DOE/ER-0668

Third International DOE/CEC Residential Radon Epidemiology Workshop February 1995

Planning Meeting Combined Analysis North America Residential Radon Studies October 1995

Radon

U.S. Department of Energy
Office of Energy Research
Office of Health and Environmental Research
Washington D.C.

Commission of European Communities
Radiation Protection Programme
Brussels, Belgium

DOE/ER-0668

Third International DOE/CEC Residential Radon Epidemiology Workshop February 1995

Planning Meeting Combined Analysis North America Residential Radon Studies October 1995

Radon

U.S. Department of Energy
Office of Energy Research
Office of Health and Environmental Research
Washington D.C.

Commission of European Communities
Radiation Protection Programme
Brussels, Belgium

FOREWORD

This report describes the Third International Department of Energy/ Commission of European Communities (DOE/CEC) Workshop on Residential Radon Epidemiology held in February 1995 in Baltimore, MD. This culminates a major effort begun 1988, co-sponsored by the DOE and the CEC Radiation Protection Programme to identify and bring together all those scientists world-wide performing epidemiological case control studies of residential radon and lung cancer. Two prior meetings were held in 1989 and 1991. The goal of this effort is to work with the investigators and to pool these studies to increase their limited statistical power and to maximize any information that could be gained from them. That goal has now been met.

At this Workshop the task moved from planning and agreement to implementation, as many of the studies were finally being completed and published. At that meeting Drs. E. Letourneau and D. Krewski of Health Canada volunteered to undertake the daunting task of actually doing the North American pooling--and a similar effort was undertaken by the CEC studies.

This report provides a summary of the Workshop as well as that of the first implementation workgroup meeting hosted by Health Canada. At this time it is proper to publically acknowledge the efforts of Dr. Jon Samet, University of New Mexico; Dr. Jan Stolwijk, Yale University Medical School, (who co-chaired all three DOE/CEC meetings); Susan Dallas, ORISE, who put all three meetings and all three booklets together; all of the very cooperative investigators and, most importantly, Drs. Letourneau and Krewski, who now must get raw data from the completed studies and put it into a meaningful whole.

Dr. Susan L. Rose
Health Effects and Life Sciences
Research Division, ER-72
Office of Health and Environmental
Research, Office of Energy Research

Dr. Jaak Sinneave
Commission of the European
Communities
Biology, Radiation Protection
and Medical Branch

PART I

REPORT OF THE

THIRD INTERNATIONAL DOE/CEC WORKSHOP

ON

RESIDENTIAL RADON EPIDEMIOLOGY

Sponsored by

U.S. Department of Energy
and
Commission of European Communities

Baltimore, Maryland

February 13-14, 1995

Third International DOE/CEC Workshop
on Residential Radon Epidemiology

February 13, 1995
Baltimore, Maryland

AGENDA

8:00 a.m. -	8:30 a.m.	**Registration/Continental Breakfast**
8:30 a.m. -	9:00 a.m.	**Welcome/Discussion of Meeting Objectives** Susan Rose, Jonathan Samet, Jaak Sinnaeve, Jan Stolwijk
9:00 a.m. -	9:30 a.m.	**Risk/Policy/Science: Equal or Not?** Congressional Viewpoint Bob Simon, Committee for Energy and Natural Resources
9:30 a.m. -	10:00 a.m.	**Recent Advances in Lung Cancer Biology** John Lechner, Inhalation Toxicology Research Institute
10:00 a.m. -	10:30 a.m.	**Break**
10:30 a.m. -	11:00 a.m.	**Are There Molecular Signatures?** William Bennett, National Institutes of Health
11:00 a.m. -	11:30 a.m.	**Concerns About Exposure Assessment** Richard Sextro, Lawrence Berkeley Laboratory
11:30 a.m. -	12:00 p.m.	**Sample Size Needs Revisited** Jay Lubin, National Cancer Institute
12:00 p.m. -	1:00 p.m.	**Working Lunch** **How to Fund the Pooling Effort: Group Participation**
1:00 p.m. -	1:30 p.m.	**The Science of Pooling** Ethel Gilbert, Pacific Northwest Laboratory
1:30 p.m. -	3:00 p.m.	**Project Status Reports**
3:00 p.m. -	3:30 p.m.	**Break**
3:30 p.m. -	5:00 p.m.	**Project Status Reports**
6:00 p.m. -	7:30 p.m.	**Reception**

TABLE OF CONTENTS

Third International DOE/CEC Workshop
on Residential Radon Epidemiology

February 14, 1995
Baltimore, Maryland

AGENDA

8:00 a.m. -	8:30 a.m.	**Continental Breakfast**
8:30 a.m. -	10:00 a.m.	**What Questions Can Pooling Address?** Ethel Gilbert, Pacific Northwest Laboratory Jay Lubin, National Cancer Institute Jonathan Samet, The Johns Hopkins University Jan Stolwijk, Yale University School of Medicine
10:00 a.m -	10:30 a.m.	**Break**
10:30 a.m. -	11:30 a.m.	**European Plans for Pooling Epidemiology** Sarah Darby, University of Oxford
11:30 a.m. -	12:30 p.m.	**Approaches for Pooling of U.S./Canadian Studies** Jay Lubin, National Cancer Institute
12:30 p.m. -	1:30 p.m.	**Working Lunch** **An Update on BEIR VI Past/Present/Future** Evan Douple, National Academy of Sciences Jonathan Samet, The Johns Hopkins University
1:30 p.m. -	2:30 p.m.	**Time Tables for Individual Studies as well as Pooling** Jonathan Samet, The Johns Hopkins University Jan Stolwijk, Yale University School of Medicine
2:30 p.m. -	3:30 p.m.	**Identification of Needs: Coordination of Future Meetings and Meeting Reports** Jonathan Samet, The Johns Hopkins University Jan Stolwijk, Identification of Needs for Coordination
3:30 p.m. -	4:00 p.m.	**Refreshments and Concluding Remarks** Susan Rose, U.S. Department of Energy Jaak Sinnaeve, Commission of European Communities

Third International DOE/CEC Workshop on Residential Radon Epidemiology

EXECUTIVE SUMMARY

Summerized by Dr. Jonathan Samet,
Johns Hopkins University, Baltimore, Maryland

Introduction

The third workshop on the epidemiologic assessment of indoor radon and lung cancer risks was held in Baltimore, Maryland on February 13 and 14, 1995. It followed two earlier workshops, one held in 1989 and the other in 1991. Like the two previous workshops, the workshop was sponsored by the U.S. Department of Energy and the Commission of European Communities. Additionally, the workshop was held in conjunction with the ongoing activities of the Biological Effects of Ionizing Radiation (BEIR) VI Committee, which is addressing the health risks of radon. The workshop was timed to coincide with the initial publications from some of the larger case-control studies and with the anticipated completion of a number of key studies in progress.

The attendees included the principal investigators for the major case-control studies that have been recently completed or are in progress. Additionally, members of sponsoring agencies were present along with invited speakers and others having a major interest and relevant expertise in the topic.

Proceedings: February 13, 1995

Following introductions by Drs. Susan Rose and Jaak Sinnaeve, representing the Department of Energy and the European Commission, respectively, and the two chairs, Drs. Jan Stolwijk and Jonathan Samet representing Yale University School of Medicine and Johns Hopkins University, the meeting began with invited presentations designed to provide a perspective on current issues in risk assessment and management, as well as the state of radon science in key areas. Separate summaries of these presentations are included in this report.

These presentations included the views of Dr. Robert Simon, (staff to the Senate Committee for Energy and Natural Resources,) on the complicated relationships among scientific research, risk assessment, and public policy. He emphasized the rapidly changing context set by the U.S. Congress. His presentation was followed by two that addressed new findings on the molecular biology of lung cancer. Dr. John Lechner, from the Inhalation Toxicology Research Institute, Albuquerque, NM, provided a broad overview of new findings on the molecular and cellular biology of lung cancer. He was followed by Dr. William Bennett from the National Cancer Institute, Bethesda, MD, who focused more specifically on research related to the possibility of specific "molecular signatures" for radon-induced lung cancer.

Dr. Richard Sextro from the Lawrence Berkeley Laboratory, Berkeley, CA, turned to the persistent problem of errors in exposure estimates and reviewed factors affecting variability of radon measurements. His presentation set a context for Dr. Jay Lubin from the National Cancer Institute. Dr. Lubin emphasized sample size needs for case-control studies in view of the present understanding of errors in exposure estimates in the case-control studies. Dr. Lubin demonstrated that plausible degrees of error lead to sample size needs that are far larger than most of the individual studies in progress.

A major purpose of the meeting was to set plans for future pooling of the data from the North American and European studies. At a working lunch, there was a discussion of potential mechanisms for funding the pooling. After lunch, Dr. Ethel Gilbert from Pacific Northwest Laboratory, Richland, WA, gave a presentation entitled "The Science of Pooling." This presentation drew on Dr. Gilbert's experience in pooling data from studies of nuclear workers. She provided a comprehensive review of the statistical aspects of pooling, and the practical issues of bringing data sets and investigators together.

Discussions at the lunch, which proceeded Dr. Gilbert's presentation, addressed the practical aspects of pooling, including funding. Two individuals who had gained practical experience through pooling studies of underground miners related their experiences. Dr. Jay Lubin described the analysis of data from studies of underground miners that had been completed in 1994 with funding from the National Cancer Institute. He pointed out that this had been a several-year project and that the investigators had enthusiastically participated. The National Cancer Institute had facilitated the project by providing funds for workshops and by supporting the staff time needed for the analysis. The pooling activity proceeded on a relatively informal basis. Dr. Sarah Darby, representing the University of Oxford University, Cornwall, England, had also pooled data from most of these same studies to address sites of cancer other than the lung. She pointed out the need for communications and the practical need to have support to facilitate communications. Dr. Lubin also commented on the difficulties and time needed to develop standardized databases for the pooling.

As the discussion evolved, it appeared that plans were already in progress for a European pooling and that a separate North American pooling was also likely. The time frames for these pooling efforts as well as for an overall pooling were discussed. Funding sources and the potential submission of a grant application were addressed.

Project Status Reports

In the afternoon of February 13, 1995, following the formal presentations, reports were made from the individual studies. See Table 1 for a listing of these studies and their current status. Table 2 provides sample sizes for the principal studies already reported.

Sarah Darby -- Cornwall, England: This study is being conducted in two counties (Devon and Cornwall) in the southwest of England, selected because of high radon levels. The cases

are ascertained at five hospitals and two controls are selected for each case: one from the hospital and the other from the community. Interviews are conducted in person. Participants are required to have lived in the area for at least 20 years, beginning 35 years previously.

The study is now at the end of its fourth year. Interviews have been completed with 1,419 persons having suspect lung cancer, of whom 986 have been confirmed as having this disease. Similar numbers of interviews have been obtained with hospital controls and community controls.

Because of the requirement for residence, the subjects have spent half of the time window of interest in their present home. There is an average of 2.3 past addresses per subject, covering the prior 35 years and ending five years before the time of interview. Only 5% of the population-time has been spent outside Devon and Cornwall.

Measurements are being made with the National Radiological Protection Board's (NRPB) alpha-track device. They are in place for six months. A study of seasonal variation has been completed and work is in progress on imputation of missing values. A database of 100,000 measurements made from homes in this area by the National Radiological Protection Board is a key resource. This database is part of the investigator's approach to addressing uncertainties in the exposure estimates. The distribution of radon measurements is not yet available, but prior measurements in this area have shown that 30% of homes have over 200 becquerels per m^3.

Margot Tirmarche -- French Case Control Studies: Dr. Tirmarche described two projects in France, the Ardennes-Eiffel Study, a collaborative effort among France, Luxembourg, Germany, and Belgium with a collaborative link to Sarah Darby in the United Kingdom project. The Ardennes-Eiffel Study is a hospital-based case-control study; the French contribution will include about 120 to 150 cases along with matched controls. Six-month measurements are made in the homes and as in the study in the United Kingdom, there is a criterion that requires residence for at least 30 years in the same region.

Dr. Tirmarche described the development of a country-wide case-control study, which is located in the regions of the country with the highest radon levels: Brittany and the Massif Centrale. A hospital-based design is being used and exposure assessment focuses on the last 30 years of residence. The final sample size is projected as 600 cases and 1,200 controls.

Andre Poffijn -- The Ardennes-Eiffel Study: This is the multicenter study previously described by Dr. Tirmarche. Cases and controls are recruited in two clinics in France, four clinics in Germany, two clinics in Luxembourg, and five in Belgium. The final goal of the study is to obtain complete data from approximately 1,200 cases and 3,600 controls, although the eventual control population may only be 2,400. The interviews were to take place between 1990 and 1994, and participants were to have lived in the region for at least 25 out of the last 35 years. A standard questionnaire was developed. Additionally, extensive emphasis was

placed on exposure assessment, although as the study has progressed, a variety of detector types have been used in the participating countries. Measurements are made in the living room and bedroom in all of the homes, although the exposure assessment is restricted to five homes per subject. To date, information has been collected from 954 confirmed lung cancer cases and approximately twice that number of controls. Dr. Poffijn anticipated that measurements would be completed in 1996. Every country will then do an analysis of its own data and then a pooled analysis of the Ardennes-Eiffel Study will be undertaken, projected to be at the end of 1996.

Dr. Poffijn also described a protocol established within the larger study to assess exposure variation. More detailed monitoring is being done in a small number of homes in each country.

Dr. Erich Wichmann -- Germany Case Control Studies: This study enrolls cases from hospitals and selects by either random digit dialing or population registries. The study began in western Germany, including the Eiffel region in the western part and the eastern portion of Bavaria, and then following unification, a portion of eastern Germany was added as well. An additional study has now been added in the Austrian Tyrol in an area with high radon concentrations. A common protocol is followed that includes a comprehensive questionnaire, charcoal canister measurements made for three days in the living room and the bedroom, and alpha track measurements made for one year in both rooms.

The study in western Germany began first and the full data set should be available by the end of 1996. The projected sample size is 2,500 cases with an equivalent number of controls, a goal that has largely been met. The timetable for eastern Germany is one year advanced so that data collection should end by the start of 1998. The sample size will be 1,500 cases and the same number of controls. The small study proposed for Austria will include 250 cases and 250 controls. The initial assessment of the distribution of measurements shows that the levels are higher in eastern Germany. Dr. Wichmann presented information showing a mean of 53 becquerels per m^3 in west Germany and of 93 becquerels per m^3 in eastern Germany.

The project includes detailed information on time-activity patterns within the home as well as on aspects of home operation that might influence the indoor-outdoor air exchange ratio. Material used to make the diagnosis of lung cancer is also being obtained including slides and paraffin blocks.

In terms of analysis, Dr. Wichmann suggested that there will be an initial pooling of the studies conducted within Germany and Austria before the data are merged into the European pooling.

Dr. Victor Archer -- Utah/Southern Idaho Case Control Studies: This is a population-based case-control study that is part of the combined two-region study supported by the National Institute for Environmental Health Sciences (NIEHS). One rationale for selecting

Utah and South Idaho originally was the high population of Mormons, a primarily non-smoking group. Case ascertainment has recently ended with selection of approximately 600 cases and an equivalent number of controls. The control collection method has provided for a balancing of the smoking habits in the case and control series.

Dr. Archer presented information on the distribution of radon levels and the relationship between occupant behavior and the measured levels. He additionally expressed concern about the effect of altitude on the measurements. He showed that in homes where the windows were kept closed that the average exposure was 72.2 becquerels per m^3 versus 52 for those keeping windows open at night. Dr. Archer estimated that 10% of homes were above the level of 148 becquerels per m^3.

Dr. Jan Stolwijk -- Connecticut Case Control Study: Connecticut represents the other field site for the NIEHS project. Interviews have now been completed on 960 cases and the same number of controls. The requirements for entry into the study included being a lifelong resident of Connecticut; the sample was further selected with stratification on smoking so as to include all never smokers and all former smokers with at least ten years of smoking. Measurements were made of radon concentration in the current dwelling and of residences back to age 25 of the subjects. Approximately 70 to 80% of the potential exposure-time has been covered. The data set includes a comprehensive questionnaire on smoking, passive smoking, occupation, and other factors. The analyses must wait for the completion of the Utah Study as the two data sets are meant to be pooled.

Dr. Ruth Kleinerman -- Gansu Province, China Case Control Study: Dr. Kleinerman described plans for a case-control study of lung cancer in a fairly remote province of China, the Gansu Province in northwestern China. In two prefectures in this province, about half of the population live in underground dwellings. In a pilot study, these dwellings were found to have concentrations that averaged 4.9 picocuries per liter. The investigators are planning a case-control study that would involve retrospective ascertainment of cases back to 1994 and then three years of prospective ascertainment. Cases will be identified through local medical facilities and confirmatory diagnostic material obtained along with tissue, if possible, for mutational analysis. Two controls, frequency match by age, sex, and prefecture, will be selected from 1991 general population census. One-year measurements will be made using alpha-track detectors. There are also plans for a pilot study that would obtain information on activity-weighted size distribution, equilibrium, and attached fraction. There are also plans to measure levels of polycyclic aromatic hydrocarbons in these dwellings.

Dr. Janet Schoenberg/Dr. William Nicholson -- New Jersey Case Control Study: This is a joint project of the Mount Sinai School of Medicine and the New Jersey State Department of Health. The cases come from five northwest counties in New Jersey which were diagnosed between September 1989 and April 1991 for males and between September 1989 and April 1992 for females. Controls were selected by random digit dialing for cases under age 65 and from the rosters of the Health Care Financing Administration for cases 65 years of age and

older. Controls and cases are matched by smoking to the extent possible. A comprehensive interview is completed. The sample size at present includes 787 cases, 54% interviewed directly, and 896 controls. An attempt was made to measure radon in all residences in which the subject had lived for two or more years in the interval 5 to 30 years before diagnosis or selection. Two 1-year alpha-track measurements were made in the living area on the first and second floor and a basement alpha-track measurement was made if the subject spent time in the basement. Two charcoal canisters were placed for four days during the heating season in the basement and on the first floor. An extensive quality control program is in place. To date, measurements have been made in nearly 2,000 homes, and the measurements should be completed in approximately one year. The data were projected to be complete by late 1995 or sometime in 1996.

Dr. William Field -- Iowa Case Control Study: This is a population-based case-control study in the state of Iowa to include 450 female cases and 600 controls during a study period that extends from October 1992 through October 1997. The study was conducted in Iowa because of the presence of a statewide cancer registry, low population mobility, and high radon levels on screening measurements. The study includes a detailed questionnaire, a one-year home radon measurement, and a histopathologic review of all lung cancer materials. While the participants are required to have lived in the same home for 20 years, the median time has been 32 years.

The project includes a detailed assessment of home characteristics. There is also an extensive time activity interview that is linked to various time periods. Up to seven alpha-track detectors are placed in the home. Some E--Perm measurements are being made, as are background gamma radiation measurements. An extensive quality control program is in place. Measurements are also being made of alpha activity in glass.

Dr. Michael Alavanja -- Missouri Case Control Study: Dr. Alavanja described a second study in Missouri to follow-up on his recently reported NCI Missouri project. This study used the same design and added one-year of cases in the state of Missouri, including smokers, former smokers, and never smokers. The study includes a total of 700 cases and 700 controls. Exposure is being assessed using alpha-track detectors, one placed in the bedroom and the other in the kitchen. Additionally, measurements are being made of alpha activity in glass using CR-39 plastic. By December 1995, it is anticipated that all of the radon measurements will be complete. Data collection includes not only the radon measurements, but review of histopathology and a detailed questionnaire. There is an extensive quality control program for the measurements. It is anticipated that about 6.5% of the population will live in homes at concentrations over 148 becquerels per m^3. Dr. Alavanja also mentioned a plan to remeasure homes where measurements had first been made in 1987. During discussion of the project, Dr. Alavanja elaborated on plans to make measurements in glass or ceramic. In Missouri, they found that most women had an appropriate piece of glass available, i.e., owned for a 25-year period of time and exposed to the living environment.

Dr. Daniel Krewski -- Canada-wide Case Control Study: Dr. Krewski described plans for a nationwide study of environmental tobacco smoke exposure and lung cancer risks that does include a component on radon. The study uses the nine provincial cancer registries and a network of collaborating hospitals in Montreal to cover the province of Quebec. A sample size of 800 histologically confirmed cases in never smokers is anticipated along with 800 population controls, all to be accrued over a three-year period from 1994 through 1997. The questionnaire to be used on environmental tobacco smoke exposure is similar to that used in a multinational study coordinated by the International Agency for Research on Cancer (IARC) and the data will eventually be pooled. The protocol for radon assessment follows that used in the Winnipeg Case Control Study. Briefly, duplicate one-year alpha track measurements will be made in all house that can be successfully included. Measurements will be made in the living area only.

In a follow-up discussion to the project, Dr. LeTourneau mentioned that house age was not predictive of radon concentration in the studies in Canada. Dr. LeTourneau also mentioned that radon concentrations in Canadian homes did not seem to track closely with indoor-outdoor exchange rate. A study of 2,000 homes has been completed in this regard. He noted that a correlation had been shown with opening the basement window, presumably not because of ventilation, but because of an altered flow of radon into the home.

Göran Pershagen -- Sweden Case Control Studies: The findings of the large Swedish case-control study had been published one year previously. Dr. Pershagen presented a summary of the findings. He then described the basis for a new project in Sweden, pooling evidence from non-smokers in various studies. In his view, a key policy question is "what are radon risks in non-smokers"? To gain a better picture of this risk, he has proposed to pool data from recent studies on lung cancer in nearly smokers in Sweden. The total of the data includes 500 lung cancer cases and nearly 2,000 controls. In some of the studies, however, radon measurements have not been made, although extensive information has already been collected. He anticipates completion of the measurements by 1998. The study has not yet been started but an effort is now underway to obtain funding.

A general discussion followed. It was pointed out that one study had not been represented at the meeting, a new Finnish case-control study to include 900 cases and 900 controls. A rough totaling of the available cases for eventual pooling yielded an estimate of approximately 16,000.

Proceedings: February 14, 1995

Discussion of Pooling

The second day of the meeting began with a group discussion of pooling. The status of the projects was reviewed along with the imperative for pooling the data to answer important policy questions in as certain a fashion as possible. There was some discussion as to the

relative merits of meta-analysis versus pooled analysis, with Dr. Jay Lubin offering a clear preference for pooled approaches. He pointed out that the pooled analysis would provide a summary, as does the meta-analytic approach while also providing finer control of confounding and assessment of effect modification. Dr. Leonard Cole, Rutgers University, provided his perspective, pointing out issues of cost, feasibility, and the need to have an answer that would impact public policy. He expressed concern that pooling could lead only to heightened ambiguity because an answer is not forthcoming. Dr. LeTourneau suggested that the investigators should focus on the science and whether something would be gained by pooling, setting aside any potential policy objectives. Dr. Krewski elaborated on this point and indicated that some outcomes of pooling could lead to useful information from a policy perspective. After further discussion, an informal polling of the principal investigators was carried out to assess their views of pooling. All were in favor of undertaking a pooling of the studies.

The group's discussion then turned to a review of the potential mechanics of pooling. The European plans were reviewed; a group is already formed and will undertake its work over the next three to five years. Other projects were discussed as potential models including the projects on underground miners and on nuclear workers.

After further discussion, Drs. LeTourneau and Krewski offered to lead organizing investigators from North America to discuss pooling. The ensuing discussion was organized around the involved regions and funding organizations. The discussion began with a reiteration of the imperative to move forward at present. Dr. Samet set out a scientific agenda of work needing to be accomplished before the data are available: such items include agreement on handling of missing values and the use of information being collected on factors modifying the exposure-dose relationship. An extensive discussion followed on scientific aspects of using epidemiologic information to address the exposure-dose relationship. There was a similarly lengthy discussion on the process for pooling.

After this general discussion, Dr. Darby presented the European plans for pooling. There had been a meeting of European investigators approximately one year previously and a funding application is being prepared for the European Commission. The aim of the European pooling will be for complete inclusion of all studies in Europe that meet specified criteria related to using long-term measurements and residence history. There was a potential pool of 15 studies possibly providing a total of just over 10,000 cases. The timetable is as follows: 1996 will be spent developing the protocol; 1997 and 1998 will involve the development of the database and the main analyses. In 1999, the final analysis would be completed. This schedule is in part driven by the completion dates of some of the larger studies. The funding request will support meetings and staff time. Dr. Darby estimated a commitment of approximately 1.5 persons for the project.

One implication of the schedule was the potential for a global pooling. It was clear that the European pooling would be completed and results reported before a combined European/North

American pooling could proceed. On the other hand, Dr. Pershagen pointed out that work could proceed jointly on various aspects of a future pooling.

At this point, the meeting divided so that the North American investigators could develop the details of a plan and also to allow for discussion among the European meeting participants.

The full meeting reconvened with reports from the European and North American groups. Dr. Darby began by reporting that the Europeans recommended the formation of some form of coordinating committee to work jointly towards the global pooling. Initial meetings were proposed as a basis for facilitating information exchange and discussion of technical issues, not to focus immediately on global pooling.

Dr. LeTourneau reported on the deliberations of the North American group. A planning meeting was proposed for Canada in the fall of 1995. This meeting would result in the drafting of a pooling protocol for North America. Dr. LeTourneau was supportive of the proposal from Sarah Darby.

The meeting ended with summary remarks from Dr. Susan Rose from the U.S. Department of Energy. She was congratulatory of the progress that had been made and the successful culmination of the process that had been started with the first workshop, six years previously and encouraged the North American effort to pool graciously proceeded by Drs. LeTourneau and Krewski. Dr. Sinnaeve was not present at the end, but is strongly supportive of the European pooling effort, already beginning preliminary planning. The North American pooling meeting in Ottawa, Canada, October 16-17, 1995 convened by Health Canada will be described by Dr. D. Krewski.

Table 1: Case-Control Studies of Radon and Lung Cancer

	In Progress	
Europe	**N (Cases)**	**Data Collected**
Cornwall/Devon	986	1995
France	600	1996
Ardennes-Eiffel	1,200	1996
Germany		
West	2,500	1996
East	1,500	1997
Tirol	250	1997
Sweden (proposed)	480	1998
Finland	900	1995
China		
Gansu	900	1998
North America		
Utah	600	1995
Connecticut	960	1995
New Jersey	787	1995
Iowa	450	1998
Missouri	700	1995
Canada	800	1998

Table 2: Completed Case-Control Studies of Radon and Lung Cancer

Completed

	N (Cases)
Europe	
Pershagen	1,360
North America	
LeTourneau	738
Schoenberg	433
Stockwell	339
(Alavanja)	538
China	
Shenyang	308

WELCOMING ADDRESS

Susan L. Rose
U.S. Department of Energy

I would like to welcome all of you to a meeting which took considerable effort to put together. Hopefully we will all benefit from what we've come here to do, and after we leave here, the remaining tasks will be the responsibility of those who are in attendance here.

My name is Susan Rose. I'm from the U.S. Department of Energy. I head the Radon Research Program in that Department and under that program we have brought the folks who are doing these studies together twice before. I would like to talk a little bit about where we have been and where we are going, but first I would like to go around the room just quickly and have everyone introduce themselves--we'll start at this end--so everyone gets an idea of who is here

...introductions were made...

I'd just like to make a few comments on what's happened since we last got together.

As you all know, and as you're going to be hearing a little bit more this morning, there have been some significant changes in terms of the science of radon and radiation generally. There have also been some important changes in the policies and the politics of radon which you are going to hear a little more detail later. I think molecular biology has certainly entered into this research area in a big way. In a way it may actually overtake the epidemiology in terms of learning what the effects of radon actually are at low levels. I think that's a very real possibility.

I think there's been some new thinking in terms of risk on this issue, risk assessment for environmental issues generally, and radon specifically. You'll hear a little bit more about that later, too.

I don't remember exactly how many years ago John Neuberger of the University of Kansas and I first talked about finding out who all of the world's radon epidemiology investigators were, but I think it was in 1987/1988. Well, we went to the trouble of identifying all the studies, and brought the study participants together twice before in Alexandria, Virginia, and our goals at those meetings, I think, were realized. I think the second meeting we all left a little depressed because the goal kept moving away as fast as we were getting toward it, it kept moving further into the future. I'm afraid we may hear a little bit about that today again. The case control studies aren't nearly finished; the more recently begun studies are maybe going to prevent the pooling effort from being done for a few more years. So, I think some of those issues were the same at the last meeting.

Among the thins we accomplished, we at least raised concerns about the exposure measurements, and if Rich Sextro does a good job you'll still be concerned today.

The smoking issues and how to handle them were discussed and because that's such an important think we hoped the studies would address those questions in similar ways. We talked about time lines, we talked about common data fields, we essentially did get to know each other, and we talked about a commitment to pooling.

I think most of us left feeling that there was a commitment. I think even beyond that--I've thought about this a lot lately--these are studies that were funded with public dollars, so, I think there is an interest in the public and the funding agencies to see that the maximum use gets made of these studies. So, there's a compelling interest beyond the investigators' own interest to join in this effort. I think we all feel pretty strongly about that.

I would like to tell you up front what our expectations are for this particular meeting. Our goal is to make the pooling happen; plan and simple. We would like to have the meeting be an interesting gift to you because we couldn't give you any financial rewards, so we have some guest speakers who are a little off our usual radon topics. Thus, the morning is devoted to some thought provoking agenda items to bring you up-to-date on cellular and molecular biology radiation, which all of you may not be acquainted with.

Later on we're going to hear a little more stuff directly related to radon but not to your studies; some discussion of BEIR VI and what is to be expected from that effort. We would also like to have the same old issues that are still out there get raised and hopefully get resolved this time. We actually would like to plan the pooling before we leave; how it's going to be done, who's going to do it; who's going to pay for it. The Department of Energy will not be able to help much with the latter, but I think that issue is out there.

Our goal here is to get the pooling affected. We did invite a lot of folks who have an interest other than directly related to a study. I would like you to feel free to get involved in question asking this morning, but once we turn the meeting over to our scientific co-chairs, Drs. Stolwijk and Samet, I would like the active participation to just be from those involved in the studies and the speakers so we can use our time to the best possible advantage.

There will be a publication again. We are recording this so that when two co-chairs put it together we will have a written record, and that way we didn't have to ask for papers. That was the first question when I asked speakers if they would come was, do we have to do a paper? When we said no, they said yes.

Lastly, I would like to introduce my colleague, Jack Sinnaeve, to say a few words on behalf of the Commission of European Communities about their perspective on this issue.

Hopefully we will all benefit from what we've come here to do, and after we leave here, the remaining tasks will be the responsibility of those who are in attendance here.

Jaak Sinnaeve

Commission of the European Communities

Good morning to all of you, and I am happy to join in with what Susan was saying. I'm much impressed by what she calls an "esteemed group" of people that is dealing with one of the issues that I do believe is actually a societal concern, the one that is dealing with Radon.

For a number of years, together with Susan, we have been trying to advance our insight on radon, in very close collaboration and consultation with the U.S., and we are still committed to bringing it all together to a good end.

Where exactly do we stand? I think there are a number of studies that are already coming to an end in the U.S. Also in Europe we do have a number of studies that lead to some what I would call preliminary conclusions that are merely dealing with regional impact assessments, but we do not have a kind of global picture.

The plan in Europe was discussed among the European participants here last night. I am very grateful to my European colleagues that are here for their agreement to have a meeting a couple of hours after their arrival in the U.S. I think our conclusions can be summarized by saying that all of the studies that are going on in Europe, let it be in Germany, in the U.K., in the Eiffel-Ardenne region, or in the Scandinavian countries, will actually come to an end towards '96-'97.

It's obvious that it's the first responsibility of epidemiologists that are working in their country to come to publication of the data coming out of their studies. But later on there is a commitment at the European level to put all of that together. I got the feeling last night that indeed, everybody is aware that we need to do that and that it will be done.

Will we have conclusive evidence out of that study even if we will have something like 5, 000 cases and 10,000 controls? I am still somewhat doubtful. We are actually facing a situation in which, if you look at the average level of exposure, even in those regions that are prone to a radon issue, the average exposure is still very low. There is the issue of the complication of smoking and all, so it's going to be difficult.

And this, from the very beginning of these collaborations, has been the justification, the motivation to go, or at least to envisage a kind of pooling of data between the U.S. and between the Europeans. And thereupon, I do agree with Susan, we're doing that effort with public resources. In Europe there are the member states, there is the Commission that is doing it; in the U.S. it's all different programs that are being implemented.

We're using a substantial amount of public resources to do that, and I think, with all respect, we are not in a situation any more where we systematically can say to the authorities, to the policy makers, we have done quite a lot but we need another number of years to give you any evidence. I think this is actually the challenge that is with all of us. We have to bring it to maybe an intermediate conclusion, but we have to do it right now.

If we are not collaborating effectively it is not only going to be a question of Susan Rose as a manager, or myself as a manager, being blamed for that lack of collaboration; it's a matter of the credibility of the epidemiological profession working on that issue to give some evidence to society whether we need to continue to use public resources to study the issue. And, I do believe that, since it is already the third time that we are meeting to discuss that, I do believe, considering the commitment all of you have to do such a thing, that it must be feasible to achieve that goal in the coming couple of years.

As far as I am concerned, I am not asking for anything that would be done next year or the year thereafter, but I think I want to know where do we stand on, what is the timing, in what way are we going to do it, in what way are we going to set up an approach that is based on a currently accepted methodology, and then we do the exercise. But, it's really something that I expect will have to be done in the two, three, maybe four years to come.

So, there is a responsibility, there is a challenge. If we have done the first analysis we will see where we go, what still needs to be done. But, we're not any longer in a situation that we can postpone providing an answer to those burning questions that are with us; is there a reason to go into intervention and remediation programs that are leading to an extremely heavy societal economical burden?

I would like you to be very aware of that because actually, if nowadays we're spending a lot of public resources, ultimately there will be the kind of commitment of all of those that may be exposed to levels of which we believe that they are unacceptable.

Let me end by saying many, many thanks to Susan Rose and Susan Dallas for having made this particular meeting possible. And, let me also thank my six colleagues from different European states that accepted on rather short notice to come here and to take part in your discussions. I hope you're going to have a very constructive and positive workshop during the coming days.

Thank you.

Jonathan M. Samet
Department of Epidemiology
Johns Hopkins University

Actually, I'm lucky to be here. I'm pleased to see so many friends. I am enjoying my new life in Baltimore. This probably the coldest few days since I've been here. I just received one of those calls while in Albuquerque, that you don't want to get, which was my Baltimore neighbor saying that the good news was that my basement was the cleanest it had ever been, and the bad news was that it had gotten that way when a pipe burst to clean it. So, I'm adjusting to the east coast.

In any case, I would like to welcome you all again to the third of these workshops. The first was actually in 1989, if I remember correctly, in the summer in Alexandria; quite a different day if I remember.

The agenda almost, I think, remains very much the same, to allow the investigators to talk to one another, to be updated on what is going on in the investigation of radon on a variety of fronts, and to look, with anticipation, to a future pooling of the data. The program has really been constructed to provide you with some news about what's going on in areas ranging from policy to molecular biology.

I really would like to, I think, re-echo Jack's sentiments about the need, ultimately, for pooling and for answering very important questions about risk. He didn't quite sound like the new congress, but he was getting there. I think that radon is really a very important test case almost for our ability to assess the risks of environmental hazards using epidemiological methods and combining them with our understanding of the effects on all biological fronts.

I think in the case of radon we really have a chance to merge epidemiology with a growing understanding at the molecular and cellular levels that Susan was mentioning.

Tomorrow we are really talking about BEIR VI, which is now in progress. Evan Douple is here, the Project Officer for that Committee, and will have a chance to talk with you about our activities, where a really important goal is to try to bring together what is happening in epidemiology, in using miner based risk models coupled with what's going on at the molecular and cellular levels to come up with our best risk models.

But, I think the world is sort of waiting for the results of these epidemiological studies and this year, with the three papers that were published, I guess the way they've been sort of scored is two to one, and I think that's exactly what we don't want to happen because that's not the way

the science really should be put together here. But, I think we've gone from the Swedish paper a year ago; risks reaffirmed, to Michael Alavanja with an intermediate stop at LeTourneau and others saying that radon may in fact just be, perhaps, another hoax.

So, I think we do have an important responsibility to sort out with these studies that are going on, and I would share the goal that Susan had, that at least we leave here with some timetable laid out for working on pooling activities over the next few years. I think there are many people waiting for the answers.

Well, I look forward to spending the next couple of days with you. I can't answer any questions about Baltimore yet, but I would try if anyone has a desperate need.

Jan A.J. Stolwijk
Department of Epidemiology and Public Health
Yale University

I am happy to be here and I am very happy to add my welcome to all of you. I think there is not very much to add to the various introductions that you've already been given, except perhaps, that the radon epidemiology is being added to several other questions that are before us in terms of very weak effects that have to be studied in large populations and are very difficult to study.

When the various studies started it was already suspected it was going to be difficult, and I think one of the things we've learned is that, it was harder than was even foreseen at the time that we started. We know a lot more about the things that limit our ability to say anything from these studies, and we have really only one answer to the difficulties that we have found to be so exasperating, and that really is a pooling effort in the hopes of trying to resolve the remaining questions that are still here.

I'm very pleased that the pooling effort is still on track, and that both the European groups and the U.S. groups are going to have an opportunity to declare themselves, and perhaps, even find ways of unifying the various studies in ways that will help overcome, to the extent possible, the difficulties that we have with this kind of study.

I hope that we make very good progress in that direction, and I'll turn it back to Susan who will introduce the speakers for the remainder of the morning.

PRESENTATIONS

Risk, Science, Policy, and Politics

Robert Simon
Committee on Energy and Natural Resources
United States Senate

It's a pleasure to be here this morning. It's an honor to be the first on the agenda for a meeting with as many distinguished people as are here.

My involvement with the radon issue is a little bit like the story of the chap who walked into an Irish bar. (Being of Irish descent I am allowed to tell this tale.) He was sitting at the bar and downing his Guiness, and he noticed a fight break out across the way. These guys were going at it, punching each other and breaking furniture, while he just sipped his Guiness. He finished it and put it down and walked over and tapped one of the guys on the shoulder and said, "Is this a private fight or can anybody get in?"

Let me tell you a little bit about what the risk/science/policy continuum looks like these days up on Capitol Hill. I have an interesting perspective as someone who is on loan from the Department of Energy to the Senate Committee on Energy and Natural Resources. I have been there since the middle of 1993 and I'll be there until the end of 1996.

I will tailor my discussion of risk, science, and policy to the issue of radon policy and how that policy might shake out in the next couple of years. I think many of the points I'm going to make about radon are generalizable to other kinds of issues on the risk/science/policy continuum.

In general, I'll say two major things. One is that, obviously, there have been big changes in the landscape up on Capitol Hill. That certainly was very noticeable last November 8, but I think that the changes that we're seeing are reflective of a bigger sea of change in how the country looks at environmental policy, a change that has been underway for quite some time.

The other message that I want to leave you with is that risk assessment and management have certainly arrived in a new way on the political and regulatory scene. Risk assessment has been used for a long time. The National Academy of Sciences report on risk assessment was issued back in 1983, 12 years ago. But, there are changes in how risk assessment is being viewed in the political environment, and I believe those changes are destined to have both a profound effect on radon policy in this country, as well as, I think, important implications for how your work will be applied in the future.

Let me talk a little bit about politics. Obviously the world has changed in Washington. I'm not working for the majority any more; I am still working for the Democrats; but now I'm working for the minority. The Republicans are in control, and I think it's fair to say, even as a Democrat, that the Democratic Presidency of Bill Clinton has been rather dramatically weakened by recent events.

I think the power shifts that are taking place in the Congress of the United States go far beyond the simple relabeling of offices, or having people move from one room down to another room, seeing a different person up on the dais when you look at CSPAN.

The way that power has shifted in Congress has a lot to do not only with political line-ups, who's got more seats in the House, but also with an intellectual line-up. One way of looking at that is to ask yourself the question, who's chairing committees in the House of Representatives these days?

For years and years and years, the tradition was that the most senior member of a particular party that was in the majority would automatically be the Chair of the committee. Well, that's not the case any more. If you look at the arguably single most important committee in the House, the Committee on Appropriations, the Republican Chair is actually ranked fifth in seniority.

What has happened is that the power of the Speaker of the House has been enormously enhanced going from the 103rd to the 104th Congress. He has reached down and selected like-minded individuals, almost irrespective of seniority, and has put them in charge of the various committees of the House. That's something that we haven't seen in this country, arguably, in 75 years.

I think that we've all heard of the "Contract With America"; some Democrats call it the Contract on America, but I think that, regardless of what you think of what's in the contract, it's undeniable that the Contract With America not only was a great marketing tool in the last political campaign, but it has left the Republicans with a very cohesive group of issues that will help them transcend the inherent factionalism within their party.

I think two of the initiatives that are in the Contract With America are going to have a direct impact on radon policy in the future. So, I will skip all the things like the Crime Bill, which probably doesn't have much to do with this particular application of epidemiology, and cut right to radon policy.

The first item, and it was Senate Bill No. 1 in the 104th Congress, is the Unfunded Mandates Bill. The Unfunded Mandates Bill essentially establishes a new Parliamentary procedure for the U.S. Congress. It kicks in when a new mandate is proposed in Federal legislation that would have the effect of costing money for state or local governments.

What the Parliamentary procedure requires under this Bill is that the Congressional Budget Office prepare a report on any Bill that proposes a Federal mandate of any size, that identifies and describes the mandate, and gives a qualitative, and hopefully if possible, quantitative assessment of costs and benefits, as well as an analysis of how these such intergovernmental mandates proceeding from the Federal level down to the state and local level might be funded.

Now, if this intergovernmental mandate is greater than a certain threshold, and the threshold is being washed out between the House and the Senate this week, somewhere in the range of $25 to $50 million, the Bill itself couldn't come up on the Floor for consideration unless the Bill contained an authorization for appropriations that cover the full direct cost of the "unfunded mandate." Also, such a Bill must incorporate a circuit breaker mechanism so that, if the appropriators don't come forth with the money, then suddenly the mandate goes on hold.

Now, there are other provisions in the Unfunded Mandates Bill and there are National Commissions and all sorts of other things, but these are the two principal provisions that would have an effect on future radon policy. For example, in the last Congress Senator Lautenberg from New Jersey proposed a radon Bill, Senate Bill 657, that would certainly have met the test of requiring this new Parliamentary procedure, and would have triggered these unfunded mandate procedures.

Now, that particular point of application of unfunded mandates to radon probably did not mean a lot to a lot of people in this country, but it didn't escape Senator Lautenberg's notice. In fact, I believe that the Senate, in its consideration of the Unfunded Mandates Bill, provided the first legislative test of where the 104th Congress is likely to go on radon policy.

In the Senate there is unlimited debate and unlimited amendment. Amendment Number 199 of the 104th Congress was offered by Senator Frank Lautenberg onto the Unfunded Mandates Bill and would have had the effect of exempting future radon legislation from the strictures of the Unfunded Mandates Bill. In fact, his amendment couched this exemption to the Unfunded Mandates Bill in terms of any law that would, quote, "Limit exposure to known human (group A) carcinogens," of which radon is one.

In spite of the somewhat indirect formulation of this issue in the Lautenberg Amendment, it is likely that many U.S. Senators, if not most U.S. Senators, going down to the Floor to vote on this Amendment knew what it was about. Senator Lautenberg's position on radon is certainly

no secret. The issue is very clearly identified with him; his colleagues are well aware of his conviction that it would be preferable that we start moving to a more mandatory Federal regime on radon policy. This amendment was the only amendment he offered on this Bill.

Now, what I think is interesting and instructive for all of us about this Amendment is what happened when the Senators went down to the Floor to vote on it. In the Senate the usual method of operation is to take a procedural vote, which is a way of disguising the substantive vote, so that you can always go back and say it was just a procedural vote. But, the first procedural vote, usually on any Amendment that comes up is a motion to table, or to kill the Amendment altogether without any further discussion. If the motion to table does not pass, then the amendment is alive for further debate and consideration.

On the motion to table Senator Lautenberg's amendment, 63 Senators voted to kill the Amendment altogether. Only 36 Senators registered a vote to keep it alive for any debate whatsoever.

I think this vote represents actually a rather striking rejection by the 104th Congress of the notion that new radon and more restrictive radon legislation is some sort of priority, and that we should accordingly lay clear the procedural path.

Let me point out that there were 40 amendments offered on the Unfunded Mandates Bill by Republicans and Democrats alike. No amendment to the Unfunded Mandates Bill got more negative votes than this one. It was a bipartisan vote; there aren't 63 Republicans in the Senate, and even environmentally oriented Senators, like Max Baucus, the Chairman of the Senate Environment Committee, and Jeff Bingman, voted against this amendment.

So, I suppose that there's a couple of messages in this. One is that, it's not likely that we're going to see a viable effort in the 104th Congress to strengthen the level of federal regulation of radon in society. I don't think, though, that this is a free pass to everybody to kick the scientific can down the road six years. I think that, actually, in the 104th Congress there's an interesting issue as to whether the Congress, not being very interested in making things tighter, will actually go in the other direction and subject the current regulatory effort related to radon to a major rethinking, or a major resizing of effort.

So, I don't think you're completely off the hook for another two years in terms of thinking about this issue and doing your science. There certainly won't be pressure on you to come up with a quick answer on whether we should increase regulation, but there might be a question some time in the next two years on whether we need to scale back what we've got.

The other part of the Contract with America that I think is significant for radon policy are the various risk assessment bills which are currently in play. In the House there is a rather complicated bill called the Job Creation and Wage Enhancement Act of 1995, H.R.9. It has many elements, the first Title is the capital gains tax cut, but Title III focuses on risk assessment, and its proponents say things like, this is a comprehensive approach to risk assessment, risk communication, and risk analysis. It all sounds good. It's certainly on a very fast track towards passage in the House. My own view is that it's probably on too fast of a track for its own good because it has so many checks and balances on regulation with risk, and studies, and peer reviews, et cetera, that it probably is unworkable in practice, and there are at least some people who think it's probably deliberately designed to be unworkable in practice, as a method of keeping more regulations from ever being written.

There is a Senate Bill offered by my boss, Senator Johnston, in collaboration with two other Senators, Senate Bill 333, that is certainly not as Draconian a measure as H.R.9. It focuses again on the use of risk assessment and public disclosure prior to the promulgation of regulations.

I think, though, that the existence of a Bill like H.R.9, and its listing on the short list of Congressional initiatives for the first 100 days, as a part of the Contract with America, is illustrative of a very profound political truth in Washington. Risk assessment and risk management are going to get more attention and are seen as ideas whose time has come in Washington.

If you look at the last two years of the rhetoric about risk assessment, you'll see the environmental movement excoriating it as one of the three members of the "unholy trinity," the other two members being takings and unfunded mandates.

The environmental groups and their Washington offices in particular have aimed their rhetoric against a much more profound or comprehensive approach towards risk assessment, but this more comprehensive approach towards risk assessment enjoys a tremendously broad political support in this country. Let me just read you a few results that came from a nationwide poll on the subject of risk assessment that was taken by Harvard University last year.

Americans were asked what they thought about the following proposition, "The government does a good job of using science in the development of environmental regulations." Fifty-two percent of Americans said, no, we don't agree with that.

They were asked what they thought about this proposition, "The government should use risk analysis to identify the most serious environmental problems and give them the highest priority in environmental spending decisions." Eight-three percent of Americans agreed.

Finally, they were asked this proposition, "When adopting an environmental regulation the government should inform the public of the benefits and costs that are expected to result from regulation." A whopping 94 percent of Americans either agreed or strongly agreed with that.

Now, why is there such tremendous support for these notions among the American public? It is always dangerous to psychoanalyze a whole population, but it might be that the general public, as well as opinion makers in the media and elsewhere, have reached their point of saturation with what might be called scare stories health and environmental issues.

Having taken one scary step to try a political psychoanalysis, I will now really get myself into even more trouble by reminding a bunch of epidemiologists of some statistics. But let me point out that by and large, Americans are not dying younger and ever more hideous deaths from environmental exposures. Life expectancy in the United States continues to increase: if you were 65 years old back in 1970, and you were a male, you could expect to live another 14.8 years, and now a 65-year-old male can expect to live for nearly 16 years more. We're not dying from a cancer epidemic in this country. If you exclude cancer caused by smoking, age adjusted mortality rate for all cancers combined has been declining since 1950.

One political scientist who died last year, Aaron Wildavsky, made the following statement (actually, he said it 15 years ago), but it's a very poignant comment. He said, "How extraordinary, the richest, longest lived, best protected, most resourceful civilization with the highest degree of insight into the consequences of its own technology is well on its way to becoming the most frightened civilization in history."

I think that the media are picking up on what Wildavsky said back in 1979. They're taking increasingly more nuanced views of environmental problems in the United States. I think if you look at such influential writers as Greg Easterbrook or Keith Schneider you can see that very clearly.

Here's something that the *New York Times Sunday Magazine* published in a major article back in last September. It says, "Forget PCB's. Radon. Alar. The world's greatest environmental dangers are dung smoke and dirty water."

Last fall as well the *Los Angeles Times* ran a very widely read and very widely syndicated series on what it termed as "cry wolf" stories on environmental health threats.

I think what's going on here is that journalists who are looking at the issue of environmental health are beginning--whether you like it or not, or think it's a good idea or not--to take these health threats and lay them side by side with more classically conceived health threats. What

they're finding is that, some of these environmental health threats have a hard time measuring up to such threats as alcohol and drug abuse, pervasive violence in society, and even such classically formulated public health threats like the emergence of drug resistant strains of tuberculosis.

I think it's not just the media that are picking up on this; I think that private citizens are beginning to have the same responses. When the House was having a hearing on risk assessment last week, they had a witness who was a school board member from suburban Chicago, a very nice lady. I met her at some time after the hearing; she and I were speaking at a program on another topic.

She recounted what she had told the House Committee. She said, "look, last week one kid killed another kid in my school district. Now, I sit back and think about all the money our school district wasted on the asbestos removal issue, $8 million in my school district; and I ask myself, what would have happened if we had spent that money on intervention activities for troubled youth? I'm sure we could have avoided one death; I'm not sure that we avoided any deaths by spending that $8 million on asbestos."

As many of you know, one of the people who's here today, a liberal Democratic political scientist from Rutgers University, Leonard Cole, has written a very compelling account about the political history of radon policy. It has all sorts of interesting stories in it, but I think the most important thing in that book is a strong plea to put all the facts, as messy and as controversial as they might be, out on the table for the American public to see and then to make a political act of faith in our fellow citizens-citizens of the best educated democracy in the history of the world-to know what to do.

Now, as experts in radon, or if you're like me, as a person with an inordinate amount of interest in the subject, we might not like the answer that comes back from our fellow citizens. We may not think it's wise. I think that's tough. We live in a democratic system and I think there's two impulses that we have to sort of be very careful to guard ourselves against, as well intentioned as they may be.

I think the first impulse that we need to avoid in all this is to pretend that our data are really better than they are, and to accordingly feed a simplified (read distorted) view of the radon issue to the public. Now, I've seen this in action. I think an excellent example of it is what went on up on the Hill after the Pershagen study was published in the *New England Journal of Medicine*. The message very clearly came up from a variety of organizations that, boy, this was a great study, you know, lots of cases, and boy, this is a compelling rationale. We just need to put more mandates into law about radon.

Here's a letter that Senator Johnston received from the Conference of Radiation Control Program Directors. It says that none of these studies will supply the definitive answer, but then it has this to say, "The important thing to remember about the current residential epidemiological studies is that each study adds to the understanding of effects of living in a radon residential environment and the studies with the largest number of cases are showing increased lung cancer risks at residential radon levels."

Well, I read the Pershagen study; I thought that it was a bit of a stretch as to how to characterize the Pershagen results. It's certainly a major stretch for trying to characterize Dr. Letourneau's or Dr. Alavanja's studies. Now that those studies have come out, there's a different marketing message we're receiving and it's, well, all these studies, you know, they're way, way, too weak. We're going to need tens of thousands of subjects to really get a conclusive link between residential levels of radon and lung cancer.

That actually may be scientifically true, but the well's been poisoned, and I think it's hard to get anybody to pay attention to that message. When you flip-flop like that you destroy your credibility in a very substantial way, and I think that groups like the Conference of Radiation Control Program Directors have a problem trying to sell that new message now.

For example, you read in publications like *Inside EPA* about this need for a study with 30,000 cases and, looking at that statement from some very crass political point of view, you sort of smell a trial balloon. You say, well, okay, what would be next is, perhaps Gary Lee will do a story about this in the *Post* and we might get Jessica Matthews to do a little Op/Ed about this, and then someone's going to try and stick it in an Appropriations Bill, or maybe a little tack on an amendment somewhere.

My view as to what would likely happen if this little sequence of events got played out is that, the notion that you need to spend tens of millions of dollars now to study tens of thousands of people of de novo, would actually have a very profound influence on the debate on radon in the United States Congress.

You have to realize that most members of Congress know that for about a decade, there have been public service ads where Fido the family pooch turns into a skeleton; you have all manner of colorful brochures that have been circulated all around the country, followed not too long thereafter by hand-wringing studies about how people aren't reading the brochures and testing their homes, and of course tons of materials for school districts to get them all excited about the topic regardless of whether schools are terribly significant epidemiological locale for radon exposure.

If after all that, we are suddenly faced with this multi-million dollar request, I think I can predict what would happen. The answer would not only be a no. It would not only be hell no. I think that what would happen is that Congress would rise up and repeal the Indoor Radon Abatement Act, and probably go looking in the U.S. Code for any other mention of radon and wipe that out too.

A well-known authority figure in the Scripture says that people who live by the sword tend to die by the sword. I think what we are seeing in the current political context is that, those who have succumbed to the impulse to make their data look a little bit better than it really was are now faced with the problem of having to live with the consequences of sending the message that we should listen to the latest epidemiological study.

Bad things happen to people who use oversimplified science to justify their cause even if they do it for the best of reasons, and even if they're good people with the best of intentions. So, I think that the impulse of making your data look better than they are is a real danger. Somewhere down the road, someone may write another book using radon as a case study of the problems of heading down that path.

I think there's another temptation that we need to avoid in all this, and that is the temptation -- it is even stronger in many ways -- to assume that, because we are experts in radon and know so much about it, that we're somehow entitled to coerce our fellow citizens to do something they're not doing, even when we don't understand why they're not doing what we're telling them to. I'd like to say a couple of things about that.

One, let me observe that we don't live in Singapore. There are places in the world that have benevolent governments that dictate the detailed behavior of citizens. We don't happen to live in one of those countries.

Another thing is that having a combination of lots of knowledge, good intentions, and noble motives still does not equal wisdom. I think that is a hard thing to accept. Most of the people who get involved in policy do so because they want to make things happen and want to make things better.

There are instances where the public's view of relative risk does not really correlate with expert assessment, and radon isn't the only one; there are many others. I think it is a real mistake to try either to get shrill or to get coercive in such cases. I think the only thing you can really do is to keep laying out the available data with all its messy glory for scrutiny by our fellow citizens. If we wander off beyond objective truth we're going to get in a lot of trouble.

I realize that what I've just said goes against at least one school of risk communication that actually advocates "simplify the message," which I translate as: "leave out the messy details." I just think that is dead wrong. Of course, this is a free country; we can all have a debate about that. I'm sure some people think that that's just the right thing to do.

When I look at the nuclear industry talking about the risks of a permanent repository in Nevada, and I see them take the risk calculation and say, well, let's divide the risk by the population of the earth. Of course, it turns out to be less than ten to the minus six when you do that. They're shading their data. The risks of a nuclear waste repository will not be distributed to the entire earth. There's a very well-characterized geological basin that will contain it all.

So, that's dead wrong, and I think they're just setting themselves up for a fall down the road. And, I think it's wrong and similarly dangerous when people who are proponents of a well-developed regulatory regime for radon present data about radon that make it seem as if some combination of policy prescriptions are going to prevent 15,000 deaths a year. That's nonsense, and that's wrong too.

I'd like to close by reading the conclusion of Leonard Cole's book; I didn't know he'd be here. He wrote it two years ago, but I think it would be very appropriate to this discussion that we're having today about risk, policy, epidemiology, and radon.

"What if epidemiological studies continue to show no relationship between cancer and radon in homes? I posed the question to dozens of government officials and scientists. The answers were unsettling. Most doubted that the government would substantially alter the current approach whatever the findings. Responses ranged from conviction that the studies will certainly show a relationship, to the belief that, if they don't, more studies would be necessary.

"There is a hint of Ptolemy in all of this. The second century astronomer conjured a complex model of epicycles to explain the apparent retrograde motion of the planets. The model was necessary to sustain the prevailing belief that all celestial bodies revolved around the earth. The model carried the wisdom of the time. When, in the 1500's, Copernicus and others placed the earth and the other planets in an orbit around the sun their ideas were scorned. The logic of their case, that is, the implicit lack of evidence for an earth-centered universe, failed to change the belief system. Even Galileo's invention of the telescope in 1610, which showed visual evidence to the contrary, initially failed to sweep away Ptolemy and his epicycles. Some experts did not believe what they saw through the telescope, and others refused to look.

"My dear Kepler," wrote Galileo to his friend about these scientists and philosophers, "what would you say of the learned here who replete with the pertinacity of the asp have steadfastly

refused to cast a glance through the telescope? What shall we make of all this? Shall we laugh, or shall we cry?

"Of course, there are important differences between the 17th Century conflict over heliocentrism and the current radon issue; yet, humans remain no less capable of sustaining beliefs out of habit, wish, or self interest irrespective of the evidence or lack of it. It is against this unhappy potential that Ptolemy's epicycles should signal caution.

"No one has a monopoly on wisdom about what a proper radon policy should be. This essential fact deserves respect from Congressional and regulatory leaders who too often speak with certitude about the matter. Since consensus is lacking in the health and science communities, differing viewpoints should be welcomed and broadcast. This is surely the healthiest approach for people in a democracy."

Recent Advances in Lung Cancer Biology

John Lechner
Inhalation Toxicology Research Institute

My charge today, originally, was to tell you some of the "exciting new things in the molecular biology of lung cancer." Lung cancer research has progressed rapidly in the last year to three or four years. As in all fields of cancer, there are two generally well- accepted types of genetic aberrations that are involved in the development of an eventual neoplasm. These are referred to as oncogenes and tumor suppressor genes, and they are the Ying Yang, or the accelerators and brakes respectively, of what makes a cell grow and not grow. It is the aberrations in these genetic processes that lead to uncontrolled growth and unfortunately often the eventual death of the individual.

Recent Advances in Lung Cancer Biology

Now, with respect to lung cancer caused by high LET radiation and radon, the primary information that is being gathered, and it is coming not as quickly as we would wish, is to study the tumors from uranium miners. That topic will be covered by Bill Bennett. I will have very little to say in my talk about the actual specifics of the miner tumors and instead will limit my talk to the generalities of what is exciting and new in lung cancer research.

One of the areas that was an old area in lung cancer research several years ago that fell in disfavor and I think is now going to come back again is the idea of an autocrine mechanism for lung cancer. Now, some of you may wonder what an autocrine is. An autocrine is typically a growth factor, but it can be a hormone, which is produced by a cell and then the cell itself has a receptor for that ligand and therefore responds. So, it is like having a perpetual motion machine where the cell makes a growth factor that causes its accelerator to move, and it just keeps going around and around and around.

Potential Autocrine Loops in Lung Cancer

A growth factor is an autocrine when it stimulates the growth of the cell that makes it.

An autocrine growth factor provides a continuous stimulus; therefore, the cell may grow continuously.

Tumor Type	Ligand	Receptor	Comment
NSCLC	TGF-α	ErbB1	
NSCLC	HGF	Met	HLGF=3p Tumor suppressor?
SCLC	SCF (stem cell)	Kit	

In the earlier days there was some evidence that for nonsmall cell carcinoma of the lung, the growth factor involved was a factor called transforming growth factor alpha. The receptor for this factor has various names, Er-B-1 is one of them, and the cells -- the airway epithelial cells and Type II cells make this factor; this receptor is on the cells and causes cells to grow.

More recently, two growth factors that were totally unrelated to lung cancer are now coming to the fore. For nonsmall cell lung cancer there is a factor which is referred to as a hepatocyte growth factor (for reasons that are totally erroneous, it was first discovered as a mitogen for hepatocytes). This factor turns out to be rather ambiguous. It is present in the lung at high levels and the receptor for it is an oncogen referred to in the early literature at MET. This system has now been shown in at least one case to serve as an auto-stimulating system where the tumor cell makes the hepatocyte growth factor and the tumor cell has the receptor and so the cell continues to grow.

One of the very intriguing aspects of this whole system, which is not well understood yet by any means, is a second factor referred to as a hepatocyte-like growth factor. These two factors are very close to each other in their actual molecular structure but one of them, a hepatocyte-like growth factor, appears to be an antagonist of this, and they both respond to the same receptor.

There is a tumor suppressor gene at Chromosome $3P_{21}$, which is a position on Chromosome 3. This factor is in that locus, so we have an exciting opportunity to try to tie all this together with a tumor suppressor gene.

In the case of small cell lung cancers, there is a stem cell factor which was originally isolated as a mitogen for leukemia cells. It is produced by the lung and the receptor kit is present in the lung, and it is now being considered as a high candidate for autocrine growth of small cell lung cancers.

As I mentioned on the first slide, there are tumor suppressor genes and one of them is located at 3P. There are several on Chromosome 3, at least three or maybe four. These losses of chromosomes are important because they give us clues as to where to look for the brakes of cell division. By losses of these brake genes then, if you're imagining the car driving, if you

can't brake it, it just keeps going until you run out of gas, and if we continue to feed the tumor, it will continue to grow.

We now know that there are some differences, again, between nonsmall cell and small cell cancers. These are very different kinds of cells when they finally form tumors, but there are some commonalities. A frequent loss of $9P_{21}$ contains at least two -- there are at least two tumor suppressor genes there for lung cancer. There are three to four on 3, and there are others: one on 17 and one on 3.

There is one here on 2, and these in bold are interesting because they seem to show up later in the process. I remind you that cancer is not a disease that occurs overnight; it's a disease that takes 20 to 40 years to develop, and there is a progression of genetic changes that occur during this time. These losses appear to be related to the actual transition of a cell from a tumor to a metastatic type of a disease. Again, the same sort of change occurs in small cell, but there are some other different losses.

There is a very exciting new technique that has been developed recently called comparative genomic hybridization. This allows one to try to monitor where other types of changes are occurring in a direct hybridization type of protocol. These losses come up using this assay. The gains, which are very new data and have only been so far done on small cell lung cancer and the nonsmall cell has not been published yet, show that in addition to losses there are some actual gains of chromosomal material that are quite frequent in lung cancers, and these are candidate genes for oncogen changes where you have too many go pedals, or too many accelerators in that causes the cell to go faster.

We have no idea what the genes are here. We do have an idea what the genes are here. This is a gene called retinoblastoma, and this one is called p^{53}, and this was called APC. But other than that we don't have any idea of what a lot of these genes are.

There's another recent exciting development in cancer, now being applied to lung cancer. This is mismatch repair or microsatellite instability.

Mismatch Repair -- Microsatellite Instability

- Replication errors corrected by Mismatch repair complex (hMSHs, exonucleases, & ligases).
- Microsatellites: 2,3 or a few basepair repeats scattered throughout the genome.
- Microsatellite mutations do not provide growth advantage; however, monoclinal microsatellite mutation is an indicator of inefficient repair.

- 50% of SCLC and 34% of NSCLC tumors have monoclinal microsatellite mutations
- Potential screening marker of premalignant disease.

What happens is that, replication errors when cells divide are corrected by a complex called a mismatch repair complex, which is a combination of many genes and many enzymes. There are things throughout the genome called microsatellites, little areas where you have two, or three, or four base pairs and they repeat themselves; we all have different lengths of these repeats called a polymorphism. You would inherit one polymorphism from your mother and one from your father and this allows us, from a genetic perspective, to trace events.

I spoke about losses and gains in the previous slide; those were in specific genes. These losses and gains are just of general markers, they don't translate to any genetic information but they do translate to a risk of something having gone wrong. So, we have now shown that about half of small cell lung cancers have these instabilities, and about a third of the nonsmall cell do. What's really exciting about this is that, these -- this loss of stability if you will, the repair process allows one a very nice potential screening marker for premalignant disease and that's an exciting area for the future. It relates not only to this mismatch repair genes, but also other DNA repair genes and other processes that control the fidelity of how well things replicate.

Another recent bit of knowledge that's come out for lung cancer is there is a very interesting relationship between two tumor suppressor genes. One of them is called Rb and another p16.

INTERRELATIONSHIP BETWEEN Rb AND p16
(Lung Cancer Cell Lines)

SCLC

	$p16^{(wt)}$ (89%)	$p16^{(mut)}$ (11%)
$Rb^{(wt)}$ (13%)	2%	11%
$Rb^{(mut)}$ (87%)	87%	0%

non-SCLC

	$p16^{(wt)}$ (32%)	$p16^{(mut)}$ (68%)
$Rb^{(wt)}$ (76%)	11%	81%
$Rb^{(mut)}$ (24%)	8%	0%

But, what's interesting is that, p16 is mutant quite often in small cell lung cancer cell lines with a very high percentage of wild type p16 and very mutant R_b in small cell and exactly the opposite wild type and mutant in the nonsmall cell.

There is a cousin gene to p16 called p15, and they are both located on chromosome 9 in the region called $9P_{21}$.

PERCENTS OF SOMATIC MUTATIONS OF p15 & p16

	$9p21^{(LOH)}$	$9p21^{(LOH)}$	$p16^{(mut)}$	$p16^{(meth)}$
Primary				
NSCLC	54-90	12	0-30	33
SC	60	0	0	0

	$9p21^{(LOH)}$	$9p21^{(LOH)}$	$p16^{(mut)}$	$p16^{(meth)}$
Metastatic				
NSCLC		23	27	
SC		0	0	
Lines				
NSCLC		50	71	
SC		0	0	

Considering recent data from Harris' lab, a lab in Japan, and David Sidransky's lab at Hopkins, including primary tumors, metastatic tumors, and cell lines, you can see that in primaries p16 varies between zero in the United States to 30 percent in Japan for nonsmall cell, and in small cell it never occurs. For metastatic disposal and cell lines the picture is confused.

The confusion may reflect the fact that this gene can be inactivated but not mutated. It's inactivated by a chemical process called methylation, and the cytosine bases have a methyl group attached to them. There's an enzyme that does that, and what appears to be going on is that there is a fair amount of inactivation before loss of the gene actually occurs, and that this gene may be playing a much larger role in lung cancer than some have suspected in the past.

We have some very interesting findings: consider this slide. This is a cell cycle; the cells divide, and here is mitosis and two cells arising. Then a cell goes in the G_1 phase, progresses along, DNA is synthesized and repackaged into metaphase chromosomes, and the cycle continues.

A number of genes are thought to be involved in lung cancer. In particular it seems that there is a lot going on in this area right here where there are some problems here; there are a lot of problems out here in a g and p53, which feeds into this. There are mutations in this gene; mutations in this gene are leading to lung cancer. Very recently in my own lab we're finding that problems in cyclin B are also involved in this area, especially in radiation-caused lung cancers in rats. We have some particular targets that we can now study and find out how frequently they're changed.

Lastly a couple of points on some other interesting areas. One is the estrogen receptor and the other is the retinoid receptor.

For reasons that we don't understand, the estrogen receptor seems to play a major role in lung cancer, even in men. It is frequently lost in nonsmall cell lung cancers and again, it seems to be due to an inactivation by methylation, not specifically a gene loss per se. In breast cancer this loss is caused by methylation and some recent evidence coming out of one of my associates' lab at the Inhalation Toxicology Research shows that this methylation correlates with radiation. In radiation-caused tumors this gene is inactivated in tumors by methylation, whereas in lung cancers caused by tobacco nitrosomines and NNK, this is not occurring.

We may have a potential signature for radiation versus spontaneous tumors but more research is needed.

With respect to the vitamin A and retinoid acid receptor, there is also interesting recent data. It's been known for a long time that vitamin A prevents squamous metaplasia. Retinoid acid beta -- receptor beta is frequently not expressed in nonsmall cell lung cancers; again, the gene is defective but without a mutation involved, implying another candidate for possible methylation inactivation; epigenetic is another term applied to this phenomenon. This is another change to assess for radiation-caused cancers.

I will now move to the possibility of taking respiratory samples to determine if people have pre-malignant disease. Now, with respect to the uranium miners that are still alive in the United States, Europe, and Asia, there are large numbers of men who have worked in the mines and received substantial doses of radiation.

Can we develop a means to obtain some of these lung cells and analyze them for genetic aberrations? Bearing on this directly is recent work from an Italian laboratory. These researchers conducted genetic and chromosomal analysis on some of the genes that I've been telling you about, and attempted to distinguish recurrences from new primaries following a first tumor.

There appears to be many people who develop a second independent tumor, and not a spread from the first tumor.

When they took samples from the uninvolved lung, other lobes, of people who had lung cancer, about half of them had genetic abhorations in "normal" cells. In other words, these were cells that had changes but not deranged to the point of producing a clinical disease. This finding suggests an opportunity and a scientific basis for taking cells from people and looking for early changes. We have done this now with a couple of miners in New Mexico and have found one individual, who now we know has a chromosomal aberration in cells in his lung, but has no evidence of cancer. Obviously, this person needs to be monitored.

In the Italian study, the people who didn't have any lung cancer had no genetic aberrations in their normal cells. However, there were only five such people so we need more information.

The most exciting, I think, in my opinion again, area of high LET radiation biology is the fantastically high level of genomic instability that is caused by these big particles. This is work that has been going on since about 1992, and is advancing rapidly.

There is early non-random chromosome instability that occurs in the progeny of cells that have been irradiated in vitro. At present, the data all come from experiments in culture. The cells are exposed to high LET radiation; in my lab we're using plutonium-238 as the source, and we're looking at 7 to 25 population doublings later, so the immediate radiation effect is long passed, the cells have grown repetitively before analysis.

A fair number of the cells show chromosomal instability, at a rate that appears higher than for any other carcinogen. The word "appears" is operative in my sentence because the comparison is to a couple of carcinogens and a few studies of X-rays. But the evidence does suggest that high LET radiation causes gene alterations that remain stable.

I will conclude with a story that I think Dr. Bennett will carry forward; that is, about two and a half years ago there was a finding of a specific mutation in the P^{53} gene that was related to radon exposures. It was a mutation in Codon 249, one of the bases in the gene.

In a collection of tumors from Grand Junction, in the Colorado Plateau mining area, about half of the tumors had this mutation of the p^{53} gene. This finding did not agree with a previous study from New Mexico.

There was a recent paper in *LANCET* that did not find this mutation with domestic radon exposure. My lab, in collaboration with Curt Harris' lab, will expose normal human bronchial epithelial cells to radiation at high doses to learn if we can measure the actual mutation. At the moment at least, it looks like this p53 mutation may not be a particularly good signature for high LET radiation.

Are There Molecular Signatures?

William P. Bennett
National Cancer Institute

Thank you very much for the invitation to tell you a little bit about our work on mutational spectrum analysis. We entered this area a couple of years ago with work on New Mexico uranium miners. My charge today is to address the question; are there molecular signatures? We've been interested in this question for a number of years, and there is now quite a bit of interest in this area. I would like to start with an introduction of some basic terms. The mutation spectrum is defined as the type and location of DNA base change. There are about five well documented examples currently. For example, G to T transversions at Codons 249 were reported in the Taylor article on the uranium miners from the Colorado Plateau as well as in aflatoxin- associated liver tumors in China and Sub-Saharan Africa. There is also the example of C to T transitions at dipyrimidine sites in sunlight-associated skin cancers.

There is growing evidence that some carcinogens cause characteristic base changes, sometimes with sequence specificities, and these have been compared to fingerprints or footprints. There is a current debate as to how specific these mutational spectra are: whether they will be found to be as unique as a human fingerprint, or more general in terms of a footprint of say a size 10D shoe worn by a 160-pound individual.

Our interest has been in whether analysis of these mutations may give insight into etiology of a variety of cancers; today I will be talking about radon- associated tumors.

Most of our work has been with the p^{53} tumor suppressor gene, shown in this schematic diagram. Along the X-axis in the multi-colored bar is a schematic representation of the protein's 393 amino acids. First discovered in 1979, it has a long checkered history that I won't go into, but since 1989, there have been several hundred papers describing its structure, functions, and protein - protein interactions.

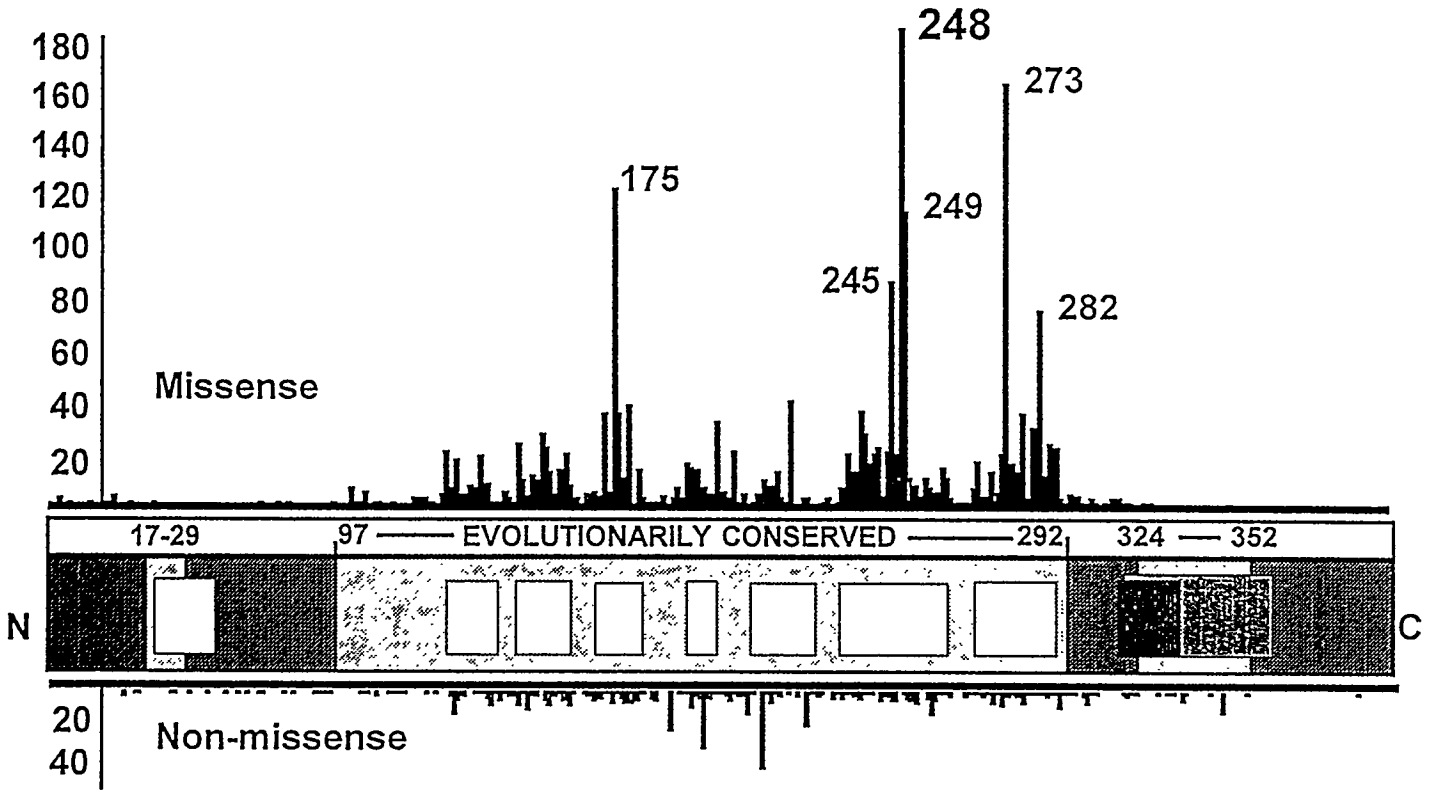


Figure Legend. Schematic representation of the codon sequences of the p53 tumor suppressor gene. Along the horizontal axis, the amino acid terminus ("N") is on the left, and the carboxyl terminus ("C") is on the right. Evolutionarily conserved sequences occur between codons 17-29 and 97-292; the regions with greatest conservation occur within the eight white boxes. "NLS" stands for "nuclear localization sequence." The location and number of point mutations are shown by vertical bars. Missense mutations are shown above the horizontal bar; mutational hotspots occur at codons 175, 145, 248, 249, 273 and 282. Non-missense murations (e.e., non-sense, insertions and deletions) are less common and are indicated below the horizontal bar.

I draw your attention to the mid-portion of this diagram, which has the lines going up along the Y-axis from the mid-portion. Those represent the mutations -- the locations of the mutations that have been identified more than 4,000 tumors to date. You'll notice that the distribution is not random, and that there are several mutational hot spots at Codons 175, 245, 248, 249, 273, and 282. These mutational hot spots are fairly characteristic of mutational spectra in a number of systems, including this one. Last year the crystal structure of the protein was solved, and it provided a rather satisfying explanation for the distribution of these mutational hot spots.

The p53 protein is a transcription factor which binds to a specific consensus sequence to activate transcription. The crystal structure of the p53 protein revealed that the normal arginine residue encoded by codon 248 inserts into the minor groove of the DNA double helix at the consensus sequence to form four critical hydrogen bonds; this structure-function relationship provides a reasonable explanation for the high frequency of codon 248 mutations. The other mutational hotspots at codons 175, 245, 249 and 273 encode amino acid residues that surround codon 248 in the three-dimensional structure and appear to provide a scaffolding to support the interaction between the arginine residue encoded by codon 248 and the minor groove of the DNA double helix.

That completes the relevant background on p53 structure-function characteristics. Now I'd like to outline the relevant literature on mutational spectra in radiation-associated tumors. Starting with ultraviolet (UV) radiation, the characteristic mutations are C>T and CC>TT mutations at pyrimidine dimers. UV radiation produces two characteristic photoproducts, either the cyclobutane-pyrimidine photodimer or the 6-4 thymine photodimer. Excision repair of these bulky, non-instructive lesions then produces the characteristic C>T or CC>TT mutations.

p53 mutations in sunlight-associated skin tumors cluster in hotspots at codons 151, 177, 196, 245, 248, 278, 286, and 294. A recent report showed that these hotspots appear to be the intersections between hotspots for UV photodamage and slow spots for DNA repair. These investigators devised an assay to detect UV photodamage hotspots at codons 151, 278, 286, and 294. Then they found slow spots for repair at codons 177, 196, 245, 248, 278, 286, and 294. Comparison of these hotspots shows that the final mutational hotspots are determined by both locations of UV damage and DNA repair.

Moving on to gamma radiation, we did a study a few years ago on some Japanese A-bomb survivors, looking for evidence of a radiation signature in these lung cancers. By design these were mostly nonsmokers, and at the end of the study we had nine cases exposed to radiation and eight nonexposed controls, mostly nonsmokers. We found mutations, but we could not find any distinguishing characteristics about these. Exposed and controls had about the same

number of mutations and the character of the mutations was approximately the same. We could not conclude that there was any characteristic radiation signature in this study.

An interesting finding was the low frequency of GC>TA transversions among these nonsmokers (note: GC>TA transversions are characteristic lesions caused by chemical carcinogens in tobacco smoke). Among Japanese smokers, the frequency of GC>TA transversions was 28% of all mutations, but among this group of Japanese nonsmokers, the frequency was 13%. When the frequency of GC>TA transversions is compared to smoking histories in pack-years, there is a dose response with an increasing frequency of GC>TA transversions correlating with increasing smoking history.

I would like to point out that smoking is a very powerful mutagen, and in trying to detect low level effects of radiation or other carcinogens, we need to control for the consequences of smoking.

This is a study of lung cancers from post-Hodgkin's patients -- Hodgkin's disease patients who received radiation for their mediastinal Hodgkin's disease and later developed lung cancer within the radiation portals.

In this series there were 11 lung cancers in these Hodgkin's disease patients, and we found six mutations. There was an interesting feature in the mutation spectrum. In spite of heavy smoking histories in these patients, which predicted G to T transversions, out of these six mutations we found no G to T transversions and a predominance of G to A transitions.

In the post-Hodgkin's lung cancers, 67 percent of mutations were G to A, in spite of heavy smoking histories, and the G to T transversions were zero, opposite to the usual smoking cases with 40 percent G to T and 24 percent G to A. The uranium miners are of course more similar to the smokers than to the post-Hodgkin's cases.

Additional information comes from some in vitro model systems, involving HPRT, as well as some shuttle vectors, but I will not discuss these studies today.

What is the bottom line from this study of the gamma-radiated Hodgkin's disease patients? These tumors may be related to either smoking, radiation, chemotherapy, or oxidative damage, but until now, there were no tools to use to determine the dominant factor, i.e., smoking, radiation, chemotherapy, or oxidative damage. Conventional wisdom has proposed that either smoking or radiation damage is the dominant mutagen and the rest are secondary forces. The data from this series of lung cancers following radiation for Hodgkins disease suggest that therapeutic radiation was the primary mutagen producing mostly GC>AT transitions through

the radiolysis of water to produce hydroxyl radicals. The implication is that smoking played a secondary role in generating these tumors. If confirmed in a planned, larger series, these data would refute the conventional dogma that radiation-related tumors cannot be distinguished from other causes.

Well, let's move on to alpha radiation, which is our main interest for today. These are the primary data from the New Mexico study, which we published a few years ago. There were some 20 patients, and about seven point mutations, including two deletions. The number of deletions is a little bit higher than in lung cancers generally. Most of these patients were smokers, and since deletions are the most common lesion associated with radiation, that is to be expected. Otherwise, the mutational spectrum was rather similar to other lung cancers.

This is a summary of the data from the Taylor et al. article published in *LANCET* in January 1994. They described 52 uranium miners, with mean radon exposure of 1,300 working level months, about five times the average level in the New Mexico miners. The mean smoking history was extensive, 41 to 59 pack years, although there were five nonsmokers in the group.

To summarize the p^{53} mutations, there were 30 mutations in 29 of the 52 tumors. These were predominantly large cell and squamous cell tumors, and there were -- out of these 30 mutations 16 of them occurred at Codon 249, a G to T transversion, producing an arginine to methionine amino acid change.

This is a rather remarkable mutational hot spot. Three of the nonsmokers had this mutation, and this particular mutation had been previously reported in only one out of 241 lung cancers.

So now let's compare the two studies. The mutation frequencies were similar, 42 percent in New Mexico, 57 percent in Colorado. The second point, the New Mexico series had two deletions, which is rather characteristic of radiation, and three G to T transversions, although there was no strand bias; that's a technical point that you could ask me about later.

In the Colorado Plateau study, 16 out of the 30 mutations were at this single site -- all in the second nucleotide position and all G to T transversions.

The conclusion of the Taylor paper was that this mutational hot spot at Codon 249 might be a molecular signature for radon exposure. They suggested that it could be used to identify cases of lung cancer related to domestic radon exposure.

Is the Codon 249 mutational hot spot a marker for radon exposure? Since publication of the Taylor paper, there have been two pertinent reports. One was a letter to *LANCET* that appeared a few months after the Taylor article suggesting that mycotoxins might produce the

Codon 249 mutational hot spot. The letter discussed the fact that Czechoslovakian uranium miners had been checked with throat swabs for cultures and that mold grew in these throat cultures. Among the molds was one that produces sterigmatiocystin, which is a mycotoxin that is a carcinogen related in structure to aflatoxin B-1.

Now, I mentioned earlier that aflatoxin has been linked to liver cancer in China and Africa, and it also causes a remarkable mutational hot spot which has been confirmed by numerous studies around the world, also at Codon 249, also a G to T transversion, and the only difference is that it is one nucleotide position away (i.e. the 3rd nucleotide position instead of the 2nd).

The letter added that sterigmatocystin, like aflatoxin, forms N7 guanine adducts and produces lung cancers in animal models, coincidentally, mostly squamous and large cell histology like the human tumors.

Last month another article in *LANCET* reported on lung cancers with known domestic radon exposure. This was a pilot study with only 17 lung cancers but with documented domestic radon exposure. Looking with a restriction enzyme analysis only at Codon 249, no mutations were found. The radon exposure levels ranged from 0.5 to 32 working level months. Recall that the Colorado miners had more than 1,300 working level months exposure, almost two orders of magnitude greater.

The Taylor study needs confirmation. I can add that Monica Holstein, one of our collaborators in Europe, is looking at some of the East German uranium miners. Preliminary data from about 35 tumors, looking I believe, at only Codon 249, has not found any of these specific mutations to date.

I'd like to tell you about our collaborative study with Dr. Alavanja and Dr. John Boice at NCI, on tumors from the study in Missouri. We are collaborating to do a laboratory study using paraffin blocks collected from the field in coordination with the exhaustive dosimetry and epidemiological information.

The design is well known here: a case-control study with numerous objectives looking at environmental radon, passive smoking, and other factors. Our approach has been to look at adenocarcinomas in never-smokers married to never- smokers. Our experimental design is to look at the p^{53} mutations in the high and low radon exposure groups. The doses at the high end are 10 to 42 working level months, and at the low doses 3 to 6 working level months.

Our series will reach about 160 patients. To date, we have screened approximately 80 of these tumors in a first pass. So far I can say that we have not, although the study is still blinded (we do not know of the dosimetry of the radon) we have not found any Codon 249 mutations in these 80 tumors.

Thorotrast is another source of alpha radiation which has produced tumors in the lung and the liver. This is another very relevant, interesting tumor series that is being analyzed. There is a Danish cohort and a Swedish cohort which have been well characterized and are being studied currently, but I don't know of any published results yet.

So let's move on to our current question and future research. Is there a molecular signature? My opinion is "possibly yes". Of course, there are a variety of opinions depending on who is asked.

For radon we have the proposed Codon 249 signature. I must stress that this needs confirmation. Like any striking mutational hot spot, it really should be confirmed because of the chance for laboratory contamination, or artifact.

For gamma radiation, we and others have observed a predominance of G to A transition in tumors. We think it's promising enough to follow-up, again, in collaboration with John Boice and others, looking at lung cancers following radiation therapy for breast cancer.

Deletions: I think this needs some further work. Let me show a figure proposed by Mark Greenblatt, who prepared a recent review of the p^{53} mutation data and is now following up with some deletion analysis. It's also been reviewed by, Ted Kunkle in North Carolina. The emerging view is that these deletions are not as random as initially thought, and you can explain many of these complex deletions and insertions through intermediate loop structures.

Another question: is p^{53} a good target for radiation-induced mutations? Again, there are a variety of opinions. Those who say "yes" will be even more affirmative if more of the Codon 249 mutations are found, if more of the G to A transitions are found in radiation-induced tumors, and certainly if better technology for deletion detection is developed.

Others will say no; we need genes more like APC, which is a colon cancer gene which selects for deletions.

In closing, what is needed to do mutation analysis on large series of human tumors? Certainly we need faster and cheaper sequencing technology and optimal gene targets, and this is the current schema for mutation analysis from archival histology section, to start with a slide --

glass slide with the tumor and stroma, do microdissection to enrich the sample for tumor, isolate genomic DNA, and then do PCR, gel purify the PCR products, and finally do sequence analysis. This is a very complex scheme. It needs automation to go quickly and without laboratory contamination.

One of my last slides: what's worth doing now? In my opinion, to find human populations and collect radiation dosimetry. Potential exposures would be therapeutic radiation, occupational exposure, or accidental exposure. Some of these populations include secondary cancers after radiation; for example, the East German uranium miners and Chernobyl survivors.

I would analyze tumors as well as collect blood for HPRT analysis if there is access to blood products.

In vitro models are also worth doing. The HPRT plus shuttle vector models for this area should use human cells because of the recent evidence showing that there are large differences in DNA repair between animal and human systems.

Again, going back to the UV light example, illustrating the importance of DNA repair in generating these mutation spectra.

We need to organize mutation databases and develop analytic software. I'd like to think this would be particularly interesting to epidemiologists; databases and software for analysis are now available by Internet.

Let's just look at the mutation spectra comparison. This particular program uses a Monte Carlo analysis to generate a P value, and at the 95 percent confidence level indicates that two spectra are not the same. We can ask: are these Colorado miners mutation profiles significantly different from those of other lung cancers? We can obtain a P value for that analysis.

While I've primarily been reviewing the literature, I would like to recognize my collaborators, particularly at NCI: Michael Alavanja, John Boice, Lois Travis, and others in the Missouri study.

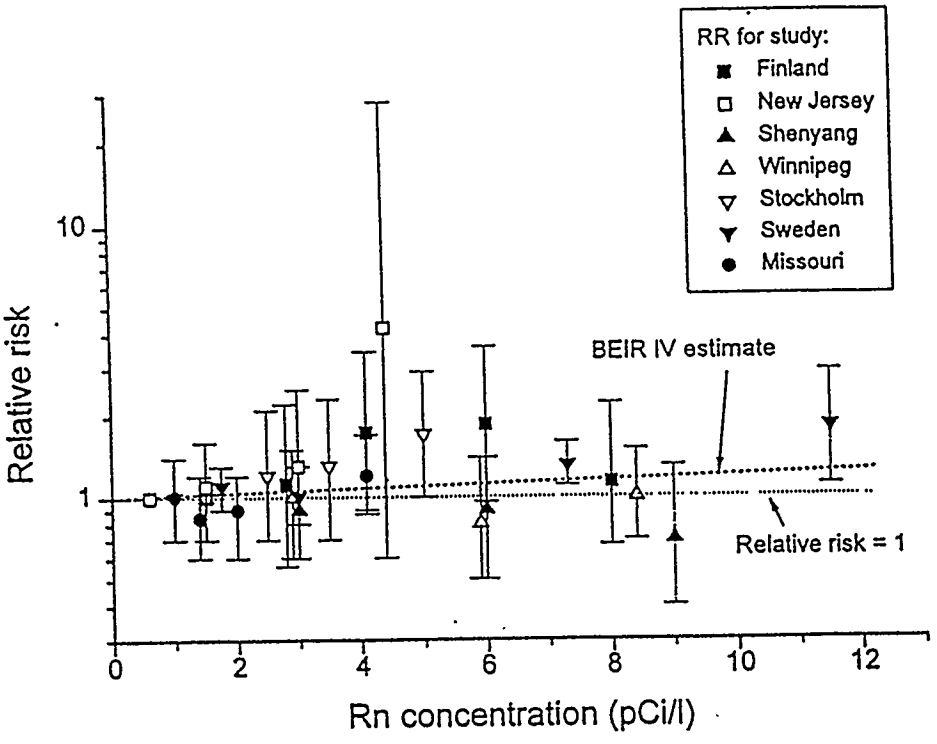
Concerns About Exposure Assessment

Richard Sextro
Lawrence Berkeley Laboratory

I will talk briefly about several issues: temporal and spatial variability of radon concentration, and house-to-house variation. These are difficult issues that I know you have already considered to some extent.

Figure 1, borrowed from Jay Lubin, shows the problem that we are facing. The data are consistent with the null hypothesis, the BEIR IV model, and the other potential models. We need to have more precise estimates at the lower levels of exposure, say below 200 Bq/m^3 (5pCi/L). It will be difficult to achieve this precision.

Figure 1.

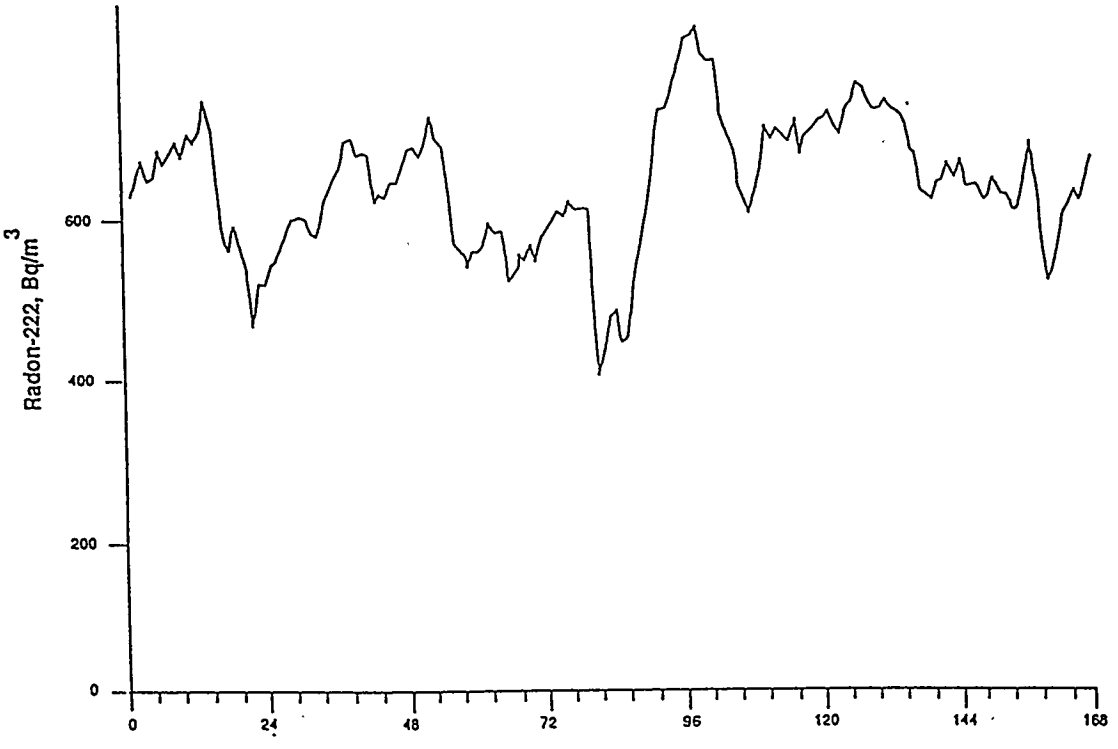


Relative risks (RR) for lung cancer by picocuries per liter (pCi/l) for the seven case-control studies of residential radon (Rn) exposure listed in table 1. Also shown are a plot of predicted relative risk for residential exposure from the age of 35–65 years using the model of the Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (2) adjusted to 1 pCi/liter as the referent exposure and a plot of a relative risk of 1.0.

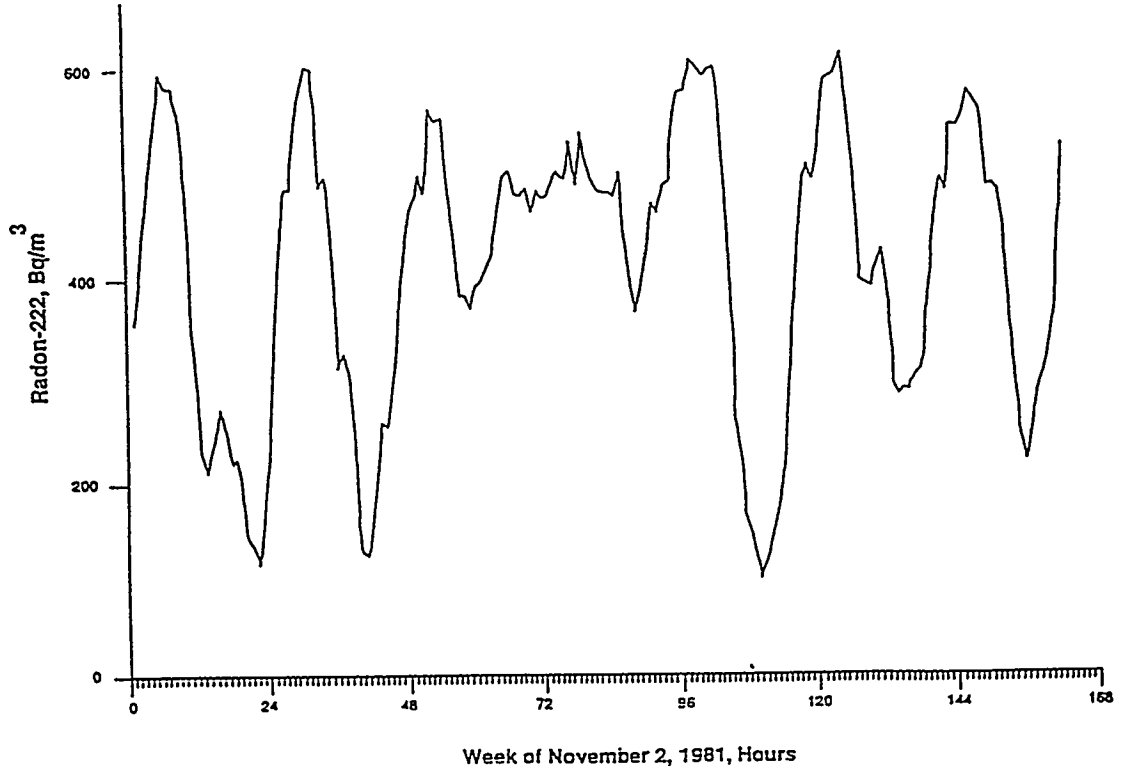
For public policy we need information at the lower levels of exposure where most people are exposed.

In estimating radon exposures, all the recently published studies have primarily relied on longer-term integrations which reduce variability. Of course, the same house has quite a bit of variability; Figure 2 shows concentrations in December and November. In the early part of November, this is probably still the tail end of the "knee season" during which occupant behavior changes. Diurnal changes also have a role, but the occupant behavior is important -- very important here because this is probably a time when the weather, during the day, was still mild and people tended to leave their houses open more.

Figure 2.



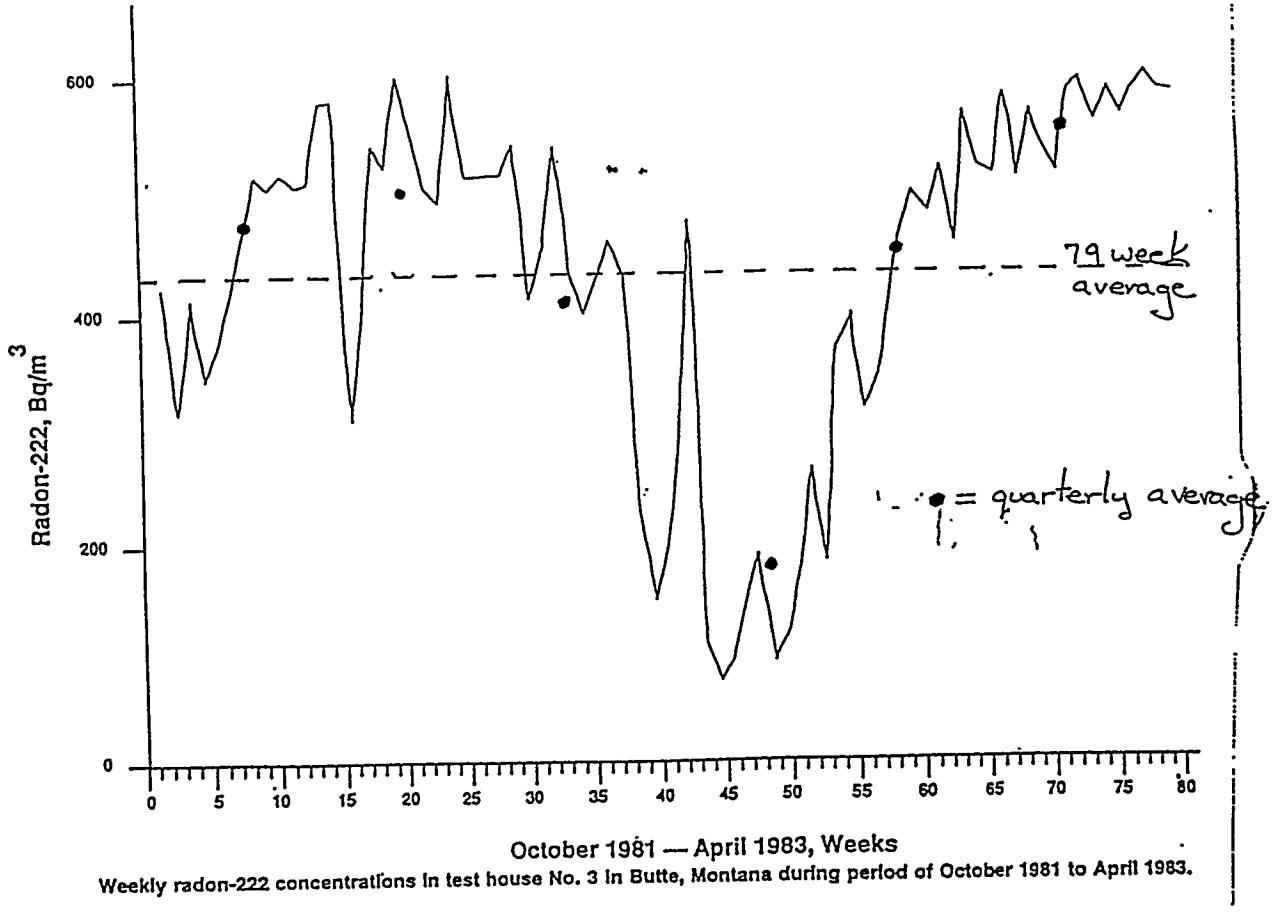
Hourly radon-222 concentrations in test house No. 3 in Butte, Montana during week of 28 Dec. 1981.



Hourly radon-222 concentrations in test house No. 3 in Butte, Montana during the week of 2 Nov. 1981.

The data shown in Figure 3 are for the same house, now showing the weekly averages for essentially a year and a half, and the dotted line shows the 79-week average, and the dark circles are the quarterly averages. Extensive variation is evident.

Figure 3.



Weekly radon-222 concentrations in test house No. 3 in Butte, Montana during period of October 1981 to April 1983.

Now, these data are from Butte, Montana, where the heating degree days, show that it's not quite as cold as the far northeast, but it's quite cold there most of the time. In fact, you can see this is almost a two-season place, winter and, as they say, Minnesota road construction season. So, making measurements over a couple of quarters in the winter time may not provide a very good estimator; in Butte it might work better because, as I said, it tends to be colder longer, perhaps similar to the Swedish and Finnish studies.

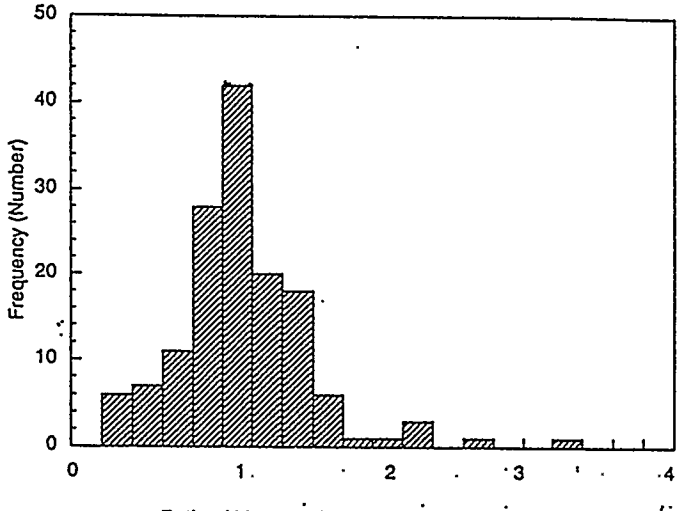
So obviously, as has been discussed, the central issue is estimation of exposures; and some of the related issues are questions of the device precision or inaccuracy.

Home occupance or occupancy fraction is also important; I was surprised to see that in the Missouri study, for example, the figure 84 to 86 percent was the average occupancy. The National Radon Residential Survey, I think, had a 65 percent occupancy, if I remember correctly.

Missing data is another big issue not well addressed. There is the related problem of how to propagate uncertainty through the risk assessment, and finally the question of using concentration and exposure as a predictor of dose.

Several studies, at least two that I looked at most recently, did some analysis of the variability and the detector uncertainties, and found a bit less of a problem. Data are shown in Figure 4 from a several year effort at Grand Junction to expose a variety of different alpha-track detectors in a chamber. They did so many times a year with different batches of detectors.

Figure 4.



Frequency distribution of measurement results for alpha-track detectors exposed in a chamber.

This figure shows the frequency distribution of measurement results for alpha track detectors. I think that these were the best results, which I think are for the Landauer Rad-Track. The comparison is what the detector determined versus the measured concentration using a highly precise measurement system.

There is about a 30 percent variability, one sigma deviation, under chamber conditions. The Rad-Track, like Terradex before it, was designed to avoid problems with other contaminants, filter loading, or from other pollutants. So the chamber conditions may a reasonable test. But nevertheless, there remains a significant problem of device uncertainty or inaccuracy.

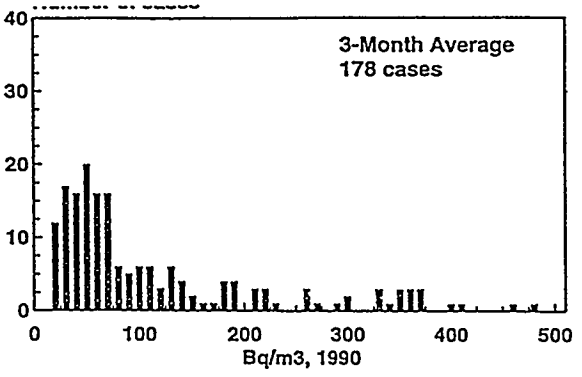
I should point out that the chamber studies at Grand Junction have shown that occasionally a bad batch is received. There may be a bad batch of detectors that, on a lot-by-lot basis, will be three standard deviations away from the normal calibration factor. In the epidemiologic studies, it's imperative to have lot-by-lot blanks and duplicates because there are these large variations on occasion.

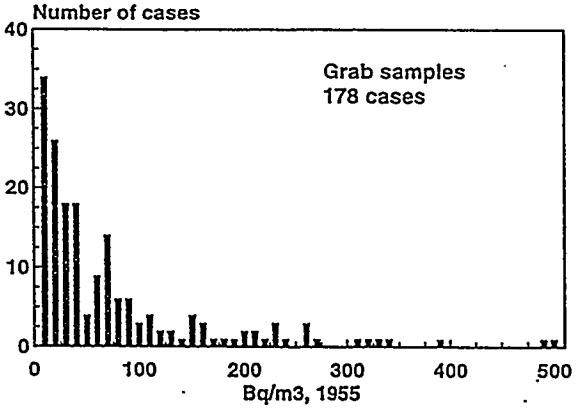
Another key issue is the question of how well measurements made in houses now reflect concentrations say 20 or 30 years ago?

There really are very few data on that subject, unfortunately. The Grand Junction group has made measurements in some contemporary houses ranging back about seven years to assess year-to-year variation. These are houses that haven't been structurally modified, and they find about a 20 percent variability, much of that weather driven. If it's a lot colder one year on average than the next, and if the radon concentrations are above one or two picocuries per liter, it's going to be dominated by adjective flow of soil acid in a house, and so that's going to be essentially related to, maybe not exactly linearly, but it's going to be related to the weather conditions because of the creation of the stack effect and so forth.

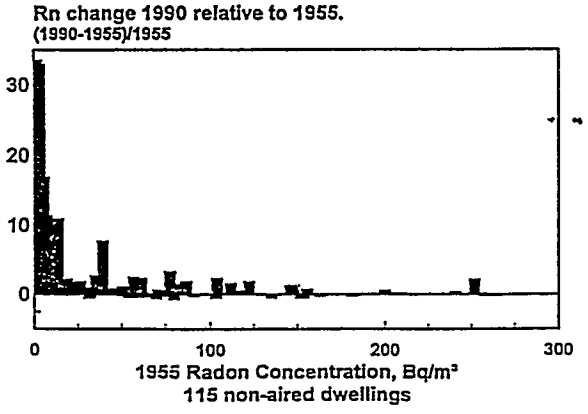
The only study that I'm aware of that has tried to look at the question of going back to some historical data -- the comparison rather of some measurements made a number of years ago versus some contemporary measurements were these data recently published by Hubbard and Swedjemark in *Indoor Air*, shown in Figure 5.

Figure 5.





Frequency distribution of all 176 cases less than 510 Bq/m³ for both 1955 and 1990.



All 115 non-aired cases. (Rn(1990) – Rn(1955))/Rn(1955) as a function of Rn 1955 in Bq/m³ plotted as a bar-chart

At the top of the Figure are measurements made in 1990 in about 170 houses, or dwellings, most of which are multi-family dwellings. Consequently these data provide little insight into the more predominant housing type in this country, and perhaps even in Sweden, which is generally single-family detached houses. But the initial measurements that were made in 1955 were predominantly done in those kind of houses; Hubbard and Swedjemark went back and tried to remeasure those same dwellings.

This is the frequency distribution and measurements made with three- month integrating detectors in 1990, and here are the original data from 1955. One of the difficulties in making these comparisons is apparent: grab samples were taken in 1955 as part of a study that, among other things, was looking at diurnal variations. They were trying to make their measurements essentially at the same time every day within these houses. I don't believe that the data they reported were in any sort of way corrected, as if to say, if you're going to measure at the same time each day, were you always at the same place on the curve, and of course, you can see that there are some places where in fact it gets very difficult because the houses don't behave exactly the same day to day.

Nevertheless, this is the one data set that allows comparisons between historical measurements made long ago and more contemporary measurements. The bottom chart here shows the change relative to the original 1955 measurements as a function of the 1955 concentration. Most of the big changes, expressed as a percentage, are not unexpected at low concentrations. At low concentrations, the accuracy of the measurements is lowest, particularly below 30 or 40 Bq/m^3 where there may be 100 percent uncertainties.

At higher concentrations the relative change is quite small, and in fact, it's kind of scattered. There are probably more changes in the sense that the 1990 measurements are a little bit higher, but at these higher concentrations, the changes aren't very large with respect to the changes at much lower concentrations.

The comparison is limited in its interpretation problems because of the differing measurements: grab sample measurements versus longer term measurements. Nevertheless, the comparison shows that the data compare somewhat out here, again, above 100 Bq/m^3.

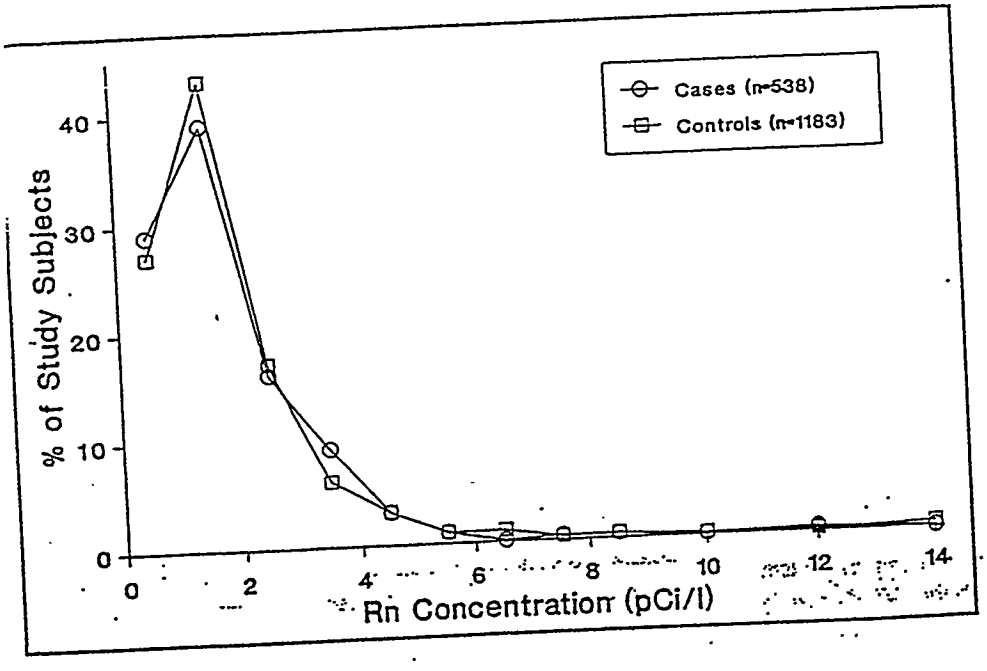
I think that, on the other hand, it is clear that one needs to pay some attention as to how to incorporate into essentially the uncertainty analysis the question of the overall measurements. If measurements are made in a house today, but the house was lived in 25 years ago, for say five or ten years by the study participant, resulting uncertainty needs to be incorporated and propagated as part of the uncertainty analysis.

Figure 6 shows data from the Missouri study. It addresses the question of methods for estimating missing data; a number of other studies that have been recently done or are ongoing also face the question of how to input missing data values.

Figure 6.

	12-mo measurements			
	Bedroom	Kitchen	Basement	
ithmetic mean, pCi L^{-1} (SD)	1.63 (1.57)	1.59 (1.48)	2.83 (1.70)	
eometric mean, pCi L^{-1} (SD)	1.19 (2.23)	1.16 (2.23)	2.37 (1.86)	
o. of measurements	2797†	2650	17	

*No. of dwellings measured for radon 5-30 years before the enrollment of case patients and control subjects in the study.
†Includes 133 side-by-side quality-control readings.



distribu
tions fc
rollmer
78.4%
radon c

OR for lung cancer by quintiles of TWA residential radon concentrat

	TWA radon levels*						
	I	II	III	IV	V	Total	Continuc
Case patients	112	112	93	99	122	538	
Control subjects	233	242	233	252	223	1183	
Total	345	354	326	351	345	1721	
Mean pCi L^{-1}	0.6	1.0	1.4	2.0	4.0		.9
OR‡	1.00–	1.01	0.84	0.90	1.20		
95% CI		0.7-1.4	0.6-1.2	0.6-1.3	0.9-1.7		

OR with additional adjustment

These are the measurements from the cases and controls in the paper by Alavanja and colleagues. The median value of the distribution was used as the missing value.

I was not clear on reading the paper as to how uncertainty in the median was considered. The uncertainty increases in time-weighted average calculation, which might cover a 15-year spread instead of a 3- or 4-year spread.

Nevertheless, I think that using the median value is probably not an unreasonable choice, given other choices that could be made. In this study, the concentrations in the houses of both cases and controls were relatively uniform so that the use of the median probably had little impact.

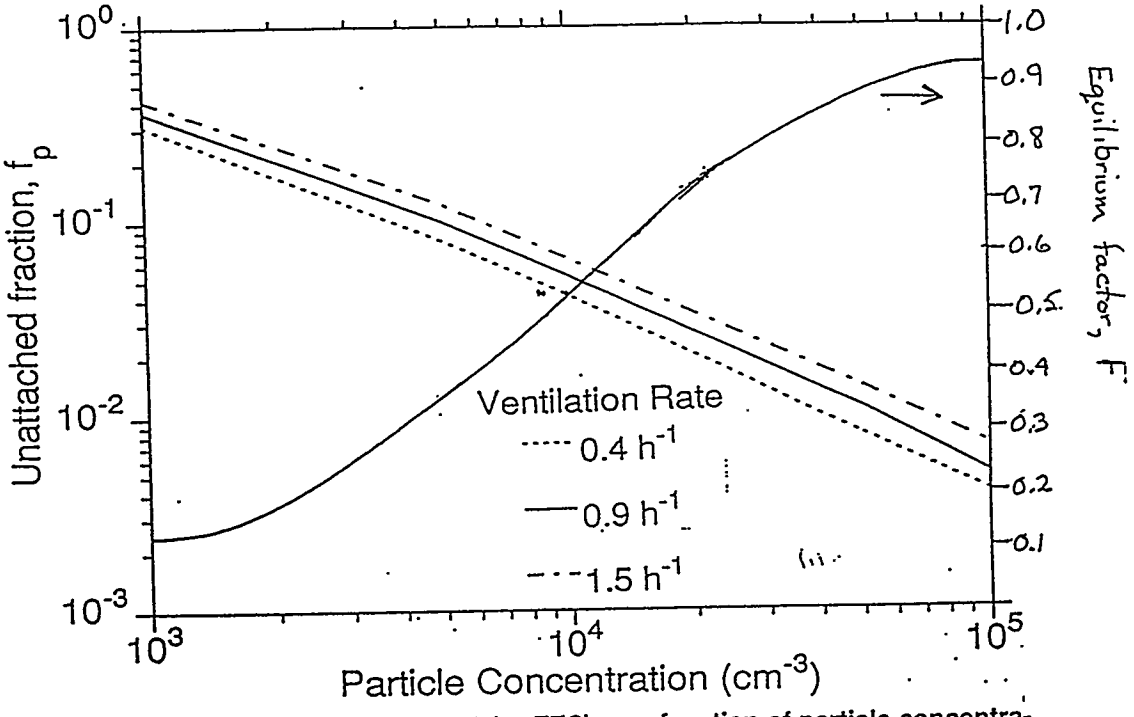
Finally I wanted to turn to this question of radon concentration measurements or estimates as an indicator of dose. Of course, you know, that it's not radon that causes lung cancer but the alpha particles from the radon decay products. The radon decay products have a somewhat dissimilar behavior indoors from radon, and deposition in the lungs and the dose that's conferred to the lungs depends heavily upon kind of the physical nature of those decay products, particularly whether they're attached to particles or not.

The deposition sites in the lung, the clearance mechanism and so forth all depend largely on where they deposit it. This is addressed in the follow-up to the BEIR IV study, the comparative dosimetry study, which presented some of the latest calculations with regard to dosimetry modeling including doses with respect to the activity size distribution of the inhaled progeny.

I will turn to the equilibrium factor F and what that means for lung dose. There seems to be a misunderstanding in the epidemiologic literature as to the distinction between the unattached fraction and F.

The equilibrium factor is basically just the ratio of the airborne radon decay products of any kind in the air versus the radon concentration itself. Figure 7 shows that as I increase the particle concentration in the air, the equilibrium fraction goes way up. The usual particles in air are like bowling balls compared to the sizes of the unattached decay products, which are nanometer-sized, and their diffusivity is orders of magnitude larger than that of the larger aerosols.

Figure 7.



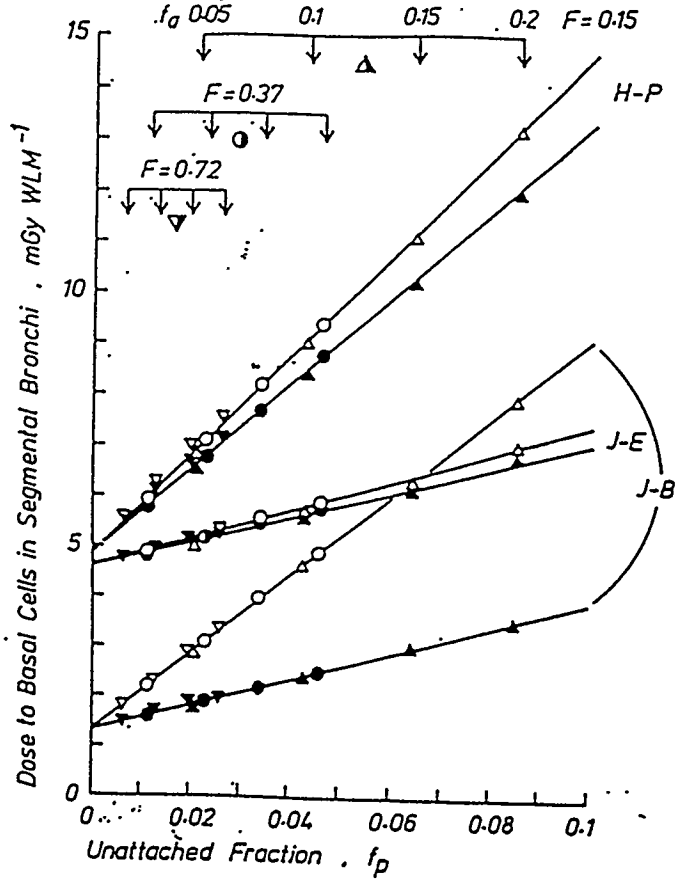
Unattached fraction of PAEC (or EEC) as a function of particle concentration; calculated for three ventilation rates using the steady-state room model.

These bowling balls are slow moving. If I sample in air at high particle counts that means I'm seeing almost an equilibrium of one to one; that is, near comparability of radon decay products attached to particles versus the radon concentration itself.

At really high particle concentrations where the equilibrium factor's very high, the unattached fraction is very low. I'll illustrate the unattached fraction issue in just a minute.

Conversely, as I go to lower particle concentrations, the equilibrium factor goes down and the unattached fraction actually goes up. So, at lower equilibrium fractions the dose to the lung, at a particular concentration, is going up, not down. That's illustrated in Figure 8 in this comparison of three different dosimetric models, Harvey-Pasternak, Jacobi Isfeld, and then the James Burchell.

Figure 8.

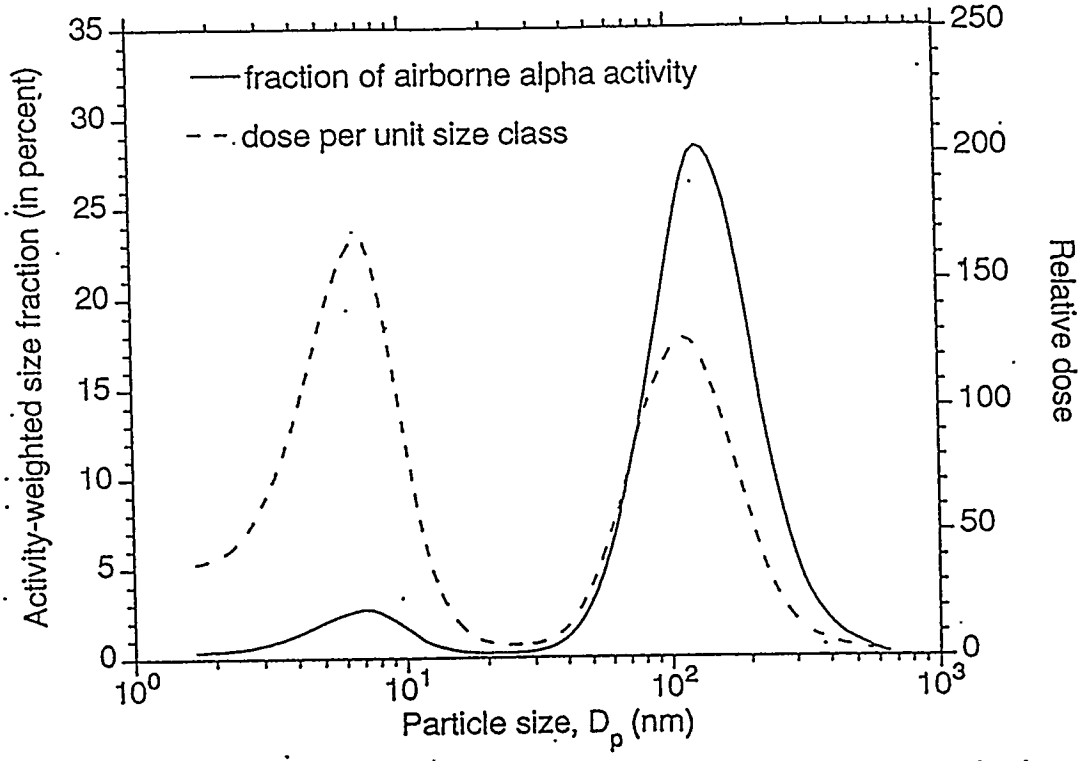


Dose (mGy/WLM) in segmental bronchi calculated as a function of the unattached fraction (f_p) and equilibrium factor (F) using different dosimetric models: Harley-Posternack (H-P), Jacobi-Eisfeld (J-E), and James-Birchall (J-B). The open symbols represent unattached Po-218 particles of 1-nm diameter, and the solid symbols represent particles of 3-nm diameter.

This illustrates the dose, in this case to the basal cells, in millirems per working level month versus unattached fraction. So, you can see, as the unattached fraction gets larger, the dose to the basal cells is higher than it is when the unattached fraction is lower.

In Figure 9, the solid line is essentially an amalgam of several measurements made in houses of activity-weighted particle size distributions. These are normal houses without smokers, but in an urban setting. There were small particles down around the five to ten nanometer size range, and then particles up here around 100 to 200 nanometers.

Figure 9.



Alpha-activity weighted size distributions and the associated relative lung dose. The solid line is a smoothed average of size distributions measured in three residences [*92*]. The corresponding dose, shown as the dashed line, is based on an average of the dose conversion coefficients for dose to secretory and basal cells as a function of particle size [*93*]. In this figure a relative dose of 100 ~ 100 mSv WLM^{-1} (~2.8 × 10^4 mSv m^3 J^{-1} h^{-1}).

Using this distribution to estimate dose, the dose per unit size class is shown by the dashed line. You can see that this bump at the small particle size is much more important to the calculation of the dose than the higher end. The relative contributions of these two modes depends on the size distribution of the indoor aerosol size distributions.

Typical indoor air concentrations, in the absence of smoking, tend to be in the 10,000 particles per cc or maybe a little lower. In houses that may not have gas- fired appliances or other sources, the currents may be lower, down to a few thousand particles per cc.

On the other hand, in a house with a smoker, the particle concentrations are higher, about 10,000 particles/cm^3, or even higher. These counts might be reached for the eight hours of the day that the smoker is smoking, but while the smoker is sleeping, presumably the particle concentration drops. Some type of averaging is needed. Consideration of particle counts would substantially shift dose estimates.

In conclusion, where does all of this put us with respect to measurement error and the fraction of missing values? Achieving an error of 25 percent in estimating exposure will be very difficult. We are probably in the range at 50 percent or more and this needs to be reflected in the newer calculations. We also need to remember the relationship between exposure and dose and address the impact of the variation in aerosol concentrations.

Errors in Exposure Assessment, Statistical Power, And the Interpretation of Residential Radon Studies

Jay Lubin, National Cancer Institute
John D. Boice, Jr., National Cancer Institute
Jonathan M. Samet, Johns Hopkins University

During the late 1980s, Jon Samet, Clare Weinberg, and I (Lubin) had discussions about shared concerns regarding the outcomes of the various projected residential radon epidemiology studies and the response to reports of the findings. We thought that exposure error and other problems inherent in doing epidemiologic studies of residential radon would lead to mixed results from the studies in progress. We wanted to anticipate these problems before the results were available. Recently we have returned to these discussions as results of some of the studies have been published.

Today I will review four issues: first, I will recapitulate the results that are currently in the literature; second, I would like to revisit the paper that we published in 1990 and discuss some more work on the effects of errors and mobility; third, I would like to consider the relationship between the true exposure that someone has and what exposure is actually being estimated; and fourth, I will present results of some new simulation studies.

Figure 1 presents the principal studies that are in the literature, in which radon levels in the homes were actually measured. These are either means or medians, depending on which was reported. The Finnish study had the highest radon measurements; a mean of 211 Bq/m^3.

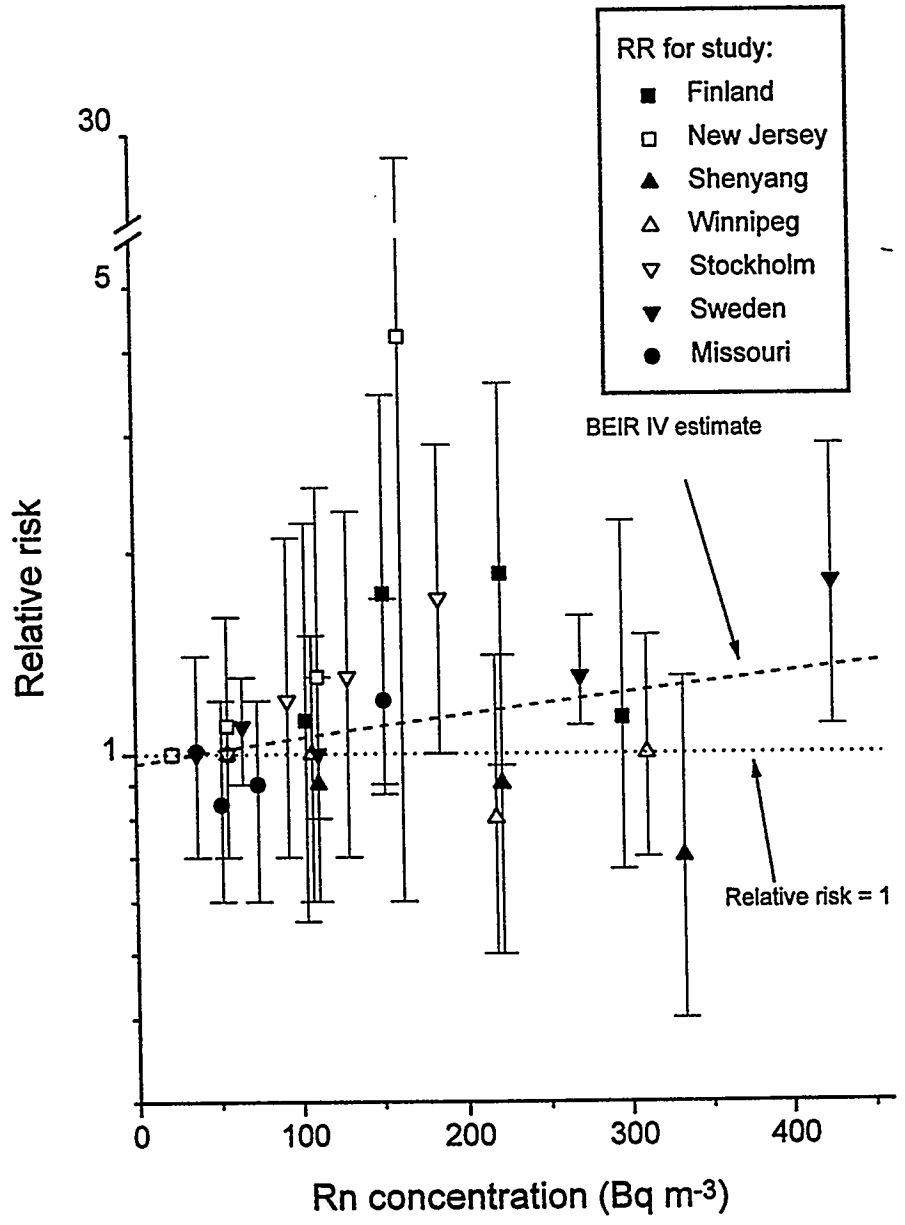
Figure 1. Summary of Lung Cancer Case-control Studies			
Study	Subjects (cases/cntls)	Rn conc (Bq/m^3)	Rn extremes
Finland*	238/434	211	40% > 174 Bq/m^3
Stockholm	210/400	128	28% > 150 Bq/m^3
Winnipeg, Canada	738/738	120	24% > 144 Bq/m^3
Sweden*	1,281/2,576	107	25% > 117 Bq/m^3
Shenyang, China	308/362	85	20% > 148 Bq/m^3
Missouri	538/1,183	67	7% > 148 Bq/m^3
New Jersey	433/402	22	1% > 148 Bq/m^3
NJ/Shenyang/Stockholm	966/1,158	73	14% > 148 Bq/m^3

* denotes studies in which radon measured for 3 months or less

A direct comparison of the results would be premature since neither the Finnish study nor the Swedish study used one year alpha-track measurements. There are a total of 3,746 cases but even so, the results of these studies are clearly ambiguous.

Figure 2 shows the relative risk of 1, a line representing the estimate from the BEIR IV model and the effect estimates with confidence intervals from the seven studies. All studies are generally consistent with either the line of no effect or the BEIR IV projection. I've changed the scale here for reasons that will become apparent later; but otherwise this is similar to the graph published in the *American Journal of Epidemiology* commentary published in 1994.

Figure 2. Summary of Risk Ratios in Published Studies



I would like to remind you that this heterogeneity reflects random variation, and problems that are intrinsic in exposure assessment, as well as the low level of risk that is of interest.

The risks are very low, and exposures are measured with great uncertainty. In referring to errors in exposure assessment, I do not mean those factors that contribute to systematic errors; for example, taking measurements only during one season, or only measures in the basement. These would generate systematic error.

I'm talking more about random misclassification; the slide shows some sources -- by no means a complete list. Of course, one of the principal sources is the measurement device itself. I have heard suggestions that the measurement devices are only accurate to within about 15 to 25 percent (if the exposure levels are low). That level of device accuracy defines the lower limit on how accurate exposure assessment can be since the exposure rate can only be measured to within 15 to 20 percent. There are other sources of error.

Errors in estimation of exposure

- Sources
  - -measurement device
  - -within house variability/measurement of 1-2 rooms
  - -occupancy
  - -current measurements of historical concentrations
  - -residential activities of current residents of previous homes
  - -house modifications
  - -unmeasured homes (mobility as a source of gaps)
  - -non-residential sources of radon exposure
  - -exposure prior to time-window
  - -relationship between exposure and lung dose
  - -calculation of exposures

There is spatial variability within the house and researchers do not measure every room. We obtain current measurements to represent historical values, an approach which may or may not be very accurate. Houses are often modified, and it's very difficult to account for those modifications.

There's also a problem with the calculation of exposures, which may not be readily apparent. When we calculate exposure, we need the time integration of exposure rate from birth to current age, or age minus five years (below, the integration on left). But, that is not what is actually done; we take the average radon concentration in the home, multiply it by the time spent in the home, and sum over index I, where I is the number of residences in an exposure time window. This approximation adds to exposure error.

Figure 3. Calculations of Total Dose for a Subject

- Cumulative exposure to age 'a'

  $\int_0^a Rn\,(t)\,dt \approx \sum_i \overline{Rn}_i \Delta_i$

  i - index of residences from 'a-30' to 'a-5' y

  Δ_i - yrs in residence

- Time weighted average (TWA)
  - 1 house; 30 yrs @ 148 Bq/m^3
  - 2 houses; 15 yrs @ 148 Bq/m^3, 15 yrs missing

As an alternative to a cumulative exposure, we often compute a time-weighted average exposure. This also can induce error, as shown by this simple example. Suppose you have two people, one person lives in a house for 30 years at some level, here 148 Bq/m^3, and a second person lives in two houses, 15 years at 148 Bq/m^3 and the radon measurement is unavailable in the second house.

In terms of time-weighted average, the two persons would have the same value; it would be calculated the same.

Due to regression towards the mean, you'd expect the second person to have, on average, a lower concentration than the first person. This suggests appropriate imputation procedures would be the preferred approach. But, even this then involves adding to the errors in exposure assessment.

Now, to be a little more specific, for those of you interested in this area I highly recommend the paper by Pierce et al.; Radiation Research 1991; 126: 36-42; there's also an RERF technical report that addresses these issues.

Figure 4. Relationship Between Observed Exposure (Z) and True Exposure (X)

- Assume:

  true exposure $X \sim LN[\mu,\sigma^2]$

  error distn $U \sim LN[0,\tau^2]$

  obs exposure $Z = X \times U \sim LN[\mu, \sigma^2 + \tau^2]$

- Error distn defined through exp(τ):

Exp (τ)	1.0	1.5	2.0	3.0
Error in exp	0%	~50%	~100%	~200%

- Use EPA NRRS, GM = 24.8 Bq/m^3 and GSD = 3.11

- For 25-y exposure in one house, GM = 3 WLM and GSD = 3.11

  25 y @ 24.8 Bq/m^3 ≈ 3 WLM

  25 y @ 74 Bq/m^3 ≈ 9 WLM

  25 y @ 148 Bq/m^3 ≈ 18 WLM

We will assume that true exposure is log normally distributed with μ and σ^2. We assume the error distribution is also log normal with parameters 0 and τ^2. We don't actually observe X. We observe Z. We'll say Z is just the product of X and U.

- $X|Z = z \sim LN[\log(z)+\{\mu-\log(z)\}\tau^2/(\tau^2+\sigma^2), \sigma^2\tau^2/(\tau^2+\sigma^2)]$

Assume Z has GM 3 WLM and GSD 3.11

Under X|Z=z, median of X falls between the median of Z and the observed z

Median of X|Z=z

	Error in exposure, exp (τ)			
	1.0	1.5	2.0	3.0
Z=3 WLM	3	3	3	3
Z=9 WLM	9	7.9	6.7	5.3
Z=18 WLM	18	14.7	11.1	7.6

One std dev range on log scale of X|Z=z

	Error in exposure exp(τ)			
	1.0	1.5	2.0	3.0
Z= 3 WLM	3	2.1-4.4	1.7-5.4	1.4-6.6
Z=9 WLM	9	5.4-11.6	3.7-12.1	2.4-11.7
Z=18 WLM	18	10.0-21.5	6.1-20.1	3.4-16.7

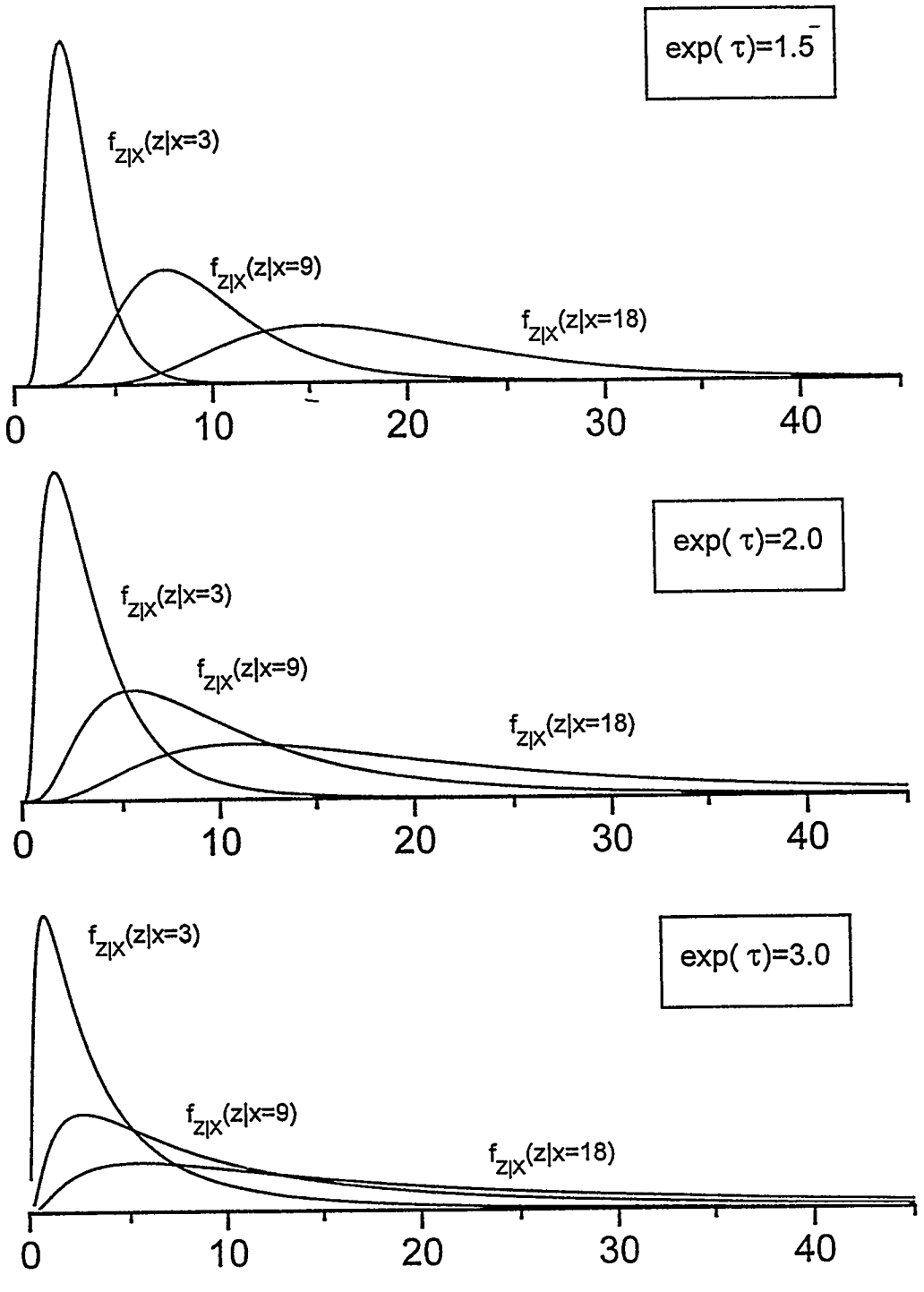
This defines a multiplicative error structure. It's easy to show that random variable Z is also log normal. The different error distributions is defined by exp(τ). If exp (τ)=1 or τ is zero, there is no error in exposure. Approximating these values for exp(τ) gives errors in this order.

So for example, if exp (τ) = 2, the exposure error is 200 percent. That is to say if someone's observed cumulative exposure is 10 WLM for example, the true exposure is between say 5 and 20 WLM.

For some of the calculations, I will assume the distribution from the EPA National Residential Radon Survey, which had a geometric mean of 24.8 Bq/m^3 and a geometric standard deviation of 3.11.

In a simple situation, if one person lives for 25 years in a single home at 24.8 Bq/m^3, then they will have an exposure of 3 WLM. If they lived those 25 years at 74 Bq/m^3 (pCi/L) they would accumulate 9 WLM; they would accumulate 18 WLM if they lived at 148 Bq/m^3 (or 4 pCi/L).

Figure 5. Cumulative Working Level Months



Now, there are two conditional distributions that should be considered. One is the conditional distribution of Z given X, which one can show to be log normal. That is, suppose someone has a particular true exposure, x, what is their observed exposure? For a certain level of X, what's the range of probable values that will be observed for that individual? Because the conditional distribution is log normal with parameter log X and τ^2, the average, or the expectation, of the observed log Z, is just log X. So everything is unbiased on the log scale.

When you transfer, however, back to the original scale, you don't get this symmetry. The median of the Z distribution is fine; it's centered at X. However, the expectation is not. If you have a true value of X, then on average, the observed Z is going to be something that's larger than the X. Here are some examples.

- $Z|X=x \sim LN[\log(x), \tau^2]$

  Under $Z|X=x$,
  - unbiased on log scale, i.e., average of log (Z) is log(x)
  - median of Z is x
  - average of Z on original scale is $x \times \exp(0.5\tau^2)$

Expectation of $Z|X=x$

	Error in exposure, exp(τ)			
	1.0	1.5	2.0	3.0
X=3 WLM	3	3.3	3.8	5.5
X=9 WLM	9	9.8	11.4	16.5
X=18 WLM	18	19.5	22.9	32.9

  - variance of X is $x^2 Var(U)$

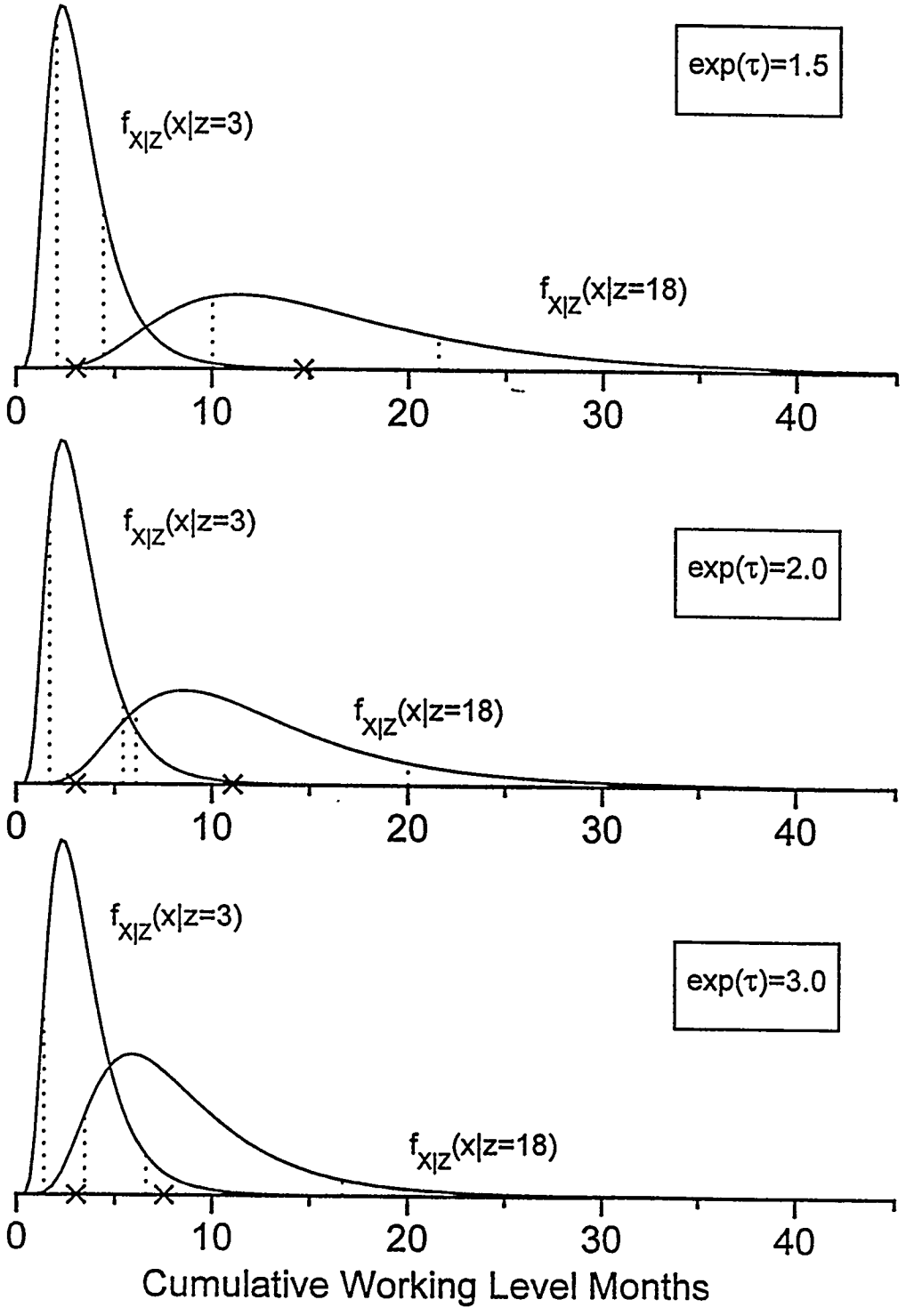
Of course, without error there is no problem. If true cumulative exposure is 18 WLM, then when there is error, the average of the observed exposure is going to be substantially larger. In addition, it's true that the variance distribution also is proportional to the square of X. Here are some examples of those distributions.

Suppose the true value is 18. What are the probable observed exposures? Well, here is the range of probable observed exposures. It gives an error of 1.5; about 50 percent.

The distribution of Z given X is not the same as the conditional distribution of X given Z, and it is this distribution that is considered in making risk calculations. You've observed to have some value of exposure Z; what is the true exposure associated with that observed? Of course, it is a distribution of possible values.

Under this conditional distribution of X given Z, and using the EPA survey results, the median of the true value always lies between three and the observed Z. If Z is on the high side, the median of the true exposures will always be less. If it's on the low side of the distribution, the median of the true exposures will always be higher. So, it's always biased towards the geometric mean. Here are some examples.

Figure 6. Cumulative Working Level Months



At 18 WLM, you can see as the error increases it tends to get closer to 3 WLM so that the value of the true exposure for high values observed is going to be less.

In fact, you can ask what the one standard deviation range is and you can see that, with very high errors, the one standard deviation range does not include the observed. The true exposure is going to be much less than observed.

Now, what's the implication for this? First, the effect of error is to induce, as known previously, a curvilinearity in the pattern excess relative risk with Z. That's because higher exposures are underestimated pulling the dose-response down at the higher level, and inducing curvilinearity.

In the time remaining, I want to present some results of recent simulation studies. Suppose we start with a standard model where the relative risk is linear in true exposure. We do the following simulation.

Figure 7. Parameters of the Simulations

- Specifications

Disease model: $\text{Odds}(D|X) = e^{\alpha}(1 + \beta X)$

Steps:

0.	set parameters;	prob of l.c. is 0.10, β=0.015, exp(τ)
1.	generate X;	sample from LN[3,1.3]
2.	determine D;	compute p(D=1|X) and sample from Unif(0,1)
3.	compute Z;	sample from LN[0,τ^2] and multiply X x U
4.	create cohort;	repeat steps 1-3 10,000 times
5.	c/c study;	select 700 cases and 700 controls and analyze
6.	repeat steps 1-5	

Extensions:

-multiple dwellings

-incomplete coverage

-enlarge c/c study to 2,000 cases and 2,000 controls

We'll first set some parameters. The probability of lung cancer is set at 10 percent. I took a risk of one and a half percent per WLM, which was the very high estimate based on the constant excess RR model from BEIR IV, and set our error distribution. The first step is to generate the true exposure, by sampling Rn rate from the EPA National Radon Survey, then multiplying by 25 years of exposure.

I determined from this risk model the probability of being diseased and then sampled from a uniform distribution. That is, if you calculate that someone's probability is .1 for example, then compare that with a uniform random number between 0 and 1 and if that is less than .1, a disease outcome will be designated. Then muddy the exposure estimate Z by sampling from another log normal distribution, multiplying that quantity times X, and obtain Z. By repeating these steps, one through three, 10,000 times, a cohort is generated. Out of that cohort, in order to mimic what's in the literature, select the case-control study.

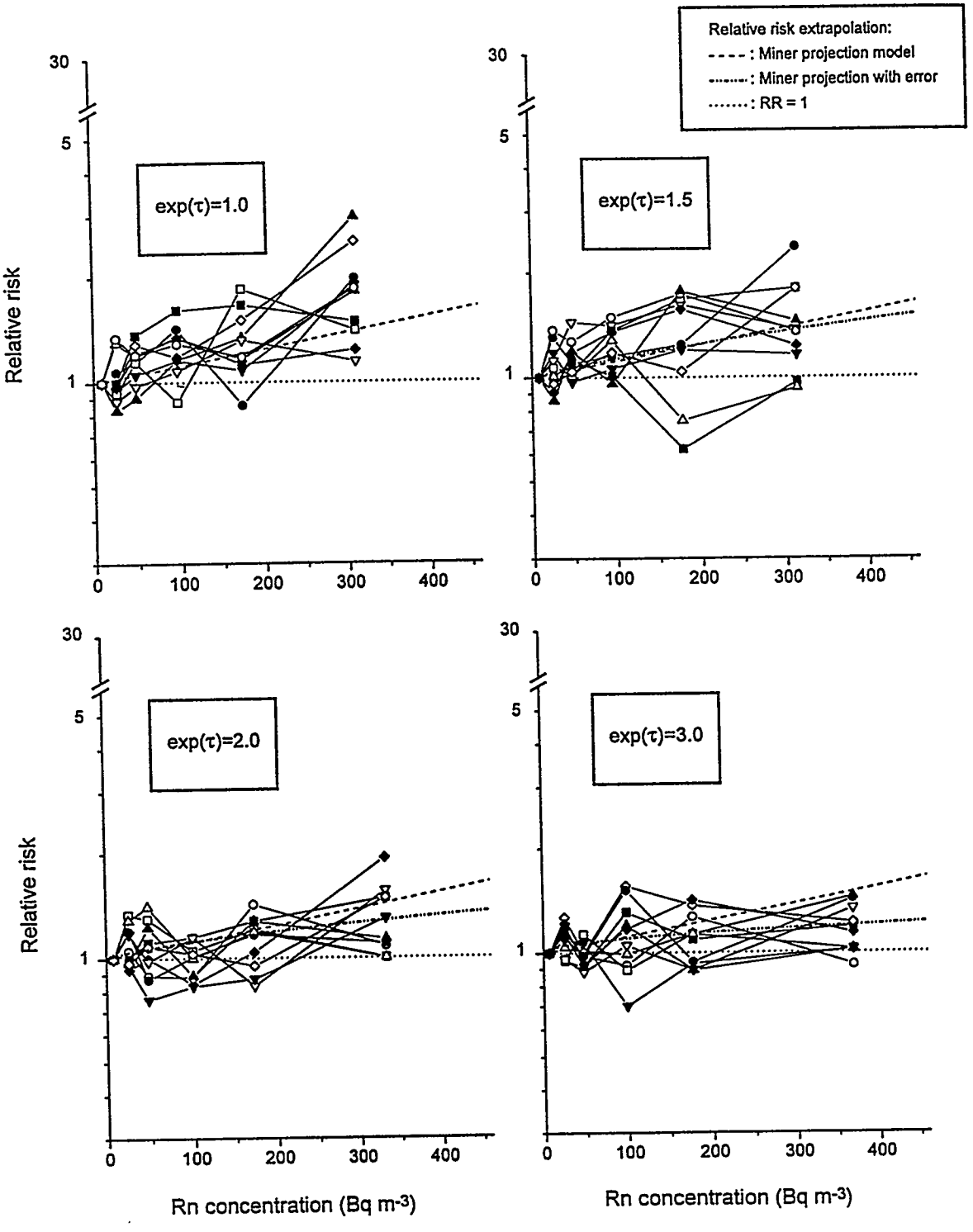
In this first set of simulations I selected fairly large studies, 700 cases and 700 controls. Repeat steps one through five for as many times as you need for the simulation.

This is a real simple simulation. It is assumed that people lived in one home for 25 years. You can extend the simulation by repeated samplings to get X so you can simulate multiple dwellings and complete the time-weighted average. In addition, you can use some of them and simulate incomplete coverage, which is the common state of affairs in most residential studies. Of course the study size can be enlarged beyond 700 cases and controls.

The first issue was to evaluate natural variation, when exposure is measured without error.

Here the top left panel of the figure shows just the natural variation that one would get.

Figure 8. Relative Risk



I should explain what I did. I just took the first ten simulations, ten case control studies of size 700 cases and 700 controls, computed RRs for categorizing of radon concentrations. The dotted and dash lines are the predicted line, based on the true exposures, and the true dose response incorporation error, respectively.

As you get more error, the true line goes down, and you can see that the ten studies tend to center around that true line, as it should of course. If the device itself has up to 25 percent error, then it's hard to argue that the error is much less than about $\exp(\tau)$ of 1.5 to 3.0.

I should also say that in the situation of no errors, if you look at the score test of trend, 4 of the 10 studies with 700 case and 700 controls rejected the null. So there was about 40 percent power. In fact, the true power is 46 percent with 700 cases and 700 controls when you characterize only 25 years of exposure.

Now, the second set of simulations provides empirical power calculations. We repeated the simulations 1,000 times so we took the 1,000 case control studies and asked, how many of the linear tests for trends were under .05? These are two-sided tests. That is, how many times would we reject the null out of 1,000? This is based on 700 cases and 700 controls.

- Simulation II: Evaluate empirical power

  For 1,000 repetitions, compute number of times the score test of no linear trend in ERR (i.e., $\beta=0$) is less than 0.05.

  -study size: 700 cases and 700 controls

  -include multiple houses: 1×25 y, 2×12.5 y and 3×8.3 y

	Number of residences in 5-30 y interval		
	1	2	3
	Percent coverage of exposure-time window		
exp(τ)	100%	100%	100%
1.0	**450**	306	282
1.5	414	266	249
2.0	294	188	94
3.0	171	118	64

It allowed us to look quite easily at mobility, so a person may live in a single home for 25 years, two homes each for 12.5 years, and three homes each for 8.3 years. The time in each home was considered fixed so there's no variability in terms of movement.

-study size: 700 cases and 700 controls

-include incomplete coverage (exposure is TWA×25)

	Number of residences in 5-30 y interval					
	1	2		3		
	Percent coverage of exposure-time window					
exp(τ)	100%	100%	50%	100%	67%	33%
1.0	**450**	306	**171**	282	**242**	**115**
1.5	414	266	**166**	249	**164**	**108**
2.0	294	188	**127**	94	**92**	**68**
3.0	171	118	**72**	64	**86**	**58**

So, if everything were perfect, the empirical power would be 45 percent. So 450 times out of 1,000 the null hypothesis was rejected. As mobility increases, power declines; this is not surprising, since the distribution of exposure narrows with increasing number of homes and with increasing exposure.

So, with an average of two or three homes in the 25-year period, we have only 20-25 percent power.

If we next used time-weighted average and added in the problem associated with not being able to have complete coverage of the time interval. For example, with one residence, clearly you've covered the whole time, with two homes, we considered that we missed one of the homes, and with three homes, missing either one or two.

If one assumes that in the 25-year exposure window, usually the average number of residences is about two, we're probably here with 10-20% power; and this is with 700 cases and 700 controls.

-increase size of c/c study: 2,000 cases and 2,000 controls

	Number of residences in 5-30 y interval					
	1	2		3		
	Percent coverage of exposure-time window					
exp(τ)	100%	100%	50%	100%	67%	33%
1.0	**898**	736	460	608	526	321
1.5	848	668	441	551	421	294
2.0	710	540	356	344	266	235
3.0	408	329	220	236	146	130

Power improves with 2,000 cases and 2,000 controls. But I wouldn't take too much heart that, even in the setting that one would reasonably say is where we're operating, we still don't have too much power; probably under about 40 percent power.

I should emphasize, this is an ideal situation, a simulation. We're not thinking of smoking, no age variation, and other factors.

Finally, in our 1990 paper we did produce some tables of sample sizes. They really are, however, out of date, so I thought as a final point I'd update those sample size calculations.

These are sample size calculations based on detecting a fairly large risk, 1.5 percent per WLM using a 30-year exposure time window.

-sample size for case-control study of indoor radon

No. of cases for radon c/c study with 1-1 matching

Error exp(τ)	1x25 y	2x12.5 y	3x8.3 y
1.0	2,033	2,447	3,408
1.5	2,521	3,292	4,879
2.0	3,716	5,365	8,484
3.0	8,429	13,530	22,694

No. of cases for radon c/c study with 2-1 matching

Error exp(τ)	1x25 y	2x12.5 y	3x8.3 y
1.0	1,488	1,810	2,530
1.5	1,846	2,437	3,626
2.0	2,724	3,974	6,311
3.0	6,183	10,034	16,895

previous calculations: 60 γ exposure, f vs exp(τ), Nero vs NRRS $\beta=0.015$, power=0.90, 2-sided 0.05-level size test no unmeasured homes

These are the number of cases that would be required. This is with one-to-one matching, 90 percent power. A study needs 7,000 to 15,000 cases and an equal number of controls, perhaps a little bit more. With two-to-one matching you do a little bit better, say 5,000 to 13,000, and have sufficient power to detect a risk. Again, this is an idealized situation.

In summary, at least it's my view, I think the graph shows that, to date the indoor studies are inconclusive, which is exactly what you would expect given the degree of error that's associated with exposure assessment, and the problems with mobility, both of which affect study power.

I think the simulation studies showed, hopefully clearly, that due to random variation, even in the best of situations, we will have "positive studies" and "negative studies." Results are going to be all over the map.

Finally, I'd just like to pose the question that, given these results in these idealized situations, what really is the likelihood, even with the data pooling, that they will produce this sort of positive weight of evidence; and then maybe the ultimate question for the group here is, is pooling really the answer to the issue of radon risk assessment in homes?

Summary

- Studies of indoor radon to date are inconclusive
- Errors plus low risk in exposure and mobility reduce study power
- Simulation studies
  -due to random variation, "positive" and "negative" studies
  -errors reduce true RR and increase the "variability" of results
  -inappropriate to highlight any particular study
  -what is the likelihood of a "positive" weight of evidence?
- Is pooling THE answer?

DR. ROSE: Let's take one wonderful question and then take our break, all right? Do you want to ask Jay?

DR. KREWSKI: Yes, I do, but I just want to say, my opinion and question is my own -- Jay, those results are extremely informative. Let me ask you a difficult question; do you think if pooling was undertaken, it would be possible to develop imputation techniques for the missing radon exposures, techniques for adjusting for measurement error that would try to accommodate for the facts that you've documented in the pooled analysis?

DR. LUBIN: Why did I feel I knew you would ask me that question? I would think no question but that you should, absolutely, if that was the most appropriate way to develop exposure estimates. On the other hand, even if you do there's a limit to how much you'll gain. Clearly you'll gain some, there's no question. But, there is a limit as to how much you can gain.

DR. KREWSKI: In idealized situations.

DR. LUBIN: Right; so I think you're absolutely right, it should be done. Second -- the second part of your question; should one apply procedures that take into account errors and variables? Absolutely, the best analyses would do that. Of course, the real problem is knowing how substantial those errors are. At the very least, some sort of sensitivity analysis

would be extraordinarily useful just because it's so hard to get a good handle on what those error distributions really are. But I think that would be a certainly worthwhile task.

The Science of Pooling

Ethel Gilbert
Pacific Northwest Laboratory

I find giving a talk under the title of "The Science of Pooling" just a bit intimidating. I can at least remind us of some of the issues that need to be kept in mind as plans for pooling of data from residential radon studies proceed.

First, it is essential to be clear about the purpose of the studies, what we hope to learn from them, and what kinds of analyses are needed to address the questions of interest.

Rationale For Studies of Persons Exposed at Low-levels

- Current estimates of risks based on extrapolation from data on populations exposed at high levels
- Radon: Underground Miners
  External Radiation: A-bomb survivors
- Low-level studies provide direct assessment of risk at levels of actual interest
- Radon: Persons exposed in residences
  External radiation: Nuclear workers

There is a close parallel between the studies of nuclear workers that I've been involved with and the studies of residential radon that are being discussed at this workshop. In both cases, estimates of risk are based on extrapolation from data at high doses. In the case of radon, studies of underground miners provide the data. For external exposure, the data come primarily from atomic bomb survivors in Hiroshima and Nagasaki, and also from persons who have been exposed for medical reasons. For both radon and external exposure, a direct assessment of the risks of lower exposures is judged to be desirable. This direct assessment is the central rationale for conducting both the residential radon studies and the studies of nuclear workers.

Concerns regarding use of "high level" exposure data for predicting "low-level" concerns

Radon (Underground miners)	External exposure (A-bomb survivors)
Other conditions in mines (dust, arsenic, etc.)	Selection from surviving initial acute effects
Primarily male adult smokers	Japanese
High exposures	High exposures
Relatively high exposure rates	Very high exposure rate
Bias and uncertainties in exposure measurements	Bias and uncertainties in exposure measurements
/rad different for miners than for residential exposures	

In both cases, there are concerns about the extrapolation process demographic characteristics of the studied populations are different from the ones for which we want risk estimates. Also, there are uncertainties about extrapolating from high exposures and high exposure rates, and in both cases there are concerns about bias related to exposure measurement problems.

Have risk models based on extrapolation from high exposure studies

- Underestimated risks, and to what extent?
- Overestimated risks, and to what extent?
- To address these questions we need to estimate risks and fully evaluate their uncertainties

I find it interesting that, in the case of external radiation, the more vocal critics have maintained that risks have been underestimated. These critics have emphasized any low-level study that seems to show some evidence of risk as supporting that claim. By contrast, with radon, the more vocal critics are claiming that residential radon risks have been overestimated.

These critics tend to indicate "negative" case-control or ecological studies as supporting that particular claim. However, with radon there is also concern about possible underestimation of risk, perhaps because of an inverse dose rate effect, or because of exposure measurement problems with the underground miner studies.

To address these questions with low-level studies, we need to estimate parameters that can be compared with those that are used in the risk models that have been used to predict risk, and we especially need to evaluate the uncertainty in the estimates of those parameters. Those that have claimed underestimation or overestimation have often more or less ignored uncertainties.

Reasons for Pooling

- Reduce uncertainty and obtain more precise estimates of risk than available from any single study (increase power for detecting risk)
- Allow more powerful exploration of modifying effects of factors such as smoking, sex, age at exposure
- Obtain the best overview or summary of studies
- Provides the best opportunity for developing an understanding of differences and similarities in studies and results (parallel analyses)
- Investigate the consistency of results from different studies

Let's turn now to pooling. By pooling I mean analysis of the original data from several studies, not meta-analysis in which summary measures from published data are analyzed.

First, I'd like to review the reasons for pooling. A major reason is to reduce uncertainty and to obtain more precise estimates of risk than would be available from any single study. We've already heard about the limitations of these studies, and the difficulty of detecting effects. Based on Dr. Lubin's presentation this morning, it's not clear whether even pooling will totally allow us to solve that problem. But certainly, analyzing combined data should offer the best hope of addressing the questions of interest.

Of course, in addition to an overall estimate, we would also like to understand the modifying effects of factors such as smoking, sex, and age at exposure. One of the difficulties with the underground miner studies is that the miners are predominantly adult male smokers, and we'd like to know about risks in other segments of the population. Addressing modifying effects usually means comparing risks in sub-groups, and thus power becomes even more limited. If we're going to have any hope of sorting out these issues, combined analyses will be very important.

Another important and very closely related reason for pooling is to obtain the best overview, or summary, of these studies. There's a tendency, on the part of the media at least, to jump on the latest study and fail to put its results in perspective by considering results of other studies.

What is the overall story? In my opinion, the best way to address that question is to conduct combined analyses. Considering the individual studies and saying the score is two to one, or whatever it is, is not a good way of summarizing, or obtaining an overview of the studies. Having the results of combined analyses available to us would be helpful in understanding and communicating what we can and cannot appropriately conclude from the residential radon studies as a whole.

Still another reason for pooling is to develop an understanding of the differences and similarities in the various studies. This is generally accomplished by conducting similar analyses of all the studies and setting them out side by side in a comparable format, so-called parallel analyses. Certainly pooling should not mean throwing all the data in the same computer and forgetting where it came from. There are many differences in these studies. The exposure measurement protocols have been different, the subjects have been selected differently, and they are of different nationalities. We obviously don't want to lose sight of those differences, and combining data offers the best chance of understanding how these differences may affect the results of the studies.

Procedures: Combined International Analyses of Nuclear Workers

- Coordinated by International Agency for Research on Cancer
- Investigators for all individual studies participated in
  planning, interpretation
- Subcommittee to
  -- develop detailed plans for analyses
  -- prepare protocol
- Dosimetry subcommittee

I would like to talk now about the practical aspects of pooling, and particularly to share my experience with the international efforts to combine data from studies in the United States, United Kingdom, and Canada. In addition, there have been efforts to pool these data on a national level, and I was involved with the United States effort.

The international analyses were coordinated by the International Agency for Research on Cancer, IARC, and the analyses were conducted at IARC. Although IARC had overall responsibility for the analyses, all the investigators for the individual studies participated. There were meetings of all investigators at the beginning and the end of the effort, and all investigators had an opportunity to review the various publications. I think this involvement was very important, and obviously this group does too, or you wouldn't be having a meeting such as this one.

We established a sub-committee that was responsible for developing detailed plans for the analyses and for setting out these plans in a protocol. This sub-committee consisted of representatives from IARC and also a representative from each of the three countries. So, we did go about this in fairly formal way, and I guess it depends on who's involved whether a more informal effort will work.

In our national pooling, we didn't do anything that formal. I essentially did the pooling. The other two participants were very cooperative, and we didn't have any problems. As the group gets larger, it may become more important to go about it in a more formal way.

We also added a dosimetry sub-committee, and I'll say just a bit more about that in a moment.

Protocol for Combined International Analyses of Nuclear Workers

- Written document setting out detailed procedures
  - -- who is responsible for what
  - -- provision of data
  - -- who will have access to data
  - -- publications (authorship)
  - -- time table
- Criteria for selection of studies to be included
- Objectives of analyses
- Approach for analyzing data
- Description of dosimetry

For the international analyses, we prepared a protocol that set out the details of how the pooling was going to proceed including who was going to be responsible for what. I've listed some of the topics that were included in that protocol.

The protocol included statements that indicated, for example, that the data would not be made available outside of IARC without express written permission of all the investigators, that the findings of the study would not be made generally available until the actual publications had appeared, and it addressed other issues with respect to publications and authorship. I think it was valuable to discuss these issues and to have them clearly set out in the protocol, because this could avoid potential misunderstandings or ill feelings that might perhaps interfere with getting analyses completed and published.

Procedures for Providing Data

- Data from all studies organized in similar manner
- List and definition of variables to be included
  -- Some may be indicated as optional
  -- Some may differ from study to study
- Need sufficient detail to allow flexibility

The protocol set out the procedures for providing data. It certainly is helpful to the person who will be doing the analyses if all data are provided in a similar manner, and our protocol actually listed all the variables, with definitions, that were to be provided. It even gave a format, although this may not have been essential.

Some of the variables might differ to some extent from study to study. For example, in our study we were interested in having a measure of socio-economic status, and it turned out that one study had data on social class, another had job category data, and still another had data on education. What we ended up doing was simply asking that everyone provide their own measure of socio-economic status with recommendations as to how it was going to be used.

We gave some consideration to providing aggregated data rather than data on individual workers, and rejected that idea because we did not think it would provide for adequate flexibility. In retrospect, I think that was a good decision. It may not be necessary, however, to provide all of the raw data. I would think, for example, that in the radon studies one would not want to provide all the raw data on exposure but would want to summarize these data by providing rates per year, or something of that sort.

A Priori Specification of "Main" Analyses

It is important to specify in advance the methods to be used in analyses that are to be emphasized in reporting results.

- Statistical methods and models
- Treatment of exposure
  -- continuous versus categorical
  -- cutpoints for exposure categories
  -- time windows
- Subjects to be excluded
- Variables for which adjustment will be made and how
- Subgroup analyses
- Modifying effects to be explored, and how

Also specify supplementary analyses to determine sensitivity to various choices that have been made.

In conducting analyses, there are many small decisions that have to be made that are more or less arbitrary: exactly what exposure time points do you use; exactly which subjects are you going to include; what variables are you going to adjust for; and exactly how are you going to do that adjustment?

Obviously more than one analysis can be conducted, but usually there's one analysis that's considered to be the main analysis - the one that gets cited in the abstract. I think it is important to set out, in advance if possible, how that main analysis is going to be done. In our case, three members of the group spent a good part of a week hammering out the precise details of exactly how we were going to perform the main analysis, as well as additional analyses that would allow us to explore the possible sensitivity of our analyses to some of the fairly arbitrary choices that were made.

Functions of Dosimetry Committee for Combined International Analyses of Nuclear Workers

- Developed questionnaire to allow documentation of dosimetry practices for each study
- Evaluated comparability and accuracy of dosimetry for each of the studies
- Made recommendations on dosimetry variables to be provided
- Made recommendations that certain subjects with poorly estimated doses be excluded from certain analyses

The dose estimates that we used in our study came from personal dosimeters worn by the workers, and I think in many ways these estimates were far less problematic than the exposure

measurements in the residential radon studies. Nevertheless, our dose estimates had limitations, and we established a sub-committee that consisted of a dosimetry expert from each of the three countries. This sub-committee developed a questionnaire to allow the documentation of dosimetry practices for each study. It evaluated the comparability and accuracy of dosimetry for each of the studies, and made recommendations as to what variables on dosimetry we wanted to have, and also about certain subjects that might be excluded from certain analyses.

Components of Pooled Analyses

- Descriptive statistics
- Parallel analyses (similar methods applied to all studies)
- Combined analyses

Here I've simply listed some of the components that go into pooled analyses: descriptive statistics, parallel analyses, and combined analyses.

Descriptive statistics are important, and even if the pooled analyses never went beyond this, presenting such statistics would be valuable. It's difficult to gain a sense of how studies compare with respect to size, exposure distributions, and other characteristics without seeing summary statistics, calculated in the same manner with the same cutpoints, for each of the studies.

Parallel Analyses

- Similar methods applied to all studies
- First step in evaluating comparability of results
- Some sub-group analyses (male/female; only complete exposure histories)
- Certain aspects of methods may differ (e.g., methods for smoking adjustment)

Parallel analyses are the second component. By parallel analyses, I mean applying similar methods to each of the studies and setting them out side by side. That is a good first step in evaluating the comparability of results among the studies. Possible reasons for discrepancies can be explored by separating results by sub-groups. For example, some of the studies are exclusively female, some include both males and females, so one might want to line up just the female component of the studies.

All the methods do not have to be exactly identical in parallel analyses. For example, the method of adjusting for smoking might differ from study to study depending on the data that were available and the particular patterns of smoking in the individual studies.

Combined Analyses

- Data from all studies considered as a single data set
- Evaluation of homogeneity across studies
- Subgroup analyses
- Overall estimate of risk with adequate evaluation of uncertainty

The distinction between parallel analyses and combined analyses is a bit blurred, but combined analyses generally focus on the overall picture, or overall summary, and usually at least some parameters are common for the various studies.

I have briefly indicated some of the components of combined analyses. These usually include evaluation the homogeneity of results across studies; subgroup analyses that allow evaluation of homogeneity for males and females, for smokers and non-smokers, etc; and of course, an overall estimate of risk with an adequate evaluation of uncertainty.

Examples of Pooled Analyses

- Lubin et al., "Radon exposure in residences and lung cancer among women: Combined analysis of three studies," *Cancer Causes and Control*, 1994
- Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Miners Studies. NIH Publication No. 94-3644, 1994
- IARC Study Group on Cancer Risk among Nuclear Industry Workers, "Direct estimates of cancer mortality due to low doses of ionizing radiation: An international study" *The Lancet*, 1994

If you're not familiar with pooled analyses, I'd suggest that you look at some examples. Most of you are familiar with the analyses of the data from New Jersey, Shenyang, and Sweden. Other good examples are the pooled analysis of the underground mining cohorts and the international worker study. Actually, only a fairly brief summary of the worker study has been published thus far, but there is a more detailed report that will be published in *Radiation Research* this spring.

Types of Analyses

- Exploration of potential confounders
- Relative risks by exposure category (with confidence limits)
- Risk estimates per unit of exposure (with confidence limits)

I am not going to go into much detail on the kinds of analyses that should be conducted. They would be similar to analyses that have been used for the individual studies. There was a good discussion of methods and approaches to analyses in the report of the last radon epidemiology meeting held in Alexandria.

Quantitative Risk Estimates Based on Case-Control Data

- Heart of the analyses
- Use excess relative risk (ERR) for comparability with miner data
- Based on linear relative risk model where relative risk is given by
  $1 + \beta z$ where z is exposure, and β is the ERR
- Risk estimates expressed as multiples of predictions from models based on underground miner studies (models include consideration of exposure rate, time since exposure, age at risk, smoking, etc.)

The heart of the analysis, in my opinion, is the presentation of quantitative risk estimates in a way that can be compared with the predictions from the risk assessment models based on the underground miner data. These might be based on a constant relative risk model, or they might incorporate certain patterns of risk that had been identified in the miners. Based on miner analyses, risks have been found to depend on exposure rate, time since exposure, age at risk, and so forth. So, one might want to weight residential exposures according to the patterns that have been identified in the miner studies, and then express risks as multiples of the predictions from the models based on miner studies. In fact, this has been done in analyses of some of the individual studies.

Excess relative risk of lung cancer per pCi/L and 95% confidence intervals

Stockholm	0.06 (-0.04, 0.34)
New Jersey	0.18 (-0.04, 0.70)
Shenyang	-0.02 (Under., 0.03)
Combined	0.00 (-0.05. 0.07)

From Lubin et al., 1994

I thought I should present at least one example. This comes from the pooled analyses of data from three residential studies. One can see that we have two positive risk estimates and one negative one. From the confidence limits, you can see readily that the results are fairly consistent for the three studies, and a formal test of heterogeneity also indicated consistency. The combined analyses yielded an estimate of almost exactly zero.

Excess relative risk of lung cancer and 95% confidence intervals

Combined residential	
per pCi/L	0.00 (-0.05, 0.07)
per WLM	0.00 (-0.01, 0.014)
Underground miners (BEIR IV)	
per WLM	0.010

From Lubin et al., 1994

At the beginning of this talk, I said that one of our major concerns was to address whether extrapolation from the underground miner studies might have underestimated or overestimated risks. To address that question we need to express estimates in terms that are more comparable to the miner studies. Here I've shown the risk estimates, originally expressed per pCi/L, converted to risk estimates expressed per working level month (WLM). I've also shown the estimate from BEIR IV adjusted to be more comparable to exposure at residential levels.

Of course, what you can see is that the confidence limits based on the residential studies include both the possibility of no risk and the BEIR IV estimate. Also, you can see that the upper limit on this confidence limit is not too much higher than the BEIR IV estimate, so we could perhaps interpret this as indicating that extrapolation from the underground miners has not seriously underestimated risks at residential levels. The results, however, are pretty uninformative regarding the possibility of overestimation since the interval includes the range from zero up to values above the BEIR IV estimate.

Now, if these confidence limits had excluded values of particular interest (for example, if the upper confidence limit had been lower than the BEIR IV estimate), then we would need to be very cautious in our interpretation because there are many sources of uncertainty that are not

reflected. Confidence limits that are calculated in the usual manner reflect only uncertainty due to sampling variation.

Uncertainties in Risk Estimates

- When all current studies are completed, confidence limits reflecting only sampling uncertainty may be fairly tight, and it may appear that the risks are estimated precisely.

- It is important to recognize that such estimates are subject to many uncertainties that are not easily quantified.

When all the studies are completed, it's possible that the confidence limit using the usual approach (that just considers sampling the variation) might end up being fairly tight, and it might appear that risk had been estimated pretty precisely. That could be rather misleading because there are many other sources of error.

Some of you may have seen a commentary in the *American Journal of Epidemiology* by Shapiro with the subtitle "Meta-Analysis-Shmeta Analysis." The main concern that seemed to be being expressed was that tight confidence limits that considered only sampling variation could be misleading. Shapiro's conclusion was that perhaps we shouldn't be doing meta-analysis. The argument might also be applied to pooled analyses.

I personally think that both meta-analysis and combined analysis are valuable and need to be done, but I share the concern about adequately expressing and communicating uncertainty.

Sources of Uncertainties in Risk Estimates

- Sampling ("Usual" statistical uncertainty)
- Heterogeneity among studies
- Confounding
- Exposure measurement errors

Here I've listed some of the sources of uncertainty that we need to worry about. Of course there's the usual sampling variation, and here it's important that the statistical methods that are used be appropriate for the models and for the very highly skewed distributions. We also need to think about the heterogeneity among studies; this needs to be investigated and if evidence for such heterogeneity is found, this ought to be reflected in the confidence limits.

Epidemiologic studies, of course, are always subject to bias that might have resulted from differential information for cases and controls and also bias resulting from unidentified, or imperfectly measured, confounders. Of course, smoking is of special concern here, and even though most of the studies residential radon have data on smoking, there are questions about whether the data are sufficiently accurate or detailed to really allow adequate adjustment for smoking.

The final uncertainty is one we've already heard quite a bit about: uncertainty resulting from exposure measurement error.

Random Exposure Measurement Errors

- Errors that are independent for measurements for different subjects
- If not accounted for, random errors can
  - -- Result in underestimation of linear regression coefficients
  - -- Reduce power for detection of effects
  - -- Distort the shape of exposure-response function
  - -- Result in underestimation of uncertainty in risk estimates

First of all, consider random error. If random errors are not accounted for, they can in general result in the underestimation of linear risk coefficients and reduce power for detecting effects. The calculations we saw this morning certainly illustrated that quite dramatically. In addition, random error can distort the shape of the dose response function and can also result in the underestimation of uncertainty in the risk estimates. This last point in combination with the first one means especially that upper confidence limits may tend to be too low if error is not taken into account.

Random Exposure Measurement Errors

- Procedures for adjusting such errors are available
  - -- Require quantification of magnitude and nature of errors
  - -- Computations very complex

There are procedures available for adjusting for random errors. These, for the most, have been developed fairly recently. In part because they're so computer intensive, we would not have even thought of doing them until relatively recently.

However, these methods require the quantification of the magnitude and the nature of the errors. We struggled with that with the workers studies, and it's a very difficult task because we simply don't have hard data on many of the sources of error. That would seem to be true in the case of radon exposure measurement as well.

Even if these errors are adequately quantified, except for a few rather simple situations, the computations that are required for adjustments are extremely complex. If one came up with a model that was a fully realistic summary or description of the exposure measurement errors, it would take some fairly complex computations to take full account of these errors. It certainly is not something that you can plug in canned software and do.

Some Suggestions

- Analyses restricted to subjects judged to have "best" exposure measurements
- Sensitivity analyses
- Simulations based on "artificial" data to illustrate potential effects

I've listed a few suggestions. One is to restrict analyses to subjects that are judged to have better measurements; that has been done in some of the individual studies. However, although it is a good idea to do that, it probably is not going to address many of the errors that we are interested in. Another possibility is to conduct sensitivity analyses. We can try some fairly simple models just to see what kind of effects they have. Finally, simulations based on "artificial" data can at least illustrate potential effects, and perhaps help communicate that this is a problem that should not just be overlooked.

It should be noted that if the pooling effort were to include substantial efforts to account for measurement error, that would probably vastly increase the amount of time and cost involved in conducting the pooling.

Systematic Exposure Measurement Errors

- Potential for bias

  Example: Bias in estimating past exposure using current measurements
- Potential may be judged to differ by study and subgroups within studies
- Postulate uncertainty distributions and incorporate these into confidence limits

So far I've just been talking about random errors. Actually, many sources of errors are probably correlated across subjects, and adequately addressing the full correlation structure would be even more complicated. There are some error sources that primarily involve systematic bias, and this is actually a little more tractable problem.

For example, there may be an overall bias in the factor one uses to estimate what fraction of time people spend in their houses, or an overall bias in using current measurements as estimates of past exposure. Of course, if you knew what that bias was, the solution would be simple and a connection could be made. The problem is, you know there's a potential for bias, but you don't know exactly what that bias might be, and the bias might be judged to differ for different studies. As I said, this is actually a reasonably tractable statistical problem. If you can postulate uncertainty factors for these biases, it is possible to incorporate those into one's confidence limits. Of course that would be a fairly subjective kind of exercise and one would probably treat it as a sort of sensitivity analysis.

Further Comments on Uncertainties

- Adjustment for uncertainties tends to weight studies and subjects by quality of exposure estimates
- For single studies, sampling uncertainty likely to dominate
- For pooled analyses based on thousands of cases, sampling uncertainty may be small, and uncertainty from other sources becomes much more important
- Important to communicate full uncertainty!

Just a few further comments on uncertainties. Adjustment for uncertainty would tend to weight studies and subjects by the quality of exposure estimates. Also, for single studies, or for smaller pooling efforts, the sampling uncertainty is probably going to dominate.

In the U.S. part of the worker studies, I made an effort to account for uncertainty resulting from systematic bias in dose estimation, and I found that even allowing a very large amount of uncertainty really didn't have very much effect on the confidence limits I was getting. The reason was that sampling uncertainty was so great that it simply dominated.

However, when we start doing pooled analyses based on thousands of cases, then the sampling uncertainty may begin to get small and it will then become rather important to consider the uncertainty from certain other sources.

Communication of Results

- Media treatment to date indicates communication is a difficult challenge
- The starting point is to perform analyses that attempt realistic quantification of uncertainty, and write papers and press releases in a way that emphasizes uncertainty
- Involvement of communication experts?

I think it's very important to communicate the uncertainties in these risk estimates, including uncertainties that go beyond just uncertainties due to sampling variation. The media treatment of these studies so far indicates that communication is certainly a difficult challenge. A first step is to perform analyses that attempt a realistic quantification of uncertainty and to try to write papers, abstracts, press releases, whatever, in a way that emphasizes that uncertainty.

Unfortunately that's no guarantee that it's going to come out the way you like in the headlines of the newspaper the next day, and I don't know what the answer is here. I'm not sure communication experts really know all the answers either, but the possibility of involving such experts is something to consider.

DR. SAMET: We have time for a question before we move on.

VOICE: So would you propose pooled analysis fooled analysis?

DR. GILBERT: Well, that's a catchy title.

DR. SAMET: Dan?

DR. KREWSKI: Dan Krewski from Canada. That was a very nice presentation, Ethel. I think really an excellent summary of all of the issues in combined analysis, and I think your experience with the three U.S. cohorts, as well as the IARC combined analysis of the nuclear workers was very, very valuable.

There are a lot of things we could talk about, let me limit myself to -- two points. One, in the IARC study there was very little evidence of heterogeneity amongst the different cohorts that were being combined. I think that probably simplified the analysis somewhat. Is it possible if you had a situation where there was appreciable heterogeneity that you may end up with less certain estimates overall when you take that into account in trying to construct a single overall summary estimate of relative risk? That's the first question.

The second one is: one of the strengths of monitoring nuclear workers is you have personal dosimeters, it is a rarity where we have that kind of personal exposure ascertainment in environmental and occupational epidemiology. But, the dosimeters are subject to varying degrees of reliability around the world, I expect different detection limits, you have got the problem of censoring below the detection limit, which can vary from organization to organization; did you try to accommodate that in the IARC analysis?

DR. GILBERT: The first question you can probably answer better than I can. The first question related to the heterogeneity among studies, and I know Dan has been working with a very elegant random effects model that addresses this. The reason I did not say too much about this is that it is not something I have had a lot of experience with.

I know Jay has made some efforts to take heterogeneity into account in the miner studies, and it did increase the width of the confidence limits on the overall estimate. I would assume that would also be the case in the worker studies, although we didn't have evidence of statistically significant heterogeneity.

DR. KREWSKI: It was a loaded question, Ethel.

DR. GILBERT: With regard to dosimetry, it was interesting that there was remarkable agreement in the dosimetry programs in the three countries that were included. I think that was largely because there was considerable communication among those developing the personal dosimetry programs, so that the systems were not independent to begin with. There was a great deal of sharing of information in developing systems for monitoring workers.

With regard to the issue of detection limits, an adjustment of dose estimates was made in some of the British studies. For the other studies, this was not judged necessary. We also talked about doing something to adjust for random measurement errors, but in fact that never happened.

VOICE: So you treated the zeros basically?

DR. GILBERT: Yes, except for some of the British studies. For other studies, this problem was carefully evaluated, and adjustments were not judged necessary.

Status Report on The National Research Council's BEIR VI Study

Evan Douple
National Academy of Sciences

I appreciate being invited to describe the work of the sixth in the series of Biological Effects of Ionizing Radiation (BEIR) committees: BEIR VI, Health Risks of Exposure to Radon. In terms of timing, it is apparent that the BEIR VI report will not be available soon enough to meet the needs of members of the U.S. House or Senate and others concerned with policy. However, the BEIR VI report should be available before most of the residential cap-control studies are published and certainly before the data are pooled.

BEIR VI began in August 1992. It is funded entirely by the Environmental Protection Agency (EPA) which asked the National Research Council (NRC) to consider whether 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 NRC in BEIR IV.

The objectives of BEIR VI are as follows:

Phase I - To assist the EPA by collecting and evaluating information on ongoing studies and results of studies published since the BEIR IV report of 1988 on the health effects of exposure to radon progeny, and to determine whether sufficient and appropriate information is available to enable a Phase II committee to reassess the health effects of exposure to radon.

Phase II - If a Phase II study is warranted on the basis of the results of Phase I, to perform a full-scale reassessment of the health effects of exposure to radon as a BEIR VI report.

In that first phase, a small committee chaired by Dr. Jonathan Samet and also including Drs. Ethel Gilbert, Eric Hall, and Warren Sinclair evaluated the information published since the BEIR IV report and the 1991 companion report on dosimetry. Based on this information and its review of research that was in progress, the committee advised EPA on whether enough new material would be available in the near future to warrant a full-blown reassessment of the risk from exposure to radon and radon progeny.

The committee published its report - a Phase I report entitled *Health Effects of Exposure to Radon: Time for Reassessment?* - in 1994. That report summarizes the new work and justifies the committee's affirmative decision: there was enough new material and experimental results

expected in animal studies, molecular biology, cellular biology, epidemiology, and other areas to indicate that a larger committee could develop an improved risk model.

Phase II started in April 1994. As with most BEIR studies, the first committee meeting in Washington was opened to members of the scientific and lay community to present information and concerns on this issue. Although that meeting was not well attended, some scientists did present their thoughts and information. The committee has thirteen members. In addition to the chairman, Dr. Jonathan Samet, Drs. Dan Krewski, Ethel Gilbert, and Jay Lubin are members of the BEIR VI committee who are attending today's meeting. Other members of the committee are Drs. Paul Ziender, Rosalyn Yallow, Roger McClellan, Philip Hopke, Eric Hall, Dudley Goulhead, David Brenner, Antone Brechs, and William Elliott. Dr. Susan Conrath is the project officer from the EPA.

The committee has been meeting approximately three times a year and has held three workshops in conjunction with those meetings. At the most recent meeting, a workshop focused on the dosimetry in mines and the uncertainties associated with the measurements of radon and other conditions in the mines. Participants included individuals instrumental in making measurements in mines and in the industry's early years and scientists who have been concerned with errors in exposures estimated for the miners. The committee tried to assess the information on exposures that might still be available and the nature and magnitude of uncertainties associated with past measurements. This productive workshop gave the committee insights into uncertainties in the exposure estimates for the miners.

The original study was scheduled to be completed in February of 1996. However, one of the recommendations of the Phase I report was that the time period be extended through December of 1996 in order to enable the committee to complete its task. That decision was not driven by the fact that some of the case-control studies will be reported during 1996. The committee, from the very beginning, made it quite clear that, although there would be important information published from the case-control studies during the tenure of the committee, it would be unreasonable to expect that pooling of the studies would be completed. The committee realizes that pooling information is not going to be available before the final BEIR VI report is completed.

On the other hand, the BEIR VI committee will monitor the progress of the studies and the report will indicate when results are likely to be published.

In order to do its work, the committee has been formed into working groups. Those working groups, which are listed below, are reflective of the major issues that have been identified as the focus of the BEIR VI committee's work.

BEIR VI WORKING GROUPS

- Miner Data Sets and Analysis
- Residential Studies
- Smoking and Radon-Smoking Interactions
- Exposure and Dosimetry
- Cellular and Molecular Studies
- Risk Models and Uncertainties
- Animal Studies

One group is working on the miner data sets and analysis and is planning additional analyses beyond those negotiated by Lubin and colleagues. Dr. Ethel Gilbert is leading this group. The analyses by Dr. Jay Lubin at NCI and his collaborators included eleven cohorts with 2,780 lung cancer deaths in 68,000 miners compared to the four cohorts with 360 lung cancer deaths in 22,190 miners available for BEIR IV. New information is available regarding various factors which might be important. For example, a Chinese study included workers under the age of twenty. Arsenic exposure may have been a confounding factor in some of the mines. Smoking as a confounder has been identified more carefully in some of the studies. The years of follow-up are substantially greater compared to the data available for BEIR IV. The BEIR VI lung cancer risk model is likely to be based on statistical analysis of miner data but it will integrate information from other sources. Dr. Lubin is coordinating a group working on residential studies.

This group is considering the case-control and ecologic studies of indoor radon. A third group is Smoking and Radon coordinated by Dr. Samet. BEIR VI will emphasize the smoking issue. In its report, the committee will try to communicate the relative contributions of smoking and radon to lung cancer and to carefully characterize the interactions of smoking with radon.

Exposure and Dosimetry is a fourth working group, coordinated by Dr. Philip Hopke. This group is assessing particle-size distributions in both mines and homes. New measurements have identified factors and physical parameters that may be useful in modeling the radiation dose to target cells in the lung. You have heard from Dr. William Bennett that a Cellular and Molecular Studies work group of the BEIR VI committee held a workshop in Phase I which reviewed the studies underway that are searching for molecular signatures of exposure to radon. It is clear that modern molecular and cellular biology will contribute important information on radon carcinogenesis.

Dr. Dan Krewski has been leading a working group on Risk Models and Uncertainties that is considering additional modeling using the miner data. Dr. Suresh Moolghavkar, Dr. Duncan

Thomas, and others have provided advice to the committee regarding proposed modeling efforts. The final working group, coordinated by Dr. Antone Brooks, is Animal Studies. Several studies are underway in laboratories around the world in which scientists are investigating the biological effects of exposure to radon carcinogenesis in animals. These experiments are also trying to test the impact of smoking and other factors in animal models. The committee's working group is assimilating the information from these studies.

Thus, the committee is reassessing key aspects of the radon problem with the goal of developing a new model for risk assessment that will better predict the risk of lung cancer. The committee has identified problem areas and determined priorities. I think that they are on schedule to produce a final report in December of 1996. That's basically where BEIR VI is and where it is going. The Academy of Sciences has been known to take on tough assignments, and I think this is right up there with some of the toughest. I remember Len Cole's earlier challenge to avoid heightened ambiguity. That is an appropriate challenge to the BEIR VI committee-to contribute a document that is going to communicate a revised risk analysis of health effects of exposure to radon in a lucid fashion so as not to heighten ambiguity.

Third International Workshop
on Residential Radon Epidemiology

ATTENDEES

Dr. Michael Alavanja
National Cancer Institute
6130 Executive Blvd.
Rockville, MD 20892

Phone: 301-496-1611
Fax: 301-402-3256

Dr. Victor Archer
University of Utah
School of Medicine
50 North Medical Drive, Bldg. 512
Salt Lake City, UT 84112

Phone: 801-585-5112
Fax: 801-581-7224

Dr. William Bennett
National Institutes of Health
Bldg. 37, Room 2C25
37 Convent Drive
MSC 4255
Bethesda, MD 20892

Phone: 301-496-4668
Fax: 301-496-0497

Dr. Gloria Caton
Oak Ridge National Laboratory
1060 Commerce Park
Room 139, MS 6480
Oak Ridge, TN 37830

Phone: 615-574-7759
Fax: 615-574-9888

Dr. Leonard Cole
Rutgers University
381 Crest Road
Ridgewood, NJ 07450

Phone: 201-427-2385
Fax: 201-652-4323

Dr. Susan M. Conrath
Environmental Protection Agency
Radon Division
401 M Street, SW
Washington, DC 20460

Phone: 202-233-9397
Fax: 202-233-9652

Dr. Sarah Darby
University of Oxford
Imperial Cancer Research Fund
Cancer Epidemiology Unit
Gibson Building
Radcliffe Infirmary
Oxford OX2 6HE

Phone: 44-1865-311933
Fax: 44-1865-310545

Dr. Evan B. Douple
National Research Council/National Academy of Sciences
2101 Constitution Avenue, NW
Washington, DC 20418

ATTN: NAS 342

Phone: 202-334-2232
Fax: 202-334-1639

Dr. Robert Ehrlich
George Mason University
Physics Department
Fairfax, VA 22030

Phone: 703-993-1268
Fax: 703-993-1269

Dr. Marvin Frazier
U.S. Department of Energy
Office of Health and Environmental Research
19901 Germantown Road
Germantown, MD 20874

Phone: 301-903-5364
Fax: 301-903-8521

Ms. Ruth Kleinerman
National Cancer Institute
Executive Plaza North, Room 408
6130 Executive Blvd., MSC 7362
Rockville, MD 20852

Phone: 301-496-6600
Fax: 301-402-0207

Dr. Daniel Krewski
Environmental Health Center
Room 109
Tunney's Pasture
Ottawa Ontario
Canada K1A OL2

Phone: 613-954-0164
Fax: 613-952-9798

Dr. E. LeTourneau
Radiation Protection Bureau
Health Canada
775 Brookfield Road
Ottawa, Ontario
K1A 1C1 Canada

Phone: 613-954-6647
Fax: 613-952-9071

Dr. R. William Field
University of Iowa
Department of Preventive Medicine
N222 Oakdale Hall
Iowa City, Iowa 52242

Phone: 319-335-4413
Fax: 319-335-4747

Dr. Ethel S. Gilbert
Battelle - Pacific Northwest Laboratories
P.O. Box 999
MS PN-82
Richland, WA 99352

Phone: 509-376-7347
Fax: 509-376-4533

Dr. Laura Kolb
U.S. Environmental Protection Agency
401 M Street SW (6604J)
Washington, DC 20460

Phone: 202-233-9438
Fax: 202-233-9652

Dr. John F. Lechner
Inhalation Toxicology Research Institute
P.O. Box 5890
Albuquerque, NM 87185

Phone: 505-845-1121
Fax: 505-845-1229

Dr. Jay Lubin
National Cancer Institute
Biostatistics Branch
6130 Executive Blvd., Room 403
Rockville, MD 20892-7368

Phone: 301-496-3356
Fax: 301-402-0081

Dr. Billy Mills
Oak Ridge Associated Universities
1019 19th Street
Suite 700
Washington, DC 20036

Phone: 202-653-8941
Fax: 202-653-5414

Dr. John S. Neuberger
University of Kansas School of Medicine
Department of Preventive Medicine
Rainbow Blvd. at 39th
Kansas City, KS 66103

Phone: 913-588-2775
Fax: 913-588-2780

Dr. Goran Pershagen
Karolinska Institute
Institute of Environmental Medicina
Box 210
S-171 77 Stockholm
Sweden

Phone: 46-8-728-7460
Fax: 46-8-31-39-61

Dr. Jerome S. Puskin
U.S. Environmental Protection Agency
ORIA (6602J)
401 M Street, SW
Washington, DC 20460

Phone: 202-233-9219
Fax: 202-233-9629

Dr. Jonathan Samet
Johns Hopkins University
School of Hygiene and Public Health
Department of Epidemiology
Suite 6039, 615 N. Wolfe Street
Baltimore, MD 21205-2179

Phone: 410-955-3286
Fax: 410-955-0863

Dr. Colin Muirhead
National Radiological Protection Board
Leader, Epidemiology Group
Chilton, Didcot
OXON, OX11 ORQ
United Kingdom

Phone: 44-1235-831600
Fax: 44-1235-833891

Dr. William Nicholson
Mount Sinai Medical Center
P.O. Box 1057
1 Gustave Levy Place
New York, NY 10029

Phone: 212-241-5822
Fax: 212-966-0407

Dr. Andre Poffijn
University Gent
Laboratory Nuclear Physics
Proeftuinstraat 86
B-9000 GENT
Belgium

Phone: 32-92-646540
Fax: 32-92-646699

Dr. Susan Rose
U.S. Department of Energy
ER-73 E-222/GTN
19901 Germantown Road
Germantown, MD 20874

Phone: 301-903-4731
Fax: 301-903-8521

Dr. Dale Sandler
National Institute of Environmental Health Sciences
Epidemiology Branch
111 T.W. Alexander Drive
Bldg. 101, South Campus, Room A306, MD A3-05
Research Triangle Park, NC 27709-2233

Phone: 919-541-4668
Fax: 919-541-2511

Dr. Jan Schoenberg
New Jersey Department of Health
Special Epidemiology Program
CN 369
Trenton, NJ 08652

Phone: 609-588-3500
Fax: 609-588-7431

Dr. Robert Simon
U.S. Senate
Committee for Energy and Natural Resources
304 Dirkson Senate Building
Washington, DC 20510-6150

Phone: 202-224-9201
Fax: 202-224-9026

Dr. Daniel Steck
St. John's University
Physics Department
Box 3000
Collegeville, MN 56321

Phone: 612-363-3186
Fax: 612-363-3202

Dr. Jan Stolwijk
Yale University School of Medicine
Department of Epidemiology and Public Health
60 College Street
P.O. Box 8034
New Haven, CT 06520

Phone: 203-785-6373
Fax: 203-785-6103

Dr. Margot Tirmarche
Departement de Protection de la
Sante de L'Homme et de Dosimetrie
Service D'Evaluation et de Gestion des Risques
Laboratorie d'Epidemiologie et d'Analyse du Detriment Sanitaire
Centre d'Etudes Nucleaires
B.P. N 6
92265 Fontenay-Auz-Roses Cedex

Phone: 33-1-46547194
Fax: 33-1-46548829

Dr. Richard Sextro
Lawrence Berkeley Laboratory
Building 90, Room 3058
Berkeley, CA 94720

Phone: 510-486-6295
Fax: 510-486-6658

Dr. Jaak Sinnaeve
European Commission
Rue de La Loi 200
1049 Brussels, Belgium

Phone: 32-2-295-4045
Fax: 32-2-296-6256

Dr. Heather Stockwell
U.S. Department of Energy
Office of Health
EH42/270CC
Washington, DC 20585

Phone: 301-903-3721
Fax: 301-903-4677

Dr. Kevin Teichman
Environmental Protection Agency
Office of Research and Development (8105)
401 M Street, SW
Washington, DC 20460

Phone: 202-260-7669
Fax: 202-260-0106

Dr. Mark Upfal
Wayne State University School of Medicine
Department of Family Medicine
4201 St. Antoine, UHC-4J
Detroit, Michigan 48201

Phone: 313-577-6857
Fax: 313-577-3070

Dr. H.-Erich Wichmann
GSF
Institute of Epidemiology
P.O. Box 1129
D-85758 Oberschleissheim
Germany

Phone: 49-89-3187-4066
Fax: 49-89-3187-3380

PART II

PLANNING MEETING FOR

COMBINED ANALYSIS OF RESIDENTIAL RADON STUDIES

NORTH AMERICA

Sponsored by

Health Canada

Ottawa, Ontario

October 16-17, 1995

Planning Meeting for
Combined Analysis of Residential Radon Studies North America

October 16-17, 1995
Tunney's Pasture, Ottawa, Ontario

AGENDA

October 16, 1995

9:00 a.m.	9:15 a.m.	**Introduction/Opening Remarks** Dan Krewski, Health Canada Ernest LeTourneau, Health Canada
9:15 a.m.	9:45 a.m.	**Summaries of Completed Studies** Ernest LeTourneau: Winnipeg Michael Alavanja: Missouri
10:15 a.m	10:30 a.m	**Coffee Break**
10:30 a.m.	11:30 a.m.	**Summaries of Other Available Data** Dale Sandler, National Institute of Env. Health Sciences Jay Lubin, National Cancer Institute
11:30 a.m.	12:30 p.m.	**Discussion on Common Data Elements**
12:30 p.m.	1:30 p.m.	**Lunch**
1:30 p.m.	2:15 p.m.	**Combined Analysis of Case-Control Radon Studies** Jay Lubin, National Cancer Institute
2:15 p.m.	4:00 p.m.	**Methods for Combining Case-Control Studies** Dan Krewski, Health Canada J.M. Zielinski, Health Canada

October 17, 1995

9:00 a.m.	10:00 a.m.	**Discussion on Common Data Format to be Submitted to Analysis Team**
10:00 a.m.	10:15 a.m.	**Coffee Break**
10:15 a.m.	11:45 a.m.	**Development of Project Working Plan**
11:45 a.m.	1:15 p.m.	**Lunch**

Health and Welfare Canada
Santé et Bien-être social Canada

Health Protection Branch
Direction générale de la protection de la santé

Room 109
Environmental Health Center
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

January 4, 1996

Dr. Susan Rose
U.S. Department of Energy
ER-73 E-222/GTN
19901 Germantown Road
Germantown, MD
U.S.A. 20874

Dear Dr. Rose:

Thank you for participating in a meeting on North American Pooling Effort held last October in Ottawa. The meeting provided an excellent forum to discuss issues involved with conducting pooled analysis of the data from case-control studies of lung cancer and residential exposure to radon. Enclosed meeting report includes appendix with common data format that will be used for submitting data to the analysis team.

We look forward to your continued collaboration on this important project.

With best regards.

E.G. Létourneau, M.D., D.Sc.
Director
Radiation Protection Bureau

D. Krewski, Ph.D., M.H.A.
A/Director
Bureau of Chemical Hazards

Encl.

Canada

Planning Meeting for Combined Analysis of Residential Radon Studies North America

EXECUTIVE SUMMARY

Objectives

Three large case-control studies of lung cancer and residential exposure to radon have been completed in North America, while several other are nearing the completion. Since some of the results of case-control studies of residential radon have been positive while others have been negative, it was decided at the Third Annual DOE/CEC International Radon Epidemiology Meeting, Baltimore, MD, that pooled analysis of the data from all North American studies would be undertaken prior to pooling with European data. A pooled analysis of their data should provide more precise estimates of the overall magnitude of lung cancer risk. A meeting to plan a combined analysis of North American residential radon studies was held on October 16-17, 1995 in Ottawa, Ontario. Principle investigators from the North American case-control studies, other key participants, and also observers from the Commission of European Communities participated in the meeting.

The four objectives of the meeting were: to consider the methods for combined analysis of case-control studies; to identify common data elements; to establish a data format to be submitted to the analysis team; and to develop an overall work plan with time lines.

The meeting was sponsored by Health Canada and U.S. Department of Energy. It was hosted by the Environmental Health Directorate, Health Protection Branch, Health Canada. The Commission of European Communities is sponsoring similar efforts for the European residential radon pooling.

Proceedings: October 16, 1995

Winnipeg

The meeting began with a description of the completed studies. Dr. E. Letourneau (Health Canada) summarized the Winnipeg study which included 738 registry identified primary lung cancer cases and 738 age/sex matched controls. One year alpha track measurements were made in basements and bedrooms of all prior residences where possible. The analyses were stratified by exposure period (5-15 or 5-30 years before study enrolment) and dosimeter location (bedroom or basement). No odds ratios were significant for any radon exposure category in any of the above strata. There was no suggestion of a positive trend in the odds ratios. The analysis controlled for smoking status, and a sub-analysis by smoking strata was not presented.

A sub-analysis was performed by histological type in which radon exposure was treated as a binomial variable. None of the odds ratios were significantly elevated.

Missouri I / Missouri II

Dr. M. Alavanja (National Cancer Institute) presented the results of the Missouri Radon I study and described the ongoing Radon II study. The Radon I study was restricted to non-smoking white, women and included 538 cases and 1183 controls who were frequency matched for age. Year long alpha track readings were made in both the kitchen and bedroom. The odds ratios for increased radon exposures were not significantly elevated and a trend in risk between exposure categories was not found. Analyses by histological type showed a positive trend in risk with increased radon for adenocarcinoma and this was significant when age and saturated fat intake were adjusted for. The Radon II study will recruit about 700 cases and will include smokers. Controls will be frequency matched for smoking category. It is anticipated that the second study will be ready for publication in October, 1996.

NIEHS Studies: Yale/Utah, New Jersey II, and Iowa

Dr. D. Sandler described three ongoing studies funded by the National Institute of Environmental Health Sciences (NIEHS). First, the NIEHS-Yale-Utah study includes 1474 cases and 1811 controls of both sexes from Utah/South Idaho, or Connecticut. Year long alpha track readings were made in living levels, bedrooms and basements of all homes inhabited for greater than one year and in the longest duration childhood home. This study is expected to be completed by December, 1996. Second, a New Jersey II study will include 787 cases of both sexes and 896 frequency matched controls. One year alpha track radon levels have been made in the living area, bedroom and basement of all residences occupied for 2 or more years. This study may be completed by December, 1996. Third, an Iowa study will include 450 cases and 616 controls and year long alpha track measurements will be made. The anticipated completion date is 1998.

Studies in China, New Jersey I

Dr. J. Lubin (National Cancer Institute) briefly described a study funded by the National Cancer Institute which was carried out in Shenyang, China. He also described an ongoing study in China which will look at radon exposures in underground dwellings. It was felt that, because of differences in housing characteristics and potential environmental and genetic confounders, it would not be appropriate to include these studies in the proposed combined analysis. A New Jersey I study was published in 1990 but was not presented at this meeting. It is planned that the New Jersey data will be used for the proposed pooled analysis.

Combined Analysis of Residential Radon Studies

Dr. Lubin pointed out that, until large studies of sufficient precision can be conducted, available studies will have to be combined and analyzed in parallel to provide the best evidence of level of risk from residential radon.

Methods for Meta-Analysis

Dr Krewski (Health Canada) presented methods used in meta-analysis of data from eleven cohorts of underground miners. Because of these differences among cohorts, a joint re-analysis of these data was conducted using a random effects regression model. By using a random-effects model, the overall effect of radon on lung cancer risk can be described by fixed regression coefficients, and variation across cohorts characterized by random regression coefficients. Specifically, a nonlinear random-effects regression model was used to describe both population average and cohort specific risks. Mixture models, which include additive and multiplicative models to describe the joint effects of radon and tobacco on lung cancer mortality, were fit to the data using generalized estimating equations. Whereas a linear relative risk model provided a good description of the excess lung cancer risk due to radon exposure in all eleven cohorts, a mixture model was used to describe the joint effects of radon and cigarette smoke in the six cohorts for which detailed information on tobacco consumption was available. Dr Krewski suggested development of methods using a similar approach, based on a random-effect model, to analyze data from several case-control studies. Here, the overall effect of radon on lung cancer risk can be described by fixed Odds Ratio Coefficient, and variation across cohorts characterized by random Odds Ratio Coefficients.

Proceedings: October 17, 1995

Common Data Format

On day two, discussion turned to the data format that will be used for the pooled analysis. A summary of the proposed format was circulated to those present. The suggested format would provide data in two "records": (1) general information and (2) radon exposure/concentration information. While a "set/stratum number" will be included for paired and frequency matched subjects, it was acknowledged that paired-matches will have to be broken for the analysis and it was felt that this should have little impact. There was considerable debate surrounding histology, and in the end it was decided to include in this variable additional category "uncertain" when reevaluation of histological material was performed and results were inconclusive. Information about residence (urban verses rural) would be problematic to come by, thus this variable was dropped. It was decided to add information on environmental tobacco smoke (ETS) including the number of cigarettes smoked in subjects' homes by others for each of the 50 years prior to the enrolment in the study. Data on occupation will not be submitted. There was general agreement on the proposed format for data on radon exposure. An additional category "glass" will be added to the measurement technique variable in order to

accommodate the studies which are now using this method. The final, revised, agreed-upon format is appended to this paper.

Results

A project working plan was developed. Nine studies could potentially be included in the pooling, and these are summarized in Table I. A Steering Committee will be established and will consist primarily of the principle investigators from the original studies. An Analysis Team will also be established which will include statistical, epidemiological, and dosimetry expertise. An initial analysis will be carried out using data from the studies which are currently available (Winnipeg, Missouri I, New Jersey I) The objective of the initial analysis will be to define the methodology for pooling. The final analysis will be completed when data becomes available from the New Jersey II, Utah-S.Idaho/Connecticut, and Missouri studies. This will likely be in early 1997. The publication format may be a paper, monograph, or both, and will be decided on at a later date. In order to protect the privacy of the studies which are ongoing at present, it was agreed that the pooled information will not be shared until the pooling has been completed, and the results have been submitted and published.

Table I. Studies available for pooling.

Study	Cases #	Date Available (if not now)
Winnipeg	738	
Missouri I	550	
Missouri II	700	October 1996
New Jersey I	433	
New Jersey II	787	December 1996
Florida	approx 200	
Louisiana	?	?
Utah/S. Idaho, Connecticut	1474	December 1996
Iowa	450	1998

DATA FORMAT FOR POOLING OF RESIDENTIAL RADON CASE-CONTROL STUDIES

For each subject, provide data in two "records".

Record 1: General information

General data:

ID	identification number	
Set number	set/stratum number, if (individually/freq) matched case-control study	
Status	case	1
	control	0
Sampling probability		number in the interval (0.0,1.0]
Histology	control	0
	squamous	1
	small/oat cell	2
	other	3
	adenocarcinoma	4
	uncertain	5

Age at interview/ascertainment
Year at interview/ascertainment

Interview type	subject	1
	surrogate	2
Gender	females	1
	males	2

Demographic data:
Education highest year in school completed:

elementary school	1
high school	2
some college or tech school	3
completed college or tech school	4
post-graduate education	5

Family income (some reasonable ranges)

Lung cancer risk factors:

Smoking type	never-smoked	1
	cigarettes only	2
	pipe/cigar	3
	mixed	4
Duration	years smoked (cigarette duration, if mixed smoker)	
Smoking rate	no/day (cigarettes/day, if mixed)	
Age started smoking	(cigarettes, if mixed smoker)	
Age ended smoking	(cigarettes, if mixed smoker)	
Cessation	years since last smoked (cigarettes, if mixed)	

Record 2: Radon exposure/concentration information

For information on residential radon concentration and ETS, provide data in terms of each year prior to interview, from one year prior to 50 years prior, i .e., $x_1, \ldots\ldots x_{50}$ where x_i is the information on the home resident in the ith year prior to the age at interview.

ID	identification number
$a_1,\ldots\ldots ,a_{50}$	Rn concentration for a house (from measurements or from an imputation approach that cannot be recreated from Rn concentration data, e.g., a regression-based imputation), if available, and zero otherwise. If more than one measurement, supply mean or "best" estimate of radon concentration.
$b_1,\ldots ,b_{50}$	type of concentration data for each year: missing/unavailable 0 estimated/imputed -1 Rn measurement from home 1 1 Rn measurement from home 2 2 etc.
$aa_1,\ldots\ldots ,aa_{50}$	for Winnipeg supply a second set of variables, $aa_1,\ldots ,aa_{50}$, to reflect basement concentrations.
$bb_1,\ldots ,bb_{50}$	type of concentration data for Winnipeg basement measurements: missing/unavailable 0 estimated/imputed -1 Rn measurement from home 1 1 Rn measurement from home 2 2 etc.
$c_1,\ldots ,c_{50}$	alpha-track meas(long-term) 1 canister meas (short-term) 2 glass meas (long-term) 3
$d_1\ldots\ldots ,d_{50}$	occupancy factor, proportion in the interval (0.0,1.0]
$e_1\ldots\ldots ,e_{50}$	number of smokers in subjects' home
$f_1\ldots\ldots ,f_{50}$	number of cigarettes smoked per day in subjects' home

To maximize use of knowledge about the local characteristics, PIs should provide their best estimate of the radon concentration ($a_1,\ldots .,a_{50}$), while still allowing for the use of simple imputation procedures, as described in Weinberg et al.

Planning Meeting for Combined Analysis of Residential Radon Studies North America

ATTENDEES

Dr. Michael Alavanja
National Cancer Institute
6130 Executive Blvd.
Rockville, MD 20892

Phone: 301-496-1611
Fax: 301-402-3256

Dr. Dalsu Baris
Atomic Energy Control Board
280 Slater Street
PO Box 1046, Station B
Ottawa, Ontario K1P 5S9

Phone: 613-992-8567
Fax: 613-943-0253

Dr. Ken Chadwick
Commission of the European Communities
Rue de La Loi 200
Radiation Protection Programme
(XII-D-3/ARTS 2-47)
B-1049 Bruxelles Belgium

Phone: 011-32-2-295-4045
Fax: 011-32-2-296-6256

Dr. Susan Conrath
Radon Division
Problem Assessment Branch 6604J
Public Health Service
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Phone: 202-233-9397
Fax: 202-233-9652

Dr. Evan Douple
National Research Council/
National Academy of Sciences
2101 Constitution Avenue, NW
Washington, DC 20418

Phone: 202-334-2232
Fax: 202-334-1639

Dr. Murray Fyfe
Community Medicine Residency Program
Department of Community Health
Sciences, Faculty of Medicine
University of Calgary
3330 Hospital Drive, NW
Calgary, Alberta, Canada

Phone: 403-220-4286
Fax:

Dr. Dan Krewski
Chief, Biostatistics Division
Environmental Health Directorate
Health Canada
Environmental Health Centre,
Tunney's Pasture
Ottawa, Ontario K1A0L2

Phone: 613-954-0164
Fax: 613-941-8632

Dr. E.G. LeTourneau, Director
Radiation Protection Bureau
Health Canada
775 Brookfield Road
Ottawa, Ontario K1A 1C1

Phone: 613-954-6647
Fax: 613-952-9071

Dr. Jay Lubin
National Cancer Institute
Biostatistics Branch
6130 Executive Blvd.
Rockville, MD 20892-7368

Phone: 301-496-3356
Fax: 301-402-0081

Mr. R.G. McGregor
Radiation Protection Bureau
Health Canada
775 Brookfield Road
Ottawa, Ontario K1A 1C1

Phone: 613-954-6677
Fax: 613-957-1089

Mr. Colin R. Muirhead
National Radiological Protection Board
Chiton, Dicot, Oxen OX11 0RQ

Phone: (UK) 235 831600
Fax: (UK) 235 833891

Dr. Susan Rose
U.S. Department of Energy
Health Effects and Life Sciences
Research Division
Washington, DC 20545

Phone: 301-903-4731
Fax: 301-903-8521

Dr. Jonathan Samet
Johns Hopkins University
School of Hygiene and Public Health
Department of Epidemiology
Suite 6039, 615 N. Wolfe Street
Baltimore, MD 21205-2179

Phone: 410-955-3286
Fax: 410-955-0863

Dr. Dale Sandler
Epidemiology Branch
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive
Building 101, South Campus
Room A306, MD A3-05
RTP, NC 27709-2233

Phone: 919-541-4668
Fax: 919-541-2511

Dr. Y. Wang
Biostatistics Division
Environmental Health Directorate
Health Canada
Environmental Health Centre,
Tunney's Pasture
Ottawa, Ontario K1A 0L2

Phone: 613-941-8013
Fax: 613-941-8632

Dr. Claire Weinberg
Division of Biometry and Risk Assessment
NIEHS
PO Box 12233, NDB3-02
RTP, NC 27709

Phone: 919-541-4927
Fax: 919-541-4311

Dr. J.M. Zielinski
Biostatistics Division
Environmental Health Directorate
Health Canada
Environmental Health Centre,
Tunney's Pasture
Ottawa, Ontario K1A 0L2

Phone: 613-954-0168
Fax: 613-941-8632