HERB LIBRARY

FINAL REPORT

OF THE

RADIATION EXPOSURE COMPENSATION ACT COMMITTEE

SUBMITTED TO THE
HUMAN RADIATION INTERAGENCY
WORKING GROUP

JULY, 1996

Appendix

Establishment of Data-Based Criteria for Radon-Associated Lung Cancer

Introduction

This appendix presents the scientific basis for suggested revisions of criteria for the compensation of lung cancer among underground uranium miners from the eligible regions of the U.S. Radioactive radon (more specifically radon-222, hereafter referred to as radon) is an inert gas and is a decay product of radium-226, the fifth progeny of uranium-238 which is ubiquitous in the crustal rock of the earth. Radon can migrate from soils and rocks and accumulate in enclosed areas, such as homes and underground mines. The carcinogenic potential of radon derives principally from alpha particles (helium nuclei) emitted during radioactive decay of the short-lived progeny of radon-222, that is, polonium-218 and polonium-214.

Since the 1970s, a substantial amount of research, epidemiologic studies in humans, experimental animal studies, and *in vitro* cellular studies, has been published, that establishes the causal link between exposure to radon and its decay products and the development of lung cancer. Periodically, the body of research material has been reviewed by expert committees. Reviews have been conducted by the National Council on Radiation Protection and Measurements (NCRP 1984) and by the International Commission on Radiation Protection (ICRP 1987). In 1988, the fourth National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiations (BEIR IV) evaluated the scientific literature, and for the first time, conducted a pooled analysis of original data from four epidemiologic studies of

miners, including a study of Colorado Plateau uranium miners (NRC 1988). The BEIR IV Committee reiterated the causal link of radon progeny exposure to lung cancer risk, and developed a risk model that described the exposure disease relationship. The BEIR IV model has been the principal model used for the evaluation of radon risks from exposures in mines and in homes. More recently, building on the work in the BEIR IV Report, scientists of the U.S. National Cancer Institute in collaboration with principal investigators of all (eleven) cohort studies of radon-exposed underground miners conducted a pooled analysis of original data (Lubin et al. 1994; 1995), including recent updates of studies of Colorado Plateau uranium miners (Hornung and Meinhardt 1987) and New Mexico uranium miners (Samet et al. 1991). The pooled analysis included a total of nearly 1.2 million person-years of observation and over 2,700 lung cancer deaths, nearly eight times the data available to the BEIR IV Committee.

The BEIR IV analysis and the NCI-led analysis showed that relative risk (RR) of lung cancer was strongly related to cumulative radon progeny exposure in units of Working Level Months[1] (WLM). The analyses indicated that the exposure-response relationship in the RR was complicated by a dependence on other factors, notably that the exposure-response relationship declined with current age (referred to as attained age) and time since the exposure occurred. These patterns indicate that the effects of exposure vary in a complex way as an individual ages. In terms of the RR, the effects of exposure lessen as the age of a miner increases and with time since cessation of radon progeny exposure. The analyses also found

---

One Working Level (WL) equals any combination of radon progeny in one liter of air which results in the emission of 130,000 MeV of energy from alpha particles. WLM is the product of time, in units of 170 hours, and WL.

an inverse exposure-rate effect, that is, for the same total exposure, exposures occurring over a shorter duration of time (at a higher exposure rate) were less harmful than exposures occurring over a longer duration (at a lower exposure rate). In the analysis of the Colorado and New Mexico data which is presented below, the inverse exposure-rate effect was not statistically significant and will be omitted. The pooled analyses also found that risk from radon progeny exposure did not depend on the age at which a miner was first exposed.

The procedures used in the BEIR IV and NCI-led pooled analyses are the same as the methods used in the analysis presented in this appendix. Specific information is provided in those reports.

RECA does not establish an entitlement program whereby all lung cancer cases are compensated, but seeks to establish a program of fairly compensating lung cancer cases for harm done during the mining of uranium. In this regard, the most appropriate basis for making such a determination is the application of the most relevant data. There have been two epidemiologic studies of uranium miners in the four state region of Arizona, Colorado, New Mexico, and Utah. One study was initiated in the 1960s by the U.S. Public Health Service and currently is being conducted by the National Institute for Occupational Safety and Health (Lundin et al. 1971; Hornung and Meinhardt 1987). A second study was initated at the University of New Mexico (Samet et al. 1991). The study populations constitute a substantial fraction of all miners eligible for compensation under RECA, and thus are directly relevant to establishing factors predictive of lung cancer occurrence. The two studies include nearly 190,000 person-years of observation and 470 lung cancer cases, and provide the data used in our evaluation of compensation criteria.

The analyses presented in this appendix use outcome and exposure information as provided by study investigators. For comparing the likelihood that an observed lung cancer in a miner is due to radon progeny exposure using non-WLM-based criteria, we assume that at a minimum a worker is able to document work history, including calendar years of underground employment.

This appendix considers five topics related to the evaluation of whether an observed lung cancer in a miner is the result of exposure to radon and its decay products accrued during time as an underground miner.

(1) Pooling data from two studies of uranium miners, risk models are developed that reflect the causal association between radon progeny exposure and lung cancer occurrence. These models form the basis for recommending new guidelines for compensation. Because the risk model is derived directly from an analysis of a substantial fraction of all eligible miners, the recommended criteria incorporates a direct evaluation of the likelihood that a lung cancer was the result of exposure to radon progeny.

(2) The scientific basis for the joint association of radon progeny exposure and cigarette use and the occurrence of lung cancer is reviewed. Based on analysis of available miner data, the most appropriate description of the joint RRs can be interpreted to specifying eligibility criteria for non-smokers which are less stringent than for smokers. However, results to date indicate that due to chance alone, the joint RRs are also interpretable as consistent with using the same compensation criteria for smokers and non-smokers.

(3) Evidence indicates that Native Americans do not smoke or are generally light smokers. Anecdotal reports suggest that radon progeny exposure may be especially deleterious in

Native Americans. Data are examined and recommendations are suggested.

(4) In response to concerns of the President's Advisor Panel on Human Radiation Experimentation on uncertainties associated with the estimation of a worker's exposure, an alternative to a WLM-based risk model is developed. This non-WLM based model is used to recommend an alternative scheme for establishing compensation eligibility when information on mine location is missing or when measurement data are missing or inadequate for accurate estimation of WLM.

(5) RECA criteria for compensation require that all exposures occurs prior to 1972, that for non-smokers total cumulative exposure should equal or exceed 200 WLM, and that for smokers exposure should equal or exceed 500 WLM or if lung cancer occurs under 45 years of age exposure should equal or exceed 300 WLM. Based on current epidemiologic findings, these criteria do not reflect a scientifically sound attribution of risk of lung cancer risk from radon progeny exposure, and therefore do not appropriately discriminate lung cancer cases that are more likely than not due to radon progeny exposure.

One issue of importance is the requisite "fairness" of the RECA compensation criteria for lung cancers in uranium miners. It is worth considering what is meant by fairness in the context of lung cancer attributable to radon progeny exposure. Compensation for lung cancer is based on whether it was more likely than not due to radon progeny exposure. This stipulation can be reflected in the probability of causation (PC), which is a probabilistic statement of the likelihood that a lung cancer case is due to radon progeny exposure. A PC equal to or greater than 0.5 indicates that the disease event was more likely than not to have

been due to the causal agent.

The validity of a PC is based on the validity of the model used to describe the disease-exposure association. If the model omits important factors or misspecifies the functional form of the relationship, then PCs computed from the model may not measure the true likelihood of the event being caused by the exposure. With observational data and without a precise understanding of the biological mechanisms of the carcinogenesis process at the level of the cell and of the organ system, the true risk relationship, and thus the true PC, can never be determined with absolute certainty. However, a risk model that provides a more accurate characterization of the observed data will necessarily result in a computed PC which has greater validity.

In the view of this Committee, fairness in the compensation criteria is reflected in the PC. The more accurate the model used to compute PCs the greater fairness there is in the determination of eligibility. The risk model which is developed below fits the pooled Colorado and New Mexico miner data significantly better than the model implied by the RECA criteria. Thus, criteria based on the new risk model would imply a greater fairness than the RECA criteria.

Current scientific understanding about the relationship between radon progeny exposure and lung cancer does not support the RECA criteria, and therefore the RECA criteria should not be viewed as the benchmark of fairness by which to judge any new criteria. It is not the case that new criteria can be fair only if greater numbers of lung cancer cases are compensated. As a result, using criteria based on a new risk model, some lung cancer cases may be eligible for compensation who would do not satisfy current RECA criteria.

Conversely, some lung cancer cases who would not be eligible under a new scheme, indicating that their lung cancer is more likely than not due to factors other than radon progeny exposure, may be eligible under current RECA criteria.

Finally, true dose to lung tissue from radon and its progeny can never be known with certainty. WLM estimates in the miner data are approximations and are themselves subject to uncertainty. Thus, any WLM-based model which is developed, while having greater validity than the RECA-based model, cannot be considered as the "gold standard" that identifies the true level of risk.

Before proceeding, we briefly review the scientific basis for the causal relationship between radon progeny exposure in miners and lung cancer, define the data available for analysis, and describe the methods of analysis, including the computation of the PC.

Scientific basis for the association of radon progeny exposure and lung cancer

Effects of radon progeny exposure in underground miners

Since the mid-1980s, expert committees have sought to characterize risk of lung cancer from exposure to radon and radon progeny. Two early reports, by the National Council on Radiation Protection and Measurements (NCRP 1984) and by the International Commission on Radiation Protection (ICRP 1987), relied on heuristic summarizations of existing results in the literature. The NCRP committee assumed that the effects of exposure directly added to the age-specific lung cancer rate in non-exposed workers, and assumed no synergistic effects of cigarette smoking. In the latter report, the ICRP committee assumed a constant RR model, whereby the effects of exposure multiple the age-specific lung cancer rate in non-exposed

workers. For exposures in miners, the multiplicative effects were assumed unchanged for all ages and without regard to years since last exposure. Recent analyses have shown that these simple characterizations of risk from radon progeny exposure are incorrect. In 1988, the NAS BEIR IV Committee was the first expert committee to conduct original analyses using modern statistical methodology. The model linking WLM and lung cancer risk was complex. The BEIR IV anlaysis showed that over a broad range of exposures RRs were generally consistent with a linear relationship; however, they also showed that the RR relationship was not constant, but decreased with current age of the individual and with time since the exposure occurred. These patterns of variation in the exposure-response relationship have since been sustained in a pooled analysis by Lubin et al. (1994; 1995) using data from 11 cohort studies, including the four in the BEIR IV Report.

Effects of smoking on risk of lung cancer due to radon progeny exposure

Cigarette smoking is the major cause of lung cancer. Several investigators have considered the effects of smoking on the estimates of risk from exposure to radon progeny. Analyses have provided convincing evidence that, although the majority of miners were smokers, the increased risk with WLM exposure is not due solely to smoking. Based on formal analyses, with the Colorado study providing the most complete information, it has generally been concluded that there is a synergistic relationship for WLM and smoking, that is, the lung cancer risk for exposure to both agents is greater than the sum of the risks for each exposure individually.

Analyses support a joint association which is most likely intermediate between multiplicative and additive, although analyses also indicate that the association is consistent

with a multiplicative association. An association which is less than multiplicative implies that the RR for radon progeny is greater in non-smokers than in smokers. In the pooled analysis of 11 cohort studies, non-smokers had a 3-fold greater exposure-response relationship than smokers. Because radon progeny exposure multiplies the background disease rate and because smokers have a much higher lung cancer rate than non-smokers, a "greater than additive" association results in a radiogenic excess that is substantially greater in smokers than in non-smokers.

Effect of radon progeny exposure in Native Americans

Because of small numbers of study subjects, analyses of Native American miners have been limited. There have been case reports of lung cancer among Native Americans of the Southwest, who were involved in mining. In the most complete analysis, Samet et al. (1984) reported on 32 lung cancer cases diagnosed between 1969 and 1982, in which 23 had a documented history of uranium mining, while none of the 64 matched controls had been uranium miners. This suggests a high RR with uranium mining in Native Americans, who traditionally do not smoke or are light smokers. However, results are insufficient for quantitative risk estimation or for comparison with non-Native American miners.

Cohort studies of U.S. uranium miners

Colorado Plateau uranium miners

Cohort definition and follow-up

The Colorado Plateau uranium miners study was one of the earliest of the modern epidemiologic studies to document increased lung cancer risk with exposure to radon progeny

(Lundin et al. 1971). Extensions of the follow-up through 1977, 1982, 1987 and 1990 were subsequently carried out. Initially established by the U.S. Public Health Service (PHS), the cohort follow-up is now under the auspices of the U.S. National Institute for Occupational Safety and Health. Work history information was available through 1969; little additional exposure is thought to have occurred after that time since many workers had retired and many uranium mines in the Colorado Plateau had closed. In contrast to the pooled analysis by Lubin et al. (1994), we include all miners and all exposures in the analysis.

All min were inclu in anal

The current analysis utilizes the most recent update with follow-up through 1990. A total of 115 workers, including 12 lung cancer cases, in the Colorado cohort qualified for and were included in the cohort study of New Mexico uranium miners (defined as all underground miners medically evaluated at the Grants Clinic, Grants, New Mexico). These miners were included only once in the pooled analysis.

Members of the Colorado Plateau study cohort included workers in the four States of Arizona, Colorado, New Mexico, and Utah, who had completed at least one month of 0underground uranium mining, who volunteered for at least one medical examination between 1950 and 1960, and who provided personal and occupational data of sufficient detail for follow-up and for exposure estimation. Information on follow-up and ascertainment of vital status was obtained from records of mining companies, state vital statistics offices, the U.S. Social Security Administration, the Internal Revenue Service, the Veteran's Administration and, most recently, the National Death Index, and by direct contact. Cause of death was determined from State death certificates.

Estimation of radon progeny exposure

Prior to 1951, only a few measurements of radon were made. During the period 1951-60, radon progeny measurements were made by the PHS, several State agencies and the U.S. Bureau of Mines. Data were considered representative of areas in which most of the miners worked. After 1960 and until the latest samples were collected in 1968, most samples were taken by mine inspectors. Between 1951-68, almost 43,000 measurements of radon progeny in 2,500 mines were obtained. However, as noted by Holaday (NRC 1988, quoted by Lundin et al. 1971), most measurements were made for control purposes and may have overestimated exposure to workers.

A little over 10% of the miners had their exposure estimated entirely from measurements taken in the mines. Measures of exposure to radon progeny were generally collected using the Kusnetz method, which was an area sample based on alpha counts collected using a filter/pump apparatus. When multiple samples were available in a given mine and year, the arithmetic mean was used to characterize annual WL levels. When measurements were not available for a given mine and year, three different methods were used to assign WL levels. (1) When data for a mine were incomplete, the annual average WL was used for the level within a maximum of two years from the measured year. (2) When gaps of greater than four years existed for a mine, averages of other mines in the same geographic area were used to estimate annual WL levels. (3) If no data existed in adjacent years or within the geographic region, estimates of WL were made based on knowledge of ore bodies, ventilation practices, and other factors thought to influence radon progeny levels.

The amount of time each miner worked underground was obtained from several sources. Initial data were collected at the time of the physical examination, one of the defining criteria

for enrollment into the cohort. This information was used to provide work histories to that point in uranium mines, as well as past employment in other hard rock mines. Additional data were collected from mining company records and from an annual census taken by the PHS and by the Colorado Bureau of Mines.

The number of hours per month underground was taken to be 170. No adjustment was made for vacations, sick leave, or overtime. However, gaps in employment histories of one month or more were recorded and, when available, taken into account in the exposure estimates.

When a census identified a miner with no work history at a particular mine, the miner was assumed to have worked in that mine for a period of six months prior and subsequent to the census date.

A relatively small proportion of the study group had WLM estimates based completely on measured data. While extrapolated data may be subject to greater error, the extent of misspecification depended largely on estimation procedure. An analysis of error found a coefficient of variation of 112% that included sampling error, counting error, and environmental fluctuations over each year (Hornung 1985). The coefficient of variation in the three estimation procedures ranged from 121% to 186%. When all estimation procedures were averaged over the number of measurements and years worked for each miner, the coefficient of variation for cumulative WLM was approximately 97%.

Exposure rates in WL have decreased dramatically over time. Figure 1 shows mean exposure rates in WL for 1950-69. The primary factor in the decline was the introduction of ventilation systems in mines. There is approximately a 20-fold reduction in mean WL for the

mines over this time period. Figure 2 shows the number of measurements made in the mines over this same period of time. The number of measurements peaked in the late 1950s and early 1960s and declined thereafter. These figures make it clear that if compensation criteria are based on duration of time spent in underground, as suggested by the Advisory Panel, calendar period of mining must also be considered.

Estimation of other mine exposures

For the present analysis, data were available on years of previous underground hard rock mining, as well as an estimate of WLM accumulated in these mines. There were no data available on other specific exposures that may have been encountered in the uranium mines, such as arsenic-containing dusts or silica, or in the previous hard rock mines.

Information on tobacco use

Data on smoking were obtained at the annual censuses of miners and from mail questionnaires, obtained on one to four occasions between 1950 and 1960 and at other times between 1963-69 (NRC 1988; Whittemore and McMillan 1983).

New Mexico uranium miners

Cohort definition and follow-up

The State of New Mexico was one of the four States included in the Colorado Plateau uranium miners study of the PHS. In 1977 a separate study cohort was established by investigators from the University of New Mexico. The cohort consisted of men who had undergone a mining-related physical examination at the Grants Clinic in Grants, New Mexico and who had worked at least one year underground in New Mexico prior to December 31,

1976 (Samet et al. 1991). The Grants Clinic opened in 1957 and performed most pre-employment as well as follow-up examinations for area mines. Although the geographic area of the New Mexico study was spatially related to the source area of workers for the Colorado Plateau cohort and although some workers qualified for inclusion in both cohorts, the New Mexico workers had substantially lower mean exposures.

Vital status was determined by searching New Mexico vital statistics records, the New Mexico Tumor Registry and State drivers' license records. The cohort was also matched against the records of the Social Security Administration and the U.S. National Death Index. Death certificates were obtained for the deceased and cause of death ascertained. After excluding men with missing work history, birth year, or follow-up information, vital status of 3,469 workers could be ascertained; 390 workers have a verified cause of death.

Estimation of radon progeny exposure

Measurements of radon and its progeny were obtained from various sources. Prior to 1968, data on radon progeny came from the State Mine Inspector, the State Health and Environment Department, and records from the Colorado Plateau study. These data were in the form of annual estimates for individual mines.

From 1967-1985, estimates of WLM exposure were taken from the WLM reports for individual miners from mining companies in the area, submitted to the U.S. Bureau of Mines or its successor agencies, the Mining Enforcement and Safety Administration, and the Mine Safety and Health Administration. Records were generally complete for the larger mining companies, while generally not available for the smaller companies (Morgan and Samet 1986).

Estimation of other mine exposures

For each worker, information from Clinic records was available on whether he previously worked in a hard rock mine.

Information on tobacco use

Clinic records indicated smoking status; current smoker, former smoker, or never smoked.

Material and methods of analysis

Pooled miner data

We developed risk models by directly pooling data from the Colorado and New Mexico studies. In the Colorado and New Mexico studies, there was a total of 7,475 miners, who accrued 187,406 person-years of observation and 470 lung cancer deaths. There were 951 Native American miners with a total of 35 lung cancers. For Colorado and New Mexico miners, mean cumulative exposures among exposed were 681 and 110 WLM, respectively.

Relative risk regression models

Poisson regression methods (more correctly called piecewise-exponential regression models) were applied to the pooled data. Methods are based on a RR model which is linear in WLM exposure, but allows for variations with other factors. These methods are similar to and are detailed in the BEIR IV Report and Lubin et al. (1994). The background risk of lung cancer among "non-exposed" miners was specified using factors for study, attained age, calendar year, previous hard rock mining experience, smoking status, and ethnicity (whites and Native Americans). These factors were adjusted in the modeling by categorizing the variables and including stratum-specific parameters.

RECA criteria and characterization of lung cancer risk

RECA criteria were meant to identify lung cancer cases which were more likely than not due to radon progeny exposure. This can be restated as a PC greater than or equal to 0.5. Since a linear model for the RR in WLM is a good first order approximation, RECA criteria can be re-expressed in terms of the RR of lung cancer for cumulative exposure (w), smoking status and age. For non-smokers, the specification of a PC of 0.5 at 200 WLM implies a linear RR model which is independent of age, namely,

$$RR_{ns}(w) = 1 + 0.005 \times w$$

For smokers, the specification of a PC of 0.5 at 300 WLM for ages under 45 years and 500 WLM at ages 45 years and older implies the following RR models,

$$RR_{smk,<45}(w) = 1 + 0.0033 \times w$$

for under age 45 years, and

$$RR_{smk,\geq 45}(w) = 1 + 0.002 \times w$$

for ages 45 years and older.

Direct analysis of data reveals that these RR patterns do not provide an adequate fit. Compared to the models developed below, the RECA-based model for the RR is statistically rejected, $p<0.001$.

For current ages 45 years and over (the majority of miners), the 500 WLM criterion implies that the excess RR of lung cancer increases 0.2% per WLM and that the increase is constant with age and other factors. The BEIR IV Report (1988) demonstrated conclusively that a model in which the RR depends only on WLM does not adequately describe the

association between radon progeny exposure and lung cancer. The BEIR IV analysis indicated that the RR of lung cancer increases with increasing WLM (as impled in the RECA-based model), but that the exposure-response relationship decreases with attained age and time since the exposure occurred. In the more recent analysis of 11 miner cohorts, analysis showed that in every cohort examined, a constant relative risk model did not provide an adequate fit to the data.

Among miners in the pooled Colorado and New Mexico studies, the RECA criterion that distinguishes lung cancer events under age 45 years has little impact on eligibility for compensation. Of the 470 lung cancer deaths in the joint population, 32 lung cancer cases occurred under age 45 years, with 27 lung cancer cases in smokers. All five non-smokers qualify for compensation. Of the 27 smokers, twenty qualify under RECA criteria. All, but two workers, had exposures above 500 WLM (and thus qualified under the general exposure criterion). Only two smokers under age 45 had exposures in the 200-300 WLM range. (Using the model defined below, all 27 smokers would be eligible for compensation, since their disease occurred at such young ages, when lung cancer is usually quite rare.)

Definition of probability of causation

Probability of causation is the chance that an observed lung cancer was due to radon progeny exposure, i.e., PC is the increase in the probability of lung cancer due to exposure. Formally, for a lung cancer cases occuring at age a, for an individual with WLM exposure w, and with other factors z, the PC is defined as

$$PC(w,z) = \frac{P(lung\ cancer\ given\ w\ and\ z) - P(lung\ cancer\ given\ w{=}0\ and\ z)}{P(lung\ cancer\ given\ w\ and\ z)}$$

Dividing the nummerator and denominator by the disease probability in the non-exposed, one obtains the PC as a function of the RR, namely,

$$PC(w,z) = \frac{RR(w,z) - 1}{RR(w,z)}$$

For a given level of exposure w and values for other factors z, the RR with exposure is determined by the risk model.

Topic 1: Modeling lung cancer risk and WLM

In modeling risk in miners, we have the benefit of having data on a substantial proportion of the population of interest, thus obviating the need for an extreme extrapolation from one population to another, possibly unrelated, population. Thus, risk levels can be based directly on relevant epidemiologic data. While the Colorado study provides limited information for exposures below 100-200 WLM, there are substantial data from New Mexico study in this range, where exposures were lower. In the New Mexico miners, mean year of first employment occurred about a decade later, in 1965, after substantial control measures had been put in place. Patterns of risk with exposure in the Colorado and New Mexico studies were consistent with patterns found in other populations of radon-exposed miners. This suggests that the observed patterns of risk in the data are not artifacts, but likely reflect underlying biological processes.

It is worth noting that, while there has been considerable advances in recent years in understanding the nature of the carcinogenic process from exposure to alpha particles,

knowledge is still incomplete. There are currently no biological markers of disease that can be used to attribute a particular case to radon progeny exposure, that is, given biological material from a lung cancer, it cannot be deduced whether the tumor was "caused" by radon exposure.

Development of risk model

Previous analysis of the Colorado data indicated that the exposure-response was non-linear, particularly at high exposures. Analyses also revealed that the exposure-response relationship varied with attained age and time since last exposure. Although our intent was to characterize risk as precisely as possible, we made several simplications to the models to enhance their usefulness in developing a practical scheme based on PCs.

For simplicity, age was categorized into four levels, <50, 50-59, 60-69 and ≥70 years of age, and time since last exposure was categorized into three levels, <10, 10-19 and ≥20 years since last exposure. The following RR model along with several variants were fit to the data:

$$RR = 1 + \beta \times w^{\kappa} \times \phi_{tsle} \times \theta_{age} \qquad (1)$$

where w is cumulative WLM and β the exposure-response parameter, κ is a "non-linear" effect of exposure, ϕ_{tsle} denotes the effects of the three time since last exposure categories, $\phi_{<10}$, $\phi_{10\text{-}19}$, $\phi_{\geq 20}$, and θ_{age} denotes the effects of the four age categories, $\theta_{<50}$, $\theta_{50\text{-}59}$, $\theta_{60\text{-}69}$, and $\theta_{\geq 70}$. For identifiability, we set $\phi_{<5}$=1.0 and $\theta_{<50}$=1.0. Results of the model fitting are shown in Table 1. The table shows that the exposure-response relationship was significantly modified by both age and time since last exposure. These models were fit assuming a multiplicative association for radon progeny exposure and smoking status.

Based on model A in Table 1, approximately 77% of lung cancer cases can be attributed

to radon progeny exposure.

Cohort differences

The populations from the two studies arise from the same mining area of the U.S., although different criteria which were used to define entry into the cohort meant that mean exposure differed substantially. Model (1) was modified to test for cohort differences by replacing the exposure-response parameter β with study-specific parameters, β_{CO} and β_{NM}. The estimates were similar; the exposure-response estimate was about 30% greater for New Mexico, but a score test revealed that this difference was not statistically significant, p=0.75.

Topic 2: Cigarette smoking and lung cancer risk due to radon

Published analyses of the Colorado data and the New Mexico indicate that data are consistent with a multiplicative relationship between smoking and WLM, but that the data are also statistically consistent with a relationship less than multiplicative. A multiplicative relationship implies that the proportion of lung cancers due to radon progeny exposure is same in smokers and non-smokers. (Because the lung cancer rate is substantially greater in smokers, the model also implies that the absolute number of lung cancer cases due to radon is greater in smokers than non-smokers.) In determining risk, a multiplicative association suggests that the same model, and therefore the same compensation criteria, should be applied to smokers and non-smokers.

Analyses indicate that the most appropriate model is less than multiplicative. This implies that the increase in the RR with radon progeny exposure is somewhat greater in non-smokers that in smokers. The difficulty in applying a sub-multiplicative relationship is

the limited amount of data on lung cancer risk in non-smokers. This leads to a lack of adequate power to estimate precisely the nature of the joint association. An estimate of the "degree of sub-multiplicativeness" depends heavily on the postulated form for the joint association. Since a multiplicative model is consistent, the difficulty in the estimation of any particular sub-multiplicative model has lead most researchers and expert committees to apply the same risk model to smokers and non-smokers. This is the approach taken by the Environmental Protection Agency in applying miner-based risk models in the estimation of lung cancer risk from residential radon exposure.

Although the precise form for the joint RR is uncertain, current analyses indicate that the absolute risk of lung cancer due to radon progeny exposure and to cigarette smoking do not simply add. In the general population the lung cancer rate among smokers is 10-20 fold greater than the lung cancer rate among non-smokers. An additive RR association for WLM and smoking would imply that the excess rate of lung cancer due to radon is the same in smokers and in non-smokers. Data indicate that more radon-attributable lung cancer cases occur among smokers than non-smokers.

In the pooled analysis, Lubin et al. (1994; 1995) separated data into smokers and non-smokers and found that the exposure-response in non-smokers was about three times the exposure-response in smoker, indicative of a sub-multiplicative association.

Because there is evidence that Native American miners either did not smoke or were light smoker, Native American miners with missing data on smoking was classified as a non-smoker. In the pooled data, 427 miners, including 6 lung cancer cases, had no information on smoking, and were omitted from the smoking analysis.

There were 464 lung cancer cases with information on smoking habits, with 47 cases among non-smokers. With so few non-smoking lung cancer cases, we could not fit a separate model for non-smoking miners. To adjust the model for smoking status, model (1) was fit to all data, Table 1. (Smoking was still included as a stratification factor in the background.) Parameter values for the effects of non-linearity (κ), age and time since exposure were then fixed, with only the β parameter free to be estimated. The model was modified by replacing the exposure-response parameter β with smoking-specific parameters, β_{ns} and β_{smk}, then fit to the data on miners with smoking information. The changes in the β_{ns} and β_{smk} relative to the overall β were then applied to the model for all data (Table 1 column A).

In the miners with smoking information, relative to the overall β, the estimate for smokers was reduced by a factor of 0.8, while the estimate for non-smokers was increase by a factor of 3.0. For all data combined, the results in Table 1 column A were modified to reflect smoking status, $\beta_{ns}=3.0\times0.22=0.66$ replaces β for non-smokers and $\beta_{smk}=0.8\times0.22=0.18$ for smokers for the computation of PCs.

Topic 3: Radon risk among Native Americans

As indicated previously, there was little quantitative information that allows comparisons of lung cancer risk with radon progeny exposure among Native American miners with non-Native American miners. There was suggestive evidence that among smokers and among non-smokers the estimated exposure-response for Native American miners was greater than for non-Native American miners; however, the difference was not statistically significant ($p=0.18$). In addition, the relative impact of smoking on the estimated radon

exposure-response for Native-American miners was less than for non-Native American miners, i.e., the difference in the exposure-response by smoking status was smaller for Native American miners than for non-Native American miners, suggesting less of a difference between Native American smokers and non-smokers. Since the data on Native American miners are too limited to estimate an exposure-response trend specific for ethniticity and since Native Americans who do smoke are generally light smokers, we classify all Native American miners as non-smokers for risk estimation purposes.

Topic 4: Risk modeling based on duration of exposure and year first exposed

The President's Advisory Panel voiced concern about the misclassification of exposures and the inability to document exposure rates in miners for individuals seeking compensation. While some estimates of exposures may over-estimate true exposures, there was particular concern about possible under-estimation of exposures, and the possibility of unfair denial of compensation. The major source of error in exposure assessment is the uncertainty in exposure rates for the various mines and tunnels.

The risk models presented in Table 1 were based on the association of WLM and lung cancer risk, with modification by age and time since last exposure. This approach may be termed a science-based approach, in that the goal is to explore the underlying relationship between exposure and disease, and provide insights into the carcinogenic process. For the purpose of compensation, however, the calculation of a miner's WLM is often problematic and perceived to be unfair by applicants. An alternative approach relates cancer risk directly to duration of exposure and calendar year of employment, along with other factors. It would

be expected that duration of exposure and year could be known and verified with great accuracy, and therefore subject to less misclassification, and would be preceived to be fairer by applicants. The approach has the advantage that the calculation of risk appears more transparent.

It should be noted that WLM is not a true measure of lung dose, but is a surrogate of the true lung dose. Likewise, exposure determined in terms of duration of underground employment (and calendar year of first exposure) is also a surrogate of the true lung dose. Because exposure rate is ignored, it must be expected that duration of exposure (and calendar year of first exposure) may be less adequate than WLM as a surrogate for the true dose.

For simplicity in risk modeling and in risk determination, we use year of first exposure, rather than year of exposure. Since periods of work histories which were free of exposure constitute a relatively small proportion of total exposure durations, modeling duration and year exposed, or duration and year first exposed will define similar levels of risk. We defined three categories for year of first radon progeny exposure, <195-54, 1955-59, and ≥1960. The RR of lung cancer was modeled in duration of exposure (denoted by d), as follows

$$RR = 1 + \beta \times d^{\kappa} \times \gamma_{yfe} \times \phi_{tsle} \times \theta_{age} \times \tau^{(age - 60)} \qquad (2)$$

where in contrast to model (1) β now denotes the duration-response parameter. The parameters γ_{yfe} denotes three parameters for categories of year of first radon exposure, <195-54, 1955-59, ≥1960, while ϕ_{tsle} and θ_{age} represent parameters for categories of time since last exposure categories and attained age, and τ represents a parameter of the effect of continuous age minus 60 years. An empirical evaluation indicated that the inclusion of continuous age significantly improved model fit.

Results of modeling are shown in Table 2. Non-linearity of the duration-response relationship is only marginally significant, while year first exposed, time since last exposure, and attained age are significant modifiers of risk.

Although not directly comparable, the deviance (a measure of model fit) was substantially smaller using model (1) then model (2); for the "full" models, deviance values were 2,509.9 on 17,218 degrees of freedom for the WLM-based model, and 2569.9 on 17,216 degrees of freedom for the duration-based model without continuous age and 2557.7 on 17,215 degrees of freedom for the duration-based model with continuous age. This suggests that model (2) does not fit the data quite as well as model (1). The attributable risk of lung cancer using the duration-year first exposure model A in Table 2 was 73%, similar to the 77% attributable risk based on model (1) using WLM. (Note this is slightly higher than reported in Lubin et al. (1994), due to the inclusion of all exposure data. Lubin et al. excluded exposures above 3,200 WLM.)

Modification of the β estimate in the duration-based model (2) for smoking status was carried out as for model (1). Model (2) was fit to the miners with smoking information, all parameters, except β, were fixed. The model then was refit with β_{smk} and β_{ns} replacing β. Relative to the overall β, the estimate for smokers was reduced by a factor of 0.9, while the estimate for non-smokers was increase by a factor of 2.4. For all data combined, the results in Table 2 column A were modified to reflect smoking status, β_{ns}=2.4 ×22.3=54.4 (with rounding) replaces β for non-smokers and β_{smk}=0.9×22.3=19.0 for smokers for the computation of PCs.

The President's Advisory Panel was concerned by the purported difficulty computing an

accurate WLM for a miner with lung cancer. In response to their concerns, the Committee developed a risk model based on duration of underground mining and year of first employment underground, factors which are likely known with a high degree of accuracy. However, another source of uncertainty that has yet to be considered arises from statistical sampling variability. The (asymptotic) statistical variability is captured in the covariance matrix of the parameter estimates. However, for the complex models described in Tables 1 and 2, calculating the variance estimate for a given set of covariates (age, time since last exposure, and WLM, or duration of exposure and year of first exposure, as well as smoking status) is not a simple matter, since one must account for the variance and covariance in the estimation of all the parameters. As suggested in the BEIR IV Report, a simple informal approximation is available, recognizing that statistical uncertainty is only one of many sources of uncertainty that burden accurate risk estimation. Stratifying on categories of attained age, calendar year of follow-up, study, ethnicity, previous mining experience and smoking status, we fit a simple constant RR model in WLM, namely,

$$RR = 1 + \beta \times w$$

Although this model does not represent the appropriate RR relationship, the estimate of β does represent a kind of average excess risk for the study population as a whole over the period of observation. Further, the estimate of variance then represents the approximate sampling variability for the data. In fitting the constant RR model in WLM to the data from the two cohorts, we obtained a multiplicative standard error of 1.25 for the estimate of β. Thus, to ensure that the computed RR for a miner captures his true level of risk with 80 percent assurance or 90 percent assurance the excess RR in model (1), i.e., RR-1, should be

multiplied by the factor $1.3=1.25^{1.28}$ or $1.4=1.25^{1.64}$, respectively. Because the approach is an approximation and the sampling variability is only one of the multiple sources of uncertainty in risk estimation, the limits are referred to as levels of assurance rather than levels of confidence which carries the connotation of a statistical confidence interval, which has a precise sampling interpretation and beyond our intended usage.

Model (2) in duration of exposure and year of first exposure lends itself to a similar approximation, using a constant RR model in duration of exposure, as opposed to WLM. In this case, the 80 percent assurance or 90 percent assurance levels are given by multiplying the excess RR in model (2) by the factors 2.2 or 2.8, respectively.

Adjusting the compensation criteria by a level of assurance decreases the number of false negative claims, i.e., rejecting claimants deserving of compensation. As a consequence, however, there is an increase in the number of false positive claims, i.e., compensating claimants who fails to meet a more likely than not criterion.

Topic 5: Comparisons PCs for data-based risk model and RECA-based models

As indicated above, the RECA-based model does not adequately account for patterns of risk, which therefore implies that RECA criteria do not adequately and fairly identify high risk workers. Using the 470 lung cancer deaths in the Colorado and New Mexico studies, we compute PCs using three different approaches: (i) based on the RRs derived from the RECA criteria, denoted PC_{RECA}; (ii) based on fitting model (1) which utilizes the relationship of risk with WLM and other factors, denoted PC_{WLM}; and (iii) based on model (2) which utilizes the relationship of risk with duration of exposure, calendar year of first exposure and other

factors, denoted PC_{dur}.

While PC_{WLM} is computed from what is thought to be the most appropriate model, any comparisons among these PC values is problematic, since the "true" relationship between exposure and disease cannot be known precisely.

Figure 3 compares PC_{RECA} with PC_{WLM}. Dotted lines denote a PC value of 0.5. The PC_{WLM} points follow curved paths of related values because of the categorical representations of age and time since last exposure. There were 296 lung cancer cases with both PC_{RECA} and PC_{WLM} greater than or equal to 0.5, termed the "true positives"; 22 cases with $PC_{RECA} \geq 0.5$ and $PC_{WLM}<0.5$, termed the "false positives", who would be compensated under RECA criteria, but not under the more appropriate risk model; 92 cases with $PC_{RECA}<0.5$ and $PC_{WLM} \geq 0.5$, termed "false negatives", who would not be compensated under RECA criteria, but would be compensated under the more appropriate risk model; and 60 cases with $PC_{RECA}<0.5$ and $PC_{WLM}<0.5$, termed "true negatives", who would not be compensated under either approach. Out of 388 (296+92) lung cancer cases who would be compensated based on the more scientifically-based model, 92 or 24% would be ineligible under RECA criteria.

As indicated, the age 45 criterion for smokers has little practical impact on determining compensation. The question might arise whether any single WLM could ever adequately identify high-risk cases. Figure 4 plots PC_{WLM}, based on model (1), by cumulative WLM exposure. As illustrated, a simple criterion based on a single WLM (which would be represented by a vertical line) is insufficient to seggregate lung cancer cases with high and low values for PC. For example, several cases with an estimated exposure of over 1,000 WLM had a value for PC_{WLM} of less than 0.5. These cases are individuals over the age of 70

at lung cancer occurrence and with more than 20 years since last exposure.

The correlation coefficient for PC_{WLM} and PC_{dur} was 0.88. Figure 5 shows a plot of PC_{WLM} and PC_{dur} for the 470 lung cancer cases. (The correlation coefficient for PC_{WLM} and PC_{RECA} is 0.65 and for PC_{dur} and PC_{RECA} is 0.57.) PC_{WLM} and PC_{dur} agree on the compensation classification of 89% (419/470) of cases. Using PC_{dur} as the sole basis for compensation, 2% (6/349) of lung cancers would be inappropriately compensated, while 45 or 12% (45/388) would be inappropriatedly rejected.

The rate of rejecting deserving lung cancer cases under a PC_{dur} scheme could be reduced by lowing the 0.5 criterion for the PC, with the corresponding consequence of increasing the number of non-deserving cases who are compensated. However, as suggested by Figure 4, no obvious and reasonable reduced standard (any vertical line) would capture a large majority of incorrectly rejected cases without markedly increasing the number of inappropriately compensated cases.

Development of model-based compensation criteria

The characterization of lung cancer events that are more likely than not due to radon progeny exposure can be re-expressed as PC≥0.5, which is equivalent to all cases with a computed RR≥2.0. Based on model (1), this characterization can be defined in terms of the level of WLM exposure for fixed categories of time since last exposure and age by solving the expression, PC=(RR-1)/RR, for w, i.e.,

Tables of exposures for fixed categories of time since last exposure and attained age were computed for RR=2.0. Table 3a shows WLM values for smokers, where β_{smk} (=0.8×β)

$$w = \left[\frac{RR - 1}{\beta \times \phi_{tsle} \times \theta_{age}}\right]^{1/\kappa}$$

replaces β from Table 1, and for non-smokers, where β_{ns} (=3.0×β) replaces β. The table illustrates the impact of age at lung cancer and time since last exposure. The older the case occurs and the more distant in time since the last exposure the less the likelihood that the observed disease was due to radon progeny exposure, and therefore the greater the WLM required to meet the more likely than not criterion. The values of WLM that are required to meet the "more likely than not" criterion with 80 percent and 90 percent assurance are shown in Tables 3b and 3c, respectively.

A similar approach for adjusting the risk model for smoking status was used with model (2), using 0.9 and 2.4 as adjustment factors for β for smokers and non-smokers, respectively. Table 4a shows duration of exposure in years that would be require to meet a "more likely than not" criterion of lung cancer causality. The values of duration that are required to meet the "more likely than not" criterion with 80 percent and 90 percent assurance are shown in Tables 4b and 4c, respectively.

The criteria defined by Tables 3 and 4 were applied to the 470 lung cancer cases occurring in the pooled Colorado and New Mexico data (Tables 5 and 6). Using model (1) and the WLM-based approach, 388 (83%) cases would be eligible for compensation, with the numbers increasing to 401 (85%) or 403 (86%) after accounting for a 80 percent or 90 percent level of assurance in the RRs. Under model (2) and the duration/year first exposed-based approach, 349 (74%) cases would be eligible, with the number increasing to 394 (84%) or 408 (87%) after accounting for the level of assurance.