APPENDIX II

QUANTITATIVE RISK ASSESSMENT OF LUNG CANCER IN U.S. URANIUM MINERS

by

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I. INTRODUCTION

A report evaluating epidemiologic studies of lung cancer in underground miners was recently sent to the Mine Safety and Health Administration (MSHA) by the National Institute for Occupational Safety and Health (NIOSH). That report concluded that prolonged exposure to radon progeny at the current standard of 4 WLM/year produced an elevated risk of death from lung cancer. It is the objective of this report to make quantitative risk estimates for various levels of cumulative exposure. In addition, other factors influencing the exposure-risk relationship will be identified and quantified whenever possible.

This report is based upon data collected from a cohort consisting of 3366 white underground uranium miners working in the Colorado Plateau (located within the states of Colorado, Utah, New Mexico and Arizona). The actual risk estimates were computed from data on 3346 members of the cohort. Ten original members were determined to have had no record of underground mining, four were non-white, and six had inadequate cigarette smoking information.

Entry into the cohort was defined by race, sex, working at least one month in underground uranium mines, volunteering for at least one medical survey between 1950 and 1960, and providing social and occupational data of sufficient detail [Lundin et al. 1971].

NIOSH has now updated the mortality experience of the cohort through December 31, 1982. Lung Cancer mortality was defined as anyone assigned an International Classification of Disease (ICD) code of 162 or 163 (same designation in Sixth through Ninth Revisions). Previous analyses of this cohort reported by Waxweiler et al. [1981] and Whittemore and McMillan [1983] considered follow-up only through 1977. Table 1 presents a comparison of vital status of the cohort at the end of 1977 and 1982.

Table 1. Status of Data Base

	1977		1982	
	Number	Percent	Number	Percent
Alive	2,388	71.4	2,132	63.7
Deceased	958	28.6	1,214	36.3
Lung Cancer	187	19.5	255	21.0
Other Causes	771	80.5	959	79.0
Total	3,346	100.0	3,346	100.0

II. PROTOCOL FOR STATISTICAL ANALYSIS

A. Type of Analysis Used

Much of the epidemiologic work in the past regarding the analysis of mortality in occupational cohorts has involved modified life table analysis. This form of analysis has a strong appeal due to its familiarity and ease of interpretation. It is mathematically straight forward since person-years at risk are simply divided into a number of strata and age-calendar year specific mortality rates from some reference population are applied to each. The U.S. population is often used as the reference population in such life table analyses. This expected mortality is then compared to the observed mortality via a ratio defined as:

$$SMR_j = \frac{\sum_i O_{ij}}{\sum_i E_{ij}}$$

where SMR = standardized mortality ratio for cause j
O_{ij} = the observed number of deaths for cause j in stratum i
and E_{ij} = the expected number of deaths for cause j in stratum i from reference population rates

If the total number of observed deaths in all of the strata of interest is large and if the reference population is the appropriate comparison group, this would be the method of choice. No modeling would be needed in such a situation. However, after stratification by age, race, sex, calendar year, other confounders, and finally the exposure of interest, there are seldom enough observed deaths to make rates in these strata reliable.

Another problem frequently encountered is a fundamental difference in certain etiologic characteristics between the study population and the reference population. For example, the study group may smoke at substantially different rates than the reference population. Often the occupational study group is "healthier" than the reference population due to selection criteria for employment (Enterline [1976]). This is usually referred to as the "healthy worker effect." An alternative to use of the modified life table approach is some form of statistical modeling. Modeling to estimate health risks is necessary when conclusions must be drawn about risk in regions of the exposure-response relationship for which data are too sparse to estimate risk directly. The use of models also permits risk estimates to be simultaneously adjusted for confounders, such as age or co-carcinogenic exposures, as well as interactions between exposure and other risk factors. This flexibility is particularly important in making risk estimates at relatively low cumulative exposures when using the Colorado Plateau data. Most miners in this cohort were exposed to high levels of radon progeny (mean exposure = 834 WLM). Since primary interest in risk estimates is below 120 WLM based on current exposures, some type of statistical model is essential.

There have been a number of types of models suggested for examination of cause-specific mortality as a function of various risk factors. The two most popular types of models are the absolute risk model and the relative risk model. The absolute risk model can be written as:

$$R(t;\underline{z}) = R_0(t) + R(\underline{z}, \beta)$$

where R9t;$\underline{z}$) is the incidence at age t for someone with risk factors $\underline{z}$, $R_0(t)$ is the baseline or background incidence at age t and $R(\underline{z},)$ is the incremental incidence as a function of the risk factors $\underline{z}$, and coefficients which are estimated from the data. This form of risk model was not used in the risk assessment since it had been rejected due to poor fit to the U.S. uranium miner data by Lundin et al. [1979].

In contrast, the relative risk model generally takes the form:

$$R(t;\underline{z}) = R_0(t)\, R(\underline{z},\beta).$$

This model assumes that excess risk is proportional to background incidence rates. Relative risk models have become increasingly popular in recent years and were found to provide good fits to the data from earlier follow-ups of the U.S. uranium miners cohort by Lundin et al. [1979] and Whittemore and McMillan [1983]. This type of model has been selected as the basic analytical method for this report.

B. The Proportional Hazards Model

A relative risk model which is particularly well-suited to longitudinal mortality studies is one proposed by Cox [1972]. This model is commonly referred to as the Cox proportional hazards model. A major advantage of this approach over the more common life table method is that it permits the use of internal comparison groups while controlling simultaneously for such confounders as cigarette smoking, age, and year of birth. In addition, time-dependent covariates such as cumulative exposure may be incorporated into the model. This is essential in any longitudinal study where follow-up and the exposure period overlap. Relative risk estimates are based on rate ratios similar to those produced in the modified life table analysis. That is, the Cox model operates in a dynamic framework by considering incidence rates over the entire period of follow-up.

The Cox model can be expressed mathematically as:

$$\lambda(t;z) = \lambda_0(t)\exp(\underline{\beta z}(t))$$

where $\lambda(t;z)$ for this study is the age-specific lung cancer mortality rate for a miner with exposure and other risk factors represented by a covariate vector $\underline{z}$. The underlying age-specific lung cancer mortality rate for the unexposed is represented by $\lambda_0(t)$. The function $\exp(\underline{\beta z})$ is generally used to model risk of death from the cause of interest which depends upon the risk factors $\underline{z}$ and the coefficients $\underline{\beta}$ which are estimated from the data.

C. Alternative Forms of the Risk Function

Although the exponential or log-linear function $\exp(\beta \underline{z})$ is the usual choice of a model for risk, any positive function may be used as long as the risk function is equal to 1.0 when the coefficients are all equal to zero. The most common alternative risk functions are the linear $(1 + \beta z)$ and the power function $(\exp(\beta \ln z) = z^{\beta})$. All three forms of risk functions were considered in modeling the U.S. uranium miners data.

D. Results of Model Development

1. Identification of Confounders and/or Effect Modifiers

Cumulative exposure as measured by total WLM for each miner was the primary exposure variable. Since cigarette smoking is known to have a strong effect upon the risk of lung cancer, cumulative smoking history as measured in pack-years was also included in the model. Another risk factor strongly associated with lung cancer mortality is age. This was tightly controlled by using age as the time dimension t in the model $\lambda(t;z)$. That is, the age at death of each lung cancer victim was recorded and all other miners alive and at risk were compared to him at that age. In this way, the cumulative exposure to radon daughters and pack-years of cigarettes were incorporated as time-dependent covariates by calculating their values at each age of death from lung cancer. This assures that proper age-adjusted comparisons were made throughout the period of follow-up.

A number of other variables were examined in developing the appropriate risk model. A list of all potential risk factors considered for inclusion in the model are provided in Table 2. These variables were considered independently as potential confounders in a stepwise fashion (both backward and forward selection procedures) and also as potential effect modifiers by assessing their interaction with cumulative radon daughter exposure.

An attempt was made to compare the fit of each of the three models during the model development stage of the analysis. However, it soon became apparent that the linear model did not fit well over the full range of radon daughter exposures and cumulative smoking levels. In fact, the iterative solution to the likelihood equations would not converge when using the linear model when both cumulative exposure and pack-years of smoking were both entered simultaneously (either as linear or linear-quadratic forms). The linear model could only be made to converge when the model was restricted to cumulative exposure below 600 WLM with no other covariates included. The restricted linear model resulted in a non-significant result in this exposure range and was subsequently eliminated from consideration.

Of the remaining two types of relative risk models (log-linear and power function), the covariates found to be most highly associated with lung cancer incidence rates were cumulative exposure (WLM), cumulative smoking (packs), and age at initial exposure (months). Table 3 illustrates the form and degree of fit as measured by the likelihood

Table 2. Regression Variables Considered in Development of Model

Variable	Units	Median	Range
Cumulative Exposure	Working Level Months (WLM)		0.3-10,000+
Average Exposure Rate	WLM/month	10.3	0.03-998
Cumulative Cigarette Smoking*	Packs	10,027	0.0-61,000
Smoking Rate	Packs/day	0.64	0.0-3.5
Age at Initial Exposure	Months	348.4	101-877
Calendar Year of Initial Exposure	Year	1954	1908-1963
Birth Year	Calendar year	1921	1877-1948
Height	Short (<68 inches) Medium (68-70 inches) Tall ($\geq$ 70 inches)		
Duration of employment	Months underground	48.0	1-371
Years of Prior Hardrock Mining**	Years	0.0	0-42

*20.4 percent never smoked.
**62 percent had no prior hardrock mining.

Table 3. Comparison of Log-Linear and Power Functions Models

Risk Factor	Coefficient	χ^2	P-value
	Log-linear Model		
Cumulative exposure (WLM)	0.897	125.4	<0.001
Cumulative cigarettes (packs)	0.063	44.6	<0.001
$(WLM)^2$	-0.089	44.5	<0.001
$(Packs)^2$	-0.002	10.5	0.001
Age at Initial Exposure (months)	0.0022	7.9	0.005
	LIKELIHOOD RATIO χ^2 = 205.8		
	Power Function Model		
Ln(Cumulative Exposure+BGR)	0.713	135.3	<0.001
Ln(Cumulative Smoking+BGS)	0.295	35.3	<0.001
Age at Initial Exposure	0.0023	8.7	0.003
	LIKELIHOOD RATIO χ^2 = 219.9		

[1]BGR - background radon exposure = 0.2 WLM/year
BGS = background cigarette smoking = 0.005 packs/day

ratio for these two models. The log-linear model required the addition of quadratic terms in cumulative exposure and cigarette smoking to provide an adequate fit. This was not necessary when developing the power function model. As shown in Table 3, the power function model provided the best fit to the data and will be used hereafter in the risk assessment.

Since the power function model involves the natural logarithms of cumulative exposure and cumulative cigarette smoking, zero values of these variables were not permitted. In order to avoid this an estimate of cumulative background exposure was added to each miner's cumulative radon daughter and cigarette totals. Based upon estimates of the NCRP (Report No. 77, 1984), 0.2 WLM per year since birth were added to each miner's exposure totals. This is the estimated background exposure in the U.S. and is also the amount used by Whittemore and McMillan [1983] in an earlier analysis. In a similar fashion 0.005 packs per day were added for each day since birth to the cumulative smoking totals based upon estimates of Hinds and First [1975].

Of particular interest is the joint effect of exposure to radon daughters and cigarette smoking. Therefore, the interaction of radon daughter exposure and cigarette smoking was included in the multiplicative power function model. The results showed a negative, borderline significant result (β=0.087,p=0.058). When a similar analysis was run with mortality data complete only through 1977, there was no indication of a significant negative effect. Therefore, based on more complete follow-up through 1982, the joint effect of radon daughter exposure and cigarette smoking appears to be slightly less than multiplicative but greater than additive. This is similar to the finding of Thomas and McNeill [1985] in their grouped data analysis of the five major radon daughter cohorts. It is still consistent with a synergistic effect of radon exposure and cigarette smoking which is usually defined as a joint effect exceeding the sum of the individual effects.

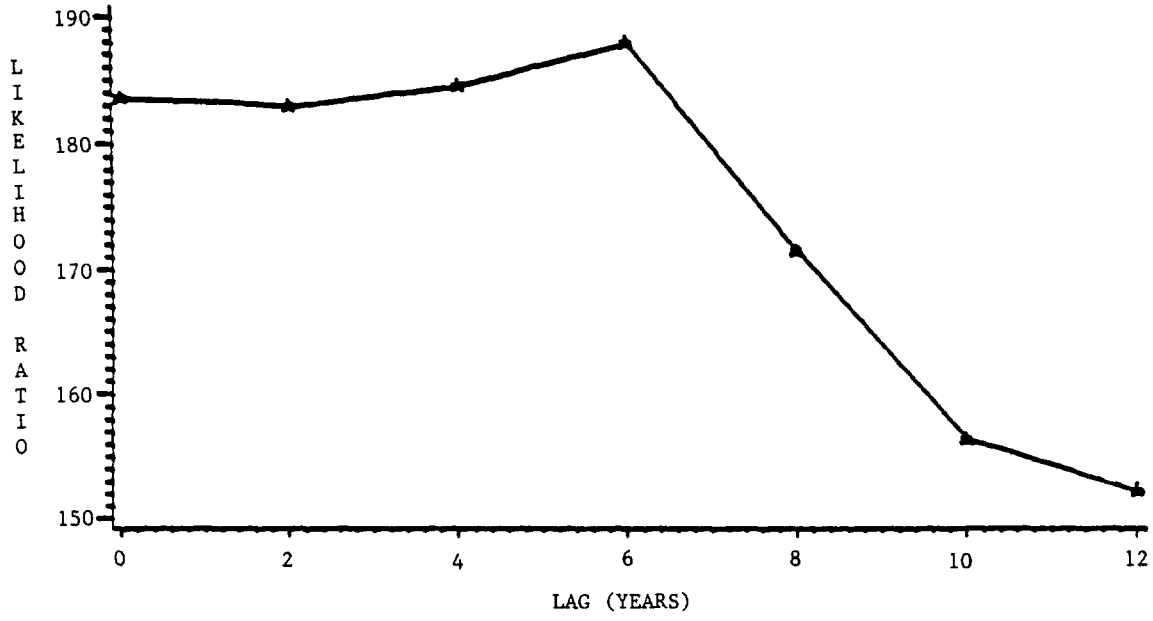
2. Weighting Exposure Over Time

An important consideration in fitting any of these models was the proper time-weighting of exposure. Since most forms of cancer, including lung cancer, have relatively long latency periods between exposure and manifestation of the disease, some weighting of exposure over time is appropriate. The most common weighting scheme is commonly referred to as lagging. This involves elimination of any exposure accumulated in a specified period of years before death from lung cancer. This provides a way of considering only that exposure that had a reasonable chance of causing death from lung cancer. Obviously exposures received in the few years immediately prior to lung cancer deaths are ineffective in the exposure-response relationship.

In order to investigate the appropriate number of years to lag exposure in this cohort, a series of lags ranging from 0 to 12 years was used. Figure 1 illustrates the results of these trials. It is evident from the improved fit, as measured by the log-likelihood of the model, that a

FIGURE 1

EFFECT OF LAGGING ON LIKELIHOOD OF MODEL



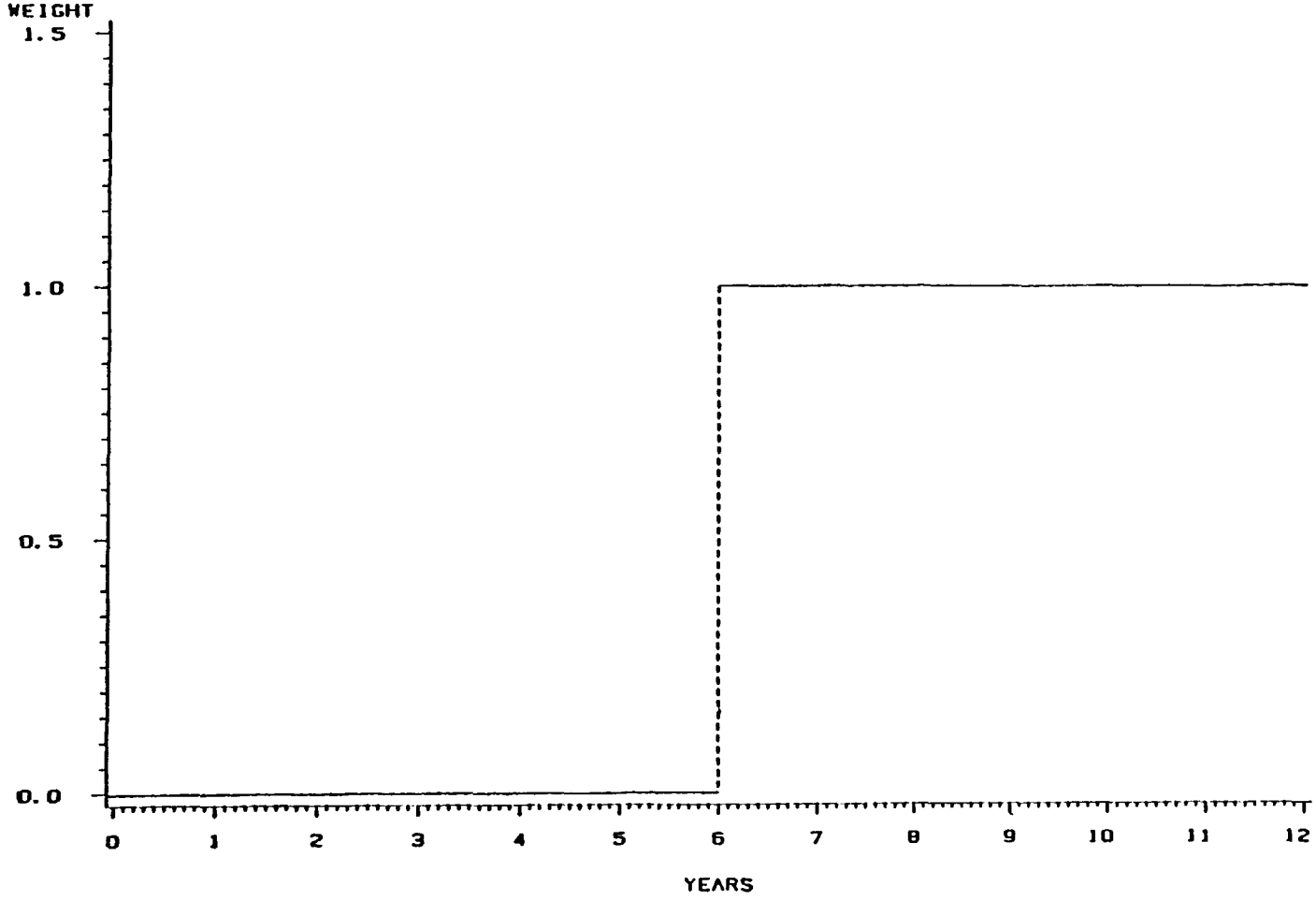
lag of 6 years for cumulative exposure is the best choice for this analysis. Cumulative cigarette smoking was rather insensitive to the amount of lag in the range of 0 to 12 years. Therefore, for the purpose of consistency cumulative smoking was also lagged 6 years. This contrasts to the lag of 10 years chosen by Whittemore and McMillan [1983] for these data and also by Muller et al. for the Canadian data. Their choices were somewhat arbitrary and largely based on knowledge that most cancers involve relatively long latency periods. The implications of a shorter lag will be discussed in a later section of this report.

An issue related to lagging of cumulative exposure and cumulative cigarette smoking is the lack of information on these variables in recent years. Radon daughter exposure was last updated in 1969. However, the absence of current exposure information should have minimal impact upon this analysis since over 90% of the miners in the cohort had retired from uranium mining for more than one year by 1969. Those few who continued mining were exposed at levels considerably less than those experienced in earlier years. Since cigarette smoking status was also unknown after 1969, all miners still smoking at that time were assumed to continue at their last recorded smoking rate. NIOSH is currently conducting a survey of radon daughter exposure and cigarette smoking status subsequent to 1969, but this information will not be available for at least another year.

The aim of lagging exposure is the elimination of exposure which is not etiologically responsible for lung cancer mortality. An implicit assumption in the use of this technique is that exposure changes from completely effective to completely ineffective at one instant in time. The actual form of this weighting function is illustrated in Figure 2. Because of the biological implausibility of such a situation, Land [1976] proposed that the effectiveness of cumulative exposure be linearly phased in over a period of several years. An illustration of such a weighting function is provided in Figure 3. Consequently, we tried various combinations of lagging and linear partial weighting with the combination illustrated in Figure 3 providing the best fit, i.e. a lag of 4 years followed by linear partial weighting in the period 4-10 years prior to death from lung cancer. This scheme provided a fit essentially the same as that of a simple lag of six years but was chosen over lagging because of its biological plausibility.

FIGURE 2

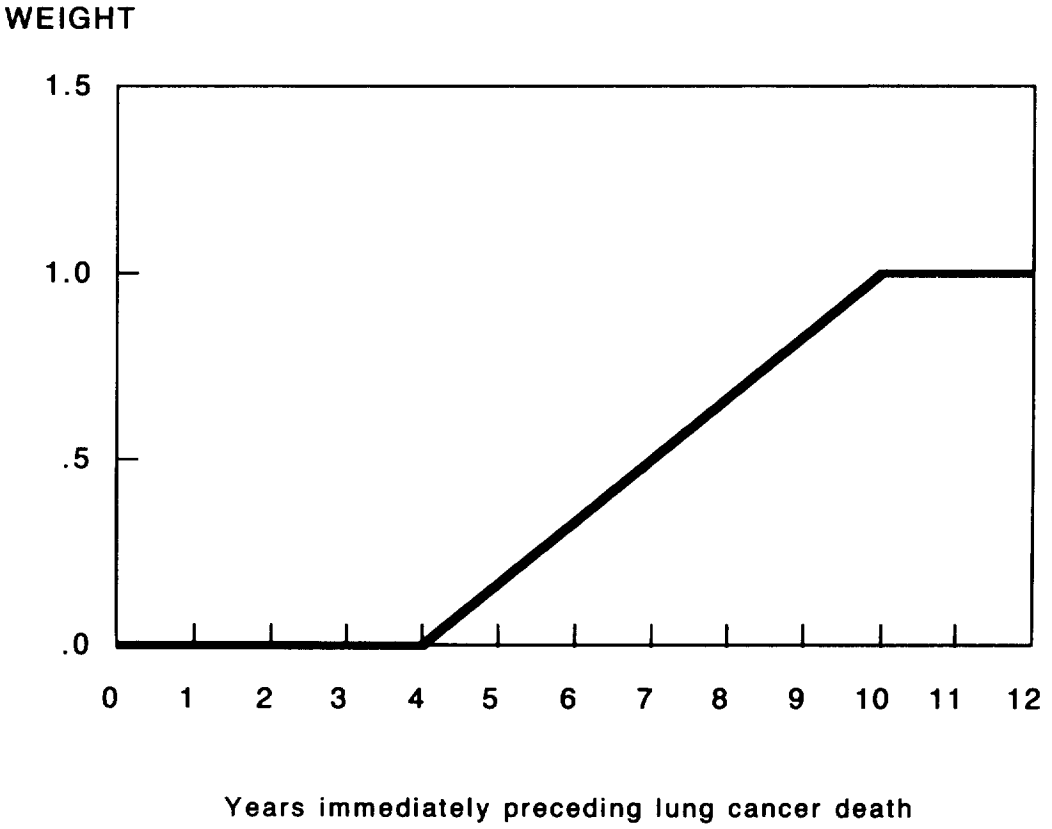
EXAMPLE OF SIX YEAR LAG WEIGHTING SCHEME



YEARS IMMEDIATELY PRECEDING LUNG CANCER DEATH

FIGURE 3

EXAMPLE OF LAGGING WITH PARTIAL WEIGHTING



III. INFLUENCE OF TEMPORAL FACTORS

A. Exposure-Rate Effect

Perhaps the most difficult aspect of producing a valid quantitative risk assessment is dealing with the effects of various time-related factors upon the exposure-risk relationship. One very important temporal influence concerns the two components of cumulative exposure itself. In most longitudinal studies the quantitative exposure index is some form of cumulative exposure. However, cumulative exposure is actually the product of duration of exposure and intensity or rate of exposure. When one uses cumulative exposure in assessing risk, the implicit assumption is that high exposure rates for short periods of time are equivalent etiologically to low exposures for long periods of time, all else being equal.

A number of investigators have examined the effect of exposure rate in the U.S. uranium miner data. Whittemore and McMillan [198]) found no statistically significant effect of exposure rate. Lundin et al. in the 1971 monograph concluded that there was no significant evidence of an exposure rate effect in the 120-360 WLM cumulative exposure range. These investigators apparently defined exposure rate as the ratio of total cumulative exposure and duration of employment (defined as the period of time between first and last employment in underground uranium mining work histories). For most forms of employment, this is the accepted definition of average exposure rate. However, underground uranium mining is a very sporadic form of employment. The actual time spent underground was often a relatively small fraction of the total employment history. Therefore, exposure rate as defined by cumulative exposure divided by the number of months actually spent underground is often a very different measure than that obtained by using duration of employment in the denominator.

Consequently, the effect of exposure rate was re-examined using the actual average exposure rate experienced while underground, eliminating any gaps in employment. Although earlier analyses using total duration of employment produced negative but non-significant results, the refined definition showed a statistically significant negative exposure rate effect (β =-0.043, $p<0.001$) as shown in Table 4. This implies that among groups of miners receiving equivalent cumulative exposures, those exposed to lower levels for longer periods of time are at greater risk of lung cancer. Because the coefficient is relatively small, however, an appreciable effect upon risk of lung cancer would not be expected unless rates were different by an order of magnitude, i.e., a miner with exposure received at a rate ten times lower than a miner of the same age, smoking habits, and cumulative exposure would have $(0.1)^{-.043}=1.104$ or 10.4% greater risk of lung cancer.

Because a negative exposure rate effect is very important and potentially controversial, it was examined in more depth. Of particular interest was the possibility that this effect was different at low versus high cumulative exposure levels. Consequently, the homogeneity of this effect across the full exposure range was examined by forming two sub-cohorts: one below the mean exposure (834 WLM) and one above the mean. The interaction of the exposure rate effect with these two strata was then tested. Results showed a significant interaction (β=0.157, P=0.019). The direction of the

Table 4. Quantitative Relative Risk Model

Risk factor	Coefficient	χ^2	P-value
Ln(cumulative exposure+BGR)(WLM)[1]	0.731	139.5	<0.001
Ln(cumulative cigarette smoking+BGS) (packs)[2]	0.291	34.5	<0.001
Age at initial exposure (months)	0.0023	8.8	0.003
Ln(exposure rate)(WLM/month)	-0.043	18.6	<0.001
Exposure Rate Interaction Model			
Ln(cumulative exposure+BGR)	0.660	101.4	<0.001
Ln(cumulative cigarette smoking+BGS)	0.292	34.8	<0.001
Age at initial exposure	0.0024	9.2	0.002
Ln(exposure rate)	-0.198	8.9	0.003
Ln(exposure rate) x exposure category:	0.157	5.5	0.019
Exposure <834 WLM = 0 Exposure ≥834 WLM = 1			

[1]Background for cumulative radon daughter exposure: BGR=0.4 WLM/year
[2]Background for cumulative cigarette smoking: BGS=0.005 packs/day

interaction indicated that the exposure rate effect was stronger in the lower cumulative exposure range (0-834 WLM). Specifically, a miner who received total exposure below 834 WLM at rate one tenth as great as another miner of the same age, smoking status and cumulative exposure would have a 58 percent greater risk of lung cancer. However, the increased risk would only be 10 percent at the lower exposure rate for miners in the 834-10,000 WLM range.

Although a statistically significant negative exposure-rate effect had not been found previously in this U.S. cohort, there is considerable evidence of such findings in animal studies of high LET radiation. Raabe et al. [1983] reported a strong low dose-rate effect in beagles exposed to internally deposited isotopes of radium and strontium. Risk of bone cancer was as much as ten times as great per unit dose for low rates as compared to the highest rates used. Cross et al. [1980] found a negative dose-rate effect for risk of lung tumors in rats exposed to airborne radon daughters. Chameaud et al. [1981] found similar results in a French study of Sprague-Dawley rats exposed to inhalation of radon decay products. Hill et al. [1982] found reduced dose rates of fission-spectrum neutrons produced significantly higher neoplastic transformation rates per rad in cell cultures of C3H mouse embryos. Although all of these studies show low dose-rate effects, no study as yet, animal or human, has investigated such effects at the very low dose rates currently found in well-ventilated uranium mines.

B. Calendar Time

It is well-known that mortality patterns change over time. Such exogenous risk factors as the prevalence of smoking and alcohol consumption, medical care, and various life style characteristics are all influenced by a changing society. Therefore, the effect of calendar time upon risk estimates, often called the cohort effect, must be controlled. The analysis of the U.S. uranium miners cohort was stratified by decade of birth so that miners dying of lung cancer were compared only to those members of the cohort at the same age and who were born within 10 years of the case. The usual assumption in a stratified analysis is that baseline mortality rates may be different from stratum to stratum but the relative risk is the same across all strata for miners with comparable risk factors. In order to check this assumption, the interaction of cumulative radon daughter exposure and birth decade was examined. Results indicated a statistically significant positive interaction (β=0.173,P=0.002). This implies that miners born in later decades are at a greater risk of lung cancer per unit of exposure when compared to miners of the same age born earlier. Since miners born in later decades were exposed at lower exposure rates, this result could be associated with the negative exposure rate effect described earlier.

C. Multistage Theory of Carcinogenesis

One of the most popular theories for explaining the temporal patterns in mortality studies of carcinogenesis is the multistage model. Originally proposed by Muller [1951] and Nordling [1953] and later refined by Armitage and Doll [1961], the multistage theory predicts an increase in cancer incidence as a function of time since exposure to some carcinogen. In

general, the theory proposes that a malignant tumor arises from a single cell which has undergone a series of heritable changes. The changes may be thought of as distinct stages in the carcinogenic process, each with a low probability of occurrence and a slow progression time in the absence of carcinogenic exposures. A carcinogen may act on any or all of the stages in this process. Carcinogens affecting the first stage are commonly referred to as initiators, while those affecting later stages are called promoters or progressors. Initiators are characterized by long latency periods between initial exposure and death, often exceeding 20 years. Promoters, on the other hand, usually have shorter latent periods since fewer stages must be transgressed before a malignant cell is produced. It is impossible to prove whether or not the mathematical form of the multistage model actually holds in a given situation. However, a number of its predictions have been verified experimentally by Peto et al. [1975]. Therefore, if one subscribes to some form of the multistage model, it is possible to predict whether exposure acts at an early or late stage in the carcinogenic process by examining the temporal patterns in the data. Whittemore [1977], Day and Brown [1980], and Brown and Chu [1983] have all reported the effect on excess relative risk of age at initial exposure and time since cessation of exposure. By examining these factors, we may better understand the underlying cancer mechanism operative in this cohort.

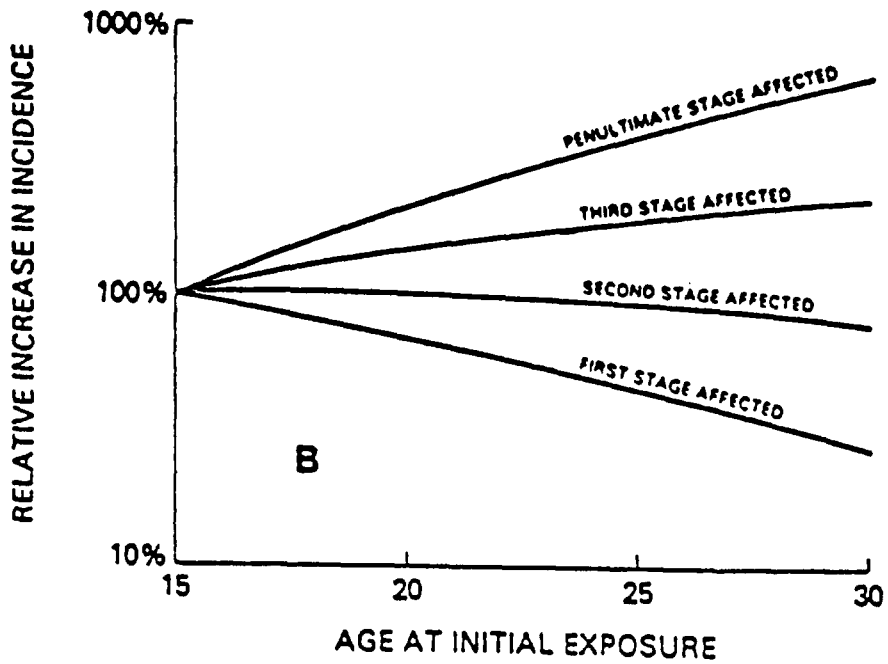
D. Age at Initial Exposure

Whittemore [1977] considered the multistage model using three exposure scenarios: single exposure at one point in time, continuous exposure at a constant rate, and exposure of varying intensity. When considering the latter category (the usual occupational situation) she found that excess relative risk was a decreasing function of age at initial exposure if an early stage was affected. When a late stage is affected by exposure, however, excess relative risk is an increasing function of age at initial exposure.

Day and Brown [1980] predicted the functional relationship between excess relative risk and age at initial exposure for the first four stages of a five-stage process when duration was held constant. Figure 4 illustrates their findings which are in qualitative agreement with those of Whittemore. Results of the analysis in our data, as illustrated in Table 4, indicate a positive and statistically significant coefficient for age at initial exposure (β=0.0023, P=0.003). This implies that miners initially exposed at later ages are at greater risk of lung cancer than those exposed at younger ages, all else being equal. Specifically, a miner with the same radon daughter exposure and smoking history who was initially exposed ten years (120 months) later in age than another miner, would have exp(0.0023x120)=1.32 or 32% higher risk of lung cancer. This result is consistent with the effect of radon daughters occurring at a late stage in the carcinogenic process. A similar age effect was reported by Mancuso et al. [1977] in an analysis of cancer risk in the Hanford workers exposed to whole-body radiation.

FIGURE 4

EFFECT OF AGE AT INITIAL EXPOSURE ON A MULTISTAGE MODEL



An analysis of age at start of smoking among miners resulted in a negative but non-significant coefficient (β=0.0016,p=0.22). This would imply that cigarette smoking in this cohort acted at an early to intermediate stage. It could also be consistent with the hypothesis of Doll and Peto [1978] that smoking acts at both early and late stages, which would tend to obscure predictive ability of age at start of smoking. A plot of the effect of age at initial exposure for both radon daughters and cigarette smoking is given in Figure 5.

E. Time Since Cessation of Exposure

Day and Brown [1980] predicted the effect upon relative risk of time since cessation of exposure when a multistage model is assumed. They found that when exposure begins some time after infancy, excess relative risk increases, peaks, and then decreases with time since termination of exposure when the first stage is affected. When the penultimate (next to last) stage is affected, relative risk strictly decreases with time after last exposure. Figure 6 illustrates their predictions for the effect of time since cessation of exposure on the first four stages in a five stage model with duration of exposure fixed at five years.

In order to investigate the effect of cessation of exposure on this cohort, all miners were identified who had indicated retirement from uranium mining during the course of follow-up. Approximately 95% of the cohort had retired for more than one year prior to 1970. The average time since last exposure was 18.0 years for those miners not dying of lung cancer and 9.9 years for lung cancer cases.

The time in months since last exposure was entered as a time-dependent covariable in the original model containing log of exposure, log of smoking, and age at initial exposure. The estimated coefficient of this term was negative and highly significant (β=-0.0056,p<0.001). Thus a miner's chances of surviving lung cancer increase dramatically with each year outside the mines. Specifically, the model predicts that the risk of lung cancer 10 years after mining uranium is exp(-0.0056x120)=0.511 relative to someone still mining with the same cumulative exposure, smoking history, and age.

When a similar analysis of time since cessation of cigarette smoking was run, the results were inconclusive. The coefficient was very small and non-significant (β=0.003,p=0.75). However, since a relatively small number of miners were ex-smokers (7.7%) there is little power for detection of such an effect even if it actually exists. Figure 7 illustrates the effect of time since last exposure for both radon daughters and cigarette smoking.

The implication of these results are essentially the same as that obtained by examination of age at initial exposure. The strong negative effect of time since last exposure implies that radon daughters act at a late stage in the carcinogenic process. The effect of stopping cigarette smoking, while based on a small amount of data, still indicates either an intermediate stage effect or a combination of early and late stage effects.

FIGURE 5

EFFECT OF AGE AT INITIAL EXPOSURE ON RISK
RELATIVE TO MINER BEGINNING AT AGE 15

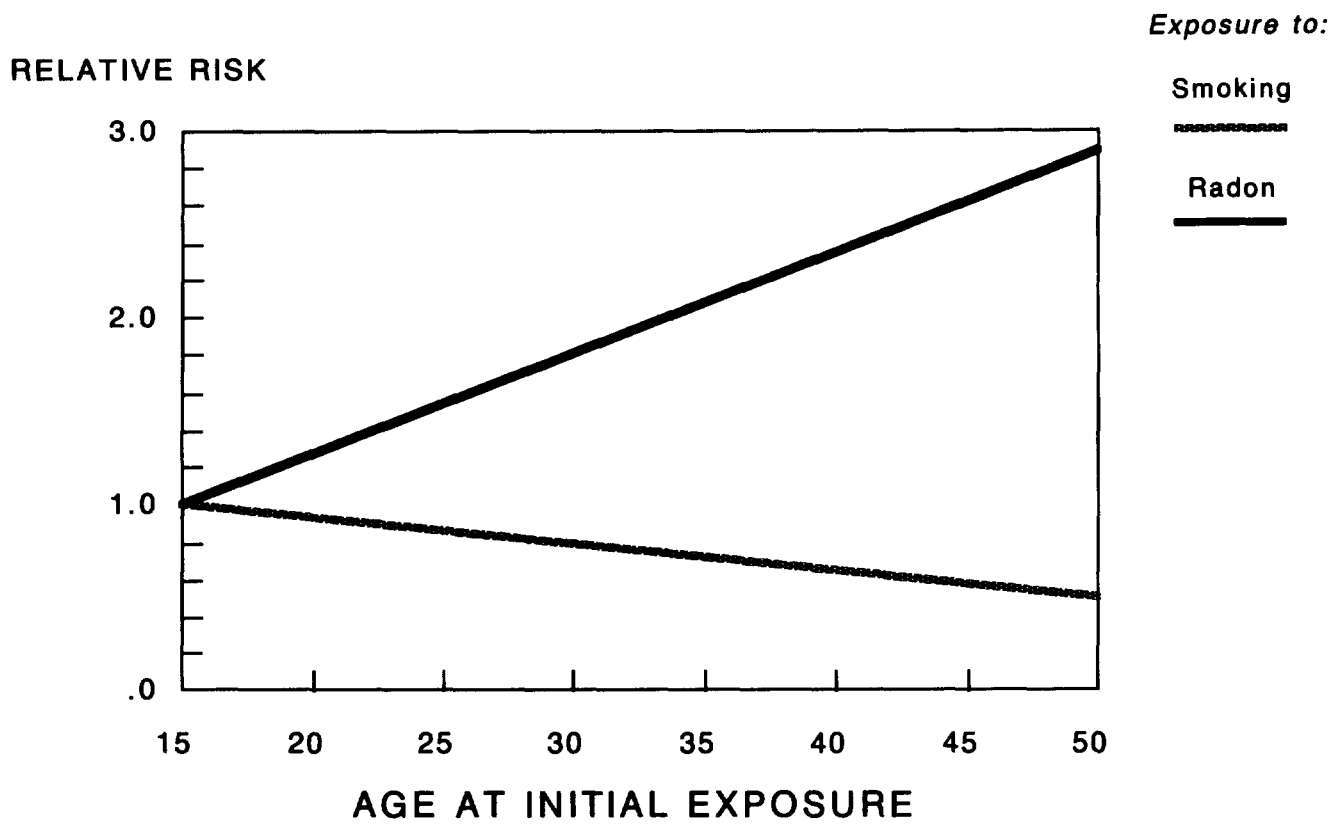


FIGURE 6

EFFECT OF CESSATION OF EXPOSURE ON A MULTISTAGE MODEL

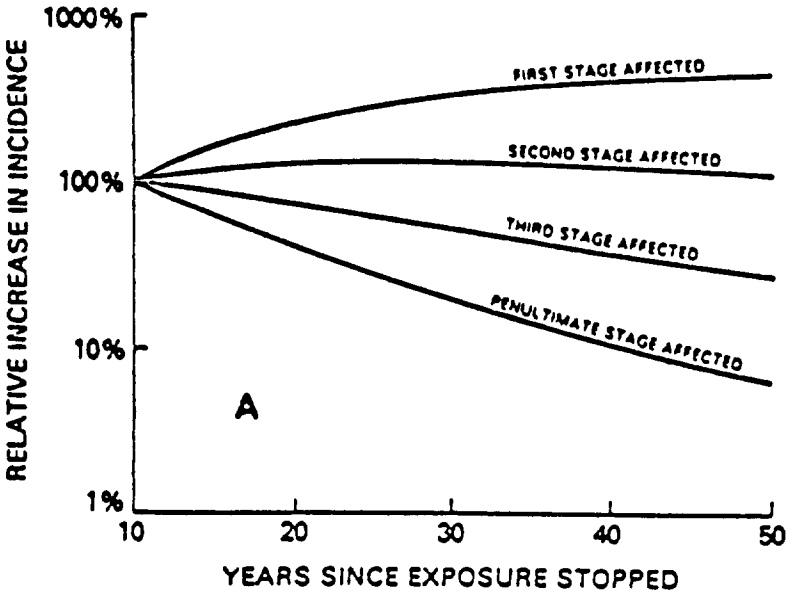
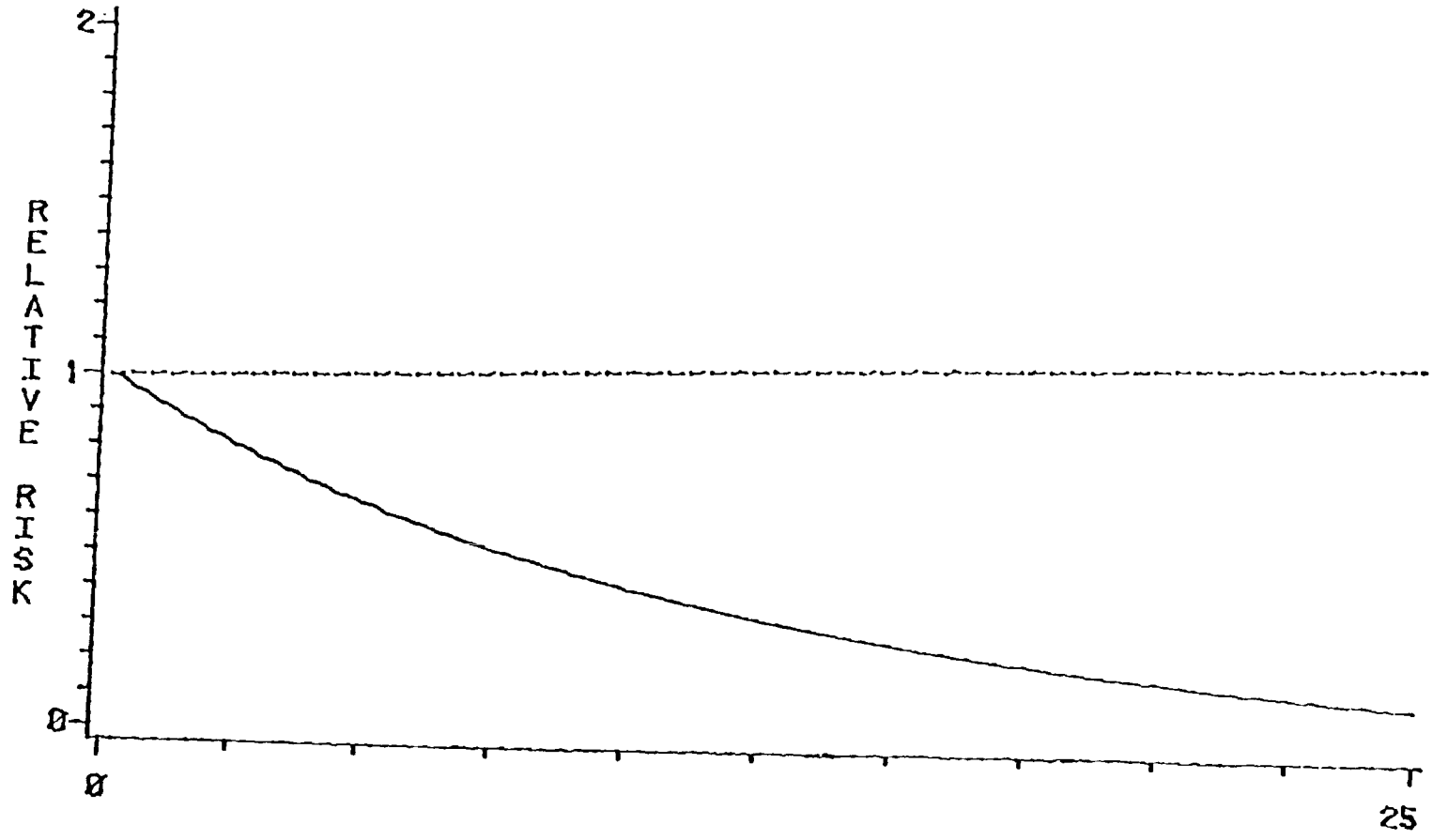


FIGURE 7

EFFECT OF TIME SINCE LAST EXPOSURE ON EXCESS RELATIVE RISK



IV. ERRORS IN EXPOSURE DATA AND THEIR EFFECT UPON RISK ASSESSMENT

In animal carcinogenesis studies, exposures or doses are usually known with a high degree of accuracy and precision. However, the same cannot be said regarding epidemiologic quantitative risk studies. In most epidemiologic studies, the actual dose to target organs can only be estimated by dosimetric modeling. This is seldom attempted in quantitative risk assessments. The dosimetry of radon daughter exposure is very complex, involving such factors as respiration rates, particle size distribution, deposition in the lung, and radon/radon daughter equilibrium. Most risk assessments are modeled as functions of some exposure index, which is the method used in this report. It is the purpose of this section to estimate the magnitude of exposure errors and their effect upon quantitative risk models. According to Lundin et al. [1971], exposures in a given mine and year were estimated in one of four ways:

1. actual measurements
2. interpolation or extrapolation in time
3. geographic area estimation
4. estimates prior to 1950 based upon knowledge of ore bodies, ventilation practices, and earliest measurements.

These methods will subsequently be called Methods 1, 2, 3, and 4. In assessing the error associated with individual exposure determinations, it is first necessary to consider the variability introduced by each of the four methods.

A. Magnitude of Error in Exposure Data

Method 1

Table 5 provides a frequency count of white miners working underground from 1950-68 and the mean number of samples taken in each mine visited in those years. The Kusnetz procedure for measuring radon daughters was most often used during the period of study (Johnson and Schiager 1981). This is an area monitoring method based on alpha counts collected on a filter/pump apparatus. The resulting data were generally thought to be of good quality (Lundin et al., 1971). Data from mines in which 5 or more measurements were taken in a given year were analyzed. These data followed a lognormal distribution with little change over the period 1951-1968. Prior to 1960, samples were taken largely by the U.S. Public Health Service, while post-1960 sampling was conducted by state mine inspectors. Therefore, data were separated into pre and post 1960 periods and estimates of the coefficient of variation (CV) were made for each period. Results indicated a slight but non-significant increase in CV's after 1960 (106.6% vs 118.3%). Since the measurements were grab samples taken at different times within each mine, the total pooled CV=112.5% over the period 1951-1968 is assumed to include sampling errors, counting errors, and environmental fluctuations over time. This estimate agrees well with the CV of 110% found in an independent study of U.S. mines in the period 1973-79 when exposure levels were much lower (Schiager et al. 1981). In other studies, however, an average CV of 30%

Table 5. Number of Miners Exposed and Mean Number of Exposure Measurements Taken by Calendar Year

Year	Number of Miners Exposed	Mean Number of Samples/Mine
1950	534	1.0
1951	668	4.2
1952	748	1.6
1953	1028	8.5
1954	1376	4.3
1955	1383	3.8
1956	1572	14.2
1957	1942	5.6
1958	1798	8.8
1959	1861	6.6
1960	1902	9.9
1961	1588	8.8
1962	1369	12.9
1963	1005	8.4
1964	828	15.6
1965	640	18.1
1966	467	18.5
1967	480	21.4
1968	336	21.9

was reported for area samples in Canadian mines (Makepeace and Stocker 1980) while fluctuations of 20-30% around daily means were found for radon measurements in non-uranium Norwegian mines (Berteig and Stranden 1981).

Method 2

In order to assess the error in interpolating for gaps in sampling of 1 to 3 years, a simulation procedure was used. Mines having the longest periods of continuous annual measurements were identified. Then the even years' averages wee omitted and the average of the two adjacent years was substituted. In this way it was possible to compare the observed annual average with the expected average had that year been missing. This strategy was repeated by imposing three year gaps in the data and again using the average of adjacent years to estimate the three intervening years.

The error variance attributable to Method 2 was then calculated by:

$$\sigma^2 = \sum_i \frac{(\log(O_i/E_i))^2}{N-1}$$

where O_i = actual measurements for intervening years
E_i = interpolated values estimated by average of adjacent years.

The resulting CV was 120.8% for 1 year interpolation and 137.3% for 3 year interpolation. Since these results were not significantly different, they were pooled to yield a CV=131.9%.

Method 3

This method used annual mine averages in the same geographic locality to estimate radon daughter levels in mines for which Methods 1 and 2 could not be used. In order to assess the error associated with this method, four of the uranium mining localities with the greatest number of annual measurements were selected. A simulation procedure similar to that used for Method 2 was employed. Annual averages for selected mines in these localities were omitted for 1 to 4 years. The averages for mines in the nearest district were substituted as the expected radon level if the annual average actually had been missing. The error variance was calculated in the same way as Method 2. The resulting CV was 148.6% for this method.

Method 4

No measurements were available in the period prior to 1950. Therefore, the estimates made using knowledge of ore bodies, ventilation, and earliest known measurements in these mines could not be verified. These estimates comprised less than 6% of the 34,120 annual averages used in exposure assessment. In addition, since only 8 percent of the total underground exposure time for the cohort occurred prior to 1950, the influence of these measurements should be minimal. However, since the

error for this method was probably the greatest of the 4 methods used, we estimated the overall CV for Method 4 to be 25% greater than that for Method 3, i.e. CV=186%.

Table 6 shows the number of annual averages for each of the four methods. Actual measurements comprised only about 10% of the data. In order to obtain an overall estimate of the relative error, a weighted average of the CV's for each method was calculated based on the number of determinations for each method. The resulting overall CV=137%.

The error associated with each miner's cumulative exposure can then be calculated using our estimate of the error in each radon daughter level (WL). The total cumulative exposure (WLM) for each miner is obtained from:

$$WLM = \sum_{i,j} (WL_{ij})(UGMON_{ij})$$

where WL_{ij} is the estimated exposure for mine i in year j and $UGMON_{ij}$ is the number of months spent underground in mine i during year j. The variance of WLM assuming independence of WL_{ij} is then:

$$Var(WLM) = \sum_{i,j} (UGMON_{ij})^2 \ var\ (WL_{ij})$$

$$= \sum_{i,j} (UGMON_{ij})^2 (CV)^2 (WL_{ij})^2$$

where CV is the coefficient of variation for the estimated exposure WL_{ij}.

If we substitute our estimate of the overall CV=137% and use total cumulative exposure divided by total months underground (WLM/TOTMON) as an estimate of WL_{ij} for each individual miner, the average CV for cumulative exposure (WLM) is 0.97 or a relative standard deviation of 97% of the total WLM for each miner. Since radon daughter measurements were taken in different areas of each mine and often at different times of the day or week, we will assume that the variance in these measurements reflects the variance in exposure levels among individual miners, i.e.

$$Var(WLM_{ij}) = \sigma^2_{ijk}$$

where σ_{ijk} = variance in exposure measurement for miner k in mine i and year j.

Table 6. Exposure Measurement Errors Due to Four Methods of Estimating Annual Radon Daughter Concentration

Exposure Assessment Technique	N	Variance of Natural Log (σ^2)	Coefficient of Variation
Actual measurements	3505	0.82	1.13
Interpolation over time	5602	1.01	1.21
Geographic area estimation	23159	1.16	1.49
Estimates prior to 1950 (assumed 1.25 x geographic error)			1.86

B. Effect on Relative Risk Estimation of Exposure Measurement Errors

There appears to be a general impression that errors in exposure measurements usually cause an underestimation of relative risk. Indeed, Bross [1954] originally demonstrated that if misclassification was equal in two comparison populations, one would tend to underestimate differences in proportions of diseased persons. Keys and Kihlberg [1963] qualified this concept by showing that relative risk is underestimated when misclassification errors are independent of disease and exposure relationships. In general, it has been shown by Copeland et al. [1977] among others, that relative risk estimates are biased too low in the presence of non-differential misclassification (equal misclassification of disease in both exposed and unexposed groups). Little work has been done concerning the effects of errors in continuous measures of exposure upon relative risk estimates obtained from statistical models. It is this situation that is a potential problem to the analysis in this report.

Prentice [1982] introduced a method for dealing with errors in individual exposure measures when using the Cox proportional hazards model. Prentice, and more recently Hornung [1985], have shown that the direction of bias in relative risk estimation depends upon the error distribution and the shape of the exposure-response model. In general, when the variability in individual exposure errors increases with the level of exposure and the relative risk model is supra-linear (curving upward), relative risk will actually be overestimated when exposure errors are ignored. The popular log-linear or exponential risk function is an example of a model which may often overestimate relative risk in the presence of errors whose magnitude increases with increasing levels of cumulative exposure.

As was reported earlier, the log-linear model did not provide the best fit to the data. Instead, the power function model which involved the logarithms of cumulative exposure and cumulative cigarette smoking provided a better fit. The effect upon risk estimates using this model was investigated when errors in exposure are lognormal as indicated in the previous section. Without presenting the statistical details, it is sufficient to say that under these conditions (power function model and lognormal distribution of exposure errors) the effect upon relative risk estimates is negligible. If the exposure measurements were generally higher than those actually experienced by the miners, as mentioned in the 1971 Monograph, relative risk per WLM would be underestimated regardless of the distribution of exposure measurement errors.

In summary, the degree of error in individual exposure measurements was quite high, an estimated CV of 97%. If, however, these individual errors were lognormally distributed about the annual average concentration in each mine, the degree of bias in relative risk estimates generated by the power function model would be minimal. Regardless of the form of the error distribution, the relative risks generated by the exposure-response model would be too low if the exposure measurements were systematically too high. Therefore, examination of the pattern of error in the exposure data would suggest that relative risks produced by the power function model are either unbiased or possibly a bit low.

V. QUANTITATIVE RISK ESTIMATES

The previous sections have outlined the protocol for the risk model development, the selection of an appropriate quantitative risk model, the temporal factors influencing risk estimation, and the magnitude and effect of exposure measurement errors. These are factors requiring careful study before attempting to make valid quantitative risk estimates.

In most risk assessments, results are reported relative to some unexposed population. In animal studies, a control group is generally used for this purpose. In life table, analyses expected mortality is obtained from some standard population, often that of the U.S. The problems inherent with the use of such external referents have been well documented [Enterline 1976]. Although a subcohort of miners unexposed to radon daughters would be ideal for a referent group, there were no unexposed miners in the U.S. cohort. Since the proportional hazards model uses internal comparisons in generating risk estimates, risk projections relative to an unexposed population necessarily involve an extrapolation to zero exposure. In the case of the power function model, a background exposure of 0.2 WLM/year of age was added to every miner's cumulative total. All risk estimates are relative to someone exposed to these background rates. Therefore, quantitative relative risk estimates are somewhat sensitive to the choice of a background exposure rate.

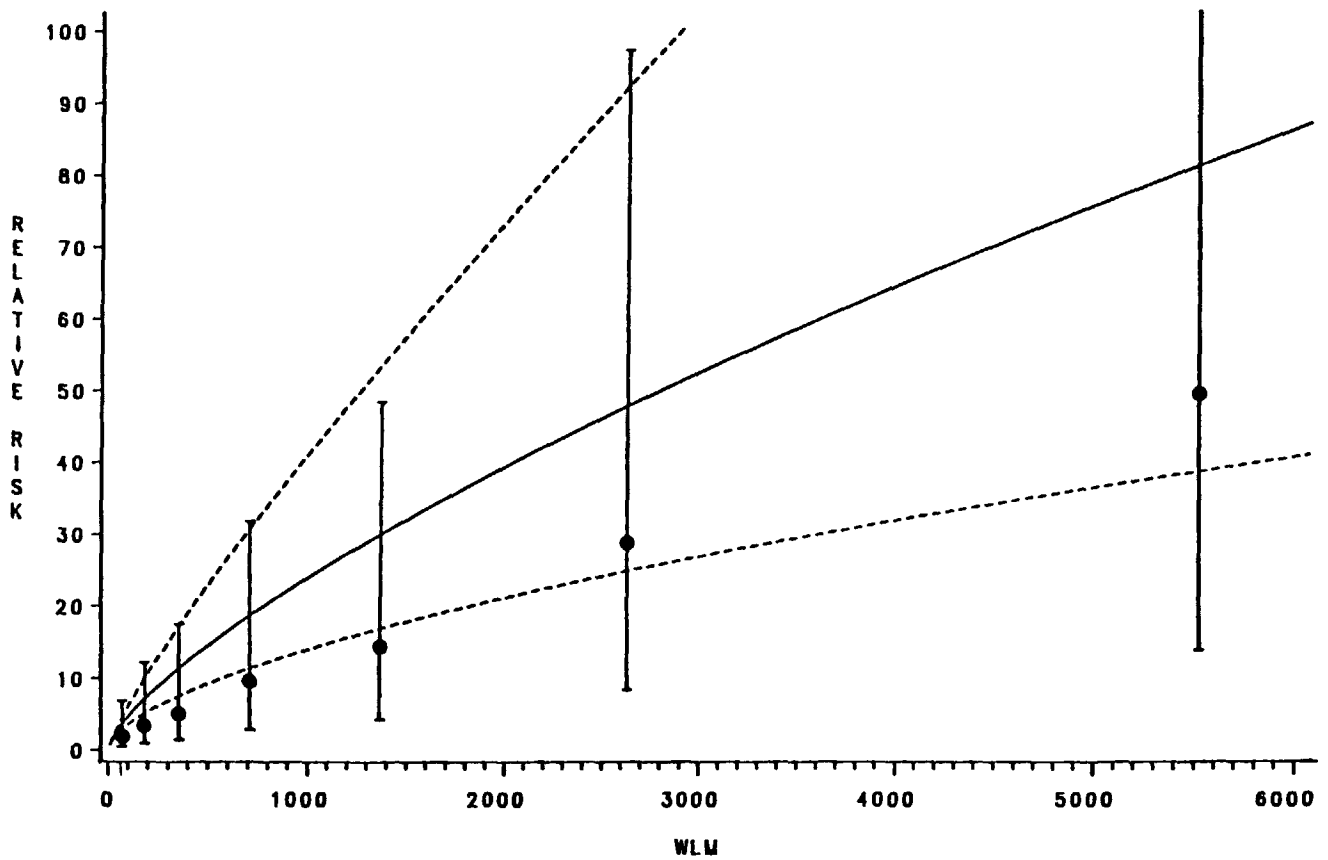
One way of checking the appropriateness of the model is to divide cumulative exposure into discrete intervals and calculate lung cancer risks in each interval relative to risks experienced in the lowest interval. In this way, relative risk estimates are free of any exposure-response function. If the risk model then fits the risk estimates in the selected intervals, one would be assured that the model is appropriate for quantitative risk estimation.

The cumulative exposure intervals chosen for this analysis were: less than 20 WLM, 20-120, 120-240, 240-480, 480-960, 960-1920, 1920-3720, and greater than 3720 WLM. Risk estimates in each interval are calculated relative to the risk in the interval less than 20 WLM. and are plotted at the mean exposure in each interval: 66.6, 179, 351, 698, 1352, 2579, and 5416 WLM, respectively. Figure 8 illustrates how these interval estimates are uniformly lower than those produced by the risk model when using 0.2 WLM/year as a background rate of exposure. The shape of the risk model, however, shows remarkably good agreement with the pattern of relative risk estimates in the selected intervals. This implies that the quantitative risk model is appropriate exclusive of the intercept. This could be due to either an improper choice of baseline exposure rate or the fact that all interval estimates are relative to exposure in the lowest interval, 0-20 WLM. If there is some level of excess risk in this interval relative to an actual unexposed population, the interval estimates would be too low.

The cumulative exposure of 0.2 WLM/year is an estimate is an estimate of the background exposure in the overall U.S. population [NCRP Report No. 77, 1984]. Exposures near ore-bearing lands are known to be considerably higher than average [NCRP Report No. 45, 1975]. Therefore, it is probable that background exposures in the Colorado Plateau area are higher than average U.S. levels.

FIGURE 8

RELATIVE RISK AS A FUNCTION OF CUMULATIVE RADON DAUGHTER EXPOSURE
BACKGROUND EXPOSURE=0.2 WLM/YEAR



DOTTED LINES AND VERTICAL BARS REPRESENT 95% CONFIDENCE LIMITS

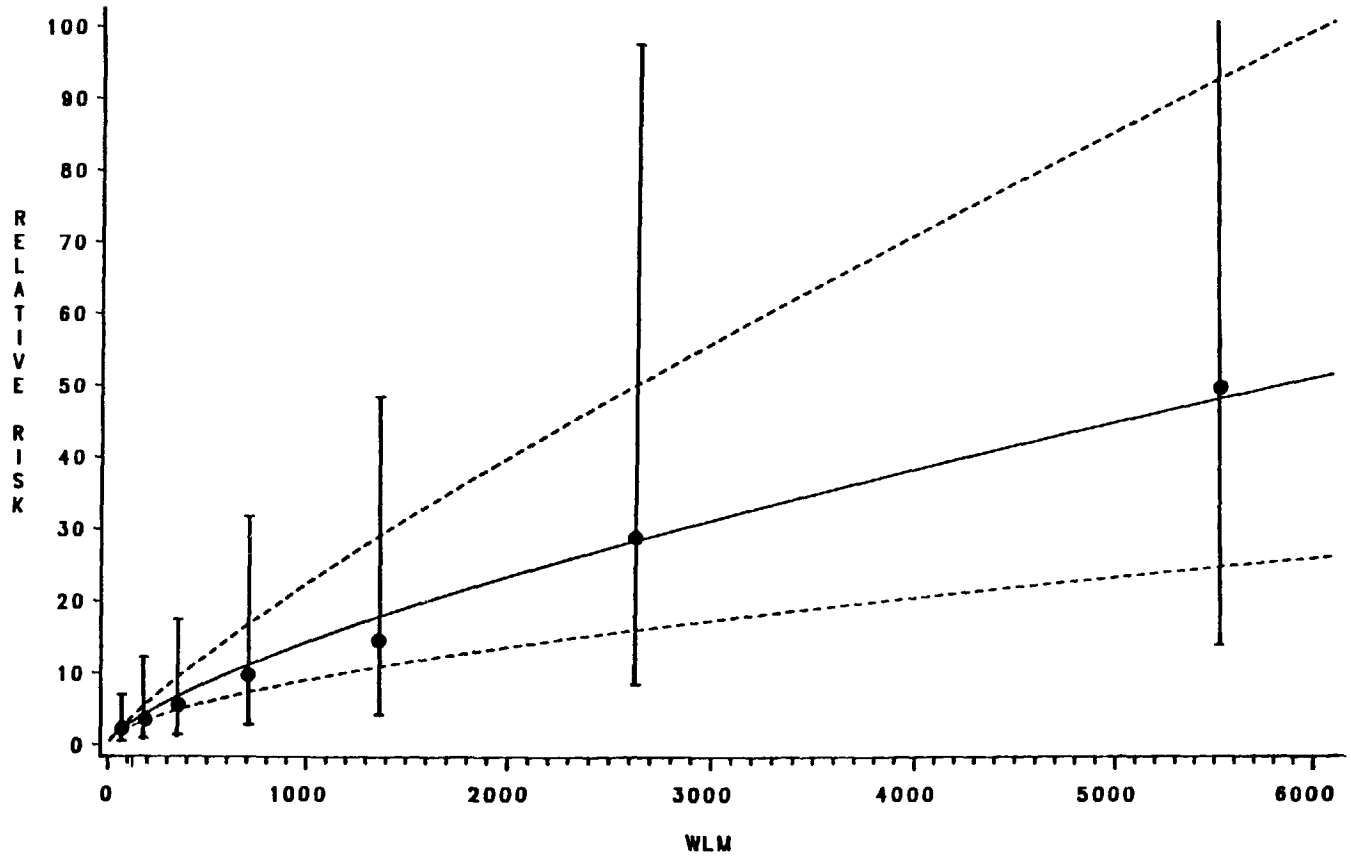
In the interest of using a background more in line with exposures received by persons living in the Colorado Plateau, the background exposure was increased to 0.4 WLM/year. This produced a quantitative risk model that agreed very well with the interval estimates, as can be seen in Figure 9.

Using this model, relative risk estimates were calculated for cumulative radon daughter exposures in the range 30 to 120 WLM corresponding to exposure levels of from one to four WLM/year over a 30-year working lifetime. These estimates range from a relative risk of 1.42 at 30 WLM to 2.07 at 120 WLM compared to someone of the same age and smoking habits with a cumulative lifetime background exposure of 24 WLM and a background exposure rate of 0.4 WLM/year. These estimates (0.9 to 1.4 excess relative risk per 100 WLM) are slightly higher than those reported by Muller et al. [1983] for the Ontario miners, but somewhat less than the estimates of Radford and Renard [1984] for the Swedish iron miners.

Obviously, these estimates are subject to the usual caveats concerning extrapolation from higher cumulative exposures and exposure rates. Because relatively few data are currently available in this cohort below 120 WLM (10 lung cancer deaths out of 709 miners), there may be some doubt that the model used actually is appropriate at these low levels. However, the pattern of relative risk estimates produced in each of the categorized exposure levels would suggest that this model fits the data well in range of 60 to 6000 WLM.

FIGURE 9

RELATIVE RISK AS A FUNCTION OF CUMULATIVE RADON DAUGHTER EXPOSURE
BACKGROUND EXPOSURE=0.4 WLM/YEAR



DOTTED LINES AND VERTICAL BARS REPRESENT 95% CONFIDENCE LIMITS

VI. SUMMARY AND CONCLUSIONS

A valid quantitative risk assessment is much more than simply fitting an exposure-response curve to mortality data. This is especially true when considering an epidemiologic risk assessment. There are a great variety of risk factors and temporal effects that may alter the interpretation of the data analysis. This report is an attempt to address such modifying influences in an effort to better understand the underlying cancer mechanisms operative in the cohort of U.S. uranium miners exposed to radon daughters.

There were a number of findings which are important in assessing the risk of lung cancer in the U.S. cohort.

1. Influence of Cigarette Smoking

The joint effect of cumulative cigarette smoking and cumulative radon daughter exposure was found to be intermediate between additive and multiplicative. This would imply a synergistic relationship in the usual definition as an effect exceeding the sum of the two relative risks.

2. Exposure-Rate Effect

Analysis of this data revealed that modeling cumulative exposure alone may not adequately predict the relative risk of lung cancer from chronic exposure to radon daughters. Miners receiving a given amount of cumulative exposure at lower rates for longer periods of time were at greater risk relative to those with the same cumulative exposure received at higher rates for shorter periods of time. This effect is supported by the convex (decelerating) shape of the exposure-response model which indicates lower exposures are more effective per unit WLM than higher exposures. Though this result may seem somewhat counter-intuitive, it is consistent with a variety of animal carcinogenesis and in vitro cellular studies after treatment with alpha radiation. This implies that results extrapolated from historical exposures at high rates may yield conservative results at current lower rates. Indeed, it is possible that lower risk estimates in the U.S. study, when compared to the four other major radon studies, as reported by Thomas et al. [1985] may be due to the higher exposure rates received by U.S. miners.

3. Late-Stage Carcinogenic Effect

Careful examination of temporal effects implies that exposure to radon daughters acts at a late stage in the carcinogenic process. All temporal factors agreed in this respect. The appropriate lag to remove redundant exposure was a relatively short six years. Older miners at initial exposure were at greater risk than those exposed at younger ages. The relative risk of lung cancer decreases with the length of time after cessation of exposure. Whether or not the mathematical form of the multistage theory of carcinogenesis applies to this cohort, the temporal patterns are worth noting.

4. Magnitude and Effect of Errors in Exposure Measurements

Analyses of the errors associated with the four methods of estimating uranium mine exposure levels indicated a lognormal distribution of errors with the relative standard deviation or CV=97 percent. Although errors of this magnitude may cause overestimation of relative risk when using the log-linear risk model, the better-fitting power function model is generally insensitive to errors of this type. In fact, if estimated exposure levels were systematically higher than those actually received by the miners [Lundin et al. 1971], relative risks per unit WLM would be underestimated for this data.

5. Quantitative Risk Estimates

Present day radon daughter exposures are considerably less than those experienced in the past by uranium miners. There is also current interest in low-level exposure to the general population from indoor radon and its decay products. Consequently, the primary cumulative exposure range of interest in risk assessment appears to be below 120 WLM. Although approximately 20 percent of the cumulative exposures in this study were below this level, there have been only 10 lung cancer deaths among this subgroup as of the end of 1982. Until this cohort is followed to extinction, epidemiologic models such as that produced in this report will be necessary to evaluate the risk of lung cancer mortality at these lower exposures.

The model developed for this report provides a very good fit to the data in the range 60 to 6000 WLM. It seems reasonable that predictions based upon this model would be reliable at least for occupational exposure to adult white males. There is little or no mortality data available regarding women and children. The risk estimates provided in Table 7 are presented as an evaluation based upon careful consideration of all factors thought to influence such long-term mortality studies. All of the caveats associated with such evaluations apply to some degree to these results.

Table 7. Quantitative Risk Estimates of Lung Cancer at Four Exposure Rates Over a Thirty Year Working Lifetime

Exposure Rate	Cumulative Exposure (30 Years)[1]	Relative Risk[2]	95% Confidence Limits
1 WLM/year	30 WLM	1.42	1.18 - 1.72
2 WLM/year	60 WLM	1.66	1.22 - 2.26
3 WLM/year	90 WLM	1.88	1.28 - 2.76
4 WLM/year	120 WLM	2.07	1.33 - 3.22

[1]Exclusive of background exposure.
[2]Risks are calculated using exposure rate interaction model in Table 6 relative to miners of the same age and smoking habits with a cumulative lifetime background exposure of 24 WLM and background exposure rate of 0.4 WLM/year.

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