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● *Paper*

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

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Abstract—**The National Institute for Occupational Safety and Health (NIOSH) has recently updated the vital status of the U.S. cohort of U miners through the end of 1982. This represents 69 additional lung cancer deaths since the last published follow-up through 1977. This more recent data was used to generate quantitative risk estimates of lung cancer after exposure to Rn daughters. Relative risks were estimated through use of the Cox proportional hazards model with an internal referent group. Results indicated that the exposure-response relationship was a slightly convex curve, predicting excess relative risks between 0.9 and 1.4 per 100 working level months (WLM) in the lower cumulative exposure range. Other findings of interest include a significant exposure-rate effect with low exposure rates more harmful per unit of cumulative exposure (WLM). Two temporal effects which modify relative risk estimates were also found. Relative risk increased with age at initial exposure to underground U mining. However, relative risk of lung cancer fell dramatically in the years following cessation of exposure.**

INTRODUCTION

A 1985 report evaluating all major epidemiologic studies of lung cancer in underground miners was sent to the Mine Safety and Health Administration (MSHA) by the National Institute for Occupational Safety and Health (NIOSH) (NIOSH85). The report concluded that, based upon recent epidemiologic studies, the current standard of 4 WLM/y should be lowered. This study is a subsequent effort 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. A technical report of this risk assessment was sent to MSHA in January 1986 (NIOSH86).

This study is based upon data collected from a cohort consisting of 3366 white underground U 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 nonwhite, and six had inadequate cigarette smoking information.

Entry into the cohort was defined by race, sex, working at least 1 mo in underground U mines, volunteering for at least one medical survey between 1950 and 1960, and providing personal and occupational data of sufficient detail (Lu71).

NIOSH has now updated the mortality experience of the cohort through 31 December 1982. Lung cancer mortality was defined as anyone assigned an International Classification of Diseases* (ICD) code of 162 or 163 (same designation in the sixth through ninth revisions). Previous analyses of this cohort considered follow-up only through 1977 (Wa81; Wh83). Table 1 presents a comparison of vital status of the cohort at the end of 1977 and 1982.

PROTOCOL FOR STATISTICAL ANALYSIS

Much of the epidemiologic work in the past regarding the analysis of mortality in occupational cohorts has involved modified life-table analysis, usually in the form of standardized mortality ratios (SMR). The SMR is the ratio of observed mortality rates to expected mortality rates obtained from a stratified referent population (often the United States). 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 with SMR studies is often the lack of comparability between the study population and the referent population. For example, the study population may smoke at different rates than the referent population or may be healthier than the referent population, especially in occupational studies (En76; McM76).

To alleviate some of these problems, in particular the relatively small number of lung cancers at low exposure levels, some type of statistical model was desirable.

* International Classification of Diseases Adapted for Use in the United States, National Center for Health Statistics, Washington, DC.

Table 1. Status of data base

	1977		1982	
	Number	Percent	Number	Percent
Alive	2388	71.4	2131	63.7
Deceased	958	28.6	1215	36.3
Lung cancer	187	19.5	256	21.1
Other causes	771	80.5	959	78.9
Total	3346	100.0	3346	100.0

Numerous types of models have been suggested for examining cause-specific mortality as a function of various risk factors. One of the most popular models in current use is the relative risk model. This has been shown to provide a good fit to earlier updates of the U.S. uranium miners cohort (Lu79; Wh83).

A relative risk model which is particularly well-suited to longitudinal mortality studies is one proposed by Cox (Co72). 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 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

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

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

Although the exponential or log-linear function $\exp(\beta\mathbf{z})$ 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 β are all equal to zero. Two of the most common alternative risk functions are the linear $(1 + \beta\mathbf{z})$ and the power function $(\exp(\beta \ln \mathbf{z}) = \mathbf{z}^{\beta})$. All three forms of risk functions were considered in modeling the U.S. uranium miners data.

There were a considerable number of variables considered for potential inclusion in the risk assessment model. Cumulative exposure as measured by total WLMs for each miner was the primary exposure variable. (A working level (WL) is defined as any combination of Rn daughters in 1 L of air which results in the ultimate release of 1.3×10^5 MeV of potential α energy. Working level months are the product of months underground (170 hours) and the Rn daughter concentration in WL.) 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 $\lambda(t;\mathbf{z})$. 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 Rn daughters and pack-years of cigarettes was 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 listed in Table 2 were examined in developing the appropriate risk model. 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 Rn daughter exposure.

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.

To investigate the appropriate number of years to lag exposure in this cohort, a series of lags ranging from 0 to 12 y 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 lag of 6 y for cumulative exposure is the best choice for this analysis. Cu-

Table 2. Regression variables considered in development of the risk model

Variable	Units	Median	Range
Cumulative exposure	Working level months (WLM)	430.4	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 (173 cm) Medium (173-178 cm) Tall (>178 cm)		
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

mulative cigarette smoking was rather insensitive to the amount of lag in the range of 0 to 12 y. Therefore, for the purpose of consistency cumulative smoking was also lagged 6 y.

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 Fig. 2. Because of the biological implausibility of such a situation, an alternative approach is to linearly weight the effectiveness of cumulative exposure over a period of several years (Ma79). An illustration of such a weighting function is provided in Fig. 3. Consequently, we tried various combinations of lagging and linear partial weighting, with the combination illustrated in Fig. 3 providing the best fit, i.e. a lag of 4 y followed by linear partial weighting in the period 4–10 y before death from lung cancer. This scheme provided a fit essentially the same as that of a simple lag of 6 y, but was chosen over lagging because of its biological plausibility.

RESULTS OF MODEL DEVELOPMENT

Of the three types of risks models used (log-linear, linear and power function), the power function model provided the best fit to the data as measured by the log-likelihood. This model is of the form $\exp(\beta \ln z) = z^{\beta}$, where z is cumulative exposure in WLM or pack-years of cigarette smoking. Since the power function model involves the natural logarithm, zero values of covariates were not permitted. To avoid this, an estimate of cumulative background exposure was added to each miner's cumulative Rn daughter and pack-year totals. Based upon estimates of background exposure in the United States, 0.2 WLM/y since birth were added to each miner's cumulative exposure (NCRP85). This was the same background used in an earlier report on lung cancer mortality in this cohort (Wh83). In a similar fashion, 0.005 packs per day were added as an estimate of passive smoking exposure for each day since birth to the cumulative smoking totals (Hi75).

Results of fitting the power function model to cumulative Rn daughter exposure and cumulative smoking are given in Table 3. Both effects are sub-linear or convex, as indicated by both coefficients less than unity.

The joint effect of exposure to Rn daughters and cigarette smoking has been an issue of particular interest in past research. Therefore, the interaction of Rn daughter exposure and cigarette smoking was assessed in the multiplicative power function model. Results showed a negative result ($\beta = -0.088$, $p = 0.06$) which, while not strictly significant, is suggestive of a departure from a multiplicative effect. When a similar analysis was run with mor-

Table 3. Radon daughter and cigarette smoking effects in the power function relative risk model

Main Effects Model: $(WLM+bgr^a)^{\beta_1}\ (packs+bgs^b)^{\beta_2}$		
Risk Factor	Coefficient	Std. Error
Cumulative exposure (WLM)	0.626	0.054
Cumulative smoking (packs)	0.298	0.050
Likelihood ratio $\chi^2=213.2$, $p<0.001$		

Interaction model: $z_1=\ln(WLM+bgr)$ $z_2=\ln(packs+bgs)$		
Risk factor	Coefficient	Std error
z_1	1.418	0.419
z_2	0.922	0.336
$z_1 \times z_2$	-0.088	0.046
Likelihood ratio $\chi^2=216.9$, $p<0.001$		

[a]bgr=background radon exposure = 0.2 WLM/year

[b]bgs=background cigarette smoking = 0.005 packs/day

tality data complete only through 1977, there was no suggestion of a significant negative effect. Therefore, based upon more complete follow-up through 1982, the joint effect of Rn daughter exposure and cigarette smoking appears to be slightly less than multiplicative but greater than additive.

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 and found no statistically significant results (Wh83; Lu71). 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 U mining work histories). For most forms of employment, this is the accepted definition of average exposure rate. However, underground U mining is a very intermittent 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 reexamined 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 ($\beta = -0.043, p < 0.001$) 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 rel-

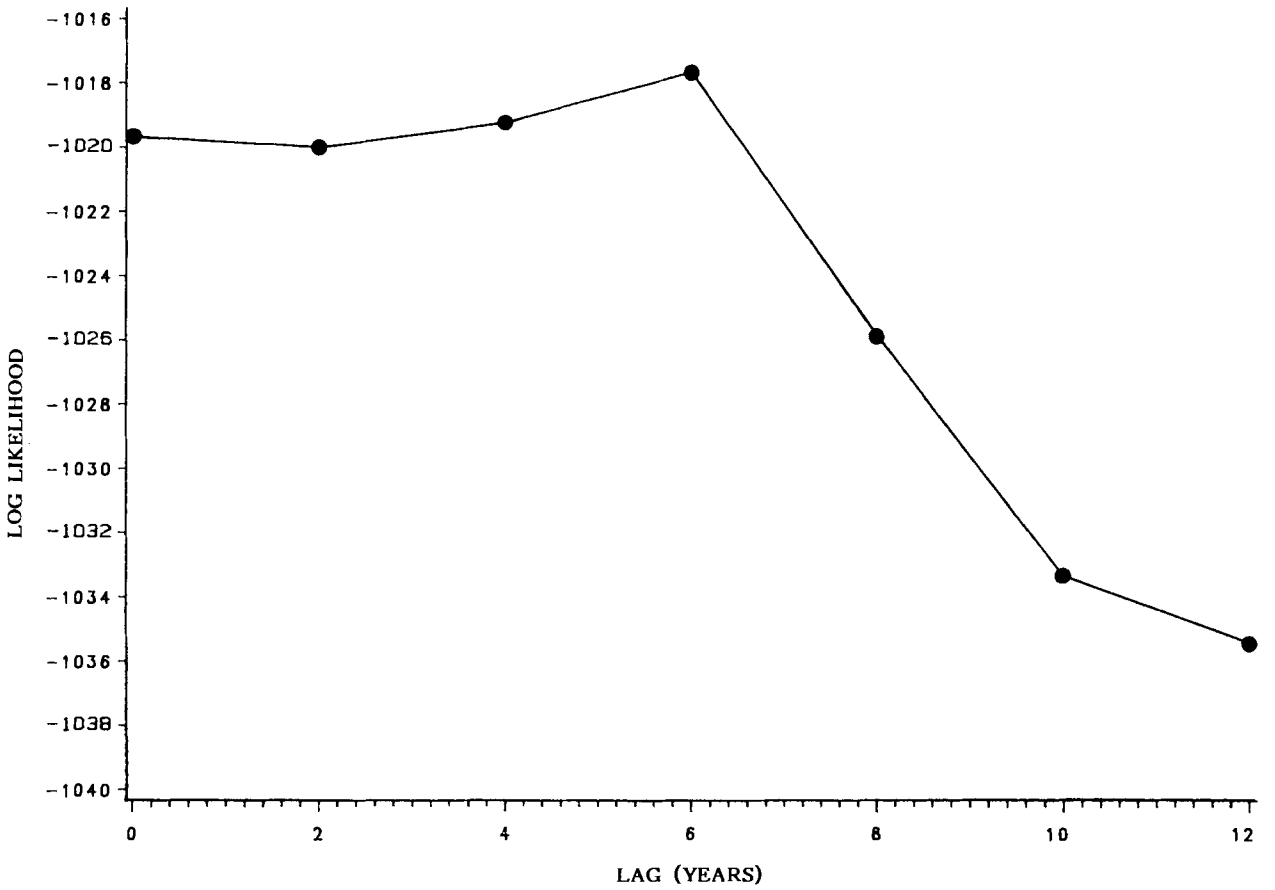

Fig. 1. Effect of lagging on the likelihood of the Rn daughter and cigarette smoking model.

atively 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 10 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 ($\beta = 0.157$, $P = 0.019$). The direction of the 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% greater risk of lung cancer. However, the increased risk would only be 10% at the lower exposure rate for miners in the 834–10,000 WLM range.

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 y 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 Rn daughter exposure and birth decade was examined. Results indicated a statistically significant positive interaction ($\beta = 0.173$, $P = 0.002$). 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.

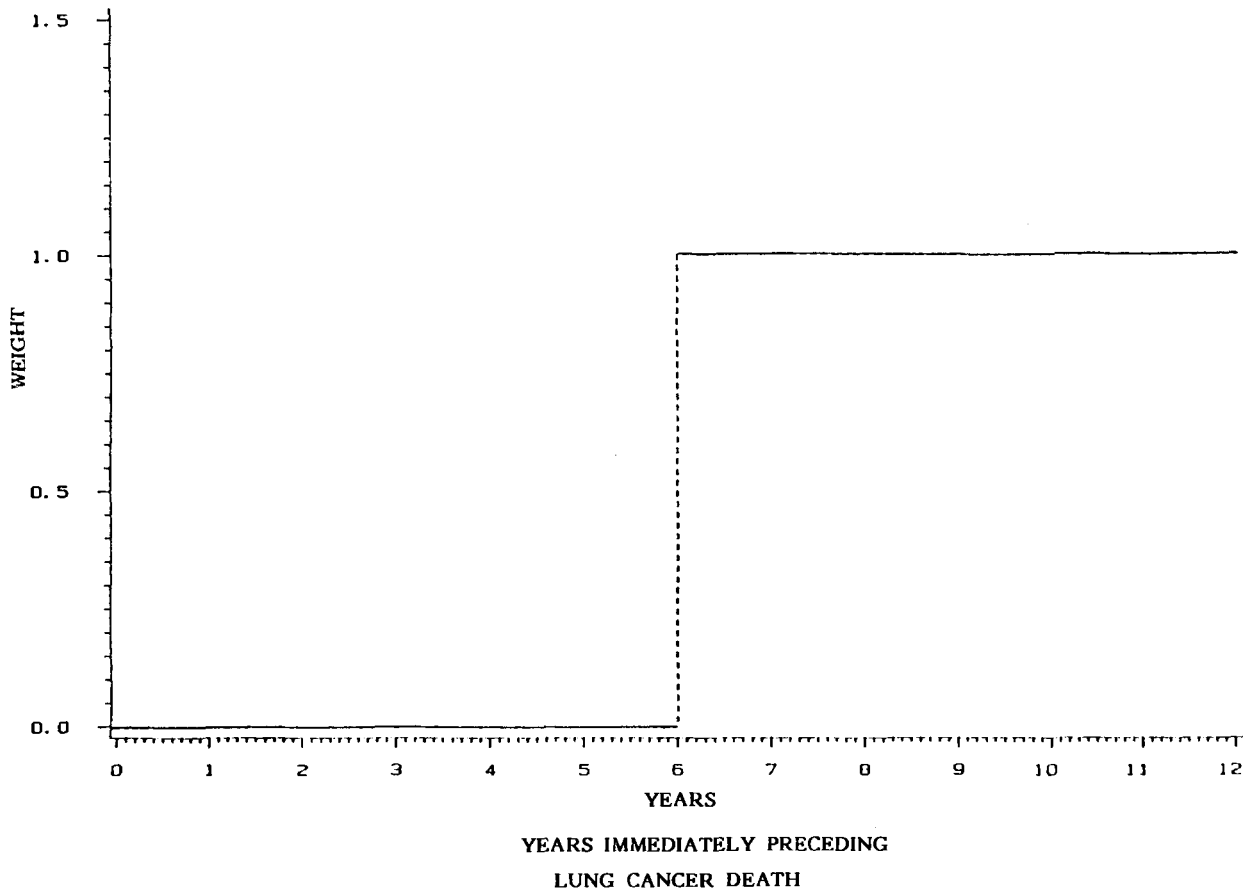

Fig. 2. Example of 6-y lag weighting scheme.

C. *Age at initial exposure*

There was a high degree of variability in the ages at which members of this cohort were initially exposed to underground uranium mining. Therefore, this variable had the potential to substantially affect risk estimates in this cohort. Results of the inclusion of age at initial exposure (in months) indicated a positive and statistically significant coefficient ($\beta = 0.0023, p = 0.004$). 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 Rn daughter exposure and smoking history who was initially exposed 10 y (120 mo) later in age than another miner, would have $\exp(0.0023 \times 120) = 1.32$ or 32% higher risk of lung cancer.

D. *Time since cessation of exposure*

To investigate the effect of cessation of exposure on this cohort, all miners were identified who had indicated retirement from U mining during the course of follow-up. Approximately 95% of the cohort had retired for more than 1 y before 1970. The average time since last exposure was 18.0 y for those miners not dying of lung cancer and 9.9 y 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 ($\beta = -0.005, p < 0.001$). 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 y after mining U is $\exp(-0.005 \times 120) = 0.549$ relative to someone who was currently mining or within 4 y of last exposure with the same cumulative exposure, smoking history and age.

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 Rn daughter exposure is very complex, involving such factors as respiration rates, particle size distribution, deposition in the lung, and Rn/Rn daughter equilibrium. Most risk assessments are modeled as functions of some exposure index, which is the method used here. It is the

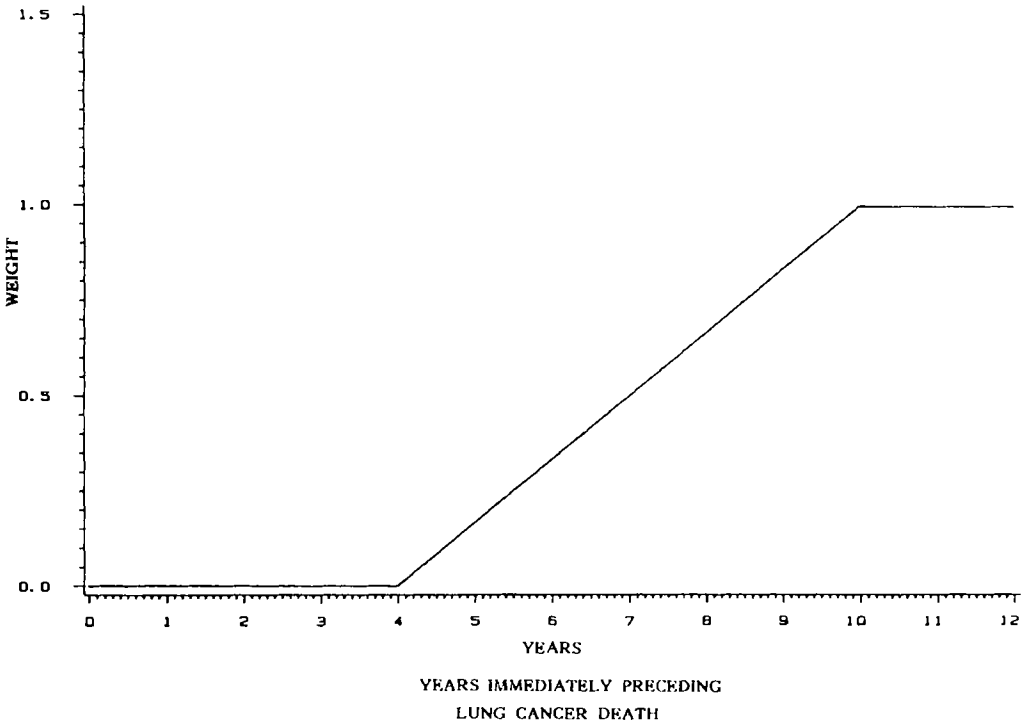

Fig. 3. Example of lagging with partial linear weighting.

Table 4. Quantitative relative risk model

Risk Factor	Coefficient	Std. Error
ln(Cumulative exposure+bgr[a])(WLM)	0.731	0.062
ln(Cumulative smoking+bgs[b])(packs)	0.291	0.050
Age at initial exposure (months)	0.0023	0.0008
ln(Exposure rate)(WLM/month)	-0.045	0.001
Likelihood ratio χ^2=228.8, p<0.001		
Exposure rate interaction model		
ln(Cumulative exposure+bgr)	0.660	0.066
ln(Cumulative smoking+bgs)	0.252	0.050
Age at initial exposure	0.0024	0.0008
ln(Exposure rate)	-0.198	0.067
ln(Exposure rate)xexposure category	0.157	0.067
Exposure <834 WLM=0 Exposure ≥834 WLM=1		
Likelihood ratio χ^2=234.2, p<0.001		

[a]bgr = background radon daughter exposure = 0.4 WLM/year

[b]bgs = background cigarette smoking = 0.005 packs/day

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

purpose of this section to estimate the magnitude of exposure errors and their effect upon quantitative risk models. Exposures in a given mine and year were estimated in one of four ways (Lu71): (1) actual measurements; (2) interpolation or extrapolation in time; (3) geographic area estimation; and (4) estimates before 1950 based upon knowledge of ore bodies, ventilation practices and earliest measurements. These methods will subsequently be called methods 1, 2, 3 and 4. Table 5 illustrates the number of measurements made in the mines by year.

A. *Magnitude of error in exposure data*

The four methods used to determine the error in exposures resulted in coefficients of variation (CVs) of 112.5%, 131.9%, 148.6% and 186%, respectively (Ho85). Table 6 shows contribution to measurement error for each of methods 1–4. Actual measurements comprised only about 10% of the data. To obtain an overall estimate of the relative error, a weighted average of the CVs 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 Rn daughter level (WL). The total cumulative exposure (WLM) for each miner is obtained from

$$\mathrm{WLM} = \sum_{ij} (\mathrm{WL}_{ij})(\mathrm{UGMON}_{ij}),$$

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:

$$\begin{aligned}\mathrm{Var(WLM)} &= \sum_{i,j} (\mathrm{UGMON}_{ij})^2 \mathrm{var}(\mathrm{WL}_{ij}) \\ &= \sum_{i,j} (\mathrm{UGMON}_{ij})^2 (\mathrm{CV})^2 (\mathrm{WL}_{ij})^2,\end{aligned}$$

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

If we substitute our estimate of the overall CV = 137% or 1.37 and use total cumulative exposure divided

Table 6. Exposure measurement errors due to four methods of estimating annual Rn 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	1.59
Estimates prior to 1950 (assumed 1.25 x geographic error)			1.86

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.

B. *Effect on relative risk estimation of exposure measurement errors*

In general, it has been shown 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) (Br54; Ke63; Co77). 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 (Pr82) introduced a method for dealing with errors in individual exposure measures when using the Cox proportional hazards model. It has been shown that the direction of bias in relative risk estimation depends upon the error distribution and the shape of the exposure-response model (Pr82; Ho85). The effect upon risk estimates using the power function 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 relatively low. If the exposure measurements were generally higher than those actually experienced by the miners (Lu71), 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 low. 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.

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 United States. The problems inherent with the use of such external referents have been well documented (McM76; En76). Although a sub-cohort of miners unexposed to Rn 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/y 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 4 illustrates how these interval estimates are uniformly lower than those produced by the risk model when using 0.2 WLM/y 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/y is an estimate of the background exposure in the overall U.S. population (NCRP84). Exposures near ore-bearing lands are known to be higher than average (NCRP75). Therefore, it is probable that background exposures in the Colorado Plateau area are higher than average U.S. levels.

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/y. This produced a quantitative risk model that agreed very well with the interval estimates, as can be seen in Fig. 5. Other significant effects found in the initial analysis were unaffected by this change in background exposure.

The risk model illustrated in Fig. 5 illustrates the estimated risk of lung cancer mortality as a function of cumulative exposure to Rn daughters in WLM units (including background). All risks are relative to persons of the same age, smoking history, and a birth decade but with only a background exposure to Rn daughters of 22 WLM. This background was obtained by multiplying 0.4 WLM/y times 55 y which is approximately the average age in the cohort less lag. The convex curvature of the model implies that the excess relative risk at lower cumulative exposure levels is greater per unit WLM than at higher cumulative exposures.

Using this model relative risk estimates were calculated for cumulative Rn daughter exposures in the range 30 to 120 WLM (excluding background exposure) corresponding to exposure rates of from one to four WLM/y over a 30-y working lifetime. The use of different exposure rates required the introduction of the negative exposure rate interactive effect (Table 4) into the model. These estimates range from a relative risk of 1.47 at 30

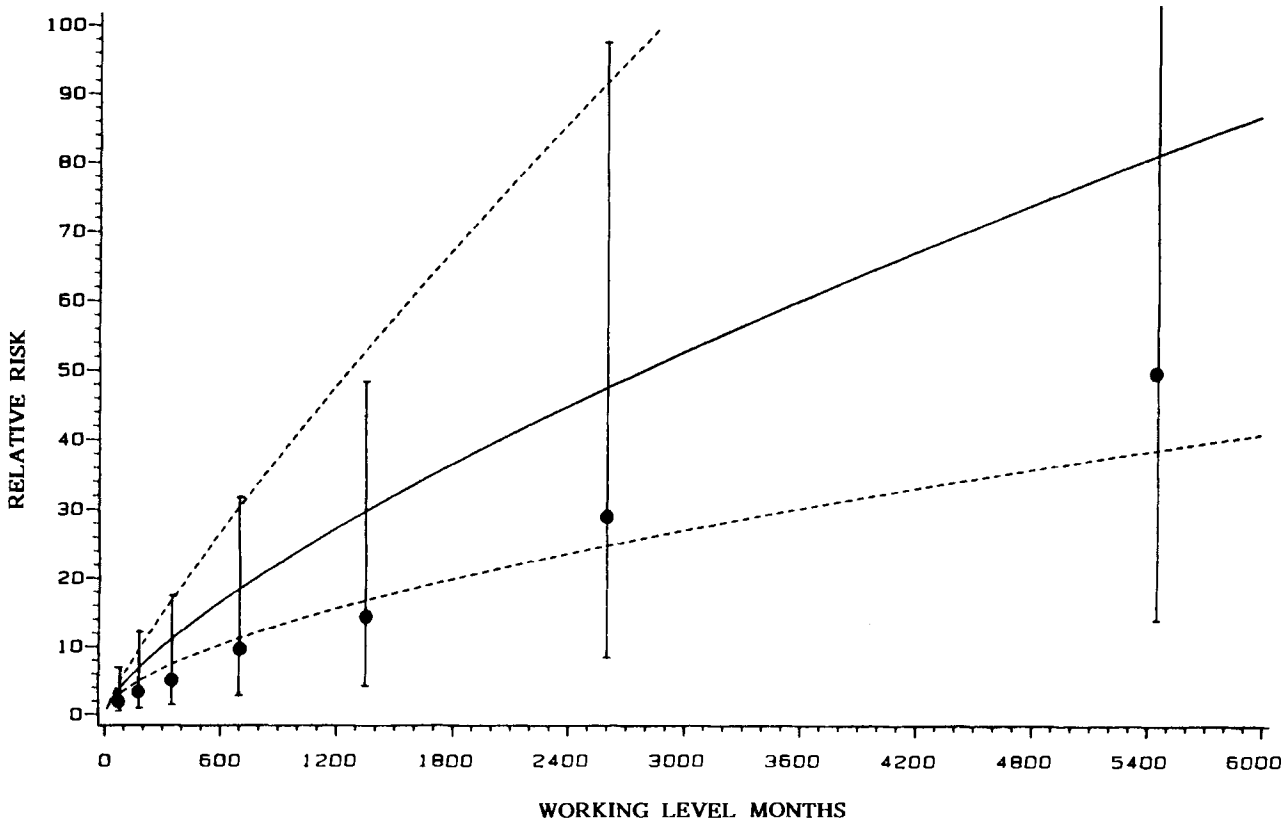

Fig. 4. Relative risk as a function of cumulative Rn daughter exposure (background exposure = 0.2 WLM/y.) Dotted lines and vertical bars represent 95% confidence limits.

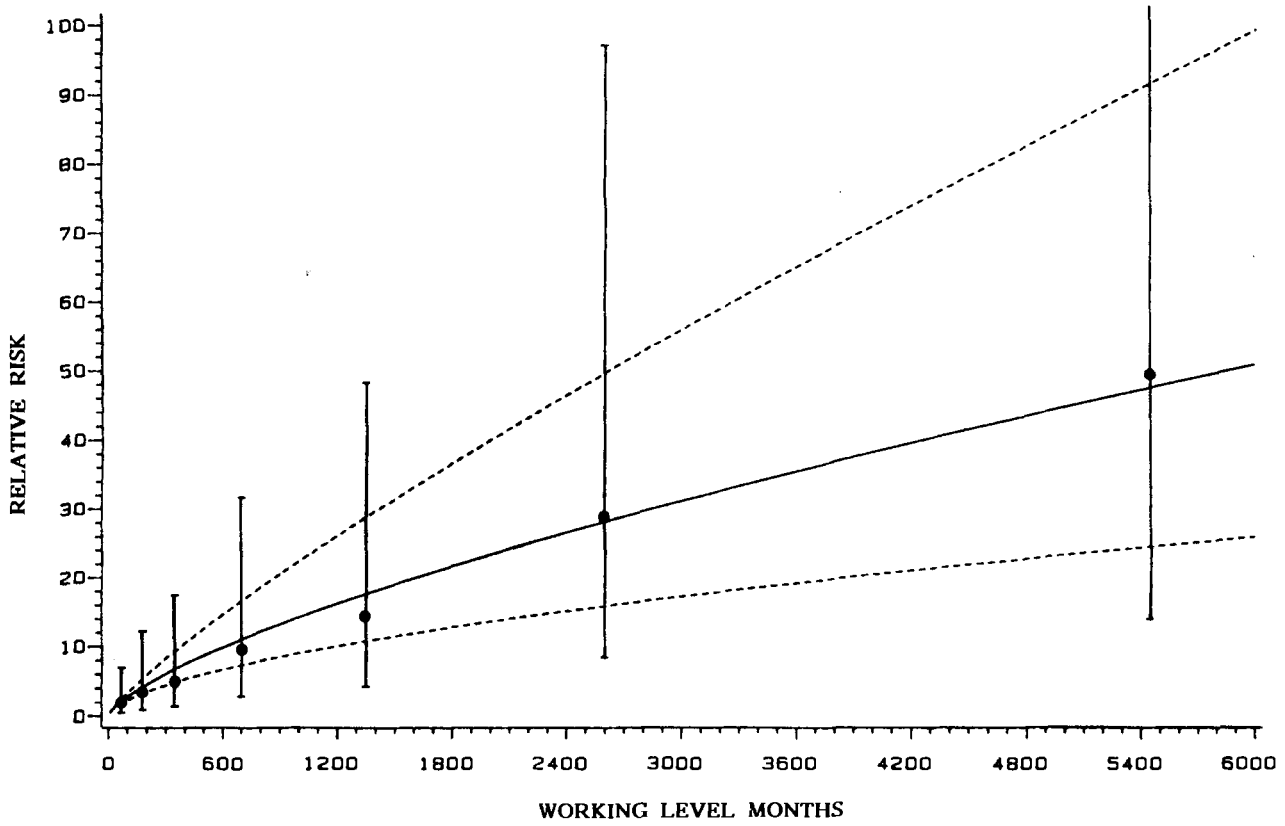

Fig. 5. Relative risk as a function of cumulative Rn daughter exposure (background exposure = 0.4 WLM/y.) Dotted lines and vertical bars represent 95% confidence limits.

WLM to 2.17 at 120 WLM compared to someone of the same age and smoking habits with a cumulative lifetime background exposure of 22 WLM and a background exposure rate of 0.4 WLM/y. These estimates (0.9 to 1.4 excess relative risk per 100 WLM) are slightly higher than those reported for the Ontario miners (Mu83), but somewhat less than the estimates for the Swedish Fe miners (Ra84). They are considerably higher than the 0.31 per 100 WLM reported in an analysis of the 1977 follow-up of this cohort (Wh83).

Obviously these estimates are subject to the usual caveats concerning extrapolation from higher cumulative exposures and exposure rates. Because relatively little data is 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.

DISCUSSION

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 analysis 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.

Influence of cigarette smoking

The joint effect of cumulative cigarette smoking and cumulative Rn daughter exposure appears to be slightly less than multiplicative. This would still imply a synergistic relationship in the usual definition as an effect exceeding the *sum* of the two relative risks. The lung cancer mortality pattern between 1977 and 1982 suggests that the joint relationship is gradually moving away from multiplicative toward additive.

For the present, however, the lack of clear-cut statistical significance ($P = 0.06$) of interaction in the power model, makes the multiplicative model the most reasonable choice. In addition, cigarette smoking is not a serious confounder in the U.S. cohort, i.e. smoking patterns are similar in the various exposure groups. Therefore, the effect of cigarette smoking is to increase the relative risk of lung cancer at all levels of Rn daughter exposure by a multiplicative factor given in Table 3.

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 Rn 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 α radiation (Ra83; Cr80; Ch81; Hi82). This implies that results extrapolated from historical exposures at high rates may yield conservative results at current lower rates. Indeed, it is possible that recently reported lower risk estimates in the U.S. study as compared to the four other major Rn studies (Th85) may be due to the higher exposure rates received by U.S. miners.

Magnitude and effect of errors in exposure measurements

Analyses of the errors associated with the four methods of estimating U mine exposure levels indicated a log-normal distribution of errors with the relative standard deviation or CV = 97%. The power function model is generally less sensitive than the linear or log-linear model to errors of this type. If estimated exposure levels were systematically higher than those actually received by the miners (Lu71), relative risks per unit WLM would be underestimated for this data.

Temporal effects

A significant positive effect of age at initial exposure was found for the U.S. data. This has the important implication that miners first exposed at later ages are at greater risk of lung cancer than younger miners, all else being equal. This effect was not found to be statistically significant in a case-control study of this cohort with 1977 follow-up (Wh83). A possible explanation is that a sample of four controls per case was not sufficient for a variable as highly skewed as age at initial exposure.

Risk of lung cancer was found to be significantly reduced with increasing time since last exposure. This reduction was in the form of an exponential decay function, i.e. $e^{-\beta t_c}$ where $\beta = 0.005$ and t_c = time in months after cessation of exposure. This predicts that excess risk of lung cancer will be reduced almost 55% 10 y after retirement from underground mining compared to miners with the same exposure, smoking history and age who were currently mining or less than 4 y from last exposure.

Multistage theory of carcinogenesis

One of the most popular theories for explaining the temporal patterns in mortality studies of carcinogenesis is the multistage model (Ar61). 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 y. 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 the mathematical form of the multistage model actually holds in a given situation. However, a number of its predictions have been verified experimentally (Pe75). 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. There has been considerable work recently concerning the effect on excess relative risk of age at initial exposure and time since cessation of exposure in the context of multistage theory (Wh77; Da80; Br83). By examining these factors, we may better understand the underlying cancer mechanism operative in this cohort.

If a late stage is affected by a carcinogen, the multistage theory predicts a rising relative risk with increasing age at exposure and a falling relative risk with increasing time since last exposure. The opposite is true for an early stage effect or initiator. Therefore, if the multistage theory is applicable to the cancer process in this cohort, exposure to Rn daughters apparently has primarily a late stage or promotional effect. This conclusion is also supported by the relatively short lag (4 to 6 y) providing the best fit to the data. Whether or not the mathematical form of the multistage theory holds for this data, the temporal effects are potentially important from an occupational and public health standpoint.

Quantitative risk estimates

Present-day Rn daughter exposures are considerably less than those experienced in the past by U miners. There is also current interest in low-level exposure to the general population from indoor Rn and its decay products. Consequently, the primary cumulative exposure range of interest in risk assessment appears to be below 120 WLM. Although approximately 20% 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 here will be necessary to evaluate the risk of lung cancer mortality at these lower exposures.

Table 7. Quantitative risk estimates of lung cancer at four exposure rates over a 30-y working lifetime

Exposure Rate	Cumulative Exposure (30 Years)[a]	Relative Risk[b]	95% Confidence Limits
1 WLM/year	30 WLM	1.47	1.23 - 1.77
2 WLM/year	60 WLM	1.73	1.29 - 2.32
3 WLM/year	90 WLM	1.96	1.36 - 2.84
4 WLM/year	120 WLM	2.17	1.43 - 3.32

[a]Exclusive of background exposure
[b]Risks are calculated using exposure rate interaction model in Table 4 relative to miners of the same age and smoking habits with a cumulative lifetime background exposure of 22 WLM and background exposure rate of 0.4 WLM/year.

The model developed for this report provides a very good fit to the data in the range 60 to 6000 WLM. However, these estimates are three to four times higher than those reported in a case-control analysis of this data using 1977 follow-up (Wh83). There are at least two potential reasons for this discrepancy. The earlier analysis used only four controls (non-lung cancers) per case of lung cancer and was based upon 5 y less observation. While this may account for small differences, it is doubtful that this could explain such a large disagreement. The most probable reason is that the earlier analysis used a lag of 10 y which has now been shown to be much too great. This degree of lag forced 18 lung cancer deaths into the baseline or referent group in the earlier analysis (0–21 WLM). This represents approximately 47% of lung cancer deaths expected in the entire cohort by the end of 1977 (Wa81). Since this baseline mortality rate appears to be too high, its effect would be to lower risk estimates in higher exposure categories relative to it.

Care was taken to use a background exposure rate and exposure weighting function that were reasonable in this risk assessment. However, since no actual unexposed occupational group was available for estimation of background rates, all risk assessments involving this cohort are somewhat sensitive to choice of a referent population and/or background exposure rates. It seems reasonable that predictions based upon the model developed in this study 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. The resulting risk assessment estimates more than a doubling of risk of death from lung cancer after a 30-y exposure to the current standard of 4 WLM/y relative to environmental levels of Rn daughters.

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REFERENCES

Ar61 Armitage P. and Doll R., 1961, "Stochastic models for carcinogenesis," in: *Proc. 4th Berkeley Symp. on Mathematical Statistics and Probability*, pp. 19–38 (Berkeley, CA: University of California Press).

Be81 Berteig L. and Stranden E., 1981, "Radon and radon daughters in mine atmospheres and influencing factors," in: *Radiation Hazards in Mining* (edited by M. Gomez), pp. 89–94 (New York: American Institute of Mining, Metallurgical and Petroleum Engineering, Inc.).

Br54 Bross I., 1954, "Misclassification in 2 × 2 tables," *Biometrics* **10,** 478.

Br83 Brown C. C. and Chu K. C., 1983, "Implications of the multi-stage theory of carcinogenesis applied to occupational arsenic exposure," *J. Natl. Cancer Inst.* **70,** 455.

Ch81 Chameaud J., Perraud R., Masse R. and Lafuma J., 1981, "Contribution of animal experimentation to the interpretation of human epidemiological data," in: *Radiation Hazards in Mining* (edited by M. Gomez), pp. 222–227 (New York:

American Institute of Mining, Metallurgical and Petroleum Engineering, Inc.).

Co77 Copeland K. T., Checkoway H., McMichael A. J. and Holbrook R. H., 1977, "Bias due to misclassification in the estimation of relative risk," *Am. J. of Epidemiology* **105,** 488.

Co72 Cox D. R., 1972, "Regression models and life tables," *Journal of the Royal Statistical Society,* Series B **34,** 187.

Cr80 Cross F. T., Palmer R. F., Dagle G. E., Busch R. H. and Buschbom R. L., 1980, "Influence of radon daughter exposure rate, unattachment fraction, and disequilibrium on occurrence of lung tumors," *Radiation Protection Dosimetry* **7,** 381.

Da80 Day N. E. and Brown C. C., 1980, "Multistage models and primary prevention of cancer," *J. Natl. Cancer Inst.* **64,** 977.

Do78 Doll R. and Peto R., 1978, "Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and life-long non-smokers," *Journal of Epidemiology and Community Health* **32,** 303.

En76 Enterline P. E., 1976, "Pitfalls in epidemiologic research: an examination of the asbestos literature," *Journal of Occupational Medicine* **18,** 150.

Hi82 Hill C. K., Buonaguro F. M., Myers C. P., Han A. and Elkind M. M., 1982, "Fission-spectrum neutrons at reduced dose rates enhance neoplastic transformation," *Nature* **298,** 67.

Hi75 Hinds W. C. and First M. W., 1975, "Concentrations of nicotine and tobacco smoke in public places," *New England J. Med.* **292,** 844.

Ho85 Hornung R. W., 1985, *Modeling Occupational Mortality Data with Applications to U.S. Uranium Miners,* Ph.D. dissertation, Dept. of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC.

Ke63 Keys A. and Kihlberg J. K., 1963, "Effects of misclassification on estimated relative prevalence of a characteristic," *Am. J. Public Health* **53,** 1656.

Lu79 Lundin F. E., Archer V. E. and Wagoner J. K., 1979, "An exposure-time-response model for lung cancer mortality in uranium miners: effects of radiation exposure, age, and cigarette smoking," in: *Energy and Health, Proc. of a SIMS Conference* (edited by N. E. Breslow and A. S. Whittemore), p. 243 (Philadelphia, PA: Society for Industrial and Applied Mathematics).

Lu71 Lundin F. E., Wagoner J. K. and Archer V. E., 1971, *Radon daughter exposure and respiratory cancer quantitative and temporal aspects,* NIOSH-NIEHS Joint Monograph No. 1 (Washington, DC: U.S. Department of Health, Education, and Welfare).

Ma80 Makepeace C. E. and Stocker H., 1980, "Statistical interpretation of a frequency of monitoring program designed for the protection of underground uranium miners from overexposure to radon daughters," *The Canadian Mining and Metallurgical Bulletin* **73,** 113.

Ma77 Mancuso T. F., Stewart A. and Kneale G., 1977, "Radiation exposures of hanford workers dying from cancer and other causes," *Health Phys.* **33,** 369.

Ma79 Mazumdar S. and Redmond C. K., 1979, "Evaluating dose-response relationships using epidemiological data on occupational subgroups," in: *Energy and Health, Proc. of a SIMS Conference* (edited by N. E. Breslow and A. S. Whittemore), p. 265 (Philadelphia, PA: Society for Industrial and Applied Mathematics).

McM76 McMichael A. J., 1976, "Standardized mortality ratios and the 'healthy worker effect': scratching beneath the surface," *J. Occup. Med.* **18,** 1965.

Mu83 Muller J., Wheeler W. C., Gentleman J. F., Suranyi G. and Kusiak R. A., 1983, *Study of Mortality of Ontario Miners,* 1955–1977 (Part 1), Ministry of Labor, Special Studies and Health Service Branch, 400 University Avenue, 8th Floor, Toronto, Ontario M7A 1T7, Canada.

NCRP75 National Council on Radiation Protection and Measurements, 1975, "Natural Background Radiation in the United States," *NCRP Report No.* 45 (Bethesda, MD: NCRP).

NCRP84 National Council on Radiation Protection and Measurements, 1984, "Exposures from the uranian series with emphasis on radon and its daughters," *NCRP Report No.* 77 (Bethesda, MD: NCRP).

NIOSH85 National Institute for Occupational Safety and Health, 1985, *Evaluation of Epidemiologic Studies Examining the Lung Cancer Mortality of Underground Miners* (report submitted on 9 May 1985 to the Mine Safety and Health Administration, 4676 Columbia Parkway, Cincinnati, OH 45226).

NIOSH86 National Institute for Occupational Safety and Health, 1986, *Quantitative Risk Assessment of Lung Cancer in U.S. Uranium Miners* (report submitted on 16 January 1986 to the Mine Safety and Health Administration, 4676 Columbia Parkway, Cincinnati, OH 45226).

Pr82 Prentice R. L., 1982, "Covariate measurement errors and parameter estimation in a failure time regression model," *Biometrika* **69,** 331.

Ra83 Raabe O. G., Book S. A. and Parks N. J., 1983, "Lifetime bone cancer dose-response relationships in beagles and people from skeletal burdens of ^{222}Ra and ^{90}Sr," *Health Phys.* **44**(suppl. 1), 33.

Ra84 Radford E. P. and Renard K. G. S. C., 1984, "Lung cancer in swedish iron miners exposed to low doses of radon daughters," *New England J. Med.* **310,** 1485.

Sc81 Schiager K. J., Johnson J. A. and Borak T. B., 1981, "Radiation monitoring priorities for uranium miners," in: *Radiation Hazards in Mining,* (edited by M. Gomez), pp. 738–745 (New York: American Institute of Mining, Metallurgical and Petroleum Engineering, Inc.).

Th85 Thomas D. C., McNeill K. G. and Dougherty C., 1985, "Estimates of lifetime lung cancer risks resulting from Rn progeny exposure," *Health Phys.* **49,** 825.

Wh77 Whittemore A. S., 1977, "The age distribution of human cancer for carcinogenic exposures of varying intensity," *Am. J. Epidemiology* **106,** 418.

Wh83 Whittemore A. S. and McMillan A., 1983, "Lung cancer mortality among U.S. uranium miners: a reappraisal," *J. Natl. Cancer Inst.* **71,** 489.