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Two-Step Model for the Risk of Fatal and Incidental Lung Tumors in Rats Exposed to Radon

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Data from 4276 rats with radon exposures up to 10,000 WLM at rates up to 1000 WL are analyzed with a two-step clonal expansion model. The age dependences of the hazard for the risks for fatal and for incidental tumors are very different. Therefore, two different parameterizations of the model are used in the two cases. In both cases radiation acts only on the initiating mutation and the clonal expansion, but not on the second mutation. Average exposure rates of 5 WL for fatal tumors and 0.5 WL for incidental tumors double the rate of spontaneous mutations. While the fatal tumors show a linear increase in the effective clonal expansion rate up to about 100 WL average exposure rate and a saturation at higher exposure rates, the incidental tumors follow a step-like behavior of this parameter. It is proposed that only the fatal lung tumors among the rats be used for generalizations to models for lung cancer in humans. The fitted model for fatal tumors shows an inverse dose-rate effect at average exposure rates above 20 WL. However, below 10 WL the lung cancer risk per unit exposure decreases with increasing duration of exposure. Between 10 and 20 WL, the difference in ERR/WLM between acute and protracted exposure is small.

INTRODUCTION

At the Pacific Northwest National Laboratory (PNNL) rats have been exposed to radon as a model for indoor radon exposure of the population and for miners exposed to radon (*1, 2*). The experimental setup allows better control over exposures and more consistent accuracy of diagnosis of lung tumors when compared to epidemiological studies of humans. The variation in duration of exposure between 2 days and about 100 weeks (about 90% of the average lifetime of the rat) allows the study of the effects of exposure and exposure rate. This is of special importance in radiation protection, as data from the atomic bomb survivors with very short exposure times (seconds) are the main source of information for radiation risk. The tumor hazard of temporally extended exposures to ionizing radiation is estimated by the International Commission on Radiological Protection to be lower by a factor of two (dose and dose-rate effectiveness factor, DDREF) (*3*). Information on the effects of exposure and exposure rates from animal experiments may be used as guidelines for extrapolations to the conditions of exposure usually encountered in radiation protection. This animal study can be used to analyze the effects of exposure rate on the two stages of mutation, and the clonal expansion rate in the two-step clonal expansion model (*4, 5*).

However, there are also drawbacks to making inferences from animal studies to humans. Differences between rats and humans include their different lung geometry and their different response to the presence of lung tumors: Rats can live a large part of their lives with a lung tumor without dying from the tumor; this may be due to slow cell growth. This observation is of great importance for the analysis of such data (*6*), and each tumor in the PNNL rats has therefore been classified as incidental or fatal. While the first analysis of this data set with a clonal expansion model treated all lung tumors as incidental (*7*), recent work differentiates between them:

Gilbert *et al.* (*8*) used an excess risk model with a spontaneous hazard proportional to a power of age in which the exponent is allowed to be different for fatal and for incidental tumors. They found an "inverse exposure-rate effect" at exposures exceeding 1000 WLM.[1] For lower exposures they did find "modest evidence" for this effect for epidermoid and adenosquamous carcinomas but not for all malignant lung tumors.

Luebeck *et al.* (*9*) used the two-step clonal expansion model and a likelihood which treats incidental and fatal tumors differently; their model does not predict the number of observed fatal or incidental tumors, only the hazard of

[1] One working level (WL) equals any combination of radon progeny in 1 liter of air which results in the ultimate emission of 130,000 MeV of energy from α particles. Working level months is a time-integrated measurement of exposure and is the product of time, in units of working months, which is taken as 170 h, and WL. In terms of SI units, 1 WLM corresponds to 3.5×10^{-3} J h m^{-3}. Residents in an average house (46 Bq m^{-3}) would experience roughly 0.2 WLM/year.

TABLE 1
Number of Lung Tumors in the Data Set

Tumor type	Cases	Fatal
Malignant lung tumor	421	174
Adenocarcinomas	301	74
Epidermoid carcinomas	104	68
Adenosquamous carcinomas	36	15
Sarcomas	35	18

Note. There are rats with several malignant tumors, and one with two fatal tumors.

a detectable tumor. Their preferred model has a stepwise increase in the effective clonal expansion rate with exposure rate. This shape is largely responsible for the inverse dose-rate effect found in their model with their estimated parameters. Uranium ore dust is always administered with radon exposure in the animals used in the study. The authors suggest that the dust is responsible for the step in clonal expansion, and therefore also for the inverse dose-rate effect.

We follow here this work of Luebeck, Moolgavkar and colleagues (*7, 9*) insofar as we also use a stochastic clonal expansion model to describe the data. But our approach differs in several respects: (a) There are more rats included in our data set; (b) we use identifiable parameters (*5*); and, most importantly, (c) we separate the modeling between appearance of a fatal or incidental tumor. Thus we estimate parameters for models which allow us to predict the hazard for fatal tumors and the hazard for incidental tumors separately. This also changes the likelihood, compared to the one used in ref. (*9*), with the four end points fatal tumor, no fatal tumor, incidental tumor and no incidental tumor.

MATERIALS AND METHODS

Data Set

We use the Pacific Northwest National Laboratory data set for 4276 rats exposed to radon. Of these 3726 lived out their life span, 418 were sacrificed according to a planned schedule, 127 were euthanized for humanitarian reasons, and 5 were killed accidentally. A total of 487 rats developed at least one lung tumor. In Table 1 the number of malignant lung tumors among these is given, together with some sub-classification. For 16 rats in the data set, it is unknown whether they had a lung tumor or not; these rats were not used in our work. For each malignant lung tumor the pathologist (in most cases G. E. Dagle) decided whether it was fatal or incidental. The tumor was considered fatal if one of the following criteria was satisfied:[2] (1) metastasis; (2) tumor size: depends on structure affected, but generally >1.5 cm diameter in the rat; (3) marked necrosis, affecting ≥50% of the lesion, with marked hemorrhage; (4) extensively invasive (into pleura, bronchi, blood vessels).

For each animal, the data set gives the exposure in WLM,[3] the uranium ore dust concentration in mg/m^3, the age (in days) at the beginning of exposure (t_b), the age at the end of exposure (t_e), and the survival time from the start of exposure (t_s). For each animal and for the four malignant lung tumor types of Table 1 there is also information on whether the tumor was present at death and was classified as fatal or incidental. Further data are given but are not used in our parameter estimation. For the description of the data, we also use the death code (natural death, sacrificed, etc.) and the nominal exposure rate.

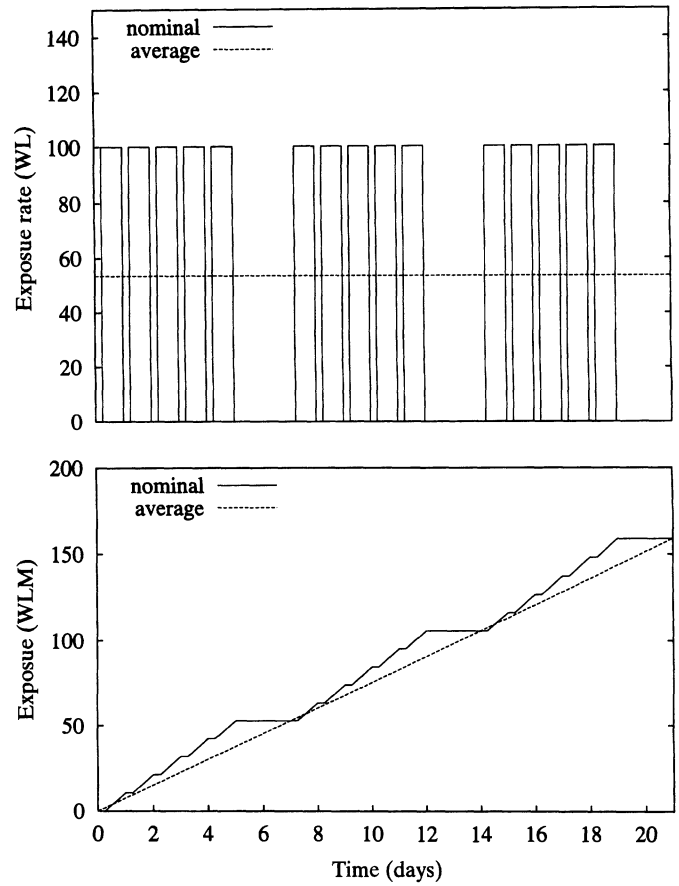

FIG. 1. Nominal and average exposure rates and cumulative exposures used in these calculations with a 3-week exposure as an example.

All exposed rats were between 75 and 110 days old (i.e. adults) at the beginning of exposure. Most rats were given constant exposure rates for 18 h/day for 5 days per week for between 2 and 705 days. Following earlier work (*7, 9*), we do not use the nominal exposure rates given in the file for fitting purposes, but we calculate average exposure rates d from the total exposure D, and the period of exposure using the formula (t_b, t_e in days)

$$d[\mathrm{WL}] = \frac{D[\mathrm{WLM}] \cdot 7.08}{(t_e - t_b)}. \quad (1)$$

One WLM is defined as an exposure at a rate of 1 WL for 170 h, or 7.08 days. A graphical presentation of the time pattern of the exposure and of the effect of this averaging is given in Fig. 1.

Groups of rats have been exposed to certain levels of exposure rate and of total exposure. In Table 2 the number of rats which lived out their life span and the numbers of malignant and fatal tumors are given for these groups. There is a clear increase in malignant and in fatal tumors with exposure, but no obvious dependence on exposure rate.

The decrease in the fraction of malignant tumors compared to all deaths in older rats (see Table 3) is related to a smaller probability for highly exposed rats to reach older ages. There is an evident decrease in the fraction of fatal tumors compared to malignant tumors as a function

[2] G. E. Dagle, P. Fritsch, F. F. Hahn, J. R. Maisin, R. Masse, M. Morin, G. Patrick and C. L. Sanders, Report of Joint U.S. Department of Energy Biological Effects Task Group and European Late Effects Project Group (BETG/EULEP) Workshop on Lung Pathology, October 12–13, 1992. *European Late Effects Project Group Newsletter*, vol. 73, pp. 24–30, 1993.

[3] The conversion of the unit WLM into SI units and the relationship between exposure and lung dose is discussed e.g. in ref (*10*).

TABLE 2
Number of All Rats That Lived Their Life Span, Rats with Malignant Tumors, and Rats with Fatal Tumors

Exposure (WLM)	Nominal exposure rate (WL)						Total
	0	10	100	250	500	1000	
0	554/7/5	—	—	—	—	—	554/7/5
20	—	—	522/9/4	—	—	—	522/9/4
40		—	460/9/6	—	—	—	460/9/6
80		348/8/3	365/15/5	—	—	—	713/23/8
160		—	174/6/1	—	—	—	174/6/1
320		101/17/5	236/14/7	—	—	200/17/3	537/48/15
640		—	141/24/6	21/3/0	21/5/3	131/11/2	314/43/11
1250		—	32/17/8	—	—	37/11/2	69/28/10
2500		—	32/22/16	—	30/15/7	84/28/11	146/65/34
5000		—	32/25/15	—	114/65/36	39/19/6	185/109/57
10,000		—	—	—	—	52/32/13	52/32/13
Total	554/7/5	449/25/8	1993/141/68	21/3/0	165/85/46	543/118/37	3726/379/164

of age: As animals with incidental tumors, by definition, are not dying of the tumor, these animals can accumulate. A more detailed description of the experiment can be found in ref. (*8*).

The age at death of the rats that lived out their life span is given in Table 4. The average lifetime of the control rats was 771 days. Rats exposed to up to 160 WLM lived longer, on average. We calculate the mean age in each group, and the standard error of the mean age, using

$$\sqrt{\frac{\overline{x^2} - \bar{x}^2}{N}}. \tag{2}$$

(The numerator is an approximation of the standard deviation of the sample.) There is a slight increase in mean age for low exposures, and a clear decrease for high exposures, when compared to no exposure. The age dependence of the estimated survival of the rats that lived out their life span is given for some of the exposure groups in Fig. 2. There is an increase in life span at low exposures that cannot be attributed to differences in treatment during the experiment. The rats with the highest exposures have clearly shortened average lifetimes, down to 541 days for the rats with 10,000 WLM exposure.

Data Selection

Only a subset of the available information was extracted from the data set and compared with the predictions of the model. We ignored the 16 rats with unknown malignancies. There were 32 rats which had incidental tumors in addition to a fatal tumor; one rat had two fatal tumors. For the risk estimation we classified a rat as having (a) a fatal tumor if it had at least one fatal tumor and (b) an incidental tumor if it had at least one incidental malignant tumor.

It would be interesting to model the tumor types given in Table 1 separately, and we hope to do this in the future; for radiation protection purposes, all malignant or all fatal lung tumors are the more relevant quantity.

TABLE 3
Number of Rats That Lived Their Life Span in Intervals of Age at Death

Age (days)	All deaths	Malignant	Fatal	Fatal/ malignant
0–100	0	0	0	
101–200	22	0	0	
201–300	31	2	2	1.00
301–400	74	5	5	1.00
401–500	131	10	6	0.60
501–600	296	41	19	0.46
601–700	602	83	38	0.46
701–800	860	101	45	0.45
801–900	913	80	29	0.36
901–1000	567	36	13	0.36
1001–1100	188	18	7	0.39
1101–1200	37	3	0	0.00
>1200	2	0	0	

Note. The numbers of malignant tumors and of fatal tumors and the fractions of fatal tumors are also given.

Models

1. Stochastic clonal expansion model

The stochastic clonal expansion model is often named after Moolgavkar, Venzon and Knudson (MVK model). As described in the Introduction, it has been applied before to the PNNL data for rats. The biologically motivated parameters of the model are the product ν of the number of susceptible cells and the first initiating mutation rate, parameters α and β for the rates of the birth (α) and death (β) process of intermediate cells, and the second mutation rate μ. Each of these parameters can depend on the exposure rate d.

From incidence data, not all of these parameters can be obtained for constant parameters, even in principle (*11, 12*). This result was extended to piecewise constant parameter sets and arbitrary exposure patterns (*5*). If arbitrary exposure rates are considered, the parameters are replaced by parameter functions of the exposure rates. As shown in ref. (*5*), an identifiable set of parameter functions is

$$\begin{aligned} Y(d) &= \nu(d)\mu(0), \\ m(d) &= \mu(d)/\mu(0), \\ \gamma(d) &= \alpha(d) - \beta(d) - \mu(d), \\ \tilde{B}(d) &= \sqrt{\gamma^2(d) + 4\alpha(d)\mu(d)} - \gamma(d). \end{aligned} \tag{3}$$

These functions are selected such that the changes of the mutation rates can be read off directly; the mutation rates themselves [e.g. $\mu(0)$] cannot be identified from incidence data.

The dependence of these parameters on exposure rate can be mathematically arbitrary and can be brought into agreement with the experimental incidence data with arbitrary precision, limited only by the quality of the data set (*5*). We assume that the first, initiating mutation rate depends linearly on radon exposure rate, with possible effects of killing of mutated cells, in the form (*13*)

$$Y(d) = Y_0[1 + Y_1 d \exp(-Y_2 d)], \tag{4}$$

and that the second mutation rate also depends linearly on the radon exposure rate,

TABLE 4
Mean Age ± SE in Days of the Rats That Lived Their Life Span

Exposure (WLM)	Nominal exposure rate (WL)						Total
	0	10	100	250	500	1000	
0	771 ± 7	—	—	—	—	—	771 ± 7
20	—	—	800 ± 7	—	—	—	800 ± 7
40	—	—	826 ± 7	—	—	—	826 ± 7
80	—	775 ± 9	786 ± 8	—	—	—	780 ± 6
160	—	—	813 ± 11	—	—	—	813 ± 11
320	—	802 ± 15	776 ± 11	—	—	711 ± 11	757 ± 7
640	—	—	792 ± 16	633 ± 28	720 ± 30	673 ± 15	727 ± 10
1250	—	—	822 ± 24	—	—	734 ± 31	774 ± 21
2500	—	—	726 ± 22	—	687 ± 20	678 ± 20	691 ± 13
5000	—	—	703 ± 21	—	565 ± 18	673 ± 20	612 ± 13
10,000	—	—	—	—	—	541 ± 18	541 ± 18
Total	771 ± 7	781 ± 7	799 ± 3	633 ± 28	607 ± 14	679 ± 7	766 ± 3

$$m(d) = 1 + m_1 d. \tag{5}$$

For the effective clonal expansion rate $\gamma(d)$ we assume a linear increase with exposure rate, with a saturation term. Sometimes we also allow an additional term for the effect of uranium dust and assume it to be constant, as suggested by Luebeck *et al.* (*9*),

$$\gamma(d) = \gamma_0 + \gamma_2\left(1 - \exp\left(-\frac{\gamma_1}{\gamma_2}d\right)\right) + \gamma_3 \text{ (if dust)}. \tag{6}$$

Note that the second summand behaves like $\gamma_1 d$ for low exposure rates and becomes a constant value γ_2 for large ones. The parameter function $\tilde{B}(d)$ describes the asymptotically constant hazard for older ages $Y(d)/\tilde{B}(d)$. As most rats were not exposed toward the end of their natural lifetime, we do not expect that $\tilde{B}(d)$ can be determined from the data as more than a constant

$$\tilde{B}(d) = q. \tag{7}$$

This parameter is characteristic of the stochastic model. For asymptotically long times after the end of exposure, the hazard rate levels off to $Y(0)/q$. A deterministic formulation does not have a constant asymptotic hazard (*11*).

The formulas for calculating the hazard rate h and the probability ψ of no malignant cells are given explicitly in ref. (*5*). The hazard rate is defined as usual by

$$h(t) = -\frac{\dot{\psi}(t)}{\psi(t)}. \tag{8}$$

We use a lag time t_l between the appearance of the first malignant cell and the time when a tumor is observable; then the probability of no tumor Ψ for each rat is

$$\Psi(t) = \psi(t - t_l), \tag{9}$$

and a corresponding time shift in the hazard for an observable tumor. This lag time is estimated from the data.

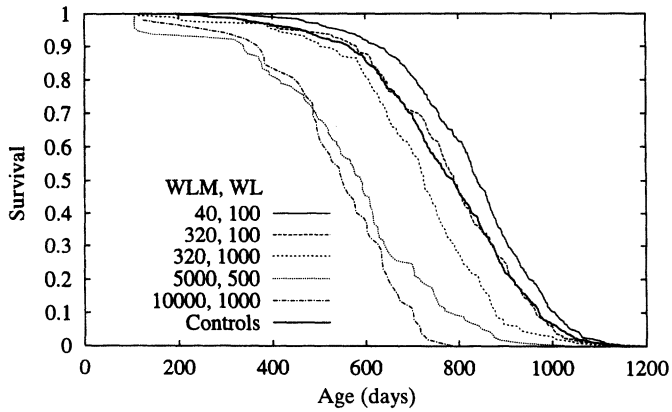

FIG. 2. Survival rate of the rats that lived their life span for some of the classes according to exposure and nominal exposure rate.

2. Excess relative risk model

For comparison, we also consider a simple heuristic model describing the rate of spontaneous cancer with a power function of age, and assuming that the excess relative risk (ERR) is a linear function of cumulative exposure D up to death:

$$h(t) = ft^p(1 + kD). \tag{10}$$

This hazard function is similar to the simplest version in Gilbert *et al.* (*8*). Using the integrated form of Eq. (8), we get

$$\ln \psi(t) = -\frac{f}{p+1}t^{p+1} - fkd\begin{cases} 0 & t < t_b \\ A(t) & t_b < t < t_e \\ A(t_e) + \dfrac{1}{p+1}(t_e - t_b) & \\ \quad \times (t^{p+1} - t_e^{p+1}) & t > t_e, \end{cases} \tag{11}$$

with

$$A(t) = \frac{1}{p+2}(t^{p+2} - t_b^{p+2}) - \frac{t_b}{p+1}(t^{p+1} - t_b^{p+1}). \tag{12}$$

No attempt has been made in this paper to optimize this model. Therefore, we did not introduce a lag time in this case.

Likelihoods

We estimate two probabilities of no tumor, Ψ_F for the fatal tumors, and Ψ_I for the incidental tumors. They require different likelihoods. For fatal tumors we use

$$\ln L_F = \sum_{\text{no fatal tumor}} \ln \Psi_{Fi} + \sum_{\text{fatal tumor}} \ln(h_{Fi}\Psi_{Fi}), \tag{13}$$

and for incidental tumors we use

TABLE 5
Values of the Deviance for the Various Parameter Estimates

Model	Fatal	Incidental
MVK	2207.3	1437.0
ERR	2256.8	1452.7

$$\ln L_I = \sum_{\text{no incidental tumor}} \ln \Psi_{Ii} + \sum_{\text{incidental tumor}} \ln(1 - \Psi_{Ii}). \quad (14)$$

The corresponding deviance in both cases is (*14*)

$$\text{Dev} = -2 \ln L. \quad (15)$$

In these likelihood functions, the surviving probability is used if no tumor was found at death, and the probability of having developed a tumor up to the given age is used for an incidental tumor. The contribution of a fatal tumor to the likelihood is the probability $-\dot{\Psi}\delta t = h\Psi\delta t$ of developing a tumor at given age in the age interval δt. As we use as the time unit one "week", δt was fixed at 1 week. The value of the likelihood depends on the value chosen for δt, but the parameter estimates and the estimated uncertainties do not. With this separation of fatal and incidental tumors we can calculate expected numbers of fatal and incidental tumors for a given subset of animals.

These likelihoods are different from earlier work: Moolgavkar *et al.* (*7*) treated all malignant tumors as incidental and Luebeck *et al.* (*9*) used a likelihood, which has one hazard function for both incidental and fatal tumors, but different contributions to the likelihood:

$$\ln L = \sum_{\text{no malignant tumor}} \ln \Psi_i + \sum_{\text{incidental tumor}} \ln(1 - \Psi_i) + \sum_{\text{fatal tumor}} \ln(h_i \Psi_i). \quad (16)$$

This approach does not allow one to calculate expected numbers of tumors.

Quality of Fit

The likelihood of the best fit is only a crude measure (if any at all) for comparing different models. To obtain a better way for judging the quality of our fits, we formed cohorts and compared the observed number of cases with the predicted number in the various groups. We used (1) age intervals of 50 days for ages up to 1200 days, and one group for age greater than 1200 days, and (2) the exposure and exposure-rate groups given in Table 2. In addition to the rats used for estimating parameters, there is also a group of 96 rats which were exposed to uranium dust but not to radon (*2*). As individual lifetimes were not available for this group, we used lifetimes from the controls to calculate the expected number of tumors for this group with our models.

The expected number of fatal tumors in each class is calculated by subtracting the cumulated hazard of a fatal tumor for each rat,

$$\int_{t_1}^{t_2} h(t)\, dt = \ln \Psi(t_1) - \ln \Psi(t_2), \quad (17)$$

at the upper end of the interval or observed time of death t_2, and at the lower end of the interval t_1, and summing over all rats. For incidental tumors, we calculated in each class the expected number of tumors by summing the tumor probabilities of all rats in that class which died. These numbers of expected cases were compared with the observed numbers in the usual way.

For each age class, we calculated the number of observed and expected cancer cases by summing over all exposures and exposure rates, and for each class of exposure and exposure rate, we summed over all ages. For these sums the Poisson-likelihood values of the observed numbers were determined. In this way of presenting the results, we follow the advice given by Peto *et al.* (*6*) for significance testing in animal experiments.

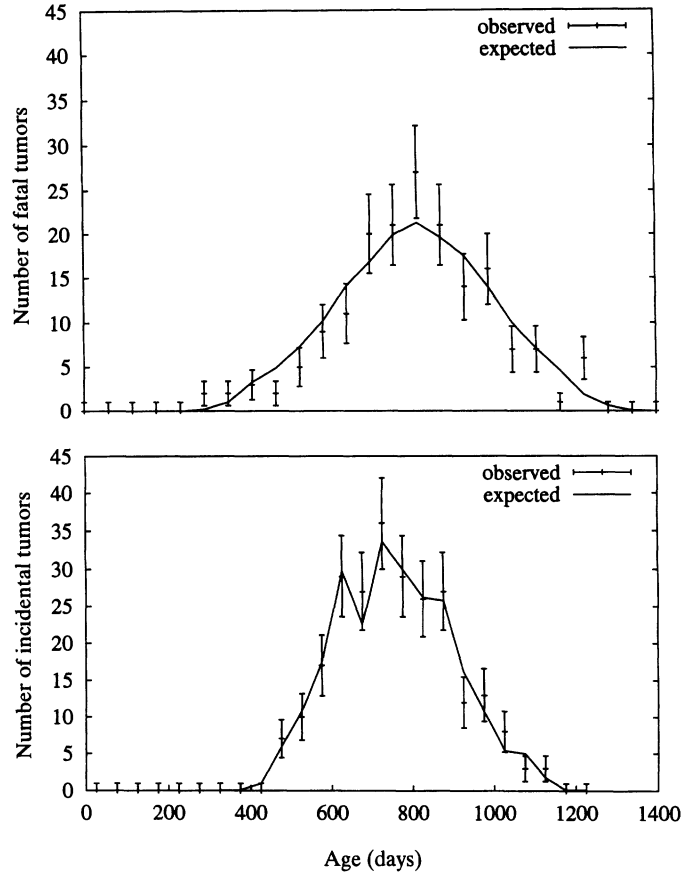

FIG. 3. Observed and expected number of fatal and of incidental tumors (per 50 days) as a function of age in the MVK model. The error bars are calculated from the square root of the number of cases or are 1 if there is no case within a class.

RESULTS

The main model we considered first has no step function in the term describing the exposure to dust, i.e. $\gamma_3 = 0$ in Eq. (6). The deviances of our various parameter estimates are given in Table 5. The ERR model has fewer parameters and gives a poorer fit. In Fig. 3 we give the observed number of tumor cases for intervals of 50 days and the number expected in the MVK model for both fatal and incidental tumors. In Table 6 we give the same numbers for the exposure and exposure-rate classes. In Table 7 we give the Poisson-likelihood values for the various models, summed over all exposures and exposure rates, respectively, over all ages. As can be seen, both the age dependence and the exposure dependence are described well by the clonal expansion models.

In Table 6 we also give the expected number of spontaneous fatal tumors based on the MVK model. From this, we calculate for each class the excess relative risk per unit exposure, based on the observed number and the predicted

TABLE 6
Observed and Expected Number of Fatal and Incidental Tumors as a Function of Exposure and Nominal Exposure Rate in the MVK Model with Two Selections in Each Case

Exposure (WLM)	Rate (WL)	Incidental		Fatal			ERR per 100 WLM	
		Observed	Expected	Observed	Expected	Spontaneous	Model	Observed
0	0	2	2.8	5	4.2	4.15		
20	100	5	4.5	4	4.9	4.16	0.9	−0.2 (−2.6–2.2)
40	100	3	5.9	6	6.0	4.38	0.9	0.9 (−0.5–2.3)
80	10	5	7.2	3	4.1	2.57	0.8	0.2 (−0.6–1.1)
80	100	10	6.7	5	4.7	2.68	1.0	1.1 (0.0–2.1)
160	100	5	5.9	1	3.6	1.43	0.9	−0.2 (−0.6–0.3)
320	10	14	7.3	5	2.6	0.97	0.5	1.3 (0.6–2.0)
320	100	11	14.4	7	7.5	1.72	1.0	1.0 (0.5–1.4)
320	1000	15	8.7	5	2.7	0.91	0.6	1.4 (0.6–2.2)
640	100	18	16.6	6	10.6	1.25	1.2	0.6 (0.3–0.9)
640	250	4	1.9	1	0.3	0.04	1.1	3.5 (−0.2–7.1)
640	500	4	2.7	3	1.0	0.14	1.0	3.3 (1.3–5.3)
640	1000	14	12.1	4	3.2	0.50	0.8	1.1 (0.5–1.7)
1250	100	9	7.0	8	5.9	0.28	1.6	2.2 (1.4–3.0)
1250	1000	9	6.2	2	2.5	0.26	0.7	0.5 (0.1–1.0)
2500	100	6	8.6	16	10.6	0.14	3.0	4.5 (3.3–5.6)
2500	500	8	8.9	7	7.4	0.07	4.0	3.7 (2.3–5.1)
2500	1000	25	27.1	12	14.5	0.35	1.6	1.4 (0.9–1.8)
5000	100	10	8.7	15	18.3	0.09	4.1	3.4 (2.5–4.2)
5000	500	31	36.8	37	36.5	0.19	3.7	3.8 (3.2–4.4)
5000	1000	17	18.7	6	7.1	0.10	1.4	1.2 (0.7–1.7)
10,000	1000	22	23.7	16	15.6	0.04	3.8	3.9 (2.9–4.9)
0	dust only	0	0.3	0	0.3	0.31		

Notes. For fatal tumors the expected number of spontaneous tumors is also given. From this number and the expected compared to the observed number of fatal cases, the ERR per 100 WLM is calculated. The uncertainty given in parentheses is ±1 SE, calculated from the uncertainties of the observed cases only.

number of fatal tumors. The confidence region given contains only one standard error of the observed number of cases. Nevertheless, the agreement is good in most classes.

In Table 8 the derived parameters are presented for the excess relative risk model and the clonal expansion model for fatal and incidental tumors. In Fig. 4 the shape of the corresponding parameter functions $Y(d)$ and $\gamma(d)$ is plotted as a function of the radon exposure rate. The estimated exposure dependence is very different for fatal and incidental tumors, although the same functional form was used in both cases.

With the estimated parameters we have a complete description of the model for the hazard of fatal and of incidental tumors. In Fig. 5 we give the hazards for various exposure patterns [the same as used by Luebeck *et al.* (*9*)] for the MVK model for fatal and incidental tumors. After the exposure, the hazard function for fatal tumors is much more dependent on age than that for incidental tumors. The hazard function for incidental tumors becomes almost con-

TABLE 7
Values of the Poisson Likelihood for the MVK and the EER Model When Summed over All Exposures over All Ages

Model	Fatal	Incidental
Age classes		
MVK	25.47	8.30
ERR	22.70	20.87
Exposure classes		
MVK	17.38	21.36
ERR	55.00	20.31

Note. There are 25 age classes and 23 exposure classes.

TABLE 8
Parameters for the Fatal and Incidental Hazard Functions

Parameter	Fatal tumors	Incidental tumors
ERR		
$f\ (w^{-(1+p)})$	$(0.26 \pm 0.62) \times 10^{-13}$	$(0.12 \pm 0.20) \times 10^{-7}$
p	4.8 ± 0.49	1.9 ± 0.35
k (WLM)	$(0.30 \pm 0.11) \times 10^{-1}$	$(0.62 \pm 0.34) \times 10^{-1}$
MVK		
$Y_0\ (w^{-2})$	$(0.59 \pm 0.23) \times 10^{-7}$	$(0.10 \pm 0.07) \times 10^{-5}$
$Y_1\ (\mathrm{WL}^{-1})$	0.34 ± 0.10	1.9 ± 1
$Y_2\ (\mathrm{WL}^{-1})$	$(0.9 \pm 0.7) \times 10^{-3}$	$(0.30 \pm 0.38) \times 10^{-3}$
$\gamma_0\ (w^{-1})$	$(0.63 \pm 0.04) \times 10^{-1}$	$(0.57 \pm 1.3) \times 10^{-2}$
$\gamma_1\ (w^{-1}\ \mathrm{WL}^{-1})$	$(0.19 \pm 0.07) \times 10^{-2}$	0.23 ± 0.55
$\gamma_2\ (w^{-1})$	0.17 ± 0.02	$(0.52 \pm 0.20) \times 10^{-1}$
$m_1\ (\mathrm{WL}^{-1})$	$(0.18 \pm 0.35) \times 10^{-2}$	$(0 \pm 0.5) \times 10^{-3}$
$t_1\ (w)$	23 ± 2	30.6 ± 4.6
$q\ (w^{-1})$	$(0.16 \pm 0.07) \times 10^{-4}$	$(0.19 \pm 0.19) \times 10^{-2}$

Note. The parameter ranges given correspond to ±1 SE, calculated from the Hesse matrix at the best-fitting value.

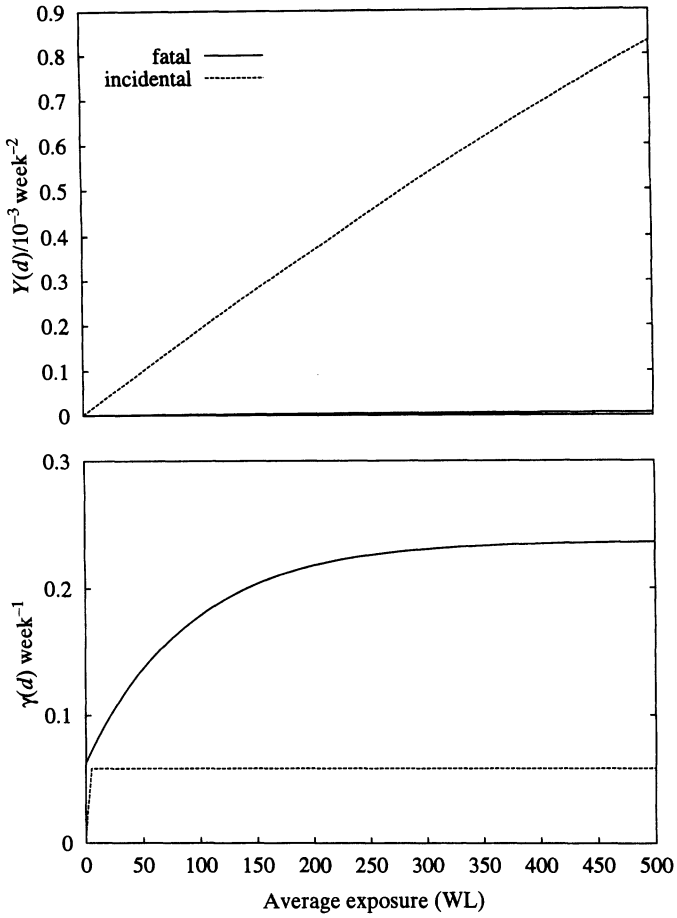

FIG. 4. Dependence of the parameters for initiation and clonal expansion on average exposure rate.

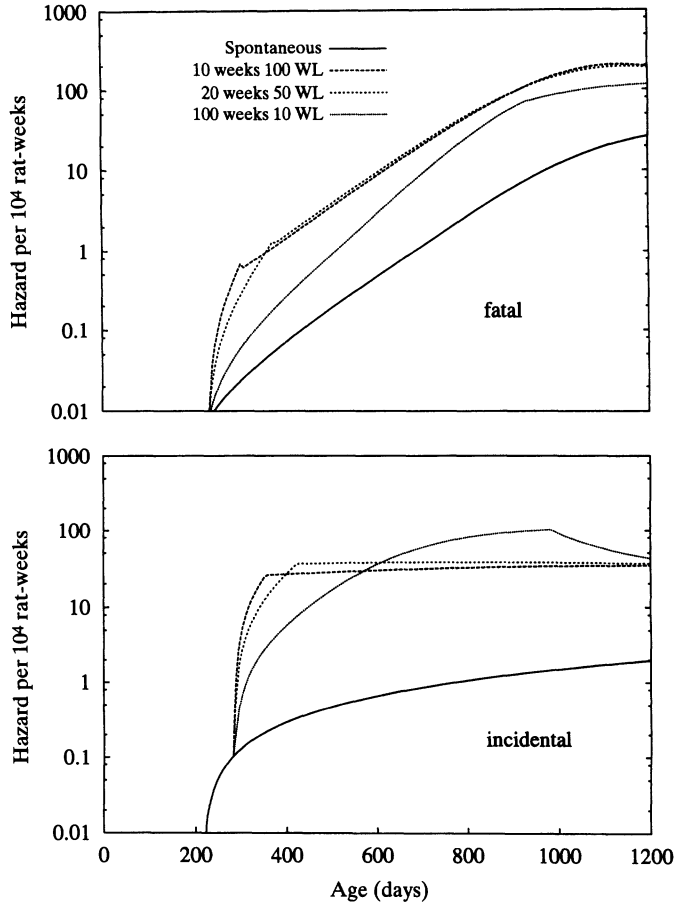

FIG. 5. Comparison of the fitted hazards for fatal and incidental tumors in various patterns of average exposure rate and exposure duration.

stant with age for the exposures with high exposure rates. The large effect of the low exposure rate comes from the step-like dependence of the effective clonal expansion rate.

In addition to estimating separate parameter values for fatal and incidental tumors, we also tried to model incidental and fatal tumor risks identically up to the state of one malignant cell and then assumed that a fixed fraction of these cells become a fatal tumor and the others develop into an incidental tumor. However, due to the large differences in the age dependence of the hazard functions, this attempt was not satisfactory.

DISCUSSION

We conclude from the different age and exposure dependence of the fatal and incidental hazard functions that they should be described separately. It could be that the development of a malignant cell into a fatal or an incidental tumor depends in a complicated way on age or on other external conditions, which do not give a fixed ratio. An alternative interpretation would be that different pathways are responsible for the two classes of tumors. For inferences regarding radiation protection for humans, we consider the analysis of the fatal tumors in rats to be more relevant than the incidental ones.

All the parameters derived carry large uncertainties; the data set is not really able to estimate so many of them reliably. However, some points can be seen:

1. The incidental tumors have a longer lag time than the fatal tumors.
2. Spontaneous parameters: The fatal tumors seem to have smaller mutation rates (Y_0) but a larger growth rate γ_0 for intermediate cells.
3. For fatal tumors, the cell-killing parameter Y_2 is not significantly different from 0. If it is forced to vanish, the best fit gives almost the same deviance of 2208.4, or $\Delta\text{Dev} = 1.2$.
4. The exposure rate which doubles the mutation rates is one of the identifiable parameters in our model. For the initiating mutation, the relevant parameter is Y_1. The doubling exposure rate for fatal tumors was found to be 3 WL, and for incidental tumors it is only 0.5 WL. The latter value was also found by Luebeck *et al.* (*9*) in their previous analysis of these data. The second mutation rate is characterized by m_1. This gives a lower bound for the doubling exposure of more than 250 WL for fatal tumors and more than 2000 WL for incidental tumors.

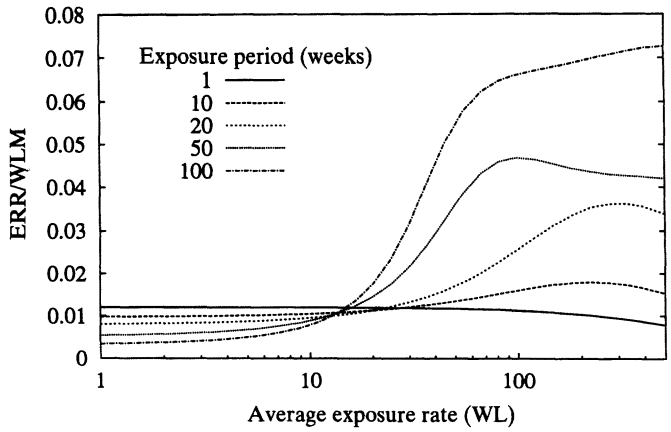

FIG. 6. The fitted excess relative risk per WLM for fatal lung tumors at an average lifetime for rats exposed from an age of 10 weeks for 1–100 weeks.

The large differences between the doubling exposure rates for the two mutations suggest a different biological nature of the two events.

5. In both cases, there is apparently no significant effect of radiation on the second mutation rate. For the fatal tumors, setting $m_1 = 0$ gives only a $\Delta\text{Dev} = 0.6$. Setting both m_1 and Y_2 to zero has a $\Delta\text{Dev} = 1.6$. This is a simpler model for fatal tumors.
6. There is a leveling off of the hazard rates at high ages; see Fig. 5. The stochastic parameter q (see Eq. 7) is significantly different from zero. Setting it to zero for fatal tumors gives a large $\Delta\text{Dev} = 11.7$.
7. For incidental tumors, the shape of the parameter function $\gamma(d)$ points to the usefulness of an indicator function for dust as proposed by Luebeck *et al.* (*9*); see Fig. 4. If γ_3 is allowed to vary, the best fit (with $\Delta\text{Dev} = -8.9$) has a negative value for γ_0 and a negative constant slope with exposure. This could be a further indication that uranium dust causes the promotion of incidental tumors.
8. The situation is different for fatal tumors: There the indicator γ_3 in Eq. (6) results in a value of $\gamma_3 = 0.013 \pm 0.011$ (w^{-1}), with a $\Delta\text{Dev} = -1.0$. This is not significant, especially as we have one additional parameter in the model. But it does not rule out completely the possibility of a small effect of uranium dust. A misclassification of some incidental tumors as fatal could also be the reason for the nonvanishing γ_3.

For comparison with radiation risk patterns in humans, we use only the analysis of fatal tumors in rats. A possible dose-rate effect is important when interpolating risk estimates for miners to indoor radon. To investigate such effects in our model for the PNNL rats, we considered the excess relative risk per exposure (in WLM) at an age of 110 weeks (close to the average lifetime of the control rats). The result is plotted in Fig. 6 for various durations of exposure. As can be seen, the model has a smaller ERR per exposure for longer-lasting exposures if the exposure rates are up to about 10 WL. This means a value of greater than 1 for the DDREF. Above about 20 WL exposure rate, the situation is reversed: More extended exposure periods have higher values of ERR per exposure; i.e., the model shows an inverse dose-rate effect. The quantity given here differs in some respects from the one given before in Table 6, but nevertheless the table gives related information on the ERR/WLM. The average exposure rates used in Fig. 6 are about half the value of the nominal exposure rates used in Table 6. Data exist at average exposure rates of 5, 50, 125, 250 and 500 WL. At 5 WL there are two classes of total exposure, namely 80 WLM and 320 WLM. The values of 3 and 5 observed fatal tumors after 80 and 320 WLM, respectively, are not sufficient to check the dose-rate effect directly from the data, but they do not contradict the conclusions. We stress that the precise exposure rate at which the reversal of the dose-rate effect occurs and the magnitude of the effect at low exposure rates are extrapolations of the model from higher exposure rates and therefore must be considered cautiously.

From the miners, an ERR/WLM of about 0.005 (95% confidence level 0.002–0.01) has been derived, which is modified by many variables (ref. *15*, Fig. 8). From a meta-analysis of eight epidemiological studies of residential radon, an ERR of 0.14 for 150 Bq/m^3 has been derived (*16*). If 25 years of exposure at 231 Bq/m^3 corresponds to 25 WLM, as used in that paper, this corresponds to an ERR/WLM of 0.009 (95% confidence level 0–0.02). According to Fig. 6, for rats at low exposure rates the fitted ERR/WLM is in the range of 0.003 to 0.012, depending on the exposure period. Thus the relative risk for radon-induced lung tumors in rats and humans is of the same order of magnitude.

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