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RADIATION RESEARCH **118,** 230–245 (1989)

Lung Carcinomas in Sprague–Dawley Rats after Exposure to Low Doses of Radon Daughters, Fission Neutrons, or γ Rays

J. LAFUMA,* D. CHMELEVSKY,† J. CHAMEAUD,‡ M. MORIN,* R. MASSE,* AND A. M. KELLERER§

*Institut de Protection et de Sûreté Nucléaire, B.P.6, F-92260 Fontenay aux Roses, France
†Institut für Strahlenschutz (GSF), Ingolstädter Landstrasse 1, D-8042 Neuherberg, Federal Republic of Germany
‡COGEMA, Laboratoire de Pathologie Expérimentale, B.P.1, F-87640 Razès, France
§Institut für Med. Strahlenkunde, Versbacher Strasse 5, D-8700 Würzburg, Federal Republic of Germany

LAFUMA, J., CHMELEVSKY, D., CHAMEAUD, J., MORIN, M., MASSE, R., AND KELLERER, A. M. Lung Carcinomas in Sprague–Dawley Rats after Exposure to Low Doses of Radon Daughters, Fission Neutrons, or γ Rays. *Radiat. Res.* **118,** 230–245 (1989).

The effectiveness of radon-daughter inhalation and irradiation with fission neutrons and γ rays in the induction of lung carcinomas in Sprague–Dawley rats at low doses is compared. Earlier reports which compared radon-daughter inhalations and neutron irradiations over a wider range of doses were based on dosimetry for the radon-daughter inhalations which has recently been found to be faulty. In the present analysis, low-dose experiments were designed to derive revised equivalence ratios between radon-daughter exposures, and fission neutron or γ irradiations. The equivalence is approximately 15 working level months (WLM) of radon daughters to 10 mGy of neutrons (the earlier value was 30 WLM to 10 mGy). The relative biological effectiveness (RBE) of neutrons is 50 or more at a γ-ray dose of 1 Gy. In these experiments with low doses and exposures, the lifetime incidences can be estimated from the raw incidences, while the derivation of the time dependence of the prevalence is essential for the estimation of RBE values and equivalence ratios.

INTRODUCTION

A current study at CEA (Commissariat à l'Energie Atomique) has been designed to compare induction of tumors in male Sprague–Dawley rats by exposure to radon daughters, fission neutrons, or γ rays. Although the study, particularly the high-dose experiments, will not be complete for several years, current interest in the relative biological effectiveness (RBE) of low doses of densely ionizing radiations and especially in the cancerogenic potential of low doses of radon (*1*) makes it desirable to present the essential findings from the low-dose part of the study now.

An added reason for this intermediate report is that it is necessary to make known changes in earlier results (*2, 3*) because these results were based on a faulty determination of the radon-daughter exposures. The revised dosimetry indicates lower radon-daughter exposures in past experiments than previously assumed. This change is substantiated by the results which are reported here and which indicate an equivalence ratio of radon-daughter inhalation relative to neutrons somewhat lower than that

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reported earlier. The equivalence ratio has been defined in (*3*) as the ratio of radon exposure and neutron dose that produce equal prevalences of lung carcinomas.

MATERIALS AND METHODS

Details of the investigations at CEA have been described in a number of reports (*2–10*). The experimental procedures may be summarized as follows.

All experiments were performed with male Sprague–Dawley rats. The animals were 3 months old (±2 weeks) at the beginning of the experiments. The animals were kept eight per cage under standard laboratory conditions (*5*). There was no random assignment of animals from different dose groups to cages, because the rats exposed to higher doses could not be kept with controls or with those animals that were exposed to lower doses.

Animals were observed daily and remained in the experiment until moribund. The lungs were fixed in Bouin–Holland fluid when gross lesions were observed or when more subtle changes, such as granulomas, were detected by palpation. The lungs were then embedded in paraffin blocks.

Serial sections, 20 μm apart, were taken until conspicuous lesions were detected; 5-μm sections were then taken from these lesions, and these were processed by conventional techniques.

Radon-Daughter Inhalations

The radon-daughter-inhalation studies were started first. They were part of a larger program to investigate the effectiveness of various α-emitters in inducing lung cancer in rats.

The experiments were performed in an inhalation chamber which was modified in 1972 (for a description see (*11*)). Measurements to determine the degree of equilibrium of radon with its daughters[1] were performed without animals in the inhalation chamber, and these measurements led to the conclusion that equilibrium was reached 3 h after the introduction of radon into the chamber. Only recently, after track detectors originally developed for the French uranium mines became available,[2,3] did it become possible to measure radon-daughter concentrations during the actual exposures. The equilibrium factor was then seen to decrease substantially when animals were present in the chamber.

The radon-daughter exposures had been calculated on the basis of the radon concentrations and the equilibrium factors. When the latter were found to be erroneous, this required simulations of the earlier

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[1] It is difficult to estimate the absorbed dose to the lung resulting from a radon-daughter inhalation. Instead of dose, one therefore utilizes the concept of *radon-daughter exposure*, E_p. This quantity (see Appendix of Ref. (*1*)) is the product of the *potential α-energy concentration*, c_p, and the duration of the exposure. The quantity c_p is defined as the sum of the total α-particle energy to be released by a mixture of short-lived radon daughters per unit volume of air. Its traditional unit, working level (WL), corresponds to 1.3×10^5 MeV/liter; it results from a concentration of 3.7 Bq of ^{222}Rn/liter of air in radioactive equilibrium with its four short-lived daughter nuclides. A familiar unit of the radon-daughter exposure, E_p, is the working level month (WLM) where the time unit, working month, is defined as 170 h. In SI units 1 WLM equals $12.7\ J \cdot m^{-3} \cdot s$.

The *equilibrium factor*, F, is the ratio of the actual value c_p to the value that would prevail if the short-lived radon daughters were in radioactive equilibrium with their mother nuclide, e.g., ^{222}Rn. Thus F determines the conversion factor from the *activity concentration* of ^{222}Rn in air to the *radon-daughter exposure rate* which equals the *potential α-energy concentration*, c_p. One can express this in the following equation between c_p in working level and the activity concentration, a, of radon in bequerel per cubic meter:

$$c_p = 0.27 \cdot 10^{-3} \cdot F \cdot a.$$

[2] P. Zettwoog, State-of-the-art of the alpha individual dosimetry in France. Presented at the International Conference on Radiation Hazards in Mining: Control, Measurement, and Medical Aspects, Golden, Colorado, October 4–9, 1981.

[3] S. Bernhard, J. F. Pineau, A. Rannou, and P. Zettwoog, One year of individual dosimetry in French mines. Presented at the International Conference on Occupational Radiation Safety in Mining, Toronto, Canada, October 14–18, 1984.

experimental conditions. These simulations have not been completed; furthermore, no simulations are possible for the exposure chamber which was used in the earlier inhalation experiments at higher doses. A decision has been made, therefore, to repeat the radon-inhalation experiments at intermediate and higher doses, and this will require several more years. The data for the present analysis are from two new experiments at low radon-daughter exposures.

No report concerning the revision of the radon-daughter dosimetry has been published, but one can make approximate corrections in the earlier results in terms of the equilibrium factors. The values range from 0.9 for the empty chamber, to 0.5 for the chamber with 50 animals, to a limit of 0.25 for the chamber with 500 animals.

The experiments were always done with the ambient aerosol. Measurements of the particle size spectrum and of the unattached fraction of radon daughters were performed, although not routinely. The median particle size was estimated to be 0.8 μm, and values for the unattached fraction[4] between 5 to 10% were found (for a description of the instrumentation, see (*12*)). As various studies have shown (*1, 13*), the unattached fraction significantly influences the dose to the upper part of the bronchial tree. The dose to the distal regions of the lungs is determined predominantly by the attached fraction. The attached fraction was, in the present experiments and according to the measurements, stable within a few percent. Masse (*14*) has argued that only the dose to the distal region of the lung is relevant in Sprague–Dawley rats, since most lung carcinomas originate distally after radon-daughter inhalation. This applies not only to the bronchoalveolar carcinomas but also to the bronchogenic carcinomas. In the present study no attempt was made to estimate, on the basis of the relevant parameters, the bronchial dose, and the reference parameter in the following is the radon-daughter exposure.

Two experiments at low radon exposure are reported here. These experiments took place in 1981. The dosimetry was performed with track detectors.[2,3] Basic data are given in Table I, which also contains information for the neutron and γ-ray experiments.

The rats were exposed to radon in sessions of 1 h, repeated approximately twice a week over 3.3 months for the group with 25 working level months (WLM) (42 sessions) and 6.3 months for the group with 50 WLM (82 sessions). The potential α-energy concentration averaged 100 WL. In these experiments continuous measurements of the potential α-energy concentration during inhalation were performed with three dosimeters positioned at three different heights in each of the two inhalation chambers. The exposure was set equal to the mean of the three dosimeter readings. A correction for the collection efficiency of 80% was applied. The results were compared for consistency with the exposure values obtained from radon-concentration measurements (made by vial samplings) and from measurements of the equilibrium factor (by brief exposures of the track-etch detectors or by the Thomas method).

Neutron Experiments

Technical details of the neutron experiments have been given previously (*15, 16*). The present analysis includes three neutron experiments.

The whole-body neutron exposures were performed in 1979 at the biological irradiation facility of the reactor "Nereid" at CENFAR. This facility permitted the simultaneous exposure of two groups of 20 animals each. The fission-neutron spectrum has been published earlier (*15*); the corresponding weighted and unweighted mean energies are 2.1 and 1.6 MeV. The neutron dosimetry was performed with polyethylene ionization chambers. Two ionization chambers were positioned in each cage, one on the front and one on the back. The ionization chambers were calibrated in the same neutron field against tissue-equivalent ionization chambers with walls 3 mm thick. The doses listed in Table I are mean values for the chambers and are rough estimates of the mean doses in the animals. A substantial γ-ray component was present in addition to the neutrons; it contributed about 25% to the total dose but is not included in the values shown in Table I. The quoted values are averages for animals in two groups of cages exposed simultaneously with somewhat different doses in each of these experiments (see Table I). The two groups in each experiment were pooled for the analysis and were assigned mean doses of 0.016, 0.08, and 0.40 Gy. Although the separate groups differ from their assigned doses by 25% in either direction, it was felt that the small number

[4] The unattached fraction here is the ratio of the unattached activity of ^{218}Po to the total activity of ^{218}Po.

TABLE I

Synopsis of the Experiments

	No. of animals examined (No. of animals at start of experiment)	*Mean lifetime (± SD) (days)*	*No. of animals with lung carcinomas*	*No. of bronchogenic carcinomas*	*No. of bronchoalveolar carcinomas*	*No. of lung sarcomas*	*Mean time to death with lung carcinoma (± SD) (days)*
Controls	579 (586)	754 (±149)	5	4	1	1	901
			Radon daughters				
25 WLM	497 (501)	730 (±135)	11	8	3	—	764 (±119)
50 WLM	496 (500)	737 (±126)	19	16	3	—	742 (±89)
Σ	993		30	24	6	—	
			Fission neutrons[a]				
0.012 Gy	149 (150)	757 (±154)	4	3	1	3	808 (±94)
0.02 Gy	149 (150)	742 (±150)	2	1	1	2	725 (±104)
0.06 Gy	77 (80)	679 (±163)	4	1	3	—	743 (±100)
0.10 Gy	75 (78)	669 (±118)	6	5	1	—	752 (±120)
0.32 Gy	72 (75)	583 (±148)	9	4	5	2	679 (±74)
0.49 Gy	74 (75)	522 (±138)	10	7	3	2	615 (±81)
Σ	596		35	21	14	9	
			γ rays				
1.0 Gy	204 (204)	700 (±146)	8	3	5	2	807 (±95)
1.0 Gy	301 (301)	706 (±146)	6	2	4	3	835 (±52)
3.0 Gy	120 (120)	648 (±160)	7	5	3	2	741 (±105)
Σ	625		21	10	12	7	

[a] In the analysis bracketed groups are pooled and the corresponding mean absorbed doses are used.

of lung carcinomas in each group required the pooling of the observations. It must also be noted that the dose to different animals in a cage has an estimated standard deviation of about 10%, due to distance variations and due to mutual shielding of the animals. The durations of exposure for the neutron experiments were 20 h for the 0.016-Gy experiment and 22 h for the others.

Gamma-Ray Experiments

The present analysis included three recent experiments with γ rays. There were earlier studies with γ rays; however, they involved considerably higher doses and are therefore irrelevant to the comparison. Two of the recent experiments utilized the same dose of 1 Gy. The data for these experiments are listed separately in Table I, but the two experiments were pooled for the present analysis.

The exposures were performed with a ^{60}Co irradiator; the duration of the irradiation was 14 h in all experiments. In each exposure, up to eight cages were exposed simultaneously, with 10 animals per cage.

The dosimetry was performed with tissue-equivalent ionization chambers. A number of simulation studies were performed with groups of rat phantoms and LiF dosimeters to estimate the average doses in the rats under actual experimental conditions. It was concluded that these averages are about 15% less than the kerma values, and the adjusted values are quoted in Table I.

Apart from the exposures, all experimental conditions were the same in the radon, neutron, and γ-ray studies. For practical reasons, animals from the same dose groups were caged together.

Earlier estimates of the rate of spontaneous lung cancer incidence among this strain of Sprague–Dawley rats were based on scanty evidence. Several additional groups of control animals were therefore followed concurrently with the recent radon, neutron, and γ-ray studies. These observations were pooled into one control group, and are also given in Table I.

The pathological classification of pulmonary malignancies was the same as that used earlier (*2, 3*). Lung carcinomas are recorded as bronchogenic or bronchoalveolar according to criteria stated by Masse (*14*). Table I gives the number of animals in each group with one or more tumors of the specified type.

In the radon-inhalation studies no lung sarcoma has been found; this is consistent with the fact that the radon daughters do not reach the pulmonary connective tissue and the blood vessels in which sarcomas originate. In the neutron and γ-ray experiments nine and seven lung sarcomas have been observed; none were observed in an animal which developed a lung carcinoma. Compared to the one sarcoma observed in the control group, the incidences of sarcomas are highly significant ($P < 10^{-3}$). The sarcomas were, with one possible exception, angiosarcomas which appeared to be rapidly lethal due to hemorrhage. To obtain dose dependencies one would have to pool angiosarcomas in all organs, and computational methods which account for lethality would have to be used. The lung sarcomas observed after neutron and γ irradiations are tabulated in Table I, but otherwise are not part of the present analysis.

CONVENTIONAL EVALUATION

Figure 1 provides a synopsis of the data. The separate panels give the distributions of death and of animals bearing a lung carcinoma at autopsy. The data are given for successive 30-day intervals after the beginning of the exposure.

In Fig. 2 the raw incidences, I_i, are compared for the three radiations. The raw incidence is defined as

$$I_i = \frac{n_i}{N_i}. \tag{1}$$

N_i is the total number of animals that died in the dose group i whose lungs were examined histologically. n_i is the number of animals among these with lung carcinomas.

The raw incidence can be a poor measure of the cancerogenic effect when there is significant life shortening due to the irradiation. At the fairly low doses considered in this analysis, life shortening is of minor importance, and the comparisons in Fig. 2 are therefore a meaningful indication of the relative effectiveness of the radiations in producing lung carcinomas.

Nevertheless, there is some degree of life shortening in the neutron experiments. In order to take this into account and to utilize the experimental information fully, a more sophisticated analysis is required which makes use of the times to tumor detection and corrects for competing risks. This will also provide additional estimates of the lifetime incidences.

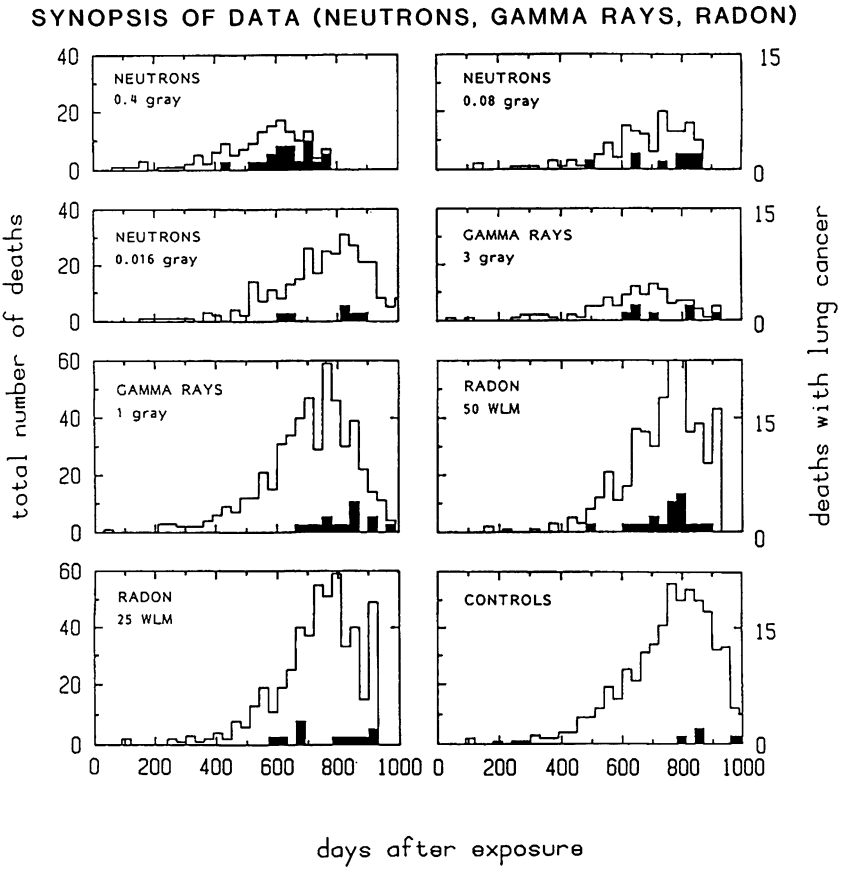

FIG. 1. Distributions of the number of animals dying at specified times after exposure (blank columns), and distribution of the number of animals dying with a lung carcinoma (solid columns). The time scale is subdivided into 30-day intervals. Note the different ordinate scales for the number of deaths and the number of animals dying with lung carcinoma.

COMPETING RISK CORRECTED ANALYSIS

Before the method of analysis is described, it is necessary to state the definitions of the required quantities (see also, e.g., (*2, 3*)).

The tumor *rate,* $r(t)$, is the probability per unit time at time t to incur the tumor; it is also termed hazard function. A closely related quantity is the *cumulative rate,* $R(t)$ (also termed cumulative hazard function):

$$R(t) = \int_0^t r(t')dt'. \tag{2}$$

In the subsequent analysis these quantities, however essential, are less central than

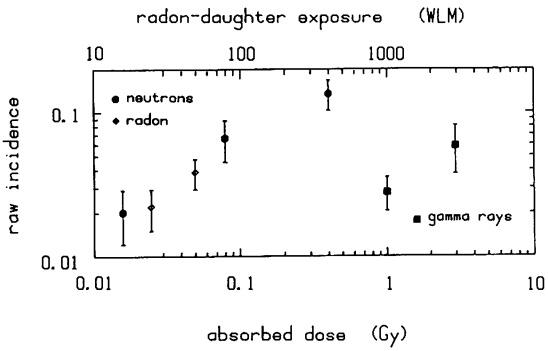

FIG. 2. Raw incidences of lung carcinomas for the different radiation modalities. The standard errors are those for the binomial distribution. The lower abscissa does not relate to the radon-daughter exposures.

a related quantity, the tumor *prevalence,* $P(t)$. This is the probability at time t that the tumor is present. If tumors and mortality are unrelated, one has a simple relation between the prevalence and the cumulative rate:

$$P(t) = 1 - \exp(-R(t)). \tag{3}$$

At small values $P(t)$ and $R(t)$ are identical; at larger values $R(t)$ exceeds $P(t)$ and, unlike $P(t)$, it can exceed unity.

If tumor rates (or tumor prevalences) are analyzed in a survival experiment, it is essential to know whether the tumors that are the cause of death are rapidly lethal, that is, the time between their initial growth and observation at autopsy is short. These tumors are in contrast to those observed incidentally at a later time when animals die for unrelated reasons or are sacrificed. Lung sarcomas are an example of a rapidly lethal tumor. For such tumors there are well-known methods of analysis. The analysis is more difficult for tumors which are incidentally observed, such as the lung carcinomas which cause, at least in the Sprague–Dawley rats, very little, if any, life shortening. For incidentally observed tumors there is no familiar method of analysis which would correspond, for example, to the proportional hazards analysis applied to the rapidly lethal tumors (*17*).

A test has been recommended by Peto *et al.* (*18*) to identify a correlation between exposure (or dose) and incidence of neoplastic changes in the lungs. It has been applied to some of the radon experiments (*19*) on the basis of the old dosimetry and has shown a highly significant correlation. The present study is designed in addition to estimate the relative efficiency of the three radiations to induce lung carcinomas. In the previous studies methods have been developed for this purpose which also apply to the present analysis. Since they have been described previously (*2, 3*), they are outlined only briefly here.

Isotonic Regression

To estimate the tumor prevalence in one dose group, one can utilize the method of isotonic regression. It is, for incidental tumors, the analog to the familiar Kaplan–

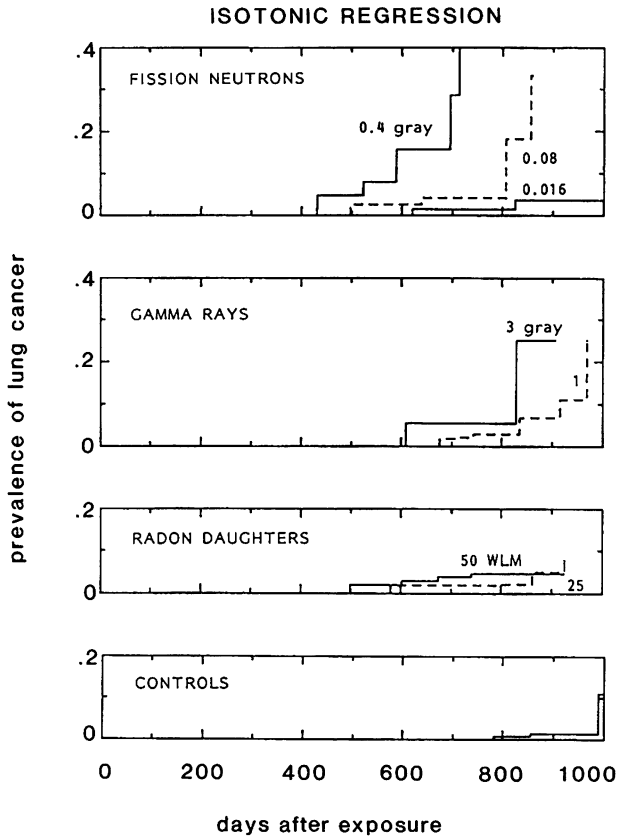

FIG. 3. Estimates of prevalences obtained by isotonic regression for the different radiation modalities and dose groups.

Meier estimate which applies to the rapidly lethal tumors. Isotonic regression is a nonparametric estimation, based merely on the plausible constraint that the prevalence be an increasing function of time. Figure 3 gives, in separate panels, the isotonic regression estimates of the lung carcinoma prevalence in the individual dose groups. Although some of the dose groups are large, there are, at these low doses, only a limited number of lung carcinomas. The magnitude of the statistical uncertainties therefore makes it difficult to assess numerically the relative efficiency of the different types of irradiation. For this reason it is necessary to utilize certain model assumptions to carry the analysis further.

Joint Analysis of Different Dose Groups

A common method of analysis is based on the choice of analytical expressions for the tumor rate or tumor prevalence as a function of dose and of time after exposure. However, such a procedure would be somewhat arbitrary in a case where the isotonic

regression estimates are not sufficiently precise to suggest, with adequate certainty, a proper analytical expression.

In their analysis of the radon experiments, Gray *et al.* (*19*) have used a Weibull model to account for the time dependence of all neoplastic changes in the lung. A nonparametric approach is used in the present study. It has the advantage that it requires fewer a priori assumptions and that the connection between the observed data and the derived prevalences is somewhat more transparent. In this approach it is sufficient to assume that the tumor prevalence is an unspecified increasing function of time after exposure, the so-called baseline function. This baseline function is assumed to change according to a relatively simple model with increasing dose or with changing type of radiation. No analytical expression is postulated for the baseline function. As with isotonic regression, the only constraint is that it increases with time. Different assumptions are, of course, possible concerning the change of the baseline function with changing radiation or changing dose. As in the earlier analysis (*2, 3*), two different models are utilized. One, the time-shift model, has been discussed in studies of life shortening and tumorigenesis after irradiation. The other, the time-acceleration model, is, next to the proportional hazards model, the most frequently used model in survival or reliability analysis. In the shifted time model the prevalence has the same time dependence at any dose,[5] D_i (the index i refers to a dose group in one of the experiments), apart from a shift in time which depends on dose:

$$P(t, D_i) = P_0(t + s(D_i)). \tag{4}$$

$P_0(t)$ is termed the baseline function. $s(D_i)$ are the time shifts; they are largest for the highest doses and are a measure for the earlier occurrence of the carcinomas.

In the acceleration model the prevalence at a dose D_i is

$$P(t, D_i) = P_0(a(D_i) \cdot t). \tag{5}$$

Again $P_0(t)$ is termed the baseline function. However, in this model the change of the prevalence function with dose is expressed not as a forward shift in time but as an acceleration of the cancerogenic process. The acceleration factors, $a(D_i)$, depend on dose and type of radiation and are a measure for the faster occurrence of the carcinomas. No analytical expression is specified for the dependence on dose or on type of radiation of the time shifts, s, or the acceleration factors, a.

The first analysis of the radon studies (*2*) also employed the familiar "proportional hazards model." It was then found that, even with considerable numbers of animals and lung carcinomas, no one model appeared to fit the data substantially better than the others. Two models were nevertheless used in the present analysis to facilitate a judgment of the amount of bias introduced by the models. The time-shift and the acceleration models are computationally similar, and their parallel use is therefore particularly convenient. The proportional hazards model loses its advantage of computational facility when it is employed with data for incidental tumors, and for this reason it is not applied in the present analysis. In the case of incidentally observed

[5] For simplicity the term dose and the symbol D are utilized in the subsequent considerations and equations, although they refer not only to the kerma of neutrons or γ rays but also to the radon-daughter exposure, E_p.

tumors, it is difficult to derive confidence intervals for the prevalences, and it was necessary to rely on an approximate procedure (see Appendix). As a check of consistency of the estimated confidence intervals, the use of two models appeared to be an added advantage.

The numerical analysis of the experimental data for either of the two models consists in identifying that baseline function and those parameters s or a which agree best with the observed data. The quantitative measure for the agreement is the so-called likelihood, i.e., the relative probability that the observed frequencies of tumors at the given death times should have occurred under the assumption of a particular baseline function and a particular set of parameters s or a. It is important to note that the baseline function is not estimated from a control group, but that it is obtained from a *simultaneous* fit to all experimental groups, including the control group. The likelihood equations have been given explicitly in the first study (*2*) and therefore need not be repeated here. As in the earlier work (*2, 3*), the numerical search for the best baseline function and best set of parameters, i.e., the ones with the highest likelihood, is performed by a nonlinear optimization algorithm (*20*).[6] This algorithm is based on the method of steepest descent to find the maximum likelihood values of the baseline function (defined on a time grid) and of the time shifts (or the acceleration factors) under constraints imposed on all or part of the variables.

In the earlier work the data included experiments over a broad range of doses with a corresponding range of tumor prevalences, and it therefore appeared justified to estimate the baseline function with a realistic, that is, a smooth, increasing function of time. In the earlier study, the constraint imposed on the prevalence function was a positive curvature (convexity from above) on a logarithmic scale of time.

In the present work with low doses we have chosen the simpler constraint of monotonicity of the prevalence function. In the computations the prevalence function $P_0(t)$ is defined on a time grid at I points ($I = 40$). Under the constraint, the prevalences at consecutive grid points, i and $i + 1$, are monotonously increasing: $P_0(t_i) \leqslant P_0(t_{i+1})$ ($i = 1$ to I).

Results of the Maximum Likelihood Analysis

One could derive separate fits for the three different radiation types. Somewhat different prevalence functions would then result, and a comparison would be difficult. Since there are no indications of systematic differences in the time course of prevalences for the different radiations, it appeared justified to postulate a joint baseline function for the different radiations and the various dose groups. This means that, in one simultaneous fit to all the data, a common baseline function, defined on a 30-day grid of intervals, and parameters s or a are estimated (see Eqs. (4) and (5)). A comparison of the effect in different dose groups of different radiations can then be based merely on the estimated values s or a for these groups. The left panels in Fig. 4 give the results of the joint fit for the shifted-time model. The right panels in Fig. 4

[6] Other optimization algorithms could be used (for a description of the various methods see (*21*)) to solve this or similar problems, i.e., to find the solution of a nonlinear equation under nonlinear (or linear) constraints on the variables.

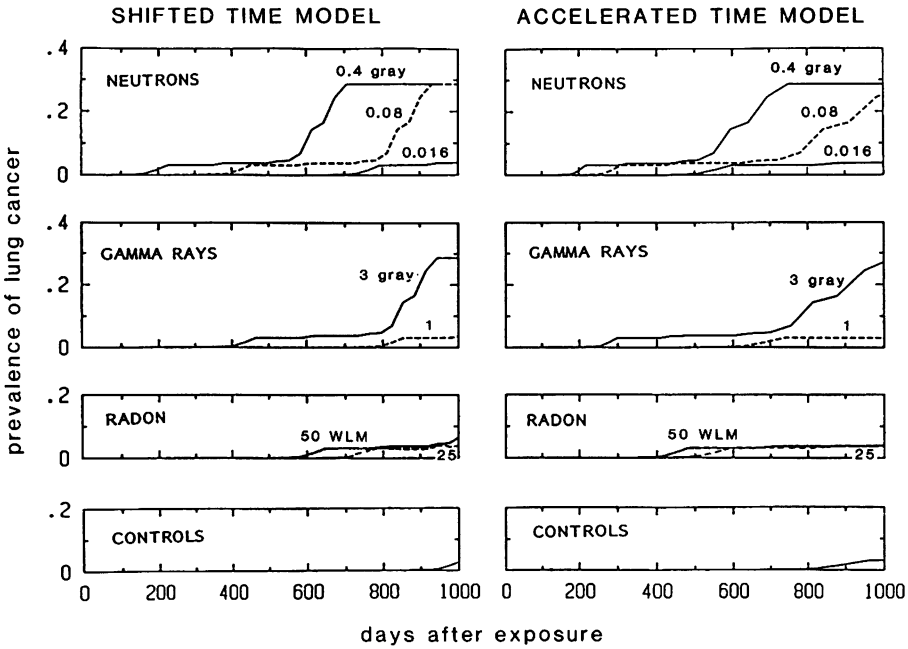

FIG. 4. Estimates of prevalences based on joint maximum likelihood fits. The left panels give the results obtained with the time shift model (see Eq. (4)). The right panels give the results obtained with the time acceleration model (see Eq. (5)).

give prevalences obtained in terms of the accelerated time model. In this case the dependencies run parallel on a logarithmic scale of time. As with the isotonic regression, the solutions are step functions, which is, of course, meaningless. However, as pointed out above, it was felt that little would be gained in this study by using numerical procedures which provide continuous solutions. This is the main difference from the earlier treatment (*2, 3*) where larger overall numbers of tumors justified more sophisticated constraints. The essential aim of the present analysis is the determination of the parameters s or a for the purpose of comparing the different radiations.

Figure 5 gives the estimated relative time shifts, s, of the prevalence and the acceleration factors, a, in two panels. The position of the points for the radon-daughter-inhalation experiments relative to those for the neutron and γ-ray exposures is arbitrary, as there is no reliable conversion factor between the radon-daughter exposure and the absorbed dose in the lung. The different reference quantities are noted on the upper and lower border of the panels. The standard errors are approximations described in the Appendix; they do not include errors in the determination of doses.

From the nature of the models it follows that an enhanced carcinogenic effect in one experiment relative to another is measured by the difference of the time shifts (or of the acceleration factors). The RBE of neutrons relative to γ rays is then, according to its definition, equal to the ratio of the γ-ray dose to a neutron dose which results in the same time shift (or acceleration factor).

From the results in Fig. 5 one estimates RBE values of neutrons relative to γ rays

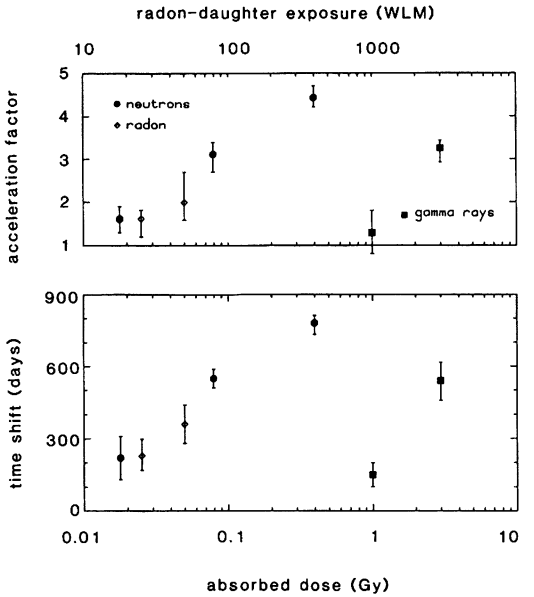

FIG. 5. Parameters obtained for the individual dose groups in the joint maximum likelihood fits. The lower panel gives the time shifts, s. The upper panel gives the acceleration factors, a. The values s and a are normalized to those for the control group. However, this is somewhat arbitrary because of the small number of only five lung carcinomas in the control group. More meaningful information is provided by the differences of the shift factors for different dose groups, and by the ratio of acceleration factors. The derivation of the standard errors is explained in the Appendix.

between 30 and 40 at a neutron dose of 0.1 Gy, and those in excess of 50 at a neutron dose of 0.016 Gy. For the comparison between radon-daughter inhalations and neutron or γ-ray exposures, one utilizes the concept of equivalence ratio which is analogous to the RBE of neutrons versus radon or of γ rays versus radon, except that one employs radon-daughter exposures instead of the insufficiently known absorbed dose produced by the radon daughters in the lung. The equivalence ratio of a radiation equals the ratio of a radon-daughter exposure to that dose of the radiation which produces equal prevalence of lung carcinomas. From the results in Fig. 5 one estimates an equivalence ratio for fission neutrons versus radon daughters of about 15 WLM to 10 mGy. For γ rays versus radon daughters one estimates an equivalence ratio of about 25 WLM to 1 Gy. These estimated equivalence ratios refer to the limited range of radon-daughter exposures between 25 and 50 WLM which are employed in the present experiments.

The estimates for the RBE and the equivalence ratios are in fair agreement with values which one would obtain from the raw incidences (Fig. 2). This may be fortuitous and does not imply that the maximum likelihood analysis is unnecessary. Nevertheless, one concludes that the results are rather insensitive to the method of the analysis.

The estimated prevalences, $P(t, D)$, can be utilized to derive standardized lifetime incidences (*3*),

TABLE II

Estimated Lifetime Incidences of Lung Carcinomas

		Estimates based on Eq. (6)	
	Raw incidences	*Time-shift model*	*Acceleration model*
		Radon daughters	
25 WLM	0.022 ± 0.007	0.028	0.032
50 WLM	0.038 ± 0.009	0.039	0.035
		Fission neutrons	
0.018 Gy	0.020 ± 0.008	0.026	0.031
0.08 Gy	0.066 ± 0.021	0.094	0.15
0.40 Gy	0.130 ± 0.030	0.23	0.25
		γ rays	
1 Gy	0.028 ± 0.007	0.021	0.028
3 Gy	0.058 ± 0.022	0.089	0.17
Controls	0.009 ± 0.004	0.009	0.016

$$I(D) = \int P(t, D)m(t)dt, \tag{6}$$

where $m(t)dt$ is the fraction of animals in the control group dying in the age interval t to $t + dt$ (see bottom right panel in Fig. 1). Integrating over the prevalences in Fig. 4 one obtains the estimated lifetime incidences which are compared to the raw incidences with their standard errors in Table II.

The raw incidences are substantially smaller than the standardized incidences for the higher neutron doses that produce substantial life shortening. But even without life shortening, the values need not agree. In the raw incidences all lung carcinomas are counted equally, regardless of the animal's age at death. In the maximum likelihood analysis which underlies Eq. (6) the age is taken into account through the estimation of the prevalence.

CONCLUSIONS

Our finding of an RBE for neutrons relative to γ rays in excess of 50 at neutron doses of a few centigray is in substantial agreement with other observations which have been the basis of a recent proposal to increase the quality factors for neutrons (*22*).

The equivalence ratio between radon-daughter inhalations and neutron irradiations of about 15 WLM to 10 mGy differs by a factor of 2 from the earlier estimate of 30 WLM to 10 mGy. This reflects the revision of the radon-daughter dosimetry which has been discussed under Materials and Methods. The average absorbed dose produced by 15 WLM in the lung of the rat is uncertain. Harley (see discussion in (*9*)) has suggested that the value is close to that for man. With the estimated dose to

the lung of 5 to 10 mGy per WLM (*1*), one would translate the equivalence ratio of 15 WLM to 10 mGy into an RBE of radon daughters versus neutrons of 0.07 to 0.14, and into an RBE of radon daughters versus γ rays of 4 to 8. It may be noted that the quality factor of 20 has been recommended for both fission neutrons and α-particles (22). The present study suggests a substantially higher effectiveness of neutrons and—with the above tentative assumption—a lower effectiveness of radon daughters.

In view of the complexities of the dose distribution in the lungs of rat or man, comparisons in terms of absorbed dose or dose equivalent are of doubtful validity. It is therefore more meaningful to consider directly the observed equivalence ratios between the radon-daughter exposure and the absorbed dose or dose equivalent of neutrons and γ rays. It should be noted that the relative effectiveness of exposures to radon daughters compared to neutrons or γ rays will be less if sarcomas of the lung are included because they are induced by neutrons and by γ rays but not by the exposure to radon daughters.

APPENDIX: DETERMINATION OF APPROXIMATE STANDARD ERRORS

There are no established methods to derive standard errors for the parameters which are computed in the time-shift or acceleration model. Standard errors have therefore been derived by an approximative method which is outlined in the following, and which avoids the need for more complicated "bootstrap" simulations. As described in the main part of the article, a simultaneous fit to all exposed groups has provided a baseline function, $P_0(t)$, of the prevalence. To take the example of the time-shift model, the estimated prevalence of lung carcinomas as a function of time after exposure is then $P_0(t + s)$. For brevity, the index which refers to the dose group is omitted here. The confidence interval of the time-shift parameter, s, is obtained by considering different values of s' and by computing for each of the assumed values the expected number of lung carcinomas and its variance $\sigma^2(s')$, which would correspond to the prevalence $P_0(t + s')$; the computations utilize the actually observed times of death in the specified groups. The standard error of s is then set equal to the range of values s' for which observed and expected number of carcinomas differ by not more than $\sigma(s')$. The variance for a specified value s' is obtained by the relation:

$$\sigma^2(s') = \sum_k N(t_k)P_0(t_k + s')\cdot(1 - P_0(t_k + s')).$$

The index k refers to the time; $N(t_k)$ is the number of animals having died in time k.

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