OFFICIAL ORGAN OF THE RADIATION RESEARCH SOCIETY

RADIATION RESEARCH

EDITOR-IN-CHIEF: DANIEL BILLEN

Volume 91, 1982

ACADEMIC PRESS

New York London
Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto

MADE IN THE UNITED STATES OF AMERICA

RADIATION RESEARCH

OFFICIAL ORGAN OF THE RADIATION RESEARCH SOCIETY

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1984: April 8–12, Orlando, Florida
1985: May 26–31, Chicago, Illinois

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VOLUME 91, 1982

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NUMBER 1, JULY 1982

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The Subject Index for Volume 91 will appear in the December 1982 issue as part of a cumulative index for the year 1982.

RADIATION RESEARCH 91, 589-614 (1982)

Maximum Likelihood Estimation of the Prevalence of Nonlethal Neoplasms—An Application to Radon-Daughter Inhalation Studies[1]

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CHMELEVSKY, D., KELLERER, A. M., LAFUMA, J., AND CHAMEAUD, J. Maximum Likelihood Estimation of the Prevalence of Nonlethal Neoplasms—An Application to Radon-Daughter Inhalation Studies. *Radiat. Res.* **91**, 589-614 (1982).

A nonparametric maximum likelihood method for estimating prevalence is described that is applicable to the analysis of nonlethal tumors which are discovered incidentally in either sacrificed animals or animals dead from other causes. The method corrects for competing risks and does not require an analytical model for the prevalence as a function of dose and time. It is applied to the results of an experiment in which numerous groups of Sprague–Dawley rats were exposed to different doses of radon daughters at different dose rates. The dependence of the prevalence on dose and time after exposure is derived, and three basic models are considered that correspond to a dose-dependent shift in time, to an acceleration in time, and finally to the proportional hazards model. Mortality-corrected risk estimates are derived from the estimated prevalences. At doses down to 65 WLM (working level months) the results are consistent with linearity in dose, or possibly with sublinearity (dose exponent less than 1); they exclude, in this dose range, a threshold or a proportionality to a higher power of dose.

INTRODUCTION

Considerable efforts have been made at a number of laboratories to assess pulmonary tumors due to inhaled radioactive substances. Recent reports (*1–3*) attest to the broad range of such investigations. They also demonstrate the difficulties

[1] Work partly supported by Euratom Contracts 099-76-1-PSA F and 208-76-BIO D.
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0033-7587/82/090589-26$02.00/0

inherent in these studies and emphasize large uncertainties of the risk estimates and the dose–effect relations.

The complexities arise largely from the multitude of different factors involved in these studies. Also an important problem is the lack of mathematical methods to separate the effect of life shortening in the survival experiments from the induction of pulmonary tumors. In the analysis of lethal cancers or cancers that can be readily discovered in the live animal, it is common practice to use the proper competing-risk-corrected quantities, for example, the Kaplan–Meier estimate (*4*). With nonlethal diseases, such as radon-induced pulmonary tumors in Sprague–Dawley rats, the situation is different; dose–effect relations are either reported for life shortening alone or, if a dose–effect relation is given for the neoplastic process, it is based on incidences uncorrected for life shortening. The failure to utilize a competing-risk-corrected analysis is striking since Hoel and Walburg (*5*) considered the problem in depth almost a decade ago and pointed out that isotonic regression can take the place of the Kaplan–Meier estimate in the analysis of nonlethal diseases in survival experiments.

The objective of the present article is to demonstrate that the method recommended by Hoel and Walburg is applicable to inhalation studies and to show that it can be considerably extended. The method will be exemplified by its application to radon-daughter inhalation studies that are part of the broader range of inhalation investigations at the Commissariat à l'Energie Atomique (*6–8*). The separate consideration of the radon studies has the advantage that complicating factors such as chemical state or particulate size need not be considered and that, accordingly, the emphasis can be on the essentials of the numerical methods.

MATERIALS AND METHODS AND BACKGROUND OF THE EXPERIMENTAL WORK

Experimental work on the carcinogenic action of inhaled α emitters began at the Commissariat à l'Energie Atomique in 1969. Research was performed mainly on male rats of the Sprague–Dawley S.P.F. (specific-pathogen free) and the Wistar A.G. inbred strains. The investigations were directed at two main objectives. The first was the assessment of the effects of the decay products of radon (*9*, *10*), a problem particularly relevant to the mining of uranium; the second was the investigation of effects of the actinides that are of concern in reactor fuel reprocessing plants (*11*, *12*).

When the experimental program began, the carcinogenic effect of radon on rodents was unknown. For this reason doses and exposure times differed widely in the initial experiments. With the intent to reach broader conclusions on basic mechanisms, the studies were subsequently extended to include investigations on the influence of factors such as sex or age at the start of inhalation (*7*). Experiments were also performed on the combined action of various cofactors which were expected to counteract the neoplastic processes, such as bleomycin, or to enhance it, such as tobacco smoke, dust, or various chemical compounds (*13–16*). For the present analysis none of the more complex investigations were utilized.

Even the radon-daughter experiments encompassed a wide range of experiments performed over the last 10 years at the laboratory of experimental pulmonary pathology in Razès that is directed by J. Chameaud (*9*, *10*, *17*, *18*). The inhalation

procedure has been described earlier (*19*). In summary, male Sprague–Dawley rats, 90 days old at the beginning of the experiments, were kept in an inhalation chamber with radon concentration at the desired levels. They were exposed to radon and its daughter products at the concentrations and for the durations specified in each individual experiment. There were 2- to 16-hr exposures two to five times a week. The experimental conditions were such that equilibrium of radon with its short-lived daughters existed. Table I gives parameters for individual experiments. In the first column the total inhalation doses and the monthly doses are listed. In columns 2 to 5 the daily durations of exposure to radon daughters, the weekly frequencies of the exposures, the total durations of the inhalation periods, and the radon-daughter concentrations are given. In columns 6–10 the total number of animals in a group, the number of animals examined, and the number of animals with pulmonary malignancies are given. The number of sacrificed animals and sacrificed animals with pulmonary malignancies are given in the last column. All times quoted in the following are to be understood as times from start of inhalation exposure.

In view of the difficult estimation of absorbed dose (*20*), the dose is given in conventional form as the product of concentration and exposure time. The unit *working level month* (WLM) is utilized. One *working level* is defined as a concentration of radon daughters which results in the ultimate release of 1.3×10^5 MeV of α energy per liter of air; it is equivalent to a concentration of 0.1 nCi radon (3.7 Bq) per liter of air in equilibrium with its four short-lived daughter products (*1*, *20*). The time unit *working month* was defined as 170 hr. The unit WLM corresponds to 3.54×10^{-3} J m^{-3} hr.

The pathological classification followed a method described in earlier articles (*21*, *22*). The pulmonary cancers were recorded as *bronchogenic* (type 1 in Table I) or *bronchoalveolar* (type 2 in Table I) according to histological criteria proposed by Masse (*22*). Epidermoid carcinomas and adenocarcinomas were, in view of the bronchic origin of their cells, given the joint pathological classification of bronchogenic cancers. For cancers with cells of more peripheral origin a common classification of bronchoalveolar carcinomas was used. Nontumorous histological changes were classified as adenomatosis, and benign tumors were classified as adenomas. Adenomatosis was very frequent in older animals, even in the nonexposed group; it is not considered in this study. For each cell type only the most severe lesion was recorded, even if other lesions were present.

In the following analysis only malignant tumors, without regard to their pathological type, are considered. It is felt that the distinction between adenomas and the malignant neoplasms is sufficiently well defined. In addition animals with adenomas only are a minor fraction ($\sim$15%) of all animals with neoplasms.

The spontaneous incidence of pulmonary malignancies in Sprague–Dawley rats is not well known. A review of data from various laboratories leads to an estimate between 10^{-3} and 5×10^{-3}. The exact numerical value is not very critical for the present analysis; we have chosen the estimate of 3×10^{-3}. This agrees with the data of Sanders and Mahaffey (*23*) and is consistent with the observation of Martin *et al.* (*24*) who found no pulmonary tumors in a life span observation of 485 Sprague–Dawley rats.

TABLE I

Summary of Protocols of the Radon-Daughter Inhalation Experiments

Dose (Dose per month) (WLM)	*Daily duration of inhalation (hr)*	*No. of inhalations per week*	*Total duration (months)*	*Radon-daughter concentration (WL)*	*No. of animals*	*No. of animals examined*	*No. of animals with pulmonary malignancy*	*No. of animals with malignancy of type 1*	*No. of animals with malignancy of type 2*	*No. of sacrificed animals (No. with pulmonary malignancy)*
0	0	0	0	0	186	159	0	0	0	0
65 (50)	2	3	1.2	360	500	490	13	7	6	0
170 (110)	3	4	1.5	390	294	244	11	9	5	4
290 (45)	5	5	6	75	81	80	2	1	1	66 (2)
860 (1500)	5	5	0.6	2,500	20	17	4	2	2	0
1,470 (1500)	5	5	0.9	2,500	30	29	5	2	3	12 (0)
3,000 (1500)	5	5	1.9	2,500	40	39	17	4	13	2 (1)
4,500 (1500)	5	5	2.9	2,500	49	48	25	15	14	11 (0)
9,250 (1500)	5	5	5.8	2,500	20	15	5	5	0	0
2,250 (4600)	16	4	0.5	3,000	25	21	7	4	3	0
3,700 (4600)	16	4	0.8	3,000	25	20	8	8	1	0
3,900 (1800)	6	4	2	3,000	50	48	16	15	1	0
5,400 (4600)	16	4	1.1	3,000	25	23	6	5	1	0
6,000 (2400)	7	5	2.3	3,000	35	35	9	6	4	0
7,000 (4600)	4	4	1.5	12,000	181	171	34	28	6	97 (12)
7,000 (7000)	5	5	0.9	12,000	33	14	3	3	0	0
8,000 (3000)	10	4	2.6	3,000	180	164	65	51	20	45 (22)
14,000 (4600)	4	4	2.9	12,000	79	72	1	1	0	12 (1)

An important question in the experimental studies of pulmonary neoplasms in animals is whether malignant neoplasms cause life shortening. In mammals with life spans much longer than the latency growth times of malignant neoplasms (primates, dogs) lethality is marked. There was no evidence of life shortening in our Sprague–Dawley rats, and there have been only a few cases where the death of an animal appeared to be related to a pulmonary tumor. As a rule, malignant neoplasms affect only limited parts of the lung tissue; furthermore, less than 1% of pulmonary malignancies were found to give rise to metastases.

Nevertheless, a pulmonary tumor could be lethal in different ways. An animal might be asphyxiated by a tumor of excessive size, or a tumor in a particular location might block the upper airways.In experiments where inhalation of plutonium was combined with benzo[α]pyrene given intratracheally, large tumor sizes were frequently obtained (*25*) and cases of asphyxiation were ascertained upon autopsy. Similar tumor sizes were never reached in experiments with radon inhalation alone.

Finally, a tumor could cause massive hemorrhage or might secrete toxins. None of these various possibilities have been observed in the radon experiments. The failure to find any instance of blocked upper airways or of internal hemorrhage is consistent with the fact that most pulmonary tumors in the Sprague–Dawley rat are peripheral. Finally, no direct evidence exists for Sprague–Dawley rats, but experiments with grafts of pulmonary tumors to Wistar rats (*26*) have led us to the conclusion that the tumors do not secrete toxins that may contribute to mortality.

The experimental data do not indicate an increased prevalence of pulmonary malignancies in nonsacrified dead animals. However, a meaningful comparison is possible only in two groups where sufficient numbers of sacrifices and deaths from other causes occur within certain intervals. In the group of 181 animals exposed to 7000 WLM between Days 400 and 500 it was found that 9 of 26 sacrificed animals had pulmonary malignancies; for the deaths from other causes this ratio was 5 to 27. In the group exposed to 8000 WLM after Day 600 there were 22 animals with malignancy among 45 sacrificed animals; the ratio for the other deaths was 22 to 41.

In view of these considerations, independence between pulmonary tumors and mortality appears to be an acceptable hypothesis for the purpose of the present study.

CONVENTIONAL ANALYSIS

This section gives numerical results obtained from a conventional analysis to facilitate the understanding of the subsequent section that deals with the more rigorous mortality-corrected analysis.

In the subsequent analysis only pulmonary malignancies—according to the criteria stated in the preceding section—are considered. The relevant information for each animal is then, apart from dose and duration of exposure, the time of its death and the presence or absence of a pulmonary malignancy. A more detailed treatment that discriminates between different types of pulmonary tumors is given in Appendix A.

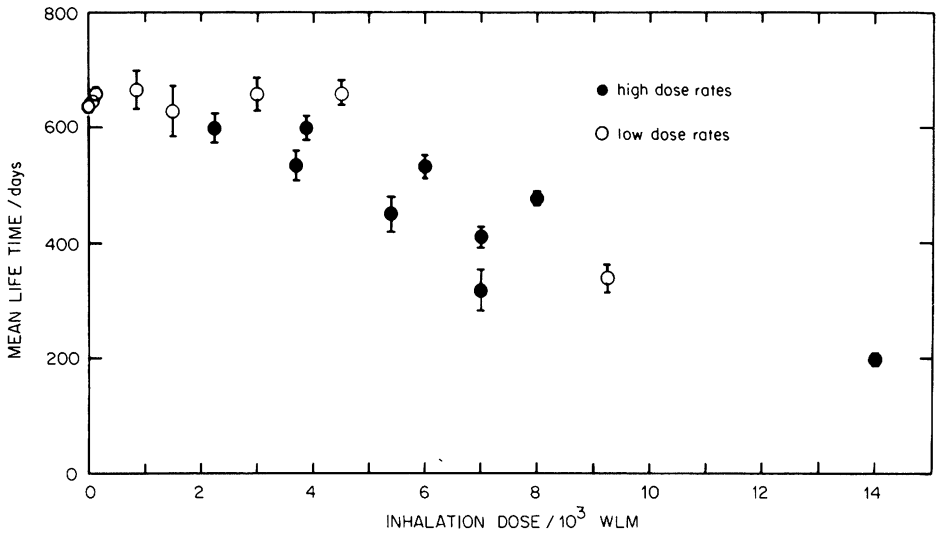

FIG. 1. The mean lifetime, with standard error, in each group as a function of inhalation dose. Data from sacrificed animals are not included. The partition between low dose rates and high dose rates is set at 1600 WLM/month.

Figures 1–3 give results of a conventional analysis; the sacrificed animals (total number = 249) were excluded. Figure 1 represents, as a function of inhalation dose, the lifetime and its standard error in the individual groups; animals that could not be examined were also included. In this, as in subsequent figures, different symbols are used for the groups exposed to less than 1600 WLM/month and those exposed to more than 1600 WLM/month. This serves merely as a visual aid to distinguish results from "moderate dose rates" and "high dose rates." The distinction has no influence on the computations.

Figure 2 gives, separately for each group, the fraction of animals dead up to the specified time and the fraction of animals dead with a pulmonary malignancy.

Figure 3 gives the raw incidence of malignancies as a function of inhalation dose, i.e., the ratio of animals dead with pulmonary malignancy to the number of examined animals in a group. These data are based only on animals that were examined, and sacrificed animals were excluded since the temporal distribution of the sacrifices could seriously bias the results. The term "raw incidence" is used to emphasize the fact that this quantity is not corrected for life shortening. Without such a correction it is unclear whether the decline of the incidence at higher doses was exclusively due to life shortening, or whether there was also an inherent decline of the induction of pulmonary malignancies at high doses.

COMPETING-RISKS-CORRECTED ANALYSIS

The Problem of Fully Censored Data

To allow for competing risks the Kaplan–Meier estimate (*4*, *27*) or similar estimates (*28*) are appropriate in the analysis of lethal diseases. These methods are

equally applicable if a tumor is not lethal, but its time of appearance can be determined; an example is the study of mammary neoplasms (*29*). Under these conditions one speaks of *right censored data*; i.e., times to the tumor are either known or are known to exceed an observed time when an animal, still without tumor, has been lost for unrelated reasons. For nonlethal diseases that can be discovered only incidentally in a dead animal, the data are times, t_i, of death with or without the disease present. The time to the effect is known to be smaller or

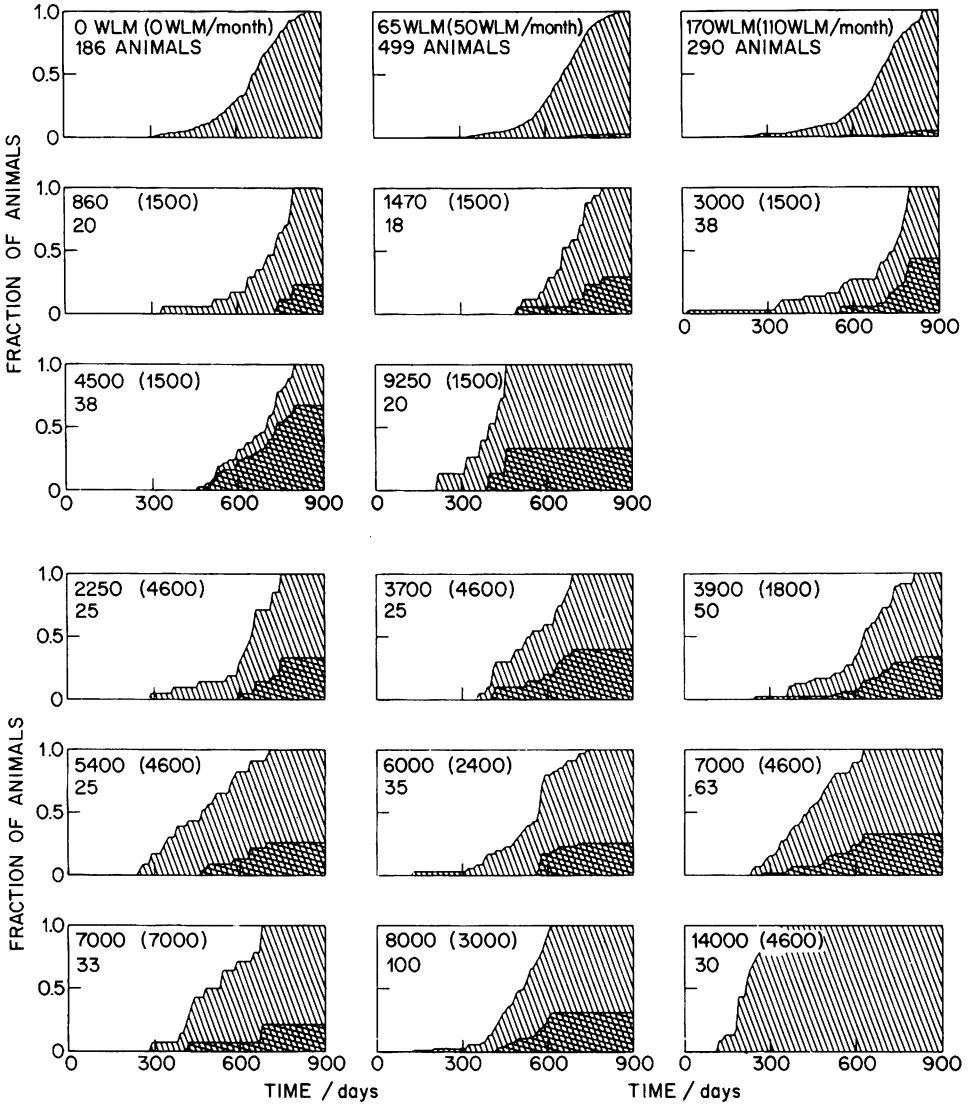

FIG. 2. The fraction of animals dead without (single-shaded area) and with (double-shaded area) pulmonary malignancies as a function of time in the different experimental groups. These calculations are based on animals with pulmonary diagnostics; they do not include sacrificed animals.

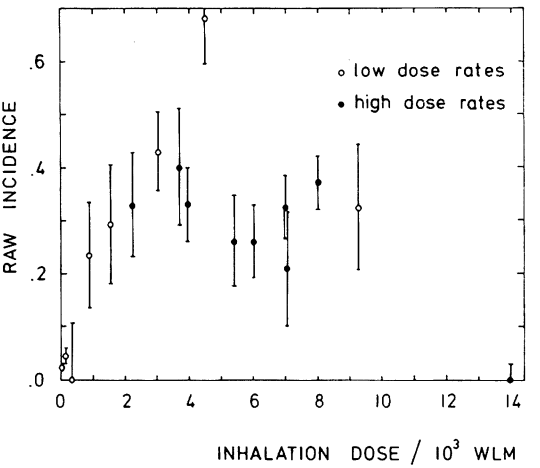

FIG. 3. Raw incidences as a function of inhalation dose. The raw incidence in a group is the ratio of the number of animals dead with pulmonary malignancy to the total number of animals. Sacrificed animals and animals without pulmonary diagnostics have been excluded. The standard errors are based on the binomial distribution. The partition between low and high dose rates is set at 1600 WLM/month.

larger than t_i; it is never actually known. One may therefore speak of *fully censored data.*[3] The mathematical analysis of such data involves the estimation of the prevalence of the disease as a function of time. The prevalence at a given age can most readily be determined by serial killing experiments, but as pointed out by Hoel and Walburg (*5*), the analysis can also be performed from survival experiments, provided the mortality rate is not influenced by the disease under study. Partially lethal diseases present a gray area where the estimation of prevalences from survival experiments is difficult or impossible.

The presence of a pulmonary tumor is determined upon necropsy in sacrificed animals, or in animals that died from other causes. Since independence of pulmonary tumors and of mortality is assumed, no distinction needs to be made between these two cases; dead animals, whether sacrificed or not, can be considered as random representatives of the animals at the specified time.

Before a discussion of the numerical methods, it is necessary to define the basic quantities which will be used. The definitions are in agreement with those in the report of the United Nations Scientific Committee on the Effects of Atomic Radiation (*31*). These definitions apply whether one deals with lethal or nonlethal diseases.

The *tumor rate*, $r(t)$, is the probability per unit time of an animal to develop a tumor at time t; in mathematical statistics this or analogous functions are termed *hazard functions.*

The *cumulative tumor rate*, $R(t)$, is the integral of the tumor rate up to time t:

[3] The term doubly censored data (left and right censored) has also been used (*30*); however, the expression fully censored appears more appropriate to a situation where there are no exact observations.

$$R(t) = \int_0^t r(t')dt'. \tag{1}$$

The *prevalence*, $P(t)$, is the probability that an animal bears a tumor at time t.

Of the three only $P(t)$ can be obtained directly in the present case; however, $R(t)$ or $r(t)$ can be inferred indirectly. For this purpose one may express the prevalence in terms of the cumulative tumor rate, $R(t)$:

$$P(t) = 1 - \exp(-R(t)). \tag{2}$$

$R(t)$ is always larger than $P(t)$, and it can exceed 1; at values of $R(t)$ much smaller than 1 there is approximate numerical equality between $P(t)$ and $R(t)$.

Maximum Likelihood Estimate of the Prevalence

As stated, there are familiar methods for estimation of the prevalence in the case of right censored data (*4*, *5*). These methods can be based on maximum likelihood considerations (*32*); however, they are sufficiently simple to be intuitively understandable without consideration of their theoretical basis.

In contrast, the estimation of the prevalence for fully censored data is straightforward only if one restricts the analysis to one preselected time when all surviving animals are sacrificed and examined for pulmonary tumors. Ullrich *et al.* (*33*) have used this approach in large-scale experiments that compare the prevalence or the mean number of pulmonary tumors in RFM/un mice 9 months after exposure to X rays or fission neutrons. The simple solution can, in principle, also be applied when the analysis is aimed at the assessment of the time dependence of the tumor prevalence; however, it requires serial sacrifice of animals so that there are enough necropsies in each preselected time interval. $P(t)$ is then estimated as the observed fraction of tumor-bearing dead animals in a time interval. The limitation of this method is its costliness due to the large number of animals required. Experiments of this type [e.g., see (*34*)] are therefore rare. In the present study, 17 groups of animals were exposed to different doses with different durations of exposure. The total number of animals was roughly 1700; it is evident that a far greater number of animals would be required if the prevalence were to be estimated separately for each group. However, it will be seen that maximum likelihood methods permit estimates even from experiments with small groups of animals.

Let t_i^+ ($i = 1, 2, \ldots, I$) be the times of death of those animals that are found to carry a tumor and let t_j^- ($j = 1, 2, \ldots, J$) be the times of death of those animals that are found to be tumor free. The likelihood, Λ, is defined as the probability for the actual outcome, conditional on the times of deaths and on the prevalence function $P(t)$:

$$\Lambda = \prod_{i=1}^{I} P(t_i^+) \cdot \prod_{j=1}^{J} (1 - P(t_j^-)). \tag{3}$$

For numerical calculations, it is more convenient to use the *log-likelihood*:

$$\ln \Lambda = L = \sum_{i=1}^{I} \ln (P(t_i^+)) + \sum_{j=1}^{J} \ln (1 - P(t_j^-)). \tag{4}$$

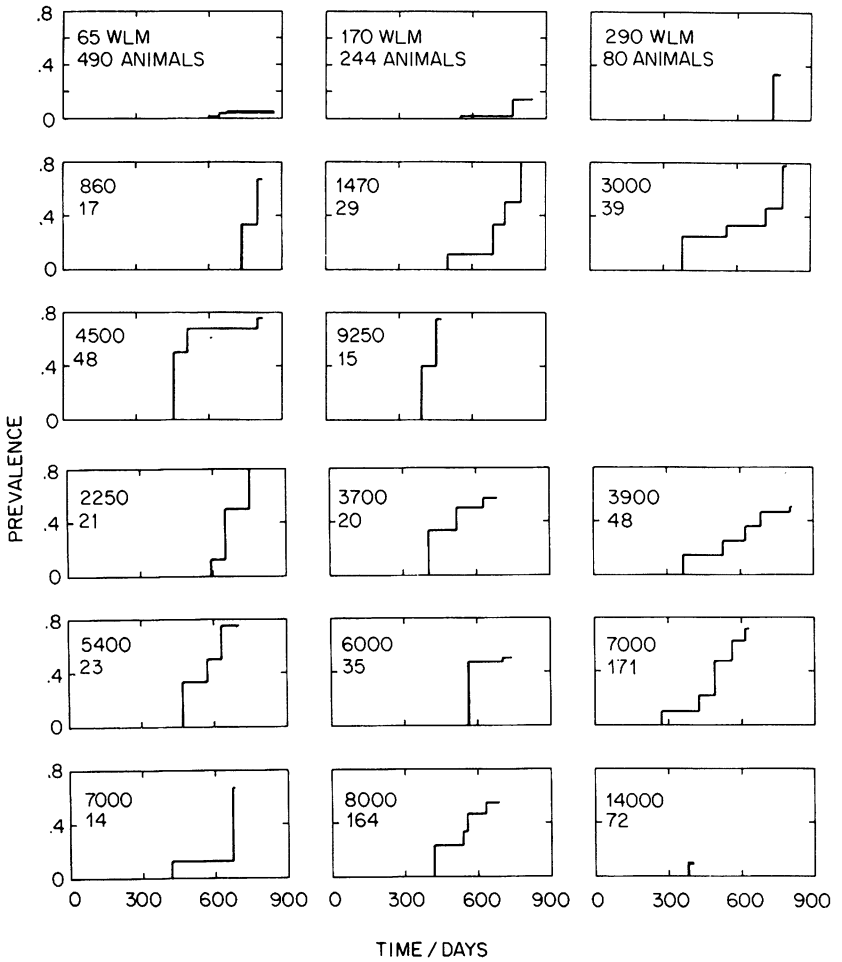

FIG. 4. Estimates of the prevalence of pulmonary malignancies from isotonic regression based on the combined data from life-span and sacrificed animals.

In Eqs. (3) and (4) it is assumed that all times t_i^+ and t_j^- are individually resolved. If multiple deaths occur at a time, a more complicated relation, corresponding to the general binomial case, applies; it is given in Appendix B.

One can calculate the theoretical function $P(t)$ that maximizes the log-likelihood. A condition for the solution is that the prevalence does not decrease in time. With this constraint of monotonicity there exists a relatively simple algorithm to obtain $P(t)$. The method, termed isotonic regression (*35*), has been applied by Hoel and Walburg (*5*) to radiation carcinogenesis studies.

Figure 4 gives the results of the isotonic regression for the 17 groups of the present experiment. In view of the small size of some of the groups it is not surprising that the shapes of the estimated curves vary widely. This type of analysis is therefore of limited value for a quantitative comparison and for the construction of dose-effect relations. A more efficient method is required that imposes additional con-

straints on the set of possible solutions. Such a method consists in postulating one underlying prevalence function (baseline function) that is assumed to vary with inhalation dose in a manner that depends on a chosen model. Inevitably the utilization of a model will introduce a degree of arbitrariness. To judge the bias that may be introduced in this way, three models will be applied and compared that have been considered in the mathematical theory of survival data.

The maximum likelihood method will be utilized in the present work in a modified form that leads to smooth curves. The monotonicity constraint is, for this reason, replaced by a convexity constraint (see Appendix B). An inconvenience of the convexity constraint is the requirement of a nonlinear optimization algorithm that takes the place of the simpler computation for isotonic regression; however, the more complex algorithm will in any case be required in the simultaneous maximum likelihood analysis of several experimental groups.

SIMULTANEOUS MAXIMUM LIKELIHOOD ANALYSIS

Three Models for the Dose Dependence of the Prevalence

Of the three models which will be considered, one—the shifted time model—has been suggested in studies of life shortening (*36*) and tumorigenesis (*29*, *37*) after irradiation. The other two have been utilized in survival analysis and reliability studies (*32*) and in clinical and experimental investigations of cancer treatment (*38*, *39*). The *shifted time model* postulates that the prevalence function, $P_D(t)$ is shifted toward earlier times in animals exposed to a dose D:

$$P_D(t) = P(t + s(D)), \tag{5}$$

where $s(D)$ is the dose-dependent shift factor.

The second distinct but related model assumes that the prevalence in the exposed animals changes in a way that corresponds to an acceleration of time:

$$P_D(t) = P(a(D) \cdot t), \tag{6}$$

where $a(D)$ is the acceleration factor, also dependent on dose. In the statistical theory of survival analysis Eq. (6) is termed the *accelerated failure time model* (*32*).

The third, the *proportional hazards model*, postulates that the tumor rate, $r(t)$, and therefore also the cumulative tumor rate, $R(t)$, change by a dose-dependent factor $\lambda(D)$:

$$R_D(t) = \lambda(D) \cdot R(t). \tag{7}$$

This model has been most extensively studied [see (*32*)] and is widely used with right censored data. Cox (*40*) has obtained a remarkably simple solution for the simultaneous maximum likelihood fit to such data; accordingly, this model is also referred to as Cox's model.

It will be sufficient to consider the accelerated failure time model in detail; the corresponding equations for the other models are cited in Appendix B. The log-likelihood in the accelerated failure time model is

$$L = \sum_{k=1}^{K} \left[\sum_{i=1}^{I_k} \ln P(a_k \cdot t_{ik}^{+}) + \sum_{j=1}^{J_k} \ln (1 - P(a_k \cdot t_{jk}^{-})) \right], \tag{8}$$

where

t_{ik}^{+} = time of death of animal i ($i = 1, \ldots, I_k$) with malignancy in group k ($k = 1, \ldots, K$),

t_{jk}^{-} = time of death of animal j ($j = 1, \ldots, J_k$) without malignancy in group k ($k = 1, \ldots, K$),

K = the number of groups.

The numerical optimization procedure yields the baseline function $P(t)$ and the acceleration factors a_k for the K groups. No analytical expression is postulated for $P(t)$. However, to ensure a smooth function convexity of ln $P(t)$ from above is used as a constraint.

Results of the Simultaneous Analysis

For each of the three models, the simultaneous maximum likelihood fit has been performed with the 17 exposed groups. The control group was excluded because no pulmonary malignancy had been observed in this group. The optimization procedure utilizes the method of steepest descent in a general-purpose computer program for nonlinear optimization developed by Abadie and Guigou. In an earlier publication dealing with the nonparametric fitting of dose–effect relations (*41*), the characteristic features and requirements of such optimization programs have been discussed. Therefore only essential information relevant to the present case is given in Appendix B.

For each of the three models, the maximum likelihood computation yields a best-fit prevalence function and a set of parameters [$s(D)$, $a(D)$, and $\lambda(D)$ in Eqs. (5) to (7)] for the individual groups. Figure 5 represents the results. In each individual panel the histogram gives the fraction of animals that have died in the specified time interval either without pulmonary malignancy (blank) or with malignancy (shaded columns). The three curves on each panel give the estimated prevalences for the group according to the three models. These estimated prevalences are extended beyond the range of observed data in the individual panels. This is done for a better indication of the characteristic differences among the three models, and also because the inferred prevalence functions are utilized in the subsequent section for the construction of dose–effect relations.

The largest value of the combined likelihood corresponding to Eq. (8) ($L = -448.2$) is obtained for the accelerated failure time model, but the values for the shifted time model ($L = -449.2$) and the proportional hazards model ($L = -448.6$) are similar. From Fig. 5 one concludes that, in spite of characteristic differences of the prevalence functions and their variation with inhalation dose, these functions are similar for the relatively narrow time ranges with actual data in the individual groups. In the subsequent section it will furthermore be found that incidences computed on the basis of the prevalence functions from the three models are similar, i.e., that the choice of the model is not critical for the resulting risk estimates. On the other hand, one would have to design experiments with a wider range of death times at each dose if a discrimination between models were to be attempted. For moderate doses this might require more early sacrifices; for

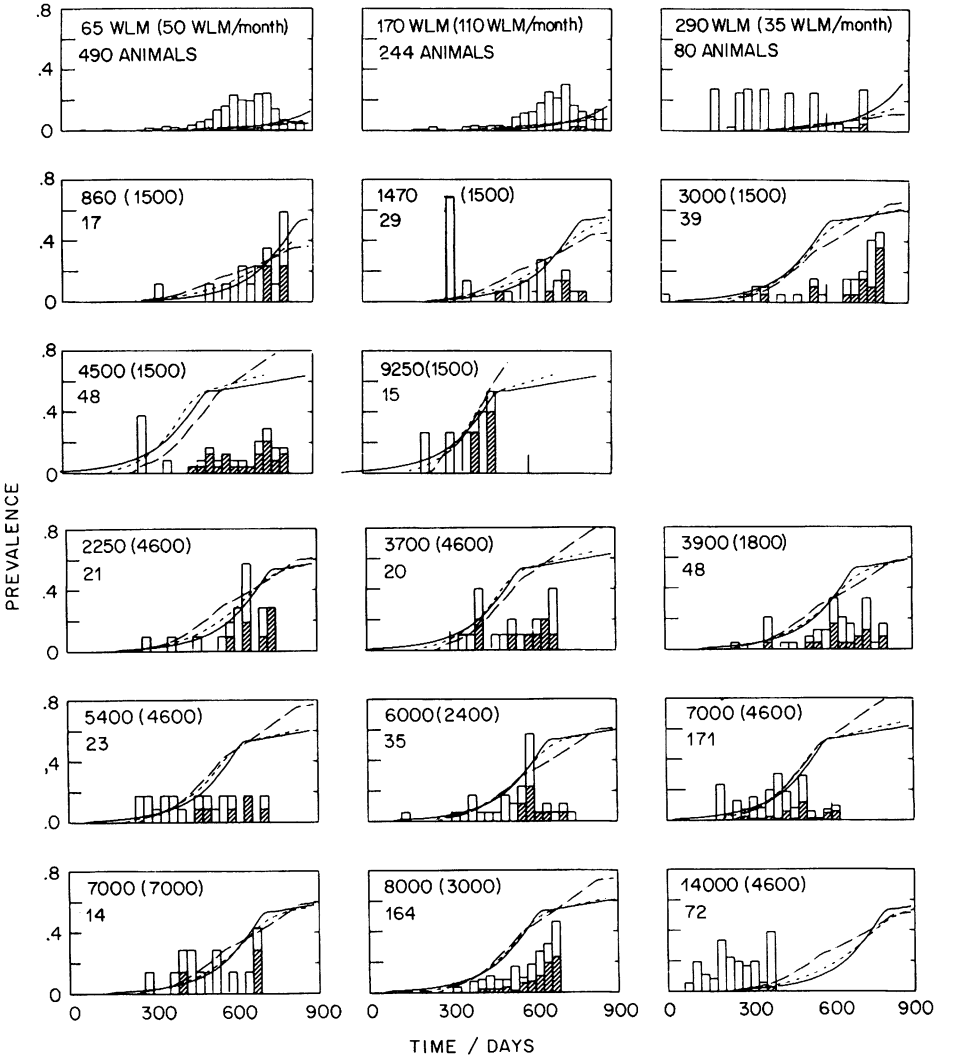

FIG. 5. The three estimates of the prevalence from the models. (Solid lines are from shifted time model; short broken lines are from accelerated time model; long broken lines are from proportional hazards model.) Each histogram gives the fraction of animals that died within each interval without (blank columns) and with (shaded columns) pulmonary malignancies. The data include sacrificed and life-span animals with pulmonary diagnostics.

high doses, where life shortening is substantial, large initial numbers of animals could be required with pulmonary diagnostics performed predominantly in animals that live relatively long.

Derivation of Mortality-Corrected Incidences

As stated earlier, the raw incidences do not represent a true dose dependence for the carcinogenic effect at dose levels where life shortening is substantial. It is

therefore desirable to compute a mortality-corrected quantity. One possibility is to define an adjusted incidence, I_D, as the probability of the animals incurring a malignancy, provided the mortality rates were those of the controls. The formal statement of this definition is

$$I_D = \int_0^{t_{max}} m(t) \cdot P_D(t) dt, \tag{9}$$

where $m(t)$ is the fraction of the control population dying per unit time interval at time t. The value $t_{max} = 850$ days has been taken as the maximum survival time. In Fig. 6 the adjusted incidences are given for all three models. The incidences for the exposed groups are plotted in Fig. 6 as excess over the assumed small control incidence of 0.003.

The adjusted incidences from the accelerated failure time model and their standard errors (see Appendix B) are compared to the raw incidences in Table II. This table also contains the acceleration factors a_k that correspond to the prevalence functions in Fig. 5. In the computations the baseline function, $P(t)$, is defined only up to an arbitrary factor in time, and, conversely, the acceleration factors are defined only up to the same common factor. However, the normalization has been chosen so that $P(t)$, i.e., the assumed prevalence for the controls ($a = 1$), yields the incidence 0.003.

It is of interest whether these results would fit a simple power function at low

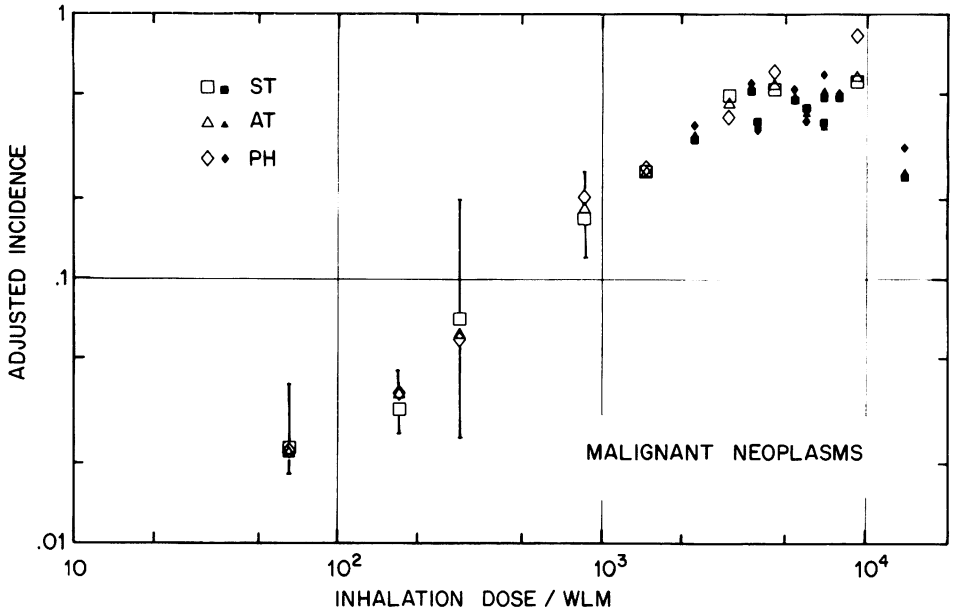

FIG. 6. Comparison of the adjusted incidences I_D (minus control incidence of 3×10^{-3}) as a function of the inhalation dose for the three basic models (ST: shifted time model; AT: accelerated time model; PH: proportional hazards model). The open symbols are used for the low-dose-rate range (<1600 WLM/month) and the solid symbols for the high-dose-rate range (>1600 WLM/month). Standard errors for all groups are given in Table II.

TABLE II

Comparison of Raw and Adjusted Incidences and Maximum Likelihood Estimates of Parameters for the Accelerated Failure Time Model

Dose D (dose per month) (WLM)	*Raw incidence*	*Adjusted incidence I_D*	*Acceleration factor a_k*
65 (50)	0.027 ± 0.007	0.025 (0.018–0.042)	1.30 (1.24–1.45)
170 (110)	0.046 ± 0.011	0.038 ± 0.011	1.48 ± 0.10
290 (45)	0 (+0.12)	0.065 ± 0.06	1.68 ± 0.39
860 (1500)	0.24 ± 0.10	0.18 ± 0.07	2.20 ± 0.25
1,470 (1500)	0.29 ± 0.11	0.26 ± 0.07	2.45 ± 0.23
3,000 (1500)	0.43 ± 0.08	0.47 ± 0.08	3.25 ± 0.49
4,500 (1500)	0.68 ± 0.08	0.54 ± 0.05	3.75 ± 0.52
9,250 (1500)	0.33 ± 0.12	0.58 ± 0.07	4.2 ± 0.78
2,250 (4600)	0.33 ± 0.10	0.35 ± 0.09	2.73 ± 0.25
3,700 (4600)	0.40 ± 0.11	0.51 ± 0.10	3.51 ± 0.71
3,900 (1800)	0.33 ± 0.07	0.39 ± 0.06	2.86 ± 0.22
5,400 (4600)	0.26 ± 0.09	0.48 ± 0.07	3.18 ± 0.31
6,000 (2400)	0.26 ± 0.07	0.43 ± 0.07	3.03 ± 0.25
7,000 (4600)	0.30 ± 0.05	0.51 ± 0.04	3.50 ± 0.24
7,000 (7000)	0.21 ± 0.11	0.39 ± 0.08	2.85 ± 0.26
8,000 (3000)	0.36 ± 0.04	0.50 ± 0.05	3.45 ± 0.35
14,000 (4600)	0 (+0.03)	0.26 ± 0.08	2.45 ± 0.26

inhalation doses. However, this requires a somewhat arbitrary selection of a dose cutoff. A regression with the data below 1000 WLM results in the fit

$$I_D = kD^p, \tag{10}$$

with

$$k = 3.4 \times 10^{-4} \pm 1.4 \times 10^{-4} \quad \text{and} \quad p = 0.92 \pm 0.07.$$

The value of k holds if D is in the units WLM.

It is evident from this result, and in particular from the observation at 65 WLM, that a sublinearity at low doses cannot be excluded, even though linearity cannot be rejected on the basis of the present data. On the other hand, a power in dose substantially in excess of 1 can be rejected.

If one assumes a linear dose dependence ($p = 1$), the linear regression yields the relation

$$I_D = c \cdot D \quad \text{with} \quad c = 2.0 \times 10^{-4}\,(\pm 0.5 \times 10^{-4})/\text{WLM} = 0.056\,(\pm 0.014)/(\text{J m}^{-3}\ \text{hr}). \tag{11}$$

I_D is not the only meaningful quantity for the construction of a dose–effect relation. It has been variously emphasized in studies of radiation risks (*42*, *43*) that a realistic assessment of detriments would have to be based not on numerical incidences but on the loss of tumor-free life. Radiation-induced malignancies that appear late in life contribute less to the decrement than early malignancies. Accordingly, it is of interest to compute a modified quantity, J_D, that represents the

average loss of tumor-free life span. Such a quantity that has been utilized in studies of mammary tumors in Sprague–Dawley rats (*29*, *37*) has been termed *effect period* in the report of UNSCEAR (*31*). The definition of UNSCEAR does not include the mortality correction. Such a correction will be applied, and the quantity effect period is then defined as

$$J_D = \int_0^{t_{max}} M(t) \cdot P_D(t) dt, \tag{12}$$

where $M(t)$ is the proportion of controls surviving at time t.

Figure 7 gives the numerical values of J_D. There is less agreement between the different models for this quantity than for the adjusted incidences, I_D.

CONCLUSIONS

The conventional analysis of the radon-daughter inhalation data permits the estimation of the dose dependence of life shortening and the dose dependence of the incidence of pulmonary tumors, uncorrected for life shortening. However, at higher doses the uncorrected incidence decreases due to life shortening. Maximum likelihood methods are required for the derivation of corrected incidences.

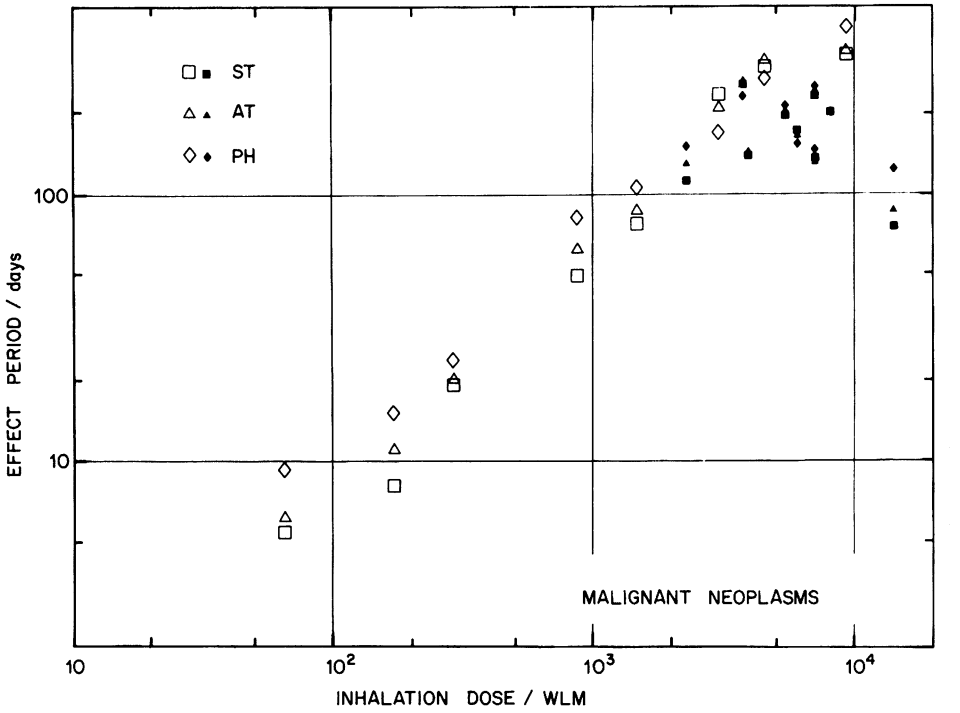

FIG. 7. The effect period J_D (see text) as a function of inhalation dose for the three basic models. (ST: shifted time model; AT: accelerated time model; PH: proportional hazards model). The open symbols are used for the low-dose-rate range (<1600 WLM/month); the solid symbols for the high-dose-rate range (>1600 WLM/month).

A further limitation of the conventional analysis results from the impossibility of mixing data from life-span experiments with data from sacrificed animals. Inclusion or exclusion of the data from the sacrificed animals can, depending on the temporal distribution of sacrifices, have considerable influence on the results. For this reason, too, the analysis of the radon-daughter inhalation experiments was based on maximum likelihood methods.

The investigation of nonlethal diseases discovered incidentally at death results in fully censored data. As Hoel and Walburg have shown (*5*), isotonic regression must be utilized instead of the Kaplan–Meier estimate that is applicable to right censored data. Isotonic regression has been applied to estimate the survival-adjusted prevalence of pulmonary malignancies as a function of time after exposure in the various groups. The results of this isotonic regression reflect the general increase of the prevalence with dose and with time after exposure. But, due to the small size of most of the experimental groups, no overall estimate of the prevalence as a function of dose and time could be inferred. For this reason the simultaneous likelihood fit was required, and it has provided the desired overall estimates. They are largely independent of the models chosen as the basis of the simultaneous fit. The same is true for the adjusted incidences obtained by integration over the prevalences.

The application of a simultaneous maximum likelihood fit is not new in itself. For right censored data a method based on the proportional hazards model has existed for some time and has been widely applied (*32*). No similar treatment had earlier been attempted with the fully censored data obtained for nonlethal diseases. As exemplified here with the radon studies, the computations require nonlinear optimization; such algorithms are widely available.

An advantage of the method is the independence from any particular model. It has therefore been applied not only with the proportional hazards models, but also with two other models that assume either a dose-dependent time shift of the prevalence function or a change of the prevalence function that corresponds to an acceleration in time. All three models were nonparametric, i.e., no analytical expression was postulated for the dose or the time dependence of the prevalence. The computational procedures are similar for the different models.

The methods that have been applied here to radon-daughter inhalation studies may also prove useful in other inhalation studies. However, they require that the pulmonary neoplasms do not appreciably contribute to mortality. While this appears to be the case with rats exposed to radon daughters, the condition may be not met in other species or with other radioisotopes.

APPENDIX A: SUMMARY OF RESULTS FOR DIFFERENT TYPES OF PULMONARY NEOPLASMS

Prevalences have been estimated in this article for pulmonary malignancies rather than all pulmonary tumors. The reason for this somewhat arbitrary restriction is the relatively small number of benign pulmonary tumors that have been found. It was accordingly felt that the advantage of a sharper pathological criterion outweighs the gain in statistical accuracy that would accrue from inclusion of the

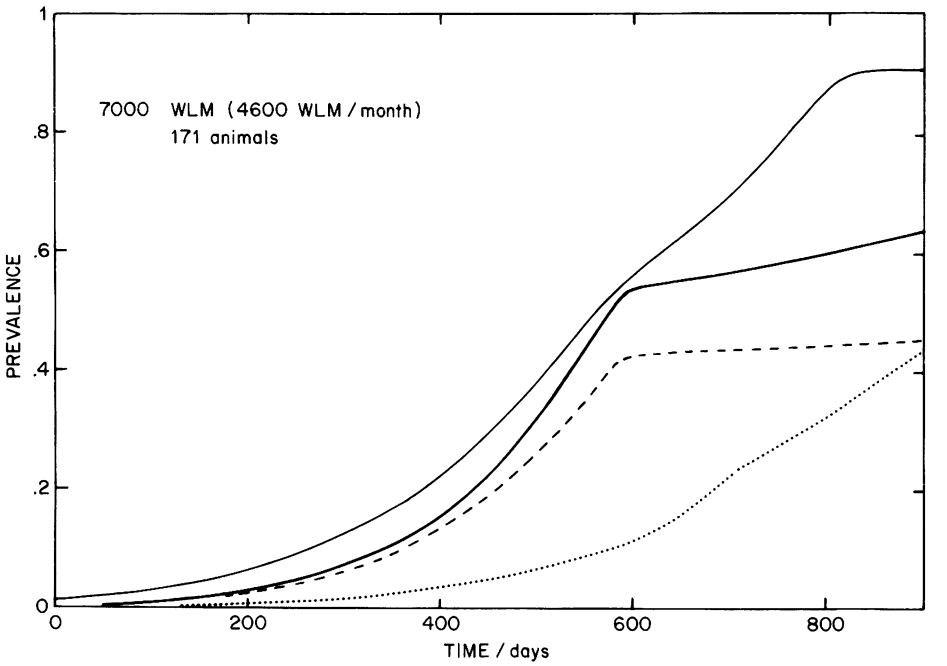

FIG. 8. Prevalance functions for the group exposed to 7000 WLM (4600 WLM/month) from the shifted time model for all pulmonary tumors (upper solid line), for pulmonary malignancies (lower solid line), for bronchogenic malignancies (broken line), and for bronchoalveolar malignancies (dotted line).

benign tumors. There is nevertheless some interest in the discrimination between benign and malign tumors and between malignancies from different cell types.

A separate analysis of benign tumors is not feasible because benign tumors have been ascertained only in the absence of malignancies of the same cell type. In the whole study, there are only 37 animals with benign tumors and no malignancies; there are, in addition, 4 animals where benign tumors have been found simultaneously with malignancies in the other cell type. In contrast there were 231 animals with pulmonary malignancies. The number with malignancies of both cell types was 15.

In view of the relatively small numbers one cannot expect to establish, with statistical certainty, possible differences in the time course and dose dependence of the prevalence between malign and benign tumors. Nevertheless, Fig. 8 gives an overall comparison of the prevalence obtained for all pulmonary tumors (upper solid line), all pulmonary malignancies (lower solid line), bronchogenic malignancies (broken line), and bronchoalveolar malignancies (dotted line). The results are from a simultaneous fit of all groups, but Fig. 8 refers only to the large experimental group with 7000 WLM (4600 WLM/month). These additional computations have been performed with the shifted time model; similar results were obtained with the other models.

The derived time shifts for the different groups and for the different types of neoplasms are not given in tabular form but in correlation diagrams in Fig. 9.

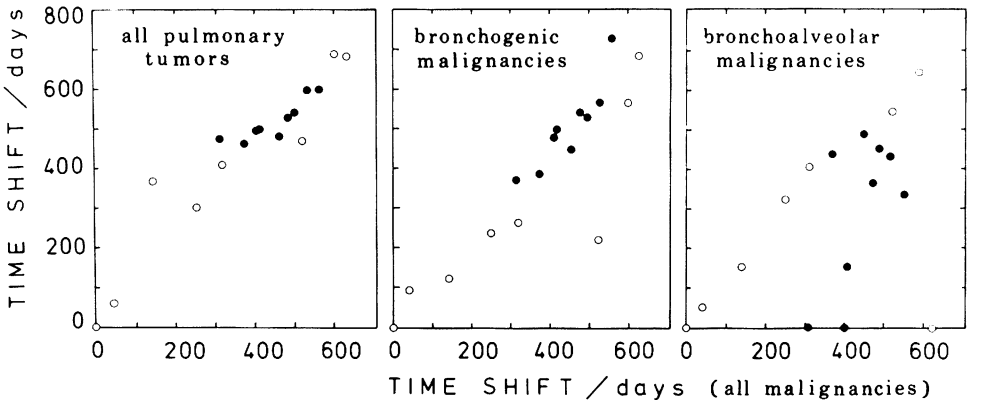

FIG. 9. Correlation diagrams of the time shifts for all pulmonary malignancies (abscissa) versus those for all pulmonary tumors, for bronchogenic malignancies, and for bronchoalveolar malignancies.

Among all pulmonary malignancies, all pulmonary tumors, and the bronchogenic malignancies no systematic difference is apparent. However, one notes that the time shifts for bronchoalveolar malignancies at high doses tend to be less than those for the other neoplasms.

Figure 10 compares the adjusted incidences for the different types of pulmonary tumors. A decrease at high doses and higher dose rates is apparent only for the bronchoalveolar malignancies. This is in line with Fig. 9.

APPENDIX B: ESSENTIALS OF THE NUMERICAL COMPUTATIONS

Likelihood Equation for Finite Time Intervals

Equation (4) for the log-likelihood contains the exact times of death of the animals. The actual computations are performed on a discrete time grid with intervals of 30 days or, in the case of the accelerated time model, with a logarithmic interval of width 0.08. The data are related to this grid by suitable interpolation. In this way the total number of variables to be optimized in a computation is reduced to the estimates at 50 grid points for the prevalence function and to 16 additional variables for the parameters for the individual groups. The log-likelihood is then

$$L = \sum_{i=1}^{I} [M_i \ln (P(t_i)) + (N_i - M_i) \ln (1 - P(t_i))], \qquad \text{(B1)}$$

where t_i ($i = 1$ to I) are the discrete times, N_i is the total number of deaths in interval i, and M_i is the number of animals with malignancy in interval i.

The simultaneous solution for several experiments requires, even for the simple constraint of monotonicity, an iterative optimization algorithm; the method of steepest descent in a computer version, GRGA, of Abadie and Guigou[4], has been applied in the present analysis. With the GRGA algorithm it is readily possible to replace

[4] J. Abadie and J. Guigou, *Gradient réduit généralisé.* Internal Report HI-069/02, Electricité de France, 1969.

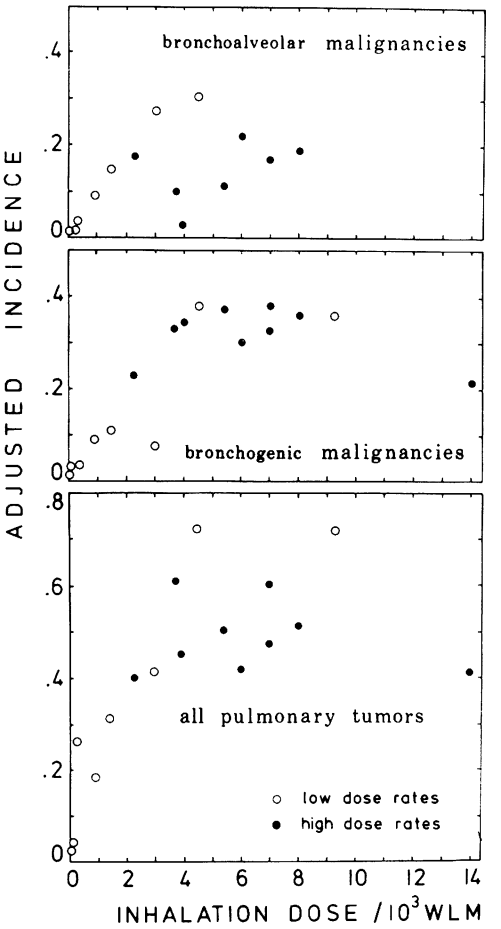

FIG. 10. Comparison of the adjusted incidences for all pulmonary malignancies, for bronchogenic malignancies, and for bronchoalveolar malignancies. Open dots are for the low-dose-rate range (<1600 WLM/month); solid dots for the high-dose-rate range (>1600 WLM/month).

the monotonicity constraint by a constraint that leads to smooth curves. The constraint actually used was therefore convexity of $\ln(P(t))$. Figure 11 uses the example of a single but relatively large group for a comparison of the naive estimates (dots), the isotonic regression with the exact times of deaths (step function), and the computation with convexity constraints (continuous curve) applied only to this individual group.

Joint Likelihood for the Shifted Time Model and the Proportional Hazards Model

From Eqs. (4) and (5) one obtains the following relation for the log-likelihood in the shifted time model:

$$L = \sum_{k=1}^{K} \left[\sum_{i=1}^{I_k} \ln\left(P(t_{ik}^{+} + s_k)\right) + \sum_{j=1}^{J_k} \ln\left(1 - P(t_{jk}^{-} + s_k)\right) \right] \qquad \text{(B2)}$$

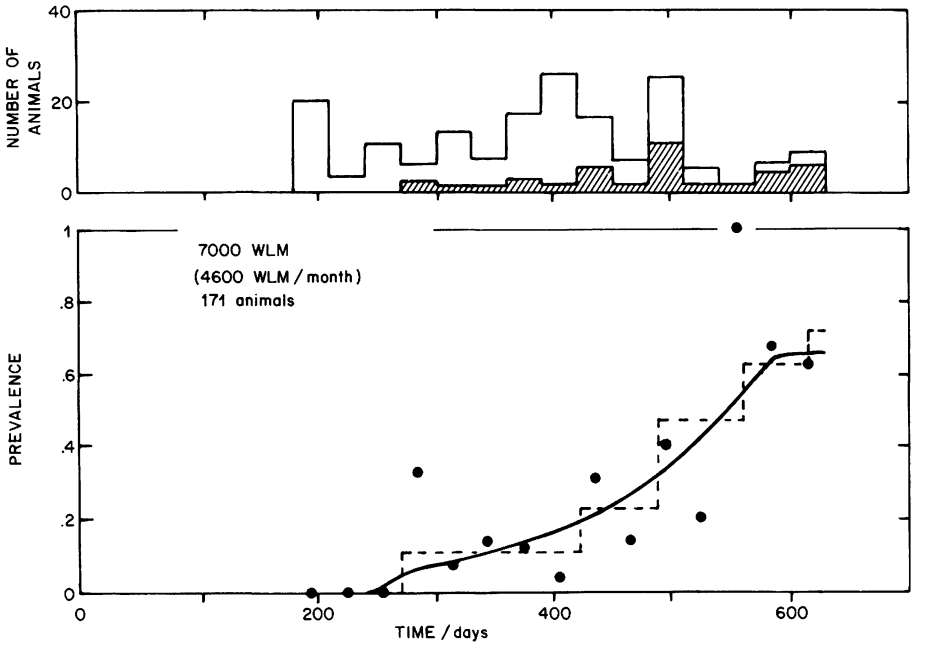

FIG. 11. Illustration of the results of maximum likelihood estimation of the prevalence by its application to a single large group of animals exposed to an inhalation dose of 7000 WLM. The upper panel represents the total number of animals which died in the intervals (blank areas: animals without pulmonary malignancies; shaded areas: animals with pulmonary malignancies). The lower panel gives the estimated prevalence functions (step function from isotonic regression; continuous function from regression with convexity constraint). Dots are the ratios of the number of animals dead with malignancies to the total number of animals dead.

[symbols as in Eq. (8)].

The proportional hazards model leads to a more complicated relation because the baseline function in this model is not the prevalence but the related quantity cumulative tumor rate, $R(t)$. With the proportional hazards assumption [Eq. (7)] and the relation [see Eq. (2)]

$$R(t) = -\ln(1 - P(t)) \tag{B3}$$

one obtains

$$P_D(t) = 1 - \exp(-\lambda(D) \cdot R(t)) \tag{B4}$$

and

$$L = \sum_{k=1}^{K} \left[\sum_{i=1}^{I_k} \ln(1 - \exp(-\lambda_k \cdot R(t_{ik}^{+}))) - \sum_{j=1}^{J_k} \lambda_k \cdot R(t_{jk}^{-}) \right]. \tag{B5}$$

The same computer program is used for both the shifted time model and the accelerated time model; this requires the utilization of the logarithm of time in the case of the accelerated time model. With the monotonicity constraint, convergence of the optimization procedure is fast and insensitive to the initial estimates. With the convexity constraint convergence can be problematic, and the proper selection

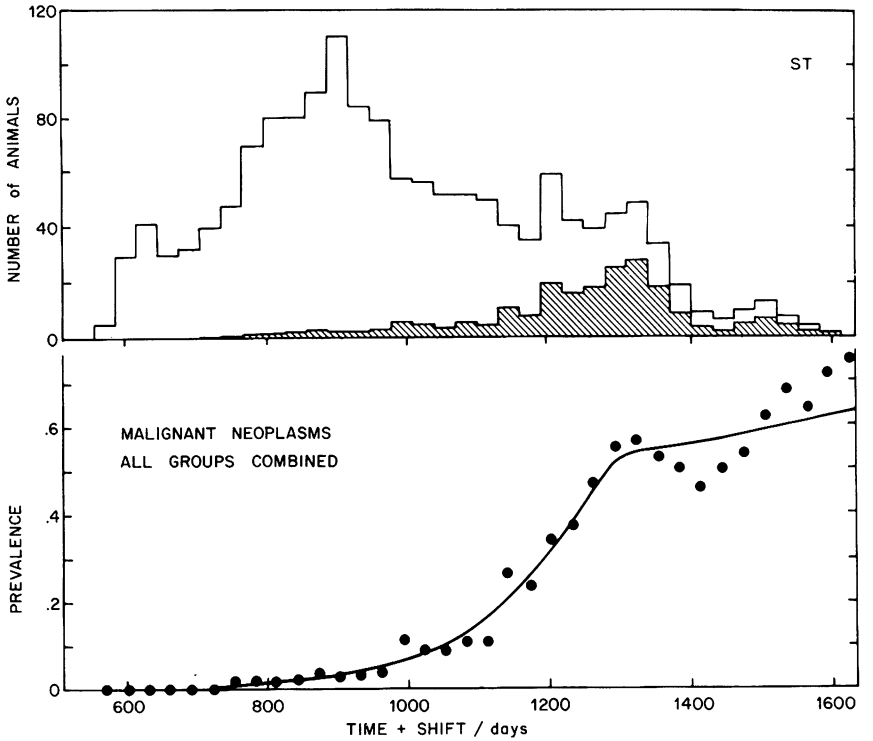

FIG. 12. The prevalence from the shifted time model as a function of converted time (actual time plus the time shift that has been obtained for each group relative to the control group). The upper panel represents the pooled total of animals from all groups that died without (blank columns) and with (shaded columns) pulmonary malignancies in each interval. Dots are the ratios of the number of animals dead with pulmonary malignancies to the total number of animals dead.

of initial estimates is critical. The initial estimates were usually obtained on the basis of the results of the simpler optimization with monotonicity as a constraint. Repeated computations with varying starting points have been performed to verify the stability of the solutions.

The maximum likelihood values that were obtained, overall and for the individual groups, were within the theoretically expected range of values. Presentation of the full data is impractical, but Figs. 12 and 13 are included to illustrate the quality of the overall fit. In these figures the individual groups of animals are superimposed according to the respective maximum likelihood shifts or acceleration factors. The resulting histograms of the total number of animals and the number of animals with malignancies are given in the upper panels of the graphs. In the lower panels the maximum likelihood prevalence is compared to the ratios of animals with malignancy to all animals in the respective intervals. These curves help in judging the applicability of the models.

The standard errors for the raw incidences in Fig. 3 were obtained by using the binomial distribution (for 0 observed events the 75% confidence range was used). The standard errors for the adjusted incidences were obtained through the standard

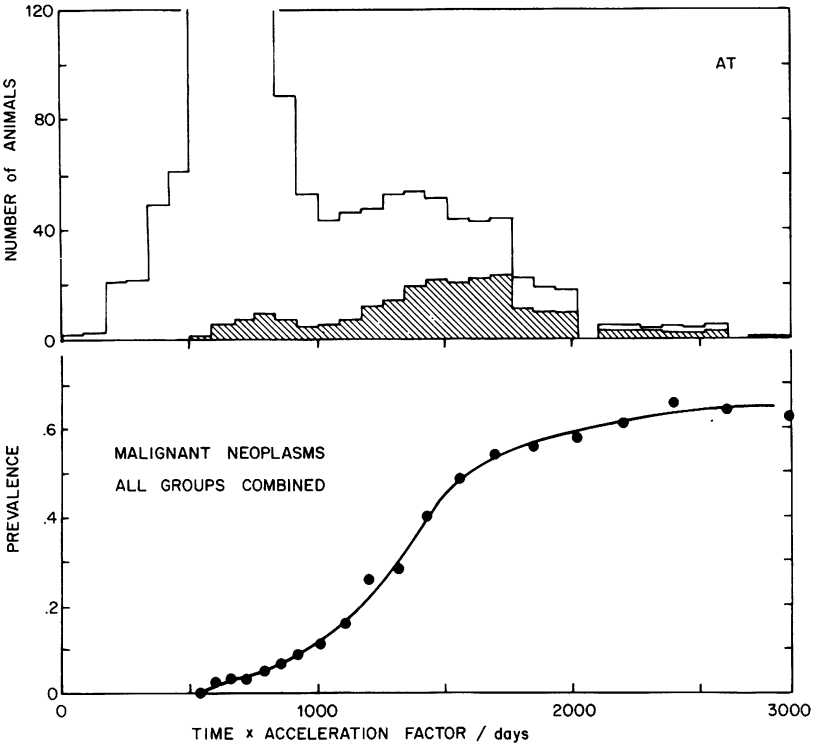

FIG. 13. The prevalence from the accelerated time model as a function of converted time (time multiplied by the acceleration factor that has been obtained for each group relative to the control group). The upper panel represents the pooled total of animals from all groups that died without (blank columns) and with (shaded columns) pulmonary malignancies. The missing part of the histogram represents 14% of all animals included in the computation. Dots are the ratios of the number of animals dead with pulmonary malignancies to the total number of animals dead.

errors of the acceleration factors or through the corresponding parameters for the other models. The standard errors of the parameters are obtained on the basis of the Fisher statistics as described in a previous application of the optimization procedure (*41*). This is an approximate method, applicable to large numbers of animals. The errors are not symmetrical but have been averaged in Table II except for the first group where the asymmetry is particularly large. The parameters and their standard errors are given only for the accelerated time model.

ACKNOWLEDGMENTS

We thank our colleagues Benno Schüllner and Štěpánka Riedmann for valuable help in the computations. Critical comments and useful advice from Drs. Harald H. Rossi and Art Petersen were greatly appreciated.

RECEIVED: September 10, 1981; REVISED: February 1, 1982

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