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RADIATION RESEARCH **98**, 519–535 (1984)

Comparison of the Induction of Pulmonary Neoplasms in Sprague–Dawley Rats by Fission Neutrons and Radon Daughters

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Pulmonary carcinomas were recorded in a life-span experiment of male Sprague–Dawley rats exposed to fission neutrons. Mortality-corrected prevalences are obtained by the method of isotonic regression. In a second part of the paper a comparison is made with data obtained earlier for radon-daughter inhalations in the same strain of rats. A simultaneous maximum likelihood analysis is applied jointly to all experimental groups from the radon inhalation and the fission neutron study. The dependence of the resulting coefficients for the different groups on absorbed dose or inhalation dose permits a derivation of equivalence ratios. At low doses the equivalence ratio is 3 WLM (working level months) of radon-daughter exposure to 1 mGy of fission neutrons. At higher doses the equivalence ratio decreases. The neutron data are also utilized to derive mortality-corrected lifetime incidences of pulmonary carcinomas in the exposed animals. At low doses the relation is consistent with linearity, but sublinearity (dose exponent < 1) cannot be excluded.

INTRODUCTION

In an experiment that is part of an ongoing investigation, groups of male Sprague–Dawley rats were exposed to different doses of fission neutrons and γ rays. The animals are allowed to live out their life, and the full spectrum of resulting neoplasms is assessed at necropsy. The γ-ray part of the experiment is unfinished and some of the exposures are still to be performed. It will therefore be several years before a final report on the experiment can be given. However, the neutron experiments are largely completed [for preliminary results see (*1*)], and an important part of the results, the data on pulmonary neoplasms, can be presented. These results are topical because they permit a comparison with the findings of the earlier radon-inhalation study (*2*). Any possibility to compare carcinogenesis by neutrons and α emitters is of particular

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interest in view of current discussions of a possible revision of quality factors for densely ionizing radiations. Furthermore, animal studies have taken added importance since the revision of the atomic bomb dosimetry (*3*) has removed, at least temporarily, what seemed to be the only source of knowledge on the induction of malignancies in man by neutrons.

Accordingly, this first report deals with pulmonary neoplasms. The data will first be given for neutrons separately; a second part of the paper contains a comparative analysis of the results of the radon-inhalation and fission-neutron experiments.

MATERIAL AND METHODS FOR THE NEUTRON EXPERIMENT

The technical details for the radon-daughter-inhalation studies have given previously (*2*). The study of fission-neutron-induced pulmonary neoplasms is part of a broader program that is aimed at a comparison of the carcinogenic effects of different types of ionizing radiations. The program started in 1969 with an extensive investigation of pulmonary neoplasms induced by inhaled α emitters. The investigation of the carcinogenic effects of whole-body neutron irradiation has been initiated more recently. Among all the observed neoplasms in the neutron experiments only the pulmonary tumors will be the objective of the present analysis because they permit a comparison of the effectiveness of neutrons and radon daughters. A comparison to the effect of γ rays must await the termination of the experiment.

As in the earlier radon-inhalation studies, male Sprague–Dawley rats were used that were 3 months old at the beginning of the exposures. The whole-body neutron exposures were performed at the biology irradiation facility of the reactor "Nereid" at CENFAR. This experimental facility permitted the simultaneous exposure of two groups of 20 animals each. Table I gives in summary form the protocol of the experiment. In the first column neutron absorbed doses are quoted; the total absorbed dose includes a γ-ray component and is larger by the factor 1.3 than the neutron absorbed dose. The energy spectrum of the neutrons has been considered in an earlier publication (*4*).

For the lower doses the exposures were performed during a period of 22 hr per day with dose rates selected accordingly. To ensure sufficient survival of the animals, the highest doses and part of the intermediate doses were given over the total periods stated in column 2 of Table I; in this case, too, there was a 2-hr interruption of the exposure each day.

Animals were kept according to standard laboratory conditions described previously (*5*). The animals were kept 10 per cage during the exposure and 8 per cage in the pre- and postirradiation periods. This differs from the conditions in the earlier radon experiments where there were 10 animals per cage, a difference that may be responsible for the somewhat longer survival times of the control animals in the neutron experiment. The neutron exposures to different doses were not performed simultaneously but over a period of 2 years; consequently a randomization of the exposed animals throughout the experiment was not feasible.

The pathological classification of lung malignancies is the same as described earlier in the radon-inhalation studies (*2*). Pulmonary carcinomas are recorded as *bronchogenic* or *bronchoalveolar* according to histological criteria proposed by Masse (*6*). Benign tumors of cells of the same origin as the carcinomas are recorded as adenomas. In the earlier radon studies there have been somewhat more stringent criteria for scoring adenomas rather than adenomatosis; a comparison between neutrons and radon that includes adenomas is therefore not possible. As in the previous studies, only the most severe lesion for each cell type was recorded, even if other lesions were present. Accordingly, Table I gives for each group the number of animals with at least one carcinoma, the number of animals with at least one carcinoma of each type, and the number of animals with either a carcinoma or an adenoma.

In the radon-daughter-inhalation studies no lung sarcomas had been observed. In the present experiment 13 pulmonary sarcomas have been registered. They are not included in the comparative analysis of the data for neutron irradiations and radon-daughter exposures. Almost all sarcomas were angiosarcomas, and they appear to be lethal since they rapidly cause severe hemorrhage. The sarcomas are reported in Table I, but are otherwise not part of the subsequent analysis.

In the earlier analysis of the radon inhalation experiments a number of reasons have been stated that the lung carcinomas do not substantially contribute to life shortening. The essential argument has been that the lung carcinomas and adenomas in the Sprague–Dawley rats grow slowly and affect only limited

TABLE I

Protocol of the Neutron Experiment with Reference to Pulmonary Neoplasms

Neutron absorbed dose (Gy)	*Irradiation period (days)*	*No. of animals*	*No. of animals examined*	*Mean life span ± standard error (days)*	*No. of animals with lung carcinomas (No. of carcinomas)*	*No. of animals with*		*No. of animals with lung carcinomas or adenomas*	*No. of animals with lung sarcomas*
						Bronchogenic carcinomas	*Bronchoalveolar carcinomas*		
0.012	1	150	148	752 ± 12	4	3	1	8	3
0.02	1	150	149	741 ± 12	2	1	1	4	1
0.06	1	80	77	679 ± 19	4	1	3	6	—
0.1	1	78	75	669 ± 14	6	5	1	13	—
0.3	1	75	71	584 ± 17	9	4	5	13	2
0.5	1	75	72	525 ± 16	10	7	3	14	2
1.5	1 14	61 40	94	487 ± 13	14 (16)	5	11	28	3
2.3	1 14	40 60	99	450 ± 12	18 (19)	9	10	26	1
3.9	23	20	20	390 ± 25	—	—	—	1	—
5.3	42	19	19	340 ± 23	4 (5)	2	3	4	1
8	42	20	20	240 ± 11	2	1	1	2	—
Totals		868	844		73 (77)	38	49	119	13

parts of the lung. Exceptions to this rule have been found only with chemical carcinogens. In the present neutron experiment, as in the earlier radon studies, the pathology has never indicated lethality due to pulmonary carcinomas. In view of these facts statistical methods are used in the subsequent analysis that apply to tumors found incidentally, i.e., in nonlethal context [for this terminology see (7)].

RESULTS OF THE NEUTRON EXPERIMENTS

Conventional Evaluation

A first synopsis of the neutron results will be given in terms of a conventional analysis, although it does not account for the influence of life shortening on tumor incidence.

Even moderate neutron doses shorten substantially the mean life span of the animals, as shown in Fig. 1. As stated, the highest doses were protracted to avoid excessive life shortening, i.e, to keep the number of surviving animals sufficiently large for the statistical analysis of neoplasms. The protraction may largely account for the bend in the curve of the mean survival time and for its more shallow decrease at higher doses.

Figure 2 gives for each group as a function of time after exposure the fraction of animals dead without (shaded areas) and with lung carcinomas (cross-hatched areas). In the graphs only the lung carcinomas are taken into account, although there have also been 13 pulmonary sarcomas. The sarcomas were excluded for the reasons stated in the preceding section.

In view of the small numbers of pulmonary carcinomas certain experimental groups were combined for Fig. 2 and for the subsequent analysis. The two groups exposed to 1.5 Gy were pooled, as were the two groups exposed to 2.3 Gy. The three groups exposed to the highest doses were also pooled and were assigned the average dose of 5.7 Gy.

Figure 3 gives the raw incidences of lung carcinomas as a function of neutron absorbed dose. In this logarithmic representation the control incidence is not subtracted; from all earlier experiments the control incidence can be taken to be about 0.003. Figure 3 indicates that the incidence never exceeds 20%, which is substantially below values observed in the radon experiments. This observation and the decrease of the raw incidences at the highest doses may be artifacts caused by the severe life shortening

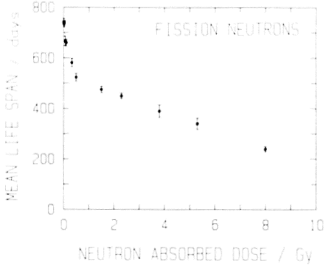

FIG. 1. The mean life span (after start of exposure at age 90 days) with standard error as a function of neutron absorbed dose. The two points at 1.5 and 2.3 Gy combine dose groups with short and protracted irradiations.

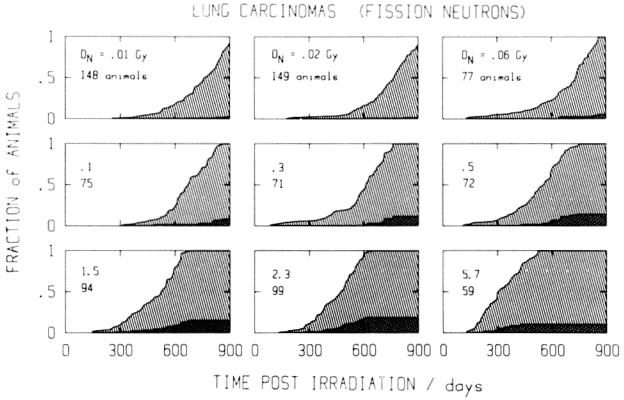

FIG. 2. The fraction of animals dead without (single-shaded area) and with pulmonary carcinomas (cross-hatched area) as a function of time after beginning of irradiation. In this and all subsequent graphs the three groups with the highest neutron doses have been pooled.

in the neutron experiment. A competing risk corrected analysis is therefore indispensable.

Although there can be no analysis of the dose dependence of the lung sarcomas, the comparison of the different types of pulmonary malignancies is of interest. Figure 4 (upper panel) indicates, for the neutron experiment, the time course of the induction of the three basic types: bronchogenic carcinomas, bronchoalveolar carcinomas, and lung sarcomas. Sum distributions of the observation times of the three tumor types are given. They are the result of the superposition of all data from all groups in the neutron study. In this representation, where the curves are normalized to the total number of neoplasms of each type, the lung sarcomas are notable for their earlier appearance. It must, however, be noted that the earlier appearance could be a mere artifact of the lethality prompting their detection. In contrast, carcinomas tend to be observed later, after death for unrelated reasons has occurred. One may further note the earlier appearance of the bronchoalveolar carcinomas in comparison to the bronchogenic carcinomas. This finding is in contrast to observations in the radon experiments where the bronchogenic carcinomas tended to appear earlier than bronchoalveolar carcinomas (Fig. 4, lower panel).

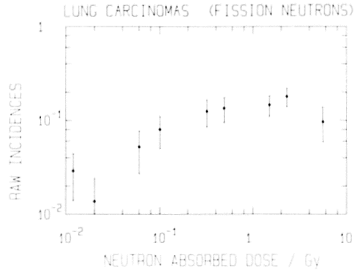

FIG. 3. Raw incidence as a function of neutron absorbed dose. The raw incidence in a group is the ratio of the number of animals with pulmonary carcinomas to the total number of animals examined.

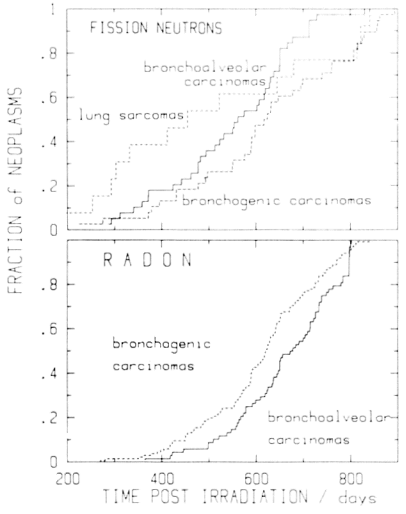

FIG. 4. Sum distribution of the times of death for animals with pulmonary malignancies of the three different types with all dose groups pooled for the neutron experiment (upper panel) and for the radon experiment (lower panel).

For the reasons stated before, only pulmonary carcinomas will be considered in the following, and no distinction will be made between the two types of carcinomas. However, the two types are considered separately in the Appendix, and this will permit the conclusion that a similar effectiveness ratio of neutrons versus radon applies.

Analysis Corrected for Competing Risks

The derivation of the time and dose dependence of the rates of radiation-induced tumors requires methods that correct for intercurrent mortality. Two characteristically different situations must be distinguished and will be considered subsequently. However, it is desirable to restate first the definitions of the quantities that will be referred to and that are essential to the analysis.

The *tumor rate,* $r(t)$, is the probability per unit time at time t for an animal still alive to develop the tumor. A quantity that can be more readily estimated is the *cumulative tumor rate:*

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

The cumulative tumor rate will be referred to in the subsequent discussion, but its estimates will not actually be derived. Instead a related, more familiar quantity, the prevalence, $P(t)$, will be utilized; it is the competing risk corrected probability of an animal to develop the tumor before time t. The relation between prevalence and cumulative tumor rate is

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

Entirely different mathematical methods must be used for the estimation of tumor rates or tumor prevalences for manifest tumors and for tumors observed incidentally. The first and more familiar case is that of manifest tumors, i.e., rapidly lethal tumors or tumors that are palpable and are therefore readily found. The resulting data are termed *right-censored,* and this expression refers to competing risks that terminate the observation for some of the animals before they have developed the tumor. For right-censored data the familiar Kaplan–Meier or product-limit estimate (*7*) can be used to obtain the competing risk corrected incidence of tumors as a function of time post irradiation. The similar and even simpler sum-limit estimate can be used to derive the cumulative tumor rate as a fuction of time postirradiation (*8*).

A second and characteristically different situation is that of *double-censored* data. Such data arise with tumors that are found incidentally because they are not directly observable and they do not contribute to lethality. In experiments with systematic serial killing the estimate of the tumor prevalence is simple, but large numbers of animals are required. In survival experiments or in experiments that combine survival data with data from sacrificed animals the estimation of the prevalence is more difficult. However, as pointed out by Hoel and Walburg (*9*) and as exemplified in our earlier report on the radon inhalation studies, the method of *isotonic regression* can, for double-censored data, take the place of the Kaplan–Meier estimate that is applicable only to right-censored data. Isotonic regression requires a relatively simple computer algorithm (*8, 10*), and provides a maximum likelihood estimate of the dependence of the tumor prevalence on time postirradiation; the underlying assumption is that the prevalence cannot decrease in time. Two recent monographs (*7, 11*) survey the available statistical methods for right- or double-censored data and the relevant theoretical background.

Figure 5 gives the isotonic regression estimates of the prevalence of lung carcinomas for the groups exposed to different neutron doses. While isotonic regression is the analog of the Kaplan–Meier estimator, it has the disadvantage that there is no simple method to derive standard errors to the resulting estimates.

It may be noted that isotonic regression does not permit the inclusion of the pulmonary sarcomas. Because these are found in a lethal context their cumulative incidence would have to be obtained separately by the Kaplan–Meier estimator; however, their total number is too small for a separate analysis.

The individual isotonic regression estimates are a first step in the analysis. However,

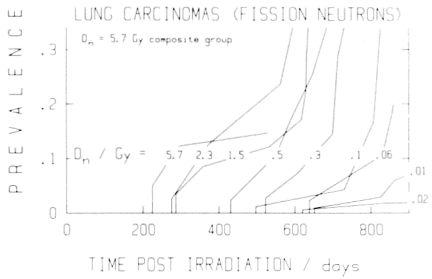

FIG. 5. Estimates of the prevalence of pulmonary carcinomas from isotonic regression.

it is evident that the separate estimates for relatively small groups are subject to considerable statistical uncertainties that make it difficult to derive coherent time and dose dependences of the tumor prevalence. More sophisticated methods are therefore required to obtain simultaneous maximum likelihood estimate of the prevalence for a set of experimental data. Such methods have been applied to the radon-daughter-inhalation studies, and they will also be utilized for the comparison of the neutron and the radon data.

COMPARISON OF THE NEUTRON AND THE RADON DATA

Principles of the Analysis

A joint estimate of the time dependences of the tumor prevalence for a number of experimental groups could be obtained by postulating an analytical expression for the prevalences as a function of time with one or more parameters dependent on absorbed dose. Examples of such approaches are the assumption of a log-normal distribution of the prevalence, or the more commonly invoked Weibull model that is based on the postulate that the tumor rates are proportional to a power of time. However, a more general approach was chosen in our analysis of the radon-inhalation experiments, and the same approach is utilized in the present comparison of the neutron and the radon data. In this treatment no specific form of the prevalence as a function of time is postulated. Instead it is assumed that the shape of the prevalence function for each experimental group adheres to the same baseline function. Apart from the evident constraint of monotonicity, the baseline function is not specified a priori. All that is required is an assumption on how the prevalence changes with dose; different simple models are considered for this purpose. With these models one can determine numerically that baseline function and those parameters of changes that bring the prevalence functions closest to the data in terms of maximum likelihood. Three different models have been utilized in the radon study, and it has been found that the results were not critically dependent on their choice.

The *proportional-hazards model* for the simultaneous nonparametric maximum likelihood analysis of tumor rates has been most common for the analysis of right-censored data. Its popularity is largely due to the simplicity of the solution developed by Cox [for the algorithm see (*12*)]. In this model the reference quantity is the tumor rate or the cumulative tumor rate, and while no assumption is made concerning the time dependence of the tumor rate, it is postulated that the influence of the treatment consists of an increase in the tumor rates or in the cumulative tumor rates by a factor that is dependent on dose but not on time. The proportional hazards factor, $\lambda(D)$, depends on the type of radiation and on absorbed dose. The formal statement of the proportional-hazards model is

$$R(t, D) = \lambda(D) \cdot R_0(t). \tag{3}$$

The proportional-hazards model has been widely applied to right-censored data, but it is evident that the assumption of a proportional change of tumor rates need not be in agreement with all experimental data on radiation carcinogenesis. Alternative models may therefore serve the same purpose, and this is particularly true in the case

of double-censored data where the proportional-hazards model loses its advantage of computational simplicity.

In the present study an analysis in terms of the proportional-hazards model is actually impracticable due to the structure of the data. Such an analysis would require a substantial overlap in the periods where deaths occur in different groups. If there is little or no overlap it is impossible to estimate proportionality factors between groups. The substantial life shortening in some of the neutron-exposed groups leads to a lack of overlap, and alternatives to the proportional-hazards model must therefore be utilized.

One alternative is the *accelerated-failure-time* model (*12*). It is based on the assumption that the treatment changes the baseline function in a way that corresponds to an acceleration of time postirradiation. Formally this can be expressed by the relation

$$P(t, D) = P_0(a(D) \cdot t). \tag{4}$$

One may note that the proportional-hazards model and the accelerated-time model are not mutually exclusive; the familiar Weibull model is a special case of both models.

The accelerated-time model has yielded the best fit to the radon-daughter-inhalation data in the earlier analysis. However, the proportional-hazards model and a further alternative the *shifted-time model* have also been consistent with the data. The shifted-time model postulates that specified values of the prevalence are reached earlier in the treated groups, with a time difference that depends on the treatment. This is expressed by the equation

$$P(t, D) = P_0(t + s(D)). \tag{5}$$

For the stated reasons only the accelerated-time model and the shifted-time model are utilized in the present analysis. The maximum likelihood equations for the different models have been given earlier (*2*) and therefore need not be repeated. The numerical methods are identical to those in the earlier study of the radon-inhalation data.

Results of the Joint Maximum-Likelihood Analysis

A comparison of the effects of radon-daughter-inhalation and fission-neutron irradiation could, in principle, be based on prevalence functions obtained independently for the radon and neutron experiments. The baseline functions obtained in the separate analyses would, however, be somewhat different, and any comparison would then contain some degree of arbitrariness. The present results were therefore derived from a simultaneous maximum-likelihood fit for all radon and neutron data together. The resulting baseline function is therefore co-determined by both data sets, and a comparison in terms of the dose-dependent parameters is straightforward; depending on the model that is utilized the parameters are the time shifts, $s(D)$, or the acceleration factors, $a(D)$.

The postulate of a common baseline function is somewhat arbitrary. For this reason a separate analysis of the neutron data has also been performed to find possible evidence for differences in the time dependence of the prevalence for neutron exposures and for the radon-inhalation studies. However, no substantial differences were seen. The acceleration factors or time-shift values obtained in the separate analyses are

consistent with those from the joint analysis. The joint analysis has the advantage of removing any element of arbitrariness in the comparison between the effects of neutrons and radon.

The computations were performed with the same computer programs as in the radon study; this includes the GRGA algorithm (*13*) for nonlinear optimization. Figure 6 gives the prevalence functions that were obtained in the simultaneous maximum likelihood analysis for neutron-exposed animals. The curves for the numerous radon-inhalation experiments are not reproduced since they do not differ appreciably from those obtained in the earlier analysis (*2*).

From Fig. 6 it is evident that the prevalence functions from the shifted-time model (ST) and the accelerated-time model (AT) are in general agreement. One concludes, as in the earlier analysis of the radon data, that the results are not critically dependent on the choice of the model.

As in the earlier analysis of the radon data, competing risk-corrected incidences are derived by integrating the estimated prevalence functions over a standardized distribution of life spans. The same life distribution as in the earlier radon study is utilized. This requires some justification. In the present experiment the mean life span for animals exposed to the lowest neutron doses is larger than with the standardized distribution. The difference may appear to be due to the fact that only 8 animals were kept per cage in the neutron experiment while there were 10 animals per cage in the radon study. This difference is an undesirable element in the present comparison, but gross errors are avoided by the fact that the analysis is corrected for changes in life spans. Nevertheless one could argue that the lengthening of life spans might be accompanied by a corresponding retardation of spontaneous or radiation-induced tumor prevalences, with a resulting decrease in prevalence at specified times. Under this hypothetical assumption the present experiment would underestimate the neutron

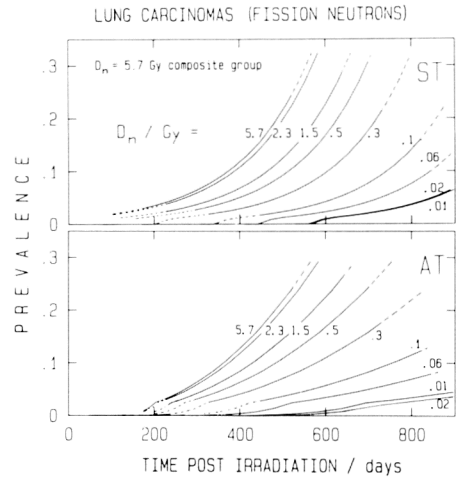

FIG. 6. Estimates of the prevalence from the two models (ST: shifted time model, AT: accelerated time model). The curves are given as broken lines when either less than four animals had already died or less than four animals are still alive in the group. The results are given only for the neutron experiment, although they have been obtained in a simultaneous analysis of the radon and neutron data.

efficiency in the comparison to the earlier radon experiment. As will be seen in the subsequent section, the relative efficiency of neutrons versus radon is remarkably high for pulmonary carcinomas. In view of the above considerations, any bias due to an increased life span of the animals would work against this result rather than for it. The point is therefore not critical to the main conclusion of the present analysis.

Figure 7 gives the competing risk corrected incidences derived from both the shifted-time and the accelerated-time models. It appears that the dose–effect relation may be linear for absorbed doses up to 0.5 Gy. At higher doses the curve flattens but does not decrease. The decline of the raw incidence at higher doses (see Fig. 3) is therefore a mere artifact of life shortening.

At the two smallest neutron doses the effects are somewhat higher than the extrapolation of the linear dose–effect relation would indicate. Since the numbers of lung carcinomas at these doses are small (four and two carcinomas at 0.012 and 0.02 Gy, respectively) and the assumed value for the control incidence (0.003) is somewhat tentative the observation is, by itself, not significant. However, it is of interest to note that it is in line with the findings in the radon experiment.

Derivation of the Equivalence Ratio

Figure 8 gives the time shifts and the acceleration factors as a function of neutron absorbed dose and of radon-inhalation exposure. The full symbols refer to the results for the neutron experiment, the open symbols to the result of the earlier radon experiment. The scales of the neutron absorbed dose in grays and the radon-inhalation exposure in working level months (WLM) are superimposed in such a way that an equivalence between 1 WLM of exposure to radon daughters and 1 mGy of neutrons would lead to coincident curves. One concludes from the results of either model that the neutron vs radon efficiency exceeds the ratio 1 WLM/mGy in the low dose range while it is below this ratio at high doses.

The lines connecting the data of Fig. 8 are simple visual fits. These lines can be utilized to construct iso-effect diagrams to compare the radon inhalations with the neutron irradiations. Such diagrams are given in Fig. 9 for both models. To construct these figures each result for a neutron exposed group is related to the interpolated

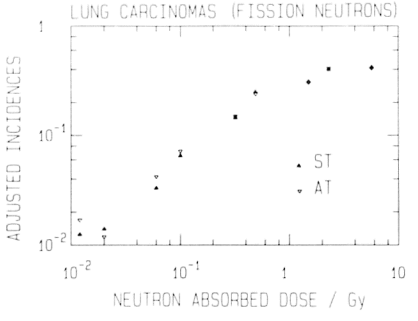

FIG. 7. Adjusted incidence (minus control incidence of 3×10^{-3}) from the two models (ST: shifted time model, AT: accelerated time model) as a function of neutron absorbed dose.

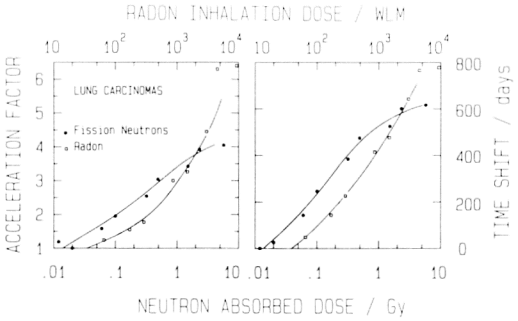

FIG. 8. Acceleration factor (left panel) and time shift (right panel) as a function of either radon-inhalation exposure (open symbols) or neutron absorbed dose (full symbols). The results are obtained from a simultaneous maximum likelihood fit of the radon and neutron data.

curve for radon and thereby to the corresponding radon-inhalation dose. The resulting values are given as full symbols. The analogous procedure is performed with the results of the radon exposed groups, and the results are given as open symbols in Fig. 9. These diagrams facilitate the assessment of the relative carcinogenic efficiency of radon-daughter inhalations and fission-neutron irradiations. At the lower doses the data are consistent with an equivalence ratio of 3 WLM/mGy that is indicated by the broken line. At higher doses the equivalence ratio is less. As stated, a radon exposure and a neutron irradiation are taken to be equivalent if the prevalence curves are equal.

Figure 10 gives the results in the more direct form of equivalence ratio versus neutron absorbed dose. The points correspond to the data in Fig. 9. The results are largely the same, whether one utilizes the shifted-time model or the accelerated-time model.

The derivation of standard errors is difficult for prevalences obtained from double-censored data. This is true both for the nonparametric maximum-likelihood analysis and for the isotonic regression. It is therefore important that the results are consistent for the multiplicity of exposed groups.

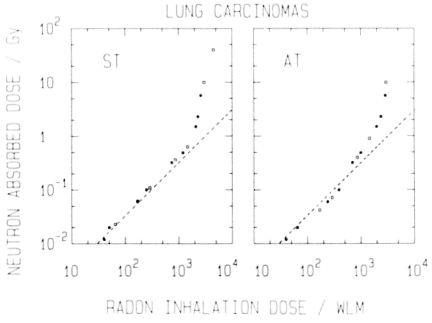

FIG. 9. Neutron absorbed dose vs equivalent radon-inhalation exposure from the two models (ST: shifted time model; AT: accelerated time model). As explained in the text, each value results from the comparison of a data point and one of the interpolated curves in Fig. 8.

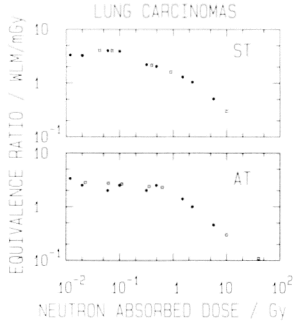

FIG. 10. Equivalence ratio as a function of neutron absorbed dose from the two models (ST: shifted time model; AT: accelerated time model). The equivalence ratio is the ratio of radon exposure and neutron dose that produce equal prevalences of lung carcinomas. As explained in the text, each value results from the comparison of a data point and one of the interpolated curves in Fig. 8.

CONCLUSIONS

From the ongoing experiment with fission-neutron-irradiated male Sprague–Dawley rats only the data on pulmonary malignancies have been utilized for the present analysis that is aimed at a comparison between the effectiveness of neutrons and of inhaled α emitters. The same nonparametric maximum-likelihood method as in the evaluation of the earlier radon-inhalation experiment has been applied.

As in the earlier experiment, estimates have first been obtained in terms of isotonic regression. From these estimates only rough conclusions on the dose and time dependence of the prevalence can be drawn. This is not unexpected; with double-censored data relatively large experimental groups would be required to obtain good statistical estimates for each group separately. More consistent results have then been obtained by the simultaneous maximum-likelihood fit to all experimental groups from the radon and the neutron study. With this method a dependence of the prevalence on time for pulmonary carcinomas has been obtained that is consistent with the relation obtained in the earlier radon study. The estimated prevalences have been utilized to derive dose–effect relations for the incidences of pulmonary carcinomas corrected for life shortening. Due to the substantial life shortening in the present neutron experiment there are considerable differences between the uncorrected raw incidences and the corrected values. The data agree with a linear dependence on dose with the coefficient 0.6/Gy; i.e., in a population of SD rats with standard lifetime distribution, the lung carcinoma incidence is increased by 6% after 0.1 Gy neutrons. In the earlier radon experiment the coefficient 0.0002/WLM has been obtained, so that 300 WLM are required for the same increase of 6%. However, in the earlier radon experiment and equally in the present experiments with fission neutrons a sublinearity (dose exponent < 1) cannot be excluded at low doses. Future studies at even lower doses will have to clarify this important point.

The effects of radon-daughter-inhalation and of fission-neutron irradiation have been compared on the basis of the pulmonary carcinomas alone. At low doses down to 0.01 Gy of fission neutrons the equivalence ratio of neutrons vs radon is close to 3 WLM/mGy (30 WLM/rad). The prevalence of pulmonary carcinomas increases

less steeply with increasing neutron doses than with radon-inhalation exposures; this leads to an equivalence ratio that is substantially below 1 WLM/mGy at high doses. The steeper increase at high radon exposures could be due to the longer inhalation times in this part of the radon experiment. The maximum protraction period in the neutron experiment has been only 6 weeks, and the possibility can not be excluded that longer protraction leads to higher tumor prevalences.

For radon inhalation there are risk estimates of lung cancer in man. There are no data for neutron irradiations. The revision of the neutron dosimetry for the atomic bomb explosion in Hiroshima has, at least for the time being, removed the possibility to derive neutron risk estimates from observations in man. Animal studies have therefore gained added importance. The findings of large neutron RBEs at low doses [see, for example, (*14–19*)] have motivated proposals to increase the quality factors for neutrons in radiation protection (*20*).

If one were to equate 1 WLM with 2.5 mGy (0.25 rad) average absorbed dose of α rays to the lung of the rat one would infer an RBE of neutrons vs radon daughters of 7.5, i.e., a value that is larger by a factor of 15 than the ratio of the quality factors presently employed for the two radiations. The disparity is even larger if 1 WLM causes an average lung dose in excess of 2.5 mGy. It is evident that the results of this study need not be representative for the effectiveness ratio of neutrons and α rays in other organs, or even for the effectiveness of neutrons relative to α-emitting actinides in the lung. The general conclusion must therefore be that either the quality factors have to be reconsidered or a distribution factor is required in the definition of the dose equivalent. Such a distribution factor has, in principle, been included in the dose equivalent (*21*); however, it has never been implemented. One may note that the relative effectiveness of neutrons is even further increased if one includes in the comparison the pulmonary sarcomas that are found after neutron irradiations but not after inhalation of radon daughters.

While the present study is not sufficient proof that α emitters have generally less carcinogenic potential at small doses than neutrons, it makes clear that high values of the neutron RBE and possible changes of the quality factor for neutrons need not necessarily be matched by corresponding changes for other densely ionizing radiations with highly nonuniform distributions of dose.

APPENDIX

Separate Consideration of Different Tumor Types

In the present analysis prevalences have been derived for pulmonary carcinomas rather than for all pulmonary neoplasms. Because the pathology for the scoring of adenomas has been altered for the present neutron experiment it is not possible to extend the comparison between fission neutron irradiations and radon daughter inhalations to carcinomas and adenomas jointly.

Any possible differences in the dose and time dependences between benign tumors and malignancies would nevertheless be of considerable interest. As stated earlier, the adenomas cannot be analyzed separately because they are registered only in the absence of pulmonary malignancies. For this reason the neutron data alone have been subjected to a further analysis equal to the one that has been described. This

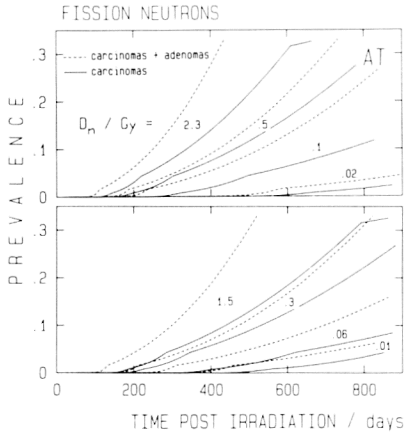

FIG. 11. Estimates of the prevalence from the accelerated time model (AT). The results have been obtained from the neutron data only. The broken lines result for adenomas and carcinomas, the solid line for carcinomas alone.

maximum-likelihood analysis has been run with all pulmonary neoplasms (broken lines in Fig. 11) and with carcinomas only (solid lines). The results indicate no basic differences of the time or dose dependences apart from an increase in the inclusive analysis that may well be independent of time and dose.

In the interest of better statistics the bronchogenic and the bronchoalveolar carcinomas have been pooled in the analysis. It is important, however, to ask whether the high relative efficiency of neutrons could be due merely to one of the two types of carcinomas. A separate analysis, although subject to larger statistical fluctuations, does not support this possibility. In the left panel of Fig. 12 acceleration coefficients are given that were obtained in a joint maximum-likelihood analysis that included

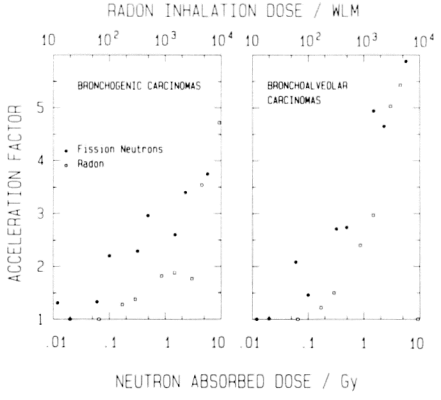

FIG. 12. Acceleration factor as a function of either radon-inhalation exposure (open symbols) or neutron absorbed dose (full symbols) for bronchogenic carcinomas (left panel) and bronchoalveolar carcinomas (right panel). The points result from a maximum likelihood analysis with the radon and the neutron data pooled.

both neutron and radon data but only bronchogenic carcinomas. From these and the analogous results in the right panel it is evident that the equivalence ratio is substantially larger than 1 WLM/mGy for either tumor type at low doses.

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REFERENCES

1. J. LAFUMA, M. MORIN, and R. MASSE, Cancer induction in rats after fission neutron irradiation with special emphasis on lung cancers. In *Proceedings, European Seminar on Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 57–73. Commission of the European Communities, Luxembourg, 1982.
2. D. CHMELEVSKY, A. M. KELLERER, J. LAFUMA, and J. CHAMEAUD, Maximum likelihood estimation of the prevalence of nonlethal neoplasms—An application to radon-daughter inhalation studies. *Radiat. Res.* **91,** 589–614 (1982).
3. W. E. LOEWE and E. MENDELSOHN, Revised dose estimates at Hiroshima and Nagasaki. *Health Phys.* **41,** 663–666 (1981).
4. A. RICOURT, M. CHEMTOB, J. C. PERRIER, C. NAUDY, C. VEAU, and R. SHUITON, Dispositif expérimental pour la surveillance de l'irradiation neutronique en continu d'animaux. In *Third Symposium on Neutron Dosimetry in Biology and Medicine,* (G. Burger and H. G. Ebert, Eds.). Commission of the European Communities, Luxembourg, 1977.
5. J. CHAMEAUD, R. PERRAUD, R. MASSE, J. C. NÉNOT, and J. LAFUMA, Cancer du poumon provoqué chez le rat par le radon et ses descendants à diverses concentrations. Comparaison de la relation dose-effet chez l'homme et chez l'animal. In *Biological and Environmental Effects of Low-Level Radiation,* Vol. 11, pp. 223–338. International Atomic Energy Agency, Vienna, 1976. (STI/PUB/409.)
6. R. MASSE, Histogenesis of lung tumors induced in rats by inhalation of α emitters: An overview. In *Pulmonary Toxicology of Respirable Particles* (C. L. Sanders, F. T. Cross, G. E. Dagle, and J. A. Mahaffey, Eds.). USDOE Technical Information Center, Oak Ridge, TN, 1980. (Available as CONF-791002 from National Technical Information Service, Springfield, VA 22161.)
7. R. PETO, M. C. PIKE, N. E. DAY, R. G. GRAY, P. N. LEE, S. PARISH, J. PETO, S. RICHARDS, and J. WAHRENDORF, Guidelines for simple, sensitive, significance tests for carcinogenic effects in long-term animal experiments. In *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* Suppl. 2, *Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal,* pp. 311–423. IARC, Lyon, 1980.
8. A. M. KELLERER and D. CHMELEVSKY, Analysis of tumor rates and incidences—A survey of concepts and methods. In *Proceedings, European Seminar on Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 209–231. Commission of the European Communities, Luxembourg, 1982.
9. D. G. HOEL and H. E. WALBURG, Jr., Statistical analysis of survival experiments, *J. Natl. Cancer Inst.* **49,** 361–372, 1972.
10. R. E. BARLOW, D. J. BARTHOLOMEW, J. M. BREMNER, and H. D. BRUNK, *Statistical Inference under Order Restrictions; The Theory and Application of Isotonic Regression.* Wiley, New York, 1972.
11. N. E. BRESLOW and N. E. DAY, *Statistical Methods in Cancer Research,* Vol. 1, *The Analysis of Case-Control Studies.* Publication No. 32, IARC, Lyon, 1980.
12. J. D. KALBFLEISCH and R. L. PRENTICE, The Statistical Analysis of Failure Time Data, Wiley, New York, 1980.
13. D. M. HIMMELBLAU, *Applied Nonlinear Programming.* McGraw-Hill, New York, 1972.
14. J. L. BATEMAN, H. H. ROSSI, A. M. KELLERER, C. V. ROBINSON, and V. P. BOND, Dose dependence of fast neutron RBE for lens opacification in mice. *Radiat. Res.* **51,** 381–390 (1972).
15. H. H. VOGEL, Mammary gland neoplasms after fission neutron irradiation. *Nature (London)* **222,** 1279–1281 (1969).

16. C. J. SHELLABARGER, D. CHMELEVSKY, and A. M. KELLERER, Induction of mammary neoplasms in the Sprague–Dawley rat by 430-keV neutrons and X-rays. *J. Natl. Cancer Inst.* **64,** 821–833 (1980).
17. C. J. SHELLABARGER, D. CHMELEVSKY, A. M. KELLERER, J. P. STONE, and S. HOLTZMAN, Induction of mammary neoplasms in the ACI rat by 430-keV neutrons, X-rays, and diethylstilbestrol. *J. Natl. Cancer Inst.* **69,** 1135–1146 (1982).
18. J. F. THOMSON, L. S. LOMBARD, D. GRAHN, F. S. WILLIAMSON, and T. E. FRITZ, RBE of fission neutrons for life shortening and tumorigenesis. In *Proceedings, European Seminar on Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 75–93, Commission of the European Communities, Luxembourg, 1982.
19. M. COPPOLA, Neutron effectiveness at low dose levels for other endpoints. In *Proceedings, European Seminar on Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 343–355. Commission of the European Communities, Luxembourg, 1982.
20. H. H. ROSSI, A proposal for revision of the quality factor. *Radiat. Environ. Biophys.* **14,** 275–283 (1977).
21. ICRP, *Radiosensitivity and Spatial Distribution of Dose.* Publication 14, International Commission on Radiological Protection, Pergamon, London/New York/Paris/Frankfurt, 1969.