MODELLING THE DOSE-EFFECT RELATIONSHIP FOR RADON-INDUCED LUNG TUMOUR IN RATS

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1. Introduction

In principle, two different approaches can be taken to model radon-induced lung tumour risk: (i) mechanistic models derived from *in vitro* cellular radiation effects, or (ii) mathematical fits to epidemiological data. While the models based on *in vitro* cellular experiments are imperative for the understanding of the mechanisms involved in radon-induced carcinogenesis, the effect of the living organism on the transformation of a normal cell to a malignant cell (e.g. the influence of the immune system) is still largely unknown. Hence, cellular carcinogenesis models are very useful tools for the determination of the relative dependence of lung cancer risk on exposure, i.e., the shape of the dose-effect curve. However, in order to predict absolute values of the lung cancer risk per unit exposure, the construction of empirical models by fitting epidemiological data through mathematical functions may be a more appropriate approach for radiation protection purposes. Thus, in the present work we have chosen the second approach.

The laboratory rat has successfully been used in the past to assess the carcinogenic risk of inhaled radon decay products [(1,2)]. While lung tumours are the most serious consequences of radon progeny inhalation, other lung damages, such as interstitial edema, alveolitis and progressive interstitial fibrosis have also been reported [(3)]. However, the observed dose-response relationship of bronchogenic carcinomas provides only information about the specific carcinogenic effects of radiation, but not about these non-stochastic radiation effects. Inhalation experiments have shown that the life span of shorter living animals can be strongly influenced by radiation-induced damages. Therefore, the life span of the laboratory rat after irradiation may be a useful indicator for assessing radon-induced radiation effects, including carcinogenesis, on the organism.

The purpose of this paper is to derive semi-empirical models for the relationship between radon progeny exposure and two kinds of experimentally observable radiation effects, lung cancer incidence and life span shortening. Based on recent experimental data from the Battelle Pacific Northwest Laboratories, two different models of the lung tumour incidence (I) and the life span (LS) as functions of the cumulative radon daughter exposure (WLM) in rats will be proposed here.

2. Analysis of experimental data

Radon progeny inhalation experiments in laboratory rats have been carried out at the Battelle Pacific Northwest Laboratories, providing experimental data about lung tumour incidences and life spans of the rats for a variety of exposure levels and exposure rates. The data used in the present analyses were taken from a recent compilation of experimental data, which are partly unpublished.

Among the 478 lung tumours that have been found in 3880 Wistar rats exposed to radon progeny at different exposure levels, 396 were malignant and 63 were benign tumours. In the corresponding control groups, 5 out of 618 rats developed tumours. Due to their relevance to human environmental exposures, the two lowest exposure groups are of particular interest. Here, lung tumours were detected in 3 out of 246 rats in the 20 WLM group, and in 10 out of 445 rats in the 40 WLM group. There were significant differences between the groups with exposure levels above 80 WLM and the control group ($\chi^2 = 7.48$, $p < 0.01$). In general, lung tumour incidence induced by radon progeny increases with rising cumulative exposure (Fig. 1): it increases rapidly between cumulative exposures of 80 up to 1280

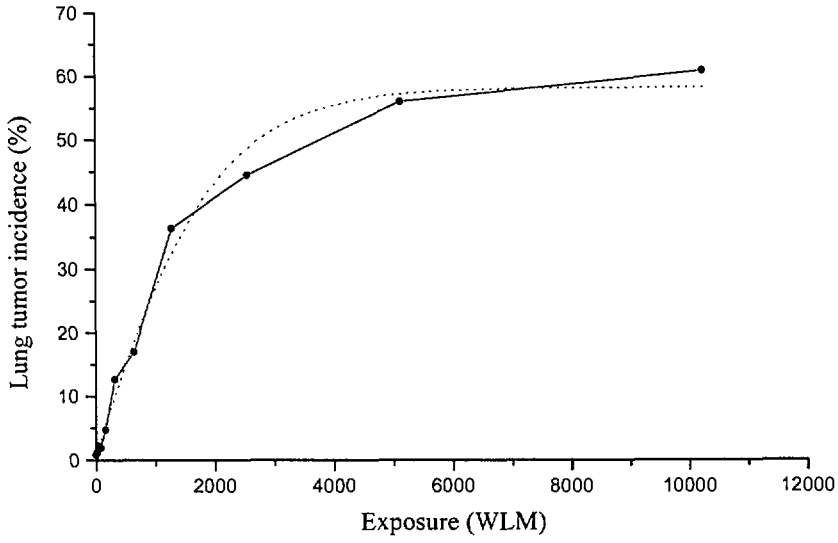
WLM, but increases less steeply up to a cumulative exposure of 10240 WLM, without dropping down at the highest exposure levels. Even at low doses (20 WLM), the incidence of the lung tumours is higher than the incidence in the control group.

The best fit of the lung cancer incidence I (in percent) as a function of cumulative exposure (in WLM) was obtained by the following mathematical expression (see Fig. 1):

$$I(WLM) = (A_1 - A_2)/(1 + exp((WLM - x_o)/dx)) + A_2 \quad (1)$$

where A_2 is the initial value, and A_1, x_o and dx are the coefficients obtained by the fitting procedure (A_1 = - 75.78, A_2=58.27, x_o = -329.31, and dx = 1127.05, χ^2 = 7.69).

Figure 1. Lung tumour incidence in Wistar rats exposed to radon progeny vs. cumulative exposure. The dotted line denotes the fit to the experimental data (equation 1).



Since the low exposure data are specifically relevant to human environmental human exposures, the same data were also fitted by a logistic function on a log-log plot:

$$log(I(WLM)) = log(N)/(1 + (WLM/O)^p) + M) \quad (2)$$

where M is the initial value on the y axis, N is the final value on the y axis, O is the center value on the x axis, and p is a fitting parameter (M = 0.9766, N = 65.14, O = 1267.31 , and p = 1.26).

Life spans of the Wistar rats were reported for 3751 animals at different exposure levels (Fig. 2). In general, the average life span drops in an exponential manner with increasing exposure, except for the lowest exposure groups (20 and 40 WLM). In both exposure groups, the mean life span is significantly higher than the average life span of the control group ($t = 4.66$, $p < 0.01$; $t = 3.53$, $p < 0.01$). However, there are no significant differences between the mean life spans at 80, 160 and 320 WLM and that of the control group ($t = 0.84$, $p > 0.05$ at 80 WLM; $t = 1.83$, $p > 0.05$ at 160 WLM; and $t = 1.15$, $p > 0.05$ at 320 WLM). From the 640 WLM group to the highest WLM group, the mean life-span is significantly lower than the life span of the control group ($t = 3.35$, $p < 0.01$). This dependence of the life span LS (in days) on cumulative exposure (in WLM) suggests to separate the data into two parts, a linear and an exponential one (Fig. 2):

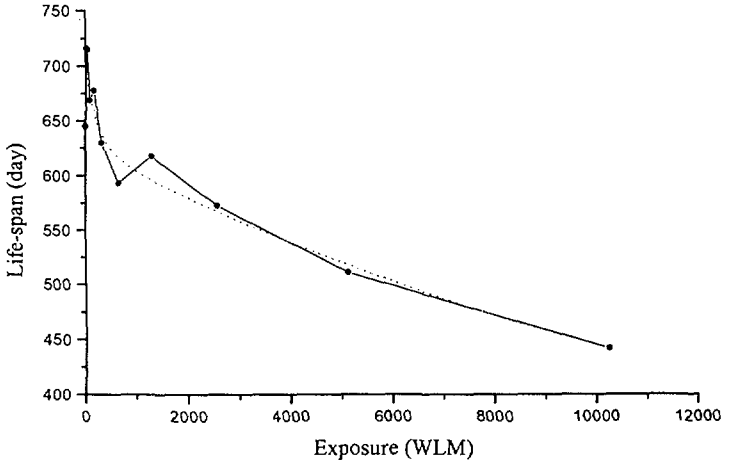
$$LS(WLM) = y_o + A_o\, WLM \quad \text{for WLM} \leq 20 \quad (3)$$

and

$$LS\ (WLM) = y_1 + A_1 \exp(-(WLM - x_o)/t_1) + A_2 \exp(-(WLM - x_o)/t_2) \quad \text{for WLM} > 20 \qquad (4)$$

where y_o and y_1 are the initial values on the y axis, x_o is the initial value on the x axis, and A_o, A_1, A_2, t_1 and t_2 are coefficients obtained by the fitting procedure (y_o = 657, A_o = 1.75, R = 0.8598; y_1 = 386.2391, x_o = 20, A_1 = 175.202, A_2 = 113.7, t_1 = 3209, and t_2 = 1.432 E4, χ^2 = 1275.95).

Figure 2. Life span in Wistar rats exposed to radon progeny vs. cumulative exposure. The dotted line denotes the fit to the experimental data (equations 3 and 4).



3. Life span normalization factor

The lifetime of an animal after irradiation is influenced by the occurrence of different post-irradiation lesions, including lung tumours [4]. Since the life span of rats after low levels of cumulative exposures is longer than in the controls, more time is available to give rise to a radon-induced lung tumour before the death of the animal. In contrast, the lung tumours may not appear during the lifetime of the animal due to the shorter lifetime of the animal after high levels of cumulative exposure. As a result of this, the real lung cancer risk may actually be lower at very low exposure levels and higher at high exposure levels than reported in the laboratory animal experiments. Hence, the experimentally determined radon-induced lung tumour risk can be modified by a linear life span normalization factor β as defined below:

$$I(\%) = \alpha . \beta = \alpha . M / M_d \qquad (5)$$

where α is the radon-induced lung tumor incidence derived from the experimental data, β is the life span normalization factor, M is the mean life span of the control group, and M_d is the mean life span of a given cumulative exposure group.

4. Discussion

The lung cancer incidence function plotted in Fig. 1 suggests that the dose-response relationship may be divided into two parts, a relatively steep linear increase with exposure below about 640 WLM, and the flattening of the curve above this level. This decrease in carcinogenic potency per unit exposure at higher exposure levels is consistent with the epidemiological observations found in uranium miner studies. Thus, rat inhalation experiments are a valuable complement to human epidemiological studies, having the additional bonus of a much better characterization of the exposure conditions.

The life span-exposure relationship plotted in Fig. 2 shows the interesting result that the life span at 20 WLM is significantly higher than that in the control group, dropping down again to the control level at

about 80 WLM. Application of the life span normalization factor defined in equation 5 to lung cancer incidences obtained in the rat inhalation experiments decreases the incidences in the exposure range from 0 up to 160 WLM.

There is sufficient experimental evidence that low dose irradiation often induces effects opposite to those observed at of high doses [5]. Low or chronic exposure to ionizing radiation can induce processes which protect the cell against naturally occurring as well as radiation-induced alterations that may ultimately lead to cell transformation. For example, studies on human lymphocytes showed that low doses could protect cells against chromosomal aberrations and radiation-induced mutations [6]. Thus small amounts of radon progeny may not be harmful to rats and, possibly, to human beings too.

5. Acknowledgements

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