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MECHANISTIC MODELS FOR RADON-INDUCED LUNG CANCER RISK BASED ON CELLULAR RADIATION EFFECTS

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ABSTRACT

Mechanistic models for radon progeny induced lung cancer risk have been developed, based on radiation mechanisms at the cellular level. The cellular effects relevant to radiation-induced carcinogenesis are transformation, cell killing, stimulated cell division, and removal from contact inhibition. Depending upon the

initiation and/or promotion properties of ionizing radiation, we distinguish between (i) an initiation-promotion-survival model, (ii) a promotion-survival model, and (iii) a survival model. Cigarette smoke or other carcinogenic substances may also act as initiators and/or promotors. Predictions of the relative lung cancer risk in each model are compared herein to published epidemiological data. Each risk model may be most efficient at a different exposure level. A composite risk model, representing combined exposures to radon progeny and other carcinogenic factors, suggests that the relative lung cancer risk for environmental exposures is significantly smaller than that derived from linear extrapolation.

INTRODUCTION

Recent comprehensive analyses of lung cancer risks associated with inhalation exposures to radon progeny have been exclusively based on epidemiological studies with underground uranium miners (ICRP 1987; NRC 1988), albeit, supplemented by data on externally irradiated atomic bomb survivors (ICRP 1987). Both scientific committees have suggested that the excess lifetime risk is linearly related to the cumulative exposure. Two epidemiological studies on lung cancer risk, however, show deviations from linearity: (i) lung cancer risk in New Mexico uranium miners, adjusted for cigarette smoking, rises in a supralinear fashion at low (say, below 1000 WLM) cumulative exposures (Samet et al. 1989); and, (ii) no excess lung cancer risk has been found in a Chinese high background area characterized by cumulative lifetime exposures of about 20 WLM (Hofmann et al. 1986).

Average environmental lifetime exposures of the general public lie typically in the range of 10 to 15 WLM. Because of practical difficulties involved in the direct determination of lung cancer risk at such low exposures, mainly because of the inevitable interaction of confounding factors, any estimate of low-level carcinogenic effects must be based on some form of extrapolation from high exposure levels at which effects are clearly demonstrable. The approaches usually taken are either theory-free curve fits to the existing epidemiological data (ICRP 1987; NRC 1988), or the application of semi-empirical functions the general form of which may be deduced from radiobiological data (NAS 1980). In the latter case, parameters are obtained through curve fits to existing epidemiological data.

In the present study, we propose an alternative rational in which both the functional form of a dose-effect relationship and its parameter values arise from radiobiological observations at the cellular and organ level (Jones 1984; Hofmann et al. 1986; 1988). The intent is to provide a coherent understanding of the in-vitro

and whole organ process of carcinogenesis. Such an approach requires a set of assumptions concerning cellular radiation effects of alpha particles relevant to radiation-induced carcinogenesis. According to the common terminology of "initiation" and "promotion" in carcinogenesis, "initiation" is considered to be a subcarcinogenic cellular stage from which cells subsequently may be transferred to a carcinogenic stage by appropriate "promotion" factors. Radiation, like all carcinogens, has properties of both initiation and promotion. We therefore shall classify the cellular effects underlying our model as either initiating or promoting events, with simultaneous consideration of cytotoxicity.

CELLULAR RADIATION EFFECTS

In line with radiobiological observations, our predictive model of lung cancer induction is based on three properties of radiation: (i) transformation of cells; (ii) inactivation of cells; and, (iii) stimulated cellular division in a stem cell population. This model has been used in a previous paper to estimate the carcinogenic risk of beta-emitting hot particles in lung tissue (Hofmann et al. 1988). In the present effort, an additional assumption has been incorporated, namely (iv) the need of a cell to be released from contact inhibition in order to express its full potential as a transformed cell (Crawford-Brown and Hofmann 1990). We emphasize that dose, D, in all following equations refers to the localized dose received by a subpopulation of uniformly irradiated cells.

The probability that a cell will be transformed and survives when receiving a dose D, PT(D) is given by the relation

$$PT(D) = a_0 + aD + bD^2 \qquad (1)$$

where a and b are constants which may depend on cell type and irradiation conditions. Equation 1 was obtained by fitting the in-vitro transformation frequencies per viable cell measured by Robertson et al. (1983) for mouse BALB/3T3 cells exposed to ^{238}Pu alpha particles, with $a_0 = 2.5 \times 10^{-5}$, $a = 1.9 \times 10^{-4}$ Gy^{-1}, and $b = 2.2 \times 10^{-4}$ Gy^{-2}.
The probability of a cell surviving an alpha dose D, PS(D), is usually expressed by single-hit kinetics:

$$PS(D) = \exp(-cD) \qquad (2)$$

where $c = 1.43$ Gy^{-1} (Robertson et al. 1983).

If cell division is a necessary condition for an initiated cell to develop into a fully transformed cell resulting in cancer (Kennedy and Little 1984; Hall and Hei 1985) then stimulated cell division should increase the probability of cancer induction. In fact, studies have demonstrated that cell killing following irradiation leads to an increase of the mitotic index of the surviving cells in a stem cell system (Sacher and Trucco 1966; Gross et al. 1987). The increase in mitotic rate may be conceived as a function of the fraction of killed cells, f(D), in the vicinity of a transformed cell, being given by the expression

$$f(D) = p(1-\exp(-cD)), \tag{3}$$

where p denotes the probability that a progenitor cell is mustdivide as a direct result of the death of an epithelial cell. Assuming 4 to 5 stages in a cell renewal system, we may let p = 0.05. The probability that an initiated cell undergoes the division-related transition under in-vivo conditions due to stimulated mitosis at a given dose D, PM(D), then becomes

$$PM(D) = k_1 [\lambda_1 + \lambda_2 p(1-\exp(-cD))]^n \tag{4}$$

where k_1 is an arbitrary scaling constant incorporating the probability of transition per division, and n may be related to the number of cellular divisions required for the necessary transition (Crawford-Brown and Hofmann 1989). This expression assumes that a cell normally has a mitotic rate λ_1, which may increase to λ_2, the rate of division under conditions of tissue replacement. For the lung, a slowly dividing tissue, we may take $\lambda_1 = 0.01\ d^{-1}$ (Frankfurt 1967; Brown and Berry 1969), and $\lambda_2 = 1\ d^{-1}$ (Sacher and Trucco 1966; Hall and Hei 1985). Consistent with an earlier simulation effort (Hofmann et al. 1988), we assume an n equal to 1 in the present calculations.

In order to express its full potential as a transformed cell, our model requires that a cell must be released from contact inhibition (Crawford-Brown and Hofmann 1990). By contact inhibition we mean any control of the information flow between cells, which may be compromised due to changes in the cell per se or its neighboring cells. Here, we assume that contact inhibition is lost whenever a transformed cell is surrounded by n or more dead cells out of N adjacent cells at the moment of division. The probability of removal from contact inhibition at dose D, PC(D), is given by the binomial distribution, $P_n(D)$:

$$PC(D) = A(B + P_n(D)) = A\left(B + \sum_{i=n}^{N} \frac{(N!)(1-\exp(-cD)^i(\exp(-cD)^{N-i}}{((N-i)!)(i!)}\right) \tag{5}$$

where B is the background probability of removal from inhibition, and A is the fraction of transformed cells having contact inhibition removed. Both A and B are assumed to be 0.1 (Crawford-Brown and Hofmann 1990). From an analysis of in-vitro transformation experiments, we let n equal 4 when N is 6 (Crawford-Brown and Hofmann 1990). Because of the bronchial epithelium's columnar cell structure we assume that the same numbers apply to in-vivo transformations as well. The product of equations 4 and 5 is, then, assumed to be the probability of promotion.

LUNG CANCER RISK MODELS FOR INHALED RADON PROGENY

Doses in each generation of a Weibel Model A (1963) lung anatomy have been calculated for an assumed reference atmosphere (Hofmann and Daschil 1986). This atmosphere contains relative concentrations, ^{222}Rn:^{218}Po:^{214}Pb:^{214}Po, of 1:0.9:0.6:0.4. This produces an exposure rate of 0.29 WLM y^{-1} for domestic exposures or 0.067 WLM y^{-1} for occupational exposures, assuming an ambient radon concentration of 37 Bq m^{-3} (1 pCi L^{-1}). The radon progeny carrier aerosol is characterized by an activity median diameter (AMD) of 0.15 μm and a geometric standard deviation of 2.5. The unattached fractions are 10% for ^{218}Po and 1% for ^{214}Pb. In deposition computations a tidal volume of 1.000 mL was used, with a breathing frequency of 15 min^{-1} Steady-state surface activities in individual airway generations were determined by using the mucociliary clearance rates reported by Lee et al. (1979). Doses under conditions of actual exposure other than the reference atmosphere then were calculated through direct scaling using the appropriate WLM ratio.

McDowell et al. (1978) have found that at least 88% of all lung cancers in humans originate in the basal and/or secretory (SMGC) cells (grouped in the subsequent text as epithelial cells). We, therefore, assume that these cells are the "cells at risk" for lung cancer induction. In our computations the respective nuclei of the secretory cells are uniformly distributed throughout the bronchial epithelium. The thickness of the bronchial epithelium within each bronchial airway generation is based upon the measurements of Gastineau et al. (1972).

The dose rate per unit surface activity, as a function of penetration depth of alpha particles into bronchial tissue, is taken from Jacobi and Eisfeld (1980), and indicates an almost linear decrease of dose rate with depth. For computational convenience, the total penetration depth, ranging from the gel-sol interface in the mucus layer to the basal lamina of the epithelium in a given airway generation, is divided into i intervals of 5 μm thickness. The first two intervals, i.e, $i = 1 - 2$, are not used in our dose calculations since they comprise the mucus sol layer and the upper part of the epithelium where cell nuclei typically do not occur

(McDowell et al. 1983). Consequently, our exposure-dose conversion factor of 2.7 mGy WLM^{-1} is less than most other reported values (James 1988).

Cumulative doses for a given exposure category are calculated assuming a median length of exposure of 4 years in all exposure categories (Hornung and Meinhardt 1987). To apply the equations presented earlier to the analysis of radiation-induced carcinogenesis, lung cancer risk must be computed using the dose delivered during the lifetimes of bronchial epithelial cells. Therefore, for the conversion of cumulative doses in each exposure group to mean effective cellular doses, we assume a mean lifetime of epithelial cells on the order of 100 days. In their analysis, Hornung and Meinhardt (1987) also investigated the role of exposure length on the related risk coefficient, finding only a slight change in it as a function of duration. As a result, here it is assumed that the same dose-response data would have been obtained if the length of exposure was lessened to the mean lifetimes of lung cells. Although a shorter exposure may change the risk coefficient slightly, the general features of the dose-reponse curve should be relatively unchanged.

For computational purposes, let us assume that a cell nucleus, located at depth interval i in the bronchial epithelium of airway generation k, receives a dose D_{ik}. Inserting D_{ik} into any combination of equations 1, 2, 4 and 5, dependent on subsequent modeling assumptions, induces a carcinogenic risk $R_{ik}(D)$ in the irradiated cell. Summation over all depth intervals i,i = 3 - I(k), where I(k) is the maximum number of depth intervals in generation k, and multiplication by the number of cells in a given generation k, N(k), which is assumed here to be proportional to the epithelial tissue mass in that generation, yields this risk function, $R_k(D)$, in generation k:

$$R_k(D) = N(k)/(I(k)-2) \sum_{i=3}^{I(k)} R_{ik}(D) \qquad (6)$$

The number of intervals is equal to (I(k)-2) since the first two intervals are not considered, as justified above. The total lung cancer risk for the whole bronchial region, R(D), is then given by the sum of the risks in the individual generations:

$$R(D) = \sum_{k=0}^{16} R_k(D) \qquad (7)$$

For this summation, we assume that the fraction of sensitive cells per unit tissue mass, and their corresponding radiosensitivities are constant for all bronchial generations.

In the present lung cancer induction model we assume five stages in the development of a cell from the initial unirradiated level (stage 1) to a fully transformed one (stage 5) (Crawford-Brown and Hofmann 1990). The intermediate steps are: production of specific DNA damage (stage 1 to 2), production of less specific DNA damage (stage 2 to 3), cellular division (stage 3 to 4) and release from contact inhibition (stage 4 to 5). Competing with these mechanisms at each transition is radiation-induced cell death. Using the terminology of "initiation" and "promotion", movement from stage 1 to 3 (step 1) may be identified as the initiation event and the two subsequent steps as promotion events. With respect to the initiating and promoting abilities of ionizing radiation we now shall discuss different lung cancer models and their applications to uranium miner data.

Initiation-promotion-survival (IPS) model:

Now, it is assumed that radiation acts both as an initiator and promotor, i.e., it carries an unirradiated cell through all intermediate stages outlined above to a fully transformed cell. The in-vitro tranformation frequency for alpha particle irradiation (see equation 1) already represents the total probability of reaching the final transformed stage of uninhibited growth, comprising all four initiation and promotion steps (this eliminates the necessity of making assumptions about a functional relationship between inititation and dose, for which there is no experimental data). Two adjustments, however, have to be made. First of all, the transformation data are usually expressed as the number of tranformations per viable cell; so to get the transformation probability per exposed cell, that corresponding value per surviving cell at a given dose must be multiplied by the survival probility at that dose. Secondly, the above transformation frequencies refer to in-vitro conditions, while we are concerned with in-vivo exposures. We do not anticipate any significant differences between the two irradiation conditions regarding intracellular DNA damage (steps 1 and 2) and release from contact inhibition (step 4). In step 3, however, cellular division within tissue occurs at a much slower rate (λ_1, see equation 4) than in a Petri dish (λ_2). It should be noted that the in-vitro rate of division is set equal to the in-vivo rate under conditions of tissue replacement. Thus the in-vitro transformation frequencies must be multiplied by the ratio of the in-vivo to the in-vitro division rates to more accurately simulate in-vivo transformation frequencies.

Utilizing the transformation data of Robertson et al. (1983), lung cancer risk at dose D_{ik}, $R_{ik}(D)$, in the IPS-model is expressed by the relation

$$R_{ik}(D) = C_1 [a_o+aD_{ik}+bD_{ik}^2)] \times [\lambda_1 + \lambda_2 p(1-\exp(-cD_{ik}))]^n/\lambda_2 \times [\exp(-cD_{ik})] \qquad (8)$$

where C_1 is an arbitrary scaling factor obtained by fitting equation 8 to epidemiological lung cancer data.

Promotion-survival (PS) model:

In this simulation we surmise that cells have been initiated prior to, or concurrent with, exposures to ionizing radiation. These transitions may result from co-carcinogenic factors (such as cigarette smoke, uranium ore dust, diesel exhausts or chemicals) or simply from a natural background rate of transition. It is assumed that radiation is the major promoting factor for the initiated cells. Two different scenarios are considered for the initiation mechanism: (i) the number of initiated cells is proportional to the number of cells in a given generation, i.e., the initiation rate or initiation probability per cell, IR_k, is a constant value for all generations k ($IR_k = r_1$), or (ii) initiation is caused by inhaled substances (other than radon progeny) and the number of initiated cells in generation k is therefore proportional to the number of deposited particles, D_k, per unit surface area, S_k ($IR_k = D_k/S_k$). In both cases, IR_k is assumed to be constant over all depth intervals i in a given generation k.

Radiation can now promote these initiated cells by stimulating cellular division (step 3) and stopping contact inhibition (step 4). At the same time, however, it can also kill the cells. Lung cancer risk at dose D_{ik}, $R_{ik}(D)$, in the PS-model can therefore be written as

$$R_{ik}(D) = C_2\,[IR_k] \times [\lambda_1 + \lambda_2 p(1-\exp(-cD_{ik}))]^n \times [A(B + P_n(D_{ik}))] \times [\exp(-cD_{ik})] \quad (9)$$

where the scaling factor C_2 is again obtained by a fitting procedure. In generations 0 (trachea) and 1 (main bronchi), the most deeply lying cells are beyond the maximum range of alpha particles. Thus equation 9 applies only to cells located in depth intervals i within the alpha particle range (i = 3 - 13). For all cells outside this range (i = 14 I(k)), the survival probability is set equal to one, and the fraction of killed cells providing the division stimulus is taken as that fraction of cells killed in depth intervals i = 3 - 13.

Survival (S) model:

Here we assume that a certain number of transformed, i.e., initiated and promoted, cells can always be found in the human body, and within the lung in particular. These are not produced by exposures to inhaled radon progeny. This probability of transformation, TR_k, may be either an event-specific transformation probability caused by other co-carcinogenic factors (previously discussed) or the natural transformation rate due to random errors in the DNA structure or the immune system. Following the procedures established above, we may assume two different cases: (i) TR_k is constant for all bronchial generations k ($TR_k = r_2$), or (ii) TR_k is proportional to the surface deposition pattern of ambient aerosols ($TR_k = D_k/S_k$). In both instances, TR_k is constant over all depth intervals i in a given generation k.

Since in this scenario cell killing is the only major effect of ionizing radiation, lung cancer risk $R_{ik}(D)$ at dose D_{ik} can be formulated as

$$R_{ik}(D) = C_3 [TR_k] \times [\exp(-cD_{ik})] \qquad (10)$$

where C_3 is once more a constant fitting parameter obtained from epidemiological data.

Cigarette smoke promotion (CSP) model:

The effects of cigarette smoke or other co-carcinogens on lung cancer risk may be manifest through inititation (with radiation acting as a promotor), promotion (after radiation-induced inititation), or both. While the first possibility has been described by the PS-model, the promotional role of cigarette smoke, or non-radiological promotion in general, will be explored in the new CSP-model. We recognize the primary promotional role of cigarette smoke as being to stimulate cellular division, based on the histopathological observations of smoke-induced hyperplasia of basal, goblet and alveolar cells, and mucus glands (Auerbach et al. 1961; Wehner et al. 1981). Thus, the promotion probability, PM(D) (see equation 4), which is used in both the IPS- and PS-lung cancer risk models, will be replaced by the combined promotion probability, PM(D,CS):

$$PM(D,CS) = k_2 [\lambda_1 + \lambda_2 CS + \lambda_2 p (1-\exp(-cD))] \qquad (11)$$

where k_2 is a constant proportionality factor, and CS represents the quantitity of cigarette smoke deposited in bronchial airways. It is assumed that dosimetry will not be affected by smoking, e.g., by either a reduced mucociliary clearance efficiency or a thickening of the tracheobronchial mucus layer.

In the absence of more substantive information, we will take CS to be proportional to the surface density of inhaled cigarette smoke particulate matter (i.e., number of particles per unit surface area), with aerodynamic diameters of 0.25 μm (Keith and Derrick 1960) -- equivalent to geometric diameters of 0.15 μm. The density of cigarette smoke in generation k, CS_k, is equal to q x S_k, where q is a proportionality constant and S_k is the surface density in generation k. While CS is thereby a function of airway generation k, it is constant over all depth intervals i within a given generation k. The observation of a multiplicative, or slightly submultiplicative, interaction between exposures to radon progeny and cigarette smoke for all exposure levels (Hornung and Meinhardt 1987; Ellett et al. 1988; NRC 1988; Samet et al. 1989) suggests that the cigarette smoke promotion term in equation (11) is more effective than the radiation-induced cell killing term for all doses considered. Depending upon the choice of p in that equation, q will be varied over a reasonable range of values in the following analyses.

LUNG CANCER RISK PREDICTIONS

For a comparison of our theoretical predictions with available epidemiological information, we have chosen the data on relative lung cancer risk in U.S. uranium miners by Hornung and Meinhardt (1987). Their results are plotted in Fig. 1 as a function of cumulative ^{222}Rn progeny exposure. The observable, large statistical uncertainty of these data, typically associated with such studies, limits to some extent their applicability for model validation.

Alpha particles emitted from radon progeny deposited on bronchial airway surfaces produce a depth-dose distribution which decreases in a quasi-linear fashion with depth in bronchial epithelium (Jacobi and Eisfeld 1980). This suggests that shallow-lying secretory cells are the cells at highest risk, if lung cancer risk is likewise related with dose. The lung cancer risk predictions for the IPS-model in the upper bronchial generations, presented in Fig. 2, indicate that the depth-risk distribution depends on the level of cumulative exposure (or dose). At low doses characteristic of enviromental exposure situations (10 WLM), lung cancer risk is nearly uniformly distributed across epithelial tissue within a generation. If the dose-dependent parts of the initiation, promotion and survival terms in equation 8 are smaller than the background incidence -- as is the case for small doses -- then the risk function is determined by the natural incidence rate, a_0, and is, therefore,

virtually independent of dose. It should be noted, however, that our value of a_0, derived from in-vitro transformation experiments (Robertson et al. 1983) may not be necessarily the same for in-vivo conditions. With increasing dose, lung cancer risk rises in cells closer to the airway lumen relative to more deeply lying cells (thereby being most effective in shallow secretory cells), approximating the depth-dose relation at some hundreds of WLMs. At high uranium miner exposures (6000 WLM), the risk function peaks at a certain depth in tissue because of the overriding effect of cell killing at sufficiently large doses. This finding suggests that the relative contributions of secretory and basal cells to lung cancer risk may not only depend on the relative numbers of cells in each generation, but also on related cumulative exposure levels.

In Fig. 3, total lung cancer risk, R(D), using the IPS-model is plotted as a function of cumulative exposure. Also shown are the epidemiological data of Hornung and Meinhardt (1987) with a least-square fit to their data. In order to facilitate comparisons of our theoretical predictions with these epidemiological findings, all relative risk functions presented here will be normalized to a relative risk of 32 at 3000 WLM. This procedure was chosen, because we do not know the proper value of a_0 under in-vivo conditions, which determines the relative risk at D = 0 (note: variations of a_0 do not affect the shape of the dose-response curve at higher cumulative exposures). Given the inherent statistical uncertainty of the epidemiological information, there is excellent agreement between the predicted and observed lung cancer risks over the entire range of cumulative exposures.

In calculating the total risk of lung cancer, the risks in each generation were summed under the assumption that all generations have the same fraction of sensitive cells with the same radiosensitivity. In order to identify the contributions of each generation to the total risk, relative lung cancer risk predictions for individual bronchial generations, normalized to the same risk at 3000 WLM, are presented in Fig. 4. Risk functions for the various generations do not differ appreciably below that value. Above it, the relative risk for upper bronchial airways (generations 2 to 8) is smaller than that predicted using the complete tracheobronchial tree. By contrast, the relative risk for the peripheral bronchial airways (generations 10 to 16) is larger. The observation that the risk approaches a saturation value (with a downward trend at even higher exposures) has been reported in many epidemiological studies (NAS 1980), and is caused by the increasing effectiveness of cell killing at sufficiently high doses (note: radiation doses in upper bronchial generations are greater than in more distal generations). This finding suggests that the contributions of terminal bronchioles to total lung cancer risk, relative to segmental and subsegmental bronchi, may increase at high exposure levels.

To obtain the total risk for the whole bronchial region (see Fig. 3), the relative contributions of individual airway generations (displayed in Fig. 4) are multiplied by the number of cells in each generation. Figure 5 shows the resulting total lung cancer risk without this selective weighting procedure. The summation of risks with equal weight is conceptually equivalent to the averaging procedure of bronchial doses as proposed by ICRP (1981). While there are practically no differences between the two risk predictions below about 4000 WLM, the total risk computed with equal weight tends to become saturated at very high exposure levels, similar to the behavior of the respective risk functions for upper bronchial airways. This indicates that the continuing rise of total lung cancer risk at sufficiently high doses (see Fig. 4) may be caused mainly by the increasing contribution of terminal bronchioles.

We shall now investigate the sensitivities of parameter variations on lung cancer risk. To begin, the radiobiological data of Robertson et al. (1983) used in the previous calculations will be replaced by transformation and inactivation data of Hieber et al. (1987) for C3H 10T1/2 cells irradiated by ^{241}Am alpha particles. In this study, the constants a_0, a, b, and c in equations 1 and 2 adopt the following values: $a_0 = 1.0 \times 10^{-6}$, $a = 2.9 \times 10^{-4}$ Gy^{-1}, $b = 5.4 \times 10^{-4}$ Gy^{-2}, and $c = 1.54$ Gy^{-1}. The effect of both radiobiological data sets on total lung cancer risk is illustrated in Fig. 6. The Hieber et al. (1987) data display a transformation background rate which is a factor of 25 smaller than the corresponding value in the Robertson et al. (1983) experiments, with larger coefficients for both the linear and quadratic dose terms of the tranformation frequency function. As a result, the IPS-model with the Hieber et al. (1987) radiobiological data leads to a slightly lower predicted risk below about 3000 WLM and a slightly higher risk above this value, without significantly changing the overall shape of the risk-exposure relation.

The parameter p in equations 3 and 4 describes the effectiveness of stimulated cellular division, caused by local cell killing, relative to the normal mitotic activity of lung tissue. Thus a value of 1 means that each killed epithelial cell will force a stem cell to divide, while values smaller than 1 indicate the existence of a multi-stage renewal system. In Fig. 7, simulations with $p = 1$ and $p = 0.25$ are compared to our previous risk predictions which used $p = 0.05$. Higher values of p lead to a higher promotional effect of cell killing and, consequently, to a slightly steeper risk-exposure curve.

In equations 3 and 4 we have assumed that "local" cell killing, i.e., cell death in the immediate vicinity of a transformed cell, gives rise to an increased mitotic activity in that cell. One might argue, however, that cells more remote from the initiated cell may also contribute to radiation-induced promotion. We therefore replaced the local dose at depth interval i in generation k, D_{ik}, by the average dose

in generation k, this being equivalent to the notion that all killed cells in generation k may promote a given initiated cell. This produces a risk-exposure function which is practically indistinguishable from the local dose case.

The effect of stimulated cell division is further illustrated in Fig. 8, in which the number of divisions required for promotion, n, is varied from 0 to 2. When n is equal to 0, stimulated mitosis plays no role in radiation carcinogenesis. The best fit to the epidemiological data is achieved for a value of n = 1, which has been adopted in all previous simulations. This suggests that stimulated division through local cell killing is an essential feature of the model, and that only one cellular division is required for promotion, possibly within a short period of time after initiation.

The distribution of risk across the bronchial epithelium in the PS-model displays the same pattern as was noted for the IPS-model (see Fig. 2). This indicates that secretory cells may play a dominant role in radiation carcinogenesis at sufficiently high doses, while the relative contribution of basal cells is most significant at relatively low doses.

The predictions of total lung cancer risk in the PS-model for the whole tracheobronchial tree as a function of cumulative exposure are presented in Fig. 9. Agreement with the epidmiological data of Hornung and Meinhardt (1987) is again very good. Lung cancer risk in the PS-model is very similar to the IPS-simulations (Fig. 3), although the theoretical predictions of the latter turn over at a slightly higher cumulative exposure. The two assumptions regarding the number of initiated cells prior to the occupational exposure of radon progeny yield practically identical curves. Furthermore, the application of the Hieber et al. (1987) cell killing data does not appreciably affect the shape of the risk function; because of a slightly greater value of c, the risk function bends downward at lower cumulative exposures. This effect can also be observed in Fig. 10 for different upper bronchial airway generations; the corresponding set of data for the IPS-model is shown in Fig. 4. Once more, the more peripheral airway generations follow the epidemiological data very closely.

The effect of removal from contact inhibition (equation 5) on the production of total lung cancer risk is illustrated in Fig. 11. The curve denoted by A = 0 represents the control case in which no contact inhibition is assumed. The lack of agreement with the epidemiological data clearly indicates that removal from contact inhibition through local cell killing plays an essential role in our cancer induction model. The assumption of a smaller background rate under in-vivo conditions leads to a reduction of risk at lower cumulative exposures and to an increase at higher exposures.

The exponential relationship of lung cancer risk with dose (equation 10) for the S-model predicts a negative slope of the risk function with cumulative exposure, in sharp contrast to the epidemiological data which indicate a positive slope. Despite this inconsistency, we shall, in the discussion section, investigate the potential role of the S-model for the calculation of lung cancer risk at very low exposures.

The additional promotional effect of cigarette smoke (equation 11) on total lung cancer risk for the whole bronchial region, incorporated into the IPS-model, is illustrated in Fig. 12. Values for q range from 0.01, where the cigarette smoke promotion term is smaller than the radiation promotion term at all doses, up to 10, where the promotional effect of cigarette smoke always exceeds that of radiation; the parameter p denoting the relative efficiency of cell killing for stimulated division being set equal to 0.05. An increase in the relative efficiency of cigarette smoke promotion produces a higher risk at low doses with a smaller risk at high doses when compared to the instance of pure radiological promotion (see Fig. 3). The same is true for the relative risk in different bronchial generations as illustrated in Fig. 13 (compare to Fig. 4). Use of the cigarette smoke promotion term in conjunction with the PS-model yields the same results as presented here for the IPS-model.

DISCUSSION

In the present study, we have developed mechanistic models for radiation-induced lung cancer based on radiation mechanisms at the cellular and organ level. This philosophy allows us to test each step of the models with laboratory evidence. Both the functional forms of the dose-effect relationships as well as the parameter values used in their functions are derived from experimental cellular studies, and only multiplicative scaling factors are obtained through fitting epidemiological data on lung cancer. In related sensitivity analyses, different parameter values were varied to explore the potential effects of differences in cell types and tissue sensitivities, and relative efficiences of cellular mechanisms on resulting lung cancer risks.

We now wish to discuss various factors which may modify the dose-effect relationhips presented in this paper:(i) In the current model we have assumed that lung cancer risk is proportional to the number of transformed cells; in other words, any factors which may subsequently modify the initial cellular response are independent of radiation dose. There may, however, exist additional modifying factors at the organ or even whole body level, such as the suppressing action of the immune system at low doses. In the absence of any conclusive formulation, we may conceptually model this effect by using a function of the form (1-exp(-aD)), as suggested by many repair concepts (Goodhead 1985). Incorporation of such a

function in our analysis would decrease the lung cancer risk at low doses relative to our current predictions.(ii) We also assumed that alpha activity is uniformly distributed among bronchial airway surfaces, thus neglecting known accumulations of radon progeny at bronchial bifurcations (Hofmann et al. 1990). Such effects would increase lung cancer risk at low cumulative exposures, without affecting risk predictions at higher exposures. This may partially compensate for a potential risk reduction at low doses due to the above suppressing factors. (iii) Within a given exposure category of an epidemiological study, differences in actual exposures and metabolic properties between individuals may influence the relationship between exposure and dose. This variability in dose for a specific exposure category may be quantified by a truncated lognormal density function (Crawford-Brown and Hofmann 1989). Inclusion of this variability into the calculation causes the predicted relative risk to continue increasing at large exposure levels, whereas the model without variability predicts, instead, a downturn.

Comparisons between the three models presented in this text show only minor differences between the risk predictions of the IPS- and PS-models over the entire range of cumulative exposures reported by Hornung and Meinhardt (1987). In contrast, the S-model does not compare well with the epidemiological data. Bearing in mind that the three models reflect different starting points in the five-stage transformation model (Crawford-Brown and Hofmann 1990) prior to exposure, one could postulate separate scenarios in which the different models are most effective at different exposure levels: 1. At very low doses only those cells which are already fully transformed, i.e., being in stage 5, can contribute to lung cancer risk prior to the onset of irradiation. Since the only effective radiation action then is cell killing, exposures to low doses are best described by the survival (S) model. 2. With increasing dosages the probabilities of removal from contact inhibition and stimulated cell division will increase, and more cells will advance from stages 3 and 4 to stage 5. This implies that cells already initiated by other non-radiological factors are to be promoted by radiation, and risk is therefore most suitably described by the promotion-survival (PS) model. 3. At ever increasing doses, cells from stages 1 or 2 will eventually reach the final stage 5; i.e., radiation acts simultaneously as an initiator and promoter. Thus at sufficiently large exposure levels, the risk function will be determined by the initiation-promotion-survival (IPS) model.

The composite lung cancer risk, $R_{comp}(D)$, which represents the most general case of a combined exposure to radiation and other co-carcinogenic factors, may then be written as the linear combination of the three individual risk functions, RIPS(D), RPS(D), and RS(D):

$$R_{comp}(D) = a(D)\,RS(D) + b(D)\,RPS(D) + c(D)\,RIPS(D) \qquad (12)$$

where a(D), b(D) and c(D) are the relative efficiences at a prediscribed dose D. These efficiencies depend on the number of cells in each stage prior to irradiation, as given by the initial state vector (Crawford-Brown and Hofmann 1990), which may be affected by a variety of factors, such as age at exposure, age at risk, health status, past exposure to other carcinogenic factors, etc. At present, however, we do not know how to extract this information from epidemiological data.

An interesting inference from equation (12) is that the composite lung cancer risk at very low doses comparable to environmental dose levels is governed by the survival model. This model predicts a decrease of lung cancer risk with increasing dose, which would lead to a deficit in radiation-induced risk relative to the natural background rate. The salient point being that radiation kills cells already transformed by other agents, thereby reducing the total lung cancer risk. Indeed, such a negative correlation of the lung cancer mortality rate in both males and females with the mean radon level in US homes has been reported by Cohen (1990), for radon concentrations as high as 259 Bq m^{-3} (7 pCi L^{-1}). Since we have no information about the relative efficiency of the survival model at low exposures, we cannot presently determine the upper bound of the exposure region in which such a potential deficit in lung cancer incidence may actually be observed.

Above the exposure region in which the survival model dominates, i.e., at low and intermediate exposures, the promotion-survival model may play the most important role. This hypothesis is supported by the epidemiological lung cancer data of Samet et al. (1989). Those findings display a rather small positive slope at exposures below about 250 WLM, followed by an increasingly steeper rise at higher exposure values. This shape of the dose-effect relationship resembles the response function of the PS-model in this exposure regime (see Figure 8). In conclusion, both the survival model at very low exposure levels and the promotion-survival model at low and intermediate exposure levels predict a significantly smaller relative lung cancer risk at low, realistic environmental exposures than that derived from a linear extrapolation of epidemiological data over the whole exposure range.

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FIGURE CAPTIONS

Fig. 1 Relative lung cancer risk as a function of cumulative ^{222}Rn progeny exposure in U.S. uranium miners (Hornung and Meinhardt 1987). Vertical bars represent 95% confidence limits.

Fig. 2 Relative lung cancer risk distribution across the bronchial epithelium in airway generation 2 for varying cumulative exposures, normalized to the same total risk. Computations are done using the IPS-model.

Fig. 3 Predictions of total lung cancer risk in the IPS-model (solid line) and comparison with epidemiological data (broken line).

Fig. 4 Predicted relative risk in the IPS-model for several bronchial airway generations as a function of cumulative exposure.

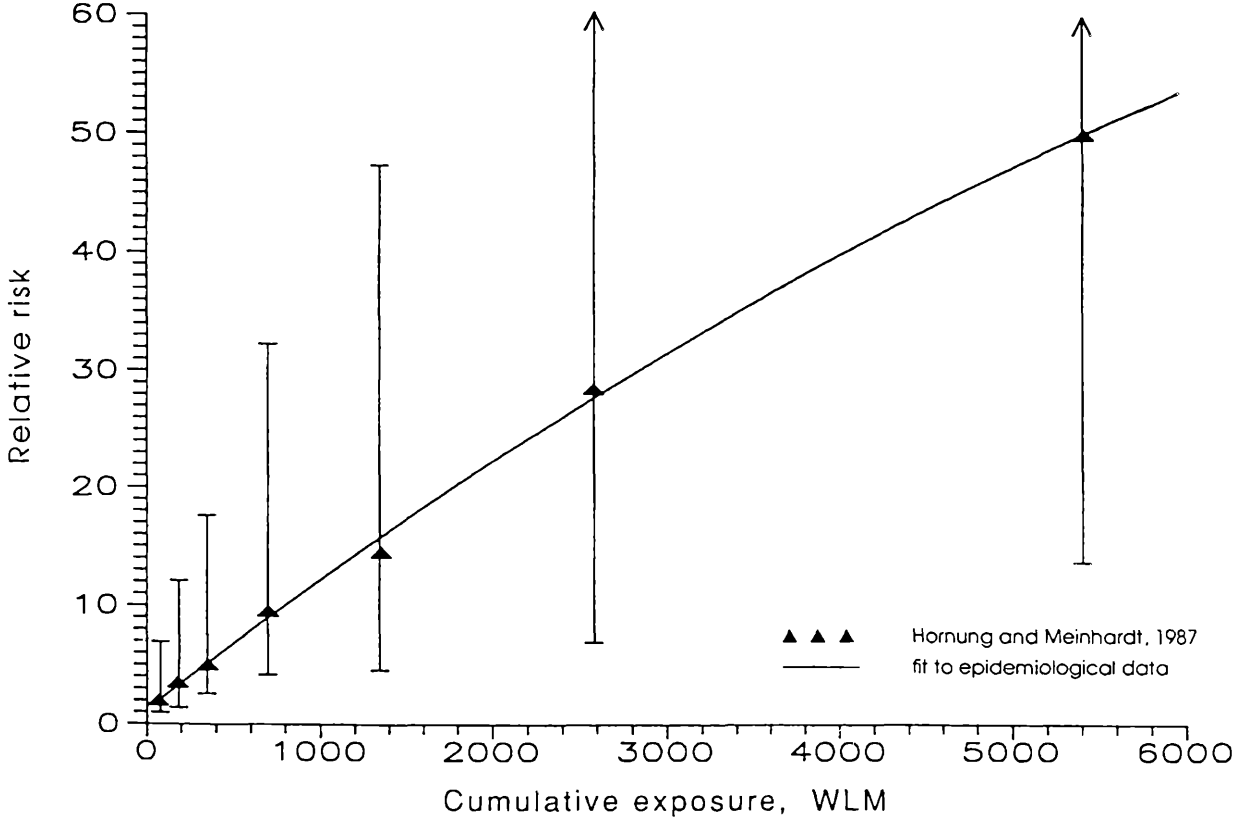
Fig. 5 Comparison of total lung cancer risk predictions (IPS-model): (a) summation of risks in individual bronchial generations, weighted by the number of cells in each generation, and (b) summation of risks in individual bronchial generations with equal weight.

Fig. 6 Comparison of the effect of two sets of in-vitro transformation and cell killing data, representing two different cell lines, on total lung cancer risk in the IPS-model: (a) Robertson et al. (1983), and (b) Hieber et al. (1987).

Fig. 7 Illustration of the promotional effect of local cell killing on total lung cancer risk in the IPS-model: variation of the fraction of killed cells inducing stimulated mitosis.

Fig. 8 The effect of stimulated cell division on total lung cancer risk (IPS-model) and its dependence on the number of cellular divisions required for promotion.

Fig. 9 Predictions of total lung cancer risk in the PS-model for two different assumptions regarding non-radiological initiation: (i) the number of initiated cells in a given generation is proportional to the number of cells in that same generation, or (ii) the number of initiated cells is proportional to the surface density of deposition.
Fig. 10 Predicted relative risk in the PS-model for several bronchial airway generations as a function of cumulative exposure.
Fig. 11 Illustration of the effect of removal from contact inhibition on total lung cancer risk in the PS-model.
Fig. 12 Predictions of total lung cancer risk in the IPS-model including the additional effect of cigarette smoke promotion. Different values of q denote the relative efficiencies of cigarette smoke promotion compared to radiation promotion.
Fig. 13 Predicted relative risk in the IPS-model, including a cigarette smoke promotion factor, for several airway generations as a function of cumulative exposure.



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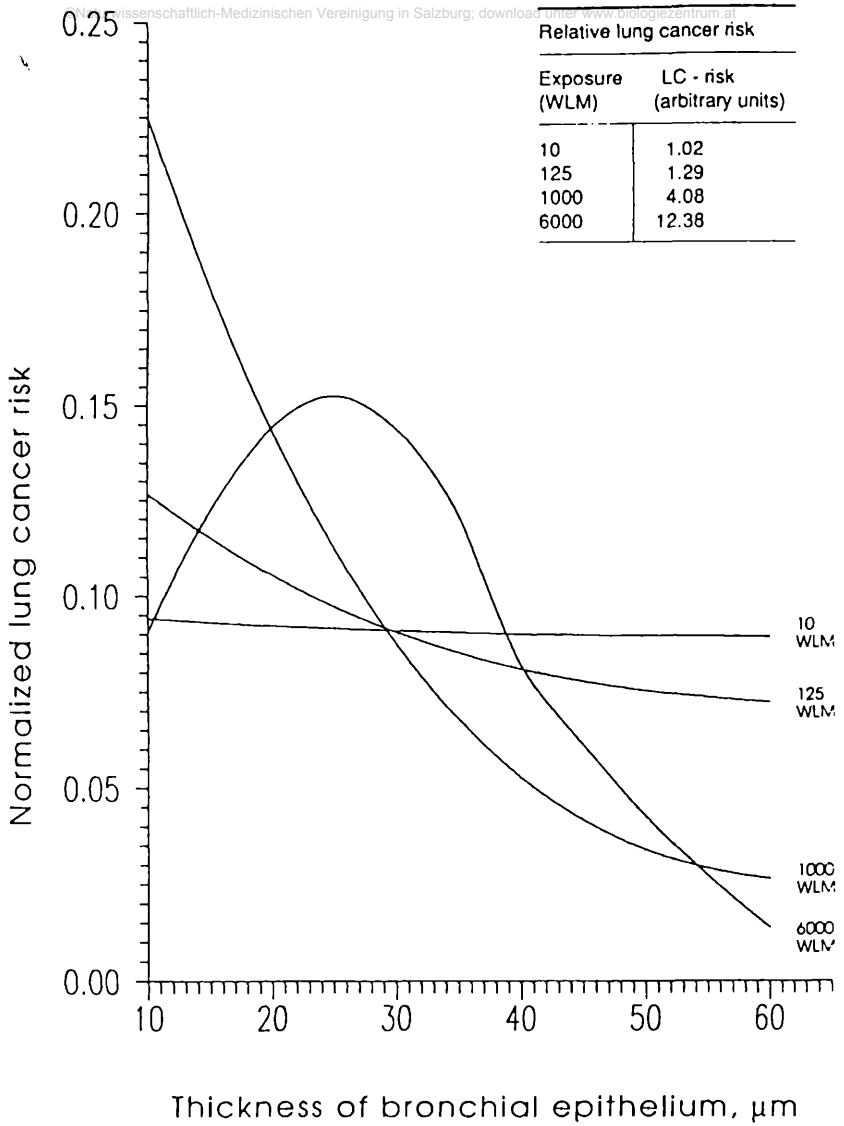

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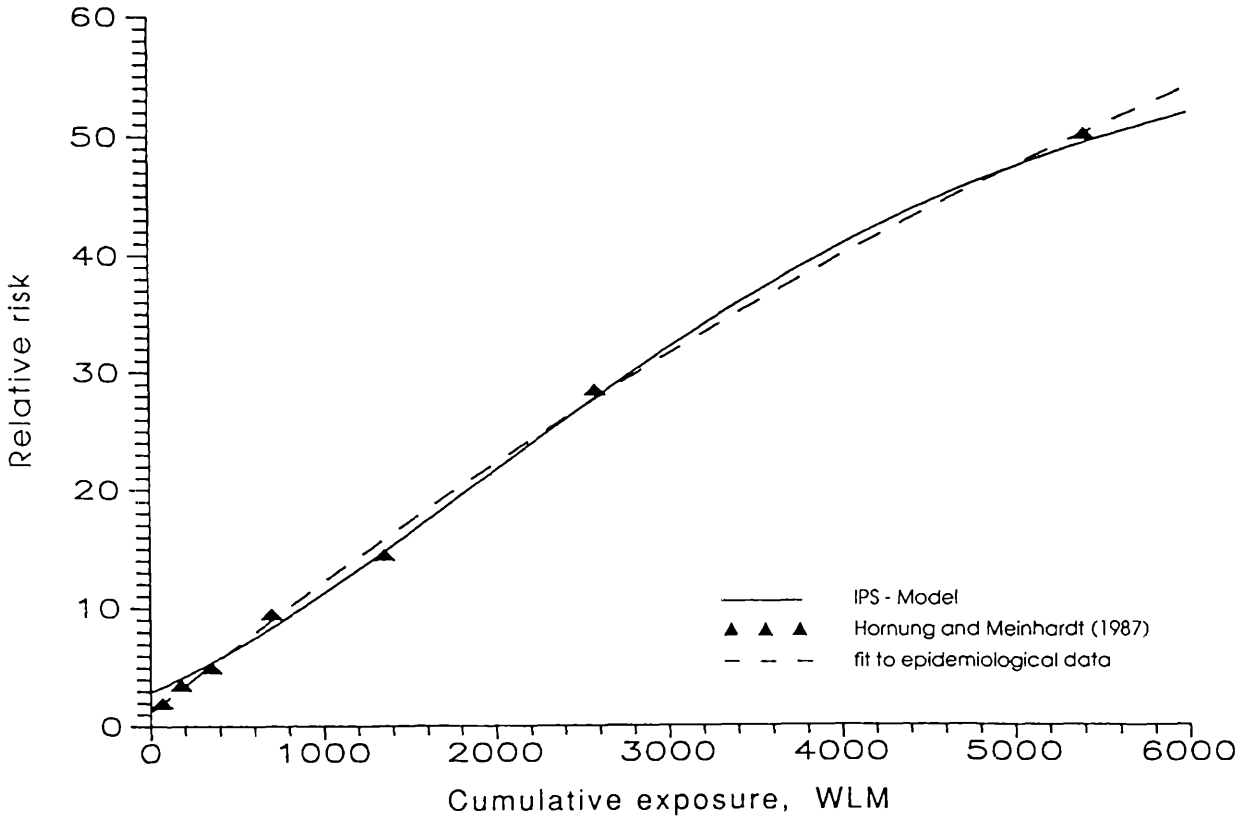

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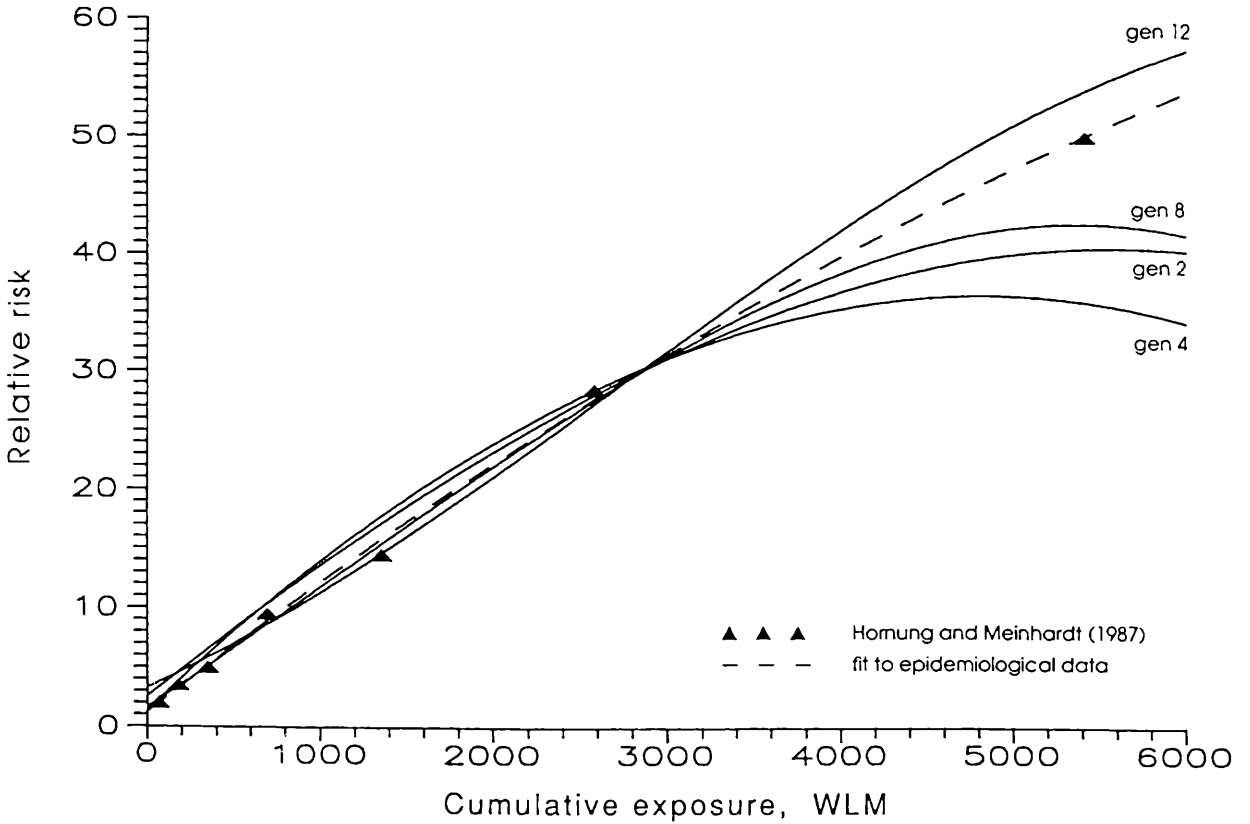

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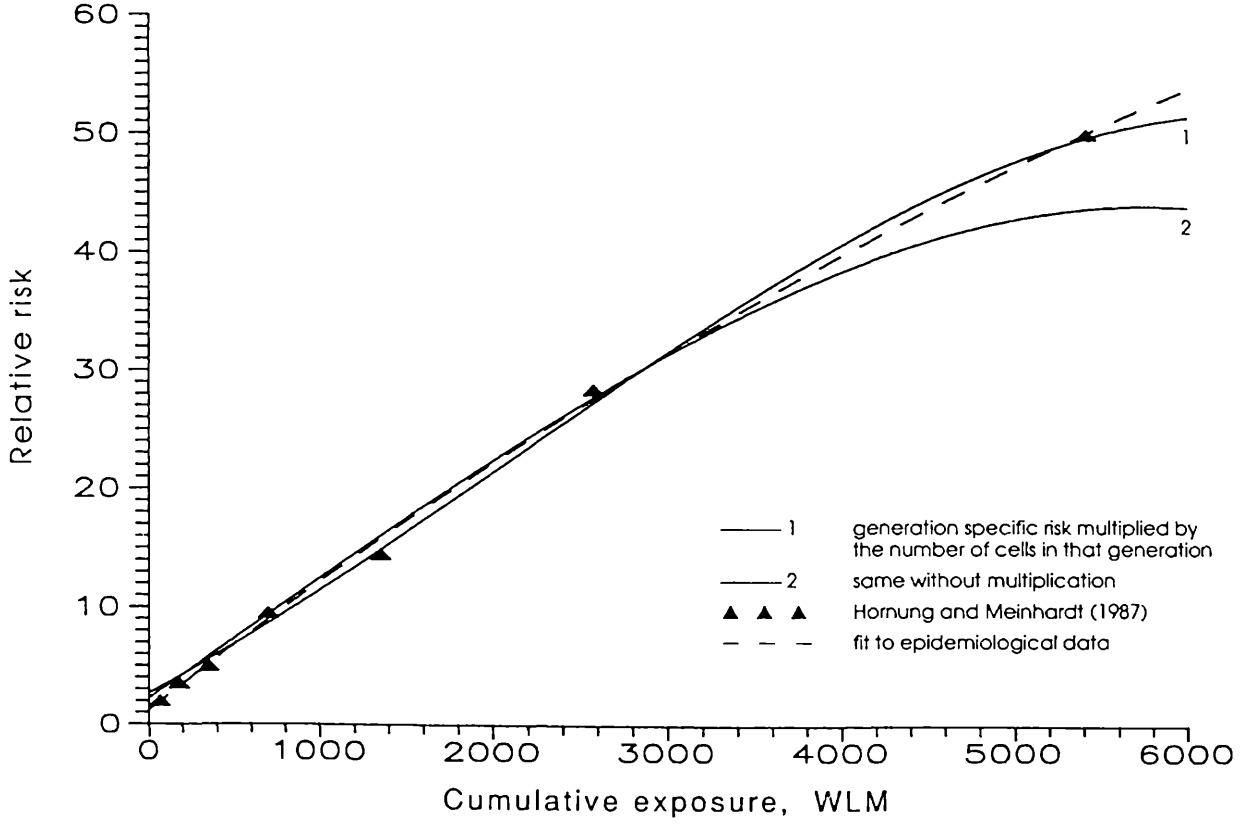

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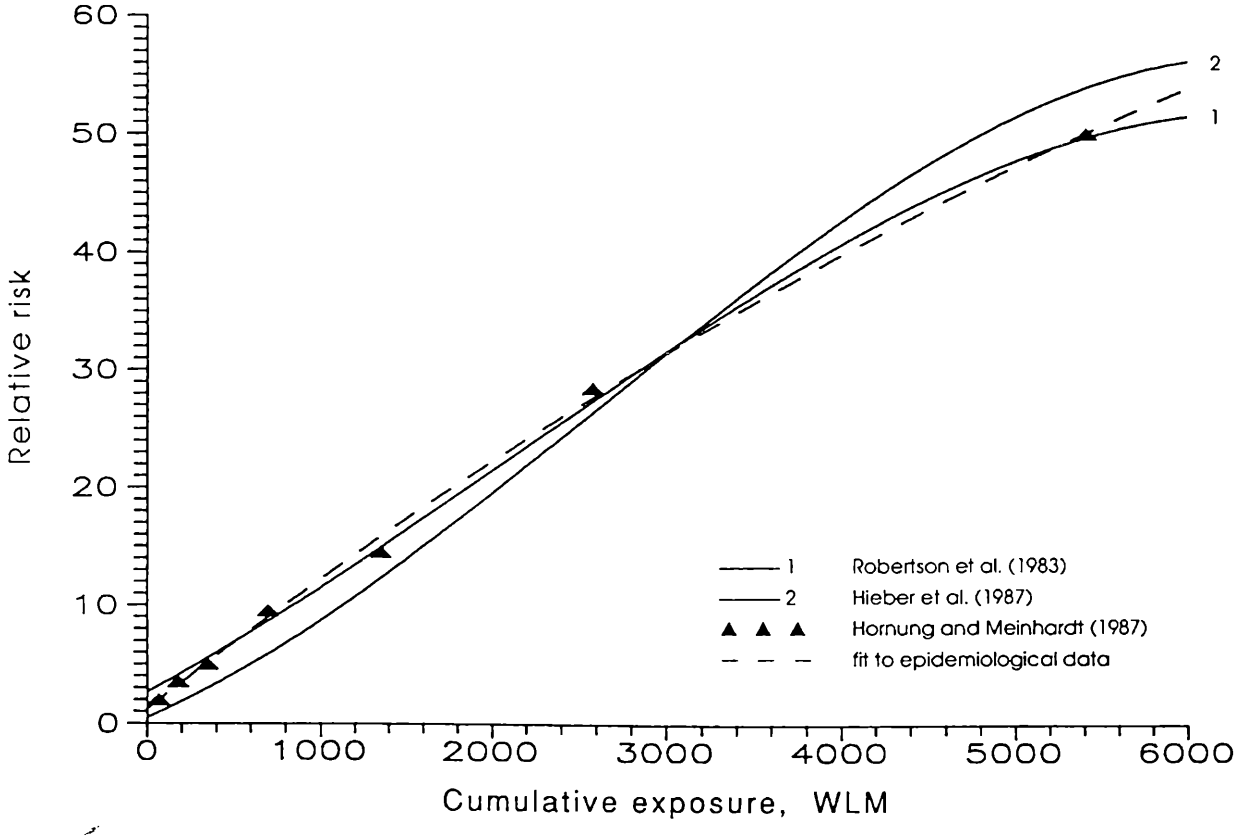

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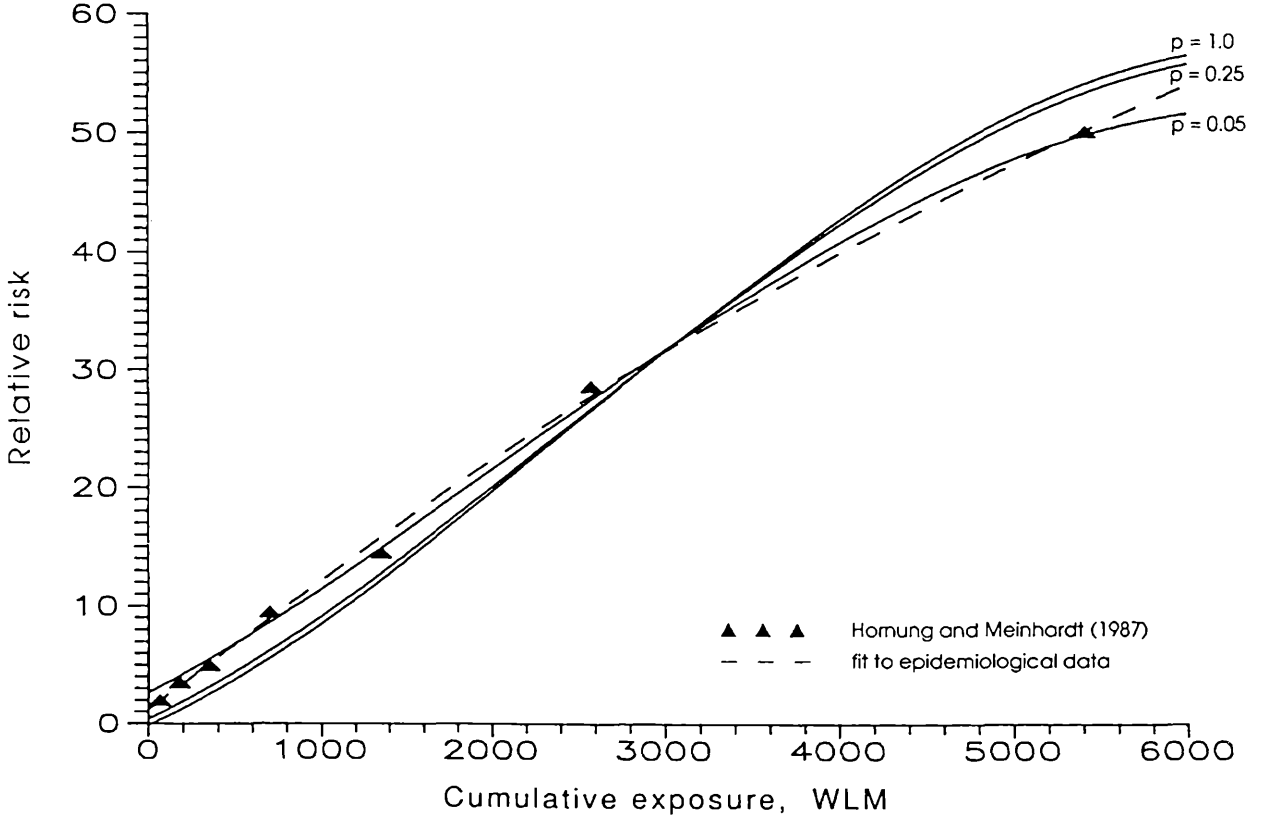

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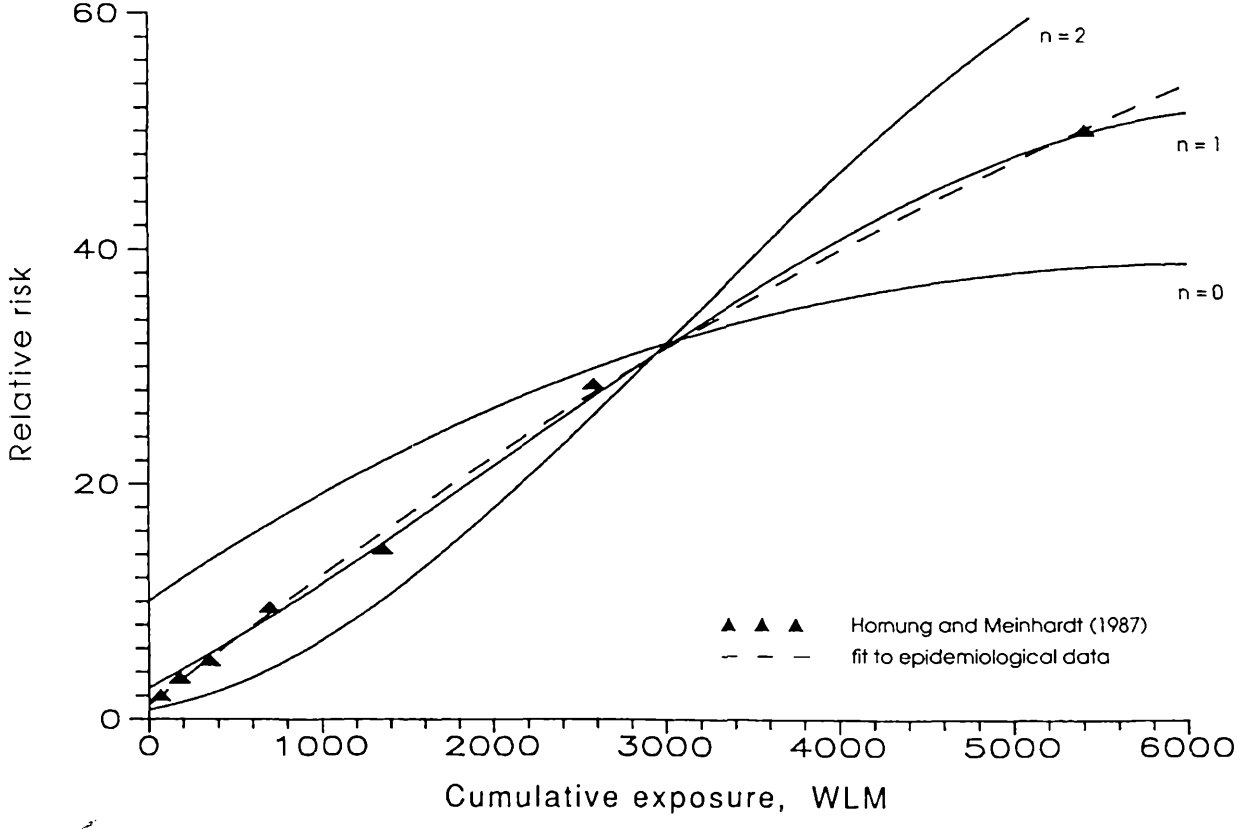

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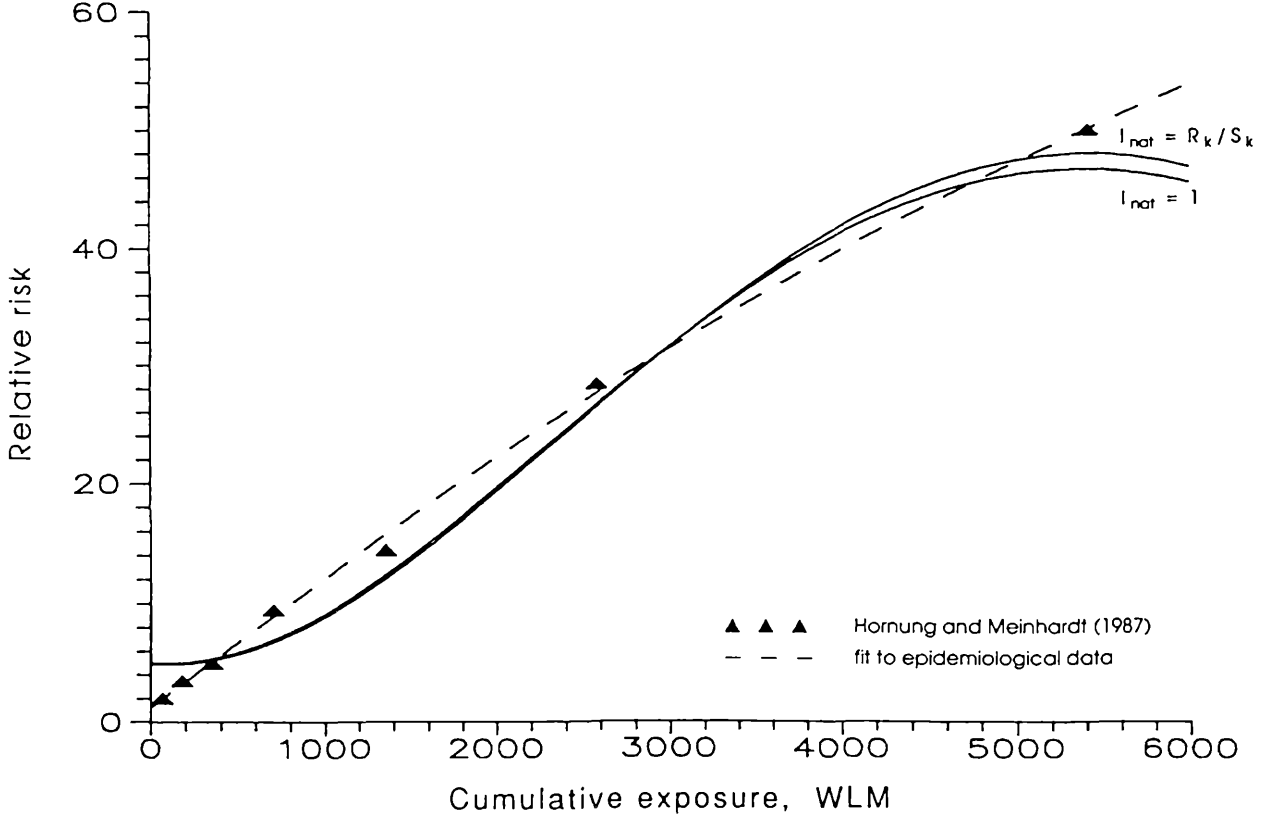

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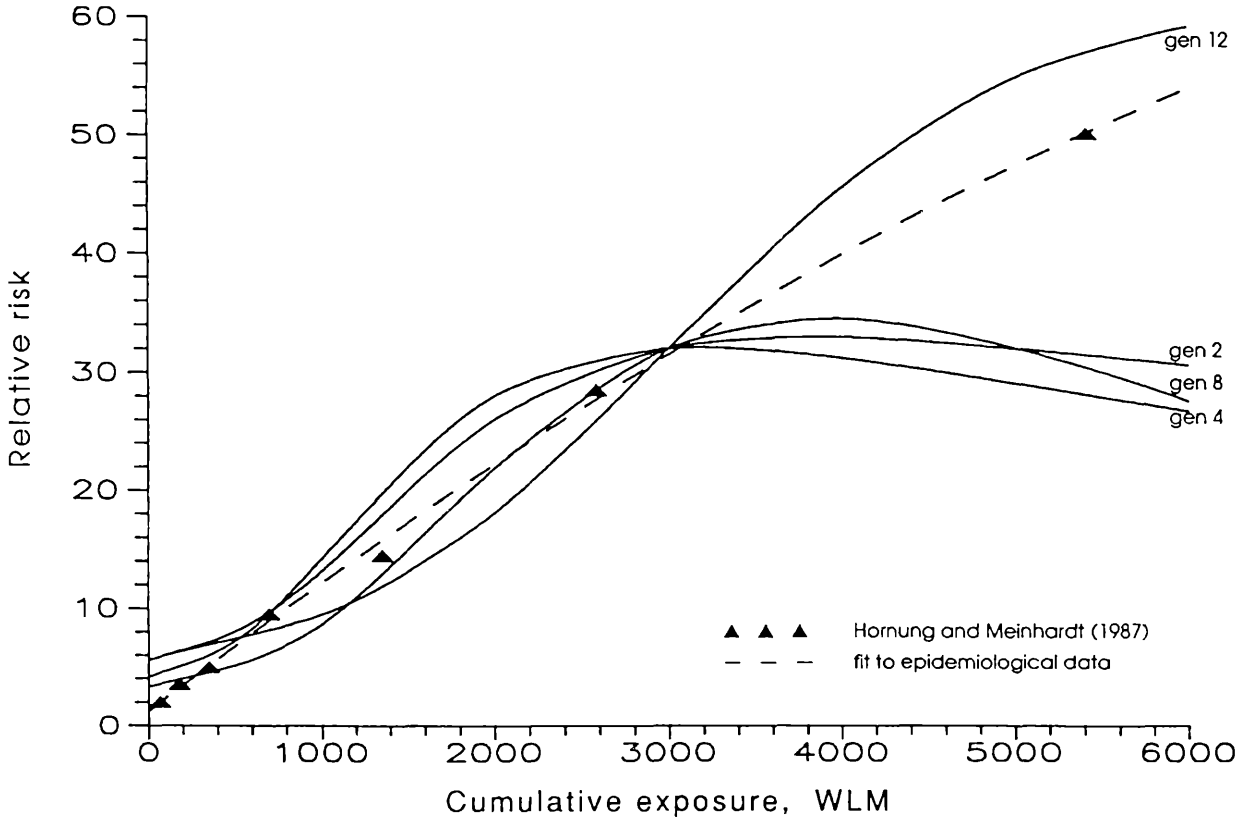

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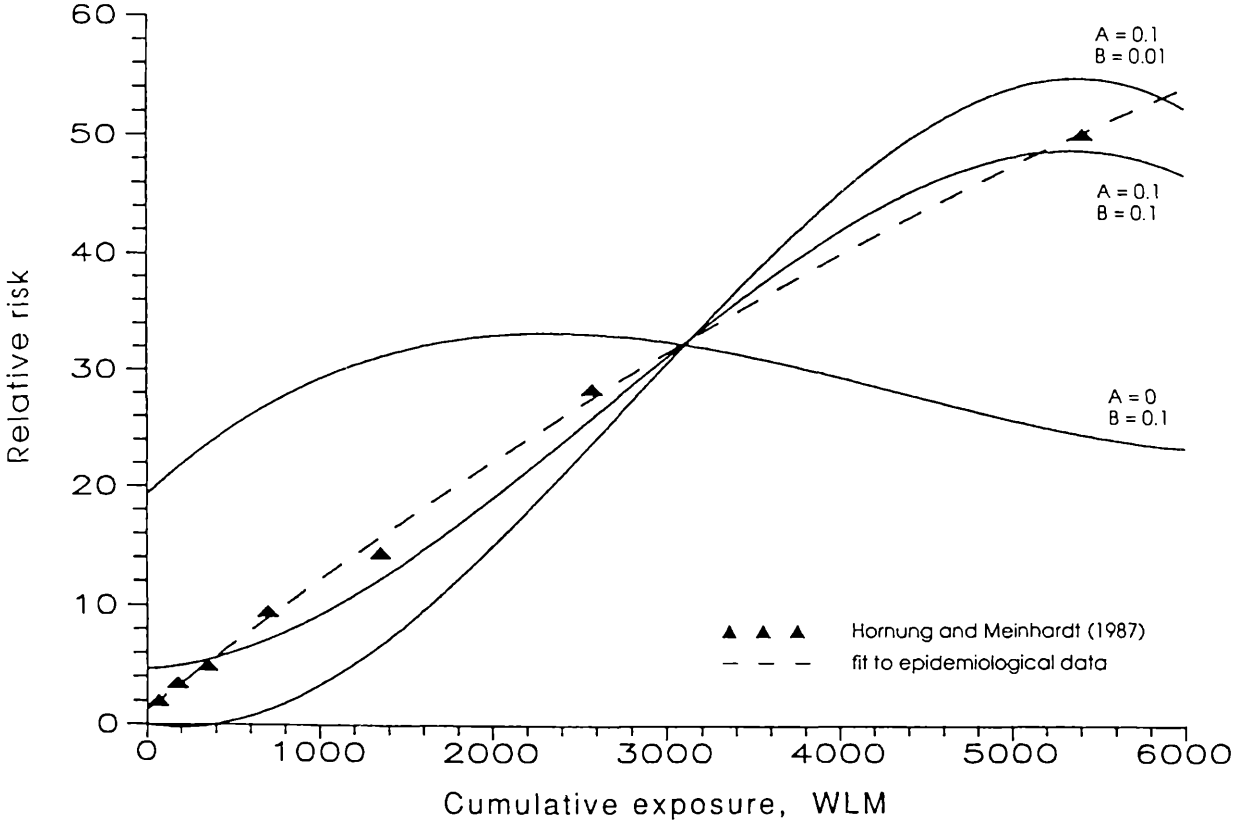

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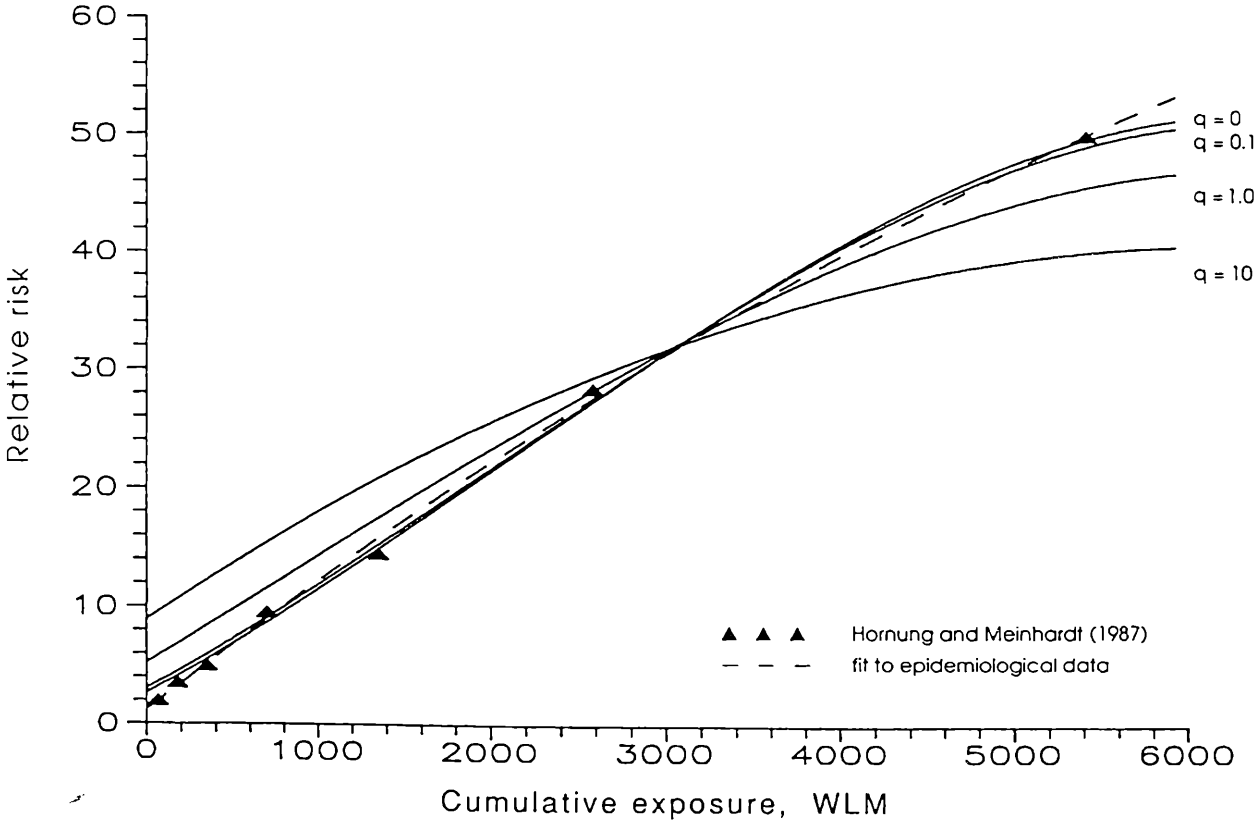

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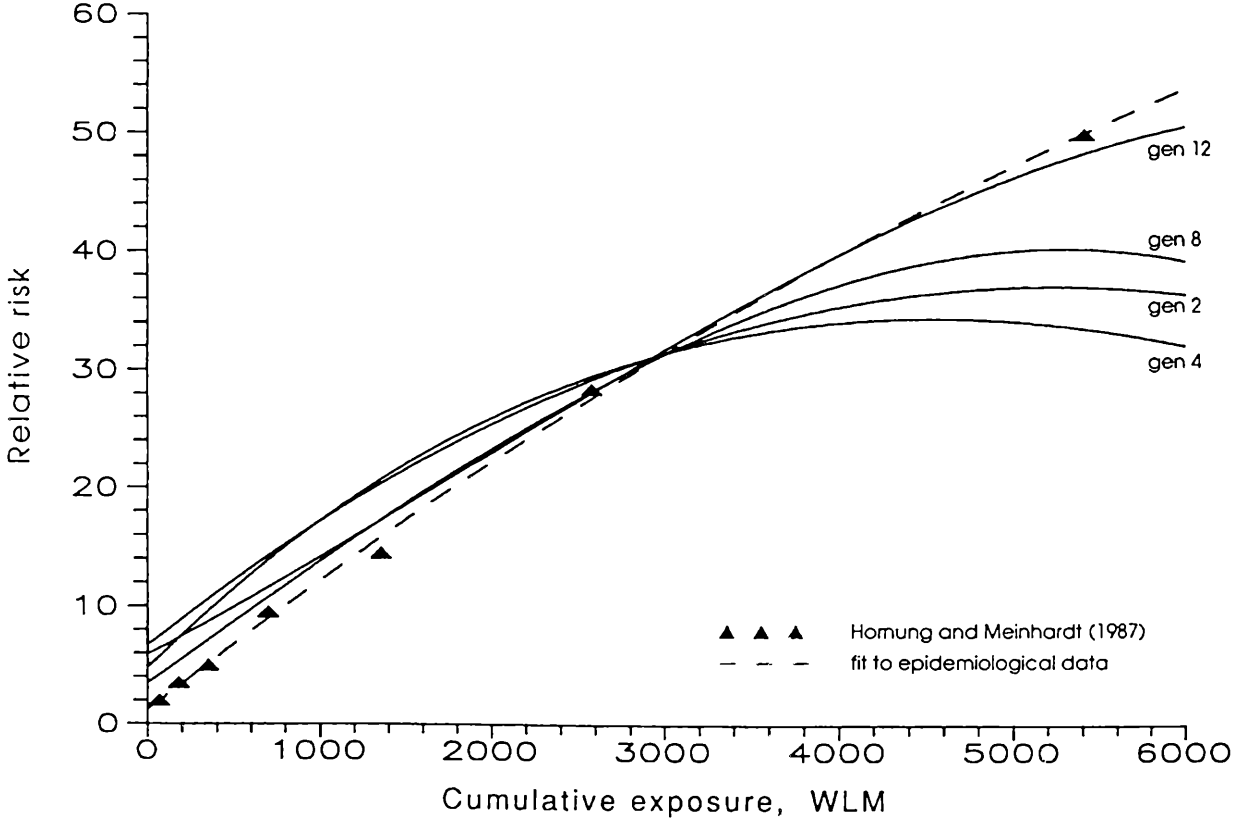

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