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Abstract

A survey of inhabitant exposures arising from the inhalation of ^{222}Rn and ^{220}Rn progeny, and lung cancer mortality has been carried out in two adjacent areas in Guangdong Province, People's Republic of China, designated as the "high background" and the "control" area. Annual exposure rates are 0.38 working level months (WLM) per year in the high background, and 0.16 WLM/yr in the control area. In 14 yr of continuous study, from 1970 to 1983, age-adjusted mortality rates were found to be 2.7 per 10^5 living persons of all ages in the high background area, and 2.9 per 10^5 living persons in the control area. From this data, we conclude that we are unable to determine excess lung cancers over the normal fluctuations below a cumulative exposure of 15 WLM. This conclusion is supported by lung cancer mortality data from Austrian and Finnish high-background areas.

A theoretical analysis of epidemiological data on human lung cancer incidence from inhaled ^{222}Rn and ^{220}Rn progeny, which takes into account cell killing as competitive with malignant transformation, leads to the evaluation of a risk factor which is either a linear-exponential or a quadratic-exponential function of the α-particle dose. Animal lung cancer data and theoretical considerations can be supplied to support either hypothesis. Thus we conclude that at our current stage of knowledge both the linear-exponential and the quadratic-exponential extrapolation to low doses seem to be equally acceptable for Rn-induced lung cancer risk, possibly suggesting a linear-quadratic transformation function with an exponential cell-killing term, or the influence of risk-modifying factors

Introduction

Although human beings are exposed to low levels of ionizing radiation during their entire lifetime, only rough and controversial information about the hazards of low levels of radiation can be derived from epidemiological investigations typically because of the synergistic interference of other environmental co-carcinogens, Among the various causes for lung cancer induction, smoking is generally considered as the dominating cause among non-radiation factors, supposedly causing about 83% of all cancer cases in men and about 43% in women (Am80). Hitherto, Rn-progeny-induced lung cancers could not be distinguished with histological-cytological methods from lung cancers initiated by other carcinogens, such as tobacco smoke (St85). Thus the biological effect of low-level Rn-progeny exposure cannot be detected directly against the high background of "natural" lung cancers in the general population.

Direct observation of Rn-induced lung cancer risk at low doses becomes a practical impossibility because the sample size needed to produce reason-

ably precise estimates increases inversely proportionally to the square of the excess, with the additional difficulty of controlling confounding factors (Th82). For this reason any estimate of the effects of low-level radiation must be based on some form of extrapolation from higher dose levels at which effects are clearly demonstrable to low dose levels. A conservative approach, *e.g.* applied by ICRP (IC81), assumes a linear no-threshold relationship between lung cancer (LC) risk and dose. Thus all risk projections for low doses depend on the validity of this relationship.

In using data for occupational exposure at high exposure levels, *e.g.* in U mines, to derive the LC risk from low-level environmental exposure, one must consider the significant environmental and physiological differences between the two exposure situations. The potential co-carcinogenic factors in the mining environment have been estimated to be responsible for about 20% of the risk coefficient of miners (Ja85). Furthermore, U miners received their exposures at high exposure rates during a period of a few years during the early phase of U mining, whereas non-occupational exposure occurs typically at considerably lower exposure rates but throughout a lifetime, resulting in a possibly increased latent period and thus reduced lifetime risk.

For all these reasons, epidemiological data for non-occupational exposure in non-polluted, high-background areas, where the natural radiation exposure is higher than the normal background levels and the natural incidence rate is low, would offer the unique chance to check current risk estimates for domestic Rn progeny exposure. Such a high background area has been found in the People's Republic of China.

In the present discussion, we seek to evaluate the effects of low doses of α particles for environmental exposure by the extrapolation of occupational miner exposure data to low doses, and to compare the result of that extrapolation to new epidemiological data obtained from a high-background area in China. A recent analysis of LC risk in U.S. uranium miners clearly demonstrates that low-dose risk estimation cannot rely entirely on epidemiological evidence, but instead requires additional scientific information (Wh83). We therefore propose a new model which incorporates current knowledge of α-particle interaction with cellular sensitive targets, and fit this model to the epidemiological data available, instead of trying to get the best mathematical fit irrespective of any biological and physical meaning.

Epidemiological Investigations in a Chinese High-Background Area

A survey of inhabitant exposures arising from the inhalation of ^{222}Rn and ^{220}Rn and their short-lived decay products, and LC mortality has been carried out by the Chinese group since 1970, in two adjacent areas in Guangdong Province designated as the "high background" and the "control" area (Hig80; Hig82). Both areas are predominantly rural with stable populations that have lived in the same area for generations. The population in each area is about 80,000. In this region of the People's Republic of China women typically do not smoke. The structure of the buildings and the living habits in these areas have not changed greatly in this century, thus ensuring that exposure rates have been the same for several generations.

The average concentrations of ^{222}Rn, indoors and outdoors, in the high-background area are 29.9 and 16.3 Bq/m^3, factors of 2.3 and 1.5 times the concentrations in the control area, respectively. The averaged concentrations of ^{220}Rn, indoors and outdoors, in the high-background region are 167.6 and 18.5 Bq/m^3, factors of 9.6 and 4.8 times the concentrations in the control area (Hig78; Zhan82). The averaged potential a energies of ^{222}Rn and ^{220}Rn daughters in air in both areas are given in Table 1.

Based on investigations of daily activities of inhabitants in both areas, most spend approximately half of their time indoors. Using the potential a energies listed in Table 1 and an occupancy factor of 0.5, the exposure rates from ^{222}Rn progeny only are 0.26 WLM/yr in the high background area, and 0.12 WLM/yr in the control area. Thus the ratio of the exposure rate from ^{222}Rn progeny in the high-background area to that in the control area is 2.2. Inhalation from ^{220}Rn progeny also contributes to the absorbed dose in bronchial tissue, although its effective dose equivalent per unit inhaled potential α energy is only about one-third of the corresponding value for the short-lived ^{222}Rn (Rn) decay products (IC81; UN82). Taking into account a weighted additional exposure from ^{220}Rn (Tn) progeny (1 WLM(Tn) = 0.33 WLM(Rn) to give the same dose equivalent), the total risk-relevant annual expo-

Table 1. Averaged potential a energies of short-lived ^{222}Rn and ^{220}Rn decay products and their standard deviations in high background and control areas.

Radionuclides	High Background		Control Area	
	Outdoor	Indoor (mWL)	Outdoor	Indoor (mWL)
Radon-222 Daughters	4.68 ± 0.62	5.20 ± 0.44	2.48 ± 0.22	2.17 ± 0.15
Radon-220 Daughters	2.75 ± 0.54	11.67 ± 0.85	1.31 ± 0.18	3.85 ± 0.36

sure to ^{222}Rn and ^{220}Rn progeny is 0.38 WLM/yr in the high-background area, and 0.16 WLM/yr in the control area. This gives then a ratio of the exposure rate from ^{222}Rn and ^{220}Rn decay products in the high-background area to that in the control area of 2.4.

In 14 years of continuous study from 1970 to 1983 (Zhai82; Hig85), the accumulated population surveyed in the two areas is nearly equal, being 767,696 person-years in the high background area and 777,482 person-years in the control area. Lung cancer deaths were found to be 23 in the high-background area and 27 in the control area (inverting the order of the radiation exposure), with the ratio of men to women being 1.1 in the high-background area and 2.8 in the control area. Annual mortality rates, adjusted according to age and sex, are 2.7 per 10^5 living people of all ages in the high-background area and 2.9 per 10^5 in the control area.

Though the number of cancers in the control area is slightly higher than in the high-background area, this difference in cancer mortality rates in the two regions is not statistically significant. We are in the region of "background noise" and cannot determine the excess cancers from these data. Although reasons have been advanced to explain such an inverse relationship with dose by "biopositive" effects (Hic83; Lu82), we rather attribute it to statistical background fluctuations. Even in such rural areas, relatively free from industrial pollution, having stable populations with comparable smoking habits, we are unable to determine the excess LC rate over normal fluctuations at an exposure level of 0.38 WLM/yr. If we take a mean effective exposure time, i.e. lifetime minus latency period, of about 40 yr, we conclude from this data that there is no observable excess LC risk below a cumulative exposure of about 15 WLM.

Further Epidemiological Evidence of Non-Occupational Exposure

The exposure rates from ^{222}Rn progeny and LC incidence in the Rn spa at Badgastein, Austria, have been studied by Pohl-Rüling *et al.* (Poh82). Most Badgastein inhabitants receive a mean bronchial dose equivalent of 39 mSv/yr (an exposure rate of approximately 0.4 WLM/yr) which is twice the value of a normal environment exposure in the Salzburg, Austria, area. The annual LC incidence rate for Badgastein is 30 per 10^5 living people of all ages, not statistically different from the observed LC cases in the whole province of Salzburg of 32 per 10^5. Although the mean exposure in Badgastein is twice that in the province, the LC mortality is again not increased but is nearly the same in both areas at about 30×10^{-5} deaths per person-year (PY). The number of persons investigated might be, however, too small to show any discernible difference.

While the corresponding high-background and control areas in Austria and the People's Republic of China have approximately the same exposure rates, the incidence rate of LC in these areas in Austria is, however, one order of magnitude higher than in the corresponding areas of China. It would appear that something other than inhaled Rn progeny is responsible for the higher incidence

in Austria. This is consistent with the generally recognized finding (Co80) that LC is more prevalent in industrialized than developing countries.

Relatively clear differences in Rn progeny exposure, ranging from 0.29 to 1.50 WLM/yr were not reflected in the geographical distribution of the incidence of LC in Finland, according to Castren *et al.* (Ca84). Here the age-adjusted incidence rates in regions with high indoor Rn concentrations were 4.7 $\times 10^{-5}$ per year for women and 69 $\times 10^{-5}$ for men. These values are lower than the national mean values for the same period, 5.3 $\times 10^{-5}$ for women and 82 $\times 10^{-5}$ for men. Consistent with the Chinese exposure experience, Rn progeny exposures in the range of 0.29 to 1.50 WLM/yr in Finland, and 0.16 to 0.38 WLM/yr in China, do not lead to clearly observable differences in LC. The age-adjusted total incidence rate for women in Finland is about two times higher than the rate for women in the surveyed area in China, while the rate for men in Finland is more than an order of magnitude higher than the rate for men in China (but is similar to the rate of both sexes in the Salzburg area).

In a nationwide indoor survey carried out in 13 Canadian cities (Le82), no evidence of any substantial association between LC rates and indoor Rn progeny exposure has been found.

A study of LC and natural radiation in the Italian province of Viterbo showed no statistically significant correlation between LC deaths and geological properties, although no Rn progeny exposure has been determined (Fo85).

Correlation studies on the domestic use of drinking water and the incidence of cancer in two American states—Maine and Iowa—indicate that LC rates for consumers of water with an elevated Ra content are higher as compared to those of users of water with a low Ra content (Bea82). However, no data is available on actual individual doses due to Rn progeny exposure.

Finally a pilot case-referent study of LC in Swedish rural areas in relation to the type of dwelling, characterized by very crude exposure categories, suggests that there might be a relationship between the structure of the houses and LC incidence (Ax79).

Risk Analysis

Current estimates of LC risk (NA72; NA80; UN77) refer essentially to mining populations, assuming a linear extrapolation to low doses. Thus the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) concludes that the most likely risk factor for LC induction ranges from 200 to 450 $\times 10^{-6}$ per WLM for at least 40 yr of exposure with a latent period of 10 yr (UN77), which translates to 6.7–15 per 10^{-6} PY-WLM. The only risk calculation referring specifically to members of the general public has been provided by Evans *et al.* (Ev80), recommending a value of 10^{-4} per WLM as an upper bound for the lifetime risk due to environmental Rn.

The Chinese epidemiological study found that no excess lung cancers could be determined. This can be interpreted in two different ways:

(1) There is actually no LC risk associated with low doses and dose rates of domestic exposure to ^{222}Rn and ^{220}Rn progenies. In this case, published risk estimates clearly overpredict LC risk at low exposure levels, e.g. the UNSCEAR-based risk estimate for the high-background area would predict 5.6–12.5 excess cases per year, while the total number of annual LC cases is only 1.6. Even the smaller figure of Evans *et al.* (Ev80) still yields 1.6 excess cases per year. We therefore conclude that a linear extrapolation to low doses is invalid.

(2) No excess risk could be determined because of the above-discussed statistical problems associated with risk estimation at low doses in the presence of other strong carcinogens, such as cigarette smoke. In this case, the Chinese study clearly demonstrates that risk assessment at low doses, even under such favorable conditions, is extremely difficult if not impossible. We therefore conclude that risk estimation at low domestic exposure levels must rely on occupational exposure data and their extrapolation to low doses.

Thus either way of interpreting the Chinese results finally leads to the question of the shape of the dose-effect curve, particularly at low doses. We seek to answer this question by developing a LC induction model based on current radiobiological information.

Besides the fact that no excess cancers have been found in the Chinese high-background area, there is the additional fact that the total LC incidence in both Chinese areas is an order of magnitude lower than in other countries (even the Chinese average

is about twice this value being 5.0 per 10^5 persons). This finding may be due to two reasons:

(1) Cigarette smoking is considered to be the primary cause for LC induction. In accordance with animal experiments, the direct carcinogenic effect of tobacco smoke seems to be rather small compared to its promoting influence (UN82). Analyses of LC mortality data of American and Czech miners suggest a strong multiplicative effect of cigarette smoking and exposure to Rn decay products (Gi84; Wh83). Since the mortality rates for men and women in the two Chinese areas are similar, and women typically do not smoke (only 1.4% in the high-background area, and 1.8% in the control area, compared to approximately 70% of men in both areas), we are led to the suggestion that cigarette smoke is less effective in these populations, e.g. because of differences in smoking habits or tobacco compounds. Assuming that the Chinese population in these areas consists mainly of "non-smokers," and applying the relative risk function for non-smokers given by Whittemore and McMillan (Wh83) to the cancer rate in United States non-cigarette smokers of 45×10^{-6}/yr (Hae58), no excess LC risk will be obtained for the high-background area. The above LC rate for U.S. non-smokers is, however, still slightly higher than the average annual LC rate in both Chinese areas at the same exposure level.

(2) After cigarette smoking, the most important cause of LC is probably general air pollution. Cohen and Cohen (Co80) conclude that the LC rate in industrialized countries early in this century, before the steep rise in LC risk in recent years, was $10–40 \times 10^{-6}$/yr. This number is comparable to the Chinese results. Since there is no reason to believe that Rn exposure has changed substantially with time, the low LC incidence in the rural, non-polluted Chinese areas suggest that factors associated with environmental pollution contribute to the higher incidence rate in industrialized countries.

From this analysis, we might characterize these Chinese populations as mainly "non-smoking" populations, living in a relatively unpolluted environment. We are, therefore, led to the suggestion that the Chinese LC rates in both areas represent a "pure" radiation effect. This is consistent with the assumption that excess cancers can be conservatively estimated from the average number of total LCs in the control and high-background areas in China. This view is supported by a recent investigation on U mining and lung cancers in Navajo men (Sa84) which demonstrates that in a rural non-smoking population most of the LCs may be attributed to a single hazardous agent, i.e. Rn progeny. The linear extrapolation used by BEIR-II, BEIR-III, and UNSCEAR to estimate the number of excess cancers would then lead on the average to a slight overestimate of the total number of observed LCs, while the smaller numbers derived from Evans *et al.* (Ev80) would be consistent with this assumption. We will check the validity of this assumption by comparing the observed total numbers to the number of excess cancers calculated by our cancer induction model.

Model for Lung Cancer Induction

From all different biological end points, LC induction represents the most important somatic hazard in the natural radiation environment. In first approximation low dose effects of α particles arise from the interaction of isolated charged particles with sensitive biological targets, neglecting inter-track effects. The low dose problem thus reduces to one of understanding the structure of a particle track in biological matter for the required variety of end points, especially for radiation-induced carcinogenesis. Since transformation and carcinogenesis can only take place in surviving cells, the observed tumor frequency always represents the product of two probabilities: one for malignant transformation and one for not being killed.

Thus the general form of the incidence function $F(D)$ as a function of dose is given by (NA80):

$$F(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2 + \ldots) \times \exp(-\beta_1 D - \beta_2 D^2) \,. \qquad (1)$$

Although the bending downwards of the LC incidence curve at higher doses suggests that cell killing is the dominant mode of interaction at high doses, track structure theory reveals the importance of this effect even at the lowest dose of high linear energy transfer radiations, that is of a single charged-particle track.

For mammalian cell killing, track theory and experimental radiosensitivity parameters allow us to construct schematic models of track structure in a biological medium (Ka82). According to track structure theory, an ion of atomic number Z, effective charge number z^*, when moving at speed β relative to the speed of light, has the probability P to inactivate a cell whose nucleus it threads, given by:

$$P = (1 - e^{-z^{*2}/\kappa\beta^2})^m , \quad (2)$$

where κ is the value of $z^{*2}/4\beta^2$ at which the plateau value of the cellular inactivation cross-section is achieved, and m is the extrapolation number for γ irradiation and possibly the number of sensitive subcellular sites which must be inactivated to inactivate the cell. Equation (2) describes the inactivation probability in the grain count regime where inactivated cells lie like beads on a string.

For a given dose D ($D = F \times L$) delivered by the fluence F of α particles with linear energy transfer L, the number of surviving cells N in a tissue volume consisting of N_0 cells can be expressed by:

$$N/N_0 = e^{-P\sigma_0 F} \quad (3)$$

where σ_0 is the plateau value of the extrapolated cross-section which approximates the geometrical cross-section of the cell nucleus. Equation (3) refers to the action of a single incident particle (ion kill). The cumulative action of overlapping tracks (gamma kill), which would become effective at α-particle doses above about 1 Gy, can be neglected here even at the highest cumulative exposures because of the wide spacing in time of α particle hits during a 30- to 40-year working history.

Histological investigations of LCs among U miners have shown that tumors occur preferentially in upper bronchial airways. While basal cells of the bronchial epithelium have been commonly regarded as the main target for LC induction (IC81; NC84), there is now growing evidence that secretory cells are the main progenitor cells for bronchial carcinoma (Mc83). Since we do not have radiosensitivity parameters for human bronchial epithelial cells, we utilize information available on other human cell lines.

For T-1 human kidney cells aerobically irradiated by alpha particles (Ba66) fits of the experimental data yield $\sigma_0 = 5.4 \times 10^{-7}$ cm^2, $\kappa = 1400$, and $m = 2.5$ (Ka71; Rot76). Radiosensitivity parameters for other cell lines or different experimental conditions lie nearby, with m being between 2 and 3, σ_0 between 5.0 and 6.6 × 10^{-7} cm^2, and κ between 750 and 1400 (Ka71). The use of different parameters more suitable for other cell lines would not change substantially the calculated inactivation probabilities or the implications of these calculations. Thus we assume that human T-1 kidney cells are representative of human lung cells, with respect to cell killing, and that these numbers derived from in-vitro experiments also apply to in-vivo irradiation.

The main dose contribution in bronchial epithelial cells from inhaled short-lived Rn progeny stems from ^{214}Po α particles. These α particles, with an energy of 7.69 MeV, have a range in soft tissue of about 70 μm. If we assume that the diameter of a cell is 10 μm and the diameter of the nucleus is 8 μm, and that the particle range is made up of a sequence of mean cellular chord lengths, then on the average, about five cell nuclei will be intersected by this α particle. Track structure calculations with aligned, close-packed T-1 cells at 10- μm intervals (Ka82) show us that out of these five cell nuclei, on the average two cells will be killed, preferably towards the end of the track. Since the inactivation probability is highest in the Bragg peak where most of the energy is delivered, about 60% of the energy deposited by a single α particle is wasted for transformation for it kills the cell it traverses. Thus only about 40% of the energy is "biologically effective," that is, has the potential of inducing a transformation.

To assess biological radiation effects in the lungs, we assume that the initial radiation damage at the organ level represents an accumulation of effects arising in single cells. Experimental evidence tells us that the probability of the final radiation effect depends on a variety of modifying factors, such as repair, hormonal influences, immune response, etc. It has, however, generally been found that the role of these biological factors is reduced for high-LET radiations, at least for cellular inactivation. More complex disease mechanisms, such as malignant transformation or carcinogenesis, require a complete mechanistic understanding which

is currently still too fragmentary. Since we do not know the function of carcinogenic risk expression from initial cellular effects to an observable tumor, we cannot apply a track structure analysis as has been found practicable for cell killing. We therefore seek to find an induction or transformation function per surviving cell, assuming that it is proportional to D^n, by fitting epidemiological data for LC induction. Taking into account the above derived survival function, the incidence function $F(D)$ adopts the form of:

$$F(D) = kD^n \exp(-P\sigma_0 D/L). \quad (4)$$

Because of the great uncertainties associated with the epidemiological LC data (St85), a more sophisticated model would be inappropriate at the current stage of our knowledge of carcinogenesis.

Results and Discussion

There is common agreement that the dose-exposure conversion factor in the mining environment is centered around 5 mGy/WLM. Track structure calculations of LC risk in bronchial airways indicate, however, that this value is applicable only at low doses, while the dose-exposure factor is significantly smaller at high doses (Ho86). If we use a dose-exposure conversion factor of 5 mGy/WLM for the low exposure region (<100 WLM), then these calculations suggest that this factor decreases with rising exposure, adopting a value of 1 mGy/WLM for exposures greater than 500 WLM.

For a mean basal cell depth of about 40 μm in segmental and subsegmental bronchioles, we calculate a mean track length of α particles emitted from airway surfaces of about 50 μm. Weighting the contributions of ^{218}Po and ^{214}Po α particles, we derive a mean LET of about 150 keV/μm, having an inactivation probability in T-1 cells of 0.35. It should be noted that the fraction of surviving cells is rather insensitive to variations in LET from about 100 to about 200 keV/μm, e.g. a smaller LET value is nearly compensated by a lower value for P in the exponential function.

The data points in Figure 1 are taken from Jacobi (Ja81) and Cohen (Co82), and consist of data on U.S. uranium miners (NA72; NA80), Czech U miners (Ku79; Se76), Canadian U miners (Arc78; Ham76), Swedish metal miners (Arc78; Ax78; Sn74), U.S. metal miners (NA72), Joachimsthal and Schneeberg miners (in *supply country*) (Arc67), Newfoundland fluorspar miners (NA72; NA80), and Japanese atomic bomb survivors (Bee78), supplemented by recent data on Ontario U miners (Mu85) and Swedish Fe miners (Ra84). The latter Canadian and Swedish studies provide valuable information on cancer risk at low exposure levels. For comparison, Figure 1 also shows the risk estimates of BEIR-II (NA72), UNSCEAR (UN77), and Evans *et al.* (Ev80), based on the linear hypothesis.

The results of the least square fits are presented in Figure 1, assigning the values of 15.5 (n = 1) and 1.8×10^{-1} (n = 2) to the proportionality constant k to get the excess LC cases per 10^6 PY and per WLM, if the dose is expressed in WLM. At intermediate and high exposures, both extrapolations seem to be equally acceptable. At low exposures, the data on Ontario U miners (Mu85) and Swedish Fe miners (Ra84) support the linear-exponential extrapolation. Cohen (Co85) argues, however, that the excess LCs in the Swedish miners are not due to Rn. Furthermore, the Ontario miner data show a clear deficit in the 12 standard WLM exposure category (for this reason the two lowest exposure groups were combined in this plot). It is interesting to note that excess LCs could be determined in the lowest exposure groups of both studies, while the Chinese investigation at comparable exposures and despite the significantly larger population surveyed, did not allow such a determination. This suggests that additional causes are responsible for LC risk at low occupational exposure levels compared to domestic exposure.

The total number of LCs in the two Chinese regions is 1.8 per 10^6 PY-WLM in the high-background area, and 4.5 per 10^6 PY-WLM in the control area. If we interpret LCs in both areas as a "pure" Rn effect, then the Chinese data would support a quadratic-exponential relationship.

From this discussion, we conclude that the quality of the epidemiological data does not allow us to rule out either hypothesis. We therefore seek to find additional scientific evidence which would support either the linear-exponential or the quadratic-exponential response.

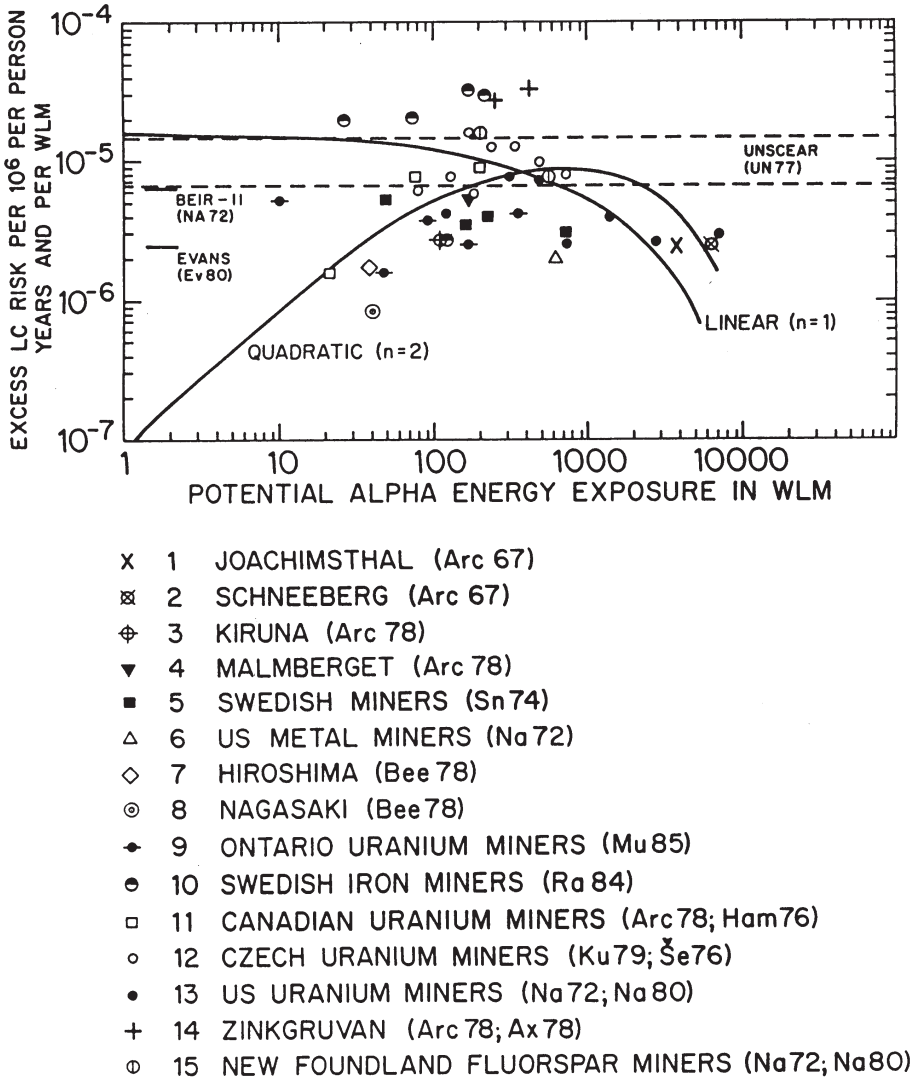

Figure 1. Excess lung cancer (LC) risk in mining populations per working level month (WLM) vs. cumulative exposure to Rn decay products in WLM.

It has been already pointed out by Mole (Mo75) that the induction process must be a power function of dose, as the result of the cooperation of at least two energy deposition events (from two different electrons) in order to get the observed linear dose-effect relationship in the low dose region. While this applies to low-LET radiations, there is experimental evidence which supports the hypothesis that LC induction by α particles requires the traversal of two α particles through the nucleus of a cell (or two α particles through two adjacent cells, if intercellular effects are assumed). For the induction of osteosarcomas in man and dog by α particles from different Ra isotopes, Marshall and Groer (Mars77) proposed a model which postulates two initiation events produced in a cell by two α particles. This agrees with the result of Rowland *et al.* (Row78) that a dose-squared-exponential function described best the incidence of bone sarcoma of female Ra dial painters exposed to ^{228}Ra and ^{226}Ra. Burch (Bu60) also advanced arguments in support of the tentative view that bone cancer induced by Ra is initiated by a highly specific two-hit mechanism. Whittemore and McMillan (Wh82) found that the osteosarcoma incidence rate among beagles exposed to ^{239}Pu can be fitted by a quadratic

function of the injected dose. Lloyd *et al.* (L179) observed even a nearly cubic dose response for transformation of mouse embryo cells with 5.6-MeV α particles. In chemical carcinogenesis, it has been suggested for a long time that a two-hit or multihit process is required for the production of a promotion-independent cell (Arm57; Pot80).

Additional information on the shape of the dose-effect curve can be supplied by animal experiments where exposure conditions are defined more accurately than for human exposures. A compilation of lifetime LC risk in rats and dogs due to inhaled Rn progeny (Ch84; Cr84) is presented in NCRP Report No. 78 (NC84), comprised of exposures as low as 20 WLM. It is interesting to note that the animal data are much more scattered than the human data, suggesting that the large scatter of the latter is caused by uncertainties in past exposure reconstruction and confounding factors. Taking the same radiological parameters as for humans, this data can be fitted only by a linear-exponential function. Since similarities exist between the dose-effect relationships in man and animals over a wide range of exposures (NC84), one might also expect a linear-exponential response in humans, at least down to about 20 WLM. However, Chameaud *et al.* (Ch85) issue a cautionary note that "direct extrapolation of results in rats for prediction of lung cancer induction by indoor exposure in non-smokers remains questionable."

Contrary to the above experimental data, lung tumor incidence in beagle dogs exposed to $^{239}PuO_2$ aerosols (Pa85) can only be approximated by a quadratic-exponential function of dose over the whole dose range.

The bending downwards of the dose-effect curve at low doses, characteristic of a quadratic-exponential incidence function per surviving cell, can also be interpreted by modifications of an originally linear-exponential relationship:

(1) Domestic exposure to low doses and dose rates suggests the existence of repair mechanisms leading to an increased latency period and thus reduced lifetime risk. In a population exposed to increased levels of Rn progeny (Badgastein, Austria), the number of chromosome aberrations remains constant below a cumulative exposure of about 20 WLM (Poh79). This finding is attributed to the induction of repair enzymes at low doses. Thus assuming an exponentially decreasing repair factor $R = (1 - e^{-\gamma D})$, with $\gamma = 13.8\ Gy^{-1}$, the linear-exponential function multiplied by R yields a dose-effect relationship very similar to the quadratic-exponential function.

(2) In the epigenetic model of carcinogenesis by Tsanev and Sendov (Ts71), factors such as cigarette smoke, ore dust, chronic bronchitis, etc., are considered as stimuli of cellular proliferation, reducing the effectiveness of repair mechanisms and, in further consequence, the latency period. A salient feature of this model is the finding that these promotion factors are most effective at low radiation doses, but rather insignificant at high exposure levels, such as in U mines. Uzunov (Uz79) therefore argues that cancer risk for non-occupational, low-level exposure should be less than for mining populations. Such a hypothesis would also explain the low LC risk in both Chinese areas by the absence of effective promotion factors. A linear-exponential dose-effect curve, modified by stimulation factors in the above-described manner, would again resemble a quadratic-exponential relationship, for extrapolation from high occupational exposures to low domestic exposures.

In the initiation-promotion concept of carcinogenesis, an initiation event has to be followed by a promotion event which acts as a stimulus for cell division. For the inhalation of Rn decay products this promotion step can be achieved by lethal α-particle interactions with epithelial cells (Mart83). Thus we identify malignant transformation of bronchial sensitive cells as the initiation event and cellular inactivation of all epithelial cells as the primary promotion event. The probability for cancer induction can then be calculated as the product of the initiation probability and the promotion probability. It should be noted that the same α particle along its path through bronchial tissue can kill a cell (with high probability) and induce a transformation (with much smaller probability). In this case, the initiation and promotion event are caused by one α particle e (single-hit mechanism), and the resulting cancer induction probability is proportional to dose D. If two different α particles are involved (two-hit mechanism), the incidence func-

tion would adopt a quadratic response. Although our understanding of the different steps in radiation carcinogenesis is still too fragmentary, we expect the linear term to dominate at low doses. The epidemiological data presented in Figure 1, however, do not allow us to derive any numbers for the relative effectiveness of either term.

Conclusions

According to BEIR-III, a linear extrapolation to low doses of high-LET radiations, such as internally deposited α-emitting radionuclides is "less likely to lead to overestimates of risk and in fact leads to underestimates." An opposite point of view is taken by Cohen (Co82; Co85) who concludes that the linear extrapolation based on observed risks at high doses grossly overestimates the effects at low doses of α particles.

If we assume an effective cumulative exposure during a 40-yr period at a mean exposure rate of 0.38 WLM/yr, we conclude from the Chinese data that there is no observable excess lung cancer risk below a cumulative exposure of about 15 WLM. This finding is consistent with epidemiological results from Austrian and Finnish high-background regions. Even in the lowest exposure category for U.S. miners (60 WLM), a deficit, though statistically insignificant, rather than an excess in lung cancers has been observed (NC84). We are in the region of "background noise" and cannot determine the excess cancers for statistical reasons. The low LC incidence in the Chinese investigation, for both high-background and control area, suggests that other factors than radiation contribute to the higher incidence rate in other countries. Since we might characterize this population as a mainly "non-smoking" population, living in a relatively unpolluted environment, we are led to the suggestion that the Chinese LC rates represent a "pure" radiation effect. We therefore may take the total LCs and interpret them as radiation-induced excess cancers.

A theoretical analysis of miner LC data reveals that this data set can be fitted by a linear-exponential as well as by a quadratic-exponential function, possibly suggesting a more complex response function. The statistical uncertainties associated with the epidemiological data do not allow to rule out either hypothesis. If we take the total cancers in the Chinese areas and interpret them as radiation-induced excess cancers, then this data would support a quadratic-exponential response. Experimental results and theoretical considerations can be supplied to support either hypothesis. The appearance of a quadratic-exponential relationship can also be simulated by modifications of a linear-exponential function, such as repair and promotion factors. At our current stage of knowledge, however, we do not feel that conclusions about biological mechanisms can justifiably be based on statistical fits of different models to the epidemiological LC data. If a linear extrapolation is to be used, the Chinese data support the upper bound for a lifetime risk due to environmental Rn given by Evans *et al.* (Ev80) of 10^{-4} per WLM.

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