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APPLICATION TO RISK ASSESSMENT**

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MICRODOSIMETRY OF RADON PROGENY: APPLICATION TO RISK ASSESSMENT*

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ABSTRACT--We developed methods for calculating radiation doses to individual cells and cell nuclei of human bronchial epithelium from radon and progeny for specified levels of exposure, breathing rates, equilibrium factors, unattached fraction of progeny, and other factors that are important in radon dosimetry. If we also know which cells are likely precursors for cancer, and we also know their locations in the respiratory tract, we then may calculate the statistical probability that these cells are irradiated by alpha particles, the number of single alpha-particle hits, and the spectrum of doses delivered (as a probability density in specific energy).

As we continue to study the relationship between microdosimetry and biological effects, we hypothesize that the corresponding probability of lung cancer is related to the specific energy imparted to nuclei of single cells in bronchial epithelium by radon and its progeny. The mathematical relationship between specific energy distribution and probability of important biological effects may be determined experimentally from results of irradiations of cultured bronchial epithelial cells and exposures of laboratory animals to radon and progeny. The concept of "hit-size effectiveness function" proposed by Bond and Varma is useful for interpreting calculated specific energy

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spectra. When applied to the lung, this concept implies that epithelial cells should be exposed to radiations of different quality and different absorbed dose levels to unfold the cell-specific transformation probability needed for predicting the dose-response function. Factors that remain to be quantified are the time course of irradiation, dose rate, linearity of the response at low levels of exposure, and relative impact of cofactors (initiators and promoters) which, in addition to the radiation dose, are important in cancer induction.

INTRODUCTION

One of the most important aspects of the study of health risks associated with environmental exposure to radon and progeny is the relationship between the radiation dose delivered to single cells and the probability of lung cancer. An understanding of the health effects of radon is particularly important because low-level radon progeny are prevalent, to varying degrees, in breathing air of homes and work places. Analyses of lung cancer risks from exposure to radon and daughter products have proceeded from the epidemiological database obtained from study of several different populations of underground miners. Laboratory animal studies have confirmed the causative relationship between radon exposure and lung cancer. *In vitro* irradiations of single cells by alpha particles have shown that the observed radiation damage includes chromosomal aberration, mutation, and transformation. These studies have resulted in some important general concepts:

- lung cancer is a rare event,
- the excess incidence of lung tumors in exposed populations is associated with radiation exposure,

- the critical targets are most likely nuclei of epithelial cells of the respiratory tract,
- there are enormous uncertainties in individual exposure levels, wide variations in the dose to bronchial epithelium, and numerous interwoven factors that influence the distribution of dose to individual cell nuclei,
- the exposure-risk relationship is approximately linear in the range of about 50-500 WLM* cumulative lifetime exposure to radon and daughter products, and
- there is tendency to try to relate relative lung cancer risk with exposure to radon progeny in air than to relate risk with actual dose at the cellular level. However, a direct association of risk with dosimetry at the cellular level should be useful for improving the quality and accuracy of risk assessments.

The purpose of *the present study* was to more closely evaluate dose distribution at the cellular level and extend the concepts of radon microdosimetry to better understand the long-term probability of lung cancer. Of particular interest were methods for predicting the biological effects of exposure to alpha particles from low-level environmental radon and progeny. An approach for extending microdosimetric concepts in radon dosimetry to risk assessment is presented in this paper.

*Working level month (WLM) is a common unit of exposure to radon progeny in air. It is defined as the exposure resulting from inhalation air with a concentration of 1 working level (WL) of radon progeny for 170 working hours. One working level (WL) is any combination of the daughter products in 1 liter of air that will result in the eventual emission of 1.3×10^5 MeV potential alpha energy.

ESTIMATED RISK OF LOW-LEVEL EXPOSURES TO RADON AND PROGENY

As many as 20 separate follow-up studies of underground mining populations show an excess of lung cancer related to cumulative exposure to radon progeny, generally at levels much greater than typically found in dwellings (National Research Council, 1988; Harley, 1989). However, the risk of cancer or other harmful effects from exposure to low-level radon and progeny is not known.

The U.S. Environmental Protection Agency and others estimated that indoor exposure to radon progeny could account for 5,000 to 25,000 lung cancer deaths annually in the United States (Lubin, 1989; USEPA, 1987; NCRP, 1984). Publication 50 of the International Commission on Radiological Protection (ICRP, 1987) reviewed current data from epidemiological studies on radon-exposed uranium miners and proposed estimates of individual risk of lung cancer from chronic indoor exposure to natural levels of radon and progeny. The ICRP considered both relative risk and absolute risk projection models, and obtained lifetime risks per 1 WLM exposure (chronic) in each year of 0.007 to 0.016, and 0.004 for non-smokers only. Each radon-induced lung cancer was estimated to reduce life expectancy by about 15 years.

The functional relationship between exposure to radon daughter radiation and long-term probability of lung-cancer mortality includes complicating factors such as age at exposure, prolongation of exposure, time since exposure, age at risk, and compounding factors such as smoking history, gender, and exposure to other environmental carcinogens. The National Academy of Sciences (BEIR IV, 1988) adopted a relative risk model to describe the rate

of lung cancer mortality per person-year at risk using data from four cohorts of underground miners:

$$\tau(\text{age, period, dose history}) = \tau_0(\text{age}) [1 + 0.025\gamma(\text{age})(W_1 + 0.5W_2)] \quad (1)$$

where τ is the age-specific risk or chance of dying of lung cancer in 1 yr, at a certain age, given that he is still alive at that age; where $\tau_0(\text{age})$ is the age-specific background risk of lung cancer from all causative agents, the dependence of risk on age $\gamma(\text{age})$ is 1.2 for age <55 yr, 1.0 for age 55-64, and 0.4 for age >65; W_1 is the cumulative exposure in working level months (WLM) incurred between 5 and 15 yr before the age when cancer develops; and W_2 is the exposure in WLM incurred 15 yr or more before this age (National Research Council, 1988).

The working level month unit of exposure to radon progeny is a convenient term for expressing an estimate of the time-integrated exposure of workers to potential alpha-particle energy from radon progeny in air. It can be calculated from airborne concentration measurements and estimates of the time spent by a worker in an area breathing air having that concentration. However, estimates of radiation dose to sensitive tissues of the respiratory tract are dependent on additional factors; the dose/WLM conversion factor may range over an order of magnitude or greater (James, 1988). These additional factors pertain to the breathing rate and whether the subject inhaled by mouth or nose, the unattached fraction of potential alpha energy, particle-size distribution and other characteristics of the aerosol that affect deposition and retention, the geometrical structure of the respiratory tract, progeny equilibrium, the thickness of the mucus and sol gel layers in which the radon

progeny are deposited and transported, the transfer of radon progeny in mucus to epithelial tissues and uptake by blood, and the spatial distribution of target cell nuclei relative to the source distribution within the epithelium. These factors can lead to wide variations in radiation dose to the sensitive cells of the respiratory tract epithelium for constant levels of exposure in working level months. A corresponding wide variation in lung cancer risk would be expected as well. We therefore consider evaluation of radiation doses to sensitive tissues to be an important step toward understanding the risks of exposure to radon and progeny. Radiation absorbed doses may be calculated directly given certain assumptions about these factors.

DOSIMETRY OF RADON AND PROGENY

Doses to epithelial tissues of the respiratory tract from inhaled radon and progeny cannot be measured directly--but may be calculated if sufficient information is known about their deposition and spatial distribution, residence times and translocation rates, and proximity to target tissues, as mentioned in the previous section. Deposition is determined by the fraction of progeny attached to inhaled particles and particle size, electrical charge, breathing rate, and airway geometry and morphometry, whereas clearance is determined by mucociliary transport, absorption into tissue and into blood, and physical decay rates. The relative distances between alpha-emitting sources and target nuclei are dependent on the distribution of sources in mucus and tissue, the size of airways, thickness of the mucus layer, and the distributions of basal and secretory cell nuclei within the respiratory tract epithelium. The dose is dependent on the number of radioactive transformations and decay energies. The number of atoms available for decay,

therefore, depends on the airborne concentration in breathing air and the degree of equilibrium of radon with progeny.

Numerous investigators have calculated "average" doses to the respiratory tract from inhaled radon and its alpha-emitting decay products ^{218}Po and ^{214}Po for a number of different exposure parameters as reviewed in the NEA Experts Group Report (1983), in NCRP Report No. 78 (1984), and in the BEIR IV Report (National Research Council, 1988). It is not our purpose to review these methods in this paper; however, we wish to emphasize that the estimated dose to lung tissue is highly variable and depends on assumptions for each of the terms used in the calculation. Published values of the dose conversion factor in NCRP Report No. 78 for various studies ranged from 0.002 to 14 rad/WLM (or 0.00002 to 0.14 Gy/WLM, NCRP 1984), with the most common factors cited ranging from 0.2 to 2 rad/WLM. The average dose varies among the different generations of the respiratory tract, with generations 2-6 receiving generally higher doses than the smaller airways of generations 7-15. Within a single airway, the differences in local absorbed dose may also vary due to nonuniform distributions of progeny. Doses may also be significantly higher at bronchial bifurcations, particularly at carinal ridges, due to the combined effects of enhanced radionuclide deposition and relatively slow clearance (Hofmann and Martonen 1988). Although the average absorbed dose per unit exposure was about 0.15 Gy/WLM, Hui, Poston, and Fisher (1990) showed that a large fraction of individual cells remained unirradiated and that the doses to individual cells with energy imparted ranged from 0.01 to more than 300 Gy. Thus, the "average" dose is clearly inadequate for describing energy depositions among

different generations, within a region of a single generation, or to single cells within a region.

STATISTICAL VARIATIONS IN DOSE AND RESPONSE

Although we know that biological effects result from discrete energy-deposition events at the cellular and subcellular level, it is difficult to establish the dose-response relationship at low levels of exposure because there are large stochastic variations in *both* the ionization densities within cell nuclei and in the types of biological response that are possible for any amount of energy imparted. A variety of different biological responses are possible at constant absorbed dose when the factors affecting hit probability at the cellular level are modified. This means that two outcomes are possible: 1) the same absorbed dose could result in different biological effects, and 2) the same biological effect could result at two different absorbed dose levels.

To analyze the dose-response relationship, two statistical variations need to be dealt with simultaneously: First, for a given average (absorbed) dose, the energy imparted to cell nuclei will be highly variable, depending on whether the cells are hit or missed by alpha particles and the ionization density (which is determined by the length of tracks and the number of tracks). The distribution of "doses" imparted to microscopic targets may be represented by a probability density in specific energy, $f(z)$. Second, for a given specific energy distribution there will be a variable biological response because of the large variety of biochemical changes that may result when radiolysis products (free radicals and ions) randomly interact with

molecular DNA. Accordingly, the dose-effect relationship was interpreted by Morstin, Bond, and Baum (1989) as an integral convolution (or inner product) of these two separate functions. Thus,

$$E(D) = \int f(z,D) \cdot \epsilon\{z, f(z,D)\} dz \quad (2)$$

where $E(D)$ is the biological response at an absorbed dose D , $f(z,D)$ is the probability density in specific energy (ICRU 1980, 1983), and $\epsilon\{z, f(z,D)\}$ is the corresponding cellular response function. Evaluation of the microdosimetric function is described in the next section.

MICRODOSIMETRIC METHODS FOR CELL-SPECIFIC DOSIMETRY

General methods for calculating $f(z)$ for irradiation of basal and secretory cells of the respiratory tract epithelium by inhaled radon and progeny (Hui, Poston, and Fisher, 1990); Fisher, Hui, and James, 1990). These methods also provide the absorbed dose (D), the probability that cell nuclei are hit once, twice, or n times, and the probability that cell nuclei are completely missed by alpha particles and secondary electrons. As with conventional radon dosimetry, these methods accounted for the many factors that influence the probability of alpha particle energy depositing in cell nuclei.

Monte Carlo techniques were applied to determine chord-length distributions for distances between alpha-emitting sources and nuclear targets. The mathematical methods of Roesch (1977) for internal emitters were then applied to determine probability densities in specific energy for any region of the respiratory tract and any set of assumptions with regard to the above variables.

The product of a microdosimetry calculation is a probability density in specific energy. An example is shown in Figure 1. This figure shows a statistical distribution of doses $f(z,D)$ to individual target cell nuclei from alpha-particle irradiations. It includes contributions from both ^{216}Po and ^{214}Po . The cell nuclei were assumed to be spherical and to have a known radius. The distribution includes a high probability of zero specific energy (0.27), meaning that 27% of the targets received no energy deposition. Thus, 73% of the targets received at least one "hit" by an alpha particle. The mean of the distribution (or the absorbed dose D) was 0.7 Gy, and the mode 0.5 Gy. The mode corresponds to the dose mean for single hits. Most targets received less than 2 Gy, but a small fraction received 2-3.5 Gy. The probability of a site receiving 1, 2, 3, or n hits may also be determined from the calculation.

A computational model for evaluating radiation dose distributions to cell nuclei from exposure to radon progeny throughout the human bronchial tree was described recently at the Third International Workshop on Lung Dosimetry (Fisher, Hui, and James, 1990). The model incorporated current information on respiratory tract geometry, nasal and oral filtration efficiencies for unattached radon progeny, characteristics of bronchial deposition by diffusive and inertial processes, mucus clearance, transfer of progeny into airway epithelium, locations of secretory and basal cell nuclei, and other factors important for assessing the probability of radiation interactions with cell nuclei. In addition, this model was used with microdosimetric theory to determine 1) probability densities in specific energy, 2) mean absorbed doses, 3) fraction of cell nuclei receiving no hits and therefore no radiation energy, and 4) hit probabilities for nuclei with single and multiple hits.

The model was used to compare these values for different total exposures (WLM) in homes or underground mines. Both soluble (transportable in epithelial tissue) and insoluble progeny were also considered. The results (Fisher, Hui, and James, 1990) are summarized in Table 1. The exposure levels chosen for comparison were 0.15 and 1.0 cumulative WLM (typical of exposures in home atmospheres) and 10 and 100 cumulative WLM (typical of exposures in underground mines).

Table 1. Calculated Values of Absorbed Dose and Alpha-particle Hit Probabilities for Secretory Cell Nuclei.

Location	Solubility	Exposure (WLM)	Mean Specific Energy (Gy)	Hit Probabilities			
				0	1	2	>2
Indoor home	Soluble	0.15	0.0034	0.996	0.004		
	Insoluble	0.15	0.0033	0.996	0.004		
	Soluble	1.0	0.023	0.974	0.026		
	Insoluble	1.0	0.022	0.977	0.023		
Underground mine	Soluble	10	0.31	0.69	0.26	0.05	
	Insoluble	10	0.28	0.75	0.22	0.03	
	Soluble	100	3.1	0.029	0.087	0.16	0.72
	Insoluble	100	2.8	0.053	0.156	0.23	0.56

These results show that single-hit interactions predominated at low exposure levels, as expected. However, we also found that more than 99% of potential target nuclei were completely uninvolved at the 0.15 WLM cumulative exposure level. The hit probability ratios and dose distributions also changed as the exposure level increased. Multiple-hit interactions were more frequent at higher levels of exposure. The resulting dose conversion factors (Gy/WLM) obtained from Table 1 ranged from 0.008 to 0.033 Gy/WLM (0.8 to 3.3 rad/WLM).

EVALUATION OF MICRODOSIMETRIC INFORMATION FOR RISK ASSESSMENT

One of the questions that we've had for many years has been, "what do we do with a probability density in specific energy $f(z,D)$, and how can this spectrum help us predict the biological effects of radiation (such as that received by the respiratory tract epithelium from radon and progeny)?" We already suggested one possible answer to this question by presenting the concept of hit-size effectiveness function. The probability density $f(z,D)$ may be useful for evaluating the biological effectiveness of radiation, using the relationship given in equation (2) if sufficient data are available for determining the cellular response function $\epsilon\{z,f(z,D)\}$. The cellular response function is not available at the present time for the irradiation of epithelial cell nuclei by alpha particles; further experiments are needed to obtain it. We can predict, however, some characteristics of this function from other information that is available.

Because radiation effects begin at the cellular level, we believe that the specific energy to the nucleus is directly related to the probability of biological effects. The transformation of cells from their normal state to a malignant state is generally believed to result from low-specific-energy interactions in the cell nucleus. These would necessarily be non-lethal energy depositions because inactivated cells cannot reproduce. The transformation response to exposure is probably linear with increasing probability of single-hits. As the probability of multiple hits increases, there may be increased probability of cell death and somewhat reduced probability of transformation per unit exposure. Therefore, a non-linear response may be anticipated with increasing levels of exposure.

Kellerer and Rossi (1972, 1978) proposed a theory of dual radiation action in which the biological response of a cell resulted from an interaction of two sublesions in a sensitive volume. The number of sublesions is proportional to the specific energy z , in the target volume, and the expectation value for the number of lesions is proportional to the square of the specific energy:

$$E(z) = Kz^2 \quad (3)$$

The mean number of lesions as a function of the absorbed dose $E(D)$, obtained by averaging over $E(z)$ for all sensitive volumes in a population, is

$$E(D) = \int_0^{\infty} Kz^2 f(z,D) dz = K\bar{z}_D + D^2, \quad (4)$$

where \bar{z}_D is the single-event dose mean specific energy (ICRU, 1983). The average diameter of the sensitive volume over which sublesions combined was approximately 1 μm . However, the sensitive volume may be the entire inhomogeneous nucleus having a diameter of 4-8 μm and a complex substructure of various sensitive sites. We therefore look to other possible interpretations of the microdosimetric spectrum.

Figure 2 shows a representation of a probability density in specific energy for a hypothetical population of cell nuclei irradiated by a 5 MeV alpha particle. We may assume that for every irradiated cell, there exists a value of specific energy z_0 above which the imparting of that amount of energy within the nucleus will be lethal to the cell, or below which the cell may survive and continue division. If we integrate this "partial area," then the

surviving fraction transformation is proportional to the integrated area (indicated with diagonal lines). This is an idea we have not tested experimentally because the value of z_0 is not a constant or a step function, but rather is more likely to be a continuous function $s(z)$, which is the survival probability of a cell receiving a specific energy z . The survival probability $s(z)$ may possibly be related to an exponential of z . Therefore, the probability of a biological endpoint for the surviving cells is an integral that incorporates $s(z)$, $f(z)$, and $\lambda(z)$ (Hui, 1989):

$$E(D) = k \int_0^{\infty} s(z) \lambda(z) f(z,D) dz \quad (5)$$

where $s(z)$ is the probability of a cell surviving receipt of a specific energy z , $\lambda(z)$ is the probability of a cell transforming or having another biological change from z , and k is a constant of proportionality. If we assume no effect at zero dose and a definitive effect at high values of z , then $\lambda(z)$ may be represented by a function shown in Figure 3. However, the function has yet to be determined experimentally. Further evaluation shows that equations (5) and (2) are mathematically equivalent and that the function described in Figure 3 is the hit-size effectiveness function. The expectation values of $s(z)$ and $\lambda(z)$ may be determined experimentally by irradiating cells at different absorbed dose levels, whereas $f(z,D)$ may be calculated for different absorbed dose levels.

SUMMARY

Alpha particles from radon progeny impart a specific energy to epithelial cell nuclei; the probability density in specific energy may be calculated from the dosimetric model and assumptions describing the physical properties of the aerosol and its deposition and clearance in the lung. Only cells having a non-lethal energy deposition event may eventually transform, and transformation is an extremely low-probability process. A hit-size effectiveness function may be unfolded from experimental data to describe the probability of a transformation for a discrete value of specific energy. This function enables one to understand the relationship between microdosimetric results and biological effects, and should be useful for risk assessment. The application of this work will be prediction of the effects of radon progeny for low-level environmental exposures. More information is needed about the response of cell populations to alpha particle radiation to evaluate the dose-response relationship. Additional factors that remain to be quantified are the time course of irradiation, dose rate, linearity of the response at low levels of exposure, and relative impact of cofactors (initiators and promoters) which, in addition to the radiation dose, are important in cancer induction.

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Figures

Figure 1. An Example of a Probability Density in Specific Energy Calculated for 6.5 μm Cell Nuclei Irradiated by 6 MeV and 7.69 MeV Alpha Particles from Uniformly Distributed Sources (^{218}Po and ^{214}Po). The mean absorbed dose is 0.7 Gy, and the fraction of unirradiated sites (δ) is 0.27.

Figure 2. Schematic Representation of a Probability Density Distribution for a Single Cell Indicating a Value of z_0 Below Which the Specific Energy Imparted is Nonlethal to the Cell.

Figure 3. Schematic Representation of the Probability of a Biological Endpoint as a Function of Specific Energy Imparted to the Cell Nucleus

Tables

Table 1 Calculated Values of Absorbed Dose and Alpha-particle Hit Probabilities for Secretory Cell Nuclei





