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MODEL FOR ASSESSING RADIATION DOSE TO EPITHELIAL CELLS OF THE HUMAN RESPIRATORY TRACT FROM RADON PROGENY*

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Abstract--A computational model was developed to evaluate radiation doses to sensitive cells from exposure to radon progeny throughout human bronchial epithelium. The model incorporated current information on nasal and oral filtration efficiencies for unattached radon progeny, characteristics of bronchial deposition by diffusive and inertial processes, mucous clearance and possible transfer of radon progeny to the airway epithelium, locations of target nuclei of secretory and basal cells in different regions of the bronchial tree epithelium, and other features. The model is useful for evaluating absorbed doses to various populations of target cell nuclei, the associated microdosimetric probability densities in specific energy, and the likelihood that target nuclei are hit one or more times by alpha-particle tracks. The model was applied to extrapolating lung cancer risks observed in underground miners to the general population exposed to low-level radon progeny in indoor home environments. The effect of increasing exposure rates by one and two orders of magnitude in both environments was modeled to determine the frequency of radiation events in target cell nuclei. The implications of dosimetric modeling for lung cancer risk analysis were also examined.

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INTRODUCTION

There have been many separate efforts to describe methods and models for estimating dose to the respiratory tract from radon and decay products[1-6]. Detailed anatomical models of the respiratory tract[7-14] were used with aerosol deposition and clearance models[6-7,11-17] to estimate equilibrium surface concentrations and resulting absorbed doses to various target tissues of the respiratory tract[18]. The equilibrium surface activity is a function of radon progeny concentration and disequilibrium ratio in breathing air, the unattached fraction, the particle size distribution, the airway model chosen (including the spatial distribution of target cell nuclei in respiratory tract epithelium, assumed mucociliary clearance rates, and diffusion of progeny ions through epithelium to blood), and the breathing rate. Uncertainties in the absorbed dose per unit exposure to radon progeny in air and the wide variation in exposure conditions, age, and breathing rates of exposed persons have resulted in large differences in estimates of the biological risk associated with exposure to radon and progeny.

The radiation absorbed dose, (D), is not the dose to individual cells or cell nuclei in the respiratory tract. Rather, it is the quotient of the amount of energy (e) imparted by ionizing radiation to matter of mass (m) over which the energy is imparted; thus $D = e/m$. For a region of tissue (as in the respiratory tract), the absorbed dose represents the mean of actual values (in specific energy) to single cells or cell nuclei. However, for alpha-particle interactions, the specific energy to cell nuclei is highly variable, depending on the length of tracks through the nuclei, the number of tracks (or "hits"),

and whether energy is imparted by track ionization events. The dose to single small sites may range from zero (when cells are completely missed by radiation) to several Gy (for cells hit multiple times by alpha particles). Energy deposition by alpha particles is also increasingly nonuniform with decreasing exposures to radon progeny.

The estimation of radiation doses from inhaled radon and progeny is further complicated by the great number of variables influencing the magnitude, character, and geometric distribution of the source term, and the number of different choices available to describe the target tissue of interest. For example, estimates of absorbed dose to radiosensitive tissues of the tracheobronchial airways per unit exposure to radon and progeny concentrations in breathing air range from about 0.002 to 0.15 Gy per working level month (WLM, a unit of integral potential alpha energy from radon progeny in breathing air; 1 WLM = 3.5×10^{-3} J h m^{-3}).

Some investigators have suggested that it is not essential to know the radiation dosimetry or microdosimetry of radon progeny, and that the risk may be inferred directly from the cumulative exposure to radon progeny in air. For instance, epidemiological studies of lung cancer incidence among underground miners exposed to airborne radon and progeny have estimated the lung cancer risk to be about 350 deaths per 10^6 WLM of collective exposure to radon progeny[19]; other such estimates have ranged from 21-54 to 1,000 lung cancer deaths per 10^6 WLM[19-20]. The lifetime risk to members of the general public from low-level exposures is not known[19]. However, biological effects result from discrete energy-deposition events at the cellular level, so that

careful microdosimetry is essential for predicting risks associated with low-level exposures to radon progeny[21].

Target tissues considered previously for evaluating environmental exposures to radon and progeny have included the whole lung, the epithelium of the respiratory tract, and the basal-cell layer of the epithelium. Recently, however, microdosimetry methods were used to calculate probability densities in specific energy for cell nuclei of the respiratory tract epithelium[21]. Both secretory cells and basal cells are currently considered to be sensitive to alpha-particle radiation for induction of lung cancer[6,22,23].

In a previous study[21], we described a method for calculating the probability density in specific energy to basal and secretory cells of the human respiratory tract epithelium. We first calculated the equilibrium alpha source distribution (disintegrations min^{-1}) in the mucus layer and the portion absorbed within the bronchial epithelium for a reference atmosphere (37 Bq m^{-3}, or 1 pCi L^{-1}) having a radon progeny equilibrium factor of 0.56 and an unattached fraction of potential alpha energy of 0.028. We also assumed a nose-breathing rate of 15 L min^{-1}, a 50% nasal deposition of unattached progeny, a mucociliary clearance velocity of 0.5 cm min^{-1} in a 15 μm-thick mucus blanket, a transfer constant of 0.4 from radon progeny in mucus to epithelial tissues, and a compromise dosimetric model of the respiratory tract[24]. Secretory cells were assumed to be distributed uniformly between the basement membrane and the epithelial surface, whereas basal cells were assumed to have a lognormally distributed depth correlating with airway diameter[24]. Monte Carlo techniques were then used to determine the

source-target geometry for microdosimetry calculations. This work resulted in the capability to determine probability densities in specific energy for any part of the respiratory tract and for any exposure conditions assumed.

In the present study, we wished to start with assumed or given values of the equilibrium surface concentration of radon progeny to study differences in the dosimetry and microdosimetry associated with exposure to radon and progeny in indoor home and underground mine atmospheres. We also wished to apply the newly proposed International Commission on Radiological Protection (ICRP) respiratory tract model (see Bair, W. J., "Revision of the ICRP Dosimetric Model for the Human Respiratory Tract," in these proceedings) as the anatomic and biokinetic basis for the calculations. The proposed ICRP model incorporates current information on nasal and oral filtration efficiencies for unattached radon progeny, the characteristics of bronchial deposition by diffusive and inertial processes, mucous clearance and possible transfer of radon progeny to the airway epithelium, and the locations of secretory and basal cell nuclei in different regions of the bronchial tree. The objective of the present study was to develop methods for calculating doses to basal and secretory cells from the 6.0 MeV ^{218}Po (range $\approx$ 48 μm in soft tissue) and the 7.68 MeV ^{214}Po (range $\approx$ 71 μm in soft tissue) alpha particles present in breathing air of atmospheres typical of underground mines or indoor homes, and to compare the dosimetric results. We developed dose conversion factors (Gy WLM^{-1}) for the respiratory tract from these comparisons.

METHODS

A dosimetric model was constructed to calculate the microdosimetry of basal and secretory cell nuclei of the respiratory tract epithelium exposed to alpha particles from radon progeny. The microdosimetric approach provides probability densities in specific energy, f(z), for any given set of exposure parameters and model assumptions.

In the present study, the dependent variables were the number of disintegrations of ^{218}Po and ^{214}Po per unit airway surface area (cm^{-2}) in the mucus layer and within bronchial epithelium, per unit exposure to potential alpha-particle energy (WLM). These values were calculated for breathing atmospheres characteristic of indoor homes or underground mines. The equilibrium surface activity is determined by the simultaneous processes of inhalation and deposition, clearance, and natural radioactive decay. The deposition of radon and progeny, clearance by mucociliary transport, and clearance to blood by diffusion were determined by mathematical modeling. Calculations were based on a scaled, 16-generation symmetric respiratory tract model, chosen to be representative of the adult male. The respiratory tract model was obtained by averaging the airway dimensions reported by Weibel[8], Yeh and Schum[11], and Phalen et al.[14], after scaling each to the normal functional residual capacity of 3.0 L[24]. This same airway model was recently proposed by the ICRP Task Group on Respiratory Tract Modeling (see W. J. Bair, "Revision of the ICRP Dosimetric Model for the Human Respiratory Tract," in these proceedings). Assumed characteristics for the airway secretory and

basal cell nuclei, aerosols, breathing rates, exposure levels, and clearance are discussed below.

Airway Model

The geometry of each bronchial or bronchiolar airway was represented by a cylindrical tube. The inner surface of the tube was characterized by a uniformly thick (5-μm) sheath of fluid mucus gel separated from the underlying epithelium by a band of hair-like cilia bathed in an aqueous sol layer (6 μm) (Figure 1). An average bronchial epithelium thickness of 55 μm was assumed to be representative of all bronchi[25]. The diameters of airways range from about 1 cm in the main bronchus (first bronchial generation after the trachea) to about 2 mm in the smallest bronchi (eighth generation), but the effect of diameter on dose to epithelial cell nuclei is negligible; for calculations, we assumed an average bronchial caliber of 5 mm.

Secretory Cell Nuclei

Secretory cell nuclei (of diameter 5 μm) were assumed to be distributed uniformly within bronchial epithelial cells at depths ranging from 10 to 40 μm below the surface[25] (Figure 1).

Basal Cell Nuclei

Basal cell nuclei (of diameter 5 μm) were assumed to be distributed between 35 and 50 μm below the epithelial surface[25] (Figure 1).

Aerosol Characteristics

Radon progeny in both indoor breathing air and underground mine atmospheres were assumed to have a disequilibrium ratio for $^{222}Rn/^{218}Po/^{214}Pb/^{214}Po$ of 1/0.8/0.4/0.2, corresponding to an equilibrium fraction of 0.4. The actual value of the equilibrium factor has only a small effect on calculated dose per unit exposure to potential alpha energy[24]. An unattached fraction of potential alpha energy f_p of 0.08 was assumed for indoor home atmospheres and an activity median diameter (AMD) of 0.15 μm for the fraction attached to airborne particles[24]. Because the thermodynamic diameter of attached particles approximately doubles in size by hygroscopic action, an AMD of 0.3 μm was used for the fraction attached to airborne particles in homes. To describe the underground mine aerosol, an unattached fraction of potential alpha energy f_p of 0.03 was assumed, as was an activity median diameter (AMD) of 0.25 μm (doubling to 0.5 μm) for the radon progeny fraction attached to airborne particles[24].

Occupant Breathing Rates

Adult male occupants of homes were assumed to spend 1/8 of their time in light work activities (1.5 $m^3\ h^{-1}$), 3/8 time at rest (0.54 $m^3\ h^{-1}$), and 1/2 time at sleep (0.45 $m^3\ h^{-1}$), for a mean breathing rate of (0.75 $m^3\ h^{-1}$). Occupancy factors were not necessary because the estimated doses were expressed in terms of exposure rates (WLM y^{-1}), and time intervals of six months (0.5 y), corresponding to the six-month turnover time for bronchial

epithelial cells. Underground miners were assumed to spend 3/4 of their time in light work activities (1.5 m^3 h^{-1}), and 1/4 time in vigorous work (3 m^3 h^{-1}), for a mean breathing rate of (1.8 m^3 h^{-1}).

Exposure Levels Modeled

The cumulative exposures to radon progeny were estimated for breathing air of indoor home atmospheres and for underground mine atmospheres over a six-month time period. Four levels of exposure to potential alpha activity in air were modeled, corresponding to 0.15 WLM and 1 WLM (typical low-level and elevated-level indoor home), and to 10 WLM and 100 WLM (low-level and elevated-level underground mine) cumulative exposures.

Clearance

The redistribution and clearance of inhaled radon progeny take place continuously throughout the bronchial tree. Deposited activity is cleared by the mucociliary escalator, but a portion may also be absorbed from the sol layer into the bronchial epithelium, where it may translocate into the blood. Figure 2 shows the clearance model used to calculate the number of alpha decays that occur in each airway generation. We assumed mucus transit times estimated by Cuddihy and Yeh[26] (Table 1).

James and Birchall in the NEA Experts Report[17] modeled the dosimetric effect of absorption of progeny into epithelium; Jacobi and Eisfeld[13] accounted for the effect of absorption into blood on the dosimetry of progeny

in each generation of the bronchial tree. Other investigators, however, have ignored these transfers and assumed that all ions clear by mucociliary action. In our study, the potential absorption from epithelium into blood was taken into account by assuming that the radon progeny were either "soluble" (partially absorbed into bronchial tissues) or "insoluble" (clearing without regional absorption). Both conditions were modeled to show the range of dosimetry results possible for lack of specific data. To model the effect of radon daughter solubility, we assumed that 30% of the daughter activity deposited in each airway generation transferred rapidly to the epithelium, where it was retained with a biological clearance half-time of 10 hours[27-28]. To model the opposite condition, we assumed no absorption from mucus into epithelium.

RESULTS

The average equilibrium surface activities for radon progeny in the respiratory tract (in disintegrations per cm^2) were calculated for indoor home and underground mine breathing atmospheres. Four exposure levels of potential alpha energy (0.15, 1.0, 10, and 100 WLM) were considered (Table 2). Two solubility conditions were also considered: soluble ions were assumed to migrate from the mucus flow into the epithelium; insoluble ions remained in the mucus (Table 2). These values for equilibrium surface activities constituted the source term for calculations of dose to target (secretory and basal) cell nuclei.

Dose to Target Cell Nuclei

Probability densities in specific energy to secretory and basal cell nuclei were calculated for each exposure condition described in Table 2. The mean specific energy (absorbed dose), probability of complete miss (n = 0, or delta function), and probability of 1, 2, 3, ... n hits were also calculated. These results are shown in Table 3 for secretory cell nuclei and in Table 4 for basal cell nuclei. These results confirm that single-hit interactions with cell nuclei predominate at low levels of exposure to radon and progeny[21], but multiple-hit interactions are common at higher levels.

Figure 3 shows plotted probability densities in specific energy for secretory and basal cell nuclei from soluble and insoluble radon progeny ions after exposure of an adult male to a cumulative indoor home exposure of 0.15 WLM. These doses represent the combined contributions of alpha-particle energy from ^{218}Po and ^{214}Po. Because of their closer proximity to cell nuclei, soluble ions in epithelial tissue cause higher doses than do insoluble ions, which are only in the mucus layer. Due to their closer proximity to the airway lumen and to the major portion of the deposited activity, secretory cell nuclei receive higher doses than do basal cell nuclei. Although doses to cell nuclei range from 0 to 3 Gy, the mean dose (or mean specific energy) is 0.0012 to 0.0034 Gy, or 0.008 to 0.031 Gy WLM^{-1} (Table 5).

Figure 4 shows probability densities in specific energy to secretory and basal cell nuclei for 100 WLM exposures to radon progeny in underground mines.

The solid and dashed lines show the differences between calculations for soluble (solid) and insoluble (dashed) polonium ions.

The absorbed dose per WLM is lower for indoor home breathing air than for underground mine air for both secretory and basal cell nuclei as targets. The absolute value of the calculated dose conversion depends on the choice of the target cell because the target cell distributions in tissue vary. The dose per unit WLM exposure was found to be higher for underground mines because the breathing rate was assumed to be higher for miners at work and the presence of larger aerosol particulates offset the counter-effect of the lower unattached fraction of potential alpha activity in air. The dose per WLM was also generally higher for secretory cell nuclei than for basal cell nuclei because secretory cells are closer to epithelial surfaces than are basal cells. The dose per WLM was also greater for assumed soluble polonium ions than for insoluble ions because soluble ions were able to migrate closer to target cell nuclei in the epithelium. The dose conversion factor was found to be in the range 0.008 to 0.0031 Gy WLM^{-1}, depending on specific conditions assumed.

Hit Probabilities

Figure 3 shows not only that the probability of alpha-particle irradiation of secretory cells is greater than for basal cells, but also that the relative doses to single cells or cell nuclei are similar. This means that the probability of receiving a hit determines the mean dose to all cells in a population exposed to radon progeny. Figure 5 shows the hit probabilities for secretory cell nuclei exposed to insoluble ^{218}Po and ^{214}Po

ions at four different exposure rates: 0.3, 2, 20 and 200 WLM y^{-1} (evaluated for 1/2 year, the mean cell turnover time). The probability of zero hits is great for each exposure rate and decreases with increasing exposure to radon progeny. Similarly, the probability of multiple hits increases with increasing exposure (Figure 5).

At low levels of exposure (<10 WLM), the shapes of the probability densities (and, therefore, the distribution of doses to target cell nuclei) were similar; the higher the cumulative exposure, the greater the probability of single hits to cell nuclei. Above 10 WLM, the shapes of the microdosimetric distributions changed significantly, showing that target cell nuclei had higher probabilities of multiple alpha-particle hits. The probability of multiple hits to secretory and basal cell nuclei was found to be negligible below cumulative exposures of 10 WLM.

The probability of alpha-particle irradiation of secretory cells was found to be greater than for irradiation of basal cells, but the probability densities in specific energy had similar shapes. In other words, the doses to secretory and basal cell nuclei were similar, but single secretory cell nuclei had a higher probability, by a factor of about 2, of being hit. The probability of multiple alpha-particle hits to cell nuclei increased with exposure above 10 WLM (Figure 5).

CONCLUSIONS

This study resulted in several advances in respiratory tract dosimetry: 1) it incorporated the proposed ICRP Task Group model of the respiratory tract; 2) it extended the concepts of internal microdosimetry[21] to a comparison of doses received by secretory and basal cell nuclei from exposures to low-level indoor radon and moderate to high-level exposures from underground mining; and 3) it estimated the range of differences in dose given various assumptions regarding the solubility and migration through epithelial tissues of ^{218}Po and ^{214}Po ions and their subsequent uptake into circulating blood. Our dosimetric model for inhaled radon progeny in the human respiratory tract allowed us to test the effects of different assumptions about the airway surface activities of radon progeny on the cell-specific radiation dosimetry. Conditions typical of exposure to indoor radon progeny and to aerosols in underground mines were selected for analysis.

These findings have important implications for lung cancer risk analysis. The transformation of cells from normal state to malignancy is generally believed to result from low-dose-per-cell (nonlethal) interactions, meaning that the transformation response to exposure is probably linear with increasing probability of single hits. As the probability of multiple hits increases, there is increased probability of cell death and somewhat reduced probability of transformation per unit exposure. We might, therefore, expect a linear increase in risk of lung cancer with increasing exposure up to about 10 WLM cumulative exposure to radon progeny, but something less than a linear response at higher cumulative exposures. This expectation may explain the

epidemiological differences in risk per unit exposure between different groups of underground uranium miners[18, 19]. This study supports the view that extrapolations of risk estimates from exposure at high levels to low levels may underestimate the risk of lung cancer at low levels of exposure.

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Table 1. Estimates of Mucus Transit Times in the Bronchial Tree[26]

Airways	Generation No.	Mucus Transit Time (min.)
Bronchi	1	11
	2	9
	3	7
	4	10
	5	11
	6	13
	7	16
	8	22
Bronchioles	9	22
	10	28
	11	45
	12	91
	13	143
	14	417
	15	1667

Table 2. Calculated Radon Progeny Equilibrium Surface Activities (disintegrations per cm^2), Averaged over the Respiratory Tract

Location	Solubility	Exposure (WLM)	Mucus		Epithelium	
			^{218}Po	^{214}Po	^{218}Po	^{214}Po
Indoor home	Soluble	0.15	5,880	12,500	1,460	4,930
	Insoluble	0.15	7,450	17,800	-	-
	Soluble	1.0	39,100	83,200	9,711	32,900
	Insoluble	1.0	49,600	118,000	-	-
Underground mine	Soluble	10	359,000	1.10×10^6	93,000	646,000
	Insoluble	10	453,000	1.56×10^6	-	-
	Soluble	100	3.59×10^6	1.10×10^7	930,000	6.46×10^6
	Insoluble	100	4.53×10^6	1.56×10^7	-	-

Table 3. 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

Table 4. Calculated Values of Absorbed Dose and Alpha-particle Hit Probabilities for Basal Cell Nuclei

Location	Solubility	Exposure (WLM)	Mean Specific Energy (Gy)	Hit Probabilities 0	1	2	>2
Indoor home	Soluble	0.15	0.0018	0.998	0.002	-	-
	Insoluble	0.15	0.0012	0.999	0.001	-	-
	Soluble	1.0	0.012	0.986	0.014	-	-
	Insoluble	1.0	0.008	0.993	0.007	-	-
Underground mine	Soluble	10	0.19	0.80	0.18	0.02	-
	Insoluble	10	0.11	0.917	0.079	0.003	-
	Soluble	100	1.9	0.107	0.239	0.267	0.39
	Insoluble	100	1.1	0.42	0.364	0.158	0.06

Table 5. Calculated Dose Conversion Factors (Gy WLM^{-1})

Location	Solubility	Target Nuclei Secretory Cells	Basal Cells
Indoor home	Soluble	0.023	0.012
	Insoluble	0.022	0.008
Underground mine	Soluble	0.031	0.019
	Insoluble	0.028	0.011

FIGURE CAPTIONS

Figure 1. Schematic model of bronchial epithelium with dimensions and spatial distributions of secretory and basal cell nuclei.

Figure 2. General model of the biokinetics of radon progeny in various bronchial generations (i) of the respiratory tract.

Figure 3. Probability densities, f(z), for secretory and basal cell nuclei in the adult respiratory tract for a cumulative indoor exposure to radon progeny of 0.15 WLM.

Figure 4. Probability densities, f(z), for secretory and basal cell nuclei in the adult respiratory tract for a cumulative underground mine exposure to radon progeny of 100 WLM.

Figure 5. Alpha-particle hit probabilities for secretory cell nuclei for different cumulative exposures to insoluble radon progeny.

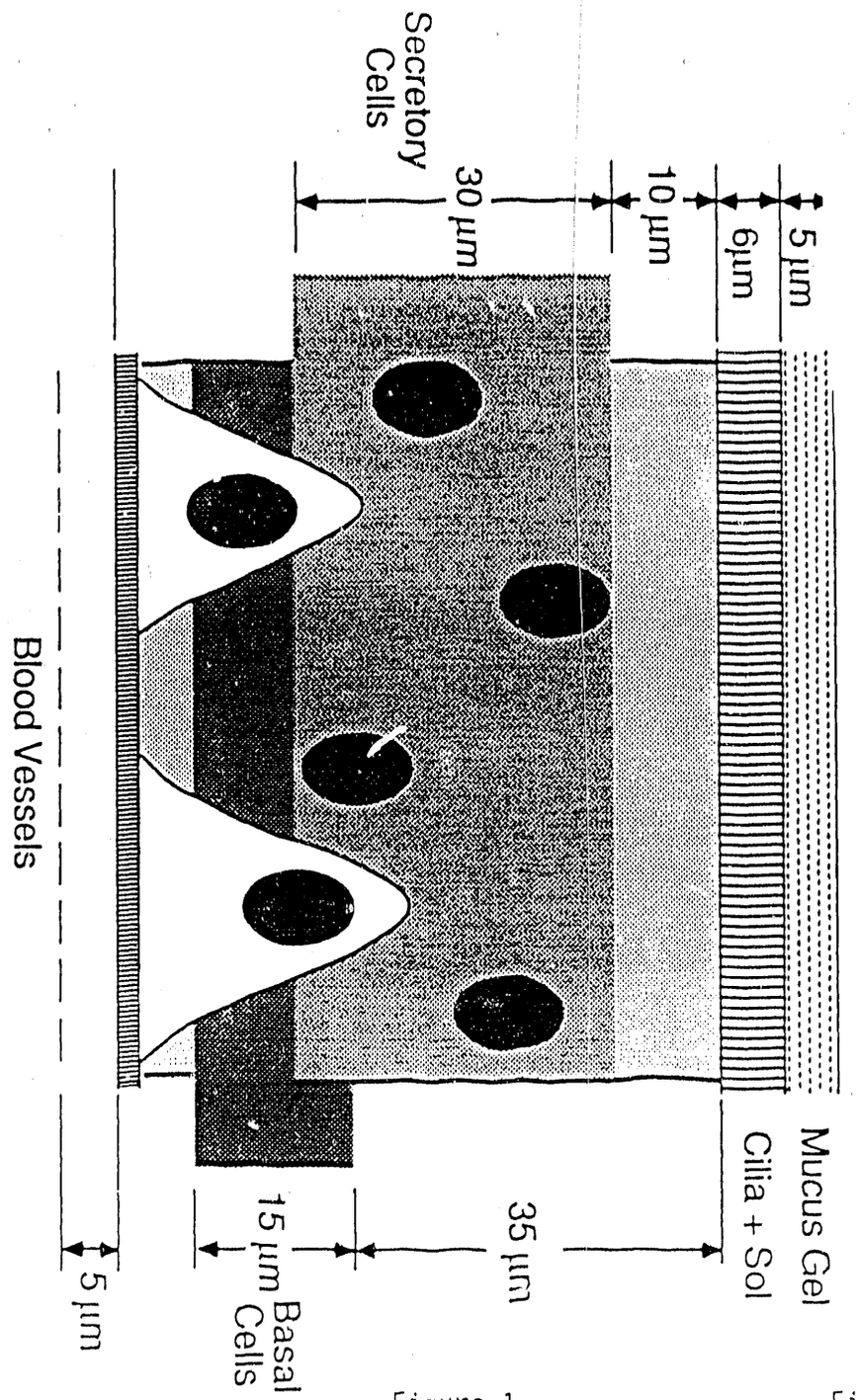

Figure 1.

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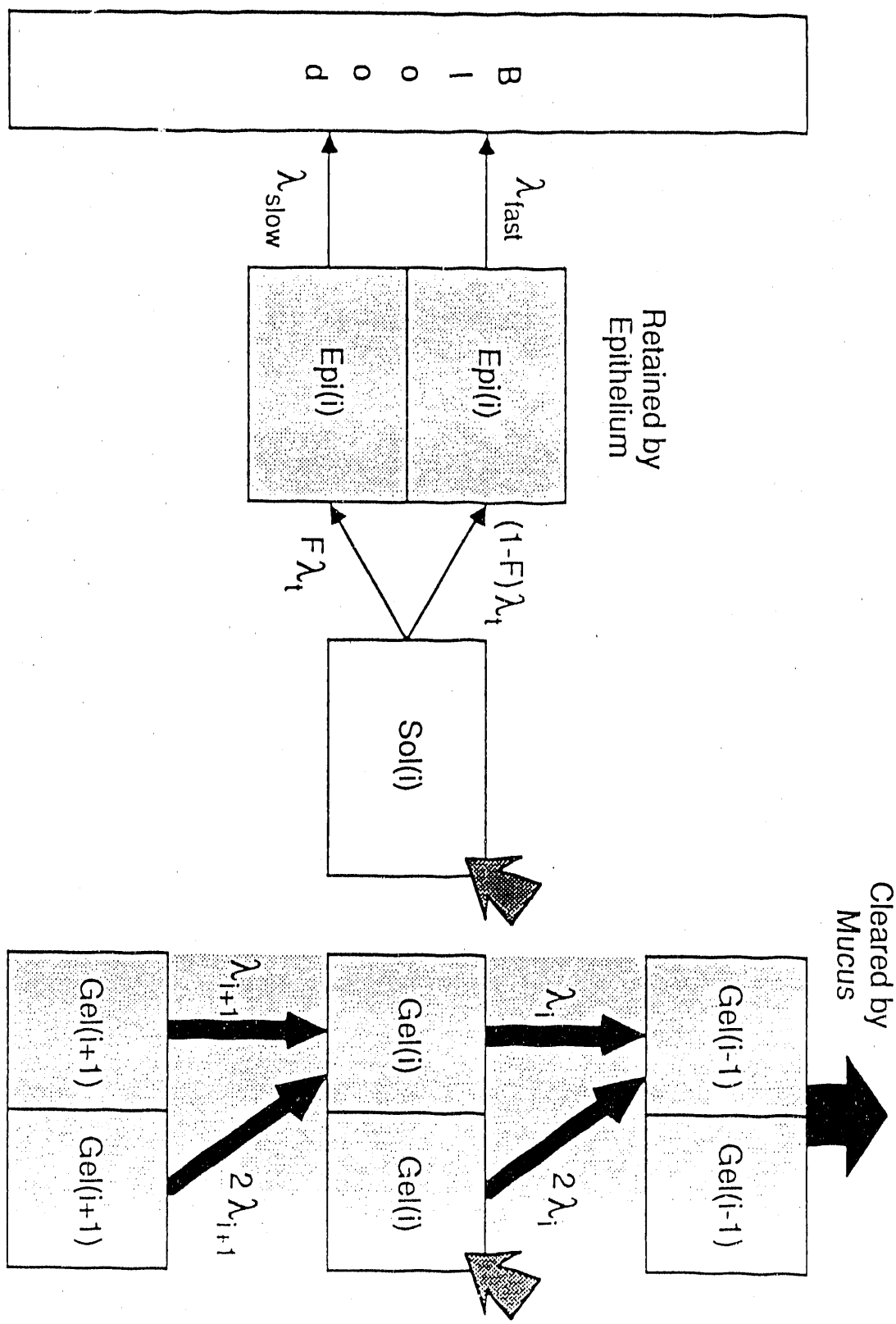

Figure 2.

Fisher/Hui/James

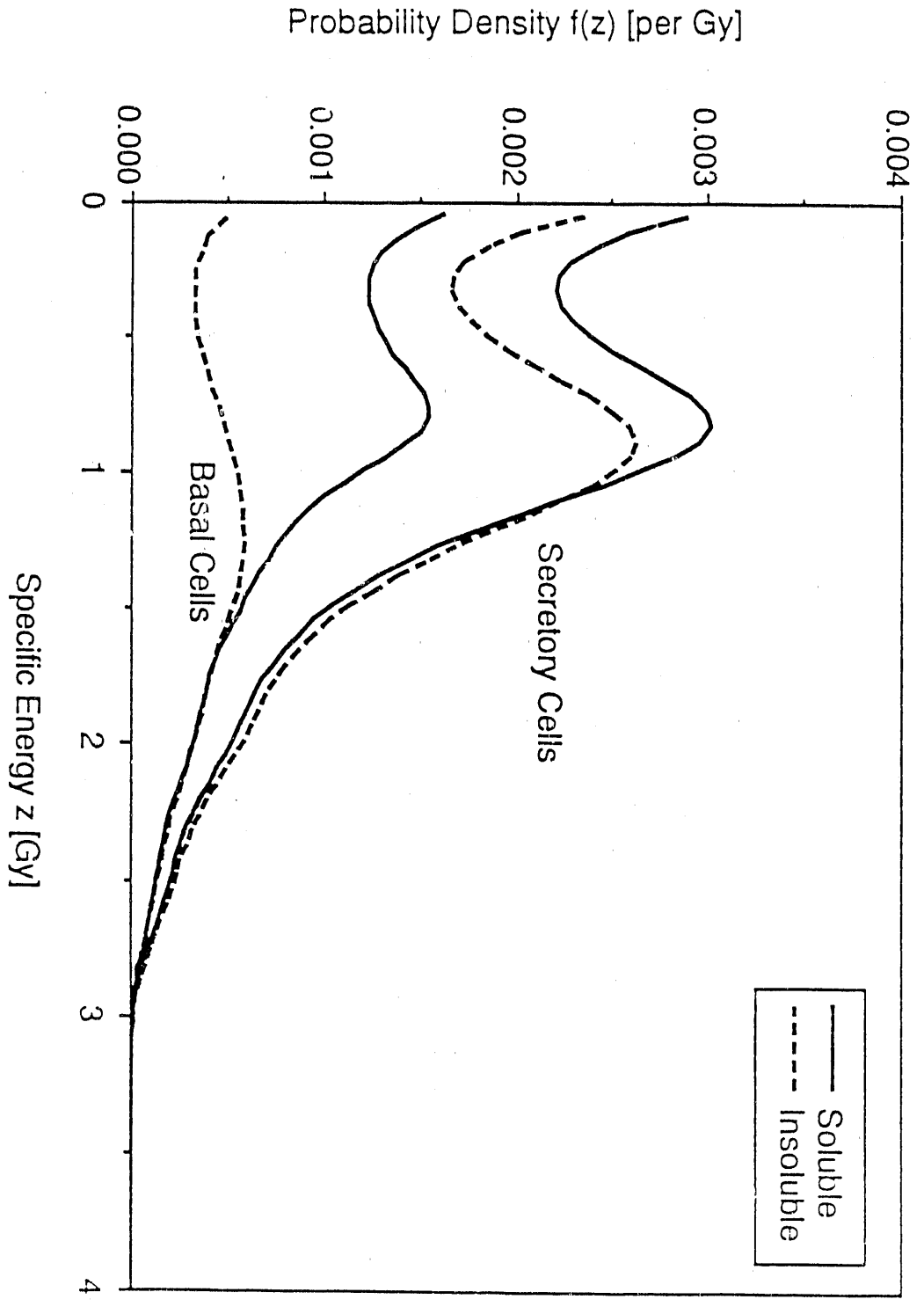

Figure 3.

Fisher/Hui/James

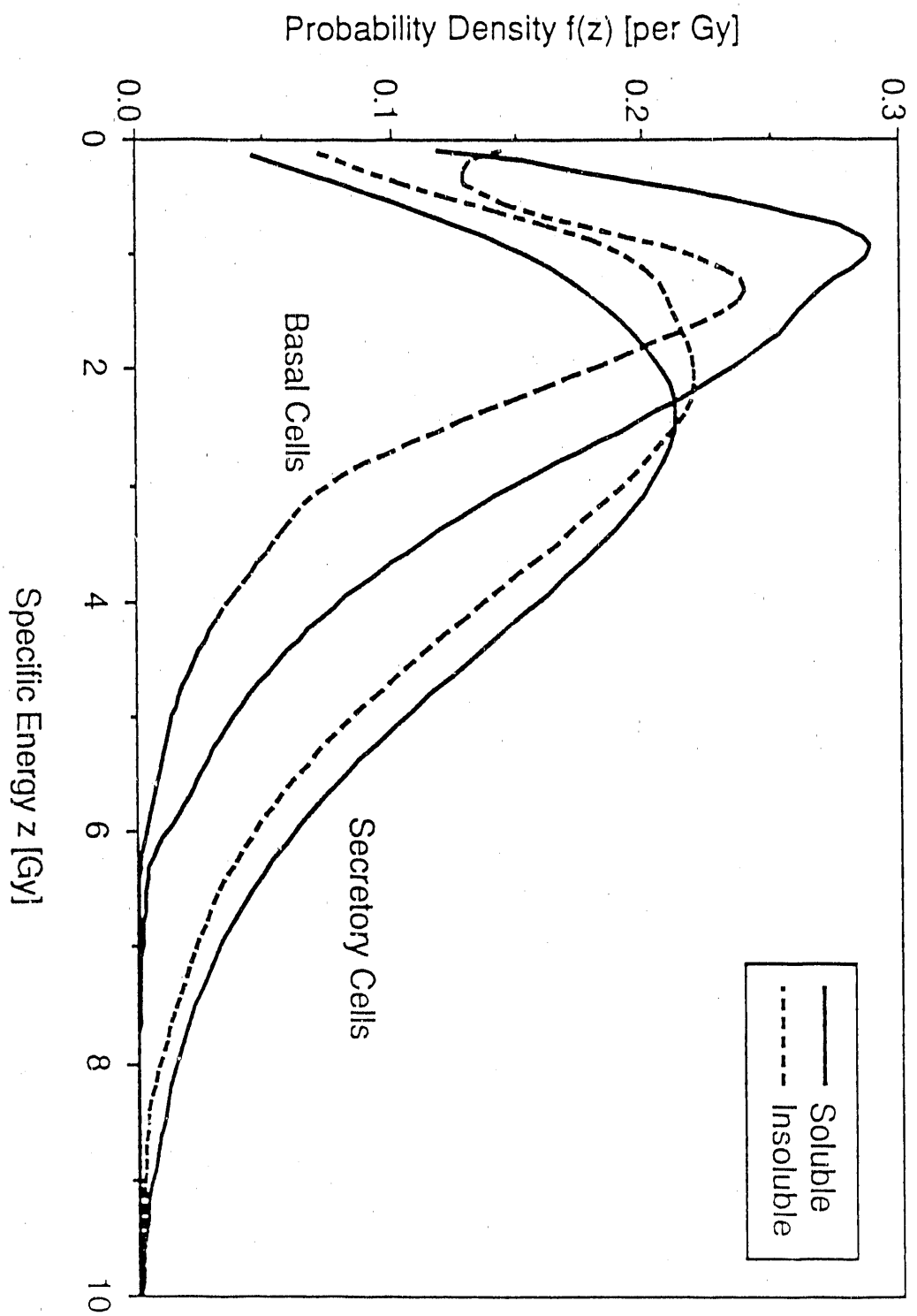

Figure 4. Fisher/Hui/James

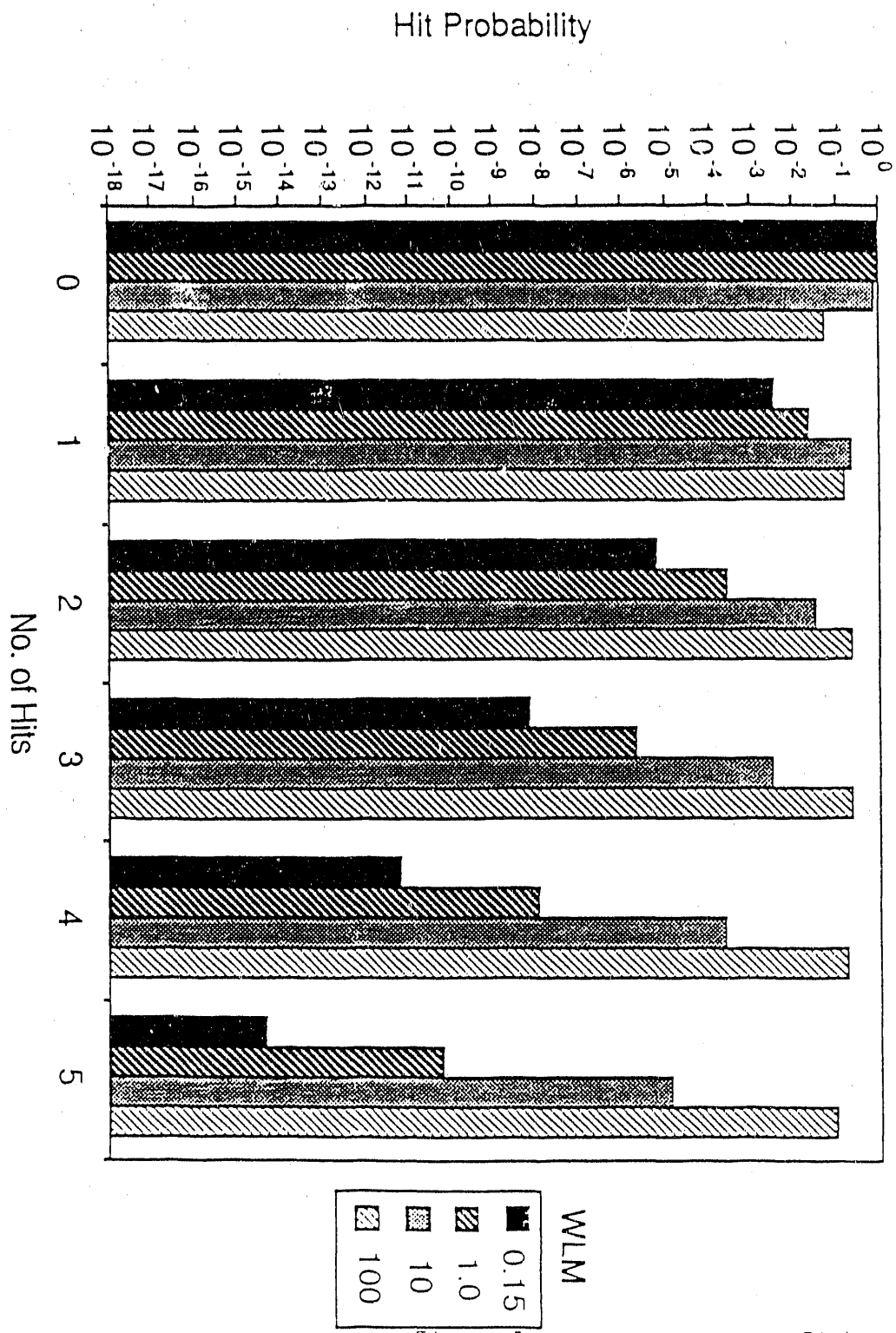

Figure 5.

Fisher/Hui/James

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