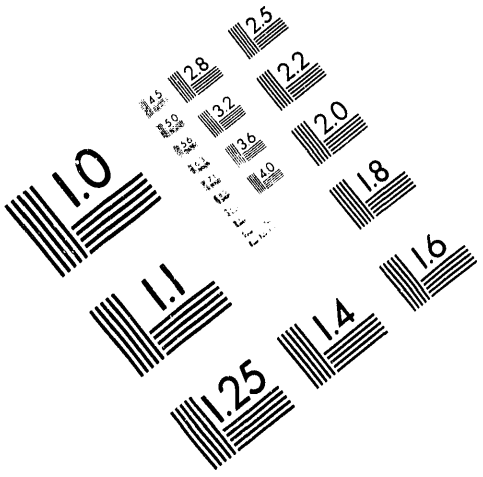

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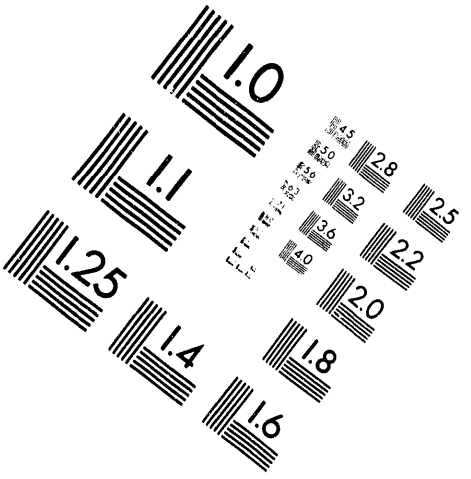

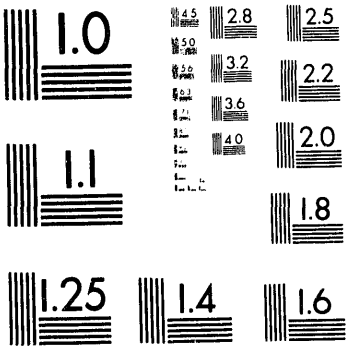

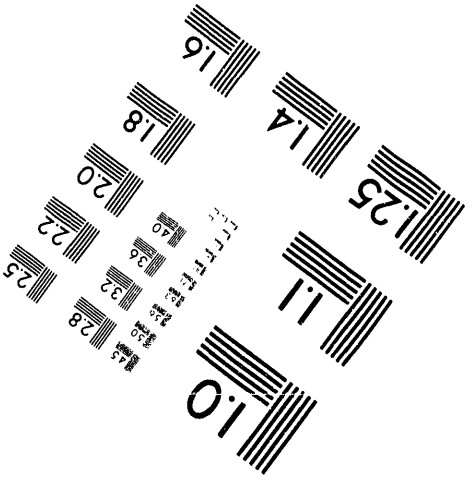

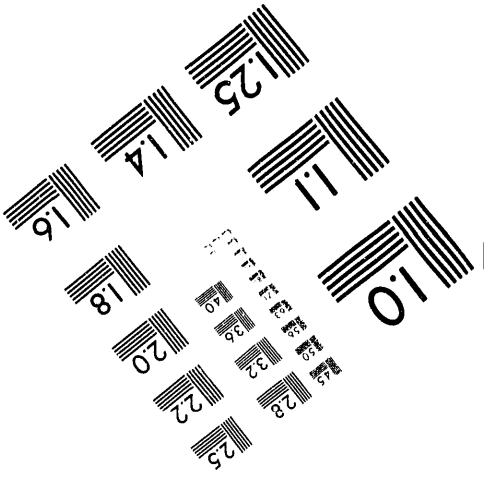

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^{222}Rn Dosimetry in the Dog Lung

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^{222}Rn Dosimetry in the Dog Lung

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ABSTRACT

The alpha dose to cells in bronchial airways in the beagle dog during historical exposures to ^{222}Rn decay products is calculated using updated information on airway morphometry, cell nucleus depth, mucus thickness, physical dosimetry and atmospheric characteristics. The alpha dose per unit exposure to basal cell nuclei in the upper airways ranges from 2 to 7 mGy WLM^{-1} (excluding the trachea) depending upon the exposure protocol used by the Institute (Battelle Northwest Laboratories versus University of Rochester). The dose to alveolar tissue is 3 mGy WLM^{-1}. In the human lung, the dose factor for the bronchial airways is 9 mGy WLM^{-1} and for the pulmonary parenchyma 0.5 mGy WLM^{-1} The human tumors appear primarily in the first few branching airway generations while the only tumors observed in the animals were in the bronchioloalveolar region suggesting a difference in cell sensitivity to alpha radiation.

INTRODUCTION

Studies with experimental animals, particularly rats (ongoing) and beagle dogs (historical experiments) have been performed to understand mechanisms of lung cancer induction by exposure to ^{222}Rn decay products. The historical studies at the University of Rochester (UR) and at Battelle Northwest Laboratories (BNWL) used beagle dogs. None of the induced lung cancers were bronchogenic in origin. For this reason, it is of value to examine the detailed dosimetry aspects in light of newer experimental data to understand possible mechanistic differences between human and experimental animal response to ^{222}Rn exposure.

Another important aspect of the dog studies at UR concerns the actual measurement of beta activity on excised tracheal tissue immediately following an exposure to ^{222}Rn and decay products. This provides the only existing experimental data supporting the modeling of bronchial alpha dose.

EXPERIMENTAL PROTOCOL IN UR STUDIES

At UR the experiments used 42 dogs with the whole body exposed to 200 to 10,000 WLM. The exposure was delivered in 1 to 50 days[1]. Histological examinations were conducted at zero, 1, 2, and 3 years post exposure. For all dose levels, the ^{222}Rn

decay product exposure atmosphere was 1800 WL with an exposure accumulation rate of 200 WLM day^{-1}. Exposure periods were 20 hours per day and 5 days per week. The aerosol was normal unfiltered laboratory room air.

The alpha dose to the trachea and major bifurcation was estimated from beta activity measurements in an experiment using 9 dogs. The dogs were first exposed for 20 hours to insure a steady state of ^{222}Rn decay products on the airways and in the lung parenchyma. After sacrifice the lungs were removed within minutes and sectioned into trachea, major bifurcation and parenchyma. The reported alpha dose was based on measurements of these tissues and an assumed absorption layer of 50 μm for the trachea and bifurcation. The exposure chamber concentration of ^{222}Rn was measured using ionization chamber measurements of air samples. The ^{222}Rn decay product concentration was determined from filtered air samples. The results of the dosimetry were stated to average 4.7±4.4 rad WLM^{-1} with a range from 0.28 to 12.5 rad WLM^{-1}, (47±44, 2.8 to 125 mGy per WLM) for the trachea and an average of 5.0±6.2 with a range of 0.36 to 20.7 rad WLM^{-1} (50±62, 3.6 to 207 mGy WLM^{-1}) for the first bifurcation[2]. The average dose to the whole lung was reported as 0.17 rad WLM^{-1} (1.7 mGy WLM^{-1}) with a range of 0.08 to 0.79 rad WLM^{-1} (0.8 to 7.9 mGy WLM^{-1}).

It was stated that different dogs exposed to the same WLM

are not likely to receive the same radiation dose and the measurements in 11 dogs indicated a range of a factor of 10.

There were no frank carcinomas in the UR study. Pathologic changes were found only in the alveolar and bronchiolar region of the lung. There was an increase in the number of small foci of chronic inflammation. The lesions appeared as small patches of thickened alveolar wall, some metaplasia of alveolar cells and some hyperplasia of bronchial epithelium.

EXPERIMENTAL PROTOCOL IN BNWL STUDIES

The other study with beagle dogs at BNWL[3] the experiments used 69 beagle dogs in 4 groups. The dogs were about 2 years old. In group 1, Twenty dogs were exposed to ^{222}Rn and decay products and carnotite (uranium ore) dust; twenty dogs in group 2 were exposed to ^{222}Rn and decay products, carnotite dust (13 ± 7 mg m^3) and cigarette smoke; twenty dogs in group 3 were exposed to cigarette smoke only and in group 4, 9 dogs were exposed to room air. Six lung cancers were observed in the group 1 animals (3 bronchioloalveolar, 2 epidermoid, 1 fibrosarcoma) and one in group 2 (bronchioloalveolar). None of the lung tumors were bronchogenic. The average exposure for group 1 and 2 dogs was 15000 WLM.

The deficit of lung tumors in the smoking dogs may be explained dosimetrically by rapid engulfment of decay products in

the parenchyma by macrophages. Tobacco smoke is well known to enhance macrophage production dramatically.

BRONCHIAL AND ALVEOLAR DOSE MODEL

The airway and parenchymal dose in the beagle dog can be modeled if the following characteristics are known. These include the airway dimensions, breathing rate, mucus clearance rate, mucus thickness, target cell nucleus depth, nasal deposition, particle deposition efficiency, aerosol diameter, unattached fraction of the ^{222}Rn decay products and the physical dosimetry. The specific information for humans has already been used in modeling their bronchial dose[4, 5, 6].

The specific information required to model the dose in beagle dog airways as compared with human dose is their airway morphometry, mucus thickness, cell nuclei depth, nasal deposition and special aerosol characteristics.

AIRWAY MORPHOMETRY

The beagle airway morphometry was reported in detail by Yeh[7]. Cohen and Briant[8] measured airway morphometry in a mongrel dog and the airway lengths and diameters were about 20% larger. Cohen also measured the flow distribution fractions to the 6 lobes of the dog lung and these are utilized in the present

model.

MUCUS THICKNESS

Mercer at al[9] measured the thickness of the human mucous layer and found the gel layer to be 1 μm and the sol layer equal to the cilia length or 7 μm, giving a total thickness of 8 μm. The total thickness of the mucous layer in the dog is not known, however, the cilia average about 4 μm in length and a total thickness of 5 μm is used in the present model.

NUCLEAR DEPTH OF CELLS IN AIRWAYS

Robbins[10], in a study of cell morphometry in dog bronchial epithelium, is determining the average depth of basal and mucous cell nuclei in tissue obtained from 26 mongrel dogs sacrificed at New York University School of Medicine. The results of measurements obtained so far (12 dogs) are used in the modeling in this study. This includes measurements on 2800 basal and 1500 mucous cell nuclei summarized in Table 1. The average nuclear depths for basal and mucous cells are 22 and 15 μm respectively. Figure 1a. shows an electron micrograph of a bronchial airway (airway generation 6) from one of the mongrel dogs in the NYU study. Figure 1b. shows an electron micrograph of the alveolar

region. These illustrate the typical morphometry of the target tissue for ^{222}Rn decay products and the location of target cell nuclei considered in the dose calculations.

NASAL DEPOSITION IN THE DOG

There is scant information on nasal deposition in the dog. Cuddihy[11] estimated nasal deposition so that he could calculate the lung deposition for inhalation studies performed at Lovelace, Inhalation Toxicology Research Institute. The nasal deposition for 3 μm diameter particles was assumed to be 60% or somewhat higher than the fractional deposition in the human nose determined by Rudolph et al[12]. Although the dog nose is possibly a more efficient particle filter than the human nose no detailed information is available for modeling. Therefore, in lieu of experimental data, the expressions for the human nasal deposition of submicron particles developed by Cheng et al.[13] and for micron size particles by Rudolph et al.[12] are used.

AEROSOL CHARACTERISTICS

The aerosol used in the UR studies was unfiltered laboratory room aerosol introduced into the 2 m^3 exposure chamber. The activity median diameter (AMD) was stated to be about 200 nm and the unattached fraction of ^{218}Po 20%[14]. The geometric standard

deviation (GSD) for this aerosol is assumed to be 2.0, the value typically reported for normal room dust[15].

In the BNWL the activity median aerodynamic diameter (AMAD) of the carnotite ore dust was stated to be 600 nm with a geometric standard deviation of 1.7. Assuming a particle density of 3.0 g cm^3 this is equivalent to an AMD of 350 nm. The unattached ^{218}Po was 3% (assumed to be expressed as a fraction of the total ^{218}Po).

BRONCHIAL DOSE MODEL

The dose model for human bronchial airways has been reported by Harley et al[4, 5, 6] and these calculations are used in the present work incorporating the information described above. The physical dose factors were recalculated using the thinner mucous layer (5 μm) and the nuclear depths of basal (25μm) and mucous cells (19 μm). The detailed dose curve for these cell nuclei as a function of depth is given in Harley et al.[6]. The results of the dose calculations as a function of inhaled particle size are shown in Figures 2 and 3. Figure 2 is the alpha dose per WLM exposure for a beagle dog breathing carnotite ore dust through the nose at an assumed rate of 4 l min^{-1}. Figure 3 is the dose per WLM for a dog breathing normal dust through the nose at 2 l min^{-1}. The curves for a dog breathing normal room dust at 4 l min^{-1} are similar to the values in Figure 2 with the exception that

the values for particle diameters greater than 1000 nm are decreased by about 30%. The BNWL exposures were nose only exposures. Mouth breathing is not calculated for UR because the particles in the UR experiments were too small to impact in the mouth.

RESULTS

The results of the dose calculation (the product of the dose factor curves with the lognormal particle size distribution) for several particle size distributions and breathing rates are given in Table 2. The base calculations are for the aerosols described above and the alpha dose is the average over upper airway generations 2 to 8. A few additional calculations increasing or decreasing the unattached fraction of ^{218}Po are also shown to indicate the effect changes in these factors have upon the calculation.

There is some indication in the published literature that there is a potential for hygroscopic growth in the lung. A calculation was also performed assuming that the laboratory room aerosol grows by a factor of 1.8[16] in the humid environment of the dog lung. Similar growth in the lung is not considered for the BNWL studies because the aerosol was uranium ore dust (75% SiO_2). This aerosol was clearly not hygroscopic unlike normal room air that has the potential for growth.

The dose to the trachea is a special case because there were measurements made at UR of the deposited activity on the trachea, major bifurcation and in the pulmonary region. It has long been known that deposition is about a factor of 10 larger in the human trachea than for subsequent airways[17] but that deposition varies markedly with flow rate and the factor is highly variable. Yu and Cohen[18] have reported that deposition in the human trachea can be expressed as a function of the Reynolds and Schmidt numbers. Their expression is,

$$Dep = 20,630\ (Re)^{-2.2}\ (Sc)^{-0.2339}\ (L/R)$$

where Dep = deposition fraction

Re(Reynolds) $= \rho\ V\ d/\eta$

ρ = density of air

V = axial airway velocity

η = viscosity of air

Sc(Schmidt) $= \upsilon\ /\ D$

υ = kinematic viscosity of air

D = diffusion coefficient

L, R = airway length and radius

The deposition in subsequent airways was calculated using the empirical expression derived by Cohen and Asgharian from measurements of particle deposition in hollow casts of the human lung[19].

DISCUSSION

The dose factors in Table 2 indicate that the average dose to the nuclei of basal cells, presumed targets for carcinogenesis in humans, ranges from 2 to 7 mGy WLM^{-1} for the BNWL and UR exposures respectively. If particle growth in the lung is possible, then the calculated dose factor for the UR experiments is 4 mGy WLM^{-1}. The dose to mucous cell nuclei is 30% higher than to basal cell nuclei.

Although the range of estimated dose factors from measurements of beta activity on the trachea and major bifurcation in the UR study is large (2.8 to 208 mGy/WLM) the modeling is least consistent with the average estimates. The average reported alpha dose is 47 mGy WLM^{-1}. In table 2 the dose to the trachea for a lognormal particle size distribution with AMD of 200 nm and GSD of 2.0 is 8.8 and 11 mGy WLM^{-1} for breathing rates of 4 and 2 l min^{-1} respectively. The wide range is most likely due to different breathing patterns among dogs and could also have been affected by changes in the particle size distribution (AMD, GSD) and unattached fraction of ^{218}Po in the exposure chamber. The empirical expression of Yu and Cohen[18] for deposition in the trachea supports wide variability with breathing rate. Given the uncertainties in modeling the tracheal dose and the different methods for calculating dose (the UR dose was estimated to a volume of tissue) the agreement is

reasonable.

The alveolar or parenchymal dose is calculated in the present work as 3.3 or 1.7 mGy WLM^{-1} depending upon the breathing rate (4 or 2 l min^{-1}). This is in good agreement with the UR reported value of 1.7 mGy WLM^{-1} if an average breathing rate of 2 l min^{-1} is assumed for the dogs.

The fact that all lung tumors in the dog were in the alveolar region in spite of the reasonable equivalence of dose to target cell nuclei in human and canine upper airways suggests differences in cell sensitivity for carcinogenesis.

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TABLE TITLES

Table 1. Measured basal and mucous nuclear depths in mongrel dog airway generations 2 to 6.

Table 2. Alpha dose to basal and mucous cell nuclei in dog bronchial airways for historical exposure to atmospheres in UR and BNWL studies.

FIGURE CAPTIONS

Figure 1a. Electron micrograph of the lining of a dog generation 6 bronchus. In addition to the ciliated cells, the pseudostratified epithelium contains the two cell types that are the most probable targets for ^{222}Rn daughter induced carcinogenesis, the mucous (M) and basal (B) cells. In comparison to the thick basement membrane seen in humans, this image illustrates the extensive network of elastic fibers that are typically found just beneath the basal lamina in the canine bronchial mucosa. Fibroblasts whose processes (arrow) partially envelop the elastic fibers closely approximate the basal lamina. Magnification 2,500X.

Figure 1b. Electron micrograph of the respiratory parenchyma of a dog lung. The lining epithelium of the alveolar airspace (A) is composed of two cell types, the cuboidal, surfactant-producing type II pneumocyte (P), and the type I cell with its extremely attenuated cytoplasm (arrow). Most of the very thin surfactant layer was lost when the lung was fixed by immersion. The interalveolar septum contains a capillary which has a red blood cell (R) in its lumen. In addition to connective tissue elements, the core of the septum contains some smooth muscle cells (S). As measured here the minimum distance from the airspace to the vascular space is approximately 0.6 μm. Magnification 10,000X.

Figure 2. Alpha dose to basal cells in mongrel dog epithelium 25 μm from the epithelial surface. Dose calculated as a function of carrier aerosol diameter. Breathing rate 4 l min^{-1} aerosol density 3.0 g cm^3 (carnotite ore)

Figure 3. Alpha dose to basal cells in mongrel dog bronchial epithelium 25 μm from the epithelial surface. Dose calculated as a function of carrier aerosol diameter. Breathing rate 2 l min^{-1}, aerosol density 1.5 g cm^3 (room air).

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	Dog Airway Generations						
	All	2	3	4	5	6	Min/Max Depth
WEIGHTED MEAN NUCLEAR DEPTH[1]							
Basal depth (μm)	22.3	25.1	25.7	22.3	19.4	17.2	15/47
SE	1.2	1.1	0.9	0.9	0.8	0.9	
Mucous depth (μm)	14.8	19.3	17.9	14.4	13.3	11.7	6/45
SE	0.2	1.4	1.3	0.7	0.7	0.7	
UNWEIGHTED MEAN DEPTH[2]							
Basal depth (μm)	24.2	24.8	27.2	23.7	20.7	19.3	
SE	8.7	4.7	11.2	9.6	4.6	5.4	
Mucous depth (μm)	17.3	19.2	20.8	16.0	13.0	12.8	
SE	7.3	3.5	9.3	7.6	3.6	2.8	

[1] Weighted average depth, wd, and weighted standard deviation, wSD, of the depth below the epithelial surface.

$$wd = \Sigma w_i d_i = \Sigma n_i d_i / \Sigma N$$

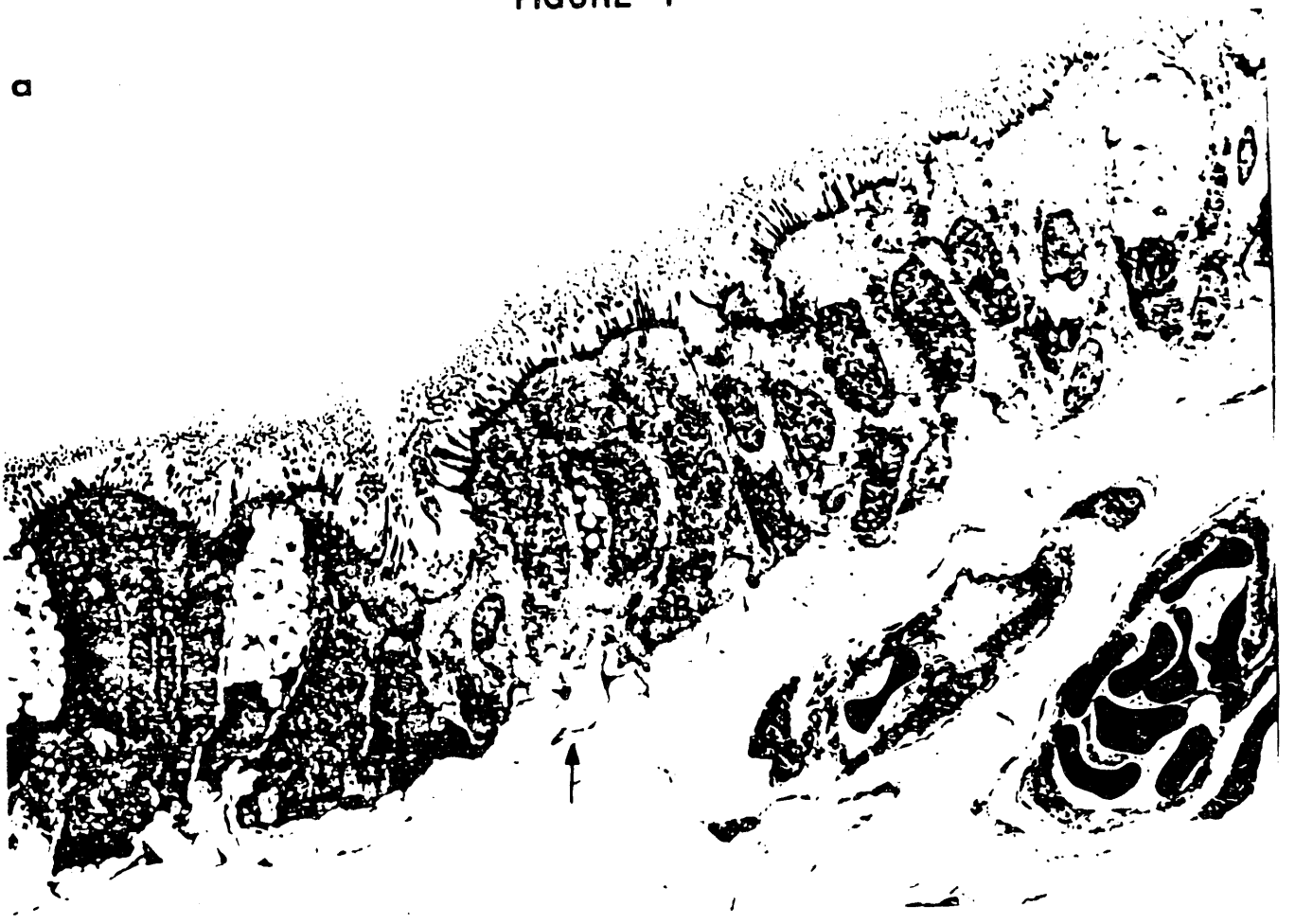
$$wSD = SQRT(\Sigma w_i^2 s_i^2 / N_i).$$

Weights use number of cells in each generation. Total number of basal cells, 2200, total number of mucous cells, 1500.

[2] Unweighted average and standard deviation of basal and mucous cell nuclei depths for 12 dogs.

FIGURE 1

a



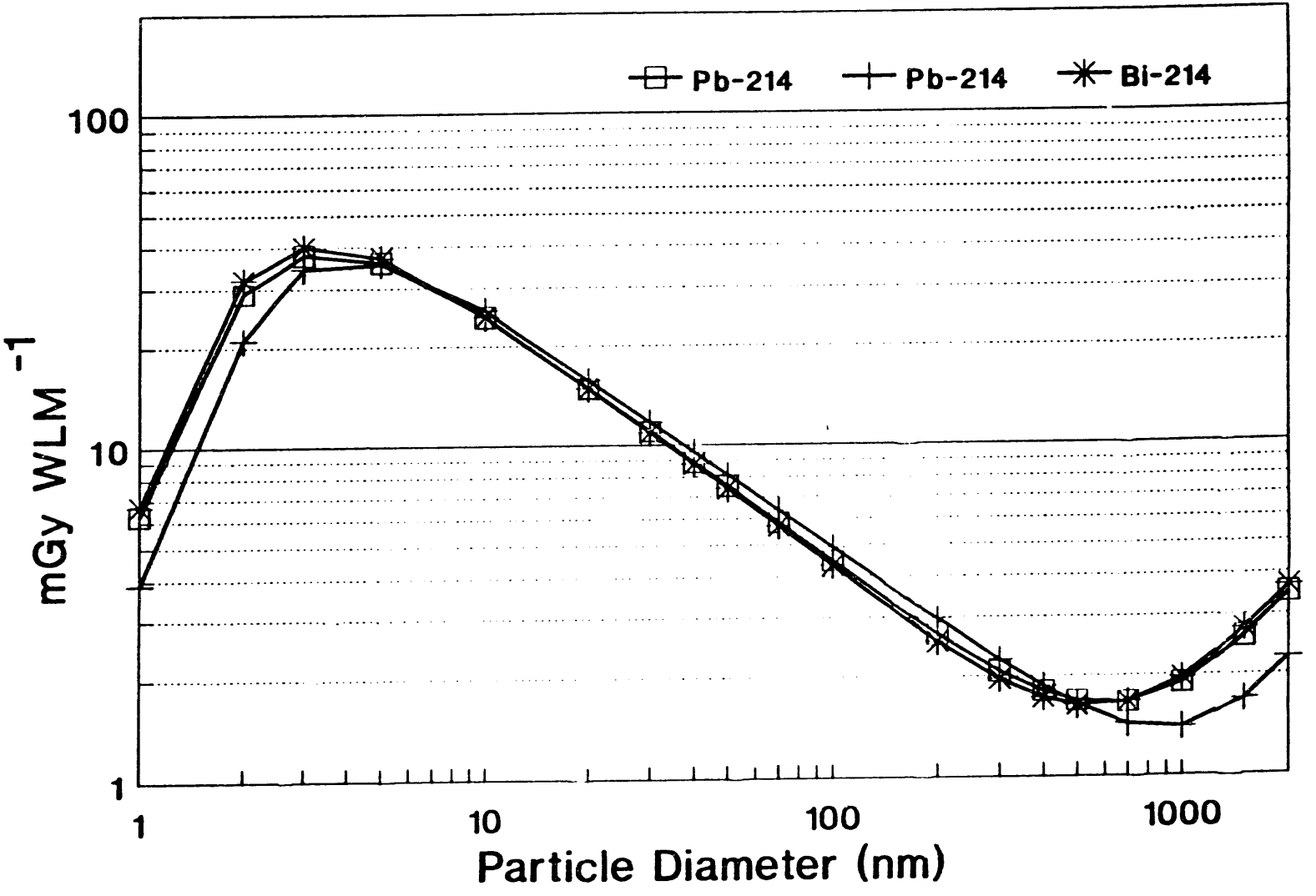
b

Site	Breathing Rate	AMD, (nm)	GSD	Unattached ^{218}Po[1] f	(f_p)	$^{222}Rn/^{218}Po/^{214}Pb/^{214}Bi$[2]	Basal Nuclei Dose (mGy WLM^{-1})[3]	Mucous Nuclei Dose (mGy WLM^{-1})[3]	Tracheal Cell Dose (mGy WLM^{-1})
UR	4 lpm	200,	2.0	20	(0.081)	100/90/40/20	5.1	6.3	8.8
	2 lpm			20	(0.081)		3.6	4.5	11
	4 lpm			10	(0.041)		4.1	5.1	
Hygroscopic Growth (x1.8)		360,	2.0	20	(0.081)		4.1	5.1	
BNWL	4 lpm	350,	1.7	3	(0.012)	100/90/40/20	2.5	3.0	
	2 lpm			3	(0.012)		1.8	1.8	
	4 lpm			10	(0.041)		3.2	4.0	

[1] The unattached fraction is given in two ways, one as a percent of the total ^{218}Po activity, f, and, two, as the fraction of total potential energy, f_{pot}. Unattached ^{214}Pb calculated as $0.1^{218}Po$ activity.

[2] The ratio of ^{222}Rn and decay products in the atmosphere considered.

[3] The dose to basal or mucous cells at an average depth of 22 µm or 15 µm below the epithelial surface. Decay product activity mixed in an 5 µm thick mucous layer. Alpha dose averaged over airway generations 1 to 7.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mGy WLM^{-1}
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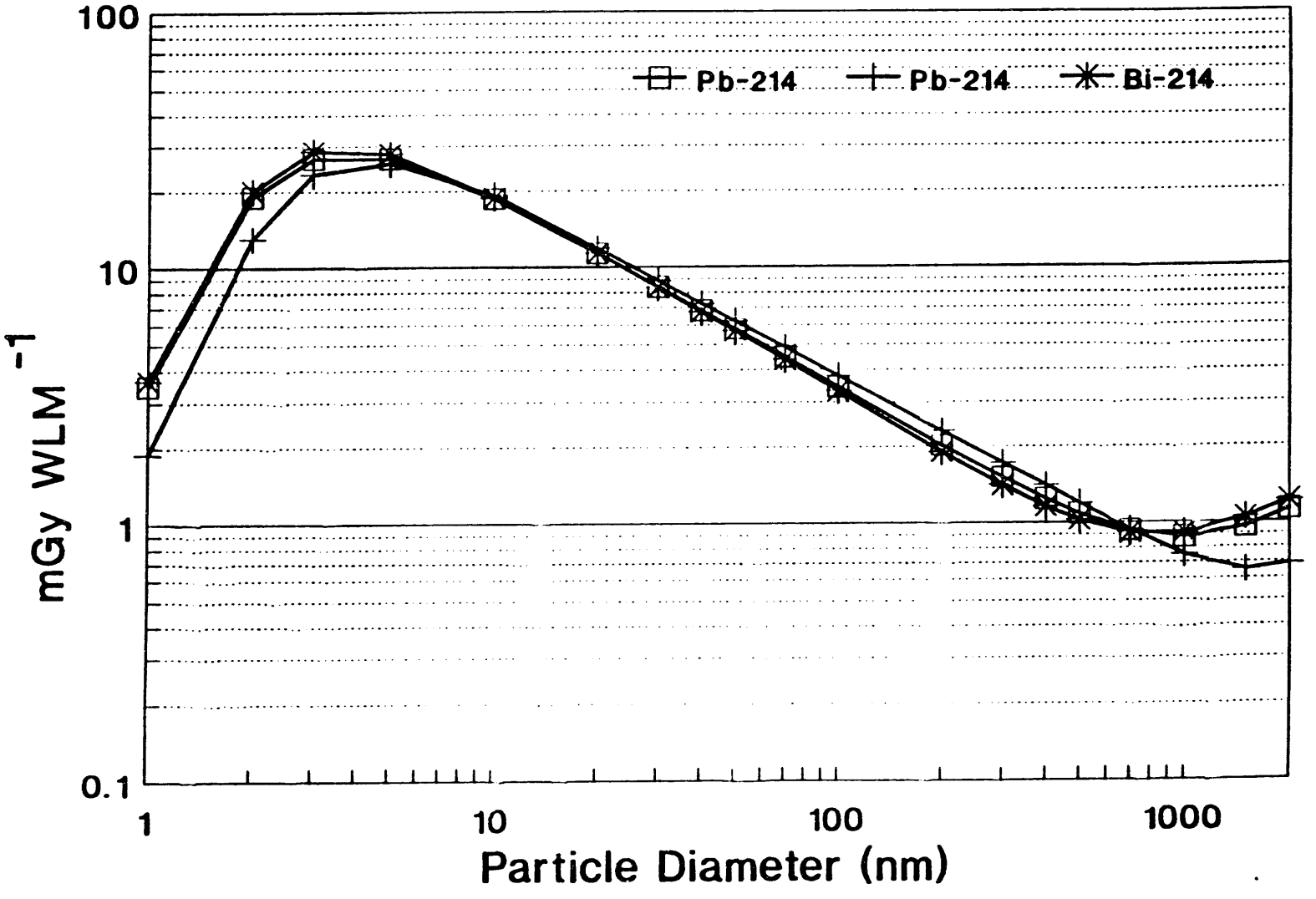
Particle Diameter (nm)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