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NEW APPROACHES TO RESPIRATORY TRACT DOSIMETRY MODELING FOR INHALED RADIONUCLIDES

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Abstract—Respiratory tract dosimetry models for inhaled radioactivity are currently being reviewed and revised by a task group of the U.S. National Council on Radiation Protection. The revised models are likely to place increased emphasis on the nasal and tracheobronchial airways because studies with laboratory animals and people have shown cancers in these regions to be associated with inhaled radioactivity or other toxic substances. A morphometric model of the tracheobronchial airways that describes a typical airway path for the respiratory tract and a clearance model based upon mucus flow velocity in conducting airways are also being evaluated. This combination of models appears to offer the greatest flexibility for dosimetry calculations applicable to people of different body size and health status. Doses to all epithelial cells lining the conducting airways will be calculated, instead of focusing exclusively on the basal cells.

INTRODUCTION

THE NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP) in the United States and the International Commission on Radiological Protection (ICRP) have parallel efforts under way to review and revise the current respiratory tract dosimetry models for inhaled radioactive aerosols. These efforts are expected to continue for about two years and lead to new methods of calculating radiation doses to tissues of the respiratory tract that are likely to have an important impact upon future radiation protection practices.

The proposed new NCRP respiratory tract dosimetry models represent a significant change in philosophy from the current ICRP Task Group models. The current models place major emphasis on providing information for calculating average dose only to the pulmonary region and deposition fractions and clearance rate constants are selected so as not to underestimate this radiation dose (TASK GROUP ON LUNG DYNAMICS, 1966; ICRP, 1979). Although information is also provided for estimating the amount of inhaled radioactivity that is expected to be absorbed into the systemic circulation and transferred to other organs or excreted, the absorbed fractions are often underestimated due to the manner in which solubility classes are assigned to different radionuclide chemical forms and the use of some inappropriate model clearance pathways. This approach makes the dosimetry models less suited for use in interpreting radiation worker exposures and bioassay measurements; however, this application of the models was not a primary goal of the TASK GROUP ON LUNG

DYNAMICS (1966). Despite these difficulties, the models have provided the best available framework for such exposure evaluations.

Additional data and computer modeling techniques are now available to improve the current dosimetry models for a broad range of important radionuclides. To accomplish this goal, the new models are being constructed to predict the most likely deposition and clearance patterns in exposed individuals, to make better use of experimental measurements from studies using laboratory animals, and to incorporate information on aerosol characteristics and bioassay data when they are available from exposure analysis.

Concerted effort is also being expended to develop respiratory tract deposition, retention and dosimetry models that are applicable not only to healthy radiation workers, but also to more heterogeneous populations. This includes males and females of different body sizes, smokers, and people with respiratory disease. Current scientific information is not adequate to accomplish the goals completely. However, new measurements of airway morphometry and of inhaled particle deposition and clearance in normal individuals, and people with compromised health status are available for constructing a new framework to evaluate individual exposures in a more detailed manner than is now possible using the current dosimetry models.

New emphasis is also being placed on dosimetry for tissues lining the airways of the nasopharyngeal and tracheobronchial regions. More than 90% of the human respiratory tract cancers occur in the conducting airways, principally in the tracheobronchial tree. Bronchial cancers are well known in people exposed to radon daughters, and both bronchial and nasal cancers have been found in laboratory animals exposed to various radionuclides (BOECKER *et al.*, 1983). Because these tissues may receive high doses from inhaled radioactive particles or may be especially sensitive to radiation, they should be considered as possible critical tissues in developing future radiation protection guidelines.

The following sections of this report highlight the most significant proposed changes in respiratory tract dosimetry being considered by the NCRP task group. They do not provide a complete description of these modeling efforts, and it is not yet clear which, if any, of the proposed changes are likely to be adopted by the NCRP.

CELLS AT RISK

The respiratory tract contains more than 30 different types of cells that all have important biological functions (JEFFERY, 1983; CRAPO *et al.*, 1983; BREEZE, 1977). These functions include providing structural support, conditioning of air, secretion of fluids, clearance of mucus and foreign matter, defense against toxic chemicals and biological agents, metabolism, gas exchange and control of ventilation. Because we cannot live unless these processes operate efficiently which requires that cells of the respiratory tract function normally, the most critical injuries are those that affect tissue repair processes including cell replacement. Probably the most important and radiation-sensitive injuries are those leading to the development of neoplastic disease. Thus, the most critical cells are those with relatively long residence times that are capable of division and responsible for replacement of other injured cells. This includes cells of the airway epithelium, except for ciliated cells, and cells of the alveolar region, except for Type I cells and migratory cells (BOWDEN, 1983; EVANS, 1982).

The current dosimetry models of the respiratory tract do not provide detailed information for calculating dose to nasal epithelium. Dose calculations for the tracheobronchial region are focused on the basal cells, and for the pulmonary region average dose is calculated by including the pulmonary lymph nodes with alveolar tissue (ICRP, 1979; NCRP, 1984).

Having considered recent studies of cell kinetics in the respiratory tract, and other factors discussed above, the current NCRP task group is likely to develop methods for calculating dose to the nasal epithelium, a region including the first four airway generations below the trachea, the terminal bronchioles, and an intermediate group of airway generations. Doses to the epithelium of conducting airways will be calculated as a function of depth in tissue from the lumen to the basement membrane. Doses to the pulmonary region and pulmonary lymph nodes will probably be calculated separately. In total, these dosimetry calculations require more extensive development of respiratory tract morphometry and deposition and clearance models than are contained in the current ICRP dosimetry models.

RESPIRATORY TRACT MORPHOMETRY

The respiratory tract morphometry model being considered for use by the NCRP task group was developed by YEH and SCHUM (1980). It is called the Typical Path Lung Model and includes 16 airway generations between the trachea and the terminal bronchioles and 9 more generations to the alveoli (Table 1). Each generation is represented by a median length (L), diameter (d), branching angle (θ), and gravity angle (ϕ). These dimensions are based on measurements obtained from a silicon rubber cast of the lungs of a 60 year old male who died of a myocardial infarction. Other lung morphometry models have been published by WEIBEL (1963), HORSFIELD and CUMMING (1968) and HORSFIELD *et al.* (1971). All of these models were based upon measurements of different lung casts, but they are sufficiently similar that the use of any of the models in predicting inhaled particle deposition fractions is likely to produce comparable results. Although the Typical Path Lung Model is a simplified representation of the complete respiratory tract, it has been used to calculate inhaled particle deposition fractions that agree well with experimental measurements (YEH and SCHUM, 1980). Also, it can readily be scaled to account for differences in body size, and it is well suited to modeling particle clearance in the tracheobronchial airways as described below.

Variability in the morphometry of the human upper bronchial tree was studied by NIKIFOROV and SCHLESINGER (in press) using replica casts obtained from 8 male adults. They showed moderate variability in the first 8 airway generations for both diameter and length. This information will be used to quantify the effect of changes in airway dimensions on particle deposition calculations using the Typical Path Lung Model.

Other studies by PHALEN *et al.* (1985) measured growth-related changes in airway sizes from casts of children and young adults who were between 11 days and 21 years of age and ranged from 48 cm to 190 cm in height. They expressed airway lengths (L_i) and diameters (D_i) as functions of body height (H) using linear relationships;

$$L_i \text{ or } D_i = a_i H + b_i \quad (1)$$

where i refers to airway generation number, a_i and b_i are fitted constants. Here, L_i , D_i and H are all expressed in cm and the constants are summarized in Table 2. These data are being used to study the impact of changing body size on inhaled particle deposition calculations.

The airway measurements and relationships to body height reported by PHALEN *et al.* are similar to those of the mathematical model derived by HOFMANN (1982). The latter model related airway dimensions to age; however, by using a typical relationship between age and height, it can be shown that the two studies generally agree within 30% in estimating the dimensions of the conducting airways.

RESPIRATORY TRACT CLEARANCE MODELS

If the airway path lengths for clearance of deposited material can be represented by a morphological model as described above, then it is possible to derive retention times in different parts of the respiratory tract in terms of mechanical transport velocities and rates of absorption into body fluids. Mechanical transport has been described in terms of a mucociliary escalator that predicts clearance of material in the conducting airways in a manner that is consistent with observed mucus transport rates and the overall time

TABLE 1. TYPICAL PATH LUNG MODEL: HUMAN—WHOLE LUNG AT TOTAL LUNG CAPACITY (REPRODUCED FROM YEH AND SCHUM, 1980)

n	Number of tubes	L (cm)	d (cm)	θ (°)	ϕ (°)	S (cm ²)	V (cm ³)	ΣV (cm ³)
1	1	10.0	2.01	0	0	3.17	31.73	31.73
2	2	4.35	1.56	33	20	3.82	16.67	48.40
3	4	1.78	1.13	34	31	4.01	7.14	55.54
4	8	0.965	0.827	22	43	4.30	4.15	56.69
5	16	0.995	0.651	20	39	5.33	5.30	64.98
6	32	1.01	0.574	18	39	8.28	8.36	73.35
7	64	0.890	0.435	19	40	9.51	8.47	81.81
8	128	0.962	0.373	22	36	13.99	13.46	95.27
9	256	0.867	0.322	28	39	20.85	18.07	113.34
10	512	0.667	0.257	22	45	26.56	17.72	131.06
11	1,024	0.556	0.198	33	43	31.53	17.53	148.59
12	2,048	0.446	0.156	34	45	39.14	17.46	166.05
13	4,096	0.359	0.118	37	45	44.79	16.08	182.13
14	8,192	0.275	0.092	39	60	54.46	14.98	197.10
15	16,384	0.212	0.073	39	60	68.57	14.54	211.64
16 ^a	32,768	0.168	0.060	51	60	92.65	15.57	227.21
17	65,536	0.134	0.054	45	60	150.09	20.11	247.32
18	131,072	0.120	0.050	45	60	257.36	30.88	278.20
19	262,144	0.092	0.047	45	60	454.81	41.84	320.04
20	524,288	0.080	0.045	45	60	833.84	66.71	386.75
21	1,048,576	0.070	0.044	45	60	1,594.39	111.61	498.36
22	2,097,152	0.063	0.044	45	60	3,188.78	200.89	699.25
23	4,194,304	0.057	0.043	45	60	6,090.97	347.19	1,046.44
24	8,388,608	0.053	0.043	45	60	12,181.95	645.64	1,692.08
25 ^b	3×10^8	0.025	0.030	45	60	—	3,871.80	5,563.88

^a Terminal bronchioles.

^b Alveoli.

n = generation number; L = airway segment length; d = segment diameter; θ = branching angle; ϕ = gravity angle with 90° corresponding to a horizontal tube; S = cross-sectional area; V = volume; ΣV = cumulative volume.

TABLE 2. CONSTANTS FOR USE IN EQUATION 1 TO DESCRIBE MODEL AIRWAY DIMENSIONS FOR PEOPLE OF DIFFERENT HEIGHTS

n^a	Airway Length		Airway Diameter	
	a_n	b_n	a_n	b_n
1	0.0500	0.150	0.010	0.0690
2	0.018	0.679	0.0069	0.0886
3	0.0070	0.246	0.0046	0.0982
4	0.0053	0.124	0.0033	0.0937
5	0.0035	0.196	0.0017	0.0999
6	0.0033	0.113	0.0014	0.0711
7	0.0022	0.112	0.0012	0.0541
8	0.0013	0.133	0.0007	0.0496
9	0.0008	0.152	0.0004	0.0499
10	0.0009	0.130	0.0003	0.0488
11	0.0007	0.129	0.0002	0.0479
12	0.0006	0.127	0.0001	0.0461
13	0.0005	0.125	0.00009	0.0452
14	0.0004	0.123	0.00006	0.0440
15	0.0003	0.121	0.00004	0.0429
16	0.0002	0.120	0.00002	0.0419

^a Airway generation number reported by PHALEN *et al.* (1985) was changed to correspond with those in Table 1.

course of particle clearance in people (YEATES and ASPIN, 1978; FOSTER *et al.*, 1982). Because few measurements of mucus flow velocity are available and these only relate to the trachea and large bronchi, it is necessary to assume a pattern of mucus flow in all other airways. By assuming that mucus is uniformly thick and that flow velocity is inversely proportional to airway circumference, Yeates and Aspin predicted clearance rates in reasonable agreement with experimental observations. This type of model fulfils many of the above requirements for calculating dose to epithelial cells lining the conducting airways, and it can readily accommodate changes in body size and mucus flow rates as observed in smokers and people with respiratory disease. It can also be applied to nasal airways.

During the time that deposited material remains in the respiratory tract, a fraction becomes available for absorption into the blood circulation. The rate of absorption mainly depends upon the solubility of the material in biological fluids and its transport across membranes. The amount absorbed depends upon the rates of dissolution and absorption compared to the rate of mechanical transport in each region of the respiratory tract. Mechanical transport of particles is most rapid in the central conducting airways and slowest from the pulmonary region to the tracheobronchial region. Studies of the clearance of relatively insoluble radiolabeled particles from the pulmonary region in people indicate that the fraction cleared per day soon after inhalation is about 0.006, but this declines to 0.002 after 200 days (Fig. 1). However, these rates include slow absorption of the radioactive label into the blood circulation, so that mechanical clearance processes may only account for a fractional daily clearance rate of about 0.001 after 200 days (BAILEY *et al.*, 1985).

A model of pulmonary clearance based upon particle solubility was described by MERCER (1967). Although this model is directly applicable to predicting lung clearance for dosimetry modeling, few estimates of the required specific surface area

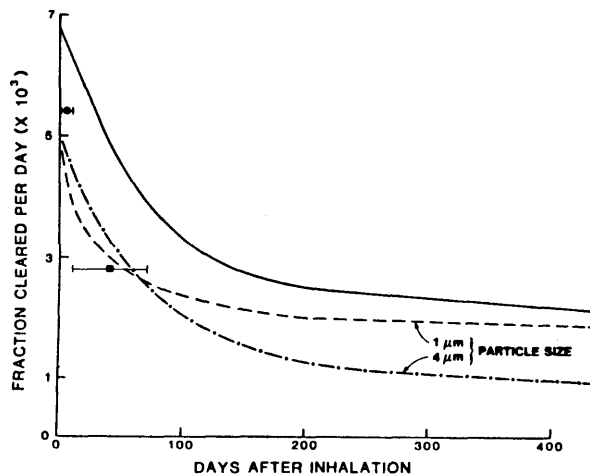


FIG. 1. Fraction of the radioactivity in the pulmonary region cleared per day. Information summarized from studies of inhaled relatively insoluble particles by BOHNING *et al.* (1982) solid line, BAILEY and FRY (1983) dashed lines, NEWTON *et al.* (1978) square, and STAHLHOFEN *et al.* (1981) circle.

dissolution rate constants are available for different radioactive materials. Also, it is not clear as to how these constants can be determined in a manner applicable to particles in lung. A further complication results from material that may dissolve in the lung, but still be retained for long periods of time. For these reasons, the NCRP task group is currently summarizing data from a variety of experimental inhalation studies to determine effective absorption rate functions for different types of inhaled materials. Most of the available studies were conducted in laboratory animals, so it must still be demonstrated that the resulting absorption rate functions apply reasonably well to human dosimetry models. Examples of this modeling approach are available for inhaled cerium (NCRP, 1978) and niobium (CUDDIHY, 1978).

REGIONAL DOSE CALCULATIONS

Dosimetry model calculations are being developed for the nasal epithelium, bronchial epithelium, pulmonary region and pulmonary lymph nodes. Doses to the nasal and bronchial epithelium are likely to be expressed in two ways; (a) local dose as a function of tissue depth and (b) average dose to a given tissue depth, both for a unit amount of radioactivity passing through the airway (Fig. 2).

This approach is being pursued because the task group cannot conclude that more weight should be given to radiation exposures of the basal cells of the epithelium than to exposures of other nonciliated cells lining the airways. Further studies are needed to relate observed radiation induced biological effects in these airways to the most appropriate expression of dose.

Dose to the pulmonary region will continue to be expressed as an average dose to the total tissue mass. However, dose to pulmonary lymph nodes will be estimated separately. Pulmonary lymph nodes can accumulate high concentrations of radio-

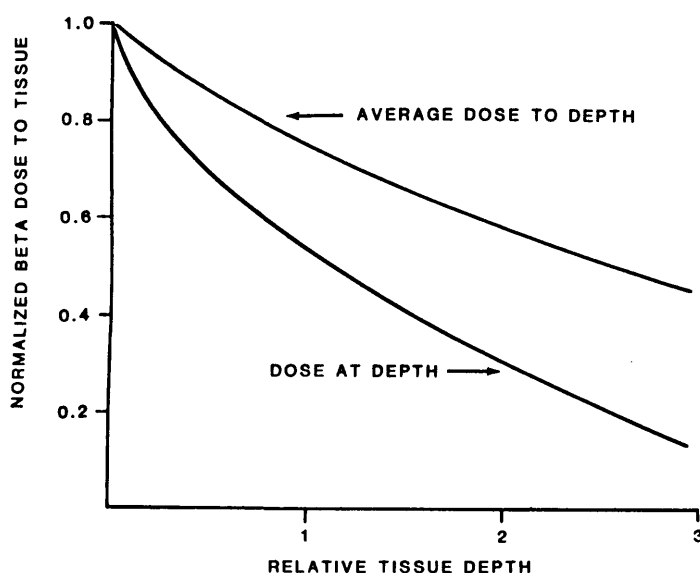


FIG. 2. Illustration of method of calculating beta dose to the bronchial epithelium from radioactivity passing through the airways lumen. The units of dose and tissue depth are arbitrary, but depend upon the energy of the radiation, the total amount of radioactivity being cleared and the mucus velocity. Doses at different tissue depths are normalized to unity at the surface of the epithelium.

activity and this has been observed to cause tissue destruction and tumors in studies with laboratory animals (HAHN and BOECKER, 1980).

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DISCUSSION

P.E. MORROW: I remember a conference on microdosimetry where radiation doses were calculated to nucleic acids. I get a little bit worried about the idea of targets when they get very small, because I don't believe we have the radiation biology to go with them. I commend the group for going after a dose to the tracheobronchial and nasopharyngeal regions and the lymphatics, but I am concerned about the progenitor cells and the differentiating cells as the targets at risk. Obviously it is the risk of cancer that you have in mind principally, but I do not know that we are sure that the environment of those cells when it's irradiated, is not also part of the picture. Is not your approach more of a refinement than we are ready for?

DR. CUDDIHY: The current ICRP respiratory tract dosimetry model provides sufficient information to calculate dose for the pulmonary region, but not for the tracheobronchial and nasopharyngeal regions. Thus, the NCRP Task Group is attempting to fill a void by providing dosimetry methods for all regions of the respiratory tract that appear to be of interest. In the future, epidemiologists and toxicologists should have a better opportunity to relate appropriate doses to the effects observed.

My discussion of cell kinetics in the respiratory tract was only meant to indicate that several types of cells in the bronchial epithelium are capable of cell division. Cells that can accumulate radiation damage over time and then divide may also give rise to respiratory tract cancers. The current dosimetry model for inhaled radon daughters estimates dose to the basal cells at a depth of 22 μm below the surface of the bronchial epithelium. In contrast, our NCRP Task Group favors a dose calculation that includes cells from the surface

of the epithelium down to the basement membrane. In terms of microdosimetry, this is less specific than the current model for dosimetry of inhaled radon daughters.

With respect to dosimetry for the different regions of the respiratory tract, the Task Group will likely provide for calculating doses to the nasal epithelium, the first four generations of bronchial airway epithelium, terminal bronchioles, the pulmonary region and lymph nodes. These are the sites at which radiation-induced cancers have been observed. However, we will not calculate doses to individual cell populations within these general regions.

P.E. MORROW: What about the endpoint of radiation fibrosis? What about injury to the vascular endothelium? When you consider all the possible short- and long-term effects of radiation in the lungs, there must be many types of cells at risk, so does not it follow that we need the dose to the lung tissues?

DR. CUDDIHY: Dose to the pulmonary region will be calculated as an average dose to the total tissue mass. This dose should apply to injuries that give rise to vascular damage and fibrosis as well as cancers.

A.S. PASCHOA: Can one safely assume that large retained particles ($\sim 10 \mu\text{m}$) are transported to other sites of the same region or even to different regions, or should one assume that they remain at one site?

DR. CUDDIHY: Inhaled large particles mainly deposit in the nasopharyngeal and tracheobronchial regions. These follow mucociliary clearance pathways rapidly, moving deposits toward the esophagus. Very few large particles deposit in the pulmonary region, but they are likely to slowly clear through mechanical means or by dissolution and systemic absorption. Fibers, such as asbestos, may also move within the pulmonary region and exhibit very long retention times.

D.C.F. MUIR: Does your deposition model take account of the inspirability of the ambient aerosol? As the particle size increases from about $1 \mu\text{m}$, the fraction of airborne particles entering the nose or the mouth falls off to about 50%. Basing calculations on the assumption that all particles are inhaled results in an overestimate of dose.

DR. CUDDIHY: The American Conference of Governmental Hygienists, Technical Committee on Air Sampling Procedures recently summarized available data on particle inspirability as a function of aerodynamic diameter. Data is available for particles up to $100 \mu\text{m}$ aerodynamic diameter, at which point the inspirable fraction is approximately 0.5. The NCRP Task Group is likely to rely upon this information and include the inspirable fraction in its inhalation dosimetry model calculations.

D.R. FISHER: In the model that you described of YEH and SCHUM, What is the mass of the lung and does it include the blood?

DR. CUDDIHY: YEH and SCHUM did not recommend a standard mass for their lung morphometry model, nor is the NCRP Task Group conducting an independent review of data on this parameter. Thus, we are likely to continue using 1000 g for the mass of the blood-filled lung as reported in ICRP Publication 23.

A.C. JAMES: In the YEH-SCHUM lung model, the cumulative volume to the end of generation 16, which is taken to be the volume of the conducting airways (dead space), is 227 ml, to which must be added the volume of the nasopharynx. This is much greater than the volume of 160 ml recommended by ICRP in Publication 23, and the volume of the dead space has a significant effect on tracheobronchial deposition calculated using theoretical models. I think the YEH-SCHUM model actually relates to an 80 kg man and therefore needs some scaling to Reference Man, but this would not bring the dead space down to anything like the volume recommended in ICRP 23. Has the NCRP Task Group considered that the YEH-SCHUM model should be scaled for 'Reference Adult Man', and if so, How?

DR. CUDDIHY: The NCRP Task Group is planning to use airway dimensions as reported by YEH and SCHUM (1980) and a method of scaling for different body sizes as recommended by PHALEN *et al.* (1985). This results in differences between some of our model parameters and those for ICRP Standard Man. However, we have not resolved these differences to date.

J.N. PRITCHARD: For hygroscopic aerosols, I think that particle growth in the lung causes deposition in the TB region to occur during exhalation rather than during inhalation. This results in local deposition patterns markedly different from those of non-hygroscopic aerosols, and I feel that account should be taken of this in dosimetry models.

DR. CUDDIHY: It will be difficult to provide an adequate treatment for describing the deposition of hygroscopic particles based upon the experimental measurements currently available. A general model treatment of hygroscopic particles would also require additional parameters to be furnished by the NCRP Task Group and by people using the model for dosimetry calculations. This has not been resolved to date, but it is not likely that we will be able to provide a satisfactory general particle deposition model to satisfy your concerns.