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Human Respiratory Tract Model for Radiological Protection



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PREFACE

A Task Group was appointed by Committee 2 to review the dosimetric model of the respiratory tract used in Publication 30, *Annual Limits on Intake for Workers*, and recommend revisions that incorporate knowledge resulting from research conducted since the development of the model in the early 1960s. The members of the Task Group were:

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During the period of preparation of this report, the membership of Committee 2 was:

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GLOSSARY

Morphology and Cytology

AI—Alveolar-Interstitial Region: Consists of the respiratory bronchioles, alveolar ducts and sacs with their alveoli, and the interstitial connective tissue; airway generations 16 and beyond.

ET—Extrathoracic Region: Consists of anterior nose (ET_1) and the posterior nasal passages, larynx, pharynx, and mouth (ET_2).

BB—Bronchial Region: Consists of the trachea and bronchi from which deposited material is cleared by ciliary action; airway generations 0 through 8.

bb—Bronchiolar Region: Consists of the bronchioles and terminal bronchioles; airway generations 9 through 15.

TH—Thoracic Region: Combined bronchial, bronchiolar, and alveolar-interstitial regions.

TB—Tracheobronchiolar: Combined regions consisting of airway generations 0 through 15.

LN_{ET}: Lymphatics and lymph nodes that drain the extrathoracic region.

LN_{TH}: Lymphatics and lymph nodes that drain the thoracic region.

BB_{bas}: Tissue in bronchial region through which basal cell nuclei are distributed.

BB_{sec}: Tissue in bronchial region through which secretory cell nuclei are distributed.

ET_{seq}: Compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages.

BB_{seq}: Compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region.

bb_{seq}: Compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region.

Basal Cells: Low cuboidal epithelial cells attached to the basement membrane of extrathoracic and bronchial epithelium and not extending to the surface.

Secretory Cells: Nonciliated epithelial cells that have mucous (mucous cells) or serous (Clara cells) secretions.

Clara Cells: Nonciliated columnar epithelial cells in bronchioles that have serous secretions.

Ciliated Cells: Respiratory epithelial cells with cilia protruding from their apical surface.

Goblet Cells: Columnar epithelial cells in extrathoracic and bronchial airways with cytoplasm distended with stored mucus.

Mucous Cells: Columnar epithelial cell of extrathoracic and bronchial airways with mucous secretory granules in cytoplasm.

Alveolar Epithelial Cells (Type I): Flattened epithelial cells lining alveolar surface through which gaseous exchange normally occurs.

Alveolar Epithelial Cells (Type II): Cuboidal epithelial cells that are precursors to alveolar Type I cells.

Lamina Propria: A layer of reticular and collagenous connective tissue and elastic fibres, containing lymphoid cells and macrophages, and delimited from the epithelium by the basement membrane.

Alveolar Macrophages: Unattached phagocytic cells found in nearly all alveoli.

Physiological Parameters

V_T : Tidal volume (in L) of exposed subject

F_n : Fraction of total ventilatory airflow passing through the nose

f_R : Respiration frequency (min^{-1})

B : Ventilation rate ($\text{m}^3 \text{h}^{-1}$)

FRC: Functional residual capacity (in L) of the exposed subject

TLC: Total lung capacity (L)

$\dot{V}$: Volumetric flow rate (in mL s^{-1}) of inspired air

$\dot{V}_n$: Component of the total volumetric flow rate (in mL s^{-1}) that is inspired through the nose

$\dot{V}_m$: Component of the total volumetric flow rate (in mL s^{-1}) that is inspired through the mouth

$V_D(\text{BB})$: Anatomical dead space (in L) of the trachea and bronchi

t_B : Time constant (in S) for conduction of air through the trachea and bronchi
 $= V_D(\text{BB})(1 + 0.5 V_T/\text{FRC})/\dot{V}$

$V_D(\text{bb})$: Anatomical dead space of the bronchioles (L)

t_b : Time constant (in S) for conduction of air through the bronchioles
 $= V_D(\text{bb})(1 + 0.5 V_T/\text{FRC})/\dot{V}$

t_A : Time constant (in S) for residence of air in the alveolar-interstitial airways
 $= \{V_T - V_D(\text{ET}) - [V_D(\text{BB}) + V_D(\text{bb})](1 + V_T/\text{FRC})\}/\dot{V}$

Deposition

Deposition: Refers to the initial processes determining how much of the material in the inspired air remains behind after expiration. Deposition of material may occur during both inspiration and expiration.

Exposure Parameters

C_A : Concentration of activity in ambient air (Bq m^{-3}).

t : Duration of exposure (h).

B : Ventilation rate of the exposed subject ($\text{m}^3 \text{h}^{-1}$).

I_0 : Activity of particles present in the volume of ambient air to be inspired $= C_A t B$.

Inhalability and Regional Deposition

η_i : Inhalability of particles, fraction of particles that enters the nose or mouth of those present in the volume of ambient air that is inspired.

η_i : Deposition efficiency of region, i , of the respiratory tract.

De_i : Deposition in region, i , expressed as a fraction of the number or activity of particles of a given size that are present in a volume of ambient air before inspiration.

Aerosol Parameters

d_{ae} : Aerodynamic particle diameter (μm). Diameter of unit density sphere that has same terminal settling velocity in air as the particle of interest.

d_{th} : Thermodynamic particle diameter (μm). Diameter of a spherical particle that has the same diffusion coefficient in air as the particle of interest.

d_v : Equivalent volume diameter (μm). Diameter of a sphere that has the same volume as the particle of interest.

D : Particle diffusion coefficient ($\text{cm}^2 \text{s}^{-1}$). Related to the mean square displacement of a particle by Brownian motion per unit time.

AMAD: Activity Median Aerodynamic Diameter. Fifty percent of the activity (aerodynamically classified) of aerodynamic diameter (d_{ae}) greater than the AMAD. A log normal distribution of particle sizes is usually assumed.

AMTD: Activity Median Thermodynamic Diameter. Fifty percent of the activity (thermodynamically classified) in the aerosol is associated with particles of thermodynamic diameter (d_{th}) greater than the AMTD. A log-normal distribution of particle sizes is usually assumed.

Scaling Parameters for Different Subjects

SF_t: The ratio of the diameter of the trachea (airway generation 0) in the reference adult male to that in the subject = $1.65/d_0(\text{subject})$

SF₉: The ratio of the diameter of the first bronchiolar airways (generation 9) in the reference adult male to that in the subject = $0.165/d_9(\text{subject})$

SF₁₆: The ratio of the diameter of first respiratory bronchiole (generation 16) in the reference adult male to that in the subject = $0.051/d_{16}(\text{subject})$

Clearance

Clearance: The removal of material from the respiratory tract by particle transport and by absorption into blood.

Translocation: The transfer of material absorbed from the respiratory tract to other tissues in the body.

Particle Transport: Processes that clear material from the respiratory tract to the GI tract and to the lymph nodes, and move material from one part of the respiratory tract to another.

Absorption: Movement of material to blood regardless of mechanism. Generally applies to dissociation of particles and the uptake into blood of soluble substances and material dissociated from particles. Includes movement of ultrafine particulate material, e.g. nanometer-size particles.

$s_i(t)$: Fractional rate of absorption of material into blood from region i at time t after an acute intake.

$g_i(t)$: Fractional rate of particle transport of material to GI tract from region i at time t after an acute intake.

$l_i(t)$: Fractional rate of particle transport of material towards regional lymph nodes from region i at time t after an acute intake.

$x_{ET}(t)$: Fractional rate of extrinsic clearance of material from the ET region at time t after an acute intake.

$\lambda_i(t)$: Overall instantaneous rate of clearance of material from region i at time t after an acute intake.

Φ_m : Modifying Factor. Amount by which a parameter should be multiplied in order to calculate doses for a specific individual or group for which the modifying factor is recommended. Transient factors apply only during exposure to the factor and are relevant only to acute intakes. Permanent factors are relevant to chronic intake.

Type F materials: Deposited materials that are readily absorbed into blood from the respiratory tract. (Fast solubilization.)

Type M materials: Deposited materials that have intermediate rates of absorption into blood from the respiratory tract. (Moderate rate of solubilization.)

Type S materials: Deposited materials that are relatively insoluble in the respiratory tract. (Slow solubilization.)

Gases and Vapours

Class SR-0: Insoluble and nonreactive.

Class SR-1: Soluble or reactive.

Class SR-2: Soluble and reactive.

Dosimetry

AF—Absorbed Fraction ($AF(T \leftarrow S)_R$): The fraction of energy emitted as a specified radiation R in a specified source tissue S which is absorbed in a specified target tissue T.

Bq—Becquerel: The name for the SI unit of radioactivity, $1 \text{ Bq} = 1 \text{ transformation s}^{-1}$.

H_T —Equivalent Dose: The absorbed dose averaged over a tissue or organ and weighted for the radiation quality that is of interest.

$H_T(\tau)$ —Committed Equivalent Dose: The time integral of the equivalent dose rate in a particular tissue that will be received by an individual following an intake of radioactive material into the body. The integration time is 50 y for adults, and from intake to 70 y of age for children.

E—Effective Dose: The sum of the equivalent doses, weighted by the appropriate tissue weighting factors, in all the tissues and organs of the body.

$E(\tau)$ —Committed Effective Dose: The time integral of the effective dose rate (defined similarly as the Committed Equivalent Dose).

w_R —Radiation Weighting Factor: Factor related to the quality of the radiation used to weight the absorbed dose.

w_T —Tissue Weighting Factor: Factor by which the equivalent dose in tissue or organ is weighted to represent the relative contribution of that tissue or organ to the total detriment due to stochastic effects resulting from uniform irradiation of the whole body.

A: Weighting factors assigned for partitioning of tissue weighting factors (w_T for lungs and for extrathoracic tissues) among all respiratory tract tissues.

Gy—Gray: The name for the SI unit of absorbed dose. $1 \text{ Gy} = 1 \text{ J kg}^{-1}$.

Sv—Sievert: The name for the SI unit of equivalent dose. $1 \text{ Sv} = 1 \text{ J kg}^{-1}$.

S—Source Tissue: Tissue or organ that contains a significant amount of a radionuclide following intake of that radionuclide or its parent into the body.

SEE—Specific Effective Energy ($SEE(T \leftarrow S)_R$): The energy (MeV), suitably modified for radiation quality, imparted per gram of a target tissue (T) as a consequence of the emission of a specified radiation (R) from a transformation occurring in source tissue (S).

T—Target Tissue: Tissue or organ in which radiation is absorbed.

ALI—Annual Limit on Intake: The annual limit on intake of any radionuclide is that intake that will result in a committed effective dose equal to the annual limit on effective dose. The ALI for any radionuclide is obtained by dividing the annual effective dose limit by the committed effective dose resulting from the intake of 1 Bq of that radionuclide.

1. INTRODUCTION

1.1. The Purpose of this Report

(1) This report describes a revision of the model used in *ICRP Publication 30* (ICRP, 1979) to calculate radiation doses to the respiratory tract of workers resulting from the intake of airborne radionuclides. This revision was motivated by the availability of increased knowledge of the anatomy and physiology of the respiratory tract and of the deposition, clearance, and biological effects of inhaled radioactive particles, and by greatly expanded dosimetry requirements. To meet fully the needs of radiation protection, a dosimetric model for the respiratory tract should:

- provide calculations of doses for individual members of the populations of all ethnic groups, in addition to workers;
- be useful for predictive and assessment purposes as well as for deriving limits on intakes;
- account for the influence of smoking, air pollutants, and respiratory tract diseases;
- provide for estimates of respiratory tract tissue doses from bioassay data; and
- be equally applicable to radioactive gases as well as to particles.

(2) In addition, large differences in radiation sensitivity among the respiratory tract tissues and the doses they receive from inhaled radionuclides argue for calculating radiation doses to specific tissues of the respiratory tract. (The current model leads to calculation of doses averaged over the total mass of blood-filled lungs.) To use these tissue doses effectively for radiation protection purposes, they must be compatible with the ICRP dosimetric system (ICRP, 1991a).

(3) Addressing all of these requirements has resulted in a dosimetry model that is more complex than previous models. This complexity is reflected in the structure of this report, which includes chapters on respiratory tract morphometry, physiology, and radiation biology or health detriment. Other chapters deal with the deposition and clearance of inhaled radioactive particles, inhalation of radioactive gases, and application of the model to estimate respiratory tract doses. The model provides most of the flexibility needed to calculate doses to the respiratory tract for a wide range of exposure conditions and for specific individuals. This flexibility also allows for revision of reference parameter values as new information becomes available without changing the model. The wide availability of personal computers allows for the easy use of the model.

1.2. The Need for a Dosimetric Model for the Respiratory Tract

(4) The respiratory tract is an important route for radionuclides and other hazardous airborne materials to enter the body, particularly for workers. However, it can also be true for the general population, especially in the case of environmental radon and the routine or accidental release of radionuclides from industrial and medical operations. Inhaled radionuclides irradiate tissues and cells of the respiratory tract as well as those of many other organs.

(5) However, whether airborne radionuclides are inhaled and enter the respiratory tract of people breathing contaminated air is determined by numerous physical, chemical, and biological factors. If the radionuclide is in a particulate form, the size,

density, and hygroscopicity will determine the extent to which the material is inhalable, i.e. can be entrained in air inspired through the nose or mouth, and either deposited in the respiratory tract or exhaled. Physical as well as chemical properties will also determine the penetration of inhaled radionuclides, the sites of deposition, the retention times or rates of clearance, and rates of absorption into blood and translocation to other tissues. Other important determinants are physiological factors, including breathing characteristics at the time of intake (e.g. respiratory rate and volume, breathing through the nose or mouth) and whether respiratory tissues are normal or altered as a result of disease, smoking, or exposure to other occupational and environmental toxicants. All of these factors, as well as the radiological properties of the inhaled material, will determine the radiation dose and, in conjunction with the sensitivity of the irradiated tissues, the health risks associated with a given intake.

(6) With the health risks of an exposure to airborne radionuclides being determined by so many variables, it would be rare for two individuals exposed under the same conditions to experience the same radiation doses and the same health consequences. Therefore, to protect workers and the general population against health effects resulting from exposures to airborne radionuclides and to project the risks to exposed or potentially exposed populations, it is necessary to devise and assign values to a set of parameters that can approximate the conditions and characteristics of the most common exposures encountered by reference populations. This was recognized during early attempts to derive limits for radionuclide exposures, thus beginning the development of dosimetric modelling of the respiratory tract for radiation protection purposes.

1.3. Model Used in ICRP Publication 2

(7) The Tripartite Conferences on Radiation Protection held from 1949 to 1953 (Taylor, 1984) addressed the need for standardized values for various parameters describing the inhalation, deposition, retention, and translocation of airborne radionuclides in workers for the purpose of deriving exposure limits. At the conference held at Chalk River, Canada, September 29-30, 1949, many aspects of particle deposition and retention were considered, and the lack of definitive information was noted. It was formally agreed, for purposes of calculating radiation doses when specific data were not available, that 50% of any inhaled aerosol reaches the lung alveoli, and that soluble particles would be totally absorbed. If the aerosol particles were insoluble, half would be retained for only 24 h and the remaining half, 25% of the inhaled amount, would be retained *in situ* indefinitely. Particles larger than 10 μm would be cleared rapidly by ciliary action. The transport of insoluble particles from lungs to lymph nodes was also recognized but not addressed quantitatively. At this and subsequent meetings, discussion of limited data from human exposures to uranium and results from animal experiments identified numerous parameters (e.g. particle size, shape, and surface area, as well as nose and mouth breathing) that could be expected to influence deposition and retention of inhaled aerosol particles.

(8) At the Arden House Conference in Harriman, New York, from the 30th of March to the 1st of April, 1953, K. Z. Morgan reported that his Subcommittee on Internal Radiation had assumed that 50% of an inhaled aerosol would be deposited in the upper respiratory tract, 25% would be exhaled, and 25% would be retained in the lungs (Taylor, 1984). These were the current ICRP values. For soluble particles, it was assumed that the 25% retained in the lungs would be absorbed and translocated to

other tissues in the body. However, for insoluble particles, 12.5% would be cleared in 24 h, and the remaining 12.5% would be retained. At the recommendation of K. Z. Morgan and Merrill Eisenbud, these values were revised to 15% being eliminated in 24 h and 10% remaining in the lung indefinitely. However, this revision was not incorporated in *ICRP Publication 2*, the 1959 report of ICRP Committee 2 on permissible dose for internal radiation (ICRP, 1960), which Dr Morgan chaired. Rather, in *ICRP Publication 2* (ICRP, 1960), it was assumed that 12.5% would be retained in the lungs, with a half-time of 120 days.

(9) This simple model of deposition, retention, and clearance of inhaled aerosols was the basis for the limits for exposure to radionuclides in *ICRP Publication 2*, and for calculations of doses to exposed individuals for both assessment and predictive purposes.

1.4. Model Used in *ICRP Publication 30*

(10) In 1964 an ICRP Task Group on Lung Dynamics, chaired by Dr Paul Morrow,¹ was appointed by ICRP Committee 2 to review the model used in Publication 2 (ICRP, 1960). In 1966 a revised lung model was published (TGLD, 1966). Although frequently used for assessment and predictive purposes, this greatly improved scheme for estimating dust deposition in and clearance from the respiratory tract was not used as a basis for lung dosimetry for calculating limits for the intake of radionuclides until Publication 30 (ICRP, 1979) was prepared. The dosimetric model used for the respiratory system was a slightly modified version of the model originally developed and published in 1966.

(11) Major innovations were introduced by this Task Group. One was a deposition model that was based on dust-sampling data and also provided for the use of such data in predicting deposition. Deposition was described for three anatomical compartments, which had both physiological and radiobiological implications. The model made it possible to consider particle sizes of inspired aerosols as well as respiratory rates with respect to fractions deposited in each of the regions: nasopharyngeal, tracheobronchial, and pulmonary.

(12) Another feature was a quantitative kinetic clearance model that accounted for removal of material deposited in each of the three regions. Perhaps of greatest impact was the classification of chemical compounds according to estimates of their expected tendency to be retained in the respiratory tract, i.e. their solubility in lung fluids. This is the D, W, Y classification; Class D is assigned to highly soluble compounds expected to be cleared from the respiratory tract with half-times less than 1 day; Class W is for less-soluble compounds, with clearance half-times of a few days to months; Class Y is for the more insoluble compounds that are expected to be retained in the respiratory tract with half-times of 6 months to years. This model also described the transfer of inhaled particles to the thoracic lymph nodes. It should be noted that the clearance rates assigned to the three classes of compounds accounted for clearance by particle transport as well as by absorption into blood.

(13) The 1966 report of the Task Group on Lung Dynamics was a major scientific accomplishment in that it used and expanded upon the total relevant technical data

¹ Other members of the Task Group were: David V. Bates, Birney R. Fish, Theodore F. Hatch and Thomas T. Mercer.

available. The deposition and retention model developed by the Task Group provided a sound scientific basis for ICRP Committee 2 to calculate radiation doses from inhaled radionuclides, leading to recommendations for annual limits on intake and derived air concentrations that appeared in *ICRP Publication 30* (ICRP, 1979). The Task Group's model went further than Committee 2 was prepared to go in some areas, such as the transfer of radionuclides to thoracic lymph nodes. (Committee 2 elected to combine the radionuclide contents of lymph nodes with the content of the lungs to calculate a dose to a composite of both tissues [mass of 1000 g].) However, the model failed to address other areas, such as the nasal passages. Nevertheless, the omissions were insignificant compared with the magnitude of the advances in dosimetry of inhaled radioactive particles made possible by the Task Group's report. It should be emphasized that the doses calculated using this model were, like those calculated using the earlier models, for the mass of the total blood-filled lungs.

1.5. Why a New Model?

(14) The publication of the ICRP Task Group's report in 1966 (TGLD, 1966) and of *ICRP Publication 30* in 1979 stimulated extensive research on the deposition, retention, clearance, and translocation to other tissues in the body of inhaled aerosols in experimental animals and in humans. It also led to the publication of numerous reports comparing experimental results with predictions based on the ICRP lung model. Not surprisingly, the model was found wanting in many cases. The most frequent criticism was directed at the D, W, Y clearance classification system because many radioactive compounds tested in experimental animals or studied in human exposures were found to clear from the respiratory tract at rates substantially different from the assigned rates. In particular, highly insoluble compounds, such as plutonium oxide, were cleared from the lungs much more slowly than the assigned rate for Class Y compounds. Other radioactive materials did not appear to fit any of the classifications. Mixtures of radioactive compounds, which are often encountered in accidental exposures, were not addressed by the 1966 model, nor by *ICRP Publication 30*. Research on deposition of inhaled aerosols has extended the particle size range beyond that of the 1966 model. This has been especially relevant to the inhalation of submicrometer-sized radon decay products. Further, in recent years interest of the radiation protection community has focused on exposure of the public to radionuclides in the environment. Since the model used in *ICRP Publication 30* was developed specifically for occupational exposures of reference Caucasian males, it lacks the flexibility to be applied with confidence to other members of the world's population.

(15) Research since the publication of the 1966 model has raised many radiobiological issues with respect to modelling the intake and dosimetry of inhaled radionuclides. As noted before, in both the 1966 model and in *ICRP Publication 30*, the calculated dose was averaged for the total mass of the blood-filled lungs to give a mean lung dose. In *ICRP Publication 30* the contents of the thoracic lymph nodes were included with those of the lungs. However, the radiation dose to the respiratory tract from inhaled radionuclides is rarely uniform. In human studies of inhaled radon, the radiation dose is estimated to be highest in the bronchial epithelium, and that is where the cancers in miners exposed to radon appear to originate. Results from animal experiments are in general agreement insofar as cancers appear where radiation dose and sensitivity are high. For example, in life-span animal studies of inhaled insoluble

forms of long-lived radionuclides such as plutonium and several fission products, the lung parenchyma receives greater radiation doses than the bronchial epithelium and is also the site of origin of resulting lung cancers. (There are no data from human exposures that contradict this finding.) However, much higher doses can be received by lymphatic tissues, but with very low risk of cancer. In several animal experiments with inhaled radionuclides, including chronic exposures to radon, cancers occurred in the nasal passages. These kinds of observations have raised questions about the validity of averaging the dose over the total mass of the lungs to calculate effective dose from the intake of radionuclides, or for assessing and predicting biological effects such as cancer from exposures to airborne radioactive particles and gases. This was recognized by the ICRP in *ICRP Publication 32* (1981), which compared epidemiologic and dosimetric approaches to deriving lung cancer risk rates. In the dosimetric approach, separate doses were calculated for the bronchial basal tissue layer and for the pulmonary region; half the lung weighting factor for stochastic risks was applied to each. This Regional Lung Dose concept was in contrast to the Mean Lung Dose concept of *ICRP Publication 30*.

(16) The "hot particle" issue in the 1970s addressed the practice of averaging the dose over the total lung mass. This issue was based on the premise that high dose rates to cells adjacent to radioactive particles deposited in the lungs led to much greater cancer risks than were represented by averaging the dose over the total lung tissue. Even though experimental animal studies have consistently refuted this premise, the "hot particle" issue drew attention to the need for refining lung dosimetry for inhaled radioactive materials.

1.6. Principal Features of the New Model

(17) Although the dosimetric model of the respiratory tract used in *ICRP Publication 30* had not been shown to be deficient for the purpose of calculating the annual limits on intake (ALI) for workers, the availability of new information to address some of the model's limitations led the ICRP in 1984 to create, for the second time, a special Task Group to review the dosimetric model of the respiratory tract and propose revisions or a new model. The members of the Task Group were selected to assure that the broad spectrum of biological, physiological, chemical, and radiological aspects of inhaled radioactive aerosols could be competently addressed. In addition, numerous corresponding members were invited to provide technical assistance and to review drafts of the Task Group's report.

(18) The new Task Group directed its efforts towards improving the model used in *ICRP Publication 30* rather than developing a completely new model. The objective was a model that would (1) facilitate calculation of biologically meaningful doses; (2) be consistent with morphological, physiological, and radiobiological characteristics of the respiratory tract; (3) incorporate current knowledge; (4) meet all radiation protection needs; (5) be no more sophisticated than necessary to meet dosimetric objectives; (6) be adaptable to development of computer software for the calculation of relevant radiation doses from knowledge of a few readily measured exposure parameters; (7) be equally useful for assessment purposes as for calculating recommended values for limits on intake, e.g. ALIs; (8) be applicable to all members of the world's population, including specific individuals; (9) allow use of information on the deposition and clearance of specific materials; and (10) consider the influence of smoking, air pollutants, and

diseases on the inhalation, deposition, and clearance of radioactive particles from the respiratory tract. These objectives have been largely met within the constraints of the available data.

(19) Results of research since publication of the report of the Task Group on Lung Dynamics (TGLD, 1966) have made it possible to model the deposition in the respiratory tract with increased confidence, especially deposition of aerosol particles in the submicrometer range. The revised model also provides for the inhalability of airborne materials (ratio of the concentration in the air entering the respiratory tract to that in the ambient air), which is dependent upon particle size but largely independent of breathing rate. Rather than partitioning material between clearance pathways as in the model used in *ICRP Publication 30* (ICRP, 1979), it is assumed in the revised model that clearance is competitive between particle transport and absorption into the circulating blood, and that the rate of the clearance by each process is a time-varying factor of the residual amount. Reference values for particle transport processes are provided. Rates for absorption into blood are intended to be derived from observations of specific radionuclide compounds in humans and/or experimental animals. In the absence of such information, default values are recommended based on the classifications in the *ICRP Publication 30* system (ICRP, 1979).

(20) The dosimetric model described in this report takes into account the potential for inhaled radionuclides to irradiate tissues throughout the respiratory tract and the large differences in their radiation sensitivity. The model also recognizes that the doses received by these tissues and the dose rates can vary substantially, depending upon the physical properties of the inhaled material and the respiratory characteristics of the intake.

(21) The calculation of doses follows the methodology of *ICRP Publication 30*, in which the committed equivalent dose in a target tissue is determined by the energy absorbed per unit mass from the radiation emitted from a source organ. The ICRP continues (ICRP, 1991a) to recommend calculating average doses for tissues and organs exposed to radiation emitted by radionuclides deposited in the body as well as to radiation from external sources. For most tissues and organs, even when radionuclides are nonuniformly distributed and the cells are not all equally sensitive, the average organ or tissue dose is adequate for radiation protection purposes. However, as noted in Paragraphs 15 and 16 in the case of the respiratory tract, the numerous tissues and cells extending from the external nares of the nose to lymph nodes in the thorax (in which radioactive particles may reach high concentrations) vary greatly in radiation sensitivity. Compounding this is the potentially great disparity in quantities of radionuclides deposited and rates of retention in the many tissues within the respiratory tract which can lead to substantial differences in radiation doses and dose rates. Since calculated average lung doses may bear little relationship to the doses received by the more sensitive tissues of the respiratory tract or to health effects that may occur, the new model provides for calculating doses to specific respiratory tract tissues in regions of the nose and other extrathoracic airways, and to tissues within the thorax. This approach extends that taken for radon and its decay products in *ICRP Publication 32* (ICRP, 1981) in which separate doses were calculated for cells of the bronchial epithelium and for the pulmonary region.

(22) The model provides for using these calculated tissue doses in the ICRP dosimetry system. Since both the radiation doses and the sensitivities of all regions determine the total radiation detriment to the respiratory tract of a given radionuclide intake, equivalent doses calculated for each tissue are weighted for the relative

sensitivity of the tissue. These weighted doses are summed separately for the tissues in the extrathoracic region and for those in the thoracic region, yielding two values of detriment-weighted equivalent dose for the respiratory tract. With application of the appropriate ICRP tissue-weighting factors, w_T , these two values are used to calculate the effective dose (ICRP, 1991a) for the intake of a given radionuclide.

(23) The model can be adapted to calculate doses from bioassay data. It is also more flexible in its application than the model in *ICRP Publication 30* because it is equally suitable for calculating limits on intake and for calculating doses required for retrospective and predictive purposes. Finally, the model can be applied to the deposition and clearance of nonradioactive materials.

1.7. Model Development

(24) The overall dosimetric model for the respiratory tract consists of six elements: (1) morphometry, which describes the structure of the respiratory tract and the important dimensions required for dose calculations; (2) respiratory physiology, which is a critical element because rates and volumes of air inhaled and exhaled determine the amounts of radioactive particles and gases that can be deposited in the respiratory tract; (3) radiation biology, which investigates the biological effects of radiation on the respiratory tract, thus determining the tissues and cells at risk and defining the focus of the modelling effort; (4) deposition, which characterises the initial distribution of inhaled radioactive material within the different anatomical regions specific to the age and gender of the subject and various physiological parameters; (5) clearance, which evaluates the rates of removal of deposited materials by particle transport and absorption into blood and, thus, the retention times of activity within the different regions, and the fractions removed to the GI tract or to circulating blood and other tissues in the body; (6) dosimetry, which evaluates the energy absorbed per unit mass of target tissue as a result of radiation emitted from each potential source organ.

(25) To provide for the use of the calculated dose in the ICRP system, additional assumptions were made with respect to the relative radiation susceptibilities of the different regions of the respiratory tract. Committed equivalent doses for the extrathoracic and thoracic regions of the respiratory tract can then be calculated, either on the basis of information about exposures to airborne radionuclides or from bioassay data.

(26) Each of the steps outlined above required the definition of a number of parameters, which can be substituted within a computational model. The degree of belief that can be attributed to the final results of such calculations is of fundamental importance to the validity of the model in its ultimate application, whether as a means to calculating dose per unit intake to set limits on intake or for exposure assessment. Therefore, the reliability of the overall model can be defined as a measure of the confidence in its capacity for making accurate predictions.

(27) The model is described in Chapters 2 through 8, beginning with the morphometric model, important respiratory physiology parameters, consideration of the biological effects of inhaled radionuclides, deposition and clearance models, inhalation of radioactive gases and vapours, and concluding with methodology for calculating radiation doses to respiratory tract tissues. The scientific background for these chapters and the tabulation of values to be used with the model are to be found in Annexes A-H. Chapter 9 addresses the application of the model, contains recommended parameter

values for reference populations, and includes an example of a dose calculation with this respiratory tract model using information in the report. Chapter 10 is a summary description of the respiratory tract dosimetry model.

(28) Literature citations in the reference section at the end of this report are limited to those specific to the overall model development. The report refers to the Annexes for supporting information and documentation, including comprehensive literature citations.

2. MORPHOMETRIC MODEL

2.1. Introduction

(29) This chapter provides a brief description of the morphological characteristics of the respiratory tract, defines the morphometric model adopted for purposes of calculating radiation doses from inhaled radionuclides, and gives central values for parameters used in the dosimetric model. Annexe A summarizes information about the anatomy and morphology of the respiratory tract that forms the basis for this morphometric model; the Annexe also describes the variability within and among individuals. While much is known about the anatomy of the respiratory tract, information about the dimensions of its numerous gross and microscopic structures is limited. Since comprehensive morphological studies have been rare, the available information consists of measurements on a small number of samples from only a few representatives of the world's population. Thus the values assigned to parameters in this morphometric model represent best judgement interpretations and extrapolations of the available information. As further knowledge of the morphology of the respiratory tract is gained, the Commission may reassess the parameter values. Because of its flexibility, this respiratory tract dosimetry model can accommodate future revisions of parameter values recommended in this report.

(30) The characteristics of air drawn into the lungs and exhaled are greatly influenced by the morphology of the respiratory tract, which causes numerous changes in pressure, flow rate, direction, and humidity as air moves into and out of the lungs. These changing characteristics and the varying tissue surfaces encountered by inspired and expired air greatly influence the rates and sites of penetration and deposition of entrained particles. For this reason the morphology and the dimensions of the structures of the respiratory tract (morphometry) are essential elements in the formulation of models to be used in the calculation of radiation doses received as the result of inhaling air containing radionuclides.

(31) The dosimetric model considers the respiratory tract as four anatomical regions (Fig. 1): (1) the extrathoracic region (ET), comprising the anterior nose (ET₁) and the posterior nasal passages, larynx, pharynx, and mouth (ET₂); (2) the bronchial region (BB), consisting of the trachea and bronchi from which deposited material is cleared by ciliary action; (3) the bronchiolar region (bb), consisting of the bronchioles and terminal bronchioles; and (4) the alveolar-interstitial region (AI), consisting of the respiratory bronchioles (bronchioles with some alveoli apposed), the alveolar ducts and sacs with their alveoli, and the interstitial connective tissue. All four regions contain lymphatic tissue (LT) or components of it. Fluid accumulated in the interstitial connective tissue is collected in lymph capillaries, from which it flows unidirectionally into lymph vessels,

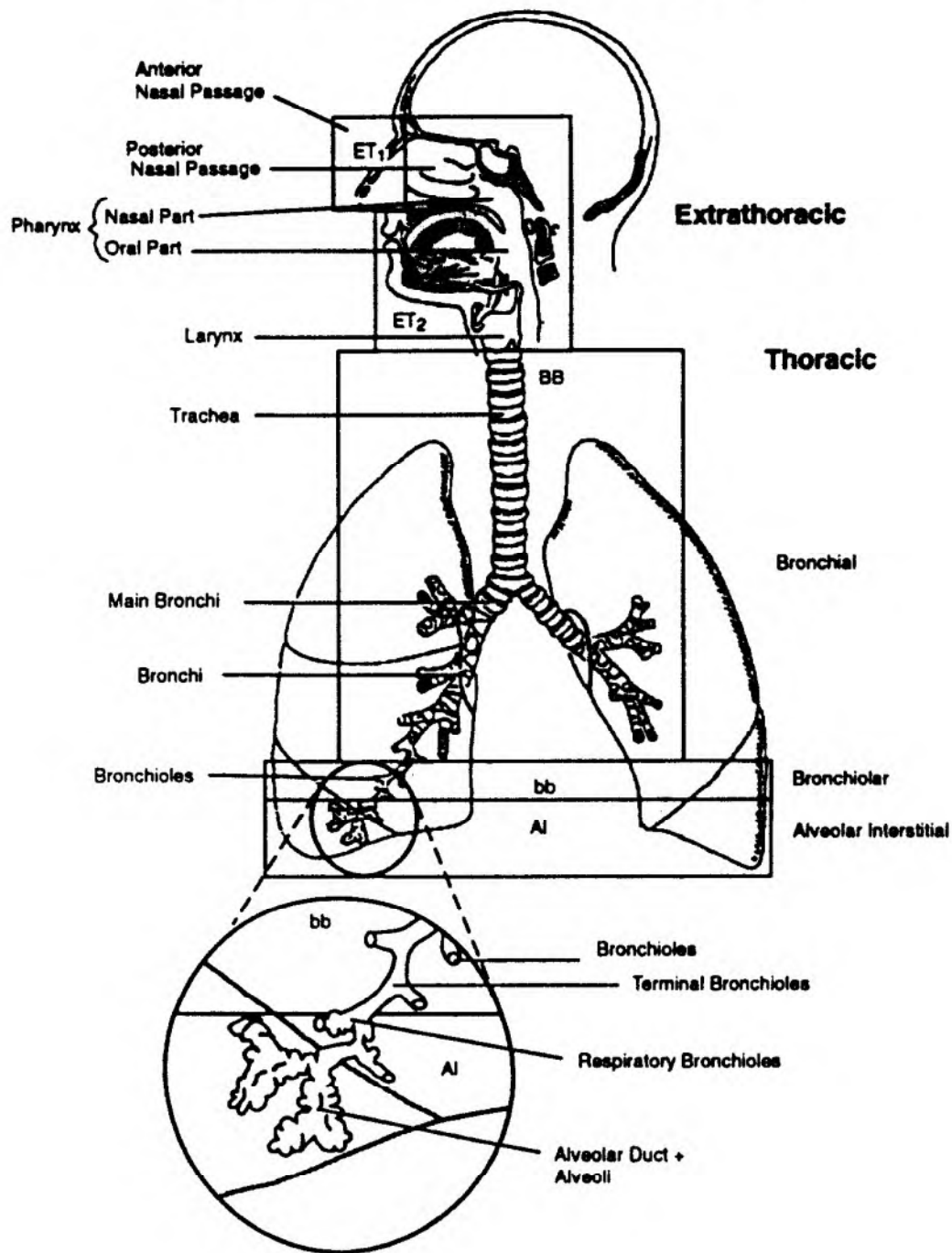
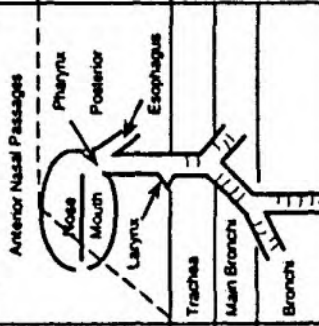
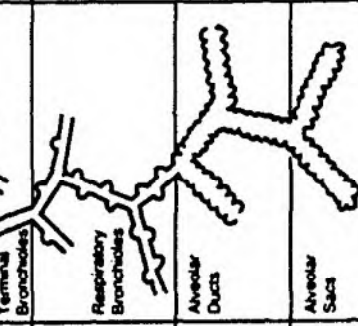


Fig. 1. Anatomical regions of respiratory tract.

and passes through one to several lymph nodes: LN_{ET} drain the extrathoracic region (ET), and LN_{TH} , which are morphologically located in the bronchial region (BB), drain this region as well as the bronchiolar (bb) and alveolar-interstitial (AI) regions. The cytology, histology, function, and structure of these regions which compose the mathematical model used in calculating radiation doses are further described in Table 1.

(32) A simplified geometrical model to represent the orientations of radionuclide sources and target tissue in airways within the ET, BB, and bb regions is the basis for later dosimetric calculations. (See Chapter 8.) In each case, a typical airway is represented by a cylindrical tube of appropriate internal calibre and wall thickness

Table 1. Morphology, cytology, histology, function, and structure of the respiratory tract and regions used in the dosimetry model

Functions	Cytology (Epithelium)	Histology (Walls)	Generation Number	Anatomy	Regions used in Model		Zones (Air)	Location	Airway Surface ^a	Number of Airways					
					New	Old #									
Air Conditioning; Temperature and Humidity, and Cleaning; Fast Particle Clearance; Air Conduction	Respiratory Epithelium with Goblet Cells: Cell Types: -Ciliated Cells -Nonciliated Cells: • Goblet Cells • Mucous (Secretory) Cells • Serous Cells • Brush Cells • Endocrine Cells • Basal Cells • Intermediate Cells	Mucous Membrane, Respiratory Epithelium (Pseudostratified, Ciliated, Mucous), Glands Mucous Membrane, Respiratory or Stratified Epithelium, Glands Mucous Membrane, Respiratory Epithelium, Cartilage Rings, Glands Mucous Membrane, Respiratory Epithelium, Cartilage plates, Smooth Muscle Layer, Glands Mucous Membrane, Respiratory Epithelium, No Cartilage, No Glands, Smooth Muscle Layer Mucous Membrane, Single-Layer Respiratory Epithelium, Less Ciliated, Smooth Muscle Layer Mucous Membrane, Single-Layer Respiratory Epithelium of Cuboidal Cells, Smooth Muscle Layers	0 1 2-8 9-14 15 16-18		ET ₁		Conditioning	Extrapulmonary	2 x 10 ⁻³ m ²	—					
					ET ₂	(N-P)			4.5 x 10 ⁻² m ²	—					
					Air Conduction; Gas Exchange; Slow Particle Clearance	Respiratory Epithelium with Clara Cells (No Goblet Cells) Cell Types: - Ciliated Cells - Nonciliated Cells • Clara (Secretory) Cells				BB		Conduction	Thoracic	2.9 x 10 ⁻² m ² (a)	511 (a)
										bb	(T-B)			2.4 x 10 ⁻¹ m ² (a)	6.5 x 10 ⁴ (a)
Gas Exchange; Very Slow Particle Clearance	Squamous Alveolar Epithelial Cells (Type I), Covering 80% of Alveolar Surface Areas Cuboidal Alveolar Epithelial Cells (Type II, Surfactant-Producing), Covering 7% of Alveolar Surface Area Alveolar Macrophages	Wall Consists of Alveolar Entrance Rings, Squamous Epithelial Layer, Surfactant Interalveolar Septa Covered by Squamous Epithelium, Containing Capillaries, Surfactant	(c) (c)		LN _{TH}	P	Gas-Exchange Transitional	Pulmonary	7.5 m ²	4.6 x 10 ⁶ (a)					
					AI				140 m ²	4.5 x 10 ⁷ (b)					

(a) See Table 2.

(a) See Table 2.

(b) See Table 3.

(c) Unnumbered because of imprecise information.

(d) Previous ICRP Model.

(e) As described in the text, lymph nodes are located only in BB region but drain the bronchiolar and alveolar-interstitial regions as well as the bronchial region.

(Fig. 2). Since information on cytological dimensions in human lungs is very limited, the average values for nuclear cell depths given in this chapter represent best judgment interpretation and extrapolation of data published by Mercer *et al.* (1991a) and Bowden and Baldwin (1989). Work of others, such as Robbins *et al.* (1990), was also considered. It is recognized that there are large variations in the dimensions within defined regions. In each type of airway, the target tissue is assumed to be distributed over a characteristic range of depths below the epithelial surface.

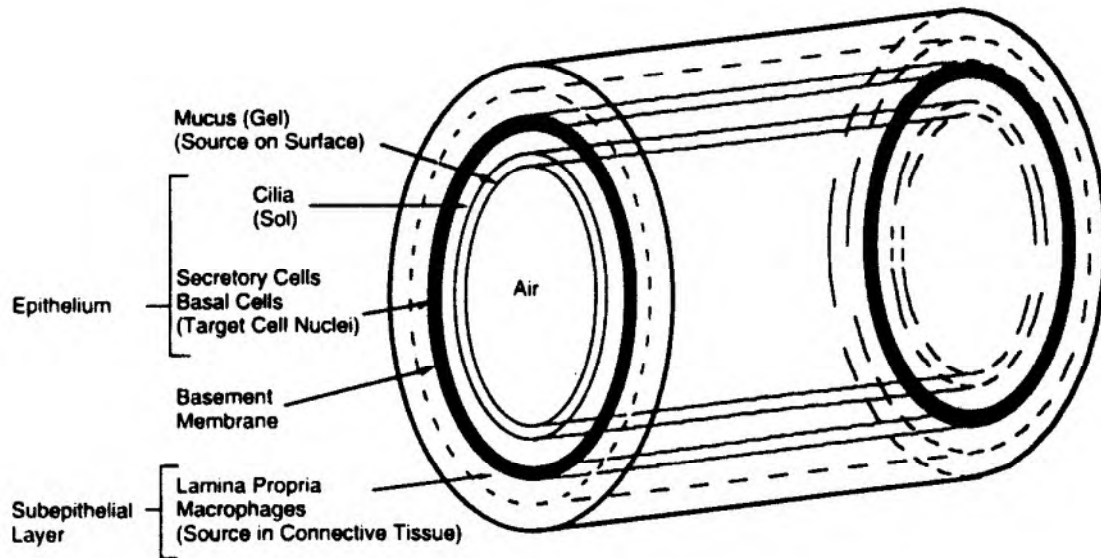


Fig. 2. Simplified geometrical model of various sources and targets involved in dosimetry of bronchial and extrathoracic epithelial tissues.

2.2. The Extrathoracic Region (ET)

(33) Under normal circumstances, air is inspired through the nose and the pharynx (nasopharynx and oropharynx) into the larynx. In case of nasal obstruction, or when ventilatory demands exceed the nasal airflow capacity, additional air is inspired through the mouth.

(34) The main task of this part of the extrathoracic region is to condition and clean the inspired air and conduct it to the trachea and the lungs. Ambient air, which is usually of lower temperature and humidity than the human body, is efficiently modified and cleansed of much particulate material before penetrating deeply into the lungs, where it comes into extremely close contact with the blood over a huge gas-exchange surface area. During nasal breathing, temperature and humidity adjustment begins at the nostrils and continues through all subsequent airways. Cleaning begins by impaction or diffusion in the anterior unciliated nares, and continues with filtration of particulate material from the inspired air as it passes through the vibrissae (hairs) behind the nasal entrance. This region also contains associated lymph vessels and lymph nodes.

(35) Inspired air flows through the anterior nares into the nasal vestibule and continues into the nasal cavity, both divided by the nasal septum. In adults the surface area of the anterior nasal passages is approximately $2 \times 10^{-3} \text{ m}^2$ (20 cm^2), increasing in the posterior nasal passages to $1.5 \times 10^{-2} \text{ m}^2$ (150 cm^2) because of the presence of convoluted turbinates, which narrow the nasal passage to slits, forcing air at increased

velocity into close contact with the walls. Most of the nasal wall is covered by respiratory mucosa, which contains a complex erectile vascular system and many glands, and is covered on average by a ciliated pseudostratified epithelium that moves a layer of mucus that is estimated to be $15\text{ }\mu\text{m}$ thick in the ET_2 region. These structures efficiently moisten and warm the inspired air. The top of the nasal cavity is covered by the olfactory mucosa, which house the receptors of smell. The paranasal sinuses, as well as the nasolacrimal ducts, originate under the turbinates as small orifices. The sinuses might act as thermal insulators in conditioning inspired air; the nasolacrimal ducts drain the lacrimal fluid.

(36) Behind the vestibule, the air stream bends and runs horizontally through the narrow passages formed by the turbinates and the nasal septum. As described in Chapter 5, these changes in direction of the air stream contribute to deposition of particulate material by impaction. Inspired air leaves the nasal cavity through the posterior nares, turns downward into the wide pharynx (nasal part) and continues vertically through the oral part of the pharynx into the larynx and trachea. The auditory tube, coming from the middle ear, runs into the nasal part of the pharynx, which is covered by respiratory epithelium. In the oral part of the pharynx, the air passage intersects the food passage. It is covered by a mucous membrane with stratified epithelium. Food is prevented from entering the trachea by the epiglottis, which covers the laryngeal tube during swallowing.

(37) The larynx contains the vocal cords, which reduce the air passage to a variable-sized slit, thus increasing the velocity of the airflow. This is the organ from which sound and speech originate, but it also prevents food particles that have gained access to the larynx from entering the trachea. These structures, however, are also a location of increased deposition of particles. The larynx is partly covered by a mucosa with stratified epithelium and partly with respiratory mucosa. Nasal breathing (normal entry route) offers better conditioning and cleaning of inspired air than oral breathing (the auxiliary route).

(38) The wall of the ET_1 region (nasal vestibule) is lined by keratinized squamous epithelium (skin), on which radionuclide sources can be deposited. Figure 3 shows the simplified model of a section through the wall of the ET_1 region used in Chapter 7 for dose calculations. The morphological dimensions assigned to the nasal vestibule (region ET_1) for dosimetry purposes are summarized as follows:

- (1) average thickness of keratinized stratified squamous epithelium, $50\text{ }\mu\text{m}$
- (2) average depth of nuclei of cells (basal) at risk, 40 to $50\text{ }\mu\text{m}$
- (3) total surface area, $2 \times 10^{-3}\text{ m}^2$ (20 cm^2)
- (4) equivalent average diameter of air passage, $5 \times 10^{-3}\text{ m}$ (5 mm).

(39) In region ET_2 , most of the wall of the nasal passages and part of the pharynx and larynx are covered by ciliated, pseudostratified epithelium. Parts of ET_2 (the oropharynx and glottic part of the larynx) are covered by stratified squamous epithelium (Fig. 4). Because the incidence of tumours in the naso-oropharynx is much higher than in the nose *per se* (see Annexe C), and the major tumour type in this region is squamous cell carcinoma, the oropharynx and part of the larynx (region ET_2) were selected for dose calculations. The morphological dimensions assigned to the sensitive oropharynx and part of the larynx (region ET_2) for dosimetry purposes, are summarized as follows:

- (1) equivalent average diameter of air passage (calibre), $3 \times 10^{-2}\text{ m}$ (3 cm)

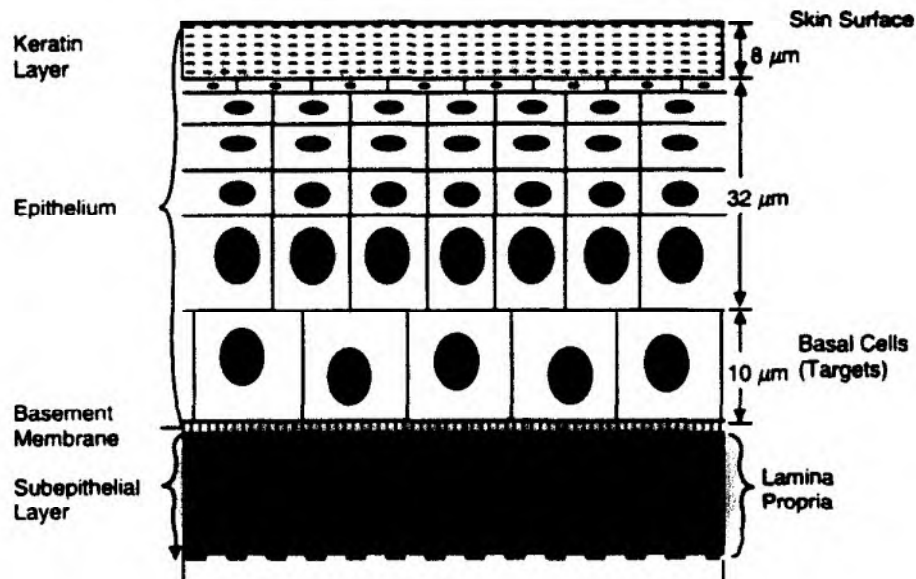


Fig. 3. Model of target cell nuclei (basal cells) in wall of ET₁ region (nasal vestibule), which is covered by keratinised squamous epithelium.

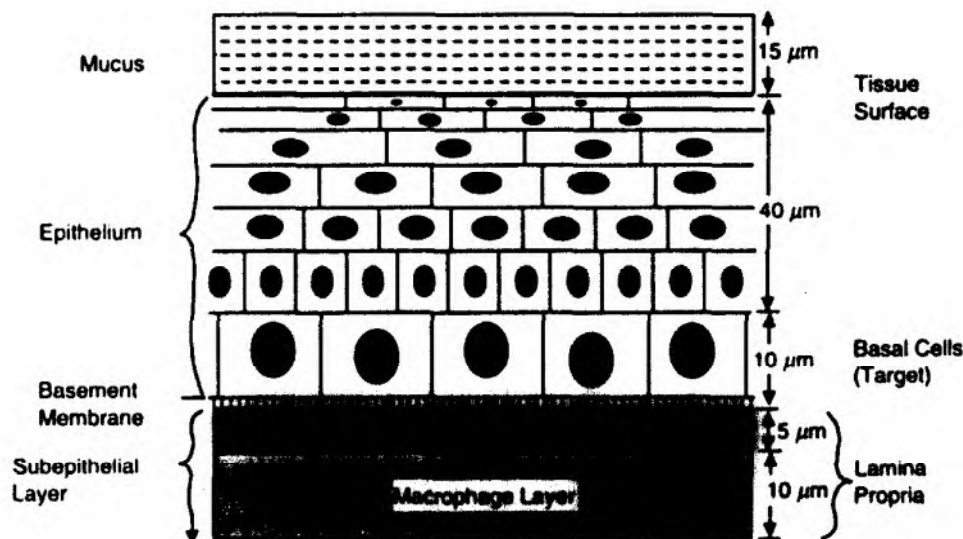


Fig. 4. Model of target cell nuclei (basal cells) in stratified squamous epithelia of oropharynx and larynx and associated sources of radioactive transformations in ET₂ region.

- (2) average thickness of mucous layer, 15 μm
- (3) average thickness of stratified squamous epithelium, 50 μm
- (4) average depth of nuclei of cells (basal) at risk, 40 to 50 μm
- (5) total surface area, $4.5 \times 10^{-2} \text{ m}^2$ (450 cm²).

2.3. The Bronchial Region (BB)

(40) This region is part of the air conducting system within the thorax and consists of the trachea, the main bronchi, and the intrapulmonary bronchi, beginning with the trachea as generation 0 and ending approximately with generation 8. The region also includes associated lymph vessels and lymph nodes.

(41) The purpose of this part of the airway tree is to conduct air. It adjusts the humidity and temperature of inspired air and is the site of the deposition of inhaled particles by impaction, sedimentation, and/or diffusion.

(42) The airway tree originates with a single tube, the trachea. On average, it is approximately 0.09 m (9 cm) long and 0.017 m (1.7 cm) in inner diameter (Table 2); its volume is approximately $2 \times 10^{-5} \text{ m}^3$. The trachea is kept open by rings of cartilage. The tracheal wall is covered by respiratory mucosa and contains many glands. The mucous sheet on top of the respiratory epithelium is moved towards the pharynx by the cilia. The bronchial wall contains cartilage plates and many glands. The bronchi are covered by respiratory mucosa, which are lined by ciliated epithelium that moves the mucous layer toward the trachea by the ciliary beat.

(43) The trachea first divides into two (extrapulmonary) main bronchi (with walls like that of the trachea), which divide into the lobar bronchi; three enter the right lung, and two enter the left lung, according to the number of lobes on each side. The lobes are covered by the pleura, from which connective tissue septa originate, subdividing incompletely the lobes into bronchopulmonary segments. Segmental bronchi, branching off the lobar bronchi, lie in the center of the segments and subdivide further. In the

Table 2. Dimensional model of tracheobronchiolar tree in adult male adopted in this report to model aerosol deposition and bronchial-bronchiolar dose (James, 1988, adapted from Weibel, 1963; Yeh and Schum, 1980; and Phalen *et al.*, 1985)^a

Region	Generation	Diameter ^b (m)	Length ^b (m)	J branch ^c (degrees)	Gravity angle ^c (degrees)
Bronchial (BB)	0 Trachea	1.65×10^{-2d}	9.1×10^{-2}	0	0
	1 Main bronchi	1.20×10^{-2}	3.8×10^{-2}	36	20
	2	0.85×10^{-2}	1.5×10^{-2}	35	31
	3	0.61×10^{-2}	0.83×10^{-2}	28	43
	4	0.44×10^{-2}	0.90×10^{-2}	35	39
	5	0.36×10^{-2}	0.81×10^{-2}	39	39
	6	0.29×10^{-2}	0.66×10^{-2}	34	40
	7	0.24×10^{-2}	0.60×10^{-2}	48	36
	8	0.20×10^{-2}	0.53×10^{-2}	53	39
Bronchiolar (bb)	9 Bronchioles	0.1651×10^{-2e}	0.4367×10^{-2}	54	45
	10	0.1348×10^{-2}	0.3620×10^{-2}	51	45
	11	0.1092×10^{-2}	0.3009×10^{-2}	46	45
	12	0.0882×10^{-2}	0.2500×10^{-2}	47	45
	13	0.0720×10^{-2}	0.2069×10^{-2}	48	45
	14	0.0603×10^{-2}	0.1700×10^{-2}	52	45
	15 Terminal bronchioles	0.0533×10^{-2}	0.1380×10^{-2}	45	45

^a There are significant differences in the adult airway dimensions measured and published by Weibel (1963), Yeh and Schum (1980), and Phalen *et al.* (1985). Because it is not apparent which set of values more appropriately apply to reference man, the dimensions from the three sources were averaged after all were adjusted to a standard functional residual capacity (FRC) of $3.3 \times 10^{-3} \text{ m}^3$ (Yu and Diu, 1982; James, 1988).

^b These values are taken to be the reference values from which tissue masses (Table 5) and airway volumes (Table 6) are derived.

^c J branch: Branching angle of the daughter segment is defined as the change in direction of the bulk airflow from the segment into the daughter segment.

Gravity angle: The inclination of the segment to gravity = angle between the bulk airflow direction during inspiration and the force of gravity. (From Phalen *et al.*, 1985.)

^d Diameter of trachea, d_0 , used to scale extrathoracic and bronchial airway dimensions in different subjects relative to the adult male.

^e Diameter of first generation bronchiole, d_1 , used to scale bronchiolar airway dimensions in different subjects relative to the adult male.

human lung, the bronchi divide in a dichotomous manner of relatively little irregularity into daughter branches that become progressively reduced in diameter. This branching pattern has been described in detail by Weibel (1963), Horsfield and Cumming (1968), Yeh and Schum (1980), and Phalen *et al.* (1985).

(44) Since the airways in the human lung branch dichotomously, the number in any generation, n , is $N_n = 2^n$, as long as all preceding generations are complete, i.e. as long as every generation divides into two branches. There are, however, exceptions where trichotomy occurs; for example, the apparent divisions of the right upper-lobe bronchus into three segmental bronchi.

(45) The dimensions and geometry of the airway branches gradually change as they penetrate deeper into the lung, Table 2. The average diameter of the branches decreases with increasing orders of generations. For example, according to the regular dichotomy model of Weibel (1963), the diameters follow a straight line plotted semilogarithmically. In the model described in Table 2, the bronchial diameter is reduced from 1.2×10^{-2} m to 0.20×10^{-2} m (1st to 8th generation), the greatest reduction occurring in the first few generations.

(46) The average length of the branches also decreases with increasing orders of generations, with the exception of the 4th generation branches, which are longer than the 3rd (Weibel, 1963).

(47) The simplified model of a section through the wall of a typical bronchus in region BB used in Chapter 8 to calculate doses is shown in Fig. 5. The nuclei of both

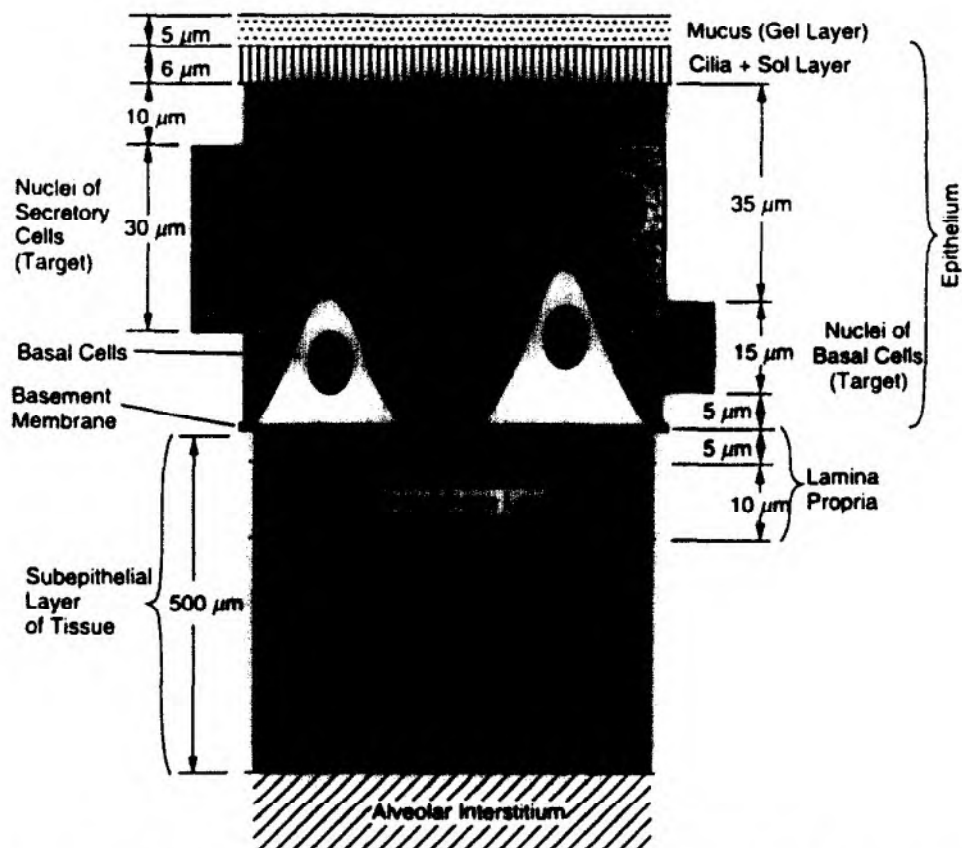


Fig. 5. Model of target cell nuclei (secretory and basal cells) and the bronchial wall in the BB region, which is covered by ciliated epithelium, and associated sources of radioactive transformations. The target tissue is shielded from radiations emitted in the alveolar interstitium by a 500- μ m-thick layer of subepithelial connective tissue.

columnar secretory and short basal cells are considered to be sensitive targets (Chapter 4). These are assumed to occur uniformly throughout a 30- μm -thick layer of tissue at 10- μm depth, and in a 15- μm layer at 35- μm depth, respectively (Mercer *et al.*, 1991a). The relative frequencies of the above-mentioned cells in humans are known only for airway generations 0 and 1: in the trachea the cell density per mm^2 basal lamina is 300, consisting of 33% basal cells, 49% ciliated cells, 9% goblet cells, and 9% of other cells. The values for the main bronchus are: 6%, 56%, 26%, and 13%, respectively (Pavelka *et al.*, 1976; Gilljam *et al.*, 1987). In contrast, basal cells in animals represent between 20% (sheep) and 32% (rhesus monkey) of the epithelial cell population, with a very irregular distribution along the intrapulmonary conducting airways. There is also a considerable variation between species as far as secretory cell types (goblet cells, Clara cells) are concerned (St George *et al.*, 1988).

(48) Doses to tracheal epithelium will not be calculated because these are generally smaller than the doses received by the epithelium of the bronchi and because the trachea is relatively insensitive to radiation exposure. The morphological dimensions assigned to the bronchi (region BB) for dosimetry purposes are summarized as follows (see Fig. 5; the variability among different members of the population is illustrated in Table A.4 of Annexe A):

- (1) volume of bronchi and trachea, $5 \times 10^{-5} \text{ m}^3$
- (2) surface area of bronchi (generations 1 to 8), $2.9 \times 10^{-2} \text{ m}^2$
- (3) bronchial wall:
 - average calibre, 5×10^{-3} (5 mm)
 - average thickness of mucous (gel) layer, $5 \mu\text{m}$
 - average thickness of cilia (sol) layer, $6 \mu\text{m}$
 - average thickness of epithelium (without cilia), $55 \mu\text{m}$
 - average depth of nuclei of secretory cells at risk, 10 to $40 \mu\text{m}$
 - average depth of nuclei of basal cells at risk, 35 to $50 \mu\text{m}$.

2.4. The Bronchiolar Region (bb)

(49) This region is the second part of the air conducting system within the thorax. It consists of the bronchioles comprising generations 9 to 15. The branches of the last generation are called terminal bronchioles; all airways beyond the terminal bronchioles carry alveoli.

(50) These airways conduct the air into and out of the respiratory region. Inhaled particles are deposited mainly by sedimentation or diffusion, depending on their size.

(51) The bronchioles branch dichotomously and are randomly orientated with respect to gravity (Table 2). The first branches have a diameter of about $0.17 \times 10^{-2} \text{ m}$ (1.7 mm), which diminishes to $0.05 \times 10^{-2} \text{ m}$. The lengths of the branches also diminish from 0.44×10^{-2} to $0.14 \times 10^{-2} \text{ m}$.

(52) Generation 15, the terminal bronchioles, is the approximate last generation of the air-conducting system; distally, all airways are alveolated to varying degrees.

(53) The bronchioles are airways without cartilage and glands. The respiratory epithelium, which consists of a single layer of columnar to cuboidal cells, contains two major cell types, ciliated and nonciliated. The latter are primarily a unique type of secretory cell, the Clara cell (see Annexe A), and are especially prominent in the terminal bronchioles, generation 15. Basal cells are rarely found in the bronchioles

(Bartels, 1983; Mercer *et al.*, 1991a). The connective tissue is reduced from that of the bronchi. It contains small lymph vessels.

(54) The simplified model of a section through the wall of a typical bronchiolus used for dose calculations in Chapter 7 is shown in Fig. 6. The nuclei of secretory (Clara) cells are considered the sensitive targets. (See Chapter 4.) These are assumed to occur uniformly throughout the 8- μm -thick layer of tissue at 4- μm depth. The morphological dimensions assigned to the bronchioli (region bb) for dosimetry purposes are summarised as follows (the variability among individual members of the population is illustrated in Table A.5):¹

- (1) volume of nonrespiratory bronchioles (generations 9 through 15), $\sim 5 \times 10^{-5} \text{ m}^3$
- (2) surface area of nonrespiratory bronchioles, $2.4 \times 10^{-1} \text{ m}^2$
- (3) bronchiolar wall:
 - average calibre, 10^{-3} m (1 mm)
 - average thickness of mucous (gel) layer, $2 \mu\text{m}$
 - average thickness of cilia (sol) layer, $4 \mu\text{m}$
 - average thickness of epithelium (without cilia), $15 \mu\text{m}$
 - average depth of nuclei of cells at risk, 4 to $12 \mu\text{m}$.

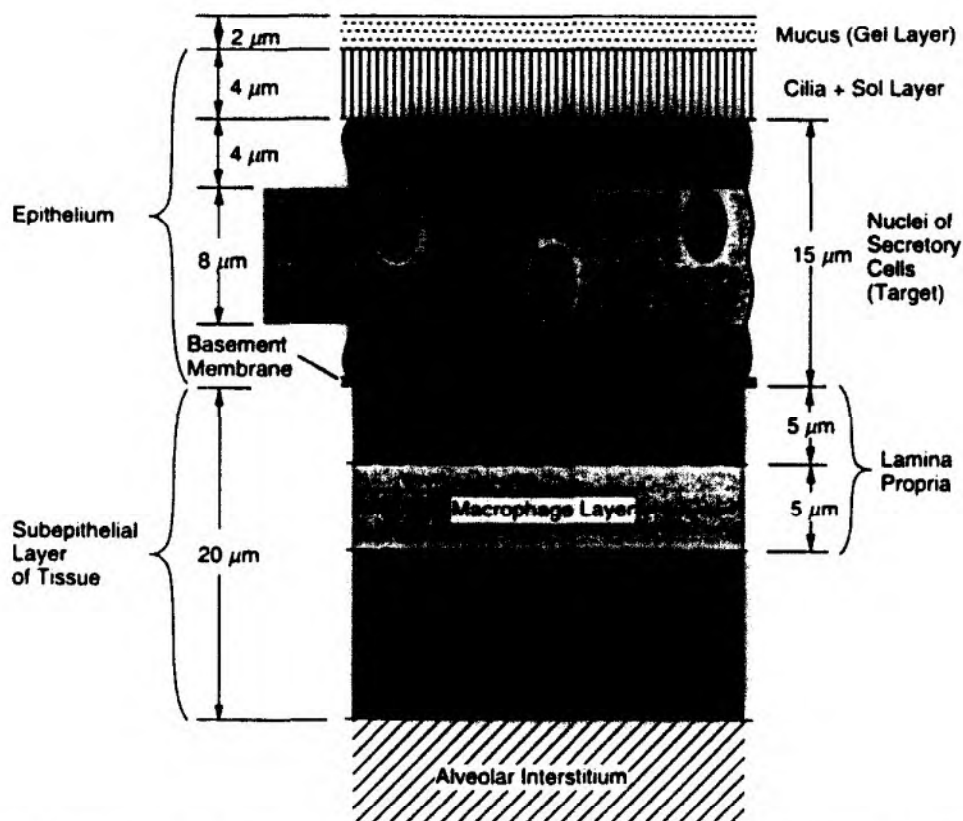


Fig. 6. Model of target cell nuclei (secretory or Clara cells) and bronchiolar wall in bb region, which is covered by ciliated epithelium, and associated sources of radioactive transformations. Target tissue is shielded from radiations emitted in alveolar interstitium by a layer of subepithelial connective tissue only $20 \mu\text{m}$ thick.

¹ For the same reasons as in the BB region, the airway dimensions have been averaged over the three sources, Weibel (1963), Yeh and Schum (1980), and Phalen *et al.* (1985), and adjusted to an FRC of $3.3 \times 10^{-3} \text{ m}^3$ according to Yu and Diu (1982) and James (1988); see Table 2.

2.5. Alveolar-Interstitial Region (AI)

(55) The alveolar-interstitial (AI) compartment comprises the respiratory tract system distal to the terminal bronchioles, i.e. approximately generations 16 to 26, which are the respiratory bronchioles and the alveolar ducts. It also includes the interstitial lymphatic tissues and lymph vessels, as well as bronchial lymph nodes. For dosimetry purposes, the interstitial lymphatic vessels do not need to be distinguished from the slow-clearing pulmonary structures. The dimensional model of this region is given in Table 3.

(56) The main function of this region is to exchange gases, although other roles are also important, for example endocrine and defence functions. Inhaled particles reaching this region are deposited by sedimentation and/or diffusion.

(57) The terminal bronchioles (generation 15) branch into respiratory bronchioles. Single alveoli or small groups of alveoli are apposed to these respiratory airways.

(58) Respiratory bronchioles branch into alveolar ducts. In these airways the whole circumference is occupied by alveoli. The gas-exchange region terminates in alveolar sacs, which are closed at the peripheral end by a group of alveoli.

(59) Since respiratory bronchioles are partly alveolated, they are considered, along with alveolar ducts and sacs, as the transitory zone between the air-conducting system and the alveoli, which in their entirety comprise the gas-exchange region of the lungs.

(60) The gas-exchange parenchyma can be subdivided into many small morphological units, the lobules, which have a volume of about 10^{-6} m^3 . They are only partially separated from each other by connective tissue but can be clearly seen on the pleura as polygonal fields. Each lobule is supplied with air by a terminal bronchiole. The lobule can be further subdivided into two functional units, the acini, each of which is supplied with air by a respiratory bronchiole of the first generation (Hansen and Ampaya, 1975; Weibel, 1963).

(61) According to Weibel (1963) the gas-exchange region of the lungs extends, on average, to generation 23. Because of irregularity in the dichotomous branching pattern,

Table 3. Dimensional model of gas-exchange region^a (calculated from Hansen and Ampaya, 1975)

Acinar generation (z)	Number of airways (N_z)	Diameter (m)	Length (m)
0 Terminal bronchioles ^b	1	—	—
1 Respiratory bronchioles	2	5.1×10^{-4c}	1.1×10^{-3}
2 Respiratory bronchioles	4	4.6×10^{-4}	9.2×10^{-4}
3 Respiratory bronchioles	8	4.1×10^{-4}	7.6×10^{-4}
4 Alveolar ducts	19	3.8×10^{-4}	6.3×10^{-4}
5 Alveolar ducts	45	3.5×10^{-4}	5.2×10^{-4}
6 Alveolar ducts	108	3.3×10^{-4}	4.3×10^{-4}
7 Alveolar ducts	254	3.1×10^{-4}	3.6×10^{-4}
8 Alveolar ducts	374	3.0×10^{-4}	3.0×10^{-4}
9 Alveolar ducts	366	3.9×10^{-4}	2.1×10^{-4}
10 Alveolar ducts	146	2.8×10^{-4}	2.1×10^{-4}
11 Alveolar ducts	58	2.8×10^{-4}	1.7×10^{-4}

^a Scaled to normal FRC of $3.3 \times 10^{-3} \text{ m}^3$.

^b Terminal bronchioles of the tracheobronchial airway model (generation 15). The total number of airways for all acini is given by $2^{15} \times N_z$ ($= 32,768 \times N_z$).

^c Diameter of first respiratory bronchioli, d_{1R} , used to scale airway dimensions in alveolar-interstitial region in different subjects relative to the adult male.

individual pathways may, however, end anywhere between the 15th and about the 30th generation. This distribution of path lengths is represented in the model of the respiratory acinus described by Haefeli-Bleuer and Weibel (1988) and by Hansen and Ampaya (1975) and Hansen *et al.* (1975). These authors traced the number of airways at each level of branching through an acinus. For computational convenience, the model of Hansen and Ampaya (1975) has been adopted (Table 3).

(62) The total volume of the respiratory bronchioles is about $2 \times 10^{-4} \text{ m}^3$, and the total surface area is about 7.5 m^2 . The air volume of the alveolar ducts and sacs, however, averages approximately $4.5 \times 10^{-3} \text{ m}^3$, and the total surface area of the alveoli is approximately 140 m^2 (Gehr *et al.*, 1978).

(63) The target cells in the alveolar-interstitial region are the secretory (Clara) cells of the respiratory bronchioli and type II epithelial cells covering the alveolar surface. While type II epithelial cells cover only about 7% of the alveolar surface, there are twice as many as the much larger type I epithelial cells.

2.6. Scaling of Airway Dimensions for Age and Gender

(64) The dimensions of the extrathoracic airways are considered to scale in proportion to the diameter of the trachea (Yu and Xu, 1987; Swift, 1989).

(65) The dimensions of the trachea and bronchi were found by Phalen *et al.* (1985) to be related to body height. The factors by which the diameter and length of airways are scaled with height H (in meters), from the values given earlier for the "reference" adult male, are given in Table 4.

(66) By age 2 the structure of the lungs is completely developed (Gehr, 1987; Zeltner *et al.* 1987; Zeltner and Burri, 1987). The dimensions of the respiratory airways are, therefore, scaled by the one-third power of the functional residual capacity (FRC). (See Chapter 3.) The morphometry of alveolated structures during the developmental

Table 4. Constants used to calculate scaling^a of airway diameter and length as a function of body height^b

Airway generation (z)	Constant (a)	
	Diameter	Length
0 Trachea	0.540	0.559
1 Main bronchi	0.530	0.468
2 Bronchi	0.507	0.474
3 Bronchi	0.489	0.502
4 Bronchi	0.429	0.431
5 Bronchi	0.441	0.476
6 Bronchi	0.452	0.441
7 Bronchi	0.405	0.359
8 Bronchi	0.333	0.273

^a Scaling factor, SF, is the ratio of airway diameter or length in the subject compared to that in reference man.

^b $SF = a(H_s - 1.76) + 1$, where H_s is height of subject in meters.

stage from birth to about 18 months is not adequately understood. In the absence of firm data, it is assumed that the full branching structure of the lung is complete at birth, but that alveolization is incomplete. It is assumed that the number of alveoli present at age 3 months is 40% of that in the adult (Zeltner *et al.*, 1987), that the number at 1 y is 80%, and that alveolization occurs uniformly throughout all respiratory airways. The corresponding dimensions of the respiratory airways in 3-month and 1-y-old infants are then obtained by appropriate scaling.

(67) The diameter of the bronchioles (generations 9 to 15) is obtained by interpolating between the reference diameter of the last generation of bronchi (generation 8) and the first generation of respiratory bronchioles (generation 16). The unique parabola, which has its minimum at the diameter of the 16th airway generation, provides a good fit to the bronchiolar airway diameters measured by Phalen *et al.* (1985) for adult subjects. This parabolic interpolation is assumed to apply to younger subjects also. In a similar manner, the lengths of the bronchioles (generations 9 to 15) are obtained by hyperbolic interpolation between the reference lengths of airways in the 8th and 16th generations.

(68) For dosimetry purposes, the mass of the AI region of the respiratory tract is assumed to vary in proportion to body weight, irrespective of age, gender, and race.

(69) The thickness and cellular structure of epithelial tissues are considered to be independent of age, gender, and body size (Gehr, 1987).

2.7. Masses of Target Tissues

(70) The masses of epithelial target tissues in the ET_1 and ET_2 , the BB, the bb, and AI regions in Caucasian subjects are given in Table 5. The tissue masses shown for women, children, and infants are derived by scaling the values given for the adult male. Target tissue mass is proportional to the product of airway surface area and thickness of the sensitive tissue in each region. The airway surface areas in ET_1 and ET_2 are assumed to scale as the square of tracheal diameter in each subject. The total areas of airway surface in BB and bb are given by the recommended morphometric model. It is assumed that the target tissue thickness is independent of the subject's size. This is taken to be 10 μm in ET_1 and 10 μm in ET_2 airways (Figs 3 and 4), 30 μm and 15 μm , respectively, for secretory and basal cell nuclei in BB (Fig. 5), and 8 μm in bb (Fig. 6).

(71) The masses of the blood-filled AI regions of the respiratory tracts in Caucasian subjects (male and female adults, children, and infants) are also given in Table 5.

(72) Values of the masses of extrathoracic and thoracic lymph nodes in Caucasian subjects that are recommended in Table 5 for use in the dosimetric model were derived by scaling the value of 1.5×10^{-2} kg (ICRP, 1975), which is assumed for the adult male, in proportion to the mass of each subject's lungs. In the absence of specific data on extrathoracic lymphatics and lymph nodes, the value of 1.5×10^{-2} kg reported in ICRP Publication 23 (ICRP, 1975) for tracheobronchial lymph nodes in adults was assumed for the mass of the extrathoracic lymphatic tissues and for the mass of the thoracic lymphatic tissues.

Table 5. Masses of target tissues in different subjects^a

Subject	Mass (kg)						
	ET ₁	ET ₂	BB _{sc} ^b	BB _{na} ^b	bb	AI ^c	LN _{ET} ^d
Adult male	2.0×10^{-5}	4.5×10^{-4}	8.6×10^{-4}	4.3×10^{-4}	1.9×10^{-3}	1.1	1.5×10^{-2}
Adult female	1.7×10^{-5}	3.9×10^{-4}	7.8×10^{-4}	3.9×10^{-4}	1.9×10^{-3}	0.90	1.2×10^{-2}
15-y male	1.9×10^{-5}	4.2×10^{-4}	8.2×10^{-4}	4.1×10^{-4}	1.8×10^{-3}	0.86	1.2×10^{-2}
15-y female	1.7×10^{-5}	3.8×10^{-4}	7.6×10^{-4}	3.8×10^{-4}	1.6×10^{-3}	0.80	1.1×10^{-2}
10 y	1.3×10^{-5}	2.8×10^{-4}	6.2×10^{-4}	3.1×10^{-4}	1.3×10^{-3}	0.50	6.8×10^{-3}
5 y	8.3×10^{-6}	1.9×10^{-4}	4.7×10^{-4}	2.3×10^{-4}	9.5×10^{-4}	0.30	4.1×10^{-3}
1 y	4.1×10^{-6}	9.3×10^{-5}	3.1×10^{-4}	1.6×10^{-4}	6.0×10^{-4}	0.15	2.1×10^{-3}
3 mo	2.8×10^{-6}	6.3×10^{-5}	2.5×10^{-4}	1.3×10^{-4}	5.0×10^{-4}	0.090	1.2×10^{-3}

^a Secondary values of two significant figures.^b BB_{sc} is the mass of bronchial epithelium through which secretory cell nuclei are distributed, and BB_{na} that for basal cell nuclei. These masses are derived from the surface areas defined by airway lengths and diameters (Table 2), which are scaled for each subject by the constants given in Table 4.^c Including blood, excluding lymph nodes.^d Mass of lymphatic tissue is assumed to be the same in extrathoracic and thoracic regions.

3. PHYSIOLOGICAL PARAMETERS

3.1. Introduction

(73) This chapter provides recommended values for respiratory physiological parameters to be used in calculating radiation doses from the inhalation of radioactive aerosols and gases and vapours. Values for workers and for members of the public are given. Annexe B contains a discussion of respiratory physiology and extensive tables of values of respiratory parameters for several ethnic groups.

(74) Radiation doses to tissues and cells of the respiratory tract are determined to a great extent by breathing characteristics and by certain respiratory parameters. Because these influence the volume and rate of air inhaled and the proportions entering through the nose and the mouth, they also determine the amounts of radioactive particles and gases inhaled, their penetration into the respiratory tract, and the quantities deposited. Breathing characteristics and respiratory parameters vary among the world's population because they are largely a function of body size, level of physical activity, state of health of the respiratory tract, and whether the individual is a smoker. Thus it is clear that a respiratory tract model that is applicable to all individuals at all times in the world's population would be very complex. This is neither feasible nor necessary to adequately protect against risks of airborne radionuclides. Reference values for the most relevant physiological parameters were derived to provide models for calculating radiation doses per unit intake of radionuclides for workers and members of the general public. An exhaustive search was undertaken to obtain respiratory physiological data for all populations in the world. This was successful to the extent that data were obtained for representative ethnic groups of both sexes, of different ages, and at different levels of activity. These data are tabulated in Annexe B.

(75) From these data, reference values representing working Caucasian males and females were selected for use in the dosimetric respiratory tract model for workers. A second set of values, representing nonworking Caucasian males and females of all ages, was selected for use in the dosimetric models for the general population. Guidance is provided to adjust these values for other ethnic groups. For purposes of assessing exposures of individuals, it is recommended that respiratory tract parameters specific to the individual and the exposure situation (at work, resting, etc.) be used in the dosimetric model. To predict radiation doses for workers and populations resulting from potential future exposures to airborne radionuclides, such as for risk assessments, Annexe B should be consulted for physiological data most representative of the population of interest. These data can be used in the dosimetric model in place of default parameters given in this chapter and in Chapters 5, 9, and 10.

3.2. Reference Values for Workers

(76) Reference values for respiratory parameters for workers (both men and women) are given in Table 6. The recommended values are not intended to be average values for the worldwide population but a coherent set of values for Caucasians. Annexe B may be consulted to determine the appropriateness of this set of recommended values for a specific population.

Table 6. Reference respiratory values for workers^{a,b}

Lung volumes	L	
TLC	6.98	
FRC	3.30	
VC	5.02	
V_D	0.146 ^c	
Ventilation rates	($\dot{V}_E$) (L min ⁻¹)	(B) (m ³ h ⁻¹)
Sleep	7.5	0.45
Rest, sitting	9.0	0.54
Light exercise	25	1.5
Heavy exercise	50	3.0
Activity	Air breathed (m ³)	
	Light work	Heavy work
Sleep, 8 h	3.6	3.6
Occupational (5.5 h light exercise + 2.5 h rest, sitting)	9.6	—
(7 h light exercise + 1 h heavy exercise)	—	13.5
Nonoccupational (4 h rest, sitting + 3 h light exercise + 1 h heavy exercise)	9.7	9.7
Total, 24 h	23	27

^a Caucasian men and women; age 30 y, height 176 cm, weight 73 kg.^b Derived in conjunction with ICRP Task Group on Reference Man.^c This is a secondary value calculated using the airway dimensions given in Table 2.TLC = Total lung capacity; FRC = functional residual capacity; VC = vital capacity; V_D = dead space.

3.3. Reference Values for Members of the General Population

(77) Reference values for respiratory parameters for the general Caucasian population are given in Tables 7 and 8. Values are included for 3-month-old infants, for children at 1, 5, 10, and 15 y, and for adults. These values are recommended for the calculation of doses per unit intake of radionuclides for the general population. To calculate doses for specific individuals or populations, Annexe B should be consulted to obtain the values most relevant to the sex, age, and ethnic group of interest. Examples of specific spirometric values are given in Table 9 for several ethnic groups. Breathing parameters are not given for ethnic groups because the existing data on ventilation parameters do not show significant differences among them.

Table 7. Reference respiratory values for general Caucasian population^a

	3 mo	1 y	5 y	10 y	15 y		Adult	
					Male	Female	Male	Female
Height (cm)	60	75	110	138	169	161	176	163
Weight (kg)	6	10	20	33	57	53	73	60
TLC (L)	0.28	0.55	1.55	2.87	5.43	4.47	6.98	4.97
FRC (L)	0.148	0.244	0.767	1.484	2.677	2.325	3.30	2.68
VC (L)	0.20	0.38	1.01	2.33	3.96	3.30	5.02	3.55
V_D (L) ^b	0.014	0.020	0.046	0.078	0.130	0.114	0.146	0.124

^a Derived in conjunction with ICRP Task Group on Reference Man. See Annexe B for published data on populations that have been studied.^b These are secondary values calculated by scaling the airway dimensions given in Table 2 for body height.TLC = Total lung capacity; FRC = functional residual capacity; VC = vital capacity; V_D = dead space.

Table 8. Reference respiratory values for a general Caucasian population at different levels of activity^a

Activity:	Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
	8			12			32			64		
Maximal workload (%):												
Breathing parameters: ^b	V_T (L)	B ($m^3 h^{-1}$)	f_R (min^{-1})	V_T (L)	B ($m^3 h^{-1}$)	f_R (min^{-1})	V_T (L)	B ($m^3 h^{-1}$)	f_R (min^{-1})	V_T (L)	B ($m^3 h^{-1}$)	f_R (min^{-1})
Age												
3 mo	0.039	0.09	38	N/A	N/A	N/A	0.066	0.19	48	N/A	N/A	N/A
1 y	0.074	0.15	34	0.102	0.22	36	0.127	0.35	46	N/A	N/A	N/A
5 y	0.174	0.24	23	0.213	0.32	25	0.244	0.57	39	N/A	N/A	N/A
10 y	0.304	0.31	17	0.333	0.38	19	0.583	1.12	32	0.841	2.22	44
15 y	0.500	0.42	14	0.533	0.48	15	1.0	1.38	23	0.667	1.84	46
Adult	0.417	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
	0.625	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	0.444	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

^a See Annex B for data from which these reference values were derived.^b V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency.

N/A = Not applicable.

Table 9. Examples of variations of respiratory values for ethnic groups^a

	3 mo	1 y	5 y	10 y	15 y	Adult	
						Male	Female
Japan							
Height (cm) ^b	62	74	—	133	—	170	158
Weight (kg) ^b	6.5	9	—	29	—	65	53
TLC (L) ^c	—	—	—	—	—	5.60	3.90
FRC (L) ^c	—	—	—	—	—	2.90	2.05
VLC (L) ^c	—	—	—	—	—	4.40	3.00
China^{d,e}							
Height (cm)	62	76	108	136	161	170	158
Weight (kg)	6.5	9.6	17	28	48	60	51
TLC (L)	—	—	—	—	—	5.40	3.85
FRC (L)	—	—	—	—	—	2.95	2.15
VC (L)	—	—	—	1.85	3.05	3.65	2.50
India^f							
Height (cm)	—	—	—	—	—	167	154
Weight (kg)	—	—	—	—	—	56	48
TLC (L)	—	—	—	—	—	—	—
FRC (L)	—	—	—	—	—	—	—
VC (L)	—	—	—	—	—	3.60	2.30
US blacks^g							
Height (cm)	—	—	—	140	—	175	162
Weight (kg)	—	—	—	38	—	80	70
TLC (L)	—	—	—	—	—	—	—
FRC (L)	—	—	—	—	—	—	—
VC (L)	—	—	—	2.35	—	4.15	3.00
Senegal							
Height (cm)	—	—	108 ^h	136 ^h	164	177 ⁱ	165 ^g
Weight (kg)	—	—	18 ^h	28 ^h	45	68 ⁱ	63 ^g
TLC (L)	—	—	—	—	—	—	—
FRC (L)	—	—	—	—	—	—	—
VC (L)	—	—	0.82 ^h	1.70 ^h	2.85	4.20 ⁱ	3.00 ^g
Zimbabwe^j							
Height (cm)	—	—	—	—	—	171	161
Weight (kg)	—	—	—	—	—	64	64
TLC (L)	—	—	—	—	—	—	—
FRC (L)	—	—	—	—	—	—	—
VC (L)	—	—	—	—	—	3.95	3.00

^a Values have been rounded.^b Tanaka *et al.* (1979).^c Nishida (1982).^d Chen (1982).^e Chen (1989).^f Kamat *et al.* (1977).^g Schoenberg *et al.* (1978).^h Seck *et al.* (1990).ⁱ Dufétel *et al.* (1989).^j Cookson *et al.* (1976).

TLC = Total lung capacity.

FRC = functional residual capacity.

VC = vital capacity.

4. RADIATION BIOLOGY CONSIDERATIONS

4.1. Introduction

(78) The dosimetric model described in this report is based on the premise that differences in radiation sensitivity of respiratory tract tissues and the doses they receive from deposited radionuclides require the calculation of radiation doses to the specific regions of the human respiratory tract described in Chapter 2. This chapter identifies the tissues and cells at risk and addresses their relative sensitivities. It also recommends factors for weighting the calculated doses to specific tissues so that the doses can be summed to give a single value for the extrathoracic region and another for the thoracic region for use in calculating effective dose. Annexe C contains supporting information.

(79) *ICRP Publication 60* (ICRP, 1991a) focuses on the concept of aggregated radiation detriment. This includes the probability of attributable fatal and nonfatal cancers, hereditary effects, and length of life lost if harm occurs. For the purposes of this report, it is assumed that the relative sensitivities of the various tissues of the respiratory tract in terms of aggregated radiation detriment are the same as for the detriment associated with fatal lung cancer.

(80) Evidence from epidemiological studies of the atomic bomb survivors and from occupational and medical exposures to radiation, supplemented by results from experimental animal studies, indicates that all regions of the respiratory tract are sensitive to radiation. At high doses, pneumonitis and fibrosis occur after exposure at times determined by the dose rate. Deterministic effects can occur at late as well as early times. There is evidence from data in exposed experimental animals, however, that deterministic effects in the lungs are not a deciding factor for dose limitation (Bair *et al.*, 1989). Exposure of the anterior part of the nose, because of its apparent low sensitivity to cancer induction, should be protected adequately by limits based upon stochastic effects recommended for exposure of skin. A further description of deterministic effects is found in Annexe C.

(81) At lower doses, in the range that might be received from occupational and environmental exposures to inhaled radionuclides, the principal concern is the incidence of cancer, which occurs with greatly different frequencies in the different regions.

4.2. Respiratory Tract Cancers

(82) Information about the types and locations of cancers observed in the respiratory tract are summarized in the following paragraphs. Emphasis is given to data obtained from human populations, but, because relatively few data are available from irradiated populations, information from radiation studies using experimental animals is also included.

(83) Knowledge of the types and locations of cancers that occur in the respiratory tract, especially after uniform radiation exposure, is helpful in identifying the most likely cells and tissues at risk. It provides a basis for judging the relative radiation sensitivity of the several anatomical regions of the respiratory tract as described in Chapter 2.

4.2.1. *Types of extrathoracic cancers*

(84) Radiation-induced cancers of the extrathoracic airways, defined as regions ET₁ and ET₂, have not been found in excess in the epidemiological studies of the atomic bomb survivors or patients treated for ankylosing spondylitis. However, nasal sinus cancers were observed amongst radium dial painters (see Annexe C); extrathoracic airway cancers have been associated with the inhalation of wood dust and airborne nickel dust.

(85) *Anterior Nose*: The external nasal skin is the most frequent site from which basal cell carcinomas arise. Risk in this region is especially related to the inhalation of large particles because of their propensity to deposit on the first surfaces with which they come into contact (see Chapter 5).

(86) *Posterior Nose*: Cancers of the nasal cavity *per se* are mainly squamous cell carcinomas (67%), arising from the lateral walls of the nasal fossae and especially the turbinates. Other tumour types encountered are nonsquamous, mainly undifferentiated carcinomas (15%); adenocarcinomas (8%); and sarcomas (<5%). Esthesioneuroblastomas arising from olfactory epithelium are extremely rare (Batsakis, 1976). Paranasal sinuses are four times more often affected than the nasal cavity. Neoplasms in the sinuses, however, may be related more to gas and vapour inhalation exposure than to particle exposure.

(87) *Nasopharynx*: The lateral walls of the nasopharynx also contain target tissues for the development of cancer. Ninety-eight percent of the tumours arising in this region are carcinomas; four-fifths are keratinizing or nonkeratinizing epidermoid carcinomas, the remainder being unclassified carcinomas and adenocarcinomas (Batsakis, 1976).

(88) On the basis of the distribution of these cancer types, it is assumed that the tissues of the nasopharynx, which give rise to the predominant squamous cell type of tumour, are the appropriate tissues for dose calculation.

(89) *Mouth*: With the exception of the lower lip, the primary site of most tumours in Western countries is the tongue (del Regato *et al.*, 1985). Other sites are the oropharynx, which includes the tonsils, buccal mucosa, and floor of the mouth. More than 90% of mouth tumours are squamous cell carcinomas.

(90) *Larynx*: About 90% of tumours in the larynx are squamous cell carcinomas (Ferlito, 1985); undifferentiated carcinomas represent about 5%, sarcomas 0.5%; the remainder are composed of rare tumour types.

(91) *Glottis*: Glottic carcinomas are most frequent in the anterior half of the chords and the anterior commissure. Subglottic carcinomas rarely arise between the inferior border of the vocal folds and the inferior margin of the cricoid cartilage (Batsakis, 1976). Epiglottic carcinomas represent about 25% of laryngeal cancers in most populations, but their incidence is much higher in Finnish, French, and Mediterranean populations.

4.2.2. *Types of thoracic cancers*

(92) Because tumours of the trachea are rare, this tissue is not considered to be at significant risk following inhalation of radioactive particles and gases.

(93) There are four major classes of thoracic cancer: (1) squamous cell carcinoma (epidermoid carcinoma); (2) small cell carcinoma, which includes oat cell and intermediate cell types; (3) adenocarcinoma, which includes acinar and bronchiolar-alveolar types; and (4) large cell carcinoma, which includes giant and clear cell types.

Primary sarcomas are rare in both humans and experimental animals (Reznik-Schüller, 1983). There are also a number of other, rare types of lung cancer. The four major classes of cancers are unevenly distributed within the lungs. A large excess of both spontaneously occurring and radiation-induced cancers are observed in the upper lobes (Yamamoto *et al.*, 1987b), but the exact location where tumours originate in the airways is not easily determined. The largest proportion of lung tumours arise from the bronchi. Half of the lung tumours arise centrally from main bronchi, to the point of division of the segmental bronchi, generation 3, and half arise distally to the segmental bronchi (Spencer, 1985). A few malignant neoplasms are thought to originate from bronchiolar epithelium and alveolar lining cells; but, according to del Regato *et al.* (1985), the percentage arising from bronchioles may be higher than 25%.

(94) A detailed discussion of the relative frequencies of the four major classes of lung cancers among human populations is given in Annexe C, where several different studies are cited. In general terms, their range of frequencies can be summarized as follows:

- Squamous cell carcinoma—one-third to one-half
- Small cell carcinoma—one-sixth to one-third
- Adenocarcinoma—one-tenth to one-third
- Large cell carcinoma—less than one-tenth to one-fifth.

The factors influencing this distribution amongst smokers, males and females, and the differences between human and experimental animal tumours are also discussed in Annexe C.

4.2.3. *Influence of smoking on cancer type*

(95) Smoking habits have a marked influence on the distribution of cancer types in human populations. A working group of the International Agency for Research on Cancer (IARC, 1986) concluded that all cancer types can be induced by active tobacco smoking. However, it is not clear that all are induced equally; adenocarcinoma occurs less frequently than squamous cell and undifferentiated carcinoma. Exposure to passive tobacco smoke, on the other hand, appears to preferentially induce adenocarcinoma (Lam *et al.*, 1987). Because everybody is exposed to passive tobacco smoke, it may well be that the generally reported excess of adenocarcinoma in "nonsmokers" is due to this type of exposure. In a comparison of lung cancer pathology in uranium miners and atomic bomb survivors, there was no suggestion that the histological types of lung cancers induced by radiation were different between smokers and nonsmokers. The proportion of squamous cell carcinoma was positively related to cigarette smoking in both populations (Land *et al.*, 1993). In the absence of clear data to the contrary, therefore, it is assumed that the regional risk of radiation-induced tumours in the respiratory tract is the same in smokers and nonsmokers. Unfortunately, little can be said about numerous other inhaled substances that may affect the relative distribution of tumour types among the regions of the respiratory tract.

4.2.4. *Influence of radiation exposure on cancer type*

(96) In a report on lung cancer and indoor radon exposure, the proportion of tumours found in the general population was highest for small cell (oat cell) carcinoma and lowest for adenocarcinoma (Blot *et al.*, 1990). In a comparison of lung cancer types in uranium miners and atomic bomb survivors, Land *et al.* (1993) found that in both

populations the relative proportion of small cell carcinoma increased and tended to occur more in persons who received the highest radiation doses. In 92 uranium miners who died of lung cancer, 62% of the cancers were small cell carcinoma, compared with 13% in 108 cases of lung cancer in atomic bomb survivors. In the male bomb survivors, of whom 90% were smokers, the distribution of tumour types was 39% squamous cell, 14% small cell, and 34% adenocarcinoma. In the female survivors, of whom 70% were nonsmokers, 23% were squamous cell, 11% small cell, and 55% adenocarcinoma. The results of the analysis did not preclude the possibility that the risk of adenocarcinoma could increase by radiation exposure. For example, adenocarcinoma has been found in excess in atomic-bomb survivors (Yamamoto *et al.*, 1987b) and in uranium miners (Archer *et al.*, 1974); and it was the only tumour type found in beagle dogs exposed to fast neutrons or photons. In the dogs, the tumours occurred in the bronchial region (Zook *et al.*, 1986). Bronchiolar-alveolar carcinoma, a form of adenocarcinoma, has also been a frequent observation in beagle dogs and in rats following inhalation of alpha-emitting and beta-gamma-emitting radionuclides. Hemangiosarcomas have been seen in animals that inhaled beta-gamma emitters (Bair, 1986). Another tumour of epithelial origin, epidermoid (squamous cell) carcinoma, also occurs in animals. This tumour probably originates from secretory and/or basal cells in the bronchial epithelium. Generally, its frequency in rats, after protracted exposure to radon and its decay products, is increased more than that of adenocarcinoma (Cross, 1992). Less frequently, hemangiosarcomas (of endothelial origin) and, occasionally, connective tissue tumours (mesotheliomas) have been reported. Large cell carcinoma does not appear to be related to radiation exposures in either humans or experimental animals.

(97) Mesenchymal tumours, which have been observed in animals heavily irradiated by beta emitters (Hahn *et al.*, 1973), have not been observed in irradiated humans. It is unlikely, therefore, that they significantly influence the calculation of risk coefficients for lung tumour assessment. A similar conclusion can be reached for tumours of the pleura. However, distal airway tumours may be the main consequence of long-term retention of insoluble radionuclides in the parenchymal region of human lungs, as has been observed in animals.

(98) Lymph nodes can be the most heavily irradiated tissue following inhalation of insoluble particles. However, in studies of experimental animals that inhaled highly insoluble alpha-emitting or beta-gamma-emitting radioactive aerosols, there has been no evidence of resulting lymphatic tumours, even after intakes that severely damaged the thoracic lymph nodes (Bair, 1986). A significant excess of non-Hodgkin's lymphomas has been observed in irradiated ankylosing spondylitis patients (Darby *et al.*, 1985), but not in atomic-bomb survivors (Preston *et al.*, 1986). Selective irradiation of a few nodes after drainage of insoluble material deposited in wounds or in subcutaneous tissues after injection has not been associated with excess lymphomas. Nor has it been possible to establish a significant excess of Hodgkin's and other lymphomas in German Thorotrast patients (van Kaick *et al.*, 1986), despite rather large amounts of material transferred to the nodes in cases where extravasation of material occurred. It should be noted that the incidence of non-Hodgkin's lymphomas was higher in the treated than in the control patients, which might indicate that the sensitivity of nodes to alpha irradiation was low, but not necessarily zero. Cancer risk in the nodes was estimated to be lower than in the liver by two orders of magnitude, assuming the doses delivered were comparable. Other limited evidence of increased prevalence of lymphatic neoplasms in occupational workers exists (Voelz *et al.*, 1989).

4.2.5. *Summary distribution of the major cancer types*

(99) Amongst nonsmokers the proportion of spontaneously occurring squamous cell carcinoma is less than in smokers, while the proportion of adenocarcinoma is greater. Thus, for nonsmokers about 30% of lung cancers are squamous cell carcinomas, 20% are small cell carcinomas, 45% are adenocarcinomas, and 5% are large cell carcinomas. For smokers, the proportion of squamous cell carcinoma may be 50%; the proportion of adenocarcinoma may be about 25%. In irradiated populations, small cell carcinoma increased disproportionately and adenocarcinoma decreased, although the results did not preclude the possibility that the incidence of adenocarcinoma was increased by radiation exposure of these populations. While direct evidence is lacking in humans, the results of animal studies are clear in demonstrating that adenocarcinoma can be a consequence of radiation exposure. There are some differences amongst ethnic groups, but differences between smokers and nonsmokers are probably greater.

4.3. Progenitor Cells of Respiratory Tract Cancers

(100) For dosimetry modelling purposes it is necessary to identify the type and location of progenitor cells of cancers likely to result from radiation exposure. It is assumed that radiation is capable of inducing all of the major respiratory tract cancer types that occur in human populations, with the exception of large cell carcinoma. There is no evidence that the rarer types of cancers are disproportionately increased as a result of irradiation in humans and experimental animals.

4.3.1. *Extrathoracic tissues*

(101) It is assumed that cells at risk in the tissues of the anterior nose are basal cells of the keratinized epithelium, distributed at a depth of 40–50 μm in the epithelium. Epithelial tissues assumed to be at risk in the posterior nose and naso-oropharynx also contain basal cells at 40- μm to 50- μm depth. Tissues at risk in the mouth and larynx are considered to be those containing basal cells at 40- μm to 50- μm depth (see Chapter 2).

(102) In summary, the majority of tumours of the extrathoracic tissues are assumed to originate in basal cells of stratified squamous epithelium that lie at about 40- μm to 50- μm depth. There is some indication that progenitor cells are located at epithelial depths greater than 50 μm from the surface, but these data are not well documented in humans (P. Gehr and R. Masse, personal observations).

4.3.2. *Thoracic tissues*

(103) There is continuing debate amongst pathologists as to the cells from which cancers arise in thoracic tissues. Identification of the progenitor cells is important, especially those that are sensitive to radiation, because their location in the epithelium of the respiratory tract determines the magnitude of radiation doses they might receive from deposited radionuclides that emit alpha or beta particles with a relatively short penetration range in tissue.

(104) One view is that the four major types of human carcinoma are derived from the same endodermic progenitors (McDowell *et al.*, 1978; Yessner, 1981). Of the numerous types of cells in the bronchial and bronchiolar epithelium, only basal and secretory cells appear to have the potential for proliferation. According to Spencer

(1985), basal cells in the bronchial epithelium are progenitors of Kulchitsky-like cells and intermediate (indifferent) cells. The former may give rise to the oat cell form of small cell carcinoma, and secretory cells may undergo metaplasia into squamous cell carcinoma. This is at variance with the conclusion of Gazdar and Linnoila (1988), who considered tall secretory cells as the most likely candidates for progenitors of all tumour types. Small cell carcinoma in humans, like squamous cell carcinoma, is mainly located centrally, progressively fewer occurring in the smaller airways.

(105) McDowell *et al.* (1978, 1987a,b) concluded that columnar secretory cells (young mucous cells) have a greater proliferative potential than basal cells and are the most likely progenitors in most bronchial lung tumours. This has been supported by studies of Johnson and Hubbs (1990), who found that basal cells repopulated denuded tracheal epithelium, but only with basal and ciliated cells, while secretory cells repopulated denuded epithelium with secretory, basal, and ciliated cells. It was postulated that, since the differentiating capacity of the basal cells seemed to be limited, the secretory cells were the likely major progenitor for the bronchial epithelium. Rats exposed to alpha emitters developed hyperplastic and metaplastic lesions in tissues made up of all cellular types of the pseudostratified epithelium except basal cells, where the only progenitors are secretory cells (Masse, 1980). Recent studies (Jetten *et al.*, 1992) indicate that keratinization in basal cells is consistent with the observation that basal cells appear during development after the columnar cells (Plopper *et al.*, 1986). These studies suggest that basal cells are derived from the intermediate cell and may not be the true stem cell in the tracheobronchial epithelium. Other observations are at variance with this conclusion in that: (1) only basal cells may be involved in late progression of human bronchial epithelium from normal to metaplastic following a transient contribution of tall columnar secretory cells (Yamamoto *et al.*, 1987a); (2) 90% pure basal cells, obtained from rabbit trachea, repopulated denuded tracheal grafts *in vitro* (Inayama *et al.*, 1988); and (3) proliferative capacity studies of basal and secretory cells separated by flow cytometry and a magnetic separation technique showed that the basal cell is the most likely stem cell of the rat tracheal epithelium (Ford and Terzaghi-Howe, 1992a,b). The latter authors believe their results differed from those of Johnson and Hubbs (1990) because they were able to achieve more complete separation of basal and secretory cells for their proliferative capacity tests. In rats exposed to tobacco smoke, both basal cells and tall columnar cells participate in the regeneration of the epithelium (Aayers and Jeffery, 1982).

(106) Despite some lack of information concerning the precise role of pre-existing basal cells in the human bronchus in the process of neoplasia, the central role of secretory cells as multipotent progenitors is not invalidated by the observation that basal cells play some role in the process of regeneration and dysplasia. Both cell types must therefore be considered as cells at risk. A National Academy of Sciences panel on dosimetric assumptions affecting the application of radon risk estimates, after considering the cells of origin of lung cancer, also concluded that secretory as well as basal cells should be included in dose calculations (NAS, 1991). In this report it is assumed that the tumours resulting from radiation exposure of the bronchial epithelium (and the cell types from which they derive) are: squamous cell carcinoma (basal and secretory cells) and small cell carcinoma (basal, secretory, or precursor cells).

(107) The bronchiolar epithelium consists of two principal cell types, ciliated columnar cells and nonciliated secretory (Clara) cells. Of these, only the Clara cell is considered to be the cell of origin of cancers (Greenberg, 1982). Clara cells are thought

to be the progenitor cells for adenocarcinoma, including those that show a bronchiolar-growth form (McDowell *et al.*, 1978).

(108) In the AI region, Clara cells, type II epithelial cells, and epithelial cells of blood capillaries are considered potential candidates from which cancers can arise (ICRP, 1980). Adenocarcinoma, in particular bronchiolar-alveolar carcinoma, is of special interest in this as well as in the bronchiolar region, because of its consistent appearance in experimental animals after inhalation of insoluble radionuclides (Bair, 1986).

(109) In summary, for dosimetric modelling purposes, it is assumed that the nuclei of secretory cells at risk in the bronchi are homogeneously distributed in the epithelium from a minimum depth of about 10 μm below the cilia, which is the average distance between the apex and upper nucleus pole of nonciliated columnar secretory cells (see Chapter 2). The nuclei of basal cells are assumed to be distributed from a minimum depth of 35 μm below the cilia. In the bronchioles it is assumed that the nuclei of secretory (Clara) cells are homogeneously distributed in the epithelium from a minimum depth of about 4 μm . Epithelial thicknesses, excluding the functional height of the ciliated sheet to the basement membrane, continually decrease from about 60 μm in the main bronchi to about 15 μm in bronchioles less than 1×10^{-3} m in diameter (Mercer *et al.*, 1991a). Surprisingly, no difference in epithelial thickness between smokers and nonsmokers was noted by Baldwin *et al.* (1991). In the AI region, secretory (Clara) cells, type II epithelial cells, and epithelial cells of capillaries are all considered target cells.

(110) Because tumours in the lymph nodes are rare both in laboratory animals and humans exposed to radiation, lymphoid cells were not considered at risk by the Commission (ICRP, 1980). Considering all the evidence, including the possibility that lymph node doses may be more than ten times the average lung dose, it is unlikely that the total risk to the nodes exceeds 1/100th of the total risk to the respiratory tract, and it is more probably approaching a risk of 1/1000th.

4.4. Partition of Detriment

(111) Although it is known that the distribution and types of radiation-induced cancers vary markedly amongst the extrathoracic regions, the airways of the lungs, and the regions of gaseous exchange, the dose-response relationships are not well enough documented to partition the risk with any degree of confidence. In seeking alternative approaches to partitioning the risk, consideration was given to applying the relative risk concept, in which it is assumed that the induction of cancer by radiation exposure is proportional to the spontaneous incidence in tissue. This approach is indirectly supported by data on the atomic bomb survivors, where the relative risk coefficient has remained constant over time (Preston *et al.*, 1986), although the age-specific absolute excess risk has increased with ageing. Current information on the relative distribution of the four major histological types of lung cancer in nonirradiated and irradiated human populations and experimental animals, and knowledge about the locations within the respiratory tract of the most likely progenitor cells for each tumour type, were reviewed to develop a basis for apportionment of the radiation detriment for purposes of summing calculated radiation doses to the extrathoracic and thoracic tissues.

4.4.1. *Partition of detriment amongst extrathoracic regions*

(112) The radiation detriment in the ET₁ region (anterior nose) is based on the assumption that sensitivity of the external nasal skin area is no different from the sensitivity of skin elsewhere on the body. The Commission (ICRP, 1991a) assigned 0.6% of the total radiation detriment to the skin. This is based on the entire skin being irradiated, an area of about 18,000 cm². Since the risk of skin cancer is proportional to the area of skin exposed to radiation, the detriment from exposure of only 20 cm² of skin of the anterior nose would be a negligible fraction of the 0.6% assigned to the total skin. There is no evidence that the risk to the remaining part of the anterior nose is any greater. The much higher radiosensitivity of the posterior nasal passages, larynx, and mouth compared with the anterior nose justifies the apportionment of a higher weighting factor to this region. Conversely, the lymphatic system in the ET region has a relatively lower sensitivity. Accordingly, detriment for the ET region is partitioned amongst the ET₁, ET₂, and lymphatic tissues as 0.001, 1.0, and 0.001, respectively. (See Annexe C.)

4.4.2. *Partition of detriment amongst thoracic regions*

(113) For an average population of nonsmokers and smokers, the distribution of cancers is assumed to be 40% squamous carcinoma, 20% small cell carcinoma, 35% adenocarcinoma, and 5% large cell carcinoma. It is only possible to approximate the sites of origin of the major lung cancer types in the three regions of the lungs defined in this report. This is because: (1) lung tumours are frequently not observed until growth of the tumour has progressed well beyond the site of origin, or there is more than one site of origin; (2) variations exist among individuals with respect to lung cytology; and (3) tumours often show mixed cell types. It is assumed that most of the squamous cell carcinomas originate in the bronchial region because they derive largely from basal cells found only in this region and/or from secretory cells found primarily in this region. Small cell carcinoma, like squamous cell carcinoma, is mainly located centrally, in the bronchial region. The cell of origin is not clear, but the tumour may arise from basal and/or secretory cells or from more primitive epithelial precursor cells (NAS, 1991). There is some evidence of small cell carcinoma occurring in the smaller airways (Matthews and Gazdar, 1982). Adenocarcinoma is mainly peripheral, although as noted above, it occurs in the bronchial region of dogs exposed to neutrons or photons. According to Spencer (1985) adenocarcinomas rarely arise from secretory cells in the epithelium of the larger bronchi; the majority arise in the lung periphery, which is interpreted to mean the bb and AI regions for the purpose of this report. Large cell carcinomas include undifferentiated tumours that examination by electron microscopy has shown to be squamous carcinomas or, more often, adenocarcinomas (McDowell *et al.*, 1978). Tateishi and Hattori (1982) found about one-fourth of large cell carcinomas in the central zone of the lungs, and three-fourths distal to the subsegmental bronchi and in bronchioli. From about 2% to 20% of all lung cancers may develop from scars and fibrosis resulting from injuries to areas devoid of bronchial tissue, i.e. mainly in the AI region, airway generations 16 and beyond (Spencer, 1982, 1985). (These scar cancers are mainly adenocarcinomas and a few squamous cell carcinomas and other rare tumour types.) For the purposes of this report, both nonsmokers and smokers must be considered. Thus, it is assumed that, in populations exposed only to background levels of radiation, about four-fifths of squamous cell and small cell carcinomas,

one-fourth of adenocarcinomas, and one-half of large cell cancers originate in the BB region, generations 1 to 8. The remaining squamous cell, small cell, and large cell carcinomas, and one-half of the remaining adenocarcinomas are assumed to originate in the bb region, generations 9 to 15. The remaining adenocarcinomas are assumed to originate in the AI region.

(114) In considering what is known about the relative induction of these four types of lung cancer following exposure to radiation, the most relevant may be the finding that small cell carcinoma was disproportionately increased in the atomic bomb survivors and in uranium miners (Land *et al.*, 1993). Small cell carcinomas originate mainly in the BB region and are considered the most malignant of all bronchial cancers (Spencer, 1985). In the atomic bomb survivors, squamous cell carcinoma, also a tumour of the BB region, was identified with smoking rather than radiation exposure, but this tumour type has been observed in experimental animals after inhalation of radon and, to a lesser extent, insoluble radionuclides. Results from experimental animal studies generally indicate that, when the lungs are reasonably uniformly irradiated, e.g. beagle dogs irradiated with neutrons or photons (Zook *et al.*, 1986), cancers occur predominantly in the BB region. There is also evidence that rats exposed to neutrons and radon develop more lung carcinomas per absorbed dose than rats exposed to inhaled insoluble alpha emitters in which the majority of the radiation dose is delivered to the AI region (Masse and Cross, 1989).

(115) It is not clear from the published literature whether adenocarcinoma (bronchiolar-alveolar carcinoma), which occurs in animals exposed to insoluble radionuclides, arises from the bb region (e.g. terminal bronchioles), from the AI region, or at the juncture of the two. Since Clara cells, one of the progenitor cells of adenocarcinoma, are found in both regions, it is assumed that adenocarcinoma originates in both regions almost equally. Adenocarcinomas were reported in the atomic bomb survivors (Yamamoto *et al.*, 1987b) and in uranium miners (Archer *et al.*, 1974), but, since the sites of origin were not clear, it can only be assumed that they were principally peripheral tumours of the bb and AI regions. In discussions of the distributions of cancer types, most authors (for example, Spencer, 1985) report that the majority of squamous cell and small cell cancers arise in the larger central airways, implying that a few probably also arise in the smaller airways of the bb region.

(116) It is not known for certain that radiation exposure results in human cancer of the AI region. However, in animals that inhaled insoluble radionuclides, bronchiolar adenocarcinoma or bronchiolar-alveolar carcinoma appeared to originate in the lung periphery from secretory (Clara) cells in the bb or AI regions or, possibly, from pneumocyte type II cells. Hemangiosarcoma also occurred in animals that inhaled beta-gamma-emitting radionuclides. In these cases the alpha radiation from inhaled radionuclides, especially from alpha emitters like plutonium, was nonuniform and was delivered mostly to the region where the tumours appeared to originate. These results indicate that the AI region is not risk free.

(117) The information summarized in the preceding paragraphs appears to indicate that uniform irradiation of the thorax is more likely to lead to the induction of cancer in the BB region than in the AI region and probably also in the bb region. However, the data are insufficient to quantify the relative sensitivity of the BB, bb, and AI regions to radiation-induced cancer, which would provide a reasonable basis for apportionment of the radiation detriment with sufficient confidence to weight calculated regional doses for purposes of summing to obtain a single value of dose to represent the total thoracic

region. In the absence of adequate quantitative information about the relative sensitivities of the different respiratory tract tissues in the thorax, and until such information is available, it is recommended that the BB, bb, and AI regions each be assigned one-third of the total risk. In addition the thoracic lymphatic tissues are assigned 0.1% of the risk, consistent with the value assigned to the extrathoracic lymphatic tissues. The apportionment of detriment, the assigned fractions of the ICRP tissue weighting factors (w_T) that are to be applied to extrathoracic and thoracic respiratory tract tissues, is given in Table 10. Because of rounding, the total for the extrathoracic region is not exactly 1, which is not significant for this purpose. The doses so weighted by these factors are summed to obtain a detriment-weighted equivalent dose for the extrathoracic region and another for the thoracic region, as follows:

$$H_{ET} = H_{ET_1}A_{ET_1} + H_{ET_2}A_{ET_2} + H_{LN_{ET}}A_{LN_{ET}} \quad (1)$$

and

$$H_{TH} = H_{BB}A_{BB} + H_{bb}A_{bb} + H_{AI}A_{AI} + H_{LN_{TH}}A_{LN_{TH}} \quad (2)$$

where H_{ET} and H_{TH} are detriment-weighted equivalent doses for the extrathoracic and thoracic regions, respectively; H_{ET_1} , H_{ET_2} , $H_{LN_{ET}}$, and H_{BB} , H_{bb} , H_{AI} , and $H_{LN_{TH}}$ are equivalent doses for tissues in the extrathoracic region and in the thoracic region, respectively; and A_{ET_1} , A_{ET_2} , $A_{LN_{ET}}$, and A_{BB} , A_{bb} , A_{AI} , and $A_{LN_{TH}}$ are factors for apportionment of radiation detriment from Table 10 for the extrathoracic region and for the thoracic region, respectively.

Table 10. Weighting factors assigned for the partition of radiation detriment among respiratory tract tissues

Tissue	Assigned fractions (A) of w_T
Extrathoracic region	
ET ₁ (anterior nose)	0.001
ET ₂ (posterior nasal passages, larynx, pharynx, and mouth)	1
LN _{ET} (lymphatics)	0.001
Thoracic region	
BB (bronchial)	0.333
bb (bronchiolar)	0.333
AI (alveolar-interstitial)	0.333
LN _{TH} (lymphatics)	0.001

4.4.3. Use of detriment-weighted equivalent doses to the respiratory tract in the ICRP dosimetry system

(118) Based on an assessment of the distribution of the aggregate radiation detriment amongst organs and tissues, the Commission developed a series of tissue weighting factors to be applied to equivalent doses to calculate weighted equivalent doses for each tissue specified. These are summed to obtain the effective dose for the individual. The purpose of this dosimetric model for the respiratory tract is to provide a means for calculating equivalent doses that can be adjusted by appropriate tissue weighting factors and to represent the total detriment to the respiratory tract from the intake of radionuclides. In *ICRP Publication 60* (ICRP, 1991a), a tissue weighting factor, w_T , of

0.12 is assigned to the lungs; other tissues of the respiratory tract are not listed. However, the weighting factor scheme assigns a value of 0.05 to remainder tissues. Although 9 remainder tissues are specified, provision is made for other tissues that may be selectively irradiated and that show a significant risk of radiation-induced cancer. When a single organ or tissue receives an equivalent dose in excess of the highest dose in any of the 12 organs and tissues for which weighting factors are specified, a weighting factor of 0.025 is to be applied.

(119) It is recommended that the tissue weighting factor, 0.12, specified for the lungs be applied to the detriment-adjusted equivalent dose calculated for the thoracic region of the respiratory tract. Distributing the weighting factor of 0.12 for the lungs amongst the thoracic tissues gives 0.04 to each of the BB, bb, and AI regions and 0.00012 to the LN_{TH} region. The extrathoracic tissues (ET_1 and ET_2 regions) are to be added to the list of remainder tissues.

5. DEPOSITION MODEL

(120) A model of the deposition behaviour of aerosols and vapours in the respiratory tract is required to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region of exposed individuals.

(121) The model is required to estimate regional deposition for a wide range of particle sizes associated with potential exposures. This range extends from atomic dimensions (approximately $0.0005 \mu\text{m}$ in diameter) to large environmental aerosols characterized by an activity median aerodynamic diameter (AMAD) on the order of $100 \mu\text{m}$, applying to various subjects, taking into account body size and the physiological factors determined by gender, age, and ethnic characteristics, as well as various conditions of exposure, taking into account the level of physical exertion.

(122) This model is also required to evaluate the bounds of uncertainty in estimates of regional deposition. Uncertainties arise from natural biological variability among individuals exposed under similar external conditions, and also from the need to interpret experimental evidence that remains inconclusive in several respects.

5.1. Deposition Compartments

(123) The clearance model, which is described in Chapter 7, identifies the principal clearance pathways within the respiratory tract that are important in determining the retention of various radioactive materials, and thus doses received, by respiratory tissues and/or other organs. The deposition model is required to estimate the amount of inhaled material that enters each input compartment shown in Fig. 7. The figure indicates those compartments in which inhaled material may be initially deposited.

5.1.1. Extrathoracic airways

(124) The extrathoracic airways are partitioned into two distinct clearance and dosimetric regions: the anterior nasal passages (ET_1), and all other extrathoracic airways (ET_2), i.e. the posterior nasal passages, the naso- and oropharynx, and the larynx. The deposition model is required to provide estimates of fractional deposition in both regions. As discussed in Chapter 7, particles deposited on the surface of the skin lining

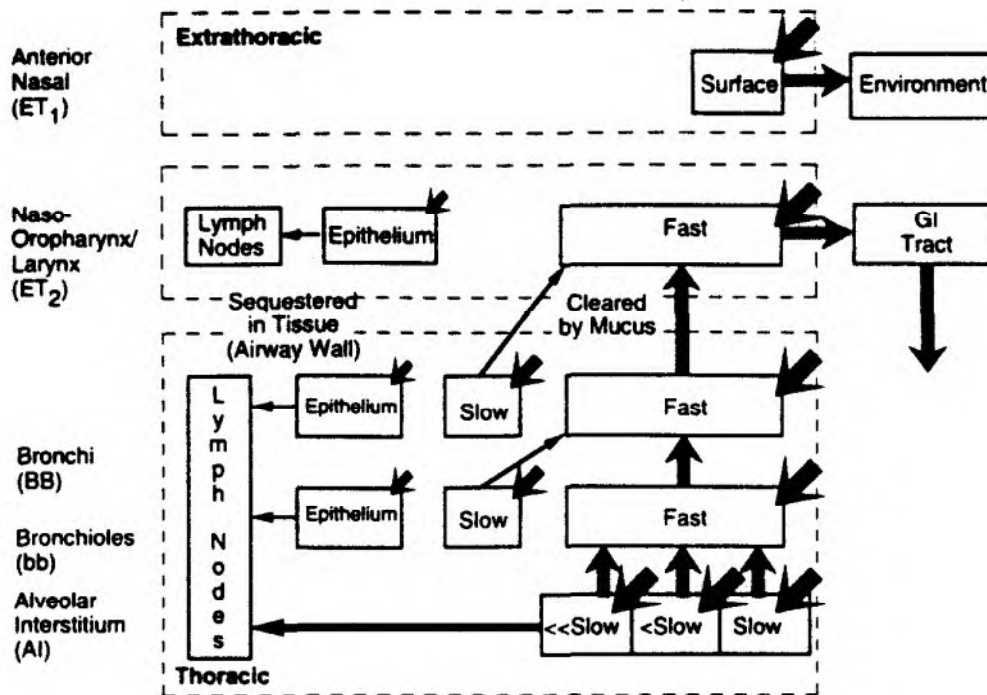


Fig. 7. Respiratory tract compartments in which inhaled particles may be deposited. See Chapter 7 for explanation of clearance pathways, clearance rates, and subfractions of activity deposited in ET₁, BB, bb, and AI committed to different pathways.

the anterior nasal passages are assumed to be subject only to removal by extrinsic means (nose blowing, wiping, etc.). The bulk of material deposited in the naso-oropharynx or larynx (ET₂) is subject to fast clearance in the layer of fluid that covers these airways.

5.1.2. Thoracic airways

(125) Activity deposited in the thorax is divided amongst the BB and bb regions (which are subject to relatively fast ciliary clearance), and the AI region (which is not subject to fast ciliary clearance). See Chapter 7.

(126) For dosimetry purposes, deposition of inhaled material is divided between the trachea and bronchi (BB), and in the more distal, small airways, the bronchioles (bb) (Fig. 7). However, as discussed in Chapter 7, the subsequent efficiency with which cilia in either type of airway are able to clear deposited particles is controversial. In this mode it is assumed that as much as half the number of particles deposited in these airways is subject to "slow" clearance. The likelihood that a particle is cleared slowly by the mucociliary system appears to depend on its physical size (Chapter 7).

(127) As described later (Chapter 7), material deposited in the AI region is subdivided among three compartments (AI₁, AI₂, and AI₃) that are each cleared slowly, but at different characteristic rates.

5.2. Model Derivation

(128) This chapter describes the model for deposition of inhaled aerosol particles. Deposition of gases and vapours is addressed in Chapter 6. The data on deposition of

inhaled particles in the human respiratory tract that are reviewed in Annexe D represent a major advance in the knowledge of the effects of aerosol size and breathing rate over that available to the previous ICRP lung model task group (TGLD, 1966). However, these data apply essentially to the adult Caucasian male; they still relate, in the main, to a particle size ranging from about 1- μm to 10- μm aerodynamic diameter, d_{ae} . Experimental information on regional deposition remains incomplete and, on close examination, controversial in several respects (Annexe D).

(129) To model particle deposition in the extrathoracic airways, an empirical method based directly on experimental data was used, as described in Annexe D. In this method, measured deposition is related to characteristic physical parameters of particle size and airflow (TGLD, 1966; Rudolf *et al.*, 1986, 1990; Stahlhofen *et al.*, 1989). Deposition efficiencies determined experimentally for adult male subjects are scaled by anatomical dimensions to predict extrathoracic deposition in women and children (Swift, 1989).

(130) In the case of thoracic deposition, substantial progress has been made in theoretical modelling of aerosol transport and deposition within the lung (Taulbee and Yu, 1975; Heyder and Rudolf, 1984), in parallel with the experimental studies of aerosol deposition in volunteer subjects. Theoretical modelling is necessary both to help interpret the data and to make predictions beyond the observations (for example, of regional deposition within the lung, and of deposition characteristics in children).

(131) A theoretical model of gas transport and particle deposition (Egan *et al.*, 1989) was applied to evaluate the subdivision of particle deposition amongst the BB, bb, and AI regions of the lungs, and to quantify the effects of a subject's lung size and breathing rate.

(132) The theoretical model is based on the work of Taulbee and Yu (1975) and Pack *et al.* (1977), which was developed further by Egan and Nixon (1985, 1987), Nixon and Egan (1987), and Egan *et al.* (1989). The model evaluates the combined effects of convective and diffusive gas transport, and aerosol loss processes, within the airways of the lungs. The structure of the lungs in different subjects is represented explicitly by a morphometric anatomical model (Chapter 2). A subject's particular breathing pattern is simulated by allowing the volumes associated with the alveolar interstitium to expand and contract from the FRC. Bulk mixing of tidal and residual air, induced by complex airflow patterns, is represented empirically by an equivalent diffusive transport of air into the lungs (Scherer *et al.*, 1975). Inclusion of this mixing phenomenon is important to represent wash-in and subsequent deposition of airborne particles of low intrinsic mobility, where equilibrium conditions are attained only after several breaths. Aerosol deposition is calculated from the combined effects of gravitational settling, inertial impaction, and Brownian diffusion. Particle settling is treated explicitly in relation to the physical airway dimensions. Treatment of inertial impaction, which is important only in the larger bronchial airways, is based on empirical observations made under realistic flow conditions in hollow casts of the human bronchi (Gurman *et al.*, 1984). Particle diffusion in the conducting and respiratory bronchioles, and in the alveoli, where airflow is dominated by viscous forces, is treated explicitly in relation to airway dimensions. In the bronchial airways, where the airflow is more complex, the physical treatment of particle diffusion is corrected empirically for the enhanced particle deposition observed in hollow airway casts, again under realistic flow conditions (Cohen *et al.*, 1990).

(133) The approach was, first, to compare the theoretical model's simulations with the available experimental information. This comparison is described in Annexe D. The model is found to predict accurately the experimental data relating total thoracic deposition to particle size and breathing behaviour. The model also succeeds in simulating the variation of regional deposition with particle size and breathing pattern that was inferred by Stahlhofen *et al.* (1980, 1983) from their measurements of thoracic deposition and retention.

(134) In common with earlier theoretical models (Yeh and Schum, 1980; Yu and Dui, 1982), the theoretical model predicts significantly less thoracic deposition for particles in the range of d_{ae} from 1- μm to 5- μm than the median values reported by Lippmann (1977) and Chan and Lippmann (1980). These data are crucial, since they represent the largest group of experimental subjects studied to date. However, as described in Annexe D, when allowance is made for the hygroscopic growth within the lungs of the particulate material used in the New York University studies, these key experimental measurements are also found to support the predictions of the deposition model.

5.3. Form of the Recommended Model

(135) To provide a model that is straightforward, yet accurate to apply, a semiempirical approach was used to describe values of regional deposition derived from experiments, and/or theory, by relatively simple algebraic approximations (as shown in Annexe D). These formulae constitute the recommended deposition model.

(136) In this model, each region of the respiratory tract is represented by an equivalent particle filter that acts in series, as shown in Fig. 8.

5.3.1. General formulation of particle deposition from tidal airflow

(137) In the empirical filtration model, each breath is represented by a tidal flow of air that carries particles through each anatomical region, which is represented by one or more filters, in series (Fig. 9). Each of these filters has two characteristic parameters: its volume and its overall efficiency for removing airborne particles. For the j th filter, these characteristic parameters are denoted by v_j and η_j , respectively.

(138) Denoting the volume of the tidal flow by V_T , the fraction ϕ_j of tidal air that reaches the j th filter on inhalation is given by Eq. (3) where v_{jj} is the volume of a preceding filter, jj .

$$\begin{aligned} \phi_j &= 1, \quad \text{if } j=0 \\ \phi_j &= 1 - \frac{1}{V_T} \sum_{jj=0}^{j-1} v_{jj}, \quad \text{if } 1 \leq j \leq (N+1)/2 \end{aligned} \tag{3}$$

and N is the number of filters, i.e. deposition regions in the respiratory tract, for the complete breathing cycle. (See Fig. 8.)

(139) Thus, on inhalation, a successively smaller fraction of the inspired air passes through each filter in turn. This fraction, ϕ , is determined by the cumulative volume of the preceding filters.

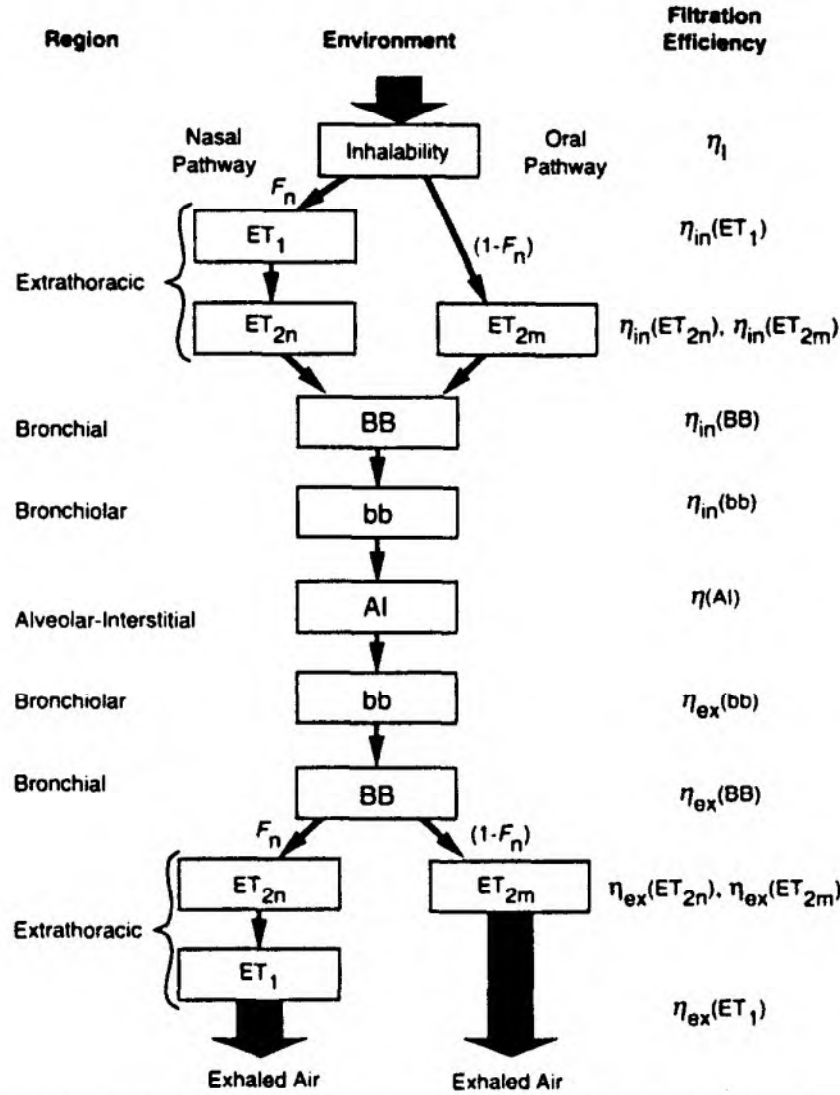


Fig. 8. Empirical representation of inhalability of particles and their deposition in the extrathoracic, bronchial, bronchiolar, and alveolar-interstitial regions of the respiratory tract during continuous cyclic breathing by transport through a series of filters. Two pathways of intake are considered: the nasal pathway, for which the fractional airflow is F_n ; the oral pathway, for which the fractional airflow is $1-F_n$. The subscripts "in" and "ex" of the filtration efficiency, η , represent the inhalation and exhalation phases of the breathing cycle, respectively.

(140) On exhalation, the volume of air returning through each filter is equal to the volume that passed through the filter on inhalation. Thus, the volumetric fraction, ϕ , on exhalation is given by Eq. (4):

$$\phi_j = \phi_{N-j+1}, \quad \text{for } j = (N+3)/2, N. \quad (4)$$

(141) In this system of sequential filters, the output of the j th filter provides the input to the $(j+1)$ th. The filtration efficiency, η_j , of the j th filter is defined as the fraction of particles entering the filter that deposits in it, or the complement of the filter output divided by its input, i.e. $\eta_j = 1 - I_{j+1}/I_j$.

(142) Taking into account both the volumetric factor, ϕ , and the efficiencies of the preceding filters in the series, the fraction DE_j of the number of particles, I_0 , sampled

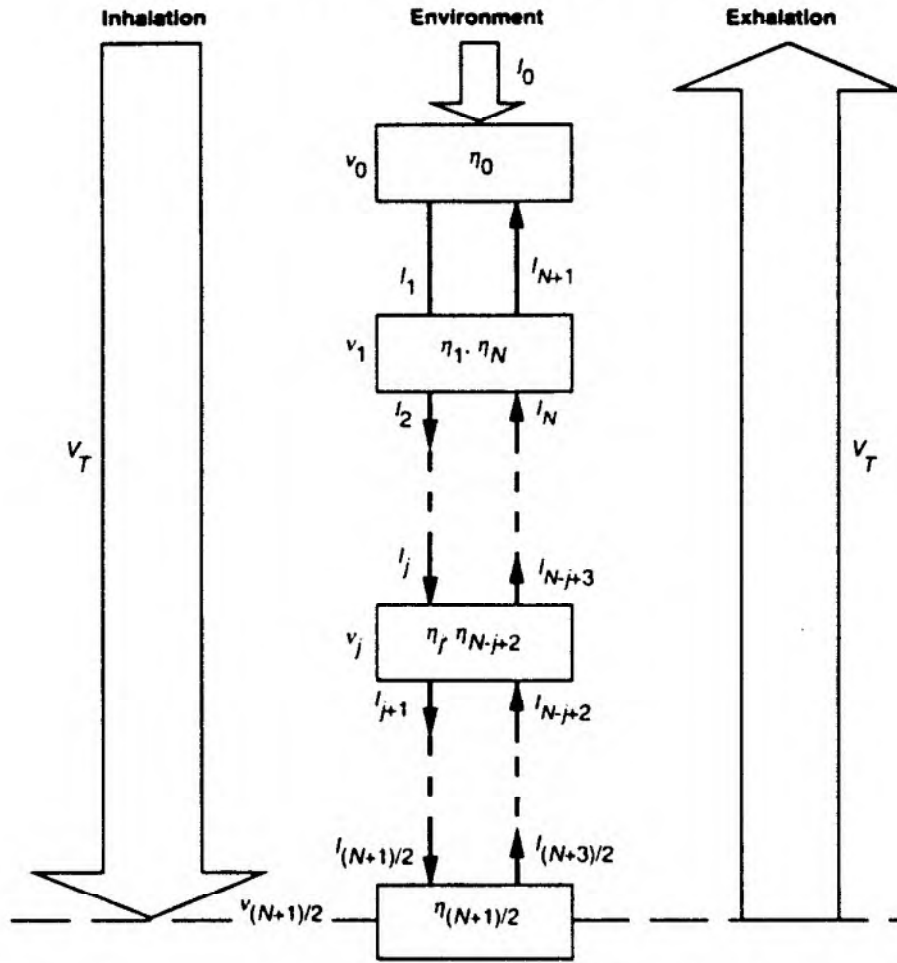


Fig. 9. General representation of aerosol deposition for tidal flow through a series of filters.

from the environment by the initial filter that is deposited in the j th filter, is given by Eq. (5):

$$DE_j = \eta_j \phi_j \prod_{n=0}^{j-1} (1 - \eta_n). \quad (5)$$

(143) Defining ξ_n as the quotient ϕ_n / ϕ_{n-1} , then ϕ_n can be replaced by

$$\prod_{n=1}^j \xi_n.$$

Thus, the expression for DE_j becomes:

$$DE_j = \eta_j \left(\prod_{n=1}^j \xi_n \right) \left(\prod_{n=1}^{j-1} (1 - \eta_n) \right). \quad (6)$$

(144) This enables fractional deposition to be expressed recursively:

$$DE_j = DE_{j-1} \eta_j \xi_j \left(\frac{1}{\eta_{j-1}} - 1 \right), \quad \text{for } j = 1, N \quad (7)$$

where N is the number of filters in series, excluding the initial (zero) filter.

(145) This recursive relationship is used to evaluate fractional deposition in each region of the respiratory tract for inhalation and exhalation in terms of that in an equivalent filter.

(146) As shown in Fig. 9, the initial filter is denoted by the subscript zero. This represents the potential loss of particles at either of the inlets to the respiratory tract, i.e. before entering the nose or mouth. The deposition efficiency, η_0 , of this imaginary prefilter is the complement of the so-called "inhalability" or intake efficiency with which airborne particles are inspired into the respiratory tract. The prefilter has no volume, i.e. $v_0 = 0$. Thus, from Eq. (3), the volumetric fraction $\phi_0 = 1$.

(147) Substitution of these parameters for the prefilter in Eq. (7) gives the fraction of the number of particles, I_0 , sampled from the environment deposited in the first filter of the respiratory tract. In this case, ϕ_1 , the volumetric fraction of the tidal flow that enters the first deposition filter is unity. Thus, the parameter ξ_1 is also unity, and the fractional deposition in the first filter of the respiratory tract is given by Eq. (8):

$$DE_1 = \eta_1(1 - \eta_0). \quad (8)$$

(148) This value of DE_1 is substituted in the recursive relationship defined by Eq. (7) to evaluate fractional deposition in each of the $(N-1)$ subsequent filters that represent deposition in specific regions of the respiratory tract.

5.4. Specification of Filtration Efficiencies

5.4.1. Intake from the environment

(149) In the general model of sequential filtration (Fig. 9), I_0 represents the intake of particles from the environment by the initial filter. In terms of the concentration of activity in air, C_A (in Bq m^{-3}), the exposure duration, t (in h), and the individual's breathing rate, B (in $\text{m}^3 \text{h}^{-1}$), the nominal intake of activity, I_0 (in Bq), is given by Eq. (9):

$$I_0 = C_A t B. \quad (9)$$

5.4.2. Regional deposition efficiency

(150) As described in Annexe D, the deposition efficiency of each respiratory tract filter is represented by two components: η_{ac} , which arises from the "aerodynamic" deposition processes of impaction and gravitational settling, and η_{th} , which arises from the "thermodynamic" process of particle diffusion by Brownian motion. Since aerodynamic and thermodynamic processes act competitively to remove particles, it can be shown (see Annexe D) that the combined deposition efficiency of region i is given by Eq. (10):

$$\eta_i = (\eta_{ac}^2 + \eta_{th}^2)^{1/2}. \quad (10)$$

(151) The component of deposition due to gravitational settling and particle inertia is represented in terms of the particle aerodynamic diameter, d_{ac} (in μm); that due to thermodynamic motion is represented in terms of the particle diffusion coefficient, D (in $\text{cm}^2 \text{s}^{-1}$).

5.5. Parameters of the Deposition Model

5.5.1. Definition of terms

(152) All special terms used below in the algebraic formulae to evaluate fractional deposition of particles and airborne activity in each region of the respiratory tract are defined in the Glossary.

5.5.2. Intake by the respiratory tract

(153) As mentioned earlier, the prefiltration efficiency, η_0 , of the respiratory tract is the complement of the more familiar term "inhalability" or intake efficiency, η_1 . Thus:

$$\eta_0 = (1 - \eta_1) \quad (11)$$

(154) Particle inhalability is assumed to depend on d_{ae} of the airborne particles and generally to decrease with d_{ae} . However, for very large particles, the inhalability is assumed to increase with windspeed (Annexe D). The following expression represents particle inhalability:

$$\eta_1 = 1 - 0.5(1 - [7.6 \times 10^{-4} d_{ae}^{2.8} + 1]^{-1}) + 1.0 \times 10^{-5} U^{2.75} \exp(0.055 d_{ae}) \quad (12)$$

where d_{ae} is in μm and U is the windspeed in m s^{-1} (for $D \leq U \leq 10 \text{ m s}^{-1}$).

(155) Particle inhalability is assumed to be the same through the nose or mouth, and also to be independent of the subject's age, gender, or ethnic group.

5.5.3. Allowance for breathing habit

(156) Since the filtration efficiencies of the nose and mouth are different, a subject's breathing habit may affect the amount of inhaled material that deposits in the lungs. At low to moderate levels of physical exertion, most subjects breathe through the nose. However, as described in Annexe D, in response to the demands of heavy exercise, normal healthy subjects typically switch to breathing partly through the mouth.

(157) Likewise, so-called habitual "mouth breathers" generally breathe oronasally (through the nose and mouth together).

(158) The values given in Table 11 represent the percentage of tidal air breathed through the nose and mouth for a normal nose-breathing adult (normal nasal augmentor), and for a mouth breather, at various levels of exertion. It can be assumed that a similar pattern applies to young subjects at equivalent levels of exercise.

Table 11. Fraction of total ventilatory airflow passing through the nose in nasal augmentors (normal nose breathers) and in mouth breathers*

Level of exertion	F_n	
	Nasal augmentor	Mouth breather
Sleep	1.0	0.7
Rest	1.0	0.7
Light exercise	1.0	0.4
Heavy exercise	0.5	0.3

* Derived from Miller *et al.* (1988a).

(159) In the model, fractionation of airflow through the nose and mouth is represented by the parameters F_n and $1 - F_n$, respectively (Fig. 8).

(160) As is also shown in Fig. 8, the total number of deposition filters in series within the respiratory tract is less for the oral pathway, i.e. $N_m = 7$, than for the nasal pathway, where $N_n = 9$.

(161) To solve the deposition model with airflow partitioned between the nose and mouth, i.e. with $F_n < 1$, use is made of the fact that the regional deposition efficiencies along the two pathways are independent. Hence, the total regional deposition for partitioned flow is obtained by summing the components contributed by the nasal pathway (with intake from the environment, I_{0n} , given by $F_n I_0$), and those contributed by the oral pathway (with intake from the environment, I_{0m} , given by $[1 - F_n] I_0$).

5.5.4. Scaling deposition efficiency for body size

(162) As described in Annexe D, the algebraic expressions that represent the deposition efficiencies in each region of the respiratory tract in a reference subject (the adult Caucasian male) are applied to subjects of different body size using simple scaling factors. These factors, which are denoted in the model by SF_t , SF_b , or SF_A , are defined by the ratio of a reference airway size in the adult Caucasian male to that in the subject. To express particle deposition in the ET and BB regions, the characteristic airway size is taken to be the diameter of the trachea, i.e. d_0 . (See Table 2.) For the bb and AI regions, the characteristic dimension is taken to be the diameter of airways in the first branching generation in each region, i.e. d_0 and d_{16} , respectively. (See Tables 2 and 3.)

5.6. Recommended Deposition Formulae

(163) Tables 12 and 13 summarize the formulae and their parametric values for evaluating aerosol deposition in the respiratory tract. The formulae are derived in Annexe D. These formulae represent the total deposition efficiency of each region of the respiratory tract for any subject, including both inhalation and exhalation. Table 12 refers to airborne particles (or activity) inhaled via the nasal pathway, and Table 13 to the fraction (if any) of the inspired and expired air that traverses the oral pathway.

(164) In both tables, each formula defining a reference deposition efficiency is expressed in terms of three parameters: a , R , and p . These parameters are combined in the general form $a \times R^p$ (Rudolf *et al.*, 1990). As discussed later (see Section 5.7), an additional factor, c , is used to multiply or divide the parameter " a " in order to estimate upper and lower confidence bounds of the estimated regional deposition.

(165) For filtration in the ET regions, the parameters $\dot{V}_n$ and $\dot{V}_m$ represent the components of the average volumetric flow rate that are inhaled (and also exhaled) through the nose and mouth, respectively. For the thoracic regions, $\dot{V}$, represents the total volumetric flow rate of the air ventilating the lungs, i.e. $\dot{V} = \dot{V}_n + \dot{V}_m$.

(166) In the thoracic regions, the deposition efficiencies also depend explicitly on the average transit time of inhaled and exhaled air through each region. The transit times are denoted by t_B , t_b , or t_A , for the BB, bb, and AI regions, respectively, where:

$$t_B = \frac{V_D(\text{BB})}{\dot{V}} \left(1 + \frac{0.5 V_T}{\text{FRC}} \right) \quad (13)$$

Table 12. Recommended parameters for substitution in the model of regional deposition for the fraction of intake inhaled and exhaled through the nose, I_{in} , for any subject, as functions of respiratory variables and anatomical size

		Regional Deposition Efficiency, η_i						Volumetric Fraction $\phi^{a,b}$	
P h a s e	Filter f	Region	Aerodynamic			Thermodynamic			
			$\eta_{ac} = 1 - \exp(-aR^p)$			$\eta_{th} = 1 - \exp(-aR^p)$			
			a	R	p	a	R		p
I n h a l	1	ET ₁ ^c	3.0×10^{-4}	$d_m^2 \dot{V}_B SF_1^3$	1	18	$D(\dot{V}_B SF_1)^{-1/4}$	1/2	1
	2	ET ₂ ^d	5.5×10^{-3}	$d_m^2 \dot{V}_B SF_1^3$	1.17	15.1	$D(\dot{V}_B SF_1)^{-1/4}$	0.538	1
	3	BB	4.08×10^{-6}	$d_m^2 \dot{V}_B SF_1^{2.3}$	1.152	$22.02 SF_1^{1.24} \psi_A^e$	Df_B	0.6391	$1 - \frac{V_D(ET)}{V_T}$
	4	bb	0.1147	$(0.056 + \frac{1}{d_m^{1.5}}) \times d_m^{1.5} \dot{V}_B SF_1^{2.3}$	1.173	$-76.8 + 167 SF_B^{0.43}$	Df_b	0.5676	$1 - \frac{[V_D(ET) + V_D(BB) + V_D(bb)]}{V_T}$
E x h a l	5	AI	$0.146 SF_A^{0.98}$	$d_m^2 f_A$	0.6495	$170 + 103 SF_A^{2.13}$	Df_A	0.6101	$1 - \frac{[V_D(ET) + V_D(BB) + V_D(bb)]}{V_T}$
	6	bb	0.1147	$(0.056 + \frac{1}{d_m^{1.5}}) \times d_m^{1.5} \dot{V}_B SF_1^{2.3}$	1.173	$-76.8 + 167 SF_B^{0.43}$	Df_b	0.5676	$1 - \frac{[V_D(ET) + V_D(BB)]}{V_T}$
	7	BB	2.04×10^{-6}	$d_m^2 \dot{V}_B SF_1^{2.3}$	1.152	$22.02 SF_1^{1.24} \psi_A^e$	Df_B	0.6391	$1 - \frac{V_D(ET)}{V_T}$
	8	ET ₂ ^d	5.5×10^{-3}	$d_m^2 \dot{V}_B SF_1^3$	1.17	15.1	$D(\dot{V}_B SF_1)^{-1/4}$	0.538	1
	9	ET ₁ ^c	3.0×10^{-4}	$d_m^2 \dot{V}_B SF_1^3$	1	18	$D(\dot{V}_B SF_1)^{-1/4}$	1/2	1

^a the parameter, ξ_j , in Eqns (9) and (10) is given by ϕ_j/ϕ_{j-1} .

^b where $V_D(BB) = V_D(BB) (1 + V_T/FRC)$.

$V_D(bb) = V_D(bb) (1 + V_T/FRC)$.

^c $\eta_{ac} = 0.5 [1 - 1/(aR^p + 1)]$; $\eta_{th} = 0.5 [1 - \exp(-aR^p)]$.

^d $\eta_{ac} = 1 - 1/(aR^p + 1)$; $\eta_{th} = 1 - \exp(-aR^p)$.

^e ψ_A is an empirical correction factor to allow for enhancement of thermodynamic deposition caused by nonlaminar bronchial airflow (see Annex D).

where $\psi_A = 1 + 100 \exp \{-[\log_{10} (100 + 10d_{AB}^{0.9})]^2\}$.

Table 13. Recommended parameters for substitution in the model of regional deposition for the fraction of intake inhaled and exhaled through the mouth, I_{no} , for any subject, as functions of respiratory variables and anatomical size

		Regional Deposition Efficiency, η_i							Volumetric Fraction $\phi_j^{a,b}$
Filter j Region		Aerodynamic			Thermodynamic				
		$\eta_{ae} = 1 - \exp(-aR^p)$			$\eta_{th} = 1 - \exp(-aR^p)$				
		a	R	p	a	R	p		
P h a s e I n h a l a t i o n	1	ET ₂ ^c	1.1×10^{-4}	$d_2^2 (\dot{V} SF_1^{0.66} (V_T SF_1^{2.3})^{-0.2})$	1.4	9	$D(\dot{V}_a SF_1)^{-1/4}$	1/2	1
	2	BB	4.08×10^{-4}	$d_2^2 \dot{V} SF_1^{2.3}$	1.152	$22.02 SF_1^{1.24} \psi_a^d$	Dt_B	0.6391	$1 - \frac{V_D(ET)}{V_T}$
	3	bb	0.1147	$(0.056 + \frac{r_b^{1.5}}{x d_{ae}^{1.5}})$	1.173	$-76.8 + 167 SF_b^{0.65}$	Dt_b	0.5676	$1 - \frac{[V_D(ET) + V_D(BB)]}{V_T}$
	4	AI	$0.146 SF_A^{0.88}$	$d_{ae}^2 f_A$	0.6495	$170 + 103 SF_A^{2.13}$	Dt_A	0.6101	$1 - \frac{[V_D(ET) + V_D(BB) + V_D(bb)]}{V_T}$
	5	bb	0.1147	$(0.056 + \frac{r_b^{1.5}}{x d_{ae}^{1.5}})$	1.173	$-76.8 + 167 SF_b^{0.65}$	Dt_b	0.5676	$1 - \frac{[V_D(ET) + V_D(BB)]}{V_T}$
	6	BB	2.04×10^{-4}	$d_2^2 \dot{V} SF_1^{2.3}$	1.152	$22.02 SF_1^{1.24} \psi_a^d$	Dt_B	0.6391	$1 - \frac{V_D(ET)}{V_T}$
	7	ET ₂ ^c	1.1×10^{-4}	$d_2^2 (\dot{V} SF_1^{0.66} (V_T SF_1^{2.3})^{-0.2})$	1.4	9	$D(\dot{V}_a SF_1)^{-1/4}$	1/2	1
		E x h a l a t i o n							

^c the parameter, ζ_j , in Eqns (9) and (10) is given by ϕ/ϕ_{j-1} .

^b where $V_D(BB) = V_D(BB) (1 + V_T/FRC)$

$V_D(bb) = V_D(bb) (1 + V_T/FRC)$.

^c $\eta_{ae} = 1 - 1/(aR^p + 1)$; $\eta_{th} = 1 - \exp(-aR^p)$.

^d ψ_a is an empirical correction factor to allow for enhancement of thermodynamic deposition caused by nonlaminar bronchial airflow (see Annex D), where $\psi_a = 1 + 100 \exp[-(\log_{10}(100 + 10/d_{ae}^{0.7}))^2]$.

$$t_h = \frac{V_D(bb)}{\dot{V}} \left(1 + \frac{0.5 V_T}{FRC} \right) \quad (14)$$

$$t_A = \frac{V_T - V_D(ET) - [V_D(BB) + V_D(bb)] \left(1 + \frac{V_T}{FRC} \right)}{\dot{V}} \quad (15)$$

(167) Separate expressions are given for the deposition efficiencies by aerodynamic and thermodynamic processes in each region, η_{ae} , and η_{th} , respectively. The resulting components of particle deposition are combined using Eq. (10) to give the overall deposition efficiency, η_i , in each region as a function of particle size and the relevant respiration parameters.

(168) To evaluate the fraction of the intake that is deposited in each region of the respiratory tract, the deposition efficiencies, together with the volumetric ratios, ξ , for each region, are substituted in Eq. (5).

5.6.1. Polydisperse aerosols

(169) The formulae given in Tables 12 and 13 define the fractional deposition of aerosols in the various regions of the respiratory tract for discrete values of particle size. In practice, it is necessary to consider that radioactive aerosols generally consist of particles distributed log-normally in size (TGLD, 1966). The parameters characterizing deposition of activity in the respiratory tract are then the AMAD, and the activity median thermodynamic diameter (AMTD), respectively, for the aerodynamic and thermodynamic components.

(170) The geometric standard deviation (σ_g) in particle size is approximately unity for vapours in the atomic size range (0.0005 μm in diameter). For unimodal aerosols with a median particle size on the order of 1 μm or larger, σ_g is likely to be about 2.5. To derive reference values of regional deposition for aerosols of intermediate size, it is assumed that σ_g is defined by Eq. (16):

$$\sigma_g = 1 + 1.5[1 - (100 \text{ AMTD}^{1.5} + 1)^{-1}] \quad (16)$$

where AMTD (in μm) is the activity median thermodynamic diameter of the aerosol considered. This assumed variation of σ_g with median particle size is discussed in Annexe D.

(171) The fractional deposition of activity, DE_A , from exposure to a polydisperse aerosol is computed from formulae representing deposition as a function of particle diffusion coefficient, $D(d_{th})$, or aerodynamic diameter, d_{ae} , using Eqs (17) and (18), respectively:

$$DE_A(\text{AMTD}, \sigma_g) = \sum_0^{\infty} DE[D(d_{th})] p_A[D(d_{th})] \delta d_{th} \quad (17)$$

where $p_A[D(d_{th})]$ is the proportion of the aerosol activity associated with the size interval δd_{th} (defined by the log-normal probability distribution) and:

$$DE_A(\text{AMAD}, \sigma_g) = \sum_0^{\infty} DE(d_{ae}) p_A(d_{ae}) \delta d_{ae} \quad (18)$$

where $p_A(d_{ae})$ is the proportion of the aerosol activity associated with the size interval δd_{ae} (also defined by the log-normal probability distribution).

5.6.2. Hygroscopic aerosols

(172) The deposition model described in the previous sections relates to the distribution of activity or mass of aerosol particles with respect to their size on entering the respiratory tract. In the case of a hygroscopic material, it is necessary to take account of the increase in particle size that occurs when such materials are exposed to the near-saturated air within the respiratory tract.

(173) To apply this model for hygroscopic materials, it is necessary to replace the single values of particle aerodynamic diameter, d_{ac} , and diffusion coefficient, D , considered in Tables 12 and 13 with the values $d_{ac}(j)$ and D_j attained in each regional filter, j .

(174) As described in Annexe D, the growth of a hygroscopic particle can be approximated in general terms as a function of its residence time in saturated air at body temperature.

(175) For a residence time t'_j , in a regional filter, j , measured from inspiration of the particle (i.e. entry to the nose or mouth), the particle aerodynamic diameter and diffusion coefficient attained by hygroscopic growth are approximately related to $d_{ac}(0)$ and $D(0)$, the respective values in ambient air (i.e. the external environment), and the values at equilibrium, $d_{ac}(\infty)$ and $D(\infty)$:

$$d_{ac}(t'_j) = d_{ac}(\infty) - [d_{ac}(\infty) - d_{ac}(0)] \left\{ \exp \left[\frac{-(10t'_j)^{0.55}}{d_{ac}(0)} \right] \right\}^{0.6} \quad (19)$$

$$D(t'_j) = D(0) - \left[\frac{d_{ac}(t'_j) - d_{ac}(0)}{d_{ac}(\infty) - d_{ac}(0)} \right] [D(0) - D(\infty)]. \quad (20)$$

(176) For a specific material, the user of the model is required to specify the degree of particle size growth at equilibrium. This generally lies in the range of two- to fourfold growth, depending on the amount of hygroscopic material associated with the particle. It is likely to be adequate to assume by default a threefold growth factor at equilibrium, for substitution in Eqs [19] and [20]. Note that the initial aerodynamic diameter, $d_{ac}(0)$, is increased by particle growth (Eq. [19]), whereas the initial diffusion coefficient, $D(0)$, is decreased (Eq. [20]).

5.7. Estimates of Variability in Regional Deposition

(177) The experimental data on regional deposition of particles in the respiratory tract (which are reviewed in Annexe D) indicate substantial intersubject variability. The upper and lower 95% confidence bounds of the data are represented by varying the coefficient, a , which occurs in each expression for deposition efficiency (Tables 12 and 13). In each case, the coefficient is taken to be log-normally distributed, i.e. $a_{upper} = a_{median} \times \sigma_g^2$, and $a_{lower} = a_{median} \div \sigma_g^2$, where σ_g is the fitted geometric standard deviation. Other confidence bounds on the predicted regional deposition efficiency are given by substituting an appropriate value of the coefficient, a , that is sampled from the defined log-normal distribution.

(178) This variability in the deposition efficiencies of each region is conveniently represented by a dimensionless scaling constant, c . Estimated values, c_j , for each regional filter j of the respiratory tract are given in Table 14. For each region, the

Table 14. Values of dimensionless scaling constant used to multiply or divide the coefficient a in model^a to estimate the upper or lower 95% confidence bounds of regional deposition

Region	Filter generation, j , and values of scaling constant, c_j					
	Nose breathing			Mouth breathing		
	j	Thermodynamic ^b	Aerodynamic	j	Thermodynamic	Aerodynamic
Inhalation phase						
ET ₁	1	1.4	3.3	—	—	—
ET ₂	2	1.4	3.3	1	1.4	3.3
BB	3	1.5	2.5	2	1.5	2.5
bb	4	1.5	2.5	3	1.5	2.5
Al	5	1.5	1.7	4	1.5	1.7
Exhalation phase						
bb	6	1.5	2.5	5	1.5	2.5
BB	7	1.5	2.5	6	1.5	2.5
ET ₂	8	1.4	3.3	6	1.4	3.3
ET ₁	9	1.4	3.3	—	—	—

^a See Tables 12 and 13.^b Estimated values.

estimated 95% upper confidence bound of the parameter a_j is given by $a_j \times c_j$, and the 95% lower confidence bound by $a_j \div c_j$.

(179) To evaluate the uncertainty distribution of the predicted deposition fractions in all five regions of the respiratory tract, i.e. ET₁, ET₂, BB, bb, and Al, it is necessary to select the values of c_j at random from their assumed log-normal distributions.

5.8. Application of the Model

5.8.1. Anatomical and physiological parameters

(180) Values of anatomical and physiological parameters that are recommended for substitution in the formulae presented above to evaluate regional deposition for Caucasian subjects at reference levels of physical activity are summarized in Table 15. Alternative parameters are recommended in Chapter 3 for some non-Caucasian subjects. In addition, to apply the model to assess particular circumstances of exposure that may differ from the reference conditions considered in this report, the user may substitute specific values of anatomical or physiological parameters where these are known or can be reasonably deduced.

(181) In the absence of specific information about the physical characteristics of the aerosol to which a subject is exposed, the following default values are recommended (see Annexe D, Section D.13):

- AMAD = 5 μm ($\sigma_g = 2.5$) for workplace exposures
- AMAD = 1 μm ($\sigma_g = 2.47$) for indoor or outdoor exposures of general public
- particle density, $\rho = 3 \text{ g cm}^{-3}$
- particle shape factor, $\chi = 1.5$.

Table 15. Values of anatomical and physiological parameters for substitution in model of regional deposition in respiratory tract

Parameter ^a	Subject							
	Male	Female	Male 15 y	Female 15 y	10 y	5 y	1 y	3 mo
•FRC (mL)	3301	2681	2677	2325	1484	767	244	148
•V _D (ET) (mL)	50	40	45	39	25	13.3	4.7	2.6
•V _D (BB) (mL)	49	40	44	39	26	15.5	6.8	4.5
•V _D (bb) (mL)	47	44	41	37	26	16.7	8.7	6.8
V _D (total) (mL)	146	124	130	114	78	46	20	14
Height (cm)	176	163	169	161	138	110	75	60
d ₀ (cm)	1.65	1.53	1.59	1.52	1.31	1.06	0.75	0.616
d _a (cm)	0.165	0.159	0.161	0.156	0.143	0.127	0.107	0.099
d _{1a} (cm)	0.051	0.048	0.047	0.045	0.039	0.031	0.022	0.020
•SF _i	1	1.08	1.04	1.09	1.26	1.55	2.20	2.68
•SF _b	1	1.04	1.03	1.06	1.16	1.30	1.55	1.67
•SF _s	1	1.07	1.07	1.13	1.31	1.63	2.30	2.58
Sleep, F _a (normal) = 1.0; F _a (mouth) = 0.7								
•B (m ³ h ⁻¹)	0.45	0.32	0.42	0.35	0.31	0.24	0.15	0.09
f _R (min ⁻¹)	12	12	14	14	17	23	34	38
•V _T (mL)	625	444	500	417	304	174	74	39
•V̇ (mL s ⁻¹)	250	178	233	194	172	133	83	50
Sitting, F _a (normal) = 1.0; F _a (mouth) = 0.7								
•B (m ³ h ⁻¹)	0.54	0.39	0.48	0.40	0.38	0.32	0.22	—
f _R (min ⁻¹)	12	14	15	16	19	25	36	—
•V _T (mL)	750	464	533	417	333	213	102	—
•V̇ (mL s ⁻¹)	300	217	267	222	211	178	122	—
Light exercise, F _a (normal) = 1.0; F _a (mouth) = 0.4								
•B (m ³ h ⁻¹)	1.5	1.25	1.38	1.30	1.12	0.57	0.35	0.19
f _R (min ⁻¹)	20	21	23	24	32	39	46	48
•V _T (mL)	1250	992	1000	903	583	244	127	66
•V̇ (mL s ⁻¹)	833	694	767	722	622	317	194	106
Heavy exercise, F _a (normal) = 0.5; F _a (mouth) = 0.3								
•B (m ³ h ⁻¹)	3	2.7	2.92	2.57	2.03	—	—	—
f _R (min ⁻¹)	26	33	36	38	45	—	—	—
•V _T (mL)	1920	1364	1352	1127	752	—	—	—
•V̇ (mL s ⁻¹)	1670	1500	1622	1428	1128	—	—	—

^a Parameters marked * are used explicitly. Refer to Glossary for definitions of symbols.

5.8.2. Illustrative examples

(182) Figure 10 illustrates values of regional deposition that are given by the recommended model for a reference adult male Caucasian engaged in light work (with an assumed average breathing rate of $1.2 \text{ m}^3 \text{ h}^{-1}$), and breathing through his nose. Figure 11 shows the corresponding values calculated for a "mouth breather" who is assumed to take 60% of inspired air through his mouth (see Table 11). These figures

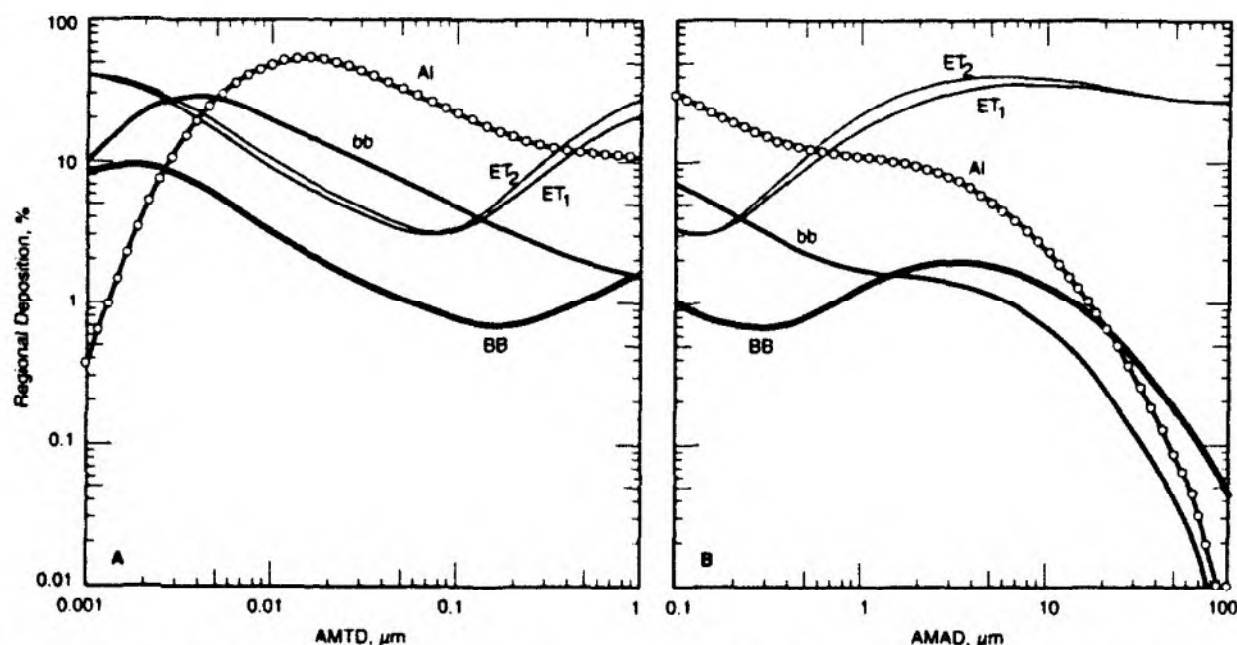


Fig. 10. Fractional deposition in each region of respiratory tract for reference worker (normal nose breather) shown as functions of (A) the activity median thermodynamic diameter, AMTD, and (B) the activity median aerodynamic diameter, AMAD. Deposition is expressed as a fraction of activity present in the volume of ambient air that is inspired, and activity is assumed to be log-normally distributed as function of particle size (for particles of density 3.0 g cm^{-3} and shape factor 1.5).

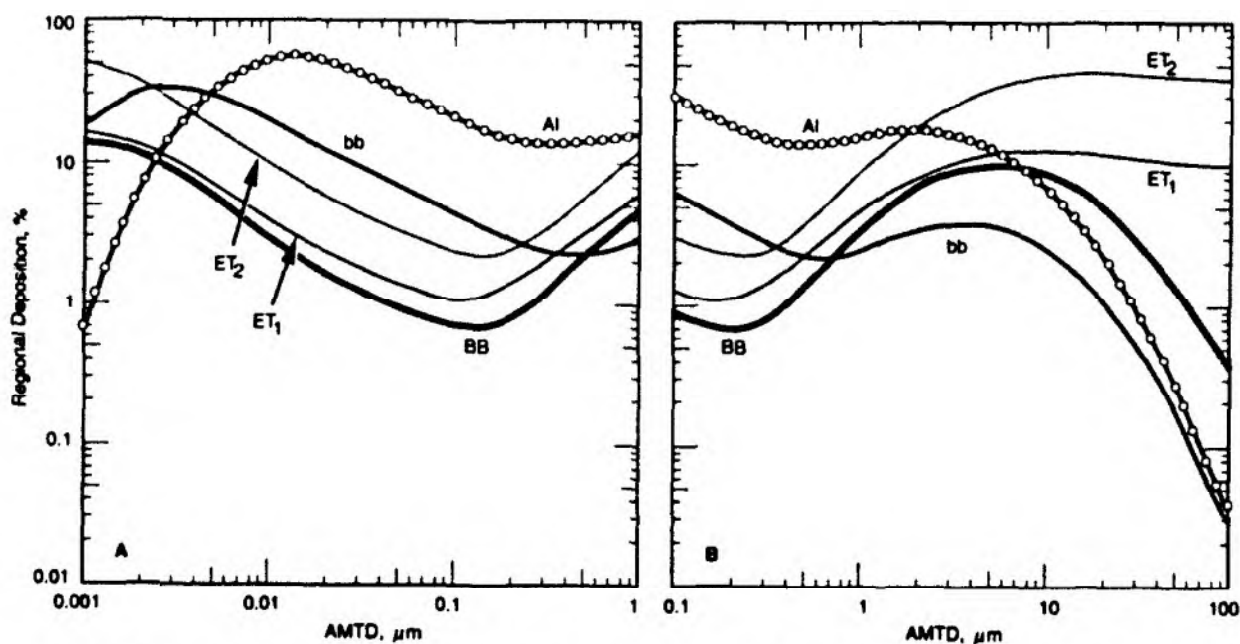


Fig. 11. Fractional deposition in each region of respiratory tract for reference worker (mouth breather).

show regional deposition calculated for polydisperse aerosols as a continuous function of the aerosol AMTD or AMAD. In these examples the particle density is taken to be 3 g cm^{-3} , with a typical particle shape factor of 1.5 (see Annexe D).

(183) Figures 12 through 15 compare the values of fractional deposition in the ET, BB, bb, and AI regions of the respiratory tract that are given by the recommended model for various Caucasian subjects. In these examples, all subjects are considered to be "nose breathers", and to be exposed outdoors. (See Table 15 for the reference anatomical and physiological parameters for each subject, and Annexe B [Table B.15A] for the fractions of time spent at different levels of exertion.)

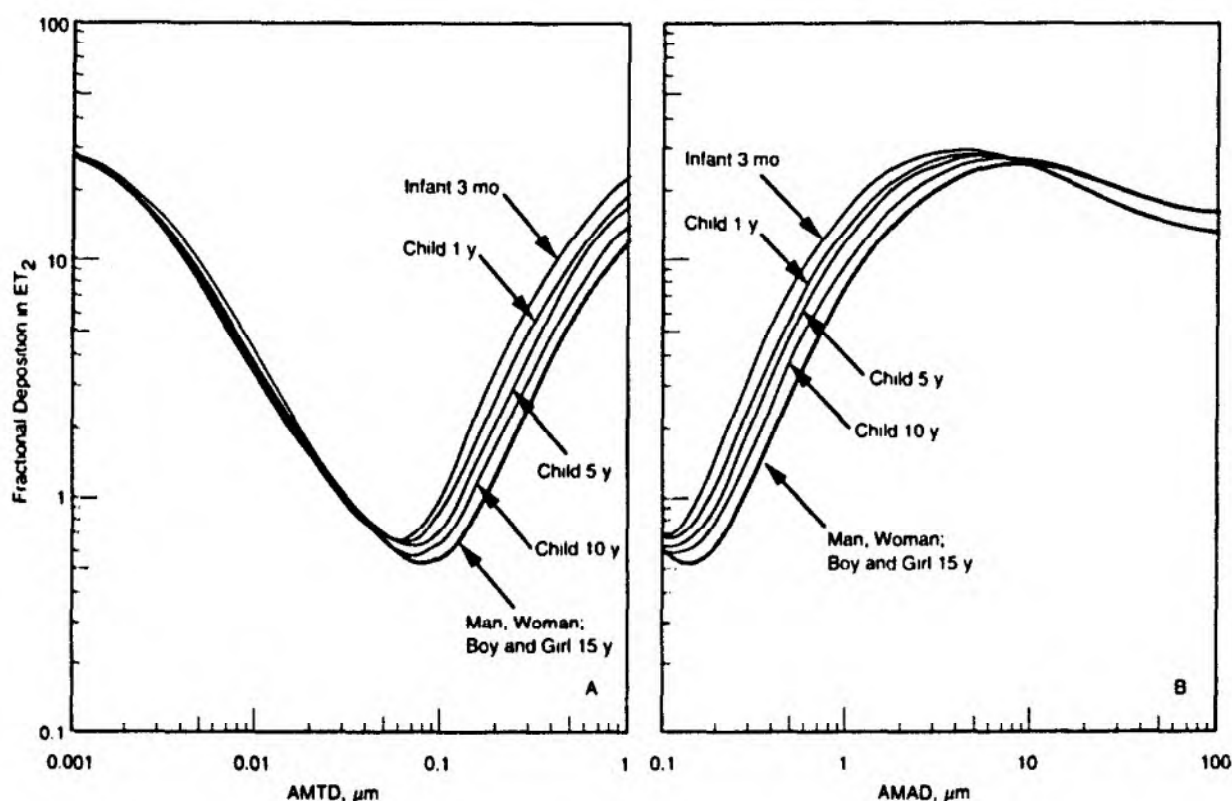


Fig. 12. Fractional deposition in the posterior nasal passages, naso-oropharynx, and larynx (ET₂) for various subjects exposed outdoors.

5.9. Reference Values of Regional Deposition

(184) Reference values of fractional deposition in each region of the respiratory tract that are predicted for Caucasian subjects at the various standard breathing rates corresponding to sleep, rest, light exercise, and heavy exercise are tabulated in Annexe F.

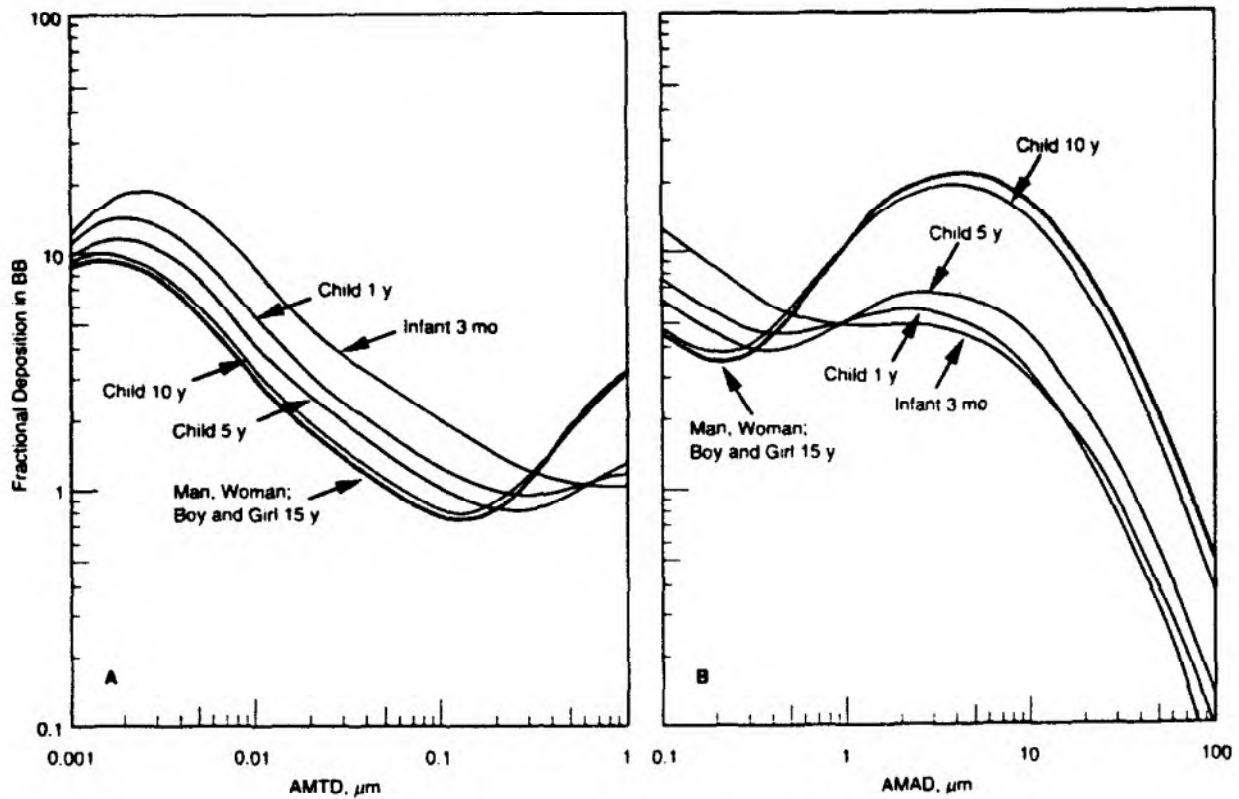


Fig. 13. Fractional deposition in bronchial region (BB) for various subjects exposed outdoors (nose breathers).

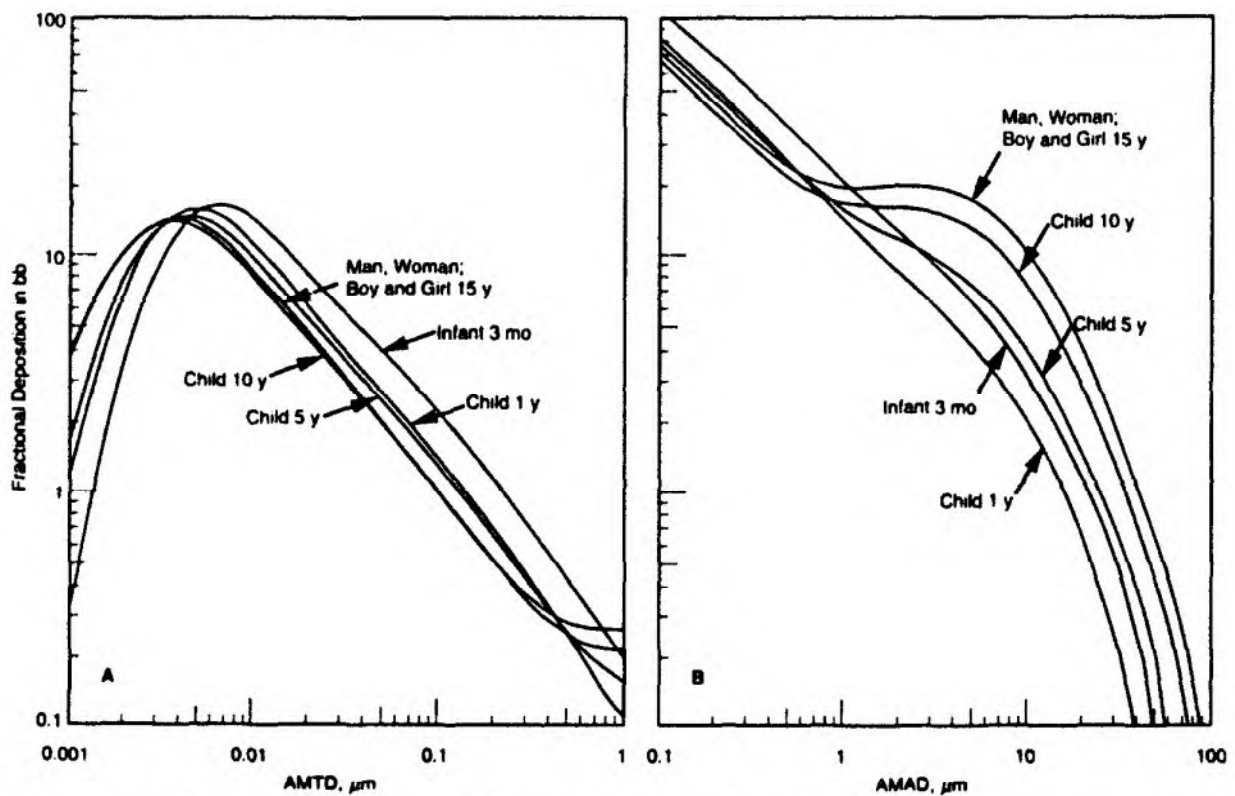


Fig. 14. Fractional deposition in bronchiolar region (bb) for various subjects exposed outdoors (nose breathers).

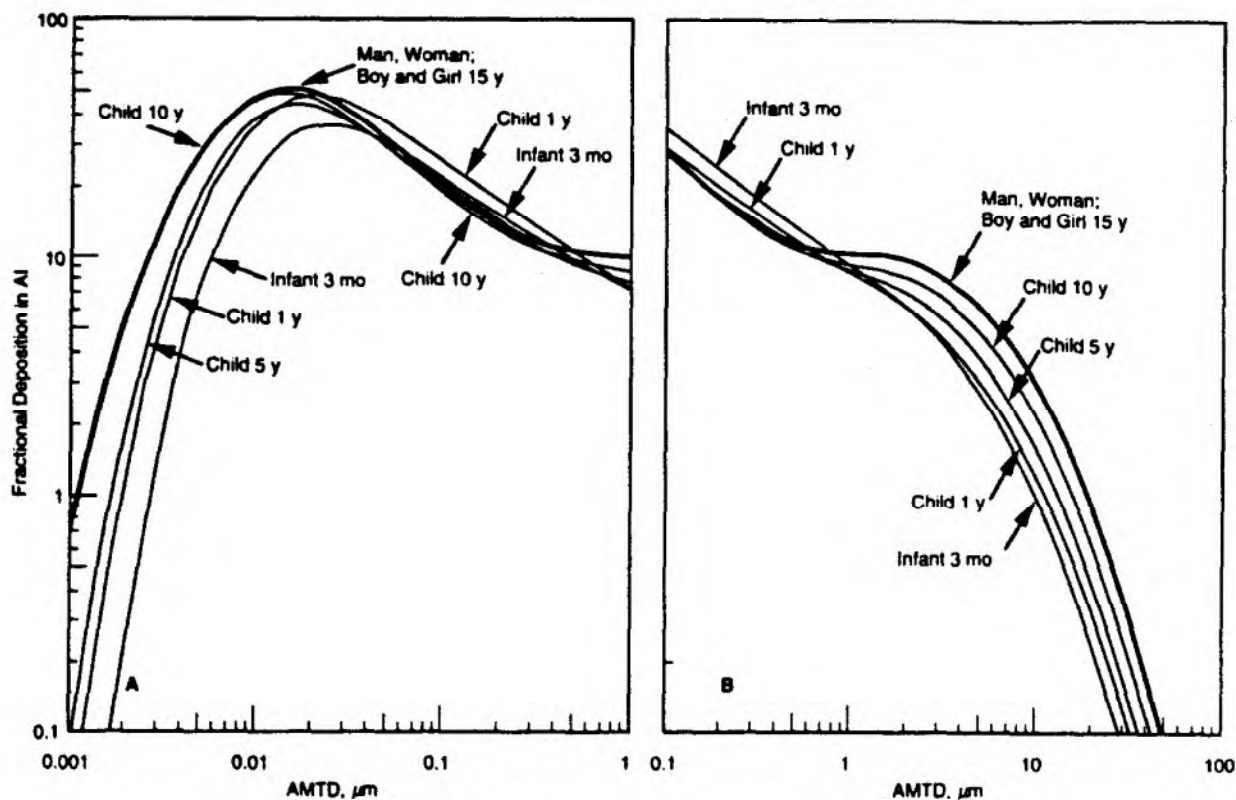


Fig. 15. Fractional deposition in alveolar-interstitial (AI) region for various subjects exposed outdoors (nose breathers).

6. GASES AND VAPOURS

6.1. Introduction

(185) Gases and vapours, like aerosol particles, also deposit throughout the respiratory tract, but do so by different dynamic mechanisms, which require separate consideration. Virtually all gas molecules contact airway surfaces during each breath, yet many of the molecules are re-entrained into the airway, where they may be exhaled. The net absorption of a gas or vapour during continuous breathing is commonly designated the "uptake" or "uptake fraction" of the gas by airway tissues. A combination of gas solubility, with its reactivity in airway liquids, results in a partition, which can be characterized by a "partition coefficient" denoted by λ , between gas dissolved in the liquid, and free gas in the lumen of the airway (Henderson and Haggard, 1943). Radionuclides taken up by liquids or tissues of the respiratory tract are cleared or metabolized as presented in Chapter 7. The main factors determining regional distribution of gas and vapour uptake are presented below.

(186) Considerable progress has been made in the understanding of aerosol particle deposition, but gas and vapour transport and uptake are not as well understood; there are still many controversies among scientists, and paradoxes found with the interpretations of data. Recent investigations have been stimulated by the realization of efficient high-frequency and constant-flow ventilation. The mechanics of respiratory ventilation are not yet fully understood. Therefore, many simplifications must be made in accordance with the empirical data available.

6.1.1. *Fluid mechanics of breathing and transport through airways*

(187) The airflow field in the airways of the respiratory tract is a three-dimensional bifurcating network that does not lend itself to simple geometric models. To account for the asymmetric nature of this geometry, computational fluid dynamics becomes extremely demanding of computer software and hardware. The most widely used model that retains some three-dimensional structure is the symmetric-bifurcation Model A given by Weibel (1963). Even this simplified structure presents an enormous task for complete fluid-mechanical modelling of the airflow field. Thus, up to now, the performance of respiratory ventilation is primarily understood by interpretation of empirical measurements.

(188) Measurements of respiratory ventilation show that air is not uniformly mixed in the pulmonary region of the lungs. Transport rates for gases are different going from tidal air into the blood stream, and from the blood stream into exhaled air. There are many fluid mechanical, chemical, and thermodynamic processes involved in this transport of gases and vapours. For some applications, such as anaesthesiology, the goal is primarily to deliver a chemical dose to achieve the desired blood-serum concentration. The region of the respiratory tract from which the anaesthetic is absorbed is not as important as transfer to the blood. In this case, the primary concern is simply total uptake of the gas. With aerosol particles, however, the region of deposition in the respiratory tract can be an important factor, as described in Chapter 5. Regional uptake of gas and vapour is also of concern, and is discussed below.

(189) Aerosol particles are much less mobile than gas molecules and tend to be carried along with the airflow. There are many paths a particle might follow in its journey through the airways. A particle of minimal intrinsic mobility is least likely to come in contact with an airway surface by inertial impaction or Brownian motion. Particles of about $0.5\ \mu\text{m}$ in diameter are at the minimum of combined inertial (aerodynamic) and diffusional (thermodynamic) motion. Very few of these particles will deposit on the airway walls as they penetrate deep into the respiratory tract during a breath. The fluid mechanics are not completely reversible on exhalation, so particles follow a different path during exhalation; but again, very few particles of minimal intrinsic motion deposit on airway walls. About 10% of these particles are not exhaled, largely owing to irreversible exchange between tidal air and resident air by actual fluid mixing. These particles are eventually deposited in the pulmonary region (AI) of the lungs.

(190) Studies of aerosol particle transport and deposition provide insight into the fluid mechanics of breathing. Larger particles are more frequently deposited on airway surfaces, especially near bifurcations where the flow changes direction. The larger the particle, the more likely it is to deposit in more central and extrathoracic airways. Smaller (ultrafine) particles have more thermodynamic mobility, which also increases probability of deposition in the more central and extrathoracic airways. The regional deposition according to particle size is presented in Chapter 5. Regional deposition of ultrafine aerosol particles smaller than $0.1\text{-}\mu\text{m}$ diameter has been given very little investigation. The modelled deposition is based on theoretical calculations of thermodynamic particle motion and measured deposition in airway casts.

6.1.2. *The size transition from particle deposition to gas uptake*

(191) As extremely small, "ultrafine" particles approach molecular size, they tend to behave more like a vapour. When they are less than about 1 nm in diameter, ultrafine

particles tend not to stick to other particles or surfaces on collision. Such particles are likely to rebound back into the air. The probability of surface capture is represented by a "sticking coefficient." Conversely, ultrafine particles larger than about 10 nm generally stick when they contact another surface. Thus, there is a continuous transition from ultrafine aerosol behaviour to gas vapour behaviour according to particle size.

(192) True gas molecules do not tend to stick to a surface; they immediately rebound to the air upon contact. However, when the surface is a liquid in which the gas is soluble, molecules have some probability of being absorbed. The concentration of the gas molecules in the liquid determines how fast molecules will be absorbed. Vapour molecules tend to stick to a surface for some period of time and are more likely to be absorbed into a liquid. Under steady-state conditions, the partition between the dissolved gas and the airborne gas establishes a partition coefficient by the ratio of equilibrium concentrations. For example, if there are 10 molecules dissolved for each airborne molecule in the same volume, the partition coefficient of 10 indicates a gas of high solubility. The uptake of this gas by the liquid is relatively fast. The partition coefficient needs to be determined for each combination of liquid and gas. This can then be used to estimate the uptake of a gas in the respiratory tract, as described below.

6.1.3. *Measurement of gas uptake in the respiratory tract*

(193) Extensive measurements of gas uptake have been made for respiration and anaesthesia gases. Respiratory physiologists have characterized oxygen uptake and carbon dioxide emission. Nitrogen is an inert carrier gas that is normally in equilibrium with liquids in the respiratory tract. Other inert gases are often used as tracers of wash-in and wash-out from the lungs. Data on uptake of some other gases may be found in the medical literature. If the endpoint is medical, uptake is usually measured as blood-serum concentration. If the endpoint is toxicology, or more specifically dose to respiratory tract tissues, uptake is measured as the uptake fraction during steady breathing. An experimental apparatus that accomplishes this measures upstream and downstream concentrations of the gas in air flowing past the nose and mouth (Dahl *et al.*, 1987; Wiester *et al.*, 1987), or at different points in a breath during inhalation and exhalation (Snipes *et al.*, 1991). This information, combined with concurrent plethysmographic measurement, allows calculation of the actual uptake fraction during normal breathing. Measurements of uptake of pollutant gases include O₃, NO₂, SO₂, HF, and CO. Few measurements of local uptake have been made in airway models (Hanna and Scherer, 1986).

6.2. Models of Gas Uptake

(194) A dynamic model of gas uptake through the entire respiratory tract is needed to model regional dose. Such a model must account for both inhalation and exhalation, and the establishment of a steady breath-to-breath equilibrium. This necessarily depends on the concentration of inhaled gas, which is assumed to be constant. A measure of regional absorption of the gas during steady breathing is the goal of the model. Owing to the complex nature of the geometry and absorption processes, a complete physical model has not been found to be practical. Thus, numerical models are being developed to simulate gas transport and absorption in the regions of the respiratory tract. Many of the parameters needed for this kind of model have yet to be defined or measured for the many gases of interest.

6.2.1. Assumptions of uptake models

(195) Several different approaches to numerical modelling of regional uptake have been presented. As these models become more sophisticated, they include more of the relevant parameters. Many assumptions must be made to arrive at a practical model at each stage. First, an airway geometry must be assumed. The most widely used geometry of thoracic airways at the present stage of modelling is the symmetric-bifurcation Model A from Weibel (1963). This allows all of the thousands of pathways through the respiratory tract to be considered equivalent. Airway dimensions can be scaled to individuals of different size and depend on tidal volume. This should ideally lead to scaling of the dose distribution studied in small animals to humans (Miller *et al.*, 1988b). Airflow in these airways is usually considered to be poiseuille, which in reality is not fully developed in many airways.

(196) The breathing pattern is an important factor. Some models assume a square-wave pattern: steady inhalation and exhalation; some assume a sinusoidal pattern. Pauses between breaths and between inhalation and exhalation, if present, should also be taken into account. Considerable transport and deposition may occur during a breath hold. Gas uptake has been found to depend on both flow velocity and time of residence in different regions of the respiratory tract (Aharonson *et al.*, 1974). Thus, the complete breathing patterns must be modelled.

(197) Critical assumptions must be made about the gas-liquid interface. Local mass-transfer coefficients have generally not been reported for the respiratory tract (Morgan and Frank, 1977). "The interaction of soluble gases with the airway mucosa during uptake or excretion is not well understood because of a dearth of experimental measurements" (Tsu *et al.*, 1991). The chemical and physical processes occurring at the interface must therefore be modelled using simplifying assumptions. It has been shown *in vitro* that first-order mass transfer coefficients describe uptake of sulphur dioxide in tissue (Ben-Jebria *et al.*, 1990). Measurements in humans confirm this, except for gases of very high solubility (Ultman and Abeles, 1987).

(198) There is an extremely wide range of partition coefficients for different gases, which has a dramatic effect on region of uptake. The solubility and reactivity of the gas in the mucus and with the underlying tissue are considered in estimations of the partition of gas between the airway lumen and walls in each region of the respiratory tract.

(199) The thickness of the liquid mucous lining the central airways, and surfactant lining the peripheral airways, are important factors in gas uptake (Miller *et al.*, 1985). Chemical reaction in the liquid can have a strong influence on mass-transfer from the air, which is determined by the capacity of the mucus for the reactant. When there is reaction or metabolism in the liquids or tissues, equilibrium is never established, unless the reaction becomes saturated. Reaction time constants need to be considered with respect to diffusion rate constants, which often dominate the uptake process.

6.2.2. Dynamics of heat and water exchange

(200) Pollutant gas uptake is not independent of other gases in the airways; there is always some interaction with water uptake and emission, and with the dynamics of heat exchange during the normal cycle of a breath. Inhaled air does not become saturated with water or become thermally uniform until it has passed through the extrathoracic airways, the trachea, and several airway generations into the bronchial tree (Daviskas

et al., 1990). During exhalation, much of the water and heat is recovered by the surfaces of these airways. This process results in variable mucous layer thickness and temperatures (Tsu *et al.*, 1988). The influence on soluble gas exchange in these regions can be substantial (Tsu *et al.*, 1991). This effect has only been modelled for one gas (ethanol), but the results demonstrate how important breathing parameters can be to the regional uptake of a gas.

6.2.3. Dynamics of local gas uptake

(201) A partition is established between a pollutant gas in the airway lumen and gas dissolved in the liquid lining of the airway. The dynamics of gas absorption by the liquid depends on solubility, chemical reactivity, and biological metabolism in the liquid and underlying tissue (Hanna and Frank, 1987; Overton and Miller, 1988). This involves several mass-transfer mechanisms that can be characterised by mass-transfer coefficients. During steady conditions, constant concentrations of the gas are established in the liquid and in the air as illustrated in Fig. 16 for gases that react at different levels of the gas-blood interface. Some conditions can be considered steady or quasisteady, but others cannot, such as solubility and concentration in the liquid lining the trachea and extrathoracic region. These vary throughout the course of each breath and have a strong influence on further penetration of the gas into the respiratory tract and local uptake in each region along the way. Because the dynamic mass-transfer is not generally known, an approximation must be made from the simple partition between liquid and gas in a representative situation.

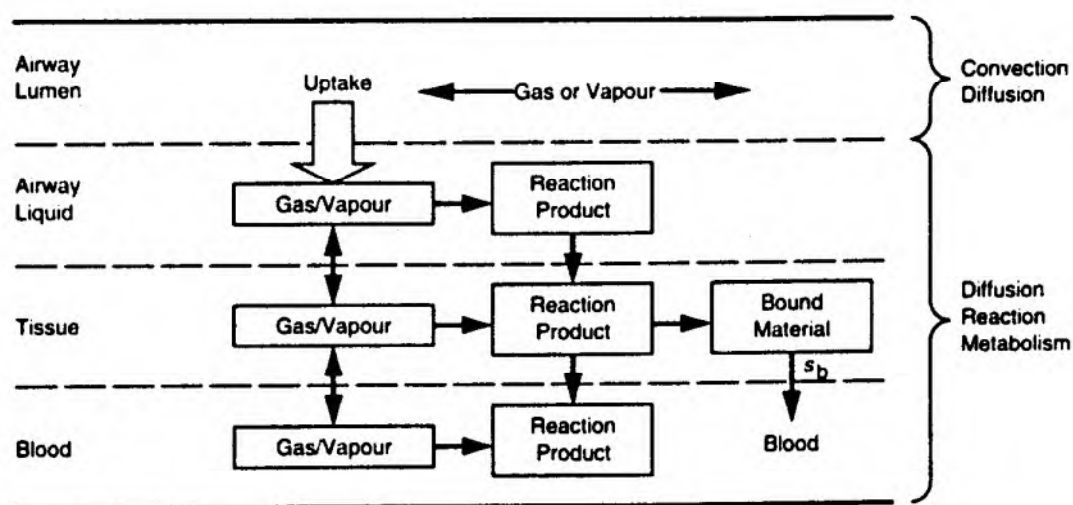


Fig. 16. Reaction of gases or vapours at various levels of the gas-blood interface.

6.3. Regional Gas Uptake

(202) Models of regional gas uptake are generally considered to be qualitative at this stage of model formulation. In some cases, qualitative analysis can lead to a quantitative conclusion. Extreme combinations of gas solubility and reactivity can result in well-characterized patterns of regional gas uptake. The transition between the extremes is what often needs to be theoretically established.

6.3.1. Penetration into the respiratory tract

(203) Penetration of a gas to the pulmonary region of the lungs depends on both limited solubility and reactivity of the gas. If the gas is both insoluble and nonreactive, then virtually all of the gas convected to the pulmonary region remains in the air, and nearly all of the gas is exhaled, resulting in practically no uptake. Helium is a good example of this. Gases of greater solubility are absorbed by bronchial and bronchiolar walls and penetrate to less depth in the lungs (Davidson and Schroter, 1983). If the gas is of high enough concentration, however, saturation of the liquids lining the conducting airways will allow deeper penetration.

(204) There is little uptake of low-solubility gases in the conducting airways; however, in the pulmonary region, with its large surface area, a large uptake can occur. Oxygen is a good example of this; it is of relatively low solubility, but of considerable reactivity in the pulmonary region. In other words, when the oxygen does get into solution in the alveolated region, it is quickly taken up by the underlying tissue, and provides for continued uptake of the oxygen. Thus, in cases of low solubility, the majority of gas absorption is in the pulmonary region, and the quantity taken up depends on concentration and reactivity of the gas. Measurements of ozone uptake differ among animal species, ranging from 47% in rats (Wiester *et al.*, 1988), to 95% in humans (Gerrity *et al.*, 1988). Mathematical models of ozone uptake (Grotberg *et al.*, 1990; Mercer *et al.*, 1991b; Miller *et al.*, 1985) showed that the majority of uptake occurs in the bb region and the proximal portion of the AI airways. This has been confirmed in animal studies (Overton *et al.*, 1987) where ozone damage was found in the distal bronchiolar and centriacinar regions.

(205) Gases of high solubility and reactivity are almost completely retained in the extrathoracic region, with very little penetrating into the tracheobronchial tree. Dosage per unit of surface area in the extrathoracic airways can be much greater than in the thoracic airways (Stott and McKenna, 1984). Sulphur dioxide has these characteristics. Experimental measurements have shown that very little SO_2 penetrates beyond the larynx. Thus, virtually all of the gas is taken up in the extrathoracic region.

(206) Tritiated water (HTO) is an example of a gas of high solubility but low reactivity. The biological half-life of inhaled HTO is about 10 days (Myers and Johnson, 1991). Although HTO is chemically similar to H_2O , there is enough difference for partition between liquid H_2O and vaporous HTO (for example, the partition coefficient between H_2O and D_2O is reported to be 0.17). Because HTO is practically nonreactive, it could easily accumulate in the BB and bb airway walls to the point of saturation. The HTO could then penetrate to the AI region in the same manner observed for acetone, which also saturates airway liquids.

6.3.2. Metabolism of retained gases

(207) Gases taken up into tissues of the respiratory tract may be metabolised or cleared depending on their chemical nature. Reactivity in the mucous layer can produce products that are metabolised or cleared at a rate that has a secondary influence on the rate of uptake (Dahl, 1990). Radioactive decay may transform an atom to a different chemical form, altering its path of absorption. All of these rates must be taken into account for the establishment of an equilibrium concentration in the *in vivo* system. Clearance of the reaction products and metabolites is treated by the model described in

Chapter 7. If an absorption rate is slow enough, concentration of the gas in the mucus may become high enough to limit local uptake and allow more distal penetration.

(208) An example of a low solubility gas that is metabolized to some degree is tritiated hydrogen (HT) gas (Peterman *et al.*, 1985). Even though only a small fraction of HT is taken up from inhalation, the resulting HTO contributes the majority of dose (Dunford and Johnson, 1987). A similar situation is found with tritiated methane (Phipps *et al.*, 1990). Thus, both solubility and reactivity must be considered when estimating the total partition and resulting uptake.

6.3.3. Partition of some radioactive gases

(209) The partition coefficient of some gases with water or biological fluids has been measured, especially for anaesthetic gases (Fiserova-Bergerova, 1983). Table 16 lists some of these values for gases and vapours that might be present as radioactive air pollutants. Other gases are included as examples to fill in the spectrum of partition. The partition of most gases in water and blood is typically very similar. Values given here have been reported for warm water, the most commonly studied liquid. One extreme is the decomposition of UF_6 , which should be considered highly soluble and highly reactive. Iodine changes phase as it dissolves, which means it should be considered reactive. Acetone is extremely soluble, resulting in a very high partition coefficient. In some literature, the partition coefficient is occasionally presented as "solubility" in terms of cm^3 of gas dissolved in 100 cm^3 of liquid, rather than in 1 cm^3 ; these values are simply divided by 100 to yield the partition coefficient. Some authors present this information in terms of Henry's law constants, ratios of which are inversely related to solubility or partition coefficient.

Table 16. Partition in warm water for gases at atmospheric pressure, along with their diffusivity in air

Gas	Molecular weight (g/mole)	Diffusivity coefficient (<i>D</i>) ($\text{cm}^2 \text{ s}^{-1}$)	Partition coefficient (λ)
H_2	1	0.84	0.017
He	4	0.75	0.009
CH_4	16	0.26	0.03
D_2O	20	0.28	0.17
N_2	28	0.24	0.014
O_2	32	0.24	0.024
CO_2	44	0.18	0.56
O_3	48	0.16	0.49
Acetone	58	0.13	395
SO_2	64	0.13	0.228
Kr	84	0.23	0.05
<i>m</i> -Xylene	106	0.07	1.7
Xe	131	0.19	0.085
SF_6	146	0.08	0.005
Rn	222	0.06	0.13
I_2	254	0.09	0.07
UF_6	352	0.07	Highly reactive

6.4. Three Classes of Gas Uptake Pattern

(210) There is a two-dimensional spectrum of gas solubilities and reactivities to be considered for modelling of regional uptake, as represented in Fig. 17. Two combinations of solubility and reactivity result in directly quantifiable uptake: a gas that has very low solubility and very low reactivity is not appreciably absorbed anywhere in the respiratory tract, and a gas that is both very soluble and very reactive is completely absorbed in the extrathoracic region. Other combinations result in some fractional uptake in each region, which must be estimated from available information. This presents three classes of gas uptake for consideration in respiratory tract dosimetry: SR-0, SR-1, and SR-2.

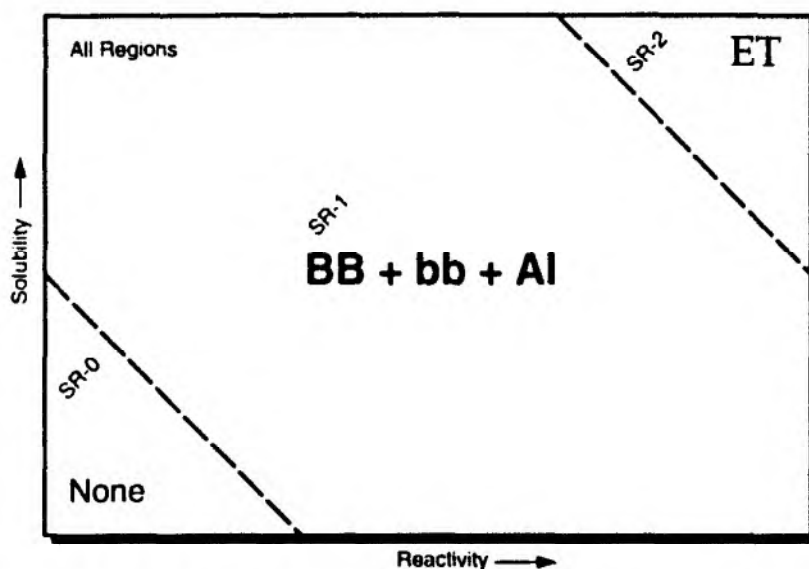


Fig. 17. Regional uptake of an inhaled gas diagrammed for combinations of solubility and reactivity. Complete uptake occurs in the upper right corner of the diagram, and no uptake in the lower left. There is partial uptake between the two extremes.

6.4.1. Insoluble and nonreactive gases—SR-0

(211) Inert gases, like H_2 , He, N_2 , and SF_6 , are relatively insoluble in the liquid lining of the respiratory tract. Radiation dose from an SR-0 gas can be calculated by simply assuming that the airways are all filled with air having the same concentration of radioactive gas, i.e. assuming that no radioactive gas is taken up by the airway tissues. Although some gas is actually taken up by airway tissues, the resulting radiation dose from the dissolved gas is calculated, for class SR-0, to be insignificant compared with that from the air spaces. In many cases, external radiation from a semi-infinite cloud of a class SR-0 gas dominates the effective dose to the body as a whole.

6.4.2. Soluble or reactive gases and vapours—SR-1

(212) Different combinations of solubility and reactivity of gases and vapours result in partial uptake by airway tissues. The simplest definition of uptake is the fraction of the gas or vapour retained in the respiratory tract during steady breathing (f_r). The region where the retention is distributed depends on the dynamics of mass transport in the airways, the mucus, and the airway tissue. This distribution has yet to be fully

modelled. Studies of O_3 , NO_2 , and H_2O have provided models of some aspects of the transport processes. These gases penetrate to the pulmonary region of the lungs, with gas retention in tissues throughout the respiratory tract (Gerrity *et al.*, 1988; Postlethwait and Bidani, 1990). Calculations of regional lung dose must then include the regional uptake fractions as inputs to respiratory tract deposition, with subsequent metabolism and clearance also considered.

(213) Some gases have much greater reactivity in the AI region than in other regions. For example, oxygen is of relatively low solubility and moderately low reactivity in the conducting airways of the ET, BB, and bb regions. The small volume of airway liquids in these regions quickly becomes saturated with oxygen, thus allowing most of the oxygen to penetrate to the AI region. Because the AI region has a very large volume (with associated surface area), much of the oxygen is rapidly absorbed into the airway liquids. The oxygen reacts by association with the large supply of haemoglobin, and never approaches saturation in the airway liquids. Thus, oxygen is almost completely absorbed in the AI region. Each gas or vapour considered to be in class SR-1 needs to be evaluated for solubility and reactivity in each region of the respiratory tract to estimate the distribution of uptake.

6.4.3. Soluble and reactive gases and vapours—SR-2

(214) Gases that are both highly soluble and reactive are completely retained in the extrathoracic airway tissues. It has been shown that some gases, such as SO_2 and HF, do not penetrate beyond the larynx. In this case, the radiation dose is more localized than in the case of an SR-1 gas. Radiation dose calculations should include the uptake as an input to the extrathoracic compartment, with metabolism and clearance also considered. Because the uptake is total, the deposition in the extrathoracic compartment (ET_2) of the deposition and clearance model is given simply by the total intake.

6.5. Uptake Model for Gases and Vapours

(215) As demonstrated by Morris and Blanchard (1992), the uptake fraction has a logarithmic relationship to the inverse of the flow rate:

$$\ln\left(\frac{C_{i+1}}{C_i}\right) = -\frac{G_i}{\dot{V}} \quad (21)$$

where G_i is the uptake rate for region i in $cm^3 s^{-1}$. This uptake rate depends on the gas concentration (C_i) entering the region, the mechanics of which have not been described in the literature.

(216) The uptake rate was shown by Morris and Blanchard (1992) to be influenced by C_i , and has the form given by Hatch and Swann (1961):

$$G_i = U_i \cdot (C_i - CD_i/\lambda) \quad (22)$$

where U_i is the overall transfer coefficient, λ is the partition coefficient, and CD_i is the concentration of gas dissolved in the walls of region i . The coefficient U_i is believed to be characteristic of a complicated time-dependent process that is not presented here. Reactivity in region i , or transfer to blood, reduces CD_i , resulting in a greater absorption rate.

(217) Combination of these two equations gives the uptake efficiency, which can be used as a filtration efficiency (as shown in Fig. 8, Chapter 5):

$$\frac{C_{i+1}}{C_i} = \exp \left(- \frac{U_i \cdot (C_i - CD_i/\lambda)}{\dot{V}} \right). \quad (23)$$

Note that this uptake efficiency depends on C_i . When the gas content of the airway wall in the region is greater than the incoming concentration, then $(C_i - CD_i/\lambda)$ is negative, and desorption occurs. Thus, when a soluble but nonreactive gas is inhaled, a substantial part of it is exhaled by desorption from the proximal regions, as demonstrated by Morgan and Frank (1977). The value of CD_i would be limited to the saturation value for this region. Regional saturation values and associated transfer rates have generally not been measured. The next stage of model development should include a database of these values and rates.

6.6. Integration with the Deposition and Clearance Model

(218) The regional uptake of a radioactive gas can be estimated from the airborne concentration, breathing parameters, and the solubility-reactivity class of the gas. For class SR-0, exposure can be modelled for submersion in a cloud, as treated in *ICRP Publication 30* (ICRP, 1979); i.e. deposition or uptake may not be a significant part of the total or regional dose. Gases of class SR-2 are completely taken up by the extrathoracic region. The total volume amount of gas breathed then determines the input to the clearance model and the dose to this region. Distribution among regions for class SR-1 is discussed in Section 6.4.2. Before making a final assignment of regional distribution, however, other factors that indirectly influence regional distribution should be considered.

6.6.1. Vapour carried by particles

(219) Vapour molecules can attach themselves to aerosol particles that coexist in the air. These vapour molecules are then carried with the aerosol particles and deposited in the respiratory tract by a completely different mechanism. This could be especially dramatic for a class SR-2 vapour that would otherwise deposit only in the extrathoracic region; the aerosol particles would deposit some of the vapour in the AI region. Gases with less affinity for aerosol particle surfaces are less apt to be carried to the AI region. To estimate the magnitude of this shift in deposition pattern, an attachment coefficient must be determined, as is done for radon progeny (Porstendörfer, 1984; Knutson, 1988).

6.6.2. Effects on respiratory physiology

(220) Some gases and vapours have a biochemical or acute toxic effect on the physiology of the respiratory tract. This could alter the breathing pattern, clearance rates, and metabolism. In some cases, the toxicological effect could outweigh the radiological effect. For example, the corrosive nature of UF_6 might cause severe edema in the extrathoracic region, owing to hydrolysis of the UF_6 . The resulting HF has been shown to be acutely lethal during inhalation, with pathologic damage confined to extrathoracic airways (Morris and Smith, 1982). Hence, rats exposed to HF apparently suffocated. Other chemicals may have much less dramatic effect, yet still have

considerable influence on breathing parameters and regional uptake (Foster *et al.*, 1991), which should be considered when evaluating regional doses.

6.6.3. Evaluation of regional uptake

(221) After considering all of the relevant factors, an uptake fraction must be assigned to each region of the respiratory tract. The simple cases of classes SR-0 and SR-2 have been described above. In the case of class SR-1, if there is no information on total uptake fraction, the conservative approach is to assume 100% total uptake. This leaves distribution among the regions to be assigned. If there is no basis to assign a large fraction of the uptake to a particular region, the regional distribution must be arbitrarily assigned: 10% ET_1 , 20% ET_2 , 10% BB, 20% bb, and 40% AI are suggested defaults. These values should be adjusted for any known uptake quality of the gas. For example, if a gas is known to be of relatively low solubility, the assignment could be shifted towards the AI region: say, 5% ET_1 , 10% ET_2 , 5% BB, 10% bb, and 70% AI.

(222) Each gas or vapour needs to be considered individually, owing to the many variables involved in determining the uptake fraction, regional absorption, clearance, metabolism, and excretion or exhalation. An example of a class SR-1 gas is radon, which is moderately soluble, but practically nonreactive. The pathways of uptake and elimination of radon gas following exposure by inhalation are shown in Fig. 18. Uptake of radon gas into the blood occurs principally in the alveolar region. The dynamics of uptake and subsequent distribution and elimination throughout body organs can be modelled by considering tissue partition coefficients and relative blood flow rates, as described by Peterman and Perkins (1988).

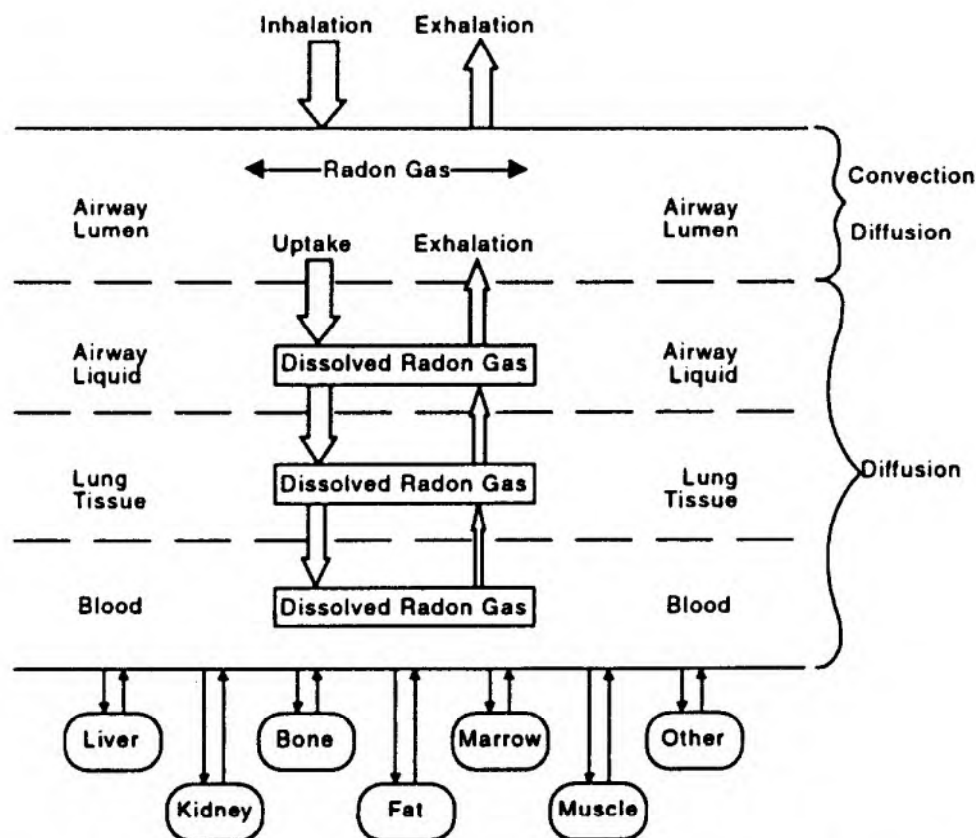


Fig. 18. Pathways of uptake and elimination of radon gas following exposure by inhalation.

6.6.4. Evaluation of regional lung retention

(223) The values of regional uptake can be substituted in the lung clearance model given in Chapter 7. Clearance and dosimetry of a dissolved gas or vapour will usually be dominated by absorption into blood, unless there is considerable local binding to tissue. Therefore, the absorption clearance rate, $s_i(t)$ from each region i is especially important. This means that uptake feeds the absorption process at the second stage, as a dissociated material. (See Chapter 7, Fig. 21.) When the clearance rate is not known, gas or vapour uptake is usually assumed to be absorption type F. Materials that react with tissues, however, can remain bound in the tissue. Retention of bound material is treated in the clearance model. (See Chapter 7, Figs 21, 23, and 24.) The distribution of dose in the respiratory tract and other organs is determined by the combined effects of regional uptake and clearance as addressed in Chapter 8.

7. CLEARANCE MODEL

7.1. Introduction

(224) A detailed treatment of clearance kinetics is required, because respiratory tract clearance rates determine not only doses to tissues of the respiratory tract itself, but also doses resulting from deposition in other organs following systemic uptake. They also govern the urinary and faecal excretion rates that are employed in biological monitoring, and this application requires further detail.

(225) Since publication of the report of the ICRP Task Group on Lung Dynamics in 1966, extensive studies of the clearance of materials deposited in the respiratory tract have been conducted. Substantial progress has been made both in understanding the processes and in quantifying the parameters involved, permitting a more systematic approach to be taken to clearance modelling. Nevertheless, major uncertainties remain, which can only be resolved by further research, associated with the kinetics of clearance of materials from each part of the human respiratory tract.

(226) Materials deposited in the respiratory tract are cleared by three main *routes* (Fig. 19):

- into blood by absorption
- to the gastrointestinal (GI) tract via the pharynx
- to regional lymph nodes (LN) via lymphatic channels.

(227) The model provides for clearance by these routes from the four regions: the ET, BB, bb, and AI. Material deposited in the ET region is also removed by extrinsic means (e.g. nose blowing).

(228) In addition, the activity of each radionuclide is reduced by transformation to decay products, which may themselves be radioactive. For simplicity, however, clearance in the absence of radioactive decay is described here.

(229) The rates at which deposited materials are cleared by each route in general depend on:

- the location of the material in the respiratory tract
- the physicochemical form of the material
- the time since deposition of the material.

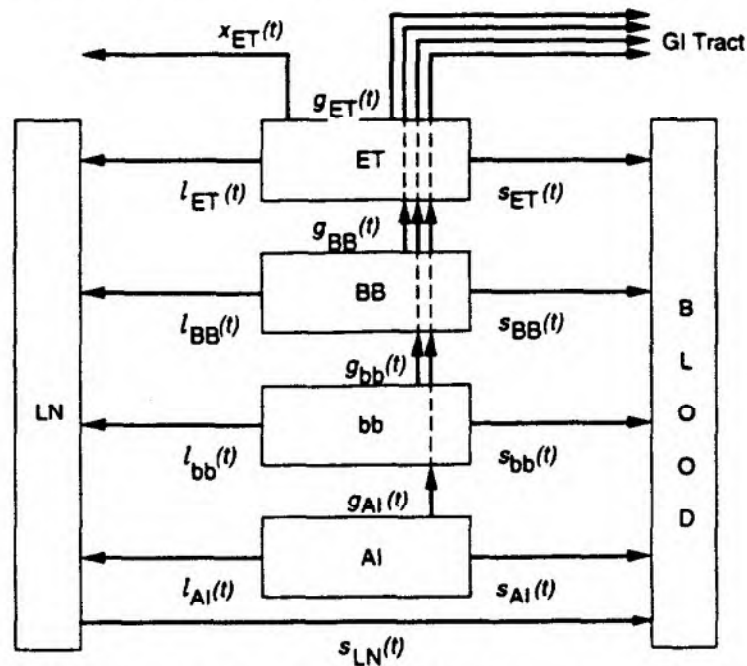


Fig. 19. Clearance routes from the respiratory tract. Symbols indicate fractional rates of clearance, at time t after an acute intake, by each route from each region: extrathoracic (ET), bronchial (BB), bronchiolar (bb), alveolar-interstitial (AI). $s_i(t)$ is the rate of absorption into blood from region i ; $g_i(t)$ particle transport towards the GI tract; $l_i(t)$ particle transport towards regional lymph nodes; $x_{ET}(t)$ extrinsic clearance from the ET region.

(230) The general approach used in this model is to treat clearance from each respiratory tract region as competitive between particle transport processes and absorption into blood (Section E.3.1).

(231) Particle transport refers to the processes that clear material from the respiratory tract to the GI tract and to lymph nodes, and move material from one part of the respiratory tract to another. The rates at which particles are cleared from the respiratory tract are determined by ongoing biological processes, such as the flow of fluids over airway surfaces, which are generally unaffected by the nature of the deposited material or indeed by its presence. They are regarded as operating primarily on particulate material, but the term includes the transport of dissociated material along these routes, which can arise through binding to mucus, or uptake by macrophages.

(232) Absorption refers to the movement of material to the blood, regardless of the mechanism involved. Generally it applies to the dissociation of particles and the uptake into blood of soluble substances and material dissociated from particles, and it is therefore controlled by the physicochemical form of the material. The term does however include any movement of particulate material to the blood, although this is only significant for particles smaller than a few nanometers (Section E.2.2).

(233) Several simplifying assumptions are made to provide a systematic basis for predicting human lung clearance kinetics for the wide range of materials required, on the basis of the limited information available, much of which necessarily comes from animal experiments. The evidence to support the assumptions, and the known

limitations, are described in Section E.3.3. Clearance kinetics are expressed in terms of fractional clearance rates, i.e.:

$$\lambda_i(t) = - \frac{dR_i(t)/dt}{R_i(t)} \quad (24)$$

where $\lambda_i(t)$ is the overall instantaneous rate of clearance of material from region i , and $R_i(t)$ is the amount of material in the region at time t after an acute intake.

(234) It is assumed in the model that:

- The clearance rates due to particle transport and absorption are independent. The overall rate of clearance from a region is thus the sum of the rates due to the individual processes:

$$\begin{aligned} \lambda_i(t) &= m_i(t) + s_i(t) \\ &= g_i(t) + l_i(t) + s_i(t) \end{aligned} \quad (25)$$

where $m_i(t)$ and $s_i(t)$ are clearance rates from region i due to particle transport and absorption, respectively; $g_i(t)$ and $l_i(t)$ are particle transport rates to the GI tract and regional lymph nodes.

- Particle transport rates are the same for all materials.
- The rate of absorption of a material into blood, which is different for different materials, is the same in all regions of the respiratory tract, including the regional lymph nodes to which the material is cleared, but excluding the anterior nasal passage. If, however, there is information available that enables different absorption rates to be determined for the different regions, this should be used.

7.2. Compartment Model for Respiratory Tract Clearance

(235) The rates of clearance from each region, by each route, generally change with time. Following an acute intake, particle transport rates tend to decrease as some sites within a region clear faster than others. Absorption rates tend to change with time since the process of dissociation alters the physicochemical form of the material. The use of time-dependent clearance functions can, however, lead to difficulties in calculating the pattern of retention and clearance following deposition, especially for protracted intakes, or where account has to be taken of radioactive decay products.

(236) To overcome the problems in using time-dependent functions, clearance from a *region* (ET, BB, bb, AI) by the three *routes* is represented in the model by a combination of *compartments*. Each compartment clears at a constant fractional rate, so that the overall clearance approximates the observed time-dependent behaviour of the region. Each compartment is cleared to other compartments by *pathways* with assigned rate constants.

(237) In selecting compartments and pathways, consideration was given to the need to quantify retention in the respiratory tract to calculate doses to radiosensitive tissues, particularly the bronchial and bronchiolar epithelia. Consideration was also given to the need to quantify clearance to the GI tract, blood, and LN with sufficient precision to calculate doses from secondary deposition sites and to interpret bioassay measurements.

7.2.1. Particle transport rates

(238) Figure 20 shows the compartment model for particle transport. It describes the behaviour of a completely insoluble material, but, as discussed in Section 7.3 below, absorption into blood generally also acts on each compartment shown, except the anterior nasal passages (represented by compartment ET_1).

(239) Reference values for each parameter are shown in Fig. 20 and listed in Table 17. Particle transport rates are expressed in d^{-1} and have been rounded. Corresponding approximate clearance half-times are also given in Table 17. A brief account of the derivation of these values follows. Full details and estimated ranges are given in Annexe E. Many of the parameters are altered by factors such as age, smoking, and disease, as described in Annexe E. Only in a few cases, however, is it possible to recommend modifying factors by which parameters should be multiplied for assessment of doses for specific individuals or groups. (See Section 7.4.)

(240) Most particles deposited in all regions are cleared by transport over airway surfaces towards the pharynx (included in compartment ET_2), where they are swallowed. However, there is evidence that a small fraction of particles deposited in ET , BB , and bb regions are retained in the airway walls, and provision is made for this by means of the sequestration compartments ET_{seq} , BB_{seq} , and bb_{seq} , respectively (Sections E.4.3 and E.5.4). Furthermore, while it is considered that most particles deposited in the BB and bb regions are cleared rapidly by mucociliary action, represented by compartments BB_1 and bb_1 , recent human studies indicate that a fraction is cleared much more slowly (Section E.5.3). This slow clearance is represented by compartments BB_2 and bb_2 , respectively.

(241) As far as possible, the parameters in the model are based on observations on humans, since particle transport rates are known to vary markedly between species (Section E.1). The main exception is for parameters quantifying particle retention in the walls of the conducting airways, which are based entirely on results of animal experiments, although the phenomenon itself has been observed in humans.

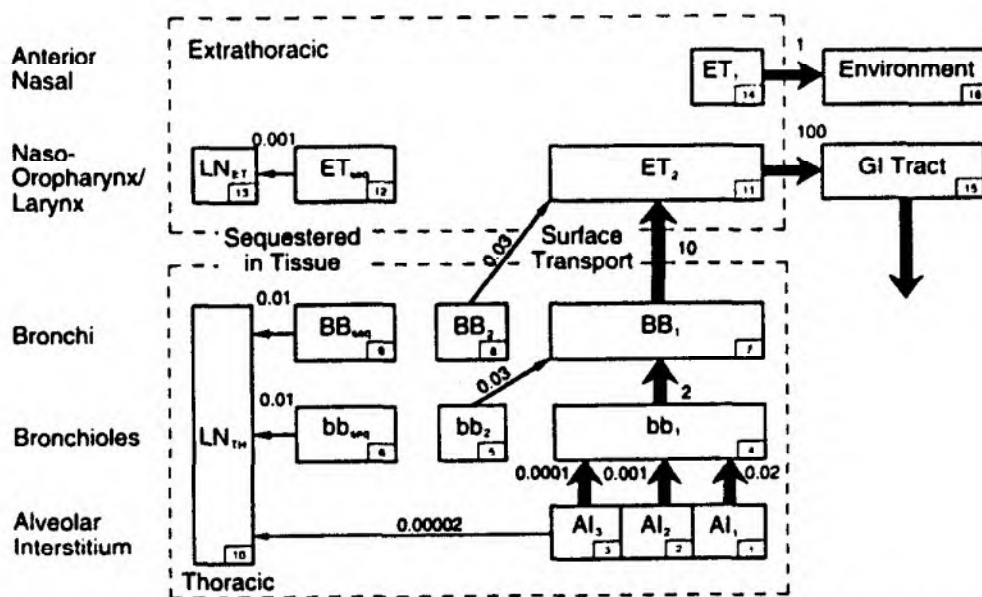


Fig. 20. Compartment model to represent time-dependent particle transport from each region. Particle transport rate constants shown beside the arrows are reference values in d^{-1} from Table 17. Compartment numbers (shown in the lower right-hand corner of each compartment box) are used to define clearance pathways. Thus the particle transport rate from bb_1 to BB_1 is denoted $m_{4,7}$ and has the value $2 d^{-1}$.

Table 17. Reference values of parameters for the compartment model to represent time-dependent particle transport from human respiratory tract

A. Clearance rates				
Pathway	From	To	Rate (d ⁻¹)	Half-time ^a
m _{1,4}	Al ₁	bb ₁	0.02	35 d
m _{2,4}	Al ₂	bb ₁	0.001	700 d
m _{3,4}	Al ₃	bb ₁	0.0001	7000 d
m _{3,10}	Al ₃	LN _{TH}	0.00002	—
m _{4,7}	bb ₁	BB ₁	2	8 h
m _{5,7}	bb ₂	BB ₁	0.03	23 d
m _{6,10}	bb _{seq}	LN _{TH}	0.01	70 d
m _{7,11}	BB ₁	ET ₂	10	100 min
m _{8,11}	BB ₂	ET ₂	0.03	23 d
m _{9,10}	BB _{seq}	LN _{TH}	0.01	70 d
m _{11,15}	ET ₂	GI tract	100	10 min
m _{12,13}	ET _{seq}	LN _{ET}	0.001	700 d
m _{14,16}	ET ₁	Environment	1	17 h

B. Partition of deposit in each region between compartments ^b		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment ^c
ET ₂	ET ₂	0.9995
	ET _{seq}	0.0005
BB	BB ₁	0.993 - f _s
	BB ₂	f _s
	BB _{seq}	0.007
bb	bb ₁	0.993 - f _s
	bb ₂	f _s
	bb _{seq}	0.007
Al	Al ₁	0.3
	Al ₂	0.6
	Al ₃	0.1

^a The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d⁻¹. A half-time is not given for the transport rate from Al₁ to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment Al₁ is determined by the sum of the clearance rates from it.

^b See Paragraph 181, Chapter 5 for default values used for relating f_s to d_{ac}.

^c It is assumed that the slow-cleared fraction f_s is size-dependent. For modelling purposes f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ac} \leq 2.5 \sqrt{\rho/\chi} \text{ } \mu\text{m and}$$

$$f_s = 0.5 e^{-0.63(d_{ac}\sqrt{\rho/\chi} - 2.5)} \text{ for } d_{ac} > 2.5 \sqrt{\rho/\chi} \text{ } \mu\text{m.}$$

7.2.2. Extrathoracic airways

(242) Studies of mucus flow patterns, and of the retention of radiolabelled particles inhaled by humans, suggest that most of the material deposited in the anterior nasal passages (compartment ET₁) is removed by extrinsic means (nose blowing, wiping, etc.), and that the retention time is on the order of 1 d (Section E.4.1). It is also likely, however, that some of the material deposited in ET₁ is transported to the posterior

nasal passages (which are included in ET_2) by mucous flow and sniffing. To take account of this, while avoiding the additional complexity of a pathway from ET_1 to ET_2 , the deposition fraction of ET_2 is rounded upwards and that for ET_1 is correspondingly rounded downwards. Thus it is assumed that the activity deposited in the nasal part of ET is equally divided between ET_1 and the nasal part of ET_2 (Section D.7.1), although for typical occupational exposures to aerosols with AMADs of a few micrometers or more, it would be expected that deposition in ET_1 would be somewhat greater than that in the nasal part of ET_2 . The reference value of the transport rate from ET_1 out of the body ($m_{14,16}$) is 1 d^{-1} ($t_{1/2} \approx 17 \text{ h}$) (Section E.4.4).

(243) The common clearance characteristic of the remaining airways of the ET region (represented by compartment ET_2) is that, although some areas of the surface are ciliated and others are not, all are largely covered by a lining of fluid that is cleared to the pharynx and swallowed, normally on a time scale of minutes. Measurements of mucous velocity in the human posterior nasal passage show a wide distribution, with a median value of $8 \times 10^{-5} \text{ m s}^{-1}$ (5 mm min^{-1}), corresponding to a transit time of 10 min. Similarly, clearance of particles deposited in the ET region during mouth breathing has been observed to be effectively complete in about 15 min. Thus, the assumed reference value for the clearance rate from compartment ET_2 to the GI tract ($m_{11,15}$) is 100 d^{-1} ($t_{1/2} \approx 10 \text{ min}$) (Section E.4.4).

(244) It has been observed in animal studies that a small fraction of particles deposited in the nasal passage is subject to prolonged retention, located near the basement membrane of the epithelium. There is no direct evidence that particles are retained in the epithelia of the oropharynx and larynx, which are regarded as being the principal tissues at risk in ET_2 , and are therefore treated as the target tissues. Nevertheless, a retention compartment in ET_2 is included in the model. This ensures that account is taken of detriment arising from retention of particles in the nasal passage. Applying it to ET_2 in the existing model will tend to overestimate the detriment, since the oropharynx and larynx are regarded as being of higher sensitivity than the nasal passage, but this is unlikely to affect the overall estimated detriment, and avoids the complication of including a separate additional compartment for the posterior nasal passage. The retained particles are represented by a sequestration compartment (ET_{seq}). The reference value for the fraction of material deposited in ET_2 that is sequestered is 0.0005 (Section E.4.4), and hence the fraction assigned to compartment ET_2 is $1 - 0.0005 = 0.9995$. During mouth breathing all the deposition in ET occurs in ET_2 , and therefore the fractions of the ET deposition going to ET_{seq} and ET_2 are 0.0005 and 0.9995, respectively. During nose breathing, however, approximately 50% of the ET deposit is in ET_2 , and the fractions of the ET deposit going to ET_{seq} and compartment ET_2 are correspondingly lower.

(245) It is assumed that the sequestered particles are cleared to lymph nodes, the reference value of the transport rate from ET_{seq} to the extrathoracic lymph nodes LN_{ET} ($m_{12,13}$) being 0.001 d^{-1} ($t_{1/2} \approx 700 \text{ d}$) (Section E.4.4).

7.2.3. Thoracic airways

(246) Retention of particles deposited in the human lungs generally shows two distinct phases. The first, which is complete within about 24 h, is considered to represent mucociliary clearance to the GI tract of most of the deposit in the BB and bb regions and is represented by compartments BB_1 and bb_1 ; the second, much slower phase represents mainly clearance of particles deposited in the AI region.

7.2.4. *Bronchial and bronchiolar regions*

(247) The velocity of mucus in the human tracheobronchial tree is considered to decrease distally from a value of about $8 \times 10^{-5} \text{ m s}^{-1}$ (5 mm min^{-1}) in the trachea. On the basis of recent models of human mucociliary clearance (Section E.5.2.5), reference values of the particle transport rates from the BB region to the pharynx, which is included in ET_2 ($m_{7,11}$), and from the bronchioles to the bronchi ($m_{4,7}$), are taken to be 10 d^{-1} ($t_{1/2} \approx 100 \text{ min}$) and 2 d^{-1} ($t_{1/2} \approx 8 \text{ h}$, respectively [Section E.5.6.1]).

(248) To provide a slow phase of clearance of material deposited in the BB and bb regions, a second compartment representing transport over the airway surfaces is included in each (BB_2 and bb_2 , respectively). Because of the limited information available, it is assumed that the same fraction of the deposit, f_s , is subject to slow clearance in both regions (Section E.5.6.1). Current information indicates that the slow-cleared fraction f_s is size-dependent. For modelling purposes, f_s is taken to be:

$$f_s = 0.5 \quad \text{for } d_{ae} \leq 2.5\sqrt{\rho/\chi} \text{ } \mu\text{m} \quad (26)$$

$$f_s = 0.5 e^{-0.63(d_{ae}\sqrt{\chi/\rho} - 2.5)} \quad \text{for } d_{ae} > 2.5\sqrt{\rho/\chi} \text{ } \mu\text{m} \quad (27)$$

Note that these formulae apply to monodisperse particles. For a polydisperse aerosol, however, the overall slow-cleared fraction will have to be calculated by convoluting f_s with the distribution of particle sizes d_{ae} . Since the deposition fraction as a function of d_{ae} is different for the bronchial and bronchiolar regions, this will result in different slow-cleared fractions in these regions. (See Paragraph 181 for aerosol default values used for relating f_s to d_{ae} .)

(249) The half-time for this slow clearance is estimated to be approximately 20 d, and, in the absence of specific information, is assumed to apply to both the BB and bb regions. Thus the reference values of the transport rate from bb_2 to BB_1 ($m_{5,7}$), and from BB_2 to ET_2 ($m_{8,11}$), are both taken to be 0.03 d^{-1} ($t_{1/2} \approx 23 \text{ d}$).

(250) There is evidence that a small fraction of particles deposited in the BB and bb regions is subject to prolonged retention in the airway wall. This is represented by the sequestration compartments BB_{seq} and bb_{seq} . The quantitative data on which the reference values are based come from studies in which particles were deposited on the rat trachea (Section E.5.4). Because of the lack of more specific information, it is assumed that the same fraction (0.007) of material deposited in the BB and bb regions is sequestered (Section E.5.6.1).

(251) It is assumed that the sequestered particles are cleared to lymph nodes. Reference values, based on experiments on rat trachea, for the clearance rates from bb_{seq} and BB_{seq} to the thoracic lymph nodes LN_{TH} ($m_{6,10}$ and $m_{9,10}$) are taken to be 0.01 d^{-1} ($t_{1/2} \approx 70 \text{ d}$) (Section E.5.6.1).

7.2.5. *Alveolar-interstitial region*

(252) Human lung clearance has been quantified in experimental studies up to about a year after inhalation. Lung retention of relatively insoluble particles over this time typically follows a two-component exponential function, with about 30% having a half-time of about 30 d, and the rest a half-time of several hundred days, giving about 80% retention at 50 d, 70% at 100 d, and 50% at 300 d (Section E.6.1). Measurements of activity in the chest after occupational exposure, and of activity in the lungs at autopsy, indicate that some material can be retained in the lungs for decades (Section E.6.1.3).

(253) Similarly, the experimental data indicate that the particle transport rate from

AI via the bronchial tree to the GI tract falls from about 0.003 d^{-1} at 25 d to 0.0008 d^{-1} at 200 d (Section E.6.2). Measurements of faecal excretion of uranium suggest that the rate continues to fall, to about 0.0004 d^{-1} at 1500 d.

(254) These results suggest that AI retention needs to be represented by three compartments, which clear at rates of about 0.02 d^{-1} (i.e. $t_{1/2}$ about 30 d), 0.001 d^{-1} , and 0.0001 d^{-1} . These are termed AI_1 , AI_2 , and AI_3 , respectively. As described in Section E.6.3, the experimental data indicate that the fraction of the AI deposit that goes to AI_1 should be 0.3; it is assumed that the fraction that goes to AI_3 is 0.1; and, hence, by difference, that the fraction that goes to AI_2 is 0.6.

7.2.6. Regional lymph nodes

(255) Autopsy tissues taken many years after exposure have shown concentrations in LN_{TH} typically about 20 times those in the lungs of nonsmokers (Section E.7). This, however, implies that the amount of material in the lungs is about three times that in LN_{TH} , since the mass of LN_{TH} (0.015 kg) is less than that of the lungs (1.0 kg). For simplicity, transport to lymph nodes is represented by a pathway from AI_3 only. The value of the transport rate from AI_3 to LN_{TH} in the compartment model ($m_{3,10}$), 0.00002 d^{-1} , was chosen to give a lymph node/lung concentration ratio of about 20 at 10,000 d after inhalation (Section E.7.5).

(256) It is assumed that there is no particle transport from LN_{ET} or LN_{TH} (Section E.7.5).

7.3. Absorption into Blood

7.3.1. Representation of time-dependent absorption

(257) As stated above (Paragraph 234), it is assumed in the model (in the absence of information to the contrary) that absorption into blood occurs at the same fractional rate, $s(t)$, in all regions, except in the anterior nasal passages (ET_1), where no absorption occurs.

(258) Absorption into blood is essentially a two-stage process, as shown in Fig. 21:

- the dissociation of the particles into material that can be absorbed into the blood. For simplicity this is termed dissolution, although other processes may be involved.
- the uptake of material dissolved from particles, or of material deposited in a soluble form.

(259) Each stage can be time-dependent. A phase of rapid absorption into blood is often observed immediately after inhalation, even with relatively insoluble materials (Section E.2.2). Uptake into blood can usually be treated as instantaneous, but, for a number of important elements, a significant fraction of the dissolved material is absorbed slowly as a result of binding to respiratory-tract components.

(260) The simplest compartment model representation of time-dependent *dissolution* is to assume that a fraction (f_r) dissolves relatively rapidly, at a rate s_r , and the remaining fraction ($1 - f_r$) dissolves more slowly, at a rate s_s (Fig. 22A). Provision is made for two such states, to avoid undue complexity, as it is considered that there would rarely in practice be sufficient information available to justify more. The main disadvantage of the system shown in Fig. 22A, however, is that it can only readily represent an overall fractional dissolution rate that decreases with time. A simple alternative, with the same number of variables, is shown in Fig. 22B. In this, the

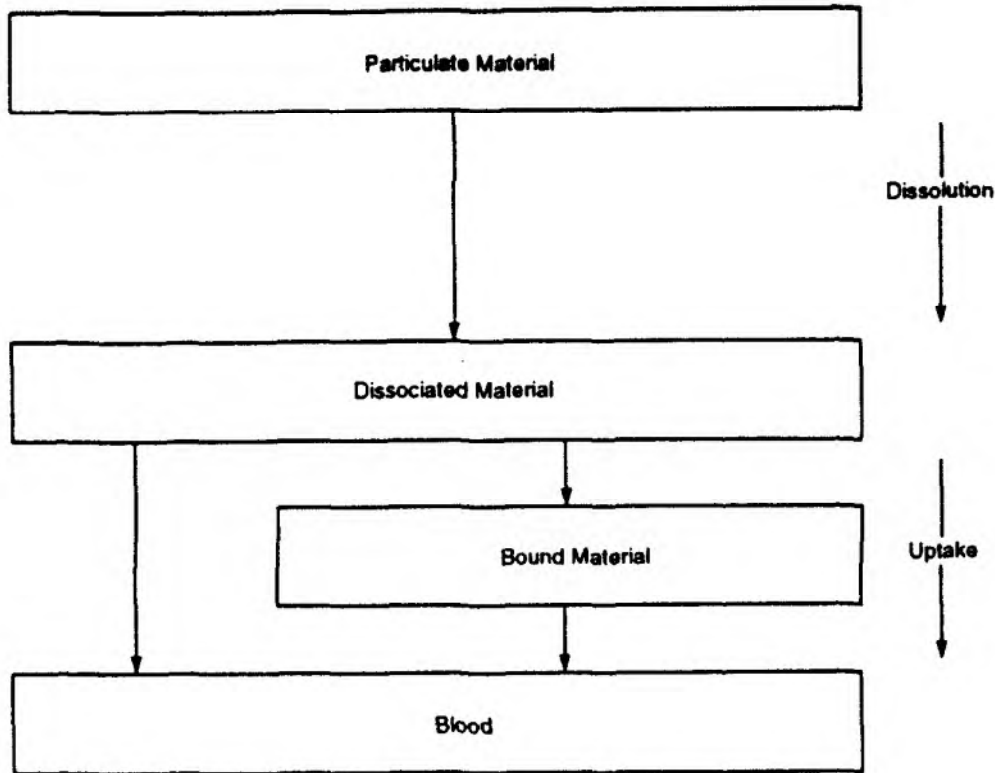


Fig. 21. Absorption into blood.

particles in their "initial" state dissolve at a constant rate s_p , but are simultaneously converted to a "transformed" state (at a rate s_{pt}), in which they have a different dissolution rate s_t . This provides the same results as the system in Fig. 22A, with the following values:

$$\begin{aligned} s_p &= s_s + f_r(s_t - s_s) \\ s_{pt} &= (1 - f_r)(s_t - s_s) \\ s_t &= s_s. \end{aligned} \quad (28)$$

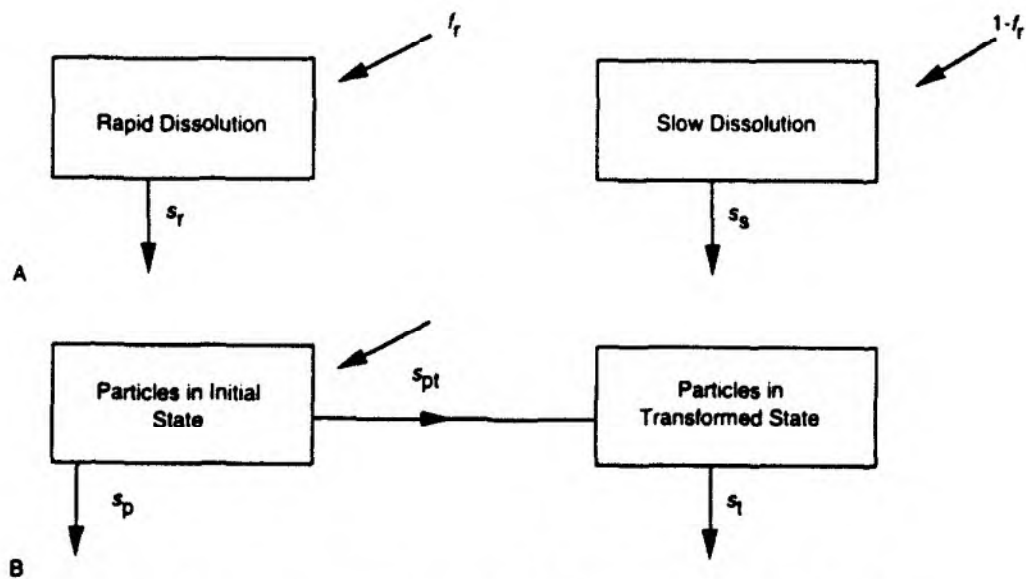


Fig. 22. Alternative compartment models for time-dependent dissolution.

With this system, the initial dissolution rate is approximately s_p , and the final dissolution rate is approximately s_t . Thus, with suitable choice of parameters, including $s_t > s_p$, an increasing dissolution rate can be represented.

(261) To represent time-dependent *uptake*, it is assumed that a fraction (f_b) of the dissolved material is retained in a "bound" state, from which it goes into blood at a rate s_b , while the remaining fraction ($1 - f_b$) goes to blood instantaneously. In the model, material in the "bound" state is not cleared by particle transport processes. (If dissociated material is bound in such a way that it is available for particle transport, e.g. taken up by macrophages, it is treated as "transformed particles".) Thus, only one "bound" compartment is required for each region.

(262) Figure 23 summarizes the model's treatment of time-dependent absorption, including both dissolution and uptake.

(263) The system shown in Fig. 23 can conveniently be regarded as an operator that acts on each compartment in Fig. 20 (except ET_1). Thus, from each compartment j ($j = 1$ through 13) containing particles in their initial state, material moves at a rate s_{pt} to the corresponding compartment j_T containing "transformed" particles (Fig. 23). The "transformed" particles are cleared by transport processes at the same rates as the particles before transformation ($m_{j,k} = m_{j_T,k_T}$ for all j and k).

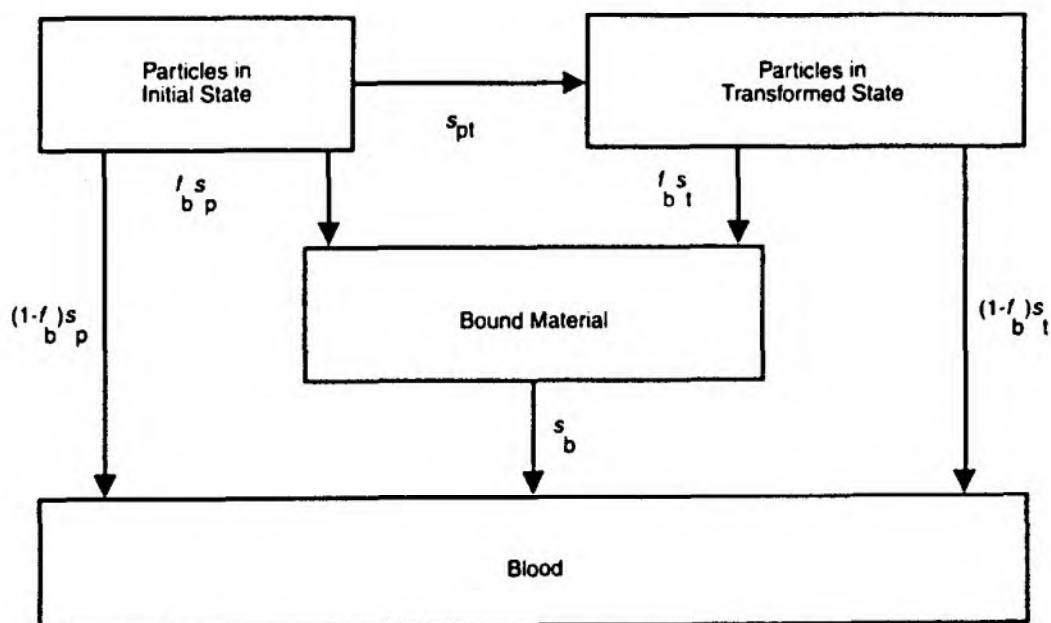


Fig. 23. Compartment model for time-dependent absorption into blood.

(264) Figure 24 shows the complete clearance model, including both time-dependent particle transport and absorption. For most materials, however, there will probably be insufficient information available to justify using anything more complex than a single, constant absorption rate (i.e. $s_{pt} = 0$ and $f_b = 0$). The requirement for time-dependent dissolution is most likely to be needed for slowly dissolving particles that show an initial rapid uptake to blood. The need to use the "bound" state will mainly arise for materials that are soluble in water but bind to tissues.

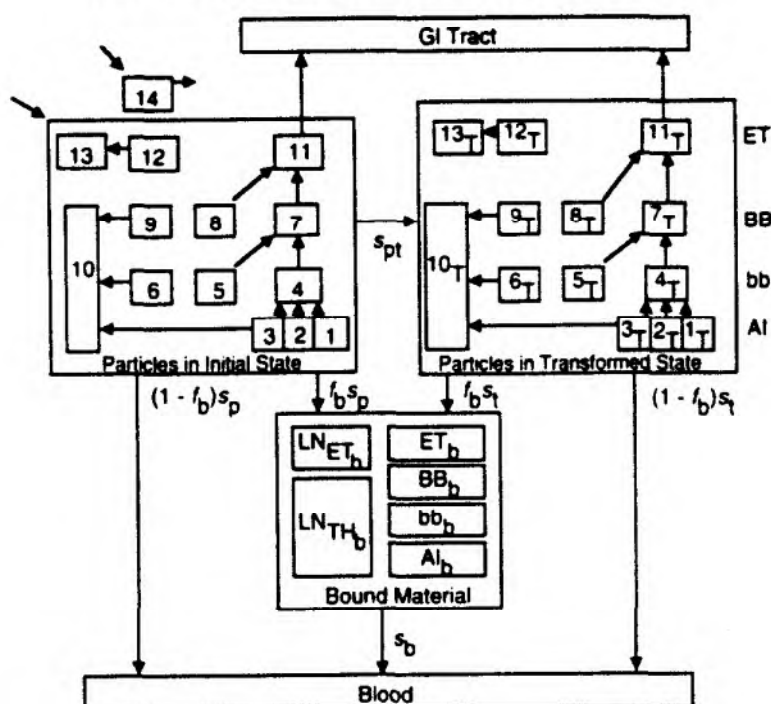


Fig. 24. Overall compartment model for respiratory tract clearance including both time-dependent particle transport and absorption into blood.

7.3.2. Determination of absorption rates

(265) Absorption rates for different materials exhibit a very wide range. At one extreme, a readily absorbed material must have a rate at least as great as the fastest particle transport rate (100 d^{-1}) so that significant absorption may occur in ET_2 , while at the other extreme, a material that remains in the lung many years must have a rate less than about 0.0001 d^{-1} .

(266) The absorption rate of a given compound may vary greatly, depending on its method of production, and history. Ideally the absorption rate of any important material should be determined from a study of the material itself. This requires *in vivo* measurements of lung clearance, and the study should be of sufficient quality to merit publication in a peer-reviewed journal. Appropriate methods of deriving absorption rates from experimental data are described in Section E.2.2.3.

(267) Recommended absorption rates for a number of compounds, based on studies that meet the above criteria, will be developed as a separate effort.

7.3.3. Default absorption parameters

(268) In the absence of absorption rate values for specific radionuclide compounds, default values are proposed for materials classified as D, W, and Y, respectively, in the *Publication 30* (ICRP, 1979) system. To simplify the discussion, they are given below in terms of the system of Fig. 22A: the fraction f_r dissolving rapidly, at the approximate rate s_r , and the approximate slow dissolution rate s_s for the remaining fraction $(1 - f_r)$. The primary corresponding parameters s_p , s_{pt} , and s_t that are recommended for substitution in the model are given in Table 18. Thus, in the absence of more specific information, a compound that was assigned to Class Y in *ICRP Publication 30* is assigned to Type S in the new scheme. It should, however, be noted that whereas D, W,

Table 18. Default absorption parameters for Type F, M, and S materials

ICRP Publication 30 class:	D (days)	W (weeks)	Y (years)
Type of absorption behaviour:	F (fast) ^a	M (moderate) ^b	S (slow) ^c
Fraction dissolved rapidly, f_r	1	0.1	0.001
Approximate dissolution rate:			
Rapid (d^{-1}), s_r	100	100	100
Slow (d^{-1}), s_s	—	0.005	0.0001
Model parameters:			
Initial dissolution rate (d^{-1}), s_p	100	10	0.1
Transformation rate (d^{-1}), s_{pt}	0	90	100
Final dissolution rate (d^{-1}), s_i	—	0.005	0.0001
Fraction to bound state, f_b	0	0	0
Uptake rate from bound state (d^{-1}), s_b	—	—	—

^a F (fast)—materials that are readily absorbed into blood (corresponding to "Class D"). There is significant absorption from ET₂ and BB, but some material in these regions will remain in solution in mucus and be swallowed, rather than be absorbed through the epithelium. Hence the default for such materials is $s_r = 100 d^{-1}$ ($t_{1/2} \sim 10$ min).

^b M (moderate)—materials with intermediate rates of absorption (corresponding to "Class W"). For such materials the percentage absorbed rapidly is on the order of 10%, and the slow-phase retention time on the order of 100 d. This is represented by $f_r = 0.1$; $s_r = 100 d^{-1}$; and $s_s = 0.005 d^{-1}$.

^c S (slow)—relatively insoluble materials (corresponding to "Class Y"). It is assumed that for most of the material the rate of absorption to blood is $0.0001 d^{-1}$. This equals the particle transport rate from the most slowly cleared AI compartment. However, it is characteristic of even very insoluble materials that some rapid uptake to blood occurs immediately after inhalation. As a default it is assumed that 0.1% of the deposited material is rapidly absorbed. While the effect of this on doses is likely to be negligible, it may significantly affect the interpretation of measurement of activity in urine. This is represented by $f_r = 0.001$; $s_r = 100 d^{-1}$; and $s_s = 0.0001 d^{-1}$.

and Y define overall clearance, F, M, and S refer only to absorption into blood; particle transport rates to the GI tract and lymph nodes are the same for the three types. The different terminology has been introduced to avoid ambiguity.

(269) The effect of these default values on the amounts of *deposited* materials reaching the blood can be summarised as follows:

- For Type F, there is rapid absorption of almost all material deposited in BB, bb, and AI, and 50% of material deposited in ET₂. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET, and for mouth breathing 50%.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET₂. Thus, for nose breathing, there is rapid absorption of approximately 2.5% of the deposit in ET, and for mouth breathing 5%.
- For Type S, there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.

This is further illustrated in Figs 25 and 26, which show the fractions of *inhaled* material reaching the blood (for a nose-breathing adult male). Figure 25 shows the time course of transfer to blood for an environmental exposure to a 1- μ m-AMAD aerosol and for an occupational exposure to a 5- μ m-AMAD aerosol. (A summary of exposure conditions and regional deposition fractions is given later in Table 28.) Figure 26 shows the effect of aerosol size on the fraction of material eventually reaching the blood, i.e. by 50 y after inhalation in an adult male, nose breather (in occupational environmental settings). For Type S, this fraction follows the dependence of AI deposition on aerosol size, since the amount reaching the blood is approximately 10 % of the AI deposit.

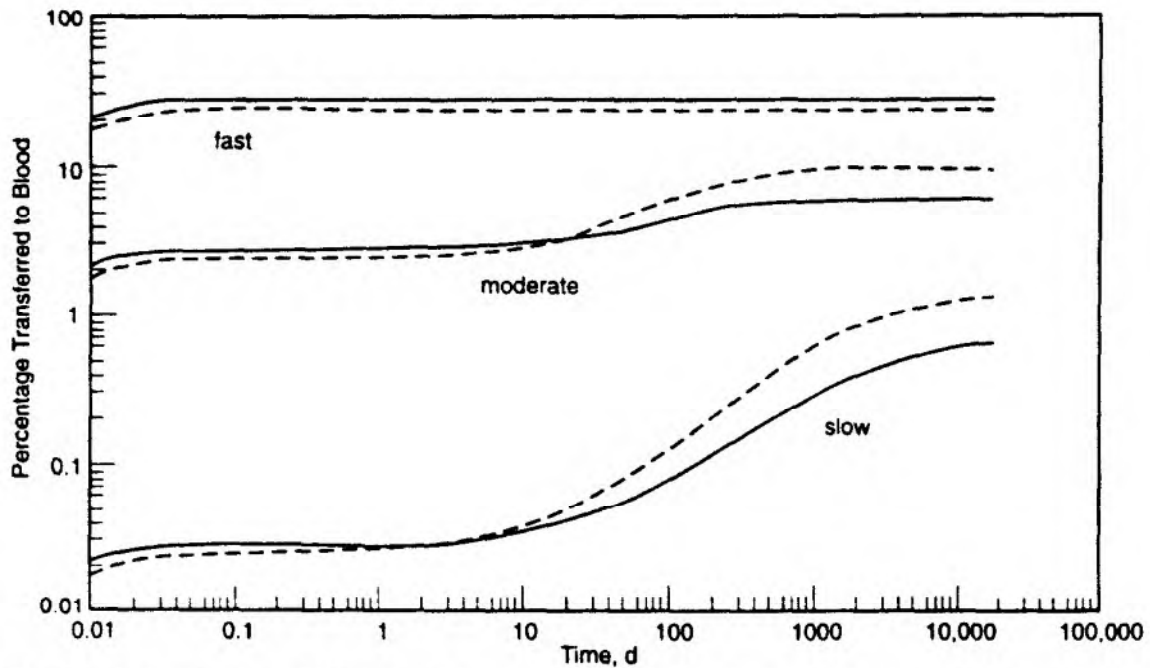


Fig. 25. Cumulative fraction of inhaled activity deposited and absorbed into blood as a function of time after intake, for each default absorption type (F, M, and S). Solid curves represent 5- μm -AMAD aerosol inhaled by a Reference Worker (Occupational) and dashed curves represent 1- μm -AMAD aerosol inhaled by a Reference Male (Environmental-Indoors). Exposure conditions and regional deposition in the respiratory tract for these subjects are given in Table 28.

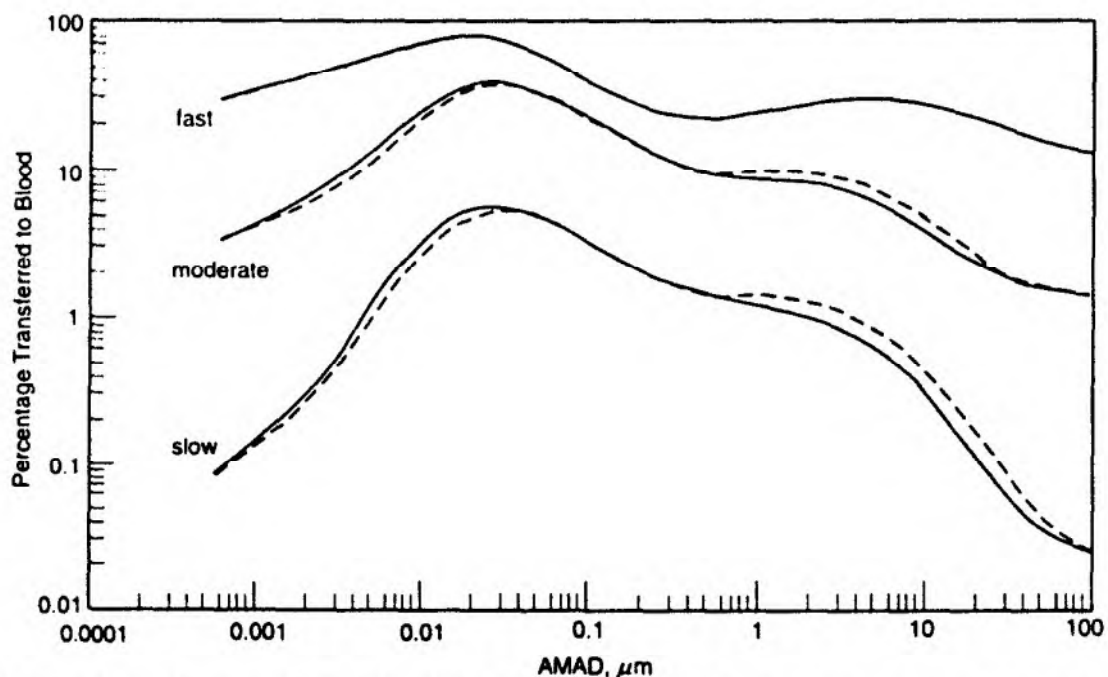


Fig. 26. Cumulative fraction of inhaled activity deposited and absorbed into blood as a function of aerosol AMAD, for each default absorption type (F, M, and S). Solid curves represent aerosols inhaled by a Reference Worker (Occupational) and dashed curves represent aerosols inhaled by a Reference Male (Environmental-Indoors). Exposure conditions and regional deposition in the respiratory tract for these subjects are given in Table 28.

7.4. Modifying Factors

(270) As discussed in Annexe E, the effects of many factors on respiratory tract clearance rates have been investigated, notably age, diseases, pharmacological agents, and air pollutants. Only in a few cases, however, is it possible to recommend modifying factors by which parameters should be multiplied for assessment of doses for specific individuals or groups. The most frequently studied factors are smoking (both acute and chronic effects) and respiratory disease; the most common endpoints have been mucociliary clearance from the nasal passage or tracheobronchial tree. However, while effects have often been observed, the results are usually qualitative, i.e. an increase or (more often) a decrease in clearance. Where sufficient data exist to enable the effect on a clearance parameter to be quantified, a recommended modifying factor is given in Table 19. At present, modifying factors are recommended for:

- the "fast" phase of particle transport from the BB and bb regions (compartments BB₁ and bb₁; Section E.5.6.2);
- the AI region (cigarette smoking only; Section E.6.3.2).

For example, in considering asthmatics specifically, the modifying factor (0.7) would be applied to the clearance from bb₁ to BB₁ (i.e. $m_{4,7}$ reduced from 2 d⁻¹ to 1.4 d⁻¹) and to the clearance from BB₁ to ET₂ (i.e. $m_{7,11}$ reduced from 10 d⁻¹ to 7 d⁻¹).

(271) Possible differences in clearance between children and adults are of particular interest in order to assess doses to the general population. However, there are almost no

Table 19. Proposed modifying factors for the compartment model to represent particle transport from the human respiratory tract

Modifying factor	Φ_m	
	Bronchial region (BB) $m_{7,11}$ (BB ₁ to ET ₂)	Bronchiolar region (bb) $m_{4,7}$ (bb ₁ to BB ₁)
Age (after 60 y)	0.6	(0.6) ^a
Sleep	0.3	0.3
Asthma	0.7	0.7
Bronchial carcinoma	0.3	0.3
Chronic bronchitis	0.5	(0.5)
Cystic fibrosis	0.5	(0.5)
Immotile cilia syndrome	0.1	(0.1)
Immunoglobulin deficiency	0.4	(0.4)
Influenza	0.2	(0.2)
Kartagener's syndrome	0.1	(0.1)
Mycoplasma pneumonia	0.3	(0.3)
Atropine	0.1	0.1
β -adrenergic agent	2	2
Cigarette smoke (acute)	1	2
Cigarette smoking	0.5	1
Sulphuric acid	1	0.7
Alveolar-interstitial region (AI)		
	a_1 ^b	$m_{2,4}$ (AI ₂ to bb ₁) $m_{3,4}$ (AI ₁ to bb ₁)
Cigarette smoking	0.3	0.7

^a Values in parentheses are adopted by analogy with BB.

^b Fraction of AI deposits that go to AI₁ (see Table 17B).

experimental data on clearance in normal children (Section E.4.4.2). Even for laboratory animals there are insufficient data to establish clear quantitative differences between immature and adult mammals, but the limited information suggests that any such differences are not large. Therefore it is not at present possible to define clearance rates specifically for each of the age groups from newborn to adult designated by the ICRP. In the absence of such information, the reference values for adults are also applied to children.

7.5. Radioactive Decay Products

(272) Generally it would be expected that the rate at which the particle dissociates is determined by the particle matrix and that, therefore, this would be the same for the decay product as for the parent. Hence s_p , s_{pr} , and s_i are assumed to be the same. A notable exception, however, is when the decay product is a noble gas, such as radon, in which case it might be expected to diffuse from the particle. The behaviour of dissociated material would, however, be expected to depend on its elemental form; therefore, f_b and s_b for a decay product would not necessarily be expected to be the same as for the parent, although in the absence of information it might well have to be assumed that they are.

8. DOSIMETRY

8.1. Introduction

(273) The purpose of the dosimetry model is to evaluate doses to each of the six tissues of the respiratory tract that are potentially at risk from inhaled radioactive materials. The target tissues within the respiratory tract were discussed in Chapters 1 and 4:

- (1) the keratinised epithelium of the skin in the anterior part of the nose (represented in the deposition and clearance model by the region ET_1)
- (2) the stratified squamous epithelium of the main extrathoracic airways (represented by the region ET_2)
- (3) the ciliated epithelium of the bronchi (represented by the region BB)
- (4) the ciliated epithelium of the bronchioles (represented by the region bb)
- (5) the alveolar-interstitium (represented by the region AI)
- (6) the thoracic and extrathoracic lymph nodes (represented by the regions LN_{TH} and LN_{ET} , respectively).

8.2. Dosimetric Principles

(274) To evaluate doses to tissues of the respiratory tract and other targets throughout the body, the formal procedure recommended in *ICRP Publication 30* (ICRP, 1979) and developed further in *ICRP Publication 56* (ICRP, 1989) and *ICRP Publication 60* (ICRP, 1991a) is applied to include contributions from all tissues in which radionuclides are retained. The committed equivalent dose, H_T , in each target

tissue, T, from radiations emitted in a tissue source, S, is determined by the product of two factors:

- (1) the total number of transformations of the radionuclide in tissue source S over a period of integration τ after intake of the radionuclide
- (2) the energy absorbed per unit mass in the target tissue T, suitably modified for the radiation weighting factor, for each radiation emitted per transformation in tissue source S.

(275) The dosimetric formulations of *ICRP Publication 30* have been extended to address age-dependence in *ICRP Publication 56*. The equivalent dose rate in target organ T includes contributions from the activity of the radionuclide present in organs of the body. The equivalent dose rate at age t in organ T of an individual of age t_0 at the time of intake, $\dot{H}_T(t, t_0)$, can be expressed as:

$$\dot{H}_T(t, t_0) = c \sum_s \sum_j q_{s,j}(t) SEE(T \leftarrow S; t)_j \quad (29)$$

where $q_{s,j}(t)$ is the activity of radionuclide j present in source organ S at age t ; $SEE(T \leftarrow S; t)$ is the total energy absorbed per unit mass in the target T; the contributions of each radiation emitted by the radionuclide are weighted by their radiation weighting factor, per nuclear transformation of the radionuclide in source region S; and c is any numerical constant required by the units of q and SEE . The equivalent dose in the target organ accumulated by age 70 y due to a single intake of a radionuclide at age t_0 , $H_T(t_0)$ is:

$$H_T(t_0) = \int_{t_0}^{70} \dot{H}_T(t, t_0) dt \quad (30)$$

that is:

$$H_T(t_0) = c \int_{t_0}^{70} \sum_s \sum_j q_{s,j}(t) SEE(T \leftarrow S; t)_j dt. \quad (31)$$

For any radionuclide, the specific effective energy SEE at age t is defined as:

$$SEE(T \leftarrow S; t) = \sum_R \frac{w_R E_R Y_R AF(T \leftarrow S; t)_R}{M_T(t)} \quad (32)$$

where w_R is the radiation weighting factor for radiation R, E_R is the energy of radiation R, Y_R is the yield of radiation R per nuclear transformation, $AF(T \leftarrow S; t)_R$ is the fraction of the energy of radiation R emitted in S, which is absorbed in the target tissue T at age t , and $M_T(t)$ is the mass of the target tissue at age t .

(276) For the adult, the SEE is not a function of time and thus:

$$H_T(t_0) = c \sum_s \sum_j U_{s,j} SEE(T \leftarrow S)_j \quad (33)$$

where $U_{s,j}$ is the total number of nuclear transformations of radionuclide j in S over the 50-y period following the intake, i.e.:

$$U_{s,j} = \int_0^{50} q_{s,j}(t) dt. \quad (34)$$

(277) When radioactive decay products are formed within the body from an intake of a radionuclide, the contribution of each product, indexed by j in the above equations, is included in the value of the committed equivalent dose per unit intake for the parent nuclide.

(278) All dosimetric discussions below are limited to the adult unless otherwise noted.

(279) The Task Group's compartment model of regional deposition in the respiratory tract (Chapter 5, Fig. 7) is used with the model of radionuclide retention (Chapter 7) to evaluate the number of radioactive decays, U_i , in each discrete source. The various source elements within the respiratory tract were illustrated schematically in Fig. 20 (Chapter 7) as compartments in which significant deposition and retention may occur:

- (1) anterior nasal passages —the airway surface
- (2) naso-oropharynx/larynx —fluid lining the airway surface
 —the airway wall
- (3) extrathoracic lymph nodes
- (4) the bronchi —mucus on the airway surface
 —the airway wall
- (5) the bronchioles —mucus on the airway surface
 —the airway wall
- (6) the alveolar-interstitium
- (7) thoracic lymph nodes.

(280) For short-range alpha, electron, and beta emitters, it is important to take account of nonuniformity of the radioactive transformations in these airways in relation to the sites of target cells. For this purpose, principles have been applied that are similar to those recommended in *ICRP Publication 30* (ICRP, 1979) for evaluating doses to the thin layer of sensitive cells at bone surfaces from sources of short-range radiation distributed more widely in skeletal tissue. In the case of photons (gamma emitters), it is necessary to consider nonuniformity of dose only between respiratory tissues within the thorax and those in the head airways. However, for photons, other source organs within the body may also irradiate the respiratory tract, and it is necessary to include these sources in the evaluation of H_e for all respiratory tissues.

(281) To evaluate doses to target tissues outside the respiratory tract, this lung model is used in the same manner as that of *ICRP Publication 30* (ICRP, 1979), together with appropriate models of radionuclide uptake and metabolism by body organs.

(282) The methods used to evaluate absorbed fractions, $AF(T \leftarrow S)$, for alpha particles, electrons, and beta particles, and the values recommended for use in the dosimetry model, together with the associated values of tissue mass M_T for the respiratory tract, are described later. For photons, the specific absorbed fractions, $SAF(T \leftarrow S)$, calculated for subjects of various age (body mass) by Cristy and Eckerman (1987a) are recommended.

8.3. Specific Absorbed Fractions for Photons

8.3.1. Extrathoracic airways and associated lymph nodes as the source

(283) The extrathoracic airways and lymph nodes have not yet been represented specifically in mathematical models (phantoms) of the human body that are used to

calculate the transport of photon energy between organs. Until specific absorbed fraction data for these tissues become available, the absorbed fractions for photon emissions in the extrathoracic airways and lymph nodes will be approximated by the absorbed fraction data for the thyroid as the source region. Thus, except for the case where the target tissue, T, is the thyroid itself, it is assumed that:

$$\left[\begin{array}{l} \text{SAF}(T \leftarrow \text{ET}_1) \\ \text{SAF}(T \leftarrow \text{ET}_2) \\ \text{SAF}(T \leftarrow \text{LN}_{\text{ET}}) \end{array} \right] \approx \text{SAF}(T \leftarrow \text{thyroid}). \quad (35)$$

(284) To approximate the specific absorbed fractions for the anterior nasal passages (ET_1), the main extrathoracic airways (ET_2), and the extrathoracic lymph nodes (LN_{ET}) when these are both source and target tissues, it is assumed that:

$$\left[\begin{array}{l} \text{SAF}(\text{ET}_1 \leftarrow \text{ET}_1) \\ \text{SAF}(\text{ET}_2 \leftarrow \text{ET}_2) \\ \text{SAF}(\text{LN}_{\text{ET}} \leftarrow \text{LN}_{\text{ET}}) \end{array} \right] \approx \text{SAF}(\text{thyroid} \leftarrow \text{thyroid}). \quad (36)$$

(285) Likewise, it is assumed that $\text{SAF}(\text{thyroid} \leftarrow \text{thyroid})$ also approximates the specific absorbed fractions for any combination of ET_1 , ET_2 , and LN_{ET} as source and target tissues.

(286) To approximate the specific absorbed fractions for the thyroid itself as target tissue, the brain is assumed to be the nearest equivalent to the extrathoracic-airway and lymph-node sources. Thus:

$$\left[\begin{array}{l} \text{SAF}(\text{thyroid} \leftarrow \text{ET}_1) \\ \text{SAF}(\text{thyroid} \leftarrow \text{ET}_2) \\ \text{SAF}(\text{thyroid} \leftarrow \text{LN}_{\text{ET}}) \end{array} \right] \approx \text{SAF}(\text{thyroid} \leftarrow \text{brain}). \quad (37)$$

(287) Values of the specific absorbed fraction of photon energy for target tissues throughout the body, calculated for the reference adult male when the radionuclide source is within the extrathoracic airways or lymph nodes, are given in Annexe G. These values are derived from Cristy and Eckerman (1987g). They apply for discrete photon energies between 0.01 and 4.0 MeV. Specific absorbed fractions for intermediate energies are obtained by linear interpolation of $\text{SAF}(T \leftarrow S)$ as a function of the photon energy. For photon energy less than 0.01 MeV, $\text{SAF}(T \leftarrow S)$ is estimated by linear interpolation from the value at 0.01 MeV to zero at zero energy. For photon energy greater than 4.0 MeV, $\text{SAF}(T \leftarrow S)$ is estimated by linear extrapolation from the tabulated values at 2.0 and 4.0 MeV.

(288) Similar tables, presented in Annexe G, give specific absorbed fractions for body tissues in the reference adult female, in children aged 15 y, 10 y, and 5 y, and in the 1-y-old, and 3-mo-old infant (Cristy and Eckerman, 1987b-f).

8.3.2. Extrathoracic airways as the target

(289) Doses received by the extrathoracic airways from photons emitted within the thorax, or from source organs elsewhere in the body, can be neglected in comparison with those received by body organs. However, for the sake of completeness, the specific

absorbed fractions for the extrathoracic airways as the target tissues are approximated by:

$$\left[\begin{array}{l} \text{SAF}(\text{ET}_1 \leftarrow \text{S}) \\ \text{SAF}(\text{ET}_2 \leftarrow \text{S}) \end{array} \right] \approx \text{SAF}(\text{thyroid} \leftarrow \text{S}), \quad (38)$$

unless the thyroid itself is the source, in which case use Eq. 37.

(290) In view of their low sensitivity, it is not necessary to consider the extrathoracic lymph nodes (LN_{ET}) as a potential target tissue for photons emitted from source tissues within the body.

(291) Values of the specific absorbed fraction of photon energy for the extrathoracic airways (or lymph nodes) as target tissues, calculated for various body tissues in the reference adult male as the source, are tabulated in Annexe G.

8.3.3. Airways within the thorax as the source

(292) It is adequate to take values of specific absorbed fraction calculated by Cristy and Eckerman (1987a-g) for the "lung" as the source in their mathematical phantoms to represent all source tissues located within the thorax. Thus, for all target tissues outside the lungs:

$$\left[\begin{array}{l} \text{SAF}(\text{T} \leftarrow \text{BB}) \\ \text{SAF}(\text{T} \leftarrow \text{bb}) \\ \text{SAF}(\text{T} \leftarrow \text{AI}) \\ \text{SAF}(\text{T} \leftarrow \text{LN}_{\text{TH}}) \end{array} \right] \approx \text{SAF}(\text{T} \leftarrow \text{lung}). \quad (39)$$

(293) Values of $\text{SAF}(\text{T} \leftarrow \text{lung})$ for photons, calculated for the reference adult male when the radionuclide source is in any tissue of the respiratory tract located within the thorax (Cristy and Eckerman, 1987f), and values of $\text{SAF}(\text{T} \leftarrow \text{lung})$ for target organs in different subjects, with lung tissues as the source, are tabulated in Annexe G.

8.3.4. Airways within the thorax as the target

(294) It is also appropriate to take values of specific absorbed fraction calculated by Cristy and Eckerman (1987a-g) for the whole "lung" as a target to represent all of the constituent lung tissues. Thus, for all sources outside the lungs:

$$\left[\begin{array}{l} \text{SAF}(\text{BB} \leftarrow \text{S}) \\ \text{SAF}(\text{bb} \leftarrow \text{S}) \\ \text{SAF}(\text{AI} \leftarrow \text{S}) \\ \text{SAF}(\text{LN}_{\text{TH}} \leftarrow \text{S}) \end{array} \right] \approx \text{SAF}(\text{lung} \leftarrow \text{S}). \quad (40)$$

(295) Likewise, for constituent lung tissues as both the source and target, it is appropriate to use the calculated values of $\text{SAF}(\text{lung} \leftarrow \text{lung})$.

(296) Values of $\text{SAF}(\text{lung} \leftarrow \text{S})$ for photons, calculated for all airways or lymph nodes located within the thorax in the reference adult male as the target, when the radionuclide source is in any tissue of the body (Cristy and Eckerman, 1987f) and values of $\text{SAF}(\text{lung} \leftarrow \text{S})$ for different subjects, with lung tissues as the target and various tissues as the source, are also tabulated in Annexe G.

8.4. Dosimetry of Short-Range Alpha, Electron, and Beta Emitters

(297) Spatial nonuniformity of the radionuclide source in relation to the target cells has been taken into account in evaluating doses to the sensitive epithelial tissues in the ET, BB, and bb regions of the respiratory tract for short-range radiations. Figure 7 illustrates two different types of sources that must be addressed in the context of the models of regional deposition, particle transport, and sensitive tissues: emissions from radionuclides undergoing "surface transport", and emissions from those "sequestered in tissue". Surface transport involves radionuclides on the surface of epithelial tissue, in the process of being transported in mucus or other superficial fluid through the bronchioles, bronchi, and naso-oropharynx/larynx; or, radionuclides awaiting removal from the surface of skin in the anterior nasal airways (external nares). "Sequestration in tissue" involves intact particles that are taken up by the airway wall.

(298) A third type of source arises for some radionuclides during the process of absorption from the respiratory tract into the blood. The absorption process may involve protracted chemical binding of the radionuclide in tissue of the airway wall. The number of radioactive transformations that occur while the radionuclide is retained in the airway wall is evaluated by the "bound material" compartment in the model of absorption into blood. This absorption model is illustrated in Figs 21-24.

(299) A simplified geometrical model shown in Fig. 2 has been applied to represent the orientations of radionuclide sources and target tissue in airways within the ET, BB, and bb regions. In each case, a typical airway is represented by a cylindrical tube of appropriate internal calibre and wall thickness. In each type of airway, the target tissue is then assumed to be distributed over a characteristic range of depths below the epithelial surface, as described in Chapter 2.

(300) In all cases, the radionuclide source is assumed to be spread uniformly in association with the airway surface. For alpha, and low-energy electron, negatron and positron emitters, the effect of a more localised distribution of radioactive transformations over part of the airway surface would be to deliver higher doses to a part of the target cell population, and low or zero doses to the remainder. However, it is assumed that the stochastic effect on the target tissue is proportional to the average dose received by the cell population as a whole (ICRP, 1977, 1980). This average dose is thus independent of the degree of localisation of the source on the airway surface.

8.4.1. *The extrathoracic airways (ET)*

(301) It is shown in Fig. 3 that the wall of the ET₁ region (nasal vestibule) is lined by keratinised squamous epithelium (skin). In this region, the radionuclide source is located only on the skin surface, since skin is considered to be impervious to both radionuclide absorption and particle sequestration (Chapter 6). Since there is no superficial fluid on the skin surface, none of the energy emitted by the source is lost in the source itself. The sensitive targets are the nuclei of basal cells. These are assumed to occur uniformly throughout a 10- μ m-thick layer of tissue at 40- μ m depth.

(302) Three distinct distributions of the radionuclide source may occur in the ET₂ region:

- (1) mucous layer of the epithelial surface (where the radionuclide concentration is assumed to be uniform within a 15- μ m-thick layer). This source is represented in the model of particle transport pathways (Fig. 7) by the "fast" surface-transport compartment.

- (2) particles sequestered by macrophages in the lamina propria (where the radionuclide concentration is assumed to be uniform throughout a $10\text{-}\mu\text{m}$ layer of macrophages at $55\text{-}\mu\text{m}$ depth). This source is represented in the model of particle transport pathways (Fig. 7) by the sequestered-in-tissue compartment labelled "airway wall".
- (3) material chemically bound in the epithelium itself (where the radionuclide concentration is assumed to be uniform throughout the epithelium, to a depth of $5\text{ }\mu\text{m}$ below the basement membrane, i.e. to a depth of $55\text{ }\mu\text{m}$). This source is represented in the overall model of clearance and absorption from the respiratory tract (Fig. 24) by the compartment labelled "ET_b".

(303) The sensitive targets in the ET₂ region are again the nuclei of basal cells. These are assumed to occur uniformly throughout a $10\text{-}\mu\text{m}$ -thick layer of tissue at $40\text{-}\mu\text{m}$ depth.

(304) The average fractions of energy absorbed by the tissue layer containing the basal cell nuclei per emission of alpha, electron, negatron, or positron radiation in each of the sources described above, i.e. the absorbed fractions denoted earlier in Eq. (32) by $AF(T-S)_R$, are calculated on the assumption that the airways in either extrathoracic region have a characteristic internal diameter (calibre). This is assumed to be $5 \times 10^{-3}\text{ m}$ (5 mm) in the nasal vestibule (region ET₁). The cross-sectional form and airway calibre vary throughout each part of region ET₂. However, the relative uncertainty in estimates of the energy absorbed by the respective target tissues that is introduced by deviations from an assumed simple cylindrical shape is not large (on the order of $\pm 50\%$). The location of the target tissue within the epithelium, and the proximity of the various sources, are more critical factors. For dosimetry purposes, the internal diameter of region ET₂ (the nose, pharynx, and larynx) is assumed to be uniformly $3 \times 10^{-2}\text{ m}$ (3 cm); see Paragraph 39.

8.4.2. The bronchial airways (BB)

(305) The simplified model of a section through the wall of a typical bronchus in region BB to be used for dose calculations is described in Fig. 5. In Section 4.3.2 it was noted that the nuclei of both columnar secretory and short basal cells are considered to be sensitive targets. These are assumed to occur uniformly throughout a $30\text{-}\mu\text{m}$ -thick layer of tissue at $10\text{-}\mu\text{m}$ depth, and in a $15\text{-}\mu\text{m}$ layer at $35\text{-}\mu\text{m}$ depth, respectively (Fig. 5).

(306) In the absence of more specific information, it is assumed that the separate populations of secretory and basal cells are equally sensitive to radiation (Chapter 4). Thus, the overall risk is assumed to be represented by the equally weighted average of the doses received by these two populations of target cells.

(307) The bronchial epithelium is assumed to be shielded from radiation emitted in the alveolar interstitium by a $500\text{-}\mu\text{m}$ -thick barrier of connective tissue. For alpha particles, this prevents "cross-regional" irradiation of the BB region from a source located in AI (and *vice versa*), but not for energetic electrons and beta particles.

(308) In the bronchial airways, five distinct distributions of the radionuclide source may occur:

- (1) mucous (gel) layer overlying cilia at the epithelial surface (where the radionuclide concentration is assumed to be uniform within a $5\text{-}\mu\text{m}$ -thick layer). This source is represented in the model of particle transport clearance pathways (Fig. 7) by the "fast" surface-transport compartment.

- (2) sol layer in which the cilia are immersed (where the radionuclide concentration is assumed to be uniform within a $6\text{-}\mu\text{m}$ -thick layer). This source is represented in the model of particle transport pathways (Fig. 7) by the "slow" surface-transport compartment.
- (3) particles sequestered by macrophages in the lamina propria (where the radionuclide concentration is assumed to be uniform throughout a $10\text{-}\mu\text{m}$ layer of macrophages at $60\text{-}\mu\text{m}$ depth). This source is represented in the model of particle transport pathways (Fig. 7) by the sequestered-in-tissue compartment labelled "airway wall".
- (4) material chemically bound in the airway wall (where the radionuclide concentration is assumed to be uniform throughout the epithelium, and to a depth of $5\text{ }\mu\text{m}$ below the basement membrane, i.e. to a depth of $60\text{ }\mu\text{m}$). This source is represented in the overall model of clearance and absorption from the respiratory tract (Fig. 24) by the compartment labelled " BB_b ".
- (5) energetic electron, negatron, and positron emitters that are retained in the alveolar interstitium (where the radionuclide concentration is assumed to be uniformly distributed throughout the mass of tissue in this region). This source includes both material retained in particulate form and that chemically bound. The former is represented by the particle transport compartments labelled "<<slow, <slow and slow" in Fig. 7, and the latter by the bound compartment labelled " AI_b " in Fig. 24.

(309) The absorbed fractions, $\text{AF}(\text{BB} \leftarrow \text{S})_R$, are calculated on the assumption that the bronchial airways have an average calibre of $5 \times 10^{-3}\text{ m}$ (5 mm), Paragraph 48.

8.4.3. The bronchiolar airways (bb)

(310) The model of a section through the wall of a typical bronchiolus used for dose calculations is shown in Fig. 6. The sensitive targets, nuclei of secretory cells, were identified in Chapter 4 and are assumed to occur uniformly throughout the $8\text{-}\mu\text{m}$ -thick layer of tissue at $4\text{-}\mu\text{m}$ depth. The subepithelial connective tissue is much thinner than that in the bronchi: it is assumed to be only $20\text{ }\mu\text{m}$ thick in the bronchioles. Therefore, significant cross-regional irradiation may occur between the AI and bb regions, even for alpha emitters.

(311) As described above for the bronchi (in relation to the model of particle transport pathways, Fig. 7), five distinct distributions of the radionuclide source may occur in the bronchioles:

- (1) mucous (gel) layer, which is assumed to be $2\text{ }\mu\text{m}$ thick
- (2) sol layer, which is assumed to be $4\text{ }\mu\text{m}$ thick
- (3) particles sequestered by macrophages in the lamina propria (in a $5\text{-}\mu\text{m}$ -thick layer at $20\text{-}\mu\text{m}$ depth)
- (4) material chemically bound in the airway wall (assumed to be uniformly distributed throughout the tissue to a depth of $20\text{ }\mu\text{m}$). This source is represented in the overall model of clearance from the respiratory tract (Fig. 24) by the compartment labelled " bb_b ".
- (5) most alpha, electron, negatron, and positron emitters that are retained in the alveolar interstitium.

(312) The absorbed fractions, $\text{AF}(\text{bb} \leftarrow \text{S})_R$, are calculated on the assumption that the bronchiolar airways have an average calibre of 10^{-3} m (1 mm), Paragraph 54.

8.4.4. The alveolar interstitium (AI)

(313) In the AI region, the interalveolar septa and the walls of blood and lymphatic capillaries are sufficiently thin to ensure that sensitive target cells are distributed homogeneously throughout the tissue mass. Therefore, it can be assumed that the average dose received by the target cells is the same as that received by the whole tissue mass.

(314) For all short-range radiations emitted within the AI region, the absorbed fraction $AF(AI \leftarrow AI)$ is assumed to be unity.

(315) Although for some radionuclides cross-regional irradiation may occur between sources in the bronchi or bronchioles and the AI target region, the relatively small amount of energy absorbed by AI tissue is shared among a much greater mass. Therefore, for short-range radiation emitted in BB or bb, the dose to the AI region is always negligible in comparison with that received by targets within the source regions themselves, and:

$$AF(AI \leftarrow BB) = AF(AI \leftarrow bb) = AF(AI \leftarrow ET) = 0. \quad (41)$$

8.4.5. The lymph nodes (LN_{ET} and LN_{TH})

(316) Both the target cells and radionuclide sources are assumed to be distributed uniformly throughout the mass of lymph node tissue, and the absorbed fractions, $AF(LN_{ET} \leftarrow LN_{ET})_\alpha$ and $AF(LN_{TH} \leftarrow LN_{TH})_\alpha$, are assumed to be unity for alpha particles.

(317) Since some of the thoracic lymph nodes are embedded in alveolar-interstitial tissue, for sources of higher energy electrons in LN_{TH} , crossfire may occur with the AI region as the target. To take account of this potential crossfire for all electrons, half the emitted energy is assumed to be absorbed in LN_{TH} and half in the AI region, i.e.:

$$AF(LN_{TH} \leftarrow LN_{TH})_{\beta,e} = AF(AI \leftarrow LN_{TH})_{\beta,e} = 0.5. \quad (42)$$

For all other tissues, $AF(T \leftarrow LN_{TH})_{\beta,e} = 0$. For the extrathoracic lymph nodes, $AF(T \leftarrow LN_{ET})_{\beta,e}$ is assumed to be zero. For alpha particles:

$$AF(T \leftarrow LN_{ET})_\alpha = AF(T \leftarrow LN_{TH})_\alpha = 0. \quad (43)$$

8.5. Scaling for Age and Gender

(318) For all short-range radiations, the airway calibre (Tables 2 and 4) is of secondary importance in determining absorbed fractions. These depend in the main on source and target thickness and their spatial separation. The epithelial thickness, and also that of superficial fluid, is determined by functional requirements rather than by age or body size (Gehr, 1987). Therefore, for dosimetry purposes, all absorbed fractions are assumed to be independent of age and body size.

8.6. Absorbed Fractions for Alpha, Electron, and Beta Emitters

(319) The methods used to calculate absorbed fractions for sources of short-range radiations within the respiratory tract are described in Annexe H. The resulting values of $AF(T \leftarrow S)$ that are recommended for substitution in the dosimetric model are shown graphically below as functions of radiation energy. Tables of $AF(T \leftarrow S)$ calculated as a

function of the energy of alpha particles, and monoenergetic electrons, or the average energy of beta particles (negatrons and positrons) are given in Annexe H. This annexe also gives algebraic formulae that approximate adequately the calculated values, but other approximations may also be appropriate.

8.6.1. Recommended values for alpha emitters

(320) Figures 27 through 30 show the absorbed fractions expressed as functions of energy for alpha particles (of between 2.0 and 11.0 MeV) emitted by each of the possible sources in the ET_1 and ET_2 , BB, and bb regions, respectively. Figure 31 shows the fraction of alpha-particle energy emitted in the AI region that is absorbed by target tissue in the bb region.

(321) For all alpha particles emitted in the AI region, the fraction of their energy absorbed by the target tissue in that region is approximated by:

$$AF(AI \leftarrow AI)_\alpha = 1. \quad (44)$$

Likewise, for alpha particles emitted in the lymph nodes:

$$\begin{aligned} AF(LN_{ET} \leftarrow LN_{ET})_\alpha &= 1 \\ AF(LN_{TH} \leftarrow LN_{TH})_\alpha &= 1. \end{aligned} \quad (45)$$

For all other combinations of alpha-emitting source and tissue target, the value of $AF(T \leftarrow S)_\alpha$ is zero.

8.6.2. Recommended values for electron emitters

(322) Figures 32 through 35 show the absorbed fractions expressed as functions of electron energy (within the range 0.01–9.0 MeV), for each possible source in the ET_1

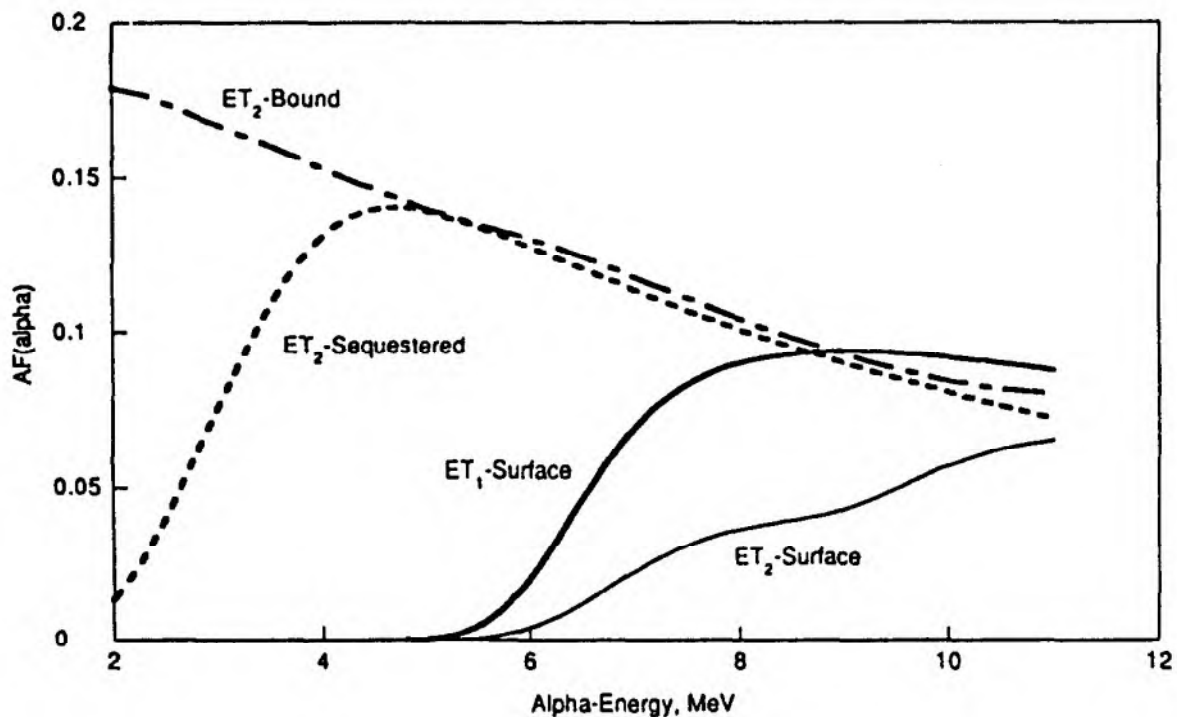


Fig. 27. Absorbed fractions for alpha emissions in the extrathoracic region. Curves are shown for various sources: surfaces of ET_1 and ET_2 , respectively, emissions from epithelium of ET_2 (bound source), and emissions from macrophages in lamina propria of ET_2 (sequestered source).

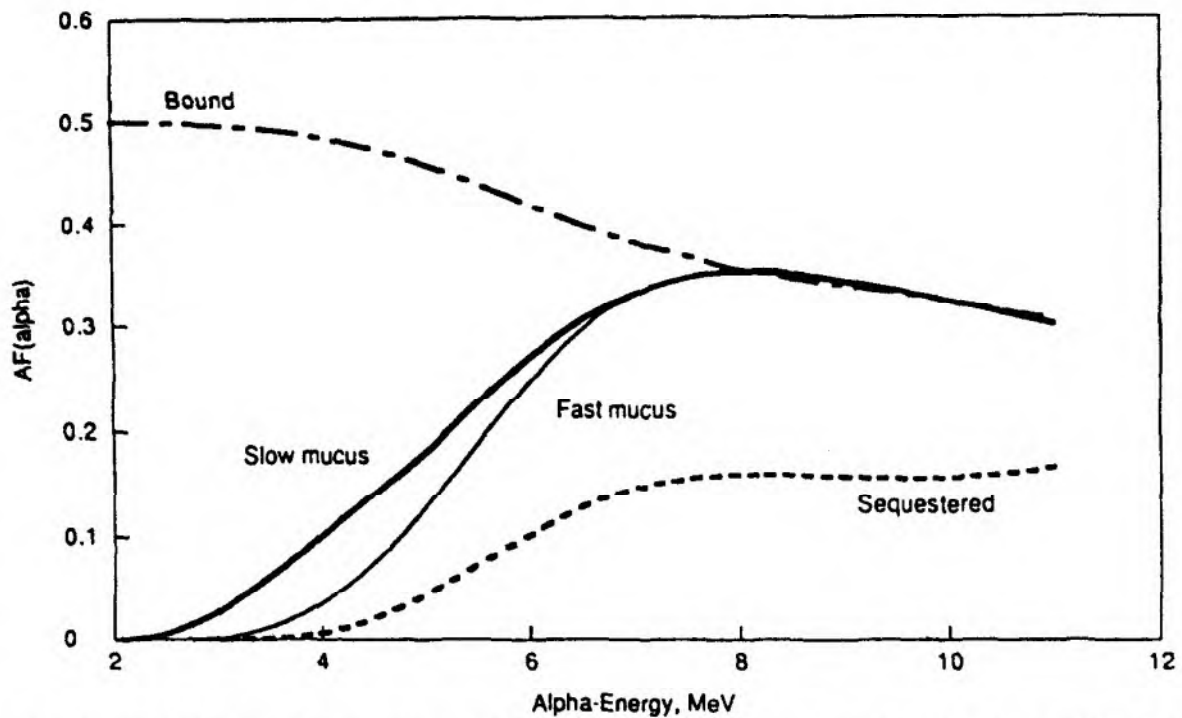


Fig. 28. Absorbed fractions for secretory cell targets from alpha emissions in bronchial region (BB). Curves are shown for emissions in the mucous gel layer (fast mucus), sol layer (slow mucus), the epithelium itself (bound), and the lamina propria (sequestered).

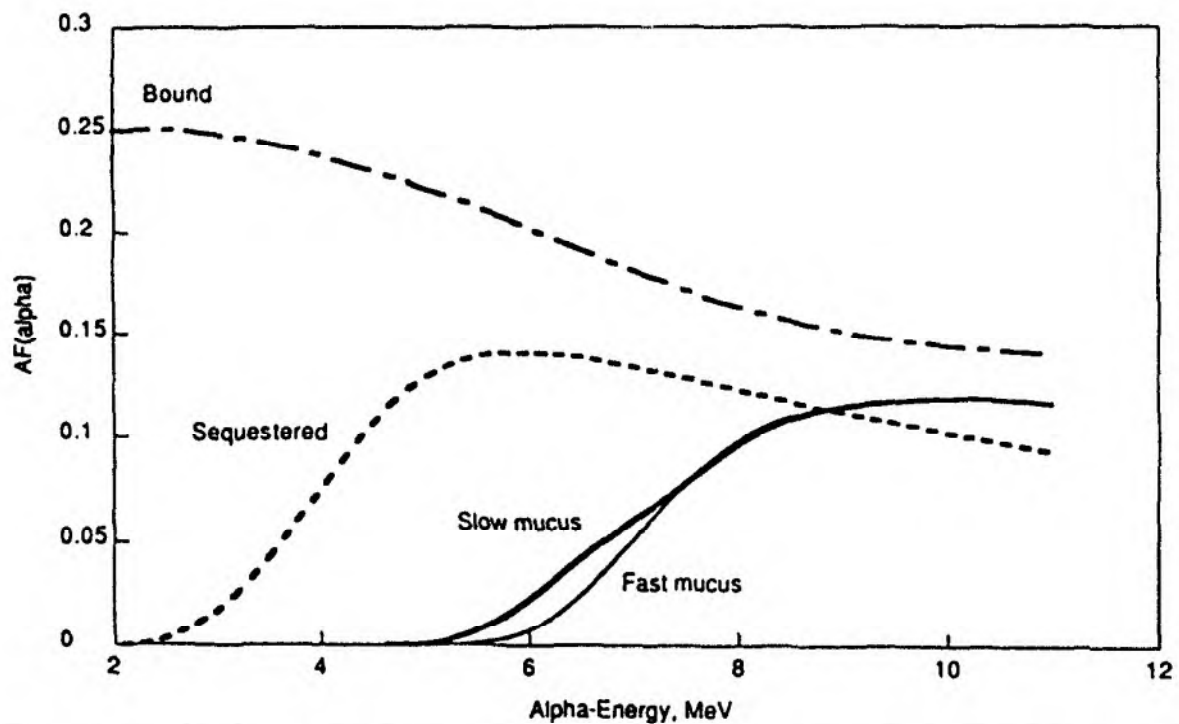


Fig. 29. Absorbed fractions for basal cell targets from alpha emissions in bronchial region (BB). Curves are shown for emissions in the mucous gel layer (fast mucus), sol layer (slow mucus), the epithelium itself (bound), and the lamina propria (sequestered).

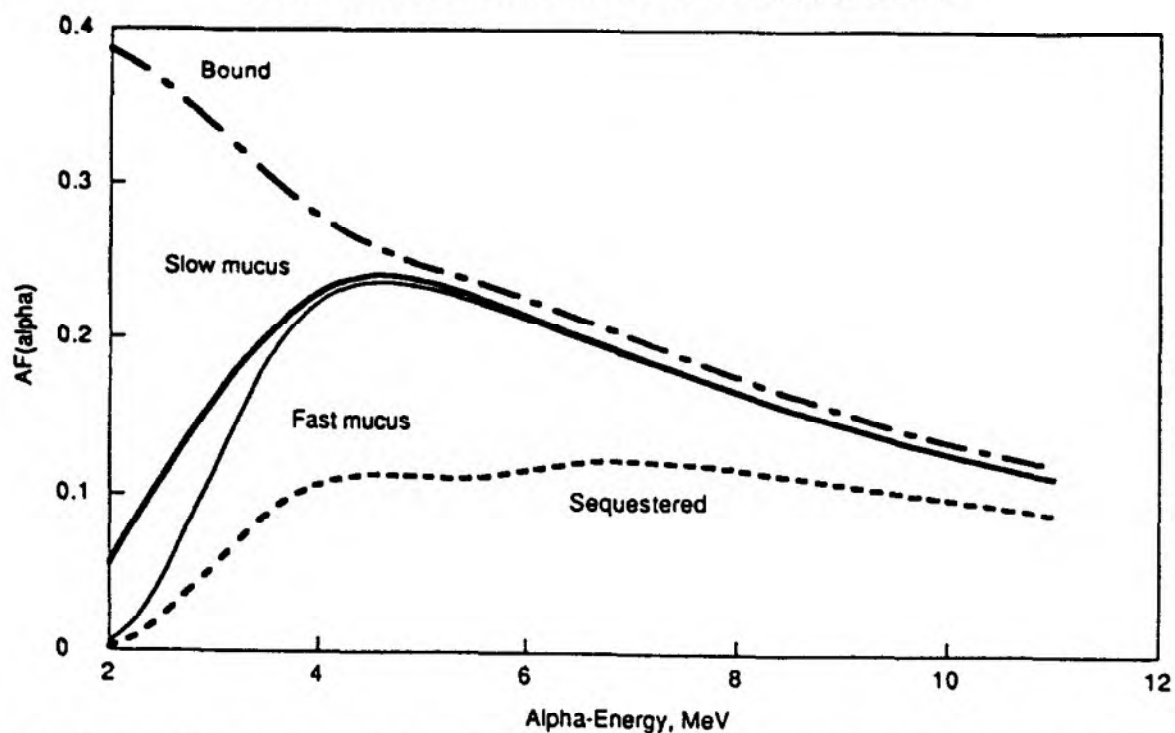


Fig. 30. Absorbed fractions for alpha emissions in the bronchiolar region (bb). Curves are shown for emissions in the mucous gel (fast mucus), sol layer (slow mucus), the epithelium itself (bound), and the lamina propria (sequestered).

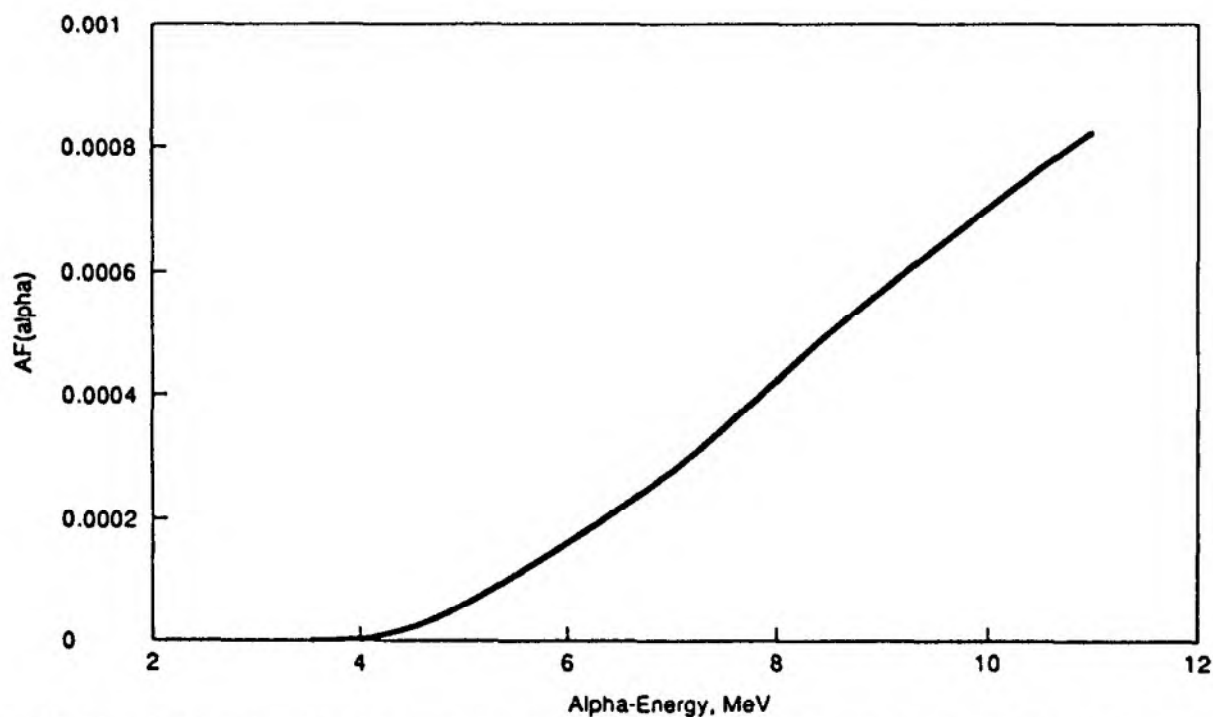


Fig. 31. Absorbed fractions for alpha emissions in the alveolar-interstitial region (AI) with target tissue in the bronchiolar region (bb).

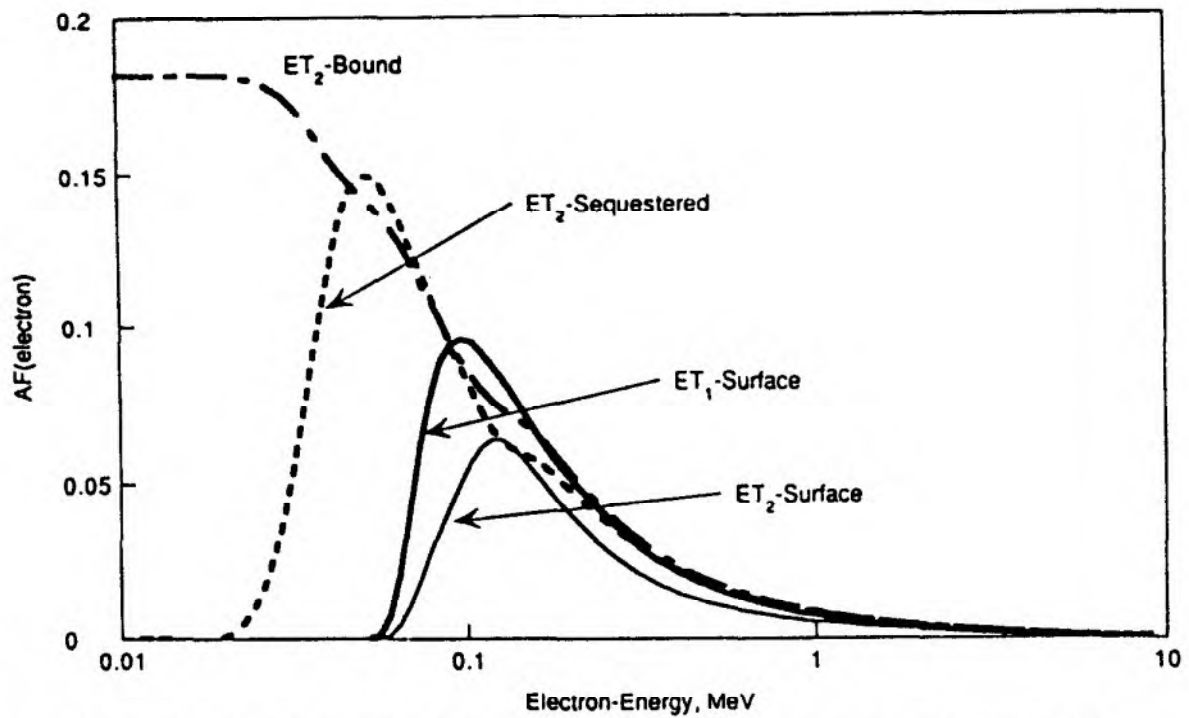


Fig. 32. Absorbed fractions for electron emissions in the extrathoracic region (ET_1 and ET_2).

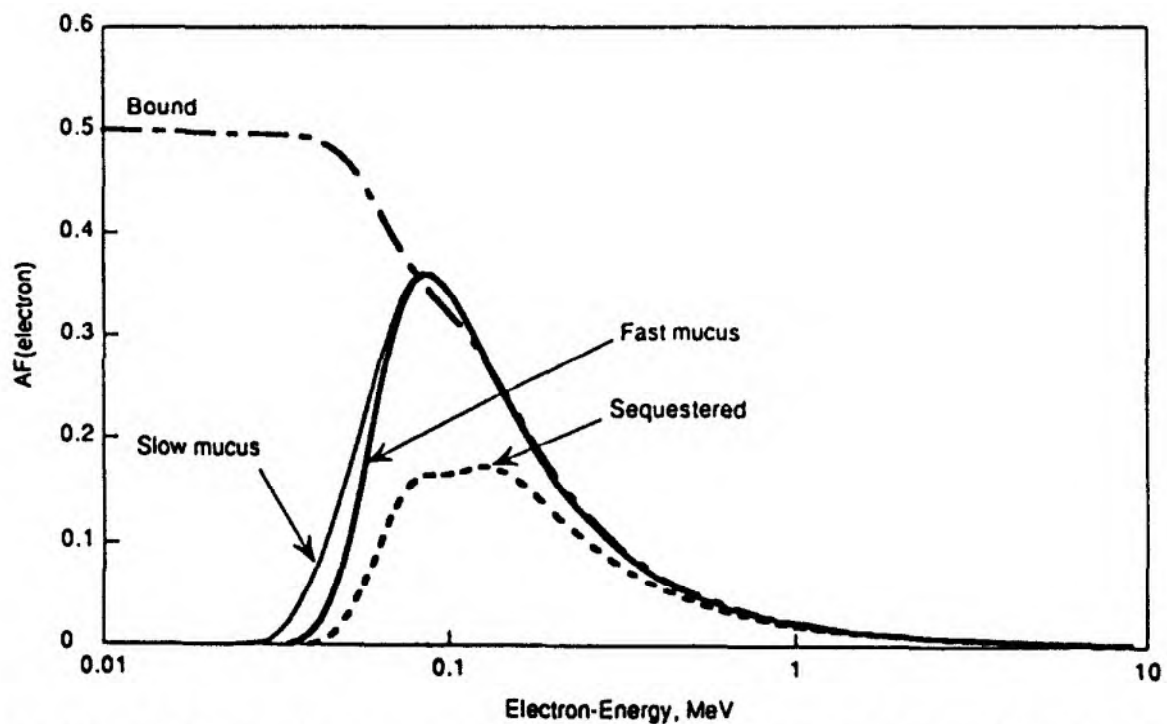


Fig. 33. Absorbed fractions for secretory cell targets from electron emissions in the bronchial region (BB).

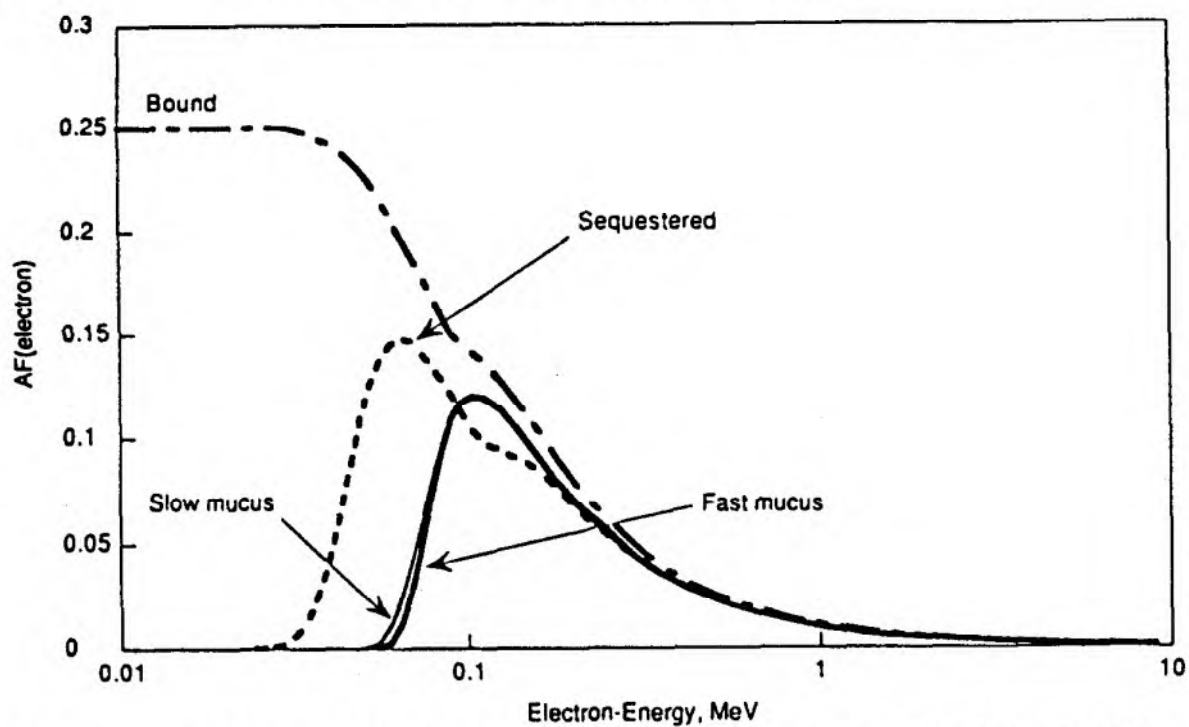


Fig. 34. Absorbed fractions for basal cell targets from electron emissions in the bronchial region (BB).

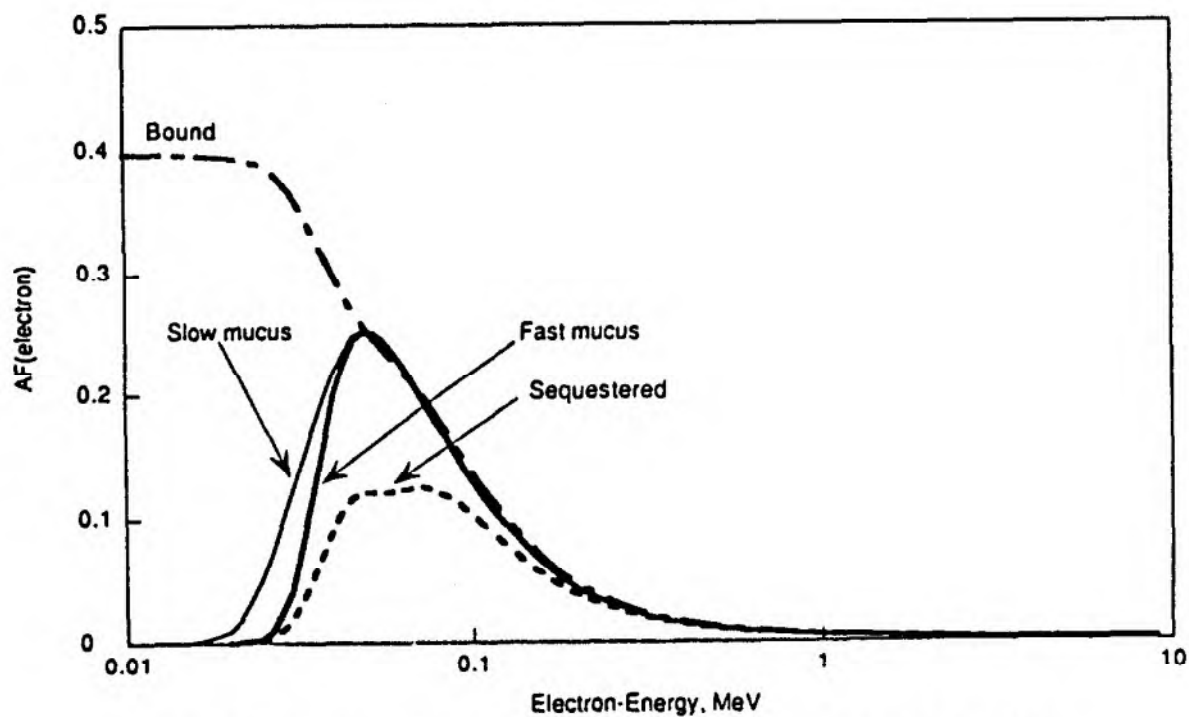


Fig. 35. Absorbed fractions for electron emissions in the bronchiolar region (bb).

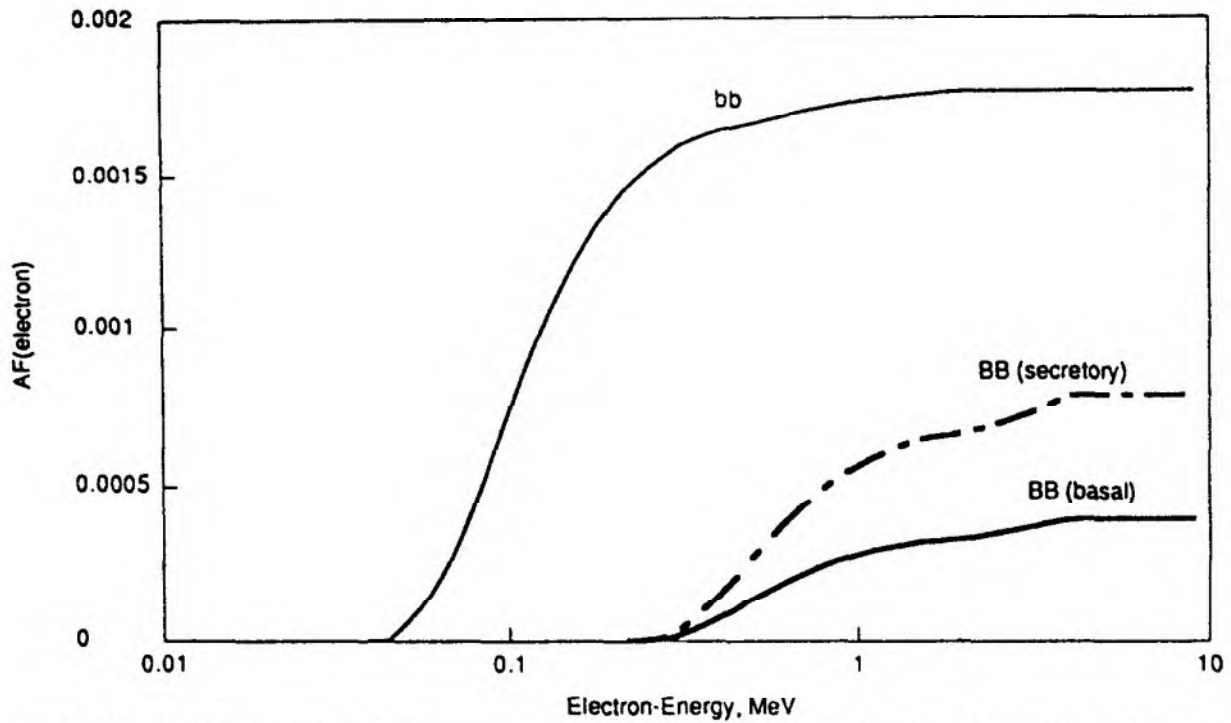


Fig. 36. Absorbed fractions for electron emissions in the alveolar-interstitial region (AI) with target tissue in both the bronchial (BB) and bronchiolar (bb) regions.

and ET_2 , BB, and bb regions, respectively. Figure 36 shows the fractions of electron energy emitted in the AI region that, for electrons of energy greater than 0.1 MeV, are absorbed by both the bronchial and bronchiolar target tissues.

(323) For all electrons emitted in the AI region, the fraction of their energy absorbed by the target tissue in that region is approximated by:

$$AF(AI \leftarrow AI)_e = 1 \quad (46)$$

and, for electrons emitted in the lymph nodes, by:

$$\begin{aligned} AF(LN_{ET} \leftarrow LN_{ET})_e &= 1 \\ AF(LN_{TH} \leftarrow LN_{TH})_e &= 0.5 \\ AF(AI \leftarrow LN_{TH})_e &= 0.5. \end{aligned} \quad (47)$$

For all other combinations of electron-emitting source and tissue target outside the respiratory tract, the value of $AF(T \leftarrow S)_e$ is assumed to be zero.

8.6.3. Recommended values for beta (negatron and positron) emitters

(324) Figures 37 through 40 show the absorbed fractions expressed as functions of average negatron or positron energy (within the range 0.001–3.0 MeV), for each possible source in the ET_1 and ET_2 , BB, and bb regions of the respiratory tract. Figure 41 shows the fractions of beta energy emitted in the AI region that, for radiations of average energy greater than 0.1 MeV, are absorbed by both the bronchial and bronchiolar target tissues.

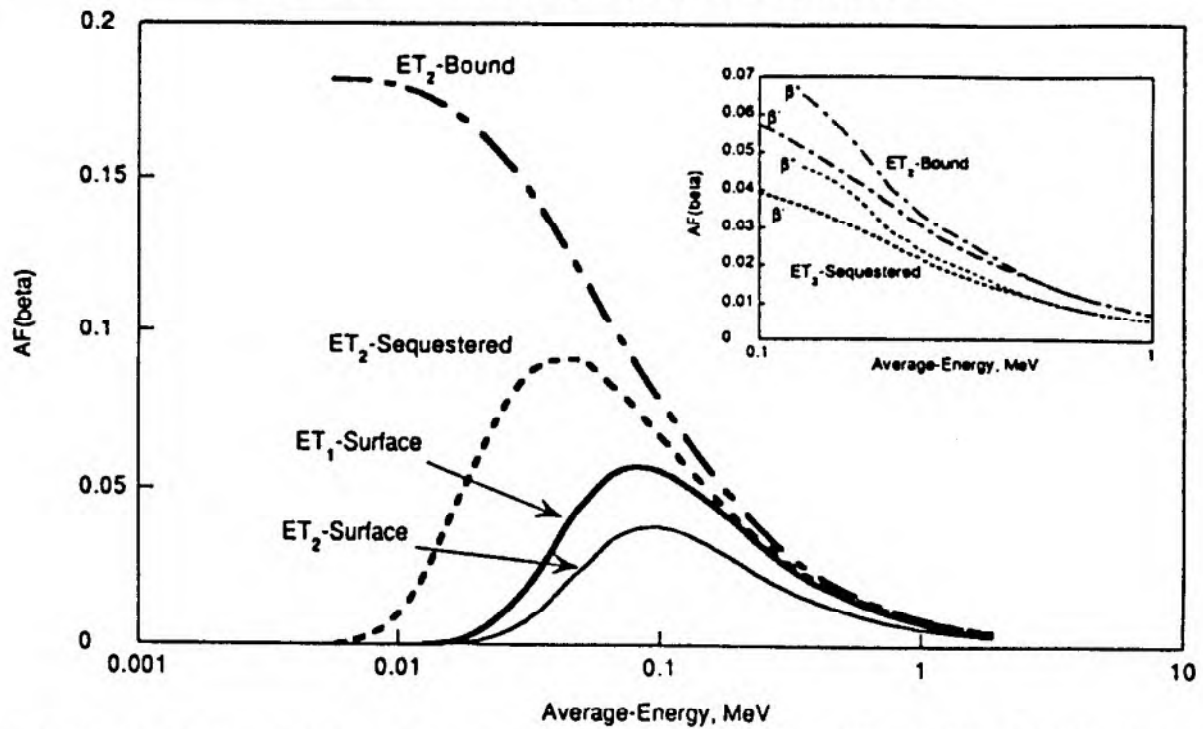


Fig. 37. Absorbed fractions for beta emissions in the extrathoracic region (ET₁ and ET₂). Main figure shows negatrons. The inset figure compares absorbed fractions recommended for positrons, over their limited energy range of 0.1–1 MeV, with those for negatrons.

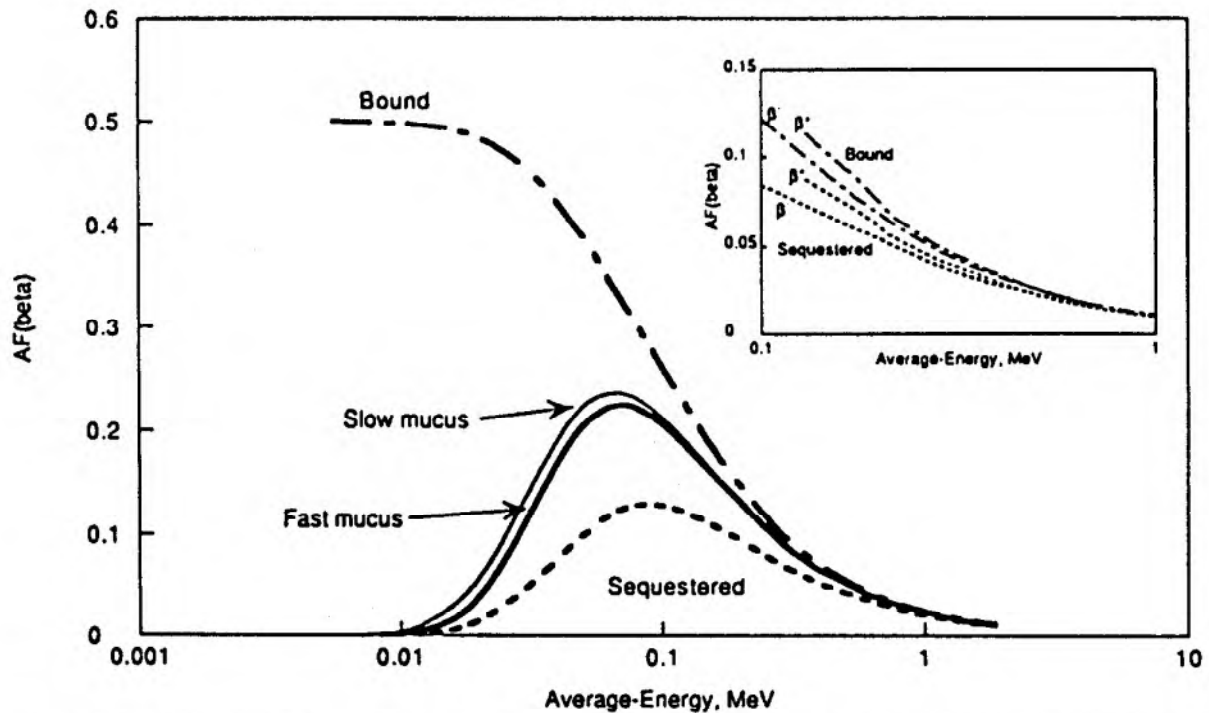


Fig. 38. Absorbed fractions for secretory cell targets from beta emissions in the bronchial region (BB). Main figure shows negatrons. Inset figure compares negatrons with positrons as described for Fig. 37.

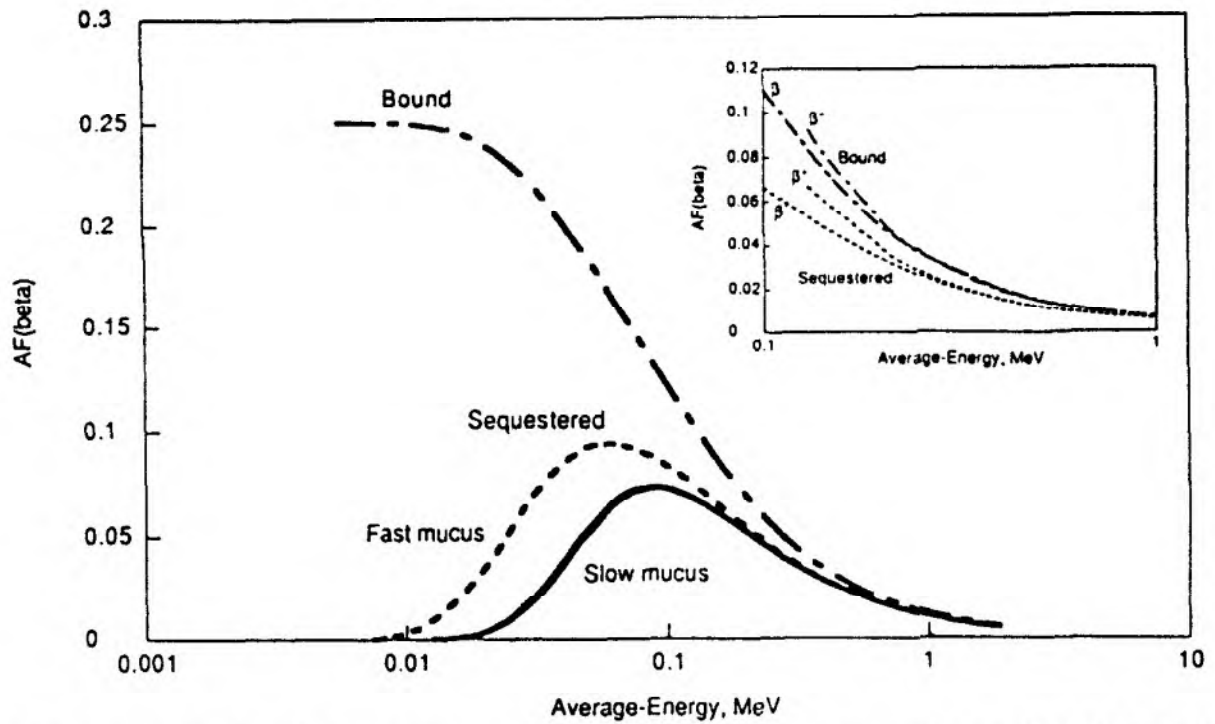


Fig. 39. Absorbed fractions for basal cell targets from beta emissions in the bronchial region (BB). Main figure shows negatrons. Inset figure compares negatrons with positrons.

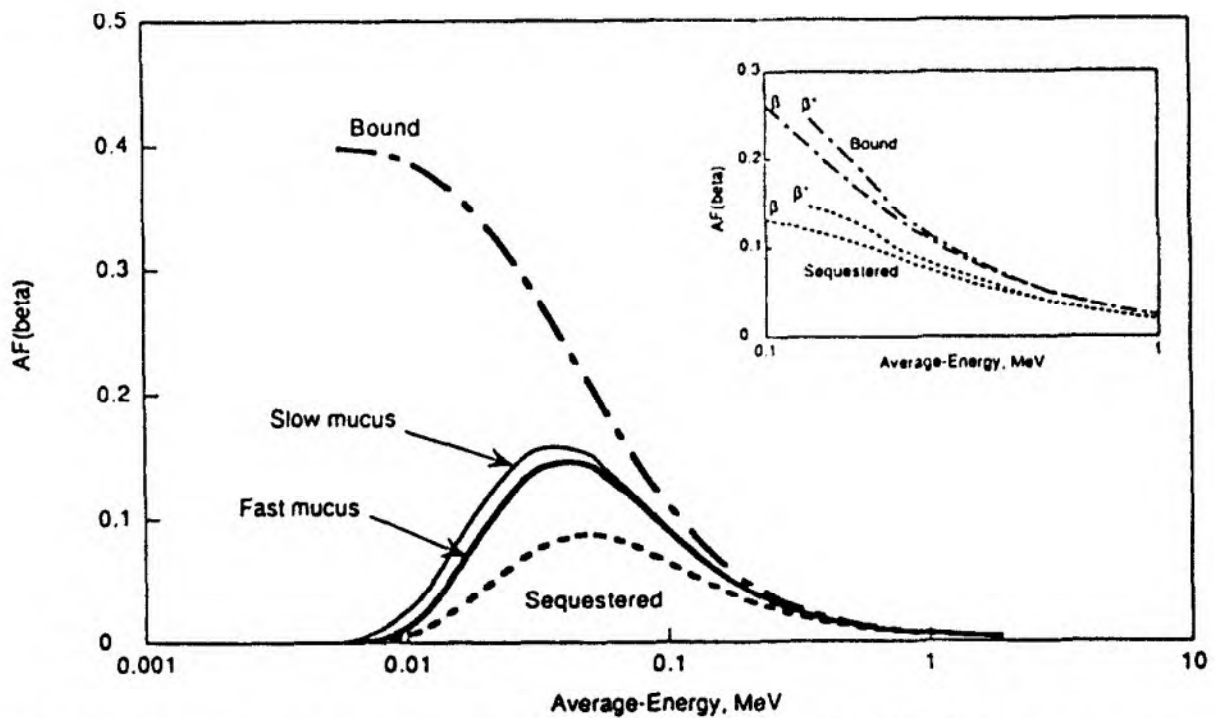


Fig. 40. Absorbed fractions for beta emissions in the bronchiolar region (bb). Main figure shows negatrons. Inset figure compares negatrons with positrons.

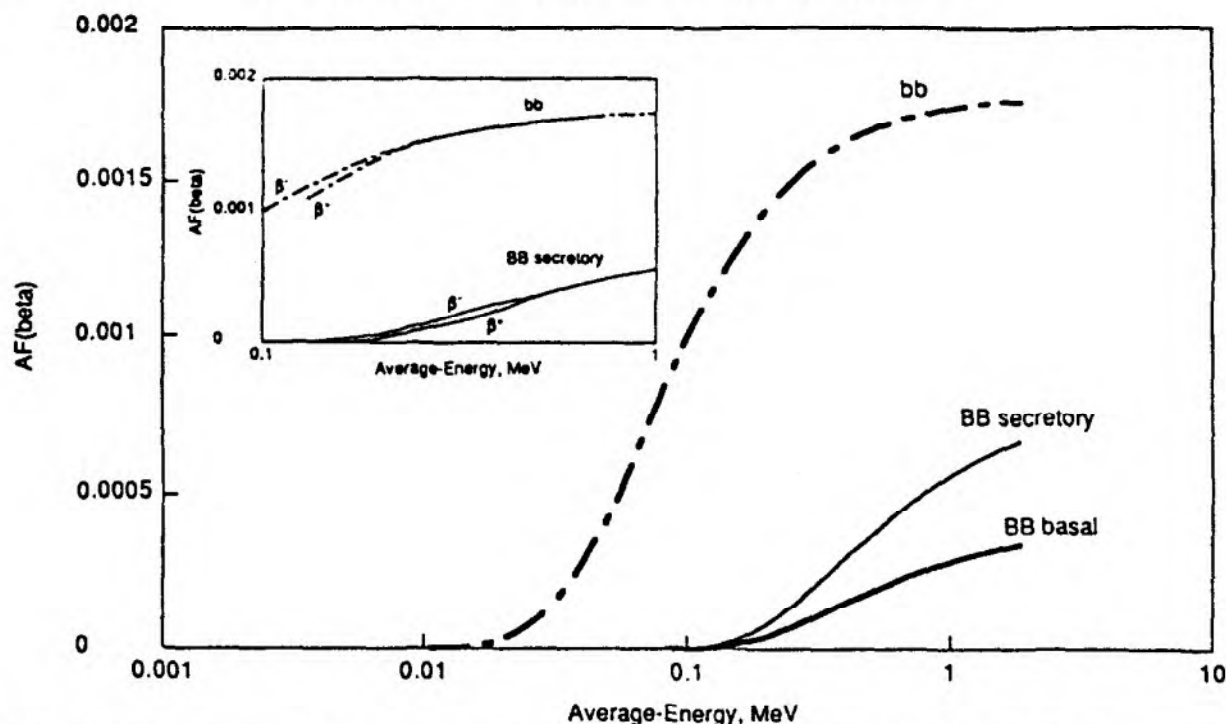


Fig. 41. Absorbed fractions for beta emissions in the alveolar-interstitial region (AI) with target tissue in both the bronchial (BB) and bronchiolar (bb) regions. Main figure shows negatrons. Inset figure compares negatrons with positrons.

(325) As assumed in Paragraph 323 for electrons, the fraction of the beta energy emitted in the AI region that is absorbed by the target tissue in AI is approximated by:

$$AF(AI \leftarrow AI)_\beta = 1 \quad (48)$$

and, for betas emitted in the lymph nodes, by:

$$\begin{aligned} AF(LN_{ET} \leftarrow LN_{ET})_\beta &= 1 \\ AF(LN_{TH} \leftarrow LN_{TH})_\beta &= 0.5 \\ AF(AI \leftarrow LN_{TH})_\beta &= 0.5 \end{aligned} \quad (49)$$

For all other combinations of beta-emitting source and tissue target, the value of $AF(T \leftarrow S)_\beta$ is assumed to be zero.

8.6.4. Application of $AF(T \leftarrow S)_R$ for short-range radiations

(326) Tables H.7-H.11 in Annexe H list the algebraic expressions and fitted parameter values recommended to evaluate absorbed fractions, $AF(T \leftarrow S)$, for sources of alpha particles, electrons, negatrons, and positrons with target tissues in the respiratory tract. These expressions can be applied to calculate the contributions of short-range radiations to $SEE(T \leftarrow S)$ for each radionuclide and isotope, as described earlier in Paragraph 258, using values of radiation energy and yield obtained from tables of radionuclide data (ICRP, 1983) and values of target tissue mass.

(327) Values of target tissue mass, M_T , for substitution in Eq. (32) are given in Table 5. These are used, together with the absorbed fractions described above, to evaluate the specific effective energies, $SEE(T \leftarrow S)_j$, for each radionuclide, j , using Eq. (32)

(Paragraph 275). For photon radiations, the specific absorbed fractions, $SAF(T \leftarrow S)_i$, (Paragraphs 283 through 296), for each source, i , are used directly to evaluate $SEE(T \leftarrow S)_j$.

8.7. Implementation of the Dosimetry Model

(328) The products of $U_{s,j}$, the total number of nuclear transformations of radionuclide j in source S over the 50-y period following an intake, and $SEE(T \leftarrow S)_j$, the total energy absorbed per unit mass in target T , weighted for each radiation emitted by the radiation weighting factor, per nuclear transformation of the radionuclide in source region S , are substituted in Eq. (33) (Paragraph 276) to calculate the committed equivalent dose, H_T .

8.8. Calculation of Number of Transformations, $U_{s,j}$

(329) The numbers of nuclear transformations of radionuclide j that occur in each source S within the respiratory tract are obtained by solving the compartment model of clearance that was described in Chapter 7 (Figs 20 and 24).

8.8.1. Source terms for photon radiations

(330) Each of the regions ET_1 , ET_2 , LN_{ET} , BB , bb , AI , and LN_{TH} is treated as a single source. The numbers of transformations in all clearance compartments within each region are therefore summed to give a value of $U_{s,j}$ for the regional source as a whole.

8.8.2. Source terms for short-range radiations

(331) For short-range radiations, the absorbed fraction $AF(T \leftarrow S)_R$, and thus $SEE(T \leftarrow S)_j$, given by Eq. (32) (Paragraph 275), depends on the locations of the source within each region of the respiratory tract (Figs 27–41). Therefore, it is necessary to calculate the number of nuclear transformations in each discrete source. The compartments in the clearance model that comprise the various sources in each region are listed in Table 20.

8.9. Factors for Apportionment of Radiation Detriment

(332) The apportionment of radiation detriment among the regions of the respiratory tract is addressed in Chapter 4, and factors to be applied to weight the equivalent doses calculated for the constituent tissues of the respiratory tract are given in Table 12.

Table 20. Equivalence between compartments in the clearance model and sources in the dosimetry model for short-range radiations

Target	Source component	Equivalent clearance components (see Fig. 24)
ET ₁	Surface deposit	14
ET ₂	Surface fluid	11 + 11 _T
	Particles in airway wall	12 + 12 _T
	Bound material	ET _h
LN _{ET}	All transformations	13 + 13 _T + LN _{ET_h}
BB	Mucous gel	7 + 7 _T
	Mucous sol	8 + 8 _T
	Particles in airway wall	9 + 9 _T
	Bound material	BB _h
	Alveolar-interstitium	1 + 2 + 3 + 1 _T + 2 _T + 3 _T + AI _h
bb	Mucous gel	4 + 4 _T
	Mucous sol	5 + 5 _T
	Particles in airway wall	6 + 6 _T
	Bound material	bb _h
	Alveolar-interstitium	1 + 2 + 3 + 1 _T + 2 _T + 3 _T + AI _h
AI	All transformations (in AI and LN _{TH})	1 + 2 + 3 + 1 _T + 2 _T + 3 _T + AI _h + 10 + 10 _T + LN _{TH_h}
LN _{TH}	All transformations	10 + 10 _T + LN _{TH_h}

9. APPLICATION OF THE MODEL

9.1. Introduction

(333) There are two primary applications for which the model is intended. The first of these, which will be its widest application in radiation protection, is the calculation of effective dose per unit of exposure and per unit of inhaled radioactivity to populations with similar characteristics, and, when required, the dose to individuals. The results of these calculations can be used to calculate standards for environmental and occupational exposures. The second application is the evaluation of doses to individuals who have been exposed, and for whom monitoring data are available.

(334) This chapter begins with a discussion of the issues involved in assessing the degree of confidence that can be placed on the values of dose that are predicted by this respiratory tract model (Section 9.2). There is, of course, always concern about how well any model describes reality, what the basis is for the estimate of the parameters used in the model, and what their variability and uncertainty are. These concerns are commonly collectively termed *model reliability*.

(335) Section 9.4 then illustrates the application of the model to calculate effective dose per unit exposure. An example of a calculation using information in this report for a hypothetical radionuclide is given.

(336) Application of the respiratory tract model to evaluate dose to an individual for whom monitoring data are available, *in vivo* counting or excreta, will be addressed in future ICRP publications.

9.2. Model Reliability

(337) The principal factors affecting the reliability of results from environmental transfer models (specification of the problem, formulation of the conceptual model,

formulation of the computational model, estimation of parameter values, and calculation and documentation of results) (IAEA, 1989) can be applied to the reliability of this respiratory tract model.

(338) The first three items in the above paragraph are concerned with the methods by which decisions are made concerning the formulation and implementation of the mathematical model; that is, how well the model describes reality.

(339) Inter-relations between these include the need for any assumptions made in formulating the model structure and associated parameter values to be consistent with the particular problem being addressed. For example, the parameter values used in calculating ALIs will tend to be different from those employed for assessing doses to individuals. Indeed, nonroutine assessments of doses to individuals in special cases should be based on specific data wherever possible, whereas reference values are necessarily required when calculating doses to populations, or in setting standards.

9.2.1. *Evaluating model reliability*

(340) It is beyond the scope of the current report to attempt a detailed quantitative assessment of the confidence that may be attached to predictions obtained using this model in any particular situation. The potential relevance of the factors discussed above are outlined, and suggestions are offered for exercising the model's capabilities.

(341) First, it can be instructive to explore the sensitivity of the model's predictions to variation of parameter values within the estimated range of uncertainty. This gives some indication of the potentially more important parameters and may provide a first indication of those areas of the model where greater knowledge might yield a significant improvement in reliability.

(342) However, simple sensitivity studies are, at best, only a weak indicator of the potential improvements to be gained from increased scientific knowledge in particular areas, since they take no account of possible interactions between parameters, or uncertainties in parameter values. A full uncertainty analysis would explore the potential impact of such combinations through the performance of repeated calculations, in which each realisation of the model contained a different set of parameter values, selected from the range of possible alternatives. Practical methods for such analyses are explored by the IAEA (IAEA, 1989). Additionally, parameters that have a large impact on the calculation of doses from estimated intakes may have little or no impact on the doses calculated from bioassay results.

(343) The requirements for such an uncertainty analysis are probability density functions for each of the model parameters, reflecting the confidence attached to the precision with which each may be defined. In addition, it is necessary to determine whether or not certain parameters may be correlated, so that unrealistic combinations of parameter values will be avoided in the model realisations. The expert judgement required to assign such distributions and correlations can be extensive, and generally needs to be coordinated by individuals trained in the art of elicitation techniques. Nevertheless, such investment is necessary if meaningful quantitative statements are to be made with respect to model reliability.

(344) The final outcome of an uncertainty analysis is a probability distribution for the endpoint of interest, which, for this respiratory tract model, might be the effective dose arising from a well-defined exposure of a specific population group to a given radionuclide. This distribution would then reflect the overall confidence that can be

attached to predictions obtained using the model, due to uncertainties in the specification of model parameters.

(345) At this stage, probability density functions reflecting the confidence attached to estimates of different parameters within this model are not available. However, an initial attempt has been made in certain areas to quantify the potential range of uncertainty for different parameters. It is seen as an important objective to progress to the specification of uncertainty distributions for all model parameters.

(346) It can be relevant in the derivation of such distributions to distinguish between the contributions from variability and those due to lack of knowledge. For example, separate parameter estimates for different ethnic groups and age groups, male and female, have been made. It is, therefore, important that any distribution should reflect the residual uncertainty and variability for each population group, rather than those applicable to the overall world population.

9.2.2. Selection of reference parameters

(347) The selection of reference parameter values to use with the model is necessary despite the large variability and uncertainty in some of them. To do this, it is useful to clearly define the differences between variability and uncertainty. Variability is used here to describe the range of values that a parameter is known to have. There will be variability between different population groups caused by different morphometric and physiological factors resulting from differences in ethnic background, age, and sex. There will also be variability that results from diseases and from different activity rates and exposure conditions within population groups. In principle these can be accounted for by the selection of appropriate model parameters, and, to a certain degree, this has been addressed in previous chapters, and has resulted in "reference parameters" given for use with selected populations.

(348) Uncertainty is used here to refer to the range that a parameter may have because of our incomplete knowledge about its actual value, or what factors may affect its value. It is well known that experimental results in animals show different deposition, retention, and clearance, even though the animals themselves are essentially identical, and efforts have been made to keep all exposure conditions identical. Similar observations have been made in humans. Where the uncertainty in parameters could result in a large difference in results, "mildly pessimistic" or "realistic but conservative" values are recommended. That is, the recommended values are intended to result in conservative estimates of dose, but not unrealistically so. Such parameters are suitable for calculating doses to population groups, but may overestimate the dose to individuals. However, the model allows the calculation of doses to individuals using individual-specific parameters when necessary.

9.3. Use of Respiratory Tract Model for Calculating Effective Dose

(349) As described in Chapter 4, the contribution to the effective dose from irradiation of the lungs is obtained by multiplying the equivalent dose to the lungs given by Eq. (2) by the Commission's recommended tissue weighting factor of 0.12 (ICRP, 1991a).

(350) When the equivalent dose to the extrathoracic region of the respiratory tract (ET) given by Eq. (1) is calculated to be higher than that to any listed organ of the

body, the risk posed by irradiation of the ET region is significant. The resulting contribution of the ET region to the total detriment is then calculated by multiplying the equivalent dose to this region by the Commission's recommended tissue weighting factor of 0.025. This weighting factor is reserved for those cases in which the most highly irradiated organ or tissue is not amongst the 12 named tissues for which a weighting factor is specified.

(351) The effective dose is then the sum of the weighted equivalent doses in all the tissues and organs of the body. It is given by the expression:

$$E = \sum w_T H_T \quad (50)$$

where H_T is the equivalent dose in tissue or organ T and w_T is the weighting factor for tissue T (ICRP, 1991a).

(352) For occupational exposure, the ALI is based on limiting the annual average committed effective dose to 0.02 Sv (ICRP, 1991a). Thus, the ALI for any radionuclide is obtained by dividing the annual average effective dose limit (0.02 Sv) by the committed effective dose (over 50 y), $E(50)$, resulting from the intake of 1 Bq of that radionuclide (ICRP, 1991b).

9.3.1. *Parameters of the lung model for reference workers*

(353) Reference parameters for substitution in the model are summarised in Chapter 10.

9.3.1.1. *Intake and regional deposition fractions*

(354) For a reference worker (an adult male), the average working day is assumed to be composed of 5.5 h of light exercise (mean breathing rate of $1.5 \text{ m}^3 \text{ h}^{-1}$) and 2.5 h rest-sitting (mean breathing rate of $0.54 \text{ m}^3 \text{ h}^{-1}$). The overall average breathing rate, i.e. the average rate of intake of air from the workplace, is therefore $1.2 \text{ m}^3 \text{ h}^{-1}$. Denoting the airborne concentration of activity (in the breathing zone of an exposed subject) by C_A , in Bq m^{-3} , the nominal rate of intake, I_0 , into the respiratory tract is therefore given by:

$$I_0 = 1.2 \times C_A \text{ Bq h}^{-1}. \quad (51)$$

(355) The actual rate of intake of activity into the respiratory tract is determined by inhalability, Eq. (12), which depends upon the aerosol size. The values of fractional deposition in each dosimetric region of the respiratory tract that are tabulated in Annexe F relate to the "nominal" intake, I_0 , i.e. they already include the loss of particles before entry into the respiratory tract.

(356) In the case of exposure to radon progeny, since estimates of lung cancer risk for workers (and for members of the public) can be made reliably from epidemiologic studies relating lung cancer in miners to radon exposure, the Commission does not recommend the assessment of risk from calculations of equivalent doses to respiratory tract tissues. In its report on radon exposure, an approach that relies more directly on an application of the epidemiologic data, and a risk projection model for specific exposure situations, is applied (ICRP, 1994). However, the use of the respiratory tract model to calculate equivalent doses to lungs may be helpful in comparing those lung doses that result from different exposure conditions.

9.4. Example Calculation of Respiratory Tract Doses

(357) The example chosen is that of a 5- μm AMAD ($\sigma_g = 2.47$, density 3 g cm⁻³, shape factor 1.5) aerosol of Type "S" long half-life alpha emitter, assuming an acute nominal intake of 1 Bq by a reference worker.

9.4.1. Regional deposition fractions

(358) The fractions of the 1 Bq nominal intake that are deposited in each region of the respiratory tract are obtained from Annexe F. Table F.1 gives, for a reference worker, i.e. a normal nose breather, and a 5- μm -AMAD aerosol, the appropriate values of fractional deposition in each initial compartment of the respiratory tract model. (See Chapter 5, Fig. 7 for an illustration of these compartments.) These values are used in Table 21 to calculate the amounts of sequestered activity. The total deposition in ET₂ is 0.40. The total deposition in BB, the bronchial region, is 1.2×10^{-2} (fast fraction) + 5.9×10^{-3} (slow fraction) = 0.0179. The slow-cleared fraction (f_s), the fraction assigned to BB₂, is 0.33. The total deposition in bb, the bronchiolar region, is 6.6×10^{-3} + 4.4×10^{-3} = 0.011. The slow-cleared fraction (f_s), the fraction assigned to bb₂, is 0.40. These values of f_s were derived for a polydisperse aerosol. (See Chapter 7, Paragraph 248.) For a monodisperse aerosol, f_s would have a value of 0.26 for both BB₂ and bb₂.

Table 21. Compartmental deposition fractions for 5- μm -AMAD aerosol (particle density = 3.0 g cm⁻³; shape factor = 1.5) inhaled by reference worker

Region	Initial deposition compartment	Deposition fraction
ET ₁	ET ₁	0.34
ET ₂	ET ₂	0.40×0.9995
	ET ₂ ^{seq}	0.40×0.0005^a
BB	BB ₁ (fast)	$0.0179 (1 - 0.33 - 0.007)$
	BB ₂ (slow)	0.0179×0.33
	BB ₂ ^{seq}	0.0179×0.007^b
bb	bb ₁ (fast)	$0.011 (1 - 0.40 - 0.007)$
	bb ₂ (slow)	0.011×0.40
	bb ₂ ^{seq}	0.011×0.007^b
AI	AI ₁	0.053×0.3^c
	AI ₂	0.053×0.6^c
	AI ₃	0.053×0.1^c

^a Sequestered fraction of ET₂ deposit (see Chapter 7, Table 17B).

^b Sequestered fraction of BB and bb deposits (see Chapter 7, Table 17B).

^c Subfractionation of AI deposit (see Chapter 7, Table 17B).

9.4.2. Disintegrations in source compartments

9.4.2.1. Particle transport rates

(359) The compartment model used to represent particle transport between each region of the respiratory tract is illustrated in Chapter 7 (Fig. 20), together with the constant transport rates applicable for each clearance pathway. These recommended rate constants are also listed in Chapter 7, Table 17A for each pathway. The notation $m_{a,b}$ is used to denote the transport rate from compartment a to compartment b. This notation is used below to calculate the residence time of the radioactive material in each compartment that results from particle transport, and thus the number of radioactive disintegrations occurring in each radiation-source compartment.

9.4.2.2. Absorption rate

(360) Absorption of a Type "S" material from each compartment of the particle transport model is represented by the assumption that 0.1% of the initially deposited material is absorbed rapidly (at the constant rate, s_r , of 100 d^{-1}), and that 99.9% of the material is absorbed at the slow rate, s_s , of 0.0001 d^{-1} . (See Chapter 7, Table 18.) This initial rapid loss of a very small fraction (0.1%) of deposited activity has a negligible effect on doses received by respiratory tract tissues, and therefore the hand calculation can be greatly simplified. Thus, for a Type "S" material the particle transport rates, m , can be assumed to compete with a single, constant absorption rate, s_s , which together determine the residence time in each respiratory tract compartment.

9.4.2.3. Compartmental residence times

(361) For a radioactive material that has an infinitely long radioactive half-life compared with the time constants for biological elimination, inspection of the particle transport pathways shown in Chapter 7 (Fig. 20) enables the residence time in each compartment of the model to be expressed simply, as shown in Table 22.

9.4.2.4. Radioactive disintegrations

(362) A compartment that constitutes a radiation source in the dosimetry model (see Chapter 8, Table 20) may be fed activity by several initial deposition compartments. These radiation-source compartments (or retention compartments) and their feed-deposition compartments are listed in Table 23, together with the component deposition-source activities (in Bq), and the resulting number of radioactive disintegrations of the radionuclide in each retention compartment. The number of disintegrations is calculated by multiplying the compartmental residence time (in d, see Table 22) by the products of the deposited component-source activities (in Bq) and the constant coefficient $86,400 \text{ (in s d}^{-1}\text{)}$.

(363) The mean residence times given in Table 22 assume that the 50-y timespan over which the committed dose is integrated is infinitely long compared with the various time constants for biological transport processes. This approximation is accurate for all

Table 22. Compartmental residence times for long-lived radionuclide

Respiratory tract region	Retention compartment (rc)	Residence time	
		$\tau_{rc}, \text{ d}$	d
AI	AI ₁	$1/(m_{1,4} + s_s)$	49.75124
	AI ₂	$1/(m_{2,4} + s_s)$	909.0909
	AI ₃	$1/(m_{3,4} + m_{3,10} + s_s)$	4,545.455
bb	bb ₁	$1/(m_{4,7} + s_s)$	0.499975
	bb ₂	$1/(m_{5,7} + s_s)$	33.22259
	bb _{req}	$1/(m_{6,10} + s_s)$	99.0099
BB	BB ₁	$1/(m_{7,11} + s_s)$	0.099999
	BB ₂	$1/(m_{8,11} + s_s)$	33.22259
	BB _{req}	$1/(m_{9,10} + s_s)$	99.0099
LN _{TH}	LN _{TH}	$1/s_s$	10,000
ET ₂	ET ₂	$1/(m_{11,15} + s_s)$	0.01
	ET _{req}	$1/(m_{12,13} + s_s)$	909.0909
ET ₁	ET ₁	$1/(m_{14,16} + s_s)$	0.9999
LN _{ET}	LN _{ET}	$1/s_s$	10,000

Table 23. Source of activity and number of radioactive disintegrations for each retention compartment from I-Bq intake of long-lived Type S radionuclide

Respiratory tract region	Retention and source compartment	Deposition compartment	Deposit (Bq)	Number of disintegrations	Total source disintegrations
Thoracic:					
AI	AI ₁	AI ₁	0.0159	68,346	4,647,546
	AI ₂	AI ₂	0.0318	2,497,745	
	AI ₃	AI ₃	0.0053	2,081,455	
	AI				
bb	bb ₁	bb ₁	0.006523	281.8	2,318.1
		AI ₁	0.0159	683.4	
		AI ₂	0.0318	1,248.8	
		AI ₃	0.0053	104.1	
BB	bb ₂	bb ₂	0.0044	12,630	12,630
	bb _{seq}	bb _{seq}	7.70 × 10 ⁻⁵	658.7	
	BB ₁	BB ₁	0.011868	102.5	604.1
		bb ₁	0.006523	56.36	
		bb ₂	0.0044	37.89	
		AI ₁	0.0159	136.7	
		AI ₂	0.0318	249.8	16,956
		AI ₃	0.0053	20.81	
		BB ₂	0.005907	16,956	
		BB _{seq}	0.000125	1,071.9	
LN _{TH}	LN _{TH}	AI ₁	0.0053	342,877 ^a	488,034
		bb _{seq}	7.70 × 10 ⁻⁵	55,250	
		BB _{seq}	0.000125	89,907	
Extrathoracic:					
ET ₂	ET ₂	ET ₂	0.3998	345.5	410.9
		BB ₁	0.011868	10.25	
		BB ₂	0.005907	5.104	
		bb ₁	0.006523	5.636	
		bb ₂	0.0044	3.802	
		AI ₁	0.0159	13.669	
		AI ₂	0.0318	24.977	
		AI ₃	0.0053	2.081	
		ET _{seq}	0.0002	15,709	
		ET ₁	0.34	29,373	
ET ₁ LN _{ET}	ET ₁ LN _{ET}	ET ₁	0.34	29,373	29,373
		ET _{seq}	0.0002	131,765 ^b	

^a Product of source activity and retention time in LN_{TH} multiplied by $[1 - \exp(-s_1 \times 18,250)] \times [1 - \exp[-(m_{1,10} + m_{1,4} + s_1) \times 18,250]]$ to correct for limited transfer of activity from AI₁ over 50-y integration period and subsequent truncation of residence in LN_{TH}.

^b Product of source activity and retention time in LN_{ET} multiplied by $[1 - \exp(-s_1 \times 18,250)]$ to correct for truncation of residence in LN_{ET}.

pathways in the model except that from AI₃ to LN_{TH}, where the mean time taken for material to reach LN_{TH} is 22.8 y. In this case, the number of disintegrations in LN_{TH} over 50 y following an intake that results from the incomplete transport of activity deposited in AI₃ is approximated by multiplying the number of disintegrations calculated as described in Paragraph 362 by the factor $[1 - \exp(-s_1 t)] \times [1 - \exp[-(m_{3,10} + m_{3,4} + s_1)t]]$, where t is 18,250 d (50 y).

9.4.3. Equivalent dose to regions of the respiratory tract

(364) The total number of radioactive disintegrations in each radiation source, S, within the respiratory tract that are given in Table 23, i.e. in ET₁, ET₂, ET_{seq}, BB₁, BB₂,

BB_{seq} , bb_1 , bb_2 , bb_{seq} , AI , LN_{ET} , and LN_{TH} , are the appropriate values of $U_{s,j}$ for substitution in Eq. (33) of Chapter 8, in order to calculate the respective contributions to the equivalent dose, H_T , in each target tissue. This calculation also requires the value of the specific effective energy, $SEE(T \leftarrow S)$, absorbed in each target tissue, T , from all radiations emitted by each source. The $SEE(T \leftarrow S)$ is defined by Eq. (32) of Chapter 8, in terms of the sum over all radiations emitted, R , of the product of the radiation weighting factor, w_R , the radiation energy, E_R , the radiation yield per radioactive disintegration, Y_R , the absorbed fraction $AF(T \leftarrow S)_R$ of the energy emitted in source S that is absorbed in target tissue T for each radiation, divided by the mass of the target tissue, M_T .

(365) If each radioactive disintegration of the radionuclide emits an alpha particle with one of several possible energies, an average alpha energy emitted per disintegration is used. In this example, it is assumed to be 5.15 MeV. The alpha emissions from most radionuclides are accompanied by low-energy electrons and photons, with average energies of a few keV per radioactive disintegration. However, since these mean energies are low compared with the assumed 5.15-MeV alpha emission, the resulting values of $SEE(T \leftarrow S)$ for these electron and photon emissions can be neglected.

(366) Table 24 summarises for each source and target tissue of the respiratory tract (both extrathoracic and thoracic), the calculated number of radioactive disintegrations

Table 24. Contributions to regional equivalent dose of disintegrations in each retention compartment for radionuclide emitting 5.15-MeV alpha particles

Target	Source	Disints.	AF(T → S) _q	Mass, kg	Equivalent dose, Sv	Assigned fraction of w _r	Weighted equivalent dose, Sv
Extrathoracic tissues							
ET ₁	ET ₁	29,373	0	2 × 10 ⁻⁵	0	0.001	0
ET ₂	ET ₂	411	0	0.00045	0		
	ET _{seq}	15,709	0.138		7.94 × 10 ⁻⁵	1	7.9 × 10 ⁻⁵
LN _{ET}	LN _{ET}	131,765	1	0.015	1.45 × 10 ⁻⁴	0.001	1.4 × 10 ⁻⁷
Total extrathoracic tissues							8.0 × 10 ⁻⁵
Thoracic tissues (lungs)							
BB basal	BB ₁	604	0	0.00043	0	0.1665	9.8 × 10 ⁻⁷
	BB ₂	16,956	0.00054		3.51 × 10 ⁻⁷		
	BB _{seq}	1,072	0.135		5.55 × 10 ⁻⁶		
	AI	4,647,546	0		0		
BB secretory	BB ₁	604	0.144	0.00087	5.90 × 10 ⁻⁶	0.1665	1.1 × 10 ⁻⁵
	BB ₂	16,956	0.192		1.65 × 10 ⁻⁶		
	BB _{seq}	1,072	0.0515		6.17 × 10 ⁻⁵		
	AI	4,647,546	0		1.05 × 10 ⁻⁶		
bb	bb ₁	2,318	0.233	0.002	0	0.1665	1.1 × 10 ⁻⁵
	bb ₂	12,630	0.237		6.44 × 10 ⁻⁵		
	bb _{seq}	659	0.111		4.45 × 10 ⁻⁶		
	AI	4,647,546	7.06 × 10 ⁻⁵		2.47 × 10 ⁻⁵		
AI LN _{TH}	AI	4,647,546	1	1.1	3.24 × 10 ⁻⁵	0.333	1.1 × 10 ⁻⁵
					6.96 × 10 ⁻⁵		
	LN _{TH}	488,034	1		5.36 × 10 ⁻⁴		
Total lungs							4.6 × 10 ⁻⁵

of the radionuclide in each radiation source, together with the appropriate average value of the absorbed fraction, $AF(T \leftarrow S)_a$, taken from Annexe H, Table H.1, and the respective tissue mass. Substitution of these values into Eqs (32) and (33) of Chapter 8, with the unit conversion coefficient, c , of 1.6×10^{-13} joule per MeV, then gives the values of "unadjusted" equivalent dose that are shown in Table 24 for each combination of source and target tissue.

9.4.3.1. *Weighting calculated equivalent doses*

(367) As described in Chapter 4 (see Table 10), the factors for apportioning radiation detriment between ET_1 , ET_2 , LN_{ET} , and BB, bb, AI, and LN_{TH} , are taken to be 0.001, 1, 0.001, 0.333, 0.333, 0.333, and 0.001, respectively. Note that the bronchial (BB) region contains two target tissues, i.e. the secretory and basal cells, respectively, for which the calculated values of $AF(T \leftarrow S)_a$ are different. In order to derive the equivalent dose to the bronchial region as a whole, it is assumed that the detriment apportionment factor of 0.333 is divided equally between secretory and basal cells.

(368) Table 24 shows the resulting weighted equivalent doses that are summed from the calculated values for the total extrathoracic tissues (extrathoracic region) and the total lungs (thoracic region).

10. SUMMARY DESCRIPTION OF RESPIRATORY TRACT DOSIMETRY MODEL

10.1. Introduction

(369) The dosimetric model for the human respiratory tract developed in this report is based on the premise that differences in radiation sensitivity of respiratory tract tissues, and the wide range of doses they receive, argue for calculating specific tissue doses rather than average lung doses for radiation protection purposes. The model enables intakes to be calculated per unit exposure (time-integrated air concentration), under a wide range of conditions, taking account of (1) inhalability, the ratio of the concentration in the air entering the respiratory tract to that in the ambient air, and (2) the subject's breathing rate, which depends mainly on body size (age) and physical activity. It defines deposition of inhaled radioactive material in and clearance from several tissues and regions of the respiratory tract and is applicable to the worldwide population of both workers and the public. The model was developed with the objective of accommodating the use of bioassay as well as exposure data to calculate radiation doses to the respiratory tract.

10.2. Respiratory Tract Morphometry

(370) For modelling purposes, the respiratory tract was divided into regions (Fig. 42) based on anatomical, cytological, physiological, radiobiological, and aerosol deposition and clearance considerations. These regions are: the extrathoracic (ET), comprising the anterior nose (ET_1) and the posterior nasal passages, larynx, pharynx, and mouth (ET_2); the bronchial region (BB), comprising the airway generations 0 through 8 (trachea through the bronchi); the bronchiolar region (bb), comprising the

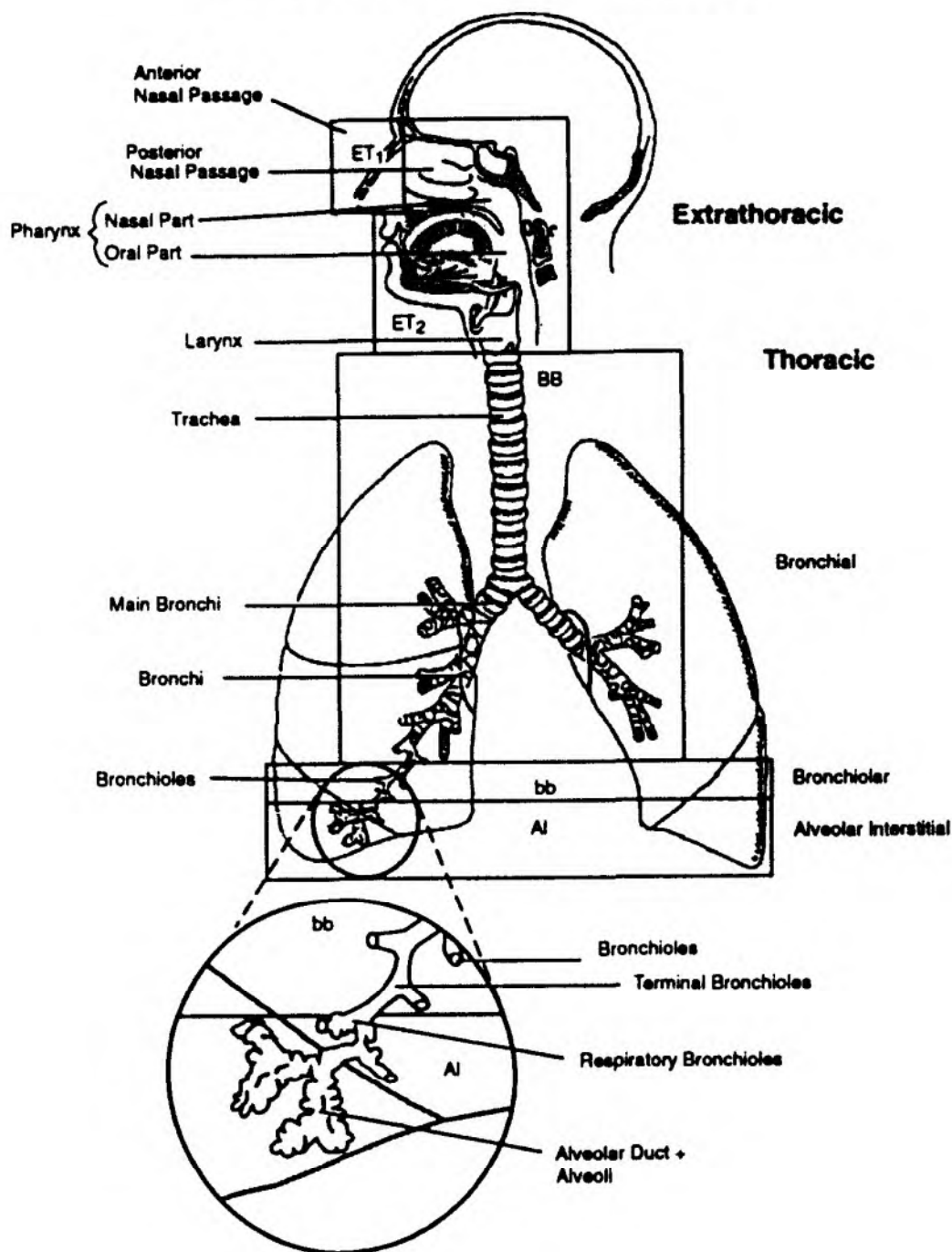


Fig. 42. Summary: anatomical regions of the respiratory tract.

airway generations 9 through 15; and the alveolar-interstitial region (AI), comprising the airway generations 16 through 26 (respiratory bronchioli through alveolar sacs). All regions contain lymphatic tissues: LN_{ET} , draining the extrathoracic region, and LN_{TH} , draining the BB, bb, and AI regions. For dosimetry purposes, morphological and cytological dimensions are assigned to these regions for the reference worker and scaled to apply to members of the general population: 3 mo olds; 1 y, 5 y, 10 y, and 15 y olds; and adults (Table 25). These dimensions define the mass of tissue containing radiation-sensitive target cells in each region for dose calculation (Table 26). These targets are epithelial basal cells in the ET regions, basal and secretory cells in the BB region,

Table 25. Summary: dimensions of target tissue (assumed to be same in all people)

Tissue	Target cells	Mucus thickness (μm)	Epithelial thickness (μm)	Depth of target cell nuclei (μm)
ET ₁	Basal	—	50	40–50
ET ₂	Basal	15	50	40–50
BB _{sec} ^a	Secretory	5	55	10–40
BB _{bas} ^a	Basal	5	55	35–50
bb	Secretory	2	15	4–12
AI	Clara and type II alveolar cells	—	—	—
LN _{ET} and LN _{TH}	Lymphocytes, endothelial, and germinal center cells	—	—	—

^a BB_{sec} is the mass of bronchial epithelium through which secretory cell nuclei are distributed, and BB_{bas} that for basal cell nuclei.

secretory cells (Clara) in the bb region, and secretory cells (Clara) and type II alveolar cells in the AI region.

10.3. Physiology

(371) The volume and rate of air inhaled and the proportions entering through the nose and mouth determine the quantity of radionuclides inspired and their penetration into the respiratory tract. Respiratory parameters vary with body size, level of activity, respiratory tract diseases, and smoking habits. Reference respiratory values are specified in Table 27. Breathing only through nose or mouth and breathing through the nose augmented by mouth breathing are all considered in the model.

10.4. Deposition

(372) The fraction of an airborne material present in a person's breathing zone that is deposited in each region is determined by particle parameters, which include size, shape, and density. It is also influenced by anatomical and physiological parameters such as airway dimensions, flow rates, and regional transit times of airborne material. Inhalability (the ratio of the concentration in the inhaled air to that in the ambient air) is determined primarily by particle size and the wind velocity. An empirical method was used to model particle deposition in the extrathoracic airways. Measured deposition was related to characteristic parameters of particle size and airflow. Deposition efficiencies determined experimentally for adult male subjects were scaled on the basis of anatomical and physiological differences to predict deposition in women and children. For the thoracic airways, a theoretical model of gas transport and particle deposition was used to calculate particle deposition in each of the BB, bb, and AI regions, and to quantify the effects of the subject's lung size and breathing rate. Regional deposition fractions have been calculated for aerosols having log-normal particle size distributions, with geometric standard deviations that are a function of the median particle size, increasing from a value of 1.0 at 0.0005 μm to 2.5 at 1 μm and above. Values of regional deposition are specified in Table 28 for an occupational exposure of a reference (light) worker to 5- μm -AMAD aerosols. Fractional deposition in each region of the respiratory tract of a reference worker as a function of aerosol size is illustrated

TABLE 26. Summary: masses of major structures in different subjects

Subject	Mass (kg)						
	ET ₁	ET ₂	BB _{sc} ^a	BB _{bas} ^b	bb	AI ^c	LN _{ET} ^d
Adult male	2.0×10^{-5}	4.5×10^{-4}	8.6×10^{-4}	4.3×10^{-4}	1.9×10^{-3}	1.1	1.5×10^{-2}
Adult female	1.7×10^{-5}	3.9×10^{-4}	7.8×10^{-4}	3.9×10^{-4}	1.9×10^{-3}	0.90	1.2×10^{-2}
15-y male	1.9×10^{-5}	4.2×10^{-4}	8.2×10^{-4}	4.1×10^{-4}	1.8×10^{-3}	0.86	1.2×10^{-2}
15-y female	1.7×10^{-5}	3.8×10^{-4}	7.6×10^{-4}	3.8×10^{-4}	1.6×10^{-3}	0.80	1.1×10^{-2}
10 y	1.3×10^{-5}	2.8×10^{-4}	6.2×10^{-4}	3.1×10^{-4}	1.3×10^{-3}	0.50	6.8×10^{-3}
5 y	8.3×10^{-6}	1.9×10^{-4}	4.7×10^{-4}	2.3×10^{-4}	9.5×10^{-4}	0.30	4.1×10^{-3}
1 y	4.1×10^{-6}	9.3×10^{-5}	3.1×10^{-4}	1.6×10^{-4}	6.0×10^{-4}	0.15	2.1×10^{-3}
3 mo	2.8×10^{-6}	6.3×10^{-5}	2.5×10^{-4}	1.3×10^{-4}	5.0×10^{-4}	0.090	1.2×10^{-3}

^a Secondary values of two significant figures.^b BB_{sc} is the mass of bronchial epithelium through which secretory cell nuclei are distributed, and BB_{bas} that for basal cell nuclei. These masses are derived from the surface areas defined by airway lengths and diameters (Table 2), which are scaled for each subject by the constants given in Table 4.^c Including blood, excluding lymph nodes.^d Mass of lymphatic tissue is assumed to be the same in extrathoracic and thoracic regions.Table 27. Summary: reference respiratory values for a general Caucasian population at different levels of activity^a

Activity:	Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
	8			12			32			64		
Maximal workload (%):												
Breathing parameters: ^b	V _T (L)	B (m ³ h ⁻¹)	f _R (min ⁻¹)	V _T (L)	B (m ³ h ⁻¹)	f _R (min ⁻¹)	V _T (L)	B (m ³ h ⁻¹)	f _R (min ⁻¹)	V _T (L)	B (m ³ h ⁻¹)	f _R (min ⁻¹)
Age												
3 mo	0.039	0.09	38	N/A	N/A	N/A	0.066	0.19	48	N/A	N/A	N/A
1 y	0.074	0.15	34	0.102	0.22	36	0.127	0.35	46	N/A	N/A	N/A
5 y	0.174	0.24	23	0.213	0.32	25	0.244	0.57	39	N/A	N/A	N/A
10 y	0.304	0.31	17	0.333	0.38	19	0.583	1.12	32	0.841	2.22	44
15 y	0.500	0.42	14	0.533	0.48	15	1.0	1.38	23	0.667	1.84	46
Adult	0.417	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
	0.625	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	0.444	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

^a See Annex B for data from which these reference values were derived.^b V_T = Tidal volume, B = ventilation rate, f_R = respiration frequency.

N/A = Not applicable.

Table 28. Summary: deposition of inhaled aerosols for occupational and environmental exposures

Region	Worker ^a (%)	Adult male ^b (%)
ET ₁	33.9	14.2
ET ₂	39.9	17.9
BB	1.8 (33% in BB ₂)	1.1 (47% in BB ₂)
bb	1.1 (40% in bb ₂)	2.1 (49% in bb ₂)
AI	5.3	11.9
Total	82.0	47.3

^a Occupational exposure. 5- μm AMAD ($\sigma_g = 2.5$), 3.5- μm AMTD, density 3.0 g cm⁻³, shape factor 1.5 (see Chapter 5); fraction breathed through nose is 1. 31% sitting and 69% light exercise; mean ventilation rate is 1.2 m³ h⁻¹. (See Table 6.)

^b Environmental Exposure (indoors at home). 1- μm AMAD ($\sigma_g = 2.47$), 0.69- μm AMTD, density 3.0 g cm⁻³, shape factor 1.5; fraction breathed through nose is 1. 55% sleeping, 15% sitting, and 30% light exercise; mean ventilation rate is 0.78 m³ h⁻¹. (See Table 16.B.)

in Fig. 43. Corresponding values are given in Annexe F for other levels of physical activity, taking account of oro-nasal breathing during heavy exercise, and for various population groups, including habitual mouth breathers.

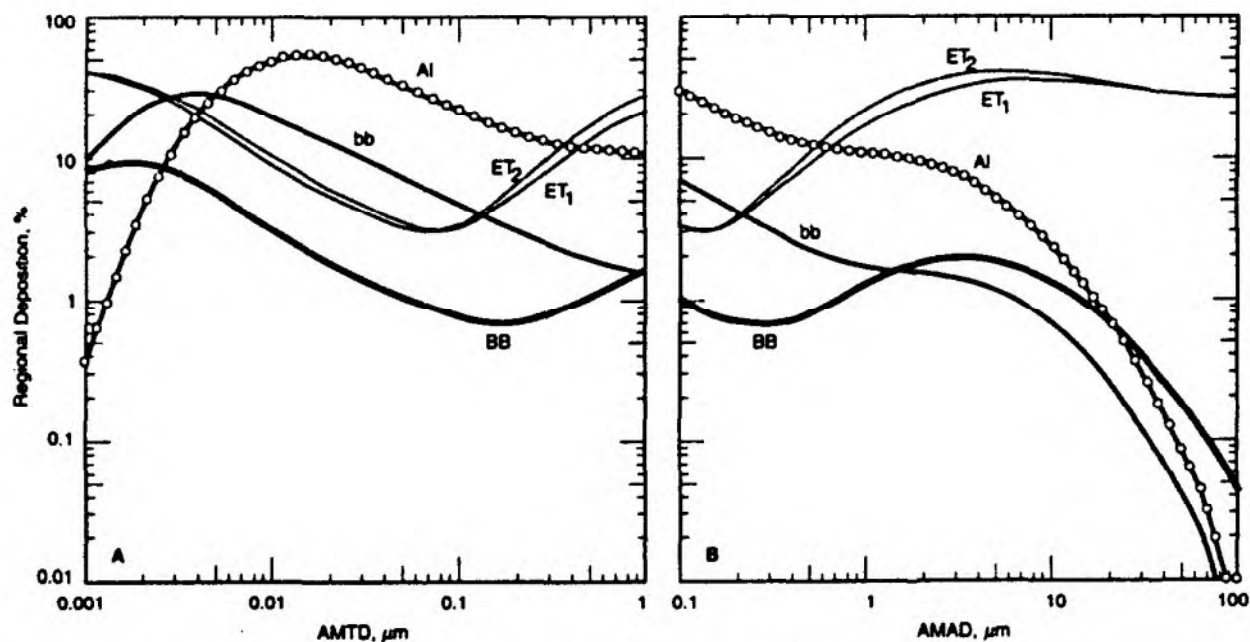


Fig. 43. Summary: fractional deposition in each region of respiratory tract for reference worker (normal nose breather). Deposition is expressed as a fraction of activity present in volume of ambient air that is inspired, and activity is assumed to be log-normally distributed as function of particle size (for particles of density 3.00 g cm⁻³ and shape factor 1.5).

10.5. Clearance

(373) The model describes three clearance pathways. Material deposited in ET_1 is removed by extrinsic processes, such as nose blowing. For the other regions, clearance of inhaled material is competitive between particle transport processes (such as macrophage uptake and ciliary action) to the GI tract and to lymph nodes, and absorption into blood. The rate of clearance by each process is a time-varying factor of the residual amount, but in the model this is represented by combinations of compartments that clear at constant rates. It is assumed that rates of clearance by both processes are independent of age and gender. Particle transport rates, which are assumed to be the same for all materials, were derived principally from studies with human subjects, and are specified (in d^{-1}) in Fig. 44 and Table 29. Guidance is provided for modifying these rates to account for the effects on clearance of particles by exposures to agents such as cigarette smoke and by respiratory tract diseases. Clearance from the BB and bb regions includes a slow phase, represented by compartments BB_2 and bb_2 . It is assumed that the same fraction of the deposit is subject to slow clearance in both regions and that the slow-cleared fraction (f_s) is size-dependent (Table 29). Provision is also made for retention of particles in the epithelium of ET_2 , BB, and bb, represented by the sequestration compartments ET_{seq} , BB_{seq} , and bb_{seq} . The fraction of the deposit in each region that is sequestered is given in Table 29B.

(374) Absorption into blood is material-specific, acts in all regions except ET_1 , and is assumed to occur at the same rate from all regions. Absorption into blood is a two-stage process: (1) the dissociation of the particles into material that can be absorbed into the blood (dissolution) and (2) the uptake of material dissolved from particles or of material deposited in a soluble form. Each stage can be time-dependent. It is assumed that time-dependent dissolution can be approximated by dividing the material into two fractions, with different dissolution rates. This is represented in the model (Fig. 45) by the material in an "initial" state dissolving at a constant rate s_p , and simultaneously

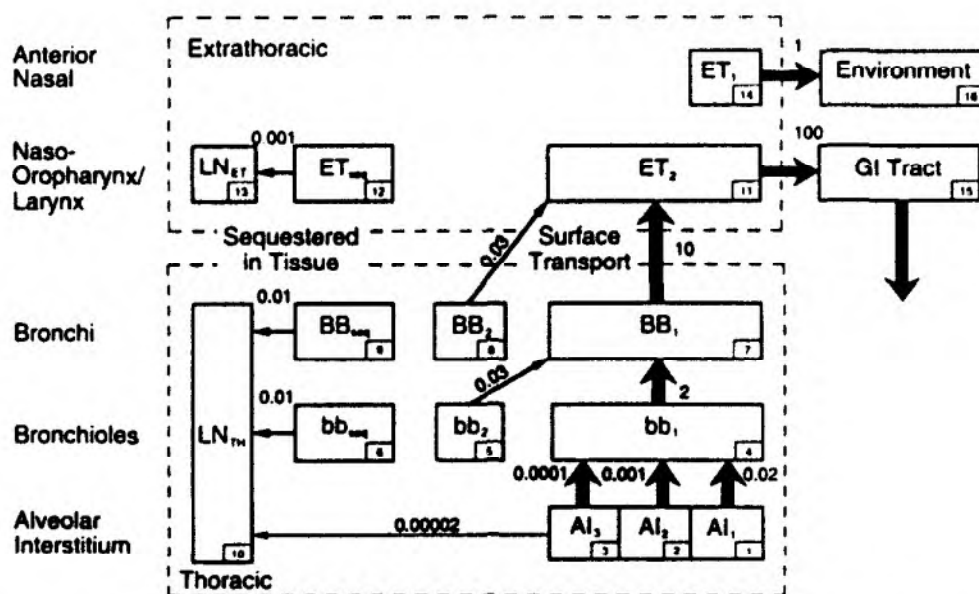


Fig. 44. Summary: compartment model to represent time-dependent particle transport from each region. Particle transport rate constants shown beside the arrows are reference values in d^{-1} . Compartment numbers (shown in the lower right-hand corner of each compartment box) are used to define clearance pathways. Thus the particle transport rate from bb_1 to BB_1 is denoted $m_{4,7}$ and has the value $2 d^{-1}$.

Table 29. Summary: reference values of parameters for the compartment model to represent time-dependent particle transport from the human respiratory tract

A. Clearance rates				
Pathway	From	To	Rate (d ⁻¹)	Half-time ^a
m _{1,4}	AI ₁	bb ₁	0.02	35 d
m _{2,4}	AI ₂	bb ₁	0.001	700 d
m _{3,4}	AI ₃	bb ₁	0.0001	7000 d
m _{3,10}	AI ₃	LN _{TH}	0.00002	—
m _{4,7}	bb ₁	BB ₁	2	8 h
m _{5,7}	bb ₂	BB ₁	0.03	23 d
m _{6,10}	bb _{seq}	LN _{TH}	0.01	70 d
m _{7,11}	BB ₁	ET ₂	10	100 min
m _{8,11}	BB ₂	ET ₂	0.03	23 d
m _{9,10}	BB _{seq}	LN _{TH}	0.01	70 d
m _{11,15}	ET ₂	GI tract	100	10 min
m _{12,13}	ET _{seq}	LN _{ET}	0.001	700 d
m _{14,16}	ET ₁	Environment	1	17 h

B. Partition of deposit in each region between compartments ^b		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment ^c
ET ₂	ET ₂	0.9995
	ET _{seq}	0.0005
BB	BB ₁	0.993 - f _s
	BB ₂	f _s
	BB _{seq}	0.007
bb	bb ₁	0.993 - f _s
	bb ₂	f _s
	bb _{seq}	0.007
AI	AI ₁	0.3
	AI ₂	0.6
	AI ₃	0.1

^a The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d⁻¹. A half-time is not given for the transport rate from AI₁ to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI₁ is determined by the sum of the clearance rates from it.

^b See Paragraph 181, Chapter 5 for default values used for relating f_s to d_{ac}.

^c It is assumed that the slow-cleared fraction f_s is size-dependent. For modelling purposes f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ac} \leq 2.5 \sqrt{\rho/\chi} \text{ } \mu\text{m and}$$

$$f_s = 0.5 e^{-0.63(d_{ac}\sqrt{\rho/\chi} - 2.5)} \text{ for } d_{ac} > 2.5 \sqrt{\rho/\chi} \text{ } \mu\text{m.}$$

changing to a "transformed" state (at a rate s_{pt}) in which it dissolves at a rate s_i . Uptake into blood is treated as instantaneous for the fraction of material absorbed immediately after dissolution. Another fraction of dissolved material may be absorbed slowly (at a rate s_b) as a result of binding to respiratory tract components.

(375) The model can use observed rates of absorption for compounds for which reliable human or experimental animal data exist. The absorption rates of other compounds are specified as "fast", "moderate", or "slow". In the absence of more

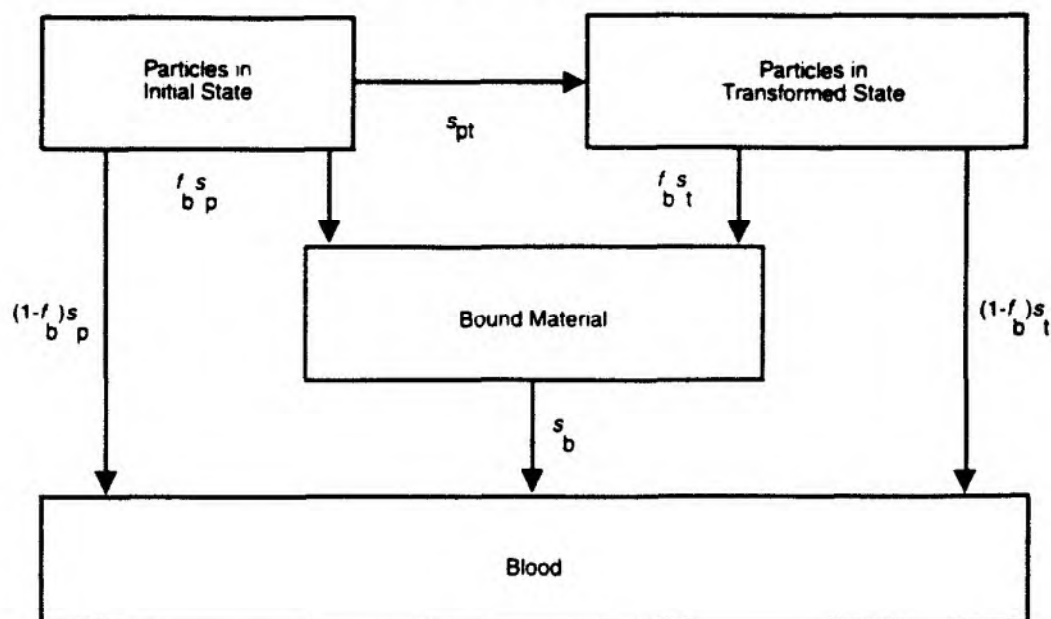


Fig. 45. Summary: compartment model for time-dependent absorption into blood.

specific information, a compound that was assigned to Class Y in *ICRP Publication 30* is assigned to Type S in the new scheme. It should, however, be noted that, whereas D, W, and Y define overall clearance, F, M, and S refer only to absorption into blood; particle transport rates to the GI tract and lymph nodes are the same for the three types. The different terminology has been introduced to avoid ambiguity. The default values are given in Table 30.

Table 30. Summary: default absorption parameters for Type F, M, and S materials

Type of absorption behaviour		F (fast)	M (moderate)	S (slow)
Initial dissolution rate (d^{-1})	s_p	100	10	0.1
Transformation rate (d^{-1})	s_{pt}	0	90	100
Final dissolution rate (d^{-1})	s_t	—	0.005	0.0001
Fraction to bound state	f_b	0	0	0
Uptake rate from bound state (d^{-1})	s_b	—	—	—

10.6. Dose Calculations

(376) The calculation of regional doses follows the method of *ICRP Publication 30* (ICRP, 1979) in which the committed equivalent dose in a target tissue is determined by the energy absorbed per unit mass from the radiation emitted from a source organ. To use these regional doses in the ICRP dosimetry system (ICRP, 1991a), it is necessary to sum those for the extrathoracic airways and those for the thoracic regions. Because the regions of the respiratory tract vary greatly in radiation sensitivity, the regional doses must be adjusted for their relative sensitivity in order for them to be summed. The Commission (ICRP, 1991a) focuses on protection of workers and the public from total radiation health detriment. This detriment includes the probability of attributable fatal and nonfatal cancers, hereditary effects, and length of life lost if harm occurs. Results

Table 31. Summary: weighting factors assigned for the partition of radiation detriment among respiratory tract tissues

Tissue	Assigned fractions (<i>A</i>) of w_T
Extrathoracic region	
ET ₁ (anterior nose)	0.001
ET ₂ (posterior nasal passages, larynx, pharynx, and mouth)	1
LN _{ET} (lymphatics)	0.001
Thoracic region	
BB (bronchial)	0.333
bb (bronchiolar)	0.333
AI (alveolar-interstitial)	0.333
LN _{TH} (lymphatics)	0.001

from studies of underground miners exposed to radon, the Japanese atomic bomb survivors, and experiments with laboratory animals and cellular systems were reviewed. It was concluded that there was no basis for deriving factors to represent regional differences in radiation sensitivity with any acceptable degree of confidence. Therefore, the weighting factors given in Table 31 are recommended. These factors may be revised by the Commission as better information becomes available. Revisions can be made without changing the respiratory tract dosimetry model itself.

(377) Regional doses, weighted with factors assigned for the partition of radiation detriment, are summed to give a value of committed equivalent dose for the extrathoracic region and another for the thoracic region, as follows:

$$H_{ET} = H_{ET_1}A_{ET_1} + H_{ET_2}A_{ET_2} + H_{LN_{ET}}A_{LN_{ET}} \quad (52)$$

and

$$H_{TH} = H_{BB}A_{BB} + H_{bb}A_{bb} + H_{AI}A_{AI} + H_{LN_{TH}}A_{LN_{TH}} \quad (53)$$

The appropriate ICRP tissue weighting factors, w_T , can be applied to these two values in calculating effective doses as described in *ICRP Publication 60* (ICRP, 1991a). The weighting factor, 0.12, specified for lungs is to be applied to the committed equivalent dose calculated for the thoracic region, while the extrathoracic region would be considered as one of the remainder tissues.

(378) The exposure parameters given in footnote a of Table 28 are recommended for calculations of effective dose per unit intake via inhalation for the reference worker. These are 5- μ m AMAD ($\sigma_g = 2.5$), 3.5- μ m AMTD, density 3.00 g cm⁻³, shape factor 1.5 (see Paragraph 181, Chapter 5); fraction breathed through nose is 1; mean ventilation rate is 1.2 m³ h⁻¹.

(379) Specific exposure parameters for calculations of the effective dose per unit intake via inhalation for members of the public will be selected from those given in this report by the ICRP Task Group on Internal Dosimetry. The Commission will be publishing a list of effective doses per unit intake for the radionuclides given in *ICRP Publication 56*, Parts 1, 2, and 3 for inhalation.

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ANNEXE A. ANATOMY AND MORPHOLOGY OF THE RESPIRATORY TRACT

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A.1. Introduction

(A1) This annexe summarises information about the anatomy and morphology of the respiratory tract that was considered in developing the morphometric model described in Chapter 2 of this report. While much is known about the anatomy of the respiratory tract, information about the dimensions of its numerous structures is limited in both quantity and quality. Since comprehensive morphological studies of the human respiratory tract have been rare, the available information consists of measurements on a small number of samples from only a few representatives of the world's population. The values assigned to parameters in the morphometric model in Chapter 2 represent best judgement interpretations and extrapolations of the available information.

A.2. General Aspects

(A2) The respiratory tract is part of a system that conducts oxygen from outside air to the mitochondria in the cells throughout the body; therefore it is the most common route of entry for toxic substances from the environment. The thin, delicate air-blood barrier in the lung, which facilitates the passage of oxygen, also reduces its effectiveness as a barrier to toxic substances. As toxic substances are transported through the airway system to the gas exchange region, they may be deposited anywhere on the epithelium, depending on a variety of factors, and enter the tissue.

(A3) Lung diseases continue to be a major health problem. In particular, there has been a rise in the prevalence of a variety of pulmonary diseases caused by the inhalation of irritant agents. Occupational exposure to toxic substances is an important cause, but smoking is undoubtedly a major contributor to these diseases. Cigarette smoking plays a major role in the development of lung cancer, chronic bronchitis, and emphysema (American Cancer Society, 1985). The risk of death from bronchial carcinoma is 13 times higher for smokers than for nonsmokers, and the number of people who die from lung cancer is still increasing (Fielding, 1985).

(A4) Another important contributor to lung cancer is, apparently, the inhalation of airborne radionuclides that occur naturally in the environment. An increased frequency of bronchial cancer has been observed, for example, among miners exposed to high radon levels (ICRP, 1987).

(A5) To help control the risks of inhaling radionuclides, the ICRP Task Group on Lung Dynamics developed, nearly 30 y ago, a dosimetric lung model based on the existing knowledge of deposition, retention, and clearance of inhaled radionuclides in the respiratory tract (TGLD, 1966). This model, which was to apply to workers, included an anatomical description separating the respiratory tract into four major compartments: the nasopharyngeal region (N-P), the tracheobronchial region (T-B), the pulmonary or nonciliated region (P), and the lymph nodes (L).

(A6) The N-P compartment comprised the anterior nares to the larynx; the T-B compartment comprised all airways from the trachea to the terminal bronchioli; the P compartment was composed of the respiratory region of the lung, consisting of the respiratory bronchioli and the alveolar ducts and sacs with their alveoli; and the thoracic lymph nodes were assigned to the L compartment. The 1966 model did not, however, include a histological and cytological description of the respiratory tract, nor did the revision of this model published in 1979 (ICRP, 1979).

(A7) In this annexe on the anatomical and morphological aspects of the inhalation, deposition, retention, and clearance of radionuclides in particular and airborne material in general, a new model is defined. It is based on the latest data on the anatomy, physiology, histology, and cytology of the respiratory tract as well as current knowledge of respiratory tract carcinogenesis resulting from exposure to radiation. The model describes the pathway of radionuclides from their entry through the anterior nares to their deposition in the alveoli, considering the architecture, geometry, and dimensions of the air-spaces and their walls (Weibel, 1963; Phalen *et al.*, 1978). Particular attention is given to the cells at risk from radiation exposure (see Annexe C and Chapter 4), which include epithelial and interstitial cells.

A.3. The Normal Structure

(A8) This annexe briefly reviews the anatomical characteristics and dynamics as well as the morphometric aspects of the normal human respiratory tract, including the thoracic lymph nodes, with respect to inhalation, deposition, retention, and clearance of potential toxicants. Although particular attention is given to inhaled radionuclides, the material in this annexe applies equally to almost all inhaled particles and gases. Comparative aspects with respect to extrapolation models are also addressed.

(A9) An anatomical and morphological overview of the respiratory tract is given in Fig. A.1. Airway dimensions of four models are given in Tables A.1A–A.1D (Weibel, 1963; Horsfield and Cumming, 1968; Yeh and Schum, 1980; Phalen *et al.*, 1985).

A.3.1. The Nose

(A10) The nose, which provides ambient air to the lungs, plays a significant role in cleaning and conditioning inspired air. During nasal breathing, temperature and humidity adjustment begins at the nostrils; final adjustment to airway conditions, however, probably occurs only in the bronchial tree. Similarly, cleaning begins by filtration, when the inspired air passes through the vibrissae (hairs) behind the nasal entrance to trap foreign material.

(A11) The nasal cavity is divided into symmetrical halves by the partly bony, partly cartilaginous nasal septum (Fig. A.2A). The stratified squamous epithelium of the facial skin continues through the nares into the vestibule (Fig. A.2B). The nostrils of adults measure 1.5 cm to 2 cm anteroposteriorly and 0.5 cm to 1 cm transversely.

(A12) The hairs and associated sebaceous glands in the nares form the first defense against the entry of particulate matter. Posteriorly, the air flows through the paired openings into the nasal cavities, which are located within the skull. The roof of the cavities is formed by the cribriform bone; the floor, by the hard and soft palate. They are smooth-sided along the septum but are interrupted laterally by bony projections (turbinates), which form narrow slits (meatus) for air passage. Their surface area totals about 140 cm² to 160 cm² and is mostly coated with a respiratory mucosa (2 mm thick) which cleans, warms and moistens the inspired air. The roof of the cavities is covered by the olfactory mucosa, which houses the receptors of smell. The epithelium of the respiratory mucosa is pseudostratified and ciliated (0.1 mm thick), carrying a mucous layer that may be 0.5 mm thick which is secreted by abundantly distributed goblet cells

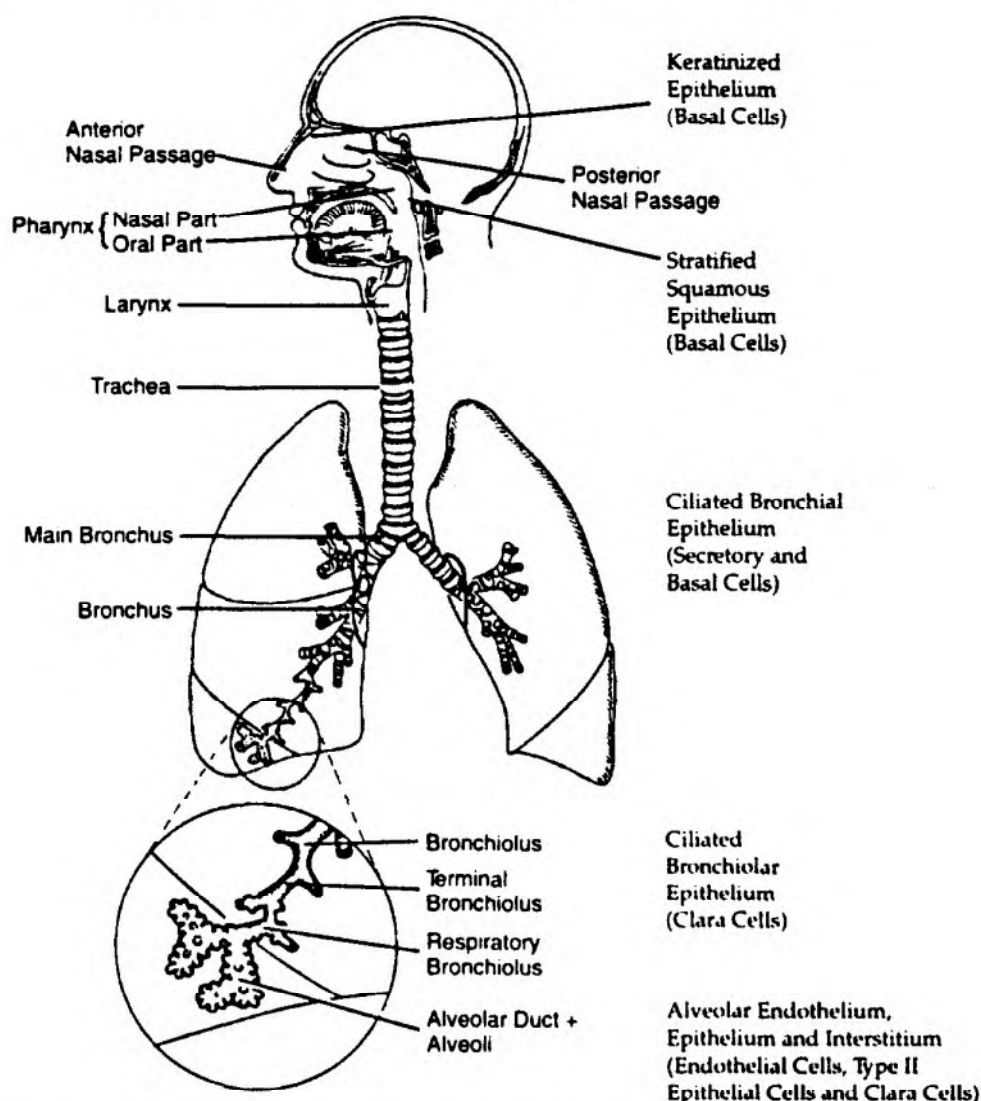


Fig. A.1. Anatomical and morphological overview of respiratory tract showing major structures, tissues, and cells.

in the epithelium and by numerous seromucosal glands located in the underlying connective tissue. The mucus, which catches particles and humidifies the air, is easily moved toward the pharynx by the ciliary beat (described in more detail in Section A.3.5).

(A13) A prominent basement lamina separates the epithelium from the subepithelial connective tissue. The connective tissue is of a fairly uniform collagenous type until it blends into the periosteal and perichondrial layers of the nasal skeleton. It also contains numerous free cells beneath the epithelium and is richly vascularised, which serves to warm the inhaled air. The vessels receive their blood from branches of the ophthalmic, maxillary, palatine, and facial arteries. The lymph is drained either into the skin covering the external nose or into the upper deep cervical nodes. The nerves include branches of the trigeminal and olfactory cranial nerves.

(A14) The paranasal sinuses, as well as the nasolacrimal ducts, originate under the turbinates as small orifices. The sinuses may contribute to conditioning inspired air by acting as an insulator and also supplement nasal secretions. The nasolacrimal ducts

Table A.1A. Dimensions of human airway model "A".^a Average adult lung with volume of 4800 mL at about three-fourths maximal inflation

Generation, z	Number per generation $n(z)$	Diameter $d(z)$ (cm)	Length $l(z)$ (cm)	Total cross-section $S(z)$ (cm ²)	Total volume $V(z)$ (cm ³)	Cumulative volume $\sum_{i=0}^z V(i)$ (cm ³)
0	1	1.8	12.0	2.54	30.50	30.5
1	2	1.22	4.76	2.33	11.25	41.8
2	4	0.83	1.90	2.13	3.97	45.8
3	8	0.56	0.76	2.00	1.52	47.2
4	16	0.45	1.27	2.48	3.46	50.7
5	32	0.35	1.07	3.11	3.30	54.0
6	64	0.28	0.90	3.96	3.53	57.5
7	128	0.23	0.76	5.10	3.85	61.4
8	256	0.186	0.64	6.95	4.45	65.8
9	512	0.154	0.54	9.65	5.17	71.0
10	1024	0.130	0.46	13.4	6.31	77.2
11	2048	0.109	0.39	19.6	7.56	84.8
12	4096	0.095	0.33	28.8	9.82	94.6
13	8192	0.082	0.27	44.5	12.45	106.0
14	16 384	0.074	0.23	69.4	16.40	123.4
15	32 768	0.066	0.20	113.0	21.70	145.1
16	65 536	0.060	0.165	180.0	29.70	174.8
17	131 907	0.054	0.141	300.0	41.80	216.6
18	262 144	0.050	0.117	534.0	61.10	277.7
19	524 288	0.047	0.099	944.0	93.20	370.9
20	1 489 576	0.045	0.083	1 600.0	139.50	510.4
21	2 097 152	0.043	0.070	3 220.0	224.30	734.7
22	4 194 304	0.041	0.059	5 880.0	350.00	1084.7
23 ^b	8 388 608	0.041	0.050 ^b	11 800.0	591.00	1675.0

^a From Weibel (1963).^b Adjusted for complete generation.

drain the lacrimal fluid. Narrow openings lead from the nasal cavities into the paranasal sinuses, which are blind pockets lined by the same (but somewhat less developed) mucosa and a mucous film, which is continuously propelled into the nasal cavity. These airspaces in the bones of the face protect the brain from blows to the front of the head.

A.3.2. The Pharynx

(A15) Behind the vestibule, the airstream bends and runs horizontally through the narrow passages formed by the turbinates and the nasal septum. It leaves the nasal cavity through the posterior nares which measure about 25 mm vertically and 12.5 mm transversely, turns downward into the wide upper part of the pharynx (nasal part), and continues vertically through the oral part of the pharynx into the larynx and trachea. The auditory tube, coming from the middle ear, runs into the nasal part of the pharynx. In the oral part of the pharynx, the air passage crosses the food passage. Food is prevented from entering the trachea by the epiglottis, which covers the laryngeal tube during swallowing.

(A16) Located behind the nasal cavities (nasopharynx), the mouth (oropharynx, intersection of air and food passages), and the larynx (hypopharynx, part of the digestive tract) is the pharynx, a musculomembranous tube, 12–14 cm long. The uppermost part is the widest (3.5 cm); in the oropharynx it is only 1.5 cm wide (Fig. A.1).

Table A.1B. Asymmetrical model of the airways derived from measurement of cast^a

Structure	Generation ^b	Number	Diameter (mm)	Length (mm)	Value of E ^c
Trachea	25	1	16.0	100	223 941
	24	1	12.0	40	123 590
	23	2	10.3	26	88 920
	22	2	8.9	18	63 973
	21	2	7.7	14	46 026
	20	3	6.6	11	33 113
	19	6	5.7	10	23 823
	18	8	4.9	10	17 140
	17	12	4.2	10	12 331
	16	14	3.5	10	8872
	15	20	3.3	9.6	6383
	14	30	3.1	9.1	4592
	13	37	2.9	8.6	3304
	12	46	2.8	8.2	2737
	11	64	2.6	7.8	1710
	10	85	2.4	7.4	1230
	9	114	2.3	7.0	885
	8	158	2.2	6.7	637
	7	221	2.0	6.3	458
	6	341	1.78	5.7	330
	5	499	1.51	5.0	237
	4	760	1.29	4.4	171
	3	1104	1.10	3.9	123
	2	1675	0.93	3.5	88
	1	2843	0.79	3.1	64
Terminal bronchiole	(-2)	27 992	0.60		8
Distal respiratory bronchiole	(-5)	223 941	0.40		1

^a From Horsfield and Cumming (1968).^b Counting upward.^c Number of distal respiratory bronchioles arising from a given branch.

(A17) The nasopharynx, lying behind the nose and above the level of the soft palate, is never completely obstructed, which is not the case for the oral and laryngeal part. Each of the lateral walls forms the opening of the auditory tubes that communicate with the middle ear. The midline pharyngeal tonsil is located on the dorsal wall. Although ordinarily small, the tonsils may become quite large when infected. The lymphoid tissue around the auditory orifices constitutes the adenoids. The oropharynx reaches from the soft palate to the upper border of the epiglottis, opening anteriorly into the mouth.

(A18) The respiratory mucosa of the nasal cavity, with its pseudostratified ciliated epithelium, continues into the nasopharynx, but is interrupted by stratified squamous epithelium where the oropharynx and larynx cross. In the pharynx the mucosa becomes thinner and generally rests directly on skeletal muscle, separated from it by a broad, fibrous, elastic layer. Numerous mucus glands, located in the subepithelial connective tissue, produce a viscous, surface-lining layer of mucus.

(A19) Branches of the facial, maxillary, and lingual arteries supply the pharynx. Lymph is drained into the deep cervical nodes, either directly or indirectly, through the retropharyngeal or paratracheal nodes. The nerve supply is derived chiefly from the pharyngeal plexus, which is formed by branches of the glossopharyngeal, vagus, and sympathetic nerves.

Table A.1C. Typical path lung model: whole lung^a

Generation ^b	Number of tubes	<i>l</i> (cm)	<i>d</i> (cm)	θ (°)	ϕ (°)	<i>S</i> (cm ²)	<i>V</i> (cm ³)	ΣV (cm ³)
0	1	10.0	2.01	0	0	3.17	31.73	31.73
1	2	4.36	1.56	33	20	3.82	16.67	48.40
2	4	1.78	1.13	34	31	4.01	7.14	55.54
3	8	0.965	0.827	22	43	4.03	4.15	59.69
4	16	0.995	0.651	20	39	5.33	5.30	64.98
5	32	1.01	0.574	18	39	8.28	8.36	73.35
6	64	0.890	0.435	19	40	9.51	8.47	81.81
7	128	0.962	0.373	22	36	13.99	13.46	95.27
8	256	0.876	0.322	28	39	20.85	18.07	113.34
9	512	0.667	0.257	22	45	26.56	17.72	148.59
10	1024	0.556	0.198	33	43	31.53	17.53	166.05
11	2048	0.446	0.156	34	45	39.14	17.46	182.13
12	4096	0.359	0.118	37	45	44.79	16.08	197.10
13	8192	0.275	0.092	39	60	54.46	14.98	211.64
14	16 384	0.212	0.073	39	60	68.57	14.54	227.21
15 ^c	32 768	0.168	0.060	51	60	92.65	15.57	247.32
16	65 536	0.134	0.054	45	60	150.09	20.11	278.20
17	65 536	0.120	0.050	45	60	257.36	30.88	320.04
18	262 144	0.096	0.047	45	60	454.81	41.84	386.75
19	425 288	0.080	0.045	45	60	833.84	66.71	498.36
20	1 048 578	0.070	0.044	45	60	1594.39	111.61	699.25
21	2 097 151	0.063	0.044	45	60	3188.78	200.89	1046.44
22	4 194 304	0.057	0.043	45	60	6090.97	347.19	1692.08
23	8 388 608	0.053	0.043	45	60	12 181.95	645.64	5563.88
24 ^d	3 × 10 ⁸	0.025	0.030	45	60	—	3871.80	

^a From Yeh and Schum (1980).^b Renumbered from original reference so that trachea is generation 0.^c Terminal bronchioles.^d Alveoli.*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.

A.3.3. The Oral Cavity

(A20) Nasal breathing offers better conditioning and cleaning of inspired air than oral breathing. Therefore, oral breathing tends to provide maximum entry for airborne irritants into the lungs. The mouth is also an auxiliary route of entry for inspired air (Fig. A.1) at elevated respiratory rates (e.g. during exercise), or if the nasal passages are obstructed. The mouth consists of an outer, smaller portion, the vestibule, and an inner, larger part, the oral cavity proper. The vestibule is a slit-like space, bounded externally by the lips and cheeks, and internally by the gums and teeth, which communicates with the exterior by the oral fissure. The oral cavity proper is bounded laterally and anteriorly by the alveolar arches, the teeth, and the gums; posteriorly, it communicates with the pharynx via the oropharyngeal isthmus, between the palatoglossal folds. The roof consists of the hard and soft palate; the greater part of the floor is formed by the anterior region of the tongue. The remainder is formed by the reflexion of the mucous membrane from the sides and undersurface of the tongue, extending to the gums on the inner surface of the mandible.

(A21) This mucous membrane is continuous with the skin at the free margins of the lips and with the mucous lining of the oropharynx at the oropharyngeal isthmus. The oral surface consists of stratified squamous epithelium, which is cornified at only a few

Table A.1D. Adult tracheobronchial airway model.^a Model applies to a person 18 y of age, 175 cm tall, with a 70-kg body mass

Structure	Adult lung model—version A					
	Generation, z	l (mm)	d (mm)	θ^b	ϕ^c	$\sum V$ (mL ^d)
Trachea	0	89.0	17.7	0	0	22
	1	38.3	13.0	36	20	32
Bronchi	2	14.7	9.1	35	31	36
	3	10.5	6.7	28	43	39
	4	8.0	4.0	35	39	40
	5	7.0	3.1	39	39	42
	6	4.9	2.7	34	40	44
	7	3.6	2.2	48	36	46
Bronchioles	8	3.3	1.8	53	39	48
	9	3.0	1.5	54	45	51
	10	2.7	1.2	51	43	54
	11	2.5	1.0	46	45	58
	12	2.2	0.82	47	45	62
	13	2.0	0.68	48	45	68
	14	1.8	0.55	52	45	75
Terminal bronchiole	15	1.7	0.46	45	45	85

^a From Phalen *et al.* (1985).

^b θ (in degrees), branching angles are assumed to be independent of age.

^c ϕ (in degrees), for gravity angle, the values of Yeh and Schum (1980) are used to generation 13, and 45° is assumed thereafter.

^d Cumulative volume, assuming each airway gives rise to two daughters.

l = airway segment length, d = segment diameter, $\sum V$ = cumulative volume.

locations (the gums and part of the tongue). Underneath lies a fine connective tissue containing free cells. The mucous membrane, covered with a mucous layer produced by numerous salivary glands located in the submucosal connective tissue, is well supplied with nerves, blood, and lymph vessels.

A.3.4. The Larynx

(A22) The larynx functions as an air passage, as a sphincter, and is used for phonation (Fig. A.1). The larynx contains the vocal cords, which also reduce the air passage to a narrow slit. This is the organ from which sound and speech originate, but it also prevents food particles that have gained access to the larynx from entering the trachea. The larynx is partly covered by mucosa with stratified epithelium and partly with respiratory mucosa.

(A23) The larynx extends from the oropharynx, at the upper border of the epiglottis, to the trachea. It projects ventrally between the great vessels of the neck (common carotid artery, internal jugular vein) and the vagus nerve, and is covered anteriorly by the skin, the fasciae, and the depressor muscles of the hyoid bone. Above, the larynx opens into the hypopharynx, of which it forms the anterior wall. It is surrounded laterally and anteriorly by the various lobes of the thyroid gland. In the adult male the larynx extends somewhat lower in the conducting airways than in the female and the child, and its length (44 mm vs 36 mm) and diameter (36 mm vs 26 mm) are larger in men than in women.

(A24) The skeletal framework of the larynx consists of the hyoid bone and cartilage, connected by ligaments and membranes and moved by a number of muscles (Fig. A.3A).

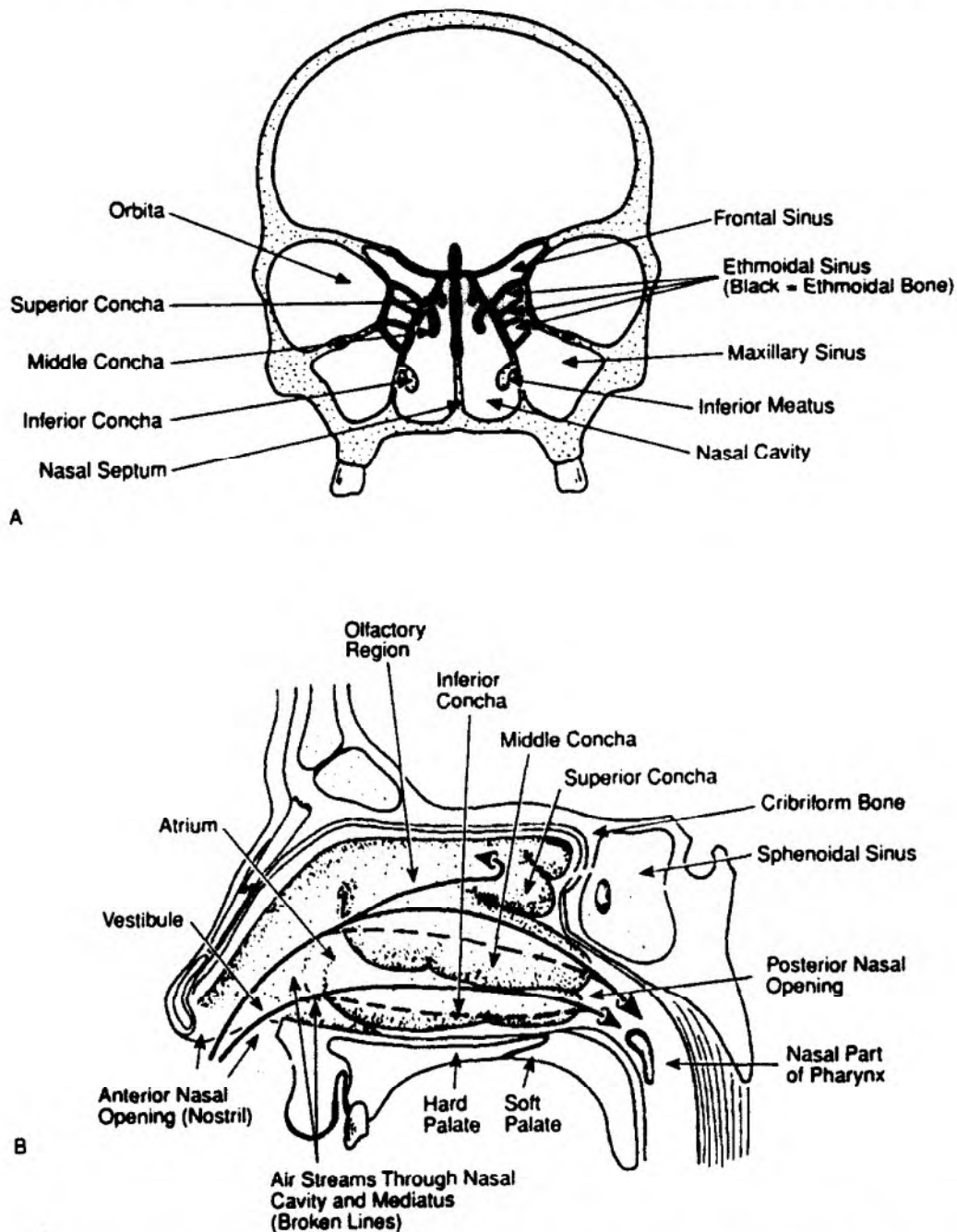


Fig. A.2. The nose. (A) Frontal section. (Redrawn from Faller, © 1988, and reprinted with permission of Georg Thieme Verlag, Stuttgart, Germany.) (B) Lateral wall of right half of the nasal cavity; internal aspect. (Redrawn from Warwick and Williams, © 1973, and reprinted with permission of Longman Group Limited.)

In effect, the larynx is suspended from the hyoid bone and slides up and down within a sleeve of connective tissue whenever the hyoid is raised or lowered. The larynx is lined with a mucous membrane, which forms three pairs of lateral folds: the uppermost, aryepiglottic folds. The middle, ventricular folds; and the lowest, vocal folds. All these folds divide the laryngeal cavity into several compartments. The mucosa of the larynx is continuous with that of the pharynx and the trachea and exhibits features of both. Stratified squamous epithelium extends from above partially into the larynx, over the aryepiglottic folds laterally, and ventrally, where it covers the entire lingual side of the

epiglottis and the upper half of its laryngeal aspect. It is also present at other points of wear, such as over the vocal folds. Elsewhere it gives way to the typical respiratory pseudostratified, ciliated epithelium, coated with a mucous layer that is moved toward the pharynx by the ciliary beat. The subepithelial fine connective tissue is rich in elastic fibres, and contains many free cells and also small lymph follicles. Underneath, the connective tissue becomes denser and connects the mucosa with the skeletal structures and the cross-striated muscles. The laryngeal glands are located here.

(A25) The chief arteries of the larynx are the laryngeal branches of the superior and inferior thyroid arteries. There are two sets of lymph vessels: the superior, above the vocal folds, which drain into the deep cervical lymph nodes near the bifurcation of the common carotid artery; and the inferior, below the vocal folds. They open into several lymph node systems: either the nodes in front of the cricothyroid ligament, or the deep cervical nodes, or the nodes alongside the inferior thyroid artery. The nerves derive from the internal and external branches of the superior laryngeal nerve, the recurrent laryngeal nerve, and the sympathetic nerves.

(A26) Between the vocal folds is the narrow glottal aperture, which is affected by movements of these folds by several small, fine striated muscles (Fig. A.3B). This system is the main structural basis for phonation. Closure of the glottal aperture also prevents penetration of the subsequent airways by foreign particles. Subsequent coughing clears foreign matter from the larynx. An expiratory effort against the closed

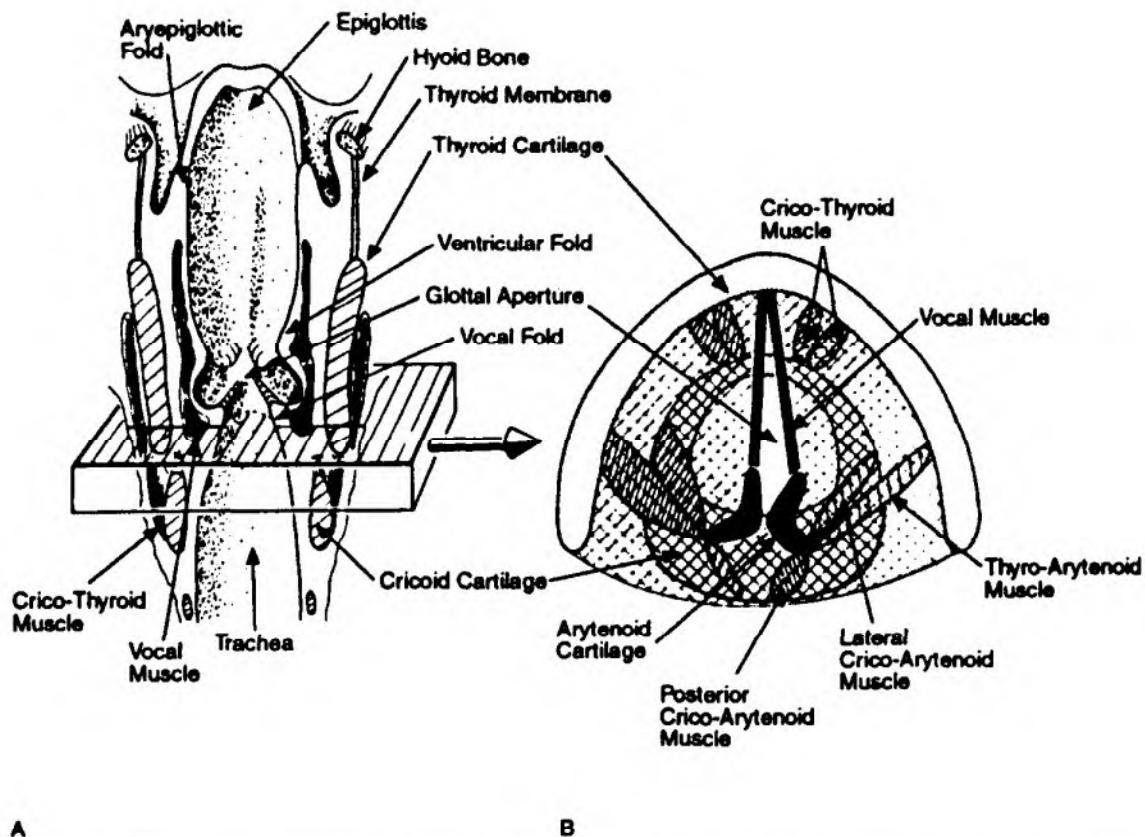


Fig. A.3. The larynx. (A) A coronal section through the larynx and the cranial end of the trachea: anterior half viewed from posterior aspect. (After Warwick and Williams, © 1973, and reprinted with permission of Longman Group Limited.) (B) Schematic representation of larynx skeleton viewed from top. Approximately what is contained in the box in Fig. A.3A. (After Faller, © 1988, and reprinted with permission of Georg Thieme Verlag, Stuttgart, Germany.)

glottis that lasts for about 0.2 s elevates pressure in the abdomen and in the pleural and alveolar spaces to a range of 50–100 mm Hg or more. The sudden opening of the glottis very rapidly forces out the air (at a rate that may exceed 12 L s^{-1}), thus expelling foreign matter (unless it is stuck).

(A27) The epiglottis, which covers the larynx, protects the lower airways during swallowing. Similarly, the upper airways are covered by the soft palate, which is proximate to the posterior pharyngeal wall during contraction of the wall muscles.

A.3.5. *The Trachea*

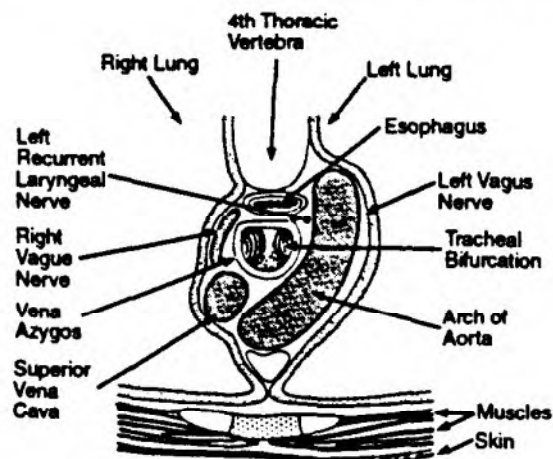
(A28) The trachea, a hollow, cartilaginous, membranous tube, about 12 cm long, originates at the base of the larynx and ends at the carina, where it bifurcates to form the primary bronchus of each lung (Figs A.1 and A.4A). It is very mobile and can extend or shorten very rapidly. It is not quite cylindrical, being flattened posteriorly; its external lateral diameter is about 2 cm in the male, a little less in the female. During childhood, the diameter in millimeters corresponds approximately to the age in years. Some morphometric measurements of the tracheal wall are given in Table A.2.

(A29) The cervical part of the trachea is covered anteriorly with the skin by superficial and deep fasciae, and it is crossed by the jugular arch. Rings two to four are crossed by the isthmus of the thyroid gland; the lower rings are near the remainder of the thymus. Laterally, the trachea is in close contact with the lobes of the thyroid gland and the common carotid artery. The thoracic part of the trachea descends through the mediastinum. Anteriorly, it is near the manubrium sterni, the arch of the aorta and other large vessels, the cardiac plexus of nerves, and some lymph nodes. Posteriorly, it is adjacent to the oesophagus, by which it is separated from the vertebral column. On the right it is near the right lung and certain vessels, among them the superior vena cava and the vagus nerve. On the left, it is situated near the arch of the aorta and other large vessels, as well as the recurrent left laryngeal nerve (Fig. A.4B).

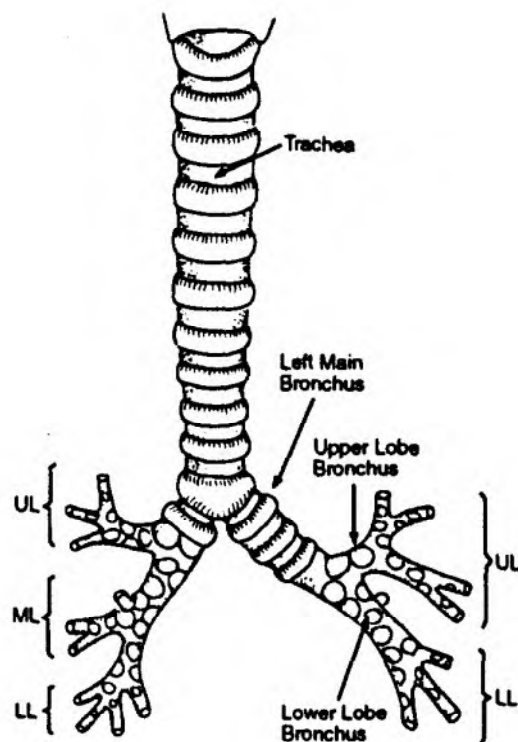
(A30) The trachea would collapse during forceful inspiration, or on inspiration against a closed glottis, were it not reinforced by a skeleton of cartilage embedded in its wall (Fig. A.4C). The wall consists of three major layers: the mucosa covering the air-space, the fibrous submucosa containing the cartilage, and the adventitia with which the trachea is embedded in the surrounding tissue.

(A31) The tracheal mucosa closely resembles that of the nose and nasopharynx and is virtually identical to that in the lower part of the larynx and in the bronchi (Figs A.4D and A.4E). It is lined by pseudostratified, ciliated, columnar epithelium, which is densely populated with ciliated cells but also contains many goblet (mucous) cells. This membrane is very sensitive to irritation and responds by thickening or may even become metaplastic. In addition to ciliated and mucous cells, basal cells populate the mucosa, their nuclei forming a row close to the basement lamina. These cells do not extend to the free surface (Fig. A.4D). Some other types of cells are present but often escape notice completely because their distinguishing features are poorly resolved by ordinary light microscopy. The epithelium is covered by a thick layer of mucus produced by the mucous cells and the tracheal glands. In addition to dead cells, granulocytes, and lymphocytes, it also contains a prominent population of surface macrophages.

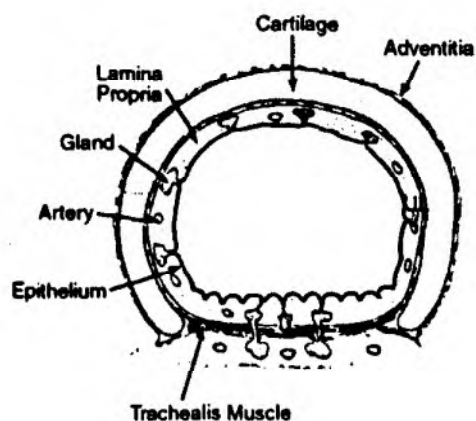
(A32) The highly viscous tracheal mucus above the cilia is moved toward the mouth by the ciliary beat. The cilia are surrounded by a low-viscosity fluid produced by the ciliated cells (Figs A.4D and A.4E).



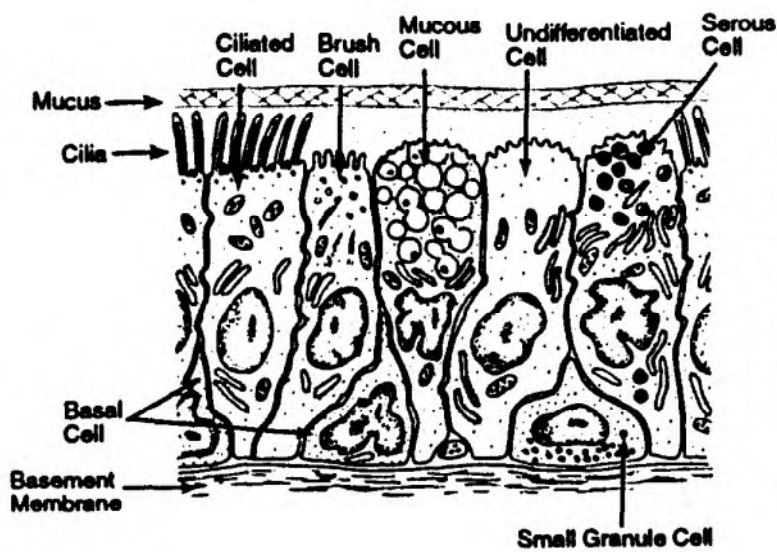
A



B



C



D



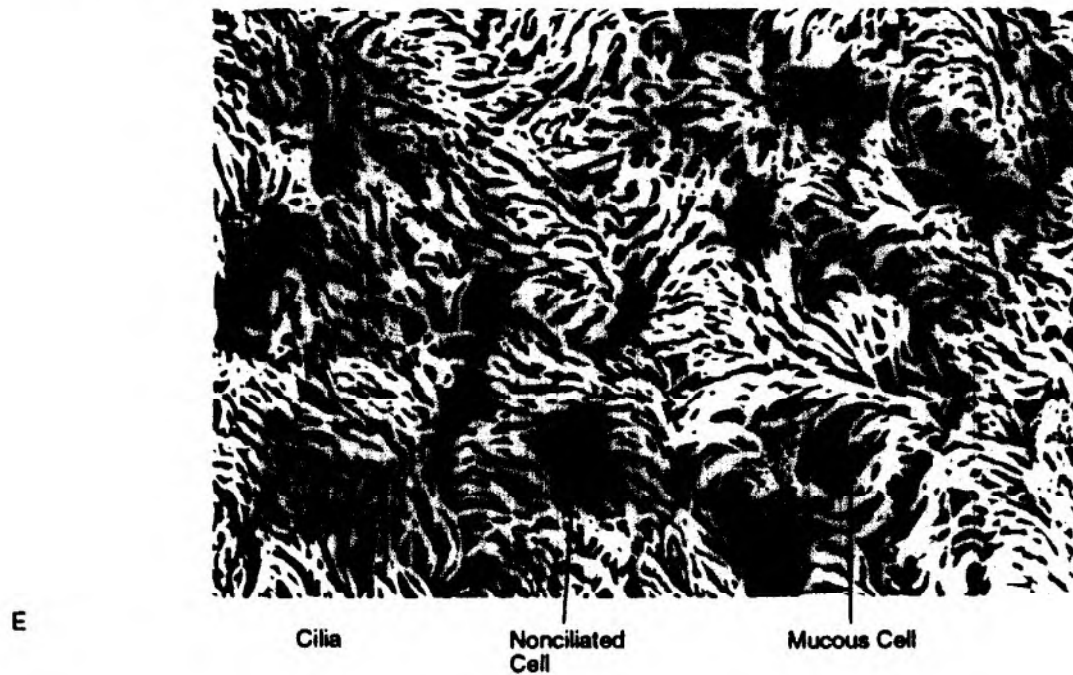


Fig. A.4. The trachea and proximal bronchi. (A) A transverse section through the mediastinum just above the tracheal bifurcation. (Redrawn from Warwick and Williams, © 1973, and reprinted with permission of Longman Group Limited.) (B) Anterior aspect of trachea and proximal bronchial tree (redrawn from Netter, 1979) UL=upper lobe, ML=middle lobe, LL=lower lobe. (C) A transverse section through a tracheal cartilage ring (Netter, 1979). (D) Epithelium of trachea and bronchi. Ciliated and goblet cells (mucous cells) predominate (redrawn from Netter, 1979). Magnification of light micrograph 1300X. (E) Scanning electron micrograph of bronchial wall viewed from top. Magnification is 3100X.

Table A.2. Estimates of dimensions of trachea, bronchus, and bronchiole.* (Giehr, unpublished preliminary data, based on a few samples only.)

	Trachea	Bronchus	Bronchiole
Outer diameter, cm	2.34	0.7	0.073
Inner diameter, cm	1.8	0.44	0.065
Wall thickness, cm	0.27	0.13	0.004
Thickness of:			
Mucus (Gel)	27 μm	5 μm	2 μm
Cilia (Sol)	8 μm	6-8 μm	4-5 μm
Epithelium	60 μm	^b	16 μm
Basement membrane	7 μm	~ 1 μm	~ 1 μm
Lamina propria	67 μm	^b	5 μm
Subepithelial layer	^b	500 μm	20 μm

* Bronchus is approximately generation 4, bronchiole is approximately generation 15, according to Weibel, 1963. See Tables A.3 and A.4. Compare also with Chapter 2.

^b Data are subject to re-evaluation.

(A33) Mucus is a mixture of a great many molecular species, of which mucins are the main component. In the respiratory tract, they are proteoglycans, consisting of a core protein and side-chains of high-molecular-weight mucopolysaccharides (glycosaminoglycans), such as sulphated amino sugar or uronic acid (sulphomucins), or sialic acid (sialomucins).

(A34) The cilia, which move the mucous layer, have a diameter of about $0.25\ \mu\text{m}$ and may vary from $5\text{--}50\ \mu\text{m}$ in length according to position and function. The pattern of movement can be subdivided into two phases: one in which the cilia are extended and move more quickly; another in which the cilia are bent and move more slowly. The first phase produces the greatest movement of mucus; therefore, it is referred to as the effective stroke.

(A35) The direction of the ciliary beat, whether in the nasal or thoracic part of the respiratory tract, is always towards the oropharynx. The beating frequency of tracheal cilia is about 22 Hz at a body temperature of 37°C , diminishing toward the periphery. The flow rate of mucus was found to be about $2\ \text{mm min}^{-1}$ in the distal bronchi, increasing to about $13\ \text{mm min}^{-1}$ in the trachea (Sleigh, 1977).

(A36) Mucus secretion and ciliary beat are independent of one another, but directional transport of mucus by cilia is an interdependent event.

(A37) Mature respiratory epithelium is composed of a variety of cell types, as determined by electron microscopy. The cellular composition changes, particularly when approaching the peripheral airways, and there are also interspecies differences. Among the heterogeneous group of nonciliated epithelial cells, a few are distinguished by the presence of long, straight, rather thick microvilli, typically in wisp-like arrangements. These brush cells are conspicuous in the tracheae of rats but are not often seen in other species. Their function is debated; they may act as receptor cells. Other nonciliated cells are immature in their structural composition. Because they are believed to develop and differentiate into mature epithelial cells of different types, they are called indifferent cells. Finally, there is another kind of small basal cell, much less frequently found, that is characterised by a cytoplasm filled with small, dense-core granules. These cells are therefore called small-granule or Kulchitsky cells and constitute a heterogeneous population of neuroendocrine cells. They are generally characterised by the ability to take up amine precursors and store them in cytoplasmic granules. They belong to the amine precursor uptake and decarboxylation (APUD) system. Occasionally, they are found in close association with pulmonary nerves; they are mostly solitary and are sparsely distributed along the intrapulmonary and extrapulmonary airways from the trachea to the alveolar ducts. They may, however, occur as clusters in the upper tracheal epithelium, close to the larynx, when they are called neuroepithelial bodies (Sorokin *et al.*, 1983). The small-granule cells are difficult to see on routine microscopic slides; with special staining methods, three different types can be distinguished in the human respiratory tract. A variety of other cell types has been described in the airway of animal lungs (Plopper *et al.*, 1988; St. George *et al.*, 1988).

(A38) Intraepithelial nerve processes may also be found in the trachea. In addition, the excretory ducts of the tracheal glands open into the tracheal lumen through the epithelium (Figs A.4C and A.5). In humans, these glands produce mixed mucus with serous crescents. Around the trachea they generally exit into the submucosa; some secretory portions may even be found in the adventitia; usually they are found in the intercartilage compartments.

(A39) The fine subepithelial connective tissue, the lamina propria, contains interwoven collagenous and, most abundantly, elastic fibres, as well as many small blood and lymph vessels, and the usual fixed and free cells of connective tissue. The elastic fibres run in a predominantly longitudinal direction. The submucosa has relatively fewer elastic fibres and more collagen than the lamina propria. It contains the distributing

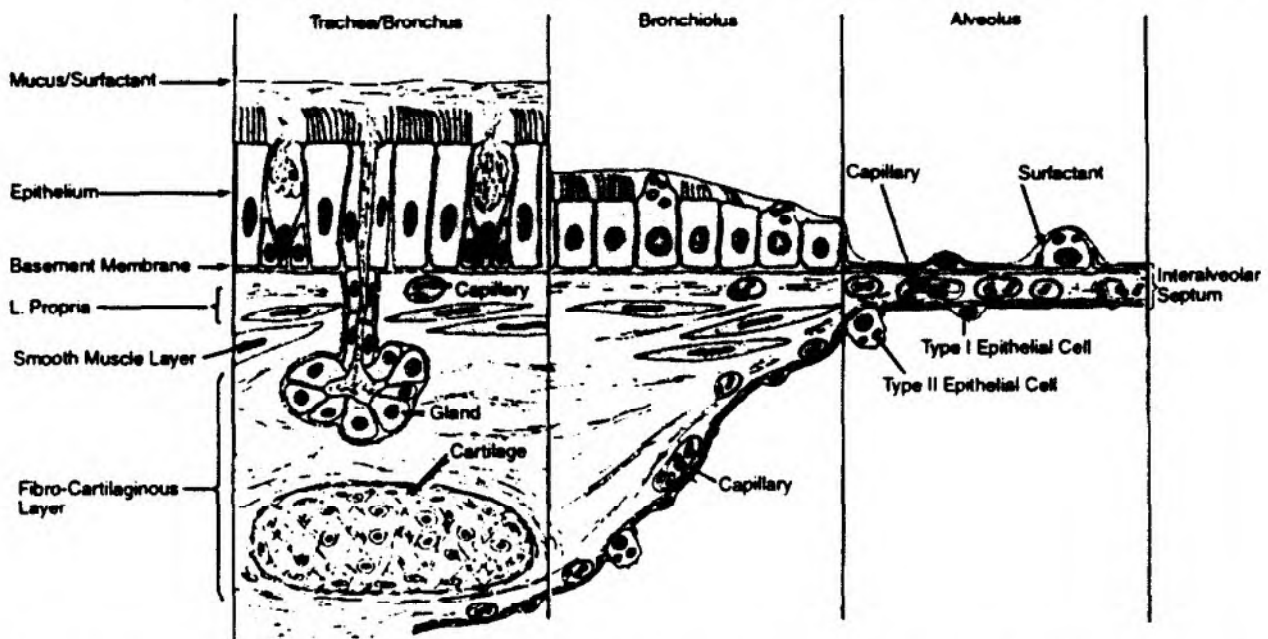


Fig. A.5. The wall structure (see also Figs A.4D and A.11C). (From Burri and Weibel, © 1973, and reprinted with permission of Hans Huber Publishers.)

vessels and lymphatics as well as the nerves of the tracheal wall. Its connective tissue surrounds the 16 to 20 C-shaped hyaline cartilage rings, which encircle the trachea on its ventral and lateral aspects. The incomplete cartilage rings are separated by spaces that are bridged by fibroelastic tissue. The posterior wall, adjacent to the oesophagus, is devoid of cartilage. Instead, a thick layer of smooth-muscle bundles runs transversely and is inserted into the dense, fibroelastic connective tissue surrounding the cartilage. The adventitia consists of loose connective tissue containing the larger vessels and nerves; the lymph nodes are attached to it (Fig. A.6A).

(A40) The arteries for the trachea derive mainly from the inferior thyroid. The lymphatics drain into the lymph nodes that accompany the trachea (Fig. A.6B). The nerves supplying the trachea arise from the recurrent branch of the vagus nerve and from the sympathetic chain, which contains small ganglia.

A.3.6. The Bronchi

(A41) The trachea divides into two main extrapulmonary branches called the primary (main or principal) bronchi (Figs A.1, A.4A and A.4B), which arise in the mediastinum at the bifurcation of the trachea (Fig. A.4A). They are smaller in diameter (about 1.2 cm) than the trachea and also much shorter. The right one is only about 2.5 cm long, a little wider than the left, and more vertically oriented; the left is about 5 cm long, a little narrower than the right, and is more transverse. Together with the main pulmonary vessels and nerves they enter the hilum of the respective lung.

(A42) The lungs occupy the thoracic cavity, which is smaller on the left than on the right owing to the position of the heart. Consequently, the right lung is larger than the left and is subdivided into a greater number of lobes: three in the right lung and two in the left. The lobes are separated from each other but are confluent at the hilum. They are covered by the pleura, a connective tissue layer of collagen and elastic fibres, and lined by squamous epithelium (mesothelium). Just as the lungs are subdivided into

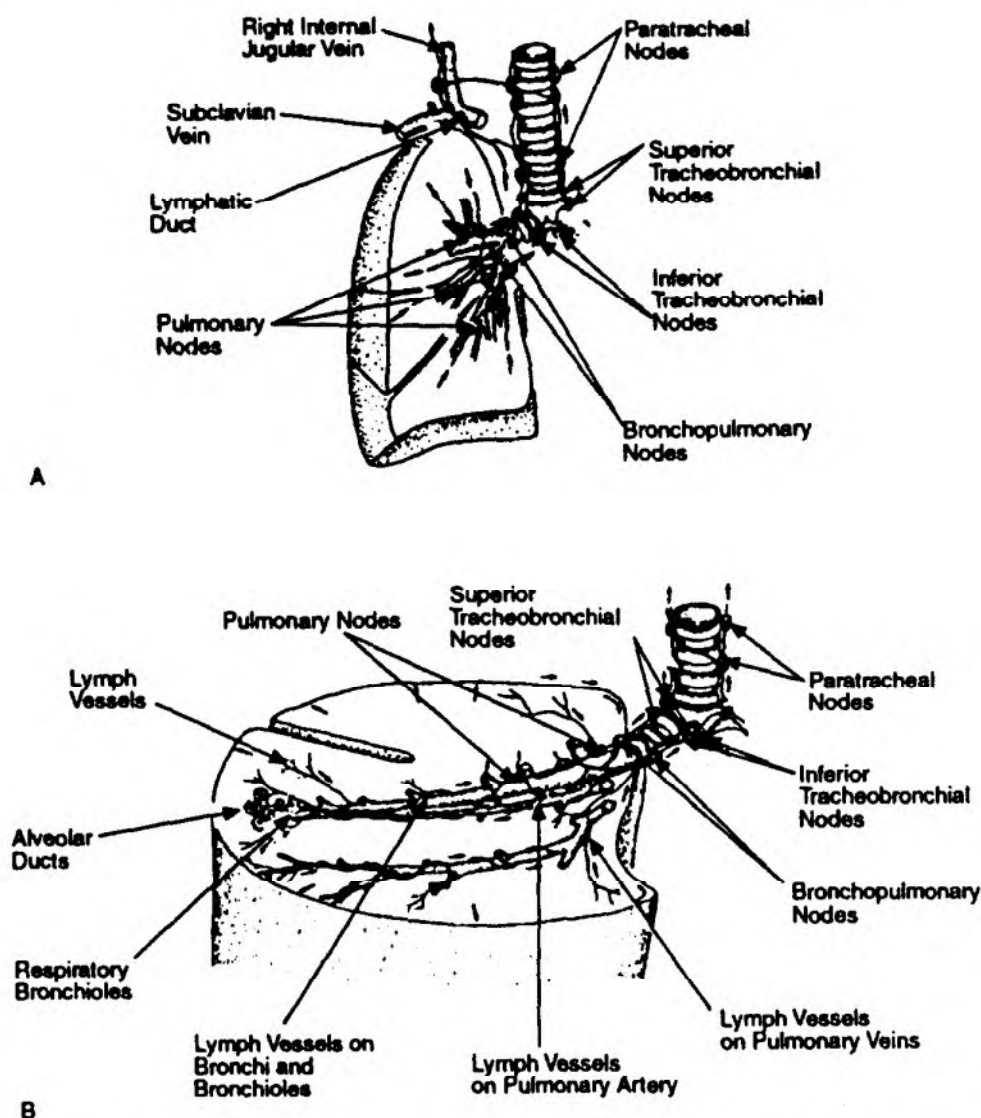


Fig. A.6. The pulmonary lymphatic system (redrawn from Netter, 1979). (A) Routes of lymphatic drainage; central aspects. (B) Distribution of lymphatics and routes of drainage.

lobes, the lobes are subdivided into smaller units (bronchopulmonary segments), which are incompletely separated from each other by connective tissue sheets originating from the pleura. The right lung is made up of ten such segments: three in the superior lobe, two in the middle, and five in the inferior lobe; the left lung can be subdivided into eight segments: four in the superior and four in the inferior lobe (Fig. A.7). Deviations from this pattern may occur. Likewise, the primary bronchi give rise to the lobar bronchi, three in the right lung and two in the left lung, which again divide into the segmental bronchi, in the same number and distribution as the above-mentioned bronchopulmonary segments. Clinical interest in the branching pattern of the human lungs extends to the level of bronchopulmonary segments. Peripherally, the airways continue this dichotomous branching pattern.

(A43) Segmental bronchi, branching off the lobar bronchi, lie in the centre of the segments and subdivide further. In the human lung, the bronchi divide in a dichotomous

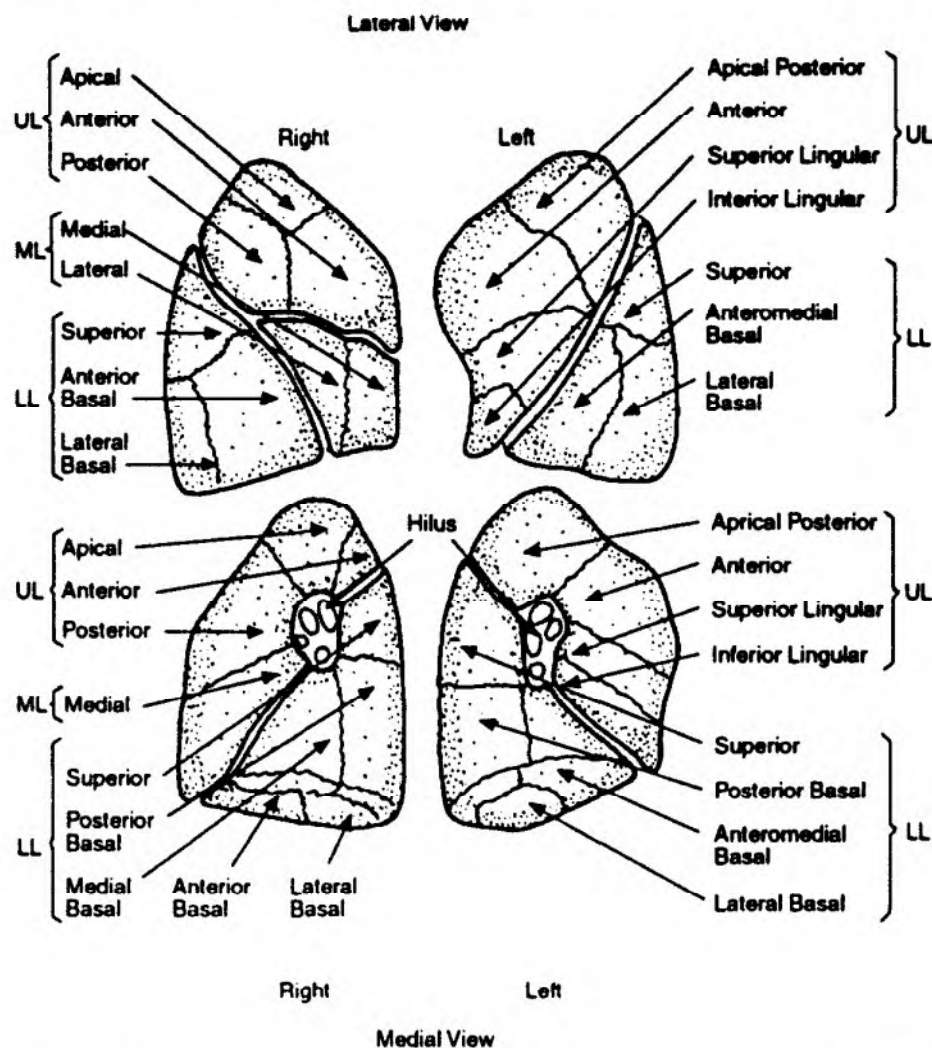


Fig. A.7. Pulmonary lobes and segments (redrawn from Netter, 1979). UL = upper lobe, ML = middle lobe, LL = lower lobe.

manner of relatively little irregularity into daughter branches that become progressively reduced in diameter. The two daughter branches often differ considerably in their dimensions as well as in their branching angles. This branching pattern has been described in detail by Weibel (1963), Horsfield and Cumming (1968), Yeh and Schum (1980), and Phalen *et al.* (1985).

(A44) Since the airways in the human lung branch dichotomously, the number in any generation z is:

$$N = 2^z, \quad (\text{A.1})$$

as long as all preceding generations are complete, i.e. as long as every generation divides into two branches. There are, however, exceptions, where trichotomy occurs, like, for example, the apparent division of the right upper-lobe bronchus into three segmental bronchi. Morphometric analysis reveals that the whole airway tree consists, on the average, of 23 generations. Because of the irregularity in the dichotomous branching pattern the airways may, however, end somewhere between the 15th and the 30th generation (Weibel, 1963).

(A45) The dimensions and geometry of the airway branches gradually change as they penetrate deeper into the lungs. The bifurcations of the bronchi are sharp (Phalen and Oldham, 1983).

(A46) The average diameter of the branches decreases with increasing orders of generations. If, for simplicity, we consider the regular dichotomy model of Weibel (1963), the diameters are assumed to follow a straight line plotted semilogarithmically. The bronchial diameter is reduced from 12.2–1.3 mm (1st to 10th generation), the greatest reduction occurring in the first few generations (Fig. A.8). It is assumed that they decrease by the exponential function:

$$d_z = d_0 \times 2^{-z/3}, \quad (\text{A.2})$$

where d_z and d_0 are the diameters in generations z and 0, respectively. This relation is known to reflect an optimal design for mass flow of air with minimal energy loss.

(A47) The average length of the branches also decreases at a constant rate with increasing orders of generations, with the exception of the 3rd generation branches, which are much shorter. Bronchial length is reduced from 47.6–4.6 mm (1st to 10th generation), the greatest reduction occurring in the first few generations. Since the diameter and length changes are not uniform, there is also a length-to-diameter ratio

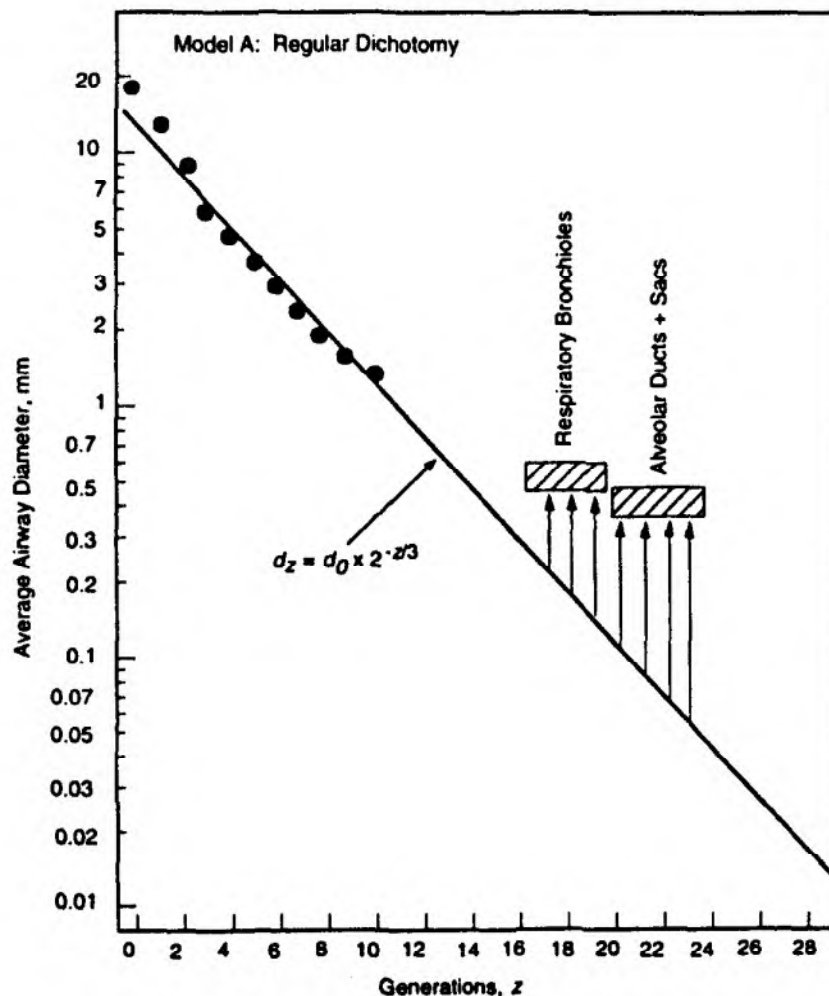


Fig. A.8. Regular dichotomy model. (From Weibel, 1984b.)

change (3.1 ± 0.6 [SD]), on the average, over all generations of this compartment. The exception, generation 3, has a value of 1.4, far from this average. Values for cumulative airway volume in this compartment, including trachea, vary from less than 50 cm^3 to more than 100 cm^3 (Tables A.1A, A.1C, A.1D); a central value for its total surface area is about 300 cm^2 .

(A48) Morphometric values for the bronchial wall, including values for infants and children, are given in Tables A.2 and A.3. The bronchi are covered by respiratory mucosa. The mucous sheet on top of the respiratory epithelium is moved towards the mouth by the ciliary beat.

Table A.3. Estimated bronchial dimensions (μm) of children, infants, and one adult. (Gehr, unpublished preliminary data, based on a few randomly selected samples only)

Age	39 y	5 y	18 mo	17 mo	16 mo	6 mo	1 mo	26 d
Body weight, W (kg)	85.0	18.0	12.5	10.0	8.8	8.2	4.1	3.0
Sex	M	M	M	F	F	M	M	M
Outer diameter	7000	1910	3100	3820	4000	2490	1600	2670
Inner diameter	4400	1380	1690	2710	2000	889	1020	1030
Wall thickness	1300	367	711	511	978	800	289	830
Cilia length	8.0	5.3	5.3	5.3	6.7	6.7	8.0	6.7
Epithelium height	33	35	27	35	27	35	34	35
Connective tissue, musculature thickness	1259	227	679	471	944	758	247	788
Ratio outer/inner diameter, R^a	1.59	1.38	1.83	1.41	2.0	2.8	1.57	2.59

^a Allometric equation for ratio of outer to inner diameter, R , is:

$$R = 2.4 \cdot W^{-0.12},$$

$r = -0.44$; r : correlation coefficient.

(A49) Where the bronchi enter the lungs (lobar bronchi), the cartilage rings disappear and are replaced by irregularly shaped, hyaline cartilage plates, which are arranged around the entire circumference of the bronchi (Figs A.5, A.9A and A.9B). As a result, the intrapulmonary airways are cylindrical rather than flattened on one side, as are the trachea and the principal (extrapulmonary) bronchi. As one follows the air passages peripherally, the cartilage plates become smaller, elastic, and irregularly distributed around the tube. A muscular layer completely surrounds the bronchus but does not form a closed ring.

(A50) The bronchial lumen is lined by respiratory mucosa very similar to and continuous with that in the trachea, consisting of respiratory epithelium covered by a mucous layer and a lamina propria (Figs A.4D, A.5, A.9A and A.9B). The epithelium is separated from the subepithelial connective tissue by a prominent basement membrane. Because of contraction of the attached smooth muscle layer, the mucosa shows marked longitudinal folding on histologic sections. Numerous elastic fibres of the lamina propria are intimately associated with the cells of the smooth muscle layer. Both components play an important part in changes in lung volume during respiration. The cartilage plates are embedded in a layer of collagenous fibrous connective tissue, with numerous mucoserous glands located between these plates (Fig. A.9B).

(A51) The outermost adventitia consists of loose connective tissue that also contains many elastic fibres and is continuous with the surrounding pulmonary tissue and with that accompanying the large vessels. Vessels of the systemic circulation (bronchial arteries), the lymphatics, and nerves are contained in this layer; lymphatic tissue is

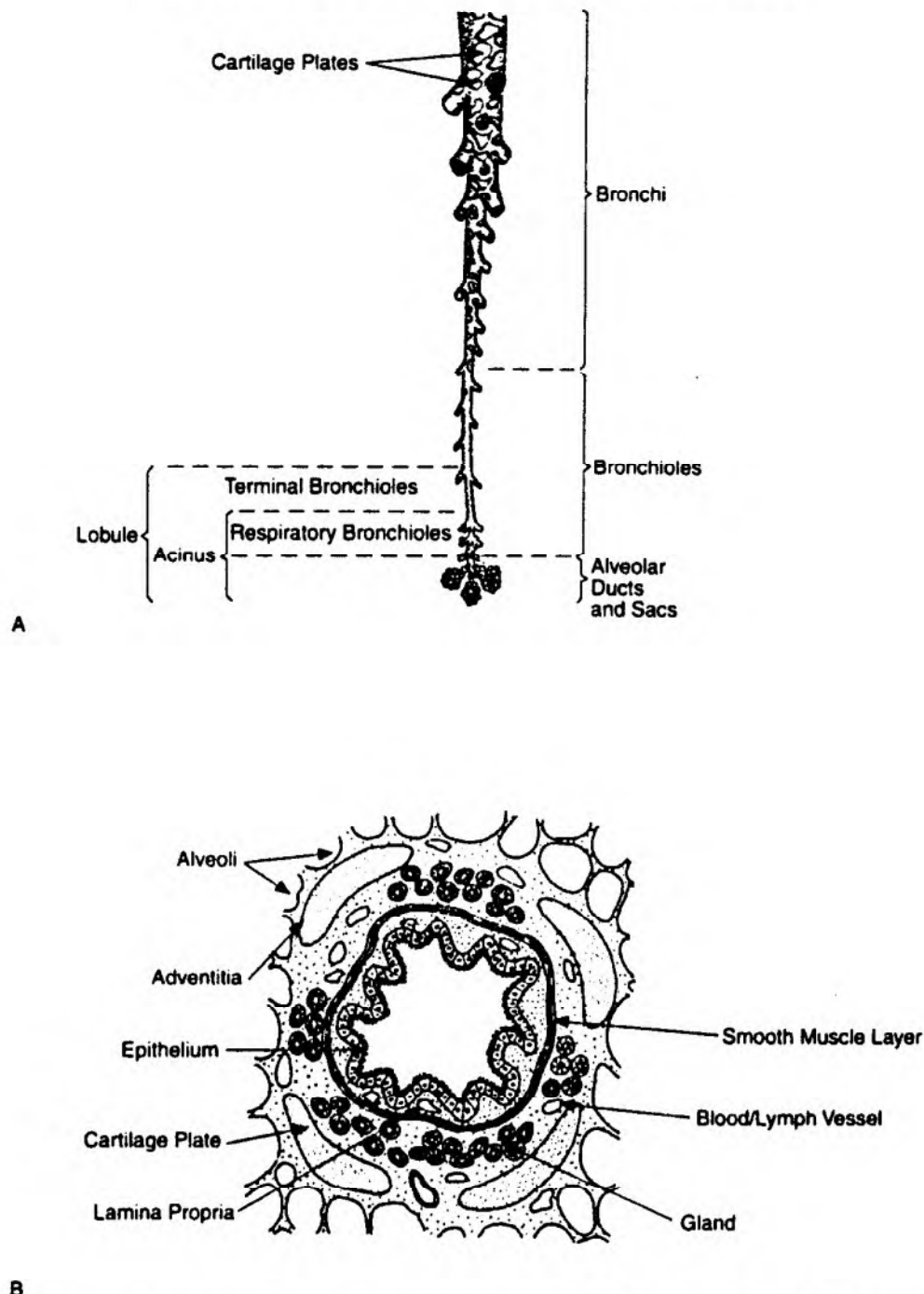


Fig. A.9. Subdivision and structure of intrapulmonary airways (redrawn from Netter, 1979). (A) Subdivision distal of segmental bronchi. (B) A transverse section through a medium-sized bronchus.

diffused throughout the mucosa and the adventitia. Lymph nodes can be found in the adventitia of larger bronchi, particularly at bifurcations (Fig. A.6B).

(A52) The bronchi are supplied by the pulmonary arteries (broncho-arterial units). The venules arise from the capillaries of the pleura and of interalveolar septa and portions of the alveolar duct. They are contained in the interlobular and intersegmental connective tissue, are independent of the arteries, and join to form the pulmonary veins (Fig. A.10). In the peribronchial and periarterial connective tissue are the bronchial

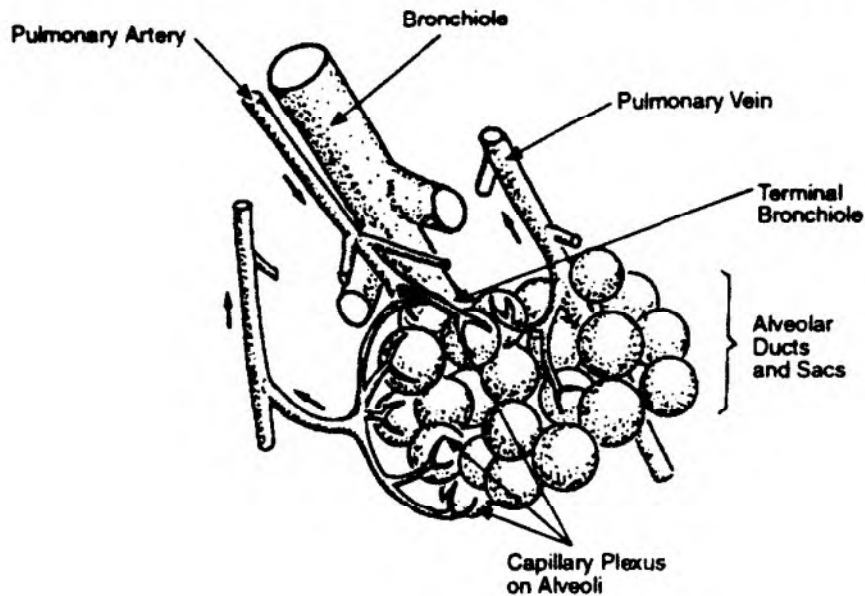


Fig. A.10. Intrapulmonary blood circulation (redrawn from Netter, 1979).

arteries and veins, the vessels of the systemic circulation. Except in the hilar region, their blood is returned by pulmonary veins. There are also arterial-venous anastomoses. The bronchial vessels do not extend beyond the bronchial tree and are much smaller than the pulmonary vessels; they arise from the aorta or from the intercostal arteries.

(A53) There are two main divisions of lymphatics, one in the pleura, the other in the pulmonary tissue. They communicate infrequently and drain into the lymph nodes at the hilum (Fig. A.6B). The relevant nerves arise from the pulmonary plexus at the root of the lung; it is formed by branches of the vagal and thoracic sympathetic ganglia (Fig. A.11).

A.3.7. *The Bronchioles*

(A54) When the diameter of the airway approaches 1 mm, the elastic cartilage plates disappear from the wall (which has gradually become thinner), and the airways are now called bronchioles (Figs A.9A and A.12A), generally airway generations 9 through 15. Gradually, other bronchial characteristics are lost, and new ones are acquired. The bronchioles are airways without cartilage, mucoserous glands, or goblet cells in the epithelium (Figs A.5, A.12B). The epithelium, which is now much thinner, is columnar to cuboidal, with a unique type of secretory cell (the Clara cells) replacing the mucous cell (Figs A.12B–D). The muscularis is relatively thicker than that of the bronchi and is also discontinuous. The attached thin connective-tissue layer consists of a fine network of interwoven collagenous and elastic fibres, which continue into the interalveolar septa. It contains small lymphatics and fine nerves. The bronchioles are accompanied by branches of the pulmonary artery. Two major cell types, ciliated and nonciliated, line the bronchioles. In the larger branches, most cells are ciliated, but the nonciliated cells usually dominate in the smaller branches. The major nonciliated cell type, the Clara cell, gives the epithelium its special character. The tall, dome-shaped Clara cells protrude into the bronchiolar lumen to the tips of the cilia (Fig. A.12C), hence the bronchiolar epithelium has a scalloped contour in sections. Clara cells are especially prominent in the terminal bronchioles. There are marked interspecies variations in the structure of

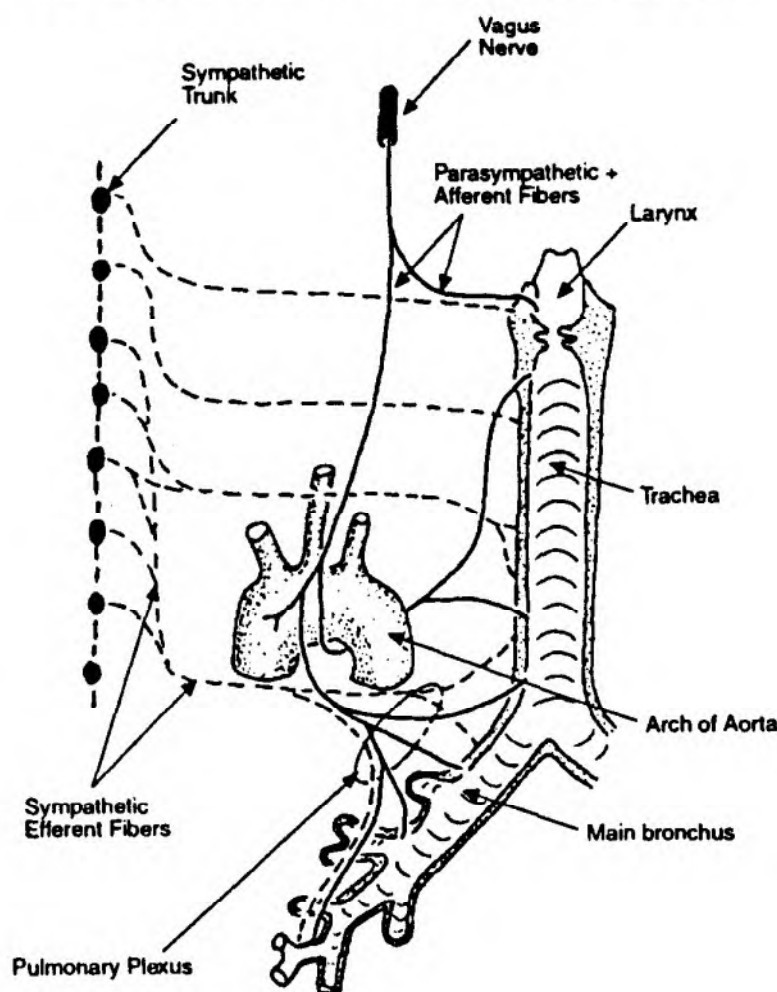


Fig. A.11. Innervation of the tracheobronchial tree (redrawn from Netter, 1979). Vagus nerve: mixed parasympathetic efferent motor fibres to smooth muscles and glands; afferent fibres from arteries and airway mucosa. Sympathetic trunk: sympathetic efferent fibres to arterial and airway smooth muscles.

Clara cells (Plopper *et al.*, 1988; St George *et al.*, 1988; Plopper and Dungworth, 1987). According to models in Tables A.1A-D, the diameters of bronchioles decrease from approximately 2 mm to 0.5 mm, and their length from approximately 5 mm to 1.5 mm. The bifurcations of the bronchioles are relatively blunt. The cumulative airway volume of these generations is about 50 cm³, and their surface area totals about 0.24 m². The bronchioles are covered by respiratory mucosa, under which lies the epithelium, which moves the mucous layer toward the mouth by the ciliary beat. Morphometric estimates of the bronchiolar wall dimensions, including values for infants and children, are given in Tables A.2 and A.4.

A.3.8. The Gas-Exchange Parenchyma

(A55) The last generation of the terminal bronchioles supplies pulmonary lobules with air (Figs A.1, A.9A, and A.12A). These lobules (about 1 mL in volume) are the structural units of the gas exchange parenchyma and are incompletely separated from each other by interlobular connective-tissue septa. The connective-tissue borders of the peripheral (subpleural) lobules reveal a typical texture on the pleural surface. (See Fig. A.17B.) The functional unit is the acinus, which is supplied with air by the first two

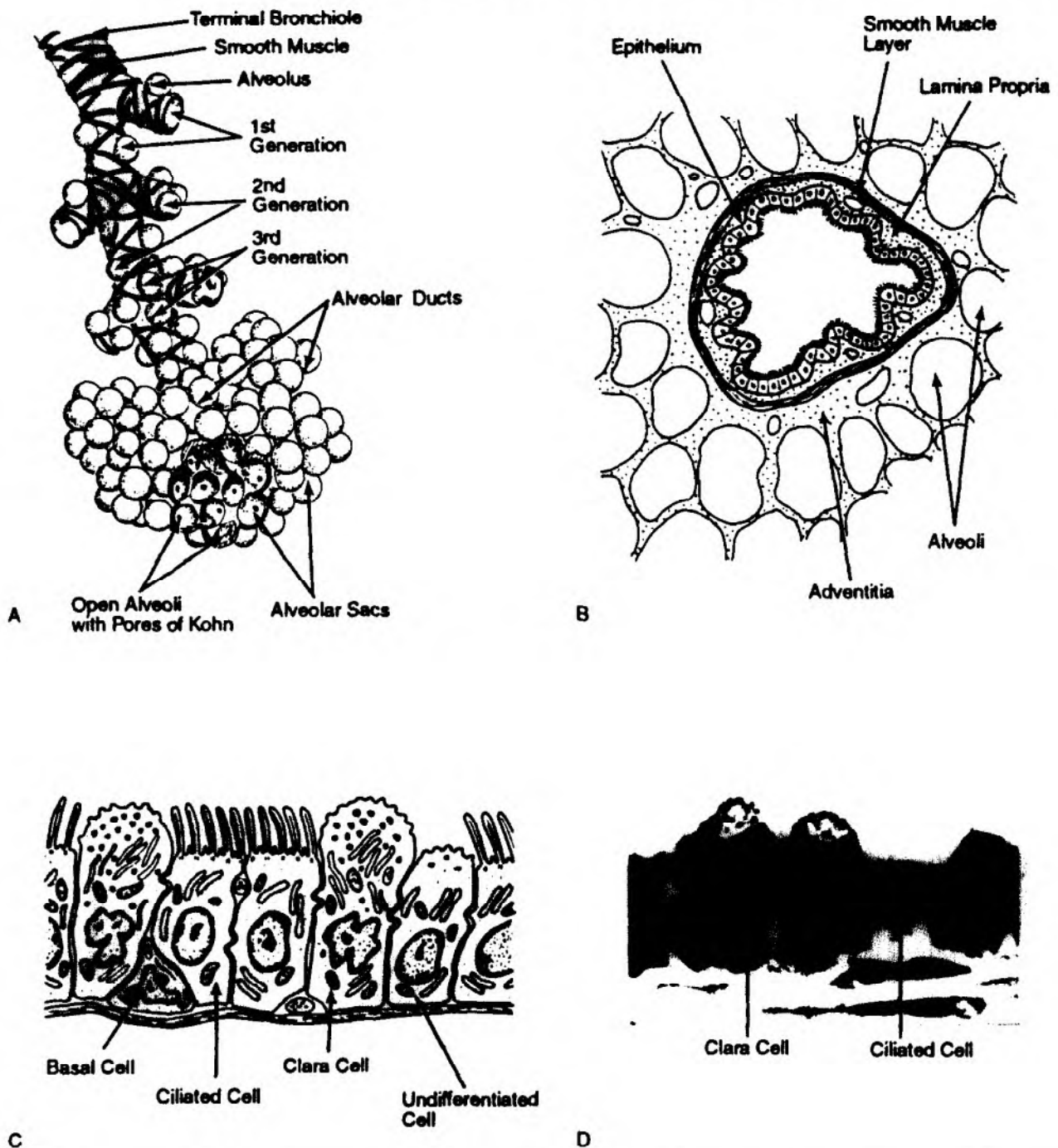


Fig. A.12. The bronchioles (redrawn from Netter, 1979). (A) Distal airways. (B) A transverse section through a bronchiole. (C) Line drawing of epithelium of bronchioli. Ciliated and Clara cells predominate. (D) Light micrograph of bronchiolar epithelium, magnification 1600X.

generations of branches after the terminal bronchioles (the respiratory bronchioles). Hence, one can say that each lobule consists of two acini (Figs A.9A and A.12A).

(A56) The respiratory bronchioles are different from the terminal bronchioles in that they have alveoli apposed to their walls: only a few in their first generation; twice as many, on the average, in their last generation. These alveoli, the first respiratory structures, are responsible for the term "respiratory bronchiole" (Fig. A.13). The average diameter of the respiratory bronchioles and alveolar ducts is only slightly

Table A.4. Estimates of bronchiolar dimensions (in μm) of children, infants, and one adult. (Gehr, unpublished preliminary data, based on a few randomly selected samples only)

Age	39 y	5 y	18 mo	17 mo	16 mo	6 mo	1 mo	26 d
Body weight, W (kg)	85.0	18.0	12.5	10.0	8.8	8.2	4.1	3.0
Sex	M	M	M	F	F	M	M	M
Outer diameter	730	640	800	600	960	853	607	447
Inner diameter	644	573	720	453	760	760	473	367
Wall thickness	43	33	40	53	93	47	67	40
Cilia length	5	5	5	5	5	5	7	7
Epithelium height	16	16	13	13	13	11	21	13
Connective tissue, musculature thickness	22	12	35	75	75	31	39	20
Ratio outer/inner diameter, R^a	1.13	1.12	1.11	1.41	1.26	1.12	1.28	1.22

^a Allometric equation for ratio of outer to inner diameter, R , is:

$$R = 1.3 \cdot W^{-0.03},$$

$r = -0.50$; r : correlation coefficient.

decreased with increasing orders of generations, from 0.54 mm in the 17th generation to 0.41 mm in the 23rd generation, according to the regular dichotomy model of Weibel (1963). When the function of the airway branch changes to include not only air conduction but also gas exchange, Eq. (A.2) can no longer be applied. To optimise the diffusion process, the diameter of this peripheral airway must increase (Fig. A.8). The average length diminishes from 1.4–0.5 mm and, hence, the length-to-diameter ratio decreases from 2.6–1.2 mm. The total volume of the respiratory bronchioles is about 200 mL, and the total surface area about 1 m². The wall structure is similar to that of the last generations of bronchioles, except that there are many fewer ciliated cells in the epithelium. At the alveolar rim the epithelium becomes continuous with the thin alveolar lining. Since this portion of the airways is conductive as well as active in gas exchange, it is called transitory.

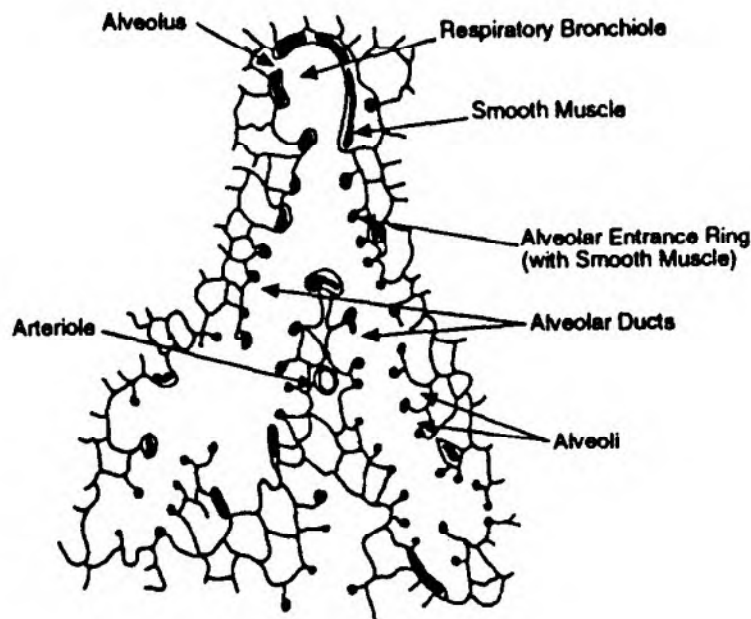


Fig. A.13. Transverse section through a respiratory bronchiole and two alveolar ducts. (Redrawn from Fawcett, 1986, and reprinted with permission of the author.)

(A57) Three generations of alveolar ducts, on the average, follow. Their walls are completely covered with alveoli. Each alveolus is entered through an entrance ring, which is a reinforcement of the interalveolar wall by collagenous and elastic fibres, and, in some species, by smooth-muscle cells. The duct wall, in fact, consists of alveolar entrance rings (Figs A.13 and A.14). The diameter of the alveolar ducts diminishes only slightly; the last generation measures approximately 0.4 mm. The ducts gradually become shorter, their length diminishing from 1–0.6 mm. The last generation, the alveolar sac, is the shortest unit (only 0.5 mm long); the diameter is unchanged, and it ends blindly; terminal alveoli cover the peripheral end of the duct. Since this part of the lung consists of gas-exchange units only, it is called the gas-exchange zone. From the respiratory

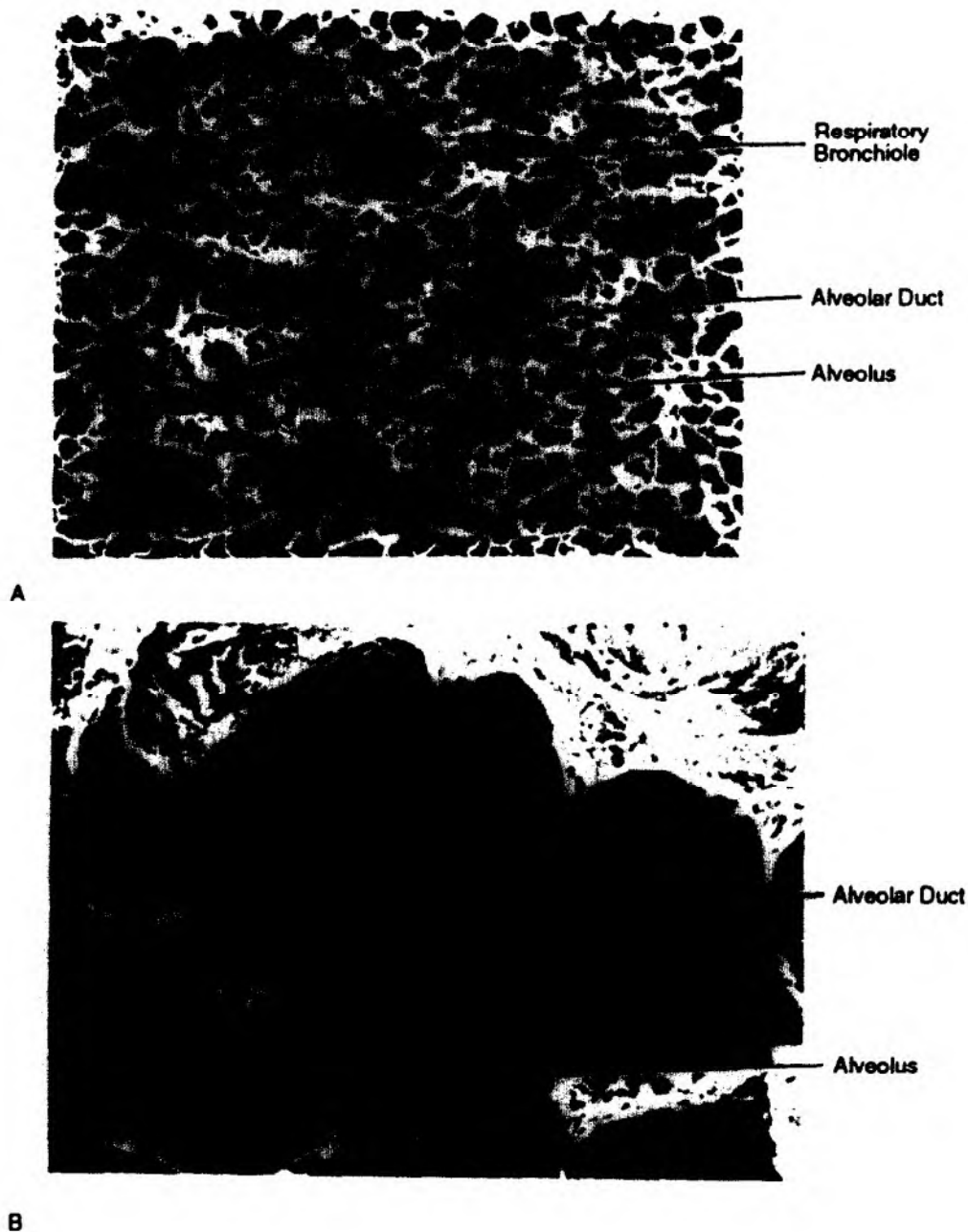


Fig. A.14. Scanning electron micrographs of gas-exchange parenchyma. (From Gehr *et al.*, © 1978a, and reprinted with permission of Elsevier Science Publishers.) (A) Respiratory bronchiole surrounded by alveoli. Magnification 80X. (B) Alveolar duct with adjacent alveoli. Magnification 240X.

bronchioles the pulmonary arteries divide; branches pass to each alveolar duct and are then distributed, in a capillary network, over all alveoli that communicate with these ducts. The venules arise from these capillaries (Fig. A.10). The interstitial fluid is drained along the interalveolar septa into the pleural, interlobular and peribronchiolar connective tissue, where it is taken up by the lymphatics. No nerves have yet been observed in interalveolar septa (Fig. A.15).

(A58) The lungs are designed to establish optimal conditions for the exchange of oxygen and carbon dioxide. Over 80% of the lung tissue of a healthy adult human is composed of gas-exchange parenchyma, which consists of about 300 million alveoli, arranged concentrically around alveolar ducts and sacs (Figs A.13, A.14A and A.14B). These densely packed alveoli provide a gas-exchange surface of 140 m² (Gehr *et al.*, 1978a), which is about the size of a tennis court (Table A.5). The air volume of the pure gas-exchange zone averages approximately 4500 mL at maximum inflation.

(A59) The structural basis for gas exchange is the alveolar wall, or, since adjacent alveoli have a common wall, the interalveolar septum (Figs A.5 and A.15A through A.15D). Here air and blood come into close contact and are separated by an air-blood or tissue barrier as thin as 2 µm, on average. Over large areas the thickness is < 1 µm (Table A.5), which is only about 1/50 as thick as a piece of airmail paper. Nevertheless, this barrier is composed of three layers: the epithelium, interstitium, and endothelium (Figs A.15C,D). Oxygen crosses this thin barrier and reaches the erythrocytes, which pass close by and frequently touch the endothelium¹. The capillaries meander around a connective-tissue frame, exposing their thin air-blood barrier to the alveolar air on either side and, thus, accumulating oxygen from two adjacent alveoli. About 200 mL of blood flows through these capillaries (Gehr *et al.*, 1978a). The techniques used to obtain these estimates, as well as several other structural parameters, have been described in detail (Gehr and Crapo, 1988; Weibel, 1979). A short summary of the stereological procedures is given in the following few paragraphs.

(A60) The delicate structures of the gas-exchange parenchyma are fixed *in situ* by instilling glutaraldehyde into the trachea (Weibel, 1984a; Gehr and Crapo, 1988). The advantage of this fixation method is that all alveoli are expanded. It is also simple and reliable, and reveals highly reproducible results if instillation pressure (25 cm H₂O above chest), osmolarity (350 mOsm), and pH (7.4) of the fixative are the same each time.

(A61) In a second step, the fixed lung is removed from the chest, and its volume is determined by water displacement. Subsequently, tissue blocks are sampled statistically, and further processed for light and electron microscopic analysis.

(A62) In the following step, the actual measurements are performed on random sections, applying stereological methods. These methods permit estimation of volumes and surfaces by counting points and intersections of a test system made up of test points and test lines that are superimposed on sections and micrographs. The ratio of points falling on a component, e.g. capillaries, P_c , to the number of points falling on the gas-exchange parenchyma, P_p , provides an estimate of the volume density of capillaries in the volume of gas-exchange parenchyma, $V_{V,c,p}$:

$$V_{V,c,p} = \frac{P_c}{P_p}. \quad (\text{A.3})$$

¹ Ninety-three percent of the alveolar surface is covered by squamous type I cells; seven percent is covered by cuboidal, surfactant-producing type II cells (Tables 1 and 7 in Crapo *et al.*, 1982).

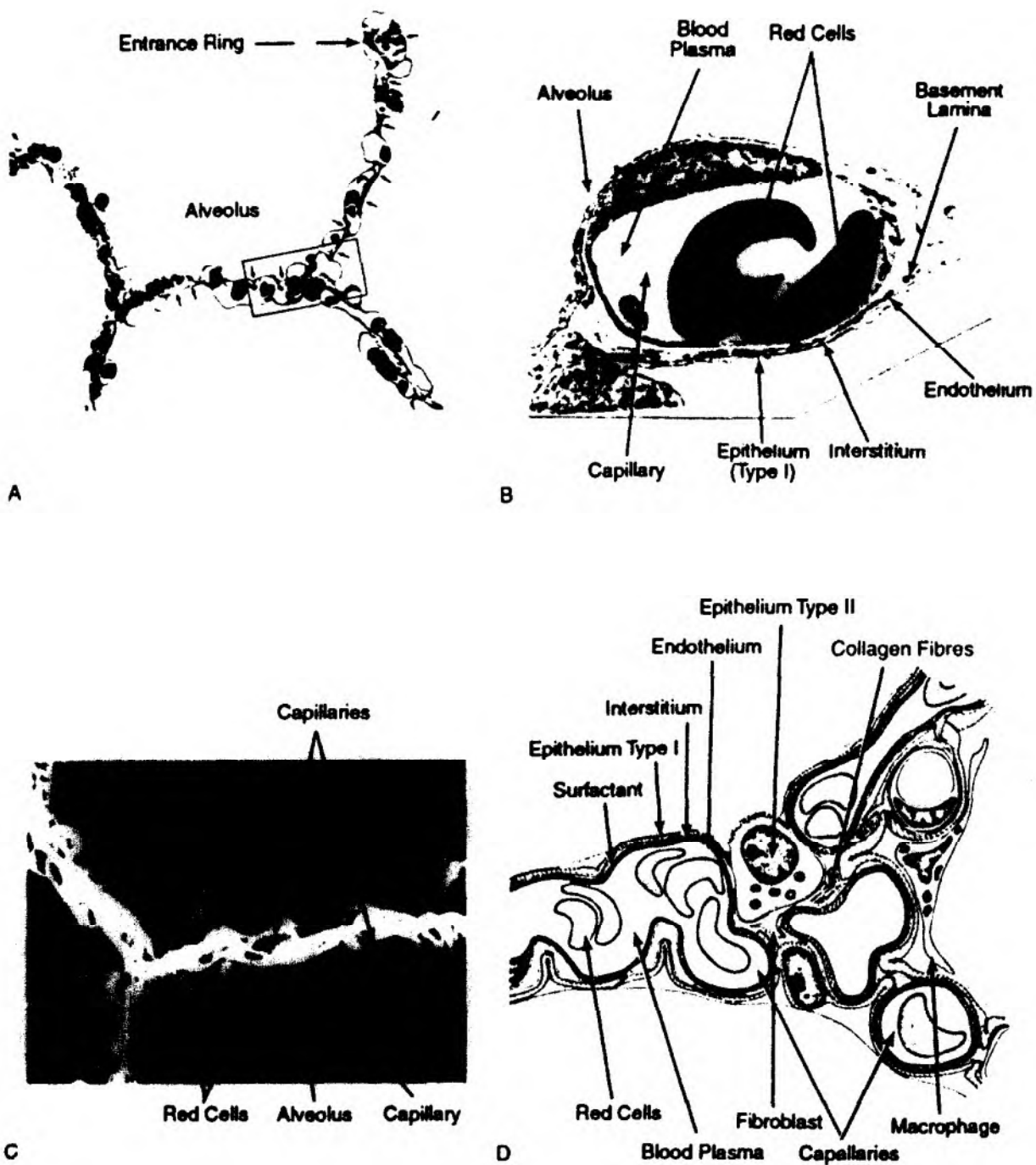


Fig. A.15. Gas-exchange apparatus; interalveolar septa. (A) Transmission electron micrograph of interalveolar septa with capillaries meandering around connective tissue frame (arrows). Magnification 2200X. (From Gehr *et al.*, © 1978a, and reprinted with permission of Elsevier Science Publishers.) (B) Transmission electron micrograph representing a cross-section through a capillary of an interalveolar septum. Magnification 530X. (From Gehr *et al.*, © 1978a, and reprinted with permission of Elsevier Science Publishers.) (C) Scanning electron micrograph of interalveolar septa, showing both a section and a surface aspect. Magnification 5100X. (D) Schematic drawing of a section through an interalveolar septum; it is idealised and shows all septal components. Represents, approximately, rectangle in Fig. A.15C. Magnification approximately 450X.

Table A.5. Mean values of morphometric parameters of structures of the pulmonary gas-exchange parenchyma for man and some other mammalian species

	Horse	Man	Dog	Rabbit	Rat	Mouse
Number of individuals	2	8	11	6	8	5
Body mass, kg	510	74	23	3.6	0.14	0.023
Lung volume, mL	37 650	4341	1406	79.2	6.34	0.74
Alveolar surface area (S_a), m ²	2456	143	83	5.9	0.39	0.068
Capillary surface, m ²	1663	126	66	4.7	0.41	0.059
Capillary volume, mL	2800	213	110	7.2	0.48	0.084
Tissue barrier, $\bar{\tau}_t$, μm	1.39	2.22	1.57	1.51	1.42	1.25

* Arithmetic mean thickness.

Any other volume densities, such as the volume density of the barrier tissue or of its individual components, i.e. of epithelium, interstitium, and endothelium (Figs A.15A, A.15B), are estimated accordingly. The interstitium, which includes cells and fibres, was found to be over 50%; the remaining volume comprises about equal parts of epithelial and endothelial cell layers.

(A63) The ratio of intersections formed by a line tracing the contours of the alveolar surface with a test line of length l_t reveals an estimate of the alveolar surface density, S_{va} , by

$$S_{va} = 2I_t. \quad (\text{A.4})$$

(A64) The surface density of capillaries, S_{vc} , which can be estimated similarly, is roughly 10% smaller than S_{va} . Multiplying these densities by the lung volume yields, for instance, the total capillary volume or the total alveolar surface.

(A65) The thickness of the air-blood barrier is another important parameter with respect to gas diffusion. The arithmetic mean barrier thickness, $\bar{\tau}_t$, is calculated from the ratio of the volume density of the tissue barrier, V_{vt} , to the barrier surface density, which is the average of alveolar and capillary surface density, S_{va} and S_{vc} , respectively:

$$\bar{\tau}_t = 2V_{vt}/(S_{va} + S_{vc}). \quad (\text{A.5})$$

(A66) The thicknesses of the individual tissue layers, (epithelium, interstitium, and endothelium) are obtained in the same manner. Table A.5 lists morphometric parameters of some of the most common mammalian species. Two interesting facts can be obtained from this table: (1) alveolar surface area S_a increases directly proportional to body mass and (2) $\bar{\tau}_t$ seems to be thicker in humans than in larger and in smaller animals. The comparative aspects of these data are described in more detail elsewhere (Gehr *et al.*, 1981a).

(A67) These morphometric parameters describe the functionally relevant respiratory structures of the lung. Changes in any of them, caused by toxic inhalants, would lead to impaired gas-exchange properties. The thickness of the air-blood barrier is rather sensitive to irritants of any kind and reacts with a drastic increase to inhaled toxic gases, as shown by the adult respiratory distress syndrome. (See Section A.5.4.) Morphometric parameters can therefore indicate the extent of damage to the lung's functionally critical structures by toxic inhalants.

(A68) In lungs fixed and processed by the methods described above, cells are counted on random sections, applying stereological methods (Weibel, 1979; Crapo

et al., 1982). The numerical cell density in the gas-exchange parenchyma, $N_{v,p}$, can be determined by counting the nuclear profiles, $N_{A,p}$, on sections, assuming that each cell has one nucleus. Since larger cells have a greater chance of being intersected by a section plane, the size of the nucleus (measured mean caliper diameter, $\bar{D}$) must be taken into consideration for this estimate, according to the formula:

$$N_{v,p} = N_{A,p} / \bar{D}. \quad (\text{A.6})$$

The total number of cells can be obtained by multiplying the numerical density by the lung volume.

(A69) Since it is not possible to estimate $\bar{D}$ reliably from independent sections, another stereological principle has been developed that allows unbiased estimation of the number of particles (e.g. cell nuclei) irrespective of their size, shape, and orientations. It requires two parallel sections with known separation and the knowledge of the reference volume². It is possible to avoid the rather difficult task of estimating the tiny separation between two parallel sections in an electron microscopic analysis by using the fractionator (Gundersen, 1986). This method is based on the same principle; however, no reference volume is needed, and, additionally, it is independent of any dimensional changes of the analysed region due to shrinkage, swelling, or compression during tissue processings.

(A70) Crapo *et al.* (1982), who counted pulmonary cells (mean caliper diameter method), showed that in the healthy human lung there is an average total of 2.3×10^{11} cells (Table A.6). This includes type I and type II epithelial cells, endothelial cells, interstitial cells (not specified), and macrophages (Figs A.15C and A.16). Type I epithelial cells cover 93% of the alveolar surface; only 7% of the surface is covered by the surfactant-producing type II epithelial cells. However, there are twice as many type II as type I epithelial cells. Each type I epithelial cell covers a huge alveolar surface area ($5100 \mu\text{m}^2$). These numbers are similar in baboons and laboratory rats (Table A.6).

Table A.6. Mean values of morphometric cell characteristics of pulmonary gas-exchange parenchyma for man and two other mammalian species (from Crapo *et al.*, 1982)

	Man	Baboon	Rat
Number of individuals	8	5	8
Body mass, kg	74	29	0.35
Total number of cells, $\times 10^9$	230	48	0.89
Percentage of total number			
Epithelial type I	8.3	11.8	8.9
Epithelial type II	15.9	7.7	14.3
Endothelial	30.2	36.3	46.2
Interstitial	36.1	41.8	27.7
Macrophages	9.4	2.3	3.0
Surface area, m^2			
Epithelial type I	5098	4004	5320
Epithelial type II	183	285	123

² See Sterio (1984) for the disector method.



Fig. A.16. Scanning electron micrograph of alveolar macrophage. (From Gehr *et al.*, © 1978a, and reprinted with permission of Elsevier Science Publishers.) Magnification 2100X.

(A71) There is, however, a large interspecies difference in the number of macrophages (Table A.6). Macrophages (Figs A.15D and A.16) comprise 9% of all cells of the human lung parenchyma (roughly 2×10^7 cells), three times as much as in the other species investigated. Human nonsmokers, however, had a percentage of macrophages similar to that in baboons and rats (approximately 3%), whereas smokers might have six times more. This strikingly close correlation of cell numbers that make up the gas-exchange region of the lungs in species that vary more than 200-fold in body size suggests structural homogeneity of the cells in the mammalian lung.

(A72) The most critical functional structures of the lungs are very vulnerable. Therefore the lungs are also responsible for protecting these structures from inhaled irritants that could impair gas diffusion. The lungs fulfill this task very efficiently, as the highly elevated number of alveolar macrophages in the lungs of cigarette smokers shows.

A.3.9. *The Connective Tissue System*

(A73) The conducting airways and their accompanying structures (blood vessels, lymphatics, and supporting structures like cartilage, musculature, glands) are surrounded by connective tissue, which originates from the hilus and extends into the fibrous network of the alveolar entrance rings in the wall of the alveolar ducts. Because of its location, it is called the axial connective tissue. Another connective tissue sheet, originating from the visceral pleura, covers the lobes and extends into the lung, incompletely surrounding the lobules (interlobular septa) and the broncho-arterial units. (Both contain pulmonary veins and lymphatics.) Because of this, it is called the peripheral connective tissue. These two systems are connected by the fine, three-dimensional fibrous system of the interalveolar septa. The whole spatial fibrous continuum forms the pulmonary connective tissue system (Fig. A.17). Because of all the histiocytes (tissue macrophages) and lymphatics located here, this compartment is particularly important with respect to long-term particle retention.

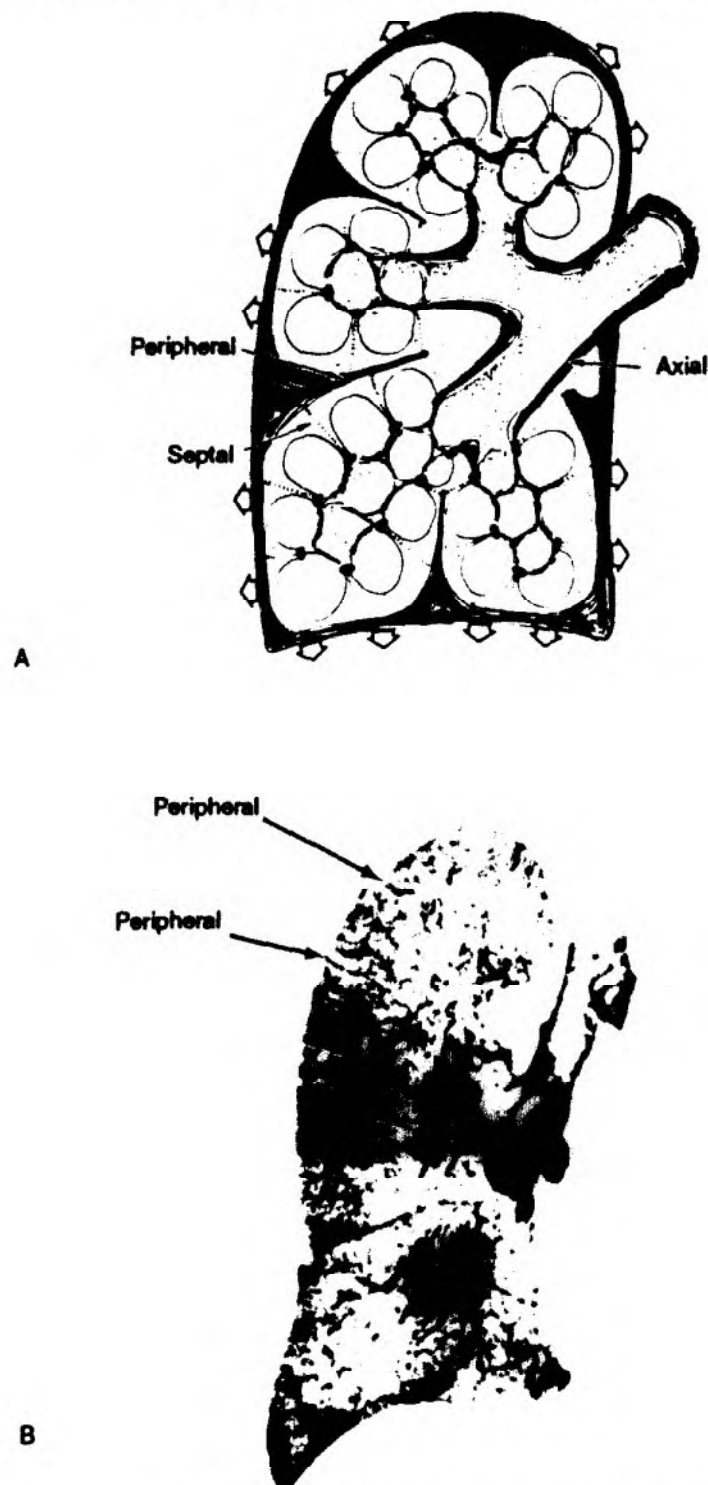


Fig. A.17. The pulmonary connective tissue system. (A) Schematic drawing. (B) Longitudinal section through dried lung (courtesy W. Weber). Peripheral connective tissue surrounds lobules. (From Weibel, © 1984b, *The Pathway for Oxygen*, and reprinted by permission of Harvard University Press.)

(A74) The interstitial space follows the continuous fibre system. Hence, the interalveolar septal interstitial space connects directly with the juxta-alveolar connective tissue system of the airways and blood vessels, and of the interlobular septa, where the lymphatics originate. Although the interalveolar septa do not contain lymphatics, the fibre system establishes a draining pathway from the septal space to the peripheral fluid sumps, where the lymph is removed by lymphatic capillaries.

(A75) Inhaled particulate matter may enter the interstitial space alone or engulfed by surface macrophages (Harmsen *et al.*, 1985). Free particles may be phagocytised by macrophages and retained permanently, or cleared directly, or ingested by the draining pathway. This material will continue into the tracheobronchial lymph nodes.

(A76) The respiratory tract lymph, which originates in the interalveolar septa flows through lymphatic vessels in the axial and peripheral connective tissue into the lymph nodes associated with the respiratory tract. These are deep cervical nodes, collecting the lymph of the upper airways and the tracheobronchial nodes, the lower airways, and the lung. In the longer term, the lymph may pass a first set of lymph nodes and continue to second-order lymph nodes, and, eventually, pass into the blood circulation at the venous angle. The respiratory tract is, therefore, provided with a unidirectional draining system that clears not only fluid but also free particles and macrophage-containing particles. Most of these particles will actually be retained in the lymph nodes, which act as filters for the lymph system.

A.3.10. *The Lymphatic System*

(A77) The lymph vessels of the lungs originate in superficial (pleural) and deep (bronchi, pulmonary arteries and veins) plexuses. In the large bronchi, the plexus consists of two networks, a submucosal and a peribronchial (adventitial). In the small bronchi there is only a single plexus, which extends as far as the bronchioles but fails to reach the alveoli; there are no lymphatic vessels beyond the alveolar ducts.

(A78) The superficial lymph vessels follow the borders of the lungs and the margins of their fissures, converging to end in the bronchopulmonary lymph nodes. The deep lymph vessels are conducted to the hilus along the pulmonary vessels and bronchi, and end, for the most part, in the same nodes. Anastomoses between the two systems are unusual.

(A79) The tracheobronchial lymph nodes are arranged in five main groups and include some of the largest nodes in the body (Fig. A.6): (1) paratracheal, at the sides of the thoracic part of the trachea; (2) superior tracheobronchial, in the angles between the lower part of the trachea and bronchi; (3) inferior tracheobronchial, in the angle between the two bronchi; (4) bronchopulmonary, in the hilus of each lung; (5) pulmonary, in the lung proper, on the larger branches of the bronchi. These groups are not sharply demarcated. The pulmonary lymph nodes become continuous with the bronchopulmonary nodes at the hilus, and they, in turn, are continuous with the inferior and superior tracheobronchial nodes; the latter are continuous with the paratracheal group.

(A80) The lymph of the upper airways is drained mostly into the upper deep cervical nodes; the lymph vessels from the anterior part of the nasal cavity pass superficially to join those that drain the skin. Eventually, they also drain into the deep cervical nodes. The deep cervical nodes, lying along the carotid sheath, are subdivided into superior and inferior groups. The efferent vessels of the superior nodes pass to the inferior nodes. The efferent vessels of the deep cervical lymph nodes then form the jugular trunk (Fig. A.18), which, on the right side, ends in the junction of the internal jugular and subclavian veins or joins the right lymphatic duct; on the left side, it usually enters the thoracic duct, although it may join either the internal jugular or the subclavian vein (Fig. A.18). Lymphatic fluid from the mouth drains into the same system.

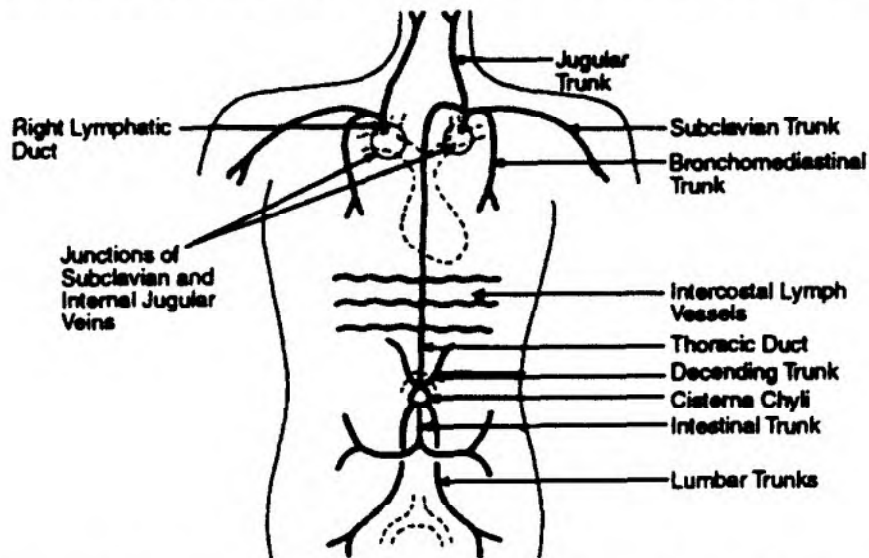


Fig. A.18. The main vessels of lymphatic drainage. (Redrawn from Roitt, © 1984, *Essential Immunology*, and reprinted with the permission of Blackwell Scientific Publications.)

(A81) The lymph passes through several lymph nodes from the periphery to its entry into the venous blood at the junction of the jugular and subclavian vein in the base of the neck. At the entrance, a bicuspidal valve faces into the vein to prevent reflux of blood into the duct.

(A82) Lymphatic vessels generally originate in connective tissue space as anastomosing capillaries. The capillaries flow into larger collecting vessels. Like blood vessels, lymphatic vessels are a tree-like system of endothelium-lined tubes. Unlike the blood vessels, they do not form a circular system but carry their contents, called lymph, in only one direction, towards the base of the neck. Lymphatic vessels recover (drain) fluids that escape into the connective tissue spaces from blood capillaries and venules and return them to the blood.

(A83) Lymphatic capillaries may reach $100\ \mu\text{m}$ in diameter. Their walls are made of flattened endothelium, which, in some cases, may have small apertures. The basement lamina is poorly developed. Collecting vessels are structurally similar to veins but without definite layers.

(A84) The lymph consists of interstitial fluid. It carries away proteins and other molecules. Its average protein content is 2 g-%, but there are considerable regional differences. The lymph vessels are, furthermore, the main channels for the clearance of material absorbed by the digestive tract, particularly for the transport of fat. The lymph also contains corpuscular matter, such as cell debris, coal particles, etc. and cells (e.g. lymphocytes, granulocytes, and macrophages). Under normal conditions and in the resting state, the amount of lymph drained is about $2\ \text{L d}^{-1}$ (Schmidt and Thews, 1977). Probably 95% comes from the liver and intestine; most of the protein originates in the liver. The flow of lymph is promoted by intermittent compression of lymphatic vessels by surrounding structures (muscles, pulsating blood vessels), respiratory movements, force of gravity, etc. The direction of flow is controlled by valves.

(A85) Dense encapsulated collections of lymphocytes, called lymph nodes, lie across collecting lymphatic vessels, and lymph percolates through them. The lymph nodes filter lymph and serve as stations for the transport of T- and B-lymphocytes and their

immunological activities. The nodes range from a few millimeters to more than a centimeter in their largest dimension. The weight of the tracheobronchial lymph nodes has been reported to be between 10 g and 30 g, with a positive correlation with age. Since there are several hundred lymph nodes in the body, the weight of all the lymphatic tissue has been estimated at between 400 g and 800 g (ICRP, 1975)

(A86) A lymph node is a capsule that encloses lymphocytes and other free cells, which are arranged on a reticulum and supplied by blood and lymphatic vessels and nerves. Its outer surface is convex and contains an indentation, the hilus, through which the efferent lymph vessels leave the node and blood vessels, and nerves enter (Fig. A.19). Afferent vessels pierce the convex surface and empty into the sinuses of the node. Between the sinuses, and partly among them, is a reticulum, a delicate meshwork of reticular fibres and reticular cells, throughout which numerous lymphocytes are dispersed. In the periphery they are closely packed, forming a layer called the cortex. Within the cortex, groups of these cells form ovoid lymphatic nodules (follicles); this is the location of B-lymphocytes. T-lymphocytes are located diffusely but densely in the perifollicular zone. Central to the cortex and extending to the hilus lies the medulla. Macrophages are distributed throughout the node. After an antigen has entered the lymph node, an immune reaction takes place. Antibodies are produced by plasma cells in the medulla and leave the node by the efferent lymphatics. Macrophages that have phagocytised particulate matter may enter lymphatics and are then transported into lymph nodes, where they can stay for long periods of time (Harmsen *et al.*, 1985).

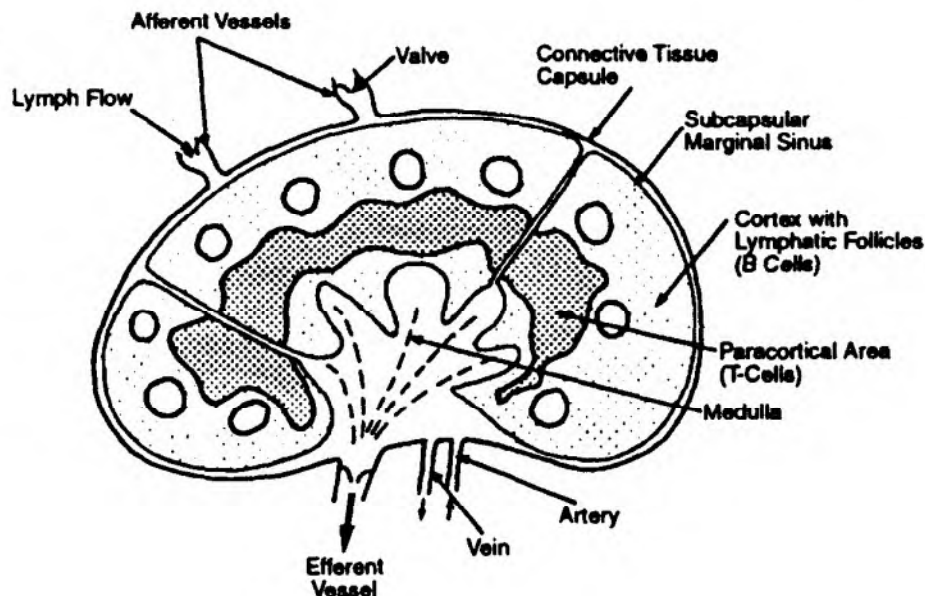


Fig. A.19. Schematic drawing of lymph node.

A.3.11. The Glands

(A87) The submucosal connective tissue of the nose, pharynx, larynx, trachea, and bronchi houses numerous glands of the branched tubulo-acinar type, which produce a mixed seromucous secretion. The secretory cells are located at the terminations of the branching duct work. Up to a dozen of such smaller ducts may lead into a collecting duct, which can be as long as 1 mm. This duct finally pours its contents into a duct-like

invagination of the airway epithelium, which is covered with ciliated cells (ciliated duct).

(A88) The glands may have a diameter of 0.2 mm, or less than one-third of the thickness of the airway wall between the surface and the fibro-cartilage layer. The density of the openings in the trachea is on the order of 1 mm^{-2} (Netter, 1979). The glands become sparser toward the distal bronchi, paralleling the decreasing amount of cartilage.

(A89) The secretion of the glands complements the secretion of the goblet cells of the surface epithelium; together they make up the mucous layer of these compartments of the respiratory tract. This mucus contains water mixed with some mucins, serum proteins filtered from the blood, secretory immunoglobulin, some immunoglobulin M, the bacteriostatic protein lactoferrin, and some uncharacterised muco- and glycoproteins derived from serous or seromucous cells that are also present in the glands. In addition there are secretions added from bronchiolar cells located deeper within the lungs. Serous cells are mostly confined to the glands, but a few may also occur in the surface epithelium (Fig. A.4D).

A.3.12. *Innervation*

(A90) The respiratory tract is mainly innervated by the autonomic nervous system. The fibres involved are the autonomic afferent, sympathetic efferent, and parasympathetic efferent (Fig. A.11).

(A91) Afferent fibres come from stretch receptors in the alveoli and from irritant receptors in the bronchi and bronchioles. They travel via the pulmonary plexus, which is located around the tracheal bifurcation, to the parasympathetic vagus nerve. Irritant receptors in the trachea and cough receptors in the larynx also reach the central nervous system via the vagus nerve. Other afferent fibres come from the chemoreceptors in the carotid and aortic bodies and pressor receptors in the carotid sinus and aortic arch; they travel via the glossopharyngeal nerve. Receptors in the nose and the paranasal sinuses give rise to afferent fibres that form part of the trigeminal and glossopharyngeal nerves.

(A92) All parasympathetic preganglionic efferent fibres to the tracheobronchial airways are contained in the vagus nerve. With short postganglionic fibres in the vicinity of or within the walls of these airways, they carry motor impulses to the smooth muscle and glands, and produce muscle contraction, gland secretion, and vasodilation.

(A93) The preganglionic efferent fibres emerge from the spinal cord and pass to the sympathetic trunks. Long postganglionic fibres carry impulses to the larynx and upper trachea. Other postganglionic fibres pass to the lower trachea, bronchi, and bronchioles, largely via the pulmonary plexus. Their stimuli relax bronchial and bronchiolar smooth muscle, inhibit glandular secretion, and cause vasoconstriction.

(A94) As a whole the intrapulmonary nerve network resembles the airway-arterial system in its pattern of branching. It mainly follows the airway tree but also accompanies the bronchial (nutritive) vessels. Some fibres run superficially in the connective tissue of the adventitia, others more deeply, inside the cartilage. After the cartilage disappears, the two bundles come together to form a single plexus in the adventitia. Ganglion cells are associated with this system. The extent and character of the innervation beyond the respiratory bronchioli remain controversial.

(A95) Intraepithelial nerve endings have been found in the trachea as well as in intrapulmonary airways. The visceral pleura receive fibres which come directly from the hilus.

A.4. Variations

(A96) Apparently, there are scarcely any systematic structural variations of the human respiratory tract that fundamentally influence susceptibility to air pollution; for example, those resulting from body size, growth, age, sex, or ethnic origin. In general, there are differences among individuals; mainly they are genetic effects and are normal. Differences in organ size are usually proportional to differences in body size. Even the growing human lung (after the age of approximately 2 y) does not seem to deviate much in structure from the adult lung (Thurlbeck, 1982a; Zeltner *et al.*, 1987). The branching pattern and morphology of the conducting airways are mature at birth. Except for the terminal bronchioles, where transformation into respiratory bronchioles may occur, the adult tracheobronchial tree is an enlarged replica of a newborn's (Hogg *et al.*, 1970; Hislop *et al.*, 1972; Burri, 1985). Between birth and adulthood these airways enlarge in length and diameter by a factor of around 3. Assuming that a given volume of tracheobronchial air supplies a constant amount of lung tissue, lung volume would be expected to grow 27-fold during this period of time. This was actually determined by Dunill (1962).

(A97) However, the effect of body size or growth has been found to be less for the deeper-lying airways of the conductive zone (trachea, bronchi, and bronchioles). From this it has been predicted that deposition is highest in the newborn and decreases with increasing age to 21 y (Phalen *et al.*, 1985). The model prediction also indicates that, in general, smaller individuals receive greater initial particle deposition within the conductive zone than larger individuals in a given ventilatory state. Under identical circumstances, Phalen *et al.* (1985) concluded that a young (small) person might be at greater risk from many types of airborne particles.

(A98) In the gas-exchange region, however, a tremendous structural transformation occurs: alveolisation, which takes place during the first 18 postnatal months. From then on, this region also grows in proportion to body mass. The connective-tissue fraction in both regions is reduced during this period of time and, perhaps, continues to diminish in the conductive zone. (See Tables A.3 and A.4; Gehr, 1987; Zeltner *et al.*, 1987.)

(A99) Some sex-specific differences have been reported in respiratory tract sizes. Up to the age of 14, boys were found to have larger lungs than girls (Thurlbeck, 1982a). There are quite remarkable differences in the size, dimensions, and structural proportions of the larynx between males and females.

(A100) Differences among ethnic groups are probably mainly dimensional, i.e. differences in body size, which cause proportional differences in respiratory-tract size.

(A101) At older ages the wall structures of the respiratory tract may experience some changes, particularly in the connective-tissue compartments. The largest morphological variations, however, are among species (Phalen and Oldham, 1983; Gehr *et al.*, 1981a; Weibel *et al.*, 1987) and may well influence deposition patterns and clearance mechanisms. Nevertheless, findings from animals have always been extrapolated to humans. In risk assessment, in particular, quantitative extrapolation is essential. Dosimetry, a major use of quantitative extrapolation, seeks to determine the amount of inhaled material that reaches a specific site in animal and human respiratory tracts after exposure to a given concentration of pollutants. Even when equivalent doses are delivered to these sites, there may be interspecies differences in the responses. Thus, species-specific sensitivity data are needed, and dosimetry and sensitivity results need to be linked to allow quantitative extrapolation from animals to humans. Selection of an

appropriate animal species is therefore important. Various scientifically valid criteria exist by which animal models can be selected for inhalation studies. Along with the breathing pattern, and physical and chemical properties of an inhaled material, the anatomy and histology of the respiratory tract will determine how much of an inhaled substance will be deposited.

(A102) Experimental data on the deposition of inhaled particles indicate that mammals of similar body size apparently have similar deposition efficiencies. (See Annexe E.) Although there are anatomical differences between human and dog lungs (Gehr *et al.*, 1978a, 1981b), there is a larger variation in deposition among humans than between human and dog, if both have been exposed under similar conditions, i.e. a similar level of activity and particle size (Cuddihy *et al.*, 1973). The structure of the gas-exchange parenchyma is very similar among mammals.

(A103) The morphometric diffusing capacity is directly proportional to body size over several orders of magnitude (Gehr *et al.*, 1981a). The principal interspecies differences lie in the conductive airway system, which is a less irregularly dichotomous branching system in humans than in all other mammals studied so far (Phalen and Oldham, 1983). Nevertheless, as mentioned above, there is little variability in deposition data if lungs of similar size are compared.

(A104) There are some other important structural differences at the level of the respiratory bronchioles. In some species they are absent; others have 3 to 5 generations (Phalen and Oldham, 1983). However, their absence or presence influences the clearance rather than the deposition of inhaled particles, since without respiratory bronchioles the mucociliary escalator is much closer to the alveolar (nonciliated) region.

A.5. Modifying Factors

(A105) From a variety of factors that modify the normal structure of the respiratory tract, four have been chosen that are considered to be of particular interest: exercise, smoking, pathogens, and disease.

A.5.1. Exercise

(A106) From experimental work with animals it can be concluded that short intense exercise, with long intervals of rest, even when performed over a long period of time, does not significantly change the structure of the respiratory tract.

(A107) Chronic, low-level exercise, on the other hand, appears to cause structural changes. These changes are probably caused by the constant increased physical activity and, hence, more-rapid metabolism or a higher oxygen requirement. Similar changes have been shown in response to low environmental oxygen pressure (pO_2) in animals and humans living at high altitude. The main modification in these species is a larger lung relative to body size, due to an increase of the gas-exchange parenchyma. Apparently, the adaptation is made during growth, and can also be shown experimentally (Burri and Weibel, 1971; Hugonnaud *et al.*, 1977; Gehr *et al.*, 1978b; Weibel *et al.*, 1987). The conducting airways, however, do not seem to adapt to the increased parenchymal volume, which may result in altered ventilation conditions.

(A108) Structural adaptations of the gas-exchange parenchyma to greater oxygen needs can also be demonstrated in animals that are physically very active. Feral species were found to have a larger gas-exchange surface area per unit lung volume than domesticated species (Gehr *et al.*, 1981a). This is a phylogenetic adaptation.

(A109) Morphological adaptations to altered living habits have also been described in the lungs of diving mammals. Nicholson (1984), who investigated Australian sea lions, found considerable reinforcement of both the peripheral airways by cartilage and the parenchyma provided by pronounced interlobular and interacinar septa. There was also general thickening of the interalveolar septa due to more connective tissue fibres. This, too, is a phylogenic adaptation.

A.5.2. *Smoking*

(A110) Smoking causes histological and cytological alterations that lead to ventilatory and circulatory problems in the lungs. Chronic bronchitis is the main result of cigarette smoking. The major histologic feature is the enlargement of the mucus-secreting glands, but there is also mucus-cell hyperplasia. Another problem is the marked narrowing of the small bronchioles, caused by goblet cell metaplasia; mucus plugging; and peribronchial inflammatory scarring (Wright *et al.*, 1983; Douglas *et al.*, 1982; Bertram and Rogers, 1981; Cosio *et al.*, 1980; Park *et al.*, 1977). In the most severe cases the lumen may be obliterated. These bronchiolar changes probably account for what is called "small-airway disease". In addition, tracheobronchial mucociliary transport may be impaired. In cigarette smokers, a large number of pulmonary arteries have reduced luminal diameter, probably due to thickening of the media and the intima. Lungs with these features may be predisposed to developing centrilobular emphysema (Hale *et al.*, 1984).

(A111) A major cytologic feature in smokers is a considerably increased alveolar macrophage population (Ando *et al.*, 1984; Crapo *et al.*, 1982). Whereas a nonsmoker usually has about 5 billion macrophages, a smoker might have as many as 70 billion (Crapo *et al.*, 1982), or more. The motility and the phagocytic activity of alveolar macrophages of smokers may be different from those of nonsmokers, and the macrophages may have an altered ultrastructure (Ando *et al.*, 1984). Furthermore, their bacterio-suppressive activity appears to be impaired. Hyperplasia of mast cells in the distal airways has also been reported in smokers (Lamb and Lumsden, 1982). In general, there is no doubt that cigarette smoke potentiates or exaggerates the effects of air contamination in the induction of respiratory disease.

A.5.3. *Pathogens*

(A112) Chemical and physical irritants (air pollutants) cause pneumoconiosis, which is mainly due to histological alterations, either cellular hyperplasia or atypia, or interstitial fibrosis, or both. The epithelium is sensitive to irritations and responds either by increasing in thickness while the mucous cells and glands beneath undergo hypertrophy or, with more intense or prolonged irritation, by producing squamous metaplasia. Some features are similar to those caused by cigarette smoking, but more severe (Crouch and Churg, 1984; Douglas *et al.*, 1982).

(A113) Oxidant air pollutants potentiate collagen synthesis. Nitrogen dioxide (NO₂) damages the bronchial and bronchiolar epithelium. High levels of oxygen initially destroy the capillary endothelium in the interalveolar septa, leading to a loss of capillaries. Type I epithelial cells are then damaged and are replaced by proliferating type II epithelial cells (repair); interstitial cells also proliferate. Narcotic addicts show alveolar and vascular lesions (fibrotic arterial walls). Diesel exhaust causes the number of Clara cells, type II cells, and alveolar macrophages to increase (Last *et al.*, 1983;

Kucukcelebi *et al.*, 1983; Plopper *et al.*, 1983; Johansson *et al.*, 1983). Asbestos exposure can lead to pleural plaques (chronic exposure) and asbestos bodies (acute exposure) (Andrion *et al.*, 1982).

A.5.4. Disease

(A114) It is not possible to give a complete overview of respiratory tract diseases here. Only a few, particularly those affecting the inhalation pathways and the gas-exchange parenchyma, will be mentioned. (See also Annexe C.)

(A115) The respiratory epithelium covering most of the inhalation pathways is very sensitive. As mentioned above, it may respond to mild irritation by increasing its height, while goblet cells and glands undergo hypertrophy. More intense or prolonged irritation may cause portions of the epithelium to assume a stratified squamous metaplasia. Islands of metaplasia, however, may occur in exposed parts of the upper airways of normal lungs, particularly at their bifurcations. In the respiratory bronchioloalveolar duct junction, on the other hand, many lesions have been detected after inhalation of noxious gases (Plopper and Dungworth, 1987). This might, therefore, be a region particularly at risk.

(A116) Structural modifications caused by bronchitis and bronchiolitis, discussed in the preceding section on smoking, are restricted to the conducting airways. Emphysema, however, severely affects the gas-exchange parenchyma by leading to a loss of interalveolar septa. It also causes chronic airflow limitation by excessive production of intraluminal mucus and may even plug small airways. Emphysema is probably the most important cause of chronic airflow limitation (Thurlbeck, 1982b).

(A117) Patchy consolidation of the lungs is the dominant characteristic of bacterial bronchopneumonia, usually causing a suppurative exudate that fills the bronchi, bronchioles, and adjacent alveolar spaces. Neutrophils are dominant in this exudate. The predominating histologic feature of viral pneumonia is an inflammatory reaction localised within the interalveolar septa. They are widened and oedematous and usually have a mononuclear infiltrate, although the alveoli may be free of exudate. It is believed that those changes reflect alveolar damage similar to that produced experimentally by exposure to high levels of oxygen, which injures endothelial cells and, subsequently, type I epithelial cells.

(A118) Pulmonary tuberculosis (secondary) produces focal lesions in the parenchyma of the apical region of the lungs. They are characteristic coalescent granulomas composed of phagocytic and epithelioid cells surrounded by a zone of fibroblasts and lymphocytes. As the lesion progresses, tubercles coalesce to create a confluent area of grossly recognisable consolidation.

(A119) Increased hydrostatic pressure, as in congestive heart failure or injury to the alveolar-capillary tissue barrier, causes pulmonary edema. The alveolar capillaries are engorged, and an intra-alveolar granular precipitate develops. Hemosiderin-laden macrophages are abundant, and fibrosis and thickening of the interalveolar septa cause the soggy lung to become firm. When the alveolar capillary damage remains localised, the oedema is overshadowed by the manifestation of infection, as in bacterial or viral pneumonia; when it is diffuse, however, it can produce acute respiratory distress syndrome. The interalveolar walls are then lined with a thick hyaline membrane. There is also focal collapse of alveoli, as well as patchy interstitial and pulmonary haemorrhage. In prolonged cases, type II epithelial cells may line the alveolar spaces, and intra-alveolar fibrosis may develop.

(A120) Four major groups of pulmonary tumours are currently distinguished: (1) squamous cell carcinoma, (2) adenocarcinoma, (3) small cell carcinoma, and (4) large cell anaplastic carcinoma. (See Chapter 4 and Annexe C.) A bronchogenic carcinoma begins as an area of cytologic atypia, which, with time, yields a small area of thickened bronchial mucosa. This small focus progressively increases in size and may produce an intraluminal mass, or it may extend into adjacent regions. Rarely occurring alveolar carcinoma is characterised by distinctive, tall, columnar epithelial cells that line up along alveolar septa and project into the alveolar spaces in numerous branching, papillary formations. A major feature is that the underlying septal structures are not destroyed. The adenoma is composed of nests, cords, and masses of cells separated by a delicate fibrous stroma.

(A121) Because of their rich vascularisation, lungs are vulnerable to radiation injury. Increased vascular permeability may lead to marked pulmonary congestion, oedema, fibrin exudation, etc.; later changes include fibrosis of interalveolar septa, which produces respiratory dysfunction. Bronchogenic carcinoma has developed after prolonged inhalation of radioactive materials, e.g. by uranium miners.

A.6. Deposition and Clearance Pathways

(A122) Inhaled particles are deposited in the respiratory tract after entering through the nose or, alternatively, through the mouth (or through both). Deposition of particles depends on the dimensions and geometry of the airspaces; on the morphology of the airspace walls; on the size, shape, and amount of particles; and, finally, on the breathing pattern. Particles can be deposited at any level in the respiratory tract, depending on the above-mentioned parameters. Particles reaching the alveoli may be retained there for long periods of time. They may eventually be cleared from this area by two main routes: (1) alveolar-bronchiolar transport, then clearance by the mucociliary escalator; or (2) after entering the interalveolar-interstitial space, clearance either by blood circulation or by the lymphatics.

A.6.1. Deposition

(A123) Structural characteristics of the respiratory tract that affect the deposition of particles are: the nasal, oral, and pharyngeal anatomy; the nasal hairs; size and shape of the laryngeal opening; tracheal and bronchial anatomy; mucus distribution; alveolar anatomy; and surface composition. Deposition of inhaled materials is discussed in detail in Chapter 5 and Annexe D.

(A124) The depth of penetration and the site of deposition in human lungs depend on the particle characteristics and the breathing pattern as well as the anatomy of the respiratory tract.

(A125) Gaseous substances that are inhaled may enter into specific chemical reactions with lung fluids and tissue elements. Insoluble gases easily penetrate the most peripheral alveoli during inspiration. During passage through the airways, a fraction of the gas can dissolve in the aqueous lining of the airways. The inspired gas diffuses into the tissue and may eventually enter the blood vessels and be transported by the blood. Inhalation of gases and vapours is discussed in detail in Chapter 6.

A.6.2. Clearance

(A126) There are several ways in which insoluble particles are cleared from the respiratory tract, depending on where they are deposited. Principally, however, the two main structural pathways are via the airways and the lymph system. Clearance of inhaled materials is discussed in Chapter 7 and Annexe E.

A.6.2.1. Airway Passage

(A127) Initially, particles that deposit on airways are swept upward by mucociliary movements. Most of the other particles will be ingested by surface (airway, alveolar) macrophages; some may penetrate the epithelium uningested. Particle-laden alveolar macrophages gradually migrate toward ciliated bronchiolar surfaces, from which they are transported upward by the mucociliary escalator, like the particle-laden macrophages in the airways (Brain, 1985; Brain *et al.*, 1977; Sorokin and Brain, 1975).

A.6.2.2. Lymph Passage

(A128) Particle-laden alveolar macrophages can also migrate into the interalveolar interstitial space, from which they are transported via interstitial fluid and lymph vessels into the thoracic lymph nodes (Harmsen *et al.*, 1985). Free particles entering the interstitial space will be phagocytised by histiocytes (tissue macrophages) and will subsequently experience the same fate as alveolar macrophages that penetrate the interstitial space.

(A129) Some macrophages may be retained in the pulmonary connective tissue for long periods (years), but their ingested particles will be slowly dissolved.

A.7. Respiratory Tract Model Considerations

A.7.1. General Aspects

(A130) Based on anatomical and morphological information presented in this annexe and on radiobiological, deposition, and clearance information given in Chapters 4, 5, and 6 and in Annexes C, D, and E, respectively, the respiratory tract is separated into four components for modelling purposes. These components are: (1) the extrathoracic region (ET), comprising the nose and mouth, pharynx, and larynx; (2) the bronchial region (BB), consisting of the trachea and the bronchi; (3) the bronchiolar region (bb), consisting of the bronchioles and terminal bronchioles; and (4) the alveolar-interstitial region (AI), comprising the respiratory bronchioles (bronchioles with some alveoli apposed), the alveolar ducts and sacs with their alveoli.

(A131) Summarised in Table A.7 is a description of the function and the structure of the regions of the respiratory tract model and a comparison with the 1966 model. Details, including morphological and cytological dimensions and scaling of these dimensions for age and gender, are given in Chapter 2.

A.7.2. Components of the Model

A.7.2.1. The Extrathoracic Region (ET)

(A132) The extrathoracic region consists of two components: the anterior nose (ET₁) and the posterior nasal passages, larynx, pharynx, and mouth (ET₂).

(A133) Under normal circumstances, inspired air moves through the nose and the pharynx (nasopharynx, oropharynx) into the larynx: nose breathing, the normal route of entry for inspired air. In case of nasal obstruction, or when ventilatory demands exceed

Functions	Cytology (Epithelium)	Histology (Walls)	Generation Number	Anatomy	Regions used in Model		Zones (Air)	Location	Airway Surface	Number of Airways
Air Conditioning: Temperature and Humidity, and Clearing: Fast Particle Clearance; Air Conduction	Respiratory Epithelium with Goblet Cells: Cell Types: - Ciliated Cells - Nonciliated Cells: • Goblet Cells • Mucous (Secretory) Cells • Serous Cells • Brush Cells • Endocrine Cells • Basal Cells • Intermediate Cells	Mucous Membrane, Respiratory Epithelium (Pseudostratified, Ciliated, Mucous), Glands			ET ₁	Old m	Conditioning	Extrathoracic	$2 \times 10^{-3} \text{ m}^2$	—
		Mucous Membrane, Respiratory or Stratified Epithelium, Glands			ET ₂	LN _{3T}				
		Mucous Membrane, Respiratory Epithelium, Cartilage Rings, Glands	0		BB	(T-B)	Conduction	Thoracic	$4.5 \times 10^{-2} \text{ m}^2$	—
		Mucous Membrane, Respiratory Epithelium, Cartilage plates, Smooth Muscle Layer, Glands	1							
Air Conduction; Gas Exchange; Slow Particle Clearance	Respiratory Epithelium with Clara Cells (No Goblet Cells) Cell Types: - Ciliated Cells - Nonciliated Cells • Clara (Secretory) Cells	Mucous Membrane, Respiratory Epithelium, No Cartilage, No Glands, Smooth Muscle Layer	2-8		bb	LN _{3M}	Gas-Exchange Transitory	Pulmonary	$2.4 \times 10^{-1} \text{ m}^2$ (a)	6.5×10^4 (a)
		Mucous Membrane, Single-Layer Respiratory Epithelium, Less Ciliated, Smooth Muscle Layer	9-14							
		Mucous Membrane, Single-Layer Respiratory Epithelium, Less Ciliated, Smooth Muscle Layer	15							
		Mucous Membrane, Single-Layer Respiratory Epithelium of Cuboidal Cells, Smooth Muscle Layers	16-18							
Gas Exchange; Very Slow Particle Clearance	Squamous Alveolar Epithelial Cells (Type I), Covering 80% of Alveolar Surface Area Cuboidal Alveolar Epithelial Cells (Type II, Surfactant-Producing), Covering 7% of Alveolar Surface Area Alveolar Macrophages	Wall Consists of Alveolar Entrance Rings, Squamous Epithelial Layer, Surfactant	(c)		AI	P	Gas-Exchange Transitory	L	7.5 m^2	4.6×10^5 (a)
		Interalveolar Septa Covered by Squamous Epithelium, Containing Capillaries, Surfactant	(c)							
				Lymphatics					140 m^2	4.5×10^7 (b)

(a) See Table 2.

(b) See Table 3.

(c) Unnumbered because of imprecise information.

(d) Previous ICRP Model

(e) As described in the text, lymph nodes are located only in BB region but drain the broncholar and alveolar-interstitial regions as well as the bronchial region

Table A.7. Morphometry, cytology, histology, function, and structure of the respiratory tract and regions used in the dosimetry model

the nasal airflow capacity, the auxiliary airway is the mouth, the pharynx (oropharynx), and the larynx.

(A134) The main task of the ET region is to condition and clean the inspired air and to conduct it to the lung. Ambient air, which is usually of lower temperature and humidity than the human body and contains pollutants, must be efficiently modified and cleansed before penetrating deeply into the lungs, where it comes into extremely close contact with the blood over a huge gas-exchange surface area.

A.7.2.2. *The Thoracic BB Region*

(A135) This region consists of the trachea, the main bronchi and the intrapulmonary bronchi, beginning with the trachea as generation 0 and ending with generation 8, and associated lymph nodes. These 9 generations of the conducting airway system comprise a total volume of only about 50 mL.

(A136) The purpose of this part of the airway tree is to conduct air into and out of the bronchiolar system. It is also involved in adjusting the humidity and temperature of the inspired air, as well as in capturing and clearing inhaled pollutants.

(A137) The airway tree originates in a single tube, the trachea. On average, it is about 10 cm long and 2 cm in diameter, and its volume is about 20 cm³. The upper part of the trachea is kept open by the cartilage rings; the lower part of the trachea and other airways are collapsible. The tracheal wall is covered by respiratory mucosa and contains many glands. The mucous sheet on top of the respiratory epithelium is moved toward the mouth by the cilia.

(A138) The trachea first divides into two (extrapulmonary) main bronchi, which divide into the lobar bronchi; three enter the right lung, and two enter the left lung. The lobes are covered by the pleura, from which connective tissue septa originate. They lead towards the hilus and subdivide the lobes into cuneiform broncho-arterial segments.

A.7.2.3. *The Thoracic bb and AI Regions*

(A139) These regions comprise the respiratory tract system distal to the bronchi, i.e. generations 9 and beyond. These are the bronchioles (generations 9 to 15), the respiratory bronchioles (generations 16 to 18), and the alveolar ducts and sacs. These regions also include the associated lymph nodes.

(A140) Generation 15, the terminal bronchioles, is the last generation of the air-conducting system; distally, all airways are alveolated. This part of the lung, which comprises 80% to 85% of the total lung volume, is therefore called the gas-exchange region (gas-exchange parenchyma). Single alveoli or small groups of alveoli are apposed to the respiratory bronchioles, whereas in alveolar ducts the whole circumference is occupied by alveoli. The last generation of the gas-exchange region, the alveolar sac, is closed at the peripheral end by a group of terminal alveoli.

(A141) Since respiratory bronchioles are partly alveolated, they are considered, along with alveolar ducts and sacs, as the transitory zone between the air-conducting system and the alveoli, which in their entirety are the pure gas-exchange zone of the lung.

(A142) The gas-exchange parenchyma can be subdivided into many small morphological units, the lobules, which have a volume of about 1 mL. They are only partially separated from each other by connective tissue but can be clearly seen on the pleura as polygonal fields. Each lobule is supplied with air by a terminal bronchiole. The lobule can be further subdivided into two functional units, the acini, each of which is supplied with air by a respiratory bronchiole of the first generation.

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ANNEXE B. RESPIRATORY PHYSIOLOGY

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B.1. Introduction

(B1) Radiation doses to tissues and cells of the respiratory tract from the inhalation of radioactive particles and gases are determined to a great extent by physiological parameters, e.g. breathing rates and lung volumes. These parameters vary slightly among different populations in the world and among individual members of these populations. It is clear that a single physiological model cannot be applied to the world's population to estimate or predict radiation doses from inhaled radionuclides. In addition, using models for every possible combination of physiological parameters would be very complex. In this annexe, the range of values for various respiratory and physiological parameters of the world's population are examined, and a range of values is identified and recommended for application to dosimetric calculations for radiation protection purposes.

B.2. General Aspects

B.2.1. Extrathoracic Regions

(B2) In spontaneous breathing, the choice of airways depends on the relative resistance of the two passages, nose and mouth, at the airflow required by ventilatory needs. This variable is linked to nasal airway morphology, described in Chapter 2 and Annexe A.

(B3) *Nasal breathing.* Nasal breathing is predominant in healthy subjects at rest. It conditions the temperature and humidity of inhaled air and filters particles. Nasal breathing is natural and comfortable for most individuals.

(B4) *Oronasal breathing.* In response to exercise, where a high rate of ventilation is needed (about $2.1 \text{ m}^3 \text{ h}^{-1}$ for adult males; Bowes and Swift, 1989), breathing becomes oronasal, because the mouth offers much lower resistance to airflow.

(B5) Three segments of the nasal passages are important for ventilation: (1) the external nares, lined with hair; (2) the constriction zone, located 2 cm behind the external nares, at the extremity of the nasal bones, and lined with mucus; (3) the area comprising two-thirds of the space posterior to the nasal passages plus the pharynx. The epithelium has mucociliary activity.

(B6) The anatomical structure of the extrathoracic regions is characterised by high resistance to airflow, half the total airway resistance value. In adults, the average total resistance for both nares is close to $0.15 \text{ kPa L}^{-1} \text{ s}$.

(B7) *Nasal cycle.* In most healthy individuals, resistances to airflow are not identical in both nostrils; moreover, anatomical asymmetry is increased by nasal congestion and decongestion that alternately raises and lowers resistances (about every 3 h) in the right and the left side. Airflow distribution can be changed as much as 20–80% between the two nostrils without any subjective discomfort. This cycle disappears in elderly people, during exercise, and during emotional upset.

B.2.2. Thoracic Regions

B.2.2.1. Conductive airways

(B8) In what is classically called the "tracheobronchial tree," inspired gases are transported but do not undergo exchanges with blood (Weibel, 1973). However, the gases can be retained in mucus, depending on their specific solubility, and transferred to

blood through the epithelium. The physiological term for this region is “the anatomical dead space,” and it increases in volume with age.

(B9) *Airway resistance to airflow.* The principal sites of airway resistance to airflow are the segmental bronchi (generations 2 to 6); adult values are close to $0.15 \text{ kPa L}^{-1} \text{ s}$, about equal to those of nasal resistance.

B.2.2.2. Alveolar regions or gas-exchange regions

(B10) In these regions, the exchange of oxygen and carbon dioxide between inhaled air and blood occurs. The alveoli that participate in gas exchange are those that receive adequate ventilation and perfusion. In healthy young subjects, at least 70% of alveoli are involved, but this proportion decreases with age. The nonfunctional alveolar region, plus the anatomical dead space, constitutes the “physiological dead space.” The parameter increases with tidal volume, especially during exercise (Morgan *et al.*, 1984).

(B11) The sequential structure of the respiratory tract causes “fresh” air to penetrate in an inhomogeneous way towards the alveoli:

- at the beginning of inspiration, air first penetrates to the hypoventilated lung apex, then to the well-ventilated bases;
- during the next inspiration, the dead volume is inspired again into the apex, and “fresh” air enters the base region.

(B12) In the deep lung, where velocity is near zero, air-mixing is progressive; according to Altshuler *et al.* (1959), no more than 11–27% of inspired air mixes with the residual volume during each inspiration.

B.3. Normal Breathing Dynamics

B.3.1. Respiratory Physiological Features

(B13) Figure B.1A gives the different measured volumes, obtained directly in respiratory function tests (e.g. tidal volume and vital capacity) and by helium rebreathing, for residual volume and calculation of functional residual capacity and total lung capacity.

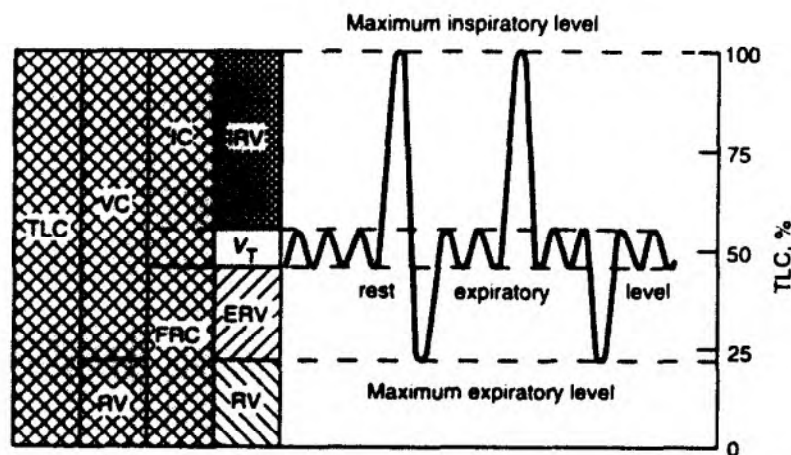


Fig. B.1A. Respiratory volumes.

Respiratory volumes

Average adult values, m³
(Quanjer, 1983)

Tidal volume (V_T)	6×10^{-4}
Inspiratory reserve volume (IRV)	2×10^{-3}
Expiratory reserve volume (ERV)	1.5×10^{-3}
Vital capacity (VC)	4.3×10^{-3}
Residual volume (RV)	1.6×10^{-3}
Total lung capacity (TLC)	5.9×10^{-3}
RV/TLC = 20–30% = constant	
Functional residual capacity (FRC)	3×10^{-3}
Anatomical dead space (V_D)	1.4×10^{-4}

Respiratory airflows

Average adult values
(Quanjer, 1983)

- Maximum (forced) expiratory volume in 1 s = FEV₁
- FEV₁/VC = 70–75% = constant $3.5 \times 10^{-3} \text{ m}^3$
- Flow volume curve: Fig. B.1B gives the different values of airflow related to the level of vital capacity during the maximum-effort vital-capacity manoeuvre
- Maximum voluntary ventilation = MV $\dot{V}$ $7.2\text{--}9 \text{ m}^3 \text{ h}^{-1}$

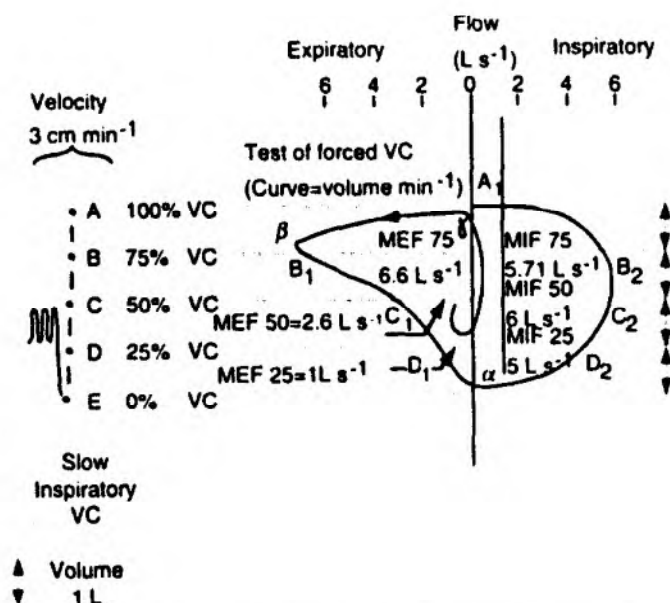


Fig. B.1B. Flow volume curve of a normal subject during maximum effort vital capacity manoeuvre.

B.3.2. Alveolar Ventilation ($\dot{V}_A$)

(B14) The fraction of global ventilation that reaches the alveolocapillary barrier is about 60–70%, excluding:

- anatomical dead space
- physiological dead space (nonperfused alveoli)

B.3.3. Dead Spaces

(B15) *Anatomical dead space*. Morphological definition: the volume of the conducting airways, i.e. airways that are not lined with respiratory exchange epithelium, measured from a cast of the bronchial tree.

(B16) *Functional dead space*. The volume of the inspired air that does not mix with alveolar gas, measured *in vivo* by the gas dilution method (Fowler, 1948).

(B17) *Alveolar dead space*. A volume of gas that mixes with gas in alveolar spaces but does not participate in alveolar exchange (a volume of gas of well-ventilated but not perfused alveoli).

(B18) *Physiological (respiratory) dead space*. The volume of gas that is inspired and expired but does not participate in alveolar exchange, measured by $\dot{V} \text{ CO}_2$ and $P_a \text{ CO}_2$, carbon dioxide expiratory flow rate, and arterial blood partial pressure.

(B19) *Physiol $V_{Dp} = \text{Anat } V_D + \text{Alv } V_D$* . Alveolar ventilation is increased for low frequencies provided minute ventilation is constant. This can be expressed as follows:

$$\dot{V}_A = (V_T - V_{Dp}) f_R \cdot \text{m}^3 \text{ h}^{-1}$$

V_T = tidal volume, m^3
 V_{Dp} = physiological dead space, m^3
 f_R = respiratory frequency, h^{-1}

The ventilation/perfusion ratio $\dot{V}_A / \dot{Q}$ (Fig. B.2) gives a picture of the distribution of alveolar function.

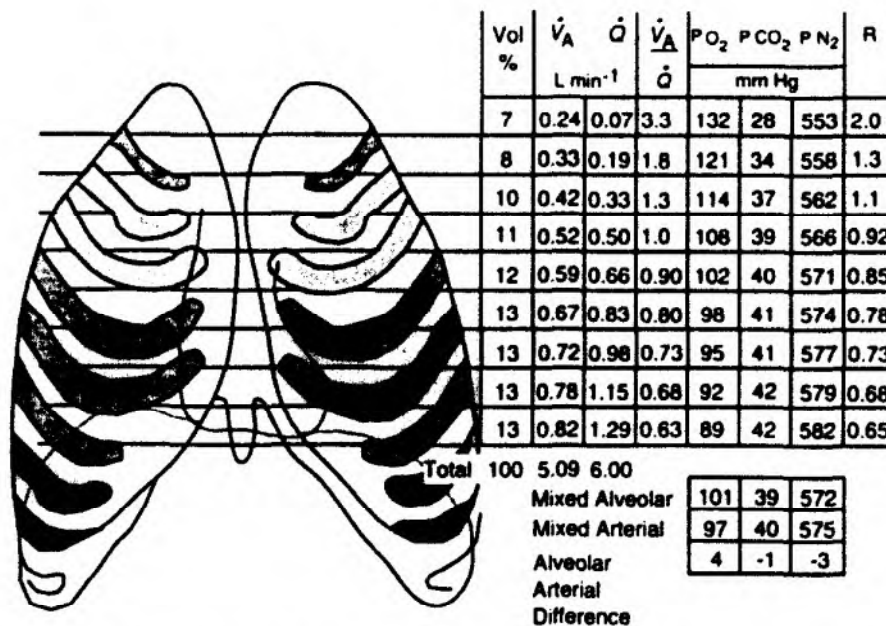


Fig. B.2. Local blood flow and ventilation effects upon regional gas exchanges. (Redrawn from West, 1966, p. 713, courtesy of Editions VIGOT Frères.)

B.3.4. Gas Compartments

(B20) Figure B.3 illustrates gas compartments and exchanges, with approximate volumes involved, pressures, and duration of the passages from venous to arterial blood.

B.3.5. Exercising Ventilation

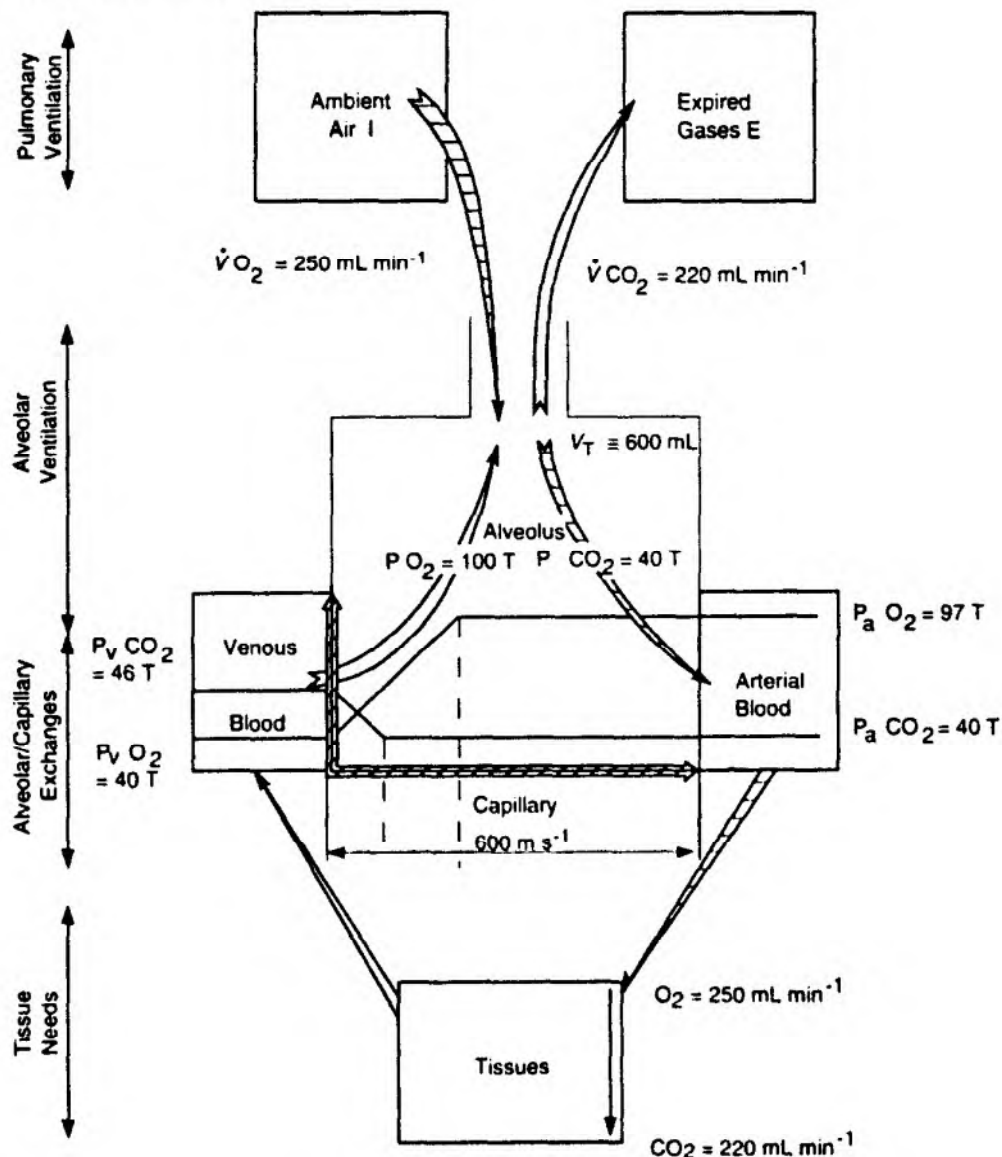


Fig. B.3. Gas compartments.

(B21) Ventilation during exercise is an important consideration in respiratory physiology. Breathing characteristics adapt to increases in energy expenditures and oxygen needs that occur during exercise.

B.3.5.1. Transformations of minute ventilation

(B22) Transformations of minute ventilation yield the following:

- increased ventilation minute volume ($\dot{V}_E$), tidal volume (V_T) (up to an average of limiting value equal to $VC/2$: Fig. B.4), and respiratory frequency (Dejours, 1963);
- increased ventilation minute volume ($\dot{V}_E$) and alveolar pressure of CO_2 ;
- increased oxygen consumption (Dejours, 1963).

Cotes (1979) proposes the following relationships:

- V_{T30} (in L) = $0.13 \text{ VC (in L)} + 0.87$ (tidal volume at frequency of 30 min^{-1});
- V_{Tmax} (in L) = $0.65 (\text{VC [in L]} - 1)$ (tidal volume at maximal value).

In the first case, V_T is roughly equal to $VC/3$; in the second, to $VC/2$.

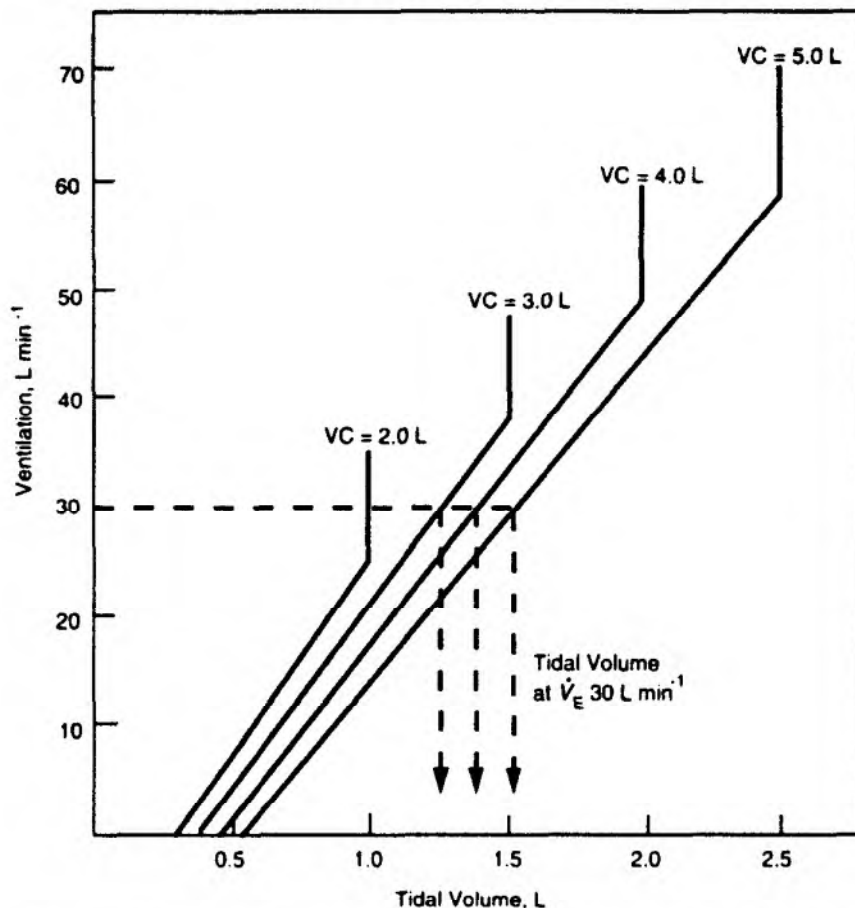


Fig. B.4. Average relationship of the exercise tidal volume to the minute volume and vital capacity for men and women of European descent. (Redrawn from Cotes, 1979, p. 383, courtesy of Blackwell Scientific Publications.)

(B23) Cotes gives a relationship between minute ventilation, $\dot{V}_E$ (in L min^{-1}), and tidal volume (V_{T10}):

- Males: $\dot{V}_E = 28 (V_T [\text{in L}] - 0.32)$
- Females: $\dot{V}_E = 33 (V_T [\text{in L}] - 0.36)$.

B.3.5.2. Transformations of dead space

(B24) In adults, the relationship between physiological dead space (V_{Dp}) and tidal volume is V_{Dp} (in mL) = $70 V_T$ (in L) + 140. Usually V_{Dp} is measured at FRC level (after expiration of a normal breath V_T), and by mouth breathing (Hart *et al.*, 1963 and Wood *et al.*, 1971) by the Fowler method with N_2 (Fowler *et al.*, 1952). With increasing V_T , V_{Dp} increases (Asmussen and Nielsen, 1956) both by alveolar V_D (but not significantly in healthy people) and by anatomical V_D stretching. Anatomical dead space comprises, therefore, an expanding fraction: $V_{D(\text{exp})}$. This fraction includes the trachea and bronchi down to the bronchioles. According to Davies (1972): $V_{D(\text{exp})} = 0.6 V_D$ (in adults). An expansion coefficient can be calculated as a function of lung volume.

B.4. Variabilities

B.4.1. Age- and Sex-Specific Effects

(B25) *Adult.* Lung volumes and airflows of a healthy subject, correlated to height and weight, are relatively constant but are affected by various factors. Vital capacity can be

increased by training the respiratory muscles. When the subject lies down, VC reduces about 7%; RV, FRC, and TLC reduce about 15% (Cotes 1979). Differences between men and women in lung volumes and airflows begin around 12 y of age; as an example, at equal height and weight, the VC in boys is about 8% greater than that in girls. After puberty the difference becomes more marked, mainly because of different body heights and weights but also because the male thorax grows more laterally and longitudinally. Adult female lung-function values are usually 20–30% lower than those for males. Pregnancy affects lung function because of changes in the chest wall and diaphragm position, and because of the rise in progesterone levels in the blood. These changes result in reduction of airway resistance, RV, and FRC. The rise in progesterone increases the ventilation response to carbon dioxide and exercise. After age 25, the respiratory function begins to decrease linearly with age: the values of VC, TLC, and FEV_1 decrease, while the values of RV, FRC, and V_D increase.

(B26) *Children.* At birth, the conductive airways are fully formed and grow regularly in length and diameter, with a constant ratio throughout the whole bronchial tree (Hislop *et al.*, 1972). Before the age of 5 y, however, a disproportion is observed in the peripheral airways (over the 16th generation), where diameters are narrower, increasing airway resistances. In the same way, V_D increases with age (Hart *et al.*, 1963). Alveoli increase in number from birth until the age of 2 y (Zeltner *et al.*, 1987), then, as a function of age, increase regularly in dimension together with lung volumes (VC, FRC, and TLC). Figures B.5 and B.6 show the resulting changes in ventilation parameters. The growth of conductive airways could be represented by a single function of age, but the alveolar and volume growth have several different functions during aging (Hofmann, 1982; Thurlbeck, 1982). This dysanaptic growth of a child's respiratory tract, and changes such as the dynamic properties of the lung and chest wall, the strength of the respiratory muscles, and changing values of arterial oxygen pressure (Burri, 1984), induce development of lung function, which is not continuous and regular but variable with age. Up to the age of 1.5–2 y, children have a different anatomical arrangement of the larynx from that of adults. The larynx in the child is situated very high in the neck and allows simultaneous breathing and swallowing. Babies, therefore, are almost entirely nose breathers (Laitman and Crelin, 1976).

(B27) Total airway and nasal resistances to airflow are higher in children than in adults. They decrease with growth and reach adult values at approximately 14 y.

(B28) Response to exercise, after allowing for body size, is similar in children and adults. For example, the maximal voluntary ventilation in $L \min^{-1}$ is in linear regression with body size (cm) (Doershuk *et al.*, 1975), but the contribution of frequency is greater.

(B29) In children, for any increase in the ventilation minute volume, the higher breathing frequency increases the dead-space ventilation at any level of alveolar ventilation. Physiological dead space is given by the relationship V_{Dp} (in mL) = $1.54 W$ (kg) + $0.049 V_T$ (in mL) + 2 (Godfrey, 1973).

B.4.2. Reference Values for Adults

(B30) A screening of recent publications of biometrical and respiratory physiological data was undertaken for several populations of both sexes and various ages. The data were retained when they were obtained by current standardised methods:

- spirometry for VC and forced expired volume in 1 s (FEV_1)
- inert gas breathing or plethysmography for RV, FRC, V_D , and TLC.

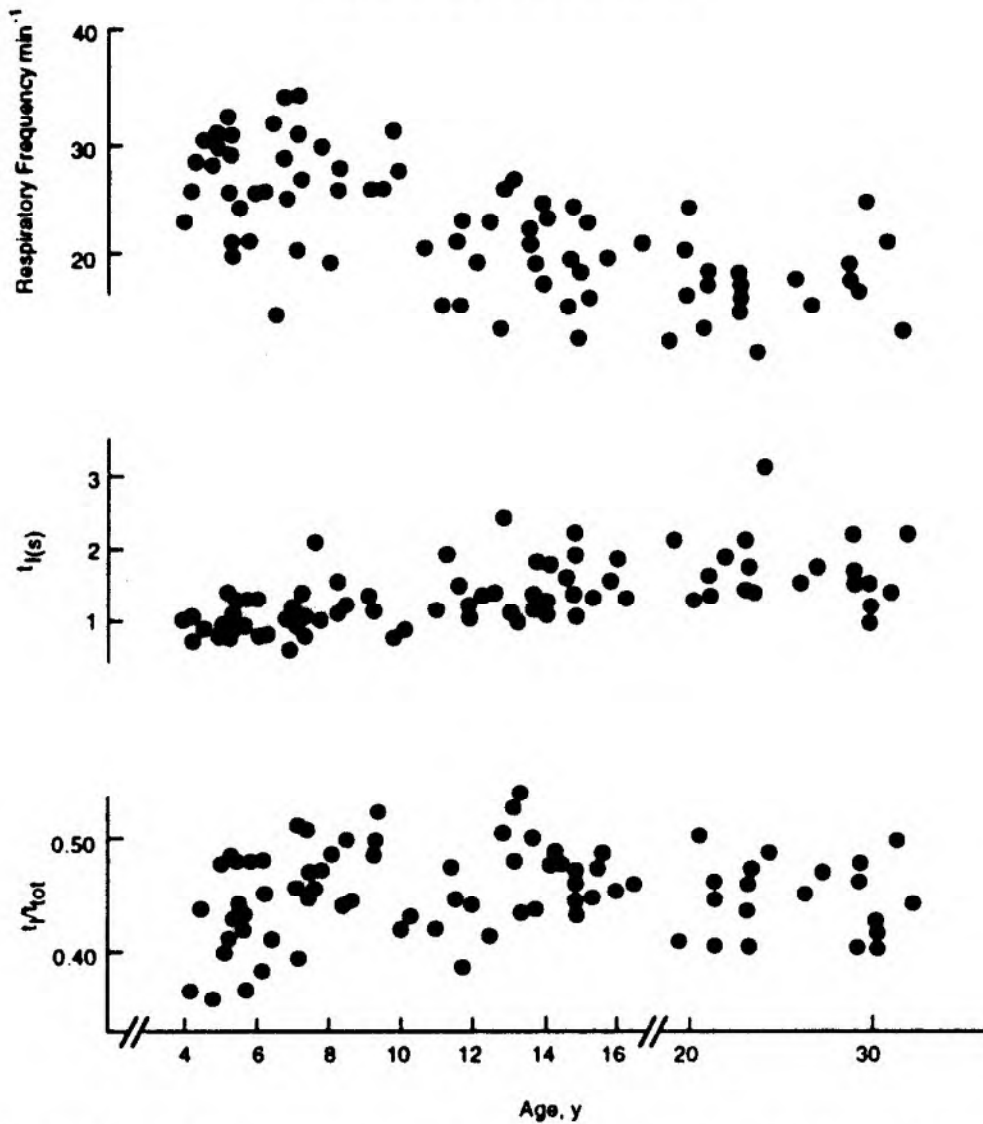


Fig. B.5. Relationship of respiratory frequency, inspiratory time (t_I), and its ratio with total cycle time (t_I/t_{tot}), and age. (Redrawn from Gaultier *et al.*, 1981, courtesy of Elsevier Science Publishers.)

Subjects studied were required to be healthy and numerous enough to provide reliable mean values and standard deviations of the parameters (at least 30 subjects in each defined group).

(B31) The results are given as regressions on age, A (in y), weight, W (in kg), and standing height, (in m). For both sexes, a residual standard deviation (RSD) is required.

B.4.2.1. Reference values for Caucasians

(B32) Cross-sectional studies in Caucasians have been compiled from authors in the United States and Europe to assess the New European Coal and Steel Community reference values (Quanjer, 1983).

(B33) Summary regressions have been derived from all authors' regression values with respect to:

- Age: 25–70 y—for subjects 18–25 y, mean value of 25 y
—for those greater than 70 y, extrapolation
- Height range: men: 155–195 cm
women: 145–185 cm

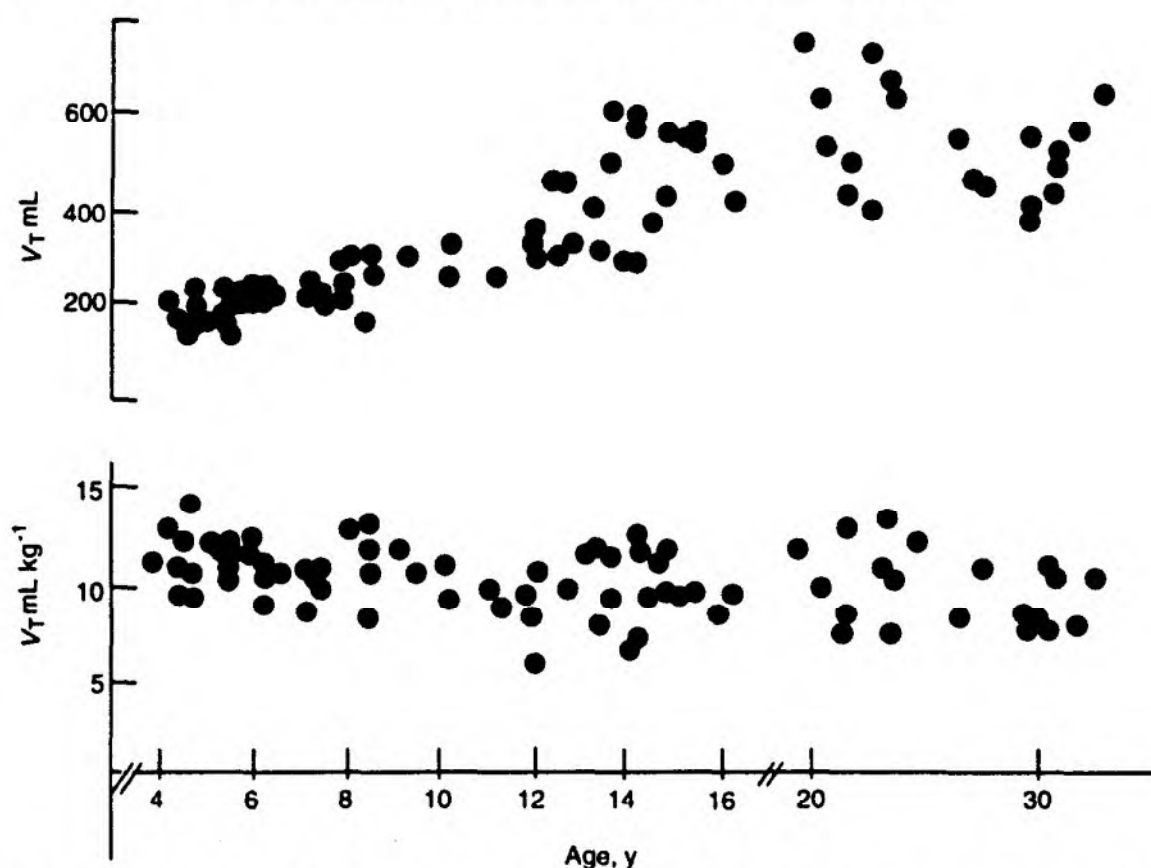


Fig. B.6. Relationship of tidal volumes, and tidal volumes normalised for body weight and age. (Redrawn from Gaultier *et al.*, 1981, courtesy of Elsevier Science Publishers.)

(B34) *Normal limits.* It is recommended that 1.64 RSD^a (average residual standard deviation from the regression equations) can be subtracted from the predicted value to estimate the lower limit.

(B35) The computation of each set of reference values was made for each combination of height and age, at 5-cm and 5-y intervals. A linear model was preferred because more complex models are not necessarily more accurate.

(B36) *Summary of regression values.* Regression equations for respiratory volumes and airflows are given for men and women in Table B.1. Regression equations for maximum voluntary ventilation are given in Table B.2; the latter apply equally to men and women. Sources of variability include origin of the population (southern or northern Europe, the United States, etc.), occupation, and seasonal or circadian variation. As an example, diurnal variations for FEV_1 are 70 mL for smokers and 40 mL for nonsmokers.

B.4.2.2. Interracial variation—ethnic group values

(B37) Because the respiratory tract model is to be applicable to all members of the world's population, it is important to give reference values of biometrical and physiological parameters useful in respiratory function for as many ethnic groups as possible. However, appropriate quantitative data are missing in several cases.

(B38) The more commonly published respiratory volume standards are those easily measured directly by spirometry: VC and FEV_1 . More difficult to find are measurements of RV, FRC, V_D , and TLC, which require more sophisticated and expensive laboratory methods, such as inert gas breathing or plethysmography.

Table B.1. Lung volumes and ventilation rates for healthy adult Caucasians

1. Reference values as functions of Age, A (in y), Height, H (in m), and Weight, W (in kg)		
VC (L)	Male: $5.76 H - 0.026 A - 4.34$ Female: $4.43 H - 0.026 A - 2.89$	RSD = 0.56 RSD = 0.43 (Quanjer, 1983)
TLC (L)	Male: $7.99 H - 7.08$ Female: $6.60 H - 5.79$	RSD = 0.70 RSD = 0.60 (Quanjer, 1983)
FRC (L)	Male: $2.34 H + 0.009 A - 1.09$ Female: $2.24 H + 0.001 A - 1$	RSD = 0.60 RSD = 0.50 (Quanjer, 1983)
V_D (L)	Male and Female: $[A + (2.2 W)] 10^{-3}$ (Cotes, 1979)	
2. Mean values at rest (Cotes, 1979)		
V_D (L)	25% of V_T at 20 y 40% of V_T at 60 y	
V_T (L)	Male: 0.4–1.5 Female: 0.3–0.85 roughly 10 mL kg^{-1}	
f_R (min^{-1} frequency)	12–20	
$\dot{V}_E$ (L min^{-1})	Male: 6–15 Female: 4–12	
3. Transformations for exercise (Cotes, 1979)		
V_D (L)	$[(70 V_T \text{ L}) + 140] 10^{-3}$ SD = 0.09	
Relationship between V_T and VC:		
$V_{T(30)}$ (L)	$= 0.13 \text{ VC (L)} + 0.87$ (roughly VC/3) SD = 0.22	
$V_{T(\max)}$ (L)	$= 0.65 (\text{VC (L)} - 1)$ (roughly VC/2)	

VC = vital capacity; TLC = total lung capacity; FRC = functional residual capacity; V_D = anatomical dead space; SD = standard deviation; RSD = relative standard deviation; V_T = tidal volume; f_R = respiratory frequency; $\dot{V}_E$ = ventilation minute volume.

Table B.2. Maximum voluntary ventilation

Value measured over 15 s (L min^{-1})	
Adult mean values: Male: 120 Female: 100	
1. Formula with FEV_1 (L)	
$\text{MV}\dot{V} = 37 \times \text{FEV}_1$	
2. Formula as a function of height, H (in m), and age, A (in y)	
Male: $\text{MV}\dot{V} = 134 H - 1.26 A - 21.4$	SD: 29 (Kory <i>et al.</i> , 1961)
Female: $\text{MV}\dot{V} = 81 H - 0.57 A - 5.5$	SD: 10 (Lindall <i>et al.</i> , 1967)

FEV_1 = maximum expiratory volume; $\text{MV}\dot{V}$ = maximum voluntary ventilation; SD = standard deviation.

B.4.2.2.1. Biometrical values.

(B39) Body heights and weights are slightly different in various ethnic groups. For adult men, 30 y old, the mean height varies from 178 cm for U.S. blacks (Rossiter and Weill, 1974) to 160 cm for New Guinea highlanders (Woolcock *et al.*, 1972). In any given ethnic group, women are about 5–8% shorter than men. Body weights follow the same pattern, but with more variability.

(B40) For comparison of respiratory function, the adult values have been chosen at 30 y of age, and the children's at the same body sizes but not the same ages.

B.4.2.2.2. *Spirometric values.*

(B41) Vital capacity is given as an example; the other lung volumes and flow rates vary in the same proportions. Among 30-y-old men (see Tables B.1 and B.3 and Section B.6.1), the highest values are found in U.S. and European Caucasians, followed by Japanese (-7%) (Nishida, 1982); U.S. blacks (-13%) (Schoenberg *et al.*, 1978); Africans (-15 to -20%) (Duf  tel *et al.* 1989); Han Chinese (-20%) (Chen, 1984); and Indians (-22%) (Kamat *et al.*, 1977).

(B42) The relationships between VC and body size (Fig. B.7) show a different pattern among various ethnic groups. FRC differences (Fig. B.8) are smaller (7 – 10%). Anatomical factors may explain these differences (Donnelly *et al.*, 1991).

B.4.2.2.3. *Ventilation rates.*

(B43) In the various ethnic groups, V_T is likely to show some differences because of variations in oxygen needs (indicated by body heights and weights) and in lung volumes (VC, for example).

(B44) Indeed, at rest, the few observed data do show some variability: Caucasians have the highest V_T values (Cotes, 1979), followed by blacks (-14%) (Cerny, 1987), Han Chinese (-20%) (Chen, 1988), and Indians (-35%) (Kamat *et al.*, 1977).

(B45) On the contrary, the respiratory frequency is increased (16 min^{-1} in Chinese, and 19 min^{-1} in Indians), compared with Caucasians (12 min^{-1}), bringing the minute ventilation ($\dot{V}_E$) to equivalent rates, around 8 L min^{-1} . In blacks, Rossiter and Weill (1974) found that oxygen diffusing capacity is lower (-8%), because of smaller alveolar volume, but that the diffusion rate is higher ($+4.6\%$) than in Caucasians; this could explain why at exercise also the minute ventilations ($\dot{V}_E$, L min^{-1}) reported by these authors are very similar in the two ethnic groups:

	Caucasians	Blacks
light exercise	26.2	25.3
higher level of exercise	38.6	37.7

Similar observations are made in children, but experimental data comparing ventilation in ethnic groups are difficult to find.

(B46) In conclusion, ethnic variability exists in lung volumes and flow rates, as well as in tidal volume. However minute ventilation at rest and at various levels of exercise does not seem to be very different between the studied ethnic groups (Roy *et al.*, 1991). The same set of values is thus suitable for all subjects.

B.4.3. *Reference Values for Children*

(B47) Complete reference values with matched regression values are not yet available for children up to 18 y; however, functional values have been given discontinuously and have been expressed in different ways (European Society for Clinical Respiratory Physiology, 1989).

(B48) *From 0 to 3 y* (Gaultier *et al.*, 1981). Volume is related not only to alveolar development but to strength of muscles and changes in chest wall and lung mechanics.

(B49) Functional residual capacity, crying vital capacity (CVC), and RV (measured), as well as TLC and ERV (calculated) are correlated with weight (kg), height (m), and the logarithm of age.

(B50) *From 6 to 11 y* (Dockery *et al.*, 1983). Volume relates to regression values (weight, size, sex); lung growth follows almost the same pattern in boys and girls until

Table B.3. Lung function for 30-y-old adults in various ethnic groups (mean and standard deviation)

1. Reference values for lung volumes as functions of age, A (in y) and height, H (in m)		China (Chen, 1984) Mean values for 120 people	India (Kamat <i>et al.</i> , 1977)
Japan (Nishida, 1982)			
VC (L)	Male: $(2.85 - [0.01 A]) H$	3.655 SD = 0.714	0.0503 H - 0.136 A - 4.488
	Female: $(2.10 - [0.007 A]) H$ (sitting position)		
TLC (L)	Male: 3.4 m	5.398 SD = 0.972	0.037 H - 0.007 A - 3.187
	Female: 2.51 m (sitting position)		
FRC (L)	Male: $(0.005 A + 1.67) H$	2.95 SD = 0.722	
	Female: $(0.007 A + 1.2) H$ (sitting position)		
2. Mean values at rest for respiratory parameters			
China		India	Ivory Coast
V_T (L)	Male: 0.594 SD = 0.183	0.454 SD = 0.148	0.750 SD = 0.215
	Female: 0.440 SD = 0.136		
Frequency (min^{-1}) V_E (L min^{-1})		0.372 SD = 0.115	0.600 SD = 0.190
		Male: 8.98 SD = 2.83	19
		Female: 7.82 SD = 2.05	

VC = vital capacity; TLC = total lung capacity; FRC = functional residual capacity; SD = standard deviation; V_T = tidal volume; V_E = ventilation minute volume.

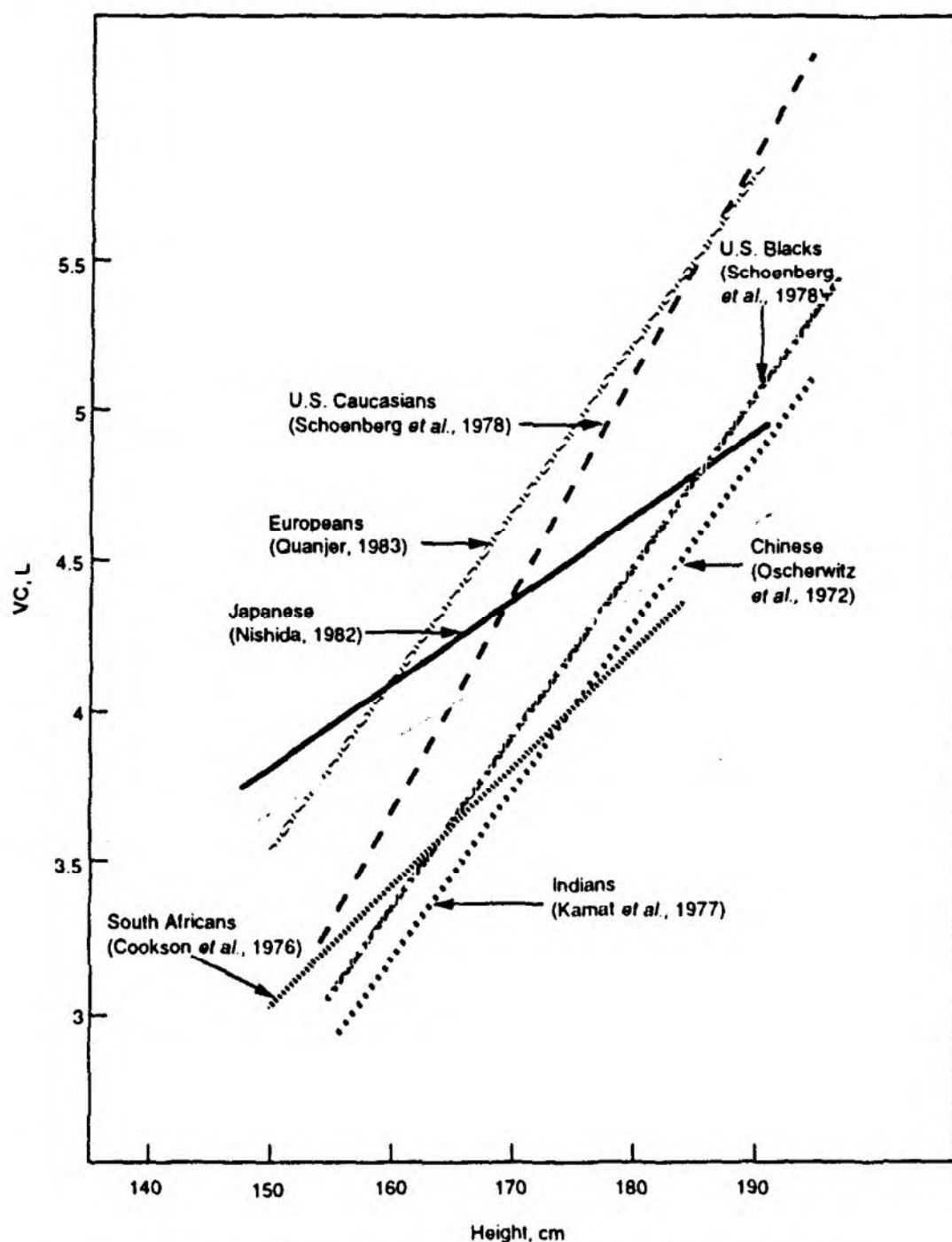


Fig. B.7. Interracial variations of vital capacity versus height in male adults.

10 or 11 y (Smeets *et al.*, 1990). Airflow follows the same pattern, but girls have somewhat lower values than boys.

(B51) *From 10 to 15 y, pubertal growth spurt* (Schrader *et al.*, 1984). The model for the relationship changes at puberty, because growth of stature and chest are not isomorphic. Specific regression values as a function of age are necessary before and after puberty (Jaeger-Denavit and Alphonse, 1990); e.g. the regression of FEV_1 for boys and girls as a function of height, H (in cm). FEV_1 can be described as a power function of height: $FEV_1 = a H^k$, where a is the slope of the log-log plot, and k is the allometric

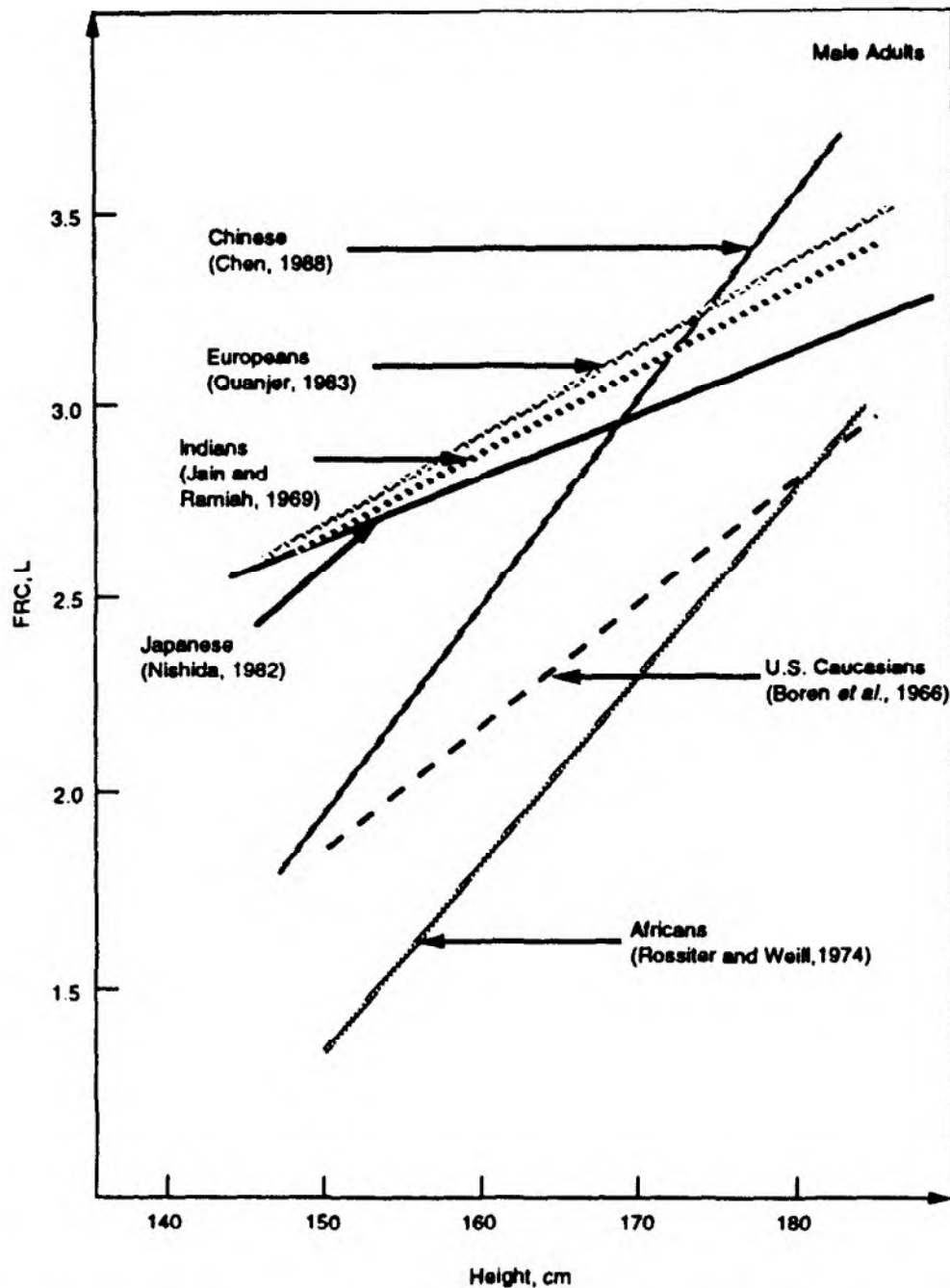


Fig. B.8. Interracial variations of functional residual capacity versus height in male adults.

constant. The allometric constant varies from 2.60 (12 y) to 3.04 (17 y) in boys and reverts to 2.4 in adults; it varies less in girls, increasing briefly before 12 y and decreasing from 2.87 to 1.95 at 15 y.

(B52) The slope of the curve is very high in boys: $1.86 < a < 7.53$ (mean = 3.99); a plateau is reached between 15 and 16 y. For girls, the slope decreases after 13 y, reaching the adult value near 15 y. This means that during puberty the relationship between lung function and height changes with age, and that a single power function will not cover the relationship from childhood to adulthood.

(B53) *Dynamic indices.*

- Maximum midexpiratory flow (MMEF) and normalized expiratory flow (MEF 25–75% FVC) are explained equally well by age and body height.
- The regression curves for flow volume (Erk and Deluniarski, 1984) are related to height by exponential model.

(B54) *From 15 to 18 y.* Volume and airflow are expressed by the model (Neukirch *et al.*, 1982):

- $y = \alpha \text{ height}^\beta \text{ age}^\gamma$ (for girls)
- $y = \alpha \text{ height}^\beta \text{ weight}^\gamma \text{ age}^\delta$ (for boys).

B.4.3.1. *Reference values for Caucasians*

(B55) Equations for calculation of lung volumes and maximal voluntary ventilation have been selected for children of various ages (Table B.4). Values for body heights and weights from birth to adulthood are given in Table B.5.

Table B.4. Lung function: reference values for Caucasian children^a

1. Reference values as functions of Age, A (in y); Height, H (in cm); and Weight, W (in kg)		
Vital capacity		
VC (mL)	0–3 y (Gaultier <i>et al.</i> , 1979) Male: $-536 + 12.27 H$, SD = 43 Female: $-527 + 11.97 H$	3–17 y (Cherniack, 1962) Male: $-3655 + 40.53 H + 51.34 A$ Female: $-2554 + 27.86 H + 90.96 A$
Total lung capacity		
TLC (mL)	0–3 y (Gaultier <i>et al.</i> , 1979) Male: $-815 + 18.17 H$, SD = 61.5 Female: $-815 + 18.17 H$, SD = 61.5	11–15 y (Dab, 1982) Male: $282 e(0.0175 H)$ Female: $309 e(0.0166 H)$
	6–14 y (Engström <i>et al.</i> , 1956) Male: $4.13 \times 10^{-3} \times H^{2.73}$ Female: $4.13 \times 10^{-3} \times H^{2.73}$	16–22 y (Dab, 1982) Male: $965 e(0.0107 H)$ Female: $1132 e(0.00826 H)$
Functional residual capacity		
FRC (mL)	0–3 y (Gaultier <i>et al.</i> , 1979) Male: $-269 + 6.9 H$, SD = 26 Female: $-204 + 5.92 H$, SD = 28.9	11–15 y (Dab, 1982) Male: $126 e(0.0181 H)$ Female: $68.2 e(0.0217 H)$
	5–17 y (Helliesen <i>et al.</i> , 1958) Male: $0.88 \times 10^{-3} H^{2.91}$, RSD = 21% Female: $0.88 \times 10^{-3} H^{2.91}$, RSD = 21%	16–22 y (Dab, 1982) Male: $225 e(0.0150 H)$ Female: $408 e(0.00989 H)$
Anatomical dead space		
V_D (mL)	0–4 y (Cook <i>et al.</i> , 1955) Male/Female: $2.5 \times W$	4–42 y (Hart <i>et al.</i> , 1963) Male/Female: $758.5 \times 10^{-6} \times H^{2.363}$ RSD: 16.9%
	7–40 y (Wood <i>et al.</i> , 1971) Male/Female: $45 \times 10^{-6} \times H^{2.92}$	
Physiological dead space		
V_{Dp} (mL)	Male: $1.54 W + 0.049 V_T \text{ mL} + 2$, SD = 22 (Godfrey, 1973) Female: $1.54 W + 0.049 V_T \text{ mL} + 2$, SD = 22	
2. Maximum voluntary ventilation (Doershuk <i>et al.</i> , 1975)		
$MV\dot{V}(\text{L min}^{-1}) = 1.28 H - 100$		

^a See also Table B.5. SD = standard deviation; RSD = relative standard deviation.

Table B.5. Mean values for height and weight in children (Fabry [1963], Tanaka *et al.* [1979], Chen [1988], Schoenberg *et al.* [1978], and Huizinga and Glanville [1968])

Age	Height, mean values, cm						Weight, mean values, kg					
	US*			Europe*			Japan			US*		
	Male	Female		Male	Female		Male	Female		Male	Female	
Birth												
1 mo			50			49.8			50			3.3
2 mo						53.5						3.2
3 mo						57						4.15
6 mo			60			59.5						4.95
9 mo			66			66						5.65
1 y			70.5			70						7.40
2 y			75			73.5						8.65
3 y			87.5			83						9.5
4 y			96			92						11.5
5 y			103			97.7						13.4
6 y			110			103						15.1
7 y			116			110						16.6
8 y			122.5			116						19.0
9 y			128			122						21.0
10 y			133.5			127.5						23.2
11 y			139			132.5						25.5
12 y			145.5			137						28.2
13 y			150.5			141.5						31.0
14 y			156			146						34.0
15 y			162.5			151.5						38.0
16 y			168.5			157						41.7
17 y			172.8			163						46.2
18 y			174.0			166.5						49.0
19 y			174.0			168						51.7
Adult	174	162		168	158		159	154		52.0	50.0	41.0
							165	166		57.5	53.0	46.5
										61.7	55.0	49.0
										65.0	56.2	52.5
										67.3	57.0	54.0
							166	154		69.5	57.8	56
							166	154		71.3	58.2	58
												50

* Caucasians.

Table B.5.—*continued*

Age	Height, mean values, cm						Weight, mean values, kg					
	Chinese		US Blacks		Equatorial Africans		Chinese		US Blacks		Equatorial Africans	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
7 y		119					20					
8 y		123			136		22		29		28	
9 y		128					25					
10 y		133			136		27				29	
11 y		138					30					
12 y		144			143		34		45		32	
13 y		151					40					
14 y	157	154			146	150	44	44			35	39
15 y	162	155					49	46				
16 y	166	156	171	157	154	157	52	48	67	56	38	44
17 y	167	157					55	49				
18 y	168	157	175	161	159	157	56	50	72	78	44	44
19 y	170	158			166	154	57	50			48	52
Adult	168	157	175	164	170	159	59	53	80	75	61	51

B.4.3.2. Other ethnic groups

(B56) Among the various populations, growth patterns with increasing age are not always similar, and adult size is not always reached everywhere at the same age (Fig. B.9). The relationships between VC and body height (Fig. B.10) show different slopes among the various ethnic groups, American Caucasians being very close to European Caucasians, Chinese close to Polynesians, and American blacks close to African blacks. The slopes for FRC are slightly different from VC (Fig. B.11).

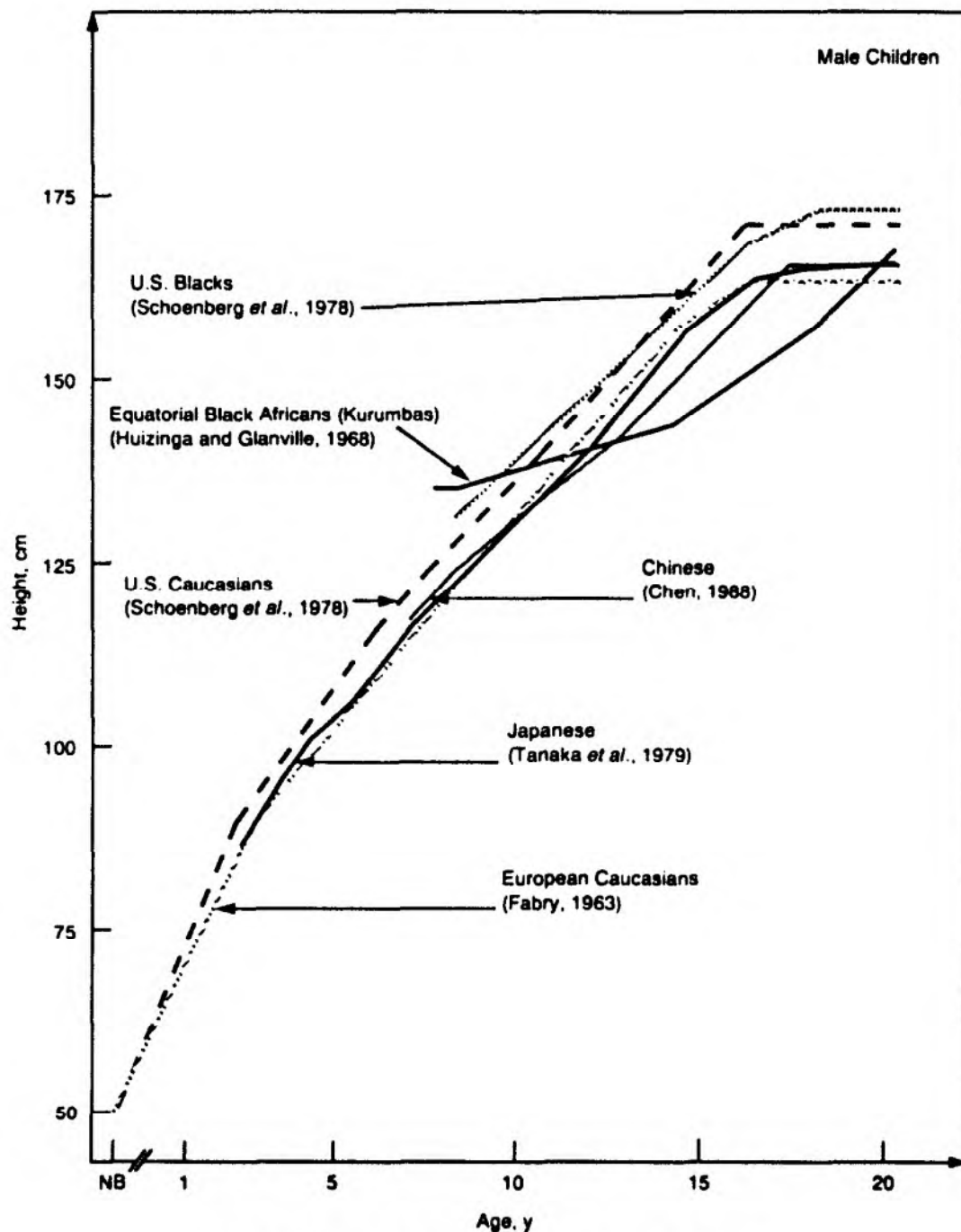


Fig. B.9. Body height versus age during growth period.

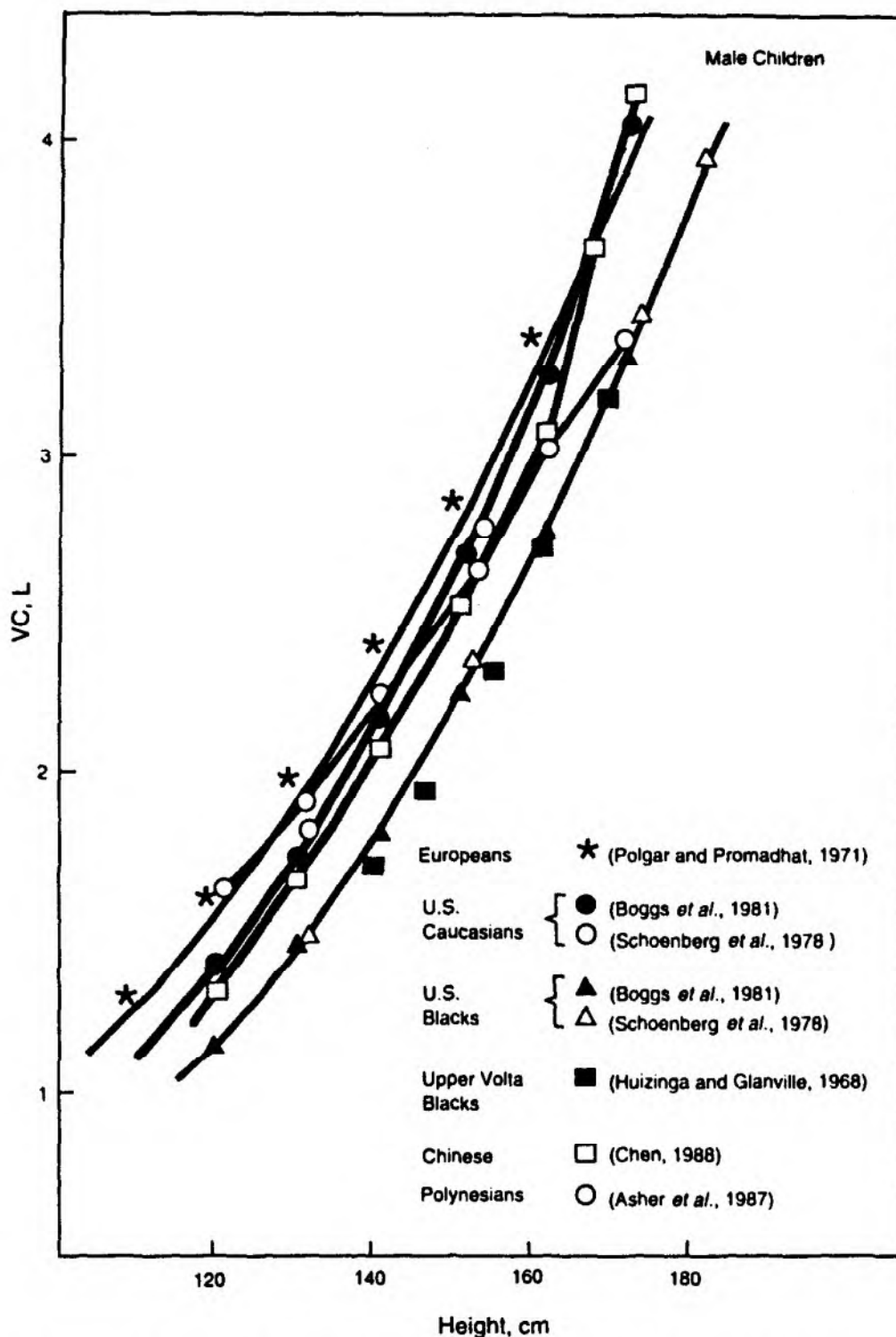


Fig. B.10. Interracial variations of vital capacity versus height in male children.

B.5. Modifying Factors

(B57) Impairment of lung function is generally the consequence of severe disease. Some circumstances, however, tend to modify lung volumes and flow rates as well as minute ventilation. Aging is known to decrease lung function; after 25 y, VC decreases about 30 mL in men and 24 mL in women every year (Bossé *et al.*, 1980). Food

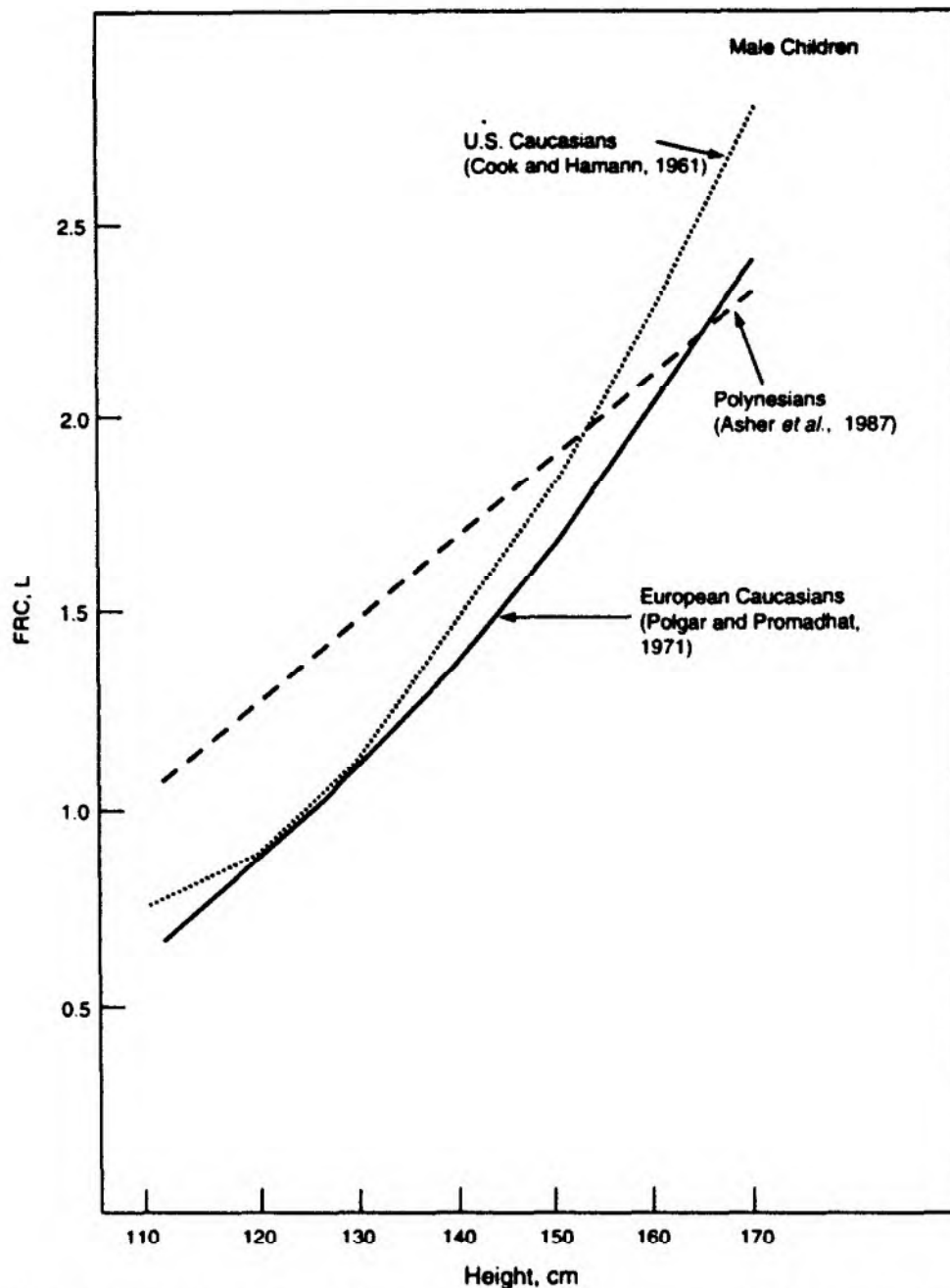


Fig. B.11. Interracial variations of functional residual capacity versus height in male children.

deprivation in children, especially lack of protein and vitamin D, is known to result in reduced lung volume. Enhanced pulmonary volume occurs among people who live at high altitudes or in cold climates, and in those who have high activity levels or who undergo physical training.

(B58) **Smoking.** Although there are very few quantitative studies, the age-dependent decline of most spirometric values appears to be qualitatively greater in smokers than in nonsmokers. It is clear now that smoking increases the risk of lung cancer; usually smoking induces pulmonary diseases, especially chronic obstructive lung disease.

(B59) **Disease.** Among patients with pulmonary disease, two principal groups of subjects have abnormal ventilation physiology: patients with restrictive lung function

(small lung volumes) and patients with obstructive lung function (low flow rates and high airway resistances). In both kinds of patients, breathing at rest is impaired, and ventilation during exercise is even more difficult because tidal volume (for restrictive function) and both tidal volume and frequency (for obstructive function) are considerably diminished and lead to dyspnea.

(B60) *Incidence of pulmonary pathology among population groups* (Epidemiological Health, 1982). Average respiratory morbidity in the Canadian population for 1978–1979 (as reported by the Canadian Health Department) was:

Disease	% Total population
Allergies	8.5
Acute respiratory diseases	3.1
Flu	2.7
Bronchitis and emphysema	2.2
Asthma	2.1
Total	18.6

For obstructive respiratory disease, the following data are available:

	Smokers (%)	Nonsmokers (%)	All (%)
United Kingdom^a			
Chronic bronchitis	5	4	5
FEV ₁			
60% of predicted value	0	2	1
80% of predicted value	12	7	10
More than one disease y ⁻¹	2	4	3
France, General Population (1986)^b			
Asthma	2.7		
Chronic obstructive pulmonary disease (COPD)	4.5		

^a Male telecommunications workers (Lloyd *et al.*, 1986).

^b Comité de lutte contre les maladies respiratoires, Paris.

B.6. Model Considerations: Parameters for ICRP Respiratory Tract Dosimetric Model

(B61) Dosimetric calculations for inhaled radioactive particles and gases require reference values for lung volumes, body heights and weights, and volumes of air breathed every day by the subjects of interest, such as workers and members of the general population.

B.6.1. Recommended Values for Specific Known Populations

(B62) Reference values from the literature for heights, weights, and lung volumes are given in Table B.6 for healthy Caucasians. The ICRP representative subjects are

- adult males and females, more than 17 y old
- children at 3 months, 1 y, 5 y, 10 y, and 15 y.

Table B.6. Biometry and lung volumes for Caucasians: children and 30-y-old adults

	3 mo	1 y	5 y	10 y	15-y		Adult	
					Male	Female	Male	Female
Height (cm)	60 ^a	75 ^a	110 ^a	138 ^a	169 ^a	161 ^a	176 ^a 168 ^b -178 ^c	163 ^a 158 ^b -166 ^c
Weight (kg)	6.0 ^a	10 ^a	20 ^a	33 ^a	57 ^a	53 ^a	73 ^a 65 ^b -80 ^c	60 ^a 54 ^b -61 ^c
TLC (mL)								
M:	307	548	1545 ^f	2869 ^f	5430 ^d	4470 ^d	6982	4968
SD:	61.5 ^e	61.5 ^e					700 ^g	600 ^g
FRC (mL)								
M:	150	244	767	1484	2677	2325	3301	2681
RSD:	28 ^e	26 ^e	161 ^h	311 ^h	562 ^h	488 ^h	600 ^g	500 ^g
VC (mL)								
M:	195	377	1012	2326	3960	3300 ⁱ	5018	3551
SD:	43 ^e	47 ^e					560 ^g	420 ^g
V _D (mL)								
M:	14 ^j	20 ^j	46 8.5 ^k	78 14.9 ^k	130 22 ^k	114 19 ^k	146 25.5 ^k	124 21 ^k

^a These values were provided by the Reference Person Task Group.

^b Sliman *et al.* (1981).

^c Schoenberg *et al.* (1978).

^d Dab (1982).

^e Gaultier *et al.* (1979).

^f Engström *et al.* (1956).

^g Quanjer (1983).

^h Helliesen *et al.* (1958).

ⁱ Cherniack (1962).

^j Cook *et al.* (1955).

^k Hart *et al.* (1963).

M = mean; SD = standard deviation; TLC = total lung capacity; FRC = functional residual capacity; VC = vital capacity; V_D = anatomical dead space.

Mean values and standard deviations are given for each parameter when possible. A residual standard deviation is given when the parameter is calculated from a regression on age, height, and weight. In adults, heights and weights include a central value, considered as the most probable for the Caucasian population, and extremes, representing the mean values of Jordanians (the lowest) (Sliman *et al.*, 1981) and U.S. Caucasians (the highest) (Schoenberg *et al.*, 1978). Reference values for some other ethnic groups are given in a similar way, when available from the literature (Tables B.7-B.13).

B.6.2. Ventilation Rates and Breathing Parameters

(B63) To assess average inspired air volumes both indoors and outdoors, it is necessary to establish modern standards for daily activities and breathing rates, according to age and gender, for several chosen groups of people: sedentary employed men, sedentary employed women, housewives with two children, housewives without children, students, school children, etc. The final aim was to assess average inspired air volume both outdoors and indoors in defined places and residences during the day (Roy and Courtay, 1991). To be consistent with the age-group divisions given in *ICRP Publication 56* (ICRP, 1989), people were separated into:

- adults: age > 17 y
- children: 3 months, 1 y, 5 y, 10 y, and 15 y.

Table B.7. Biometry and lung volumes in Japanese

		Adults				
		3 mo	1 y	10 y	Male	Female
Height (cm) ^a	M	62	74	133	170	158
	SD				5.6	5
Weight (kg) ^a	M	6.5	9	29	64.5	52.8
	SD				8.8	6.7
TLC (mL) ^b	M				5580	3910
	SD				690	490
FRC (mL) ^b	M				2890	2040
	SD				630	370
VC (mL) ^b	M				4370	3000
	SD				490	390

^a Tanaka *et al.* (1979).^b Nishida (1982).

TLC = total lung capacity; FRC = functional residual capacity; VC = vital capacity; M = mean; SD = standard deviation.

Table B.8. Biometry and lung volumes in Chinese

		Adults ^a						
		3 mo ^a	1 y ^b	5 y ^b	10 y ^b	15 y ^b	Male	Female
Height (cm)	M	62	76	108	136	161	168	157
	SD						5.5	5
Weight (kg)	M	6.5	9.6	17	28	48	59	53
	SD						5.7	5.4
TLC (mL)	M						5398	3845
	SD						972	538
FRC (mL)	M						2950	2122
	SD						722	38
VC (mL)	M				1850	3050	3656	2511
	SD				281		710	460

^a Chen, X. A. (1984, personal communication [1989]).^b Chen (1982).

TLC = total lung capacity; FRC = functional residual capacity; VC = vital capacity; M = mean; SD = standard deviation.

Table B.9. Biometry and lung volumes in Asian Indian adults^a

		Male	Female
Height (cm)	M	166.8	153.7
	SD	6.4	6.5
Weight (kg)	M	56.2	48.4
	SD	7.6	8.3
VC (mL)	M	3590	2310
	SD	540	420

^a Kamat *et al.* (1977).

VC = vital capacity; M = mean; SD = standard deviation.

Table B.10. Biometry and lung volumes in US blacks^a

		10 y	Male	Female
Height (cm)	M	140	175	162
	SD	12	6.4	3.6
Weight (kg)	M	38	80	70
	SD	12	16.7	15.4
VC (mL)	M	2350	4140	2990
	SD	640	370	480

^a Schoenberg *et al.* (1978).

VC = vital capacity; M = mean; SD = standard deviation.

Table B.11. Biometry and lung volumes in Senegalese

		Adult ^b				
		5 y ^a	10 y ^a	15 y ^a	Male	Female
Height (cm)	M	108	136	164	176	165
	SD	4.5	6.6	7.7	6	5
Weight (kg)	M	18	28	45	67.5	63
	SD	2.4	4.5	7.5	9.4	11.9
VC (mL)	M	823	1715	2825	4210	2970
	SD	140	291	480	490	490

^a Seck *et al.* (1990).^b Dufétel *et al.* (1989).

VC = vital capacity; M = mean; SD = standard deviation.

Table B.12. Biometry and lung volumes in Rhodesian African adults^a

		Male	Female
Height (cm)	M	171	161
	SD	7.1	5.9
Weight (kg)	M	64	64
	SD	13.9	8.9
VC (mL)	M	3940	3010
	SD	650	420

^a Cookson *et al.* (1976).

VC = vital capacity; M = mean; SD = standard deviation.

Table B.13. Biometry and lung volumes in Native American adults^a

		Male	Female
Height (cm)	M	172.1	158.8
	SD	6.4	6.2
Weight (kg)	M	78.3	68.6
	SD	12.8	15.1
VC (mL)	M	4710	3400
	SD	780	570

^a Crapo *et al.* (1988).

VC = vital capacity; M = mean; SD = standard deviation.

B.6.2.1. Time budgets

(B64) Values have been previously published in *ICRP Publication 23* (ICRP, 1979), UNSCEAR (1982), *ICRP Publication 50* (ICRP, 1987), and UNSCEAR (1988); the latter used Brown's data (Brown, 1983), which were based on a 1978 British Broadcasting Corporation survey of time budgets of people over 5 y of age in Great Britain. Such data have also been gathered by the Multinational Comparative Time Budget Research Project, and discussed by Szalai in 1972. About 30,000 people from 12 countries in Europe, the United States, Peru, and the Soviet Union participated in this study. These data were later used by Moschandreas (1981) to evaluate exposure to airborne pollutants. To update the subject, more recent information was noted on daily activities of categories of populations. Economic surveys provided time budgets and activities (INSEE, 1988, 1989a,b,c,d). They led to values of the time spent indoors higher by 5–10% than those published by Anderson *et al.* (1985) in a U.S. Environmental Protection Agency report giving detailed time budgets of the U.S. population.

(B65) Two groups of workers were not included in the INSEE surveys: outdoor workers (farm workers, construction workers, etc.) and miners; for outdoor workers, we assumed the same time-budget as for sedentary workers, but the exercise level was assumed to be higher.

B.6.2.2. Ventilation parameters

(B66) It was necessary to estimate respiratory frequencies (f_R), V_T , and ventilation minute volumes ($\dot{V}_E$) according to age and level of exercise. In untrained adult men, four main activities were selected, and the corresponding values of work load and minute ventilation were taken from the literature (ICRP, 1975; Dejours, 1982; Scherrer, 1981). (See Table B.14.)

Exercise levels were chosen as follows for adults:

- Light exercise: one-third of highest work load completed ($W_{\max}$ measured by Godfrey *et al.*, 1971); this level of exercise corresponds to:
 - working in laboratories and workshops
 - active housecleaning
 - painting, woodworking, etc.

Table B.14. Relationship between workload and minute ventilation in adult men

Activity	Workload		$\dot{V}_E$ (L min ⁻¹)	B (m ³ h ⁻¹)
	Watts	% Maximum workload ($W_{\max}$) completed ^a		
Sleep	20	8	7.5	0.45
Sitting	30	12	9	0.54
Light exercise	80	32	25	1.5
Heavy exercise	160	64	50	3

^a Maximum workload = 250 W.

$\dot{V}_E$ = ventilation minute volume; B = ventilation rate.

- Heavy exercise: two-thirds of $W_{\max}$ is appropriate for periods of time not exceeding 2 h d⁻¹ for:
 - firemen, construction workers, farm workers
 - athletes, etc.

These levels of exercise or work are consistent with *ICRP Publication 23* (ICRP, 1975). They are slightly lower than those given by Anderson *et al.* (1985), who emphasized high activity levels.

(B67) In women and children, breathing parameters were scaled from the values for males according to published experimental data (Table B.15):

- 3 month: V_T were calculated from Gaultier (1978), for:
 - sleep, 6 mL kg⁻¹
 - light exercise, 10 mL kg⁻¹ or CVC/3.

f_R come from Gaultier (1978) and Taussig *et al.* (1977).

- 1 y: V_T were calculated from Gaultier (1978) for:
 - sleep, 6.5 mL kg⁻¹
 - sitting awake, 9 mL kg⁻¹
 - light exercise, 11 mL kg⁻¹ or CVC/3.

f_R come from Gaultier (1978) and Taussig *et al.* (1977).

- 5 y: V_T and f_R , for:
 - sleep and sitting awake come from Taussig *et al.* (1977)
 - light exercise come from Godfrey *et al.* (1971).
- 10 y and 15 y: V_T and f_R , for:
 - sleep come from Gaultier *et al.* (1981)
 - sitting awake come from Gaultier *et al.* (1981) and Zapletal *et al.* (1987)
 - light and heavy exercise come from Godfrey *et al.* (1971), Godfrey (1973), Cooper and Weiler-Ravell (1984), Flandrois *et al.* (1982).
- adults: V_T and f_R , for:
 - sleep and sitting awake come from Cotes (1979)
 - light and heavy exercise come from Cooper and Weiler-Ravell (1984).¹

B.6.2.3. Volumes of air breathed daily

(B68) Standard activities were attributed to defined periods of the day; ventilation rates were associated with each of them for defined categories of people:

- In the general population and in sedentary workers, daytime was calculated to be spent:
 - indoors (at home, work, or elsewhere), while sleeping, or awake, one-third of the time sitting and two-thirds in light exercise;
 - outdoors (in the open air or in cars, trains, buses, etc.), one-half of the time sitting, three-eighths in light exercise and one-eighth in heavy exercise.
- In heavy workers (in the open air, or in factories), seven-eighths of the time was spent in light exercise and one-eighth in heavy exercise (Monod and Flandrois, 1985).

(B69) Tables B.16A and B.16B give these data for all the population categories including workers; the volumes of air breathed per day are summed for each situation.

¹ Values for 17-y-olds are presumed to apply to adults.

Table B.15. Ventilation parameters by age and gender

Maximum workload, % completed:	Activity ^{a,b}											
	Resting (sleeping)				Sitting				Light exercise			
	f_R (min ⁻¹)	TV (L)	$\dot{V}_E$ (m ³ h ⁻¹)	f_R (min ⁻¹)	TV (L)	$\dot{V}_E$ (m ³ h ⁻¹)	f_R (min ⁻¹)	TV (L)	$\dot{V}_E$ (m ³ h ⁻¹)	f_R (min ⁻¹)	TV (L)	$\dot{V}_E$ (m ³ h ⁻¹)
8					12			32			64	
Breathing parameters												
Age												
3 mo	38 ^{c,d}	0.039 ^c	0.09 ^{c,d}				48 ^{c,d}	0.066 ^c	0.19 ^{c,d}			
1 y	34 ^{c,d}	0.074 ^c	0.15 ^{c,d}	36 ^{c,d}	0.102 ^c	0.22 ^{c,d}	46 ^{c,d}	0.127 ^c	0.35 ^{c,d}			
5 y	23 ^d	0.174 ^d	0.24 ^d	25 ^d	0.213 ^d	0.32 ^d	39 ^c	0.244 ^c	0.57 ^c	44 ^{c,f}	0.841 ^{c,f}	2.22 ^{c,f}
Male												
10 y												
Male and female	17 ^e	0.304 ^e	0.31 ^e	19 ^{e,h}	0.333 ^{e,h}	0.38 ^{e,h}	32 ^{c,f}	0.583 ^{c,f}	1.12 ^{c,f}			
Female												
Male	14 ^e	0.500 ^e	0.42 ^e	15 ^{e,h}	0.533 ^{e,h}	0.48 ^{e,h}	23 ^{c,f,i,j}	1.0 ^{c,f,i,j}	1.38 ^{c,f,i,j}	46 ^{c,f}	0.667 ^{c,f}	1.84 ^{c,f}
15 y										36 ^{c,f,i,j}	1.352 ^{c,f,i,j}	2.92 ^{c,f,i,j}
Female	14 ^e	0.417 ^e	0.35 ^e	16 ^{e,h}	0.417 ^{e,h}	0.40 ^{e,h}	24 ^{c,f,i,j}	0.903 ^{c,f,i,j}	1.30 ^{c,f,i,j}	38 ^{c,f,i,j}	1.127 ^{c,f,i,j}	2.57 ^{c,f,i,j}
Male	12 ^e	0.625 ^e	0.45 ^e	12 ^e	0.750 ^e	0.54 ^e	20 ^{e,h}	1.25 ^{e,h}	1.5 ^{e,h}	26 ^{e,h}	1.923 ^{e,h}	3.0 ^{e,h}
30 y												
Female	12 ^e	0.444 ^e	0.32 ^e	14 ^e	0.464 ^e	0.39 ^e	21 ^{e,h}	0.992 ^{e,h}	1.25 ^{e,h}	33 ^{e,h}	1.364 ^{e,h}	2.7 ^{e,h}

^a ICRP (1975).^b Scherrer (1981).^c Godfrey (1973).^d Gaultier (1978).^e Taussig *et al.* (1977).^f f_R = frequency, TV = tidal volume, $\dot{V}_E$ = ventilation minute volume.^h Godfrey *et al.* (1971).ⁱ Godfrey (1973).^j Gaultier *et al.* (1981).^k Zapletal *et al.* (1987).^l Cooper and Weiler-Ravell (1984).^m Flandrois *et al.* (1982).ⁿ Cotes (1979).

(B70) In Table B.17 workers are treated apart from the general population and separated into "sedentary" and "heavy"; an average working day was divided into three periods of 8 h each, according to ICRP recommendations.

B.6.2.4. Comparison with previous reference values

(B71) *ICRP Publication 23* (ICRP, 1975) recommended dividing the day into three periods of 8 h of activities and ventilation minute volume ($\dot{V}_E$, L min⁻¹):

	Male	Female	10 y	1 y	Newborn
8 h working	20	19	13		
8 h nonoccupational	20	19	13	4.2 (10 h)	1.5 (1 h)
8 h resting	7.5	6	4.8	1.5 (14 h)	0.5 (23 h)
Total air (m ³ d ⁻¹)	22.8	21.12	14.78	3.78	0.78

Later, UNSCEAR (1982) and *ICRP Publication 50* (ICRP, 1987) established the following values for men in the general population:

	UNSCEAR (1982)	ICRP (1987)
Indoors 19 h	5.5 h at 20 L min ⁻¹ 8 h at 7.5 L min ⁻¹ 5.5 h at 12.5 L min ⁻¹	19 h at 0.75 m ³ h ⁻¹
Outdoors 5 h	2 h at 20 L min ⁻¹ 3 h at 12.5 L min ⁻¹	1.0 m ³ h ⁻¹
Total air (m ³ d ⁻¹)	18.975	19.25

(B72) In 1988, the UNSCEAR report simplified its dosimetric coefficients. The same mean breathing rate of 0.8 m³ h⁻¹ was assumed both for indoor and outdoor residence. Thus the mean daily breathing volume was 19.20 m³.

(B73) Compared with *ICRP Publication 23*, the total volume of air breathed every day at each age, calculated by this method, is almost equal for adult males and for 10-y-old children, but slightly lower for adult females and higher for 1 y olds and newborns in the general population. The values attributed to adults are close to the ones recommended by *ICRP Publication 50*, which are average values, for males and females.

(B74) The values obtained for workers (Table B.17) are close to those recommended by *ICRP Publication 23* (ICRP, 1975); however, to take into account higher ventilation rates required by some workers (firemen, construction workers, farm workers) a "heavy-worker class" is added, so as not to underestimate their exposure under possible critical situations.

(B75) Recently, Layton (1993) proposed a different approach for the evaluation of daily ventilation rates based upon daily energy expenditure among various age cohorts of both genders. This methodology deals with daily intakes of food from dietary surveys made in California. Average energy expenditure was either calculated as a ratio to basal metabolism or was calculated from time/activity surveys. The basis of this method is the estimation of a breathing rate, using the ventilatory equivalent, by estimating the oxygen

Table B.16A. Recommended values of daily ventilation rates for dosimetric modelling: children in general population

Age		3 mo	1 y	5 y	10 y	15 y (M)	15 y (F)
		Duration of activity and ventilation rates					
Location	Activity	h d^{-1}	$\text{m}^3 \text{h}^{-1}$	h d^{-1}	$\text{m}^3 \text{h}^{-1}$	h d^{-1}	$\text{m}^3 \text{h}^{-1}$
Indoors	Sleep	17	0.09	14	0.15	12	0.24
	Housework, free time, etc.	7	0.19	5	0.31 ^a	6	0.49 ^a
	TOTAL air breathed, $\text{m}^3 \text{d}^{-1}$	2.86	3.65	3.65	10.06	10.71	11.15
	Work + other			3	0.87 ^a	4	0.93 ^c
At work or elsewhere	TOTAL air breathed, $\text{m}^3 \text{d}^{-1}$		1.24	1.47	2.61	3.72	2.55
	TOTAL air breathed indoors, $\text{m}^3 \text{d}^{-1}$	2.86	4.89	7.29	12.67	14.43	13.70
	Heavy work						
Outdoors	Travel, sports, etc.			1	0.31 ^a	3	0.87 ^a
	TOTAL air breathed outdoors, $\text{m}^3 \text{d}^{-1}$		0.31	1.47	2.61	5.67	2.02
	GRAND TOTAL, $\text{m}^3 \text{d}^{-1}$	2.86	5.20	8.76	15.28	20.10	15.72
ICRP (1975), $\text{m}^3 \text{d}^{-1}$		(0.780)	(3.780)	(14.784)			

^a Ventilation rate: 1/3 sitting + 2/3 light exercise.^b Ventilation rate: 1/2 sitting + 3/8 light exercise + 1/8 heavy exercise.^c Ventilation rate: 1/2 sitting + 1/2 light exercise.^d Ventilation rate: 2/3 light exercise + 1/3 heavy exercise.

Table B.16B. Recommended values of daily ventilation rates for dosimetric modelling: adults over 17 y in general population

Location	Activity	Sedentary Workers									
		Housewife		Male				Female			
		Duration of Activity and Ventilation Rates									
		h d ⁻¹	m ³ h ⁻¹	h d ⁻¹	m ³ h ⁻¹	h d ⁻¹	m ³ h ⁻¹	h d ⁻¹	m ³ h ⁻¹	h d ⁻¹	m ³ h ⁻¹
Indoors	At home										
	Sleep	8.5	0.32	8.5	0.45	8.5	0.32	8.5	0.45	8.5	0.45
	Housework, free time, etc.	13.5	0.96 ^a	7	1.18 ^a	9.5	0.96 ^a	7	1.18 ^a	7	1.18 ^a
	TOTAL air breathed, m ³ d ⁻¹	15.68		12.09			11.84		12.09		12.09
Elsewhere	Miscellaneous	1	0.96 ^a	6.5	1.18 ^a	4	0.96 ^a	1	1.18 ^a		
	TOTAL air breathed, m ³ d ⁻¹	0.96		7.67			3.84		1.18		
	TOTAL air breathed indoors, m ³ d ⁻¹	16.64		19.76			15.68		13.27		
Outdoors	Heavy work ^d										
	Travel, sports, etc.	1	1.00 ^c	2	1.21 ^c	2	1.00 ^c	6	1.69 ^b	1.5	1.21 ^c
	TOTAL air breathed outdoors, m ³ d ⁻¹	1.00		2.42			2.00		11.96		
GRAND TOTAL, m ³ d ⁻¹		17.64		22.18			17.68		25.23		
ICRP (1975), m ³ d ⁻¹		(21.120)		(22.800)			(21.120)				
ICRP (1978), UNSCEAR (1982), and UNSCEAR (1988)				(18.975)							

^a Ventilation rate: 1/3 sitting + 2/3 light exercise.^b Ventilation rate: 7/8 light exercise + 1/8 heavy exercise.^c Ventilation rate: 1/2 sitting + 3/8 light exercise + 1/8 heavy exercise.^d The mean ventilation rate estimated for underground miners engaged in heavy manual work is not significantly higher than the 1.18 m³ h⁻¹ assumed for sedentary workers (see Section B.76.).

Table B.17. Recommended values of daily ventilation rates^a for dosimetric modelling: adult workers

Activity	Sedentary worker		Heavy worker
	Male	Female	Male
Sleeping (8 h)	3.6 (3.6) ^b	2.6 (2.9)	3.6 (3.6)
Occupational (8 h)			
1/3 sitting	9.6 (9.6)	7.9 (9.1)	
2/3 light exercise			
7/8 light exercise			13.5 (9.6)
1/8 heavy exercise			
Nonoccupational (8 h)			
1/2 sitting			
3/8 light exercise	9.7 (9.6)	8.0 (9.1)	9.7 (9.6)
1/8 heavy exercise			
Total air breathed (m ³)	22.9 (22.8)	18.5 (21.1)	26.8 (22.8)

^a Volumes of air (m³) breathed in a working day.^b Values in parentheses from *ICRP Publication 23* (ICRP, 1975).

uptake associated with nutrient oxidation for production of energy. However, evaluating breathing rates from food intake requires several assumptions, some of which lead to underestimation because of nonlinearity in relationships and high individual variability of some factors; for example, the yield of food intake to energy expenditure and the oxygen quantity required for its oxidation. However, the major uncertainty lies in the value of the respiratory equivalent, relating oxygen uptake to ventilation minute volume; this relationship is nonlinear with activity levels among individuals, and also varies broadly with dietary habits and metabolic characteristics, such as production of organic acid and the pH balance in the organism maintained by adaptive carbonic acid elimination by breath.

(B76) Because respiration is not exclusively an oxygen supply mechanism, average daily ventilation rates have been estimated directly from ventilation minute volumes required to support time-weighted physical activities of standard individuals from the population of interest. With this method, uncertainty arises more from the evaluation of daily activity levels than from the associated breathing rates derived from experimental data. To verify these estimates, experimental ventilation data in individuals performing various daily activities would be of interest. This has been done recently in South Africa among workers in conventional gold mines. In this study, 620 subjects² wore individual expired air analyzers while working; the oxygen consumption was related to their own heart frequency. Even if this method altered their relative respiratory parameters, tidal volume, and respiratory frequency (at least during the first minutes), it still gave a reliable value of the overall ventilation minute volume required for a variety of tasks. This study indicated that 70% of the miners performing heavy work had a ventilation rate greater than 1.2 m³ h⁻¹, and 15% greater than 1.5 m³ h⁻¹. The mean ventilatory rate estimated for underground workers was approximately 1.3 m³ h⁻¹. This rate applies to heavy workers and not to those in a more mechanised working environment.

² South African Chamber of Mines Research Organization. Underground Environment. Preliminary Report on Ventilation Rate of Mine Workers. D. G. Wymer and A. Van der Linde, personal communication, 1992.

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ANNEXE C. EFFECTS OF RADIATION ON THE RESPIRATORY TRACT

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C.1. Nonstochastic Risk

(C1) Early effects, acute and subacute, and late stochastic effects, can be expected following irradiation of the respiratory tract. The mechanisms of early damage to the respiratory tissues have been dealt with in great detail in *ICRP Publication 31* (ICRP, 1980a). Tissues at risk from nonstochastic effects do not need further investigation for radioprotection purposes. There is evidence, from data in beagle dogs, that deleterious nonstochastic effects in the lung do not provide a basis for dose limitation (Bair *et al.*, 1989). To improve radiotherapeutical applications of lung irradiation, additional data are

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needed on radiation necrosis of the extrathoracic airways, radiation pneumonitis, lung fibrosis, and impairment of local immunity defences. However, this aspect is beyond the scope of this report.

(C2) The lung parenchyma is the only tissue at risk for early effects. Whether exposure is by external irradiation or internal emitters, the changes in lung (radiation pneumonitis and fibrosis) are generally the same in animals and, presumably, the same in humans (NRC, 1985). The three clinical phases are: (1) early, up to about 2 months; (2) intermediate, from 2 months to 9 months; and (3) late. Early damage involves increased capillary permeability in the epithelial and endothelial lining of the alveoli, resulting in oedema and accumulation of inflammatory cells. Later, fibrosis of the alveolar septa predominates.

(C3) Experiments in animals have provided invaluable details on the response of the tissue in the case of continuing or multiple exposures. Occlusive vascular lesions were more prominent in dogs exposed to inhaled beta emitters than in those exposed to brief external x-irradiation (Slauson *et al.*, 1976, 1977). The severity of the reaction depends on the total dose (Collis and Steel, 1982; Phillips and Margolis, 1972), dose rate (Travis *et al.*, 1983; Depledge and Barrett, 1982), type of radiation (Mauderly *et al.*, 1980), and spatial clustering heterogeneity of class W and Y alpha emitters (Masse *et al.*, 1975).

(C4) Therapeutic modalities, notably corticosteroids (Gross, 1977) and pulmonary lavage in the case of inhaled radionuclides (Muggenburg *et al.*, 1976; Nolibé *et al.*, 1977), can influence the course of radiation pneumonitis.

(C5) Dose-effect relationships have been considered only in relation to lethality, but it can be inferred from the work by Mauderly and colleagues (1973, 1980) that the threshold dose for morbidity is about half the LD₅₀.

(C6) Available mortality data have been summarised (NRC, 1985) in the form of hazard functions (Fig. C.1). The effect of protraction is obvious. There are no available data for children, but experiments in animals suggest that children may be twice as sensitive as adults (McClellan *et al.*, 1982).

(C7) Cancer is the main detrimental effect associated with irradiation of the respiratory tract in workers or the general public. Cancers may develop in all tissues of the respiratory tract, but the regional sensitivity for carcinoma induction may vary strongly with histological type, genetic background, and lifestyle.

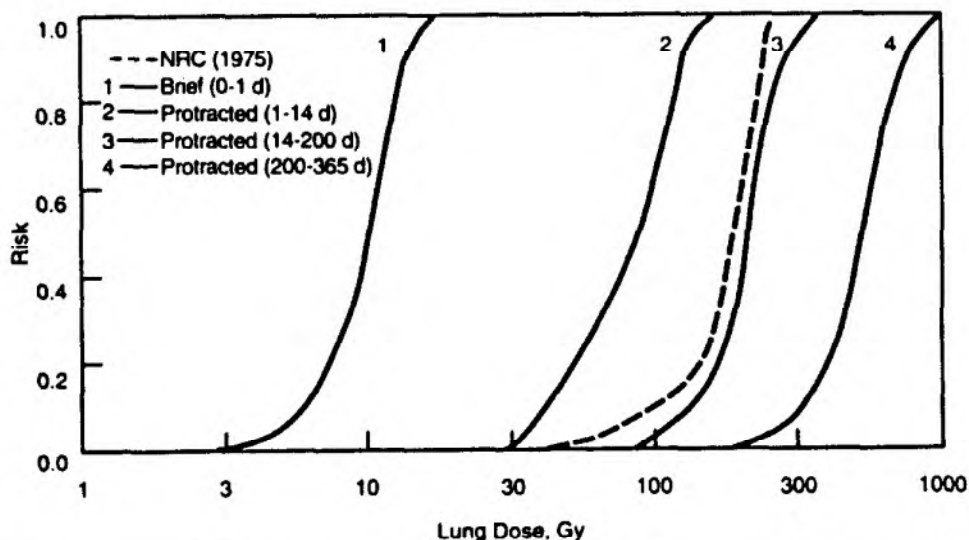


Fig. C.1. Dose-response functions for mortality from pulmonary syndrome criterion used in consequence model.

C.2. Basic Epidemiology of Respiratory Tract Cancers**C.2.1. Extrathoracic Airway**

(C8) Extreme variability exists in worldwide risks of upper airway cancers. Among the population of southern China, up to 18% of all malignant neoplasms may occur in the nasopharynx, compared to 0.25% in a worldwide survey among Caucasians (Batsakis, 1976). Age-adjusted mortality rates of laryngeal cancer vary by a factor of 70 in males and 15 in females in the worldwide population (Staszewski, 1985; see Table C.1).

Table C.1. Age-adjusted mortality rates per 100,000 for cancer of the larynx (Staszewski, 1985)

Location	Males	Females
France	12.34	0.37
Spain	7.39	0.21
Uruguay	7.24	— ^a
Italy	6.57	0.35
Hungary	6.11	0.44
Portugal	5.63	0.55
Yugoslavia	5.62	0.59
Cuba	5.13	0.86
Luxembourg	5.11	—
Romania	4.82	0.57
Singapore	4.77	—
Belgium	4.77	0.39
Poland	4.76	0.32
Czechoslovakia	4.47	0.14
Greece	4.29	0.48
Austria	3.89	0.27
Bulgaria	3.72	0.31
Hong Kong	3.67	—
Puerto Rico	3.12	1.09
Switzerland	3.08	0.30
Venezuela	2.63	1.08
Finland	2.63	—
Canada	2.43	0.27
Germany, F.R.	2.40	0.15
Chile	2.35	0.29
Australia	2.28	0.17
United States	2.26	0.37
Germany, D.R.	2.17	0.07
New Zealand	2.13	—
Ireland	2.07	0.82
Israel	2.04	—
Netherlands	1.92	0.16
Denmark	1.89	—
England and Wales	1.81	0.33
Mexico	1.74	0.59
Northern Ireland	1.73	0.82
Ecuador	1.65	—
Scotland	1.62	0.64
Japan	1.39	0.19
Sweden	0.94	—
Norway	0.90	—
Philippines	0.60	0.32
Thailand	0.18	—

^a No data available.

(C9) The prognosis for upper-airway cancers, though less dramatic than for lung cancer, depends strongly on the location of the tumour. Most basal cell carcinomas of the external nares are definitely cured by appropriate treatment. The incidence of cancers of the mouth, pharynx, and larynx is strongly influenced by smoking and alcohol consumption. Epstein-Barr virus may be associated with genetic factors in high-risk areas of nasopharyngeal cancers. Some occupational exposures, for example in former nickel refinery plants, in chromium industries, in places contaminated with isopropyl oil vapours, and in wood and leather industries (WHO/IARC, 1981) have been correlated with higher nasal tumour rates (especially adenocarcinomas).

(C10) Excess nasal and laryngeal cancers have been observed in luminiser workers and in patients receiving head and neck exposures (Batsakis, 1976), but not in atomic-bomb survivors or in patients treated for spondylitis (Darby *et al.*, 1985). Sinonasal cancers were described in humans (Evans *et al.*, 1969; Finkel *et al.*, 1969) as a result of systemic contamination by radium. Although the role of radon emanating from radium decay has been suspected as a cause, the incidence of sinonasal cancers is not greater than average in uranium miners; thus, the possible role of radon from radium decay is not clear. Nasal-cavity tumours have been observed in animals exposed to both alpha and beta emitters (Benjamin, 1983). Intranasal injection of radionuclides has resulted, both in humans and in animals, in a high incidence of epithelial cancer (Grampa, 1971; Jasmin *et al.*, 1977).

(C11) The lifetime probability for nasal cancer (excluding skin and nasopharyngeal tumours) in the United States is 0.4% of all cancers; for mouth and oropharyngeal (excluding lips), 3%; and for laryngeal, 1.4%. Male-to-female sex ratios are: nasopharyngeal, 2:3; mouth, 2:3; and laryngeal, 7:3. The incidence of upper-airway cancers (age-adjusted to the U.S. population of 1970) was 36% of all cancers in the respiratory tissues, compared with a mortality rate of 23% (OTA, 1982).

C.2.2. *Tracheobronchiolar Airways and Lung*

(C12) Tracheal tumours are rare, and there is no evidence that tracheal cancers are induced by ionising radiation. For epidemiological purposes, bronchial cancers are referred to as lung cancers.

C.2.2.1. *General population*

(C13) Lung cancer is the number one cause of death in males in industrialised countries; it is the number two killer of females in the United States. Recent results from U.S. epidemiological surveys indicate that lung cancer accounts for about 21% of all newly diagnosed cancer cases and 32% of all deaths in Caucasian males. In Caucasian females, this cancer represents about 8% of all new cancers and 13% of all cancer deaths.

(C14) Lung cancer incidence rates differ considerably throughout the world (WHO, 1983); the ratio between the lowest and highest rates is approximately 5 in males and 10 in females (Table C.2).

C.2.2.2. *Irradiated populations*

(C15) Several populations that received relatively large radiation exposure have been considered by the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and the Biological Effects of Ionizing Radiation (BEIR) committees to estimate cancer

Table C.2. Examples of high and low cancer rates in various populations. (Numbers given are age-standardised annual incidence rates per 100,000 population (WHO, 1983))

Site of cancer	Sex	High cancer incidence		Low cancer incidence	
		Population	Rate	Population	Rate
Nasopharynx	Males	Hong Kong	30.0	German Democratic Republic	0.3
		Singapore (Chinese)	18.1	England and Wales (rural)	0.3
		New Zealand (Pacific Polynesian Islanders)	14.1	Finland	0.3
Lung	Males	United States, New Orleans (black)	110.0	United States, Los Angeles (Filipino)	21.7
		United Kingdom, Scotland	91.1	Iceland	24.7
		Singapore (Chinese)	73.4	Sweden	25.3
	Females	United States, Alameda (white)	33.3	Italy, Ragusa	2.8
		China, Tiamin	28.8	France, Doubs	2.8
		United Kingdom, West Scotland	28.6	Spain, Tarragona	3.3

risk for different organs. Three populations can be considered relevant for assessing risk to lungs: miners irradiated by inhaling radon and its decay products; Hiroshima and Nagasaki survivors of the atomic bomb (Kato and Schull, 1982; Yamamoto *et al.*, 1987a; Preston *et al.*, 1986); and therapeutically irradiated patients, especially those with ankylosing spondylitis (Darby *et al.*, 1985). Other populations have provided limited evidence of radiogenic lung tumours.

(C16) *Uranium miners.* Available data (Table C.3) were reviewed in *ICRP Publication 50* (ICRP, 1987). Since the publication of that document, a number of new reports have appeared dealing with health risks of radon and other internally deposited alpha emitters (NRC, 1988); uranium miners in the Canadian Northern Territories (Howe *et al.*, 1987) and New Mexico (Samet *et al.*, 1989); tin and haematite miners in China (Chen *et al.*, 1990; Lubin *et al.*, 1990); tin miners in Cornwall (Hodgson and Jones, 1990); and nonsmoking uranium miners from the Colorado Plateau (Roscoe *et al.*, 1989). These studies are in fair agreement with the conclusions of *ICRP Publication 50* (ICRP, 1987).

(C17) The increased lung-cancer frequency observed among uranium miners indicates a strong correlation with cumulative radon-progeny exposures. This conclusion is confirmed by the survey of other small groups of underground miners exposed to radon, e.g. fluorspar miners in Newfoundland and elsewhere in Canada, and iron ore miners in Sweden, China, and the United Kingdom.

(C18) *Atomic-bomb survivors.* In the 48,275 people that survived exposure to more than 0.01 Gy (T65), delivered at a very high dose rate, an excess of 17 lung cancers over the corresponding normal incidence in Japan was observed from October 1950 to December 1978 (Kato and Schull, 1982). An excess of 31 tumours was found when unexposed and lower-exposed Hiroshima and Nagasaki residents were considered as controls (Darby *et al.*, 1985). However, this is a relatively small number of cases. Prentice *et al.* (1983) selected a cohort whose smoking habits could be established and for whom doses received (<0.1 Gy, 0.1–1 Gy, >1 Gy) could be estimated. They

Table C.3. Basic data for epidemiological studies on uranium miners (modified from ICRP, 1987)

Quantity	Colorado ^a USA 1950–77	Bohemia ^b CSSR 1948–75	Ontario ^c Canada 1955–81	France 1947–83
Initial number of miners	3,366	2,433	ca. 13,400	1,957
Average follow-up period per miner (y)	19	26	15	25.9
Surviving fraction at end of follow-up (%)	72		ca. 80	81
Median age at start of U-mining (y)	30	35–40	ca. 25	ca. 30
Average working period in U-mines (y)	9	10	ca. 2	11.4
Number of person-y at risk	62,556	ca. 60,000	202,785	50,784
Mean cumulative exposure (WLM)	820	310	60 ± 25	^d
Chronic cigarette smokers (%)	ca. 70	ca. 70	50–60	ca. 70
Number of lung cancer cases during follow-up				
Observed	194	ca. 250	82	36
Expected	40	ca. 60	57	18.8
Excess	154	ca. 190	25	17.2
Relative risk (observed/expected cases)	4.8	ca. 4.2	1.45	1.9

^a White miners only.

^b Study group A only; the total group involved 4,364 miners (Schüttmann, 1982; Sevc *et al.*, 1971).

^c Only uranium miners without prior gold mining experience.

^d Exposure data not yet available.

WLM = working level months.

established a dose dependence of radiation-induced cancers after correcting for smoking habits.

(C19) The expanded cohort in the life-span study (Preston *et al.*, 1986) comprised 27,569 and 9,604 control subjects in Hiroshima and Nagasaki, respectively; irradiated subjects (doses > 0.01 Gy) numbered 32,901 and 21,157, respectively. Bronchial and lung tumours totaled 232 in the control group and 421 in the irradiated group, resulting in a relative risk of 1.33 (1.19–1.50) at 1 Gy.

(C20) *Therapeutically irradiated patients.* For therapeutically irradiated patients we must consider data cautiously because of the possible interaction between irradiation and the medication that was administered, and the possibility that patients may be immunologically compromised. However, because no other data are available from humans exposed at low fractionated doses, some useful indications may be obtained. An excess of lung tumours was observed in patients irradiated for malignant diseases such as Hodgkin's and breast cancer (Boice, 1988). Excess lung tumours were also observed in radiologists in the United States with, in addition, evidence of cancer excess in the mouth and pharynx (Matanoski *et al.*, 1984). Surprisingly, there was no excess in women fluoroscopically followed for pneumothorax (Davis *et al.*, 1989) and no excess in patients who received Thorotrast (van Kaick *et al.*, 1986). In the group of spondylitis patients, an excess of 30 tumours was noted (Darby *et al.*, 1985).

(C21) *Other populations.* Nuclear energy workers did not develop significant excess of lung or lymphatic-system cancers (S. C. Darby, personal communication, updating Doll and Darby, 1988). In the 224 men exposed to plutonium since 1974 during employment at Los Alamos, and who had estimated body burdens of more than 370 Bq, no excess of lung cancers and lymphatic tumours was observed (Voelz *et al.*, 1983). Members of the public exposed to elevated radon concentrations have provided controversial data; however, most of the case-control studies suggest an association of cancer excess with higher exposure indicators (Samet, 1989). A large excess of carcinoma of the paranasal sinuses and mastoid air cells is known to have occurred in radium dial painters. Amongst the 2,403 subjects for whom there is an estimate of the bone uptake, 31 tumours have been observed (NRC, 1988).

C.3. Tumour Type, Histogenesis, and Target Tissues

(C22) This section refers mainly to tumours observed in general populations and an assessment of target tissues. There is some evidence that the relative frequency of tumours in the respiratory tract is similar in homogeneously irradiated tissues (Yamamoto *et al.*, 1987b), although some more recent evidence refutes this (Land *et al.*, 1993). This is not the case when the dose delivered to different parts of the organ is heterogeneous. In that case, induction of the different tumour types reflects the absorbed dose in the compartments and, eventually, their specific sensitivities. This may account for the specific high induction rate of central lung tumours in uranium miners exposed to radon (Saccomanno *et al.*, 1971).

C.3.1. Nose and Nasopharynx

(C23) The skin of the nose is the most frequent site for cancer in the nasal region. Basal cell carcinoma of the nose, the most frequently encountered tumour of the skin after the age of 60 (Headington, 1976), arises from skin basal cells located 40 μm and

deeper below the surface of the skin. Irradiation of these basal cells by alpha emitters is unlikely, although penetration can occur through discontinuity of the keratin layer around the hairs and via the adnexal glands (Osanov and Filatov, 1976).

(C24) The nasal cavity opens in the external nares and communicates with the nasopharynx through the choanae, or turbinates. Paranasal sinuses, including the maxillary antrum, ethmoid sinus, sphenoid sinus, and frontal sinus, communicate with the nasal cavity through small ostia.

(C25) Cancers of the nasal cavity *per se* are mainly squamous cell carcinomas, arising from lateral walls of the nasal fossae; 50% originate from the turbinates. Septa, vestibula, posterior choanae, and floors are less frequently affected. Fifteen percent of nasal tumours are nonsquamous, mainly undifferentiated carcinoma. Sarcomas represent less than 5% of all tumours; esthesioneuroblastomas arising from olfactory epithelium are extremely rare (Batsakis, 1976).

(C26) Paranasal sinuses are four times more often affected than the nasal cavity. The maxillary antra are the primary site (60% of all tumours are in the nose region), followed by the ethmoid sinuses (17%). Other sinuses are rarely involved (Batsakis, 1976). Worldwide cancer registries (Muir and Nectoux, 1980) indicate that 67% of these tumours are squamous-cell, 15% are undifferentiated, and 8% are adenocarcinomas. Sarcomas make up less than 4% of all tumours. Up to 5% of nasal tumours are adenoid cystic, mucoepidermoid, mixed types and oncocytomas, strongly suggesting tumours arising from salivary glands. Accessory (minor) salivary glands are scattered throughout all tissues of the upper airways.

(C27) Apart from the anterior part of the nares, which is covered by Malpighian (stratified) epithelium, the progenitor cells for epithelial cancers are the dividing cells of the pseudostratified epithelium layering the nose cavities. Under normal conditions this epithelium is evenly distributed and of the ciliated columnar type (Proctor and Chang, 1983). Basal cells are supposed to be progenitors, but secretory cells cannot be excluded. In accessory glands, secretory cells are progenitors. Cytokinetics is not documented in humans, but observations in patients suffering from viral rhinitis have shown that 2-6 weeks are necessary for normal reconstruction of the desquamated mucosa (Camner *et al.*, 1973).

(C28) Chronic rhinitis and sinusitis were found associated with cancer, sometimes preceding it by 10 y (Collan, 1983; Hiyama *et al.*, 1983). This produces metaplastic changes of the ciliated epithelium to the squamous type, where dividing cells may be found throughout the thickness of the epithelial layer. The nasopharynx is the most cephalad part of the pharynx; the roof is limited by the sphenoid; the floor lies on the soft palate. Lateral walls are of great importance for the development of cancers, especially the depression located above and behind the eustachian tubes, the fossa of Rosenmüller. The posterior wall is delimited by the occiput and the two upper cervical vertebrae.

(C29) Ninety-eight percent of the tumours in the nasopharynx are carcinomas; four-fifths are keratinising and nonkeratinising epidermoid carcinomas; approximately 20% are unclassified carcinomas and adenocarcinomas (Batsakis, 1976).

(C30) Pseudostratified epithelium of the nasopharynx is continuous only in infants (Yeh, 1962). After 10 y of age, rather large areas covered by squamous cell types are unevenly distributed. About 80% of the posterior wall, 50% of the lateral walls, and 60% of all the nasopharyngeal mucosa are covered by metaplastic epithelium (Ali, 1967). Dividing basal cells of the squamous epithelium, and basal and secretory cells of

the pseudostratified epithelium, are the probable progenitors for squamous tumours; a large number of adenocarcinomas probably derive from scattered accessory salivary glands. Intermediate epithelium, made up of five or six layers of cells devoid of cilia on their apical edges, may be found in patches that are especially abundant over the pharyngeal tonsils. These cells may also be important in the histogenesis of some poorly differentiated tumours (Batsakis, 1976).

C.3.2. Mouth

(C31) Lips, buccal mucosa, gums, tongue, palate, oropharynx, palatine arch, tonsils, and hypopharynx are the anatomical locations of interest to clinicians. Generally speaking, the frequency of tumours increases from the anterior to the posterior tissues. More than 90% of tumours in this area are squamous cell carcinomas. Their histogenesis is very similar since stratified epithelium covers all areas except the openings of glandular ducts. With the exception of the lips, the primary site of most tumours is the tonsillar region. Worldwide, with the exception of nasopharyngeal cancers in some Asiatic areas, the tonsils are the second most common site in the upper airways, after the larynx. Precancerous epithelium in the buccal cavity is often keratinised and is referred to as leukoplakia when cytological atypia is observed.

C.3.3. Larynx

(C32) Histologically, the larynx and epiglottis are more complicated than the oropharynx and consist of pseudostratified, stratified, and glandular components. The normal covering of the larynx consists of nonkeratinised squamous cells, except for the lining of the laryngeal ventricle and the subglottic areas, which have columnar ciliated epithelium. Keratosis occurs very frequently in middle-aged men: 82% of males whose average age was 51 y (Norris and Peale, 1963).

(C33) For clinical considerations, the larynx is divided into glottic, epiglottic, and subglottic compartments. Glottic carcinoma is the most frequent, primarily in the anterior half of the cord and the anterior commissure. Subglottic carcinoma rarely arises between the inferior border of the vocal folds and the inferior margin of the cricoid cartilage (Batsakis, 1976). Epiglottic cancers represent about 25% of laryngeal cancers in most populations, but they are most frequent in people from Finland, France, and the Mediterranean countries.

(C34) About 90% of all tumours in the larynx are squamous cell carcinoma (Ferlito, 1985); undifferentiated carcinoma represents about 5%, sarcoma 0.5%, and there are many rare tumour types.

(C35) The histogenesis of laryngeal tumours has been reviewed by Ferlito (1985) and is summarised in Table C.4.

(C36) Laryngeal cancer has been associated with irradiation of the neck (Hueper, 1966) and, in one study, is significantly higher in atomic-bomb survivors from Hiroshima (Kurihara *et al.*, 1981).

(C37) In conclusion, most of the cancers arising in the upper airways originate from stratified epithelium, either physiological or metaplastic. Although the cytokinetics of these tissues is not documented in humans, there is some indication that progenitor cells are located at distances deeper than 50 μ m from the surface.

(C38) Tumours of the trachea are rare; one cancer of the trachea occurs for every 180 cancers of the bronchi. Fifty percent of tracheal cancers are squamous cell carcinomas and occur distally (Batsakis, 1976); their histogenesis is supposedly the

Table C.4. Histogenesis of laryngeal tumours

Tumour type	Incidence (%)	Cells of origin
Squamous	90	Basal cells in Malpighian epithelium
<i>in situ</i>	2	Dividing cells in metaplastic ciliated epithelium
Proper	84.4	Basal cells in Malpighian epithelium
Verrucous	3.8	Epithelial dysplasia
Spindle	1	Basal cells in Malpighian epithelium
Undifferentiated	5.4	Controversial, including mesenchymal
Adenocarcinomas	0.4	Mucous gland cells
Adenosquamous	0.4	Ducts of mucous glands
Clear cell	0.1	Salivary duct cells
Mucoepidermoid	0.8	Salivary duct cells
Small cell	0.4	Endodermal precursor of Kulchitsky's cells

same as that of bronchial tumours. Twenty to thirty-five percent of the tumours are adenoid cystic (cylindromas), which probably originate from intercalary ducts of salivary glands (Batsakis and Regezi, 1977) or myoepithelial cells. These tumours occur in the upper one-third of the trachea, as do other adenocarcinomas.

C.3.4. Bronchi and Bronchioles

(C39) As in the other parts of the respiratory tract, epithelial tumours predominate. The vast majority originate from the pseudostratified epithelium, although some rare tumours originate from bronchial glands. Six main cell types are implicated in the histogenesis of bronchial cancers (McDowell *et al.*, 1978). Goblet and ciliated cells are fully differentiated and do not participate in cancer production. Poorly differentiated young mucous cells, characterized by small mucous granules, can be distinguished in nonciliated cells. Bidifferentiated cells, exhibiting both incomplete ciliogenesis and mucous granule production, are seldom observed. Undifferentiated or poorly differentiated cells are more frequent; they have no secretory granules but many short apical microvilli, much the same as in the brush cells described in other species. The apices of all these cells extend into the bronchial lumen beneath the mucus. They are able to divide their nuclei, which are located below the superior one-third of the mucosa. The basal cells and the neurosecretory cells (Kulchitsky counterpart) are layered on the basement membrane. Basal cells divide, but neurosecretory cells appear to divide only in tumourous tissues. Judging from other species, the progenitor cell in the bronchioles is the Clara cell.

(C40) The cytodynamics of the human bronchus is poorly documented because *in vivo* labelling is not possible in humans; thus, a large part of our knowledge is extrapolated from animal studies. However, direct measurement of the DNA content of selected histological samples is now feasible using flow cytometry. From *in vitro* labelling it has been observed (Harris *et al.*, 1975) that fresh human bronchus explants incorporate ^3H -thymidine. Two cell types are involved: two-thirds basal cells, one-third small mucous granule cells. In the noninflammatory bronchus, 0.48% of all cells observed were in S and late S phase (Greisen, 1970). The doubling time for adult bronchial cells plated on de-epithelialised trachea has been estimated to be about 15 d (Terzaghi and Klein-Szanto, 1980). Intimate contact with normal mesenchymal substrate was necessary for normal bronchial reconstitution.

(C41) Additional data can be obtained from hyperplastic and metaplastic bronchi. Mucous hyperplasia and squamous hyperplasia are common events after irritation by toxicants or following infectious diseases. In squamous metaplasia, basal cell hyperplasia occurs, along with incomplete differentiation of intermediary cells, with no mucous granules and no cilia, but persisting mitotic activity, up to the luminal part of the epithelial sheet. Bidifferentiated cells, with mucous granules and cytokeratin filaments (as observed in stratified epithelium), are frequently seen. Increasing mitotic activity is observed in small mucous granule cells, which seem to be the main progenitors for the lesion (Trump *et al.*, 1978).

(C42) It is interesting to contrast these observations with cytokinetic data obtained with *in vivo* labelling to study the histogenesis of the induction of lung cancer in rats after inhalation of radionuclides (Rhoads *et al.*, 1983; Masse, 1980). Turnover time of airway epithelium has been estimated as 47.6 d (Bertalanffy, 1951); nor is it more rapid in the distal airways in healthy animals. However, it is three times faster in the young than in the adult animal (Bolduc and Reid, 1976). Higher turnover has not been correlated with an increased susceptibility to tumour induction in ^{239}Pu exposures. Exposure of neonates to $^{239}\text{PuO}_2$ aerosols resulted in an extremely low lifetime incidence (D. Nolibé, personal communication; Griffith *et al.*, 1992). In extrapulmonary airways, basal cells account for 67% of the cells incorporating thymidine; secretory cells for 27%; and undifferentiated cells for 6% (Aayers and Jeffery, 1982). Tobacco smoke accelerates the production of secretory cells. Local damage is a direct stimulus for the cells in the vicinity to divide (Gordon and Lane, 1980). In the intrapulmonary airways, secretory cells are the only progenitors. In the distal airways, poorly differentiated Clara cells are progenitors and differentiate into ciliated and mucous cells as well as brush and other Clara cells. Squamous metaplasia is often observed in alveoli adjacent to the bronchioles through a process known as alveolar bronchiolisation (Nettesheim and Szakal, 1972). It occurs in areas devoid of basal cells; bronchiolisation introduces secretory cells as direct progenitors of stratified epithelium. However, it is possible that type II pneumocytes are the progenitors of stratified epithelium since they were shown to repopulate denuded trachea with bronchiolar-like cells (Johnson *et al.*, 1990).

(C43) Increased labelling indices were observed in precancerous lesions, around fibrotic areas, in adenomatosis and squamous metaplasia foci (Rhoads *et al.*, 1983).

(C44) Where tumours originate in the human bronchi is not easily determined. It is generally accepted that one-third to one-half of cancers arise centrally from large bronchi; the central zone includes the main bronchi to the point of division of the segmental bronchi (Spencer, 1977). Up to 60% of lung tumours are suspected to arise distally to a segmental bronchus, with almost 20% originating peripherally from lung tissue in which distal airways cannot be seen with the naked eye (Spencer, 1977). There is a clear upper-lobe predominance of lung cancer in the United States, including all major histological types, in both sexes, and in blacks and Caucasians of all ages. The age-adjusted ratio of lung cancers in upper lobes versus lower lobes is greater than 2:1 (Byers *et al.*, 1984).

(C45) Lung tumour classification has been revised by WHO (1981). The most frequently occurring epithelial tumours should fall in one of the four following categories: squamous cell carcinoma (epidermoid), adenocarcinoma, small cell carcinoma (including, notably, oat cell carcinoma), and large cell carcinoma. The purpose of this revision is to provide the clinician with the best criteria for prognosis and treatment.

(C46) Pathologists may disagree concerning the classification of poorly differentiated tumours. In a review panel of three pathologists evaluating 476 lung tumours (Stanley and Matthews, 1981), all three agreed on 67% of the cases. In 94% of the cases, two pathologists agreed on the major classification. Small cell carcinoma and epidermoid carcinoma were those most consistently evaluated.

(C47) Small cell carcinoma is mainly central in the lobe, as is squamous cell carcinoma; however, there is some evidence that squamous tumours of peripheral origin are largely underestimated (Spencer, 1977). This is confirmed by a study in tin miners in China (Sun Shiquan, personal communication). Although these miners have probably been exposed to high concentrations of radon, 44% of all tumours were peripheral, and 59% of those were epidermoid. Adenocarcinoma is mainly peripheral. Large cell carcinomas include undifferentiated tumours that electron microscopy has shown to be squamous carcinomas and, more often, adenocarcinomas (McDowell *et al.*, 1978).

(C48) Differential distribution of the major epithelial types in the general population can be deduced from a review of 28,000 cases, including reports from a cross section of pathologists from the National Cancer Institute (Percy and Sobin, 1983). According to the revised WHO classification, these were 32% squamous cell carcinoma, 16.5% small cell carcinoma, 26.5% adenocarcinoma, and 7.5% large cell carcinoma. With the exception of a few rare tumours, the remaining reported cases (undifferentiated bronchogenic carcinomas) could not be included in the classification.

(C49) Adenocarcinoma is significantly more frequent in females. In areas where lung cancer incidence in females is high, for example in Hong Kong (Kung *et al.*, 1984), it comprises up to 56% of all tumour types, compared with 34% in males. In a recent study in France (Tredaniel, personal communication), adenocarcinoma represented about 50% of lung tumours in nonsmokers of both sexes. Eighty-five percent of the tumours were in males, of whom 88% were smokers; 70% of the female cases were nonsmokers. There was no evidence of a role of gender in the prevalence of adenocarcinoma in nonsmokers. The partition of tumour types in females was 34% squamous carcinoma, 17% small cell (oat cell) carcinoma, and 40% adenocarcinoma, compared with the group distribution (both sexes) of 50% squamous, 15% oat cell, and 22% adenocarcinoma. In a case-control study in Sweden (Damber and Larsson, 1986), the differential distribution in males was 54% squamous carcinoma, 28% small cell carcinoma, and 13% adenocarcinoma in smokers versus 36% squamous, 13% small cell, and 42% adenocarcinoma in nonsmokers. Other incidence studies substantiate the point that, in both sexes, adenocarcinoma became a dominant type in the 1970s (Vincent *et al.*, 1977). Among 108 cases of lung cancer in Hiroshima/Nagasaki survivors, 60% were in males, of whom 90% were smokers; distribution of tumour types was 39% squamous, 14% small cell, and 40% adenocarcinoma (Land *et al.*, 1993). In females, of whom 70% were nonsmokers, 23% of the tumour types were squamous, 11% small cell, 55% adenocarcinoma (including large cell adenocarcinoma). Interestingly, this study was able to show that small cell carcinoma was the most likely to be induced by radiation exposure. While there was no evidence of a proportional increase in adenocarcinoma in irradiated populations, the results did not preclude the possibility of adenocarcinoma being induced by radiation.

(C50) Histological types in irradiated groups can be identified with certainty only in male miners, where a large excess of lung cancer is observed. Early reports (Saccomanno *et al.*, 1964, 1971; Horáček *et al.*, 1977) indicated that exceptionally high rates of small cell carcinoma occurred. A 66% incidence of this tumour type was

observed in a cohort of Colorado Plateau miners (reviewed in Yessner, 1981). However, newly diagnosed cases among Caucasians in the Colorado Plateau cohorts (Saccomanno *et al.*, 1982) do not confirm a high ratio for small cell carcinoma; squamous carcinoma became predominant, and small cell carcinoma decreased (progressively) to 22%. Adenocarcinoma increased up to ~15% in those who started mining when they were age 20–29 y.

(C51) Although some suggestions have been made, taking into consideration the latency period, the age at the time of diagnosis, and total cigarette consumption, the origin of this tumour-type shift remains obscure. Age-adjusted incidences do not indicate significant differences between tumour types and onset in people not exposed to radon (Greenberg *et al.*, 1984).

(C52) In the Chinese tin-miner study (Sun Shiquan, personal communication), small cell carcinoma was rare; epidermoid (squamous) tumours represented 71% of all cancers, and an unexpectedly high number of adenocarcinomas, of the bronchiolo-alveolar type, were noted.

(C53) Interestingly, the cohort studied by Yamamoto *et al.* (1987a), which comprised 82,000 Hiroshima/Nagasaki survivors, indicated that the differential distribution of tumour types in the irradiated group followed that of the control group, even though a steeper slope was noted for oat cell carcinoma (Land *et al.*, 1993). This observation indicates that, in different tumour types, the relative sensitivities to induction by irradiation do not differ significantly.

(C54) From the viewpoint of histogenesis, there is little doubt that the four major types derive from the same endodermic progenitors (McDowell *et al.*, 1978; Yessner, 1981), despite the obscure origins of oat cell carcinoma, including cells derived from the neural crest and macrophages.

(C55) Columnar secretory cells are the most likely candidates as progenitors in thoracic lung tumours (Trump *et al.*, 1978). There is direct evidence of their implication in epidermoid lung tumours since they can give rise to fully differentiated squamous carcinoma in bronchial glands devoid of basal cells. Further evidence of secretory cell involvement in radiation carcinogenesis is found in the paper by Harley and Robbins (1992).

(C56) Basal cells are very similar to the germinal cells of the epidermis. Since they divide and have been shown in animals to differentiate into secretory cells, they may be progenitors; however, recent results (Johnson *et al.*, 1990) have shown that their role may be limited.

(C57) Most cells with neurosecretory granules, which make up the specificity of oat cell carcinoma and are seldom observed in normal epithelium, appear to derive from pre-existing epithelial cells that did not possess dense-core, granular, endocrine specialisation (McDowell *et al.*, 1978). Histological patterns of the four main tumour types reflect their common origin. There is a continuous dynamic histopathological spectrum of phenotypes (Yessner, 1981), influenced by poorly understood host factors.

(C58) Cells at risk in the tracheobronchiolar region should therefore be considered homogeneously distributed in the thickness of the epithelium. A minimal distance of 10 μm , including the functional height of the ciliated sheet and the distance from the nucleus pole to the cell apex, is suggested for refined dosimetry as the threshold distance from the emitting particles deposited on bronchial mucus. A minimal distance of 4 μm between the apex and nucleus pole of nonciliated, columnar secretory cells applies to bronchiolar tissues.

C.3.5. Lung Parenchyma

(C59) Tumours originating from alveolar pneumonocyte type II cells (Coalson *et al.*, 1973) and from Clara cells (McDowell *et al.*, 1978) are extremely rare in humans. They are frequently induced in mice (Kauffman *et al.*, 1979; Masse, 1980), in hamsters (Kennedy *et al.*, 1977), in rats (Sanders *et al.*, 1977; Cross *et al.*, 1982a), and in dogs (Hahn *et al.*, 1988). Distal airway tumours may be the main consequence of long-term retention of insoluble radionuclides in the alveolar region of the human lung, as in animals. However, distal tumours are also found in animals treated with arsenic, beryllium, nickel sulphides, vinyl chloride, etc. instead of the tumour locations usually found in exposed people. It is more likely that distal tumours in animals reflect a specific animal sensitivity of the distal airways. However, it would be unwise to neglect parenchyma as a tissue at risk, because scar tumours, mainly adenocarcinomas, may represent an important contribution in some instances where scarring is a common process, as in workers exposed to asbestos and in cured tuberculosis patients.

(C60) Mesenchymal tumours (angiosarcomas, fibrosarcomas, etc.) have been observed in exposed rodents and were predominant in dogs heavily irradiated by beta emitters (Hahn *et al.*, 1973). These tumours were observed only after high doses in animals exposed to insoluble alpha emitters and not in animals exposed to more soluble compounds (Rhoads *et al.*, 1983). They were not observed in hamsters intravenously given insoluble ZrO_2 microspheres tagged with $^{239}PuO_2$, despite high doses delivered locally to the vascular cells (Anderson *et al.*, 1979). Since they were also absent in irradiated people, it is unlikely that they will significantly influence risk coefficients for lung tumour assessment in humans. A similar conclusion can be reached for tumours of the pleura, a few of which have been described in rats after inhalation of alpha emitters (Dagle *et al.*, 1980, 1992).

C.3.6. Lymph Nodes and Cells Involved in Surveillance

(C61) Lymph nodes may be the most heavily irradiated tissue following inhalation of insoluble particles, especially particles made up of alpha emitters. A significant excess of non-Hodgkin's lymphomas has been observed in irradiated ankylosing spondylitis patients (Darby *et al.*, 1987) but not in Hiroshima and Nagasaki survivors (Preston *et al.*, 1986). This indicates that the induction of lymphomas after whole-body irradiation in the general population is not a significant contribution to the total risk. Selective irradiation of a few nodes after drainage of insoluble material deposited in wounds or in subcutaneous tissues after injection has not been associated with excess lymphomas. Nor has it been possible to establish a significant excess of Hodgkin's and other lymphomas in German Thorotrast patients (van Kaick *et al.*, 1986), despite rather large amounts of material transferred to the nodes in the 30% of the cases where extravasation of material occurred. It should be noted that the incidence of non-Hodgkin's lymphomas was higher in the treated than in the control patients, which might indicate that the relative sensitivity of nodes to alpha irradiation was low, but not zero. One may roughly estimate that the cancer risk in the nodes was lower than in the liver by two orders of magnitude, assuming the doses delivered were comparable. There was no excess of lymphomas in the Rocky Flats cohort of workers exposed to

plutonium, although some limited evidence of increased prevalence of international classification of diseases numbers 200 to 209 has been suggested (Voelz *et al.*, 1989). No excess of lymphomas was observed in the workers exposed to plutonium at the Los Alamos Laboratory who had depositions of 370 Bq or more. Two studies (Archer *et al.*, 1973; Waxweiler *et al.*, 1981) have reported observation of a few lymphomas in uranium mill workers, accounting for two deaths from giant follicular lymphomas, three from lymphosarcomas, and three from Hodgkin's disease. There was no excess of lung tumours. The numbers are too small to draw any correlation with a possible irradiation of tracheobronchial nodes by uranium and thorium particles.

(C62) A few tumours (hemangiosarcomas) were observed in beagles following inhalation of beta emitters (Hahn and Boecker, 1980). Some lymphomas were induced in certain strains of rats following inhalation of radionuclides, but no dose response could be established, and, consequently, lymphoid cells were not considered at risk by the Task Group to Committee 1 of the ICRP (ICRP, 1980a).

(C63) Overall, it is impossible to determine whether local irradiation of the lymph nodes makes any significant contribution to direct induction of cancer. Indirect effects, such as the killing of T-lymphocytes in the parafollicular areas of the nodes, may be more important, but the effect of lymph node irradiation on tumour occurrence in upper or lower airways has not been substantiated. Neither has the role of thymus-derived lymphocytes on lung tumour surveillance been confirmed. Thymectomised neonatal rats did not develop more or earlier lung tumours than controls after inhalation of plutonium dioxide particles (Nolibé *et al.*, 1981). Neither was any decrease of tumour incidence observed in $^{239}\text{PuO}_2$ -exposed rats previously treated with bacillus Calmette-Guérin (Nolibé *et al.*, 1980).

(C64) It is not known whether lymphopenia, which was found to follow deposition of plutonium in the lung (ICRP, 1980a), is due to irradiation of lymphocytes in the nodes or in the lungs. In experiments with dogs that received mean lung doses from radon decay products comparable to the doses received from plutonium exposures, no lymphopenia was observed (Cross *et al.*, 1986). Thus, it appears that lymphopenia observed in plutonium exposures may be due to irradiation of the tracheobronchiolar lymph nodes, which contain both circulating lymphocytes and fixed lymphoid tissue. Whether lymphopenia follows alpha irradiation of lymph nodes in other species remains unknown.

(C65) As already noted, mesenchymal-epithelial interaction governs the differentiation of the cells grown *in vitro* from human explants (Terzaghi and Klein-Szanto, 1980). Irradiation of mesenchymal cells may play a role in cancer induction. The radiosensitivity of endothelial and connective tissue cells is extensively documented in *ICRP Publication 31* (ICRP, 1980a).

(C66) Less attention has been paid to irradiation of intracapillary cells; a selective decrease of natural killer (NK) cells has been noted after PuO_2 inhalation (Nolibé *et al.*, 1983). The decrease of NK cells was correlated with a decreased ability of the lung to kill intravenously injected tumour cells grown from syngeneic radio-induced lung tumours. Since no depression of NK activity could be established in circulating blood, a selective local inhibition was postulated. This would lead to the concept that alveolar macrophages are cells at risk. Studies have shown that alveolar macrophages are severely depressed after alpha irradiation of the lungs (Moore *et al.*, 1986), but a threshold for the impairment of NK activity in plutonium dioxide exposures was noted below 37 Bq/g fresh lung weight (Nolibé *et al.*, 1985).

C.3.7. *Nonrespiratory Cancers*

(C67) Depending on the solubility of the radionuclide in the lungs, it is possible that nonrespiratory tissues and organs accumulate more absorbed dose than the lungs after inhalation. This depends strongly on the metabolic behaviour of the radionuclide. Some, such as iodine, are avidly retained in specific organs, some are distributed in the whole organism, and others are retained, to a greater or lesser degree, in bone and liver. Computation of the dose equivalents is given in Publication 30 (ICRP, 1979a,b, 1980b, 1981b,c, 1982a,b). As a consequence, target cells may differ for the same element, depending on the specific isotope: $^{239}\text{PuO}_2$ induces lung cancers in animals, and $^{238}\text{PuO}_2$ induces both lung and bone cancers (ICRP, 1980a).

(C68) Inhaled insoluble compounds are transported to the oropharynx and are swallowed. They deliver some dose to the GI tract. This dose, however, cannot be more than an insignificant fraction of the doses delivered to the respiratory tract, because of the larger volumes irradiated and the shorter retention times in the GI tract.

C.4. *Modifying Factors*

(C69) Some factors are known to be associated with an increased incidence of lung cancer. They may be due to lifestyle and genetic factors and, in some instances, to possibly unknown factors, as is suspected with Maoris and Hong Kong women. The most important factor is smoking; however, as already stated, respiratory-tract cancers are also often associated with alcohol consumption.

C.4.1. *Smoking Effect*

(C70) Smoking is, by far, the most important etiologic factor associated with cancer in both sexes. From Doll and Peto (1981), it is estimated that, in 1978 in the United States, among the 71,006 deaths due to lung tumours in males, 64,567 were due to tobacco; among the 24,080 lung tumours in females, 18,626 were due to tobacco.

(C71) Cancers of the mouth, pharynx, larynx, and oesophagus are also influenced by smoking. In 1978, the incidence of this group of tumours amounted to one-fifth the incidence of lung tumours; 71% of the tumours were caused by tobacco in males, as were 42% in females (Doll and Peto, 1981). Maximum exposure to cigarettes in the United States probably occurred among men who are now in their seventh and eighth decades. Smoking decreased after 1950, resulting in less exposure to men now in their third or fourth decade. By contrast, peak exposure to smoking among women probably occurred in those who are now in their fifth or sixth decade, because the decrease in the number of women who smoke came later. Since smoking habits differ widely in different parts of the world, differences can be expected with regard to smoking-related cancer incidence.

(C72) Lung cancer mortality is also strongly influenced by smoking rate and by yields of tars in different cigarettes (IARC, 1985).

(C73) Cessation of smoking is rapidly followed by decreased risk. After 5 y, ex-smokers have a relative risk two to four times lower than that of smokers. After 10 y, the relative risk is one-fifth to one-tenth that of smokers but remains two times higher than the risk of persons who never smoked (OSH, 1979). Though it has been thought that squamous and small cell carcinomas were the only tumours influenced by smoking (Kreyberg Group 1), it is now clear that adenocarcinoma is also increased in men and

women smokers (Lubin and Blot, 1984; Stayner and Wegman, 1983) nonoccupationally exposed to radon. Interaction between exposure to radon, or ionising radiation in general and smoking, in terms of relative risk, cannot be excluded.

(C74) The effect of smoking inferred from radon-exposed miners is a matter of debate, partly because smoking habits in miners may differ from smoking habits in control populations. There is an apparent synergism (see Reif, 1984 for a definition) in three studies (Lundin *et al.*, 1969; Whittemore and McMillan, 1983; Hornung and Meinhardt, 1986): additivity in one (Radford, 1981), and antagonism in another (Axelson and Sundell, 1978). The role of other potential carcinogens present in the mine is totally unknown. Whether or not lymphopenia follows alpha irradiation of lymphoid tissue as observed in some animal studies also remains unknown. Evidence of a substantial hazard of lung cancer in nonsmoking uranium miners has only been substantiated in two studies. The first study (Samet *et al.*, 1984) dealt with Navajos from the New Mexico Tumor Registry. The second study (Roscoe *et al.*, 1989) was carried out in the Colorado Plateau cohort, in 516 nonsmoking white miners followed up from 1950 to 1984. In the latter, 14 deaths were observed though 1.1 were expected. Reassessments of the whole data have led to the conclusion that the joint effect of tobacco and radon was more than additive and less than multiplicative (Samet *et al.*, 1989; Hornung and Meinhardt, 1986; Lubin, 1988). The less-than-multiplicative pattern is strongly illustrated in the studies by Samet *et al.* (1984) and Roscoe *et al.* (1989), in that the relative risks in the nonsmoking groups were much higher than in other studies where smokers were included.

(C75) Experiments in animals have shed some light on these different observations (Archer, 1985). Antagonism was noted in beagle dogs exposed alternately, but on the same day, to radon and tobacco smoke (Cross *et al.*, 1982b). However, rats exposed to tobacco after exposure to radon exhibited a strongly increased response, indicating a promoter role of tobacco smoke (Chameaud *et al.*, 1982). Current evidence in animal studies suggests that the duration of cigarette smoking is at least as important, if not more important, than the number of cigarettes smoked daily (Cross, 1994). An earlier paper by Doll and Peto (1978) regarding British doctors who smoked presented the same conclusion, although this conclusion was not shared by other modellers of the data (Moolgavkar *et al.*, 1989) who used an approximate solution of the two-mutation model in their analysis. Using the exact solution in a recent reanalysis of the British doctors data in conjunction with the Colorado Plateau uranium miners data has confirmed, as do the radon animal experiments, that cigarette smoke is a promoting agent exerting its interaction with radon in a supra-additive but submultiplicative way (Moolgavkar *et al.*, 1993).

(C76) The effect of smoking in the survivors of Hiroshima and Nagasaki indicates a submultiplicative function of the relative risk, combining dose and amount smoked for all nonhaematologic cancers. The relative risk of lung cancer could not be distinguished from either a multiplicative or an additive form (Prentice *et al.*, 1983). Some evidence has been given (Kopecky *et al.*, 1986) that whole-body irradiation and tobacco smoking may combine in a more complicated way. The excess relative risk was assigned to be the sum of two components, one due to irradiation that increased with decreasing age at the time of bombing; the second, due to smoking, obviously increasing with tobacco consumption and consequently with aging. One consequence is that the apparent relative risk for exposed people is highest in nonsmokers and decreases with tobacco consumption. Since most men were smokers and most women were

nonsmokers, sex differences in terms of relative risk may result only from different smoking habits.

C.4.2. *Other Combined Effects*

(C77) Historically, exposure to arsenic, nickel, chromium, bis-chloromethylether, mustard gas, and merphalan were associated with higher levels of lung cancer. Asbestos exposure in the workplace is also an important factor, particularly in smokers. The effect of indoor exposure to asbestos remains a matter of debate; however, the ubiquitous presence of asbestos fibres could make it a very real problem. Formaldehyde has been suspected, although not definitely established, as a carcinogen for humans. In many instances, increased incidences of lung cancer could not be established as the consequence of exposure to an identified carcinogen at the workplace, even though the work was considered hazardous (Dubrow and Wegman, 1983). The effects of alcohol and tobacco consumption, which varies considerably among groups and is a highly confounding factor, must also be considered. They may explain the fact that income status is strongly associated with lung cancer risk (Dayal *et al.*, 1984; Ernster *et al.*, 1982). It should be noted, however, that above-ground uranium workers, not exposed to radon daughters, but exposed to other airborne toxic materials, did not show an excess of lung cancer (Waxweiler *et al.*, 1981).

(C78) The effects of combined exposures in animals are poorly documented. Urethane exhibited an antagonistic effect with PuO_2 (Brightwell and Heppleston, 1977); asbestos fibres exerted a subadditive effect in alpha-irradiated lung (Sanders, 1975), but some evidence of synergy could be observed after intrapleural injection of different types of fibres in rats pretreated with radon (Bignon *et al.*, 1983). Ore dust was not found to exert a significant effect on the lifetime risk of rats exposed to radon (Cross *et al.*, 1982a). Beryllium oxide was not observed to increase the risk of lung cancer in PuO_2 -treated rats (Sanders *et al.*, 1978); results with beryllium metal (André, 1984) indicated that lifetime risks were additive. Moreover, very significant life shortening from lethal lung tumours was observed in rats receiving both beryllium and PuO_2 . Benzo(a)pyrene exerted a multiplicative effect when combined with PuO_2 (Métivier *et al.*, 1984), whereas nitrosamine failed to exhibit any combined effect (Métivier *et al.*, 1983).

C.4.3. *Initiation-Promotion*

(C79) Probably no one would support a one-step theory of lung cancer induction based on a single rare mutation in a single cell at risk. The age-dependence of lung cancer prevalence and evidence from exfoliative cytology are sufficient to nullify such a theory. However, it appears very likely that tumours arise from single cells. Whether as the result of a rare final genetic arrangement or the result of clonal selection, cancer induction is a multistage phenomenon whose modelling has been debated for many years. Almost all models refer to the initial work by Armitage and Doll (1954), which states that k numbers of events occurring in a fixed order are necessary. Since it has been observed that the logarithm of the age-specific cancer incidence increases linearly with the logarithm of age (y), it has been possible to identify the slope of the curve with the number k . There is, of course, some approximation in this analysis, but a k number of 6 is generally accepted for lung-cancer induction (ICRP, 1987).

(C80) These models (see Whittemore and Keller, 1978, for a review) cannot refer explicitly to the nature and the time sequence of each of the supposed steps. This drawback does not appear in the two-stage model proposed by Moolgavkar and Knudson (1981). The two-stage model favours the concept of recessive oncogenicity, according to which inactivation of both alleles of specified genes (possibly antioncogenes) leads to cancer (Knudson, 1986). Although it does not refer to oncogene activation (initiation, promotion, progression) as a limiting step towards cancer, nor to contact and paracrine control from neighbouring cells, it does take into account the role of cell proliferation, which may well be the final result of these intermediate steps; cell proliferation is probably implicitly included in promotion and progression concepts. At the cellular level it postulates that a normal cell (1) transforms into an intermediate cell (2), which can reverse, increase in number, and transform again into an irreversible, malignant stage (3). In this theory there is a spontaneous rate of transformation from 1 to 2 and from 2 to 3. Thus a carcinogen can act either by increasing the transformation rate, which is the most frequently investigated step, or by increasing the number of intermediate cells without necessarily interacting with the cell genome. The main interest of this model is that its mathematical formulation provides a good fit to relevant experimental data (Moolgavkar *et al.*, 1990) and epidemiological data (Moolgavkar and Knudson, 1981).

(C81) Intermediate cells can divide or differentiate, or disappear (by cell death). The disappearance of initiated cells may be considered an important factor in tumour-induction modelling, as suggested in NCRP (1984). There is indirect evidence for the disappearance of cells transformed by radon with a longer latency time in young miners (Archer *et al.*, 1979). A "time-since-exposure" effect has been modelled in epidemiological studies of underground miners (NRC, 1988). A decrease in hazard with time after exposure was also modelled in rats exposed to radon (Gilbert, 1989; Moolgavkar *et al.*, 1990). Finally, the observation that promotion of radon-induced tumours in the rat significantly decreased with the time elapsed between irradiation and promoter application is a good argument for that assumption (Lafuma *et al.*, 1982).

(C82) Clonal expansion of Stage 2 cells proceeds to benign tumours. Thus, benign tumours, while not guaranteeing malignancy, indicate that production of intermediate cells is abnormally high.

(C83) Findings on oncogenes have focused attention on the possible mechanisms leading to lung carcinogenesis. In humans, oncogenes *myc* (c,N) have been shown to be amplified in small cell lung cancer (SCLC) (Wong *et al.*, 1986); *k-ras* was found to be mutated in adenocarcinoma (Rodenhuis *et al.*, 1987). Vähäkangas *et al.* (1992) have reported mutations in exons 5 through 9 of the p53 tumour suppressor gene, but not in codons 12 or 13 of *k-ras* in lung cancers from uranium miners. In contrast, preliminary data on radon-induced rat lung tumours reported by Cross *et al.* (1992a) and G. L. Stiegler (personal communication) have reported codon 13 *k-ras* activating mutations (where the sequence TGC replaced GGT (Cys for Gly) in some tumours and GAC replaced GGC (Asp for Gly) in others), and a possibly unique activating lesion at codon 62 in the *H-ras* second exon (where GAA is mutated to GAT, bringing about a glutamate-to-aspartate substitution). The potential of this latter mutation to induce *ras* activation is not known.

(C84) Additional mechanistic evidence includes: epidermal growth factor receptor (EGF-R) has been shown to be overexpressed in non-SCLC (Dazzi *et al.*, 1989) in humans and bombesin to be overexpressed in both radon-induced rat lung epidermoid

carcinoma and in uranium miner SCLC (Leung *et al.*, 1992). Also, inactivation of 40–50% of p53 has been observed both in SCLC and non-SCLC (Takahashi *et al.*, 1989). Oncogene polymorphism, therefore, is a potential tool for an estimate of prognosis and predisposition to lung cancer (Willey *et al.*, 1988).

(C85) In irradiated people (or animals) it is not clear which is the dose-related limiting step in multistage carcinogenesis. It is generally believed that genetic events are responsible for the lifetime increased risk of cancer. Epigenetic events in initiated cells, or the consequence of dose delivery to surrounding tissue, may also influence the tumour type and the time to tumour. Additionally, signals to initiated cells for mitosis, resulting from death of adjacent cells or from distant injured tissue (notably vascular and alveolar), may also play a role in lifetime risk. This point has been taken into account in *ICRP Publication 32* (ICRP, 1981a), which considered the whole lung at risk, with equal weighting factors for the bronchial tree and parenchyma.

(C86) It has been observed that the time to tumour could be significantly reduced in rats exposed to radon when 5-6 benzoflavone, a nonmutagenic specific promoter, was administered (Lafuma *et al.*, 1982; Poncy *et al.*, 1992). The main detectable effect was specific induction to mitosis of epidermoid-like cells (Stage 2 precursors). A similar effect was obtained with rats treated with tobacco smoke (Chameaud *et al.*, 1982; Cross *et al.*, 1992b); in the French experiments, multiple primary tumour nodules could be detected early, and increased numbers of animals bearing tumours were observed when tobacco smoke was given after radon inhalation.

(C87) In humans nonoccupationally exposed to radon, there is a strong suggestion that smoking acts mainly as a promoter, as it does in rats, since a decreased incidence of cancer follows almost immediately when smoking is terminated.

(C88) As previously mentioned, in miners exposed to radon, promotion by cigarette smoking appeared to cause a shift in time to onset of tumours. Independent epidemiologic studies carried out in irradiated people have led to three different estimates (synergism, additivity, and antagonism) of the effect of smoking on the lifetime risk. The conflicting results have been reconciled by Reif (1984), with the following interpretation: "The apparent synergism observed in the study by Lundin *et al.* (1969) in which observations were made relatively early after radon exposure, may be due to the promotional effect of tobacco smoke on the initiation effects produced by radiation. The additive result observed after a longer period may indicate that the promotional effect of tobacco smoke was much lower by this time. Finally, the inhibition observed after the longer follow-up time may mean that cancers induced much earlier by radiation had already been expressed previously in smokers, whereas those induced in nonsmokers were finally now being expressed." A similar conclusion was reached by Archer (1985).

C.4.4. Sex and Age

(C89) Currently, women in occidental countries are much less prone than men to the development of spontaneous cancer in the respiratory tract. Sex ratios for the larynx, bronchi, and bronchioles are shown in Tables C.1 and C.2.

(C90) It may be expected that sex ratios of respiratory-tract tumours will decrease in the next few decades because of changes in smoking habits. An extrapolation of the incidence trends with time in the United States allows us to predict that women and men will reach the same incidence by the twenty-first century (Horn and Asire, 1982).

Lung cancer mortality rates are increasing so fast among females in some U.S. areas that they have surpassed breast cancer as the leading cause of death. The male-to-female sex ratio is increased in countries where the lung cancer incidence is spontaneously high in females; in Hong Kong, the male-to-female sex ratio for mortality increased from 1.1 in 1960 to 1.8 in 1981 (Kung *et al.*, 1984).

(C91) The importance of gender as a factor in sensitivity to radiation-induced tumours is not well documented. Squamous cell carcinomas and adenocarcinomas of the lung in Hiroshima and Nagasaki seemed to develop more rapidly in males than in females, but there was no difference after smoking habits were taken into account (Hayabuchi *et al.*, 1983). It has been suggested (Kopecky *et al.*, 1986) that, after correction for smoking, males and females are equally sensitive to lung-cancer induction. The follow-up of a group of women irradiated by fractionated doses of x-rays after pneumothorax failed to show an elevated incidence of lung cancer, in contrast to breast cancer. This suggests that dose fractionation may be more of a factor for lung cancer than for breast cancer (Davis *et al.*, 1989).

(C92) Age-specific onsets of tumours do not differ markedly in either sex; they can be described as 6th-power functions of age, graphically displayed by parallel lines on log-log scales. There is good evidence, from the survey of irradiated groups, that a minimal latent period (probably close to 10 y and possibly shorter [Hornung and Meinhardt, 1987]) after exposure is necessary for a cancer to develop in the lung. As previously mentioned, there is also evidence that the age-specific incidence of radio-induced lung cancers follows that of spontaneous cancers (ICRP, 1987).

(C93) The very strong age-specific dependence of tumour onset makes it difficult to understand the role of age at time of exposure, on the basis of an absolute excess of tumours, after an incomplete follow-up of the cohort. Moreover, it seems that the latent period is age-dependent, as is well illustrated in uranium miners. Latent periods declined from about 45 y to about 10 y in those who started mining at 20 y or 60 y, respectively (Archer *et al.*, 1979). Evidence is most convincing that the relative risk coefficient can, however, be considered age-independent in adults (ICRP, 1987). Higher sensitivity in infants is uncertain, particularly in radon exposures, where a decrease in hazard is noted with time following exposure. For example, tin miners who started work at age 13 showed no greater risk for lung cancer than miners who started work at an older age (Lubin *et al.*, 1990). In Hiroshima and Nagasaki for survivors less than 10 y of age, the relative risk coefficient for lung cancer induction was twice that of adults (Shimizu *et al.*, 1990). The BEIR-V committee, however, found no effect of age at time of exposure on relative risk (NRC, 1990).

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ANNEXE D. DEPOSITION OF INHALED PARTICLES

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D.1. Introduction

(D1) This annexe describes the experimental data on total and regional deposition of aerosol particles in the human respiratory tract on which the deposition model (Chapter 5 in the main text) is based. Detailed reviews of the development of these data, which include discussions of the physical factors influencing particle deposition in the respiratory tract, are available in the literature (Altshuler *et al.*, 1957; Altshuler, 1961; Hatch and Gross, 1964; Lippmann and Albert, 1969; Albert *et al.*, 1973; Aharonson *et al.*, 1976; Swift and Proctor, 1976; Lippmann, 1977; Brain and Valberg, 1979; Lippmann *et al.*, 1980; Heyder *et al.*, 1980a,b; Raabe, 1982; Clarke and Pavia, 1984; Stahlhofen, 1984; Morén *et al.*, 1985; Morrow and Yu, 1985; Miller *et al.*, 1988; Vincent, 1990). The deposition of particles in the respiratory tract, and the underlying physical mechanisms that determine regional deposition, have been, and continue to be intensively studied. However, in the main, experimental data are still available only for the adult Caucasian male, and for a limited range of particle size (from about 1- μm to 10- μm aerodynamic diameter), whereas the application of this human respiratory tract dosimetry model is required to be much broader. Furthermore, the published experimental determinations of regional deposition within the lungs rely on the premise that particles deposited in distinct anatomical regions, i.e. the ciliated tracheobronchiolar airways or the respiratory airways of the alveolar interstitium, are cleared with distinctly different rates. Recent studies of human subjects, for whom a special inhalation technique was used with the aim of restricting the inhaled particles to a so-called "bolus" within the ciliated airways, have suggested that the fundamental assumption of uniformly rapid ciliary clearance might not be valid. In these studies, according to the current understanding of the behaviour of an inhaled bolus, deposition would have occurred in the tracheobronchiolar region; yet a substantial fraction of the deposited particles was cleared slowly, at a rate that is indistinguishable from alveolar-interstitial airway clearance (Stahlhofen *et al.*, 1987, 1990; Scheuch and Stahlhofen, 1988). These new observations necessitated further review of the regional deposition characteristics of the human lungs. (See also Annexe E for discussion of the data that indicate slow bronchial clearance in relation to the recommended model of regional lung clearance.) Because of the additional need to

extrapolate the available data to aerosol particles and vapours from atomic dimensions up to very coarse wind-borne particles, and also to subjects of different body size and level of physical exertion, it was decided to apply both theoretical and/or empirical modelling methods, as appropriate, to develop the predictive deposition model that is recommended in Chapter 5. Section D.8 of this annexe provides a summary of the primary experimental data used to evaluate total and regional deposition of aerosol particles in the human lungs.

(D2) Since the publication of ICRP's current deposition model (TGLD, 1966; ICRP, 1979), substantial progress has been made in theoretical modelling of aerosol transport and deposition within the lungs (Taulbee and Yu, 1975; Pack *et al.*, 1977; Yu, 1978; Nixon and Egan, 1987). The development of this theoretical modelling approach has been reviewed by Heyder and Rudolf (1984). The particular formulation described by Egan and Nixon (1985), and later improved by Egan *et al.* (1989), as the basis for modelling regional aerosol deposition in the lungs of different subjects as a function of their respiratory characteristics was adopted for this respiratory tract dosimetry model. The aim of Section D.9 is to show that this theoretical treatment of aerosol transport and deposition provides a working predictive model of regional lung deposition.

(D3) In parallel with this more fundamental approach to modelling in purely physical terms, substantial developments have occurred in the analysis of measured particle deposition in the respiratory tract in terms of empirically defined parameters (TGLD, 1966; Davies, 1972; Rudolf *et al.*, 1986, 1990). The parametric analysis of regional lung deposition developed by Rudolf *et al.* (1990) to represent the results of complex theoretical modelling by relatively simple algebraic approximations was adopted for this model. These formulae constitute the recommended deposition model (Chapter 5). Their derivation is described in Section D.10.

(D4) Section D.11 presents an evaluation of intersubject variability and/or uncertainty in estimating the regional deposition throughout the respiratory tract of an individual subject. This section also discusses experimental data that indicate effects of airway disease on regional deposition.

(D5) Section D.12 describes the derivation of the model recommended to calculate deposition for hygroscopic aerosols. The final section, Section D.13, discusses the parameters needed to define the aerosol exposure in order to adequately represent regional deposition. These parameters are: (1) the characteristic median physical or aerodynamic diameter; (2) the characteristic particle shape factor; (3) the particle density; (4) the geometric standard deviation of the particle activity with respect to particle size; and (5) the degree of hygroscopicity of the aerosol particles.

(D6) First, however, before modelling the regional deposition of particles within the respiratory tract quantitatively, it is necessary to model the effects of particle size and any other factors on the entry of particles from the exposure environment. This characteristic is termed the "inhalability" of the ambient aerosol, and it can vary markedly depending on the conditions of exposure. The following section, D.2, shows the experimental data used to evaluate aerosol inhalability, and describes the empirical expression that is recommended for use in the deposition model.

(D7) Section D.3 discusses the experimental data used to define the "breathing habit" of various subjects, i.e. the factors that determine whether a subject breathes through the nose, the mouth, or a combination of both.

(D8) Sections D.4 through D.7 then describe the experimental data on which the models of particle deposition in the nose and naso-oropharyngeal passageway are

based, and the derivation of the recommended algebraic formulae that represent these data.

D.2. Inhalability

(D9) Inhalability is the ratio of the number concentration of particles with a particular aerodynamic diameter inspired through the nose or mouth to the number concentration of particles with the same aerodynamic diameter present in the inspired volume of ambient air. In terms of the notation used in Chapter 5, the nominal intake, I_0 , is defined as the total activity of aerosol particles in the volume of air to be inspired. The actual intake of activity into the nose or mouth, I_1 , is then given by Eqn. D.1:

$$I_1 = \eta_1 I_0 \quad (\text{D.1})$$

where η_1 is the inhalability of the aerosol, i.e. the intake efficiency.

(D10) Several authors have studied the inhalability of aerosol particles as a function of their aerodynamic diameter (Ogden and Birkett, 1977; Vincent and Mark, 1982; Armbruster and Breuer, 1982, 1984). These studies involved sampling ambient aerosols through the nose or mouth orifices of a mannequin placed in a wind tunnel at various angles to the direction of airflow. The published data were reviewed and supplemented by a study of the effect of windspeed by Vincent *et al.* (1990). These authors concluded that "effects associated with differences in windspeed and breathing parameters are relatively weak over quite wide ranges. So, too, are effects associated with nose-versus-mouth breathing and facial structural features."

(D11) Vincent *et al.* (1990) presented a synopsis of the measured aspiration efficiency through the mouth in a model of the human head and torso, averaged over 360° horizontal orientation to the direction of the wind. These data are shown in Fig. D.1. At low windspeeds, the intake efficiency decreases with increasing particle size, reaching a value of approximately 0.5 for particles larger than about 20- μm aerodynamic diameter. To reflect this characteristic pattern of intake into the respiratory tract when sampling aerosols in the workplace, the American Conference of Governmental Industrial Hygienists (ACGIH, 1985) recommended that the intake efficiency of a sampler as a function of aerodynamic diameter should be within $\pm 10\%$ of the following empirical expression:

$$\eta_1(\text{sampler}) = 0.5[1 + \exp(-0.06 d_{ae})]. \quad (\text{D.2})$$

The curve of intake efficiency versus aerodynamic diameter defined by this expression is shown in Fig. D.1.

(D12) For very large particles at high windspeeds, the recent data of Vincent *et al.* (1990) (Fig. D.1) show that there is a clear tendency for the intake efficiency to increase with particle size, and even to exceed unity at the highest windspeed tested, i.e. at 9 m s^{-1} . To represent this characteristic in a sampling instrument, these authors proposed that the ACGIH expression should be modified by the addition of a term containing the windspeed, U , as defined by Eqn. D.3:

$$\eta_1(\text{sampler}) = 0.5[1 + \exp(-0.06 d_{ae})] + 1 \times 10^{-5} U^{2.75} \exp(0.055 d_{ae}). \quad (\text{D.3})$$

(D13) To increase the accuracy of representing the experimental data on the intake efficiency of the human head, I_1 , for particles less than about 10- μm aerodynamic

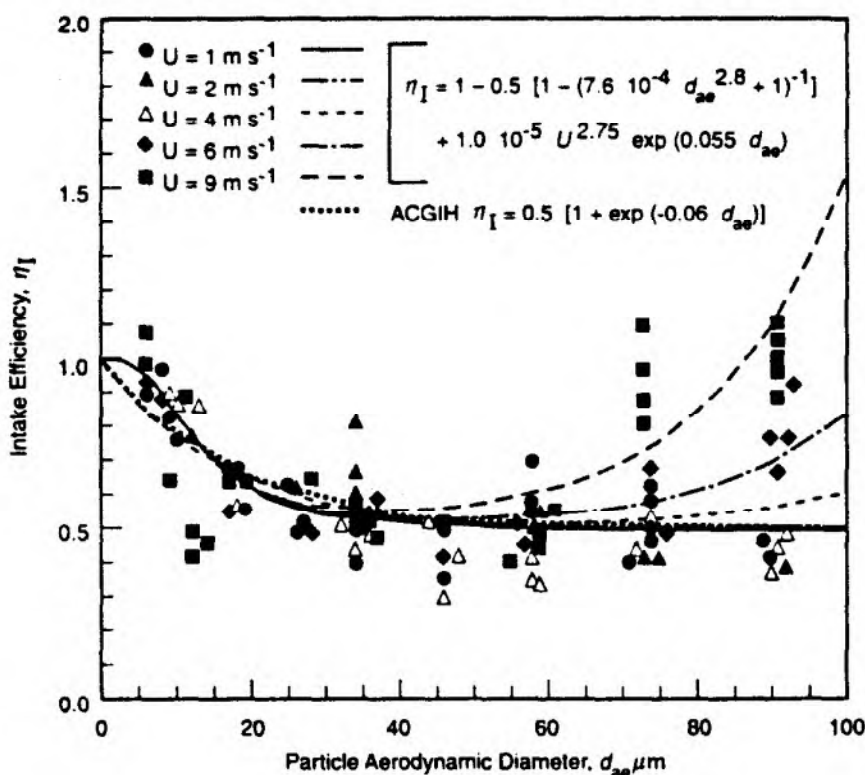


Fig. D.1. Intake efficiency of the human head at random orientations to moving air. The data were obtained by Vincent *et al.* (1990) using a mannequin rotated through 360° in a large wind tunnel. The curves show the representative empirical function recommended in this report (for various windspeeds), and the standard for sampling instruments recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).

diameter (for which I_1 is close to unity), the expression defined by Eqn. D.4 is recommended:

$$\eta_I(\text{head}) = 1 - 0.5 \{ 1 - [7.6 \times 10^{-4} (d_{ae})^{2.8} + 1]^{-1} \} + 1 \times 10^{-5} U^{2.75} \exp(0.055 d_{ae}). \quad (\text{D.4})$$

The curve of intake efficiency as a function of windspeed given by this expression is shown in Fig. D.1.

D.2.1. Inhalability in Still Air

(D14) The data discussed above apply to the intake efficiency of the human head for particles carried in moving air. Breyse and Swift (1990) published the only study of particle inhalability in still air. These authors measured the efficiency of nasal aspiration of radiolabelled pollen and wood dust in four subjects at normal resting breathing rates. Their data are shown as a function of particle diameter in Fig. D.2.

(D15) For comparison with these data for intake efficiency in still air, the figure also shows the intake efficiency function (defined by Eqn. D.4) fitted to data for moving air. It is seen that this expression tends to overestimate the aspiration efficiencies measured for 30- μm diameter particles by Breyse and Swift (1990) in still air. However, for the purpose of standard-setting, it is prudent to apply Eqn. D.4 to evaluate the aspiration efficiency of the human head under both still and moving air exposure conditions.

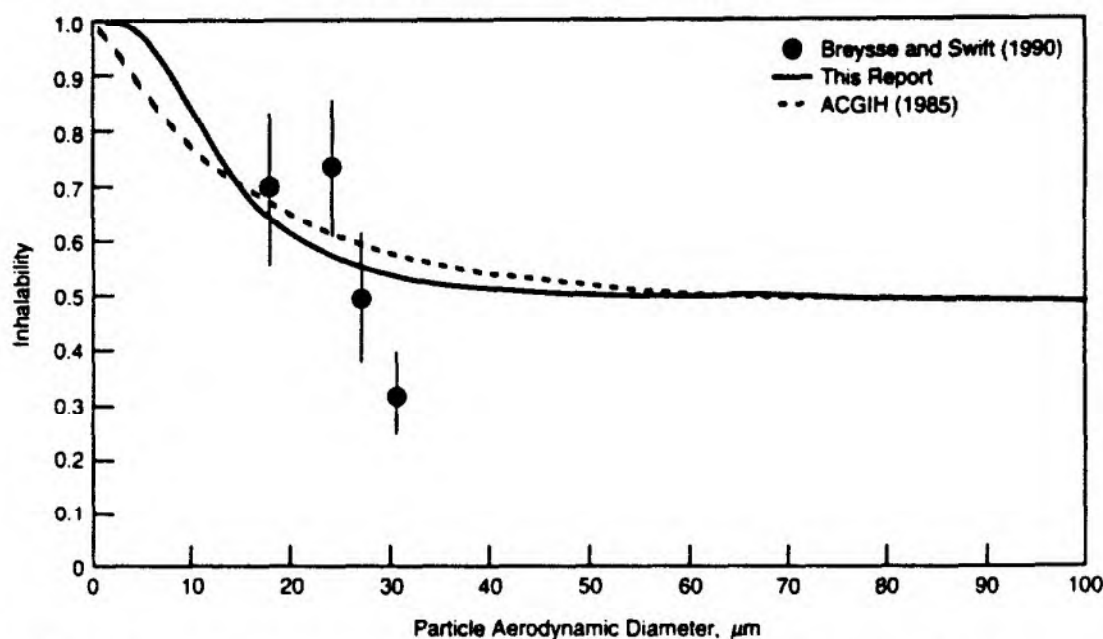


Fig. D.2. Inhalability of particles from still air measured by Breysse and Swift (1990) in four human subjects. The data are the average values ± 1 standard deviation of results from repeated measurements. The curves are described in Fig. D.1.

D.3. Breathing Habit

(D16) The head warms and humidifies the inspired air, and also acts as a particle filter for the thoracic airways. Since the nose is more efficient than the mouth in conditioning the inspired air, breathing at rest usually occurs through the nose. However, during physical exercise, oral breathing is used to supplement airflow through the nose.

(D17) Since the filtration efficiencies of the nose and mouth are different, a subject's breathing habit affects the amount of inhaled material that deposits in the lungs. Niinimaa *et al.* (1980, 1981) found that, in response to exercise, most subjects switch to breathing partly through the mouth. In studies of healthy young adults, these authors found that twenty of thirty subjects tested switched to oro-nasal breathing, typically at a ventilation rate of about $2.1 \text{ m}^3 \text{ h}^{-1}$. Five other subjects continued to breathe through the nose even when exercising vigorously. Another four subjects, who were habitual "mouth breathers," were found to breathe oro-nasally (through the nose and mouth together) at all levels of exercise.

(D18) These data were reviewed by Miller *et al.* (1988), who concluded that, for the purpose of deriving radionuclide intake limits, it is unrealistic to consider the case of a pure mouth breather. Based on the review of Miller *et al.*, it is recommended that the patterns of change between nasal and oral breathing shown in Fig. D.3 be taken to typify the breathing habit of an adult male as a function of ventilation rate.

(D19) Recommendations for the percentage of total ventilatory airflow passing through the nose in normal nasal augmenters (nose breathers) and in mouth breathers at reference levels of physical exertion are summarised in Table 15 of Chapter 5. In the absence of specific data, it must be assumed that the same breathing habits apply to healthy young subjects as apply to normal, healthy adults.

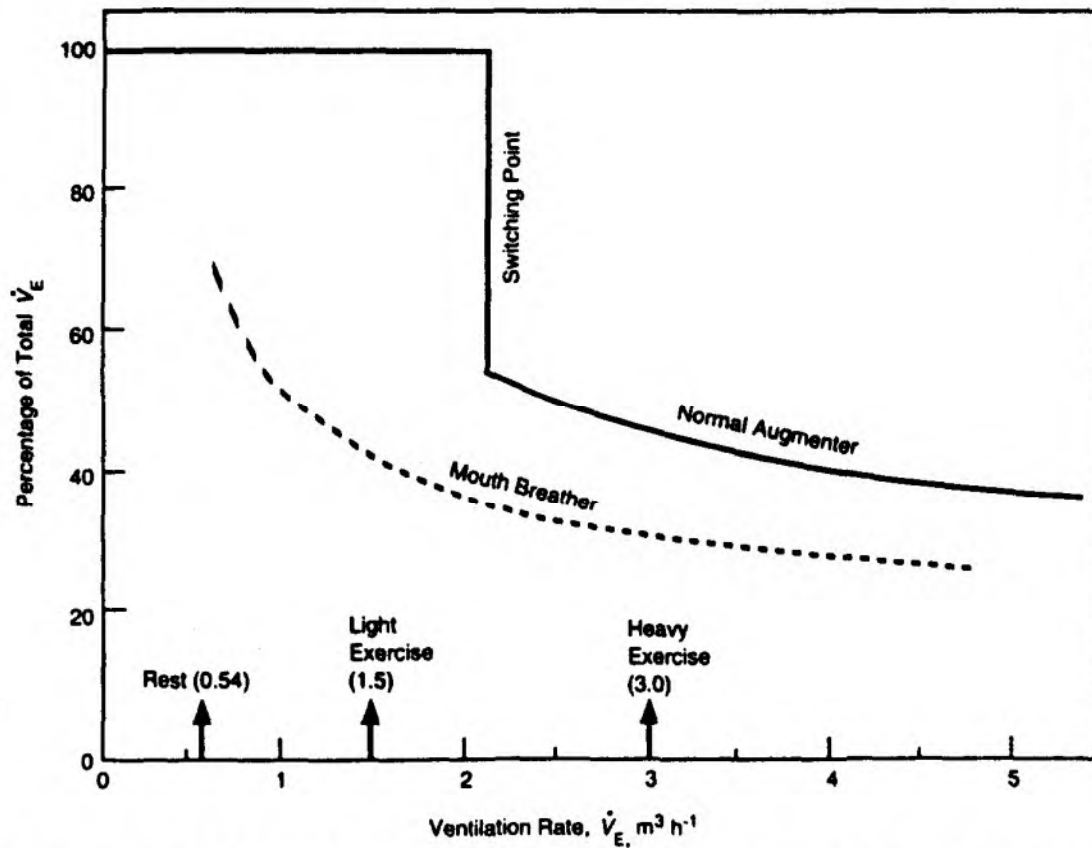


Fig. D.3. Percentage of total ventilatory airflow passing through the nasal route in "normal augmenters" (solid curve) and in habitual "mouth breathers" (dashed curve).

D.4. Empirical Modelling of Deposition Data

(D20) The term "deposition" denotes the mean probability of an inspired particle being deposited. The fraction of the number of inhaled particles deposited in the whole respiratory tract is referred to as "total" deposition. The fraction of the number of inhaled particles deposited in a single region of the respiratory tract is referred to as "regional" deposition. The total deposition is therefore the sum of the regional deposition values.

(D21) The term "deposition efficiency" denotes the fraction of the number of particles that enter a single region of the respiratory tract that is deposited in that region. In the recommended model (see below and Chapter 5) the deposition efficiency of each region is formulated separately for the inhalation and exhalation phases of a breath.

(D22) The processes that govern deposition of particles in the extrathoracic region of the respiratory tract, i.e. the nose, naso-oropharyngeal passages, and larynx, depend strongly on particle size (as they do within the thoracic airways). In broad terms, particles with an aerodynamic diameter larger than about $0.5 \mu\text{m}$ are deposited primarily by the so-called "aerodynamic" transport processes of inertial motion, referred to as "impaction", and gravitational settling, referred to as "sedimentation". For very large particles and fibres, interception with surfaces in the extrathoracic airways also contributes to their deposition. Particles with an equivalent physical diameter less than a few tenths of a micrometer are deposited primarily by the "thermodynamic" transport process of Brownian "diffusion".

D.4.1. Aerodynamic Deposition

(D23) The physical properties of a particle that determine its aerodynamic transport are combined in a unique parameter, the aerodynamic diameter:

$$d_{ae} = d_e \left[\frac{\rho C(d_e)}{\chi \rho_0 C(d_{ae})} \right]^{1/2} \quad (D.5)$$

where d_e is the equivalent volume diameter, i.e. the diameter of the spherical particle with the same volume as the particle considered, χ and ρ are the particle shape factor and mass density, and ρ_0 is unit density (1 g cm^{-3}), with the slip correction (often called the Cunningham factor), $C(d_e)$ or $C(d_{ae})$, for particle slip caused by the relative velocity of gas molecules at the particle surface. (See Hinds [1982] for an introductory discussion of these parameters.)

D.4.1.1. Slip correction factor

(D24) The slip factor was derived by Davies (1945) in the form of Eqn. D.6:

$$C(d_e) = 1 + (\lambda/d_e) \{2.514 + 0.800 \exp[-0.55(d_e/\lambda)]\} \quad (D.6)$$

where $\lambda = 0.0712 \text{ } \mu\text{m}$ and is the mean free path of the air molecules at 37°C , 100% relative humidity and 76 cm Hg atmospheric pressure (Briant, 1990). The mean free path is a function of both temperature and pressure (Willeke, 1976). The correction for particle slip in the human respiratory tract at 37°C is conveniently expressed in terms of d_e (μm) and the atmospheric pressure, P (cm Hg), by:

$$C(d_e, P) = 1 + (1/P d_e) [13.571 + 4.312 \exp(-0.1022 P d_e)]. \quad (D.7)$$

D.4.1.2. Aerodynamic shape factor

(D25) The aerodynamic shape factor is a dimensionless constant used to relate the drag force experienced by an irregular particle moving in air to the particle's equivalent volume diameter. According to Stokes' law, the drag on an irregular particle is given by Hinds (1982):

$$F_D = 3\pi\mu u d_e \chi \quad (D.8)$$

where μ = dynamic viscosity of air, i.e. 1.90×10^{-4} Poise (Briant, 1990),

u = particle velocity,

d_e = the equivalent volume diameter, i.e. the diameter of a sphere having the same volume as the particle, and

χ = the dynamic shape factor, typical values of which lie in the range 1 to 2 (Hinds, 1982).

(D26) When a particle achieves its terminal settling velocity, u_g , this drag force is balanced by the force of gravity, g . Thus:

$$u_g = \frac{\rho d_e^2 C(d_e) g}{18\mu\chi} = \frac{\rho_0 d_{ae}^2 C(d_{ae}) g}{18\mu} \quad (D.9)$$

The solution of Eqn. D.9 for aerodynamic diameter, d_{ae} , yields Eqn. D.5.

D.4.1.3. Aerodynamic deposition efficiency

(D27) Gravitational deposition efficiency can usually be described as a function of $d_{ae}^2 t_r$, where t_r is the mean residence time of a particle in a given region of the respiratory tract. Inertial deposition efficiency can be described as a function of $d_{ae}^2 \dot{V}$, where $\dot{V}$ is the volumetric flow rate through a particular region.

(D28) The effects of inertial and gravitational transport are summed using Eqn. D.9 to give the overall efficiency of the aerodynamic deposition processes, η_{ac} , in terms of the "impaction," η_i , and "sedimentation," η_s , components:

$$\eta_{ac} = 1 - (1 - \eta_i)(1 - \eta_s). \quad (D.10)$$

D.4.2. Thermodynamic Deposition

(D29) The mean square displacement of a particle by Brownian motion per unit time is:

$$\frac{\overline{x^2}}{t} = 2D = \frac{2C(d_e)kT}{3\pi\mu d_e} \quad (D.11)$$

where D is the so-called "diffusion coefficient" of the particle, which is defined in terms of the additional parameters k , Boltzmann's constant, and T , the absolute temperature. The diffusion coefficient has the unit $\text{cm}^2 \text{s}^{-1}$.

(D30) The particle properties that determine thermodynamic transport can also be used to define the thermodynamic diameter of the particle:

$$d_{th} = d_e = \frac{kTC(d_e)}{3\pi\mu D} \quad (D.12)$$

where d_{th} is considered to be equal to the particle volume equivalent diameter. In practice, the thermodynamic diameter is determined by a measured diffusion coefficient D .

D.4.2.1. Relating thermodynamic to aerodynamic diameter

(D31) A particle's thermodynamic diameter is given in terms of its aerodynamic diameter by Eqn. D.13 (derived from Willeke, 1976):

$$d_{th} = d_{ac} \sqrt{\frac{\chi\rho_0}{\rho} \times \frac{C(d_{ac})}{C(d_{th})}} \quad (D.13)$$

where $C(d_{th})$ is the slip correction for a particle of thermodynamic diameter, d_{th} , ρ is the density of the particle, and $C(d_{ac})$ is the slip correction for a particle of aerodynamic diameter, d_{ac} . These slip correction factors are given by substituting either d_{th} or d_{ac} , respectively, for d in Eqn. D.14:

$$C(d) = 1 + \frac{\lambda}{d} \left[2.514 + 0.800 \exp \left(-0.55 \frac{d}{\lambda} \right) \right]. \quad (D.14)$$

Note that in Eqn. D.13 the thermodynamic diameter, d_{th} , appears in the expression for $C(d_{th})$. Thus, in order to express d_{th} uniquely as a function of the aerodynamic diameter, d_{ac} , it is necessary to solve Eqn. D.13 recursively. This solution can be approximated by initially setting $(d_{th})_1 = d_{ac} \sqrt{(\chi/\rho)}$. It can be shown that the iterative solution then converges rapidly ($n < 10$) to the correct value for d_{th} .

D.4.2.2. Correction of thermodynamic diameter for extremely small particles

(D32) For extremely small particles, which approach molecular dimensions, i.e. for particles less than 2-nm equivalent volume diameter, Ramamurthi and Hopke (1989)

showed that Eqn. D.10 must be modified in order to calculate the diffusion coefficient. These authors found that the real equivalent volume diameter, d_e , should be replaced in Eqns D.7 and D.11 by a thermodynamic diameter, d_{th} , defined by Eqn. D.15:

$$d_{th} = d_e [1 + 3 \exp(-2.20 \times 10^3 \times d_e)] \quad (D.15)$$

where d_e is in μm . This correction reduces the diffusion coefficient (Eqn. D.10) calculated for a 0.0005- μm -diameter particle by approximately a factor of two, which agrees with the diffusion coefficient of molecular clusters in a gas derived from kinetic theory (Loeb, 1961; Porstendörfer, 1968; Raabe, 1969).

D.4.2.3. Diffusional deposition efficiency

(D32) Diffusional deposition in a particular region of the respiratory tract is described as a function of the diffusion coefficient, D , usually in combination with the residence time, t_r , in the form $(Dt_r)^{1/2}$.

D.4.3. Combining Thermodynamic and Aerodynamic Deposition

(D33) For a given particle, deposition by Brownian diffusion is a stochastic process, in contrast to deposition by aerodynamic transport, which is determined by airway geometry and airflow characteristics. Fuchs (1964) showed that the transport length from two deposition processes acting simultaneously, when at least one of these processes is stochastic in nature, is given by quadratic addition of the two components. It can be shown that, providing the deposition efficiency, η , is less than about 0.3, this quadratic form of superimposition can also be applied to the respective deposition efficiencies, i.e.:

$$\eta = (\eta_{th}^2 + \eta_{ac}^2)^{1/2}. \quad (D.16)$$

(D34) Heyder *et al.* (1985) studied experimentally the interaction of diffusional and gravitational particle transport in various types of aerosol filters. They found empirically that the interaction can be described by:

$$\eta = \eta_D + \eta_G - (\eta_D \times \eta_G) / (\eta_D + \eta_G). \quad (D.17)$$

(D35) By replacing η_D and η_G in Eqn. D.17 by η_{th} and η_{ac} , respectively, it can be shown (J. W. Gentry, University of Maryland, personal communication) that the relationship derived empirically by Heyder *et al.* (1985) is equivalent to the first term in the series expansion of Eqn. D.16. Thus, Eqn. D.16 is recommended, on the basis of conceptual considerations, to express the combined effects of thermodynamic and aerodynamic deposition processes.

(D36) Within any particular region of the respiratory tract, simultaneous thermodynamic and aerodynamic transport can only be significant for particles in the size range from about 0.1- μm thermodynamic diameter to 1- μm aerodynamic diameter. For smaller or larger particles, either thermodynamic or aerodynamic transport predominates, respectively. Thus, it is appropriate to use Eqn. D.16 to combine the thermodynamic and aerodynamic deposition efficiencies in all parts of the respiratory tract.

D.5. Nasal Deposition: Human Data and Models

D.5.1. Aerodynamic Deposition

D.5.1.1. Experimental studies

(D37) Because it is more easily studied experimentally, the aerodynamic filtration efficiency of the nose is much better documented than that of any other part of the respiratory tract. A large number of studies have been reported for aerosols with aerodynamic particle diameters above $0.2 \mu\text{m}$. These studies have been reviewed by Mercer (1975), Lippmann (1977), Yu *et al.* (1981), Schlesinger (1985), and Stahlhofen *et al.* (1989).

(D38) Different experimental techniques and evaluation procedures have been used in the various studies, so that the published data are not all directly comparable. In some studies, nasal deposition has been determined directly by external detection of deposited radioactivity after inhalation of labelled particles (Lippmann and Albert, 1969; Lippmann, 1970). An earlier experimental technique involved measuring the change in particle concentration when an aerosol was drawn in through the nose and out through the mouth during breath holding (Landahl and Black, 1947; Landahl and Tracewell, 1949; Landahl, 1950; Pattle, 1961; Fry, 1970; Hounam *et al.*, 1971). This artificial technique was later replaced by measuring the total respiratory tract deposition during different breathing manoeuvres, i.e. during pure nose breathing, pure mouth breathing, nose-in mouth-out, and mouth-in nose-out breathing (Dennis, 1971; Giacomelli-Maltoni *et al.*, 1972; Märtens and Jacobi, 1973; Rudolf, 1975; Heyder and Rudolf, 1977). By applying all four of these manoeuvres, Heyder and Rudolf (1977) were able to determine separately the efficiencies of nasal deposition during inspiration and expiration.

D.5.1.2. Discussion and empirical model

(D39) Figure D.4 shows the experimental data on the aerodynamic deposition efficiency of the nose during normal inspiration, plotted as a function of the inertial impaction parameter, $d_{ac}^2 \dot{V}$, where d_{ac} is the aerodynamic particle diameter (in μm), and $\dot{V}$ is the volumetric flow rate (in $\text{cm}^3 \text{s}^{-1}$).

(D40) On the average, the nasal deposition efficiency is seen in Fig. D.4 to be related to the impaction parameter. The data from all four of the available studies are consistent. However, the studies by Lippmann (1970), Giacomelli-Maltoni *et al.* (1972), and Rudolf (1975) exhibit a large degree of variability. This is due mainly to the measured variability in nasal deposition between different subjects.

(D41) Since the bulk of aerodynamic nasal deposition occurs near the junction between the anterior and posterior nasal passages, the dead space can be neglected. Thus, the nasal deposition measured on inhalation is a close approximation of the deposition efficiency of the nose. By statistical least-squares analysis of these data, Rudolf *et al.* (1986) and Stahlhofen *et al.* (1989) expressed the mean aerodynamic deposition efficiency of the nose on inhalation, $\eta_{ac}(N_i)$, in terms of the impaction parameter, $d_{ac}^2 \dot{V}$, by Eqn. D.18 (as shown in Fig. D.4):

$$\eta_{ac}(N_i) = 1 - [3.0 \times 10^{-4} (d_{ac}^2 \dot{V}_n) + 1]^{-1}. \quad (\text{D.18})$$

In this expression, $\dot{V}_n$ represents the volumetric flow rate through the nose, which might consist of only part of the total inspiratory flow. (See Chapter 5, Fig. 8.)

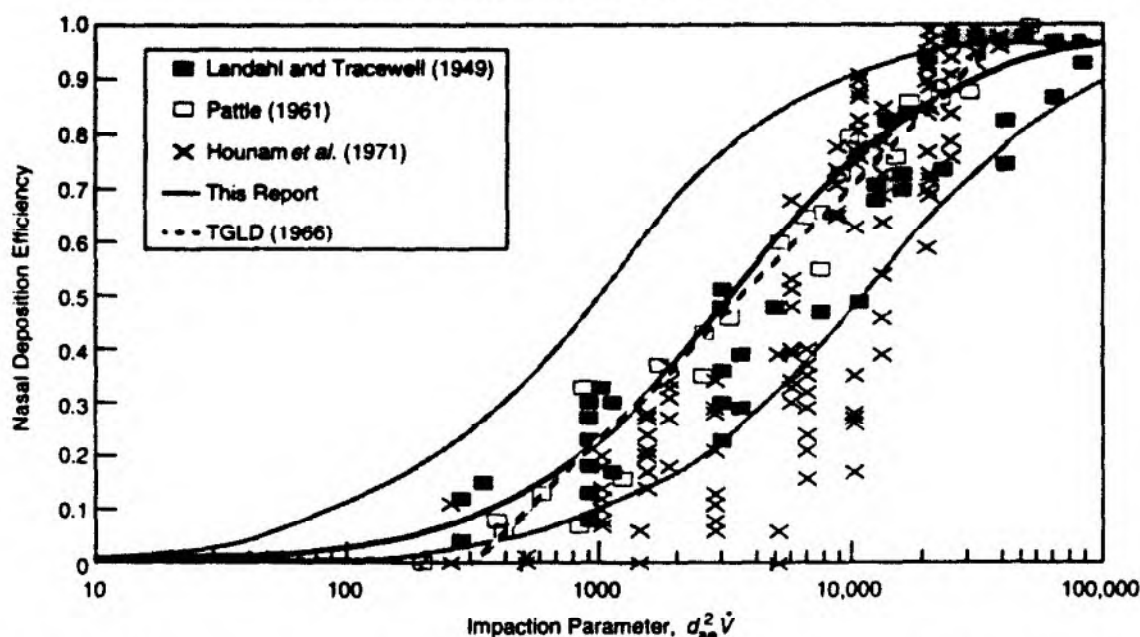


Fig. D.4. Nasal deposition efficiency measured in adult Caucasian males during normal breathing. The solid curve shows the expression given by Stahlhofen *et al.* (1990) to represent the mean of these data as a function of the impaction parameter, $d_{ae}^2 \dot{V}$. The two outer curves show estimates of the upper and lower 95% confidence limits for the modelled nasal deposition efficiency. The dashed curve shows the expression for nasal deposition efficiency used in the ICRP Publication 30 lung model (TGLD, 1966).

(D42) This approximation accounts for the observed slow increase in deposition efficiency for low values of $d_{ae}^2 \dot{V}$, and predicts an asymptotic approach to unity for high values of this impaction parameter. As shown in Fig. D.4, for intermediate values of $d_{ae}^2 \dot{V}$, the predicted deposition efficiency is similar to that given by Pattle's (1961) log-linear approximation, which was adopted by the Task Group on Lung Dynamics (TGLD, 1966).

(D43) The expression for deposition efficiency recommended in this report (Eqn. D.18) has the general hyperbolic form:

$$\eta = 1 - 1/(aR^p + 1) \quad (\text{D.19})$$

where the parameters a and p are dimensionless constants. In this case, the value of a is 3.0×10^{-4} , and p is unity.

D.5.1.3. Estimation of uncertainty

(D44) The 95% confidence bounds of the experimental data estimated by a statistical analysis procedure (G. Rudolf, personal communication) are shown in Fig. D.4. In the main, these reflect the intersubject variability of nasal deposition on inhalation for particles in the aerodynamic-size range. These bounds are defined numerically by increasing or decreasing the parameter a in Eqn. D.19 by the constant factor c of 3.3. Thus, the upper 95% confidence bound is obtained by substituting $a = 1.0 \times 10^{-3}$, and the lower bound by substituting $a = 9.0 \times 10^{-5}$.

D.5.1.4. Data for aspirated flow through the nose and mouth

(D45) Earlier studies of nasal deposition in human subjects used the artificial technique of drawing an aerosol in through the nose and out through the mouth (Landahl and Tracewell, 1949; Pattle, 1961; Hounam *et al.*, 1971). The results obtained

by these authors are shown in Fig. D.5, where they are compared with the nasal deposition efficiency predicted by the recommended expression (Eqn. D.18). It is seen that, except for at high values of the impaction parameter, artificial aspiration of particles through the nose tended to give lower measured values of nasal deposition. This tendency is particularly marked in the case of the study by Hounam *et al.* (1971).

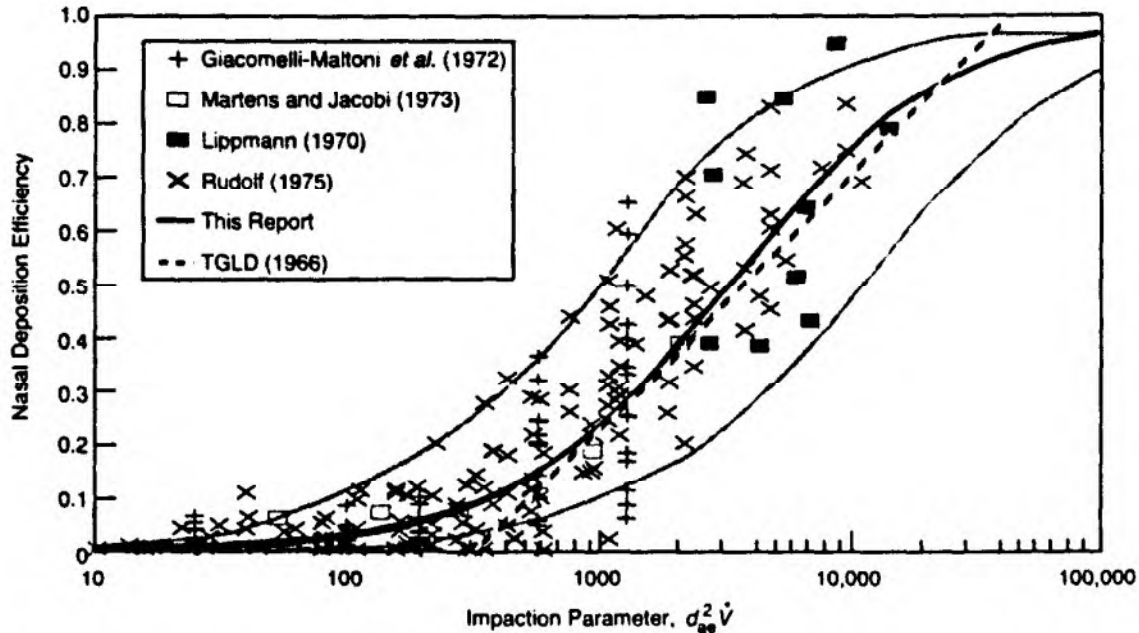


Fig. D.5. Nasal deposition efficiency measured in adult Caucasian males when particles are drawn artificially through the nose and out through the mouth. The curves show the recommended model for nasal deposition during normal inhalation, and the expression for nasal deposition used in the *ICRP Publication 30* lung model (TGLD, 1966), as shown in Fig. D.4.

D.5.1.5. Deposition on exhalation

(D46) Heyder and Rudolf (1977) derived from their data the separate expressions for nasal deposition efficiency on inhalation and exhalation given by Eqns D.20 and D.21, respectively:

$$\eta_{ac}(N_i) = -1.15 + 0.47 \log_{10}(d_{ac}^2 \dot{V}) \quad (D.20)$$

$$\eta_{ac}(N_e) = -1.01 + 0.43 \log_{10}(d_{ac}^2 \dot{V}). \quad (D.21)$$

(D47) For values of $d_{ac}^2 \dot{V}$ greater than 1000, these expressions give estimates of nasal deposition efficiency within several percent of each other. For lower values of $d_{ac}^2 \dot{V}$, the predicted efficiencies for inhalation and exhalation diverge. However, in this region of the data, the log-linear regression no longer provides an acceptable fit, and any systematic difference between the efficiencies of deposition on inhalation and exhalation is not detectable in the data. Thus, for application of the dosimetry model, it is considered that Eqn. D.18 is appropriate to evaluate nasal deposition for both inhalation and exhalation. When the overall nasal deposition is high, most of this will have occurred on inhalation, since particles not already deposited in the nose are likely to deposit in the lungs.

D.5.1.6. Scaling for body size

(D48) Nasal deposition has not been studied systematically in children, nor has the degree to which the intersubject variability measured in adult subjects relates to

variation in anatomical dimensions. In the absence of data, it is recommended that the scaling procedure proposed by Swift (1989) be applied to Eqn. D.18 to predict the effect of a subject's body size on nasal deposition of particles in the aerodynamic size-range.

(D49) Eqn. D.18 represents particle deposition in the nose of the adult Caucasian male in terms of the product, $d_{ac}^2 \times \dot{V}$, of particle aerodynamic diameter and volumetric inspiratory flow rate. The equation can be rewritten in terms of the Stokes inertial parameter:

$$Stk = \frac{\rho_0 d_{ac}^2}{18\mu L} u \quad (D.22)$$

where ρ_0 = unit density, 1 g cm^{-3} ,

u = air velocity, cm s^{-1} ,

μ = dynamic air viscosity, $\text{g cm}^{-1} \text{ s}^{-1}$,

L = characteristic airway dimension, cm.

For u being the average velocity across an airway of characteristic diameter L , the ratio u/L is proportional to the ratio $\dot{V}/L^3$.

(D50) Yu and Xu (1987) and Swift (1989) have applied the factor $1/L^3$ to scale inertial effects in the nose for airway dimensions. In the absence of direct measurements of the critical linear dimension of the nasal passageway in different subjects, these authors assumed that this parameter is scaled in proportion to the diameter of the subject's trachea. This scaling convention to evaluate nasal deposition in adult and child subjects by reference to that in the adult Caucasian male is adopted in this report. Thus, to scale the inertial deposition efficiency of the nose in terms of a characteristic linear dimension of the subject, Eqn. D.18 is modified as follows:

$$\eta_{ac}(N) = 1 - [3.0 \times 10^{-4} (d_{ac}^2 \dot{V}_n SF_1^3) + 1]^{-1} \quad (D.23)$$

where SF_1 is the ratio of tracheal diameter in the reference adult male Caucasian to that in the subject.

D.5.2. Thermodynamic Deposition

D.5.2.1. Human data

(D51) Deposition in the nose by Brownian diffusion is significant not only for adsorptive gases, but also for particles below about $0.1 \mu\text{m}$ in diameter. However, nasal deposition for these submicron-sized particles has not been studied intensively in human subjects. George and Breslin (1969) measured nasal deposition of radon progeny in three subjects by drawing laboratory air containing either "unattached" or "attached" progeny in through the nose and out through the mouth at various flow rates. They recorded deposition values of a few percent for the attached progeny, and about 60% for the unattached progeny. Unfortunately, when these experiments were performed, it was not known that the diffusion coefficient of unattached radon progeny varies markedly with the trace constituents present in room air. The general assumption at that time was that unattached radon progeny had a characteristic diffusion coefficient of approximately $0.05 \text{ cm}^2 \text{ s}^{-1}$. Later work in the same laboratory showed that the so-called "unattached" progeny may actually consist of molecular clusters with a characteristic diffusion coefficient an order of magnitude lower. Therefore, the interpretation of George and Breslin's (1969) measurements as defining the nasal deposition efficiency of unattached radon progeny is uncertain.

(D52) The later study by Schiller *et al.* (1986, 1988) measured total deposition in a typical group of human subjects who inhaled aerosol particles at a constant flow rate, first in through the nose and out through a mouthpiece, and then *vice versa*. By assuming that deposition in the oropharynx and larynx is negligible, these authors estimated nasal deposition efficiencies of about 15% and 4% for 0.005- μm - and 0.01- μm -diameter particles, respectively. However, as discussed below, it is now known that oropharyngeal and laryngeal deposition of submicron-sized particles cannot be neglected in comparison with that in the nose.

D.5.2.2. Experimental studies with hollow casts

(D53) In the absence of definitive studies of nasal deposition in human subjects, reliance must be placed on surrogate measurements of deposition in hollow casts of nasal passages, naso-oropharynx, and larynx. Anatomically accurate casts constructed from magnetic resonance imaging (MRI) scans of subjects taken *in vivo* have been used by several authors to measure the deposition efficiency of the head airways and larynx for ultrafine particles, as a function of the particle diffusion coefficient and airflow rate (Cheng *et al.*, 1988, 1989; Swift *et al.*, 1992). In a study involving three different casts (one from an *in vivo* MRI scan of an adult male, one taken from an adult male *postmortem*, and one from an *in vivo* MRI scan of a 1.5-y-old child), consistent experimental results were obtained in three different laboratories (Swift *et al.*, 1992). These authors' results are shown in Fig. D.6, together with their fitted relationship between naso-oropharyngeal-laryngeal deposition efficiency and an empirical deposition parameter $D^{1/2} \dot{V}^{-1/8}$.

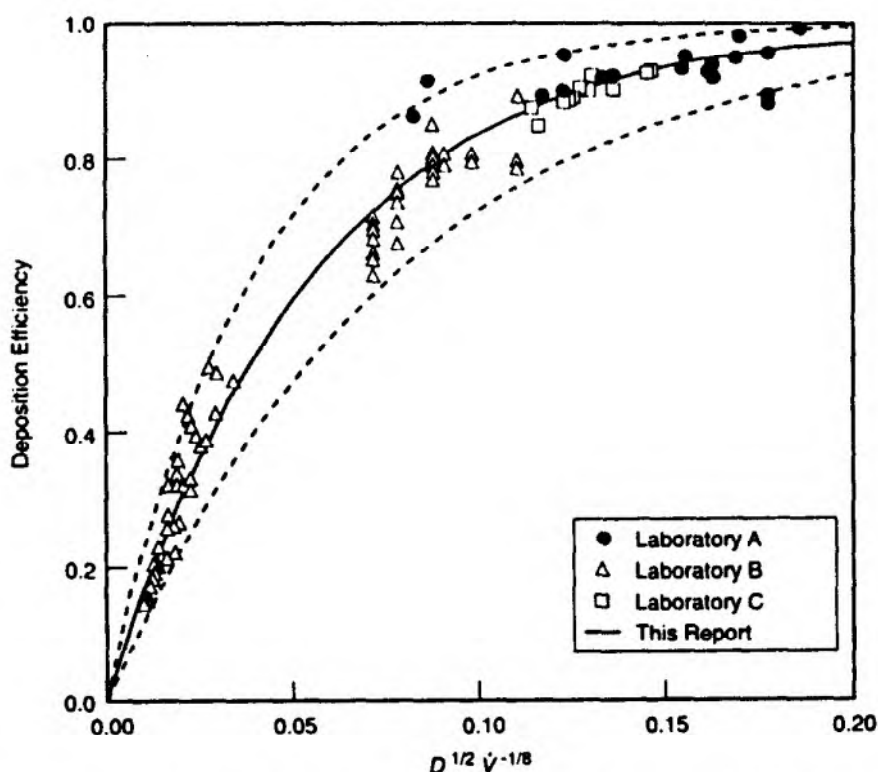


Fig. D.6. Deposition efficiency measured in replicate casts of the human naso-oropharyngeal passage and larynx by Swift *et al.* (1992) as a function of the empirical deposition parameter, $D^{1/2} \dot{V}^{-1/8}$. The dashed curves show assumed 95% confidence limits in using the fitted curve to predict nasal deposition for an actual human subject.

D.5.2.3. Empirical model and estimated uncertainty

(D54) The hollow casts measured by Swift *et al.* (1992) comprised the nasal and naso-oropharyngeal passages and larynx in series. In the notation used in this report, these airways comprise both regions ET_1 and ET_2 , so that the thermodynamic deposition efficiency measured by Swift *et al.* (1992) corresponds to that of the ET region as a whole, for inhalation via the nasal route, i.e. $\eta_{th}(ET_1)_n$. This measured deposition efficiency is represented by Eqn. D.24:

$$\eta_{th}(ET_1)_n = 1 - \exp(-18D^{1/2}\dot{V}_n^{-1/8}) \quad (D.24)$$

where $\dot{V}_n$ is the volumetric flow rate through the nose.

(D55) Swift *et al.* (1992) noted that when the experimental data were plotted as a function of the parameter $D^{1/2}\dot{V}_n^{-1/8}$, the results for the three different casts (including that from the 1.5-y-old child) were indistinguishable. Thus, any effect of the markedly different anatomical dimensions of the three casts was masked by the intrinsic variability of the experimental measurements.

(D56) In the absence of confirmatory human data, it is assumed that the variability in measured deposition efficiency shown in Fig. D.6 provides a reasonable estimate of the uncertainty in predicting thermodynamic extrathoracic deposition *in vivo*. The dashed curves shown in Fig. D.6 are estimates of the upper and lower 95% confidence bounds on the modelled deposition efficiency.

(D57) Eqn. D.24 has the general form:

$$\eta = 1 - \exp(-aR^p). \quad (D.25)$$

In this case, the constant a is 18, the composite parameter R can be set equal to $D\dot{V}^{-1/4}$, and p is 1/2 (as is applied in Chapter 5, Table 12).

(D58) The 95% uncertainty bounds in modelling thermodynamic deposition in the extrathoracic region are estimated by multiplying or dividing the constant a in Eqn. D.22 by the constant factor c of 1.4.

D.5.2.4. Deposition on exhalation

(D59) Yamada *et al.* (1988) found that the thermodynamic deposition efficiency measured for particles between about $0.005\ \mu\text{m}$ and $0.2\ \mu\text{m}$ in a hollow nasal cast was approximately 10% higher for flow in the expiratory direction than for inspiration. Since this difference is relatively slight, it is recommended that Eqn. D.24 be used to estimate nasal deposition on both inhalation and exhalation. As mentioned earlier for aerodynamic deposition (Paragraph D44), when the thermodynamic nasal deposition is high, very few particles will escape from the lungs on exhalation to be deposited in the nose.

D.5.2.5. Scaling for body size

(D60) To model the effects of anatomical dimensions on nasal deposition for particles in the thermodynamic size range, the flow rate $\dot{V}_n$ in Eqn. D.24 can be replaced by the dimensionless Reynolds number Re (Cheng *et al.*, 1988):

$$Re = Lu/\nu \quad (D.26)$$

where L is a hydraulic diameter, cm,

u is the fluid velocity, cm s^{-1} ,

ν is the kinematic fluid viscosity, $\text{cm}^2 \text{s}^{-1}$.

Substituting the volumetric flow rate $\dot{V}$ for u in Eqn. D.23 then gives:

$$\begin{aligned} Re &= k' L \dot{V} / L^2 \\ &= k' \dot{V} / L \end{aligned} \quad (\text{D.27})$$

where k' is a constant term.

(D61) Therefore, the scaling factor to be applied to $\dot{V}$ in Eqn. D.24 is L_{ref}/L_s , where L_{ref} is a characteristic airway dimension for the reference adult male, and L_s is the corresponding anatomical dimension for the subject considered. The diameter of the trachea provides an adequate index dimension. Thus, for any subject, the ratio of tracheal diameter in the reference adult male to that in the subject, SF_t , is used to modify Eqn. D.24, and:

$$\eta_{\text{th}}(\text{ET})_n = 1 - \exp\{-18[D(\dot{V}SF_t)^{-1/4}]^{1/2}\}. \quad (\text{D.28})$$

D.6. Oropharyngeal-Laryngeal Deposition: Human Data and Models

D.6.1. Aerodynamic Deposition

D.6.1.1. Experimental studies

(D62) Most experimental studies have been performed with mouth breathing through a tube, since this is a convenient method for aerosol administration. The oral deposition was measured by repeated mouth washings directly after inhalation. The remainder of the extrathoracic deposition, i.e. that in the oropharynx and larynx, was measured by external gamma counting (Foord *et al.*, 1978; Chan and Lippmann, 1980; Emmett and Aitken, 1982; Stahlhofen *et al.*, 1980). In the study by Stahlhofen *et al.* (1980), the activity in the stomach immediately after inhalation was also measured and considered to be part of the extrathoracic deposition. This activity must have originated from particles swallowed within a short time of deposition in the extrathoracic airways.

(D63) Measurements of extrathoracic deposition are not rigorously comparable in the various studies, since different experimental procedures and mouthpieces have been used. For example, the inner diameter of the mouthpiece tube influences the measured deposition; for the same respiratory flow rate, the smaller the tube diameter, the higher the velocity of inspired air, and thus the higher the inertial deposition. The position of the mouthpiece tube in relation to the tongue may also influence deposition. Furthermore, Dennis (1961) and Swift (1985) have observed that normal mouth breathing tends to give higher extrathoracic deposition than when the same subjects breathe through a mouthpiece tube. These authors' results indicate that deposition in the oral cavity during natural mouth breathing depends on the position of the tongue and the degree to which the mouth is open. Hence, the experimental data are not sufficient to model quantitatively deposition in the mouth and oropharynx itself. However, by using a scanning-bed gamma counter, Emmett and Aitken (1982) showed that, for particles less than about 10- μm aerodynamic diameter, the bulk of the extrathoracic deposition during mouth breathing occurs in the larynx. This conclusion was reinforced by Rudolf *et al.* (1983), and Stahlhofen *et al.* (1980, 1983, 1984b), who found that the extrathoracic deposition measured in their studies was largely accounted for by inertial deposition in the larynx.

(D64) Figure D.7 compares the experimental data on extrathoracic deposition during mouth breathing through tube mouthpieces obtained by Lippmann (1977), Chan

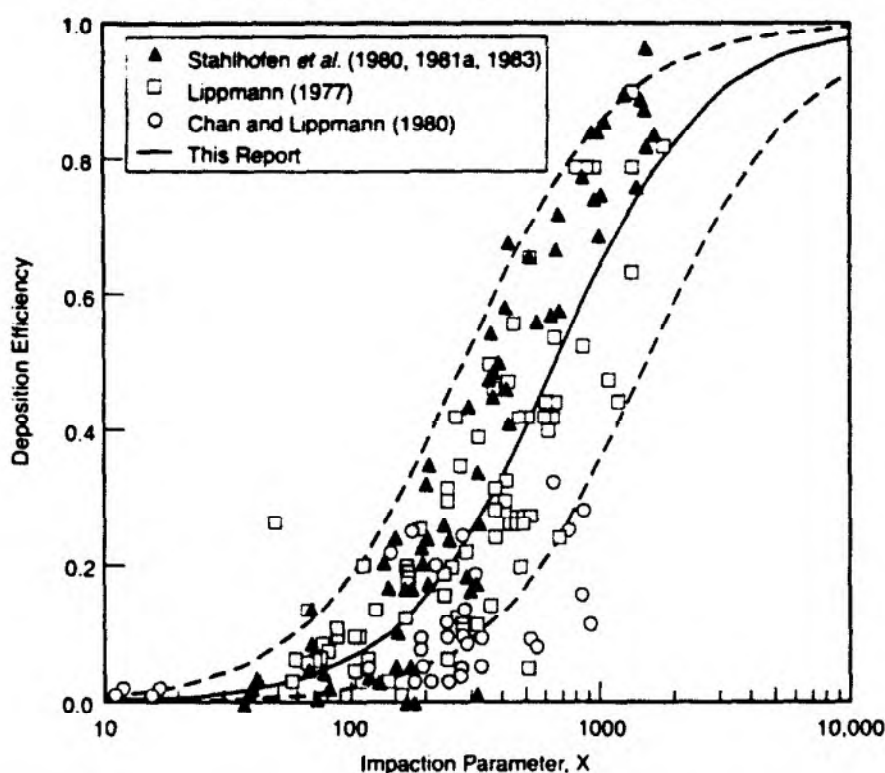


Fig. D.7. Experimental data on extrathoracic deposition when particles are inhaled and exhaled through a mouthpiece. The solid curve shows the empirical model. Dashed curves on either side represent the estimated 95% confidence bounds in predicted deposition based on variability of the data. Impaction parameter: $d_{ae}^2 V_T^{-0.6} V_I^{-0.2}$, $\mu\text{m}^2 \text{cm}^{1.2} \text{s}^{-0.6}$.

and Lippmann (1980), and Stahlhofen *et al.* (1980, 1981a, 1983). These studies involved 22, 26, and 15 different subjects, respectively.

(D65) Figure D.7 shows that the measured variability in extrathoracic deposition is high. The curves shown in the figure represent the empirical model adopted to describe the underlying trend of deposition efficiency as a function of an impaction parameter, and the upper and lower 95% confidence bounds of this estimate (G. Rudolf, personal communication), as described below. Figure D.8 compares the predicted extrathoracic deposition efficiency and its 95% confidence bounds with the additional data obtained by Foord *et al.* (1978), Emmett and Aitken (1982), Svartengren *et al.* (1987a,b, 1989a,b), and Anderson *et al.* (1990).

D.6.1.2. Empirical model and estimated uncertainty

(D66) Rudolf *et al.* (1983) and Rudolf (1984) showed that the inspiratory extrathoracic efficiency is not a unique function of the impaction parameter. The geometry of the airways in this region, and the flow conditions, suggest that deposition is in fact due to impaction. However, the characteristic dimension of the ET region during mouth breathing increases with increasing flow rate and with increasing tidal volume. Thus, the oropharyngeal-laryngeal passageway appears to behave like a "dynamic" impactor. The glottis is known to exhibit this type of behaviour by opening further with increasing flow rate and tidal volume.

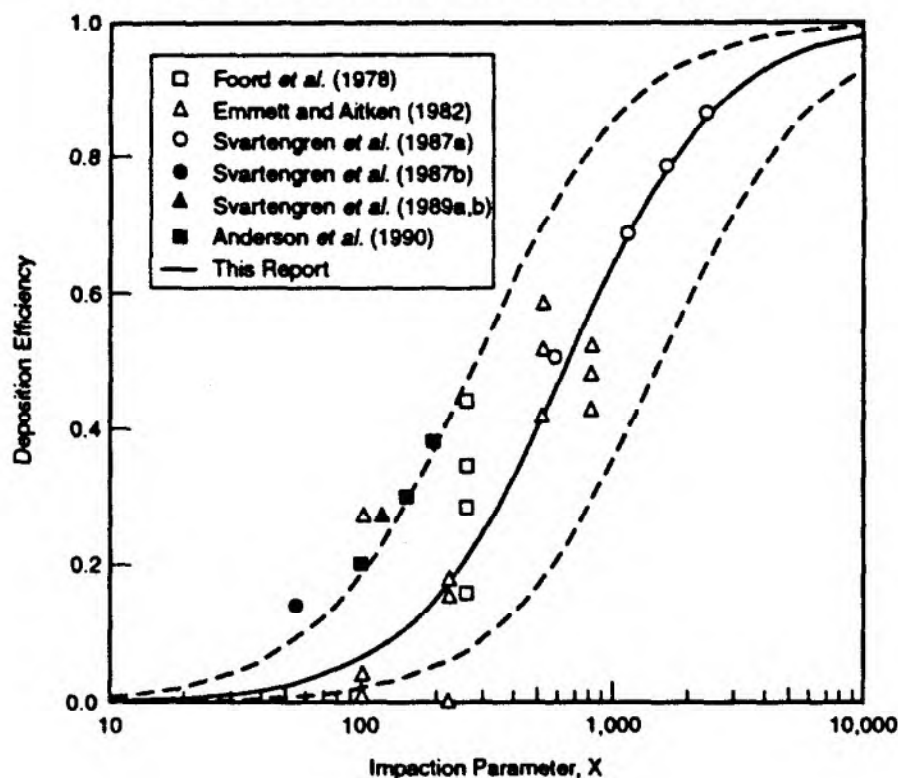


Fig. D.8. Comparison of model of extrathoracic deposition when breathing through a mouthpiece (showing 95% confidence bounds) with additional experimental data. Impaction parameter: $d_{ac}^2 \dot{V}^{0.6} V_T^{-0.2}$, $\mu\text{m}^2 \text{cm}^1 \text{s}^{-0.6}$.

(D67) Statistical analysis of all the available data (which are shown in Figs D.7 and D.8) gives the following revised expression for the estimated mean deposition efficiency of the larynx as a function of the impaction parameter $d_{ac}^2 \dot{V}^{0.6} V_T^{-0.2}$:

$$\eta_{ac}(\text{ET})_{\text{larynx}} = 1 - [1.1 \times 10^{-4} (d_{ac}^2 \dot{V}^{0.6} V_T^{-0.2})^{1.4} + 1]^{-1} \quad (\text{D.29})$$

where d_{ac} is the aerodynamic particle diameter, $\dot{V}$ the volumetric flow rate, and V_T the tidal volume (Rudolf *et al.*, 1990).

(D68) This expression has the same general form as Eqn. D.19, which was found to represent inertial impaction in the nasal passages. However, in the case of laryngeal deposition, the impaction parameter R depends on the tidal volume in addition to the volumetric flow rate, and this parameter is raised to the power 1.4. The constant term a is found to be 1.1×10^{-4} . The estimated upper and lower 95% confidence bounds in the modelled laryngeal deposition (see Figs D.7 and D.8) are given by multiplying or dividing a by the factor c of 3.3. This same value of c was estimated from the measured variability in nasal deposition (Paragraph D44).

(D69) Use of Eqn. D.29 is recommended to evaluate extrathoracic deposition for mouth breathing, and also the additional deposition that occurs in the larynx during nose breathing. The appropriate value of $\dot{V}$ for substitution in this expression is therefore the total volumetric flow rate, $\dot{V}$, i.e. the sum of that inspired through the nose and that (if any) inspired through the mouth.

D.6.1.3. Deposition on exhalation

(D70) In the absence of specific data, it is recommended that Eqn. D.29 also be applied to calculate extrathoracic deposition for particles exhaled via the oral pathway.

D.6.1.4. Scaling for body size

(D71) As discussed in Paragraphs D48 through D50 in relation to nasal deposition, the scaling factor for the volumetric flow rate, $\dot{V}$, in Eqn. D.29 that is necessary to correct for anatomical dimensions is SF_t^3 , the cube of the ratio of tracheal diameter in the reference adult Caucasian male to that in the subject. Adequate adjustment for the relatively smaller effect of the tidal volume, V_T , is achieved by multiplying this parameter by SF_t^2 . The extrathoracic (laryngeal) deposition in any subject is therefore given by Eqn. D.30:

$$\eta_{ac}(ET)_{larynx} = 1 - \{1.1 \times 10^{-4} [d_{ac}^2 (\dot{V} SF_t^3)^{0.6} (V_T SF_t^2)^{-0.2}]^{1.4} + 1\}^{-1}. \quad (D.30)$$

D.6.1.5. Intersubject variability and effects of laryngeal disease

(D72) The biological variability of extrathoracic deposition during mouth breathing (through a mouthpiece) has been discussed by Stahlhofen *et al.* (1981a). This study employed a constant inspiratory flow rate of $250 \text{ cm}^3 \text{ s}^{-1}$, and a constant inspiration time of 4 s. The distribution of extrathoracic deposition measured in individual subjects is illustrated in Fig. D.9. This large intersubject variability is most likely due to differences in the morphology and physiology of this region, especially of the larynx and vocal cords.

(D73) The high degree of variability in laryngeal deposition is further illustrated when deposition in healthy subjects is compared with that in patients with early stages of laryngeal carcinoma (Fig. D.10). These data are taken from Stahlhofen *et al.* (1984b), who measured laryngeal deposition in both pre- and postoperative laryngeal carcinoma patients. It is seen that the mean laryngeal deposition in preoperative patients is higher than that in healthy subjects. This is higher still in postoperative patients, presumably as a result of altered mobility of the regenerated vocal cords; no substantial morphological changes were observable in these patients by laryngoscopy.

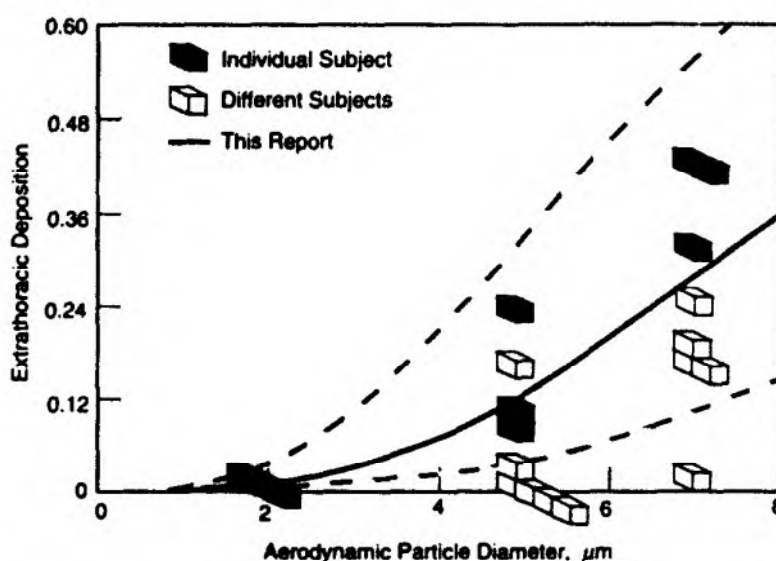


Fig. D.9. Distribution of extrathoracic deposition measured in individual subjects who inhaled particles through a tube inserted into the mouth.

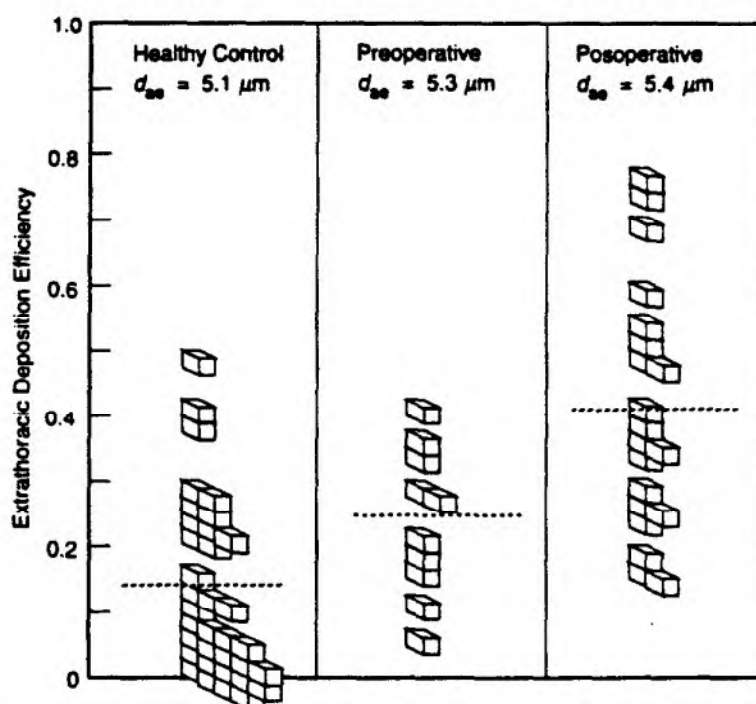


Fig. D.10. Comparison of extrathoracic deposition measured in normal healthy subjects and in pre- and postoperative laryngeal carcinoma patients. The dashed lines indicate the average value for each group.

D.6.2. Thermodynamic Deposition

D.6.2.1. Experimental studies with hollow casts

(D74) Deposition of small particles in the oropharyngeal-laryngeal airways has not been studied systematically *in vivo* in human subjects. As is the case for nasal deposition of particles in the thermodynamic size range (Paragraph D53), reliance must be placed on surrogate studies of particle deposition in hollow airway casts. Initial studies with a cast of the oral passageway taken *postmortem* gave slightly higher deposition than that for the nasal passageway of the same individual (Cheng *et al.*, 1990). However, in the oral cast the tongue was much closer to the roof of the mouth than it would have been during mouth breathing *in vivo* (D. L. Swift, personal communication). Measurements of the thermodynamic deposition efficiency in a hollow cast constructed using *in vivo* MRI data (Swift *et al.*, 1994) are shown in Fig. D.11.

D.6.2.2. Empirical model and estimated uncertainty

(D75) In the absence of additional data, it is assumed that the deposition efficiency of the oral pathway during mouth breathing, $\eta_{th}(ET)_m$, is given by Eqn. D.31:

$$\eta_{th}(ET)_m = 1 - \exp\{-9[D(\dot{V}_m SF_1)^{-1/4}]^{1/2}\} \quad (D.31)$$

where $\dot{V}_m$ is the volumetric flow rate through the mouth, and SF_1 is the anatomical scaling factor described in Paragraph D71.

(D76) Eqn. D.31 has the general form of Eqn. D.25, i.e. $\eta = 1 - \exp(-aR^n)$. It is assumed that the upper and lower 95% confidence bounds are represented by multiplying or dividing the coefficient a by the same constant factor c of 1.4 that was recommended for nasal deposition (Paragraph D58).

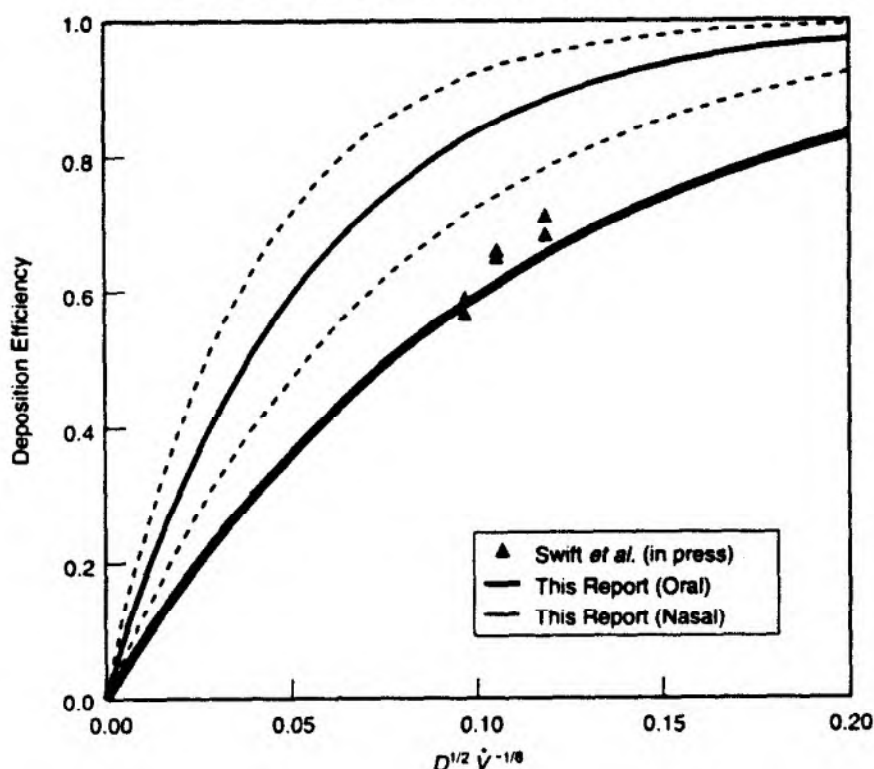


Fig. D.11. Deposition efficiency measured in replicate cast of the human oral passageway and larynx constructed from *in vivo* MRI data (Swift *et al.*, 1994). The lighter solid curve shows the mean deposition efficiency measured in casts of the nasal passageway, with the upper and lower 95% confidence bounds (dashed curves). The heavy curve shows the deposition efficiency predicted when the coefficient a in Eqn. D.25 is assumed to be 50% of the value for the nasal pathway.

D.6.2.3. Deposition on exhalation

(D77) The deposition efficiency of the oral pathway on exhalation is likely to be the same as that on inhalation. Eqn. D.31 is therefore recommended to predict the thermodynamic deposition from both the inhalation and exhalation phases of a breath.

D.7. Partitioning of Extrathoracic Deposition Between ET_1 and ET_2

D.7.1. Nose Breathing

(D78) No systematic studies have been carried out of the partitioning of extrathoracic deposition for nose breathing between the distinct clearance regions ET_1 and ET_2 . However, on the basis of the available experimental data on the subsequent clearance behaviour of particles deposited in the human nose (Chapter 7, and Annexe E), it can be assumed for dosimetry purposes that the activity deposited in the nasal part of ET during nasal inhalation is partitioned equally between the anterior nares (ET_1) and the posterior nasal passages (which are part of the main extrathoracic region, ET_2).

D.7.1.1. Aerodynamic deposition

(D79) The aerodynamic deposition efficiency of the ET_1 region for the fraction of the inhaled and exhaled volumetric flow that passes through the nose at a rate, $\dot{V}_n$, is assumed to be given by Eqn. D.32:

$$\eta_{ac}(ET_1)_n = 0.5 \{ 1 - [3.0 \times 10^{-4} (d_{ac}^2 \dot{V}_n SF_1^3) + 1]^{-1} \}. \quad (D.32)$$

(D80) An equal amount of deposition is assumed to occur in the posterior nasal passages. However, the total aerodynamic deposition in the ET_2 region will include a contribution from that in the larynx (which is given by Eqn. D.30). It can be shown that, when the ET_2 region is treated as a filter in series with ET_1 , the equivalent deposition efficiency of ET_2 is represented by Eqn. D.33:

$$\eta_{ac}(ET_2)_n = 1 - [5.5 \times 10^{-5} (d_{ac}^2 \dot{V}_n SF_1^3)^{1.17} + 1]^{-1}. \quad (D.33)$$

D.7.1.2. Thermodynamic deposition

(D81) In a similar manner, the thermodynamic deposition efficiency of the ET_1 region for the fraction of the inhaled and exhaled volumetric flow that passes through the nose is assumed to be given by Eqn. D.34:

$$\eta_{th}(ET_1)_n = 0.5 (1 - \exp\{-18[D(\dot{V}SF_1)^{-1/4}]^{1/2}\}). \quad (D.34)$$

(D82) By treating the ET_2 region as a filter in series with ET_1 , it can be shown that the equivalent deposition efficiency of ET_2 is represented by Eqn. D.35:

$$\eta_{th}(ET_2)_n = 1 - \exp\{-15.1[D(\dot{V}SF_1)^{-1/4}]^{0.538}\} \quad (D.35)$$

D.7.2. Mouth Breathing

(D83) In the case of pure mouth breathing, all of the extrathoracic deposition occurs in the ET_2 region, and essentially all in the larynx. Therefore:

$$\eta_{ac}(ET_2)_m = \eta_{ac}(ET)_{larynx} \quad (D.36)$$

where $\eta_{ac}(ET)_{larynx}$ is given by Eqn. D.30. The corresponding thermodynamic deposition efficiency is given by Eqn. D.31.

D.8. Lung (Thoracic) Deposition: Human Data and Models

D.8.1. Measured Total Deposition

(D84) Total deposition in the respiratory tract has been more widely studied than regional deposition since it can be measured relatively simply. For particles between about $0.01\text{-}\mu\text{m}$ and $3\text{-}\mu\text{m}$ aerodynamic diameter inhaled through a tube inserted in the mouth, deposition in the extrathoracic region is small, so that a measurement of total deposition approximates that for the lungs. The total deposition, which is denoted by DE , is obtained simply by measuring the number of inspired and expired particles per breath, N_i and N_e :

$$DE = 1 - N_e/N_i. \quad (D.37)$$

(D85) To determine deposition during steady breathing as a function of the aerosol properties and the characteristics of the breathing pattern, it is necessary to use a periodic respiratory flow rate, $\dot{V}$, and a constant particle number concentration of the inspired aerosol particles during each inhalation. For particles in the size range $0.2\text{--}3\text{ }\mu\text{m}$, which have relatively low deposition from a single breath, it is also necessary to allow a sufficient number of breaths to ensure that the so-called "wash-in" of particles is complete (Davies *et al.*, 1972). The total deposition, DE , can then be derived from a

continuous measurement of the particle concentration, volumetric flow rate, and time for inspiration and expiration, as described by Heyder *et al.* (1980b):

$$DE = 1 - \frac{N_e}{N_i} = 1 - \frac{\int_{t_e} c |\dot{V}| dt}{\int_{t_i} c |\dot{V}| dt} \quad (D.38)$$

(D86) By applying various photometer techniques to measure the particle number concentration in inhaled and exhaled air, Muir and Davies (1967), Davies *et al.* (1972), and Heyder *et al.* (1975) obtained total deposition values of particles of 0.5- μm and 1- μm diameter, which are in excellent agreement. All these measurements were done during steady-state breathing at normal functional residual capacity of the subjects. The total deposition data of Tarroni (Heyder *et al.*, 1978) and Melandri *et al.* (1983) are based on a different measurement technique whereby the particle number concentration of the exhaled aerosol was averaged over several breathing cycles. The particle concentration of the inspired aerosol was determined separately. A comparison of these techniques by Heyder *et al.* (1975) and by Tarroni (Heyder *et al.*, 1978) yielded consistent results.

D.8.2. Comparison of Measured and Modelled Deposition

(D87) In Fig. D.12, the data for unit density particles of diameter between 0.2 μm and 3 μm that were obtained by Heyder *et al.* (1975, 1980b) are compared with data given by Hiller *et al.* (1982), Heyder *et al.* (1978), and Melandri *et al.* (1983). The agreement among data from these different laboratories is generally good. Figure D.12 also shows the total deposition in the thoracic airways that is predicted by the theoretical model adopted in this report (Egan *et al.*, 1989; see Paragraphs D92 through D99 below), together with the total deposition in the respiratory tract as a whole calculated by including extrathoracic deposition modelled by Eqns D.29 and D.31. It is seen that the models predict somewhat higher total deposition for particles of 1- μm and larger diameter than that measured in three subjects by Heyder *et al.* (1975, 1980a). However, when all of the data shown in Fig. D.12 (which apply to a total of 15 subjects) are considered, the model described in this report is seen to provide a representative prediction.

D.8.3. Influence of Breathing Characteristics

D.8.3.1. Controlled versus spontaneous breathing pattern

(D88) The data shown in Fig. D.12 apply to controlled breathing at a constant inspiratory and expiratory flow rate, whereas, during normal spontaneous breathing, the flow rate varies throughout each breath in an approximately sinusoidal manner. However, Heyder *et al.* (1982) showed in a study of 20 different subjects that the mean total deposition for spontaneous breathing is virtually identical to that for controlled breathing at the same average flow rate (Fig. D.13). For both controlled and spontaneous mouth breathing, there is a large amount of variation between different subjects, although in any one subject under controlled breathing conditions, total deposition measurements are highly repeatable (Heyder *et al.*, 1982).

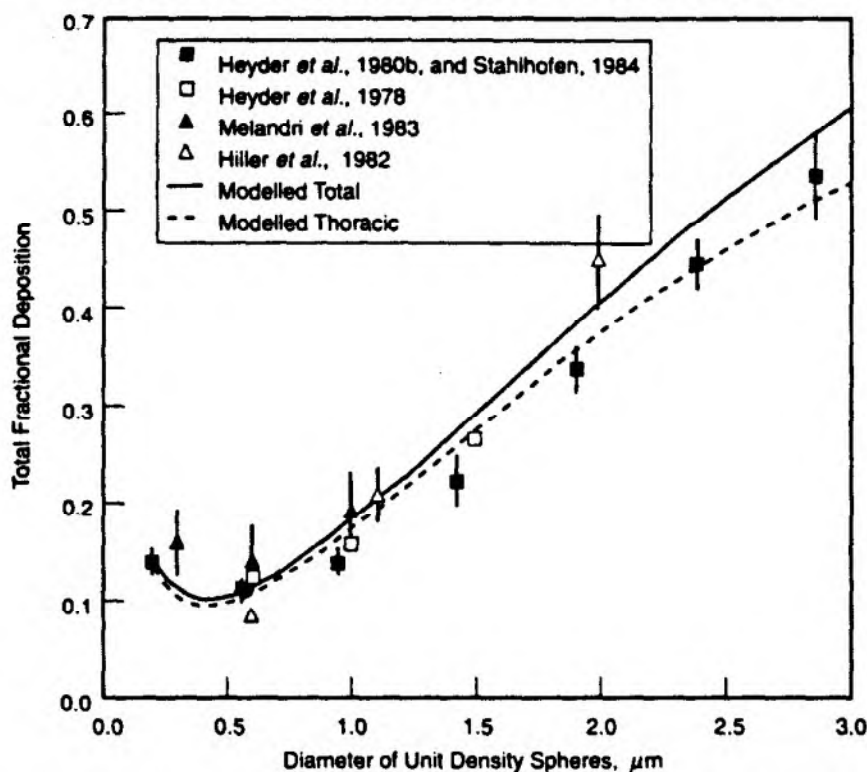


Fig. D.12. Comparison of total deposition data (including extrathoracic deposition) for subjects who breathed monodisperse particles through a mouthpiece at a flow rate of 500 (400) $\text{cm}^3 \text{s}^{-1}$ and respiratory frequency of 15 (12) min^{-1} . (Values in parentheses refer to study by Hiller *et al.*, 1982.) Curves show values given by the deposition model recommended in Chapter 5; dashed curve is thoracic deposition, solid curve includes extrathoracic deposition.

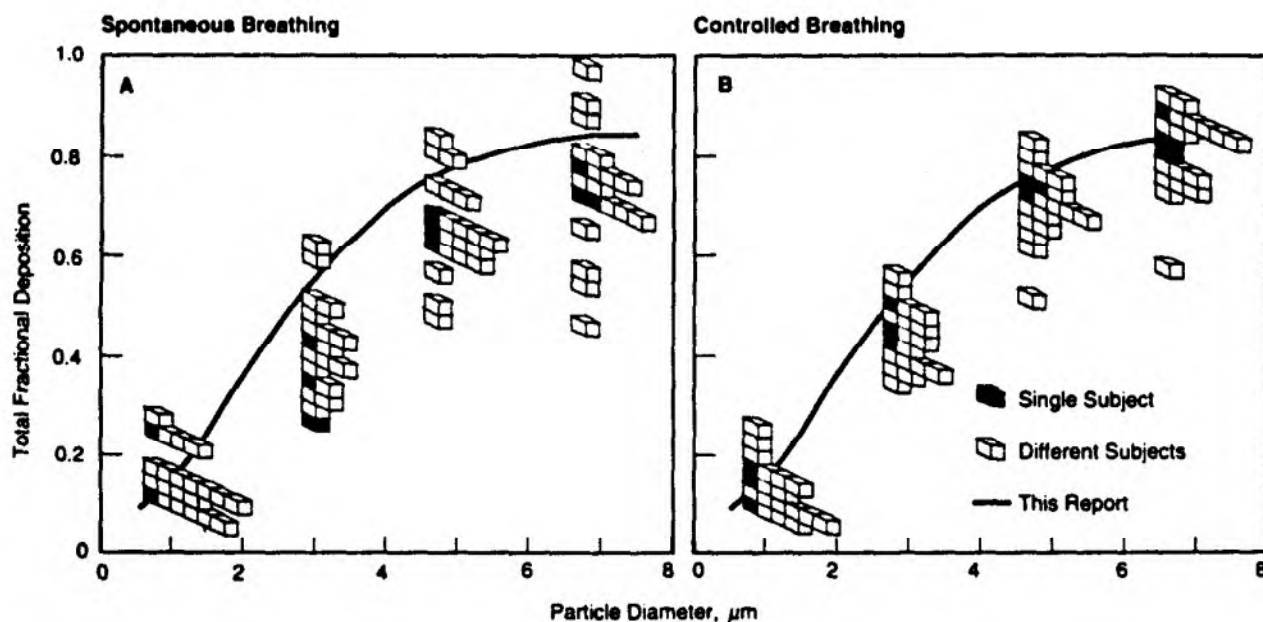


Fig. D.13. Comparison of the distributions of total respiratory tract deposition measured in 20 different subjects (A) breathing spontaneously at rest, or (B) breathing at a controlled rate at rest. In case (A), the individual mean flow rate on inspiration varied from 220 to 740 $\text{cm}^3 \text{s}^{-1}$, with a collective mean value of 380 $\text{cm}^3 \text{s}^{-1}$. In case (B), the mean flow rate was held constant at 400 $\text{cm}^3 \text{s}^{-1}$ for each subject. Each box shown in the figure represents one experimental measurement. Shaded boxes represent repeat measurements on a single subject. The curves show values predicted by the algebraic deposition model recommended in Chapter 5.

D.8.3.2. Effects of tidal volume and flow rate

(D89) Heyder *et al.* (1980b) reported experimental studies of total deposition during mouth breathing for a smaller group of subjects. (Each reported result was the average value obtained from at least three subjects.) However, these authors used nine very different, controlled breathing patterns. Their experimental data provide a stringent test of predictive models of respiratory tract deposition as a function of particle size and breathing behaviour. Fig. D.14 shows that the algebraic deposition model recommended in Chapter 5 succeeds in providing a good overall prediction of the measured total deposition in the human respiratory tract for particles in the aerodynamic size range of equivalent diameter greater than several tenths of a micrometer.

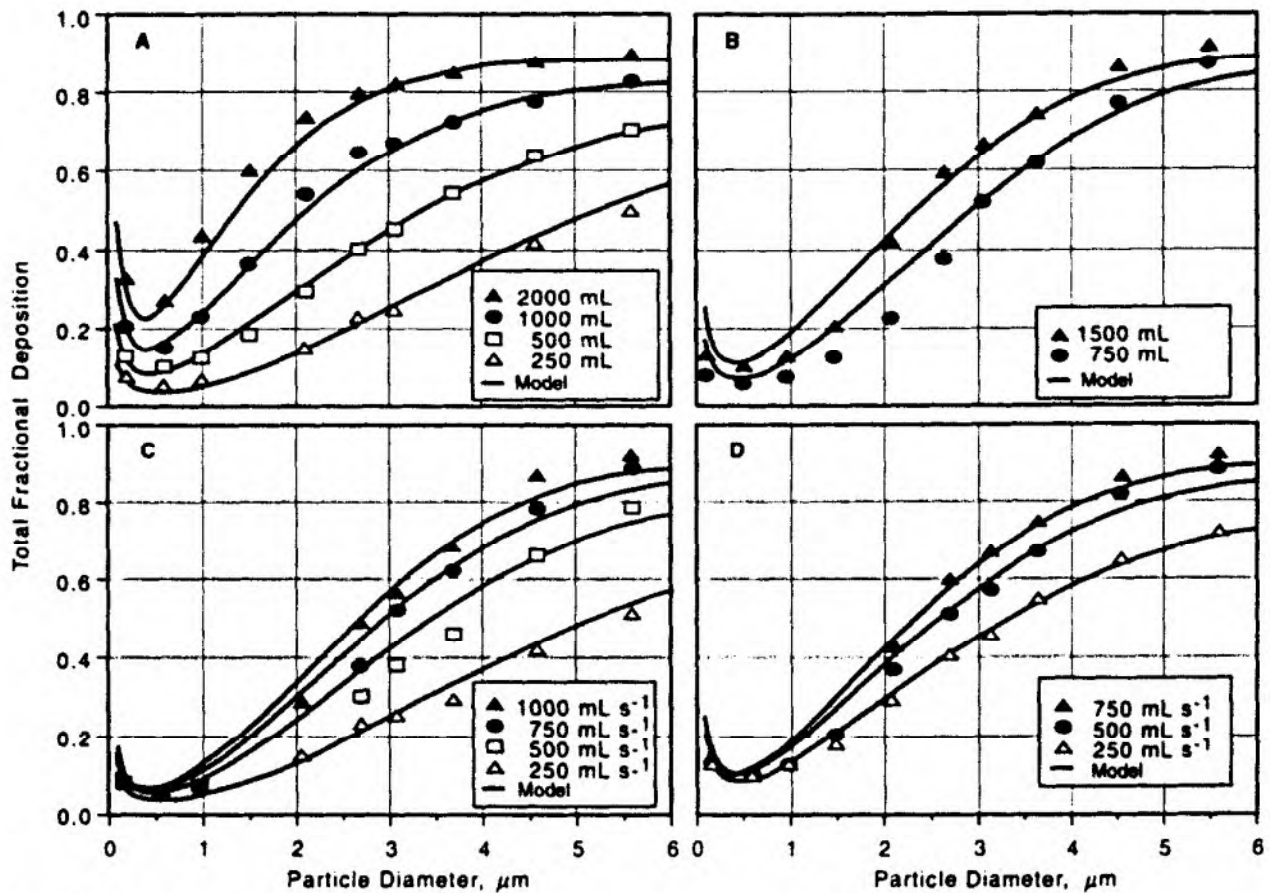


Fig. D.14. Comparison of total respiratory tract deposition measured by Heyder *et al.* (1980b) in several mouth-breathing subjects with the values predicted for an adult male by the algebraic model recommended in Chapter 5: (A) breathing at a controlled flow rate of $250 \text{ cm}^3 \text{ s}^{-1}$, with tidal volumes between 250 cm^3 and 2000 cm^3 ; (B) breathing at a controlled flow rate of $750 \text{ cm}^3 \text{ s}^{-1}$, with tidal volumes of 1500 cm^3 or 750 cm^3 ; (C) breathing at a mean residence time of 1 s, with controlled flow rates between $1000 \text{ cm}^3 \text{ s}^{-1}$ and $250 \text{ cm}^3 \text{ s}^{-1}$; and (D) breathing at a mean residence time of 2 s, with controlled flow rates between $750 \text{ cm}^3 \text{ s}^{-1}$ and $250 \text{ cm}^3 \text{ s}^{-1}$. In all cases the subjects breathed monodisperse droplets of di-2-ethylhexyl sebacate, of density 0.91 g cm^{-3} , through a mouthpiece.

D.8.4. Particles in the Thermodynamic Size Range

(D90) For particles in the thermodynamic size range with equivalent diameter between about 5 nm and $0.2 \mu\text{m}$, extrathoracic deposition during mouth breathing (in the oral cavity and larynx) is small compared with that in the lungs. Schiller *et al.* (1986) measured the total respiratory tract deposition for several subjects exposed *via* a

mouthpiece to monodisperse, uncharged spherical particles of silver over a range of particle diameter extending from 5 nm to about 0.2 μm . These experimental results were corrected by Gebhart *et al.* (1989) for the effects of instrumental dead space, which tended to reduce the measured deposition fraction for nanometer-sized particles. Egan and Nixon (1989) compared the resulting mean values of total thoracic deposition with the values predicted by the theoretical model developed by Egan *et al.* (1989). Figure D.15 shows that, for the two values of tidal volume tested, i.e. for tidal volumes of 500 cm^3 and 1000 cm^3 (at a controlled flow rate of 250 $\text{cm}^3 \text{ s}^{-1}$), the calculated fractional deposition in the lungs matches the measured values reasonably well.

(D91) Figure D.16 shows that the calculated values are also consistent with the earlier data obtained for hydrophobic submicron-sized spheres of aluminosilicate by Tu and Knutson (1984).

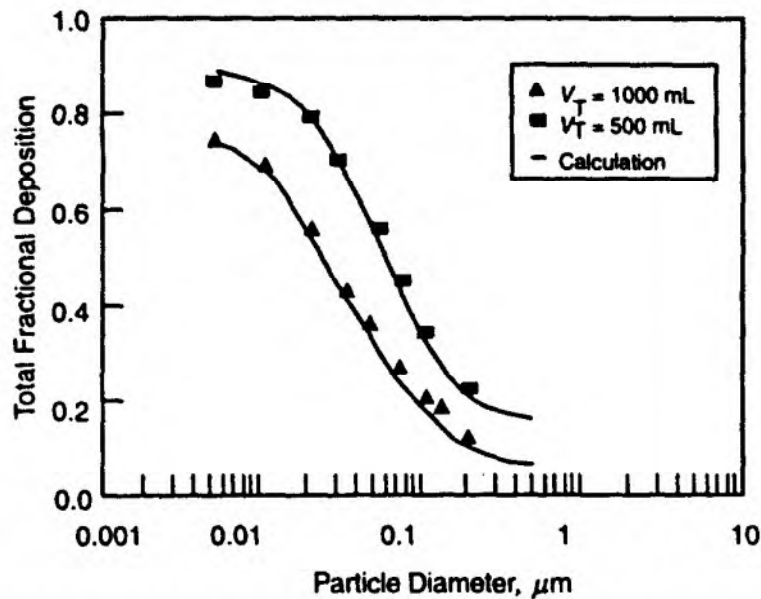


Fig. D.15. Comparison of the mean values of total respiratory tract deposition measured in several different subjects by Schiller *et al.* (1986, 1988), as corrected for instrumental dead space by Gebhart *et al.* (1989) with the total thoracic deposition calculated as a function of particle diameter by Egan *et al.* (1989).

D.9. Theoretical Model of Regional Lung Deposition

(D92) Whereas the experimental data obtained for the adult human male are sufficient to model empirically the deposition efficiency of the lungs as a whole, as a function of breathing behaviour and particle size (Rudolf *et al.*, 1983, 1986), they are not complete enough nor mutually consistent enough to define: (1) regional deposition in the adult male, or (2) the effects of different airway size in other subjects. The theoretical model referred to in Chapter 5, and in Paragraph D87 above, was used to predict the effects of breathing behaviour and airway size on the deposition of particles in discrete anatomical regions of the lungs, i.e. in the bronchial (BB), bronchiolar (bb), and alveolar-interstitial (AI) airways, of various subjects. These theoretical predictions formed the basis for the simplified algebraic model of regional deposition in the lungs of various subjects that is recommended in Chapter 5 for practical and general application.

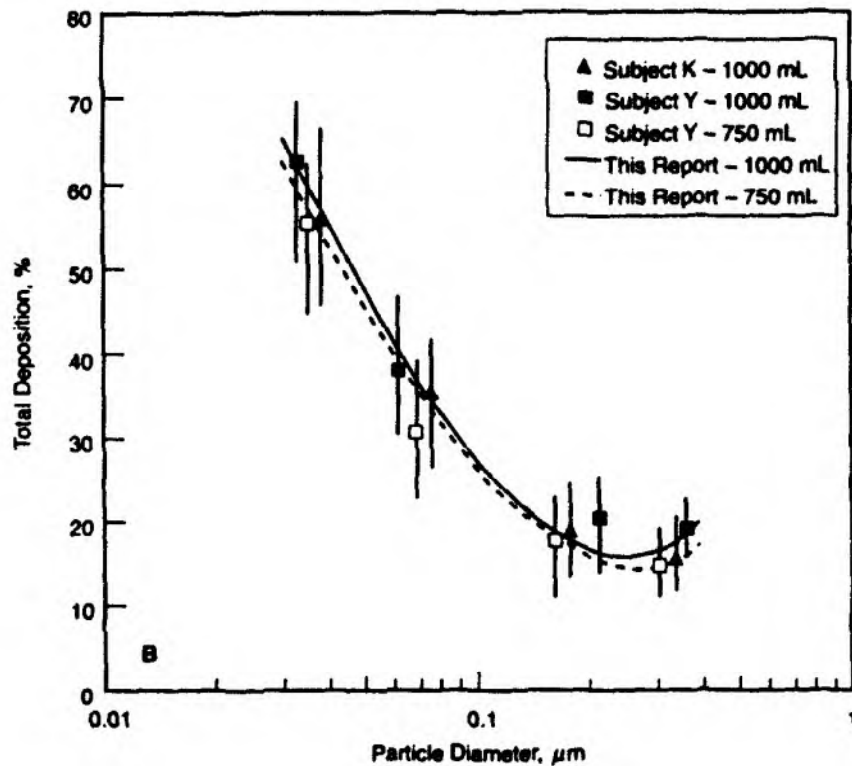
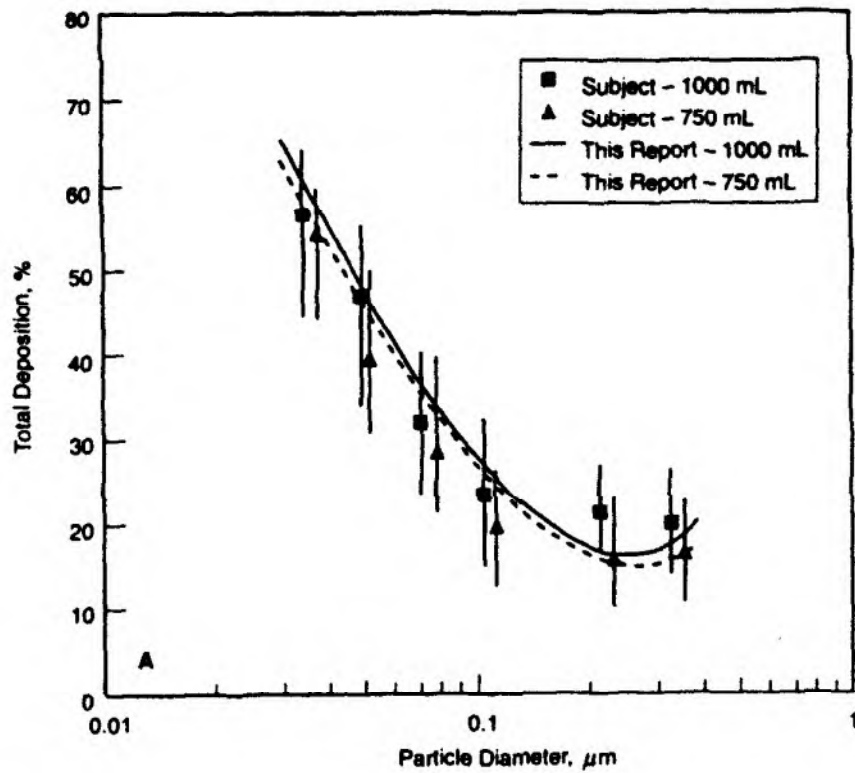


Fig. D.16. Comparison of total respiratory tract deposition of submicron-sized aluminosilicate particles measured by Tu and Knutson (1984) in one subject (A) and in two other subjects (B) with the values calculated as a function of particle diameter by Egan *et al.* (1989).

(D93) The theoretical model used in this report, which was also adopted by NRC (1991) to evaluate the comparative dosimetry of radon progeny in mines and homes, was developed by Egan and Nixon (1985), Nixon and Egan (1987), and updated by Egan *et al.* (1989). The model evaluates the combined effects of convective and diffusive gas transport, and aerosol loss processes, within the airways of the lungs, on the basis of the mathematical formalisms introduced by Taulbee and Yu (1975) and Pack *et al.* (1977). The summary description of the theoretical deposition model that follows is taken from NRC (1991).

(D94) The lungs of various subjects (adults, children, and infants) are represented by the regular system of branching airways that is described in Chapter 2 (and discussed in Annexe A). In this model, each airway branch within one generation is taken to have identical dimensions, which are a characteristic of the subject. Each point within the lungs is then characterized by its axial distance, x , from the origin of the trachea. The properties of the airway generation at that level in the lungs are associated with the value of x , for example, the number of branches, the branch diameter and length, and the number of alveoli. Within these model airways, the variation of aerosol concentration, $c(x,t)$, is governed by convection at velocity $u(x,t)$ through the airways; diffusion along the airways, which is represented by an effective diffusivity $D(x,t)$; and deposition onto the various airway surfaces. Particle deposition is characterised by the deposition rate per unit length of airway, $L(x,t)$. As described by Egan and Nixon (1985), the combined effects of these processes is represented by Eqn. D.39:

$$\frac{\partial}{\partial t} (A_T c) = - \frac{\partial}{\partial x} (A_A u c) + \frac{\partial}{\partial x} \left(A_A D \frac{\partial c}{\partial x} \right) - L. \quad (\text{D.39})$$

(D95) In this formalism, $A_A(x,t)$, which is represented in Eqn. D.39 by the simpler term A_A , is the cross-sectional area for aerosol transport. This is summed over all airways at distance x from the entrance of the trachea. Similarly, $A_T(x,t)$ is a cross-sectional area function that allows for the alveolar volume associated with the respiratory airways, where $(A_T - A_A)/l$ is the additional alveolar volume associated with an airway generation of length l . All of these variables are functions of time, t , and distance, x .

(D96) Eqn. D.39 is solved numerically for $c(x,t)$ over several breaths, until ventilation and deposition rates reach equilibrium. The breathing process is simulated by allowing the cross-sectional areas of the bronchial, bronchiolar, and alveolated airways to expand and contract about their mean values. Thus, for both A_A and A_T :

$$A(x,t) = A(x)f(t) \quad (\text{D.40})$$

where $A(x)$ is the mean cross-sectional area, and $f(t)$ is a function of time. The function $f(t)$ is chosen to represent the subject's breathing pattern. A sinusoidal pattern with no pause between inhalation and exhalation was assumed.

(D97) The flow fields that are produced in the lungs during breathing are complicated, and they induce irreversible mixing between the tidal and reserve air within the lungs. The characteristics of this mixing process were investigated experimentally by Scherer *et al.* (1975). These investigators represented the dispersion of tidal flow that they measured in a hollow airway cast by an axial diffusion coefficient. The diffusion coefficient was found to be higher on inhalation than on exhalation. This process has the effect of "washing in" particles of relatively low intrinsic mobility, i.e. submicron-sized particles of diameter greater than about $0.1 \mu\text{m}$, so that their deposition in the lungs

increases over several breaths until a steady state is reached (Egan and Nixon, 1987). On the basis of analysis by Scherer *et al.*, the theoretical deposition model of Egan *et al.* also represents the effective diffusivity of particles within the lungs (denoted by $D[x,t]$ in Eqn. D.39) by:

$$D(x,t) = D + 1.08 u(x,t) d \quad (\text{for inspiration})$$

$$D(x,t) = D + 0.37 u(x,t) d \quad (\text{for expiration})$$

where D is the particle diffusion coefficient (which was defined earlier by Eqn. D.11 in terms of the equivalent particle diameter and slip factor), $u(x,t)$ is the convective flow velocity, and d is the diameter of an individual airway through which the flow is being represented (Pack *et al.*, 1977; Egan and Nixon, 1985).

(D98) The deposition term $L(x,t)$, or L in Eqn. D.39, represents the rate at which particles are removed from the airstream per unit length of airway because of the combined effects of impaction, gravitational settling, and Brownian diffusion. The contribution to $L(x,t)$ made by inertial impaction is modelled directly from the experimental data obtained with hollow casts of human lungs (Gurman *et al.*, 1984). Figure D.17 shows that the efficiencies, η_i , with which particles are deposited by

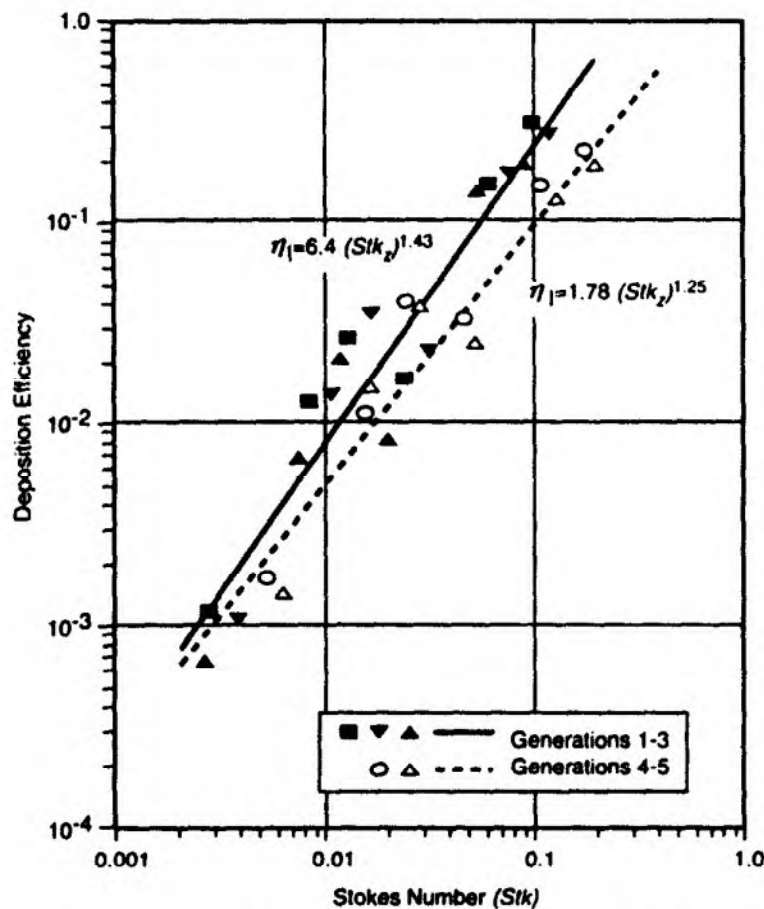


Fig. D.17. Efficiency of particle deposition by impaction measured by Gurman *et al.* (1984) in a hollow cast of a human trachea and five generations of bronchial airways. The symbols show the mean deposition efficiencies measured in each airway generation (1-5) as a function of Stokes' number. The Stokes' number was varied experimentally by changing both the particle size and the airflow rate through the cast.

impaction in each bronchus of a particular airway generation, z , can be approximated by an expression of the form:

$$\eta_1 = \alpha Stk_z^\beta \quad (D.41)$$

where Stk_z is the Stokes inertial parameter of the flow in that airway generation (which was defined earlier by Eqn. D.22). This parameter is proportional to u_z , the mean flow velocity, and inversely proportional to d_z , the airway diameter, respectively, in generation z . The values of the constants α and β are found to be significantly higher in generations 1 through 3 than they are thereafter. The values shown in Fig. D.17, which were used to simulate bronchial deposition during natural cyclic breathing, were fitted to the experimental data obtained under a sinusoidally varying flow (Gurman *et al.*, 1980, 1984). The corresponding coefficients fitted to experimental data of Gurman *et al.*, obtained under constant flow through the bronchial casts, were found to be significantly different (Egan *et al.*, 1989). These coefficients for constant flow were used to simulate the experimental data that are described in Paragraphs D106 through D111 below (Stahlhofen *et al.*, 1980, 1981a,b, 1983) on "fast-cleared" and "slow-cleared" thoracic deposition measured in human subjects who breathed test aerosols at a controlled flow rate.

(D99) The bulk of deposition by gravitational sedimentation and Brownian diffusion occurs in the smaller airways, where the air velocity is low and the flow field is less complicated than that in the bronchi. Therefore, at least in these airways, it is reasonable to apply theoretical treatments to represent deposition by sedimentation and diffusion. The model of Egan *et al.* (1989) uses Pich's (1972) sedimentation theory, which was found by Heyder and Gebhart (1977) to predict the observed deposition of particles by sedimentation in inclined circular tubes. For diffusion, the model uses the theoretical expression derived by Ingham (1975) for fully developed laminar flow (which assumes that the characteristic parabolic flow profile is fully developed in each airway).

D.9.1. *Correction of Modelled Thermodynamic Deposition in the Bronchi for Nonlaminar Flow*

(D100) The applicability of Ingham's (1975) expression for particle deposition by diffusion in laminar flow to predict particle deposition behaviour under the disturbed flow conditions present in the larger bronchi has been tested experimentally by Cohen (1987) and Cohen *et al.* (1990). These authors measured the particle deposition efficiency of individual airways in several hollow casts of the human bronchial tree. They compared deposition efficiencies measured for monodisperse aerosol particles of diameter about 0.04 μm , 0.15 μm , or 0.2 μm , at four different ventilation rates, with the values calculated for each individual airway using the theory of Ingham (1975). In these studies the casts were ventilated using the cyclic flow pattern and apparatus developed by Gurman *et al.* (1984) to simulate the natural breathing cycle. As is seen in Fig. D.18 (which is derived from Cohen and Asgharian, 1990), the measured deposition efficiencies of individual airways were found to vary substantially about the predicted values. On average, however, the measured deposition efficiency tended to be higher than the predicted value. There was no distinguishable trend of deposition enhancement with the generation number of the airways studied. On average, the deposition enhancement was reasonably uniform over the six airway generations included in the casts.

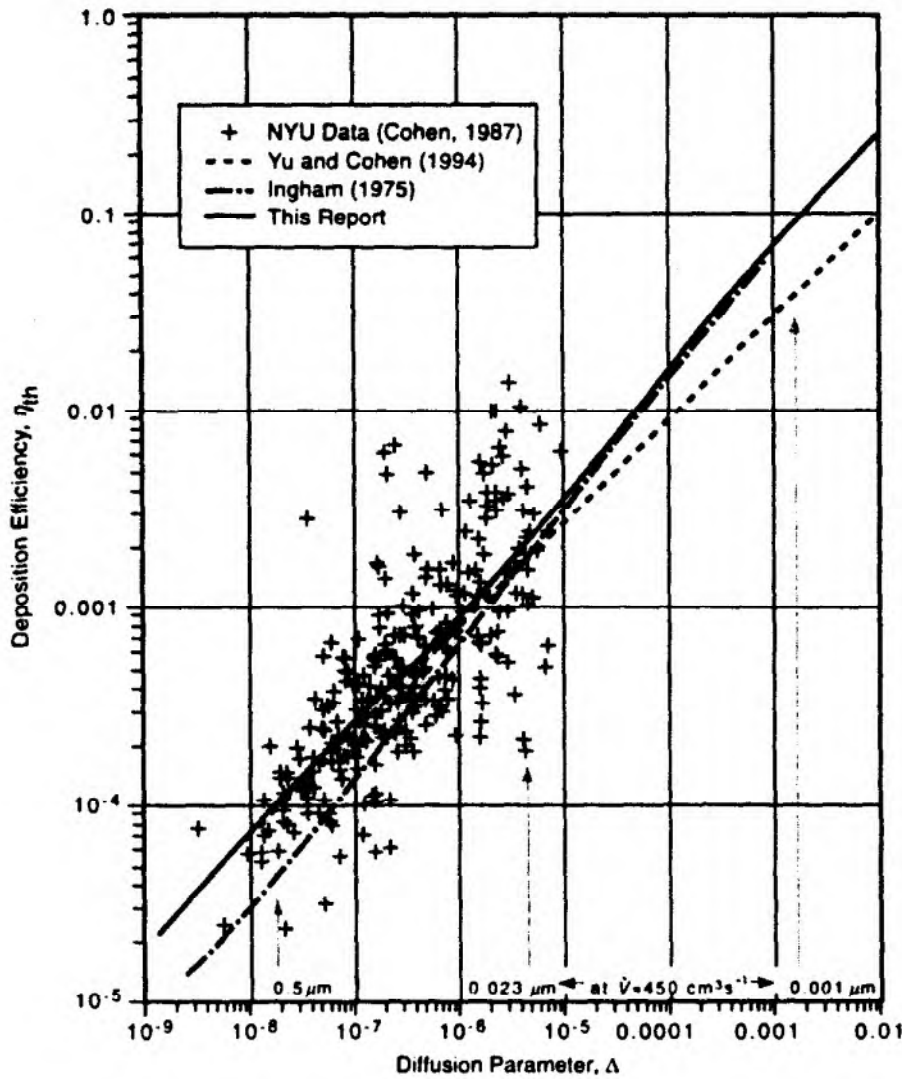


Fig. D.18. Deposition efficiency, η_{th} , of individual airways in hollow casts of the human bronchial tree measured by Cohen (1987), plotted against the diffusion parameter, Δ . Dashed curves show the relationship between η_{th} and Δ predicted for diffusional deposition in laminar flow by Ingham (1975), and for nonlaminar flow by Yu and Cohen (1994). The solid curve shows the relationship adopted in this report, which converges with Yu and Cohen's curve for small values of Δ , and with Ingham's prediction for high values of Δ .

(D101) Ingham (1975) gave the following expression for deposition efficiency in a cylindrical tube with parabolic, laminar flow:

$$\eta_{th} = 1 - 0.819e^{-14.63\Delta} - 0.0976e^{-89.22\Delta} - 0.0325e^{-228\Delta} - 0.0509e^{-125.9\Delta^{1/3}} \quad (D.42)$$

where $\Delta = \pi l D / (4 \dot{V})$ and is the dimensionless diffusion parameter with airway length l , flow rate $\dot{V}$, and particle diffusion coefficient D . The enhanced deposition was described by Cohen *et al.* (1991) to be caused by deviation of the flow field, from the parabolic shape of laminar flow, to one that has a greater coefficient of transfer to the airway surface in bifurcating airways. By considering this deposition to be a convective diffusion process, Yu and Cohen (1994) derived an expression for the thermodynamic deposition efficiency of the form given in Eqn. D.43:

$$\eta_{th} = a Re^b Sc^c \left(\frac{l}{R} \right)^d = a \left(\frac{2 \dot{V}}{R \pi \nu} \right)^b \left(\frac{\nu}{D} \right)^c \left(\frac{l}{R} \right)^d \quad (D.43)$$

where the Reynolds number (Re) and the Schmidt number (Sc) include the airway radius, R , and kinematic viscosity, ν . Yu and Cohen found that the coefficients $a = 1.2027$, $b = -0.6067$, $c = -0.5108$, and $d = 0.5081$ gave the "best fit" to the experimental cast data. Both Ingham's (1975) expression and Yu and Cohen's (1994) empirical expression are plotted in Fig. D.18, together with the experimental data.

(D102) For relatively small particles (of diameter less than about 20 nm), where there are no experimental data, the deposition efficiency predicted by Yu and Cohen's (1994) empirical expression is seen in Fig. D.18 to cross below that predicted by Ingham's expression for laminar flow. This particle size range is important dosimetrically because it includes ultrafine types of aerosols produced from vapours by condensation and also the unattached radon progeny (of diameter approximately 1 nm). Since, on physical grounds, a lower deposition efficiency than that predicted for laminar flow is not expected, a modified form of Yu and Cohen's analysis to represent the experimentally observed enhancement of diffusional deposition in the bronchial airways was adopted. The expression, which provides a smooth transition between Yu and Cohen's analysis of the experimental cast data for the relatively large particle sizes studied and Ingham's (1975) expression for ultrafine particles, i.e. for $\Delta > 10^{-5}$, is also shown in Fig. D.18.

(D103) Yu and Cohen's (1994) analysis of the experimental data showed that the enhancement of diffusional deposition in the bronchial airways depends relatively weakly on the average flow rate. The ventilation rate used in the cast experiments varied from $0.45 \text{ m}^3 \text{ h}^{-1}$ to $3.6 \text{ m}^3 \text{ h}^{-1}$, yet the modelled deposition enhancement factor (for $0.1\text{-}\mu\text{m}$ -diameter particles) increased by only about 10% (from 1.52 to 1.67). Because of this weak dependence on flow rate, the following expression for the deposition enhancement factor simply in terms of the particle thermodynamic diameter, d_{th} (in μm), was derived:

$$\psi_{th} = 1 + 100 \exp \left\{ - \left[\log_{10} \left(100 + \frac{10}{d_{th}^{0.9}} \right) \right]^2 \right\}. \quad (\text{D.44})$$

(D104) This expression defines the empirical correction factor, ψ_{th} , recommended in Chapter 5 (Tables 12 and 13) to allow for the enhancement of the modelled thermodynamic deposition efficiency of the bronchi caused by nonlaminar bronchial airflow. The resulting deposition enhancement factor varies from about 2 for particles of diameter larger than $0.5 \mu\text{m}$ to unity for particles smaller than 20-nm diameter.

(D105) The theoretical calculations of Egan *et al.* (1989) did not include any allowance for the enhanced thermodynamic deposition efficiency of the bronchial airways. However, the calculated values of bronchial deposition efficiency for particles in the thermodynamic size range can be corrected retrospectively using Eqn. D.44. A similar expression was derived and used by NRC (1991), although their expression (which was fitted to earlier, less complete data) predicted somewhat greater deposition enhancement than Eqn. D.44.

D.9.2. Comparison with Experimental Data from the GSF Frankfurt Laboratory

(D106) Stahlhofen *et al.* (1980, 1981a,b, 1983) measured the fractional deposition of insoluble monodisperse aerosols of iron oxide particles labelled with ^{198}Au , in a total of nine different subjects under closely controlled breathing conditions. In these tests, the subjects inhaled and exhaled particles of various sizes through a mouthpiece, at a

constant flow rate of either $250 \text{ cm}^3 \text{ s}^{-1}$ or $750 \text{ cm}^3 \text{ s}^{-1}$. Four different tidal volumes were studied: 250 cm^3 , 500 cm^3 , 1000 cm^3 at the flow rate of $250 \text{ cm}^3 \text{ s}^{-1}$, and 1500 cm^3 at the flow rate of $750 \text{ cm}^3 \text{ s}^{-1}$. The fraction of inhaled gamma activity deposited initially in the thorax was measured using a calibrated and well-characterised array of collimated NaI(Tl)-detectors. The retention of the deposited iron oxide particles in the lungs (obtained by correcting the thorax measurements for the activity of particles cleared to the stomach) was followed in each subject for several days. In general, two distinct phases of particle retention were observed: an initial rapid phase, succeeded by continued slow clearance with a fitted half-time of several tens of days. The exponential clearance curve fitted to the "slow-cleared" fraction was extrapolated back to the time of exposure to define the complementary "fast-cleared" fraction of the initial lung deposit. As discussed in Chapter 7 and Annexe E, the "slow-" and "fast-cleared" fractions of the thoracic deposit are conventionally assumed to represent particles deposited in the AI region and tracheobronchiolar airways (BB and bb regions), respectively.

(D107) To simulate these experimental data, the theoretical deposition model of Egan *et al.* (1989) was used to calculate the expected fractional deposition summed for all airways in the AI region and the combined BB and bb regions. For these calculations, their values for the coefficients alpha and beta in Eqn. D.41 (which define the efficiencies of bronchial airways for inertial impaction, η_i , under constant flow conditions) were used. The calculations were carried out at the United Kingdom Atomic Energy Authority's Safety and Reliability Directorate, Culcheth, Cheshire. Figures D.19 and D.20 compare the theoretical predictions of tracheobronchiolar and alveolar-interstitial deposition, respectively, with the "fast-" and "slow-cleared" fractions of thoracic deposition measured at the GSF Frankfurt Laboratory.

(D108) It is seen from these figures that both measured fractions of the thoracic deposition exhibit substantial variability under otherwise identical experimental conditions (as does the total thoracic deposition). It is also seen that, overall, the calculated deposition curves provide an accurate prediction of the trends in measured values with particle aerodynamic diameter.

(D109) In Fig. D.19, except for the experiments carried out at a flow rate of $250 \text{ cm}^3 \text{ s}^{-1}$ and a low tidal volume of 250 cm^3 (Fig. D.19D), it is seen that the predicted curves match the measured "fast-cleared" fractions. The closest match is obtained for the experiments carried out at a flow rate of $750 \text{ cm}^3 \text{ s}^{-1}$ and tidal volume of 1500 cm^3 (Fig. D.19B), which approximates the breathing rate of a "reference worker". (See Chapters 3 and 5.) The apparently poor match to the data at low flow rate and low tidal volume arises principally from the two measurements for $12\text{-}\mu\text{m}$ -aerodynamic-diameter particles. Bronchial deposition efficiency for these particles should clearly be substantially higher than for the next smallest particles (of $7.5\text{-}\mu\text{m}$ aerodynamic diameter). The fact that the measured efficiency is lower suggests an experimental artifact in correcting for extrathoracic particle losses.

(D110) On the whole, the predicted deposition fractions are seen to match the data with increased accuracy as the particle aerodynamic diameter is increased. For several of the smallest particle sizes studied, there is a general tendency for the predicted tracheo-bronchial deposition to be higher than the measured "fast-cleared" fraction. However, for these particles (with aerodynamic diameter less than about $5 \mu\text{m}$), the fit of the predicted curves to the measured values is significantly improved by allowing for the incomplete "rapid" clearance of particles deposited in the human tracheobronchial

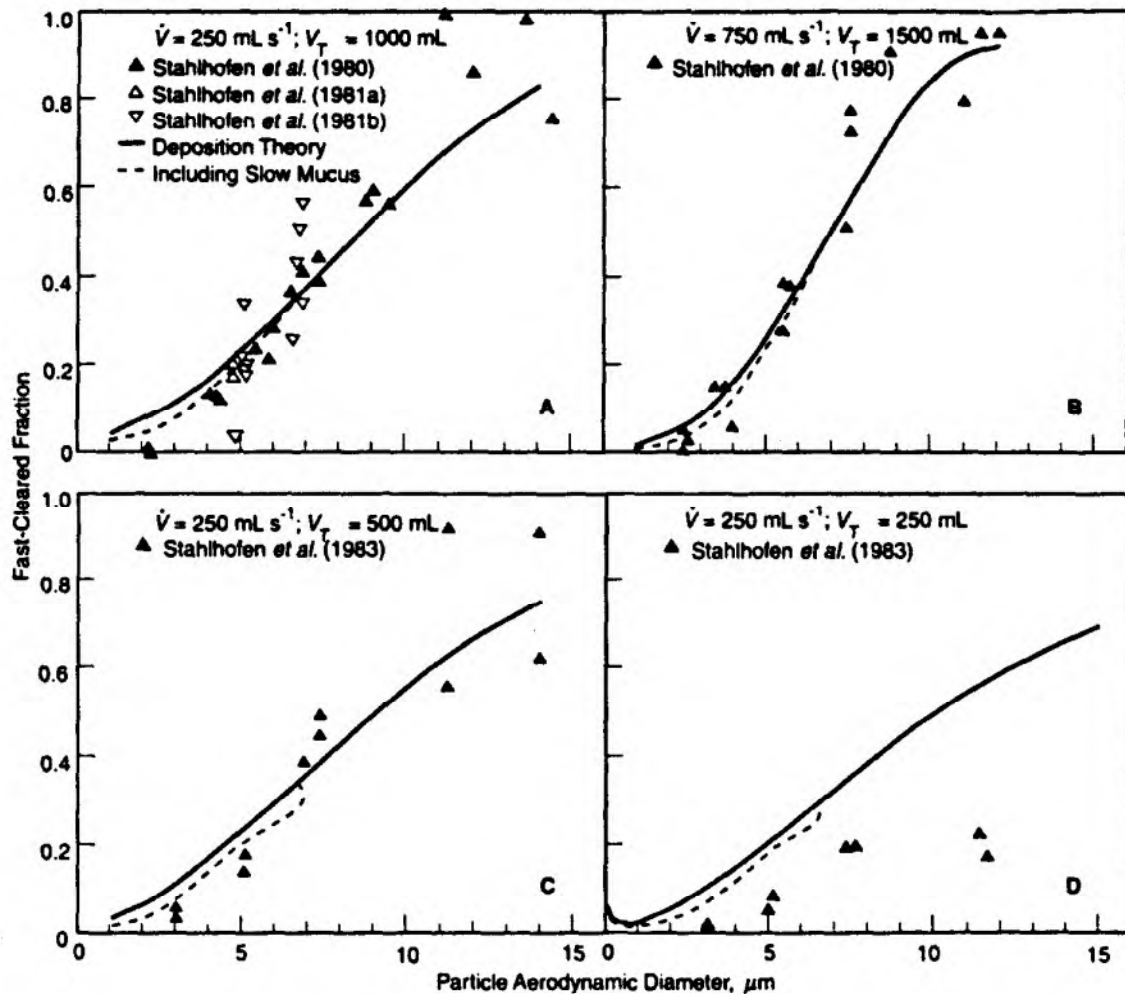


Fig. D.19. Comparisons of the fast-cleared fraction of lung deposition in human subjects measured at the GSF Frankfurt Laboratory with the tracheobronchiolar deposition predicted by the theoretical model (shown by the solid curves) of Egan *et al.* (1989). The dashed curves show the effect on the predicted fast-cleared fraction of allowing for slow clearance of a fraction of the number of particles deposited in the tracheobronchiolar airways.

tree that has been observed directly in other experimental studies. Those studies are discussed in Annexe E (Section 5.3.2). Based on that discussion, it was concluded that, for particles with a physical diameter of $2.5 \mu\text{m}$ or less, only 50% of the number deposited in the tracheobronchial airways is cleared rapidly. The remaining 50% is cleared at a rate that is indistinguishable experimentally from particles deposited in the alveolar-interstitial airways. For larger particles, the fraction of the tracheobronchial deposition that is cleared slowly is found to decrease steeply with particle size. The dashed curves shown in Fig. D.19 make allowance for slow clearance of a part of the tracheobronchial deposition. It is seen that, by making this allowance, the fit of the predicted "fast-cleared" fraction to the measured values is improved.

(D111) Figure D.20 compares the experimental data and theoretical predictions of the complementary "slow-cleared" fraction of lung deposition. For particles with aerodynamic diameter $5 \mu\text{m}$ or greater, the fit between predicted and measured values is generally good. Allowance for part of the predicted tracheobronchiolar deposition being cleared slowly is again seen to improve the predictions for smaller particles.

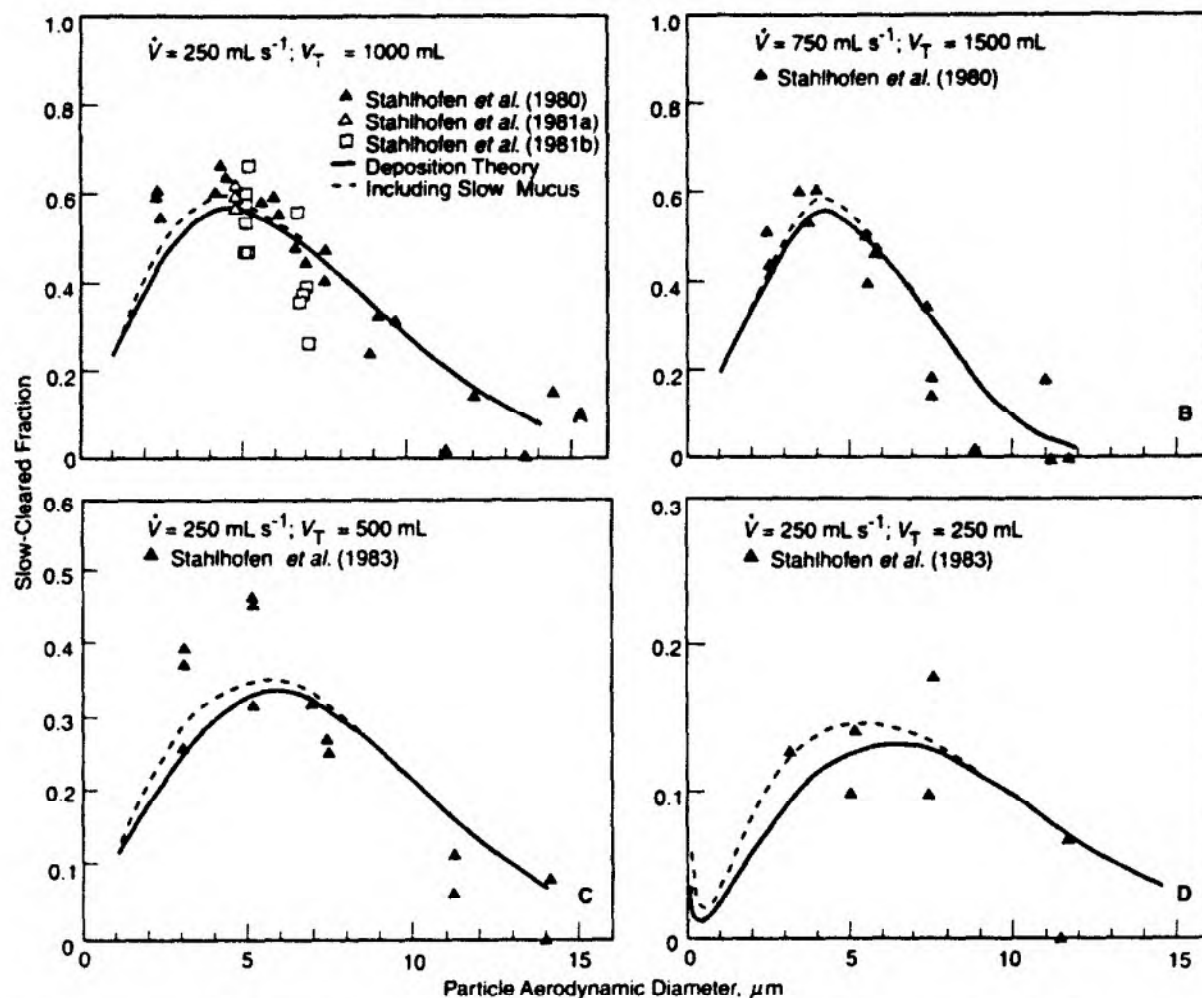


Fig. D.20. Comparisons of the slow-cleared fraction of lung deposition in human subjects measured at the GSF Frankfurt Laboratory with the alveolar-interstitial deposition predicted by the theoretical model (shown by the solid curves) of Egan *et al.* (1989). The dashed curves show the effect on the predicted slow-cleared fraction of allowing for additional slow clearance of a fraction of the number of particles deposited in the tracheobronchiolar airways.

D.10. Recommended Algebraic Model for Regional Lung Deposition

(D112) For more general application, a set of algebraic expressions is recommended in Chapter 5, which give (when used with the coefficients listed in Tables 12 and 13) reliable estimates of regional deposition within the lungs for various subjects, and for widely variable breathing conditions. The functional forms of these expressions have been taken from the empirical analyses developed by Rudolf *et al.* (1983, 1986, 1990) to represent the deposition efficiencies of each region of the lungs in terms of components contributed by aerodynamic and thermodynamic deposition processes. This approach is an extension of that used to predict the deposition efficiencies of the nasal passages and larynx (Paragraphs D37 through D83).

(D113) This section describes how the numerical coefficients listed in Tables 12 and 13 of Chapter 5 were derived. These coefficients are derived from the particle deposition probabilities calculated for the BB, bb, and AI regions of the lungs in the adult male, adult female, and 10-y-old, 5-y-old, and 1-y-old children using the

theoretical model of Egan *et al.* (1989). The analysis of Rudolf *et al.* (1990) was extended to model the discrete deposition efficiencies of the BB and bb regions on inhalation and exhalation. Representation of lung deposition as a sequential process that occurs in each region of the lungs in turn (see Fig. 8 in Chapter 5) enables the effects of particle hygroscopicity to be modelled (as described later, and in Paragraphs 172 through 176 of Chapter 5).

(D114) The recommended algebraic model of regional lung deposition is defined by the recursive convolution of deposition efficiencies in a series of filters (see Eqns 6 and 7 in Chapter 5). The filtration efficiency, η_j , of each filter, j , in the series is evaluated simply as the root sum of squares of the aerodynamic and thermodynamic deposition efficiencies of that filter. (See Eqn. D.16.) Both the aerodynamic and thermodynamic efficiencies of each of the lung regions are expressed by Eqn. D.25, i.e. $\eta = 1 - \exp(-aR^p)$, where a and p are dimensionless constants, and R has a characteristic functional form that is different in each region. The functional forms were given in Tables 12 and 13 of Chapter 5. The deposition efficiencies in BB, bb, and AI are identical whether the subject breathes through the nose (Table 12) or mouth (Table 13). The functions describing regional deposition in the lungs are summarised in Table D.1.

(D115) Regional deposition is calculated simply by substituting into Eqn. 6 and the recursive Eqn. 7, given in Chapter 5, specific combinations of aerosol parameters, volumetric constants of the subject's lungs, and the flow rate and residence time constants associated with a particular breathing pattern. These equations were implemented in the software code LUNG Dose Evaluation Program (LUDEP), which was described by Birchall *et al.* (1991).

D.10.1. Derivation of Constant Factors a and p

(D116) Appropriate values of the constants a and p in each expression of aerodynamic or thermodynamic regional deposition efficiency, i.e. in Eqn. D.25, were

Table D.1. Functional forms and aerosol and breathing parameters to represent regional lung deposition

Phase	Lung Region	Regional Deposition Efficiency, η_R					
		Aerodynamic			Thermodynamic		
		$\eta_a = 1 - \exp(-aR^p)$			$\eta_t = 1 - \exp(-aR^p)$		
		a	R	p	a	R	p
Inhalation	BB	4.08×10^{-6}	$d_m^2 \dot{V} SF_1^{2.13}$	1.152	$22 SF_1^{1.24} \psi_a^*$	DI_B	0.6391
	bb	0.1147	$(0.056 + t_b^{1.13}) \times d_m^{1.24}$	1.173	$-76.8 + 167 SF_b^{0.65}$	DI_b	0.5676
	AI	$0.146 SF_A^{0.98}$	$d_m^2 t_A$	0.6495	$170 + 103 SF_A^{2.13}$	DI_A	0.6101
Exhalation	bb	0.1147	$(0.056 + t_b^{1.13}) \times d_m^{1.24}$	1.173	$-76.8 + 167 SF_b^{0.65}$	DI_b	0.5676
	BB	2.04×10^{-6}	$d_m^2 \dot{V} SF_1^{2.13}$	1.152	$22 SF_1^{1.24} \psi_a^*$	DI_B	0.6391

* ψ_a is an empirical correction factor to allow for enhancement of thermodynamic deposition caused by nonlaminar bronchial airflow. (See paragraphs D.100 through D.105.)

derived using a parameter optimization procedure (Graphically Interactive General Algorithm for FITting [GIGAFIT]; A. Birchall, T. E. Hui, and A. C. James, Pacific Northwest Laboratory). This procedure varied all 12 parameters simultaneously to minimize the χ^2 statistic for the values of regional deposition calculated as a function of particle size and breathing pattern compared with the values predicted by the theoretical model of Egan *et al.* (1989).

(D117) Figure D.21 shows the optimal fits obtained with the 12-parameter algebraic model given in Chapter 5 to the regional lung deposition calculated for the adult male breathing at the rates recommended in Chapter 3 as representative of sleep, sitting (at rest), light exercise, and heavy exercise, respectively. Since the algebraic model matches accurately the complex changes of regional deposition with particle diameter that occur in the lungs of the "reference adult male" at four discrete combinations of average flow rate and tidal volume, it is reasonable to expect this empirical model to predict accurately the regional deposition for any other combinations of intermediate flow rate and tidal volume.

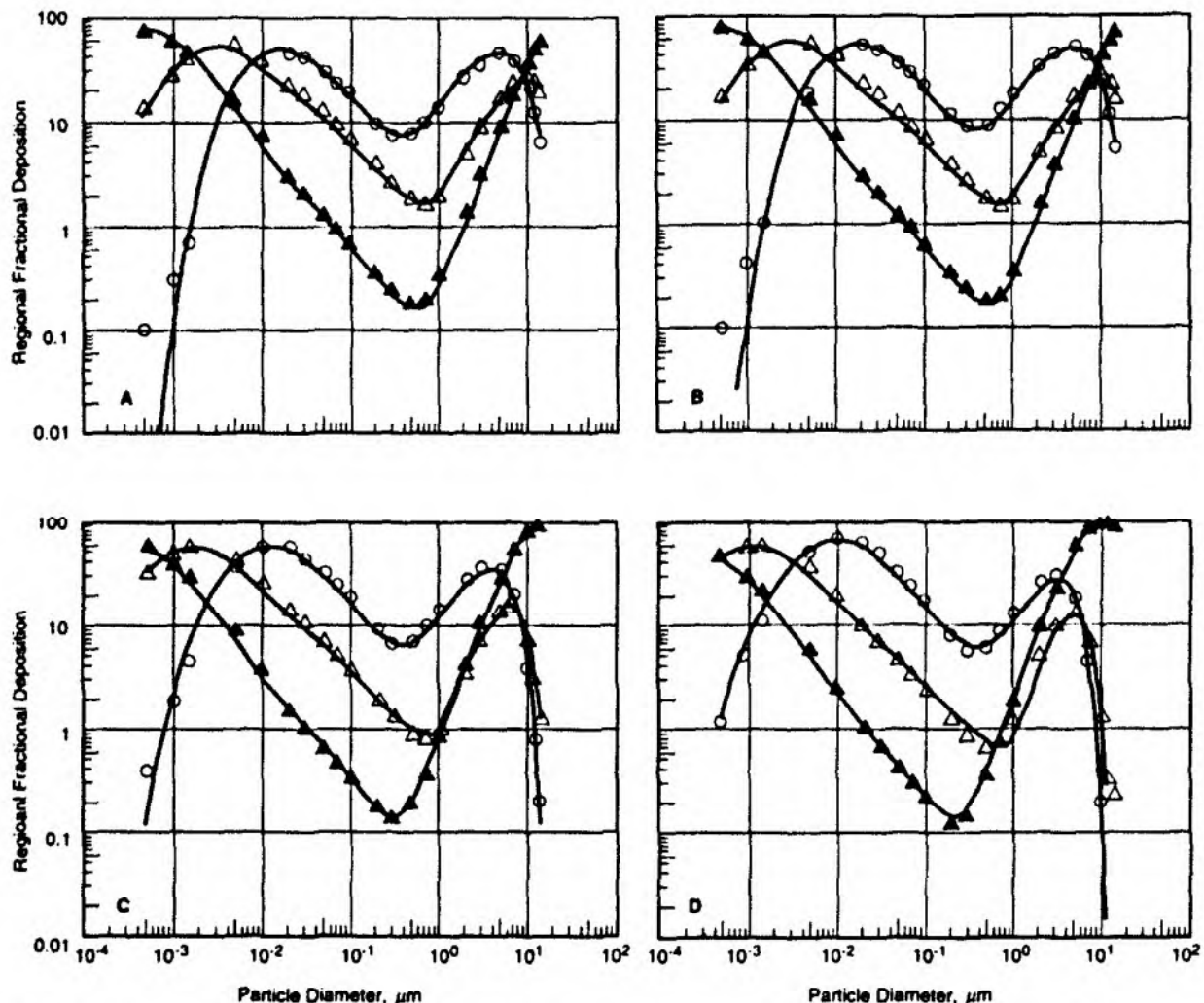


Fig. D.21. Fits to the values of regional lung deposition in an adult male calculated using the theoretical model (data points) of Egan *et al.* (1989) given by the empirical algebraic model (solid curves). The calculated and fitted values apply to each of the four reference levels of physical exertion: (A) sleep; (B) rest (sitting); (C) light exercise; and (D) heavy exercise. Δ = BB theoretical, $\triangle$ = bb theoretical, $\circ$ = AI theoretical, — algebraic model.

(D118) The fitted values of the parameters a and p , which are recommended to evaluate the expected regional lung deposition in a reference adult male, are given in Table D.1.

D.10.1.1. *Aerodynamic deposition in BB on exhalation*

(D119) The deposition efficiency by impaction in the bronchial airways on exhalation is generally neglected when modelling lung deposition. This was also assumed to be negligible by Egan *et al.* (1989). Thus, the parameter a in Eqn. D.22 for the BB region was constrained to be zero when deriving the six unknown values of a from the calculated values of regional deposition. Although particle deposition in the bronchi by impaction on exhalation has not been quantified in experimental studies with bronchial casts, and this is bound to be negligible for large particles which would all deposit deeper in the lungs, consideration of the airflow characteristics at airway confluences indicates that some additional deposition would occur for smaller particles. In order not to underestimate the overall bronchial deposition, the plausible assumption is made that the aerodynamic deposition efficiency of the bronchial region on exhalation is one-half that on inhalation, i.e. the appropriate value of the constant a for the BB region on exhalation is 2.04×10^{-6} .

D.10.2. *Derivation of Scaling Exponents, SF^n , for Different Subjects*

(D120) Estimates of extrathoracic deposition efficiencies in different subjects were obtained in Sections D.5.1.6 and D.5.2.5 by introducing a dimensionless scaling factor, SF_t , which represented the ratio of the tracheal diameter in the reference adult male to that in the subject. The recommended algebraic model of regional deposition in the lungs enables the same scaling principle to be applied to evaluate lung deposition for any subject in terms of reference anatomical dimensions. The algebraic deposition model automatically takes account of differences between subjects in air residence times for the various lung regions, and in volumetric dead spaces.

D.10.2.1. *Thermodynamic deposition efficiencies*

(D121) For thermodynamic deposition, the scaling factor for anatomical dimensions is included in the parameter a . (See Table D.1.)

(D122) For the BB region, the deposition efficiency in any subject (on both inhalation and exhalation) is evaluated by multiplying the constant a derived for the reference adult male by $SF_t^{1.24}$, giving $22 \times SF_t^{1.24}$, where SF_t is the dimensionless scaling factor determined by the ratio of tracheal diameter in the reference male to that in the subject.

(D123) For deposition in the bb region, the dimensionless scaling factor is determined by the ratio of diameter of the 9th generation airway in the reference adult male to that in the subject, which is denoted by SF_b . The scaled value of a is $-76.8 + 167 SF_b^{0.65}$.

(D124) For deposition in the AI region, the dimensionless scaling factor is determined by the ratio of diameter of the 16th generation airway in the reference adult male to that in the subject, which is denoted by SF_A . The scaled value of a is $170 + 103 SF_A^{2.13}$.

D.10.2.2. *Aerodynamic deposition efficiencies*

(D125) For aerodynamic deposition, the scaling factor for anatomical dimensions is a little more complex. (See Table D.1.)

(D126) For the BB region, the deposition efficiency in any subject (for both inhalation and exhalation) is evaluated by multiplying the composite parameter R by $SF_i^{2.3}$, giving $d_{ac}^2 \dot{V} SF_i^{2.3}$, where SF_i is the dimensionless scaling factor determined by tracheal diameter.

(D127) For aerodynamic deposition in the bb region, which occurs predominantly by gravitational sedimentation, scaling between different subjects is adequately accounted for by the appropriate time constant, i.e. the mean residence time t_b in the bb airways. An additional scaling factor for airway dimensions was not found to be necessary.

(D128) For the AI region, the dimensionless scaling factor, SF_A , which is applied to the constant a , is determined by the diameter of the 16th generation airway. The optimum form of this scaling factor is $SF_A^{0.98}$.

D.10.2.3. Fit of algebraic model to lung deposition calculated for different subjects

(D129) Figure D.22 shows the correspondence between regional lung deposition evaluated simply using the algebraic model and the values calculated by Egan *et al.* (1989) for women, and children of age 10 y, 5 y, and 1 y who are assumed to breathe at

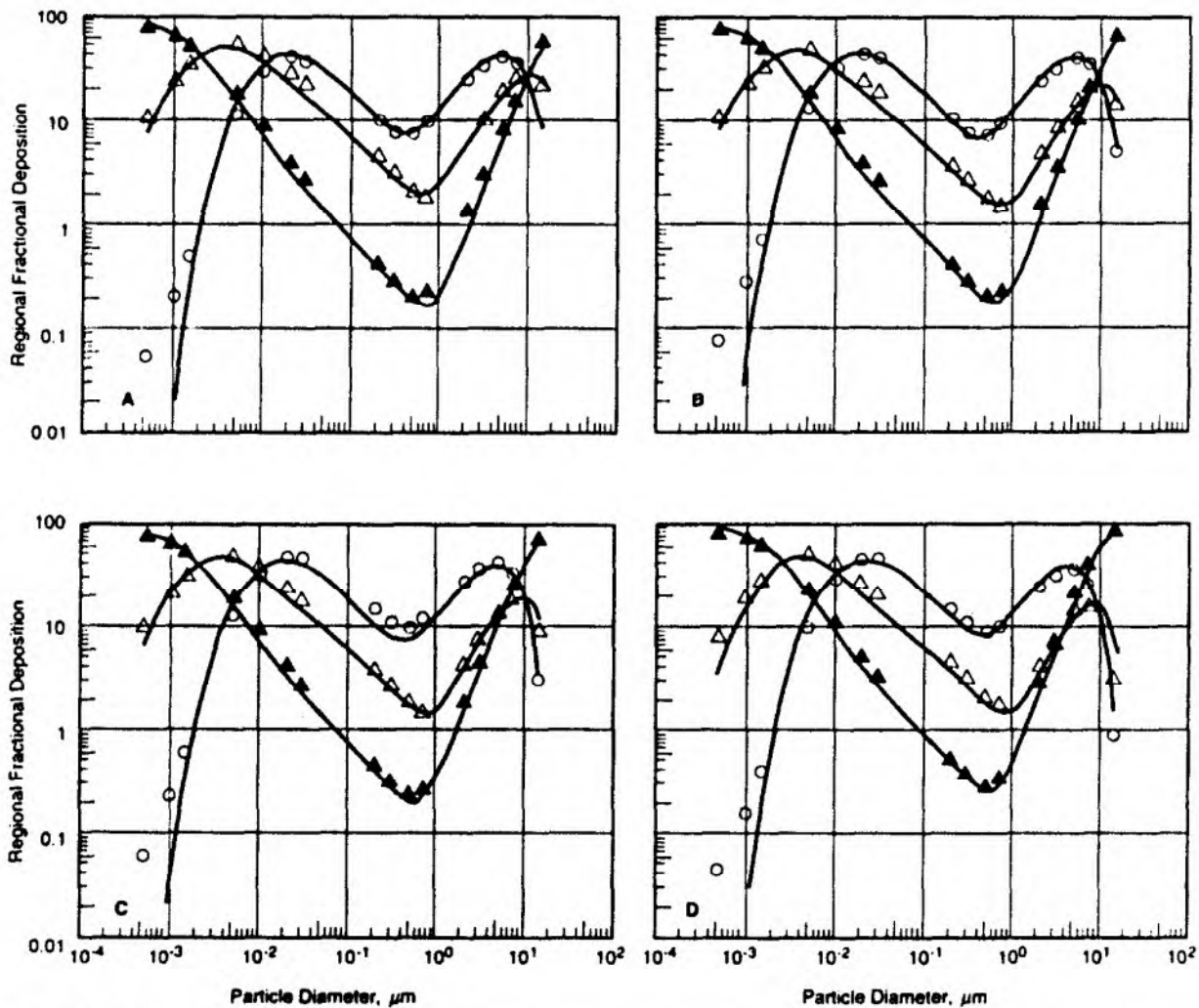


Fig. D.22. Fits to the values of regional lung deposition in various subjects calculated using theoretical model (data points) of Egan *et al.* (1989) given by the empirical algebraic model (solid curves). The calculated and fitted values apply to subjects engaged in light exercise: (A) woman; (B) child 10 y; (C) child 5 y; (D) infant 1 y. $\blacktriangle$ BB theoretical, $\triangle$ = bb theoretical, $\circ$ = AI theoretical, — algebraic model.

the rates recommended in Chapter 3 to characterize light exercise. This correspondence was obtained by optimizing the seven variable exponents of the scaling factors, SF, described in Paragraphs D121 through D128.

(D130) Figure D.23 shows that a similar correspondence between regional deposition evaluated by the algebraic model to the values calculated by Egan *et al.* (1989) is obtained when the parameters representing breathing rates for sleeping subjects are substituted into the model.

D.10.3. Test of Predicted Total Deposition in Children

(D131) There are no experimental data on regional lung deposition in children that can be used to test the predicted values shown in Figs D.22 and D.23. However, Becquemin *et al.* (1991), and Schiller-Scotland *et al.* (1992, 1994) have measured the total respiratory tract deposition in groups of children. The latter authors reported results for two separate groups: first of 23 children with an average age of 10.6 y (± 2 y standard deviation), and second of 6 children with an average age of 5.3 ± 1.5 y. For the analyses presented below, we have excluded from the first group 6 subjects who were

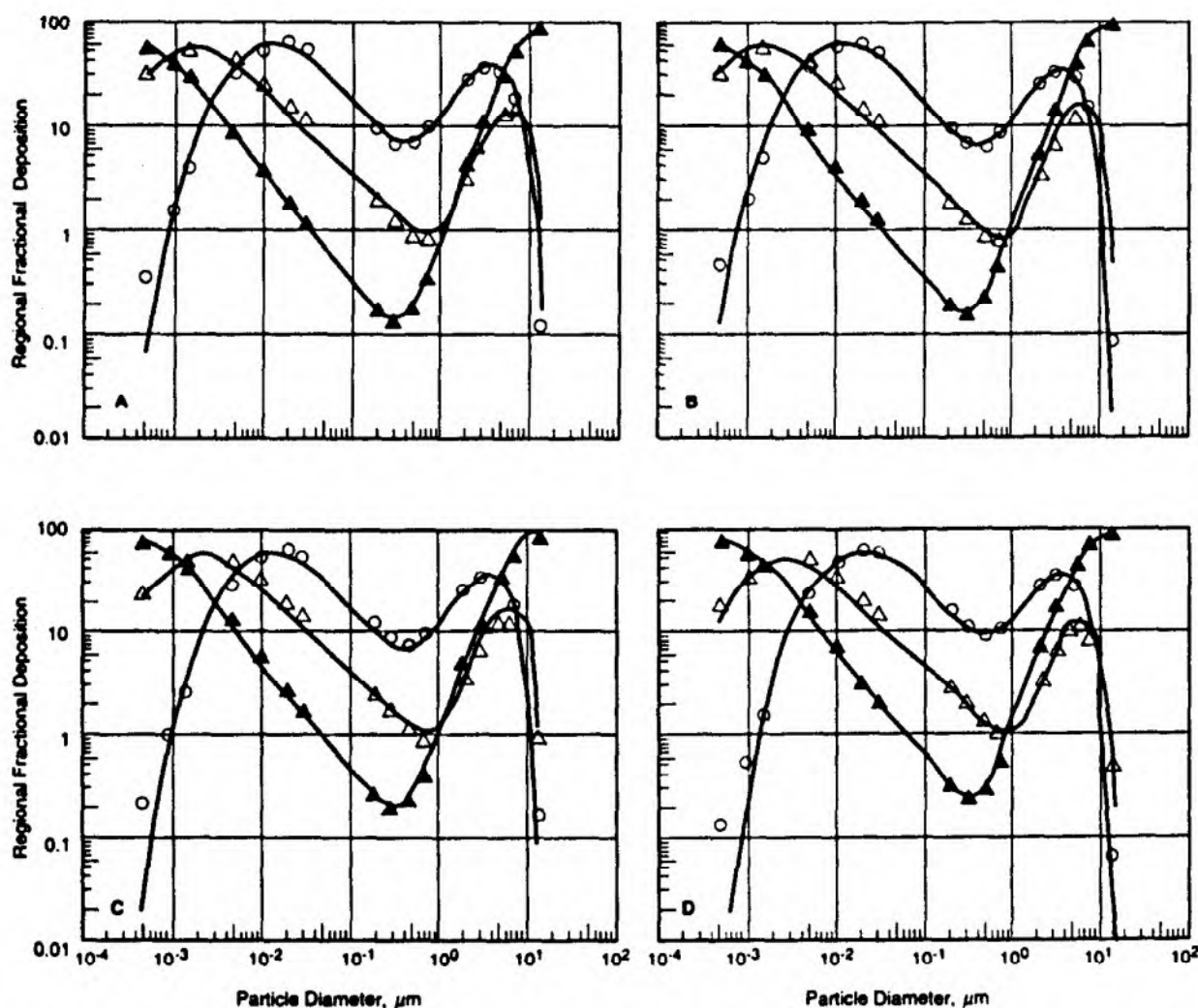


Fig. D.23. Fits to the values of regional lung deposition in various subjects calculated using theoretical model (data points) of Egan *et al.* (1989) given by the empirical algebraic model (solid curves). The calculated and fitted values apply to sleeping subjects: (A) woman; (B) child 10 y; (C) child 5 y; (D) infant 1 y. $\blacktriangle$ = BB theoretical, $\triangle$ = bb theoretical, $\circ$ = AI theoretical, — algebraic model.

older than 12 y, and thus reduced the average age of this group to 9.5 y (± 1 y). These two groups of children then provide a representative sample to simulate the 10-y-old and 5-y-old reference subjects for which the values of anatomical dimensions and respiratory tract volumes are recommended for substitution in the algebraic model.

(D132) Schiller-Scotland *et al.* measured the total deposition in each subject exposed via a mouthpiece to monodisperse aerosol particles of approximately 1- μm , 2- μm , or 3- μm diameter. In each experimental test the average tidal volume and flow rate were measured for each breath, when the subject breathed either spontaneously or at a controlled flow rate. The 5-y-old subjects were not able to maintain a controlled breathing pattern, so we examine below their results together with those for the 10 y olds also breathing spontaneously.

(D133) Figure D.24 plots values of the total respiratory tract deposition measured in individual tests on 10-y-old children with the values predicted by the algebraic model for the specific experimental conditions. Figure D.24A shows that the measured deposition is generally higher than that calculated for an adult male at the same tidal volume and flow rate. However, when the lung deposition model specifically for a 10-y-old child is used (Fig. D.24B), most of the measured values lie within $\pm 20\%$ of the predicted values.

(D134) It is of interest to note that the highest values of total deposition for 2.3- μm -diameter and 3.2- μm -diameter particles occurred in the same subject (of age 10.4 y), although the measurement obtained from this subject for 1- μm -diameter particles was close to the predicted mean value. The next highest total deposition value for 2.3- μm -diameter particles, and the highest value for 1- μm -diameter particles, were obtained with another subject (for whom no measurement was made with 3.2- μm -diameter particles). It is reasonable to conclude that the residual scatter in measured values is a reflection of intersubject variability in respiratory tract deposition efficiencies. The recommended treatment of intersubject variability is discussed later.

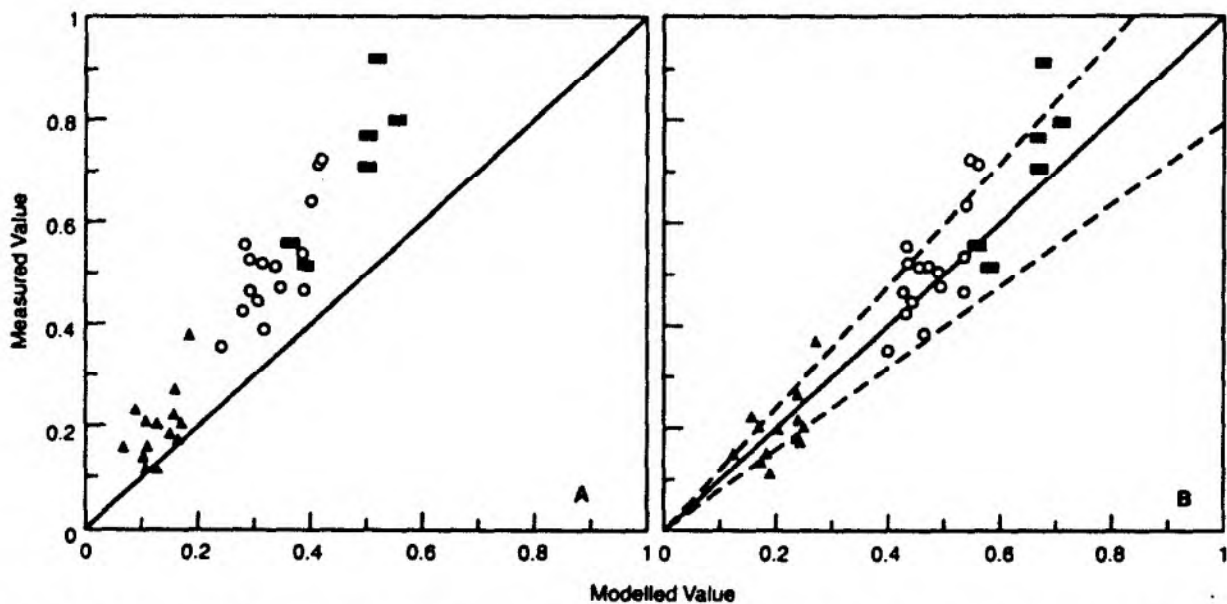


Fig. D.24. Total respiratory tract deposition in 10-y-old children measured by Schiller-Scotland *et al.* (1992, 1994) plotted against values predicted by the recommended algebraic model (1:1 ratio, solid line): (A) using the model for the reference adult male, and (B) using the model for the reference 10-y-old child; $\pm 20\%$ tolerance (dashed lines). Δ = 1- μm particles, $\circ$ = 2.3- μm particles, $\blacksquare$ = 3.2- μm particles.

(D135) Figure D.25 shows the measurements of total respiratory tract deposition made by Schiller-Scotland *et al.* (1994) in a group of 6 children about 5 y of age. In Fig. D.25A, the measured values are seen to be substantially higher than those predicted for an adult male at the same values of tidal volume and flow rate. Figure D.25B shows that the model specifically for the 5 y old provides reasonably close predictions of the measured values, although the modelled values are generally about 20% too high.

(D136) Further experimental data for young children may enable the scaling factors used in the algebraic model to be refined. However, in the interim, the predictive accuracy of the recommended algebraic model for children is considered to be adequate for radiological protection purposes.

D.10.4. Comparison of Model Predictions with Experimental Data on Regional Deposition in Adult Males

(D137) This section compares regional lung deposition predicted for the adult male by the recommended algebraic model with the substantial body of experimental data obtained using aerosols, exposure administration procedures, and lung-counting apparatus that differed from those used at the GSF Frankfurt Laboratory. The GSF Laboratory used a so-called "academic" breathing pattern, in which the subject inhaled and exhaled at a closely controlled rate. Other investigators have exposed their subjects under so-called "spontaneous" breathing conditions, where the subject maintains a more natural variation in flow rate through the breathing cycle, but is trained to achieve a relatively constant tidal volume and respiratory frequency.

D.10.4.1. Polystyrene particles

(D138) Foord *et al.* (1978) measured the fractional deposition of ^{99m}Tc -labelled polystyrene particles in the mouth and lungs of 15 different subjects. The lung deposition was divided into a "tracheobronchiolar" fraction, which was assumed to

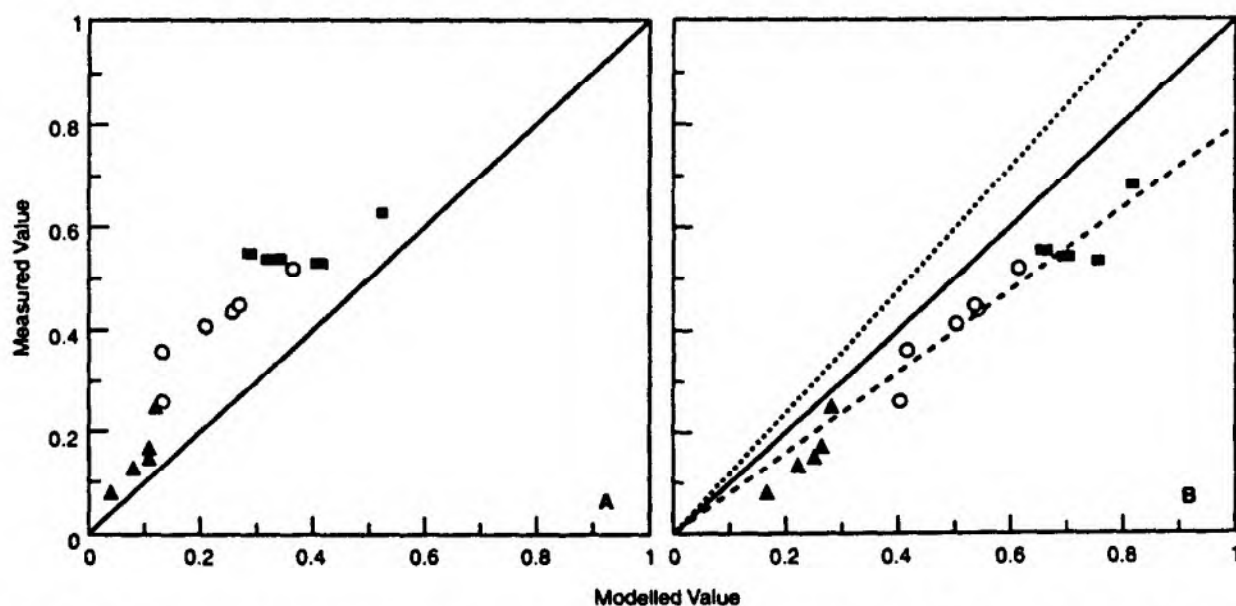


Fig. D.25. Total respiratory tract deposition in 5-y-old children measured by Schiller-Scotland *et al.* (1992, 1994) plotted against values predicted by the recommended algebraic model (1:1 ratio, solid line): (A) using the model for the reference adult male, and (B) using the model for the reference 5-y-old child; $\pm 20\%$ tolerance (dashed lines). Δ = 1- μm particles, $\circ$ = 2.3- μm particles, $\blacksquare$ = 3.2- μm particles.

consist of the activity cleared from the lungs within 24 h of inhalation, and the remaining "pulmonary" fraction. These authors used three different sizes of particles, i.e. 2.5- μm , 5- μm , and 7.5- μm diameter, and studied regional deposition for several different breathing patterns.

(D139) The experimental data obtained for an average tidal volume of 1 L, and a mean respiratory frequency of 10 min^{-1} , are shown in Fig. D.26. Foord *et al.* studied six different subjects under these conditions. Figure D.26 also shows the deposition of $^{99\text{m}}\text{Tc}$ -labelled polystyrene particles in the mouth and lungs of 12 different subjects (divided into four groups, each exposed to particles of one of four different sizes) measured by Emmett and Aitken (1982), using the same breathing pattern.

(D140) Figure D.26A shows that, after correcting for the extrathoracic deposition measured for each test, the recommended lung deposition model accurately matches the trend of tracheobronchiolar deposition with particle size measured by Foord *et al.* For the 2.5- μm particles, a better match to the average reported tracheobronchiolar "deposition" is obtained when the modelled deposition in the BB and bb regions is reduced by an assumed fraction of 50%, representing particles deposited in these airways but not cleared within 24 h.

(D141) The tracheobronchiolar deposition reported by Emmett and Aitken (1982), i.e. the activity deposited in the lungs that is cleared within 24 h, is generally higher than that found by Foord *et al.*, with relatively little variability between the three subjects studied at each particle size.

(D142) Figure D.26B shows the measured values of activity deposited in the lungs that was retained longer than 24 h. In this case, the data of Foord *et al.* are generally higher than the modelled values, and Emmett and Aitken's values are lower by a similar factor. Both sets of data show a similar trend of "slow-cleared" lung deposition with

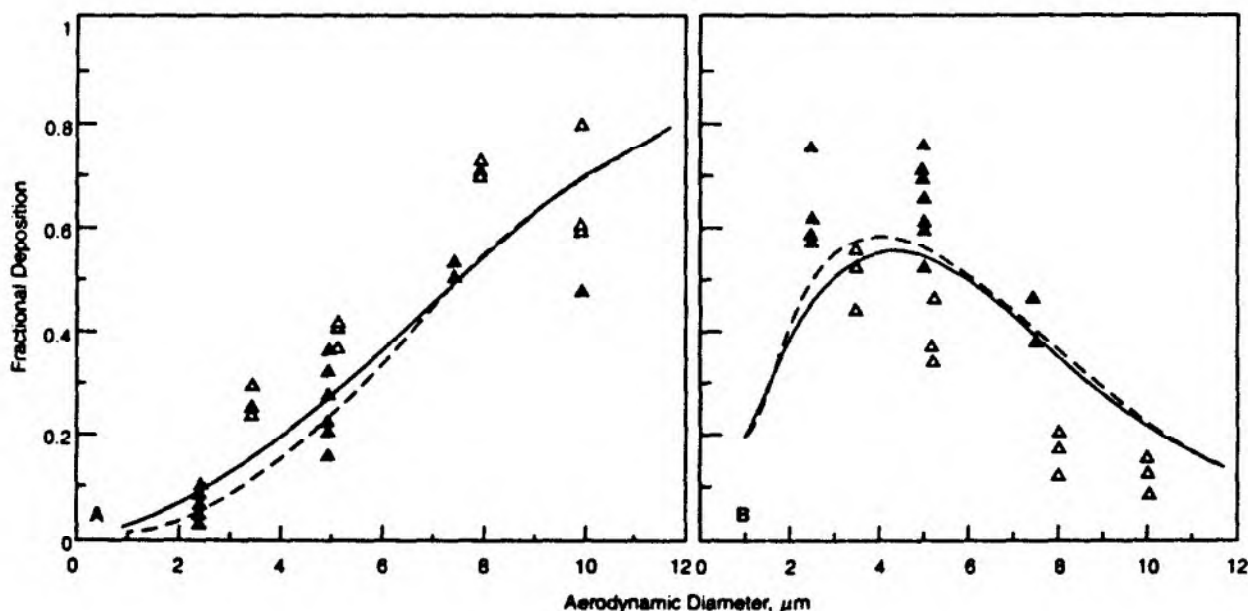


Fig. D.26. Comparison of fractional lung deposition measured by Foord *et al.* (1978) ($\blacktriangle$) and Emmett and Aitken (1982) ($\triangle$) with values given by the recommended algebraic model. The fractional deposition shown has been adjusted to correspond to zero extrathoracic deposition, where (A) is the measured fast-cleared deposition, and (B) the slow-cleared deposition. The solid curves represent the modelled tracheobronchiolar and alveolar-interstitial deposits, respectively; and the dashed curves, the corresponding modelled fast- and slow-cleared fractions.

particle size to that modelled, but with higher or lower absolute values, respectively, for the same breathing pattern.

(D143) Foord *et al.* (1978) also studied the effect of varying the tidal volume on regional lung deposition (at a mean respiratory frequency of 15 min^{-1}), for two different sized particles, in three different subjects. Figure D.27 shows substantial intersubject variability in the measured lung deposition, both for the fast- and slow-cleared fractions. On the average, however, the measured fast-cleared lung deposition (Fig. D.27A) is matched well by the values modelled as a function of the subject's tidal volume. It should be noted that for the $3.5\text{-}\mu\text{m}$ -diameter particles, the modelled tracheobronchiolar deposition is reduced by 25% to allow for the recommended slow-cleared fraction, and for $6.5\text{-}\mu\text{m}$ particles by just 3.1%. As noted in the previous paragraph for the experiments carried out with a tidal volume of 1 L and respiratory frequency of 10 min^{-1} , the slow-cleared lung deposit measured as a function of tidal volume at $15 \text{ breaths min}^{-1}$ tends to be higher than the modelled values. However, the data obtained for a tidal volume of 2 L are (on average) well represented by the model.

(D144) Figure D.28 shows a similar pattern for the fast- and slow-cleared lung deposition measured by Foord *et al.* (1978) as a function of the respiratory frequency (at a tidal volume of 1 L). On average, the fast-cleared lung deposition is well represented by the recommended model, but the values of slow-cleared lung deposition measured for $3.5 \mu\text{m}$ are generally higher than those predicted.

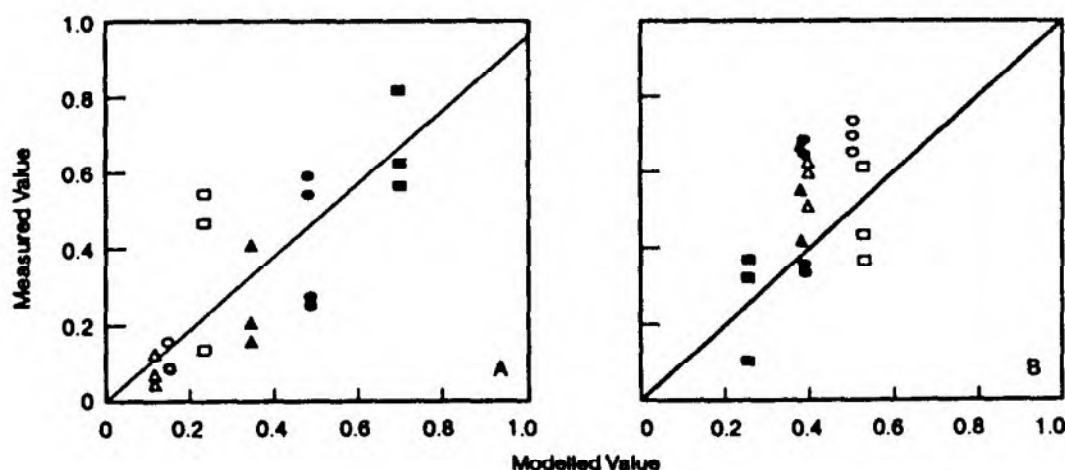


Fig. D.27. Plot of (A) fast-cleared lung deposition, and (B) slow-cleared lung deposition, measured by Foord *et al.* (1978) in three subjects as a function of tidal volume (at a mean breathing frequency of 15 min^{-1}) against the values predicted by the recommended algebraic deposition model. $3.5\text{-}\mu\text{m}$ particles at 0.5 L (Δ), 1.0 L ($\circ$), and 2.0 L ($\square$); $6.5\text{-}\mu\text{m}$ particles at 0.5 L ($\blacktriangle$), 1.0 L ($\bullet$), and 2.0 L ($\blacksquare$).

D.10.4.2. Teflon particles

(D145) Camner (1971) described the production and use of test aerosols of fluorocarbon resin (Teflon) particles labelled with insoluble radionuclide tags to measure regional lung deposition in human subjects. Measurements of the ratio of fast- to slow-cleared lung deposition made by this group in Stockholm have been intercompared with measurements at the GSF Frankfurt Laboratory (Stahlhofen *et al.*, 1980). Results for the same subject exposed under the same conditions in both laboratories were found to agree within about 10%.

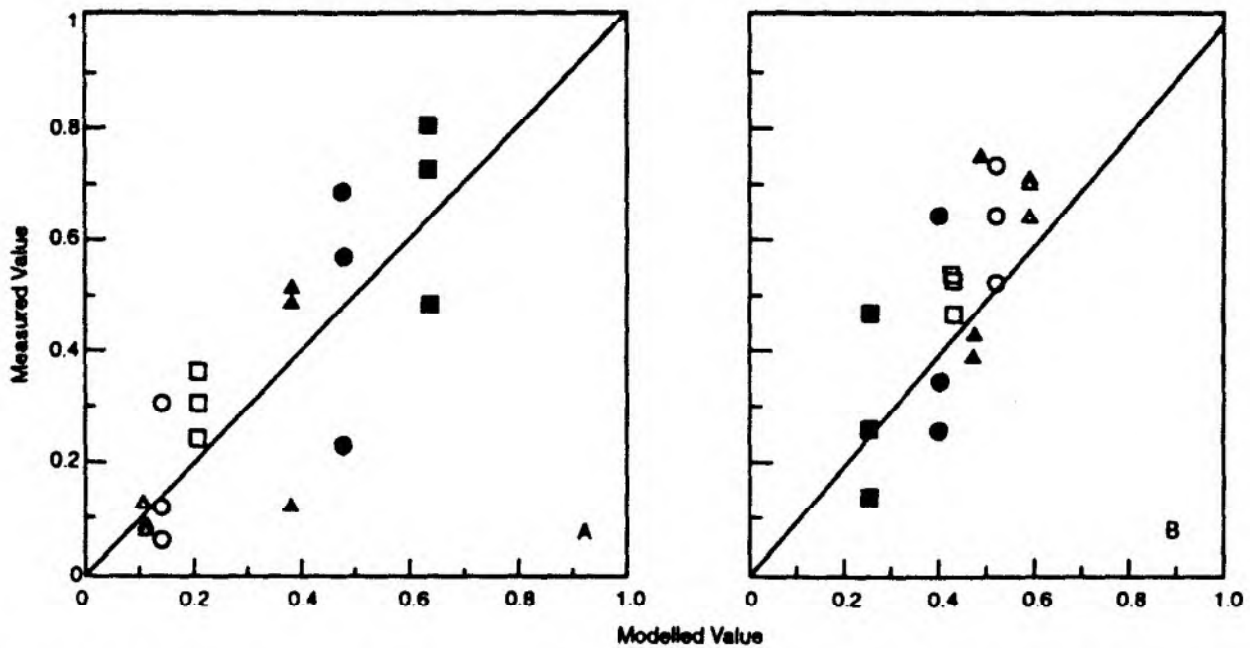


Fig. D.28. Plot of (A) fast-cleared lung deposition, and (B) slow-cleared lung deposition, measured by Foord *et al.* (1978) in three subjects as a function of breathing frequency (at a mean tidal volume of 1 L) against the values predicted by the recommended algebraic deposition model. 3.5- μm particles at 10 min^{-1} (Δ), 15 min^{-1} (O), and 25 min^{-1} ($\square$); 6.5- μm particles at 10 min^{-1} ($\blacktriangle$), 15 min^{-1} ($\bullet$), and 25 min^{-1} ($\blacksquare$).

(D146) Studies carried out in the Stockholm laboratory have employed a breathing pattern designed to detect broncho-constriction and other symptoms of airway disease by their effects on regional lung deposition (Camner and Philipson, 1978; Svartengren *et al.*, 1984, 1987a,b, 1989a,b). This has generally involved inhalation exposure to radiolabelled particles through a mouthpiece at a constant flow rate of about 500 $\text{cm}^3 \text{s}^{-1}$. The breath is normally taken to the subject's maximal lung inflation (between 3 L and 4 L tidal volume). Anderson *et al.* (1990) also studied the effects of the inspiratory flow rate on regional lung deposition. Figure D.29 compares the mean values of regional deposition measured in these various studies (averaged for groups of between six and ten subjects) with the values predicted by the recommended algebraic deposition model for the appropriate breathing patterns.

(D147) Figure D.29 shows that, for relatively high values of the impaction parameter (which correspond to particles with an aerodynamic diameter greater than about 8 μm), both the predicted fast-cleared lung deposition and extrathoracic deposition are in good agreement with the measured data. However, for smaller particles, both the measured tracheobronchiolar and extrathoracic deposition were significantly greater than expected from the model, i.e. from the other available experimental data (for example, compare with the extrathoracic deposition shown in Fig. D.8). In fact, for the experiment with 2.5- μm -aerodynamic-diameter particles ($d_{\text{ac}}^2 \dot{V} \approx 3000 \mu\text{m}^2 \text{cm}^3 \text{s}^{-1}$), the average measured extrathoracic deposition is about 4-fold higher than expected, and for 3.6- μm particles ($d_{\text{ac}}^2 \dot{V} \approx 6500 \mu\text{m}^2 \text{cm}^3 \text{s}^{-1}$) it is 2.5- to 5-fold higher. This apparently high extrathoracic (and tracheobronchiolar) deposition may be an experimental artifact explained by the tendency of small Teflon particles to form larger aggregates at the high particle concentrations achieved in the Swedish studies (G. Scheuch, GSF Laboratory, Frankfurt, personal communication).

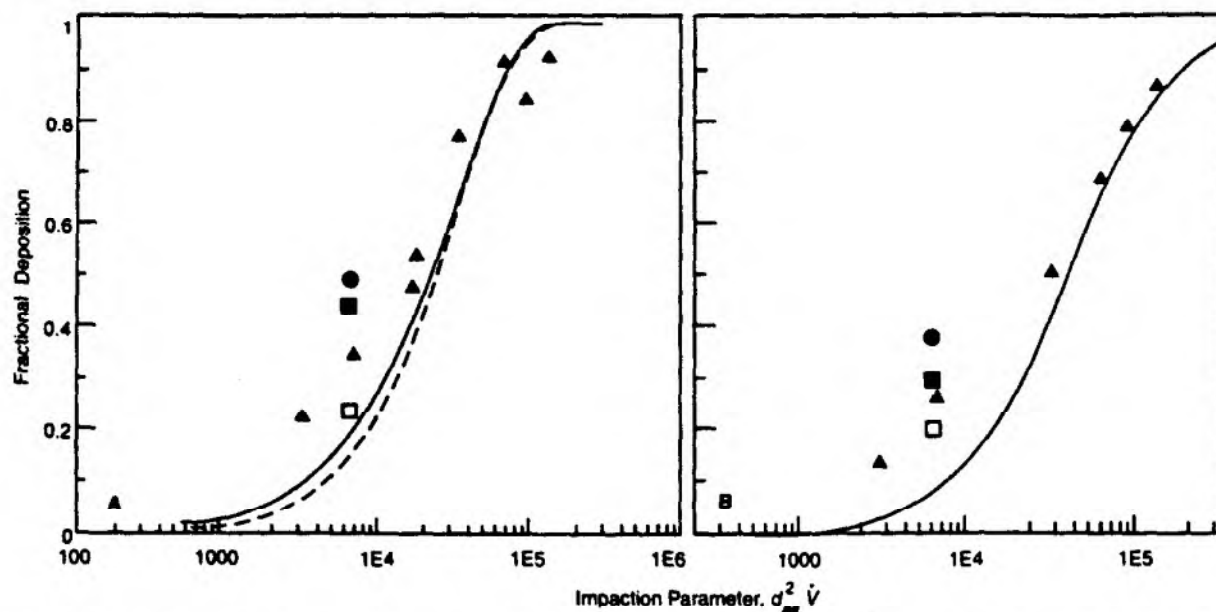


Fig. D.29. Comparison of fractional deposition measured at the Karolinska Institute, Stockholm, for (A) fast-cleared lung activity, and (B) extrathoracic activity, with values predicted by the algebraic deposition model. Fractional deposition is plotted against the impact parameter, $d_{ae}^2 \dot{V}$. In (A), the solid curve represents this report's predicted tracheobronchiolar deposition, and the dashed curve the fast-cleared fraction. In (B) the solid curve represents this report's predicted extrathoracic deposition. $\blacktriangle = 500 \text{ mL s}^{-1}$; $\square = 400 \text{ mL s}^{-1}$; $\blacksquare = 800 \text{ mL s}^{-1}$; $\bullet = 1200 \text{ mL s}^{-1}$.

D.10.4.3. Iron oxide particles

(D148) Lippmann (1977) and Chan and Lippmann (1980) reported measurements of lung deposition and 24-h retention in a large number of different subjects at New York University (NYU). These studies involved iron oxide particles tagged in aqueous suspension with ^{99m}Tc (Wales *et al.*, 1980). Each subject was allowed to breathe normally, and the average tidal volume and breathing frequency were monitored. Typical values of these respiratory parameters were $500 \text{ cm}^3 \text{ s}^{-1}$ and 15 min^{-1} , respectively.

(D149) Figure D.30 shows the values of fast- and slow-cleared lung deposition obtained in these studies at NYU (adjusted to zero extrathoracic deposition from the measured value). In common with the earlier theoretical lung deposition models described by Yeh and Schum (1980) and Yu and Diu (1987), the recommended algebraic deposition model predicts substantially less bronchial (fast-cleared) deposition for particles of aerodynamic diameter larger than $1 \mu\text{m}$ than is indicated by the bulk of the NYU data. Likewise, the predicted alveolar (slow-cleared) deposition for particles of about $1\text{-}\mu\text{m}$ aerodynamic diameter is also low compared with the NYU data.

(D150) These data provide an excellent measure of intersubject variability in the deposition efficiencies of the tracheobronchiolar and alveolar-interstitial regions of the lungs. However, in absolute terms, the interpretation of these results is complicated by the likelihood that the labelled iron oxide particles used may have grown hygroscopically in the humid air of the respiratory tract. Monodisperse iron oxide particles are produced by atomisation of an aqueous suspension of colloidal iron oxide with a spinning top generator (Albert *et al.*, 1964; Lippmann and Albert, 1967; Stahlhofen *et al.*, 1979). The colloidal suspension is prepared by converting iron chloride in aqueous solution by hydrolysis to iron oxide. In order to remove all traces of

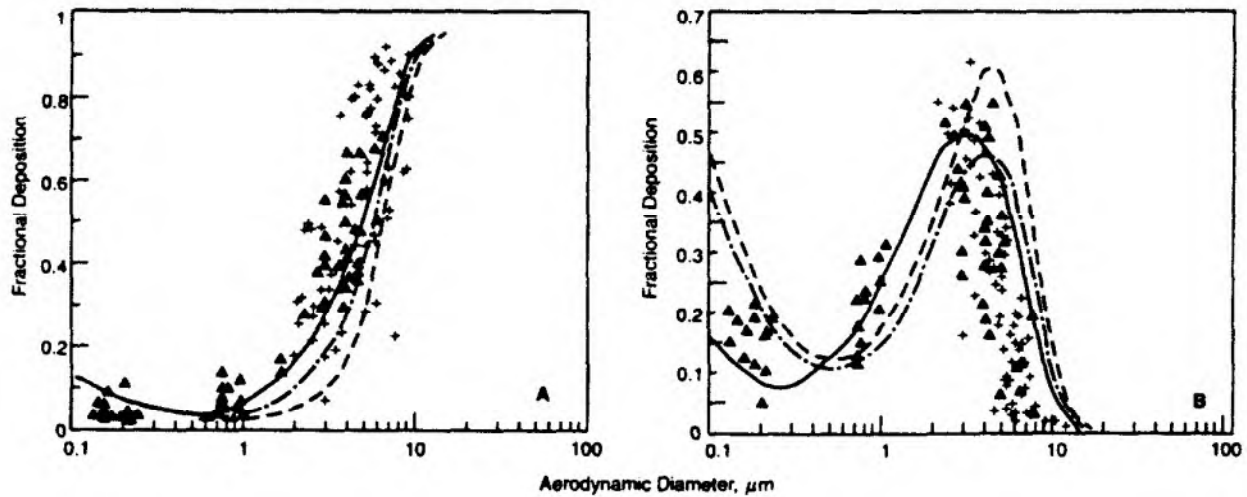


Fig. D.30. Fractional deposition in the lungs of (A) fast-cleared, and (B) slow-cleared particles measured at New York University, compared with values predicted by the algebraic deposition model. The lighter solid curves show the calculated tracheobronchiolar and alveolar-interstitial deposition, respectively. The dashed curves show calculated deposition corrected for the expected slow-cleared fraction of bronchial deposition. The heavier solid curves show calculated deposition corrected for hygroscopic growth of iron oxide particles estimated from the study by Gebhart *et al.* (1988). The measured and calculated values are normalised to zero extrathoracic deposition. $\blacktriangle$ = Chan and Lippmann (1980), $+$ = Lippmann (1977).

the dissolvable chloride, the aqueous iron oxide colloid must be dialysed extremely thoroughly.

(D151) Gebhart *et al.* (1988) used light-scattering photometry to examine the effect of the degree to which a suspension of colloidal iron oxide is dialysed on the hygroscopicity of the resulting monodisperse particles, by comparing the physical properties of these particles on inhalation and exhalation. These authors found that even when the particles are produced from extremely well dialysed iron oxide there is a distinct change in light-scattering properties between the inhaled and exhaled particles. Since the total respiratory tract deposition of these particles was indistinguishable from that of oil droplets of the same aerodynamic size in ambient air, Gebhart *et al.* (1988) concluded that their measured shift in optical properties was caused by the presence of a thin film of condensed water on the surface of the exhaled particles.

(D152) Using this same technique on a sample of the dialysed iron oxide suspension prepared at NYU, Gebhart *et al.* found a much greater shift in light-scattering properties of the final monodisperse particles between inhalation and exhalation. This observed shift in light-scattering properties was accompanied by increased total respiratory tract deposition compared with that of oil droplets of the same aerodynamic size in ambient air. The deposition measured under identical exposure conditions was found to increase from 44% for the hydrophobic oil droplets to 68% for the iron oxide particles. The same change in measured respiratory tract deposition would be obtained by inhaling oil droplets of 3.8- μm aerodynamic diameter in place of the 2.4- μm -aerodynamic-diameter iron oxide particles.

(D153) The recommended method for extending the algebraic deposition model to evaluate regional lung deposition for aerosols that are subject to hygroscopic particle growth is described in Section D.12 below. Figure D.30 shows the effect on the modelled fast- and slow-cleared lung deposition of allowing for a degree of hygroscopic growth of the NYU iron oxide particles. (See Section D.12.5.) It is seen that this

correction of the modelled lung deposition improves substantially the overall fit of the predicted values to the measurements. However, some further correction of the calculated values may be necessary to account for the additional particle growth resulting from residual chloride introduced by radiolabelling with ^{99m}Tc carried by sodium pertechnetate in stannous chloride (G. Scheuch, GSF Laboratory, Frankfurt, personal communication).

D.11. Evaluation of Intersubject Variability

(D154) Primarily on the basis of the variability in regional lung deposition within the large group of subjects studied by Lippmann (1977) and Chan and Lippmann (1980), Rudolf *et al.* (1994) have estimated the upper and lower 95% confidence bounds for predicting the regional lung deposition in an individual subject. These confidence bounds are estimated by applying the dimensionless scaling constants given in Table 14 of Chapter 5 to multiply or divide the coefficient a in Eqn. D.25. The constants so derived for the aerodynamic deposition efficiencies of the BB, bb, and AI regions are 2.5, 2.5, and 1.7, respectively. For submicron-sized particles, the available experimental data on regional lung deposition are too sparse to provide an equivalent estimate of the variability in thermodynamic deposition efficiencies. However, multiplication or division of the coefficient a in Eqn. D.22 by the factor 1.5 in order to estimate the 95% confidence bounds on the thermodynamic deposition efficiencies of the BB, bb, and AI regions appears to be a reasonable working assumption.

(D155) Figure D.31 compares the estimated 95% confidence bounds on the fast- and slow-cleared fractional deposition in the lungs of human subjects exposed under the same average breathing conditions (tidal volume and breathing frequency) with the experimental data obtained by Foord *et al.* (1978) and Emmett and Aitken (1982). It is

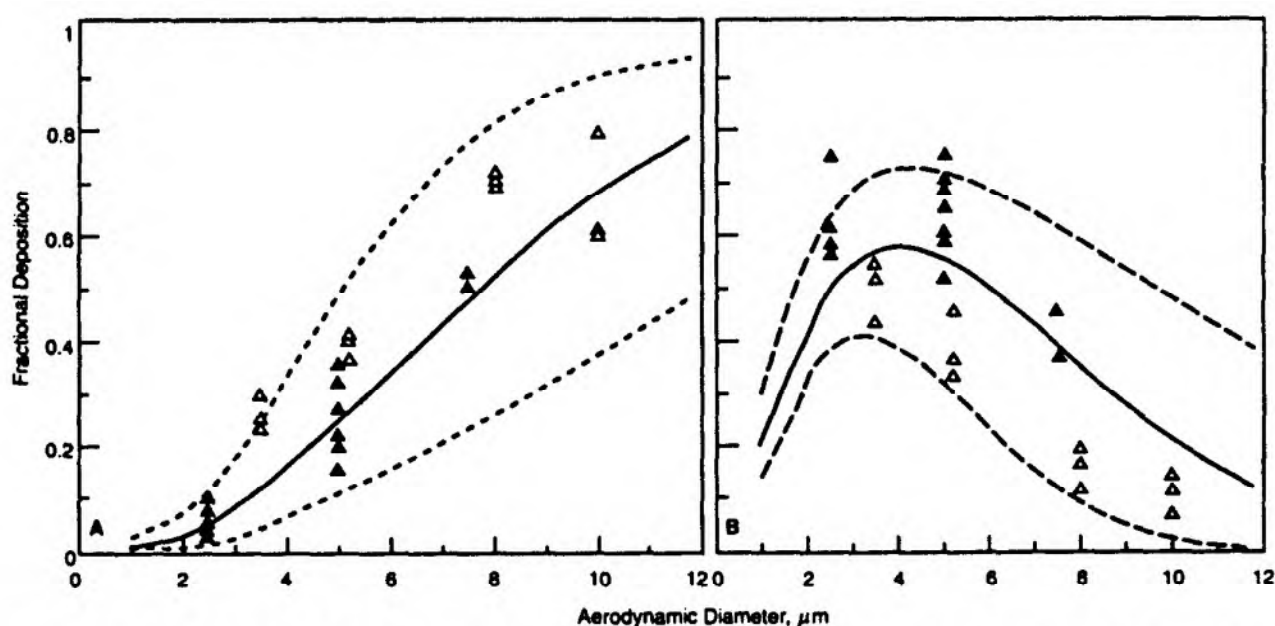


Fig. D.31. Comparison of the estimated 95% confidence bounds on regional lung deposition efficiency with experimental measurements by Foord *et al.* (1978) (▲) and Emmett and Aitken (1982) (△). These data were shown earlier in Fig. D.26. The solid curve represents this report's predicted deposition, and the dashed curves the upper and lower 95% confidence bounds.

seen that the estimated confidence bounds on the predicted regional lung deposition envelope the variability of the data from these two studies. However, it is likely that some of this variability in experimental results may have arisen from systematic differences in measurement procedures. The net variability in the actual lung deposition efficiencies between subjects, may therefore be less than is indicated here.

(D156) The experimental data on regional lung deposition presented in this section were normalised to remove the effects of the measured variability in extrathoracic deposition. Thus, multipliers and divisors of the coefficient a in Eqn. D.25 were derived to express the confidence bounds on the deposition efficiency of each of the three lung regions considered in isolation. The probability distribution of the overall fractional deposition in each region is then determined by convoluting the probability distributions of each regional deposition efficiency.

(D157) To estimate the overall probability distribution of regional lung (and extrathoracic) deposition, it would be reasonable to assume that the deposition efficiencies of each region are not correlated, and that these are sampled at random from normal distributions centred on the predictions of the recommended algebraic model. Anatomically defined factors that do lead to correlations of regional deposition efficiencies, such as body height, are already incorporated in the model.

D.11.1. Pathogenesis and Disease

(D158) Few experimental data are available in the literature on the effects of lung pathology and disease on aerosol deposition. In general, quantitative studies have instead examined the effects of lung disease on clearance, as described in Annexe E.

(D159) However, Stahlhofen *et al.* (1984a) were able to show that the presence of bronchitis does modify the fractionation of particle deposition between the tracheobronchial and alveolar-interstitial regions of the lungs to a measurable degree. These authors studied thoracic deposition in a group of 27 dental technicians. Some of their subjects had symptoms of bronchitis; others had been exposed occupationally for more than 10 y to both airborne silica and heavy metals. The fractionation of fast- and slow-cleared thoracic deposition in these bronchitic and dust-exposed subjects was compared with that in a control group of normal, asymptomatic subjects. The results are shown in Fig. D.32.

(D160) The figure shows that, in addition to the expected intersubject variability within each group, the majority of the dental technicians with symptoms of bronchitis exhibited a substantially smaller slow-cleared fraction of thoracic deposition than normal subjects. Furthermore, dental technicians with more than 10 y occupational exposure also tended to exhibit a smaller slow-cleared fraction of thoracic deposition than did normal subjects, or peers exposed for less than 10 y.

(D161) Table D.2 gives the average values of total respiratory tract deposition, DE , and the fractional deposition in the thoracic and extrathoracic airways, DE_{TH} and DE_{ET} , respectively, that were measured in these different subject groups. The table also shows the measured subdivision of thoracic deposition into fast- and slow-cleared fractions, $DE_{TH}(F)$ and $DE_{TH}(S)$, respectively, together with the ratio of $DE_{TH}(S)$ to total thoracic deposition, DE_{TH} , which was shown in Fig. D.32.

(D162) It is seen from the table that, on average, the total respiratory tract deposition, DE , is essentially the same for each group of subjects. However, the extrathoracic deposition efficiency, DE_{ET} , tends to be increased with occupational

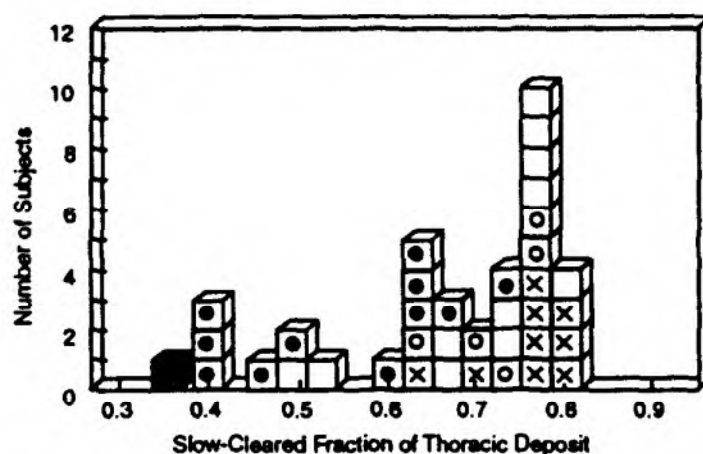


Fig. D.32. Ratio of slow-cleared to total thoracic deposition measured by Stahlhofen *et al.* (1984a) in different subjects who inhaled 5- μ m-diameter unit density particles under the same breathing conditions. X = normal subjects; O = dental technicians (DT) with <10-y exposure; (open box) = DT with >10-y exposure; ● = DT with bronchitis symptoms; (shaded box) = patient with bronchitis.

Table D.2. Total and regional respiratory tract deposition measured for three different groups of dental technicians compared with results for nonoccupationally exposed control subjects

Deposition fraction	Nine subjects (control)	Five dental technicians < 10-y exposure	Eleven dental technicians > 10-y exposure	Eleven dental technicians > 20-y exposure (with bronchitis)
Total	0.79	0.81	0.80	0.80
ET	0.08	0.14	0.16	0.20
TH _{total}	0.71	0.67	0.64	0.60
TH _{fast}	0.17	0.19	0.19	0.27
TH _{slow}	0.54	0.48	0.45	0.33
TH _{slow} /TH _{total}	0.76	0.72	0.70	0.55

exposure, and to be highest on the average in the bronchitic subjects. Conversely, therefore, the thoracic deposition, DE_{TH} , tends to decrease with occupational exposure, and to be lowest in bronchitic subjects.

(D163) As was shown in Fig. D.32 for the distribution of values measured in individual subjects, the average fractionation of thoracic deposition into fast- and slow-cleared material exhibits a more marked dependence on exposure history and bronchitis. The average slow-cleared fraction of thoracic deposition was found to decrease markedly from 0.76 in normal subjects to 0.55 in bronchitic subjects.

(D164) Table D.3 shows that the observed differences in regional lung deposition amongst these four groups of subjects are not reflected in similar changes in lung function. The measured values of standard clinical lung function parameters show some correlation with exposure history and bronchitis, but all of the group average values lie within the normal range.

Table D.3. Clinical lung function parameters measured for three different groups of dental technicians compared with results for nonoccupationally exposed control subjects

Functional parameter	Nine subjects (control)	Five dental technicians < 10-y exposure	Eleven dental technicians > 10-y exposure	Eleven dental technicians > 20-y exposure (with bronchitis)
FEV ₁ (L s ⁻¹)	3.83	3.58	3.67	3.78
FEV ₁ [*] (%)	108	95	100	90
R _{aw} (kPa L ⁻¹ s ⁻¹)	1.82	2.44	2.40	2.68
FEV ₁ /VC (L)	75.4	75.6	73.6	69.1

FEV₁ = forced expiratory volume in 1 s; FEV₁^{*} = fraction of expected value; R_{aw} = airway resistance; VC = vital capacity.

D.12. Data and Model for Hygroscopic Aerosols

(D165) Most studies of particle deposition in the lungs have used nonhygroscopic or minimally hygroscopic materials. However, many materials of concern are hygroscopic, such as soluble inorganic salts and organic materials like tobacco smoke. Hygroscopic particles absorb water, and can grow rapidly to many times their original size when they experience an increase in relative humidity. The resulting deposition in the respiratory tract is then complicated by the dynamics of hygroscopic particle growth (Morrow, 1986). The rate of growth depends on several parameters, including relative humidity, temperature, particle size, and particle composition.

(D166) In the absence of hygroscopic growth, particles that start out with 1- μ m diameter in normal room air are expected to have a relatively low deposition probability in the lungs. Over the course of a breath, however, hygroscopic particles of 1- μ m initial diameter may grow to approximately 4- μ m diameter. This growth would result in much greater deposition in the lungs. On the other hand, particles that start out with 0.1- μ m diameter have reduced thermodynamic mobility when they grow to about 0.5- μ m diameter, resulting in reduced deposition in airways. Thus, both total and regional lung deposition are affected substantially by hygroscopic particle growth.

D.12.1. Human Data

(D167) The total lung deposition of hygroscopic aerosols has been measured in human subjects (Hänel and Heyder, 1980; Blanchard and Willeke, 1984; Tu and Knutson, 1984). It is generally found that dry particles in the size range of 0.2–2.0 μ m grow enough to substantially increase deposition, while growth of smaller particles tends to decrease deposition. Growth factors have been found to be in the range 3–7. For sodium chloride, the dry-particle size having minimum deposition has been found to be 0.08 μ m (Blanchard and Willeke, 1984; Tu and Knutson, 1984; Hicks *et al.*, 1986). This corresponds to a particle size of 0.5 μ m for a nonhygroscopic material, i.e. to a growth factor of 6.

(D168) The regional deposition of hygroscopic aerosols has not been measured. The soluble nature of hygroscopic materials obviates most methods of regional deposition measurement. A possible exception would be particles composed of a mixture of soluble and insoluble material: an insoluble core could be tagged for regional deposition measurement, while a hygroscopic surface causes substantial particle growth. (See Paragraph D183 below for discussion.) However, for dry particles larger than about

1 μm , where total deposition of the hygroscopic aerosol is high, a shift of aerodynamic deposition from peripheral to more central airways is expected when compared to nonhygroscopic particles. At the other extreme, for dry particles very much smaller than 0.1 μm , thermodynamic deposition of hygroscopic particles is expected to shift from central airways to more peripheral airways. Morrow (1986) presented a review of these fundamental problems arising from the growth of particles in humidified air, and described the factors determining hygroscopic aerosol deposition in the human airways.

D.12.2. *Modelling of Hygroscopic Particle Growth*

(D169) Ferron (1977) applied his theory of hygroscopic particle growth to the particle deposition model of the Task Group on Lung Dynamics (TGLD, 1966) to illustrate how hygroscopic growth would affect lung deposition. Using the tidal volume of 750 cm^3 , an inspiration time of 1.74 s, an expiration time of 2.06 s, a pause of 0.2 s before expiration, and constant airflow rates, Ferron computed the mean residence time of particles in the nasal passages, tracheobronchial tree, and pulmonary parenchyma. Taking $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ as an example of a hygroscopic salt, and an assumed relative humidity (RH) of 0.995, he showed graphically how the deposition of a CoCl_2 aerosol would differ from that of a nonhygroscopic aerosol.

(D170) Such models for calculation of particle growth in the human respiratory tract depend on presumed RH and temperature profiles in the lungs (Ferron *et al.*, 1985, 1988). Measurements of particle growth during transport in human lungs have found the effective RH to be 0.995 of saturation (Ferron, 1977; Blanchard and Willeke, 1984; Tu and Knutson, 1984; Anselm *et al.*, 1986). Profiles of temperature and RH are calculated to reach normal lung values within the first few generations of the bronchi (Ferron *et al.*, 1988). The effect of these profiles may be approximated by introducing an effective time delay of 0.1 s before the onset of hygroscopic growth, as suggested by Ferron *et al.* (1988).

(D171) The growth of hygroscopic particles in the respiratory tract is rapid enough for deliquescence to occur in the ET_2 region. This growth can continue through successive regions, on both inhalation and exhalation. Therefore, to calculate the deposition efficiency of each region of the lungs (for example, using the recommended algebraic deposition model) it is necessary to calculate first the amount of particle growth that occurs in each region.

(D172) The dynamics of hygroscopic growth of aerosol particles have been analysed by Ferron (1977). The composition of the growing particle may be complicated by the fact that it may consist of an insoluble core, which is coated with a layer of salt. As the particle absorbs water from the air, the liquid layer grows to an equilibrium size, where the rate of evaporation is balanced by the rate of absorption. In this case, the dynamics of the composite particle's growth are similar to those of pure salt particles.

(D173) Calculation of the growth in aerodynamic diameter of a hygroscopic particle is complicated by the fact that the particle density may decrease rapidly when a dry particle of relatively high density absorbs water. Thus, a dramatic growth in the geometric diameter of a particle may not herald a similar growth in aerodynamic diameter. For example, iron oxide particles with a surface coating of sodium chloride are calculated to grow in geometric diameter by a factor of 3.3, while the growth in aerodynamic size is only 1.8. (See Paragraph D183 below.)

(D174) To quantify particle growth as a function of time, it is useful to consider the growth fraction, $F(t)$. This is defined as the fractional growth from the dry particle size

to the equilibrium particle size at 0.995 RH. Ferron found this time-dependent factor to be similar for a variety of salts. It can be shown that the particle growth fraction, $F(t)$, calculated by Ferron (1977) for a typical salt as a function of time, can be approximated by Eqn. D.45:

$$F(t) = \frac{d_{ac}(t) - d_{ac}(0)}{d_{ac}(\infty) - d_{ac}(0)}$$

$$= \frac{d_{ac}(\infty) - [d_{ac}(\infty) - d_{ac}(0)] \left[\exp \left(\frac{-(10t)^{0.55}}{d_{ac}(0)} \right) \right]^{0.6} - d_{ac}(0)}{d_{ac}(\infty) - d_{ac}(0)} \quad (D.45)$$

where $d_{ac}(0)$ is the initial aerodynamic diameter of the particle, $d_{ac}(t)$ is the aerodynamic diameter at time, t , and $d_{ac}(\infty)$ is the aerodynamic diameter at hygroscopic equilibrium.

(D175) Growth curves obtained by evaluating Eqn. D.45 for three different values of $d_{ac}(0)$ are shown in Fig. D.33. These curves are direct representations of the values given in Fig. 4 of Ferron (1977).

(D176) To calculate the regional deposition of hygroscopic particles, their growth as a function of time is needed in order to give a reference particle size for computing deposition in each compartment of the respiratory tract model. Growth of aerodynamic particle size is extracted from Eqn. D.45 in terms of t and $d_{ac}(\infty)$:

$$d_{ac}(t) = d_{ac}(\infty) - [d_{ac}(\infty) - d_{ac}(0)] \left[\exp \left(\frac{-(10t)^{0.55}}{d_{ac}(0)} \right) \right]^{0.6} \quad (D.46)$$

and the particle has a diffusion coefficient, $D(t)$, given by:

$$D(t) = D(0) - \frac{d_{ac}(t) - d_{ac}(0)}{d_{ac}(\infty) - d_{ac}(0)} [D(0) - D(\infty)] \quad (D.47)$$

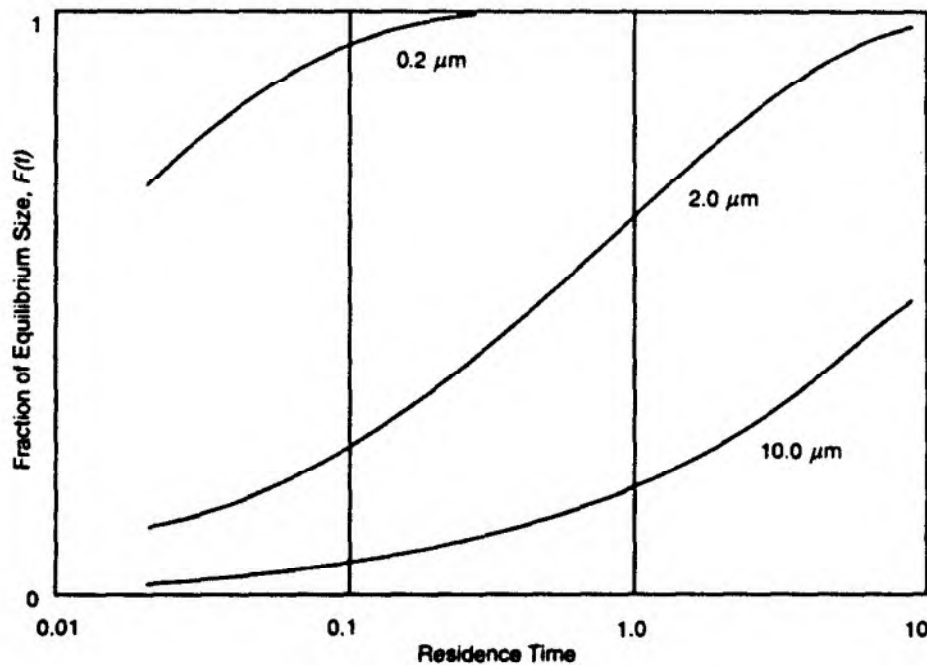


Fig. D.33. Variation of the hygroscopic growth fraction, $F(t)$, as a function of time calculated for three initial sizes of dry particle (using Eqn. D.45).

where $d_{ae}(\infty)$ is not an independent variable, but must be determined for each hygroscopic material of interest.

(D177) From a measured (or assumed) initial particle size, $d_{ae}(0)$, the equilibrium particle size, $d_{ae}(\infty)$, is calculated at 37°C and 0.995 RH (using the equations given by Ferron, 1977) for each starting (dry) particle size of a given material. For a range of particle size (such as that represented by the log-normal particle size distribution of a typical aerosol) this procedure is simplified by using a descriptive function. For example, Eqn. D.48 adequately describes the growth of pure NaCl particles within the respiratory tract solely in terms of time, t :

$$d_{ae}(t) = d_{ae}(0) + 6.28t^{0.8} \log_{10}[1 + 4.13t^{-1}d_{ae}(0)^{0.5}]\{1 - t^{-0.031} \exp[-t^{-0.3}d_{ae}(0)]\} \quad (D.48)$$

for $d_{ae}(0) > 0.2 \mu\text{m}$. The growth of smaller particles is more accurately described by the function:

$$d_{ae}(t) = 6.288d_{ae}(0)^{1.347} \quad (D.49)$$

for $d_{ae}(0) \leq 0.2 \mu\text{m}$.

D.12.3. Application of the Algebraic Model to Hygroscopic Aerosols

(D178) For comparison with the regional lung deposition curves derived by Ferron (1977), Eqns D.48 and D.49 were used with the recommended algebraic model to calculate the regional deposition values shown in Figs D.34 through D.37. These figures compare the deposition of nonhygroscopic and hygroscopic particles in the ET, BB, bb, and AI regions that is calculated for an adult male (breathing at the rate of 15 breaths min^{-1} , with a tidal volume of 750 cm^3).

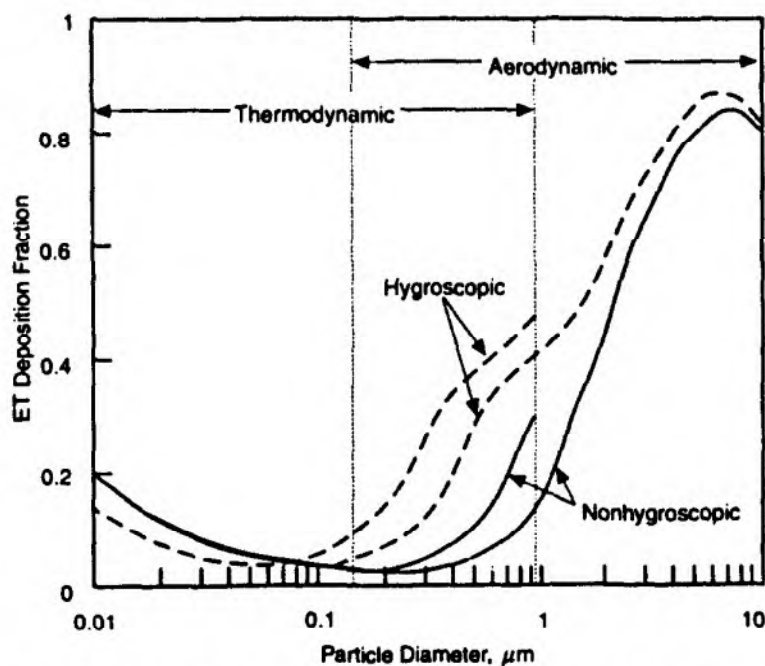


Fig. D.34. Effects of hygroscopic particle growth on extrathoracic (ET) deposition modelled for an adult male breathing through his nose at the rate of 15 breaths min^{-1} , with a tidal volume of 750 cm^3 . The solid curves show ET deposition calculated for nonhygroscopic particles, and the dashed curves the values calculated for hygroscopic particles of NaCl (plotted as a function of the "dry" particle size).

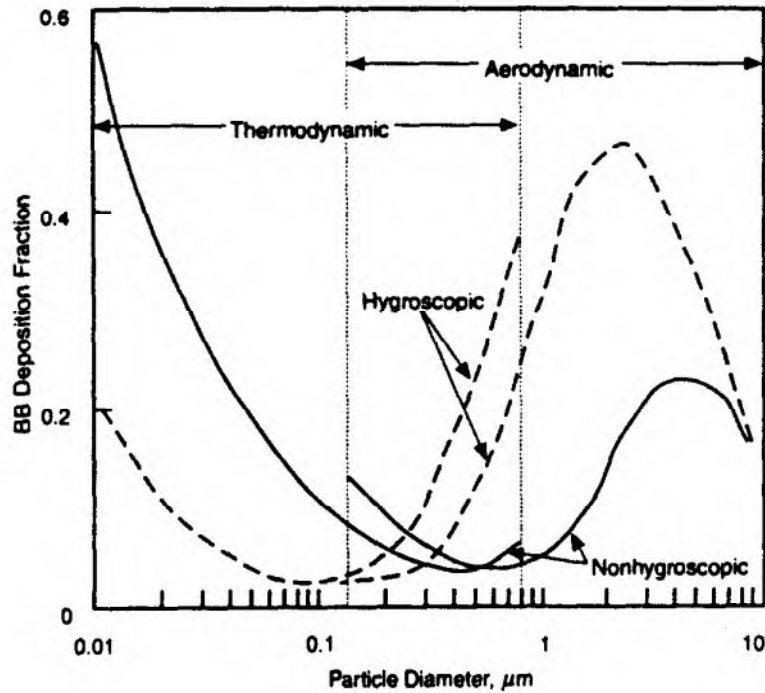


Fig. D.35. Effects of hygroscopic particle growth on tracheobronchial (BB) deposition modelled for an adult male breathing through his nose at the rate of $15 \text{ breaths min}^{-1}$, with a tidal volume of 750 cm^3 . The solid curves show BB deposition calculated for nonhygroscopic particles, and the dashed curves the values calculated for hygroscopic particles of NaCl (plotted as a function of the "dry" particle size).

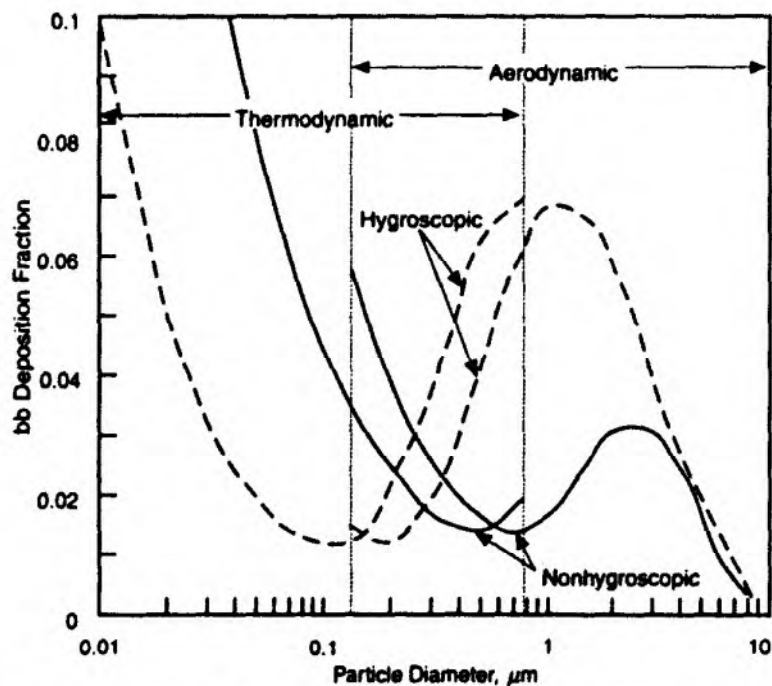


Fig. D.36. Effects of hygroscopic particle growth on bronchiolar (bb) deposition modelled for an adult male breathing through his nose at the rate of $15 \text{ breaths min}^{-1}$, with a tidal volume of 750 cm^3 . The solid curves show bb deposition calculated for nonhygroscopic particles, and the dashed curves the values calculated for hygroscopic particles of NaCl (plotted as a function of the "dry" particle size).

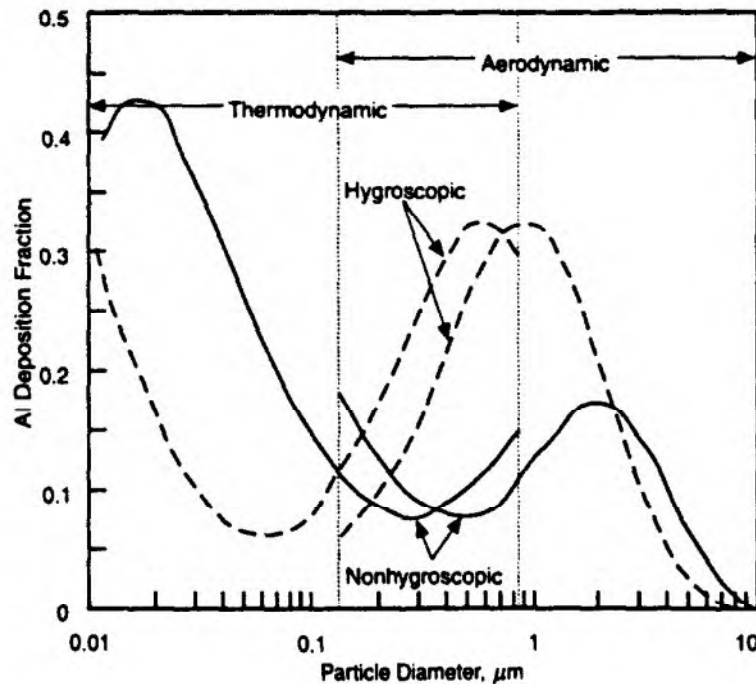


Fig. D.37. Effects of hygroscopic particle growth on alveolar-interstitial (AI) deposition modelled for an adult male breathing through his nose at the rate of 15 breaths min^{-1} , with a tidal volume of 750 cm^3 . The solid curves show AI deposition calculated for nonhygroscopic particles, and the dashed curves the values calculated for hygroscopic particles of NaCl (plotted as a function of the "dry" particle size).

D.12.4. Comparison of Modelled Lung Deposition with Experimental Data

(D179) Experimental studies of the growth of hygroscopic particles in tubes or tube systems with air at different RH have been reported by Scherer *et al.* (1979), Jähnert (1982), Martonen *et al.* (1982), Hicks and Megaw (1985), and Li *et al.* (1992). These measurements generally confirm the theoretically predicted growth rates for hygroscopic particles.

(D180) Direct measurements of the total lung deposition in human subjects have been made for NaCl aerosol particles by Blanchard and Willeke (1984) and Tu and Knutson (1984). In Fig. D.38, these data are compared with the values predicted by the algebraic model with and without hygroscopic growth of the NaCl particles into droplets.

(D181) Figure D.38 shows that the algebraic deposition model predicts a substantial change in total lung deposition when hygroscopic growth of the NaCl particles within the respiratory tract is included in the model. It is seen that minimum total deposition is predicted to occur for NaCl particles of about 0.08- μm diameter in the dry state, whereas for stable particles the minimum deposition occurs at a diameter of about 0.3 μm . The predicted shift in particle size for minimum deposition is confirmed by the experimental data. Since only a few subjects were tested in these experiments, the fact that the deposition values measured by Blanchard and Willeke (1984) are all higher than predicted may not be significant, in view of the expected variability between subjects.

(D182) The model of hygroscopic particle growth presumes a temperature of 37°C and RH of 0.995 in all regions of the respiratory tract (model compartments), except the ET region on inspiration. Ferron *et al.* (1988) suggests that an effective time delay

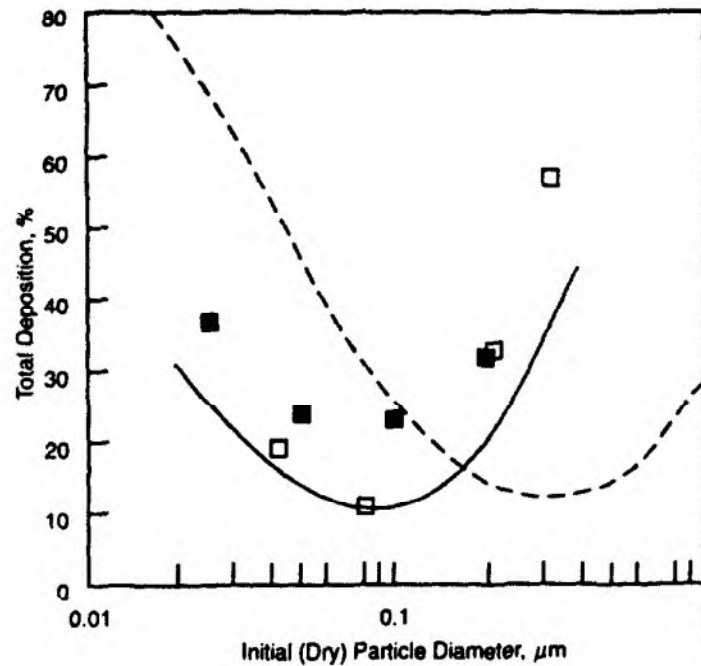


Fig. D.38. Total lung deposition of monodisperse NaCl aerosol measured in human subjects by Tu and Knutson (1984) ($\square$) and Blanchard and Willeke (1984) ($\blacksquare$) compared with values given by the algebraic model for dry NaCl particles (dashed curve) and hygroscopically grown droplets (solid curve). The data and calculated values are plotted as a function of the initial (dry) particle diameter.

of 0.1 s corrects for the temperature and humidity profiles that occur during oral inspiration. This delay in particle growth is assumed to occur entirely in the ET region, which has a transit time on the order of 0.1 s. Nasal inspiration raises the temperature and humidity of the inspired air much more rapidly. Therefore, an effective time delay of only 0.01 s is used for nasal breathing.

D.12.5. Hygroscopic Growth of Iron Oxide Particles

(D183) The function $F(t)$ (defined by Eqn. D.45) can also be used to calculate the equilibrium diameter of the incompletely dialyzed particles of iron oxide studied by Gebhart *et al.* (1988) in the respiratory tract. In this case, the particles had an average residence time of 2.0 s in the respiratory tract. For the starting size, $d_{ac}(0)$, of $2.4 \mu\text{m}$, and the estimated equivalent "deposition" size, $d_{ac}(2)$, of $3.8 \mu\text{m}$, the equilibrium size, $d_{ac}(\infty)$, is calculated to be $4.3 \mu\text{m}$. (See Table D.4.) Calculation of the amount of NaCl needed to cause the growth of a liquid layer at the particle surface $0.7 \mu\text{m}$ thick gives an estimate of 8.7% salt by mass for these iron oxide particles.

(D184) By presuming that the ratio of total salt mass to total particle mass is constant for all preparations of different particle size, the salt content of each particle is calculated from the calibrated value for $2.4\text{-}\mu\text{m}$ iron oxide particles.

(D185) Iterative computation gives the equilibrium aerodynamic diameter for other starting particle sizes, using the equations given by Ferron (1977). Because $d_{ac}(\infty)$ depends on the composition and geometry of the particle, an array of equilibrium sizes is associated with a range of initial particle size for each aerosol. As for pure NaCl discussed in Paragraph D177, a descriptive function was devised from the computed values given in Table D.4:

$$d_{ac}(t) = d_{ac}(0) + \log_{10}[1 + 5.5t^{0.5}d_{ac}(0)^{0.1}]\{1 - \exp[-d_{ac}(0)]\}. \quad (\text{D.50})$$

Table D.4. Fraction of equilibrium particle size, $F(t)$, attained by hygroscopic iron oxide particles studied by Gebhart *et al.* (1988) calculated as a function of residence time in the respiratory tract

Residence time	0.2 s			1.0 s			2.0 s			4.0 s			Equilibrium growth factor ^a
	$d_{e0}(0) (\mu\text{m})$	$d_{e0}(0.2) (\mu\text{m})$	$F(0.2)$	$d_{e0}(1.0) (\mu\text{m})$	$F(1.0)$	$d_{e0}(2.0) (\mu\text{m})$	$F(2.0)$	$d_{e0}(4.0) (\mu\text{m})$	$F(4.0)$	$d_{e0}(\infty) (\mu\text{m})$			
0.1	0.1	0.09	1.00	0.09	1.00	0.09	1.00	0.09	1.00	0.09	0.93		
0.2	0.2	0.24	0.99	0.24	1.00	0.24	1.00	0.24	1.00	0.24	1.18		
0.3	0.3	0.40	0.95	0.41	1.00	0.41	1.00	0.41	1.00	0.41	1.36		
0.4	0.4	0.57	0.89	0.59	1.00	0.59	1.00	0.59	1.00	0.59	1.47		
0.5	0.5	0.72	0.83	0.77	0.99	0.77	1.00	0.77	1.00	0.77	1.54		
0.6	0.6	0.87	0.77	0.95	0.97	0.95	0.99	0.96	1.00	0.96	1.59		
0.7	0.7	1.02	0.71	1.12	0.95	1.14	0.99	1.14	1.00	1.14	1.63		
0.8	0.8	1.15	0.67	1.29	0.93	1.32	0.98	1.33	1.00	1.33	1.66		
0.9	0.9	1.28	0.62	1.46	0.91	1.50	0.97	1.51	0.99	1.52	1.68		
1.0	1.0	1.41	0.58	1.62	0.88	1.67	0.96	1.69	0.99	1.89	1.70		
1.1	1.1	1.53	0.55	1.77	0.86	1.84	0.94	1.88	0.98	1.70	1.72		
1.3	1.3	1.77	0.49	2.08	0.81	2.17	0.91	2.23	0.97	2.26	1.74		
1.5	1.5	2.00	0.44	2.36	0.76	2.49	0.87	2.58	0.95	2.64	1.76		
1.7	1.7	2.23	0.40	2.63	0.71	2.80	0.84	2.92	0.93	3.01	1.77		
2.0	2.0	2.56	0.36	3.03	0.66	3.24	0.79	3.41	0.90	3.57	1.79		
2.2	2.2	2.77	0.33	3.28	0.62	3.52	0.76	3.73	0.87	3.95	1.79		
2.4	2.4	2.99	0.31	3.53	0.59	3.80	0.73	4.03	0.85	4.32	1.80		
2.7	2.7	3.31	0.28	3.89	0.55	4.19	0.68	4.48	0.82	4.88	1.81		
3.0	3.0	3.62	0.25	4.24	0.51	4.58	0.65	4.91	0.78	5.45	1.82		
3.5	3.5	4.14	0.22	4.81	0.46	5.20	0.59	5.60	0.73	6.38	1.82		
4.0	4.0	4.65	0.20	5.37	0.41	5.80	0.54	6.26	0.68	7.32	1.83		
4.5	4.5	5.17	0.18	5.92	0.38	6.38	0.50	6.89	0.64	8.26	1.84		
5.0	5.0	5.68	0.16	6.46	0.35	6.95	0.46	7.51	0.60	9.20	1.84		
5.5	5.5	6.18	0.15	6.99	0.32	7.50	0.43	8.11	0.56	10.13	1.84		
6.0	6.0	6.69	0.14	7.52	0.30	8.06	0.41	8.70	0.53	11.07	1.85		
6.5	6.5	7.20	0.13	8.04	0.28	8.60	0.38	9.28	0.50	12.01	1.85		
7.0	7.0	7.70	0.12	8.56	0.26	9.14	0.36	9.85	0.48	12.95	1.85		
7.5	7.5	8.21	0.11	9.08	0.25	9.67	0.34	10.41	0.46	13.89	1.85		
8.0	8.0	8.71	0.10	9.59	0.23	10.20	0.32	10.97	0.43	14.82	1.85		
8.5	8.5	9.21	0.10	10.11	0.22	10.73	0.31	11.52	0.42	15.76	1.85		
9.0	9.0	9.72	0.09	10.62	0.21	11.25	0.29	12.06	0.40	16.70	1.86		
9.5	9.5	10.22	0.09	11.13	0.20	11.78	0.28	12.60	0.38	17.64	1.86		
10.0	10.0	10.72	0.08	11.65	0.19	12.30	0.27	13.14	0.37	18.58	1.86		

^a Ratio of equilibrium aerodynamic diameter to the starting aerodynamic diameter.

(D186) Aerosols with other salt contents or particle geometries (such as different core density or composition) will have somewhat different descriptive functions than Eqn. D.50. However, once an appropriate function has been developed for a particular material, since this is a function only of time, t , it can be used directly in the algebraic deposition model to calculate the hygroscopic growth in particle size in each compartment of the model.

D.13. Reference Aerosol and Exposure Parameters

(D187) Setting aside anatomical and physiological factors, the regional deposition of activity in the respiratory tract from an inhaled aerosol depends on one or both of the AMAD and/or the AMTD. Whether regional deposition is determined primarily by the AMAD or the AMTD depends in turn on whether the bulk of the aerosol activity is carried by particles in the aerodynamic or thermodynamic size ranges, respectively. For spherical particles of unit density, the transformation between aerodynamic and thermodynamic dominance occurs for a particle diameter of about $0.5\ \mu\text{m}$. For these particles, the overall lung deposition is at an approximate minimum when neither the aerodynamic nor the thermodynamic deposition process is very efficient. The precise particle size for which this minimum occurs depends on the breathing rate, on anatomical factors for the subject, and on the region of the respiratory tract considered. (See Chapter 5, Figs 10 through 15.) In general, though, spherical particles of unit density that are larger than $1\text{-}\mu\text{m}$ diameter are deposited primarily by aerodynamic processes, and those smaller than $0.1\text{-}\mu\text{m}$ diameter primarily by the thermodynamic process of diffusion.

(D188) In practice, however, it is rare for the material of concern to consist of spherical, unit density particles. Most radioactive aerosols are composed of particles of more complex shape, with mass density significantly greater than unity. Although, in theory, these additional aerosol parameters and the geometric standard deviation of the particle size distribution could be measured, this is rarely a practical possibility. Therefore, in order to relate aerosol exposures by inhalation to lung and other tissue doses, it is usually necessary to make plausible assumptions about the "typical" values of the physical aerosol parameters that determine lung deposition.

(D189) The practical significance of particle shape and mass density is that these factors determine the relationship between the aerodynamic and the thermodynamic diameter. Thus, for example, a particle of uranium oxide that has an aerodynamic diameter of $1\ \mu\text{m}$ and a mass density of about $10\ \text{g cm}^{-3}$ would have a thermodynamic diameter of approximately $0.3\ \mu\text{m}$, where the precise value of the thermodynamic diameter would depend on the particle's shape. Deposition efficiencies for such a particle would include a significant thermodynamic component.

D.13.1. Aerodynamic Shape Factor

(D190) In practice, aerosol particles can be divided into two general shape categories, as either "fibres" or "particulates." Fibrous aerosols are usually produced by disturbing a fibrous material. There are special considerations associated with the deposition, clearance, and pathological effects of fibres that are not addressed in this report, but have been addressed elsewhere (for examples see: Timbrell, 1982; Asgharian and Yu, 1989; Wehner and Felton, 1989; Balashazy *et al.*, 1990).

(D191) The particles that comprise a "particulate" aerosol are generally not spheres, so they have an aerodynamic shape factor greater than unity. Typical values of this shape factor range from 1.1 to 1.9, for a wide range of materials (Mercer, 1973). In the absence of specific information about the aerosol of concern, the value recommended to be used as a reference, or typical, aerodynamic shape factor is 1.5.

D.13.2. *Particle Density*

(D192) As shown by Eqn. D.13, for a particular aerodynamic diameter, d_{ac} , the ratio of aerodynamic shape factor, χ , to the particle density, ρ , determines the thermodynamic equivalent diameter.

(D193) Particle density varies over a wide range that can have substantial influence on the thermodynamic size of particles in relation to their aerodynamic size. The chemical composition, crystalline structure, and hydration all enter into the mass density. A reference value of 3 g cm^{-3} is recommended because it is typical of many natural materials.

D.13.3. *Typical Activity Median Aerodynamic Diameter*

(D194) Particle diameter is the most important and most widely ranging variable of the aerosol parameters. The particle size distribution is determined by the mechanism of aerosol generation and the available time for coagulation or gravitational settling. In the simplest situations, these processes jointly result in a single mode of log-normal size distribution, which can be characterised by a mean or median particle diameter and geometric standard deviation (GSD). If there are two or more mechanisms involved in generating an aerosol, the size distribution can be bimodal, or even multimodal, as is found for the normal particulate burden of the atmosphere (Davies, 1974).

(D195) For radiological protection purposes, in the absence of more specific information, it is generally assumed that the radioactive material of concern is distributed log-normally as a function of particle aerodynamic diameter (TGLD, 1966).

(D196) For occupational exposure settings, a reference AMAD of $5 \mu\text{m}$ is recommended as being representative. (See, for example, Stevens, 1969.) For exposures in the general environment, a smaller value of $1\text{-}\mu\text{m}$ AMAD may be appropriate.

D.13.4. *Typical Aerosol-Size Dispersion*

(D197) The dispersion in particle size of an aerosol is expressed by the GSD. This may vary from unity, for example for freshly formed single ions of the short-lived radon progeny, to about 2–2.5 for single log-normal modes of multimodal, aged aerosols (Davies, 1974).

(D198) For ultrafine aerosols produced when vapours condense, the GSD will often depend on the age of the aerosol, and the degree of growth attained. This process results in a GSD of some intermediate value between unity and the upper bound of about 2.5. In the absence of specific knowledge of the GSD of particle size in an aerosol of interest, this parameter can be estimated by Eqn. 16 given in Section 5 (NRC, 1991). The form of this expression is shown in Fig. D.39.

(D199) As noted by the Task Group on Lung Dynamics (TGLD, 1966), the precise value of the GSD has less impact on lung deposition (and thus on calculated doses) than the median particle size of a radioactive aerosol. However, the assumption of an unrealistically high value for the GSD will bias the resulting estimate of lung deposition.

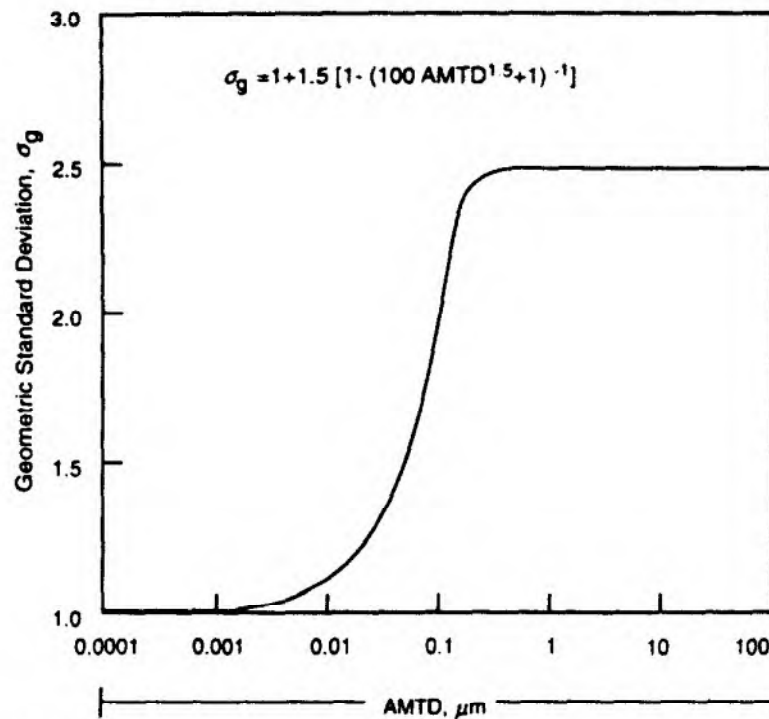


Fig. D.39. Variation of geometric standard deviation of particle size with the activity median diameter of an aerosol that is assumed in modelling aerosol deposition in the respiratory tract.

For example, values of the GSD of 4 or more are sometimes assumed when cascade impactor results indicate an overly wide spread in particle size. A very broad spread in particle size is more likely to arise from two or more distinguishable aerosol particle populations, each having a moderate GSD.

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