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Development of a model for human and rat airway particle deposition: implications for risk assessment

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Preface

Computer models have proven to be important tools to analyse PM dosimetry. Because these models use an explicit set of equations which describe real-life processes, either empirically or based on first principles, they are especially suited to analyse effects of scenarios, such as particulate exposure control strategies. In a review paper by RIVM (Freijer *et al.*, 1997) modelling of dosimetry has been evaluated for possible use at RIVM. In the above-mentioned study several models are discussed, among which the ICRP dosimetry model. The ICRP model may be successfully used to analyse dosimetry in healthy humans, but is not suited to analyse dosimetry in animals and people with airway diseases or breathing abnormalities. Also, the model does not provide insight in the variability of deposition within the lung. One of the main conclusions of the explorative study was that there is a need at RIVM and possible else where for a detailed dosimetry model that can be used in fields of exposure and risk analysis and to perform inter and intra species extrapolation of concentration-dose-effect relationships.

At CIIT scientists have extensive experience in the development of empirical and deterministic models for the deposition of particles in the respiratory tract. This was the opening for a RIVM-CIIT collaboration starting in January 1998. The intention of this collaboration was to achieve a technology transfer on the use of various computer-based dosimetry models for animals and humans enabling the assessment of exposures to PM and their impact on particulate dose to critical regions of the lung. The collaborative project was financed by Chemical Industry Institute of Toxicology (CIIT), the Ministry of Housing, Spatial Planning and the Environment (VROM), and The National Institute of Public Health and the Environment (RIVM). At the National Institute of Public Health the above-described issues have been identified as study areas in order to characterise the complete source-effect-risk assessment chain for ambient PM.

Contents

Samenvatting

Fijnstof is een verzamelbegrip voor zeer kleine deeltjes die zweven in de lucht en die met het blote oog niet zichtbaar zijn. Het gaat om alle deeltjes kleiner dan 10 µm, ook wel aangeduid als PM10. De chemische samenstelling van PM10 is heel complex en verschilt van dag tot dag. Deze deeltjes ontstaan deels door verkeer, industrie, energie opwekking, landbouw maar zijn ook van natuurlijke oorsprong zoals zeezout en opwaaiend stof. Expositie aan PM10 wordt geassocieerd met toename aan cardiopulmonaire aandoeningen en (vervroegde) sterfte. Er is echter nog onvoldoende bewijs dat PM10 echt deze effecten veroorzaakt en welke chemische of biologische stoffen daarvan dan verantwoordelijk zijn. Het is belangrijk om aan te kunnen geven welke de bronnen zijn die deze schadelijke stoffen in de lucht brengen. De overheid kan met deze informatie gericht beleid voeren om de uitstoot van bepaalde stoffen te verminderen. Omdat verder terugdringen van de niveaus van luchtverontreiniging grote maatschappelijke kosten met zich mee brengt is het van essentieel belang vast te stellen wat de causale factor(en) is (zijn), welke de in bevolkingsonderzoek waargenomen gezondheidseffecten kunnen verklaren. Alleen dan kan de bron-tot-effect keten voldoende en adequaat worden beschreven om een gericht kosten-effectief bestrijdingsbeleid te formuleren. Onderdeel van deze keten is het schatten van de geïnhaleerde dosis van fijnstof op basis van de uitwendige concentratie en fysische karakteristieken van het fijnstof. In dit rapport wordt een beschrijving gegeven van een recent door het Chemical Industry Institute of Toxicology (CIIT) en het RIVM ontwikkelt computerprogramma[1] MPPDep (Multiple Pathway Particle Deposition model). Het programma is grotendeels gebaseerd op in de literatuur beschreven ‘multiple path’ modellen voor aerosolen, wat als belangrijk voordeel ten opzichte van bestaande modellen heeft dat het gebruik maakt van de morfologische gegevens van een individu. Het omvat zowel modules voor het bepalen van de gedeponeerde dosis in zowel de mens als in proefdieren (rat). De modellen zijn in staat om op basis van bestaande morfologische en functionele gegevens de dosis en flux in een bepaald segment of regio van de luchtwegen vast te berekenen. Daarnaast kunnen binnen een zekere range de functionele parameters als ademhalingsfrequentie worden aangepast om hiermee bepaalde luchtwegaandoeningen te kunnen simuleren. Een andere belangrijke modificatie is het toevoegen van functies voor de inhaleerbaarheid van aerosolen, het invoeren van gegevens over poydisperse aerosolen. Het softwarepakket is gebruikersvriendelijk door toepassing van een grafische interface en geschreven voor een MS-Windows 9x/NT. Het model kan gebruikt worden voor het onderzoeken van verschillen in doses en depositie tussen mensen en proefdieren (rat) voor extrapolatie doeleinden en risk assessment. Ook het effect van ademhalingsgedrag op de depositie van aerosolen (rust versus activiteit, oud versus jong, ziek versus gezond) of de invloed van de grootte van een fijnstof deeltje op de gedeponeerde massa kan hiermee in kaart worden gebracht. In de nabije toekomst zal dit model verder moeten worden uitgebreid met modules voor klaring en retententie van de deeltjes in de luchtwegen.

[1] Het MPPDEP computerprogramma (RIVM Publicatie 650010 019)kan bij het RIVM worden besteld. Neem contact op met de Bureau Rapporten Beheer van het instituut, postbus 1, 3720 BA Bilthoven, fax: 31 - 30 - 274 4404; e-mail: rivm.reports@rivm.nl

Abstract

Particulate matter is a collective term for very small-suspended particulates in ambient air that cannot be observed by the human eye. They are also referred to as PM10, particles with an aerodynamic diameter smaller than 10 µm. The chemical composition of PM10 is complex and varies from day to day and they can origin from traffic, industry, energy generation, and agricultural activities but also from natural sources like sea salt and resuspended dust. Exposure to PM10 has been associated with an increase in cardiopulmonary diseases and mortality. However, there is still lack of (causal) evidence to prove that PM10 really is responsible for causing these effects and what chemical or biological components can be held responsible for these effects. Policy makers and governments will need information on the causally related agents to outline a policy for reducing emissions of certain particulates. Since this will go together with an increase in the cost for the general society, it is essential to have a good description of the whole source-health effect chains with a well-formulated targeted cost-benefit analysis. Part of the source-effect chain is the estimation of inhaled dose based on exposure concentrations and physical characteristics of the particles. This report described a recently by Chemical Industry Institute of Toxicology (CIIT) and the RIVM developed software package[2] MPPDep (Multiple Pathway Particle Deposition model), for airway particle deposition. The program is largely based on in the literature described multiple path models for particle deposition and morphological data, which is a major advantage above the already existing models. It encompasses both modules for human and experimental animal (rat) calculations. The software is capable to calculate the dose ratio and flux of particulates in certain segments or regions within the airways. By adjusting the functional parameters like breathing frequency or tidal volume, the influence of certain respiratory diseases on particle deposition can simulated. Another important modification is the addition of functions for the inhalability of particulate matter and the option to calculate the deposition of both mono and poly disperse aerosols. The software package is user-friendly by the application of a graphical interface for a MS Windows 9x/NT computer operating system. The model can be used to investigate the differences in doses and deposition between humans and experimental animals for extrapolation purposes and risk assessment. Also, the effect of the breathing pattern on the deposition of particles (resting versus exercise, old versus young, healthy versus diseased) or the impact of the size (distribution) of particulate matter on the deposited dose (rate) can be mapped. In the near future, the model has to be extended with modules for clearance and retention of particles in the airways.

[2] The MPPDep software (RIVM Publication 650010 019) can be obtained from the Dutch National Institute of Public Health and the Environment. Contact the Bureau Rapporten Beheer of the institute at P.O. Box 1, 3720 BA Bilthoven, telefax: +31 - 30 - 274 4404; e-mail: rivm.reports@rivm.nl

1. Introduction

Epidemiological time series analyses have indicated that associations exist between PM levels and daily mortality. PM concentrations are often expressed as PM_{10} or $PM_{2.5}$ concentration levels, which are surrogates for a broad class of chemically and physically diverse particles of varying size. A better understanding of PM air quality and its effects on health is needed to assess the source-effect chain for PM and to devise appropriate risk reduction strategies (Fig. 1). This includes research on what specific size or chemical fractions are responsible for health effects and the variability of dose and health effects in the population.

An important component in the source effect chain for inhaled particles is the link between concentration of particles in the air and the doses to various regions of the respiratory tract. This relationship is not a simple one, because many processes influence the apparent concentration-dose relationship, such as transport through the lung, deposition by impaction, sedimentation, and diffusion, interaction between PM and tissues, and clearance. Lung morphometry, structure of the extrathoracic regions, breathing pattern, and particle properties effect the local conditions in the respiratory tract for deposition, and show a large variation within species but also between species.

Four important topics in dosimetry have been addressed in the last decades that have to be studied in order to assess the variability in concentration-dose relationship.

a. Interspecies differences

Deposition of PM in the respiratory tract varies between animals when exposed to identical aerosols. This is because of differences in breathing pattern (breathing frequency and tidal volume), lung morphometry (lung volume, branching, and symmetry) and structure of the upper respiratory tract between species, which influences the local conditions at sites where particle deposition occurs. At equivalent exposure conditions (ambient concentration and particle diameter) deposition in humans and animals may differ significantly. Knowledge on this difference is critical for making interspecies dosimetric adjustments when extrapolating animal toxicological results to humans (Jarabek et al., 1989) and for identifying human exposure scenarios that would results in comparable doses at critical target sites established in animal toxicological studies.

b. Intraspecies differences

Even within one species differences in deposition of PM can be expected, due to differences in level of exercise (which has effects on the breathing rate), age, disease, and the presence of breathing abnormalities. When evaluating the exposure of populations to PM, knowledge on these differences is imperative, because only then it becomes apparent what physiological conditions are connected with the highest doses.

c. Distribution of deposition dose through the lung

The lung is a highly non-symmetric structure, which causes deposition of PM not only to vary between airway generation, but also between each path and acinar end. In order to assess the risk from exposure to PM and its health effect one is especially interested at what sites the highest dose occurs, and how this dose relates to the average dose to the whole lung, or generation.

d. Experimental study design and risk analysis

Knowledge on differences in the concentration-dose relationship can improve both explorative experimental studies and risk analysis. When dosimetry in experimental subjects can be regarded as *a priori* knowledge exposure conditions and duration can be adapted to simulate realistic human dosing scenarios in these settings. For risk analysis it becomes possible to identify the distribution of doses in the population at a given concentration level, and to identify the physiological and morphological factors causing these differences. Groups with relatively high risks for being exposed by doses at target tissues can thus be identified.

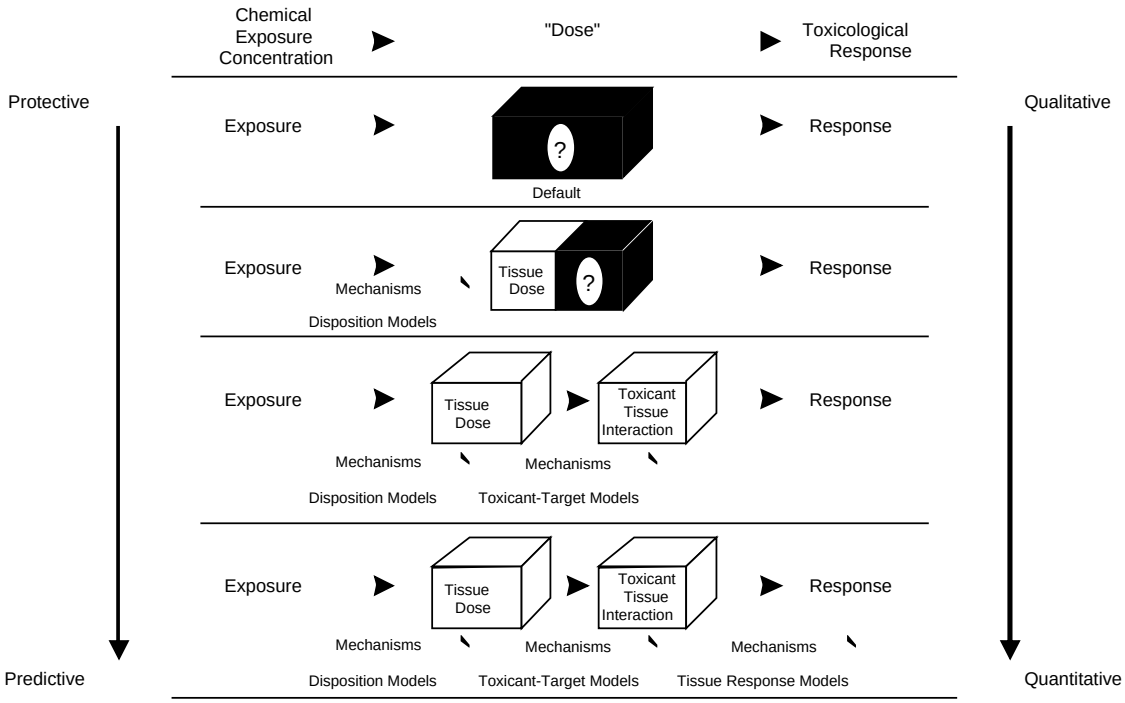

Fig. 1 Concepts of concentration-dose-effect relationships
(US EPA, 1996)

2. Methodology

The model, which was used in the current project, is based on the work on a multiple path model for particle deposition in the rat by Anjilvel and Asgharian (1995). The mathematical approach of the model for each individual path segment is similar to that of the single path model (Yu, 1978). The major advantage of a multiple path model is that it makes use of the data from lung airway measurements and thus incorporates asymmetric features of actual lung geometries. It calculates deposition for every airway of the lung structure. The multiple path model allows deposition calculations among different alveolar groups, and thus, it can predict the dose distribution in this region. In the project this model was extended. The following major features were added:

- The model is now suited to treat the lungs at different levels of detail: (i) as a single path model for a symmetric lung; (ii) as a multiple path model for the upper branches with symmetric structures for each lung lobe, and (iii) as a full multiple path lung architecture. The treatment of the architecture is generic, such that data on new species can easily be added in future. Currently, the theory for a single path model for humans (Yeh and Schum, 1980), a 5-lobe model for humans (Yeh and Schumm, 1980) and a multiple path model for the rat (only) is available (Raabe et al., 1975)
- Functions for inhalability have been added for rat and human
- New functions for nasal and oral deposition for rat an human have been added.
- The model was made suitable for polydisperse aerosols with lognormal particle distributions as well as for monodisperse aerosols.
- The model can calculate deposition rates for repeated sets of input data. This enables evaluation of multiple particle diameters as well as the evaluation of 24 hr activity patterns.
- New design of computer code in a modular structure to allow future additions.
- Connection to a windows 95/NT user interface, which allows the user to alter a large number of input parameters and to display he results graphically as well as to generate detailed reports of output. This feature is especially interesting for interactive working, which is desired for calculating different scenarios and to optimize experimental designs. In both cases the user wants to review different options and reach his goals iteratively.

A full description of the model is presented in chapter 4.

3. Model description

Construction of models for airflow and deposition of particles in animal and human lungs has required idealization of lung morphometry to varying degrees. The most commonly used among such models treat the airway branching structure in rat and human lungs as symmetric at each generation (Weibel, 1963; Yeh *et al*., 1979). Airway branching is assumed to be dichotomous. Each airway branch is assumed to be cylindrical and straight and is characterized by a length, diameter, the angle the airway makes with its parent, and a gravity angle. This allows simulating average regional deposition but does not provide estimates for localization or inhomogeneities in deposition patterns. The lower airways of the human lung are reasonably well characterized in a symmetric fashion. However, there are major asymmetries in the upper few airways of the human thoracic cavity that lead to different deposition patterns in these airways as well as to differences in the apportionment of air flow to the different lung lobes. Because of its monopodial nature, the rat lung is highly asymmetric, and a typical path characterization is expected to lead to significant errors in predictions of deposition.

3.1 Multiple vs. single path method

The here presented Multiple Path Particle Deposition model (MPPDep) is based upon a multiple-path method that is capable of incorporating all the asymmetries in the airway branching structure if the morphometric details are available. Detailed morphometric mapping up to the level of the terminal bronchioles was available for the Long Evans rat. For the human lung, on the other hand, such detailed data are not yet fully available, requiring a combination of multiple- and single-path analyses of the airflow.

In the Single-Path Model a single symmetric tree represents the lung geometry. Such a construction leads to a "typical" or "single" path for airflow from the trachea to the alveolar region. The deposition results provided by such a model are averages for a particular generation of the airway structure. The MPPD model uses the symmetric structure provided in the compilation by Yeh (1980) for the human lung. The deposition results are very similar to those obtained by Yu and Diu (1982).

The multiple-path formalism (Anjilvel and Asgharian, 1995) incorporates asymmetry in the lung branching structure and calculates deposition at the individual airway level by using detailed information on lung geometry. Morphometric information at such a level of detail was available for the rat lung, where the entire set of airway measurements collected by Raabe et al. (1975) for the 2404 conducting airways of a Long Evans rat have been used. A symmetric 8-generation model acinus was attached to the end of each terminal bronchiole to model the acinar region in the rat lung (Yeh *et al*., 1979; Anjilvel and Asgharian, 1995). While the lung measurements correspond to that of an adult Long Evans rat, one may develop

approximate models for other rat strains using the same morphometry. This can be done by uniformly scaling the total Long-Evans lung volume to correspond to the functional residual capacity of the other strain. The airway volumes are scaled uniformly to a specific functional residual capacity.

For the human lung, a full multiple-path approach could not be implemented due to the lack of complete conducting airway measurements. Therefore, the option to use either a symmetric geometry or limited multiple-path geometry has been provided for the human. The limited multiple-path geometry for the human consists of characterizing the asymmetry completely at only the level of the major segmental bronchi leading to the five lobes of the lung. Each lung lobe is then represented as a separate symmetric tree and deposition is simulated at each generation within the individual lobes. The symmetric representations for the whole lung as well as the lobar data were obtained from Yeh and Schum (1980). To use these representations for individuals with specific lung capacities, the airway volumes of the Yeh and Schum models are scaled uniformly to the functional residual capacity of the individuals.

3.2 Breathing cycle

The breathing cycle is assumed to consist of an inspiratory and an expiratory stage, which may have a different duration. The model does therefore allow asymmetric breathing patterns. In each stage flow rate is assumed to be constant with time. At an airway entrance, uniform flow is assumed to be at the average parabolic velocity for a given volumetric flow rate at that point. The flow rate at this point is determined to be proportional to the lung volume distal to it. Such a rule for flow partitioning between a parent and daughter airways allows for inclusion of the expansion and contraction of the lung during inspiration and expiration. This dynamic change of volume is assumed to be uniform across the lung, including the tracheobronchial and alveolar airways.

3.3 Deposition mechanisms in the lung

The predominant mechanisms for deposition of particles are diffusion and sedimentation within an airway and impaction at the airway bifurcations. Deposition by interception is not considered to be relevant for spherical particles between 0.01 and 10 microns. Aerosol concentration at either end of an airway is determined using numerically derived efficiencies for deposition that, depending on the mechanism of deposition, are functions of the air velocity, airway dimensions, bifurcation angle, gravity angle and particle density. The specific functional formulation for each mechanism may be obtained from Cai and Yu (1988) for impaction in rat airways, Zhang et al. (1997) for impaction in human airways, Ingham

(1975) for diffusion, and Wang (1975) for sedimentation. The mass entering or exiting an airway for a given duration of time is calculated from the aerosol concentration and the flow rate at either end of the airway. The aerosol concentration within an airway is interpolated from the concentration values at the airway ends and integrated over the airway to obtain the remaining mass at the end of inspiration. The deposition fraction for each airway is then determined using the principle of mass balance. The calculation for exhalation is similar except that the initial mass at the start of the expiratory cycle is not zero for any airway, and is a function of time. Deposition fractions for individual airways are calculated after accounting for the filtering effect of the airways previously traversed by the air front, and then extended to obtain regional and overall respiratory tract deposition fractions. The regional and overall deposition fractions incorporate the filtering effect of the head.

3.4 Deposition efficiency in nasal and oral regions

Efficiencies for deposition by impaction in the head region are as given by Zhang and Yu (1993) for rats and by Rudolf *et al.* (1990), Rudolf *et al.* (1986) and Stahlhofen *et al.* (1989) for human nasal and oral breathing. Deposition by impaction in the mouth during expiration is considered to be negligible, while in the nose, deposition efficiencies during expiration and inspiration are considered to be the same. Diffusion deposition in the head during inspiratory and expiratory breathing is also included using efficiency functions for the human nose (Swift *et al.*, 1992) and mouth (Cheng *et al*., 1993), and for the rat nose (Cheng *et al.*, 1990). In the human, head deposition during mouth breathing is considered to occur primarily in the larynx, while during nose breathing both nasopharyngeal and laryngeal deposition is considered to occur (ICRP, 1994). The deposition efficiency used for modeling laryngeal deposition is the same as that used for deposition in the oral cavity, as suggested by ICRP (1994). There is no aerosol deposited in the rat mouth, as rats are obligatory nose breathers. For a comprehensive discussion of efficiency functions reported in the works cited above for deposition in the human head (ICRP, 1994). Partitioning of airflow for combined nose and mouth breathing (oronasal breathing) are as given by Niinima et al (1981).

3.5 Inhalability

While deposition of coarse mode particles increases significantly with particle size because of impaction either in the head or tracheobronchial (TB) region, increased inertia poses a limitation to the ability of particles to enter the head region. This reduction in the inhaled fraction of the aerosol with increasing particle sizes may be significant for nasal breathing and more so for rats than for humans. An inhalability adjustment is made to the inhaled concentration using empirical curves derived by Menache et al. (1995).

4. Model capabilities and user interface

The computer algorithms in the software calculate the deposition of monodisperse and polydisperse aerosols in the respiratory tract of rats and humans for particles ranging from ultrafine (0.01 microns) to coarse (10 microns) sizes. The models are based upon the single-path and multiple-path methods for tracking air flow and calculating aerosol deposition in the lung. The single-path method calculates deposition for a typical path, while the multiple-path method is capable of incorporating the asymmetry in lung structure and providing lobar specific and airway specific information. Within each airway, deposition is calculated using theoretically derived efficiencies for deposition by diffusion, sedimentation and impaction within the airway or airway bifurcation. Filtration of aerosols by the head is determined using empirical efficiency functions. A detailed description and literature references are presented in section 5.

The model has been connected to a user-friendly interface that works under the MS Windows 95/98 and NT operating systems. The interface employs menus and dialog boxes for input arrangement (an example is displayed in Fig. 2). The program has a detailed help manual with five tutorials and explanations on its algorithms and operation. The user-interface enables the user to:
1. specify different combinations of input parameters
2. generate comprehensive output files
3. display different graphical presentations of the results
4. save input settings for later use.

A detailed overview of the input and output option of the software is provided in Appendix 1. Some examples of the output are displayed in Figs 2 to 5. An explanation of each input section is given below:

4.1 Lung morphometry

Two options are provided for idealizing the geometry of the human lung. One uses a symmetric geometry for the whole lung. The second option captures the asymmetry in the lobar structure, but treats the geometry within each lung lobe in a symmetric fashion. Both models are constructed using morphometric data compiled by Yeh and Schum (1980). The rat lung is modeled using a multiple-path geometry that captures the complete asymmetry of the tracheobronchial (TB) tree as provided by Raabe et al. (1975) and that represents the acini at the end of each terminal bronchiole as an 8-generation symmetric tree.

The user provides as input particle characteristics, the breathing scenario and breathing parameters, the functional residual capacity (FRC), and the upper respiratory tract (URT) volume. A set of computer files giving the lung geometries are included with the software package but these files cannot be modified by the user.

Results for the deposition fraction and mass deposited are provided in graphical and text formats. Simulation results are provided for total, regional and lobar deposition, and as a function of airway generation number. An advanced feature that fully exploits the features of the multiple-path formalism is provided for the rat lung. This feature provides a histogram of the frequency distribution of the acini as a function of the deposition fraction per acinus.

4.2 Aerosols

Calculations may be done for monodisperse or lognormally distributed polydisperse aerosols. Further, the calculations may also be carried out for monodisperse particle sizes ranging from the ultrafine through coarse, so that a plot of deposition vs. particle size may be obtained.

4.3 Breathing patterns

Various breathing patterns may be simulated: endotracheal, nasal, oral, and combined nasal and oral (oronasal). The exposure scenario may be constant or variable. For the variable scenario, the user may specify different breathing patterns either on an hourly basis during the day or activity patterns for variable time durations. Adjustment for inhalability of the particle is also included as an option.

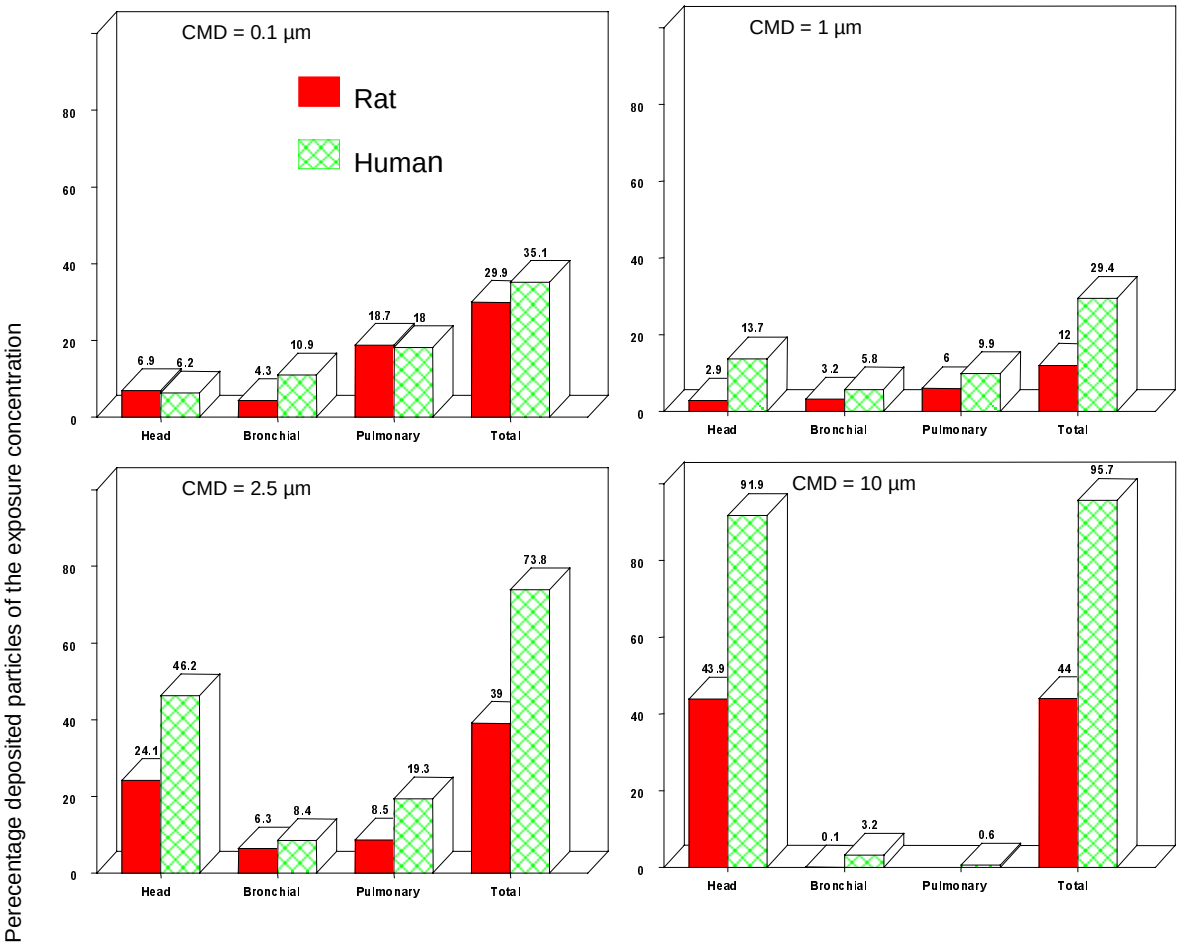

Fig. 2 Example of simple output of deposition percentage for a monodisperse aerosol (density 1.0 g cm^{-3}) adjusted for inhalability and assuming. Input for the human model: tidal volume 750 ml and a breathing frequency of 20 min^{-1}. Input for the rat model: tidal volume 1.5 ml and a breathing frequency of 130 min^{-1}.

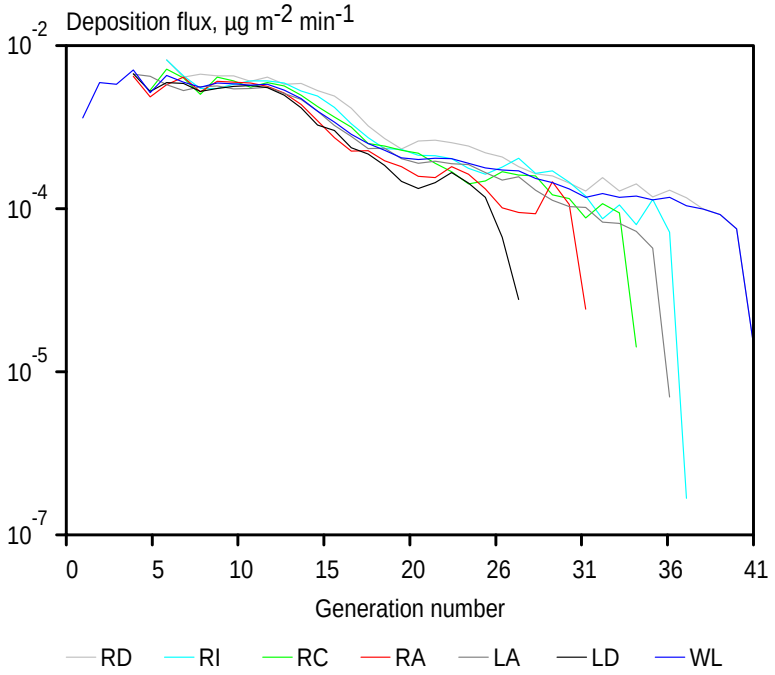

Fig. 3 Examples of deposition fraction and flux vs. generation number for the rat multiple path lung model with nasal breathing and inhalability adjustment. Tidal volume 2.1 ml and breathing frequency 102 min^{-1}; monodisperse aerosol with particles diameter 0.135 µm and density 4.1 g cm^{-3}. Abbreviations: RD = right diaphragmatic, RI = right intercostal, RC = right cardiac, RA = right apical, LA = left apical, LD = left diaphragmatic, WL = whole lung

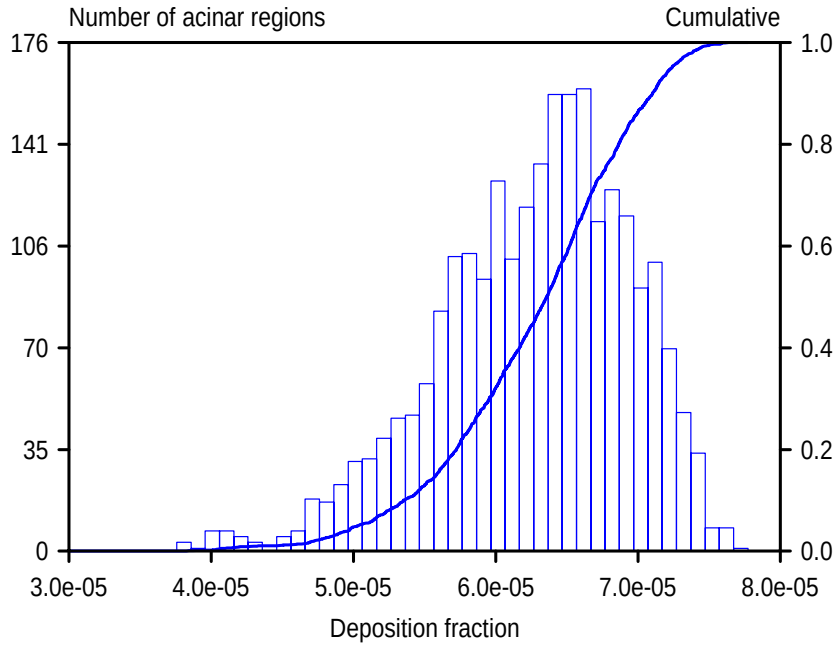

Fig. 4 Example of deposition distribution in the acini using the rat multiple path lung model with nasal breathing and inhalability adjustment. Tidal volume 2.1 ml and breathing frequency 102 min^{-1}; monodisperse aerosol with particles diameter 0.135 µm and density 4.1 g cm^{-3}.

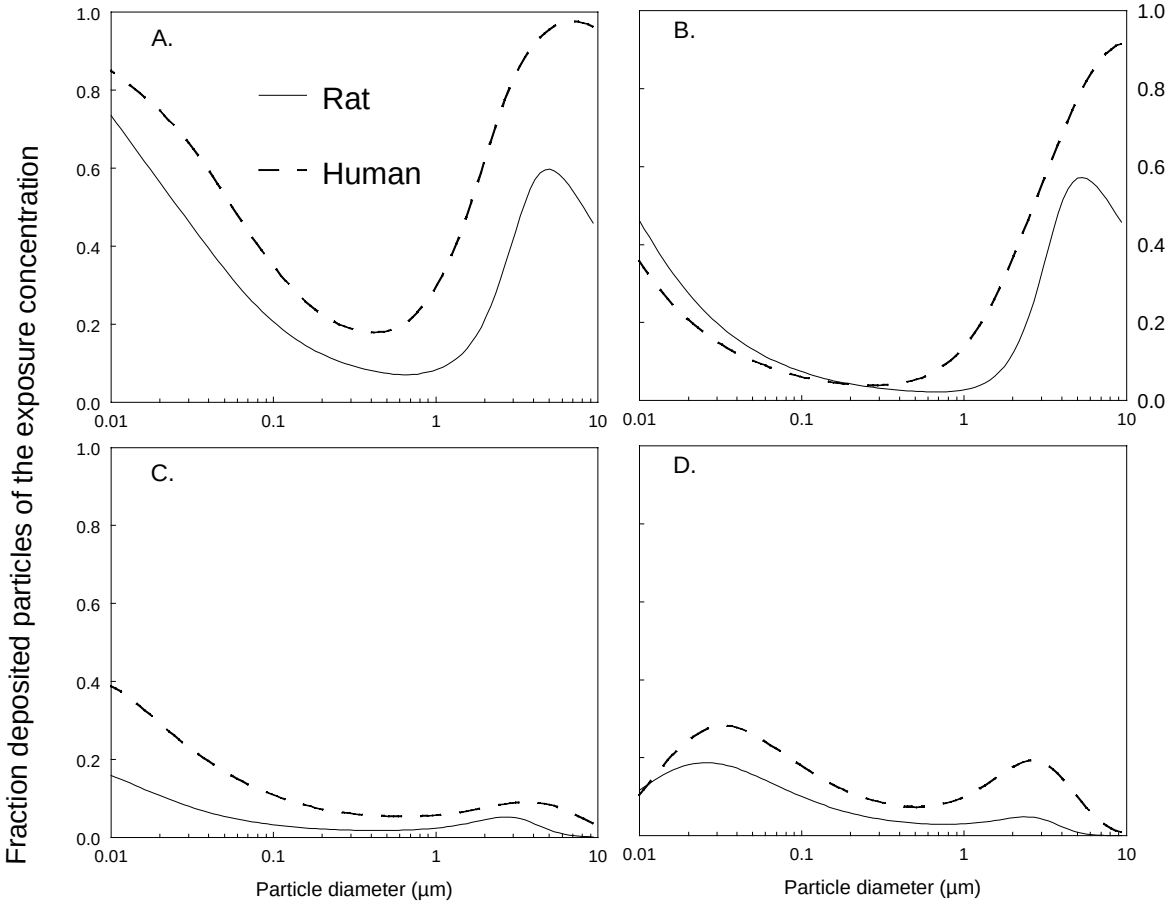

Fig. 5 Example of deposition fraction vs. particle diameter for monodisperse aerosol with particle density of 1.0 g cm^{-3} and adjusted for inhalability and assuming nasal breathing. For the multiple path rat lung model a tidal volume 1.5 ml ml and a breathing frequency of 130 min^{-1}.was used. And for the human whole lung model a tidal volume 625 ml and a (nasal) breathing frequency of 12 min^{-1}has been applied. A. Total airway deposition; B. Head deposition; C. Tracheo-bronchiolar deposition; D. Alveolar deposition.

5. Perspectives and applications

PM is tied to a specific size of particles, such as PM-10 or PM-2.5, and represents a mixture of a myriad of different types of particles. Developing a software program that can handle the deposition and clearance of all these species of particles, while doable, is a major undertaking that likely would require resources about an order of magnitude above those associated with the current project. However, the need for such a program goes without question. Control strategies for PM are projected to be extremely costly. There will be a premium on having tools available that allow exposure and response information to be integrated in PM assessments in a manner by which the “bad actors” in the PM mixture can be identified. A schematic representation of the way information will need to be integrated is shown in fig. 6. As shown in fig. 6, dosimetry computations will need to provide various dose metrics to analyse what best explains a particular type of health outcome. The deposition software developed in this project can serve as the kernel around which a software program that also includes clearance can be built.

The current work provides a tool that can directly be used to give answers to many questions concerning the relationship between breathing characteristics and lung morphometry of individuals and particulate matter deposition. The current model can be used to:

- analyse differences in dose and deposition between humans and rats at identical levels of exertion and aerosol properties. This allows for a animal-human extrapolation of dosimetry, e.g. as proposed by Jarabek et al. (1989) and to use of animal data for human risk assessment.
- analyse the impact of breathing behaviour on deposition. Within the human population breathing behaviour changes as function of age, the presence of disease, and level of exertion.
- analyse the differences in dose and deposition in healthy individuals and individuals with breathing/lung abnormalities due to diseases.
- identify the crucial moments in deposition as effected by diurnal variation in breathing behaviour and aerosol concentration.
- analyse the deposition variability within the lung in longitudinal sense (differences between airway generations) as well as in lateral sense (differences between airway paths). For rats this can explored in very detail, because the morphometry of the lung is fully known. For humans this is limited to the level of lobes, because the structure of the human lung is not fully known.
- Estimations of the dose at certain exposure conditions en the recognition of groups that receive relatively high doses.
- The possibility to link this model to a population based exposure model AirPex.
- Implementation in risk assessment with the use of human clinical data.

6. Future research needs

Dosimetry refers to estimating or measuring the amount (mass, number, surface area, volume, etc.) of particles at specific target sites at a particular point in time. Thus, dosimetry encompasses both deposition, which is the process of removing particles in various regions of the respiratory tract during the breathing of particle-laden air, and clearance, which refers to the rates and routes by which deposited particles are removed from the respiratory tract. Typically, the term “retention” in particulate inhalation toxicology refers to the amount of particles (sometimes called retained deposits) present at specific respiratory tract sites that is the net difference between deposition and clearance processes. The current software program is only intended to calculate the deposition of particles in the lung. While this is the critical first step in dosimetry modeling of particulate matter, establishing PM dose-effect relationships for any human exposure scenarios lasting longer than 24 hours requires also the clearance of particles to be addressed. To be an effective tool in PM health risk assessments, the software program needs to be extended to incorporate clearance of particles as well.

Research is also needed on developing lung geometries for individuals with chronic obstructive pulmonary disease (COPD) since these individuals have been shown to be particularly susceptible to PM. Current deposition and clearance models use lung geometries for healthy, normal adults. However, COPD individuals have about three fourths of the air inhaled going to only about one fourth of their lung surface. Thus, even greater differences in lobar-specific deposition of particles can be expected to occur in individuals with COPD. This means that the kind of multiple path approach to particulate deposition used in the current project for rat needs to be extended to the human situation.

Also, the MPPDep model needs to be evaluated with (existing) animal and human experimental data.

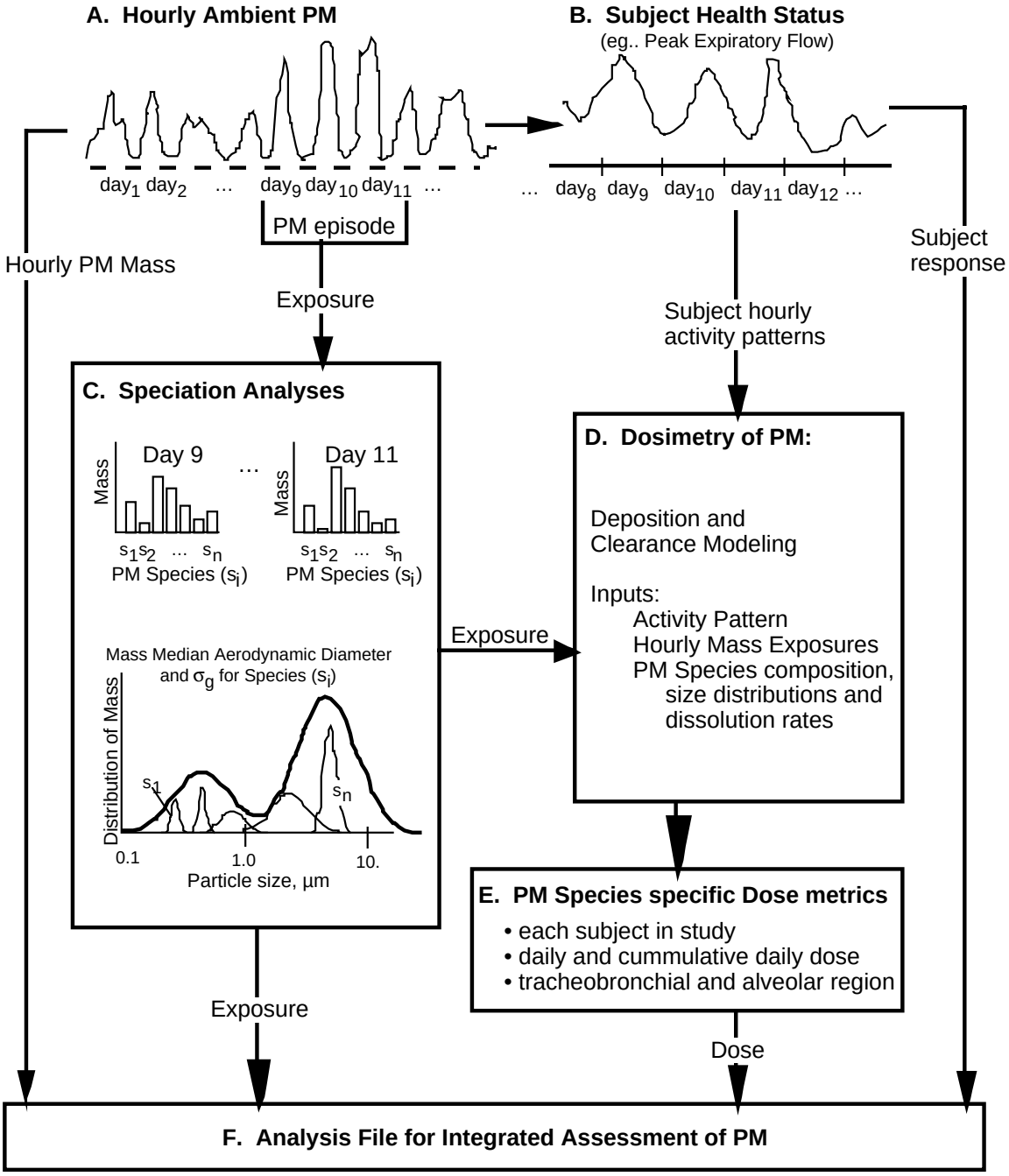

Fig. 6. Schematic showing the interrelationships among exposure, dose, and response data that must be integrated for PM health risk assessment analyses.

Future research is recommended on the following issues:

Multiple path lung geometry

The above analyses require data on lung morphometry and breathing parameters. Although much of these data have been presented in literature the last 10 decades, data on the asymmetry in lungs is poorly available. In the current model we used a comprehensive multiple path geometry for the rat and a limited multiple path geometry for humans based on 5 connected lobes (Yeh and Schum, 1980). Accordingly, there is a need for multiple path geometries for humans and laboratory animals other than rat. Also, data on the geometry for subjects with disease is important, in order to evaluate the effect of abnormalities and to estimate to what extend enhanced doses may contribute to their increased susceptibility.

Clearance and retention

The current model is only intended to calculate initial deposition in the lung. In order to establish dose-effect relationships a mass balance of particulate matter in the lung needs to be evaluated. From this mass-balance the retention of PM in the lung can be determined for each different location by looking at input fluxes (deposition) and output fluxes, (uptake and clearance). The latter mechanisms have not been incorporated in the model yet. We propose to extend the deposition model to include clearance and uptake mechanisms, so as to enable the software package to be an effective tool in particulate matter health risk assessment.

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Certification and disclaimer

The version of the software program that has been developed is designated as MPPDep_VI.I.

The software program was developed as a collaborative effort between CIIT and RIVM scientists. Since the goal is to have this user-friendly software readily available (without charge but with acknowledgment of the source) for use by scientists, neither CIIT nor RIVM will distribute the code until a mechanism for user access has been determined.

The source code and the user manual contain the following: "Disclaimer–While significant effort has been expended to ensure the accuracy and functionality of the source code, neither the Chemical Industry Institute of Toxicology nor the National Institute for Public Health and the Environment En Mileu warrant the source code to be error free. Users of MPPDep_VI.I assume full responsibility for the validity of any results obtained using the code."

Users of the software program (MPPDep_VI.I) who are not affiliated with CIIT or RIVM are required to acknowledge these organizations when they publish any results using the program. The source code and user manual address this in the following manner: “Acknowledgment Required–Implicit to users not affiliated with the Chemical Industry Institute of Toxicology (CIIT) or the National Institute for Public Health and the Environment (RIVM) is the requirement to acknowledge CIIT and RIVM for use of the program whenever publishing results obtained using MPPDep_VI.I”.

Appendix 1 Examples of input and output of the software

Table 1 Outline of input data entries

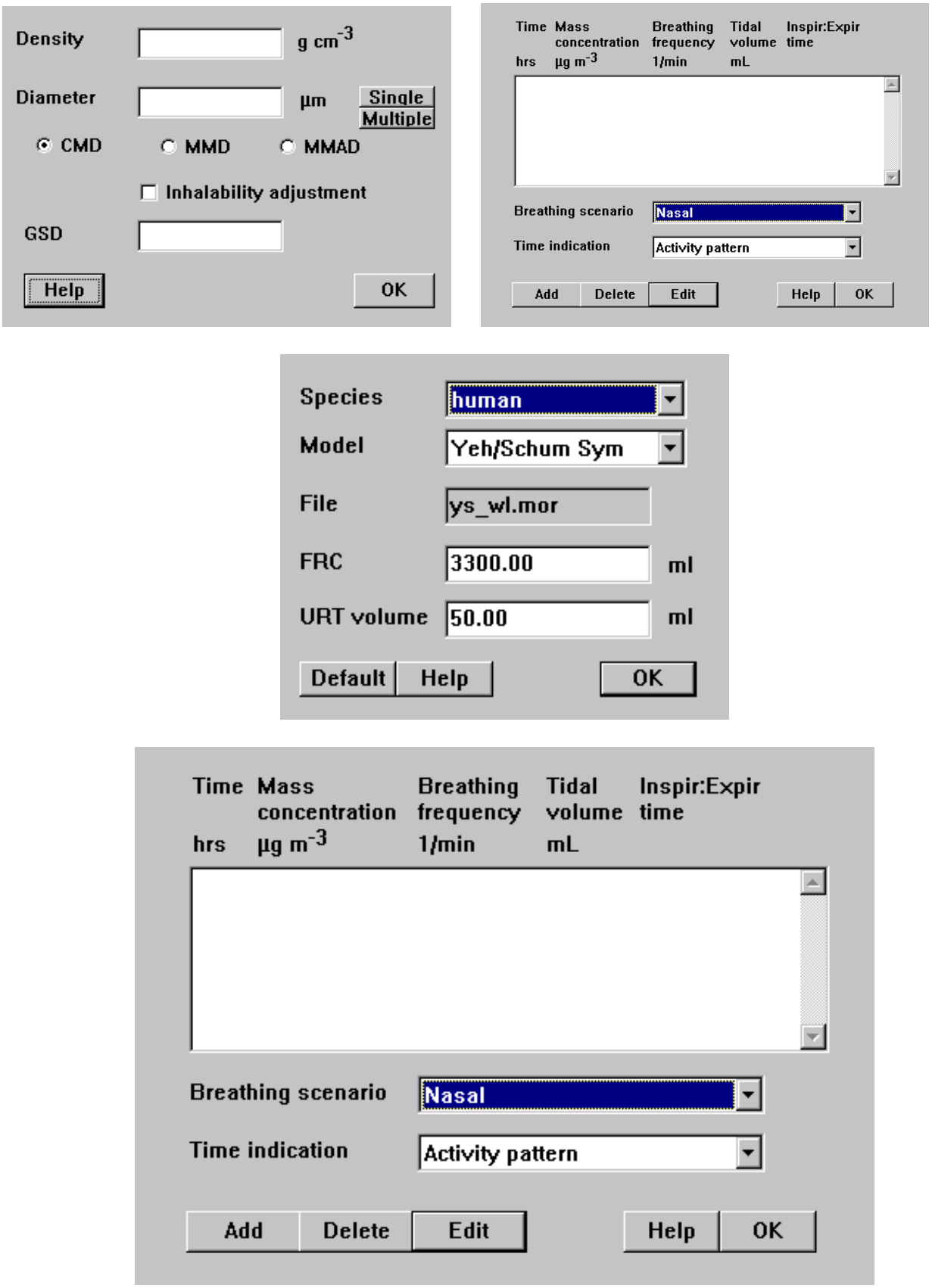
Entry	Item	Choices/ranges
Airway morphometry	Species	• Human • Rat
	Model	Human: • Yeh and Schum whole lung • Yeh and Schum 5-lobe model Rats: • Multiple path lung
	Functional Residual Capacity (FRC)	Human: 150.0-4500 Rat: 2.0-8.0
	URT	Human: 2.0-60 Rat:0.30-0.50
Particle properties	Density	0.010-50.0
	Diameter	multiple single
	Inhalability adjustment	on|off
	Geometric Standard Deviation	1.0-4.0 (<1.3 is interpreted as monodisperse)
Exposure condition	Aerosol concentration	0.0-1.0e5
(constant)	Breathing frequency	Human: 10.0-50.0 Rat: 60.0-200
	Tidal volume	Human: 40.00-2000 Rat: 0.40-3.0
	Inspiration/Expiration time	0.20-0.80
	Breathing Scenario	Human: nasal, oral, oronasal-mouth breather, oronasal-normal augmenter, endotracheal Rat: nasal, endotracheal
Exposure conditions*	Aerosol concentration	0.0-1.0e5
(variable in time)	Breathing frequency	Human: 10.0-50.0 Rat: 60.0-200
	Tidal volume	Human: 40.00-2000 Rat: 0.40-3.0
	Inspiration/Expiration time	0.20-0.80
	Breathing Scenario	Human: nasal, oral, oronasal-mouth breather, oronasal-normal augmenter, endotracheal Rat: nasal, endotracheal

* Data records can be entered as an activity pattern, in which duration is specified or as an hourly pattern, in which hour of the day is specified.

Table 2 Graphical Output Possibilities

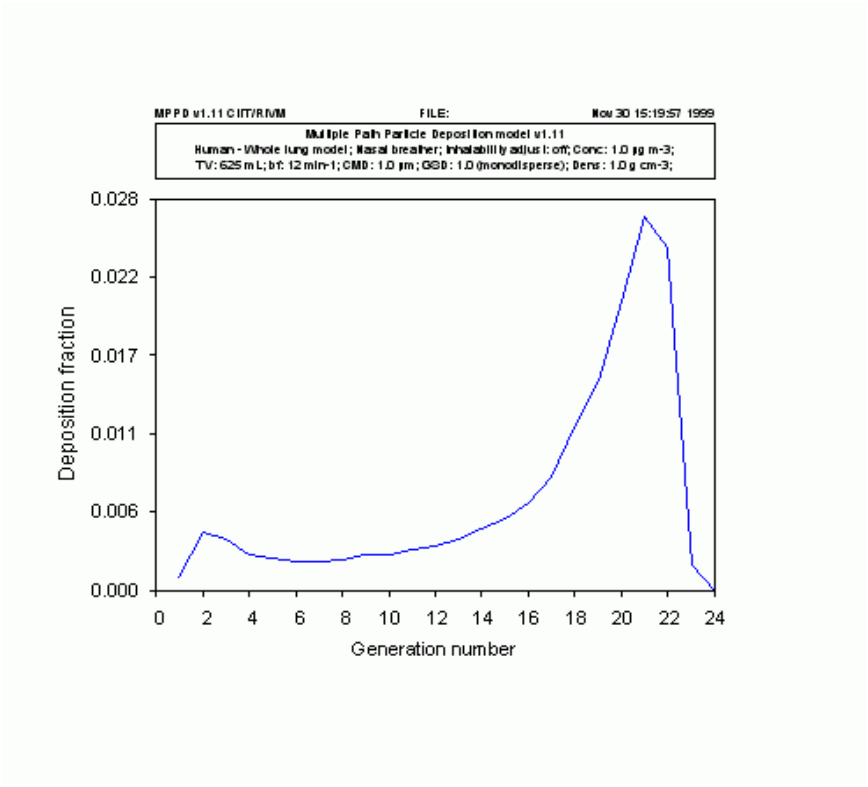
Graph entry	Subentry	Input selections		
		Morphometry	Diameter	Breathing
Deposition distribution	Lobar	rat multiple path, human 5-lobar	single diameter, mono disperse	constant
	Acinar	rat multiple path	single diameter, mono disperse	constant
Regional deposition	Regional fraction	rat multiple path, human 5-lobar, human whole lung	single diameter, mono and poly disperse	constant
	Fraction vs. gen. #	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	constant
	Mass rate vs. gen. #	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	constant
	Mass flux vs. gen. #	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	constant
	Mass/Area vs. gen. #	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	constant
Deposition vs. diameter	Regional	rat multiple path, human 5-lobar, human whole lung	multiple diameter, mono disperse	constant
	Thoracic	rat multiple path, human 5-lobar, human whole lung	multiple diameter, mono disperse	constant
Deposition vs. time	Accumulated mass	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	variable
	Dep. mass rate	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	variable
	Dep. fraction	rat multiple path, human 5-lobar, human whole lung	single diameter, mono disperse	variable

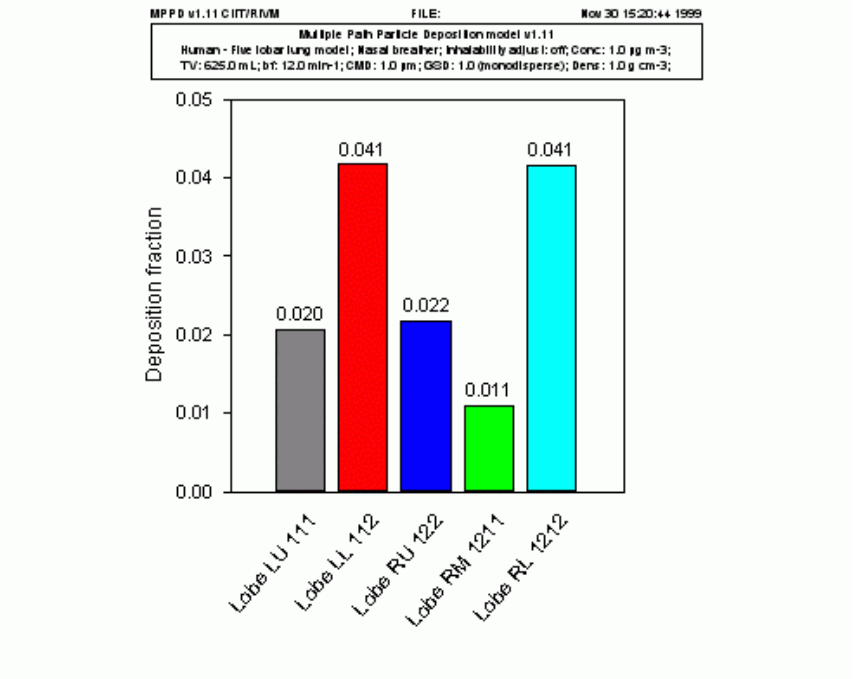
Appendix 2 Examples of input dialog boxes



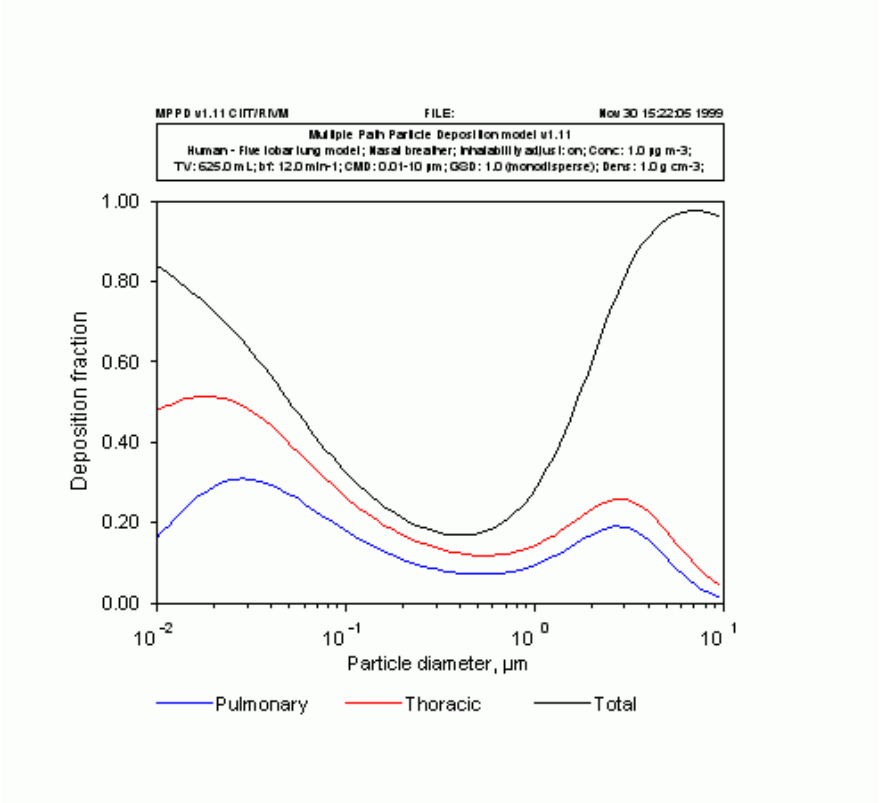
Screen lay-out for the input of the MPPDep depostion model.

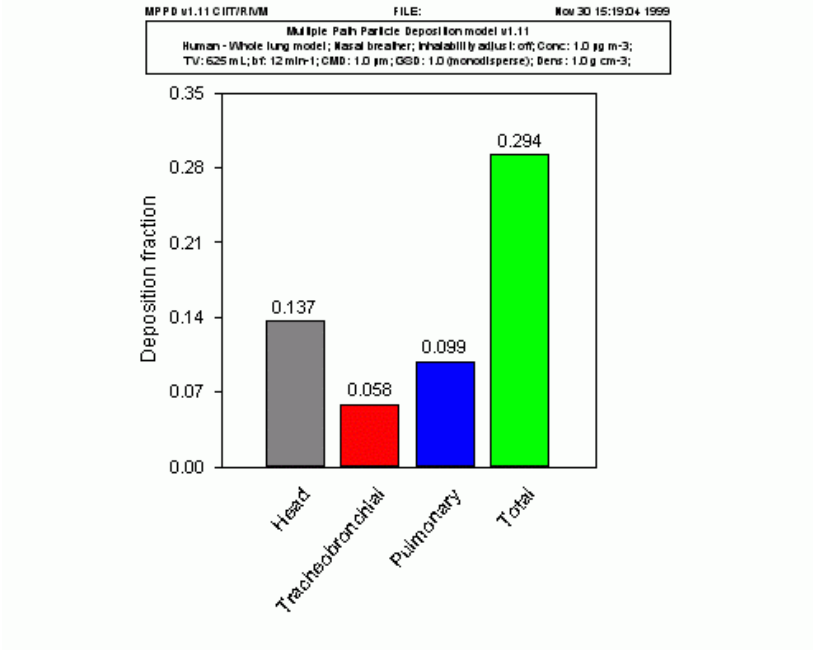
Appendix 3 Examples of graphical output





Screen lay-out for the output of the MPPDep depostion model.





Screen lay-out for the output of the MPPDep depostion model.

Appendix 4 Examples of data output files

Rat data

Using data file: rat.mor
Scaling tree by 0.663892
(TLC-->FRC)CGS (cm, gm, s) Units troughout, unless otherwise stated

BREATHING PARAMETERS and TIMES
Breathing frequency: 130.0 Tidal volume: 1.50
Nasopharyngeal Dead Space: 0.420
Inhalation Time: 0.231 Exhalation Time: 0.231
Volumetric inhalation flow rate at trachea: 6.500
Volumetric exhalation flow rate at trachea: -6.500
Time spent in NP space during inhalation: 0.065
Lung inhalation time: 0.166
Lung exhalation time: 0.166
PARTICLE diameter and density: 1.00e-04 1.00e+00

MORPHOMETRY
Number of segments: 24039
Lung volume: 3.999
Rescale FRC dimensions by 1.06 (Lung Vol = FRC + 0.5 TV)
Number of acini (alveolar segments) = 2404

DEPOSITION FRACTIONS for RANGE of MONODISPERSE PARTICLE SIZES

Diam	Total	TB	Alv	Inh	Exh	Nasal Inh	Nasal Exh	Inhalability
9.33e-04	4.60e-01	1.26e-03	6.66e-05	1.30e-03	2.47e-05	4.58e-01	2.82e-06	4.61e-01
8.71e-04	4.80e-01	1.79e-03	1.38e-04	1.89e-03	3.90e-05	4.78e-01	4.43e-06	4.82e-01

<data in between are removed to save space>

1.00e-06	7.36e-01	1.58e-01	1.16e-01	2.49e-01	2.58e-02	3.49e-01	1.13e-01	1.00e+00
1.00e-06	7.36e-01	1.58e-01	1.16e-01	2.49e-01	2.58e-02	3.49e-01	1.13e-01	1.00e+00

Human data

Using data file: ys_wl.mor
Scaling tree by 0.865932
(TLC-->FRC)CGS (cm, gm, s) Units throughout, unless otherwise stated

BREATHING PARAMETERS and TIMES
Breathing frequency: 12.0 Tidal volume: 625.00
Nasopharyngeal Dead Space: 50.000
Inhalation Time: 2.500 Exhalation Time: 2.500
Volumetric inhalation flow rate at trachea: 250.000
Volumetric exhalation flow rate at trachea: -250.000
Time spent in NP space during inhalation: 0.200
Lung inhalation time: 2.300
Lung exhalation time: 2.300
PARTICLE diameter and density: 1.00e-04 1.00e+00

MORPHOMETRY
Number of segments: 24
Lung volume: 3612.525
Rescale FRC dimensions by 1.00 (Lung Vol = FRC + 0.5 TV)
Number of acini (alveolar segments) = 65536

DEPOSITION FRACTIONS for RANGE of MONODISPERSE PARTICLE SIZES

Diam	Total	TB	Alv	Inh	Exh	Nasal Inh	Nasal Exh	Inhalability
9.33e-04	9.64e-01	3.80e-02	9.35e-03	4.44e-02	2.87e-03	9.02e-01	1.52e-02	9.67e-01
8.71e-04	9.70e-01	4.41e-02	1.39e-02	5.41e-02	3.86e-03	8.92e-01	1.91e-02	9.73e-01

<data in between are removed to save space>

1.00e-06	8.52e-01	3.89e-01	1.04e-01	4.59e-01	3.41e-02	3.17e-01	4.19e-02	1.00e+00
1.00e-06	8.52e-01	3.89e-01	1.04e-01	4.59e-01	3.41e-02	3.17e-01	4.19e-02	1.00e+00