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From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats.

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Abstract

Particulate matter (PM), consisting of solid particles and droplets, is present in ambient air. Particles with an aerodynamic diameter of less than 10 μm can be inhaled by humans. Knowledge on the tissue-specific internal dose of PM povides a critical link between individual external exposure and health effects. Being especially suited to analysing effects of scenarios, such as particulate exposure control strategies, computer models have proven to be important tools in the analysis of PM dosimetry. The Multiple Path Particle Dosimetry model (MPPD), developed by the Chemical Industry Institute of Toxicology (CIIT) in the USA in close collaboration with RIVM, allows PM deposition fractions and exposure doses for humans and rats to be calculated; this model also includes age-specific human lung models. Here, the results are described of mono-disperse aerosol deposition calculated with the MPPD model and its sensitivity to various parameters. Regional, lobar and alveolar depositions were calculated for the human adult using a stochastic lung model. Age dependency on PM deposition was studied for children and young adults, while the dependency of regional deposition on physical exertion was studied for adults. Coefficients for the rat–human deposition extrapolation were determined for three levels of human physical exertion (sleep, rest and light exercise).

Preface

The National Research council has identified dosimetry, the deposition and fate of particles, in the respiratory tract of individual belonging to presumed susceptible subpopulations as one of there ten Research Priorities for Airborne Particulate Matter (NRC, 2001). A clear understanding of exposure-dose-health-effects relationships is an important necessity to understand the variation among normal and particularly susceptible humans. This in turn can give direction for risk assessment for ambient PM. Although the dose after inhalation of PM is difficult to assess, sophisticated computer models have been developed to estimate this relationship. In a collaborative effort that started in 1998, RIVM and CIIT have developed the Multiple Path Particle **Deposition** model (Freijer et al.; 1999, Cassee et al., 1999 and Asgharian et al., 1999). Although this user-friendly model was already a significant improvement of existing models, it could only be used to estimate a deposition in an adult or rat for very short exposure durations.

In the recent years the new version of this model was developed which includes major additional capabilities. The new model (Multiple Path Particle **Dosimetry** model) can now calculate the deposition as well as the clearance of particles from the respiratory tract of adult humans and rats for various (prolonged) exposure scenarios. A unique feature is the ability to examine particle deposition in the lungs of children from infancy through adolescence. 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.

The dosimetry program will prove to be a critical and effective tool for use in PM health risk assessments, source apportionment of human lung burdens, and control strategy analyses. There is an option to link the current model with an air-pollution-population-exposure model like AirPex (Freijer et al., 1998).

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Contents

Samenvatting

Fijn stof bestaande uit vaste deeltjes en druppels is aanwezig in binnen- en buitenlucht. Deeltjes met aerodynamische diameter kleiner dan 10 μm kunnen ingeademd worden door mensen. Kennis van weefsel specifieke dosis van fijn stof is een kritische schakel tussen individuele blootstelling en gevolgen voor de gezondheid. De dosis is een functie van de depositie in de luchtwegen en longen alsook van processen binnen het lichaam om deeltjes effectief te verwijderen (klaring). Het netto resultaat wordt retentie genoemd en slaat op de hoeveelheid deeltjes die achterblijven in de luchtwegen op specifieke tijden, wat toxische responsen beïnvloedt. Depositie van ingeademd fijn stof is hoofdzakelijk afhankelijk van blootstellingsconcentraties, fysieke eigenschappen van deeltjes, morfometrie van de longen en ademhalingsparameters, en kan niet makkelijk gemeten worden. Computer modellen zijn belangrijk gereedschap om fijn stof dosimetrie te analyseren. Doordat deze modellen een expliciete set van vergelijkingen gebruiken, die reële processen beschrijft, of wel empirisch, of wel gebaseerd op fundamentele principes, zijn ze zeer geschikt om effecten van scenario's te analyseren, zoals controlestrategiën voor blootstelling aan fijn stof.

Het Multiple Path Particle Dosimetry (MPPD) model is ontwikkeld door CIIT (Chemical Industry Institute of Toxicology, VS) in samenwerking met het RIVM. Het MPPD model biedt de mogelijkheid om depositiefracties en blootstellingsdosis aan fijn stof te berekenen voor mensen en ratten, en bevat leeftijdafhankelijke humane longmodellen. Het model kan gebruikt worden om blootstelling – dosis – respons verhoudingen, waargenomen in milieu-epidemiologische studies, beter te begrijpen, maar ook voor extrapolatie van studies in experimentele dieren naar mensen. Bovendien kan inzicht in factoren die leiden tot grotere gevoeligheid worden verbeterd. Dit rapport beschrijft resultaten van de berekeningen met het MPPD model van depositie van monodispers aërosol en de gevoeligheid van het model voor verschillende parameters.

- De longdepositie (tracheobronchiale en pulmonaire depositiemassa) van grove deeltjes (5-10 μm) is significant hoger gevonden voor kinderen en adolescenten van een specifieke leeftijdsgroep dan voor volwassenen (18 jaar en ouder), voornamelijk vanwege de hogere depositie in het hoofd voor volwassenen. Toenemende grootte van de grove-deeltjesdiameter van 5 μm naar 10 μm verlaagt de ondergrens van deze leeftijdsgroep van 8 jaar naar 2 jaar en vergroot het verschil in longdepositie tussen kinderen en volwassenen. Pulmonaire depositiemassa per alveole is hoger voor kinderen in de leeftijd van 8-14 jaar vergeleken met volwassenen voor deeltjes van ongeveer 5 μm. Pulmonaire depositiemassa per oppervlakteeenheid groeit ongeveer lineair tussen de leeftijd van 20 en 80 jaar met ongeveer 30%.

- Toenemende fysieke inspanning resulteert in een hogere longdepositie. De longdepositie van ultrafijne deeltjes is hoger dan de longdepositie van fijne en grove deeltjes voor lichte tot matige inspanning. Op het moment dat neusademhaling verandert in een mondneus ademhaling, verandert het gedrag van longdepositie van fijne en grove deeltjes – voor modale tot zware inspanning is de longdepositie hoger voor grotere deeltjes.

- Variaties in functionele restcapaciteit (FRC), het longvolume aan het einde van normale uitademing, kunnen pulmonaire depositiefracties substantieel beïnvloeden.

- In geval van mond- of mondneus-ademhaling zijn long depositiefracties van grove deeltjes hoger dan in het geval van neusademhaling.

- De longdepositie is afhankelijk van deeltjesgrootte 45 – 200 keer hoger voor mensen dan voor ratten bij rust.

Samengevat, de leeftijd van persoon, de functionele capaciteit van de longen en ademhalingsparameters alsook de individuele longmorfometrie zijn factoren die depositie van deeltjes significant beïnvloeden en de gevoeligheid van subpopulaties kunnen verklaren.

Summary

Particulate matter (PM) consisting of solid particles and droplets is present in the ambient air. Particles with an aerodynamic diameter less than 10 μm can be inhaled by humans. Knowledge of the tissue-specific dose of PM is a critical link between individual exposure and health outcomes. The dose is a function of the deposition in the airways and lungs as well as the processes within the body to remove the particles effectively (clearance). The net result is called retention and refers to the amount of particles that remains in the respiratory tract at specific times, which affects the toxic responses. Deposition of inhaled PM depends primarily on exposure concentrations, physical characteristics of the particles, lung morphometry and breathing parameters and cannot easily be measured. 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.
A Multiple Path Particle Dosimetry model (MPPD) has been developed by CIIT (Chemical Industry Institute of Toxicology, USA) in close collaboration with RIVM. The MPPD model allows calculation of PM deposition fractions and exposure doses for humans and rats, and includes age-specific human lung models. The model can be used in the future to improve understanding of the exposure-dose-response relationships observed in environmental epidemiological studies, but also for extrapolation of studies in experimental animals to humans. In addition, factors resulting in increased susceptibility can be studied. This report describes the results of monodisperse aerosol deposition calculations with the MPPD model and its sensitivity to various parameters.

- Coarse mode particles (5-10 μm) lung deposition (tracheobronchial and pulmonary deposited mass) is found to be significantly larger for children and adolescents of a specific age group compared to adults (age 18 and older), mainly due to the larger deposition in the head for adults. Increasing coarse particle size from 5 μm to 10 μm reduces the lower boundary of this age group from 8 years to 2 years and increases the difference in lung depositions between children and adults. Pulmonary deposition per alveolus is higher for 8-14 years old children compared to adults for particles of about 5 μm. Pulmonary deposition per unit surface area increases nearly linear between the ages of 20 and 80 years by approximately 30%.
- Increasing physical exertion results in a higher lung deposition. The lung deposition of ultrafine particles is higher than the lung deposition of fine and coarse mode particles for light to modest exercise. When breathing is changed from nasal to oronasal the lung deposition behaviour of fine and coarse particles changes - for modest to heavy exercise the lung deposition of larger particles is higher.
- Variations in functional residual capacity (FRC), the lung volume at the end of normal expiration, can substantially affect the pulmonary deposition fractions.
- In case of oral or oronasal breathing lung deposition fractions of coarse particles are higher than in case of nasal breathing.
- Lung deposition depending on particle size is 45-200 times larger for humans than for rats at rest.

In conclusion, age of the subject, the functional capacity of the lungs and breathing parameters as well as the individual lung morphometry are factors that significantly affect the particle deposition and can explain the susceptibility of subpopulations.

1. Introduction

Aerosols or Particulate Matter (PM) consisting of solid particles and droplets are present in the atmosphere and in the ambient air. Primary aerosols are emitted from the sources as traffic and industry or consist from soil particles and sea spray transported by wind. Secondary aerosols are formed in the atmosphere by chemical reactions from sulphur dioxide (SO_2), nitrogen oxides (NO_x), ammonia (NH_3) and volatile organic compounds (VOC).
Thus, aerosols can be antropogenic (man-made) or natural and have a wide range of particle sizes. Particles with an aerodynamic diameter less than 10 μm are inhaled by humans. Increasing inertia disables the inhalation of larger particles. Inhalable particles are divided in ultrafine particles (0.01 – 0.1 μm), fine particles (0.1 – 2.5 μm) and coarse particles (2.5 – 10 μm). Particle size distribution as well as aerosol concentration varies considerably in time and space.

Epidemiological time-series studies have shown associations between daily levels of PM and hospital admissions and mortality in the Netherlands as well elsewhere in the world (NAP, 2002). Definitive conclusions on the mechanisms of the PM associated health effects can not be made yet. The particle size distribution, concentration, chemical speciation and bioavailability of aerosols is information that is needed to understand the health effects of PM.

For risk assessment it is essential to have a good description of a whole source – effect chain. The estimation of inhaled aerosol dose and regional deposition patterns in the airways based on exposure concentrations, physical characteristics of the particles, lung morphometry and breathing parameters is a part of the source-effect chain.
A Multiple Path Particle Dosimetry model (MPPD) was developed by CIIT (Chemical Industry Institute of Toxicology, USA) in collaboration with RIVM. This model enables the assessment of exposures to PM and their impact on particulate dose to critical regions of the lung. The MPPD model could be a part of the complete source-effect-risk assessment chain for ambient PM.

Deposition in respiratory tract and lungs strongly depends on particle size distribution. Aerosols entering the respiratory tract deposit by impaction, sedimentation and Brownian diffusion. Particle loss by impaction is especially important for coarse particles in the upper airways. Sedimentation is gravitational settling which is important for coarse particles in the lower airways. Brownian diffusion is important for small particles deep in the lung.
The human lung structure is shown in Figure 1. There are three major regions where deposition can be modelled. The head or upper respiratory tract (URT) is an area from nose and/or oral cavity down to the trachea. The tracheobronchial (TB) region is an area from the trachea down including usually 16 (humans) or 15 (rats) conducting airway generations where the mucociliary clearance occurs. The pulmonary (P) or alveolar region includes 8 to 12 respiratory airway generations for humans and 26 for rats. The lungs are subdivided in bronchopulmonary segments named lobes. Human lungs consist of 5 lobes and rat lungs consist of 6 lobes. Lobar deposition can be modeled as well by MPPD model. When breathing the air flows through the airway tree consisting from tubes and ending with alveolar sacs. Each tube has morphometric parameters such as length, diameter, branching angle and gravity angle. When morphometric parameters are known the deposition can be modelled on the level of an individual airway. The lungs expand and contract during breathing. Breathing

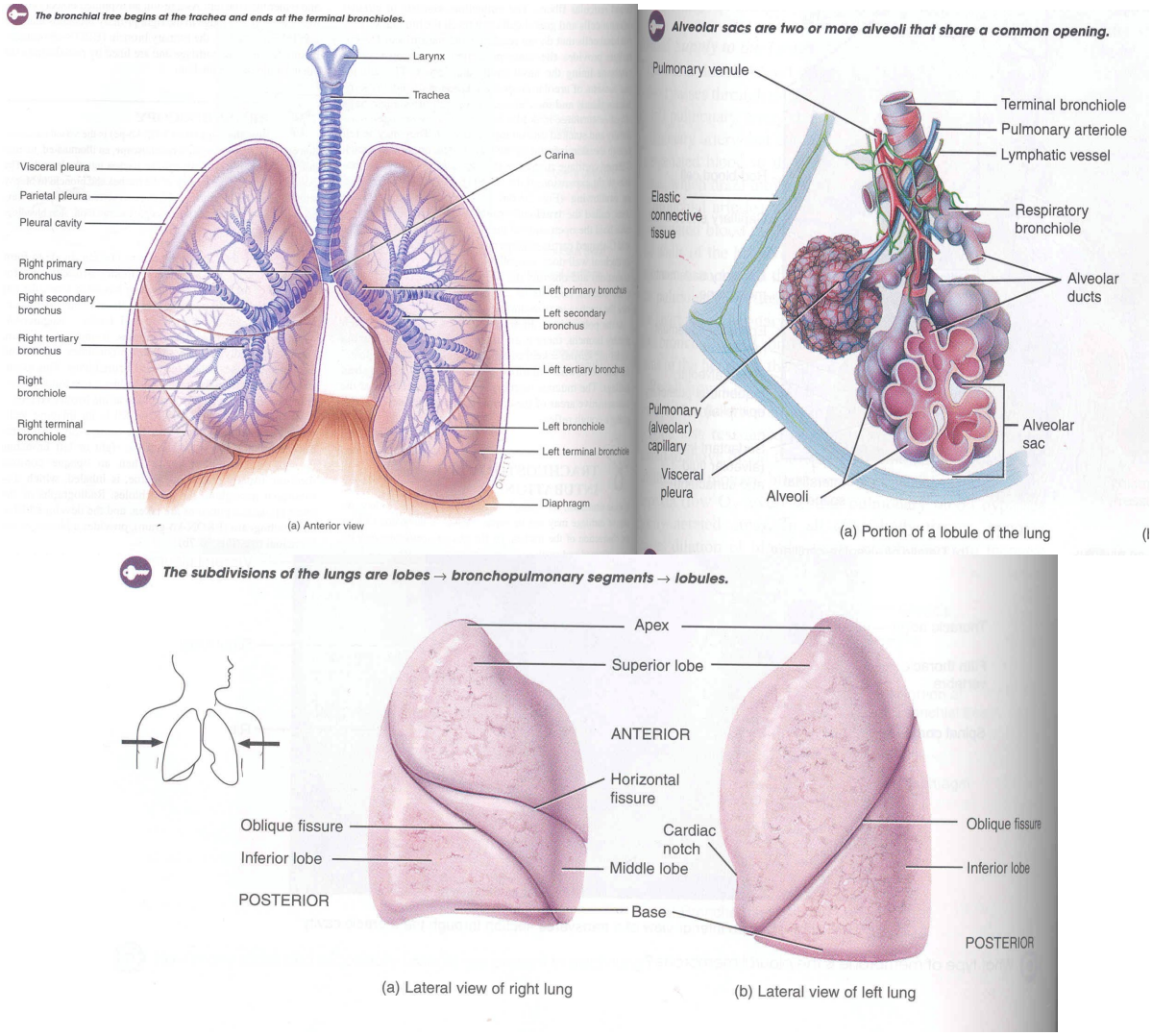

Figure 1. Human lungs: bronchial tree in relation to the lungs (top left), alveolar sacs (top right), the subdivision of the lungs in lobes (bottom).

is a periodic process. By quiet breathing an air volume of about 0.5 l is inhaled and exhaled by humans (the whole lung volume being about 6 l) with a frequency of about 12 min^{-1}.
This report describes the results of monodisperse aerosol deposition calculations with the MPPD model and its sensitivity to various parameters. In chapter 2 the differences between the new MPPD version 1.0 (2002) and the old version MPPDep v. 1.1 are highlighted and the submodels of the MPPD are described. In chapter 3 the regional and lobar deposition fractions as well as alveolar deposition fraction distributions in human adults as a function of particle aerodynamic diameter calculated by a stochastic lung model are presented. Chapter 4 describes how the deposition calculation is performed, and describes the dependency of regional deposition and standardised deposition on age especially for children. Chapter 5 describes deposition as a function of physical exertion. Chapter 6 describes results of a sensitivity analysis to model input parameters. Chapter 7 describes the rat-human extrapolation of PM deposition for monodisperse particles. Finally, chapter 8 summarises the conclusions.

2. CIIT/RIVM MPPD model v. 1.0 (2002).

The MPPDep (Multiple Path Particle Deposition model) version 1.11 (Freijer et al., 1999; Cassee et al., 1999; Asgharian et al., 1999) was developed by Chemical Industry Institute of Toxicology (CIIT, USA) and the RIVM and was restricted to model only aerosolised particulate matter (<10 μm) deposition in the lung of an adult human and rat. The new version called MPPD (Multiple Path Particle Dosimetry model) was developed by the CIIT Centers for Health Research in close collaboration with the RIVM and is available on CD (Price et al., 2002). The MPPD model has the following major additional capabilities:

- The new version models both the deposition and clearance of particles from the respiratory tract of adult humans and rats for constant exposure scenario.

- In the new version the capability has been added to examine particle deposition in the lungs of children from infancy through adolescence. Two series of lung geometries for children are available – symmetric and 5-lobe symmetric.

- Two stochastically generated asymmetric lung geometries for adult human were added. The large lung with most airways yields the greatest predicted total respiratory tract deposition of particles and the small lung with the least airways predicts the least deposition. The results obtained from calculations using these two lung geometries provide the user the range for total deposition that can be expected in the adult population.

- The new version of the model accounts for particle losses during pause between inhalation and exhalation for humans.

- The new version of the software was written in Java, universal programming language, the old version was in C++.

The present model calculates the deposition and clearance of monodisperse and polydisperse aerosols in the respiratory tract of rats and humans for particles ranging from ultrafine (0.01 μm) to coarse (20 μm) sizes. The MPPD model v. 1.0 (2002) contains the following submodels:

1. Multiple-path asymmetric model for the rat lung. Incorporates asymmetries in rat airway structure. Deposition is calculated at the individual airway level. Both deposition and clearance calculations are enabled for constant exposure scenario (fixed aerosol concentration and breathing patterns). Deposition calculations in case of variable exposure scenarios are possible.

2. Single- or typical-path Yeh-Schum symmetric model for human adult. Allows correct calculation of average regional depositions (head deposition, tracheobronchial (TB) deposition and pulmonary (P) or alveolar deposition) and of average depositions per airway generation. Both deposition and clearance calculations are enabled for constant exposure. Deposition calculations in case of variable exposure scenarios are possible.

3. Yeh-Schum 5-lobe model for human adult. Incorporates asymmetries in the upper airways of the human tracheobronchial tree. Limited multiple-pass or 5-lobe model includes an asymmetric tree for the first few airways followed by 5 symmetric but different lobar structures. Allows correct calculation of average regional depositions and average depositions per airway generation. Lobar depositions are calculated as well. Both deposition and clearance calculations are enabled for constant exposure. Deposition calculations in case of variable exposure scenarios are possible.

4. Stochastic lung model for human adult (2 individual lung geometries available). Random selection of morphometric parameters is made for every airway generation. Deposition is calculated at the individual airway level for the individual lung structure. Both deposition and clearance calculations are enabled for constant exposure scenario. Deposition calculations in case of variable exposure scenarios are possible.

5. Age specific single- or typical-path Yeh-Schum symmetric models for ages of 3, 21, 23, 28 months old and 3, 8, 9, 14, 18, 21 years old. Allows correct calculation of average regional depositions and average depositions per airway generation. Only deposition calculations are possible.

6. Age specific Yeh-Schum 5-lobe models for ages of 3, 21, 23, 28 months old and 3, 8, 9, 14, 18, 21 years old. Allows correct calculation of average regional depositions and average depositions per airway generation. Lobar depositions are calculated as well. Only deposition calculations are possible.

The results described in this report are obtained using the early version of MPPD model. The only difference with MPPD version 1.0 is the availability of only one mid-size stochastic lung geometry instead of two (small and large).

3. Deposition in adults

A major limitation for realistic deposition models is the degree to which the lung geometry can be accurately reconstructed. Unfortunately, morphometric data for the entire airway tree of the human lung are not available (Asgharian et al., 2001) and we have to use models in which certain assumptions are made. The CIIT/RIVM particle deposition model (Anjilvel and Asgharian, 1995; Asgharian et al., 1999 and 2001; Cassee et al., 1999) includes three models of idealised geometry of the human lung. The Yeh-Schum symmetric model uses a symmetric geometry for the whole lung. The lower airways of the human lung can be reasonably characterised as symmetric, but there are major asymmetries in the upper airways of the human tracheobronchial tree that lead to different deposition patterns in these airways as well as in the apportionment of airflow to the different lung lobes. The Yeh-Schum 5-lobe model captures the asymmetry in the lobar structure, but treats the geometry within each lung lobe in a symmetric fashion. Raabe et al. (1976) made limited measurements of human upper airway parameters. The stochastic lung model accounts for an asymmetric geometry of the tracheobronchial region (Koblinger and Hofmann, 1985; 1990) using data of Raabe et al. (1976). The CIIT/RIVM model (the early version of MPPD) includes one individual stochastic lung representative of the general human population. The geometry of a lung in all models is based on morphometric data from Yeh and Schum (1980). Particle deposition in typical-path symmetric model was compared with the ones in the five-lobe symmetric and in the stochastic multiple-path human lung geometry models (Asgharian et al., 2001). The models showed very similar regional and generation-by-generation deposition results. Lobar deposition was found to be strongly dependent on the detailed morphometry of the lung

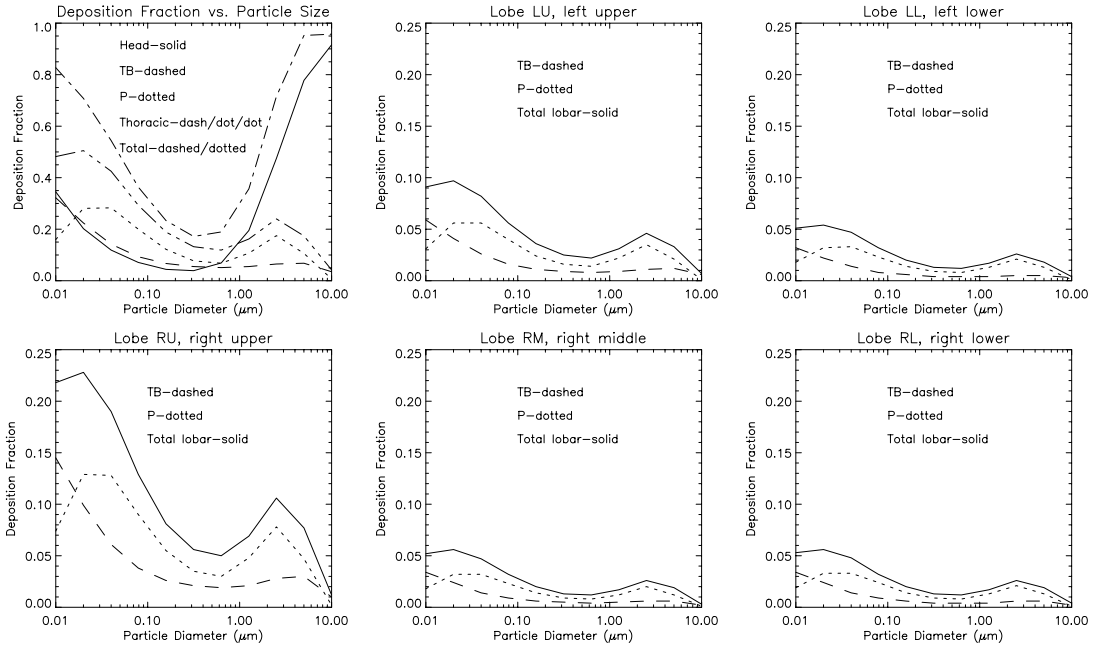

Figure 2. Aerosol deposition fractions (head, tracheobronchial (TB), pulmonary (P), thoracic, total and lobar) in human adult as a function of particle aerodynamic diameter. Stochastic lung model input parameters: fractional residual capacity 3.3 l, upper respiratory tract volume 50 ml, particle density 1 g/cm^3, breathing frequency 12 min^{-1}, tidal volume 625 ml, the nasal breathing scenario was used with equal breathing time during inhalation and exhalation, and no pause in between.

structure that was used. Results using the CIIT/RIVM model show good agreement with experimental data for regional deposition in the human lung (Heyder et al., 1986).
Deposition calculations were performed with a stochastic lung model for monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 μm to 10 μm. The growth of aerosols within the airways due to the high humidity in the lungs was neglected. Results on regional (head, tracheobronchial, pulmonary, thoracic, total) and lobar aerosol deposition fractions as a function of particle size are shown in Figure 2. Here it should be emphasised that large individual differences exist between persons in fractional residual capacity and breathing parameters leading to significant differences in aerosol deposition. Concerning lobar depositions shown in Figure 2 it should be noted that an up to three fold variation in deposition fraction was observed among various stochastic lungs having a differing geometry, indicating that individuals may receive different doses in the various lobes (Asgharian et al., 2001).

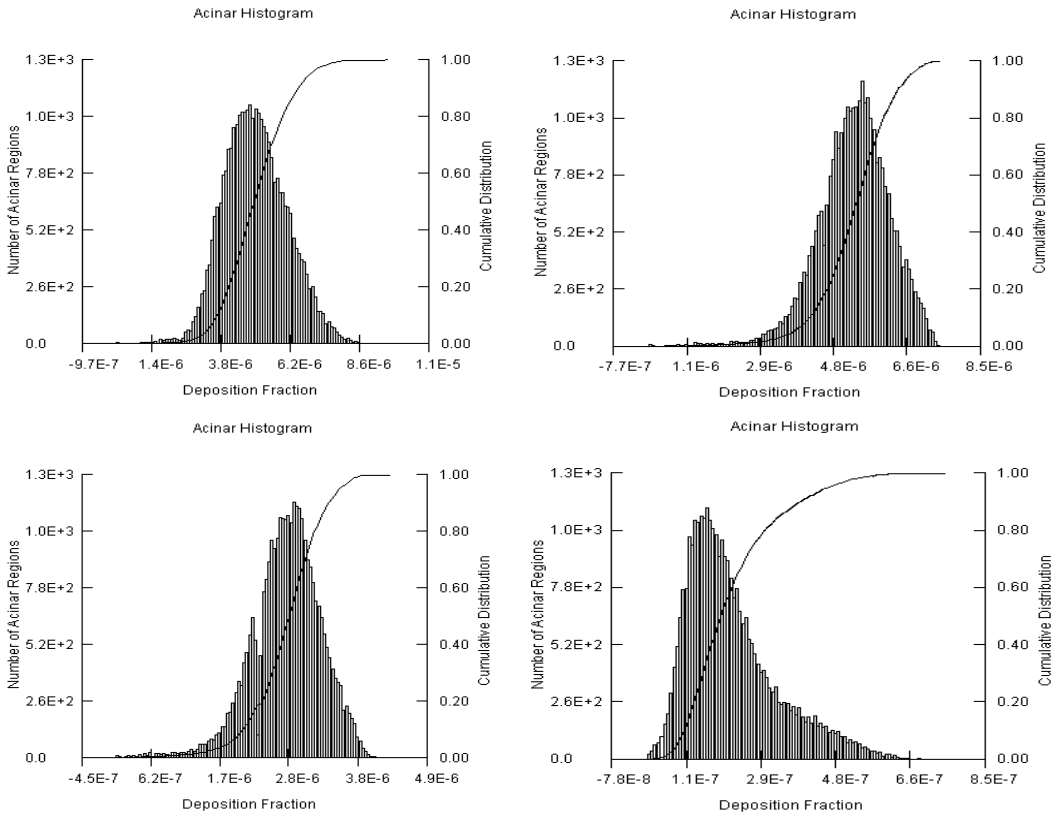

Figure 3. Alveolar deposition fraction distribution from stochastic model for particle sizes of 0.01 μm (top left), 0.1 μm (top right), 1 μm (bottom left) and 10 μm (bottom right). Model input parameters are the same as in Figure 2.

The initiation of lung injury in alveolar regions is most likely directly related to the initial deposition of particles (Asgharian et al., 2001). There are 31,926 terminal bronchioles and alveolar regions in CIIT/RIVM stochastic lung geometry, representing the $3 \cdot 10^8$ alveoli of an average adult. Not all alveolar regions receive the same dose. To examine regional variation of alveolar or pulmonary deposition, the alveolar deposition fraction frequency distribution is shown in Figure 3 for particle sizes of 0.01 μm, 0.1 μm, 1 μm and 10 μm. Up to 2-3 fold differences in deposition fractions exist among various alveolar regions. The alveolar deposition fraction frequency distribution of 10 μm particles has a long tail, therefore deposition fractions in various alveolar regions differ up to 8 fold.

4. Deposition in children

An important issue in risk assessment is the age dependency of PM deposition, especially for children. The CIIT/RIVM particle deposition model includes age-specific lung models. These models are modifications of the basic Yeh-Schum symmetric tree single path model (Yeh et al., 1979; Yeh and Schum, 1980). The size and structure of the tree is dependent upon the age of the child or young adult (ages of 3, 21, 23, and 28 months and 3, 8, 9, 14, 18, and 21 years are available). These lungs were generated by M.G. Menache (University of New Mexico, USA) based on the morphometric measurements of Mortensen et al. (1983; 1988). Typical path symmetric models allow the simulation of average regional deposition in the head, tracheobronchial and alveolar regions, deposition results are average values for each generation (Asgharian et al., 1999). Appropriate anatomical and physiological parameters used are shown in Table 1. Functional residual capacity (FRC) is from Overton and Graham, 1989; Phalen et al., 1985; Dunhill, 1962; Altman and Dittmer, 1971 based on Mortensen et al. (1983; 1988) lung dimensions. Upper respiratory tract (URT) volume or head volume comes from Overton and Graham, 1989; Hart et al., 1963. Tidal volume (TV) and breathing frequency (BF) for respective ages in case of rest are from Hofmann, 1982.

Table 1. Parameters used in age dependent calculations of the CIIT/RIVM deposition model.

Age	FRC, ml	URT volume, ml	Breathing frequency, min^{-1}	Tidal volume, ml	Minute ventilation, l/min
3 month	27.36	2.45	39	30.44	1.19
21 month	64.46	6.52	28	81.22	2.27
23 month	78.45	6.94	27	86.79	2.34
27 month	100.67	7.92	26	100.1	2.60
3 years	95.43	9.47	24	121.3	2.91
8+ years	437.34	21.03	17	278.2	4.73
9+ years	513.12	22.44	17	295.8	5.03
14 years	881.47	30.63	16	388.1	6.21
18 years	1,935.34	37.38	15	446.7	6.70
21 years	1,854.54	42.27	14	477.2	6.68

Calculations were performed for monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 μm to 10 μm, particle density of 1 g/cm^3, the nasal breathing scenario was used with equal breathing time during inhalation and exhalation, and no pause in between. Total and regional deposition fractions were calculated as well as the deposition fraction per generation. The mass depositions were calculated for aerosol concentration of 140 $\mu g/m^3$. The deposited mass per breath (DMB), the deposited mass rate (DMR), the standardised deposited mass per breath (SDMB) and the standardised deposited mass rate (SDMR) are expressed as following:

$$DMB_i = DF_i \cdot N(t) \cdot TV \cdot 10^{-6}$$

$$DMR_i = DF_i \cdot N(t) \cdot TV \cdot BF \cdot 10^{-6}$$

$$SDMB_i = \frac{DMB_i}{S_i}$$

$$SDMR_i = \frac{DMR_i}{S_i},$$

where DMB is deposited mass per breath in µg, DF is deposition fraction, N is aerosol concentration in µg/m^3, t is time, TV is tidal volume in ml, DMR is deposited mass rate in µg/min, BF is breathing frequency in min^{-1}, SDMB is standardised deposited mass per breath and per unit area in µg/m^2, SDMR is standardised deposited mass rate per unit area in µg/(min m^2) and S is the lung region surface area in m^2, i is the lung region. Standardised deposition rates are much more adequate deposition metrics because they include the target area. The total deposited mass in µg is:

$$DM_i = \int_0^T DMR_i(t) \cdot dt,$$

where T is the exposure time in min.

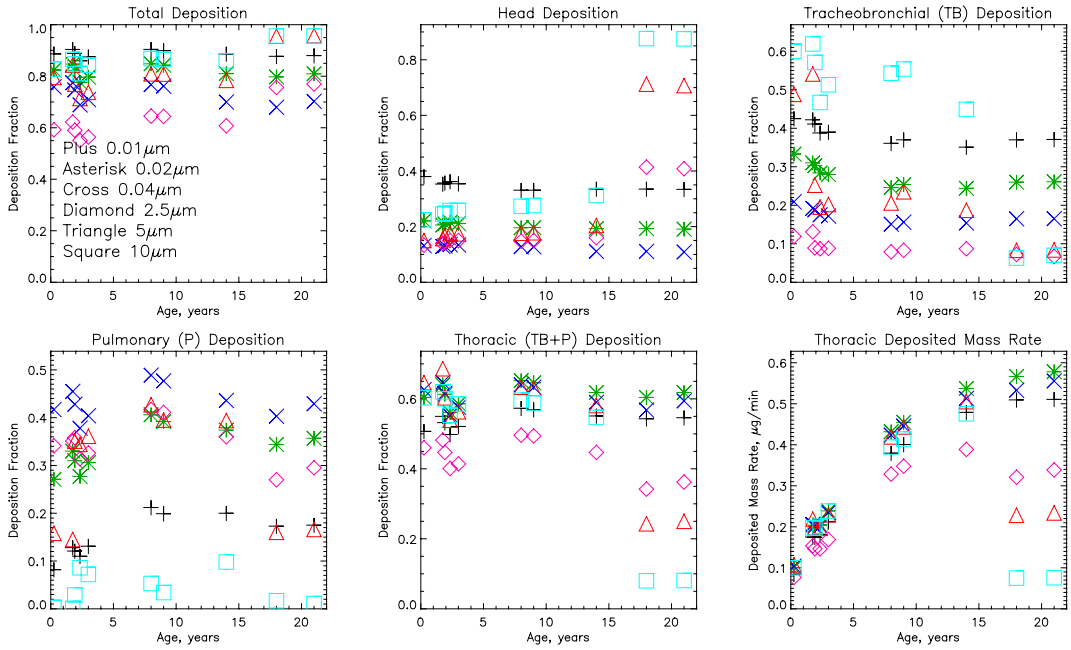

Figure 4. Age dependency of human aerosol deposition for different particle sizes. Total (top left), head (top middle), tracheobronchial (top right), pulmonary (bottom left) and thoracic (bottom middle) deposition fractions, deposited thoracic mass rate (bottom right). Aerosol concentration used for mass calculation is 140 µg/m^3.

Results of age-dependent deposition are shown in Figure 4. The head deposition fractions by impaction are based on the data from Becquemin et al. (1991). For coarse particles the adult (here 18 and 21 years old) head deposition fractions are larger than the head deposition fractions in children. The thoracic deposition fraction (which is a sum of tracheobronchial and pulmonary deposition fractions) of ultrafine particles does not change with age. For coarse particles (5µm and 10 µm) tracheobronchial and thoracic deposition fractions are significantly larger for children (ages of 0-15 years old) than for adults, mainly due to the increase in head deposition from children to adults. The difference in tracheobronchial and thoracic deposition fractions between children and adults increases with particle size.

Pulmonary or alveolar deposition fractions of 5 µm particles for 8-14 years old children are higher than for adults. Deposited aerosol mass rate in the thoracic region increases with age for ultrafine particles. For coarse particles the deposited aerosol mass rate in the thoracic region increases with age up to the age of 14 years. The increase of deposited mass rate is due to the growing tidal volume (Table 1). For coarse particles the deposited aerosol mass rate in the thoracic region of 8-14 years old children for 5 µm particles and of 2-14 years old children for 10 µm particles is higher than in adults (18 and 21 years old). Here it should be emphasised that the age dependency of deposited mass is determined by the age dependencies of head deposition and minute ventilation (tidal volume multiplied by breathing frequency), and that the age dependency of head deposition is based on a limited number of measurements (Becquemin et al., 1991).

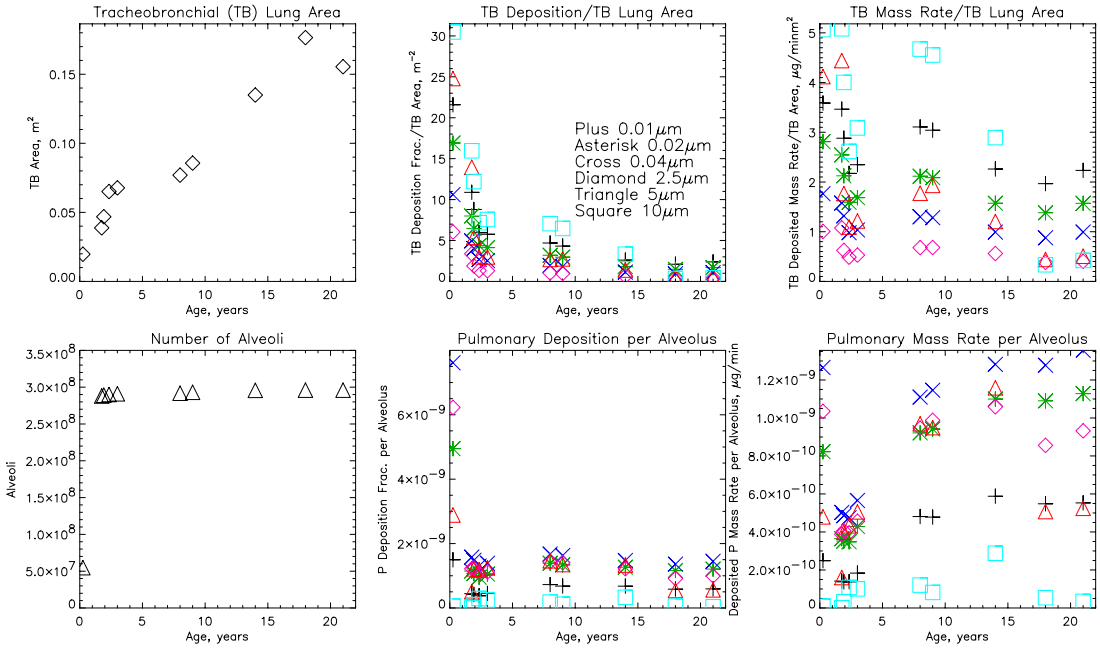

Figure 5. Age dependency of human standardised aerosol deposition for different particle sizes. Tracheobronchial (TB) lung area (top left), TB deposition fraction per unit of TB lung area (top middle), deposited TB mass rate per unit of TB lung area (top right), total number of alveoli (bottom left), pulmonary (P) deposition fraction per alveolus (bottom middle), deposited P mass rate per alveolus (bottom right). Aerosol concentration used for mass calculation is 140 µg/m^3.

The standardised aerosol deposition is shown in Figure 5. The CIIT/RIVM model calculates lung surface area per airway generation, the first 16 generations belong to the tracheobronchial region. The tracheobronchial lung area, tracheobronchial deposition fractions per unit of surface area and deposited tracheobronchial mass rates per unit surface area are shown in the top of the Figure 5. The tracheobronchial surface area grows monotonously from about 197 cm^2 at birth to about 1,554 cm^2 at the age of 21 years. Tracheobronchial deposition fractions per unit surface area are decreasing with age for all particle sizes due to increasing tracheobronchial lung area with age. Tracheobronchial deposition fractions per unit surface area are up to 10 times (for ultrafine particles) and 68 times (for coarse particles) higher for 3 month old babies compared to adults; up to 4 times (ultrafine) and 27 times (coarse) higher for the age of 2 years compared to adults. For ultrafine particles the deposited aerosol mass rates in tracheobronchial region per unit surface area for 3 month old babies are up to 1.8 times larger than for adults and seem to decrease

monotonously with progressing age. However, small deviation in tracheobronchial surface area at the age of 2.3 and 3 years, due to the differences in lung geometry, leads to almost same tracheobronchial deposited mass rates per unit surface area as for adults. For coarse particles of 2.5 μm, 5 μm and 10 μm the deposited aerosol mass rates in tracheobronchial region per unit surface area for 3 month old babies are respectively 2.5, 8 and 12 times larger than for adults, for 2.3 years old children respectively 1.2, 2.2 and 6.2 times larger than for adults, and for 8 years old children respectively 1.7, 3.5 and 11 times larger than for adults. The age dependency of tracheobronchial deposited mass per unit surface area is determined by the age dependencies of head deposition, minute ventilation and tracheobronchial surface area.

The total number of alveoli, pulmonary deposition fractions per alveolus and deposited pulmonary mass rates per alveolus as a function of age are shown in the bottom part of the Figure 5. There are approximately $50 \cdot 10^6$ alveoli at birth and about 85% of alveoli are added after birth, the adult number of about $300 \cdot 10^6$ is attained by 20 years (Mauderly, 1979). Alveolar multiplication is extremely rapid in the first few years of life and then slows down. The time of cessation of alveolar multiplication is still not settled. The older view was that alveolar multiplication continued to 8 years of age, newer data put this at an earlier date, perhaps 2 years of age (Thurlbeck, 1988). Pulmonary deposition fractions per alveolus are up to 5 times (for ultrafine particles) and 6 times (for coarse particles) higher for 3 month old babies compared to adults. For children of the age of about 2 years and older the pulmonary deposition fraction per alveolus does not change significantly. Deposited pulmonary mass rates per alveolus are lower for the age of 2-3 years compared to adults for ultrafine and 2.5 μm particles and 1.8 to 2.2 times higher for 8-14 years old children compared to adults for 5 μm particles. The age dependency of pulmonary deposition per alveolus is determined by the age dependencies of head deposition, minute ventilation and alveolar multiplication.

Alveolar surface area obtained from 8 normal adult human lungs by Gehr et al. (1978) is 143±12 m^2. The airway surface area for generations above 16 belonging to the pulmonary region calculated from the model is 9.35 m^2. Therefore, the adult tracheobronchial deposition fraction and mass rate per unit surface area are 2,078 to 377 times (for 0.01 μm to 0.04 μm particles) and 223 to 6,238 times (for 2.5 μm to 10 μm particles) larger than adult pulmonary deposition fraction and mass rate per unit surface area. Progressive morphological changes in the senescent adult lung result primarily in a loss of alveolar surface area and altered elastic properties. Alveolar septal membranes weaken and stretch, causing an enlargement of alveoli and a reduced surface area. Changes occurring in the alveolar septal wall result in a nearly linear decrease of surface area between the ages of 20 and 80 years, such that by 80 years the surface area is reduced by approximately 30% (Mauderly, 1979). There is little age-related change of breathing patterns of adults at rest although there is a slight trend toward a larger minute ventilation with age. The minute ventilation during exercise increases with age (Mauderly, 1979). Thus, the pulmonary deposition fraction, mass rate and deposited mass per unit surface area increase nearly linear between the ages of 20 and 80 years by approximately 30%.

5. Deposition and physical exertion

Earlier studies (Freijer et al., 1997) indicate the PM deposition dependency on the level of physical exertion. Information on this dependency as well as on the activity patterns is necessary for an estimate of the actual exposure of a whole population. The CIIT/RIVM Yeh-Schum 5-lobe limited multiple-pass particle deposition model is used to calculate aerosol deposition in human adult at different levels of physical exertion. The model uses data made available by Yeh and Schum (1980) that characterises individual airways at the level of the segmental bronchi, but describes the airways within each lobe in a single-path manner. A separate symmetric tree represents each of the five lobes. Levels of physical exertion for adults, corresponding representative activities and corresponding minute ventilation (CARB, 1987) used in the calculation are presented in Table 2. Default human breathing frequency and tidal volume during resting breathing in CIIT/RIVM model is 12 min^{-1} and 625 ml (ICRP, 1994). The breathing frequency and tidal volume for different physical exertion levels (Table 2) is calculated from minute ventilation keeping the ratio of breathing frequency

Table 2. Levels of physical exertion for adult, corresponding representative activities and breathing parameters.

Minute ventilation, l/min	Breathing frequency, min^{-1}	Tidal volume, ml	Exertion level	Representative activity
5	10	500	Rest	Sleep
7.5	12	625	Rest	Awake
13	16	813	Light	Walk (4 km/h); washing clothes
19	19	1,000	Light	Walk (5 km/h); bowling; scrubbing floors
25	22	1,136	Light	Dance; push a 15 kg wheelbarrow; building activities; piling firewood; walk (7 km/h)
30	24	1,250	Modest	Quiet cycling; pushing a 75 kg wheelbarrow; using a sledgehammer
35	26	1,346	Modest	Climb 3 stairs; play tennis; digging soil
40	28	1,429	Modest	Cycle (23 km/h); walk in snow; digging a trench; jogging
59 (55-63)	34	1,735	Heavy	Skiing cross-country; mountaineering; climbing stairs with weight
72	37	1,946	Very heavy	Squash and handball; chopping wood;
85	40	2,125	Very heavy	Running (18 km/h); cycle racing
100 (>100)	44	2,273	Extremely heavy	Marathon; triathlon; cross-country ski race

and tidal volume nearly constant. For normal augmenters, the switch to oronasal breathing (combined nose and mouth breathing) is considered to occur at a minute ventilation of 35.3 l/min. Partitions of airflow between the nose and mouth as given by Niinima et al. (1981) are used for the oronasal breathing. The partitioning flow is assumed to be the same for inhaled and exhaled air. For minute ventilation lower than this value, breathing is only through the nose. Therefore, the calculations present a discontinuity at this point. Calculations are performed for monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 µm to 10 µm and with a particle density of 1 g/cm^3. The deposited mass rates were calculated for an aerosol concentration of 140 µg/m^3.
Results on aerosol deposition as a function of physical exertion for different particle sizes are shown in Figure 6. The head deposition fractions for 1.3 µm, 2.5 µm and 5 µm particles increase from rest to light exercise. They decrease with a factor of respectively 2.3, 1.8 and 1.5 and further stay about constant when breathing is changed from nasal to oronasal at modest and heavy exercise with minute ventilation of 40 l/min and higher. The head deposition fraction of ultrafine particles decreases slightly from rest to light exercise.

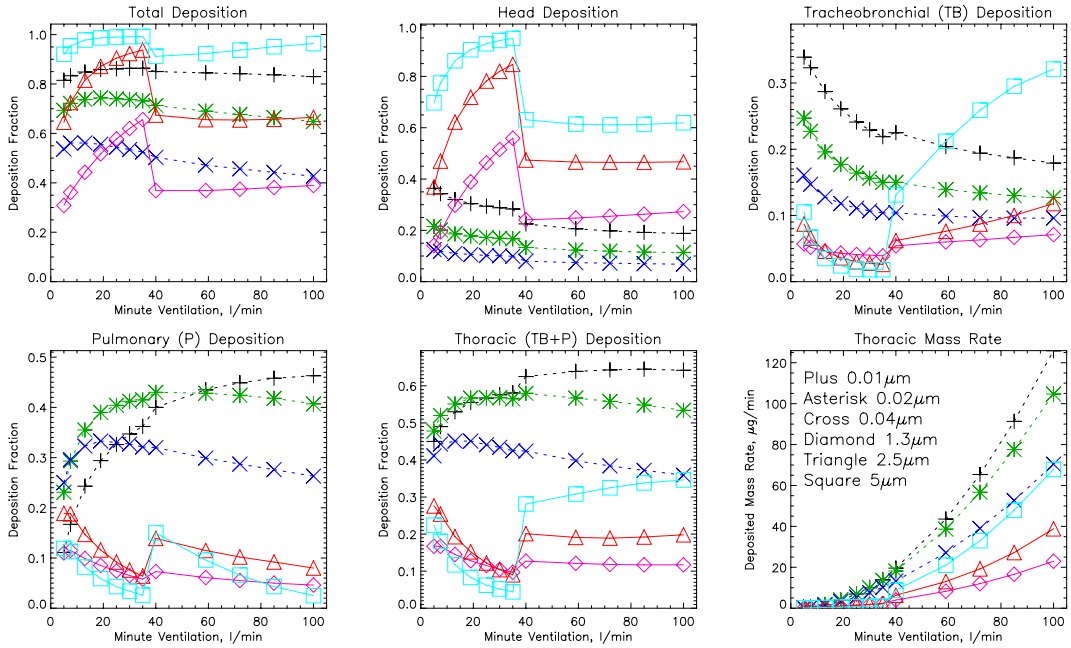

Figure 6. Dependency of aerosol deposition in human adults on physical exertion expressed as minute ventilation for different particle sizes. Aerosol concentration used for mass calculation is 140 µg/m^3.

Tracheobronchial deposition fractions for ultrafine particles of 0.01 µm, 0.02 µm and 0.04 µm decrease from rest to light exercise, decrease slightly further to heavy exercise for 0.01 µm particles and stay constant for 0.04 µm particles. Tracheobronchial deposition fraction for coarse particles decreases slightly from rest to light exercise and rises when breathing is changed from nasal to oronasal. It increases from modest to heavy exercise especially for 5 µm particles. Tracheobronchial deposition fraction of ultrafine particles is larger than deposition fraction of coarse particles at rest, light and modest exercise, however, at heavy exercise the deposition fraction of 5 µm particles is larger than that of ultrafine ones. Pulmonary or alveolar deposition fraction of ultrafine particles increases from rest to light exercise, deposition fraction of coarse 2.5 µm and 5 µm particles decreases from rest to light exercise, rises when breathing is changed from nasal to oronasal and decreases slightly from

modest to heavy exercise. Thoracic deposition fraction shows a light increase for 0.01 μm and 0.02 μm particles and a decrease for 2.5 μm and 5 μm particles from rest to light exercise. Deposited thoracic mass rate increases with increasing physical exertion, faster for heavy exercise. At light exercise with a minute ventilation of 25 l/min the deposited thoracic mass rate is 13 times larger than at rest awake (7.5 l/min) for 0.01 μm particles and 4 times larger for 5 μm particles. At modest exercise with minute ventilation of 40 l/min the deposited thoracic mass rate is 36 times larger than at rest awake (7.5 l/min) for 0.01 μm particles and 44 times larger for 5 μm particles.

6. Sensitivity analysis to model input

6.1. Functional residual capacity

The CIIT/RIVM Yeh-Schum 5-lobe symmetric particle deposition model is used to calculate aerosol deposition in human adults for different input parameters. First, the dependency on functional residual capacity (FRC) was investigated. FRC is defined as the volume of the lung at end of a normal expiration. The default value used in the model for FRC is 3,300 ml (ICRP, 1994). FRC values for human lungs have been correlated with age and height for adult Caucasian males and females by Morris et al. (1984), who suggested the empirical relationship shown in Figure 7. However, standard deviation of the individual FRC from this relationship was ±1,060 ml for women and ±1,460 ml for men. Aerosol deposition fractions calculated with FRC 2,000 ml, 3,300 ml and 5,000 ml are presented in Figure 8. Tracheobronchial deposition fractions are almost the same for al three FRCs. Pulmonary or alveolar deposition fractions are most influenced by FRC. The smallest FRC gives the largest deposition fractions. The difference in FRC of 1,300 ml leads to at least 25% difference in pulmonary deposition fractions and at least 10% in thoracic deposition fractions for a whole range of particle sizes, and less than 10% in tracheobronchial deposition fractions for coarse particles.

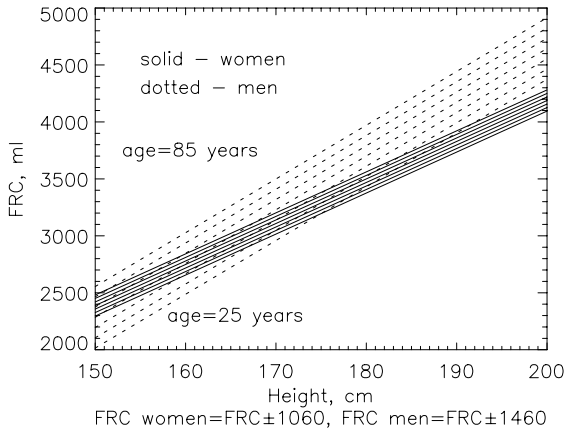

Figure 7. Empirical relationship of FRC as a function of height and age between 25 and 85.

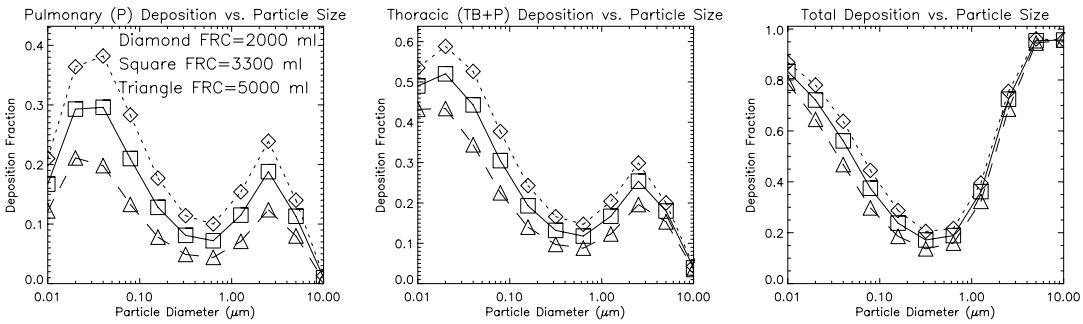

Figure 8. Pulmonary, thoracic and total aerosol deposition fractions in human as a function of particle diameter for FRC 2000 ml (diamonds), 3300 ml (squares) and 5000 ml (triangles).

6.2. Upper respiratory tract or head volume

The upper respiratory tract (URT) volume is the volume of the respiratory tract from the nostril or mouth down to the pharynx. In humans, the oral cavity and nasal passages are assumed to occupy the same volume. Calculations were performed with the URT or head volume of 20 ml (corresponding to an age of 8 years), 50 ml (default value in the human model) and 70 ml. Smaller URT volume leads to larger thoracic deposition fractions. However, the dependency on URT is weak. The change of URT volume from 50 ml to 70 ml and from 50 ml to 20 ml leads to decrease and increase, respectively, in tracheobroncial deposition of 3-4.5% and 4-7%; in pulmonary deposition of up to 9% and 8-12%; in thoracic deposition of 2-7% and 6-10%.

6.3. Particle properties

Calculations were performed for aerosol particle densities of 0.9 g/cm^3, 1 g/cm^3 and 1.1 g/cm^3. No significant differences were found in deposition fractions. Aerosol concentration has no influence on deposition fractions. To determine deposited aerosol mass, mass rate or the number of deposited particles, deposition fractions have to be multiplied by aerosol concentration.

6.4. Nasal, oral and oronasal breathing

Deposition calculations were performed for nasal, oral and oronasal breathing. In case of nasal breathing inspiration and expiration is through the nose so that head deposition is restricted to the nasopharyngeal passages. The URT volume specifies the total volume of the nasal passages. In case of oral breathing inspiration and expiration is through the mouth only and therefore head deposition is restricted to the mouth cavity. The URT volume specifies the total volume of the mouth cavity. Head deposition by impaction and diffusion is determined using empirical functions discussed in ICRP (1994). Oronasal breathing is combined nose and mouth breathing. The airflow partitioning between the nose and mouth is as given by Niinima et al. (1981). Two types of individuals have been considered, normal augmenters and mouth breathers. For normal augmenters, the switch to oronasal breathing is considered to occur at a minute ventilation of 35.3 l/min; for minute ventilation below this value, breathing is through the nose only. Habitual mouth breathers are considered to breathe through the nose and mouth simultaneously, even at rest. Figure 9 shows the head, tracheobronchial and pulmonary deposition fractions in human for nasal, oral and oronasal breathing. Due to reduced head deposition, the thoracic deposition fractions are largest for oral breathing and lowest for nasal breathing, the deposition fractions for oronasal breathing lay in between. Tracheobronchial and pulmonary deposition fractions are largest for oral breathing, especially for coarse particles, respectively of 5 μm-10 μm and 2.5 μm-5 μm. In case of oral breathing tracheobronchial and pulmonary deposition fractions of 5 μm particles are 3 times larger than in case of nasal breathing. The difference between quiet and heavy oral or oronasal breathing is qualitatively the same as discussed for nasal breathing in 4.2.4.
Thus, persons with chronic obstructive pulmonary diseases (COPD) often having oral breathing pattern have a larger risk concerning coarse particle deposition than nasal breathers.

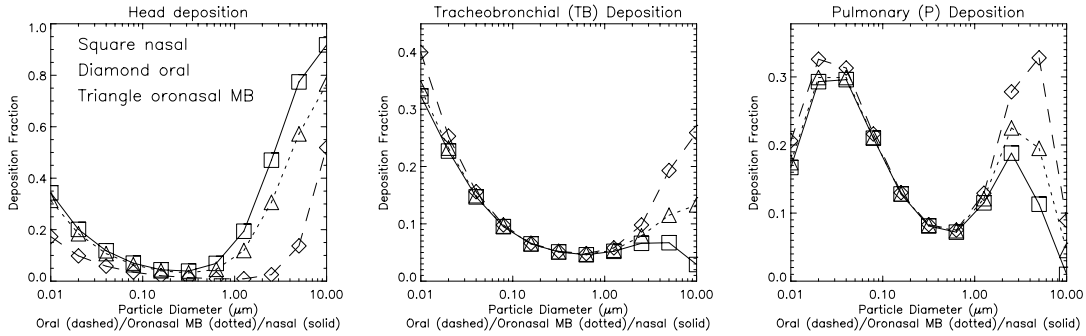

Figure 9. Head, tracheobronchial and pulmonary deposition fractions in human for nasal, oral and oronasal breathing.

6.5. Expiration fraction and pause fraction

Chronic obstructive pulmonary diseases (COPD) comprise asthma, bronchitis and emphysema. For deposition calculations of COPD patients a common respiratory abnormality in these three conditions is a slower rate of forced expiration (Freijer et al., 1997). Obstructive airways diseases also affect the breathing patterns, airway diameter and respiratory tract geometry. The influence of a longer than normal expiratory fraction is studied. Other breathing parameters and lung morphometry are kept constant. Figure 10 shows head, tracheobronchial and pulmonary deposition fractions in humans with expiratory fraction of 0.75 (COPD), quiet (7.5 l/min) or heavy (35 l/min) breathing and an expiratory fraction of 0.5 (normal). The head deposition is larger for coarse particles when exhalation time is longer, especially in case of heavy breathing. This leads to lower tracheobronchial deposition and lower pulmonary deposition for coarse particles. However, the pulmonary deposition for ultrafine particles is larger, especially in case of heavy breathing.

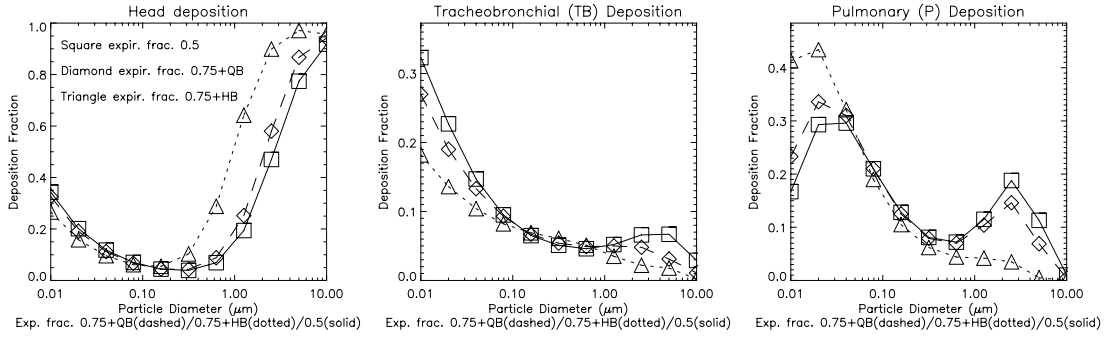

Figure 10. Head, tracheobronchial and pulmonary deposition in human for expiratory fraction 0.75 (person with COPD) quiet and heavy breathing, and 0.5 (normal) quiet breathing.

Alterations in the pattern of breathing may also include the pause-time between breaths (Freijer et al., 1997). Calculations were made with the pause fraction of 0.3, which means the ratio of the time spent during the pause between the inhalation and exhalation to the total breathing period. Other breathing parameters and lung morphometry are kept constant. Figure 11 shows head, tracheobronchial and pulmonary deposition fractions in human with pause fraction of 0.3 (COPD), quiet (7.5 l/min) or heavy (35 l/min) breathing and without the pause between inhalation and exhalation (normal). The tracheobronchial deposition is slightly larger when there is a pause between inhalation and exhalation, it is decreasing from quiet to

heavy breathing due to increasing head deposition. The pulmonary deposition is larger when there is a pause between inhalation and exhalation. For heavy breathing the pulmonary deposition of ultrafine particles is increasing, the pulmonary deposition of coarse particles is decreasing.

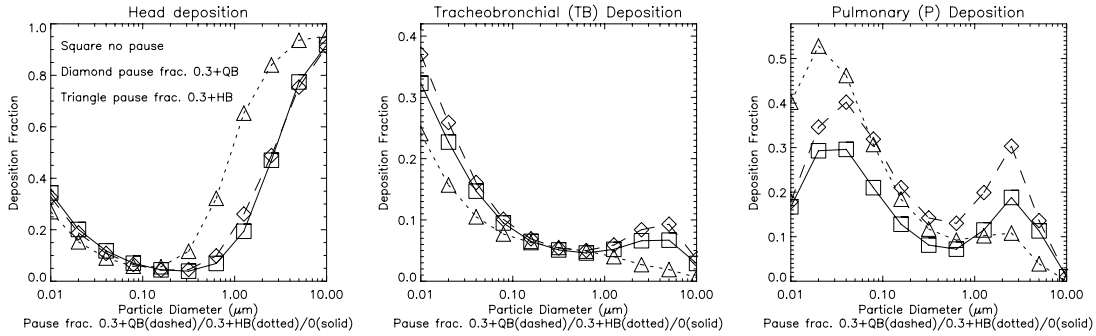

Figure 11. Head, tracheobronchial and pulmonary deposition in human with no pause between inhalation and exhalation and quiet breathing, and with pause fraction of 0.3, quiet and heavy breathing.

In general, humans with compromised airways exhibit a larger tidal volume and a higher breathing frequency than healthy humans (Goldberg and Lourenco, 1973). This leads to higher aerosol mass and mass rate deposition even if deposition fraction is equal. However, to estimate aerosol deposition fractions in persons with COPD the corresponding lung morphometries should be developed and included into the model.

7. Deposition in rat and human

An important issue in human risk assessment is animal-human extrapolation of dosimetry. The multiple-path aerosol deposition model for a rat (Anjilvel and Asgharian, 1995) incorporates asymmetry in the lung branching structure and calculates deposition at the individual airway level. Detailed morphometry up to the level of the terminal bronchioles was available for the 2,404 conducting airways of a Long Evans rat (Raabe et al., 1976), which in addition does not display significant inter-individual variation (Menache et al., 1991). 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). For the acinar regions, the model provides average deposition results for each generation. The airways are separated so as to identify the six lobe structure of the rat lung. Results using this model show good agreement with experimental data for regional deposition in the rat lung (Raabe et al., 1975; Anjilvel and Asgharian, 1995).
Here, analysis of differences in deposition between humans and rats at identical levels of exertion and aerosol properties is performed. Deposition calculations were performed with the 5 lobe lung model for humans and with the multiple-pass model for rats. Monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 μm to 10 μm and particle density of 1 g/cm^3 are considered. The deposited mass rates were calculated using the aerosol concentration of 140 μg/m^3. Following model input parameters were used: fractional residual capacity of 3,300 ml for humans and 4 ml for rats, upper respiratory tract or head volume of 50 ml for humans and 0.42 ml for rats. Breathing frequencies and tidal volumes at different levels of exertion for humans and rats are shown in Table 3, the nasal breathing scenario (rats are obliged nose breathers) was used with equal breathing time during inhalation and exhalation, and no pause in between.

Table 3. Definition of respiratory parameters for specified human physical states (sleep, rest, light exercise) and corresponding respiratory parameters for rats.

Rat			Human		
Breathing frequency, min^{-1}	Tidal Volume, ml	Minute Ventilation, ml/min	Minute Ventilation, ml/min	Breathing frequency, min^{-1}	Tidal Volume, ml
83	1.7	143	5,000	10	500
102	2.1	214	7,500	12	625
162	3.3	543	19,000	19	1,000

The respiratory conditions in the Table 3 describe three states of human physical activity: sleep, awake rest and light exercise (CARB, 1987). A correlation between respiratory states for humans and rats was established through the minute ventilation, the minute ventilation for rats increases by the same factors as for humans. The increased physical activities analogous to human conditions can be simulated in rats by elevated concentrations of CO_2 inhaled (Martonen et al., 1992). The breathing frequency and tidal volume for humans and for rats awake or at rest are respectively from ICRP (1994) and from Mauderly et al. (1979). The ratios of breathing frequency and tidal volume are kept nearly constant.

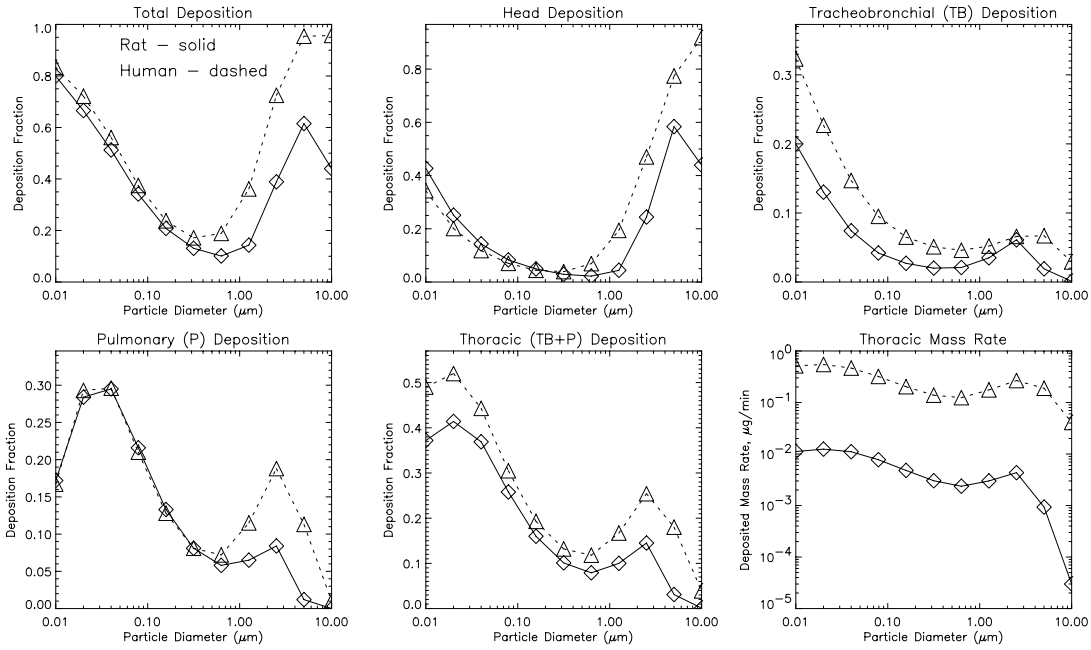

Figure 12. Comparison of total, head, tracheobronchial, pulmonary, thoracic aerosol deposition fractions and deposited thoracic mass rate in rats and humans for different particle sizes. Fractional residual capacity is 3300 ml for humans and 4 ml for rats, upper respiratory tract volume is 50 ml for humans and 0.42 ml for rats. Minute ventilation corresponding to awake rest is 7500 ml/min for humans and 214 ml/min for rats. Aerosol concentration used for mass calculation is 140 μm/m^3.

Comparisons of total, upper respiratory tract, tracheobronchial, pulmonary, thoracic aerosol deposition fractions and deposited thoracic mass rates for humans and rats at awake rest are shown in Figure 12. While deposition of coarse mode particles increases significantly with particle size because of impaction either in the head or tracheobronchial 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 is relevant for particle sizes larger than 3-4 μm for rats and sizes larger than about 8 μm for humans and is more significant for rats than for humans. Inhalability adjustment (Menache et al., 1995) does not change significantly deposition results for humans, the tracheobronchial deposition fraction reduces 3.5% and thoracic deposition fraction 2.5% for 10 μm particles. For rats the nasal deposition fraction during inhalation reduces about 1.5 times for 5 μm particles and more than 2 times for 10 μm particles when accounting for inhalability. As a result tracheobronchial and pulmonary deposition fractions are reduced about 25% for 5 μm particles.
Upper respiratory tract deposition fractions are larger for humans than for rats for fine and coarse particles (larger than 0.3 μm), and slightly lower for ultrafine particles. Tracheobronchial and thoracic deposition fractions are larger for humans than for rats. Pulmonary deposition fractions are larger for humans than for rats for fine (larger than 0.3 μm) and coarse particles. Deposited thoracic mass rates are 45-200 times larger for humans than for rats. It should be noted, that the acinar deposition distributions for large particles have significant tails (see Figure 3) for humans and for rats. This means that significant differences in deposition fractions of large particles exist among various alveolar regions (Asgharian et al., 2001; Anjilvel and Asgharian, 1995).

Table 4. Human-rat extrapolation coefficients $k_i(d)$ for tracheobronchial, pulmonary and thoracic aerosol deposition fractions for sleep, rest and light exercise.

Particle size, μm	Tracheobronchial human/rat	Pulmonary human/rat	Thoracic human/rat
Minute Ventilation = 5,000 ml/min (human) and 143 ml/min (rat)			
0.01	1.67	0.93	1.40
0.02	1.78	1.03	1.32
0.04	2.01	1.00	1.25
0.08	2.22	0.96	1.20
0.16	2.43	0.94	1.22
0.32	2.55	1.00	1.33
0.63	2.47	1.29	1.61
1.26	2.04	1.90	1.94
2.51	1.61	2.15	1.94
5.01	3.18	4.41	3.73
Minute Ventilation = 7,500 ml/min (human) and 214 ml/min (rat)			
0.01	1.62	0.97	1.32
0.02	1.75	1.03	1.26
0.04	1.99	1.00	1.20
0.08	2.26	0.97	1.18
0.16	2.41	0.96	1.21
0.32	2.55	1.00	1.31
0.63	2.19	1.24	1.49
1.26	1.49	1.77	1.67
2.51	1.08	2.24	1.75
5.01	3.53	9.42	5.81
Minute Ventilation = 19,000 ml/min (human) and 543 ml/min (rat)			
0.01	1.54	0.98	1.18
0.02	1.75	1.01	1.16
0.04	2.07	0.99	1.15
0.08	2.38	0.99	1.18
0.16	2.54	0.99	1.24
0.32	2.36	1.01	1.32
0.63	1.52	1.11	1.25
1.26	0.73	1.27	1.02
2.51	0.80	3.52	1.95
5.01	6.00	59.00	16.60

Table 4 shows calculated human-rat extrapolation coefficients $k_i(d)$ for tracheobronchial, pulmonary and thoracic aerosol deposition fractions for sleep, rest and light exercise. The human exposure to aerosols can be extrapolated from the rat exposure by following equations:

$$^{H}DF_i(d) = k_i(d) \cdot {}^{R}DF_i(d)$$

$$^{H}DMR_i(d) = k_i(d) \cdot V \cdot \frac{t_H}{t_R} \cdot \frac{N_H}{N_R} \cdot {}^{R}DMR_i(d)$$

$$^{H}SDMR_i(d) = k_i(d) \cdot V \cdot \sigma_i \cdot \frac{t_H}{t_R} \cdot \frac{N_H}{N_R} \cdot {}^{R}SDMR_i(d),$$

where DF is deposition fraction, DMR is deposited mass rate in μg/min, SDMR is standardised deposited mass rate per unit area in μg/(min m^2) or per alveolus in μg/min, H stands for human, R stands for rat, i is the lung region, k_i are rat-human extrapolation coefficients from Table 4, d is particle aerodynamic diameter, V is the minute ventilation coefficient human/rat, σ is the lung surface area coefficient or alveolar number coefficient rat/human, N is aerosol concentration in μg/m^3, t is exposure time. The minute ventilation coefficient V human/rat is 35.014 (see Table 3). The lung surface area coefficients and the alveolar number coefficient rat/human are shown in Table 5. In contrast to the stabilising of lung surface area in young adult humans, the lung surface area of rats continues to increase beyond the age of sexual maturity. The lung surface area for the rats increases rapidly from about 0.55 m^2 at the age of 4 month to about 0.8 m^2 at the age of 8 month, and continues to increase at a slower rate to about 0.88 m^2 at the age of 16 month (Mauderly, 1979). The human lung surface area is a sum of the alveolar surface area of 143±12 m^2 (Gehr, 1978) and the airway surface area of 7.3 m^2 calculated from the 5 lobe human model. The tracheobronchial surface area for humans is calculated from the 5 lobe model as a sum of surface areas of the first 16 airway generations. The tracheobronchial surface area for rats is calculated from the multiple-pass model for rats as a sum of surface areas of the first 15 airway generations. The alveolar number coefficient rat/human comes from the multiple-path rat model and the 5 lobe human model. To achieve exposure levels for rats, which are identical to exposure levels of humans, one can change aerosol concentration or exposure time, or both in order to satisfy above equations.

Table 5. The thoracic and tracheobronchial rat/human lung surface area coefficients σ_i, and the rat/human alveolar number coefficient σ_i.

Rat age, months	Thoracic surface area coefficient rat/human	Tracheobronchial (TB) surface area coefficient rat/human	Alveolar number coefficient rat/human
4	$3.66 \cdot 10^{-3}$	$7.96 \cdot 10^{-3}$	$4.05 \cdot 10^{-2}$
8	$5.32 \cdot 10^{-3}$		
16	$5.86 \cdot 10^{-3}$		

8. Conclusions

The CIIT/RIVM particle deposition model allows calculation of PM deposition fractions and deposited mass for humans and rats, and includes age-specific human lung models. Human regional depositions for different particle sizes were calculated for a default set of physiological and breathing parameters as well as lobar depositions and alveolar deposition distribution for a stochastic human lung. Large individual variations exist in regional deposition due to the differences in fractional residual capacity (FRC) and breathing parameters, in lobar and alveolar deposition due to differences in lung geometry.

For coarse particles (5 μm and 10 μm) tracheobronchial and thoracic deposition fractions are significantly larger for children (ages of 0-15 years old) than for adults (18 and 21 years old), mainly due to the increase in head deposition from children to adults. The difference in tracheobronchial and thoracic deposition fractions between children and adults increases with particle size. Pulmonary or alveolar deposition fractions of 5 μm particles for 8-14 years old children are higher than for adults. For coarse particles deposited aerosol mass rates in the thoracic region of 8-14 years old children for 5 μm particles and of 2-14 years old children for 10 μm particles are higher than in adults (18 and 21 years old). Deposited aerosol mass rates in tracheobronchial region per unit surface area decrease with progressing age, however, individual differences in the tracheobronchial surface area and in the tidal volume can disturb this dependency leading to even equal depositions per unit surface area for infants and for adults. Pulmonary deposition fractions per alveolus are higher for babies compared to adults, for children of the age of about 2 years and older pulmonary deposition fractions per alveolus does not change significantly. Deposited pulmonary mass rates per alveolus are lower for the age of 2-3 years compared to adults for ultrafine and 2.5 μm particles and higher for 8-14 years old children compared to adults for 5 μm particles. The pulmonary deposition per unit surface area increase nearly linear between the ages of 20 and 80 years by approximately 30%.

Aerosol deposition in human adults was calculated at different levels of physical exertion. Tracheobronchial deposition fraction of ultrafine and coarse particles decreases slightly from rest to light exercise. Tracheobronchial deposition fraction for coarse particles rises when breathing is changed from nasal to oronasal and increases from modest to heavy exercise. Pulmonary deposition fraction of ultrafine particles increases from rest to light exercise, deposition fraction of coarse particles decreases from rest to light exercise, rises when breathing is changed from nasal to oronasal and decreases slightly from modest to heavy exercise. Deposited thoracic mass rate increases with increasing physical exertion, faster for heavy exercise. The thoracic deposition of ultrafine particles is higher than the thoracic deposition of fine and coarse mode particles for light to modest exercise. When breathing is changed from nasal to oronasal the thoracic deposition behaviour of fine and coarse particles changes - for modest to heavy exercise the thoracic deposition of larger particles is higher.

Variations in fractional residual capacity (FRC) affect mostly the pulmonary deposition fractions. Increase in FRC of about 1.5 l leads to at least 25% decrease in pulmonary deposition fractions.
In case of oral breathing tracheobronchial and pulmonary deposition fractions of coarse particles are larger (3 times for 5 μm particles) than in case of nasal breathing.

A longer than normal expiratory fraction leads to slightly lower tracheobronchial deposition of ultrafine and coarse particles and to slightly lower pulmonary deposition of coarse particles, however, the pulmonary deposition of ultrafine particles is slightly larger. The tracheobronchial deposition is slightly larger for ultrafine and coarse particles when there is a pause between inhalation and exhalation. The pulmonary deposition is larger for all particle sizes when there is a pause between inhalation and exhalation.

Tracheobronchial and thoracic deposition fractions are larger for humans than for rats. Pulmonary deposition fractions are larger for humans than for rats for fine (larger than 0.3 μm) and coarse particles. Deposited thoracic mass rates depending on particle size are 45-200 times larger for humans than for rats at rest. Coefficients for the rat-human extrapolation of deposited mass and standardised deposited mass have been determined for three levels of human physical exertion (sleep, awake rest and light exercise), which allows to achieve equal exposure levels for rats and humans by changing the aerosol concentration or exposure time.

9. Future directions

The current MPPD model is still under development. The ultimate goal is to develop a risk-assessment software package for which dose computation is only the first component of the dose-response prediction. Toward that goal, a number of enhancements to the software package are possible. Various potential additional features and capabilities are briefly discussed below (Miller, 2002).

Asymmetric lung geometry for children
Symmetric lung geometries have limited applicability since only regional predictions can be satisfactorily addressed. The onset of lung injury and disease is site-specific rather than uniformly occurring on airway surfaces. Notably, emerging technologies are enabling toxicologists to examine responses in specific locations at the cellular level. Thus, site-specific dose-response relationships will increasingly need to be examined in PM risk assessments. Current lung geometry models for children are based on symmetric structures. The methods used to generate structurally accurate asymmetric lung geometry for adults can be extended to develop similar models for children. Realistic site-specific, lobar, and regional dose predictions are feasible by generating a pool of age-related stochastic lungs to study the mean and range of deposition in a given age-group.

Deposition of polydisperse particles
Regional and lobar deposition fractions of polydisperse particles are currently being calculated mainly because most of the provided lung geometries have typical-path structure. Only the stochastic lung in humans and Long-Evans rat lung geometry comprise a complete lung airway structures in the current version. Site- and airway-specific deposition calculation of polydisperse aerosol can be included in the software package once more detailed lung structures become available for other cases.

Additional stochastic lung geometries for adults
There are significant lung variations within the population. To be able to study the mean as well as the distribution of dose in the population, a large number of stochastically generated lung geometries need to be developed and various analyses conducted using these geometries. Currently, we do not have a clear understanding of how to select from among the stochastically generated lungs those that would provide insights on regional variation in dose and how this variation contributes to the broader issue of intersubject variability.

Particle clearance with variable exposure scenarios
The current version of the software supports clearance calculations for a given exposure concentration and fixed breathing parameters. The exposure scenario remains similar throughout (i.e., given hours per day, days per week and so on). This is particularly useful for controlled laboratory settings. Such scenarios will not encompass more general situations where a change in environment and activity levels are common occurrence. For example, in chronic exposures as in the case of animals, the lung and breathing parameters change due to animal growth. Both exposure concentration and breathing and lung parameters change in the case of humans in daily life (uncontrolled environment) due to change of environment and activity level. These cases can be covered by including ‘Variable Exposure’ case that is currently supported for deposition calculations only. The addition would require substantial change in the structure of the code that can be included in the next version of the code as a separate task.

Hygroscopic particles
Particles that are composed of inorganic salts such as chlorides or sulfates, or other water-miscible species, are hygroscopic. As these particles travel through the high humidity of the respiratory system, they will grow, which will affect the site of deposition. Therefore, the amount and rate of growth of hygroscopic particles needs to be taken into account for site- or generation-specific deposition calculations

The rate of growth of the particles in the respiratory system has been calculated based on empirical (Xu and Yu, 1985) or mechanistic models. The latter models are based on the rate of diffusion of water vapor to a particle (Hinds, 1982). The models incorporate corrections for molecular diffusion through the noncontinuum regime; they may incorporate multiple volatile materials, change in droplet temperature, and mixtures of soluble materials (Ferron, 1977; Persons et al., 1987; Soderholm and Ferron, 1992; Robinson and Yu, 1998). A model based on these principles can be developed and implemented to calculate particle growth.

As inputs to the model, the particle composition must be specified, including the various inorganic salts and other components that are deliquescent. This composition needs to be presented as a function of particle size. The relative humidity of the ambient air and the change in relative humidity through the respiratory tract also needs to be input into the model. The relative proportion of nasal to oral breathing needs to be specified as the relative humidity in various compartments of the model (nasal passages, oral-pharynx area, trachea, etc.) are influenced by the route of breathing.

The change in particle size can be calculated based on the particle composition within a particle size interval. The particle initially can be assumed to be in equilibrium with the ambient relative humidity. As the particle enters the respiratory system, the relative humidity increases to greater than 99%. Particle growth as a function of the increasing humidity and the length of time spent in the entry region can be computed. The deposition efficiency can be recalculated at the new particle size for the entry region. Particles that are not deposited in the previous generation and that are not yet at their equilibrium size can provide inputs for calculations in the next airway generation.

COPD modeling
Research is needed on developing lung geometries for individuals with chronic obstructive pulmonary disease (COPD) since these individuals have been shown to be particularly susceptible to airborne particles. Current dosimetry models use lung geometry 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 rats needs to be extended to the human situation.

Lung geometry developed for normal adults can be modified by including various degrees of restriction/obstruction and rescaling of the airway dimensions to represent the lungs of individuals with COPD.

Other lung geometries

There are efforts underway in various laboratories to make morphometric measurements of the lung airways in mice and monkeys and to make geometric models of the lung based on the measurements. These models can be included in the MPPD once becoming available. The addition of multiple lung geometries of animals allows for across species exposure data extrapolation from animals to humans.

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