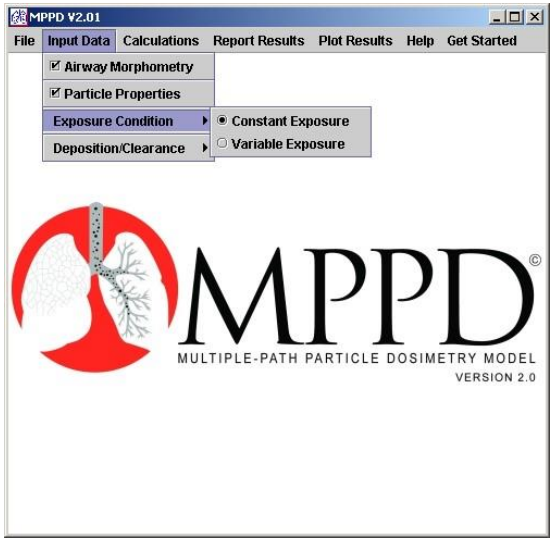
Multiple Path Particle Dosimetry (MPPD) model and its Applications

Bahman Asgharian

Applied Research Associates, Inc., Raleigh, NC



APPLIED RESEARCH ASSOCIATES, INC.®
An Employee Owned Company

Introduction

Why use computational tools to inform dose-response models and toxicological risk assessment?

- Computational dosimetry modeling complements in vitro and inhalation studies.

- Modeling can be faster, cheaper, and can fill gaps not addressed by inhalation studies.

- Dosimetry modeling can be used as a tool for interspecies dose extrapolation.

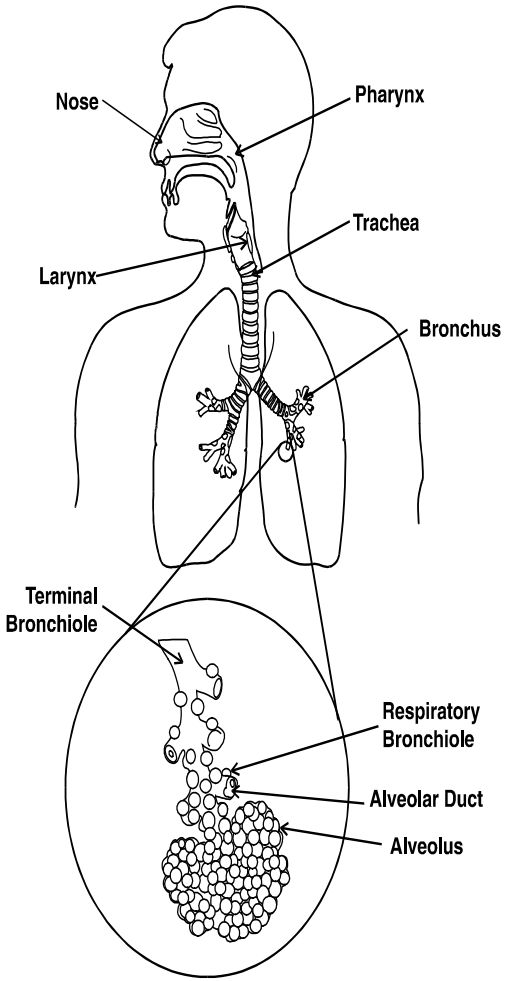
Objectives in Dosimetry Modeling

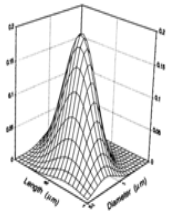
- Develop mechanistic models based on the physical and physiological parameters that govern transport within the respiratory tract.
- Predict total, regional, lobar, and local deposition in the lung.

Modeling approaches:

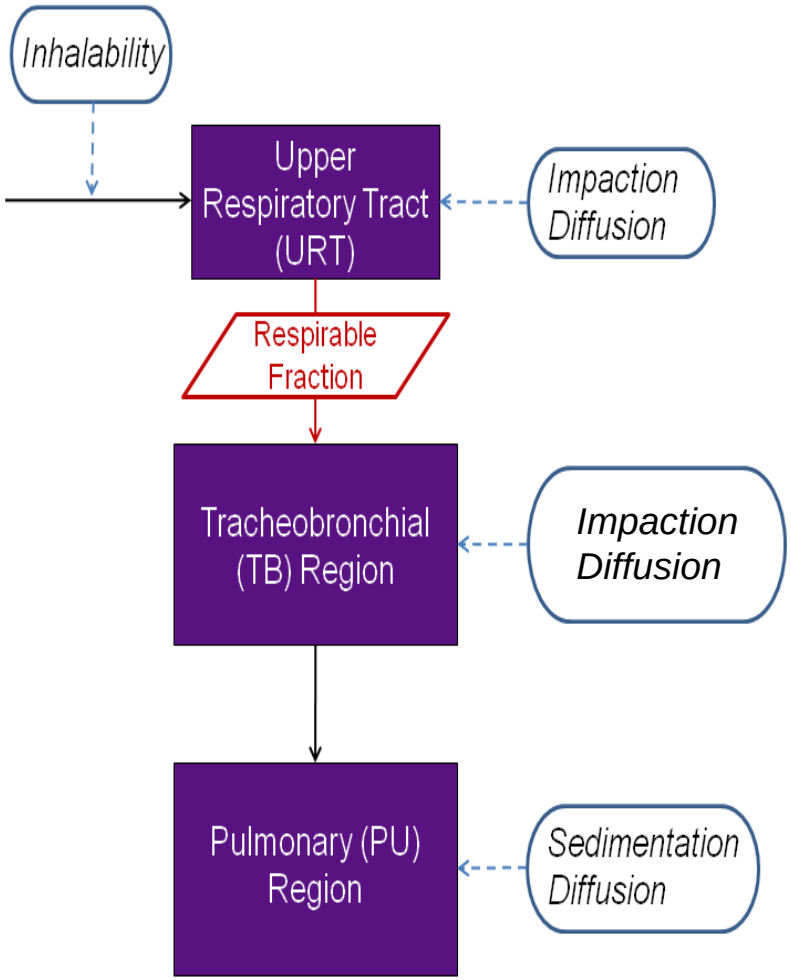
1. Site-specific modeling → Scanned imagery & CFD based
2. Whole-lung modeling → MPPD
3. Hybrid modeling (combining 1 & 2)

Building a Computational Dosimetry Model



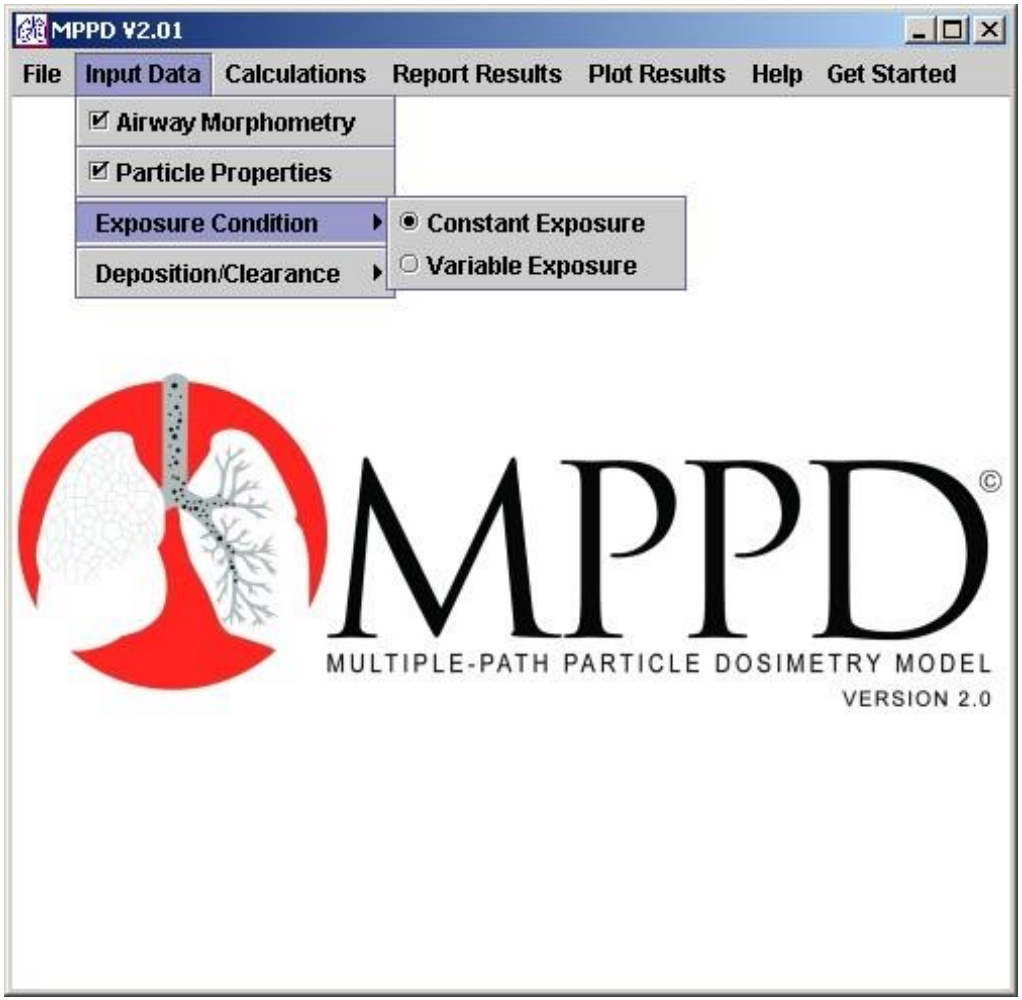


Aerosol size distribution



Multiple Path particle Dosimetry Model

Freely available: http://www.ara.com/products/mppd.htm



Development Team:

ARA & CIIT

- B. Asgharian
- F.J. Miller
- R. Subramaniam
- O.T. Price

Dutch Ministry of Health

Ministry of Housing, Spatial Planning and the Environment

- J. Frier
- Flemming Cassee

Funding

- CIIT/The Hamner
- Dutch Ministry of Health
- CDC/NIOSH, NIH, ONR

NCRP, ICRP, MPPD

	NCRP	ICRP	MPPD
Mathematical model:	Semi-empirical	Semi-empirical	Deterministic: multiple-path
Species	Humans (adults and children), two strains of mouse	Humans (adults and children)	Humans (adults and children), multiple species
Lung geometry	Symmetric lung geometry, asymmetric recently reported	Symmetric lung geometry	typical-path, 5-lobe symmetric, asymmetric
Particles	monodisperse & polydisperse	monodisperse, polydisperse	monodisperse, polydisperse
Breathing routes	nasal & oral (user can define % each pathway)	nasal & oral (user can define % each pathway or used defaults	nasal, oral, oronasal-normal augmenter, oronasal- mouth breather, endotracheal
Clearance	22 total compartments, 17 for lung and TB airways, one for lymphatic system, and four for extrathoracic airways.	three-compartmental alveolar region plus lymph node	TB Mucous clearance many one-compartmental alveolar region plus lymph node
Interface	Must program	Dos & Windows menu driven	Graphical interface with help menu / tutorials

Key MPPD Features

- Calculation of various dose metrics to address intrahuman and interspecies variability
  - Dose in **adults** (symmetric, asymmetric/stochastic lungs)
  - Deposition in **children** of different age groups
  - Dose in **Rats** (Long-Evans & Sprague Dawley)
  - Dose in **Mice** ($B_6C_3F_1$ & BALB/c)
  - Deposition in **rhesus monkeys**, **guinea pigs**, **pigs**, **sheep**, **dogs**, **rabbits**

MPPD Inputs

- Exposure characteristics (mass/number concentration with uniform distribution)
- Particle characteristics (diameter and size distribution)
- Breathing parameters (BF and tidal volume)
- Breathing route (nasal, oral, oronasal, endotracheal)
- Lung parameters (FRC, URT volume)
- Adjustment for inhalability of particles

MPPD Output

Outputs:

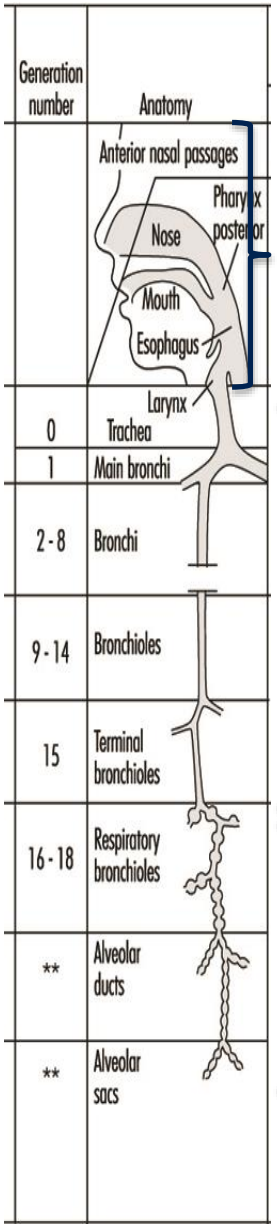
Textual - input parameters, predictions
Graphical - Deposition per generation, lobe, and region
Data files - export to other graphical packages and spreadsheets

The latest version of MPPD can be downloaded from:

https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304

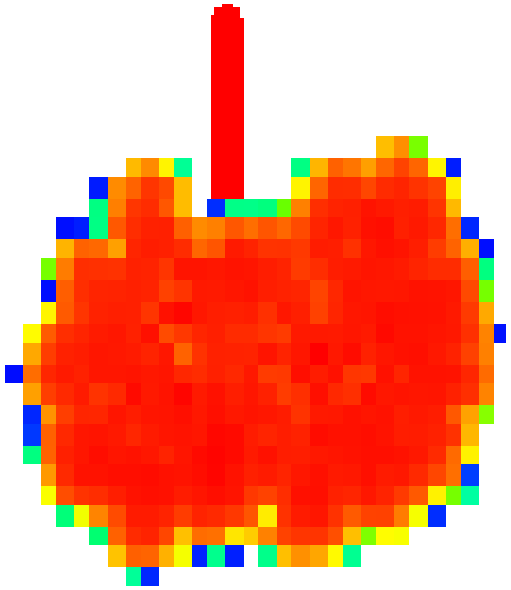
Model Predictions

- **Deposition Predictions**
  - Entire respiratory tract
  - Regional (URT, Tracheobronchial, Alveolar)
  - By Generation (Trachea -> Bronchi . . . Bronchioles -> Alveoli)
  - Lobar (RU, RM, RL, LU, LL)
  - Airway-specific for asymmetric models
- **Retained dose predictions**
  - Airway, generation for TB
  - Regional for PUL
- **Dose Metrics**
  - Deposition fraction (mass deposited / inhaled)
  - Deposited mass (mg)
  - Deposited mass rate (mg/min)
  - Deposited mass per surface area (mg/cm^2)
  - Deposited mass flux ($mg/min/cm^2$)
  - Retained mass (after clearance)



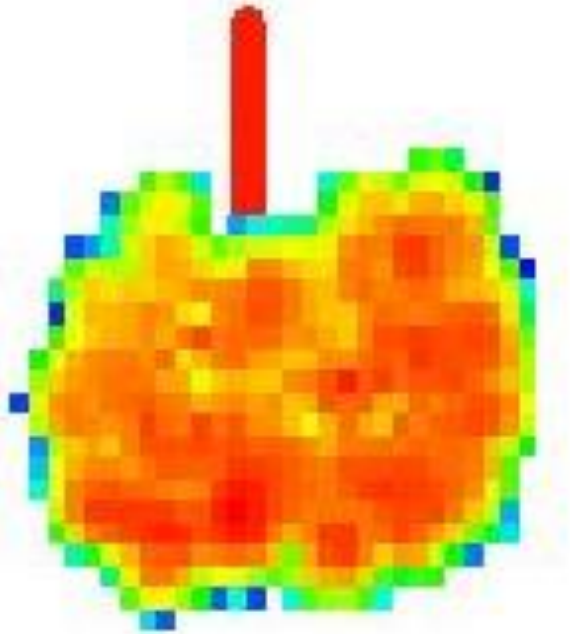
Deposition Distribution

2 nm



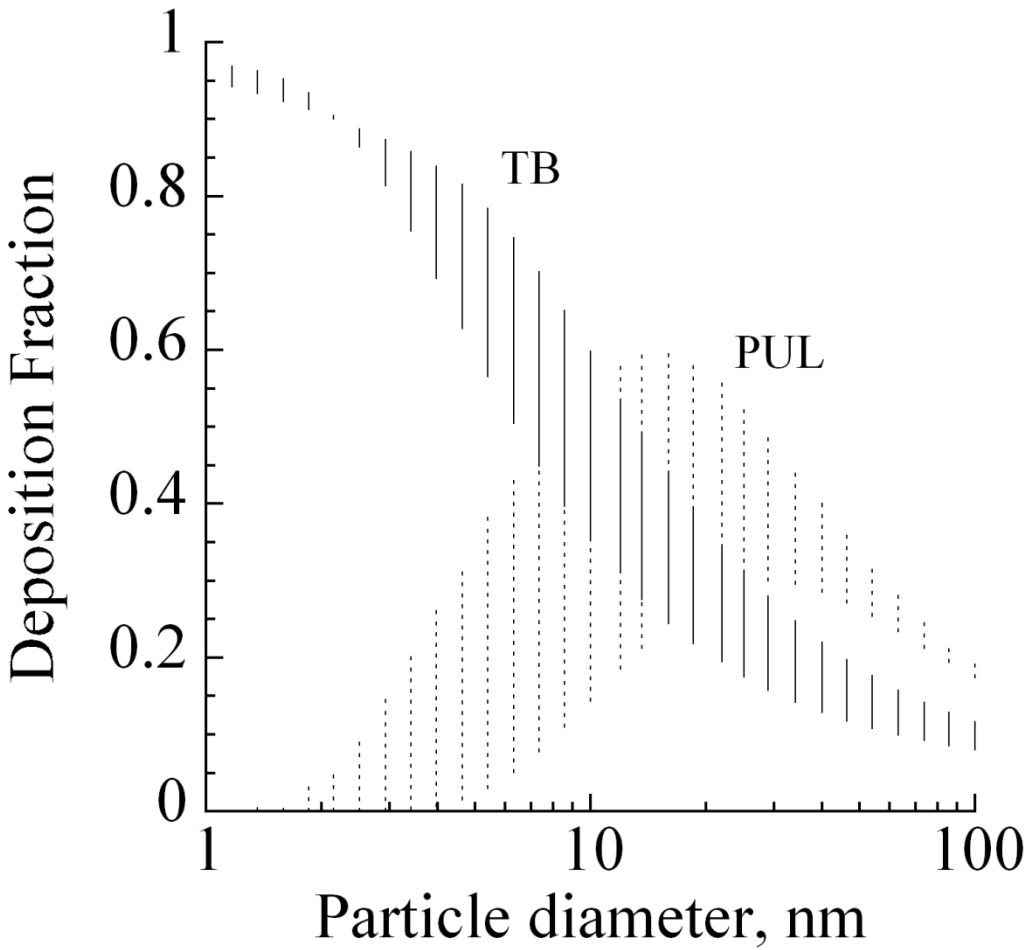
5 nm

10 nm



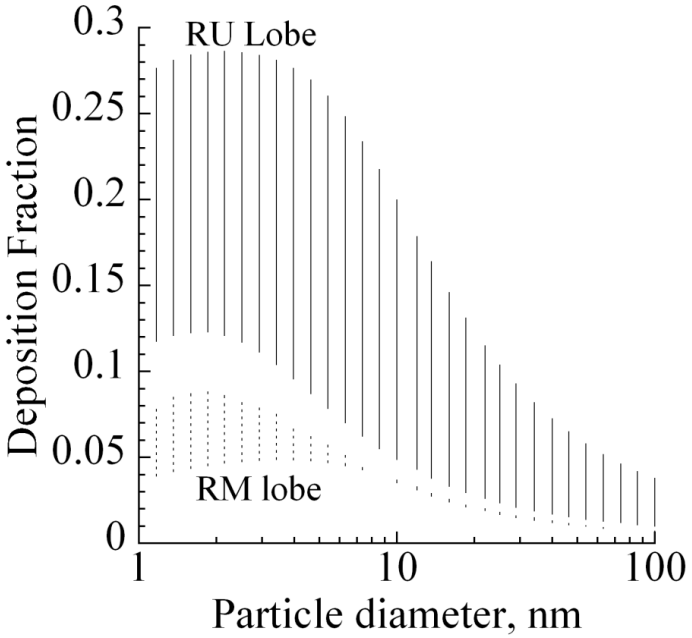
- More homogenous deposition with decreasing particle size (behave like gases)

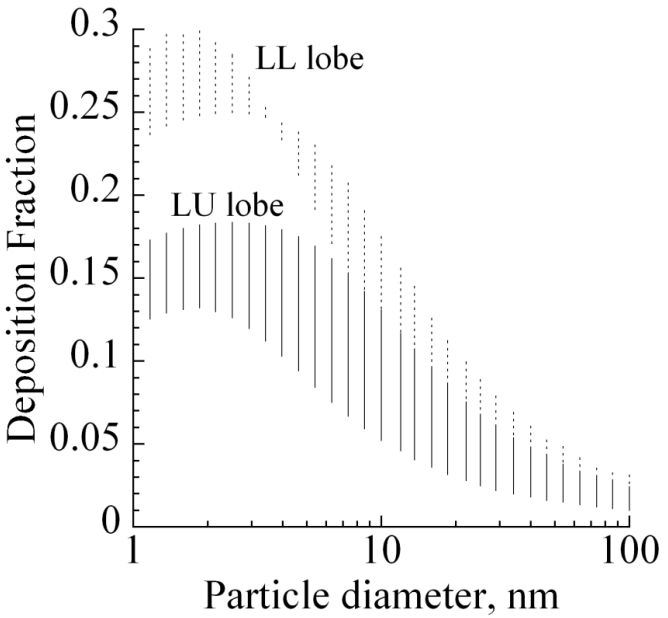
Inter-subject Variability (30 stochastic lungs)

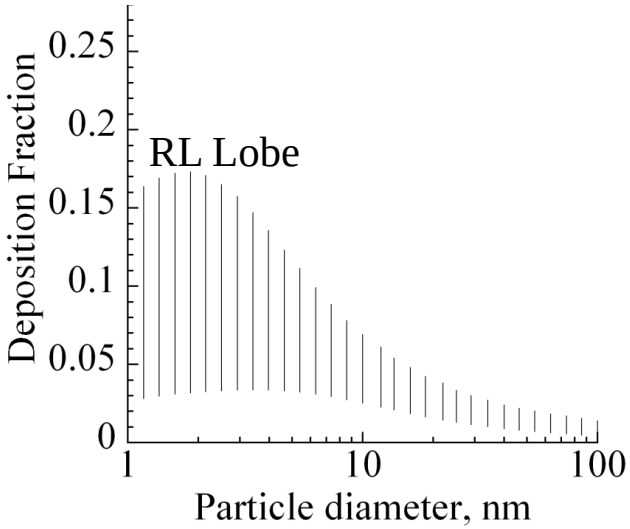


- Less variation in TB and more variation in PUL deposition.

Lobar Deposition

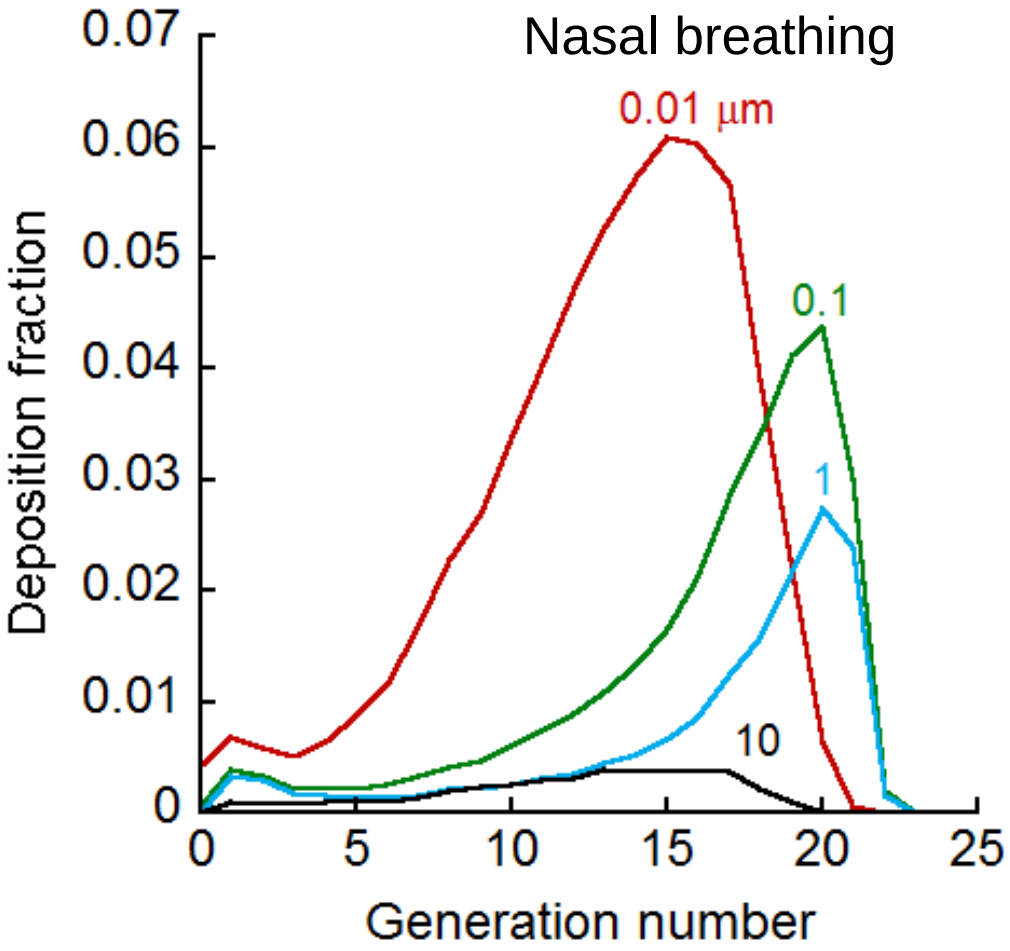






- More variation in RU & RL lobes.
- Highest deposition in RU & LL lobes

Deposition by Generation



Applications of MPPD

Applications in risk assessment

- Establishes comprehensive exposure-dose-response – characterization
- Improves interspecies dose-metric adjustment and extrapolation
- Interfaces with PBPK models to reduce uncertainty
- Aids in design of inhalation exposure studies
- Aids in design of toxicological and human clinical studies.

Other Applications

- Drug delivery by inhalation route
- Protect against CBRN (Chemical, biological, radiological and nuclear) threats

Closing Remarks

- MPPD can be used to predict deposition in the lungs of humans and several other species.
- It predicts the retained dose in humans and rats.
- Can make interspecies extrapolation based on various dose metrics.
- MPPD can be used to predict drug delivery for inert compounds.
- Is a mechanistic model: has potential for extension to different particle types.

References

Asgharian, B., and Price, O.T. (2007). Deposition of Ultrafine (nano) Particles in the Human Lung, *Inhalation Toxicology* 19:1045-1052.

Asgharian, B., Price, O.T., and W. Hofmann, W. (2006). Prediction of Particle Deposition in the Human Lung Using Realistic Models of Lung Ventilation, *Journal of Aerosol Science* 37:1209-1221.

Asgharian, B., Price, O.T., and Oberdörster, G. (2006). The effect of gravity on airflow distribution and particle deposition in the lung, *Inhalation Toxicology* 18(7):473-481.

Asgharian, B. (2004). A Model of Deposition of Hygroscopic Particles in the Human Lung. *Aerosol Science and Technology* 38(9):938-947.

Subramaniam, R.P., Asgharian, B., Freijer, J.I., Miller, F.J., and Anjilvel, S. (2003). Analysis of lobar differences in particle deposition in the human lung. *Inhalation Toxicology* 15:1-21.

Asgharian, B., Hofmann, W., and Bergmann, R. (2001). Particle deposition in a multiple-path model of the human lung. *Aerosol Science and Technology* 34:332–339.

Cassee, F.R., Freijer, R., Subramaniam, R., Asgharian, B., Miller, F.J., Van Bree, L., and Rombout, P.J.A. (1999). Development of a model for human and rat airway particle deposition: implications for risk assessment. *National Institute of Public Health and the Environment Bilthoven, the Netherlands* report no. 650010 018.

Asgharian, B., Miller, F.J., and Subramaniam, R.P.(1999). Dosimetry software to predict particle deposition in humans and rats. *CIIT Activities* 19(3):1-6.

Anjilvel, S., and Asgharian, B. (1995). A multiple-path model of particle deposition in the rat lung. *Fundamental and Applied Toxicology* 28:41–50.