Using Inhalation Dosimetry Models to Predict Deposition of Ultrafine Particles

P. Shade, P. Georgopoulos • Computational Chemodynamics Laboratory (www.ccl.rutgers.edu)
Environmental and Occupational Health Sciences Institute, a Joint Institute of UMDNJ-Robert Wood Johnson Medical School and Rutgers University, Piscataway, NJ

Abstract

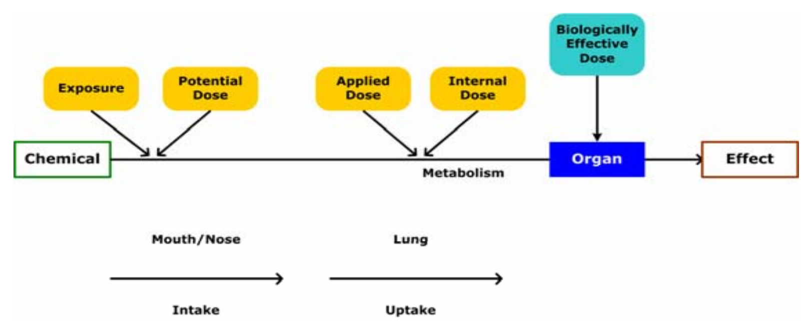
The results of several epidemiological studies suggest that exposure to particulate matter (PM) in ambient air may be associated with an increase in respiratory and cardiovascular morbidity and mortality. Due to certain features and their prevalence in ambient air, ultrafine particles (UFP) may contribute to these adverse health effects. Although ambient concentration is what is measured and regulated, the ultimate biological response is dependent upon the target tissue dose.

Inhalation dosimetry plays a key role in determining the link between environmental exposure to airborne contaminants and observed human health effects. Due to the limited availability of human experimental data and the complex nature of exposure-dose-response scenarios, mathematical modeling is an important tool in studying the mechanisms which dictate the inhaled "dose." Numerous factors affect the inhaled dose, and models include an extensive amount of information regarding physiological and anatomical parameters.

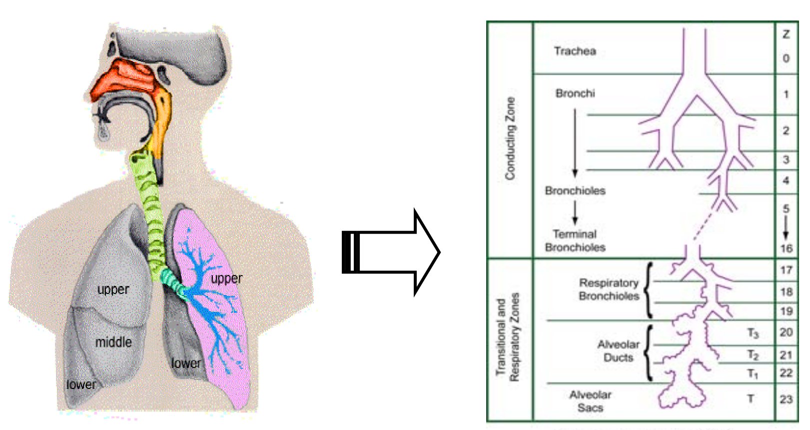
An inhalation module was developed at the Computational Chemodynamics Laboratory (CCL) as part of the Modeling ENvironment for TOtal Risk (MENTOR) system which accounts for the variation in delivered dose due to age, gender, and physical activity. Several models are available which determine the deposition of ultrafine particles in the human airways. These model predictions are compared to one another and to available experimental data.

Inhalation Route: Exposure to Airborne Contaminants

- Exposure is the concentration of a chemical at the boundary of the body.
- The anatomy and physiology of the airways determines the concentration in inspired air (potential dose)
- Determination of the biologically effective dose is key in risk assessment.



Factors Affecting Inhaled Dose

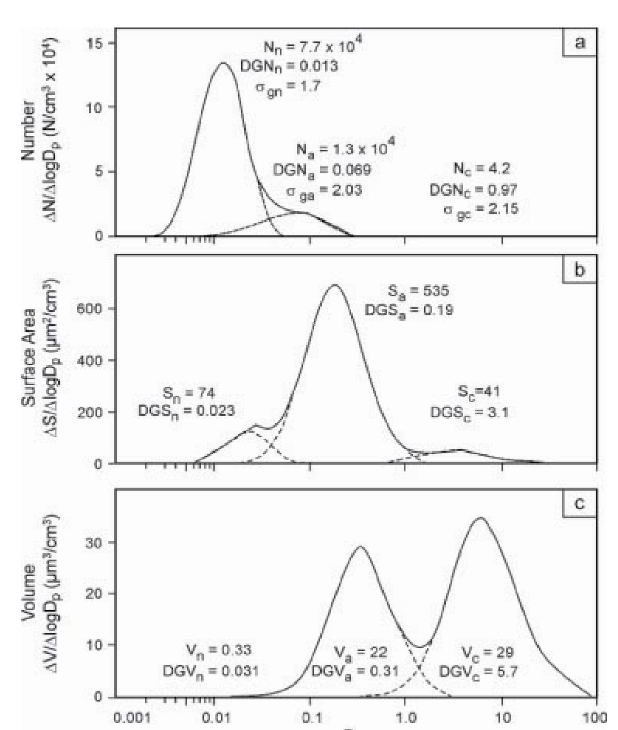


Weibel Model A (1963)

- Particle geometry & physicochemical properties
  - Size, shape, surface area, hygroscopicity, chemical composition, charge, density, solubility
- Lung morphology
  - Respiratory tract (RT) altered by disease, inflammatory state
- Respiration physiology
  - Ventilation rate, activity level, age, gender
- Environmental conditions
  - Humidity, temperature, ambient concentration

Ultrafine Particles:
What Are They & Why Are They Important?

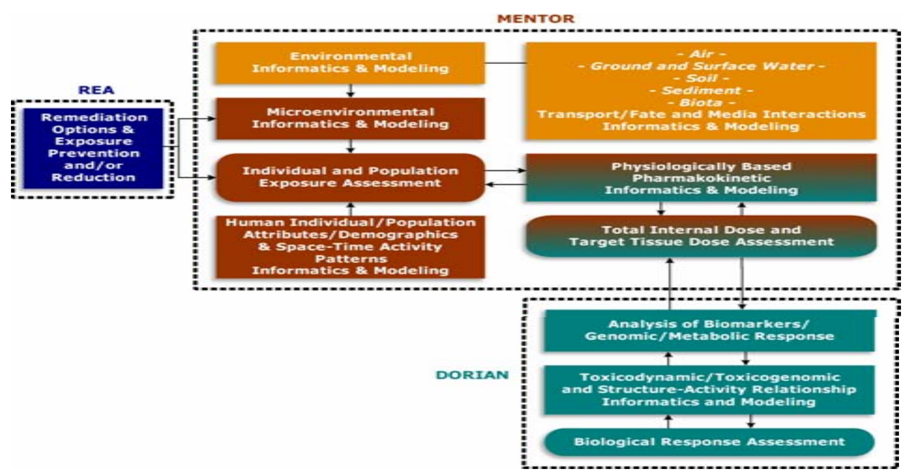
- Particles are classified according to size or aerodynamic diameter (AD) and many terms are used interchangeably. Particles > 100 µm are not generally considered as respirable.
  PM_{10} (coarse): AD < 10 µm $PM_{2.5}$: AD < 2.5 µm
  Fine, Accumulation Mode: AD < 1 µm
  Ultrafine, Nuceli Mode: AD < 0.1 µm
  Nano: AD < 0.01 µm
- UFPs often ignored due to small contribution to overall particle mass
- UFPs often present in high numbers in the atmosphere with measured number concentrations as high as 1×10^7 particles/cm³
- Animal studies suggest UFPs induce greater airway inflammation than similar mass concentrations of larger particles
- Predominant mechanism of deposition is diffusion; the probability of diffusion increases as particle size decreases
- Smaller particles should be favored in the distal airways and alveoli because reduced airflow increases residence times in these regions



Source: Whitby (1978)

MENTOR/SHEDS: Source-to-Dose Exposure Analysis

The Modeling ENvironment for TOtal Risk (MENTOR) / Stochastic Human Exposure and Dose Simulation (SHEDS) framework facilitates the consistent multiscale, source-to-dose, modeling of exposures to contaminants for both individuals and populations.

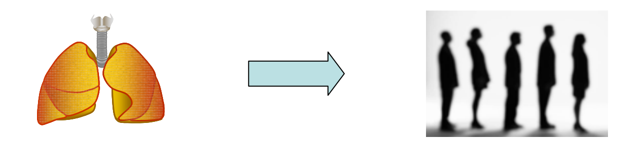


- Both respiratory PM deposition and multimedia/multipathway PBPK models have been implemented with a flexible design.
- Modules are interactive with databases of anatomic and physiological parameters
  - physiological variability due to age, gender, weight, etc.
- continuous temporal variability due to physical activity (metabolic expenditure)

Inhalation Dosimetry Models

Model Attributes
- Standard dosimetry models available to calculate particle deposition and retention

Advantages/Disadvantages
- Empirical and semi-empirical models allow for scaling from individual to population level
- Determination of cumulative lifetime risk
- Expansion to "source-to-outcome" framework; flexible applications



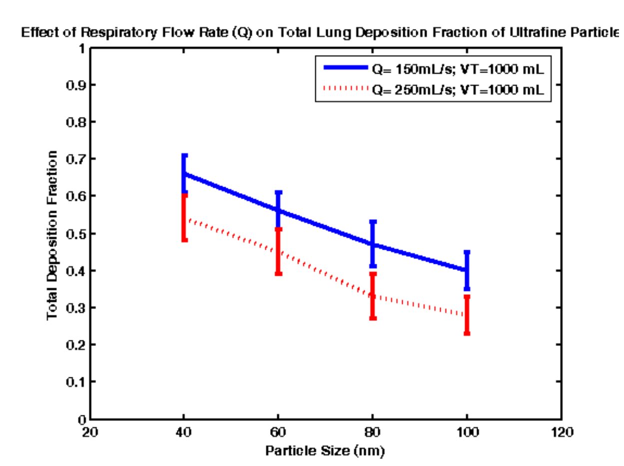
International Commission on Radiological Protection (ICRP)
- Developed to determine deposition and clearance of radionuclides in occupational setting
- Semi-empirical model

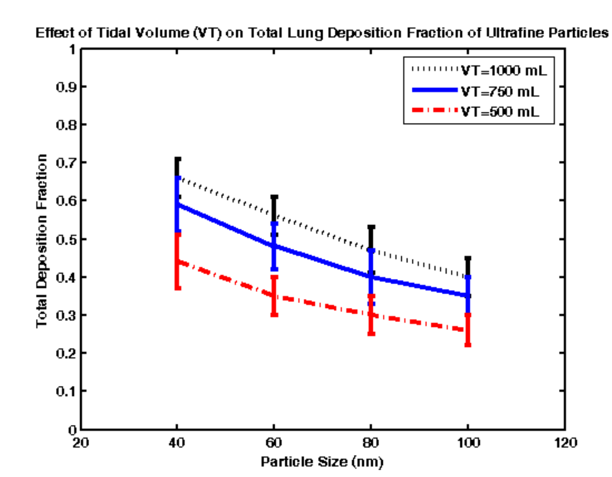
HUMTRN-based model (CCL)
- MATLAB-based semi-empirical model developed at the Computational Chemodynamics Laboratory (CCL)
- Variant of the HUMTRN program developed at Los Alamos National Laboratory
- Age-dependent inhalation rate and dose

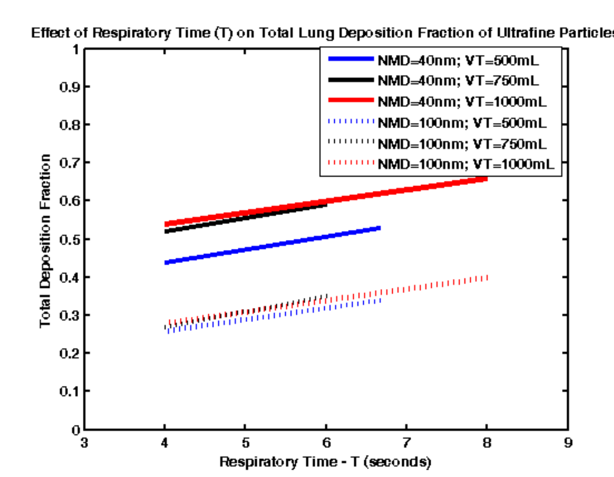
Multiple Path Particle Dosimetry (MPPD2) model
- Windows-based program developed at CIIT
- GUI to assign input parameters; age-dependent morphology for less than 21 years of age
- Creates report for deposition (and clearance if available) and associated plots

Deposition of Ultrafine Particles During Rest and Exercise: Evaluation of Experimental Data and Comparison of Experimental Data to Model Predictions

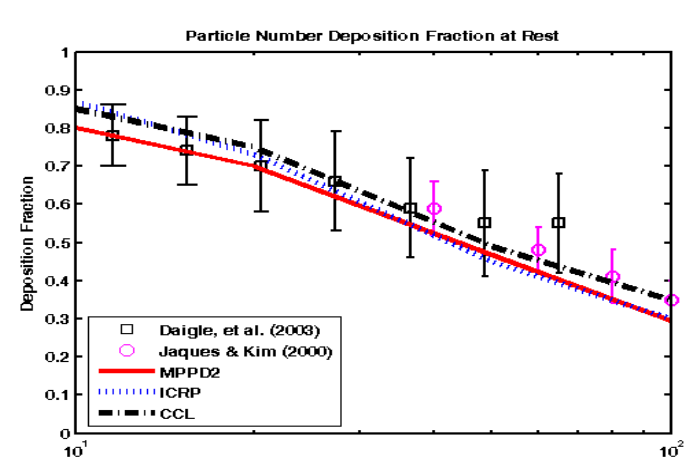
- Experiments conducted by Jaques & Kim (2000) and Daigle, et al. (2003) compare the deposition of UFPs in adults during rest and exercise – the experimental data is then compared to model predictions
- Experimental deposition of UFPs exceeds that predicted by models
- Probability of diffusion increases as particle size decreases
- Diffusional deposition of UFPs (as compared to larger particles) favored in distal airways and alveoli because reduced airflow increases residence time in these regions
- Total Deposition Fraction (TDF) varies with breathing pattern
  - Increase in TDF expected with increased activity level
  - Larger tidal volume (V_T) should penetrate deeper into the lung where airway diameter is small and wall surface area is large
- No gender difference in TDF of UFPs appreciated
- Additional experimental work by Kim & Jaques (2005) shows no significant difference between healthy elderly and young adults

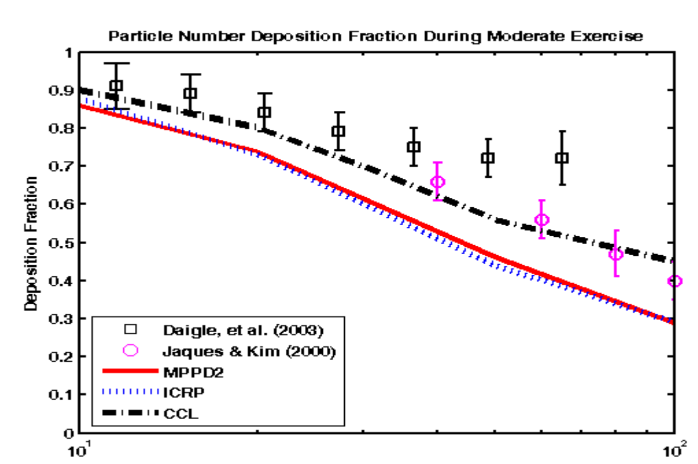




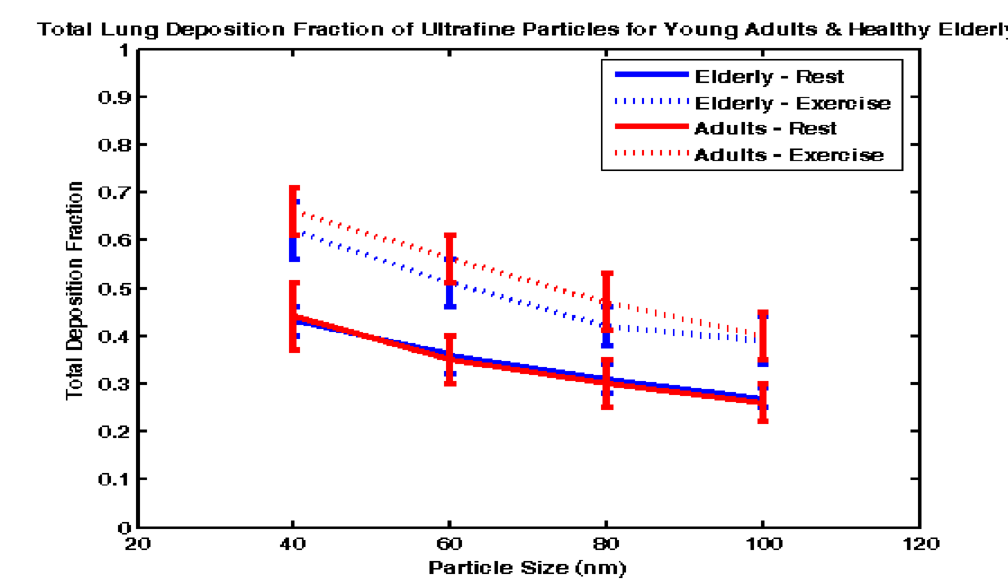


- Based on experimental data by Jaques & Kim (2000)
- Increase in TDF expected with larger tidal volume V_T (with constant flow rate, Q) due to penetration deeper into the lung where airway diameter is small and wall surface area is large
- Deposition by diffusion is time-dependent and expected to increase with longer residence time





- TDF measured in Jaques & Kim (2000) and Daigle, et al. (2003) studies at rest and during moderate exercise
- Experimental data compared to model predictions using MPPD2, ICRP, and HUMTRN-based model developed at CCL; experimental conditions used as model inputs
- Effect of exercise:
  - Tidal volume increases to a greater extent than respiratory rate which may favor diffusional deposition
  - Effects of exercise important because particle intake may increase 6-8x during exercise based only on the increase in minute ventilation
  - Deposition fraction at rest increases as particle size decreases
  - Deposition fraction during exercise increases as particle size decreases
  - Models underpredict the effects of exercise



Comparison of Young Adults to Healthy Elderly to Examine the Effects of Aging on Ultrafine Particle Deposition
- Additional measurements of total lung deposition of UFPs performed by Kim & Jaques (2005) on healthy elderly subjects during controlled breathing
- Breathing patterns equivalent to resting and an activity slightly above resting
- No difference appreciated between healthy elderly and young adult subjects

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Acknowledgements

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