Multiple Path Particle Dosimetry (MPPD) model and its Applications

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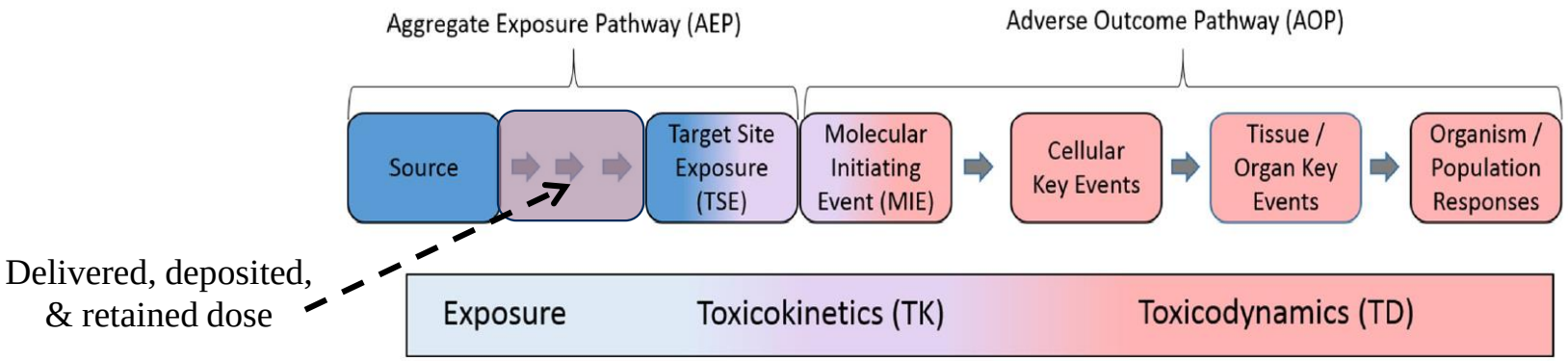
Outline

- Dosimetry modeling
- Modeling approaches
- Description of dosimetry model (MPPD)
- Features of MPPD
- Application of MPPD
  - Example 1: Influence of breathing route & activity level
  - Example 2: Intersubject variability
  - Example 3: Human Equivalent Concentration (HEC)
- Concluding Remarks

Dosimetry Modeling

Computational tool to inform exposure-dose-response models and toxicological risk assessment:



Dosimetry Modeling

Description:

- Mechanistic models based on the physical and physiological parameters that govern transport within the respiratory tract.
- Predicts deposition and retained dose in the lung.

Benefits:

- Computational dosimetry modeling complements/replaces 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.

Modeling Approaches

1. **Site-specific:** Focus on a small section of the lung to study mechanisms and local effects.

2. **Whole lung:** Consider entire lung geometry to predict regional and total dose

3. **Hybrid:** Combine 1 and 2 to use best knowledge available for

Comparison of Approaches

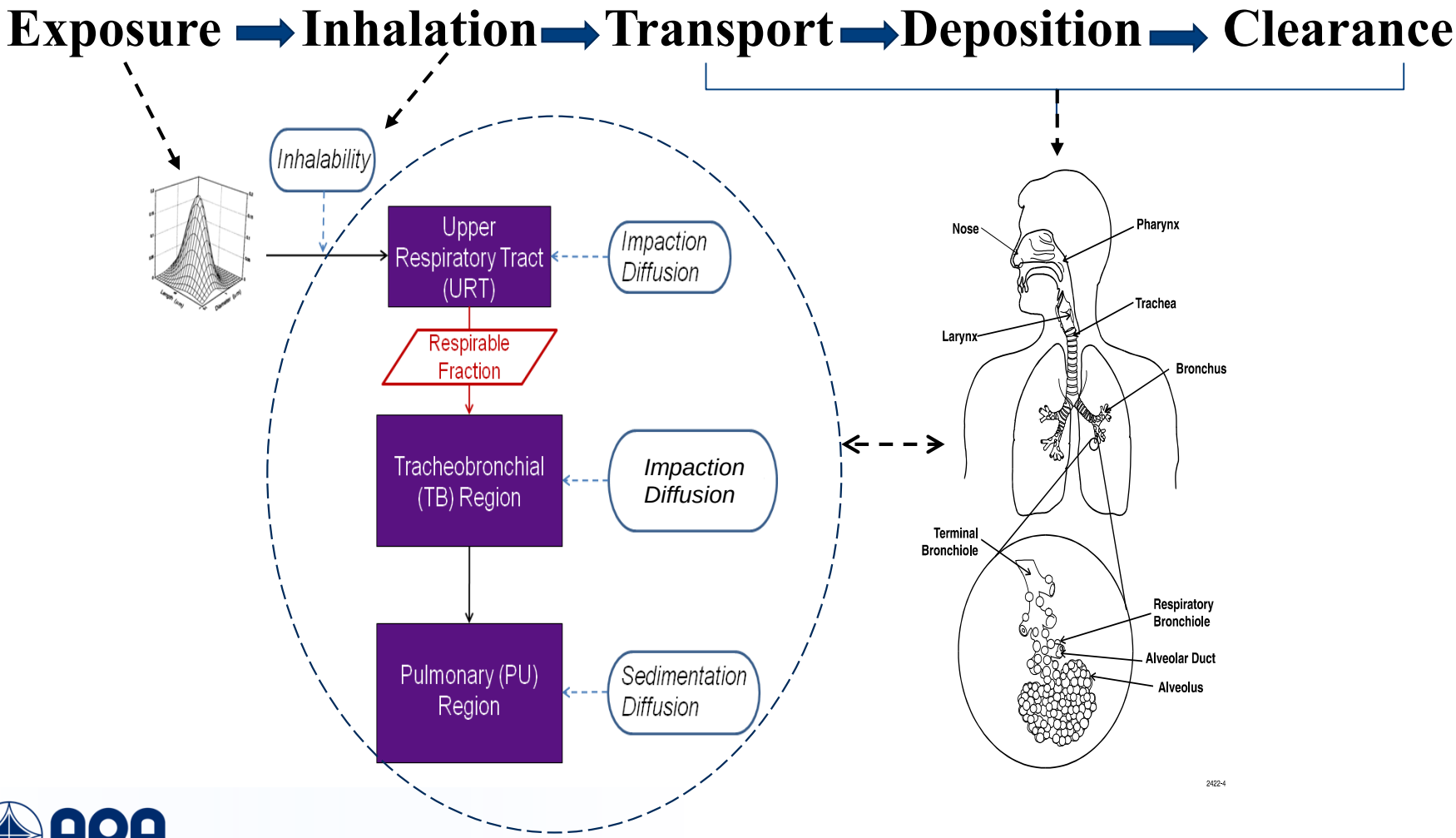
Approach	Strength	Challenges
Site-specific	- Few assumptions - Detailed 3D modeling	- Unknown boundary conditions (lung ventilation) - Requires realistic geometry - Cannot model entire respiratory track reliably (Section by section not justified)
Whole-lung	- Models entire respiratory tract - Used for risk assessment	- Requires various simplifying assumptions. - Predicts average deposition.
Hybrid	- Provides a framework for next generation modeling to include emerging data & information. - Most accurate predictions	- Early stages

Whole Lung Modeling

Overview of Major Models:

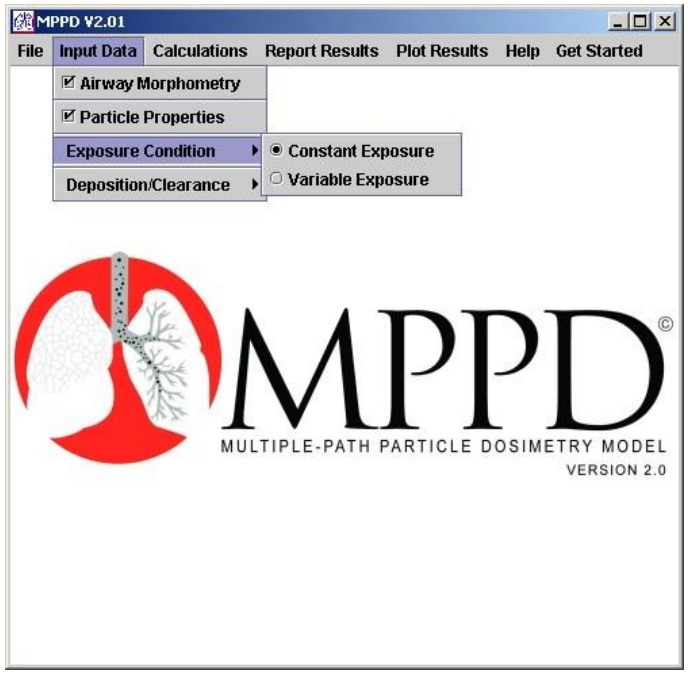
	NCRP	ICRP	MPPD
Mathematical model:	Semi-empirical	Semi-empirical	Deterministic: multiple-path
Species	Humans (adults and children), two strains of mouse	Humans (adults and children)	Humans (adults and children), Multiple species
Lung geometry	Symmetric lung geometry, asymmetric recently reported	Symmetric lung geometry	Symetric, 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	Mechanistic TB Mucous clearance, One alveolar compartment for each VU, lymph node
Interface	Must program	Dos & Windows menu driven	Graphical interface with help menu / tutorials

MPPD Internal Structure



Current State: MPPD

Input: Exposure characteristics



Output: Dose-deposition predictions

MPPD Inputs

- **Exposure characteristics:** (mass/number concentration with uniform distribution)
- **Particle characteristics:** dimensions, size distribution, correlation
- **Breathing parameters:** BF and tidal volume
- **Breathing routes:** nasal, oral, oronasal, endotracheal
- **Lung parameters:** FRC and URT volumes
- **Inhalibility** adjustment for particles

MPPD Output

Textual - input parameters, predictions

Graphical - Deposition per generation, lobe, and region

Data files - export to other graphical packages and spreadsheets

Model Predictions

1. Deposition:

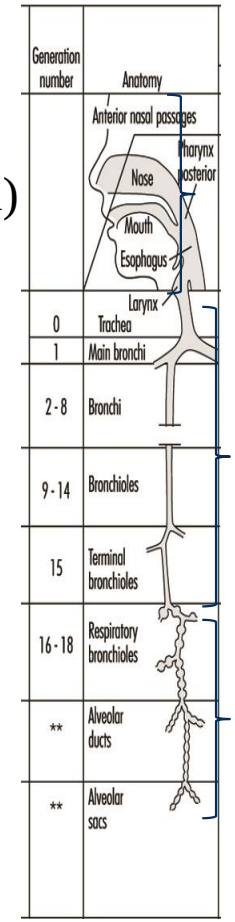
- Entire respiratory tract
- Regional (URT, Tracheobronchial, Alveolar)
- By Generation (Trachea -> Bronchi . . . Bronchioles -> Alveoli)
- Lobar (RU, RM, RL, LU, LL)
-Airway-specific

Adults and children of different age groups
Rhesus monkeys, guinea pigs, pigs, sheep, dogs, rabbits

2. Retained dose:

- Airway generation for TB
- Regional for PUL

Human adults (symmetric, asymmetric/stochastic lungs)
Rats (Long-Evans & Sprague Dawley)
Mice ($B_6C_3F_1$ & BALB/c)



Metrics for interspecies extrapolation

- 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

Applications of MPPD

Applications in risk assessment

- Characterizes exposure-dose-response relationship
- Improves interspecies dose-metric adjustment and extrapolation
- Interfaces with PBPK models to predict fate in the body
- Aids in design of inhalation exposure studies

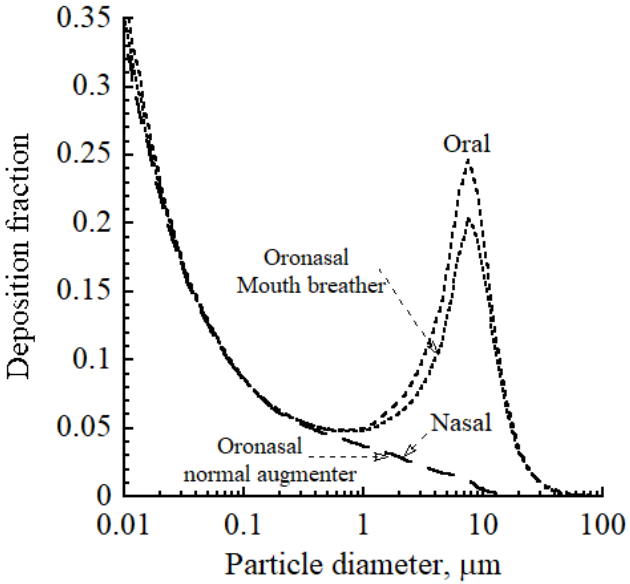
Other Applications

- **Drug delivery:** Aids in drug formulation and assessment of efficacy
- **Threat assessment:** Prediction of deposition of CBRN (Chemical, biological, radiological and nuclear) agents in the respiratory tract

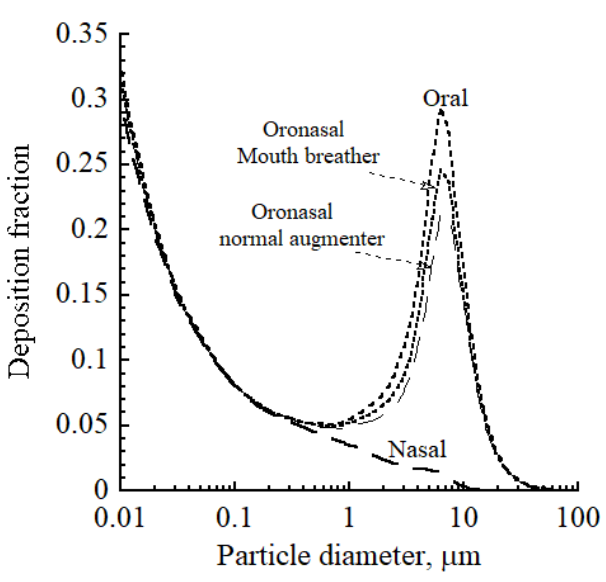
Example 1
Influence of Breathing Route & Activity Level

Deposition in TB Region

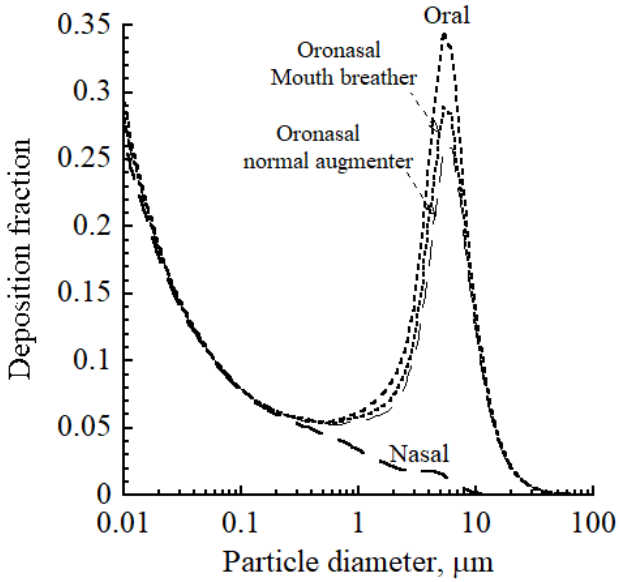
Light



Moderate



Heavy

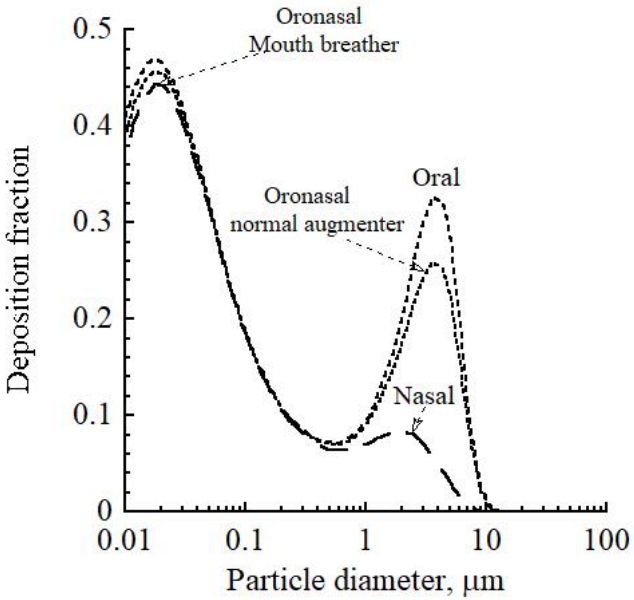


- Oral→ Mouth breather→ augmente → nasal
- Fine particles ↓ with activity level
- Coarse particles ↑ with activity level

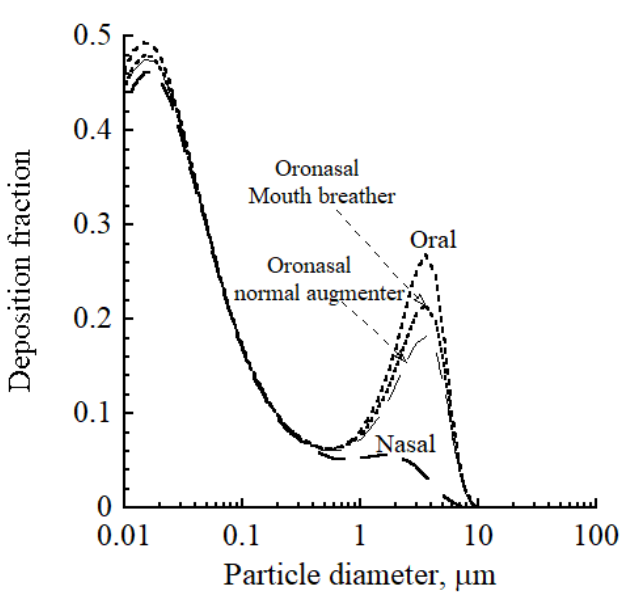
Light: $BF = 21.9$ $\dot{V}_E = 30.3LPM$ $V_T = 1450\,mL$
Moderate: $BF = 47.4$ $\dot{V}_E = 26.5LPM$ $V_T = 1860\,mL$
Heavy: $BF = 31.9$ $\dot{V}_E = 72.3\,LPM$ $V_T = 2300\,mL$

Deposition in PU Region

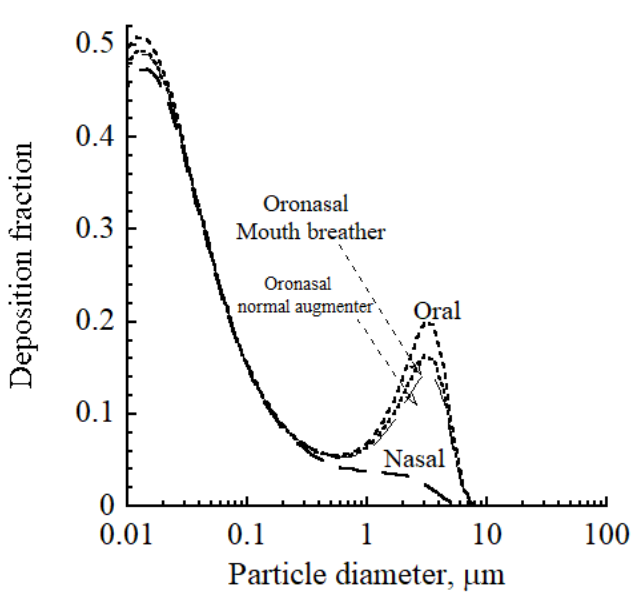
Light



Moderate



Heavy



- Oral→ Mouth breather→ augmente → nasal
- Fine particles↑ with activity level
- Coarse particles ↓ with activity level

Light: $BF = 21.9$ $\dot{V}_E = 30.3LPM$ $V_T = 1450\,mL$
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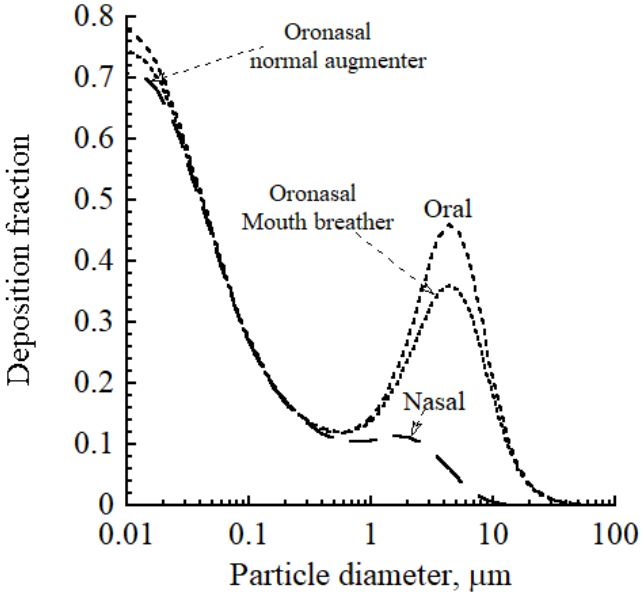
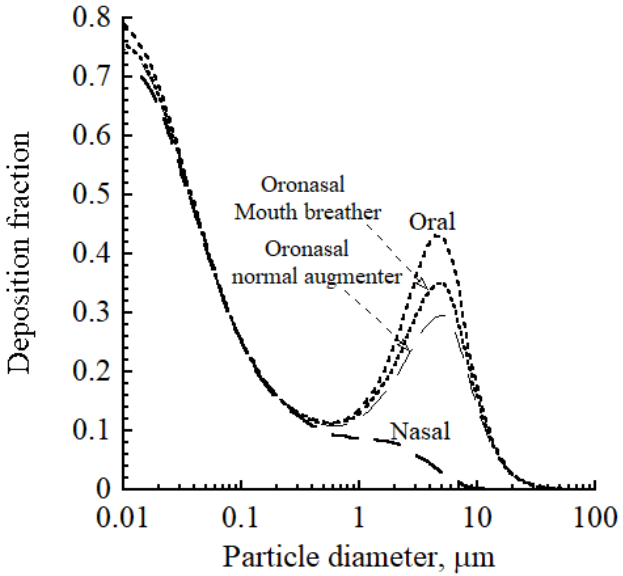
Deposition in LRT

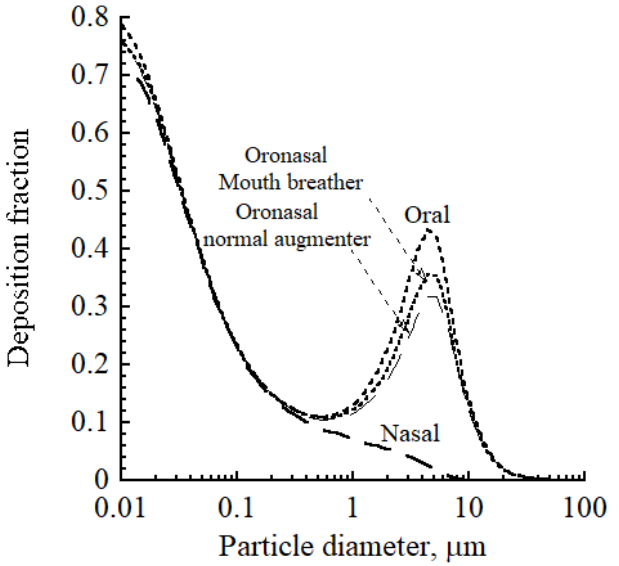
Light



Moderate



Heavy

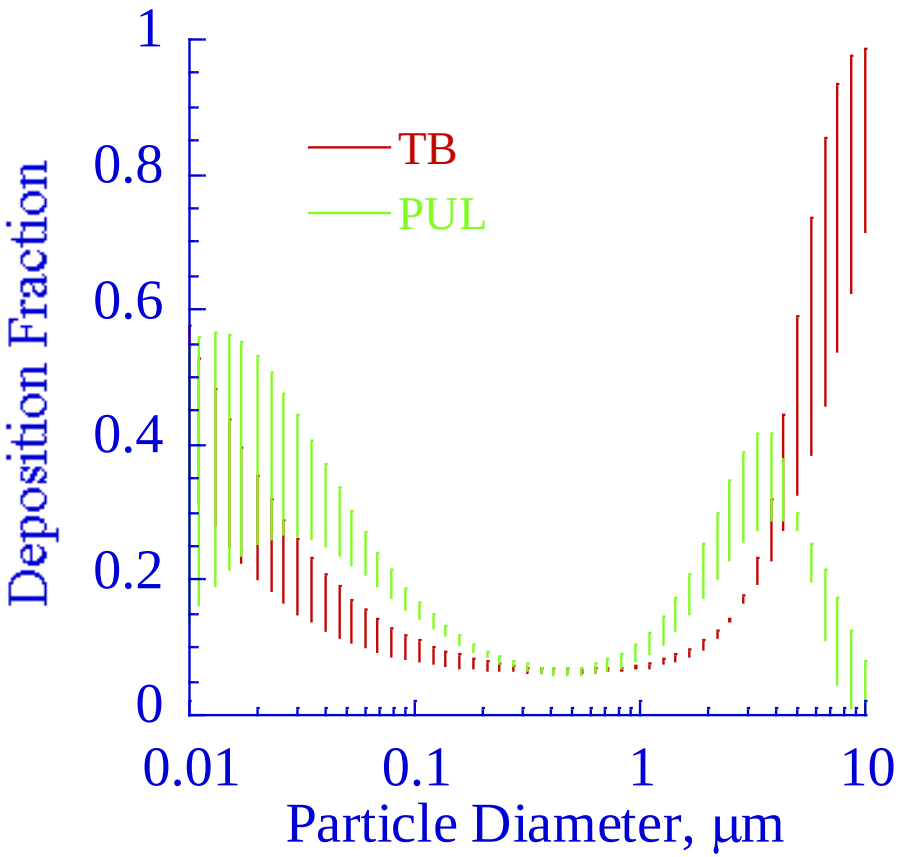


- Oral→ Mouth breather→ augmente → nasal
- Similar pattern with activity level except for augmenter

Light: $BF = 21.9$ $\dot{V}_E = 30.3LPM$ $V_T = 1450\ mL$
Moderate: $BF = 47.4$ $\dot{V}_E = 26.5LPM$ $V_T = 1860\ mL$
Heavy: $BF = 31.9$ $\dot{V}_E = 72.3\ LPM$ $V_T = 2300\ mL$

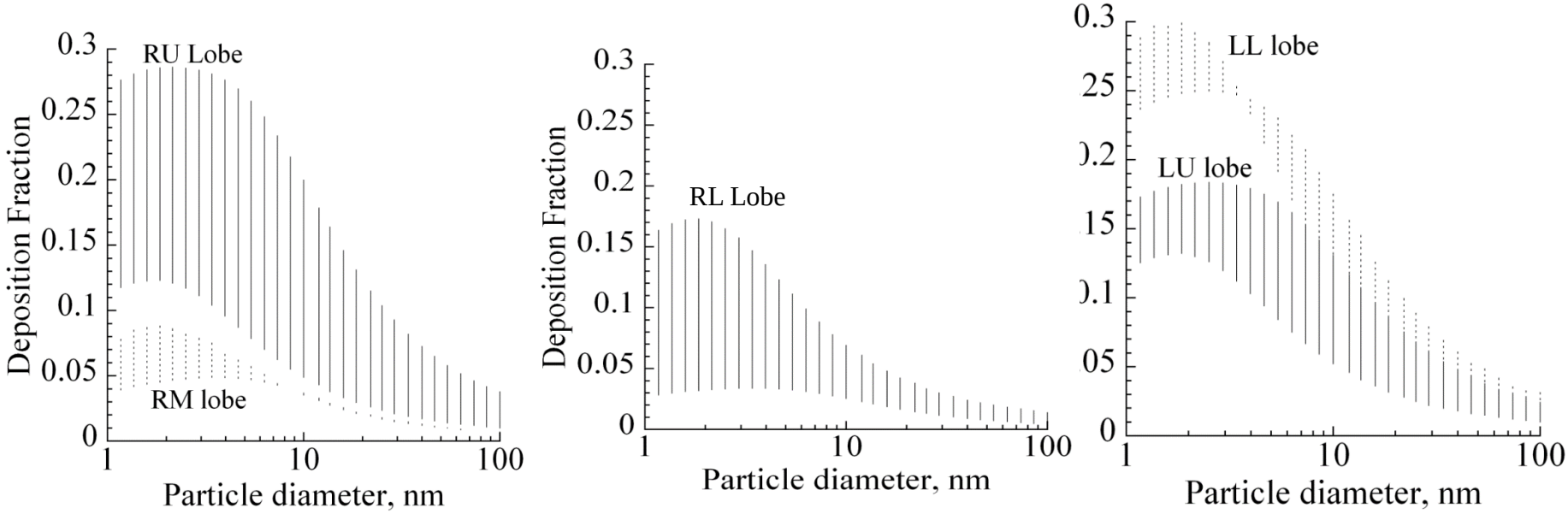
Example 2
Inter-subject Variability

Regional Deposition Fraction



- Significant variability for ultrafine and coarse particles

Lobar Deposition Fraction



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

Example 3
Human Equivalent Concentration (HEC)

HEC Predictions Based on Deposition

1. Acute exposure:

Dose metric based on deposited mass/surface area

$$\begin{pmatrix}\text{deposited}\\ \text{mass}\end{pmatrix} = \begin{pmatrix}\text{deposition}\\ \text{fraction}\end{pmatrix} \times \begin{pmatrix}\text{exposure}\\ \text{concentration}\end{pmatrix} \times \begin{pmatrix}\text{minute}\\ \text{volume}\end{pmatrix} \times \begin{pmatrix}\text{exposure}\\ \text{time}\end{pmatrix}$$

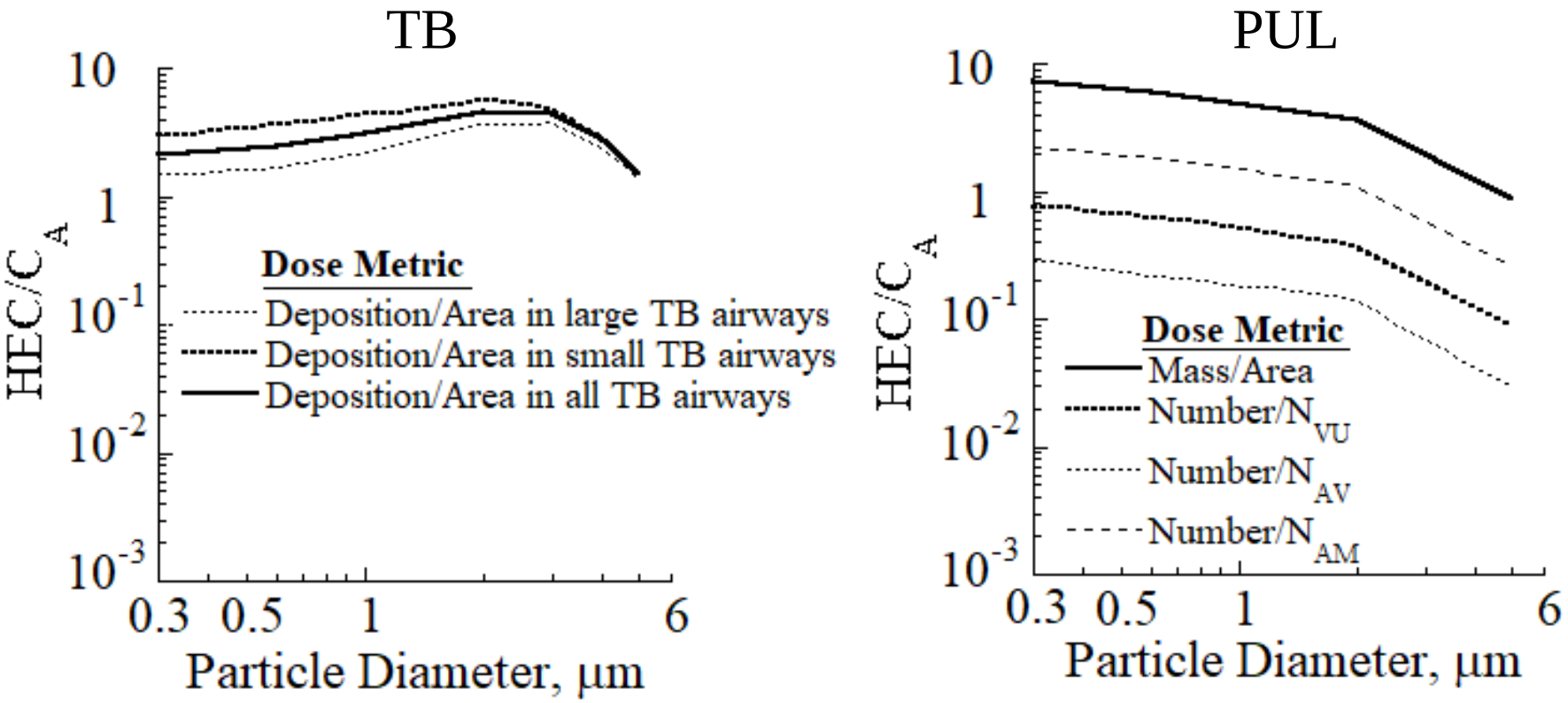
$$\boldsymbol{Mass} = \boldsymbol{DF} \times \boldsymbol{C} \times \boldsymbol{\dot{V}_E} \times \boldsymbol{\delta t}$$

$$\left(\frac{\text{Mass}}{\text{SA}}\right)_{\text{H}} = \left(\frac{\text{Mass}}{\text{SA}}\right)_{\text{A}}$$

$$\Rightarrow \quad HEC = \frac{\left(\dot{V}_E\right)_A}{\left(\dot{V}_E\right)_H} \times \frac{(DF/SA)_A}{(DF/SA)_H} \times \frac{\delta t_{\ A}}{\delta t_{\ H}} \times C_A$$

HEC Predictions - Deposition

Jarabek, Miller, and Asgharian (2005). Inhal. Tox. 17:317-334.

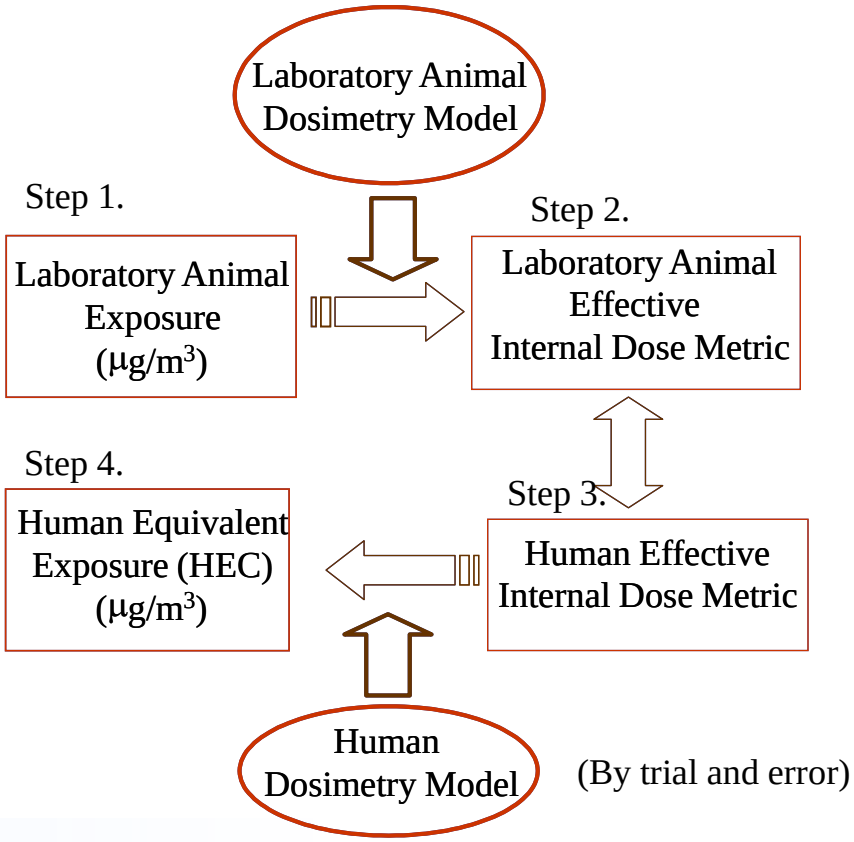


- $HEC/C_A > 1$ Using C_A is conservative & vice versa

HEC Predictions Based on Retained Dose

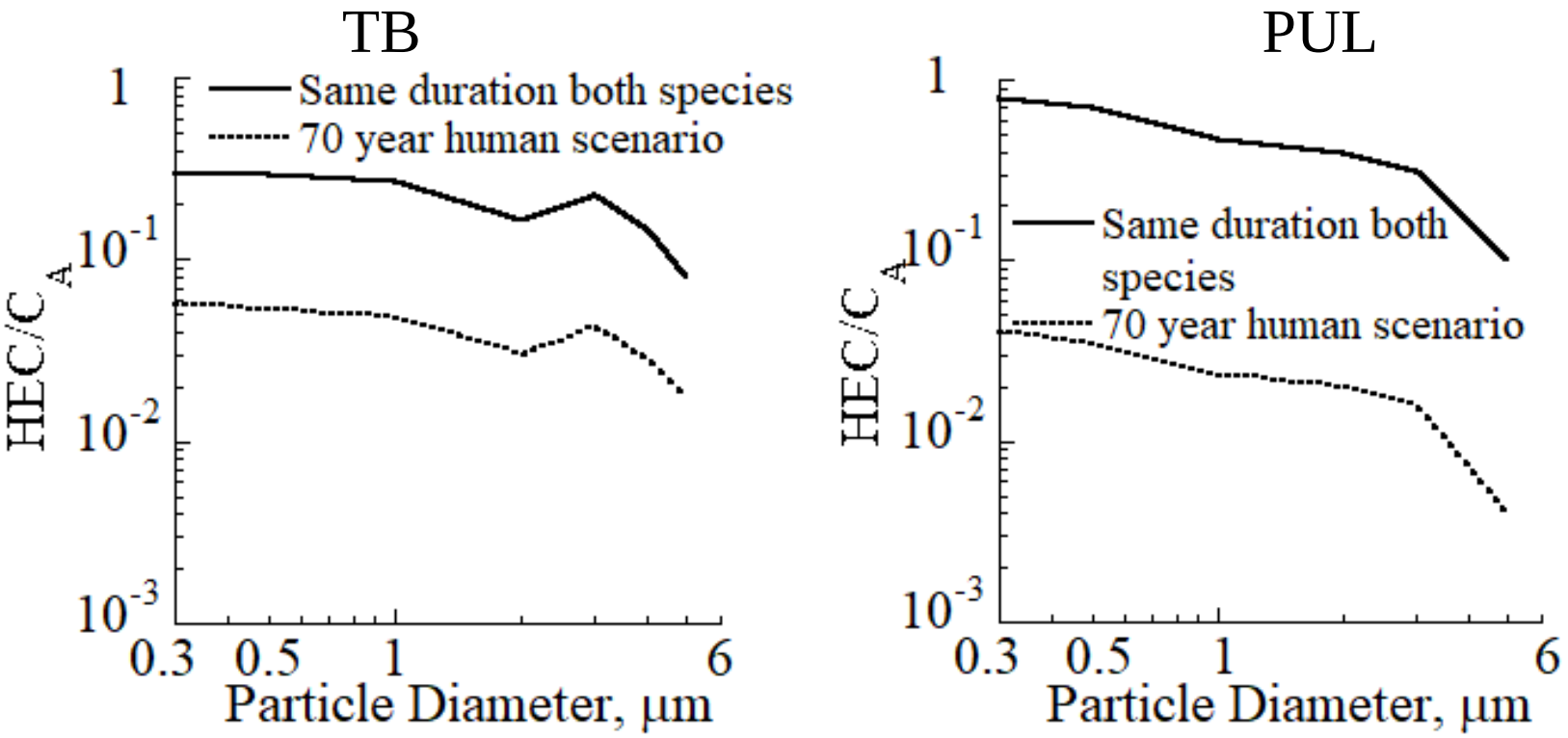
2. Chronic (life stage) exposure

Dose metric based on Retained Mass



HEC Predictions - Retained Dose

Jarabek, Miller, and Asgharian (2005). Inhal. Tox. 17:317-334.



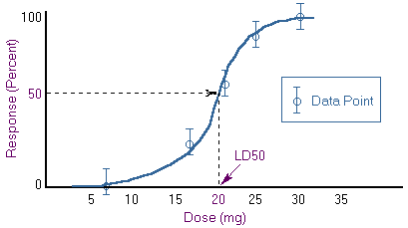
- Assessment based on equal exposure duration leads to over-prediction of exposure and under-prediction of risk

Closing Remarks on MPPD

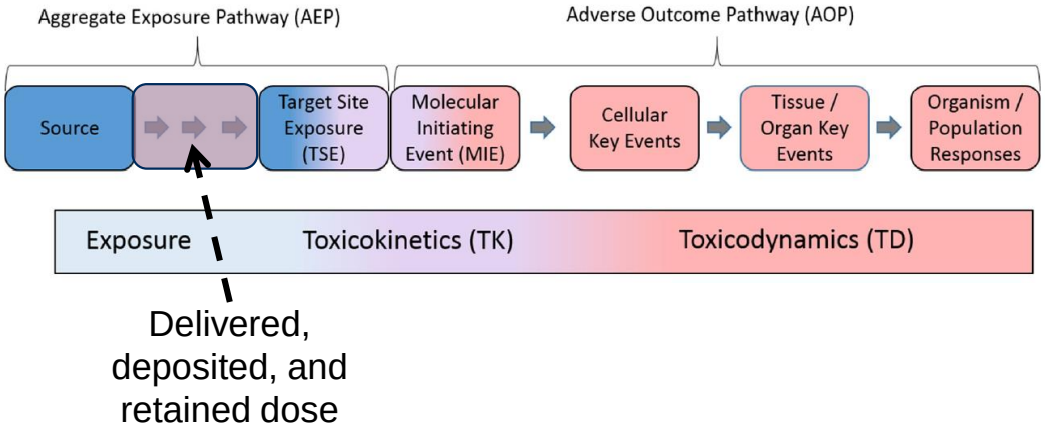
- **Mechanistic**. Has potential for extension to different particle types.
- **Deposition Fractions**. Can be predicted in the lungs of humans and several other species.
- **Retained dose**. Can be found in humans, rats, and mice.
- **Interspecies extrapolation**. Is based on various dose metrics: Deposition, DF/A in TB, PU, and entire lung.
- Need to include **case studies** in MPPD Help Menu to aid users in applications of MPPD.

Dosimetry Modeling

Toxicity testing:
Inhalation toxicity is expressed as point estimate of median lethal concentration (LC50); probit analysis of E-R data and benchmark dose analysis.
It does not offer site or mechanism information.



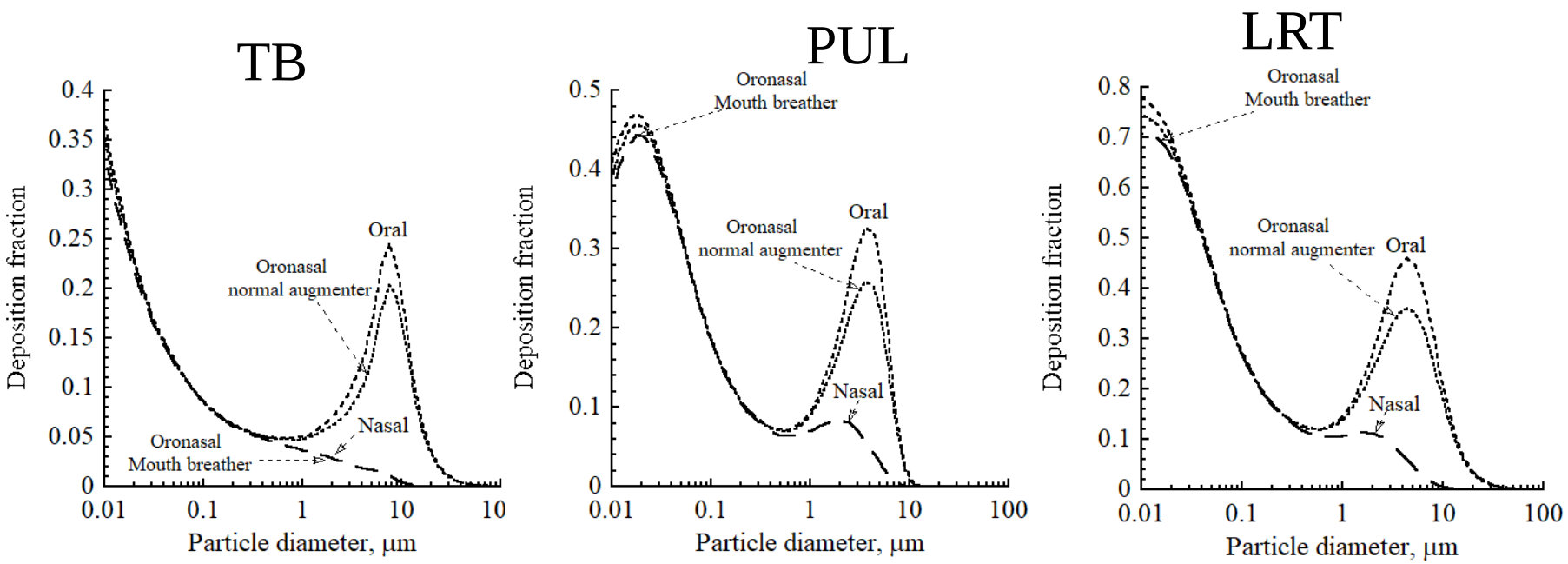
Non-animal approaches offer a predictive tool for establishing hazard and :
Organize existing mechanistic evidence by connecting key events from molecular to population levels based on an adverse outcome.



Example 1: Influence of Breathing Route/Ventilation

Light activity

($BF = 21.9, \dot{V}_E = 30.3 LPM, V_T = 1450\ mL$)

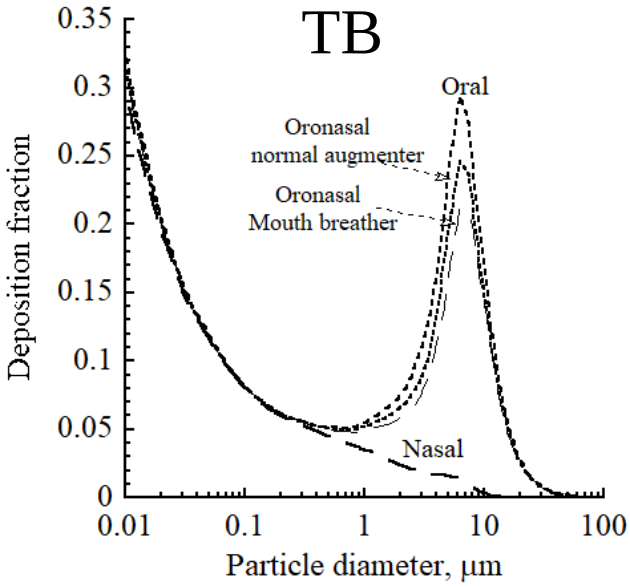


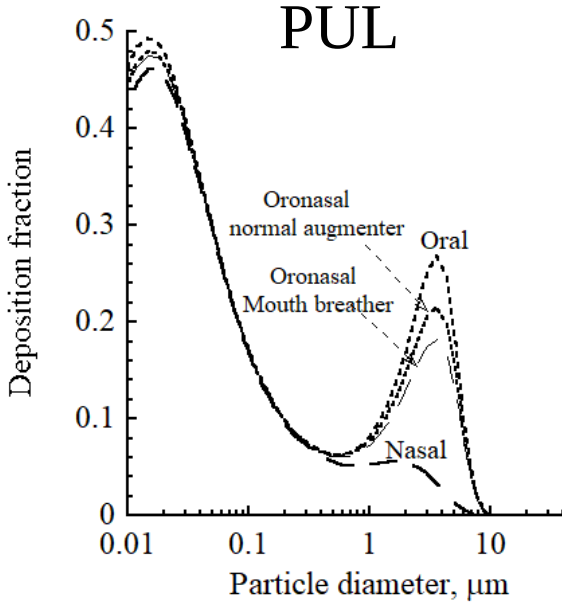
- Deposition of fine particles is independent of breathing route
- Oral and nasal breathing create the bounds
- Normal augmenter is higher than mouth breather

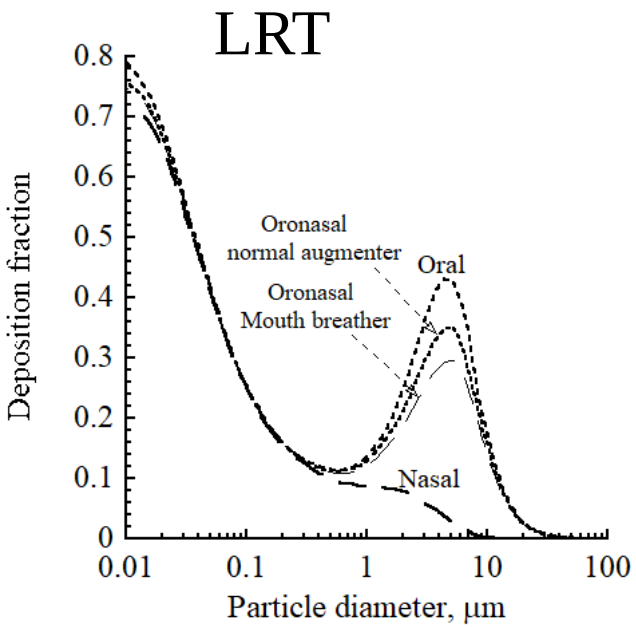
Example 1: Influence of Breathing Route/Ventilation

Moderate activity

$(BF = 47.4, \dot{V}_E = 26.5LPM, V_T = 1860\,mL)$







Example 1: Influence of Breathing Route/Ventilation

Heavy activity

($BF = 31.9, \dot{V}_E = 72.3\ LPM, V_T = 2300\ mL$)