Computational methods for characterization of aerosol dynamics and dosimetry in humans

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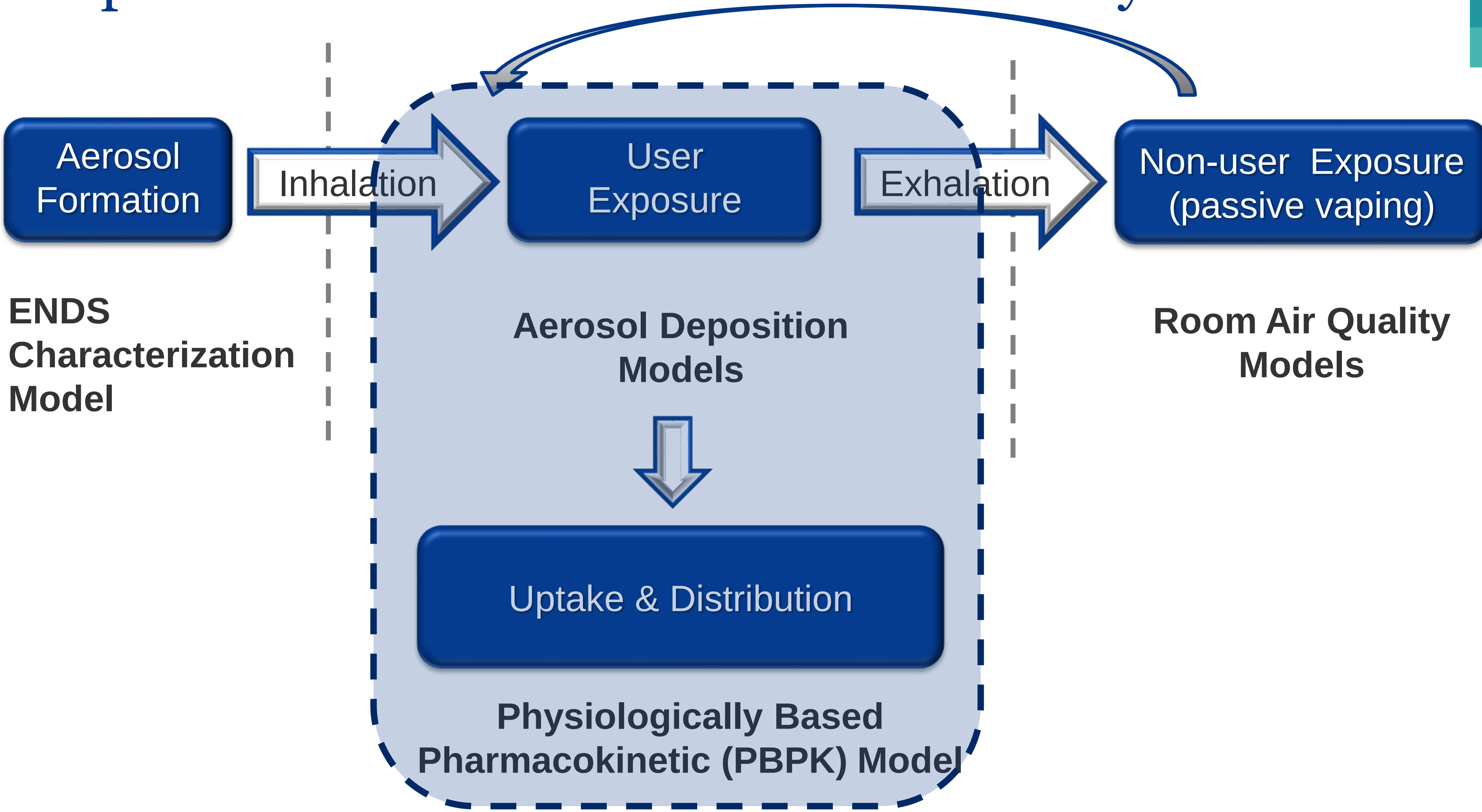
Exposure Characterization and Dosimetry Models



These are physics-based models that include fluid, mass and heat transfers along with thermodynamic and kinetic interactions and physiological parameters.

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ENDS Aerosol Dynamics

ENDS* aerosol has some unique properties

- Multi-constituent
- Volatile constituents- vapor and liquid phases dynamically coexist
- Hygroscopic
- High number density: 10^9-10^{10} particles/cc
- Initial temperature different from body temperature

Complex aerosol dynamics

- Interface mass transfer
- Particle size and concentration changes
- Particle composition changes
- Both vapor and particle deposition contribute to uptake
- Regional deposition flux are different for different constituents
- Thermal exchange

*Electronic Nicotine Delivery System

Three approaches to characterize aerosol deposition in Respiratory Tract

Question: How much of each constituent , in what form (vapor or liquid), and where in the airway is absorbed?

Upper Airway

- Air flow is key to the aerosol dynamics
- More realistic geometry down to G5-6
- 3D transient approaches are used:
  - **Particle Tracking- Lagrangian Approach**
  - **Eulerian Approach**

Whole Airway

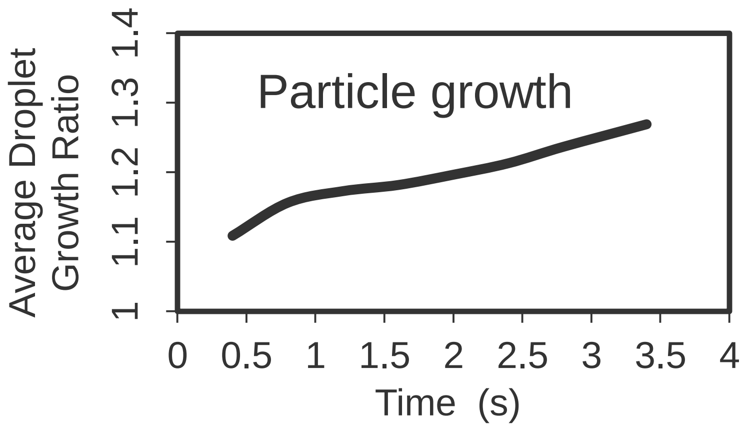
- Diffusion is key specially in lower airways
- Simplified geometry
- More physics can be incorporated
  - **1D transient approach (similar to MPPD*, but including oral cavity)**

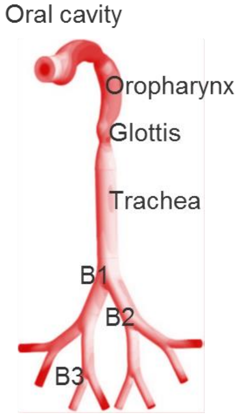
* MPPD: Multipath Particle Dosimetry Model

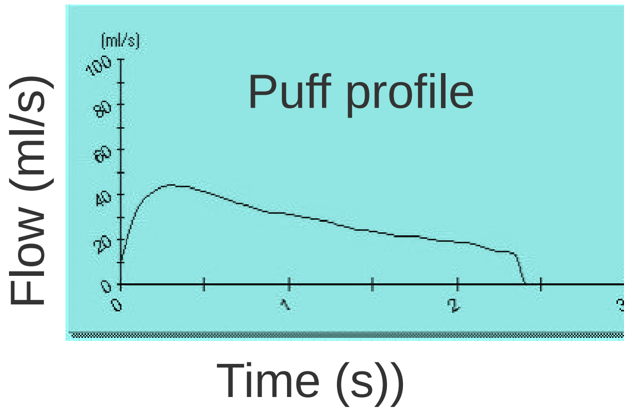
Lagrangian Approach

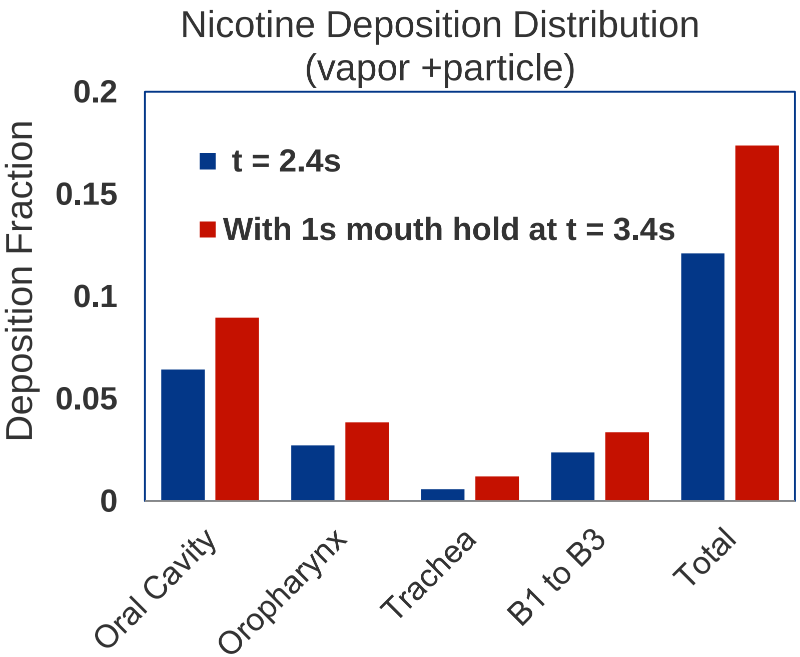
A limited number of particles represent all particles. It accounts for

- Vapor absorption and particle deposition on the wall
- Particle composition changes
- Particle size Change
- Interface mass transfer
- Thermal effects









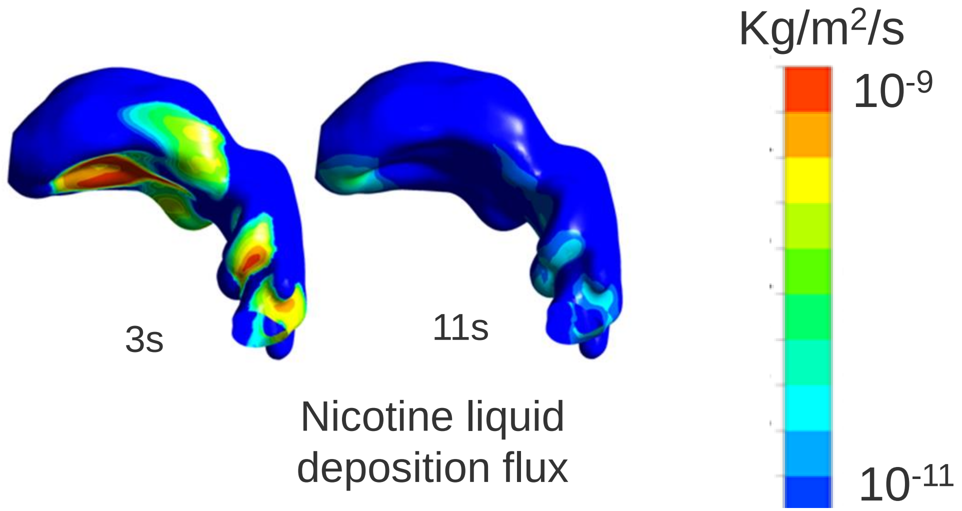
Y. Feng C. Kleinstreuer, A. A. Rostami, "Evaporation and condensation of multicomponent electronic cigarette droplets and conventional cigarette smoke particles in an idealized G3–G6 triple bifurcating unit", Journal of Aerosol Science 80 (2015) 58–74

Yu Feng, Clement Kleinstreuer, Nicolas Castro , Ali Rostami "Computational transport, phase change and deposition analysis of inhaled multicomponent droplet– vapor mixtures in an idealized human upper lung model" Journal of Aerosol Science 96 (2016) 96–123.

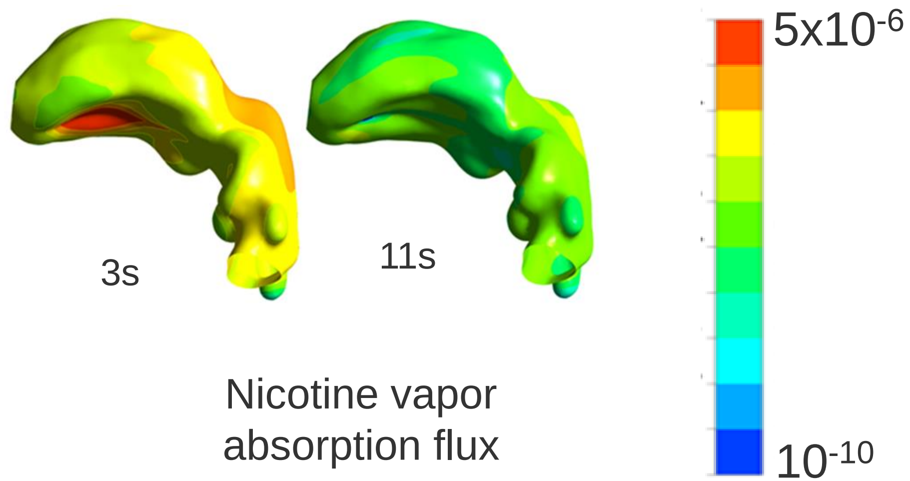
Eulerian Approach

- Particles are treated as a species with variable composition
- All processes mentioned earlier are accounted for
- VLE* approximation is used for particle-vapor interface mass transfer

3s puff duration followed by 8s air wash



Nicotine liquid deposition flux



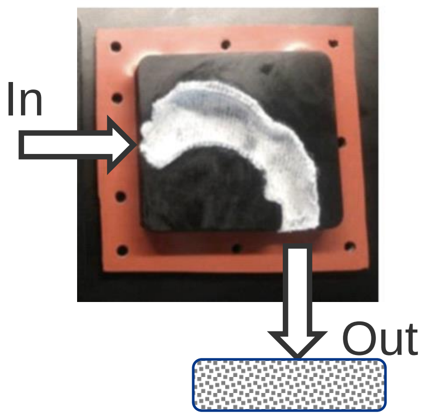
Nicotine vapor absorption flux

Similar contour plots were generated for PG and glycerin.

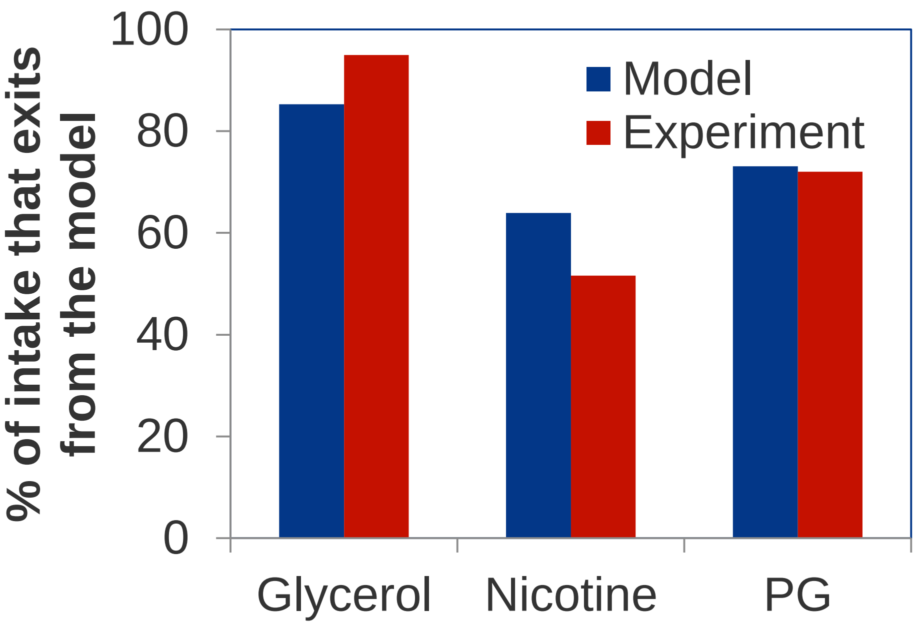
H. Pourhashem, M. P. Owen, N. D. Castro and A. A. Rostami, Eulerian modeling of aerosol transport and deposition in respiratory tract under thermodynamic equilibrium condition” under review, J. Aerosol Science.

* VLE: Vapor Liquid Equilibrium

Comparison to Experiment



- 3s intake, 8s wash
- Inner surface covered with moist cloth
- Test unit placed in a 37°C oven to mimic body temperature



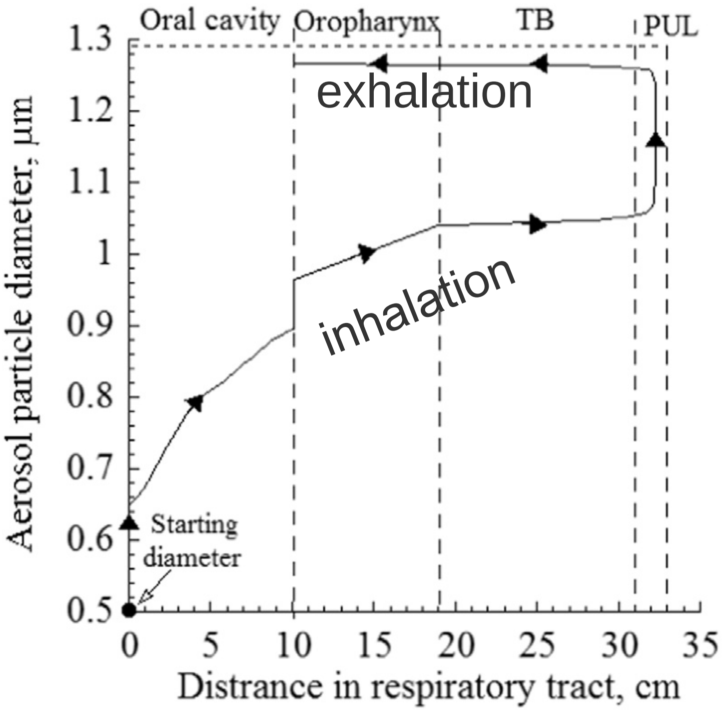
Subtract from 100 to get (deposited + suspended)

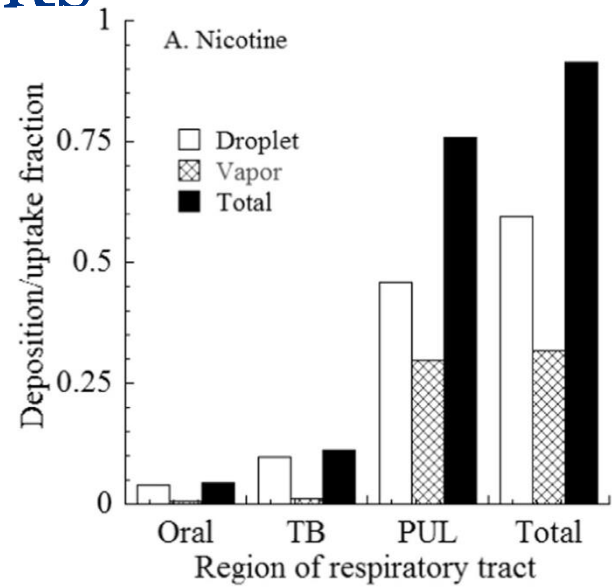
Whole Airway Model

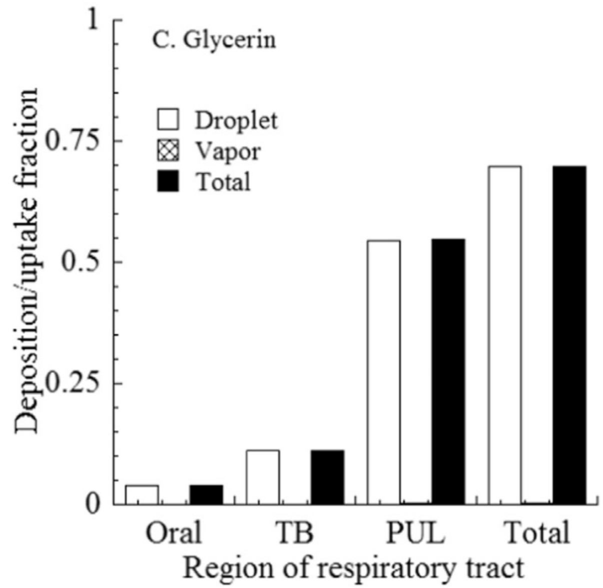
- 1D transient for the entire airways.
- Allows for full vaping topography including puff, mouth hold, inhalation with additional air, lung hold and exhalation.
- Key processes affecting aerosol mixture dynamics (coagulation, interface mass transfer, hygroscopic effects, mixing and dilution, gravitational effects) are accounted for.
- A realistic oral geometry and a typical path lung geometry was used.
- Dilution with reserved air volume in lower airway was accounted for.

Bahman Asgharian, Owen T. Price, Ali A. Rostami, Yezdi B. Pithawalla, "Deposition of inhaled electronic cigarette aerosol in the human oral Cavity", Journal of Aerosol Science 116 (2018) 34–47
Bahman Asgharian, Ali A. Rostami, Owen T. Price, Yezdi B. Pithawalla, "Regional deposition of inhaled aerosol constituents from Electronic Nicotine Delivery Systems (ENDS) in the respiratory tract", Journal of Aerosol Science 126 (2018) 7–20

Whole Airway Model: Results







Particle diameter grows to 2.5 times the initial diameter.

Glycerin total uptake less than nicotine due to lower volatility

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TB: Tracheobronchi, PUL: Pulmonary

Nicotine PBPK Model

- Uptake will be used as inputs to a PBPK model.
- PK profile (shape, C_{max}, t_{max} and area under curve) depends on the location of uptake in the airway.
- The differences are related to the surface area of airway region and tissue thickness (air-blood barrier)
- Faster permeation to blood in LRT than URT and oral cavity
- We introduce a Physiologically Based Pharmacokinetic (PBPK) model that accounts for these variables.

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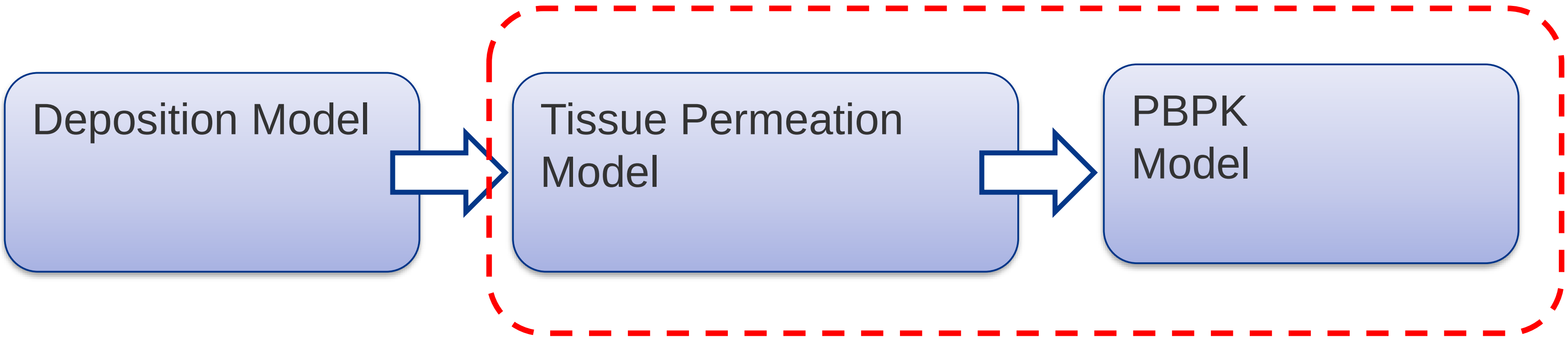
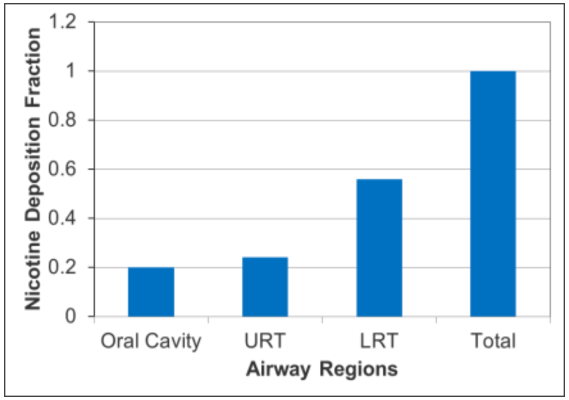
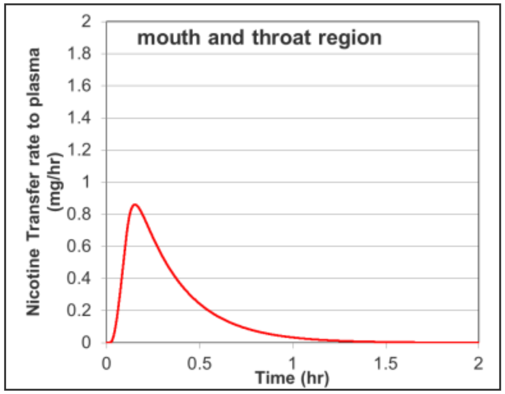
LRT: Lower Respiratory Tract, URT: Upper Respiratory Tract

Deposition-PBPK Modeling Approach

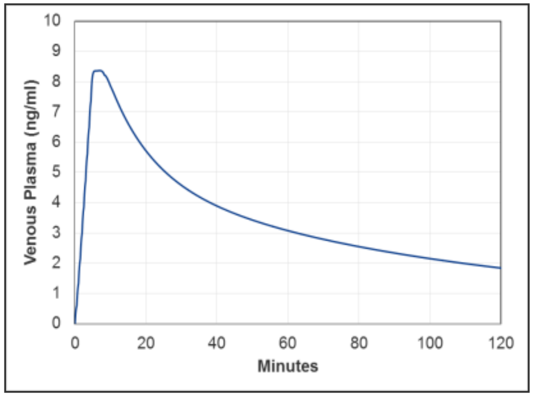




Regional deposition



Transfer rate to plasma



Plasma concentration

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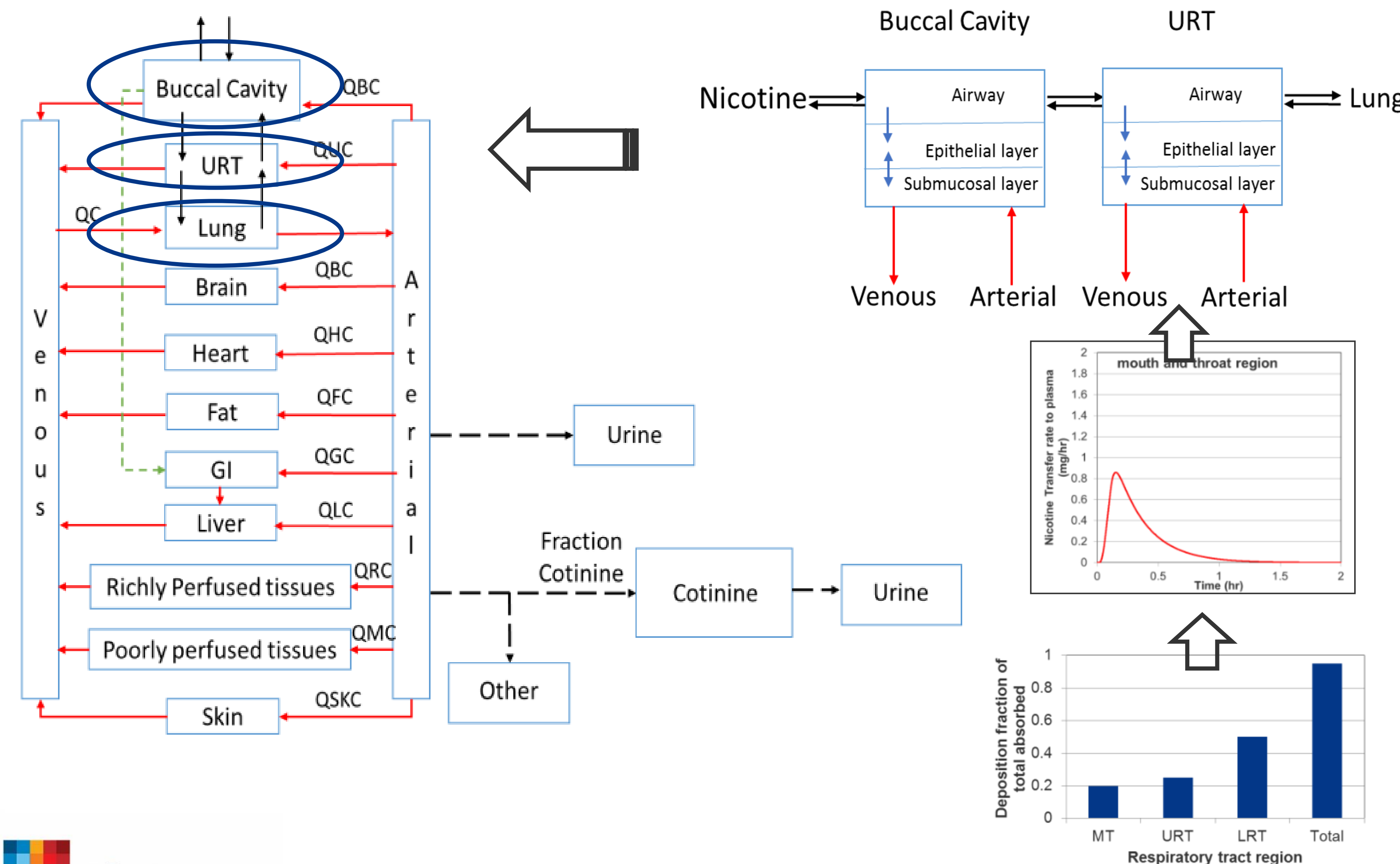
PBPK Model Structure Unique Features



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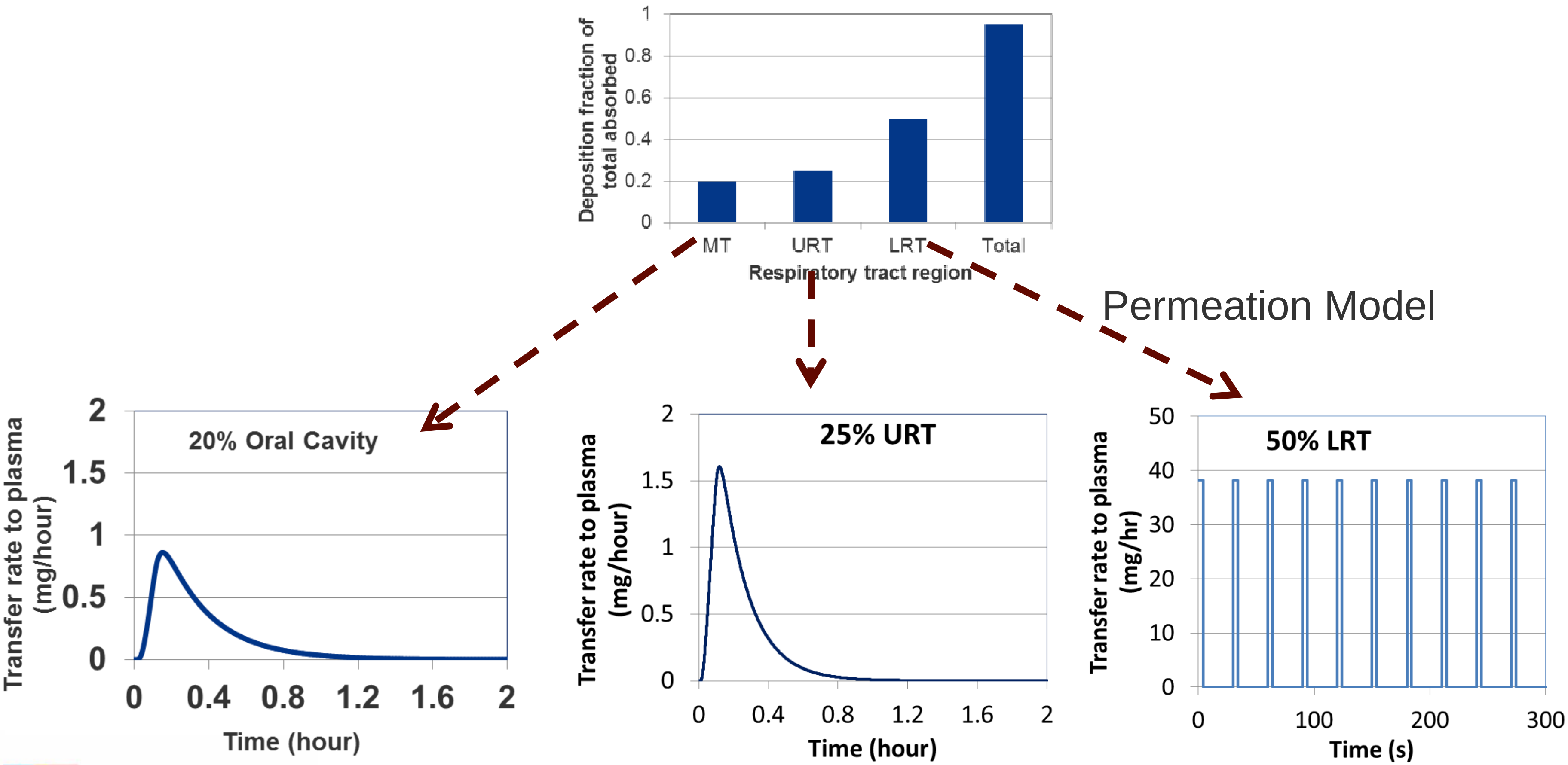
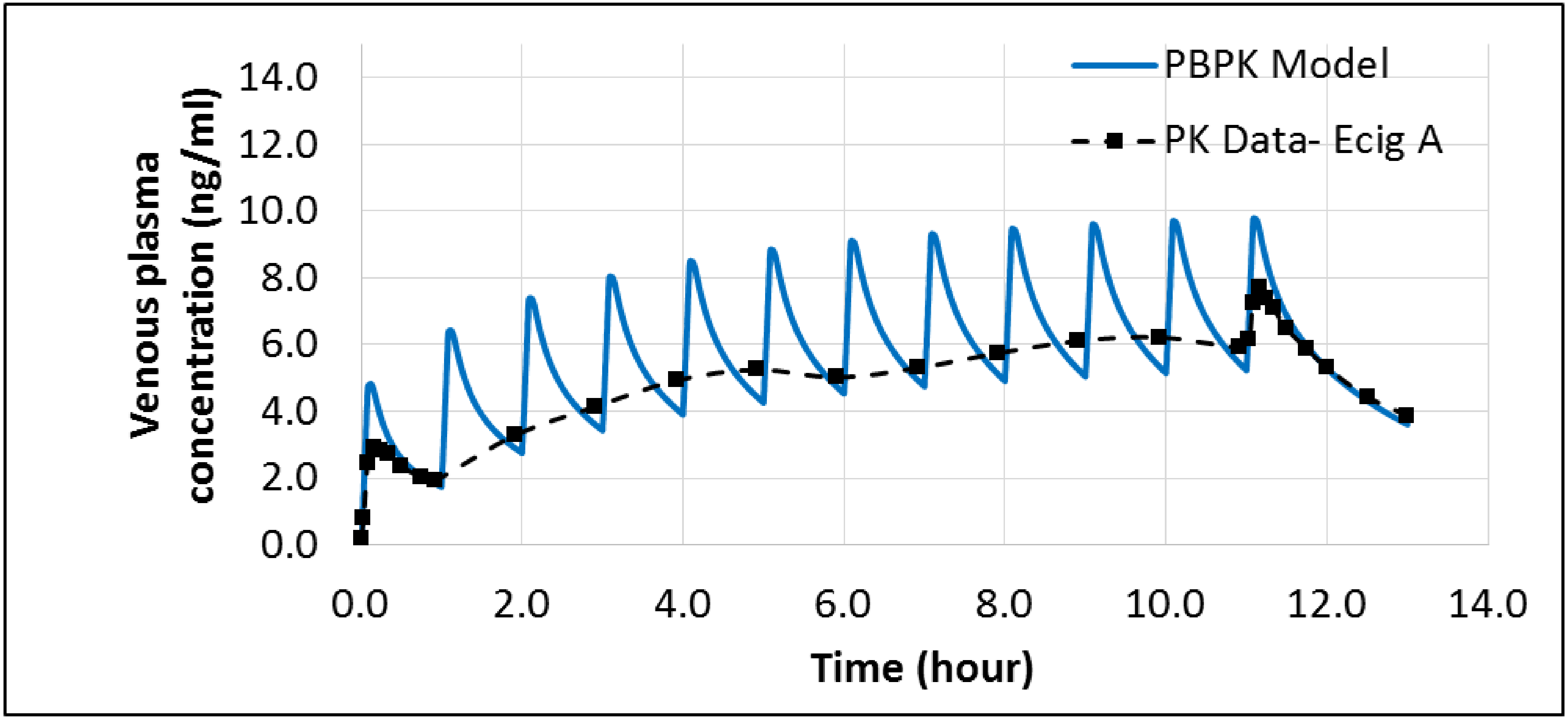
E-Vapor Example

- In a clinical study, 27 participants used MarkTen e-vapor product
- Each took 10 puffs, 5s duration, 30s intervals, once every hour for 12 hours
- Average nicotine uptake among participants was 0.85 mg/puff



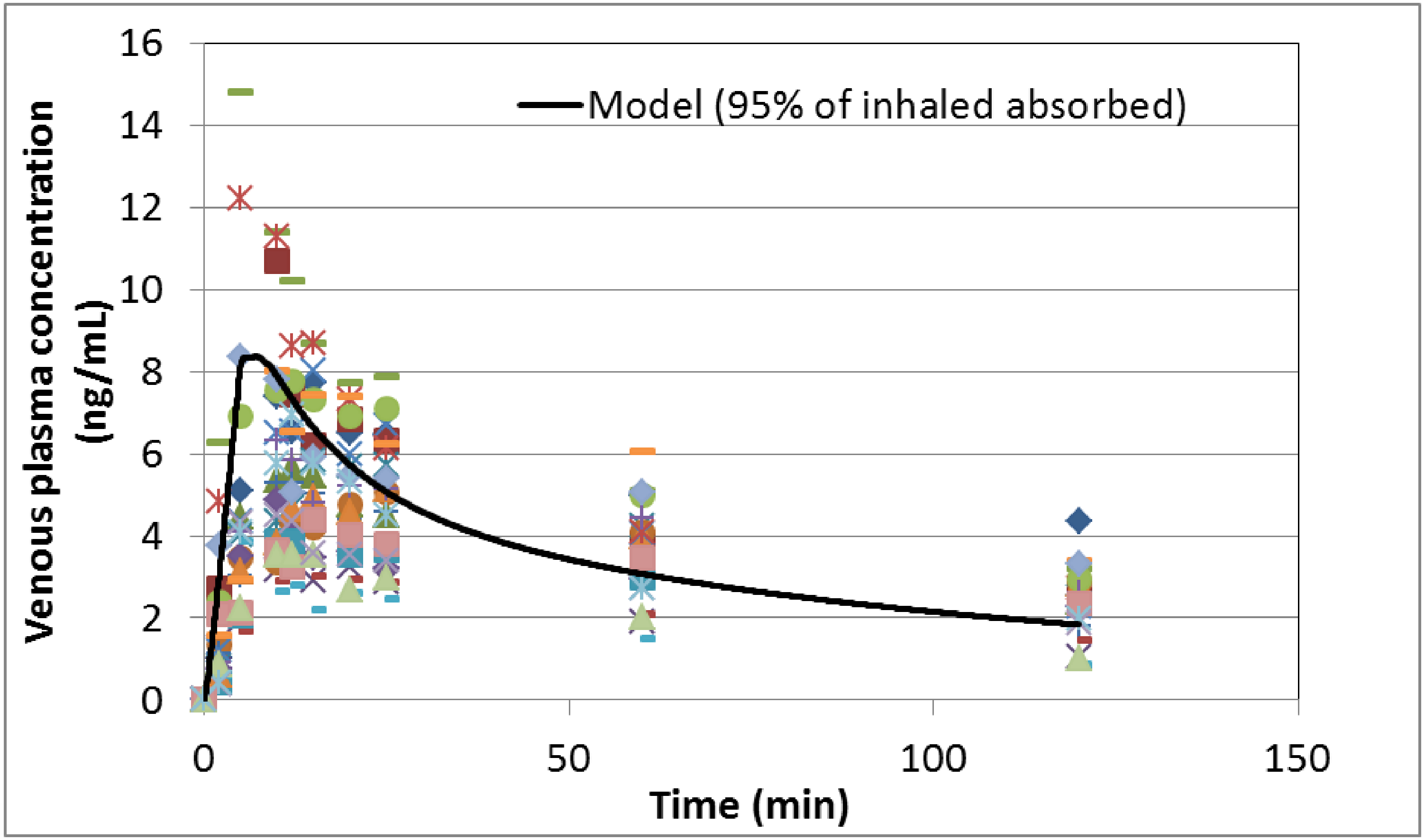
Blind Test: PBPK Model vs PK Data*



* Liu, J.; Liang, Q.; Connell, C.; Rimmer, L.; Edmiston, J.; Sarkar, M., A Pharmacokinetic Study to Determine Plasma Nicotine Profile from Two Electronic Cigarette Prototype Products in Adult Cigarette Smokers , 20th (SRNT), Seattle, WA, February 5-8, 2014

Comparison with Experiment (One Session)

- 27 participants used MarkTen e-vapor product
- Each took 10 puffs, 5s duration, 30s intervals
- Average nicotine uptake among participants was 0.85 mg/puff



Summary

- We have developed a number of computational models to characterize human airway dosimetry and internal nicotine exposure after using ENDS
- Results from the aerosol deposition models are used as inputs to the PBPK model
- The PBPK model presented here allows for distributed airway dosimetry
- Models can be used to study individual users PK variability resulting form different topography.

Thank You!