Physiologically based Pharmacokinetic Modeling of Inhaled Aerosol

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Problem Formulation

• Development of appropriate Physiologically Based Pharmacokinetic (PBPK) models
  • Need to bridge the gap between exposure, time and dosimetry for inhaled evolving liquid aerosol

• Can a unified or general methodology be developed?

• We are looking for panel input in developing such a model

• Potential partners for co-development of such models and validation use cases

• Need for open access and benchmarking their applicability

• Role of such models in risk assessment
Agenda

• Background

• Objectives

• Review of existing approaches
  o Physicochemical Properties of Aerosol
  o Inhalation Topography and Airway Anatomy & Physiology
  o Aerosol Deposition Models
  o Inhalation PBPK Models

• PBPK Modeling at Philip Morris International R&D (PMI)

• Future Work

• Challenges
Background - Research @ PMI

- Reduced Risk Products (RRP)
  - Offer alternatives to adult smokers who want to continue using nicotine products
  - Potentially reduce individual risk and population harm
  - Tobacco Heating System (THS) is a candidate RRP

Toxicological assessment requires an understanding of
  - Exposure
  - Time
  - Dose

Note: Reduced-Risk Products (“RRPs”) is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.
Physiologically based Pharmacokinetic Models

**Oral**

- Solubility
- pH
- Lipophilicity
- Controlled release rate
- Particle size distribution
- GI transit time
- GI fluid hydrodynamics
- GI fluid composition
- GI fluid pH
- GI fluid volume
- Permeability
- Etc.

**Dermal**

- Modeling dermal formulations
- Stratum corneum
- Viable epidermis
- Dermis
- Systemic

**Inhaled**

- Pfizer – PulmoSim

Gastroplus – TCAT model

- https://www.simulations-plus.com/software/gastroplus/additional-dosage/
Reduced Risk Products: Aerosol Inhalation

Nicotine
- Cigarette, Gum, Oral Snuff, Chewable Tobacco
- Transdermal Patch, Nasal Spray
- E-Cigarette, THS (Aerosol)

THS Generates Nicotine Containing Aerosol by Heating Tobacco

Cigarette Smoke

THS
Objectives

Develop methodologies based on PBPK modeling for dose estimation of nicotine contained in aerosols by

• Identifying the key requirements for PBPK modeling of inhaled aerosol

• Accounting for the specificity of inhaled RRPs aerosols
Review of approaches for inhaled aerosol dosimetry

Administered Aerosol → Exposure → Delivered (Deposited) Dose → Internal Dose → Biological Effect

Chemical & Physical Characterization of Aerosol
Inhalation Topography
Lung Morphology

PBPK modeling
Coupling Dosimetry and PBPK
Risk Assessment (In vitro to In vivo)

Computational tools
Review of approaches for inhaled aerosol dosimetry

Exposure
- Chemical & Physical Characterization of Aerosol
- Inhalation Topography
- Lung Morphology

Dose
- PBPK modeling
- Coupling Dosimetry and PBPK
- Risk Assessment (In vitro to In vivo)

Aerosol dosimetry

Computational tools
Physical Aerosol Characterization

Particle size distribution (PSD):
particle number density and particle size

- Instruments based on various measuring principles:
  - Inertia and aerodynamic drag
  - Light scattering

- Challenges:
  - Invasive techniques
  - Not applicable for high particle number densities
  - Often need dilution thus lead to aerosol evolution
Chemical & Physical Characterization of Aerosol

Aerosol Evolution

- nucleation
- evaporation / condensation
- coalescence / breakup
- drift (inertia, diffusion)
- deposition (inertia, diffusion)

Mechanisms of Aerosol Transport in Respiratory Tract

Nordlund and Kuczaj, 2015
Hinds, 2012
Review of approaches for inhaled aerosol dosimetry

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Aerosol dosimetry

Computational tools
Inhalation Exposures

**Short Exposure:** Single Inhalation Cycle
- Medical Products
- Self-administered → Guidance available

**Short Exposures: (intermittent) Multiple Puffs/Inhalation Cycles**
- Aerosols in Critical Care
- Administered under supervision
- Consumer Products
- Self-administered
- No guidance

**Long Exposures:**
- Environmental or occupational exposures
- Self-administered

**Concentration**
- Seconds
- Minutes
- Hours/Day
Inhalation Topography

**Tidal breathing patterns**

**Standard**

Flow rate

Inspiration | Expiration

0  | 1.5  | 4.6

**Expiration** | **Inspiration**

0     | 3   | 7

**Flow rate**

**Expiration** | **Inspiration**

Flow rate

**Inhalation topography influences the deposited dose and thereby the pharmacokinetics**

**Real-time inhalation cycle**

Flow rate (L/min)

- Puff Volume
- Inhalation Volume
- Inhalation Duration
- Exhalation Volume
- Exhalation Duration

Time (s)

(Vas 2015)

- Single individual
- Measured flow rate during inhalation cycle
- Each step can vary across population

**Standard**

Slow inspiration and breath hold

Forced inspiration

• Single individual
• Measured flow rate during inhalation cycle
• Each step can vary across population

Inhalation topography influences the deposited dose and thereby the pharmacokinetics
Review of approaches for inhaled aerosol dosimetry

Exposure
- Chemical & Physical Characterization of Aerosol
- Inhalation Topography
- Lung Morphology

Dose
- PBPK modeling
- Coupling Dosimetry and PBPK
- Risk Assessment (In vitro to In vivo)

Aerosol dosimetry

Computational tools
Lung Morphology

Airway dimensions

Branching pattern

- Limited data on deposition
- Humans: Lovelace Morphometry Report (1976)
  - Measurements for lungs
- Rodents: limited information concerning strain differences
  - Cast based measurements (Phalen, 1973)
- Individual-specific versus population-relevant

(Mouse Lung) Internal data

SOT Presentation, 2019

Respiratory Tract Heterogeneity Across Species

Expression of cells

- Absorption could be different across the respiratory tract (RT)
  - Differential expression of cell types
  - Wall Thickness
  - Mucociliary clearance rates

Wall thickness
(Human Respiratory Tract)

Mucus clearance

<table>
<thead>
<tr>
<th>Measured (mm/min)</th>
<th>Rat</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal Mucus Velocities</td>
<td>1.9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

(Hofmann 2002)
Aerosol dosimetry is complex
- No control over breathing pattern
  - Rodent to human exposures → difficult to translate
- Scaling of aerosol and airway diameters is critical
- Deposited dose and tissue exposures vary in time

**Aerosol vs Airway Diameter Ratio**

- Human: Aerosol → Airway → Deposition in Lower RT → Delivered Dose & PK
- Rodent: Aerosol → Airway → Deposition in Upper RT → Delivered Dose & PK

**Duration of Exposures are Different**

- Human: Seconds → Delivered Dose & PK
- Rodent: Minutes → Hours → Delivered Dose & PK
Review of approaches for inhaled aerosol dosimetry

Exposure

Chemical & Physical Characterization of Aerosol
Inhalation Topography
Lung Morphology

Dose

PBPK modeling
Coupling Dosimetry and PBPK
Risk Assessment (In vitro to In vivo)

Aerosol dosimetry

Computational tools
Fate of Nicotine after Inhalation

Kinetic process after nicotine inhalation are
• Absorption
• Metabolism
• Clearance
Existing Inhalation PBPK Models

- Models based on exposures and increasing complexities

1 compartmental RT  3 compartmental RT  4 compartmental RT

• Modeled exposures for risk assessment of acetone, vinyl acetate and styrene
• Prolonged exposures – hours/days

Ramsey & Andersen, 1984
Kumagai & Matsunaga, 1995
Bogdanffy, 1999; Sarapaneni, 2002
Existing Inhalation PBPK Models

Category of gases
(based on water solubility and reactivity)

<table>
<thead>
<tr>
<th>Gas Category Scheme</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: Do not penetrate to blood</td>
<td>Extrathoracic absorption</td>
</tr>
<tr>
<td>(e.g., highly water soluble/rapidly</td>
<td>Entire tract absorption</td>
</tr>
<tr>
<td>reactive)</td>
<td>Predominantly pulmonary absorption</td>
</tr>
<tr>
<td>Category 2: Water soluble/Blood accumulation</td>
<td></td>
</tr>
<tr>
<td>Category 3: Water insoluble/Perfusion</td>
<td>Example – Styrene</td>
</tr>
<tr>
<td>limited</td>
<td>solubility in water = 0.03 % (20 °C)</td>
</tr>
</tbody>
</table>

Model types for gases
• Fraction penetration model
  • absorption in ET region
  • concentration entering TB region

• Ventilation perfusion model
  • PU region

U.S. EPA, Methods for derivation of inhalation reference concentrations and applications of inhalation dosimetry, October 1994; (EPA/600/8-90/066F)
Review of approaches for inhaled aerosol dosimetry

- Exposure
  - Chemical & Physical Characterization of Aerosol
  - Inhalation Topography
  - Lung Morphology

- Dose
  - PBPK modeling
  - Coupling Dosimetry and PBPK
  - Risk Assessment (In vitro to In vivo)

Aerosol dosimetry

Computational tools
Coupled Inhalation PBPK Models

- Anatomical Lung representation in PBPK model
- Predict PK of inhaled powders (non-evolving aerosols)
- Dosing → single puff
- Determine Regional deposition and then input values into PBPK model

Particle size distribution

Estimated regional deposition (impaction, sedimentation, Diffusion)

Upper airways

Peripheral Lung

Central Lung

Mucociliary clearance

Gut

Liver

Richly perfused

Poorly perfused

Adipose

Upper airways (Nose)

Peripheral Lung

Central Lung

Particle dissolution

Surface Lining Liquid

Airway Tissue

Alveolar Dissolution Space

Mucociliary clearance

Gut

Liver

Richly perfused

Poorly perfused

Kidney

“No real coupling”

Boger, 2016 AstraZeneca

Caninga, 2016 Merck
Coupled Inhalation PBPK Models: Mechanistic

ICRP 66 model:
Particle filtration efficiency

ICRP 66 model:
Particle filtration efficiency

Mimetikos Preludium

Gastroplus – Inhalation module

Gastroplus – pulmonary module (Adapted from Boghart 2015)
https://www.simulations-plus.com/software/gastroplus/additional-dosage/
Inhalation PBPK Models: Non-Mechanistic

- **PulmoSim (Pfizer)**
  - No particle physics
  - No airway anatomy description
  - PulmoSim
    - Meeting report available but model descriptions are not available
    - Cannot really evaluate its applicability

- **SimCyp Simulator (Certara)**
  - Deposition
  - Airway Mucus
    - Absorption
    - Diffusion
  - Lung Tissue
    - Bound ↔ Unbound
  - Systemic PK
    - Absorption
  - GI tract

**Applicability for Aerosols?**

- Meeting Report Collingwood, 2012
- Backman, 2018
Review of approaches for inhaled aerosol dosimetry

Exposure
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Dose
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Aerosol dosimetry

Computational tools
Inhaled Dose Calculation

• Association of Inhalation Toxicologists, recommend standard delivered dose calculation in aerosol inhalation studies

\[
DD = \frac{C \times RMV \times D \times IF}{BW}
\]

(Alexander 2008)

DD = Delivered Dose
C = concentration of substance in air
RMV = respiratory minute volume
D = duration of exposure
IF = inhalable fraction
BW = Body weight

• More holistic determination of dose calculation must account for at least the following:
  o Aerosol physics
  o Inhalation topography
  o Lung Morphology

Aerosol Physics: Computational Fluid Dynamics

Increasing complexity and level of details

Mass conservation
\[ \frac{\partial}{\partial t} \rho + \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho u_j) \right) = -\sum_{j} \left[ (1 - \gamma) f_j \right] \]

Momentum conservation
\[ \frac{\partial}{\partial t} (\rho u_i) + \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho u_i u_j) \right) = -\frac{\partial}{\partial x_i} (\rho v) + \sum_{j} \left( \mu \frac{\partial u_i}{\partial x_j} \right) \quad ; \quad i = 1, \ldots, 3 \]

Energy conservation
\[ \rho c_p \left( \frac{\partial}{\partial t} (T) + u_i \frac{\partial}{\partial x_j} (T) \right) = \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho u_i \tau_{ij}) \right) + \sum_{k} \left( \rho \frac{\partial \tau_{ik}}{\partial x_j} \right) + \frac{\partial \rho}{\partial t} \frac{\partial T}{\partial t} \]

Transport of compounds in gas phase
\[ \frac{\partial}{\partial t} (\rho \tau_{i}) + \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho \tau_{i} u_j) \right) = \sum_{j} \left( \tau_{i} \frac{\partial Y_j}{\partial x_j} \right) + \sum_{k} \left( \rho \frac{\partial Y_j}{\partial x_k} \right) \quad ; \quad n = 1, \ldots, N \]

Transport of compounds in liquid phase
\[ \frac{\partial}{\partial t} (\rho Z_n) + \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho Z_n u_j) \right) = \sum_{j} \left( Z_n \frac{\partial Y_j}{\partial x_j} \right) + \sum_{k} \left( \rho \frac{\partial Y_j}{\partial x_k} \right) \]

Transport of particle number density
\[ \frac{\partial}{\partial t} (\rho M_q) + \sum_{j} \left( \frac{\partial}{\partial x_j} (\rho M_q u_j) \right) = -\sum_{j} \left( \rho M_q \frac{\partial M_q}{\partial x_j} \right) + \sum_{j} \left( \rho D_q \frac{\partial M_q}{\partial x_j} \right) + \sum_{k} \left( \rho \frac{\partial M_q}{\partial x_k} \right) \quad ; \quad q = 1, \ldots, Q \]

Longest & Kleinstreuer, Aerosol Sci. Technol., 2005
Finlay, Mechanics of Inhaled Pharmaceutical Aerosols, 2001
Rostami, Inhal. Tox. 2009
Corley et al., Toxicol. Sci., 2012

Inhalation Dose: Whole-lung models

- These models are based on following assumptions:
  - Lung morphometry data
  - Semi-empirical correlations
  - Single-path / Multiple-path
  - Deterministic / Stochastic


- Limited airways geometries
- Limited available correlation data
- Developed for solid (non-evolving) particles
Semi-Descriptive Rat Inhalation PBPK Model @ PMI

- Verifying applicability of different compartmental models

For model development validation experiments
- Cigarette smoke (CS) and nebulized nicotine in water were exposed to rats (nose-only exposure)
  - CS: MMAD < 1.0 μm, GSD ~ 1.3
  - Nebulized nicotine aerosol: MMAD 1.0-2.5 μm, GSD ~ 2.0

On the basis of developed model:
- Good predictions were obtained assuming that part of the aerosol is not inhaled
- Need for multi-compartmental model to account for aerosol physics and deposition in the upper respiratory tract

Predicted Nicotine fraction entering RT ($f_0$) using PK

<table>
<thead>
<tr>
<th>Compound</th>
<th>Respiratory tract ($f_0 \times (1-f_{alv})$)</th>
<th>Alveoli ($f_0 \ times f_{alv}$)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Gastrointestinal tract</th>
<th>Respiratory tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Semi-Descriptive Human Inhalation PBPK Model @PMI

- Clinical trial comparing Electronic Vapor product (EVP) and Cigarette smoke (CS)
- Fraction deposited are fitted to PK
- Electronic vapor product showed marked deposition in upper airways

Challenges
- Without aerosol physics the model cannot predict delivered dose for other compounds
- Data cannot be translated across population
- As expected model indirectly predicted increased absorption of nicotine in the upper respiratory tract for EVP
Ongoing Work

Airway anatomy

Deposition of evolving aerosol
- nucleation
- evaporation / condensation
- coalescence / breakup
- drift (inertia, diffusion)
- deposition (inertia, diffusion)

Physiological process

Physiological process

Mucus velocities in airway generation

Inhalation topography

Flow rate (L/min)

Puff Volume

Mouth Hold Time

Inhalation Volume

Inhalation Duration

Breath Hold

Exhalation Volume

Exhalation Duration

Time (s)

Deposition of evolving aerosol

Dose

Physiological process

Mucus velocities in airway generation

Inhalation topography

Flow rate (L/min)

Puff Volume

Mouth Hold Time

Inhalation Volume

Inhalation Duration

Breath Hold

Exhalation Volume

Exhalation Duration

Time (s)
Discussion

Challenges involved in PBPK modeling of Nicotine containing Inhaled Aerosol
PBPK Modeling of Inhaled Aerosol

Aerosol dosimetry
(airway anatomy, aerosol physics and inhalation patterns)

Volume/surface estimations
Whole-lung models
CFD-based models

Single-path
Multiple-path
Lagrangian
Eulerian

Stochastic
Deterministic
One-way Coupled
Fully Coupled

1-3 Segments
Multi-segments
Discrete/continuous (CFD-PBPK coupled)

1-3 Segments
Multi-segments
Discrete/continuous (CFD-PBPK coupled)

EXPOSURE
DOSE
TISSUE CONCENTRATIONS

Increasing complexity and level of details
Challenges: Aerosol Physicochemical Properties

- Chemical composition of aerosol formulation impacts transport, evolution and deposition of aerosol mixture in respiratory tract.

- Partitioning of the aerosol mixture phases influences deposition and absorption, which subsequently impacts dose response of the compound under investigation.

- Transport of an evolving aerosol is influenced by several factors including changes in pH, influence of spatio-thermal and humidity conditions along the respiratory tract.

Aerosol Composition of THS

- Water: 76%
- Nicotine: 12%
- Glycerin: 9%
- Others: 3%

Schaller, 2016

https://en.wikipedia.org/wiki/Vapor
Challenges: Inhalation Topography

• Inhalation topography (breath hold, mouth hold and deep/shallow inhalation) effects the pharmacokinetics of short interval exposure.

• Inhalation patterns vary across individual subjects resulting in different exposures, thus there is a requirement to analyze and benchmark patterns of absorption, distribution, metabolism and excretion following aerosol exposures for development of population-based PBPK modeling.

• Do we need to consider breathing pattern –

Breathing pattern

• In reality – its unsupervised and varies across population
Challenges: Lung Geometry

• There is a limited knowledge deposition of mouth and nose geometries on the delivery of aerosols for rodents and humans.

• Current data on rodent and human lung geometries are limited. They are not representative for the population differences.

Mouse nose geometry – (source: PNNL, Corley)

Lung volume differences

Donnelly 1991
Challenges: Aerosol Dosimetry + PBPK

- The outcomes of a PBPK model show the actual deposited dose in the lung (respiratory tract) and gastrointestinal (swallowed directly) vary due to dependence on the aerosol inhalation process.

- Various methodologies were developed to determine and validate regional deposition of aerosol in the respiratory tract, but they lack generalization concerning dependence on chemical and aerosol physical properties.
Challenges: Aerosol Dosimetry + PBPK

- There is limited knowledge concerning the partitioning coefficients of compounds in various regions of the respiratory tract (e.g., extra-thoracic, thoracic, bronchiolar and alveolar regions) especially considering the varied tissue thickness and transfer rates.

- The aerosol exposure to delivered dose calculations as per Association of Inhalation Toxicologists [13] does not account for aerosol physics with an inclusion of transport, evolution and deposition mechanisms.
Challenges: Aerosol Dosimetry + PBPK

- What level of respiratory tract complexity is needed to improve predictions of aerosol dosimetry from a PBPK modeling perspective?

- Which computational dosimetry approaches (whole-lung or CFD-coupled) are recommended for development and coupling while simultaneously accounting for accuracy vs feasibility and practical use?

- Is there an optimal (required or sufficient) number of lung segments to be used for dosimetry prediction and subsequent linking to PBPK compartments?
Challenges: ADME+ PBPK

• Methodologies to predict the rates and amounts of selected compounds cleared by mucus based on physiochemical properties of aerosols are not published. A detailed inclusion of mechanistic biology (e.g., inclusion of expression of cytochrome P450 enzymes, transporters etc.) of the respiratory tract would be beneficial.

• Reliability of in vitro tools for measurements

Measure Aerosol Deposition

Measurement of Mucus Dissolution Rates

Metabolism and Transport in 3D Airway Tissues

Cilia Beating Frequency

Informing PBPK model
Quantitative in vitro to in vivo Extrapolation (QIVIVE)

- Improvement of dose-response extrapolations of in vitro concentrations to in vivo outcomes is needed. Quantitative translation strategies need to be adapted for determining such doses.

- There is a need to develop strategies for employing in vitro tools and preclinical in vivo studies to further support the quantitative extrapolation of inhaled aerosol dose-exposure-response paradigm.

- What might be the best validation experiments in preclinical species that are pertinent to humans for evolving and non-evolving aerosols especially considering anatomical and physiological differences?

- How to appropriately apply QIVIVE in scaling of the lung geometry and aerosol particle size distributions to facilitate such extrapolations?
Model Comparison to Identify Best Applicability

• Head-to-Head comparison of PBPK models
  o Predict transport, deposition and transfer of Aerosol
  o Influence of aerosol mixtures

• Any interest in open source platform development
  o Aerosol deposition and exposure modeling
  o Exchange of knowledge and mathematical models
  o Advance field of multidisciplinary science
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