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Alliance for Risk Assessment (ARA) Workshop 2019, Austin, TX

Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment

Physiologically based Pharmacokinetic Modeling of Inhaled Aerosol

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The research described in this presentation was sponsored by Philip Morris International.

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

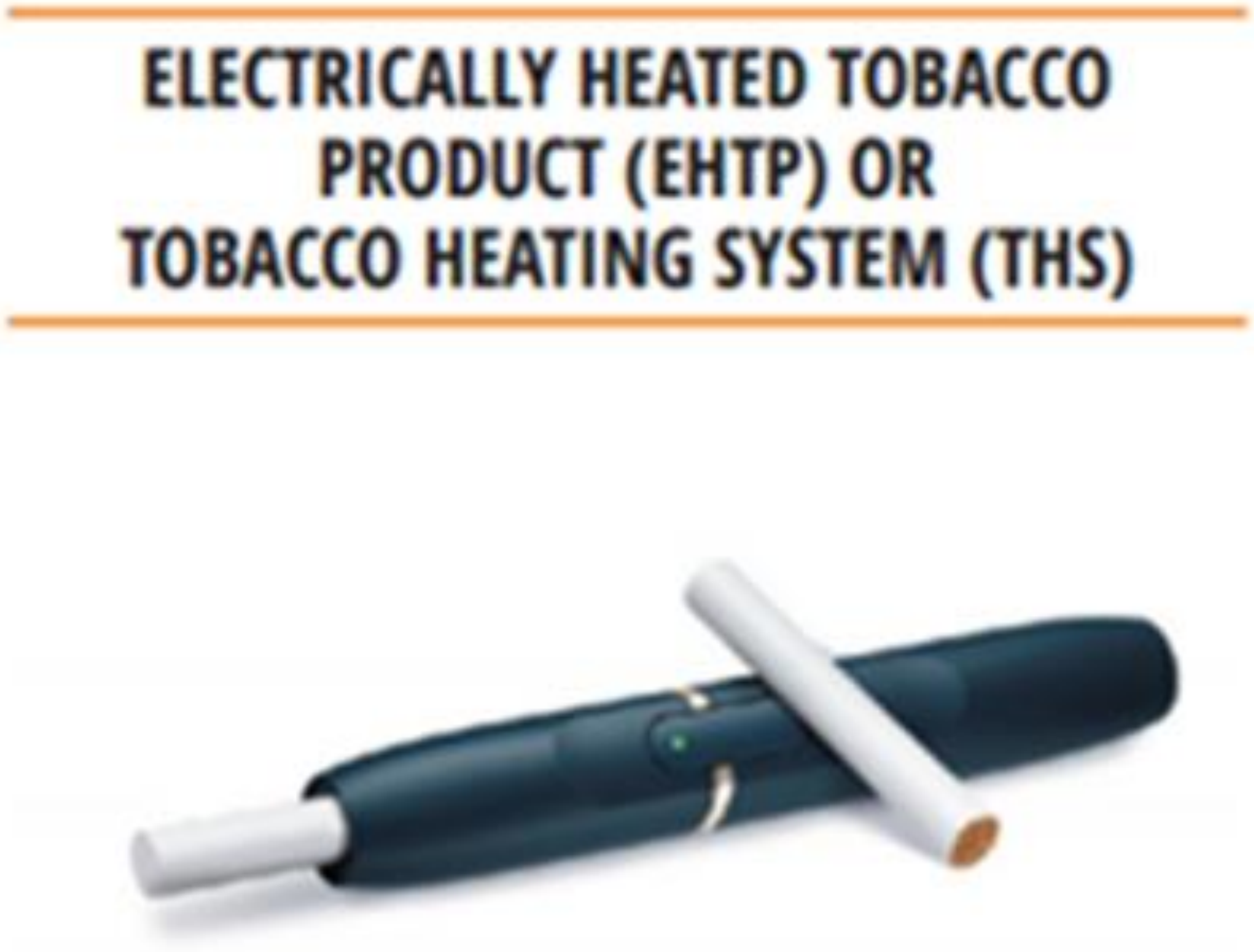
Agenda

- Background
- Objectives
- Review of existing approaches
  - Physicochemical Properties of Aerosol
  - Inhalation Topography and Airway Anatomy & Physiology
  - Aerosol Deposition Models
  - 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

HARM REDUCTION = REDUCED-RISK PRODUCT x PRODUCT ACCEPTANCE AND USAGE

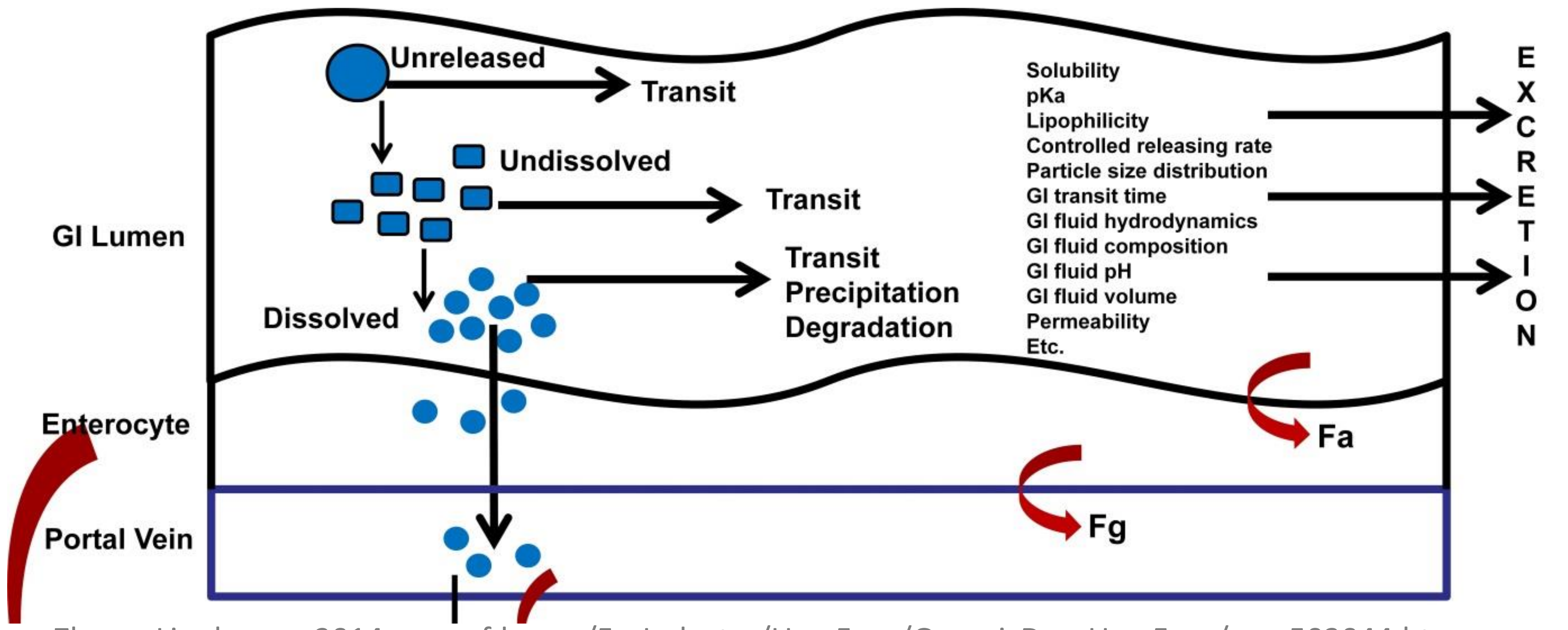


- Toxicological assessment requires an understanding of
  - Exposure
  - Time
  - Dose

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.

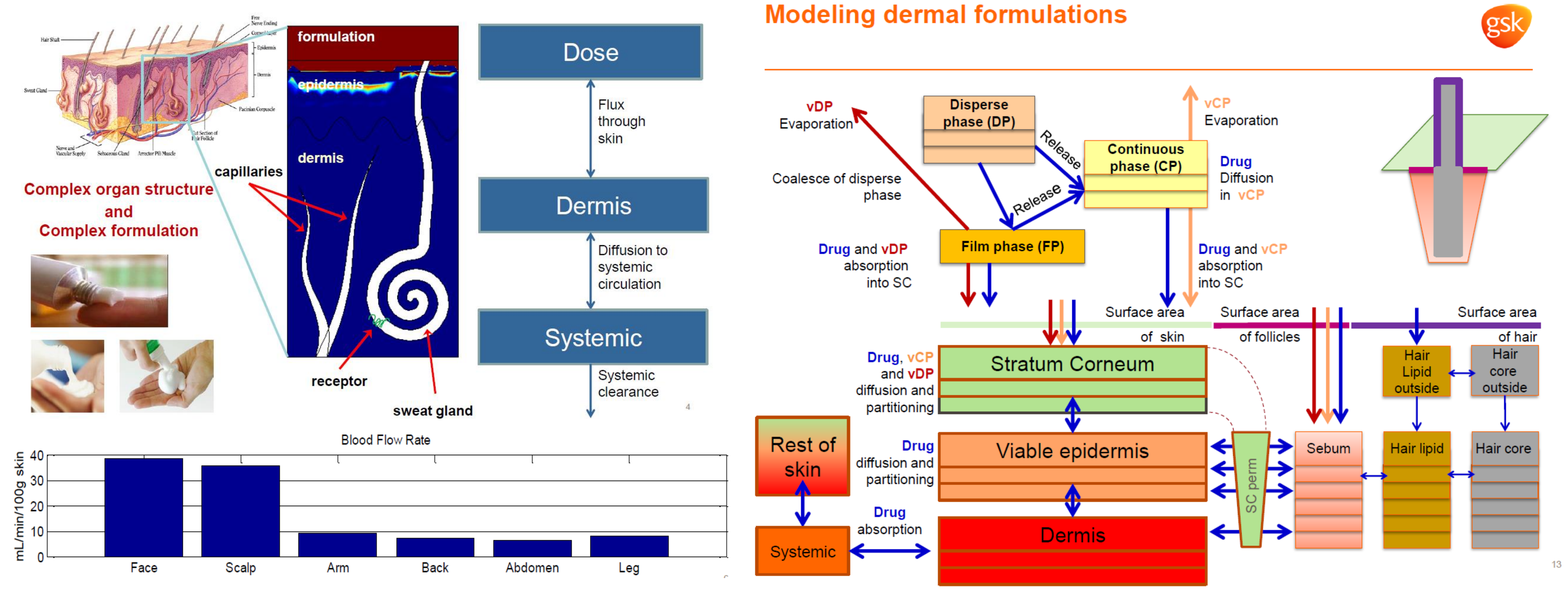
Physiologically based Pharmacokinetic Models

Oral



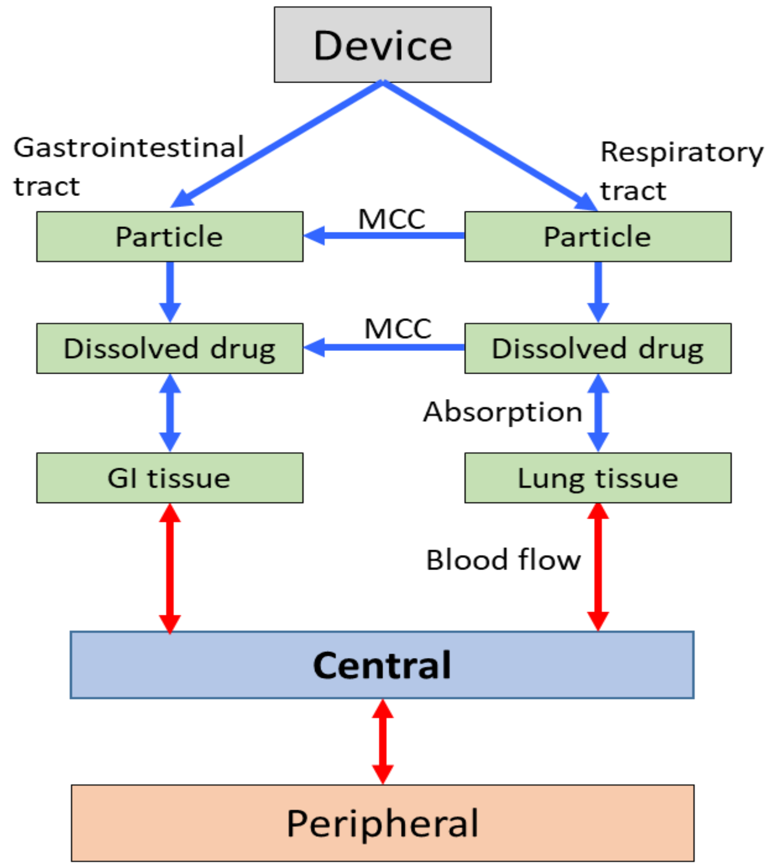
Zhang, Lionberger 2014; www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503044.htm

Dermal

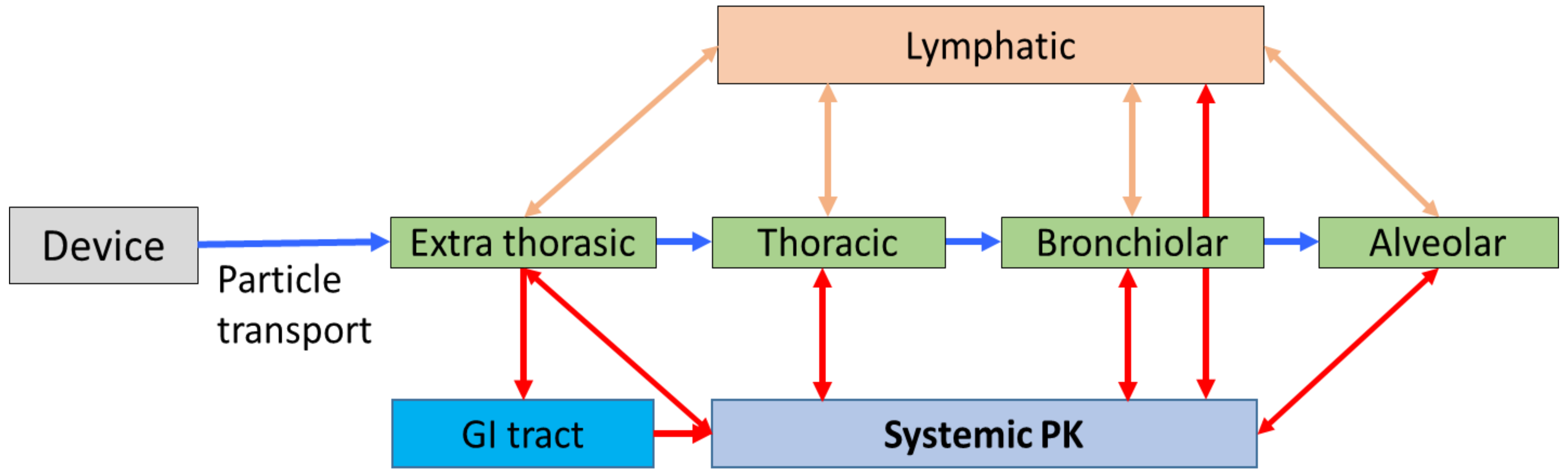


https://www.toxicology.org/groups/ss/BMSS/docs/SOT_2017_Dermal_Drug_Webinar.pdf

Inhaled



Pfizer – PulmoSim



Gastroplus – TCAT model

https://www.simulations-plus.com/software/gastroplus/additional-dosage/

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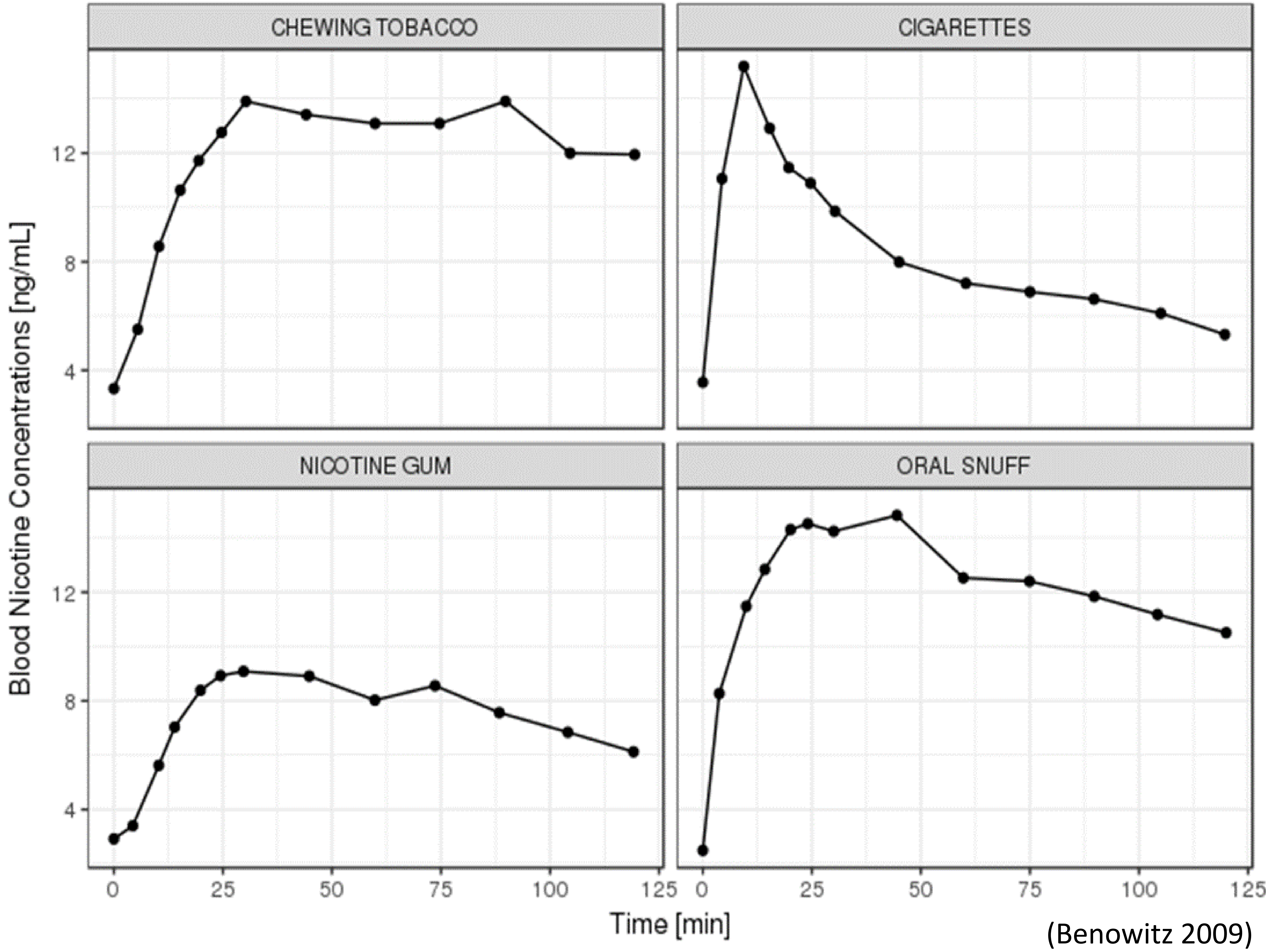
Reduced Risk Products: Aerosol Inhalation

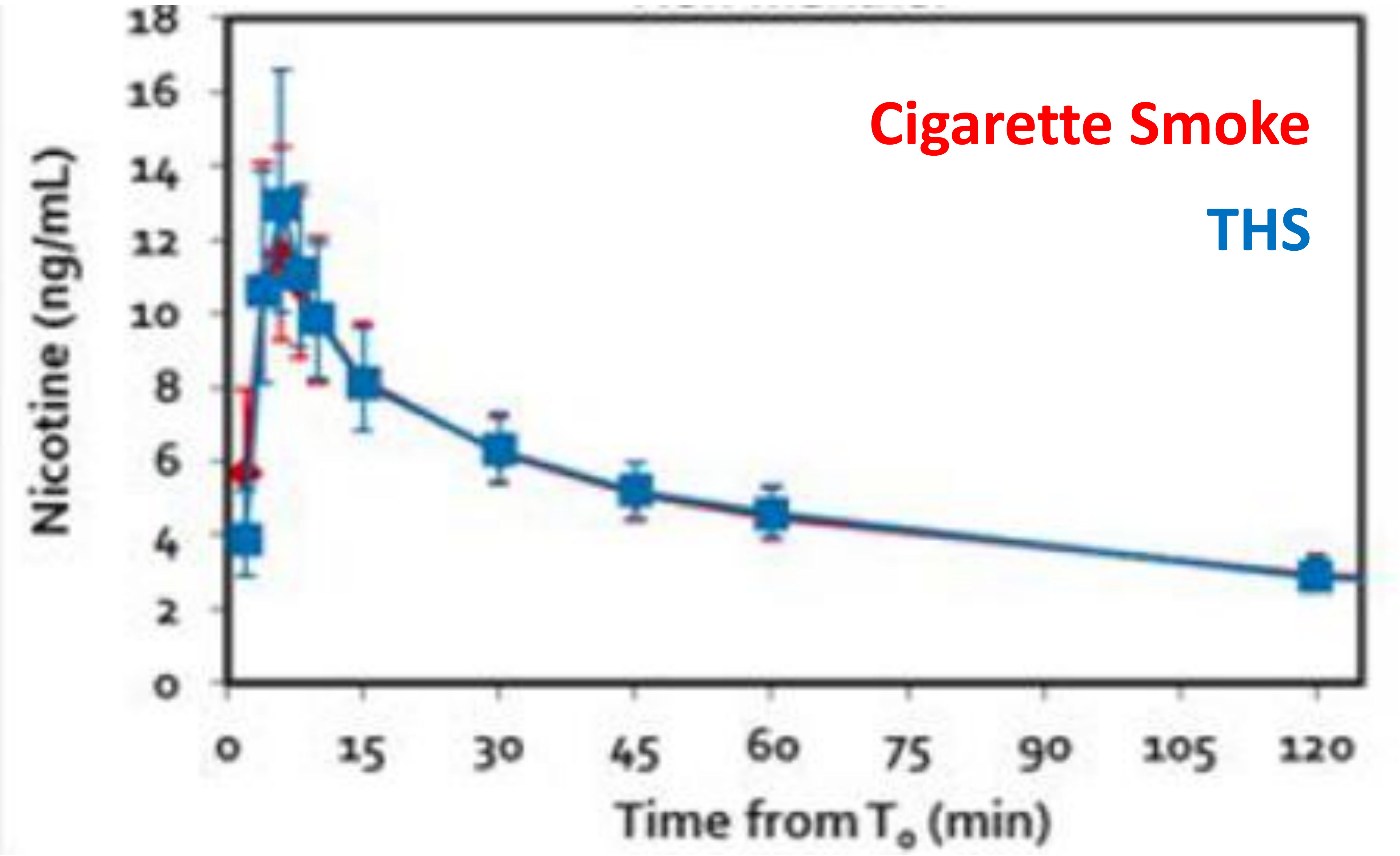
Nicotine

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



(Benowitz 2009)

THS Generates Nicotine Containing Aerosol by Heating Tobacco



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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

Aerosol dosimetry

PBPK modeling

Coupling Dosimetry and PBPK

Risk Assessment (In vitro to In vivo)

Computational tools

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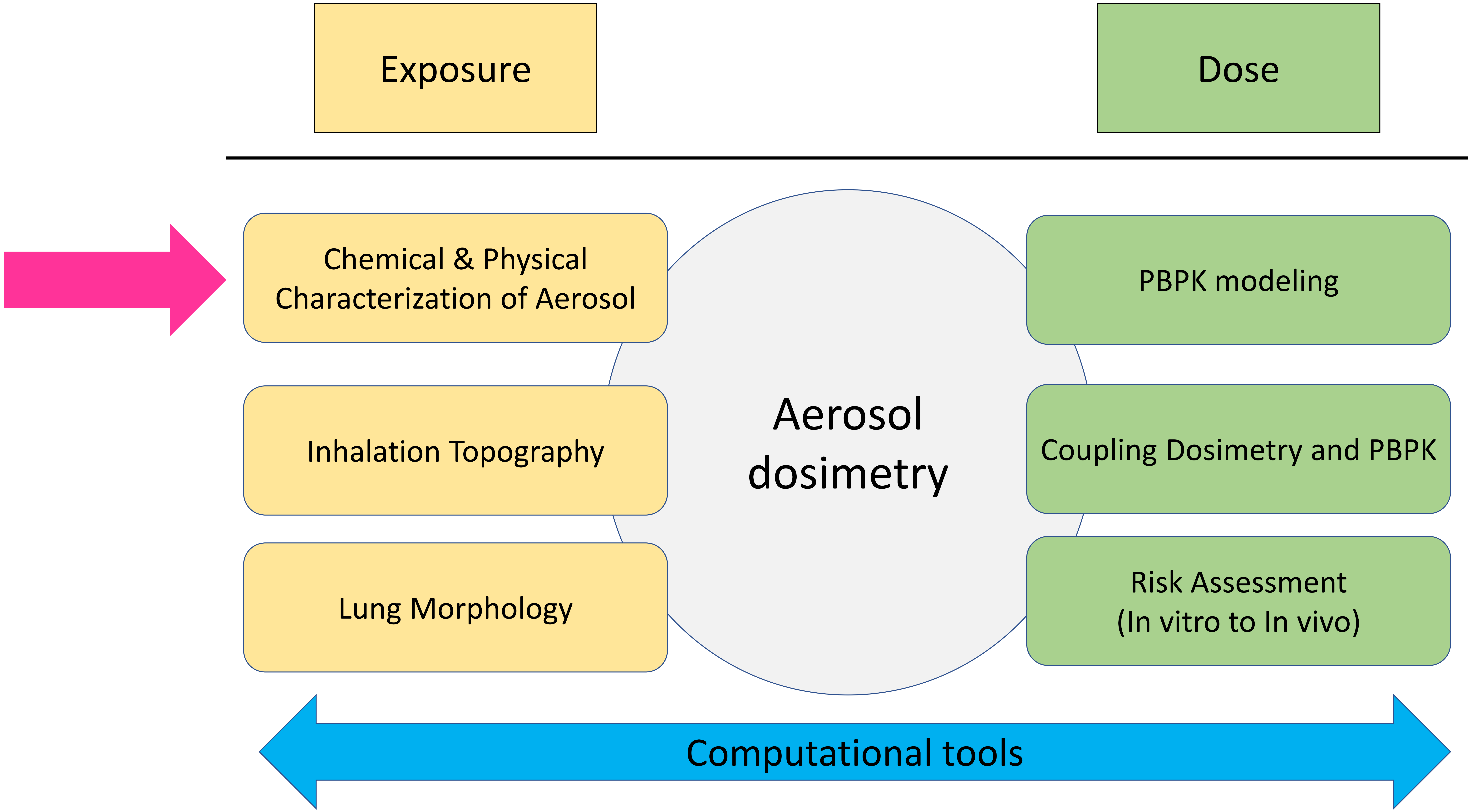
Review of approaches for inhaled aerosol dosimetry



Chemical & Physical Characterization of Aerosol

PIXE Cascade Impactor

Source: www.pixeintl.com

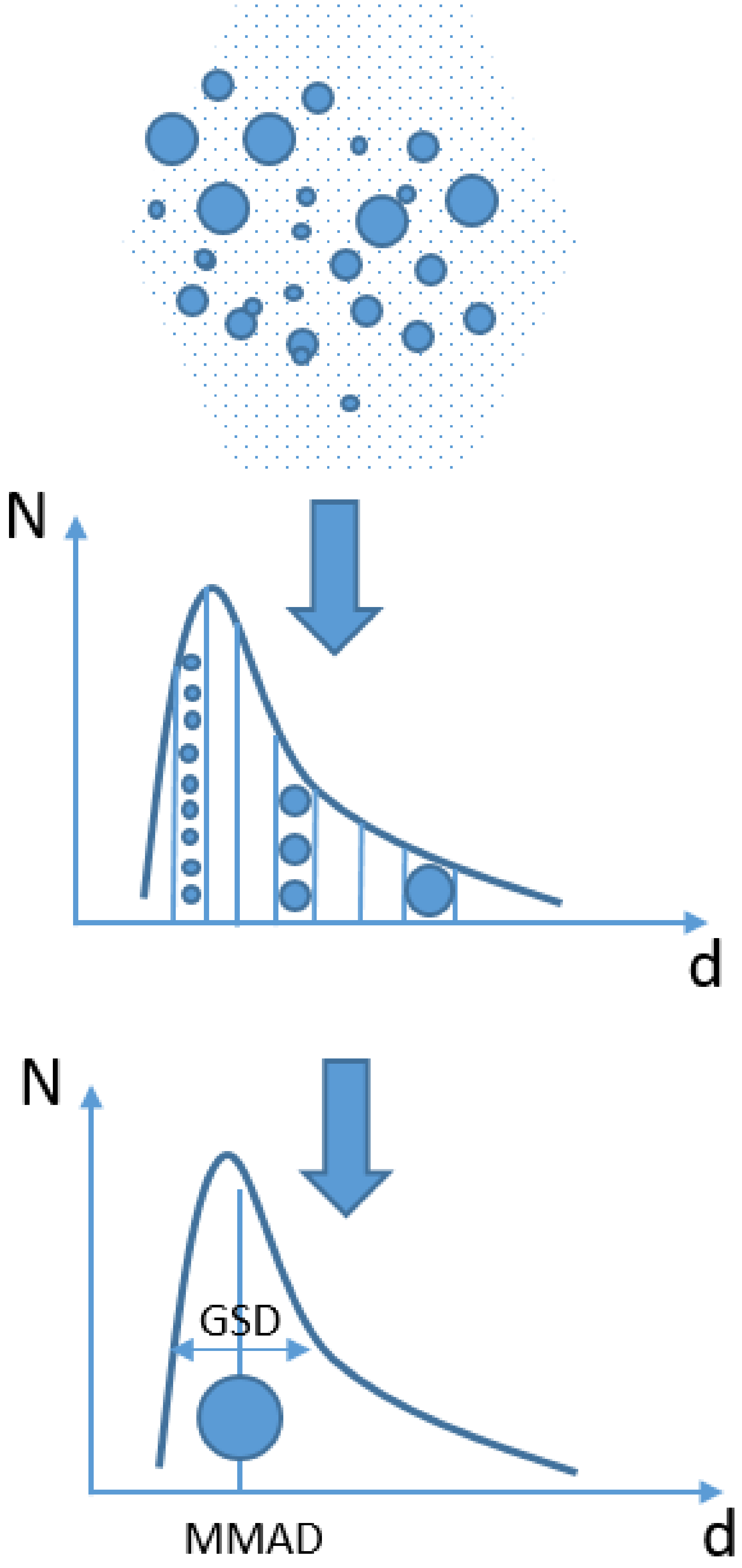
Physical Aerosol Characterization

Particle size distribution (PSD):

particle number density and particle size

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

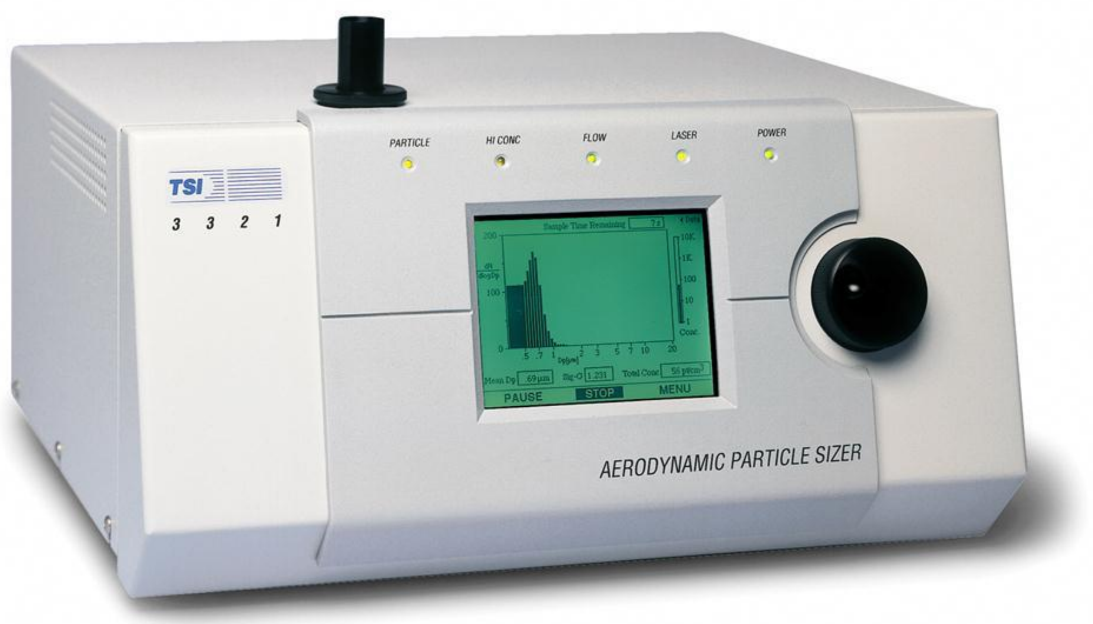
- Invasive techniques
- Not applicable for high particle number densities
- Often need dilution thus lead to aerosol evolution



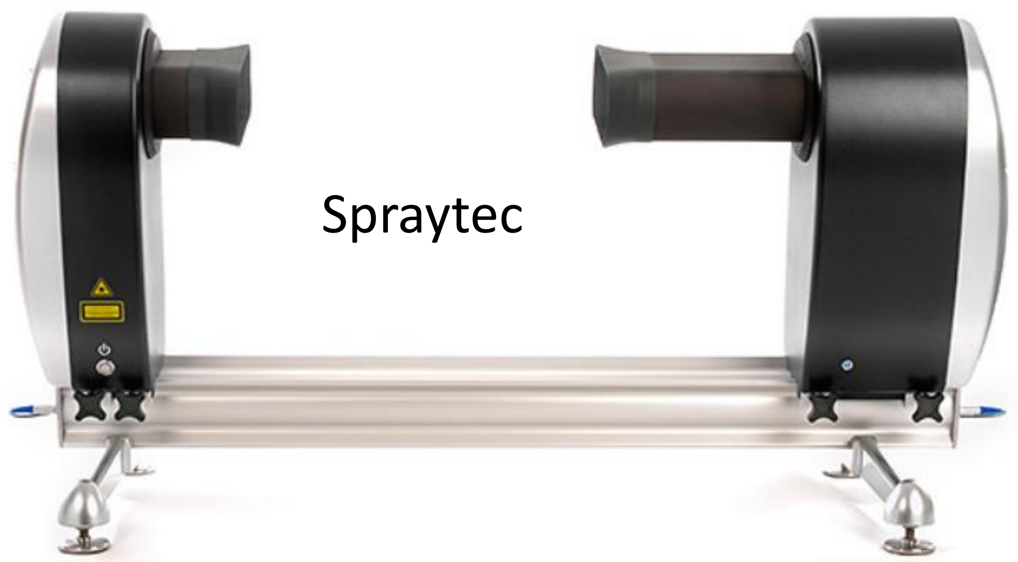
Andersen Cascade Impactor

Source: www.copleyscientific.com

Aerodynamic Particle Sizer



Source: www.tsi.com



Spraytec

Source: www.malvernpanalytical.com

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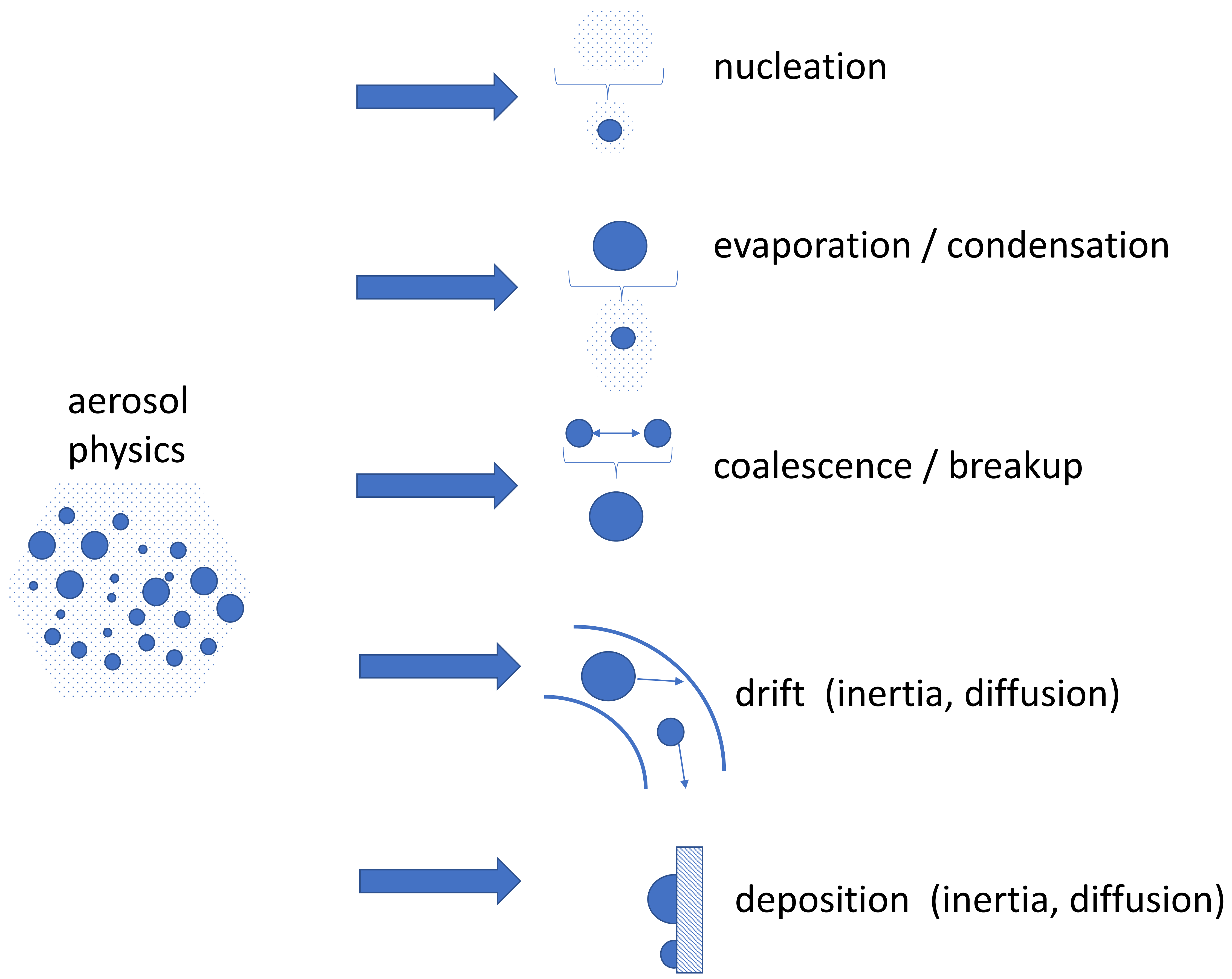
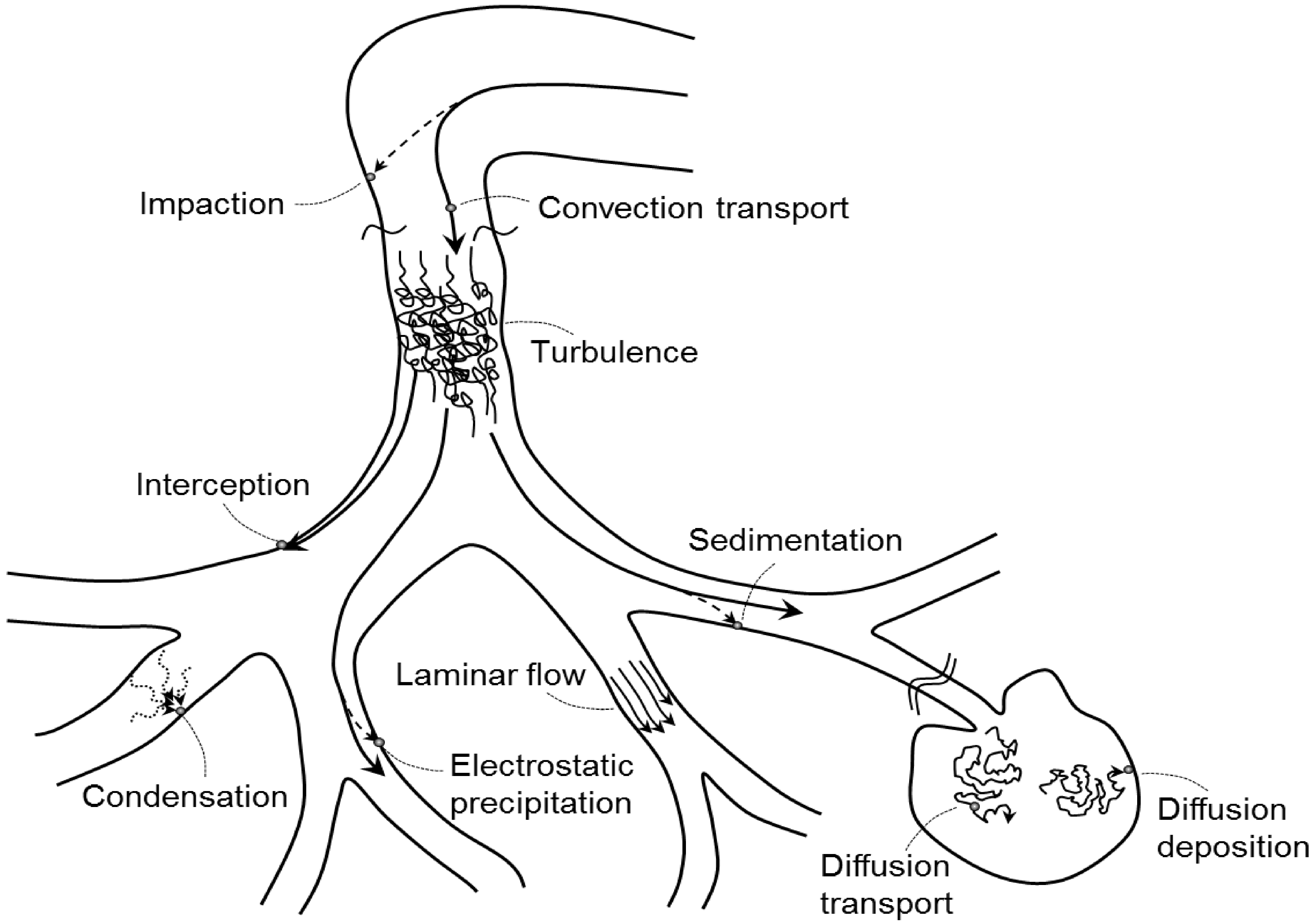
Chemical & Physical Characterization of Aerosol

Aerosol Evolution



Mechanisms of Aerosol Transport in Respiratory Tract



Nordlund and Kuczaj, 2015
Hinds, 2012

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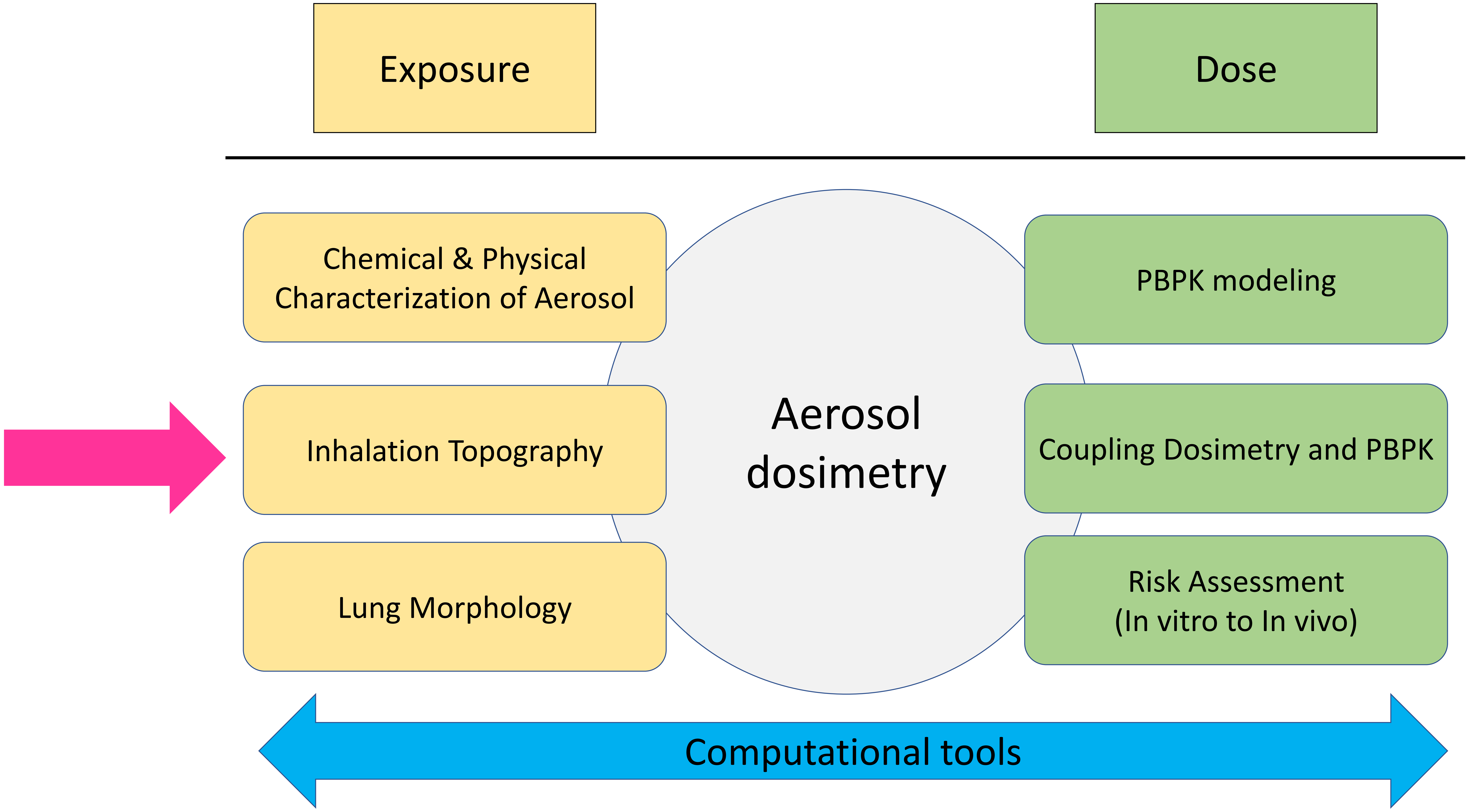
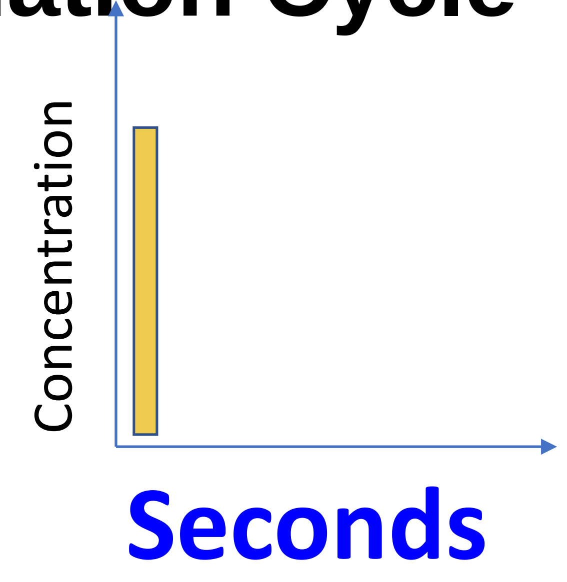
Review of approaches for inhaled aerosol dosimetry



Inhalation Exposures

Seconds → **Minutes** → **Hours/Day**

Short Exposure: Single Inhalation Cycle

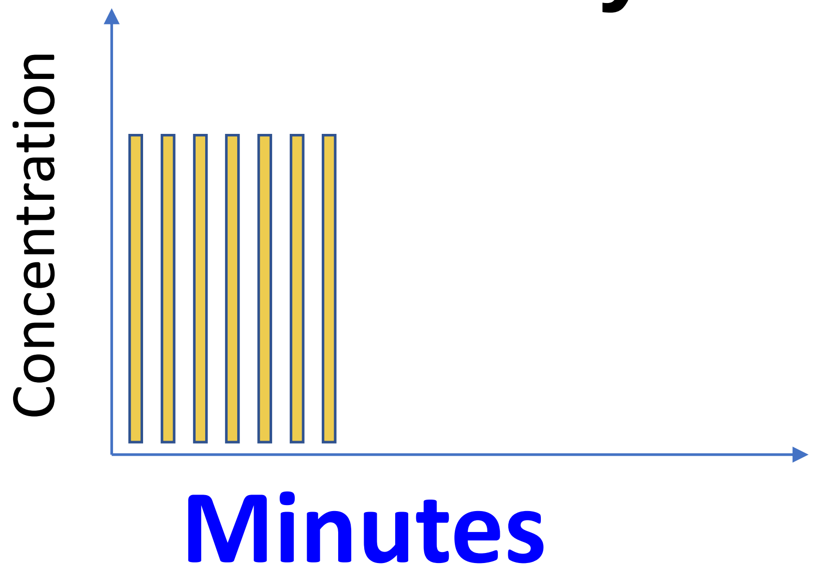



Wikipedia:Metered-dose inhaler


Wikipedia:Neubulizer

- Medical Products
- Self-administered →
- Guidance available

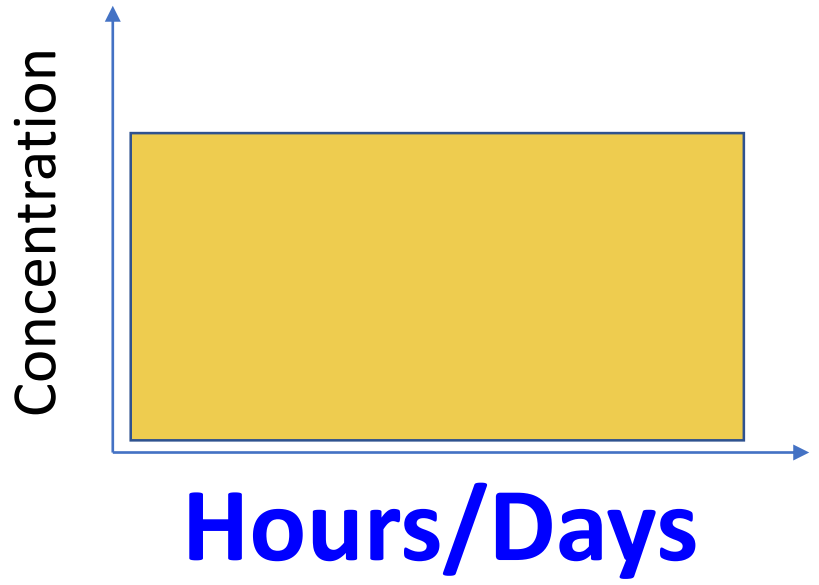
Short Exposures: (intermittent) Multiple Puffs/ Inhalation Cycles

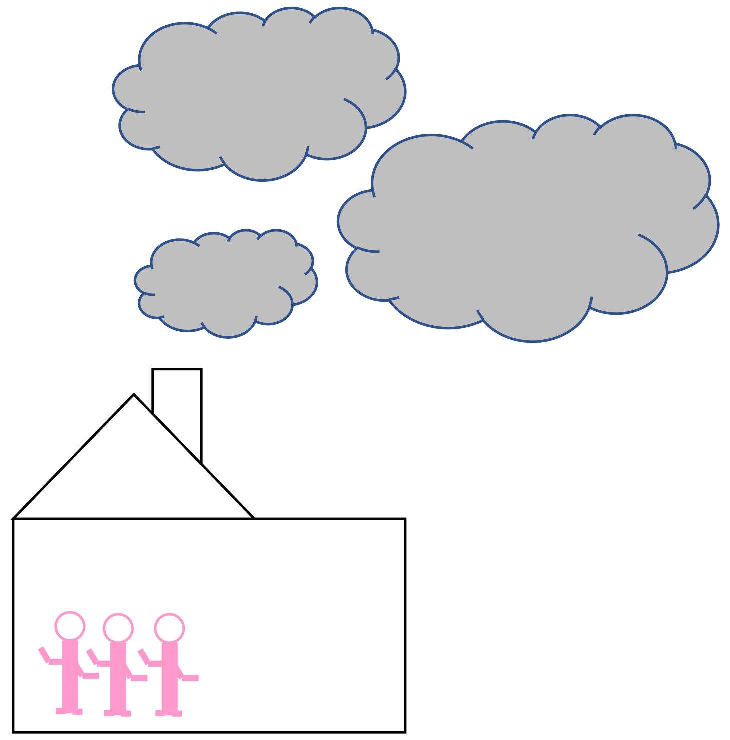


- Aerosols in Critical Care
- Administered under supervision

- Consumer Products
- Self-administered
- No guidance

Long Exposures:

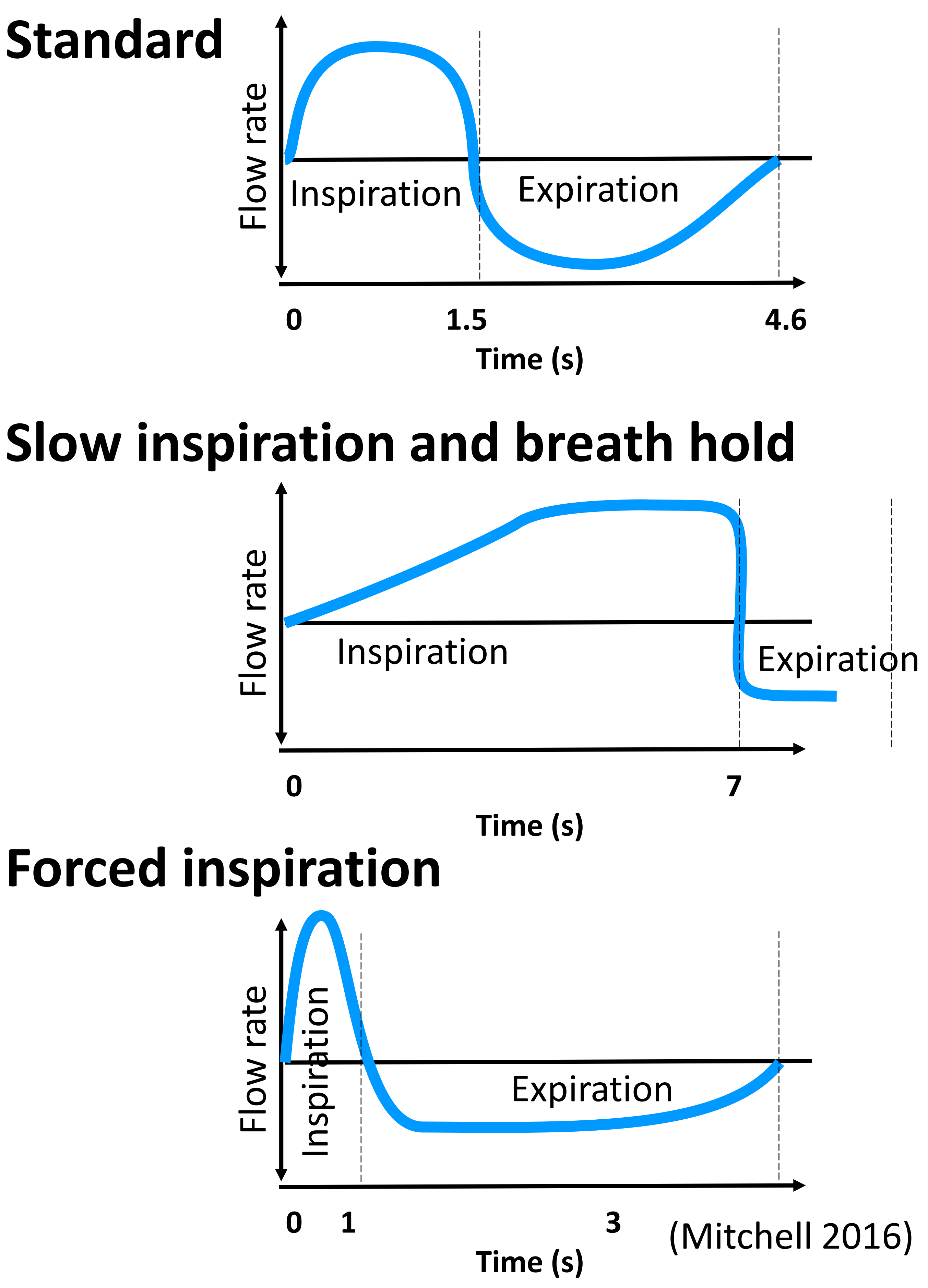




- Environmental or occupational exposures
- Self-administered

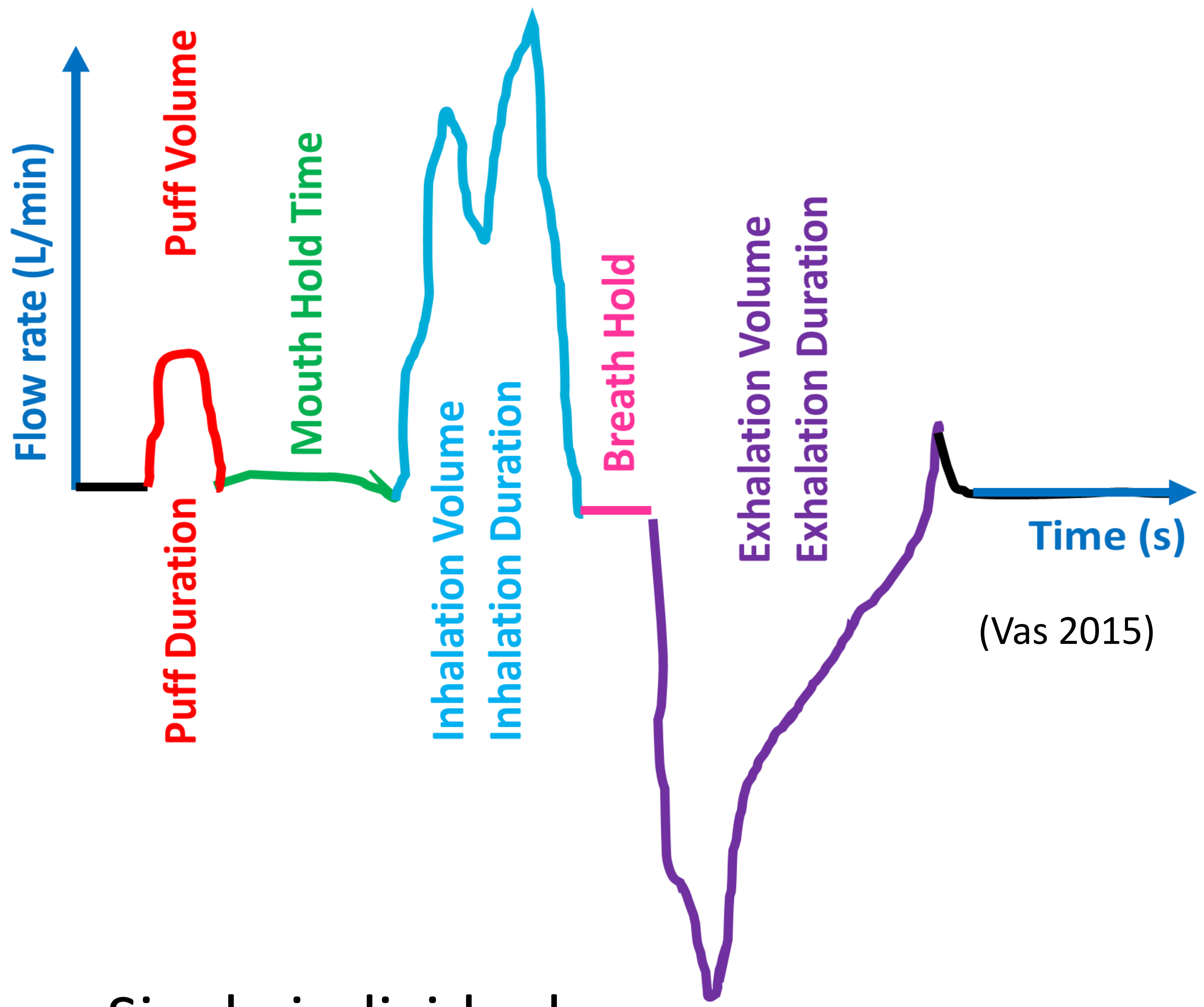
Inhalation Topography

Tidal breathing patterns



(Mitchell 2016)

Real-time inhalation cycle



(Vas 2015)

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

Inhalation topography influences the deposited dose and thereby the pharmacokinetics

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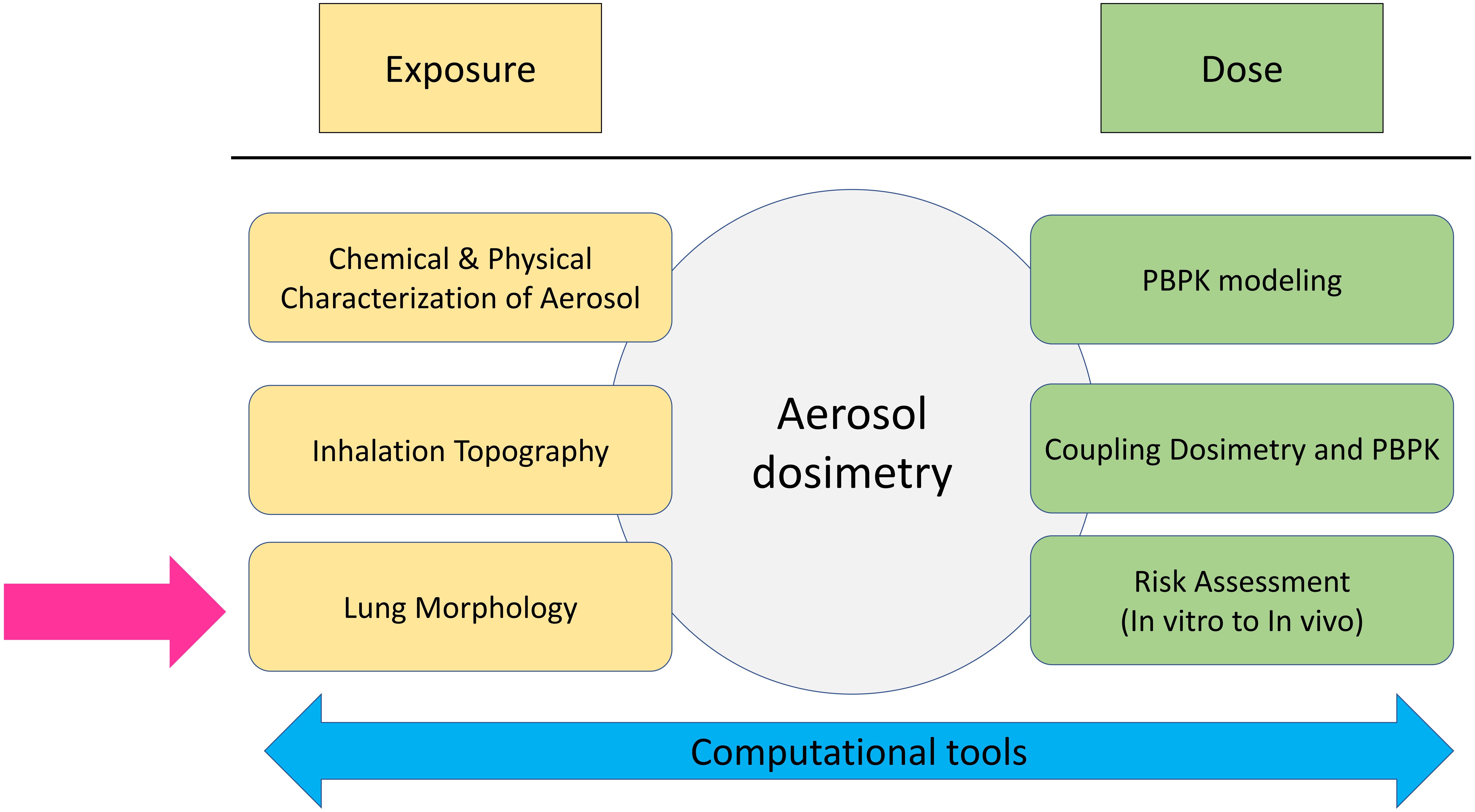
Review of approaches for inhaled aerosol dosimetry



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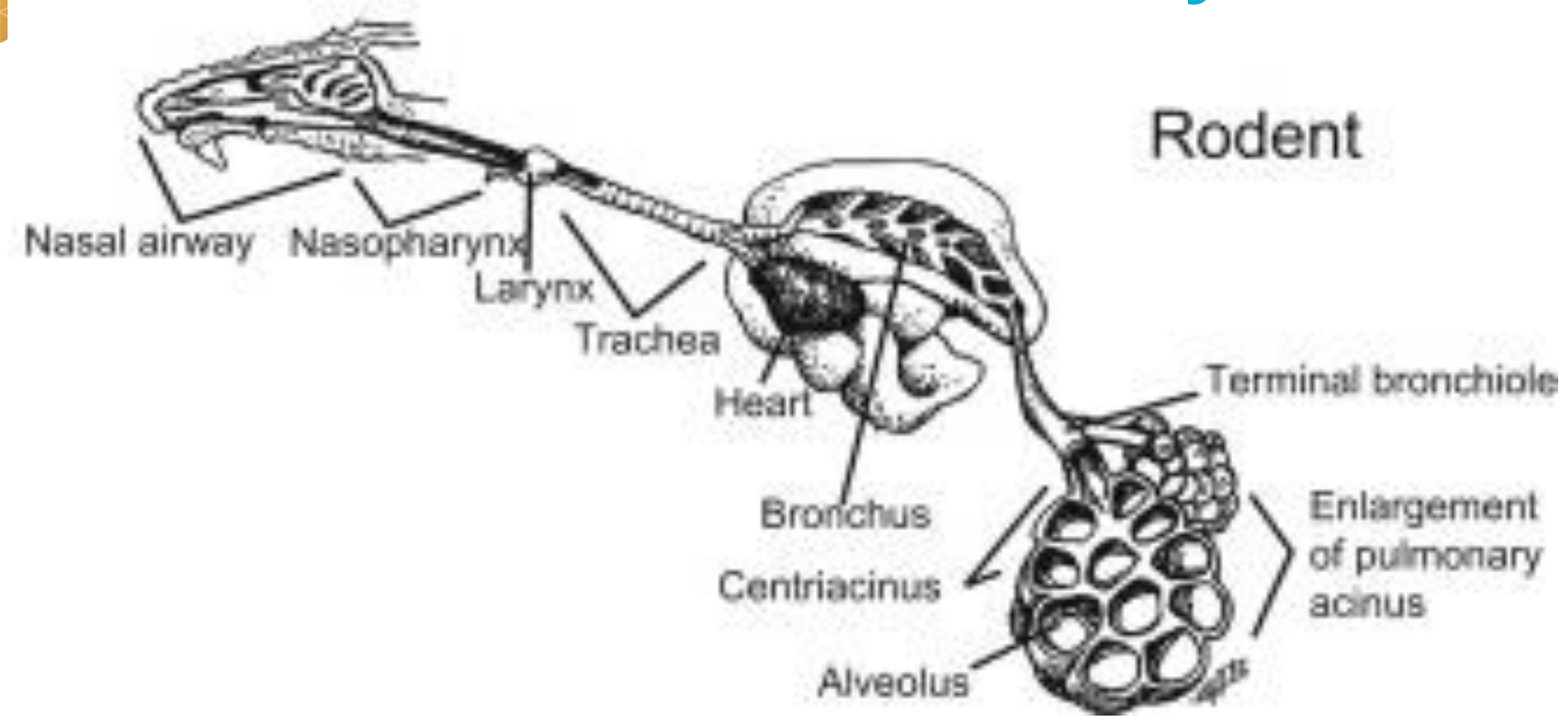
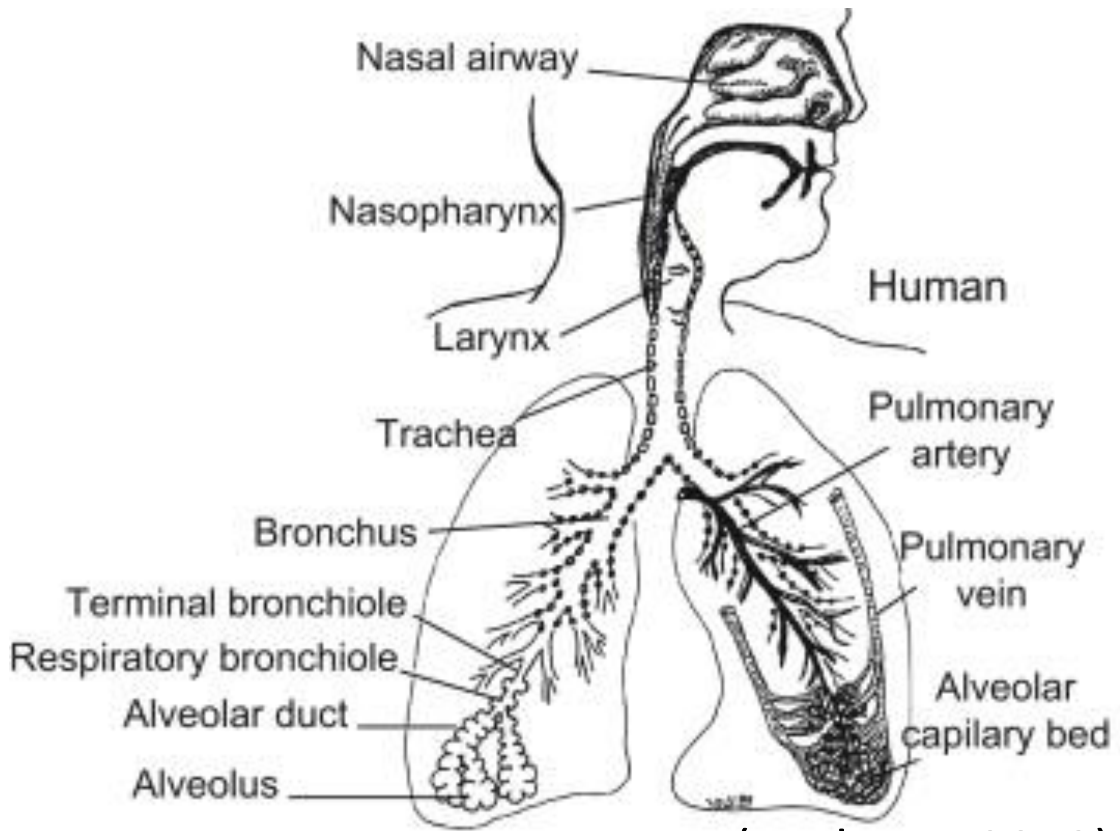
Lung Morphology

Airway dimensions

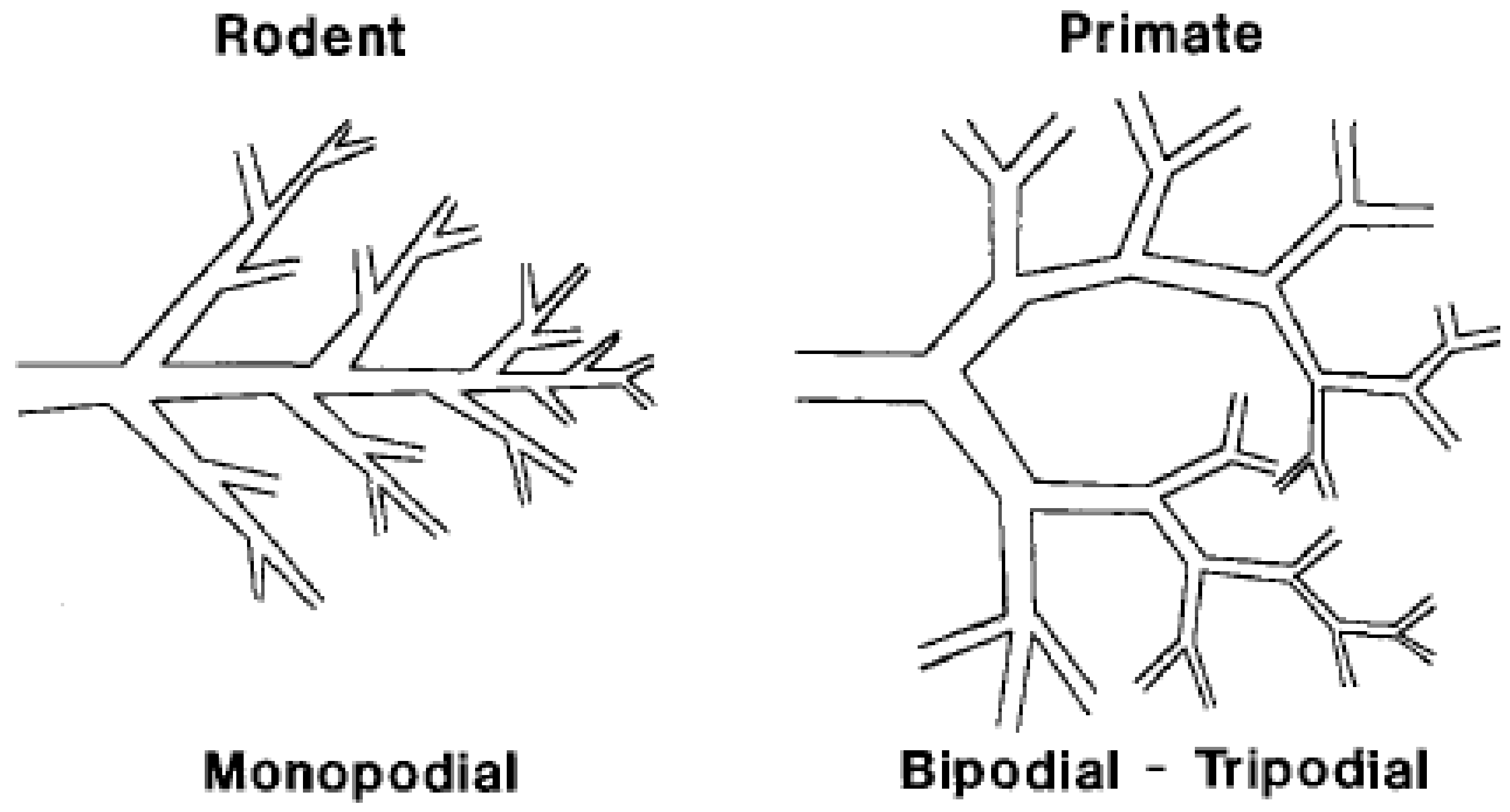


(Harkema 2013)

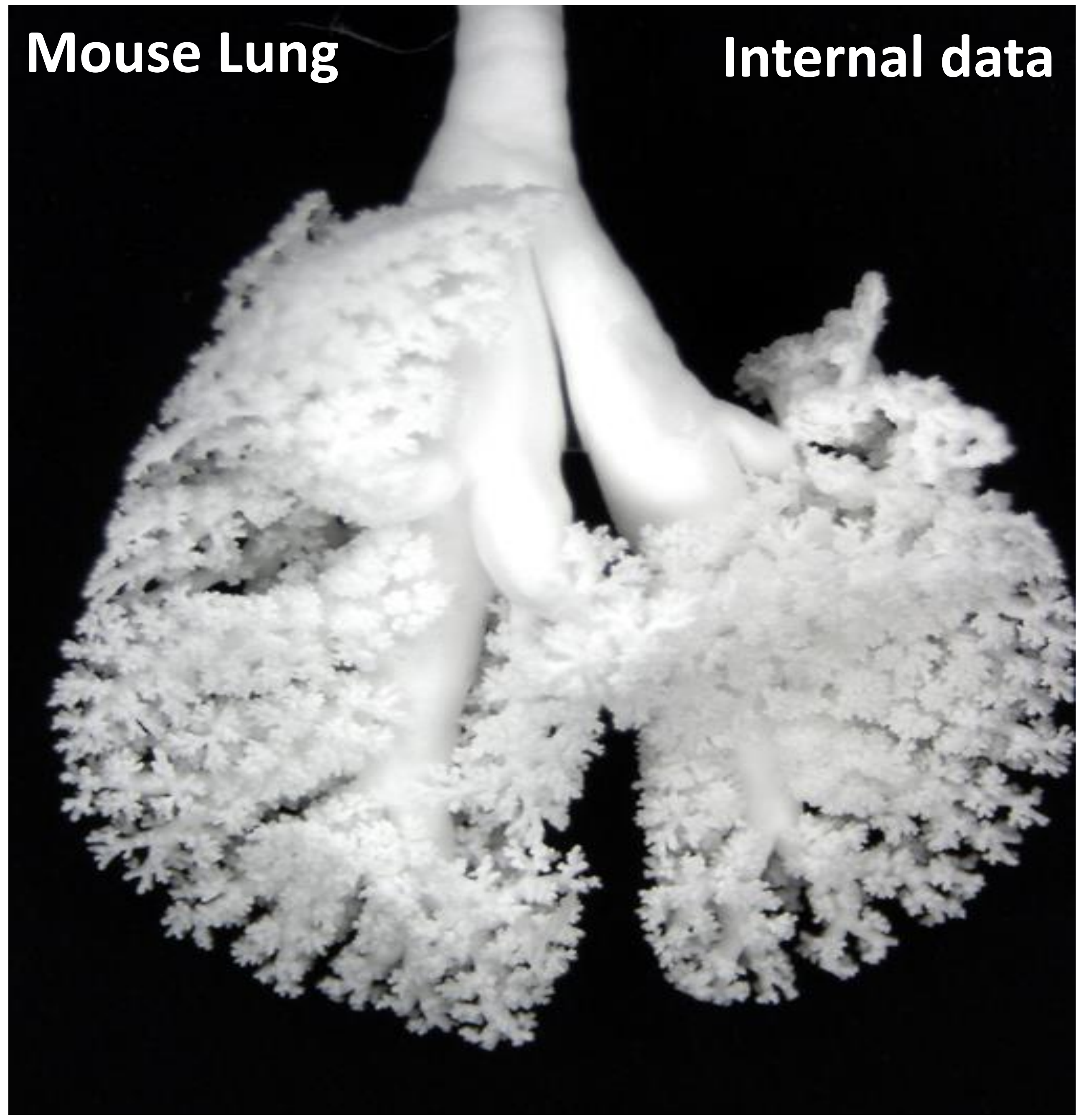


(Harkema 2013)

Branching pattern



(J. F. Miller, J.D. Crapo, 1993)



SOT Presentation, 2019

- 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

Phalen et al. Casting Lungs in-Situ. Anat Rec. 1973;177(2):255–63.

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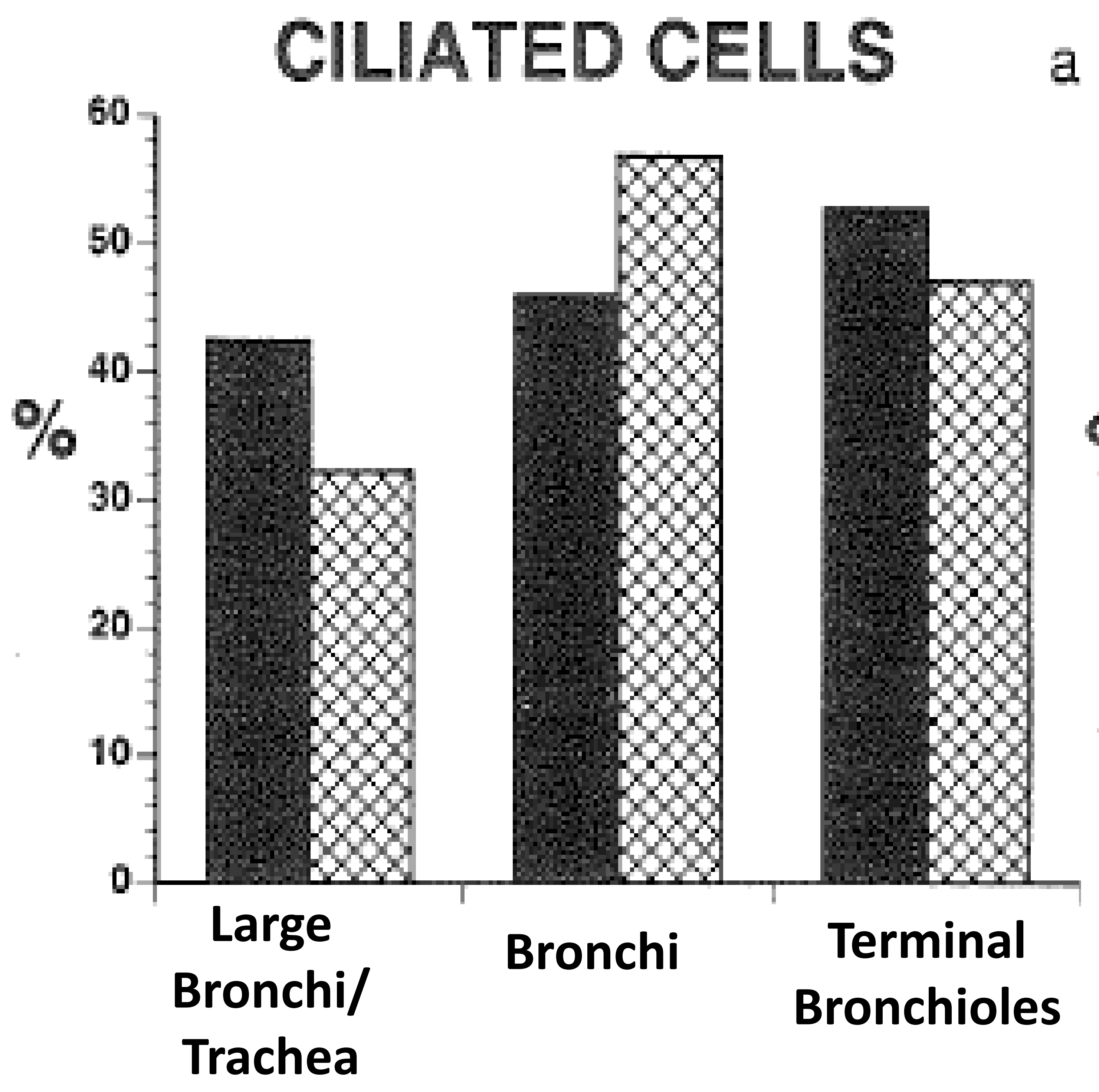
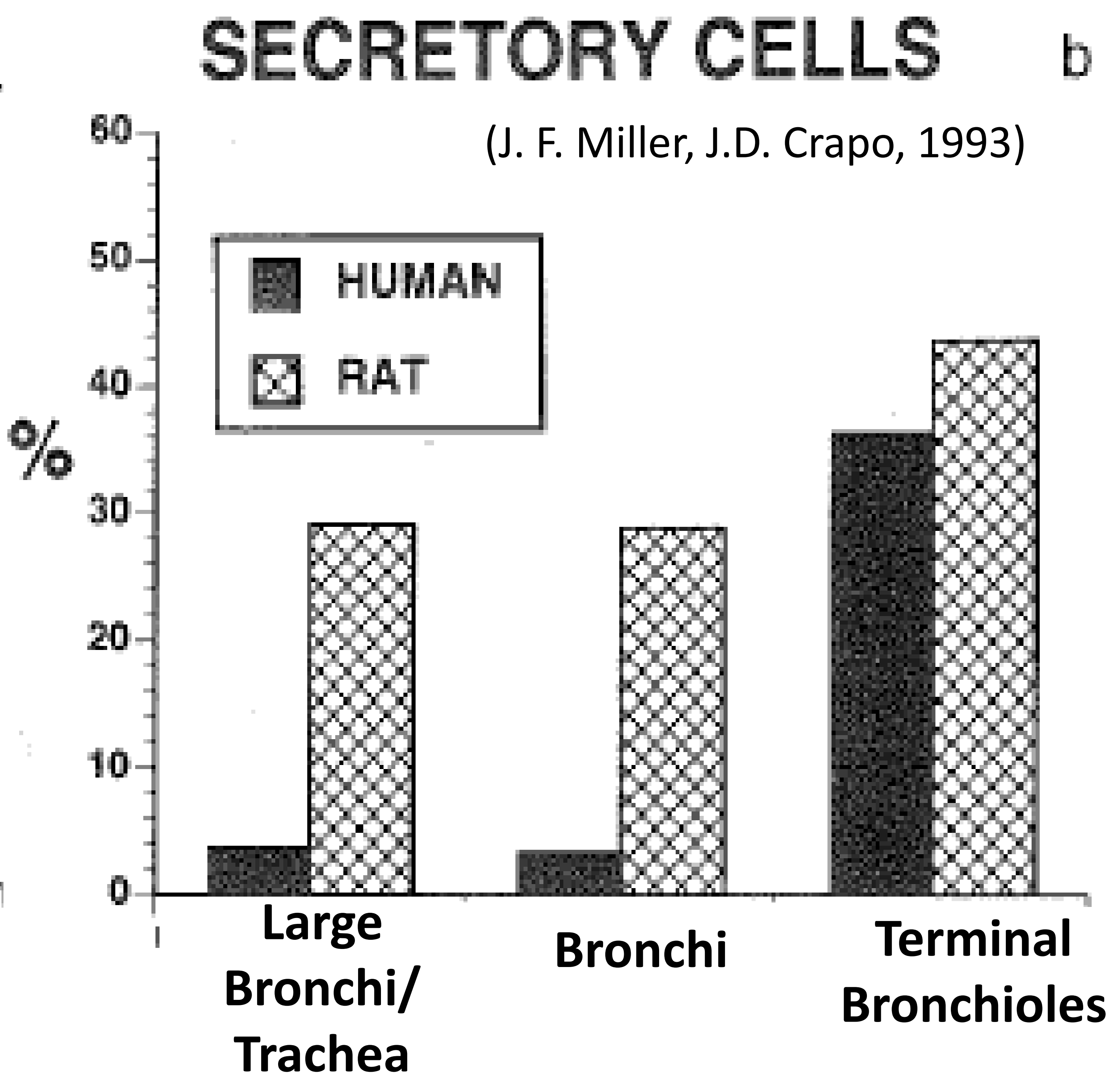
Respiratory Tract Heterogeneity Across Species

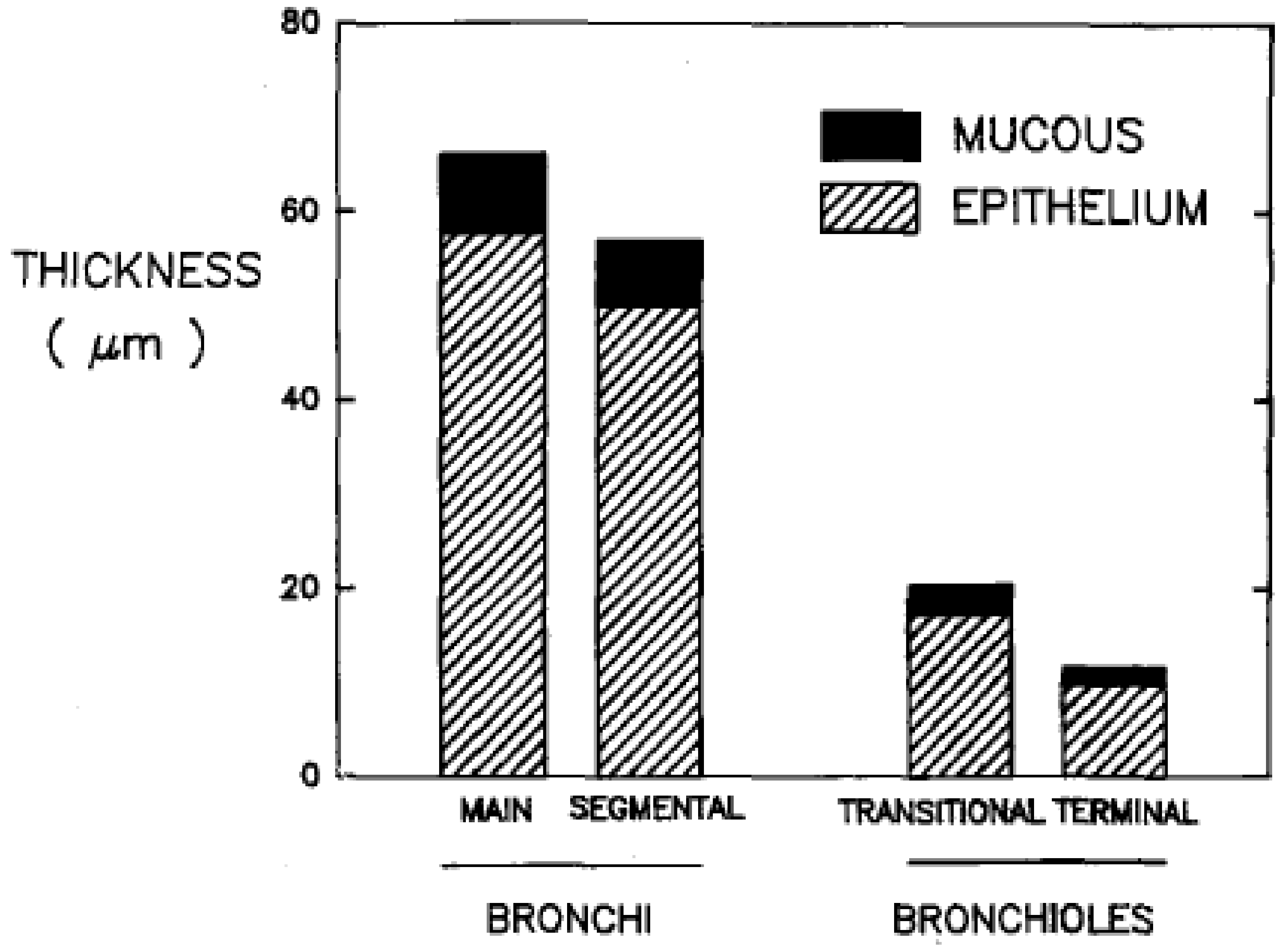
Expression of cells





Wall thickness

(Human Respiratory Tract)



Mucus clearance

Measured (mm/min)	Rat	Human
Tracheal Mucus Velocities	1.9	5.5

(Hofmann 2002)

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

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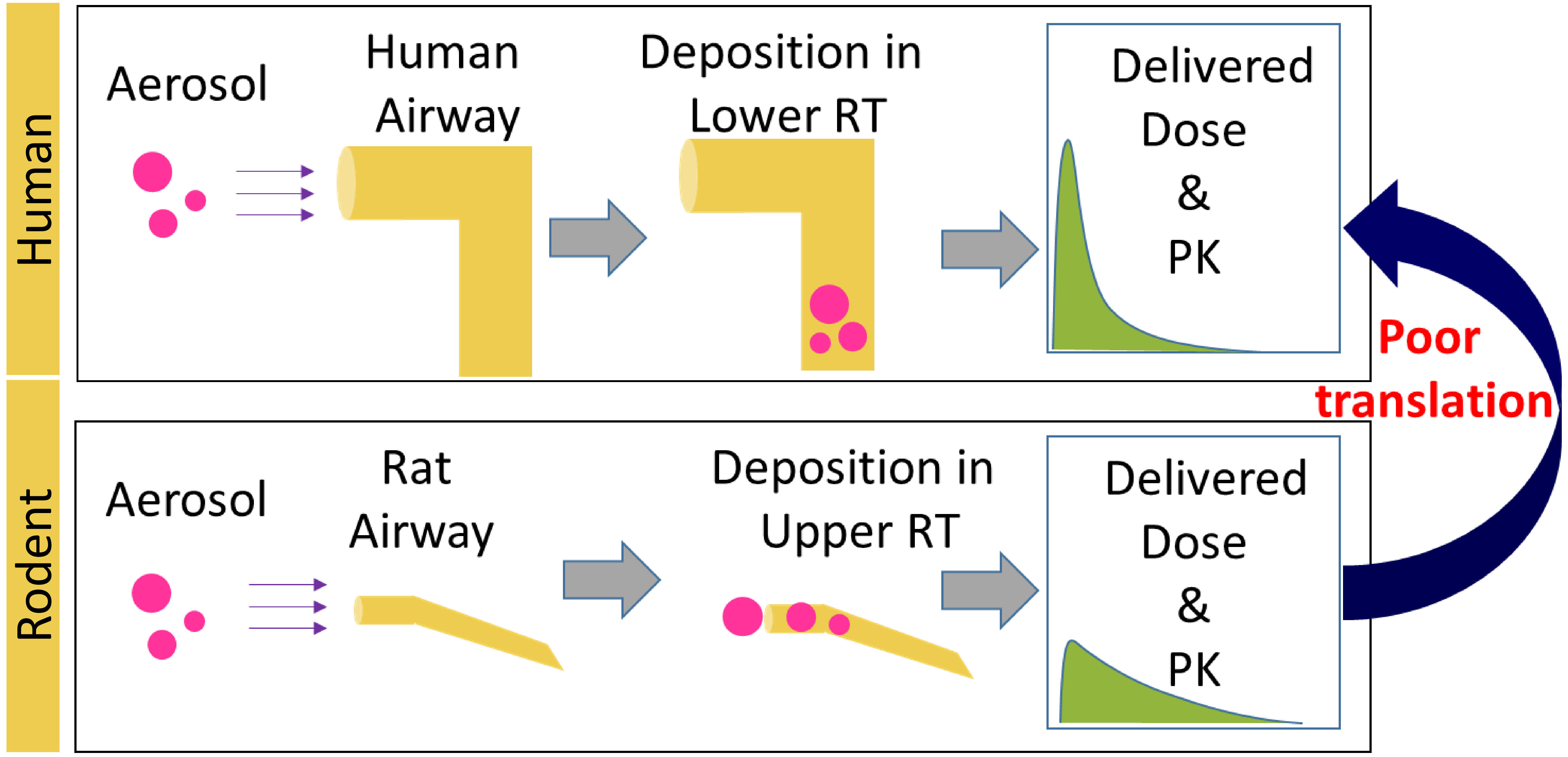
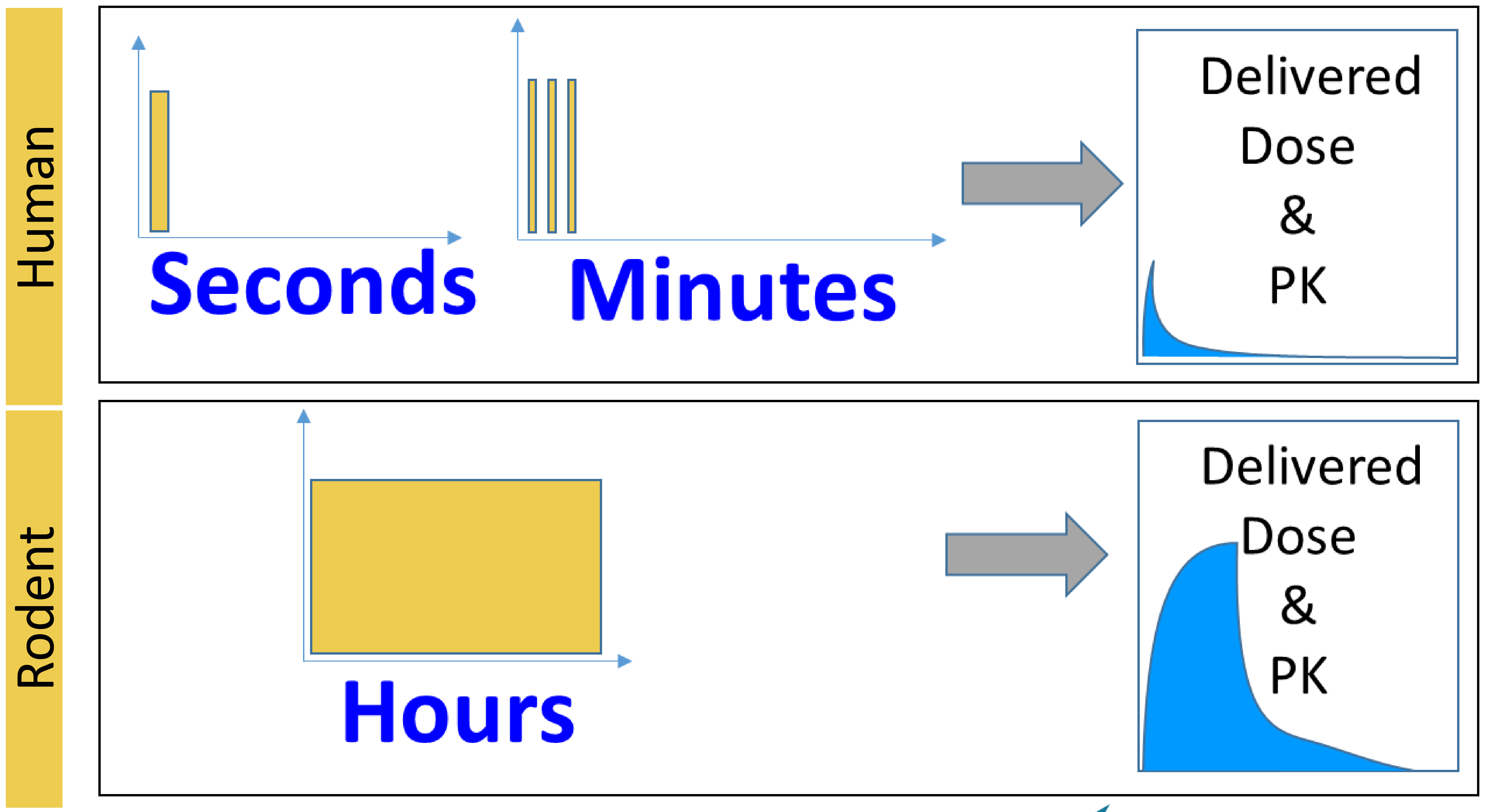
Translation of Exposures Across Species: Rodent to Human

- 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

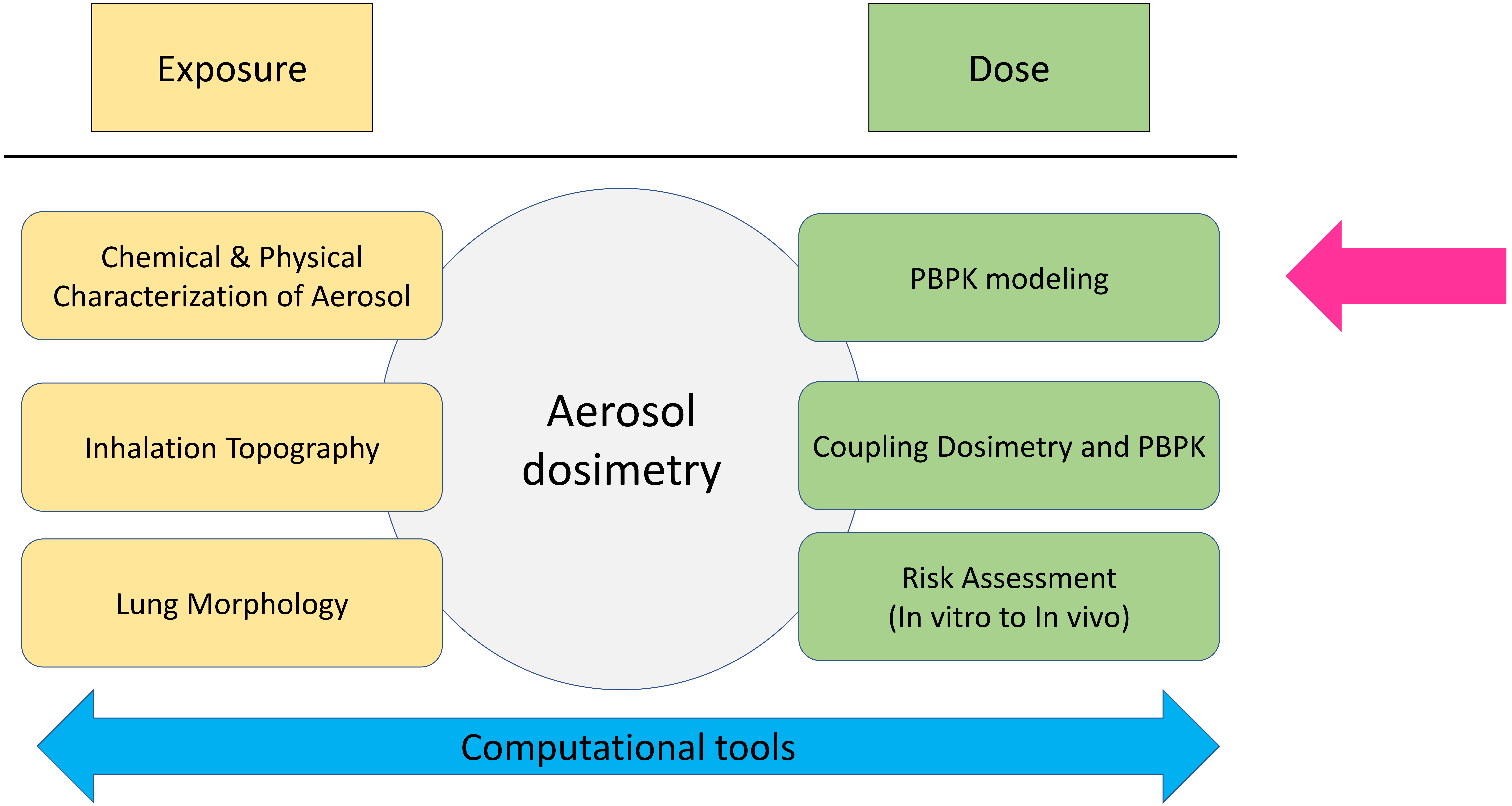
Aerosol vs Airway Diameter Ratio



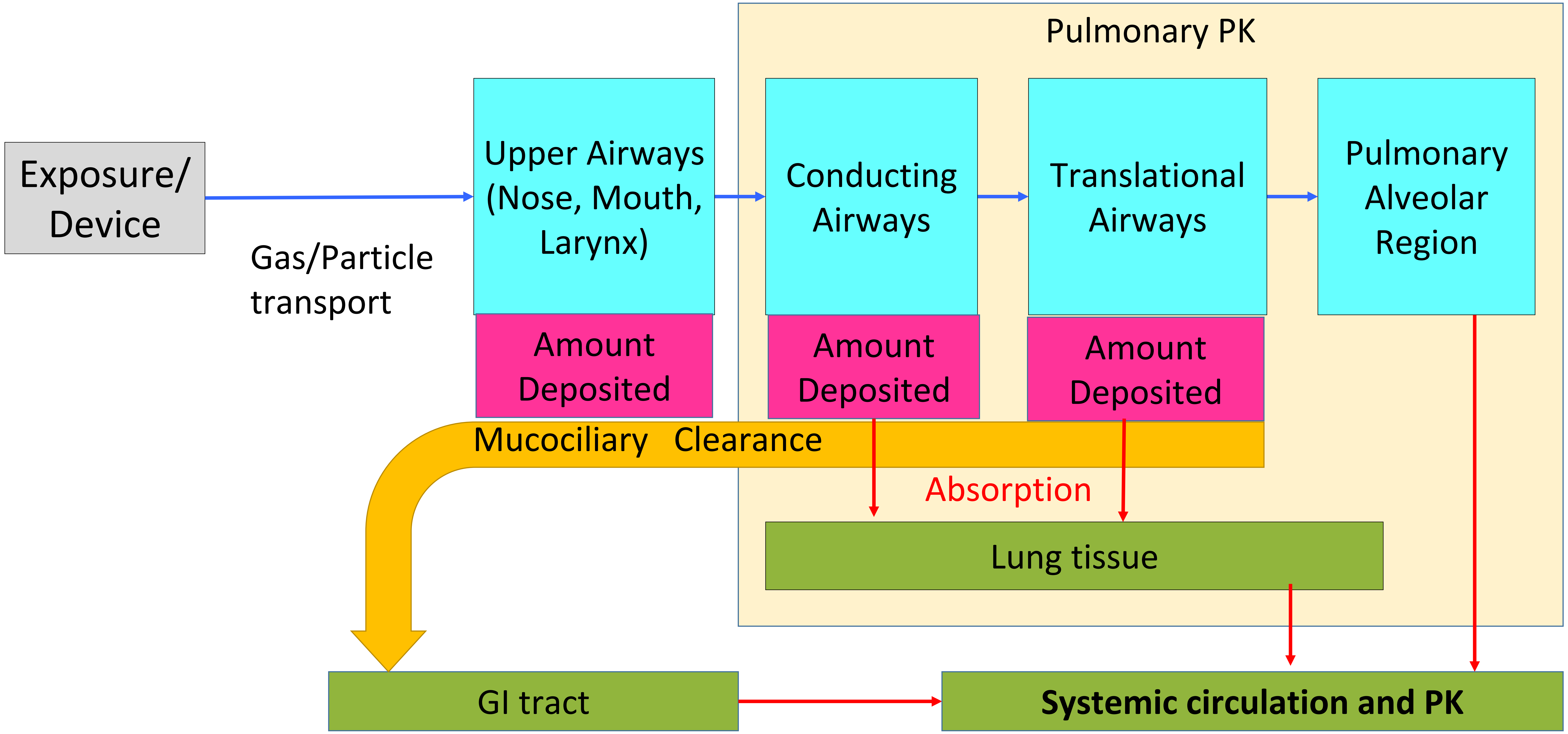
Duration of Exposures are Different



Review of approaches for inhaled aerosol dosimetry



Fate of Nicotine after Inhalation



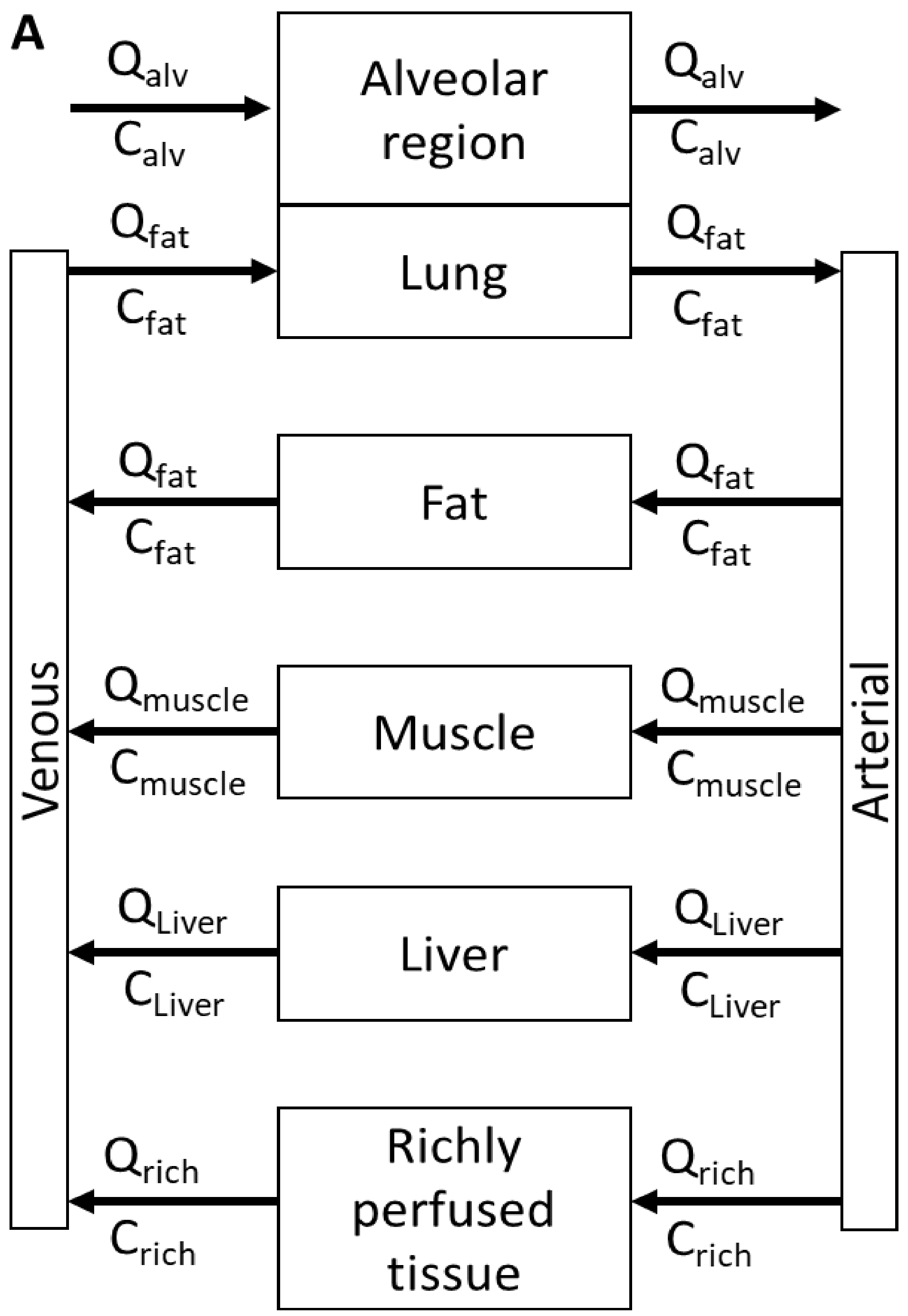
- Kinetic process after nicotine inhalation are
  - Absorption
  - Metabolism
  - Clearance

(Borghardt, 2015)

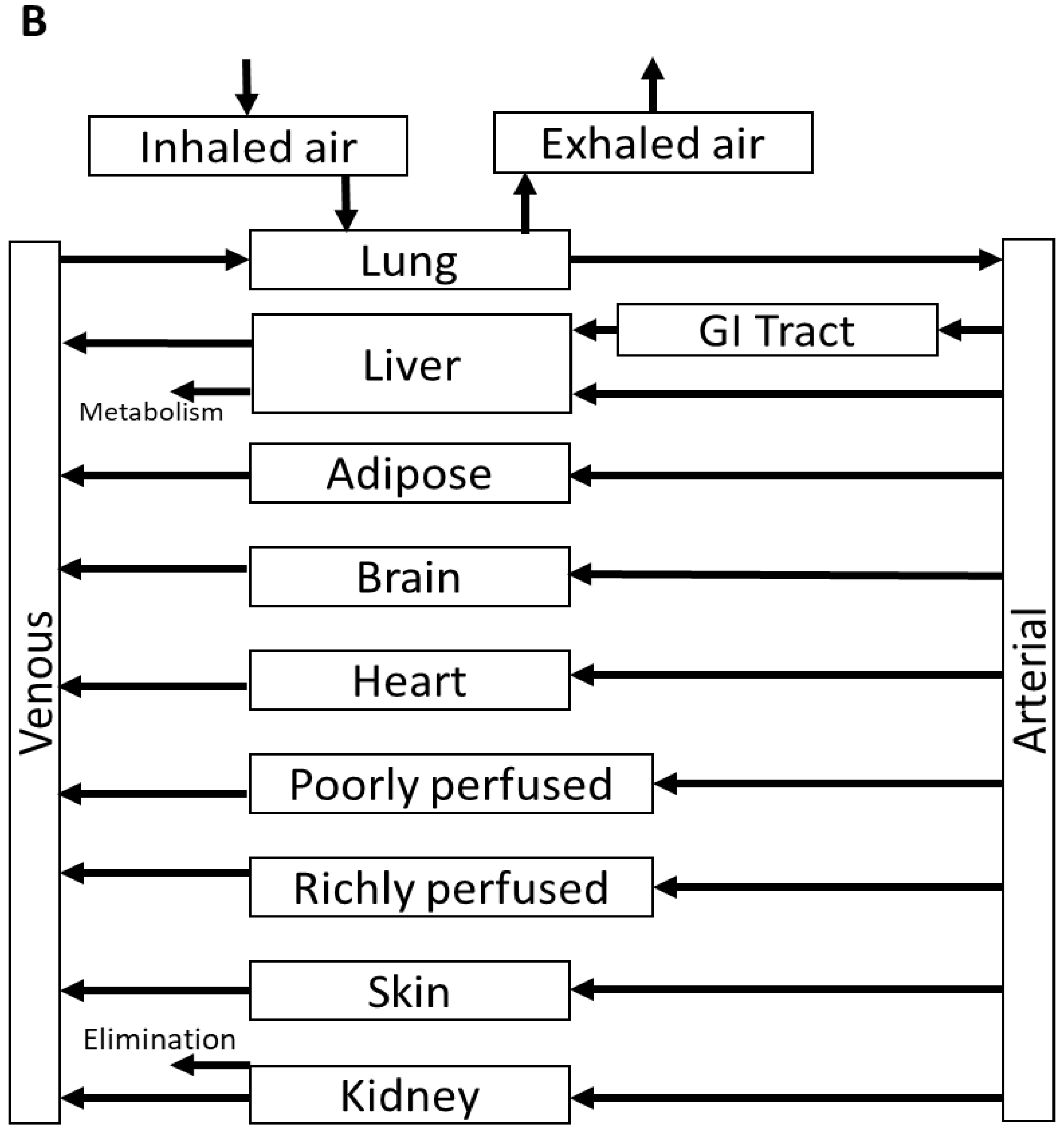
Existing Inhalation PBPK Models

- Models based on exposures and increasing complexities

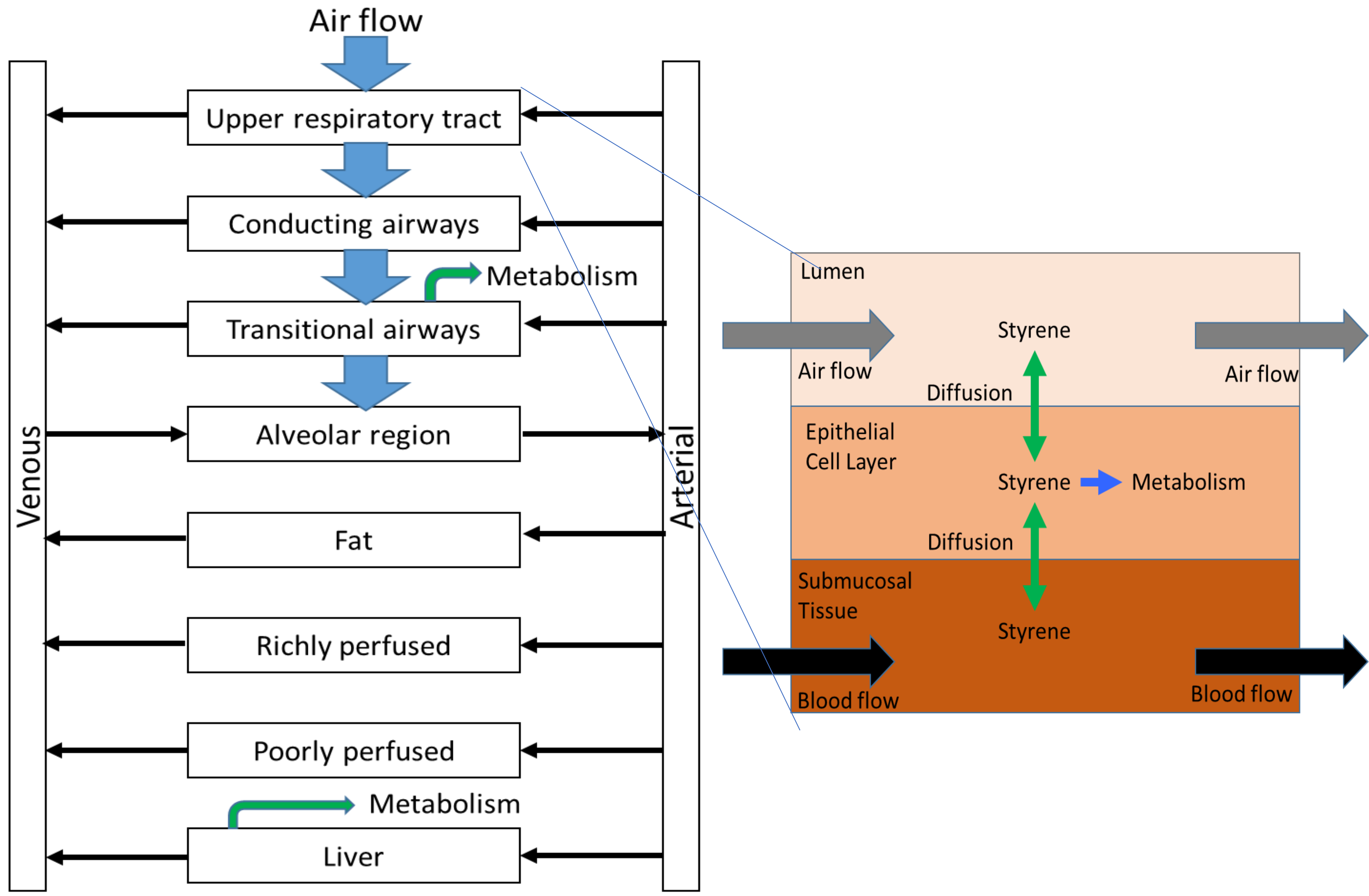
1 compartmental RT → 3 compartmental RT → 4 compartmental RT



Ramsey & Andersen, 1984



Kumagai & Matsunaga, 1995



Bogdanffy, 1999; Sarapaneni, 2002

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

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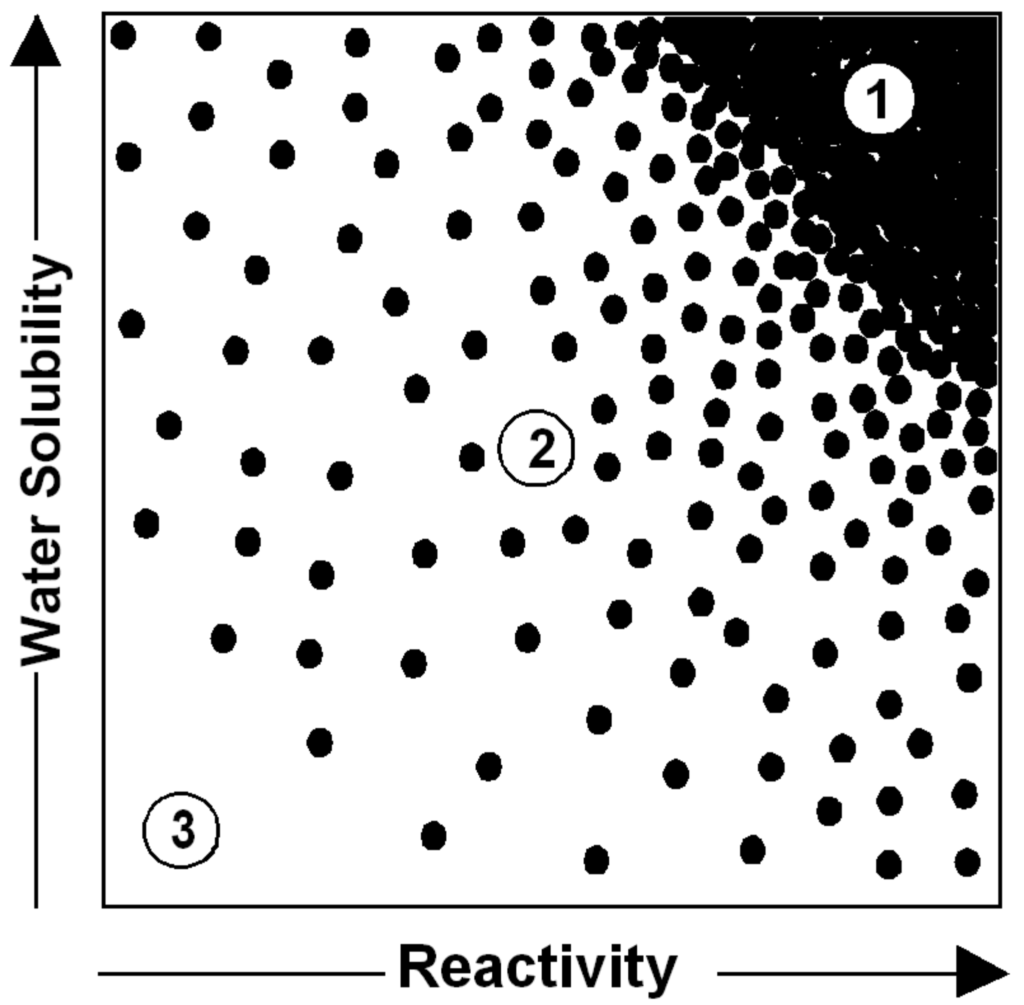
Existing Inhalation PBPK Models

Category of gases

(based on water solubility and reactivity)



Gas Category Scheme

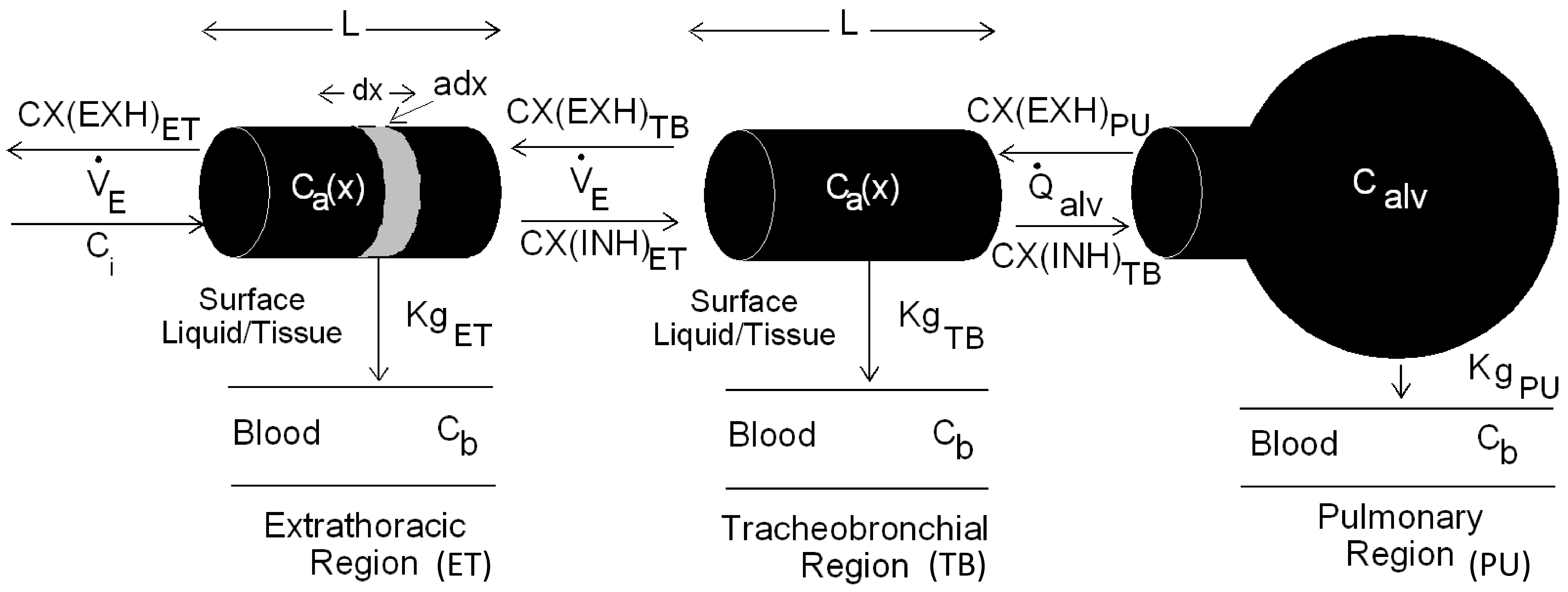
Category 1: Do not penetrate to blood (e.g., highly water soluble/ rapidly reactive)
Category 2: Water soluble/Blood accumulation
Category 3: Water insoluble/ Perfusion limited

Location

- ■ Extrathoracic absorption
- ◙ Entire tract absorption
- □ Predominantly pulmonary absorption

- Example – Styrene
- solubility in water = 0.03 % (20 ^{0}C)

Inhalation PBPK model: Gases



Model types for gases

- Fraction penetration model
  - absorption in ET region
  - concentration entering TB region
- Ventilation perfusion model
  - PU region

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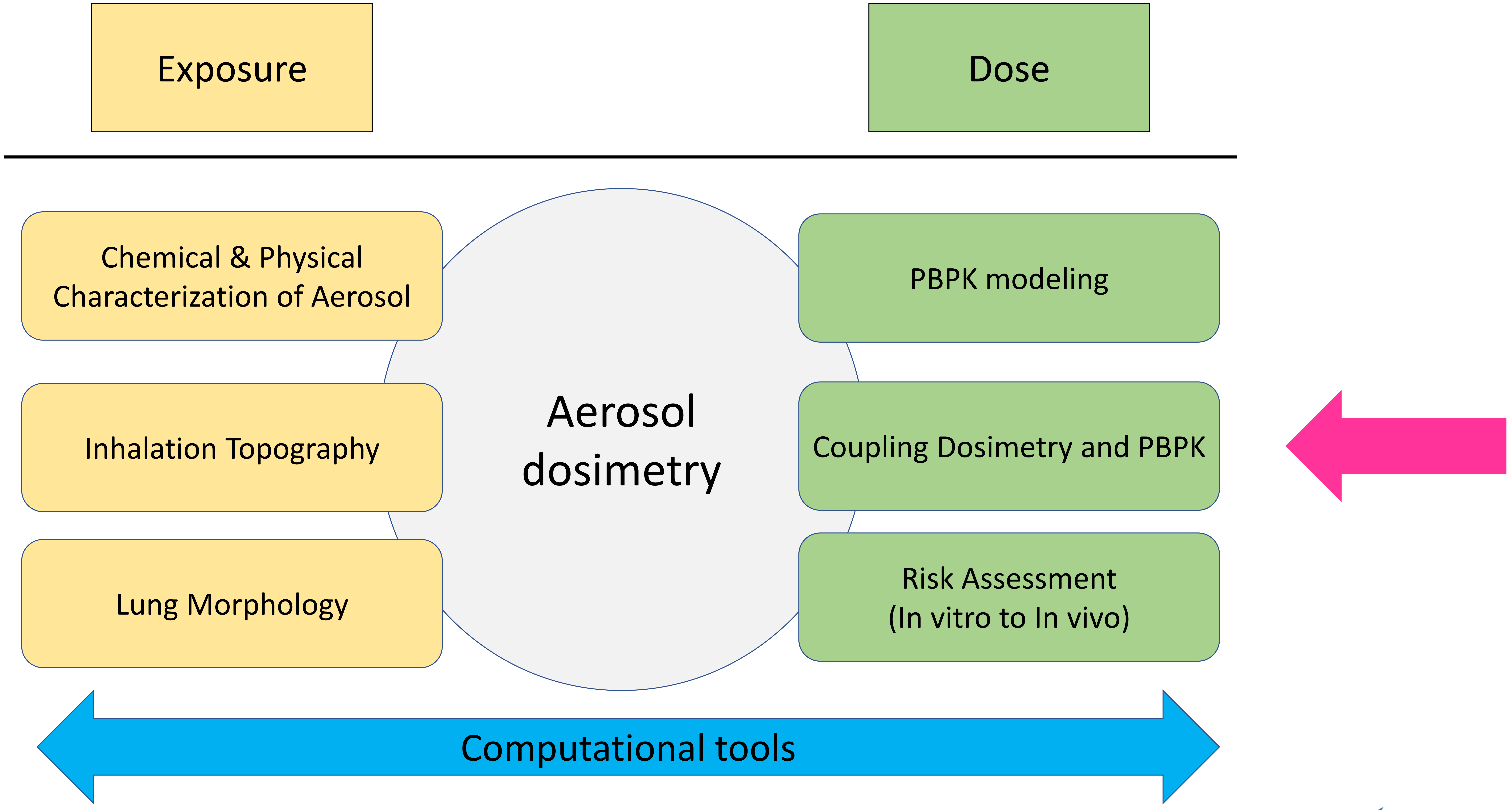
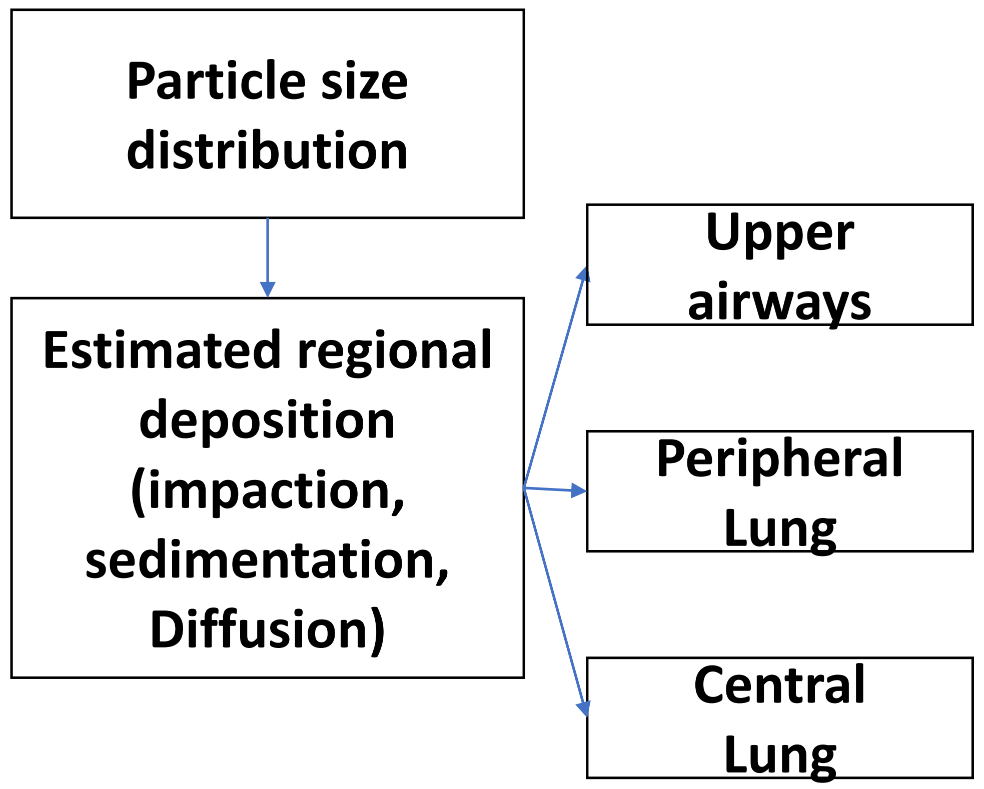
U.S. EPA, Methods for derivation of inhalation reference concentrations and applications of inhalation dosimetry, October 1994; (EPA/600/8-90/066F)

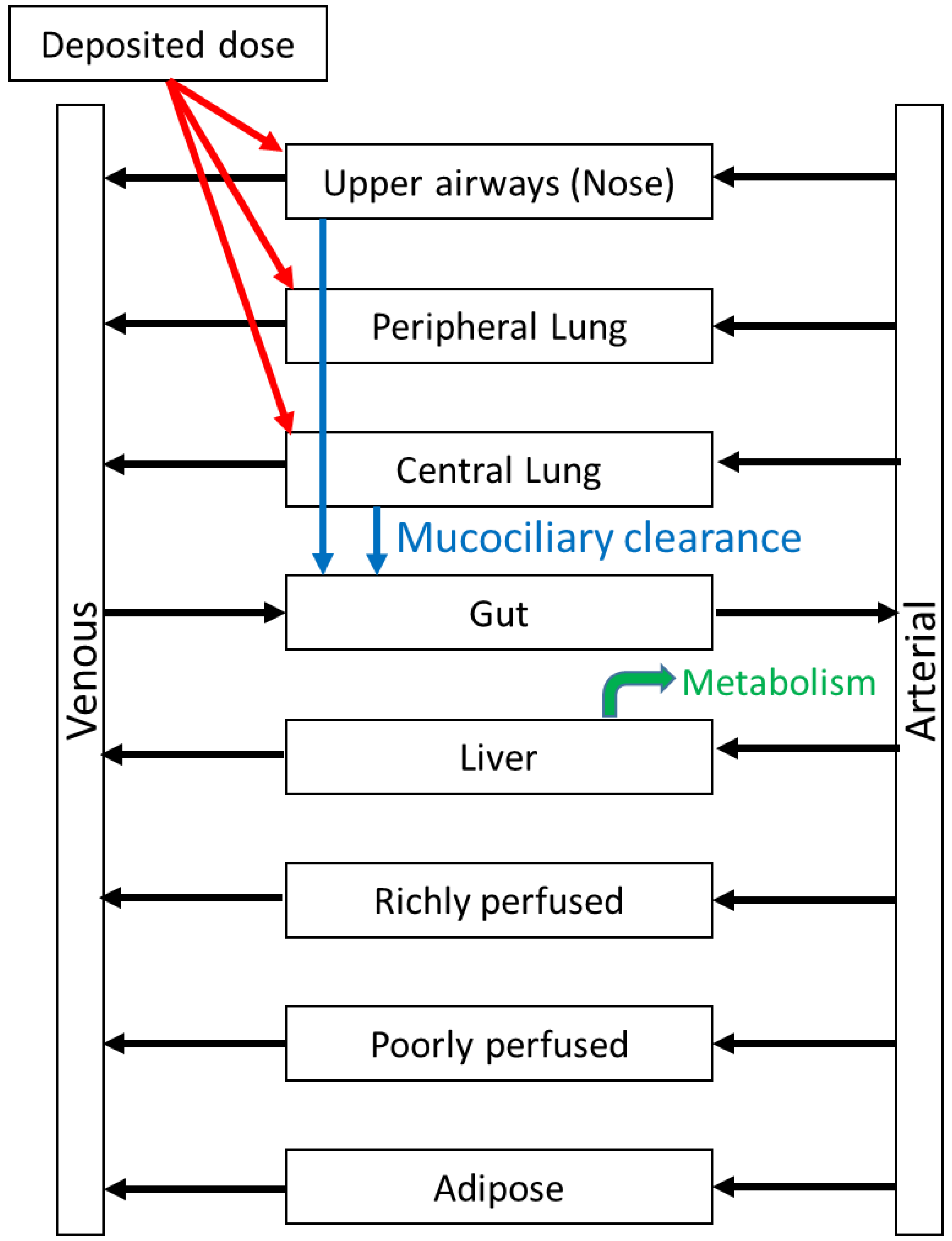
Review of approaches for inhaled aerosol dosimetry



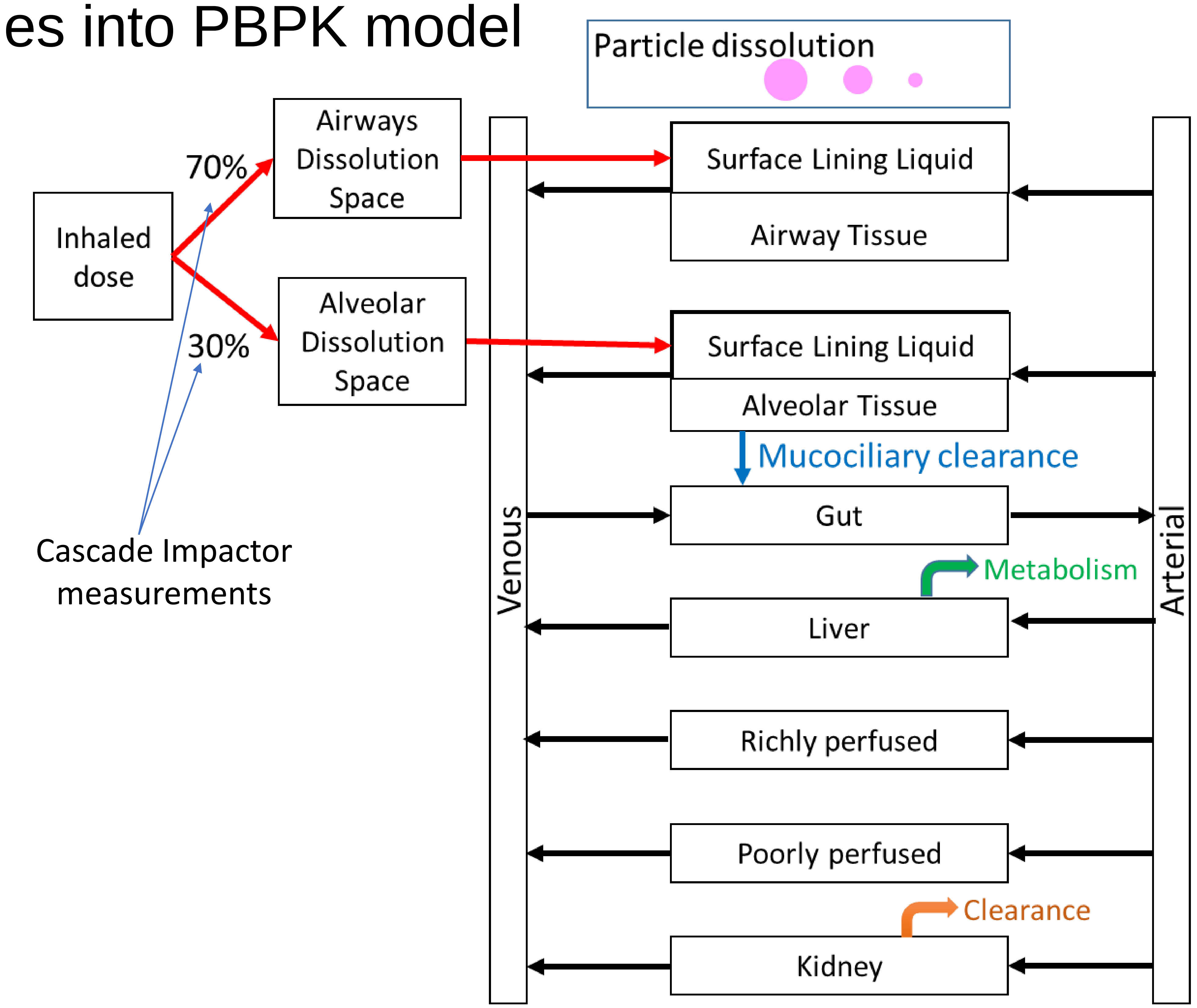
Coupled Inhalation PBPK Models

- 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





Boger, 2016
AstraZeneca



Caninga, 2016
Merck

"No real coupling"

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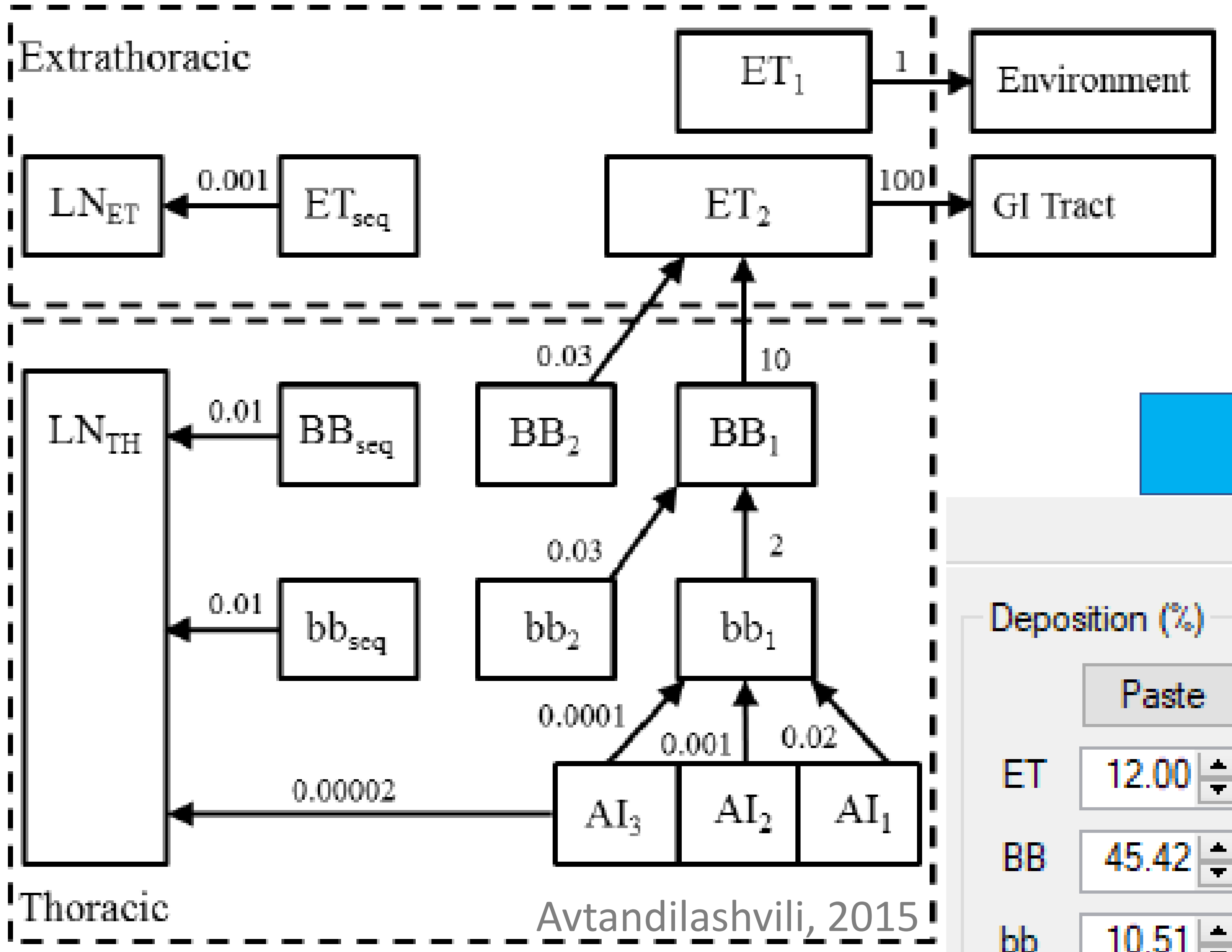
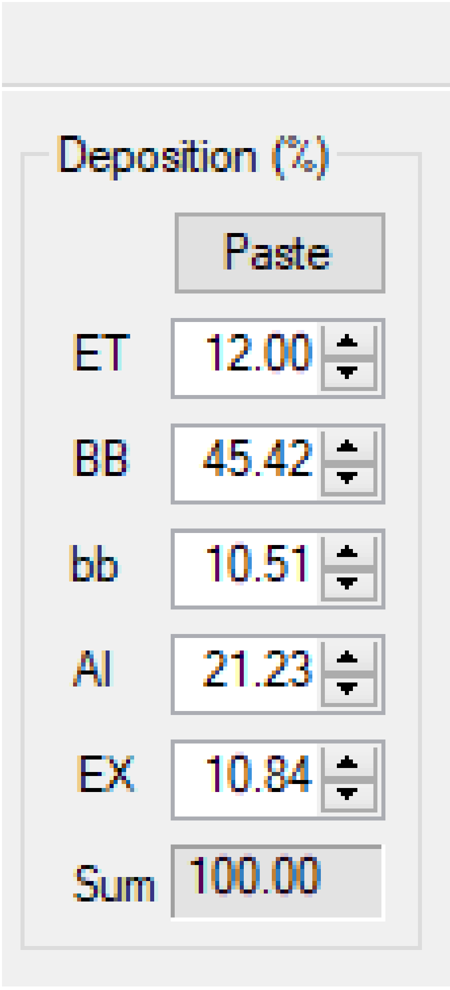
Coupled Inhalation PBPK Models: Mechanistic

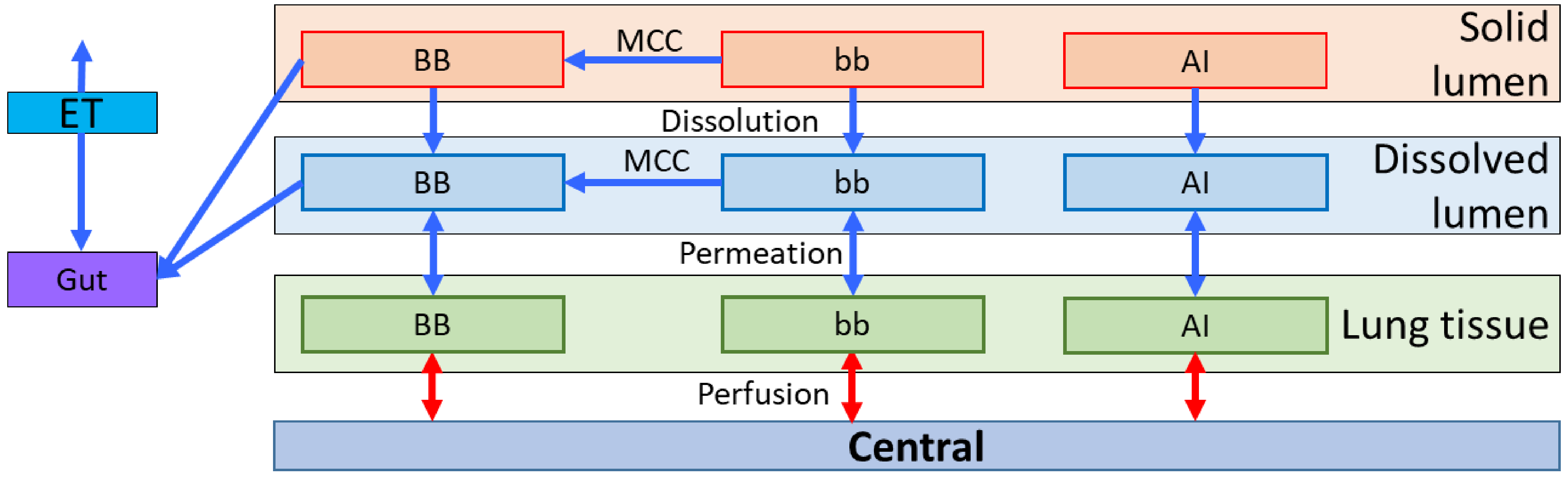
ICRP 66 model:
Particle filtration efficiency





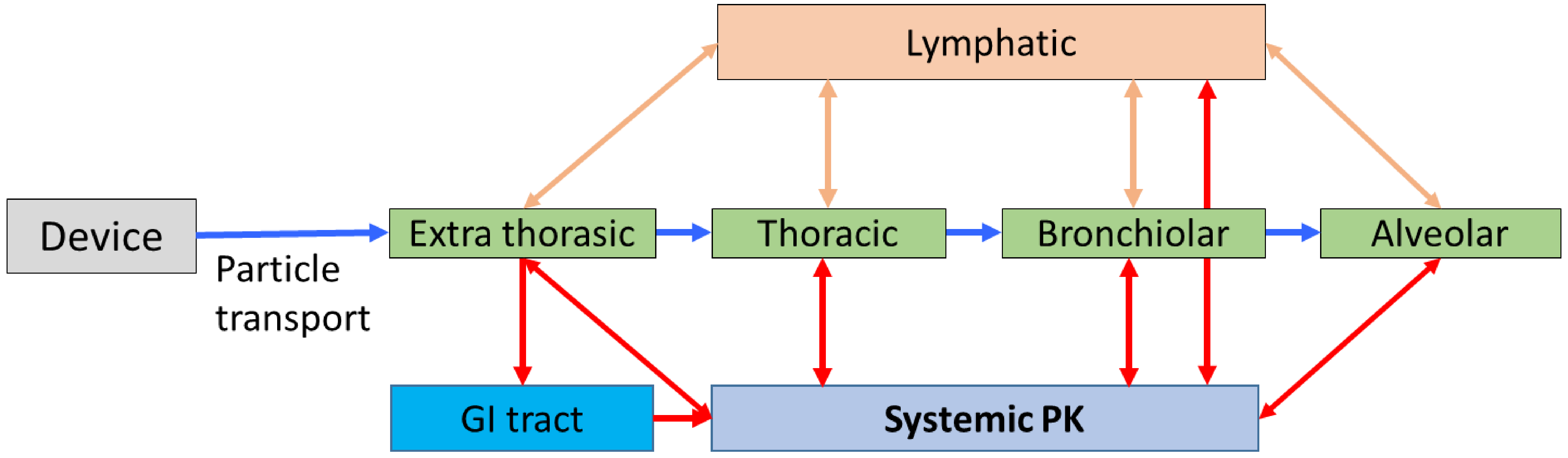
http://www.icrp.org/publication.asp?id=icrp%20publication%2066

Mimetikos Preludium



https://www.emmace.se/mimetikos-preludium/

Gastroplus – Inhalation module



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

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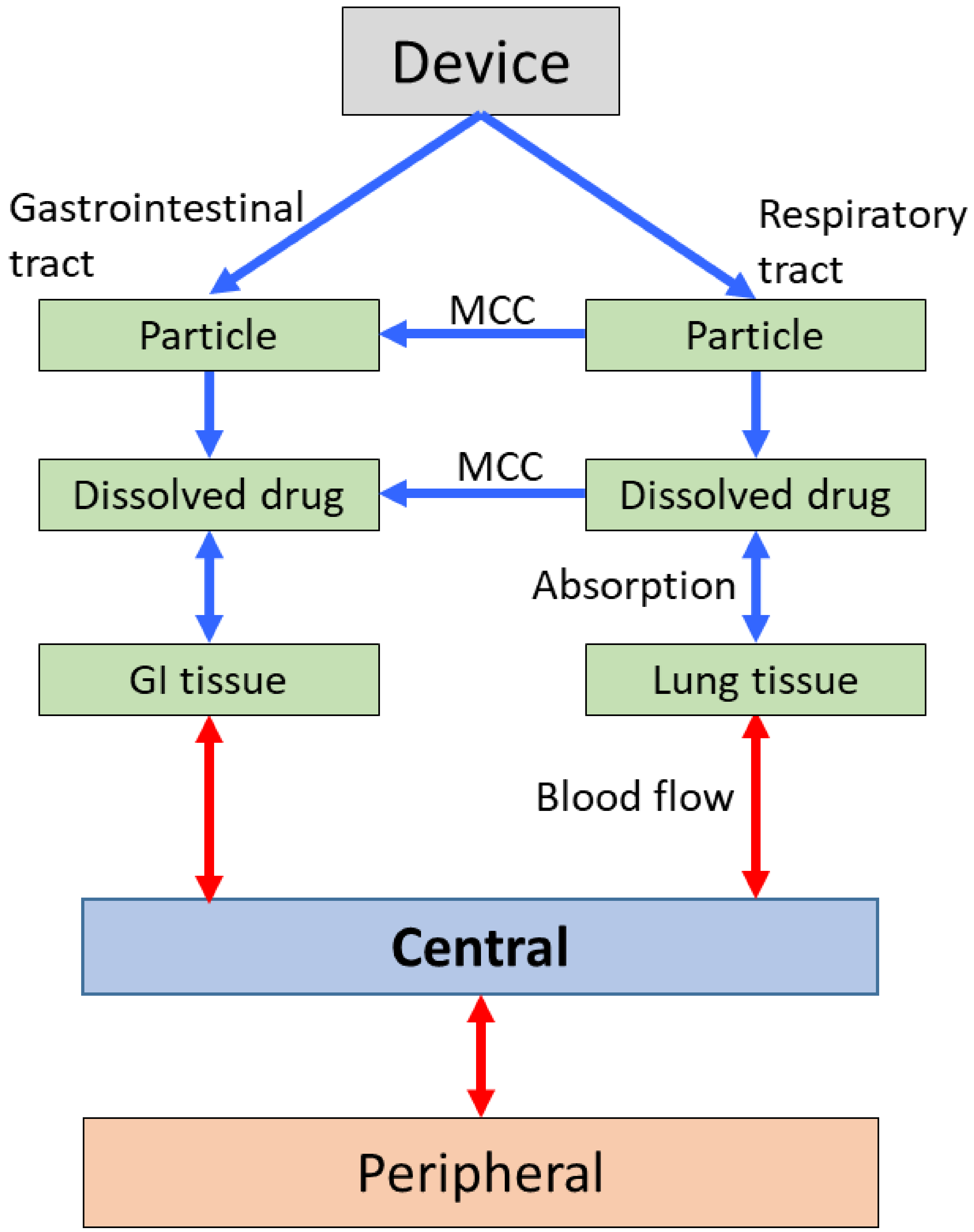
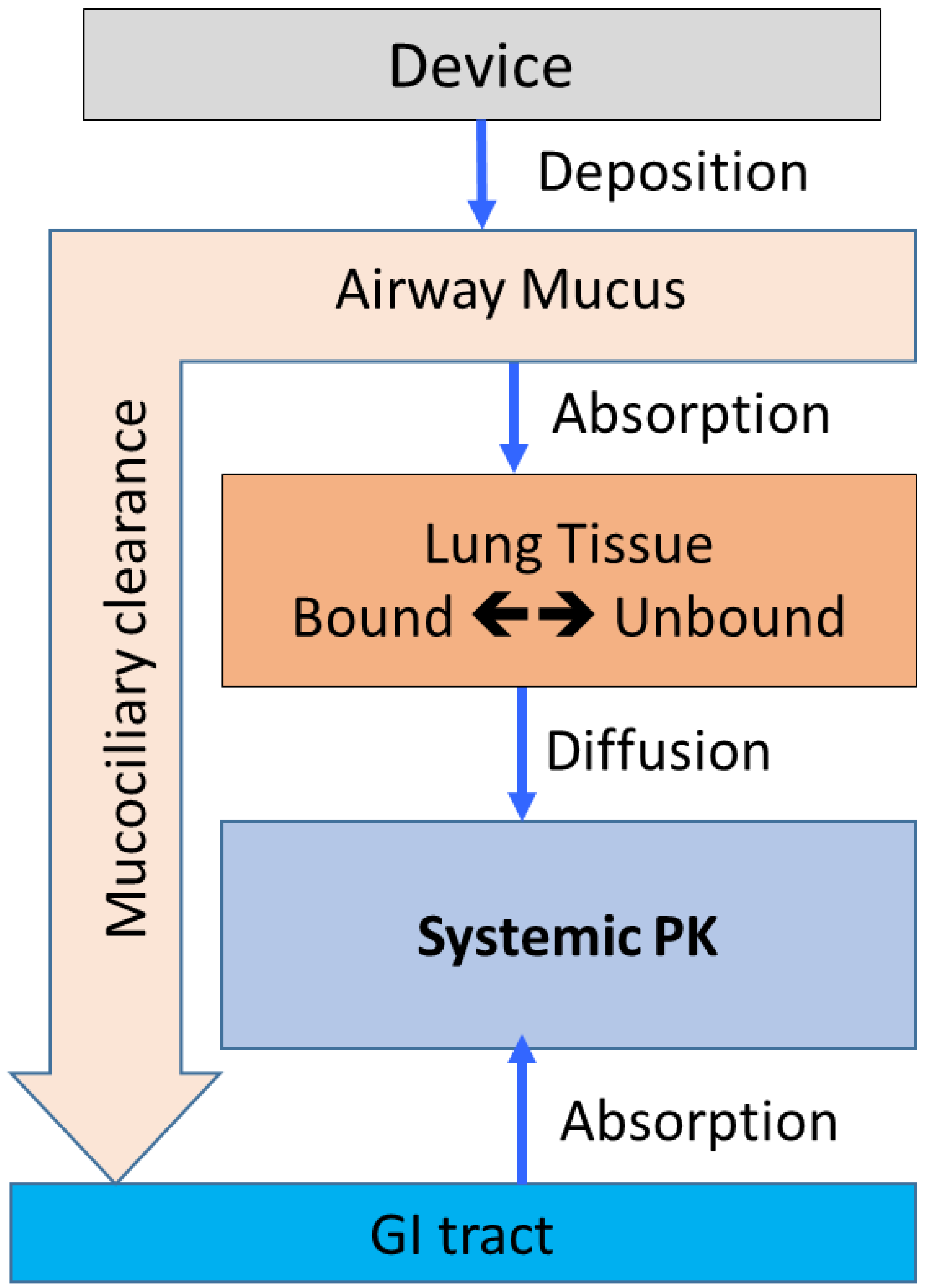
Inhalation PBPK Models: Non-Mechanistic

PulmoSim (Pfizer)



Meeting Report
Collingwood, 2012

SimCyp Simulator (Certara)



Backman, 2018

Applicability for Aerosols?

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

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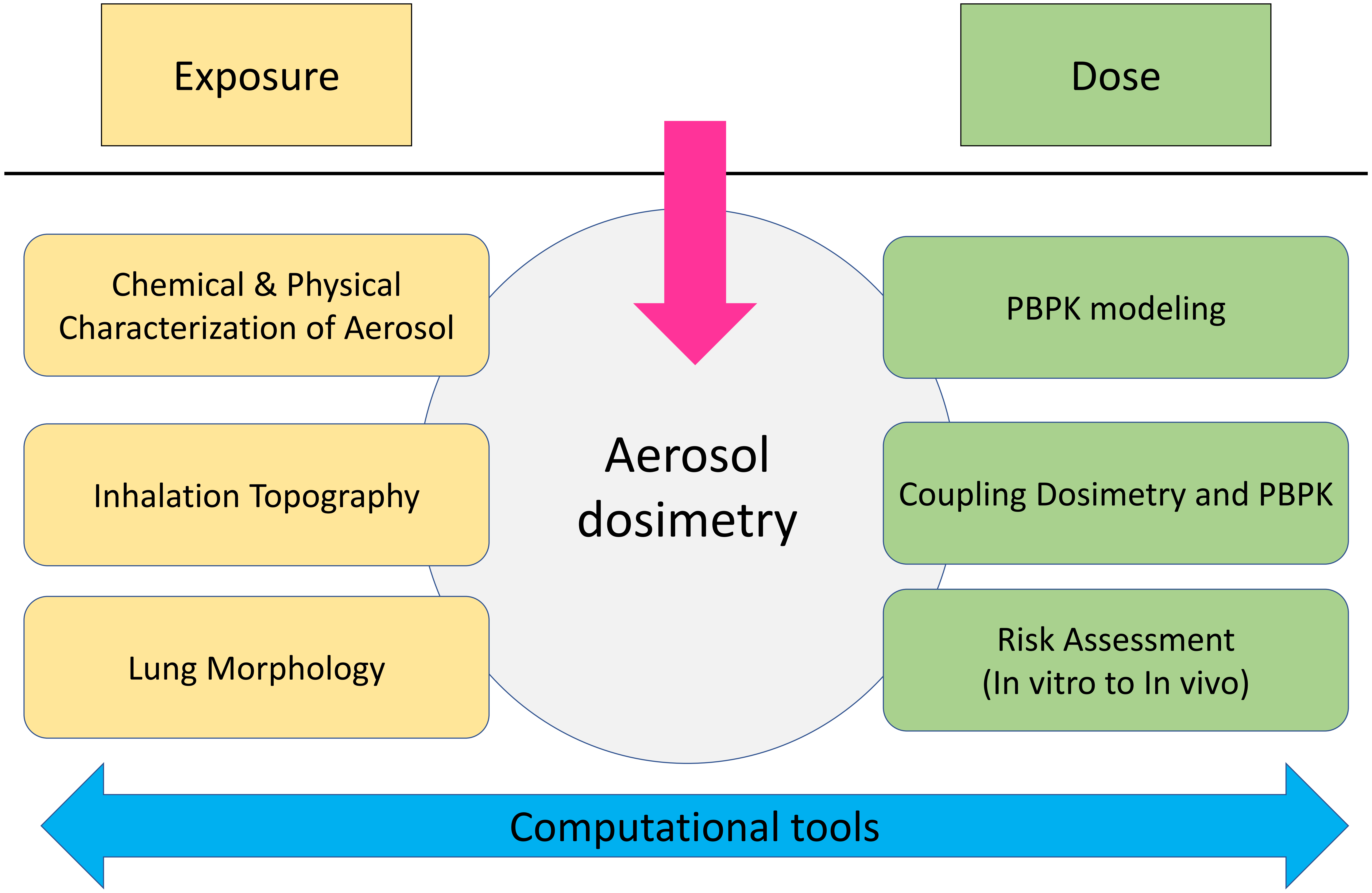
Review of approaches for inhaled aerosol dosimetry



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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

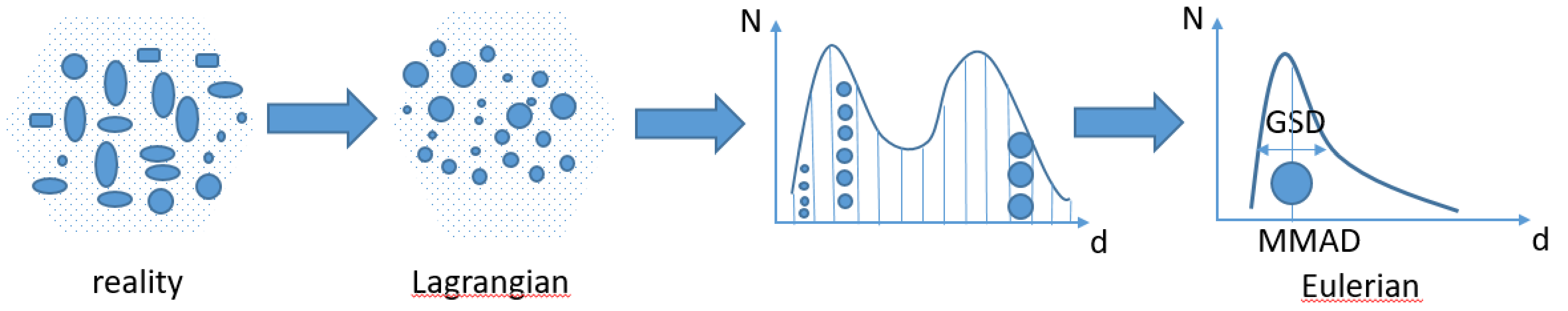
- More holistic determination of dose calculation must account for at least the following:
  - Aerosol physics
  - Inhalation topography
  - Lung Morphology

Reference: Alexander et al, Association of Inhalation Toxicologists (AIT) Working Party Recommendation for Standard Delivered Dose Calculation and Expression in Non-Clinical Aerosol Inhalation Toxicology Studies with Pharmaceuticals, Inhalation Toxicology 2008

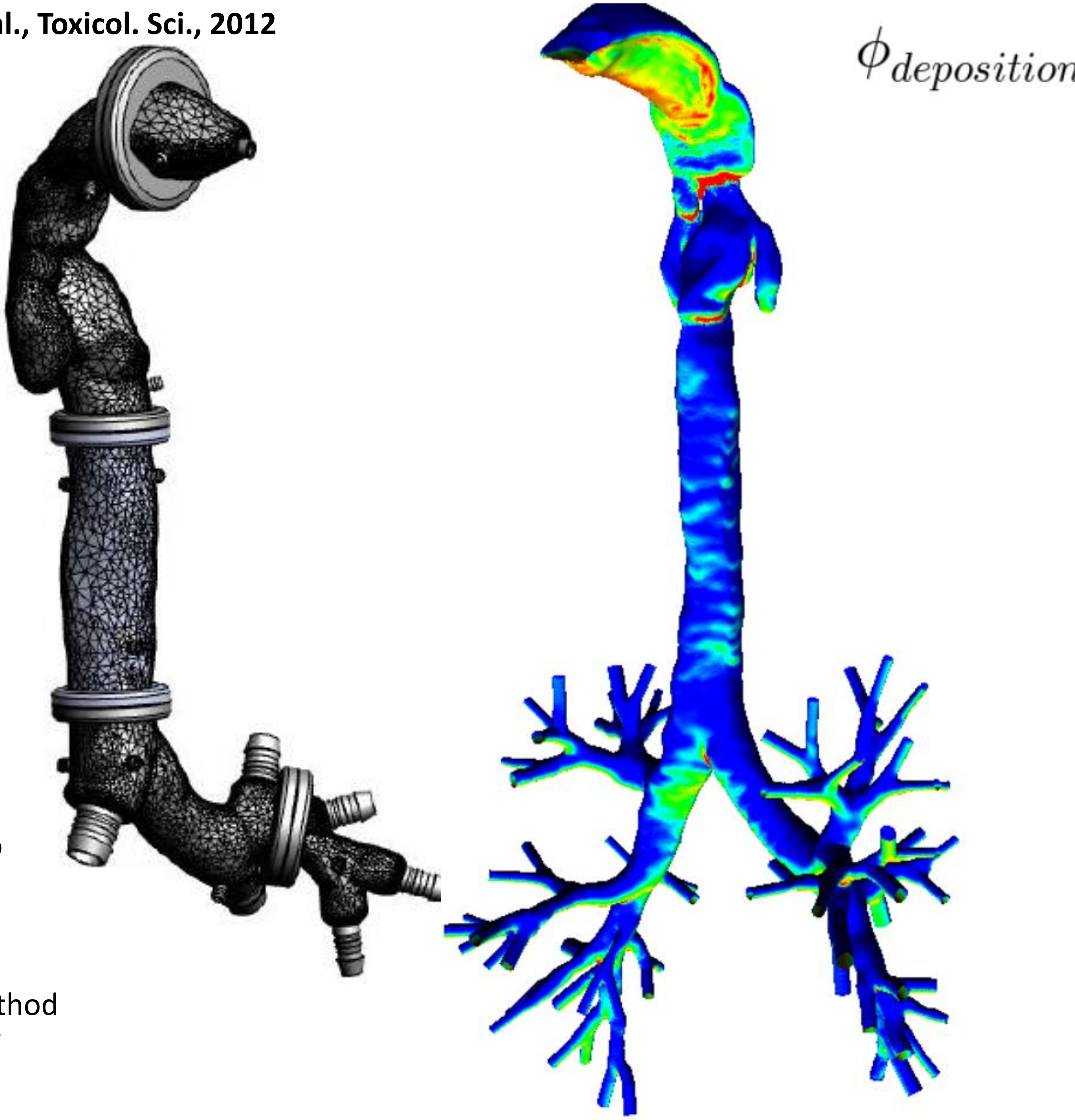
Aerosol Physics: Computational Fluid Dynamics

Increasing complexity and level of details

whole-lung models



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



Mass conservation

$$\partial_t \rho + \partial_j(\rho u_j) = -\partial_j[(1-\gamma) f_j]$$

Momentum conservation

$$\partial_t(\rho u_i) + \partial_j(\rho u_i u_j) = -\partial_i p + \partial_i(\mu \tau_{ij}) \quad ; \qquad i = 1,\ldots,3$$

Energy conservation

$$\rho c_p(\partial_t T + u_j \partial_j T) = \partial_j(k \partial_j T) + \partial_j(\mu u_k \tau_{kj}) + \Im_h + Dp/Dt$$

Transport of compounds in gas phase

$$\partial_t(\rho Y_n) + \partial_j(\rho Y_n u_j) = \partial_j(Y^{-1} f_j Y_n) + \Im_{Y_n} \quad ; \qquad n = 1,\ldots,N$$

Transport of compounds in liquid phase

$$\partial_t(\rho Z_n) + \partial_j(\rho Z_n u_j) = \partial_j(Z^{-1} \gamma f_j Z_n) + \Im_{Z_n}$$

Transport of particle number density

$$\partial_t(\rho M_q) + \partial_j(\rho M_q u_j) = -\partial_j(\rho M_q u^l_{j,q}) + \partial_j(\rho D_q \partial_j M_q) + \Im_{M_q} \quad ; \qquad q = 1,\ldots,Q$$

AeroSolved

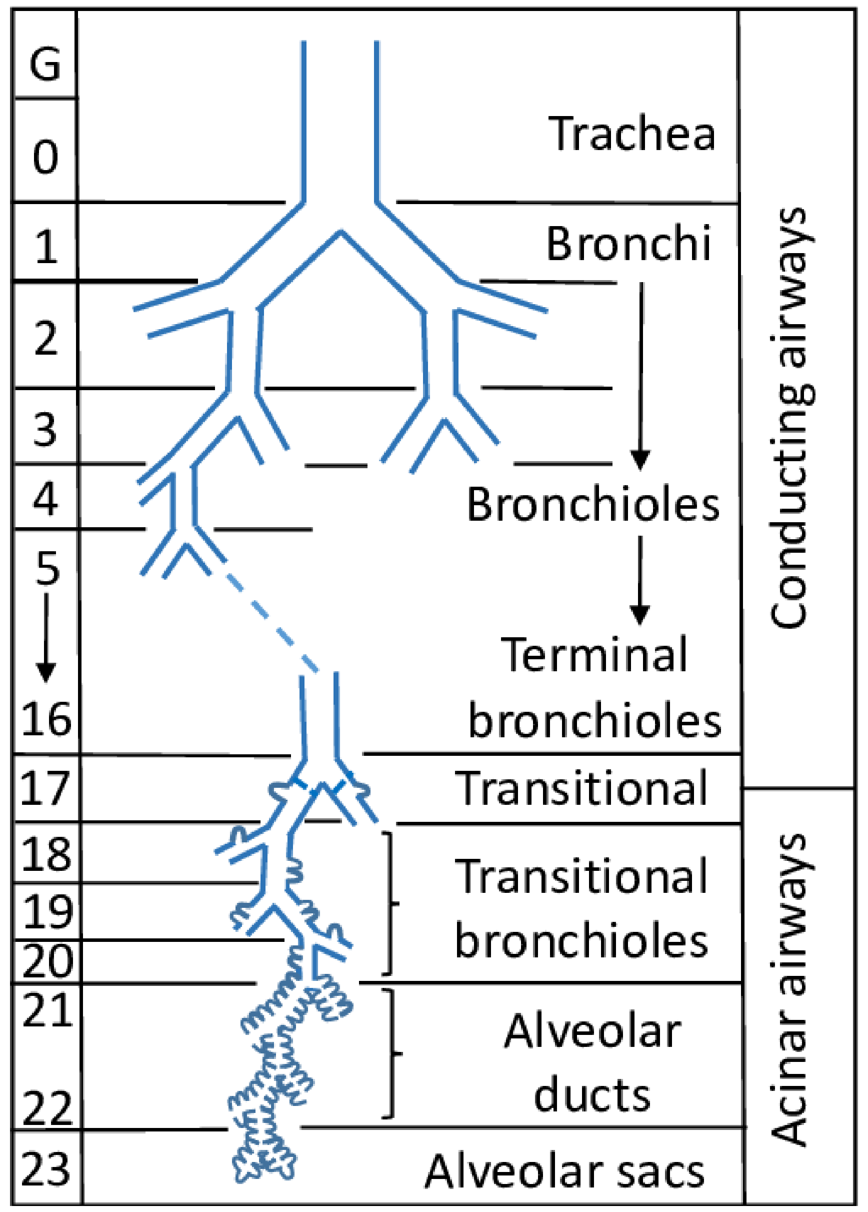
http://www.aerosolved.com

- Frederix, E. M. A. Eulerian modeling of aerosol dynamics. From nucleation to deposition, PhD thesis, 2016
- Frederix, E. M. A. et al. Characteristics-based sectional modeling of aerosol nucleation and condensation, J. Computational Physics, 2016
- Frederix, E. M. A. et al. Application of the characteristics-based sectional method to spatially varying aerosol formation and transport. J. Aerosol Science, 2017

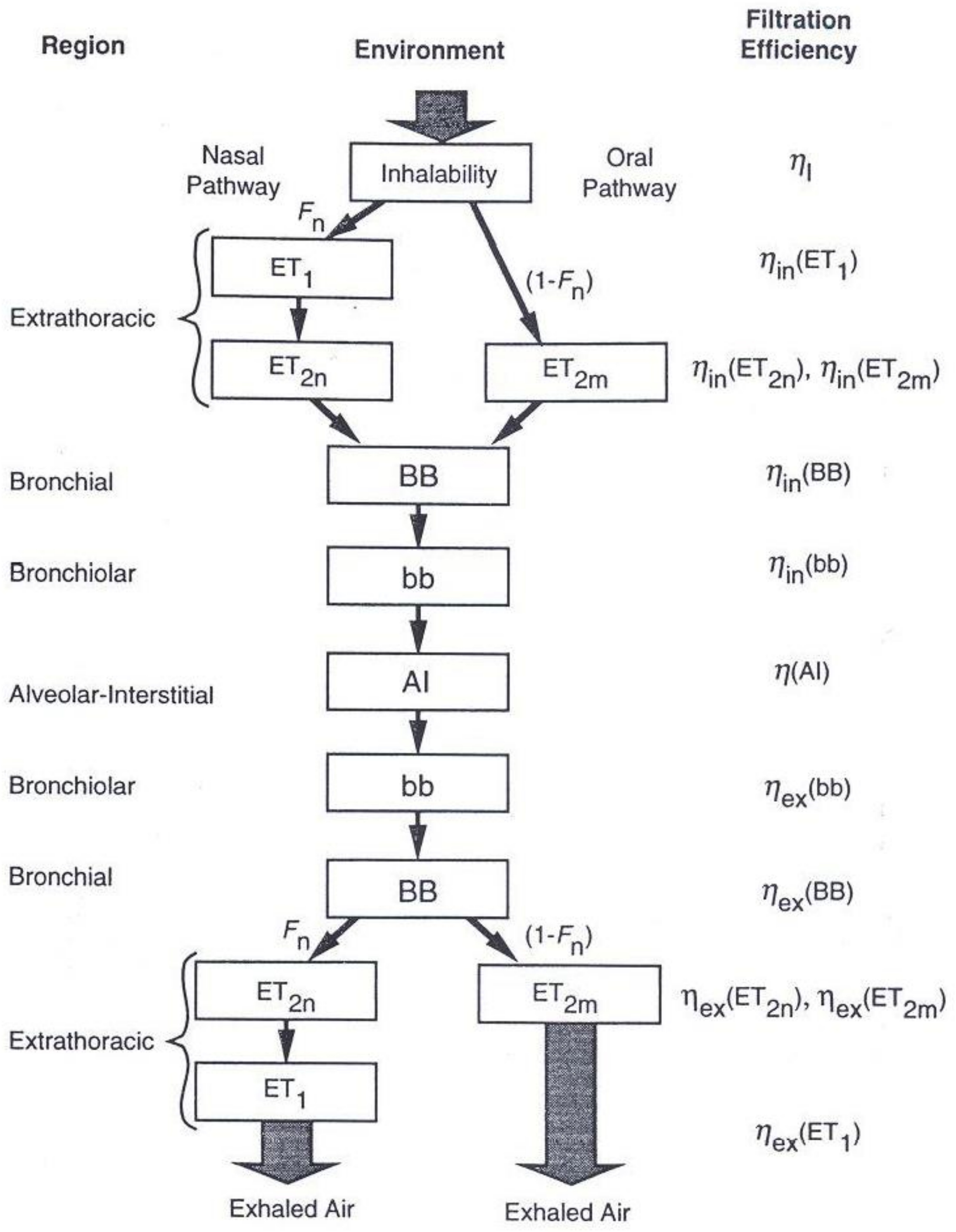
Inhalation Dose: Whole-lung models

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

- Stahlhofen et al, J. Aerosol Sci., 1983
- Yeh, Bull. Math. Biol., 1980
- Anjilvel &Asgharian, Fundam. Appl. Toxicol., 1995
- Hofmann, Journal of Aerosol Science, 2011



Weibel 1963, Raabe et al. 1976



ICRP Publication 66, 1994

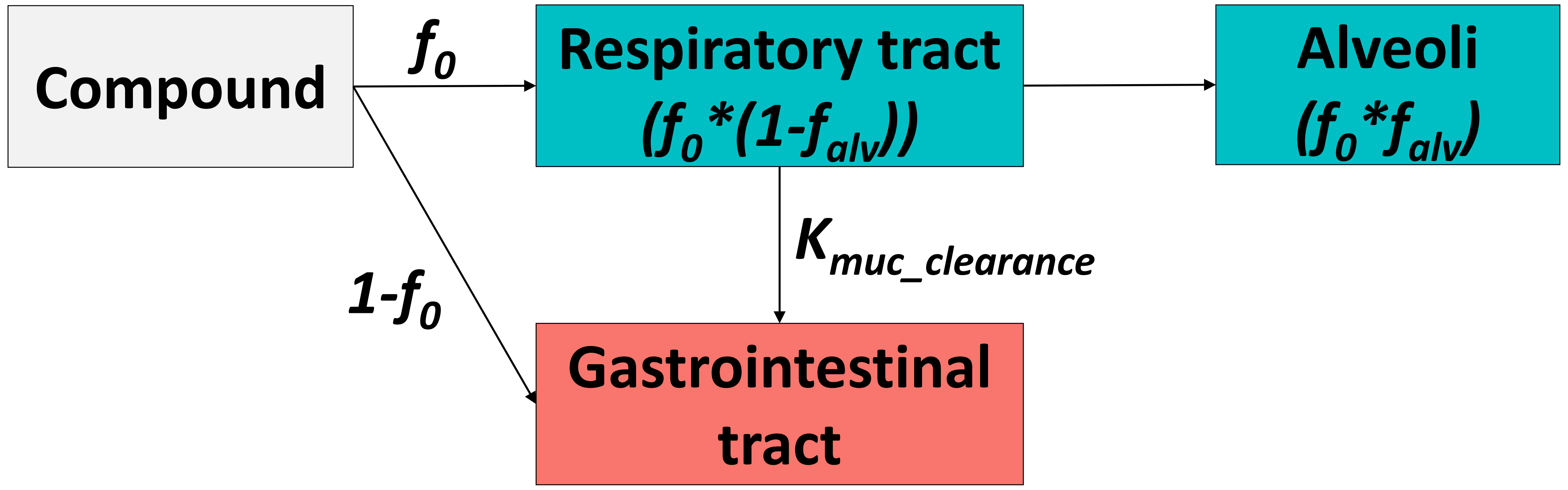
MPPD
MULTIPLE-PATH PARTICLE DOSIMETRY MODEL
VERSION 2.0

Multiple-Path Particle Dosimetry Model
ARA
Asgharian et al. 1995 -2016

- **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



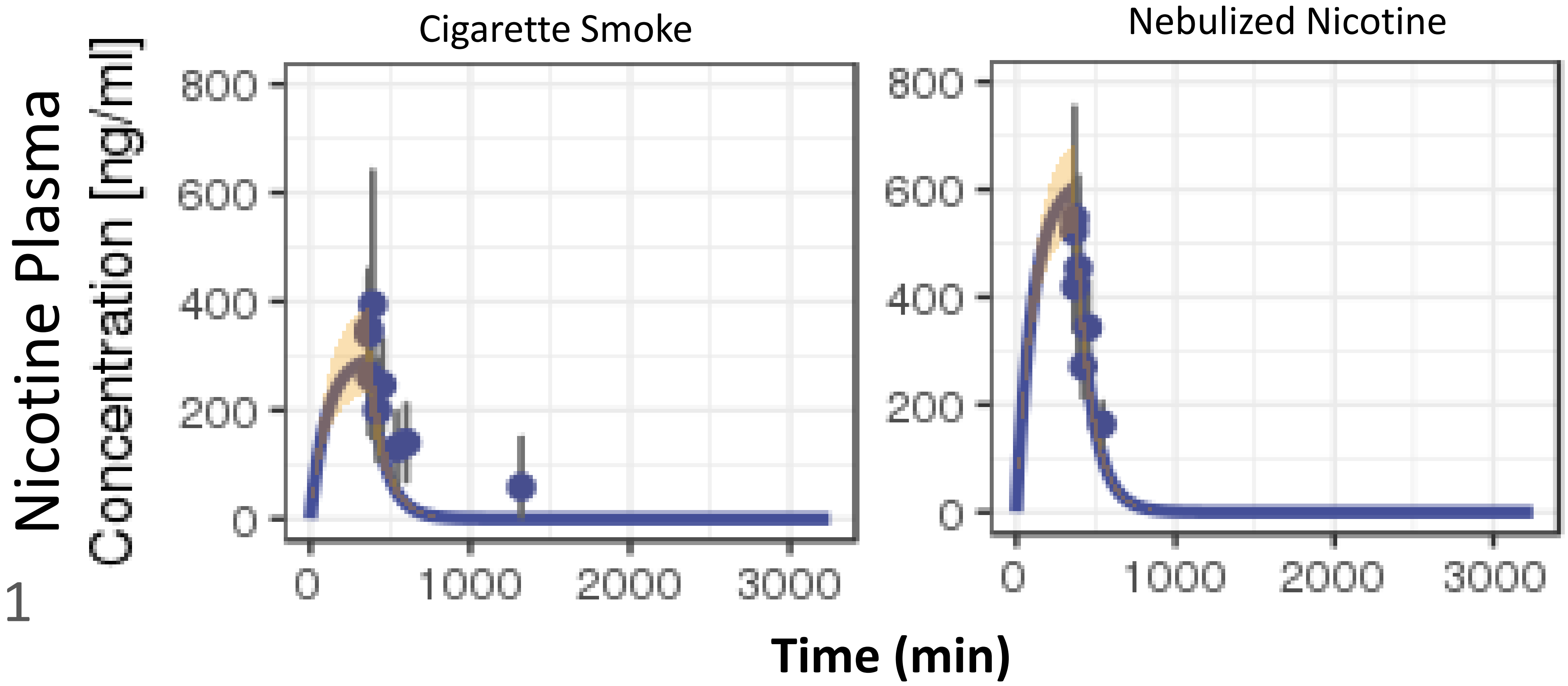
- Predicted Nicotine fraction entering RT (f_0) using PK

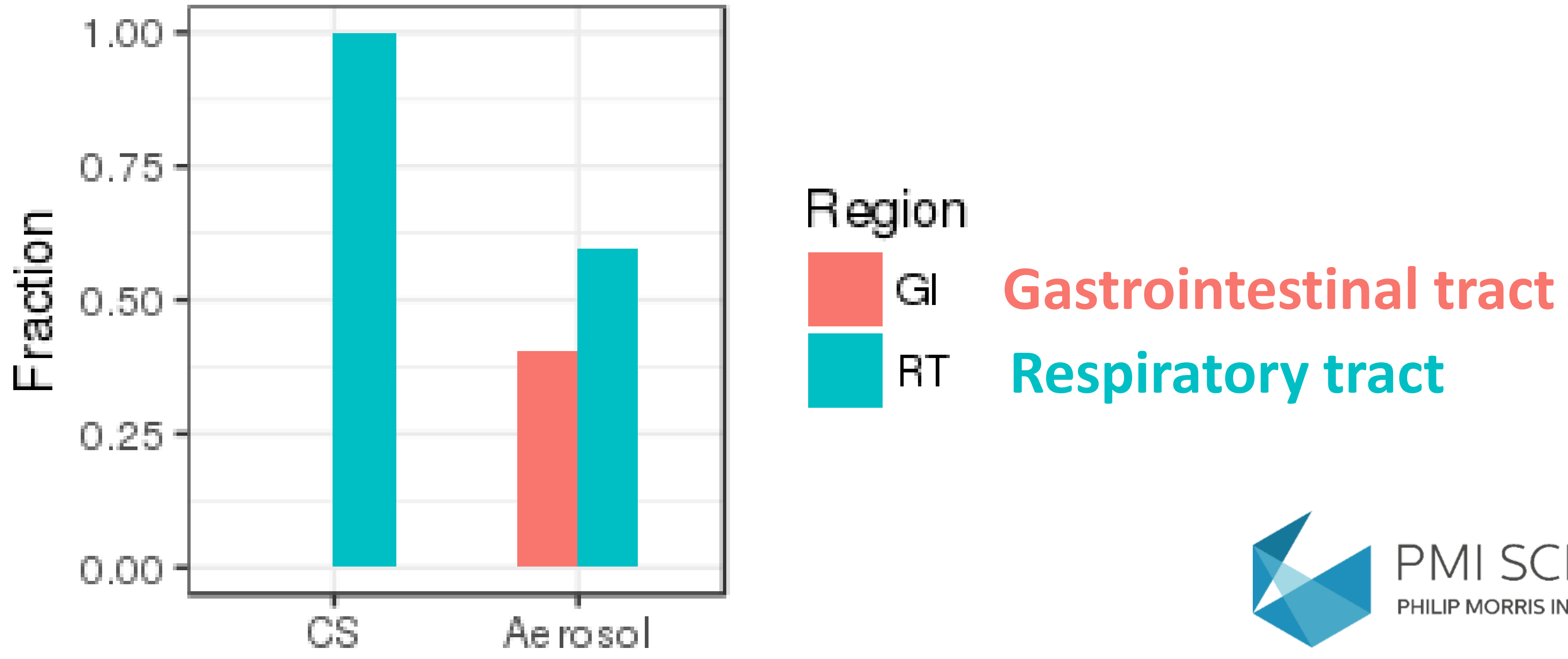
For model development validation experiments

- 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:

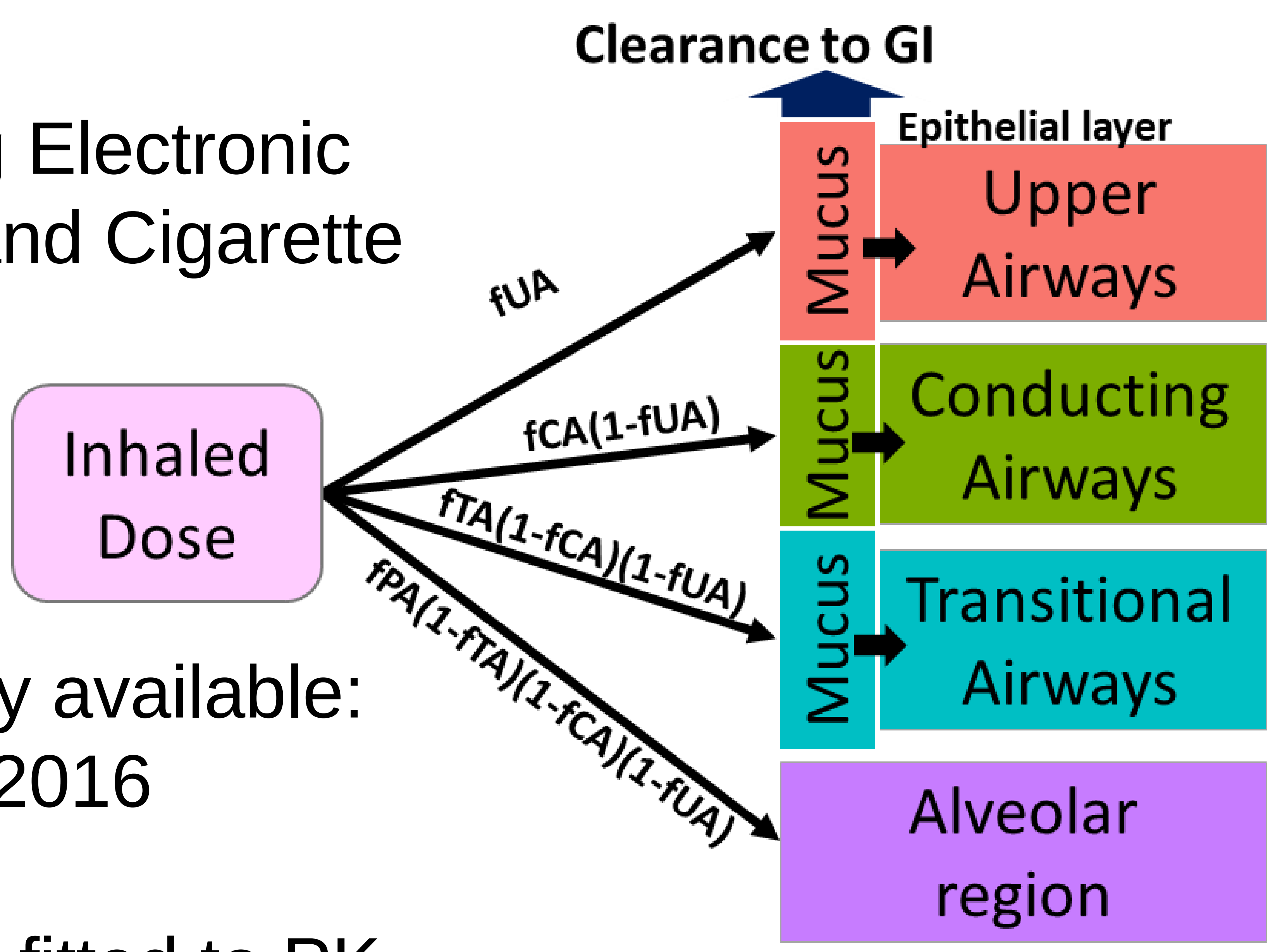
- Good predictions were obtained assuming that part of the aerosol is not inhaled
- Need for multi-compartmental model to account for aerosol physics and deposition in the upper respiratory tract



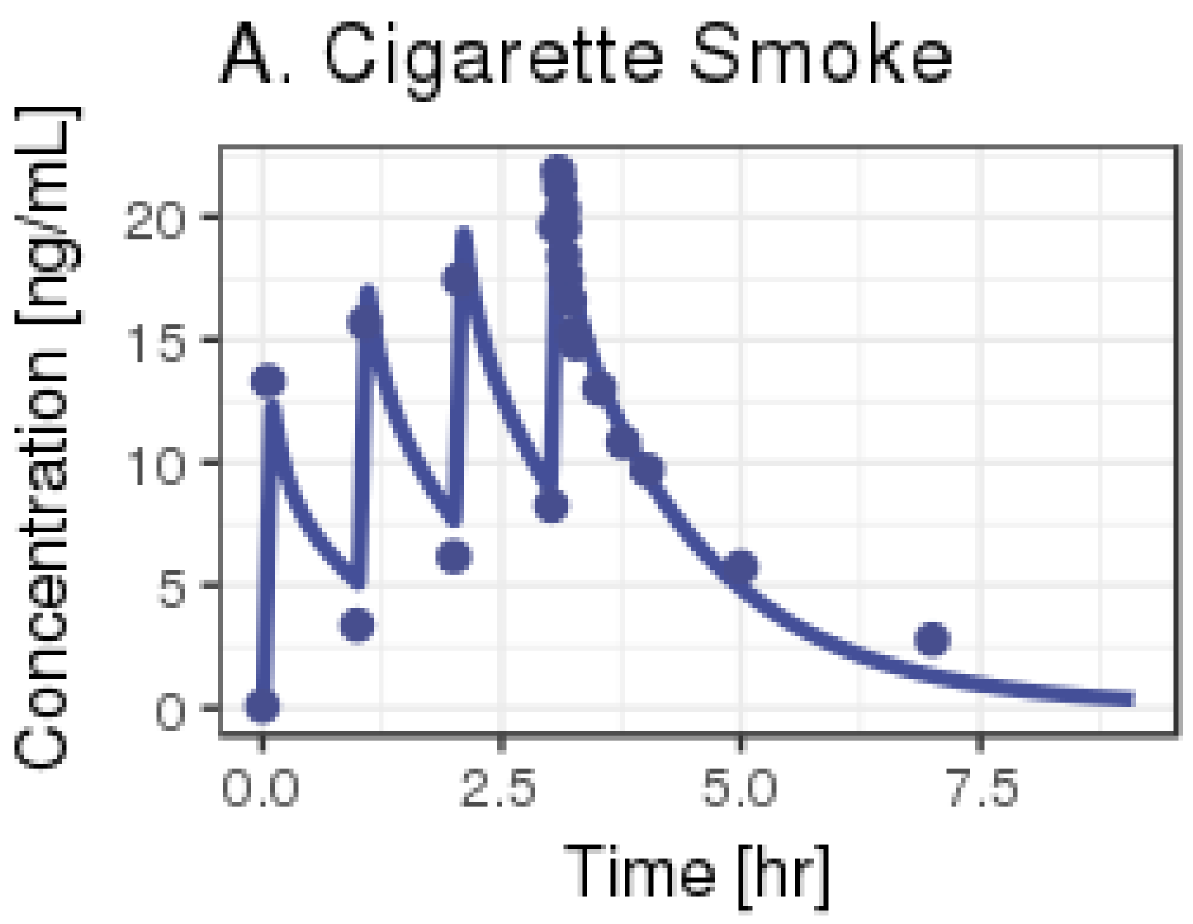


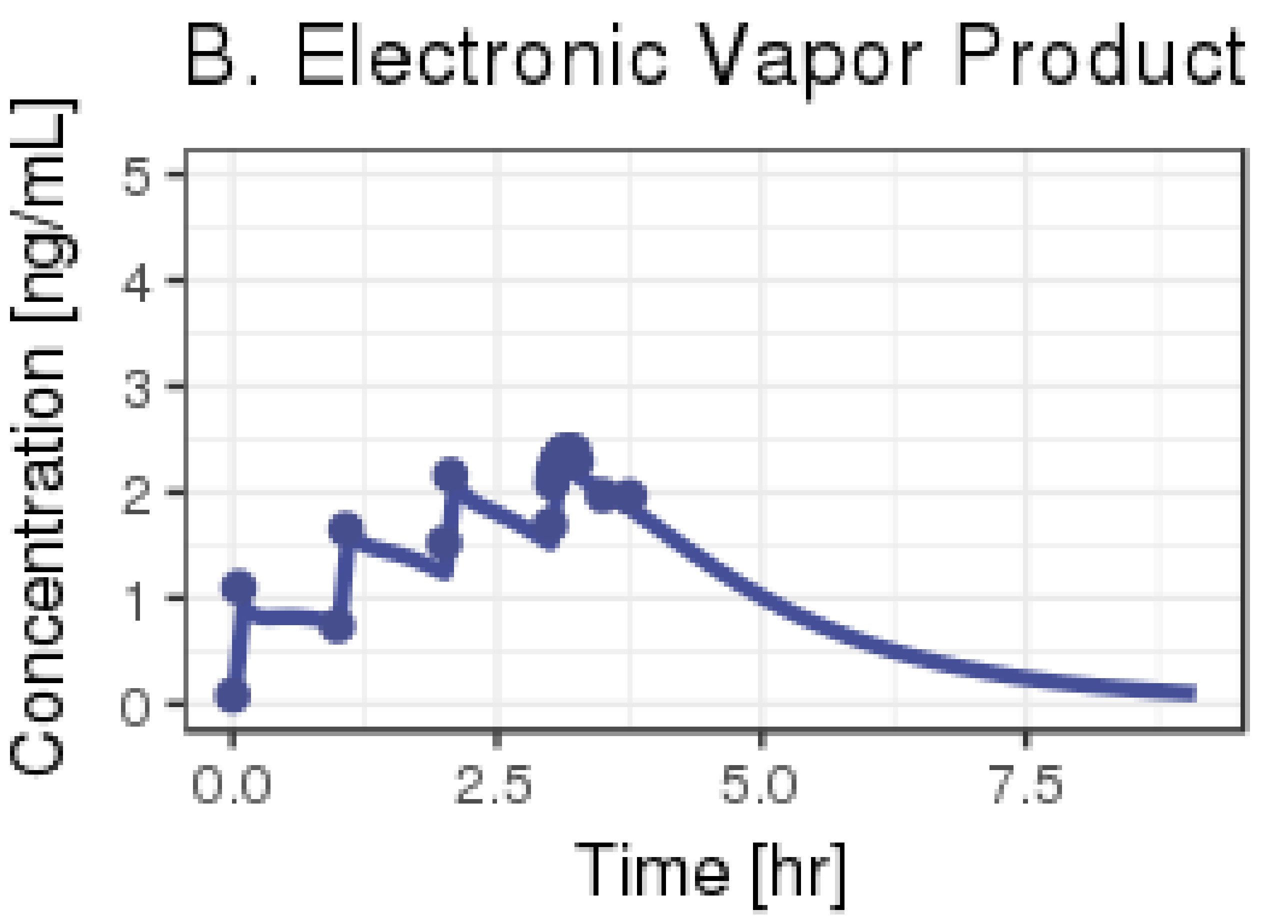
Semi-Descriptive Human Inhalation PBPK Model @PMI

- Clinical trial comparing Electronic Vapor product (EVP) and Cigarette smoke (CS)

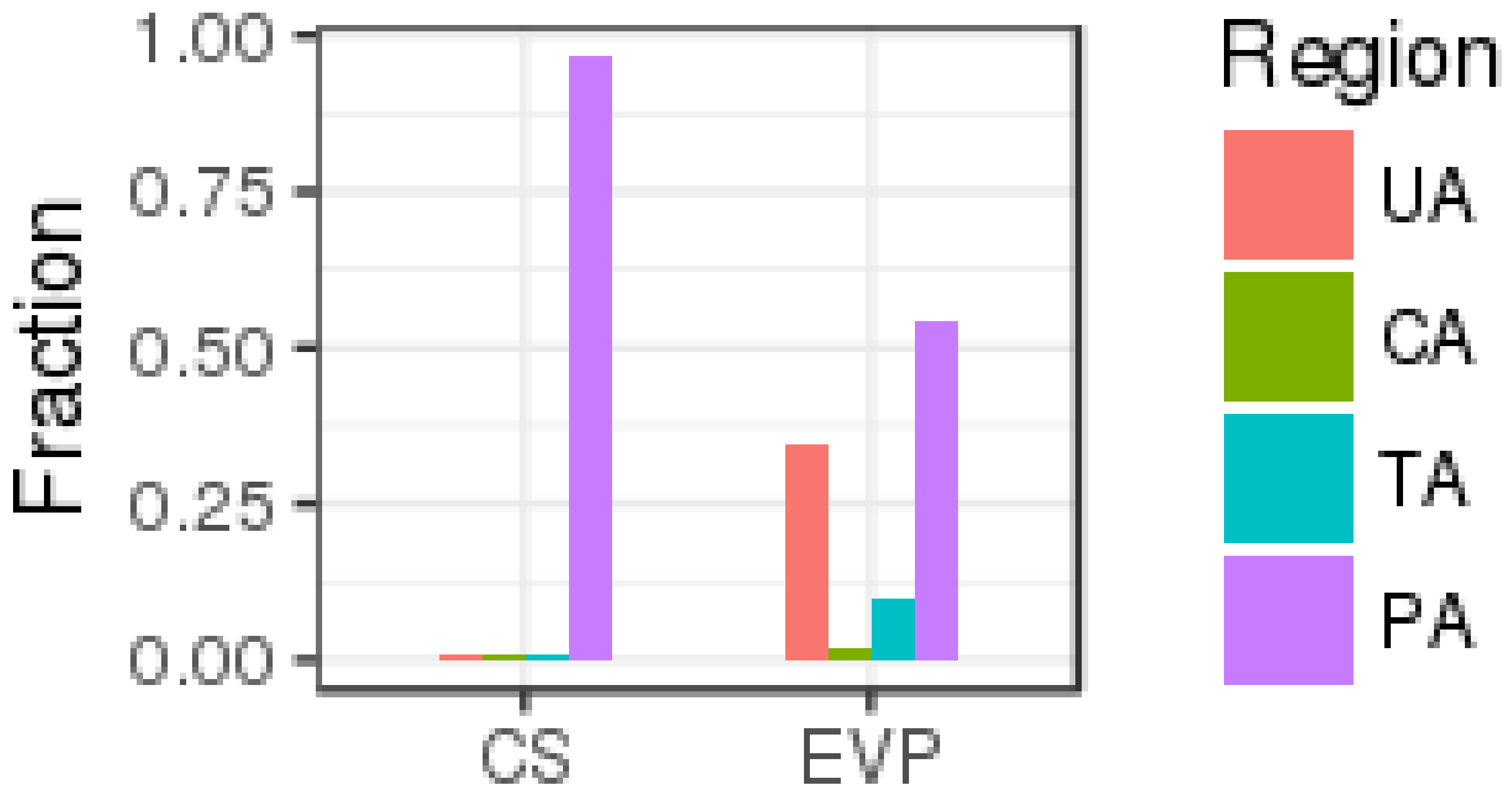


- Source of data: publicly available: Walele, Sharma et al. 2016
- Fraction deposited are fitted to PK





- 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

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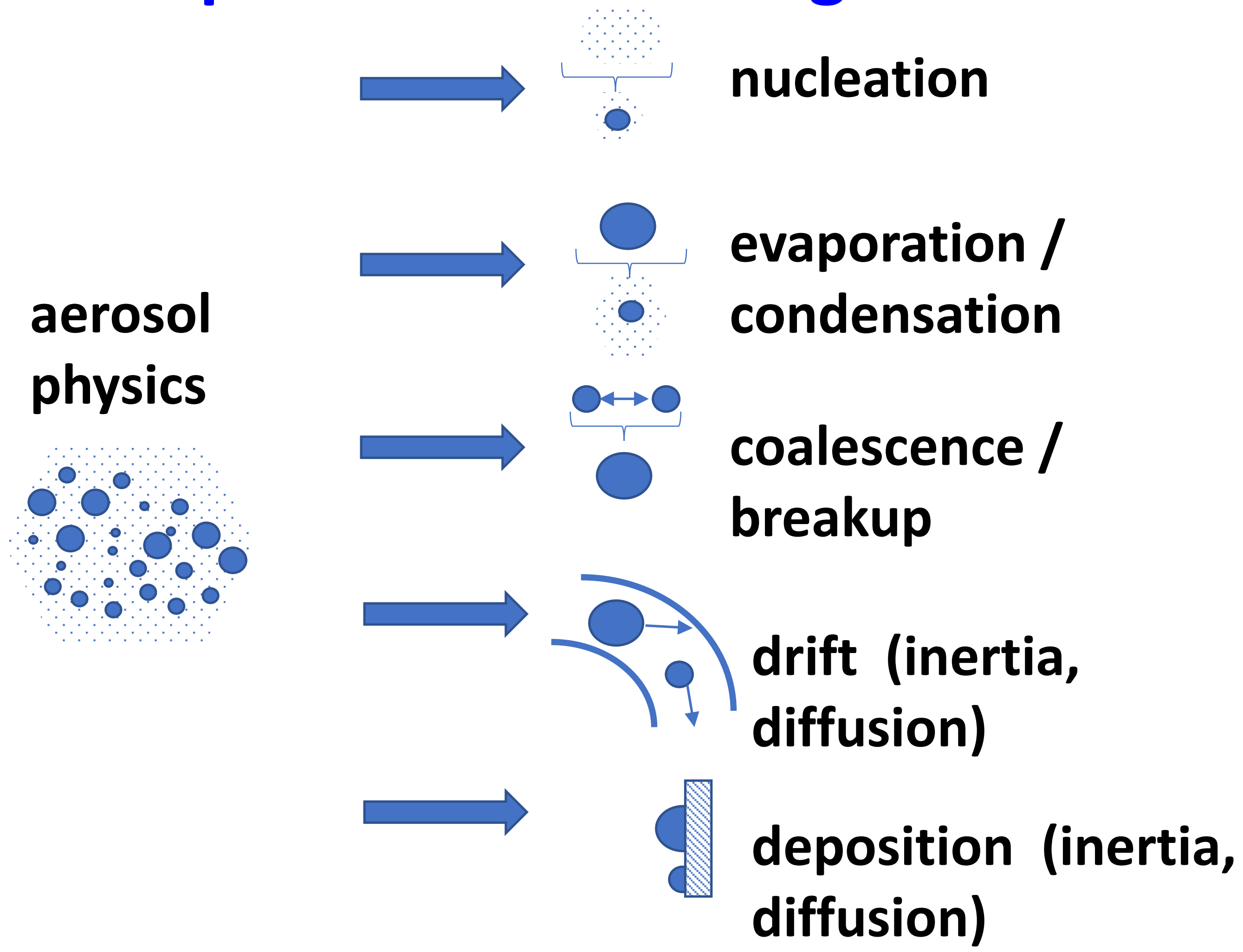
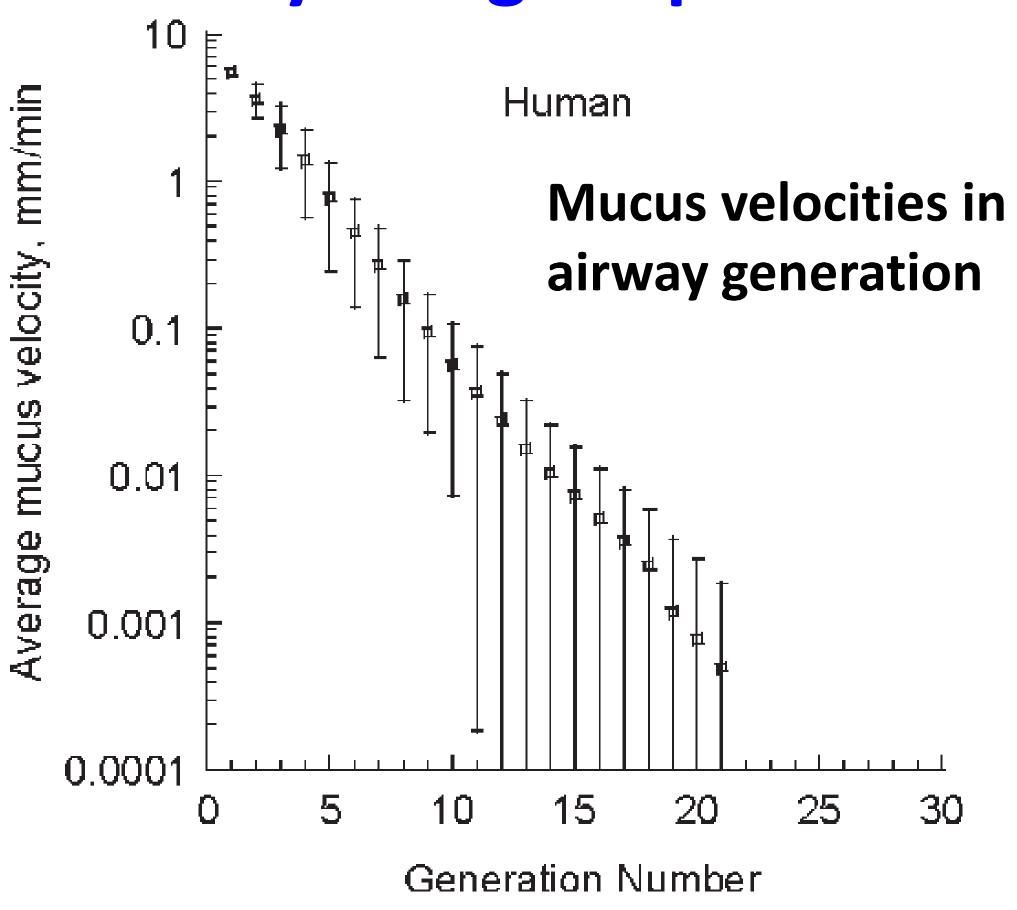
Ongoing Work

Airway anatomy

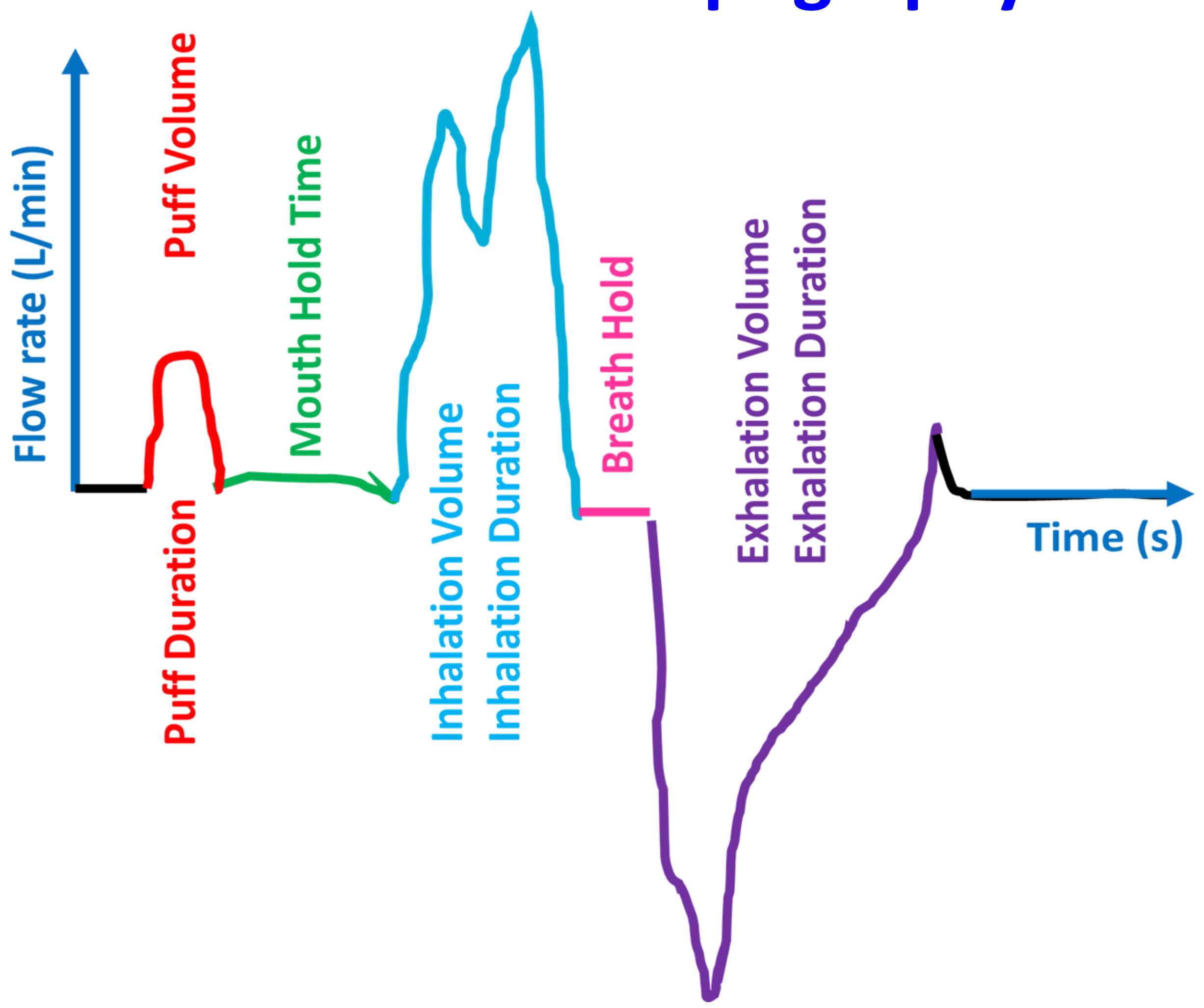
Deposition of evolving aerosol



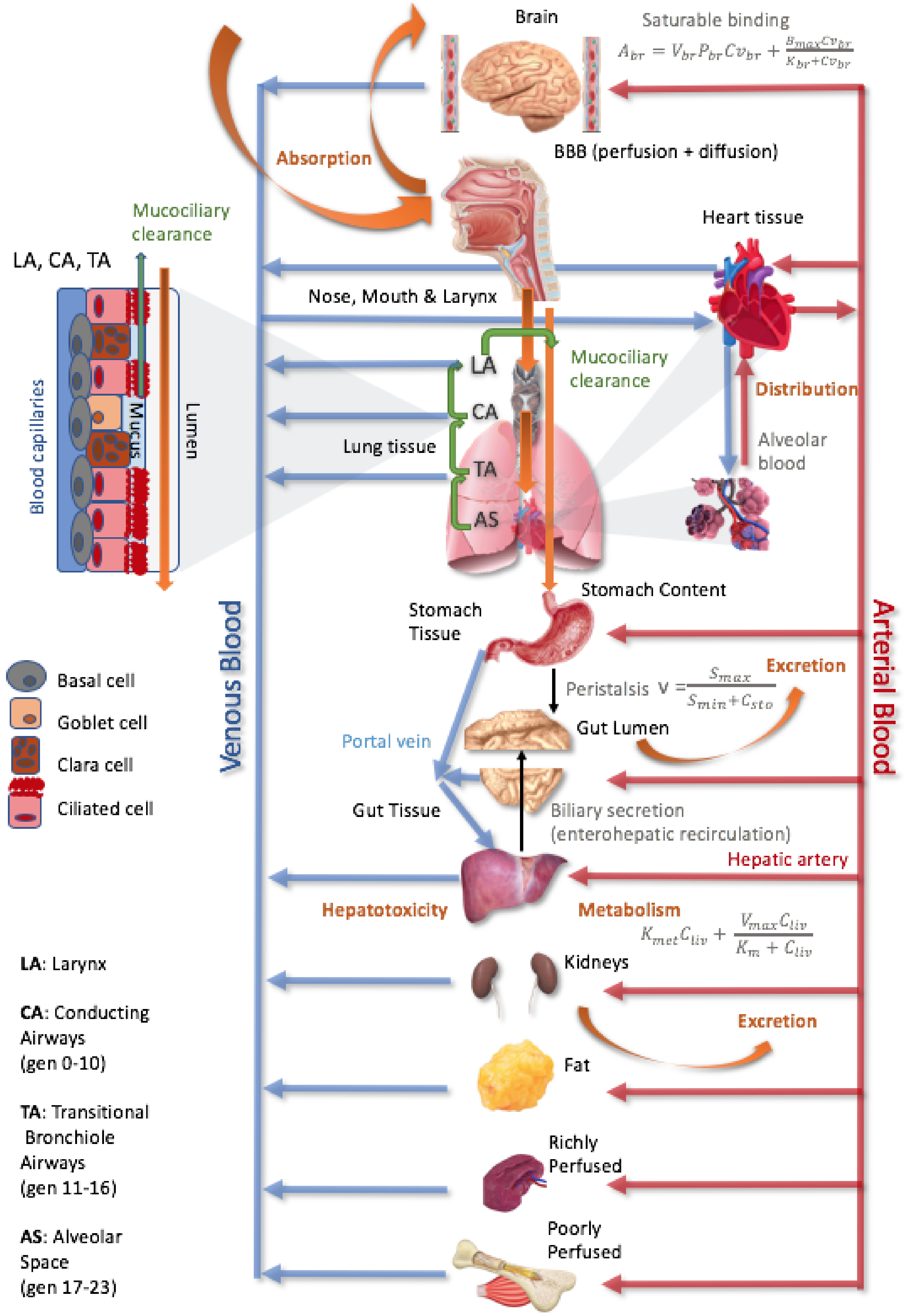
Physiological process



Inhalation topography

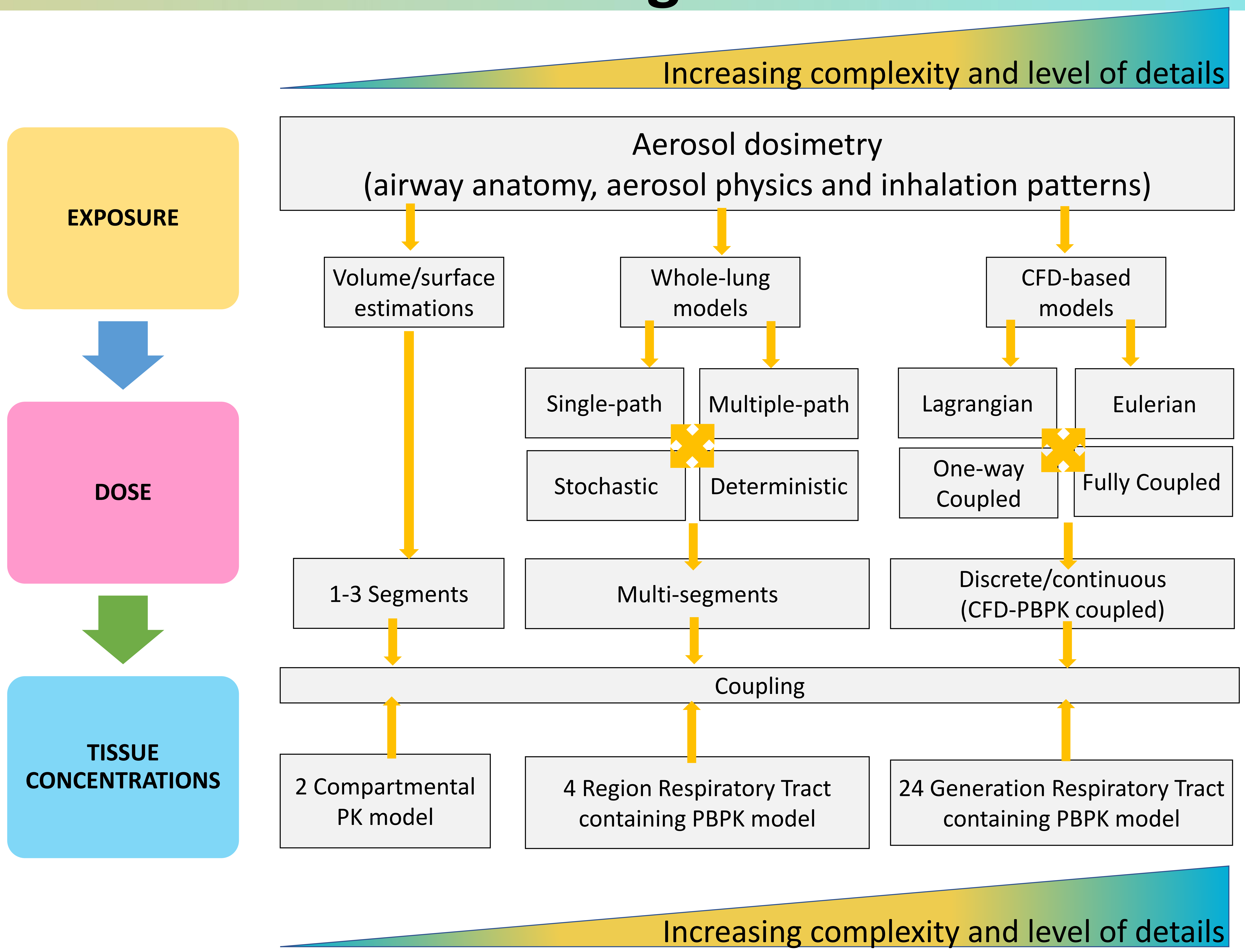


Dose



Challenges involved in PBPK modeling of Nicotine containing Inhaled Aerosol

PBPK Modeling of Inhaled Aerosol



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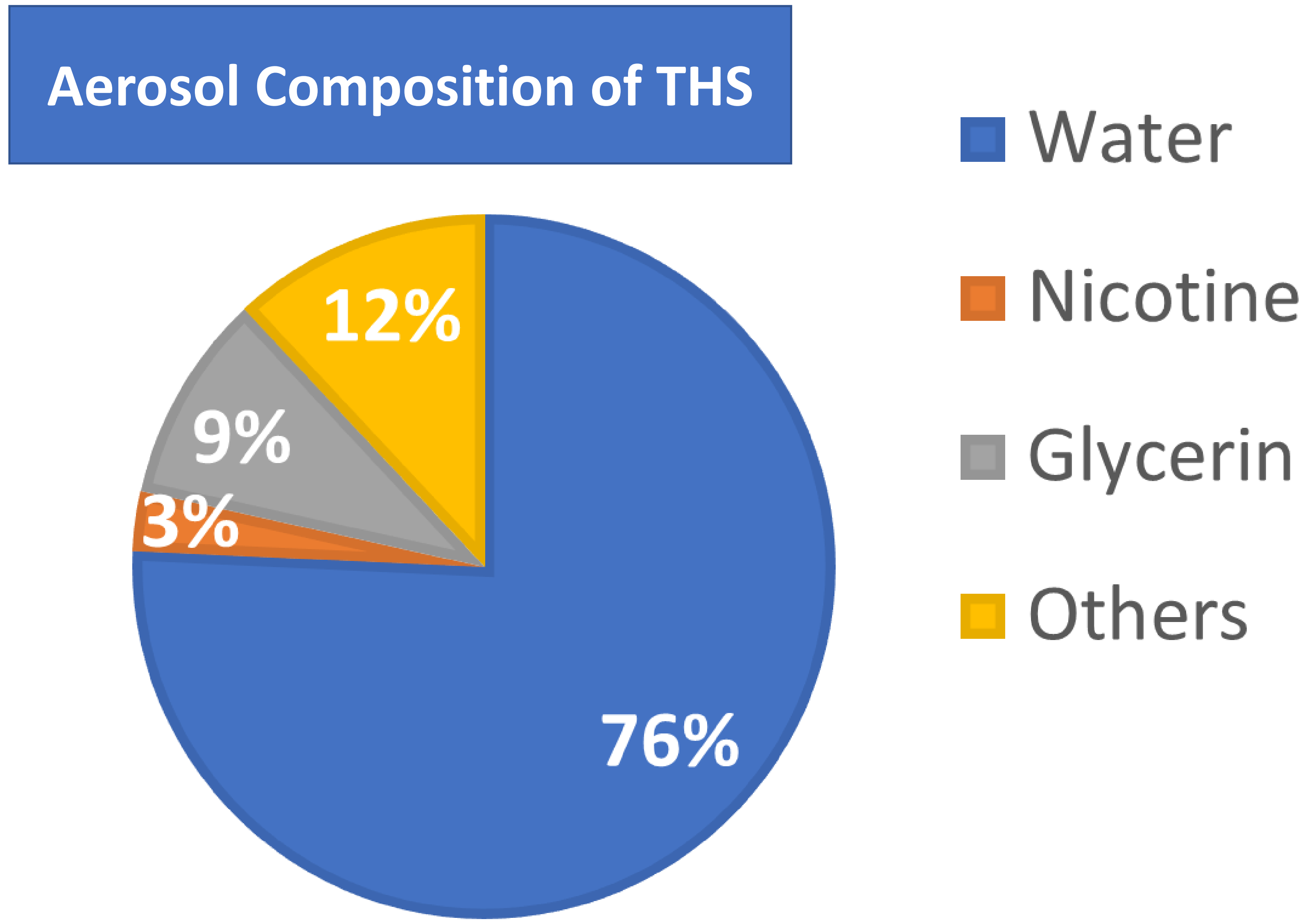
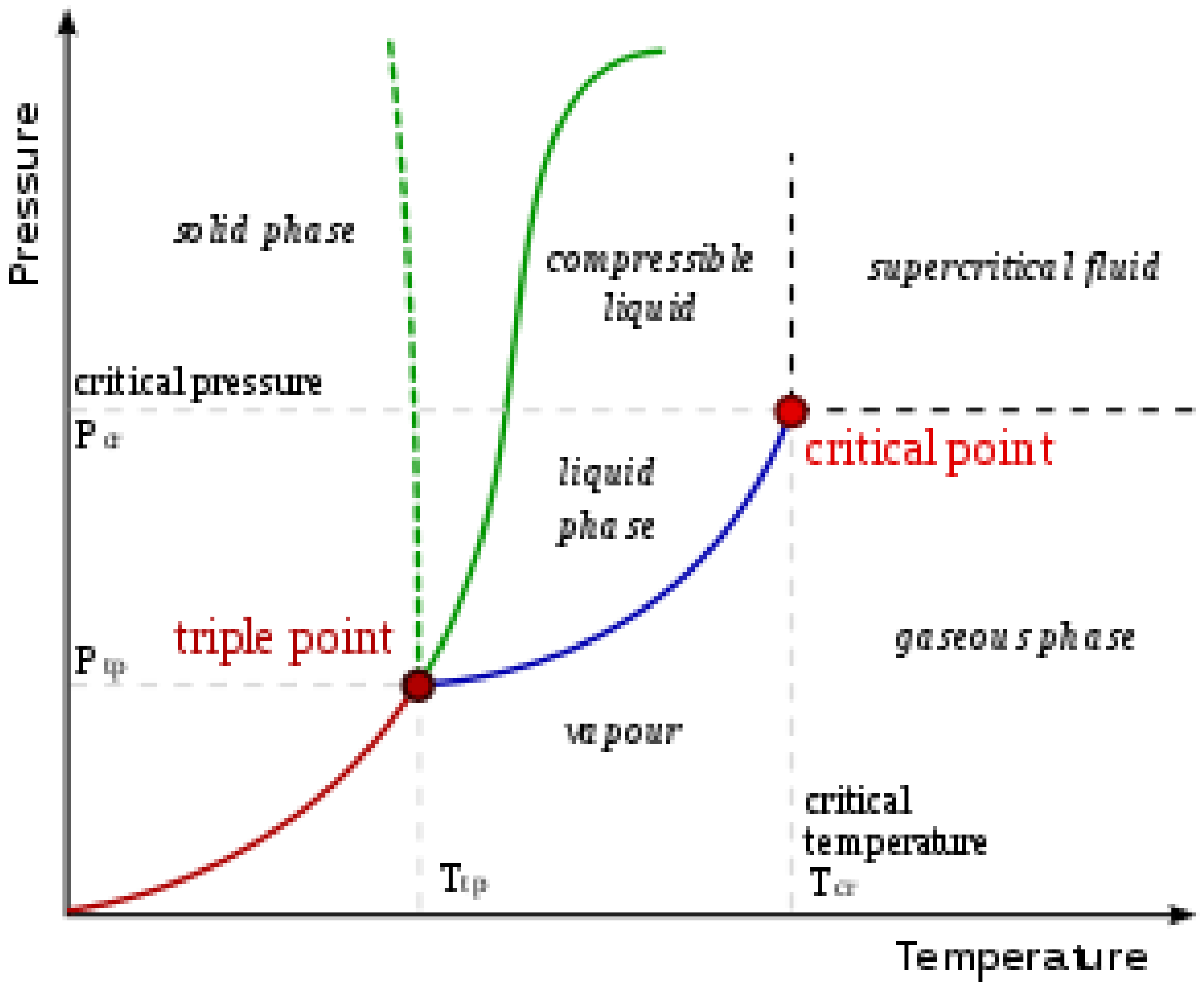
Challenges: Aerosol Physicochemical Properties

- 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.



Schaller, 2016



https://en.wikipedia.org/wiki/Vapor

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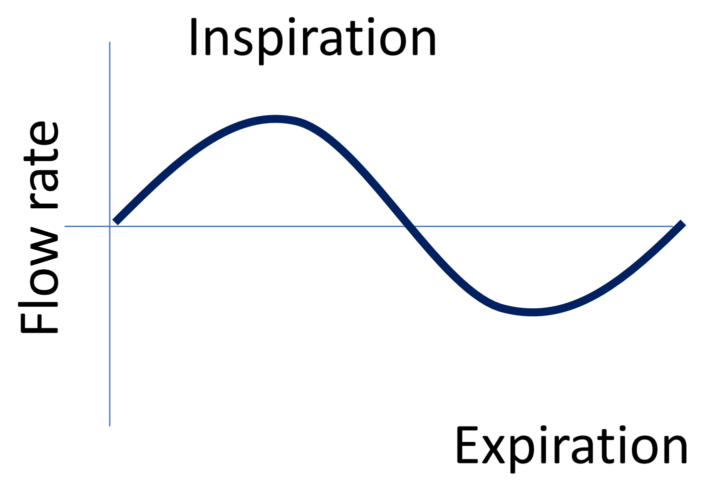
Challenges: Inhalation Topography

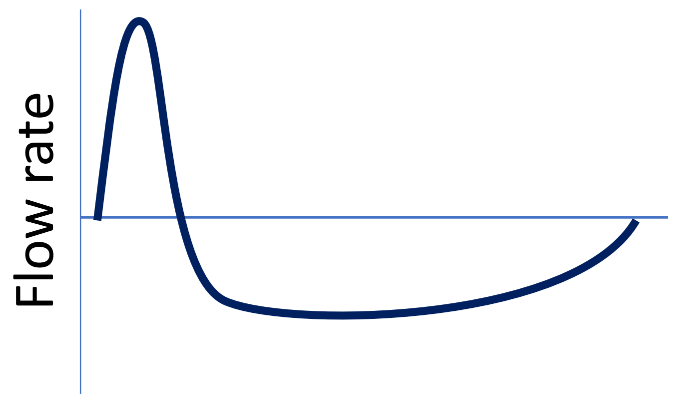
- Inhalation topography (breath hold, mouth hold and deep/shallow inhalation) effects the pharmacokinetics of short interval exposure.

- 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

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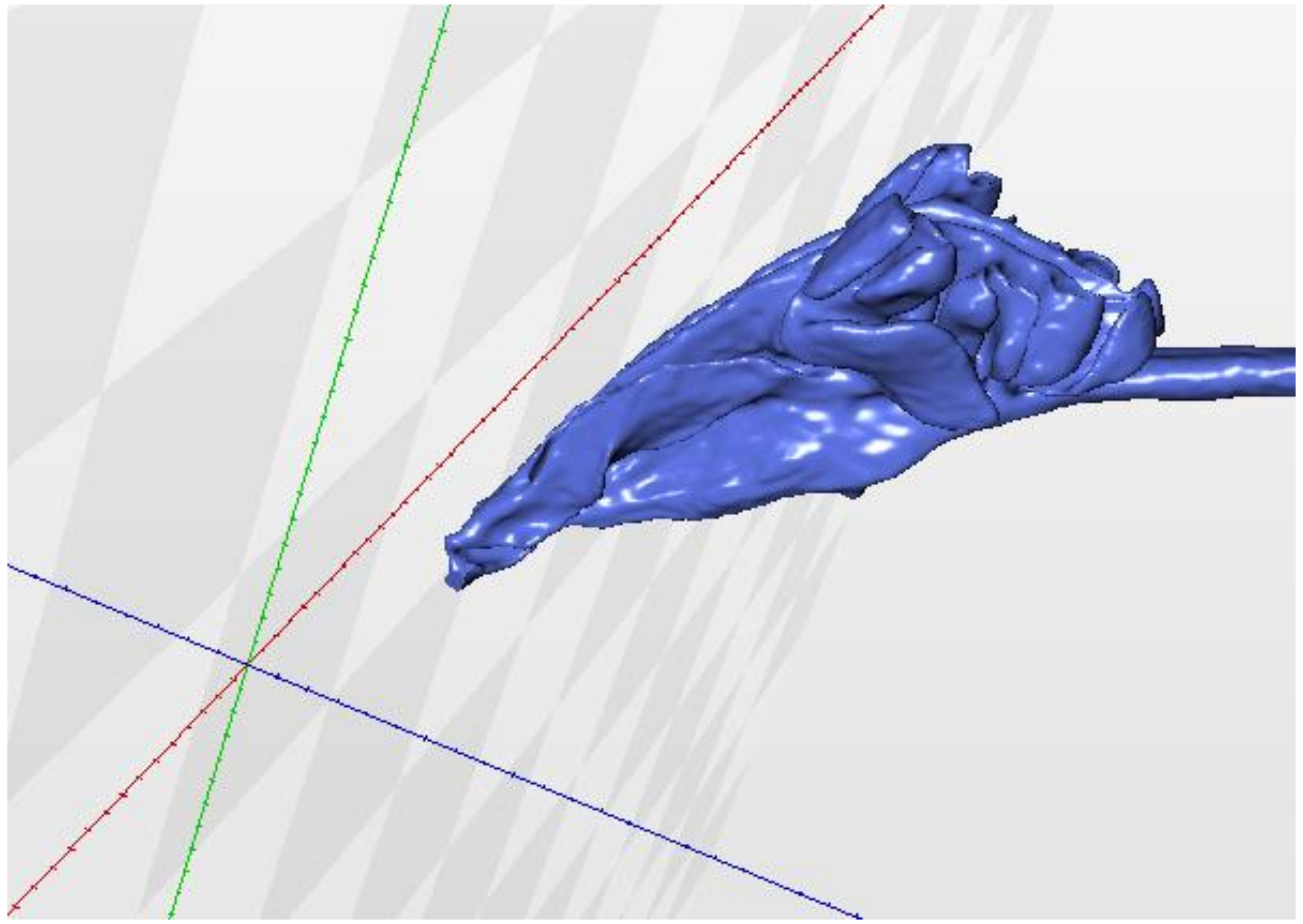
Challenges: Lung Geometry

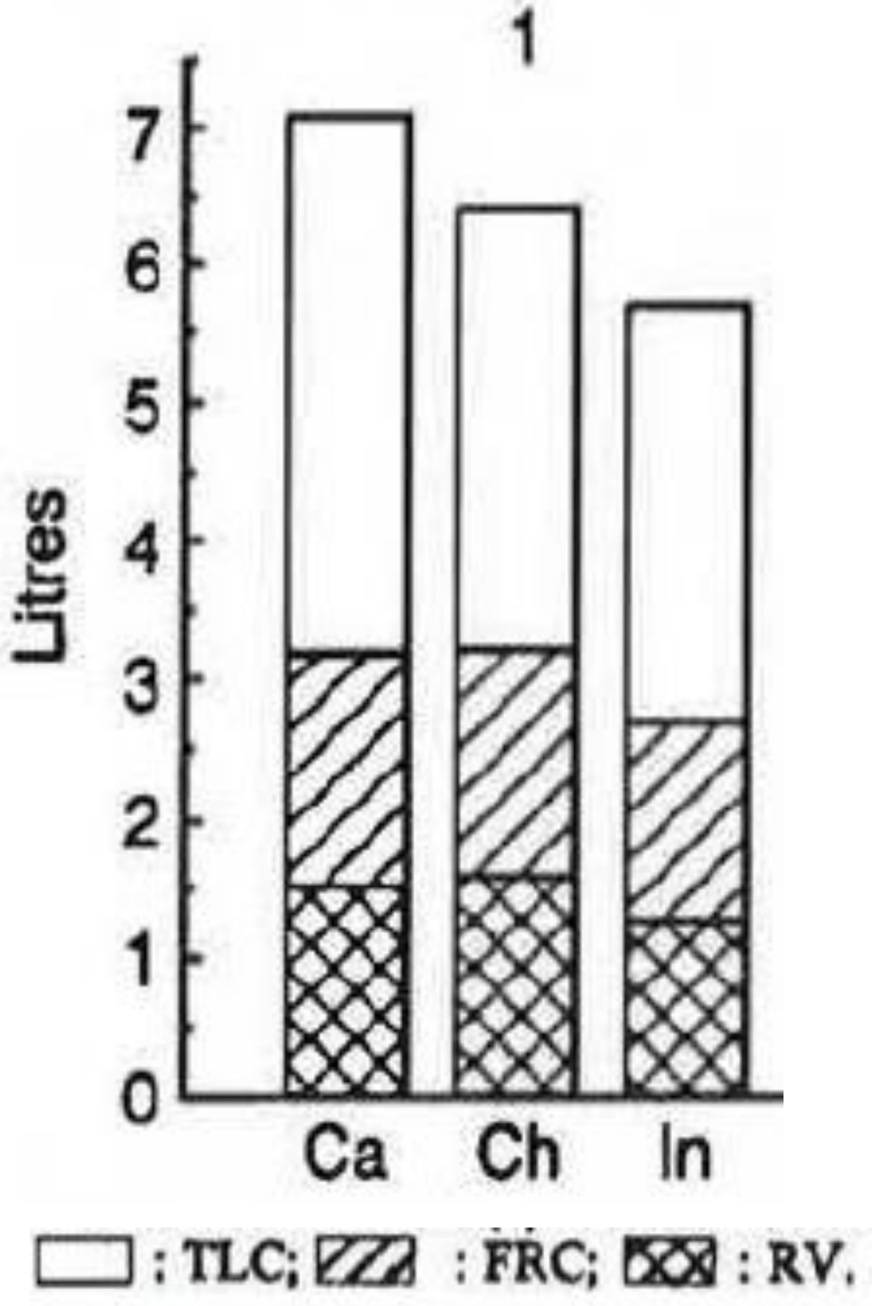
- There is a limited knowledge deposition of mouth and nose geometries on the delivery of aerosols for rodents and humans.

- 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

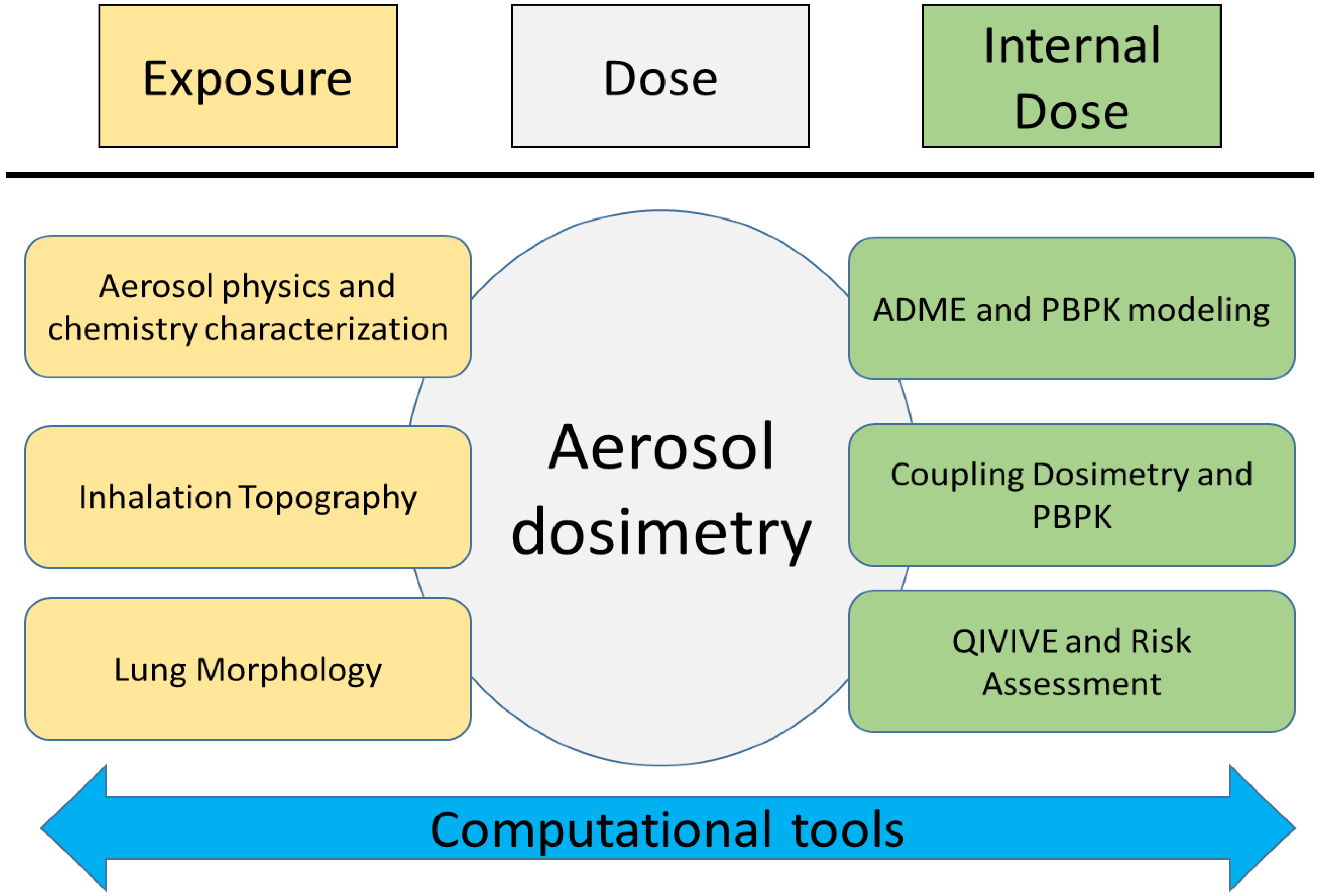


Donnelly 1991

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.



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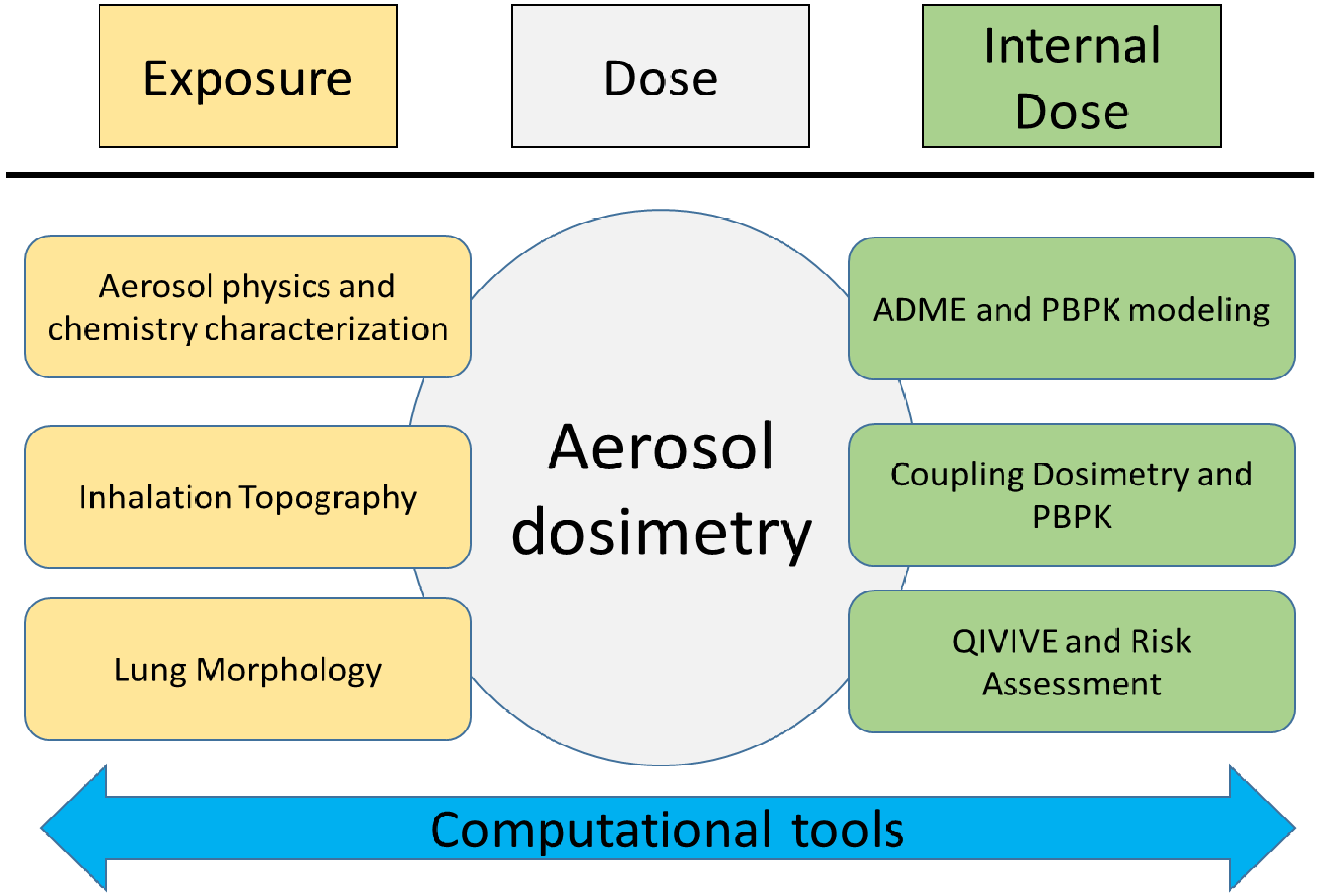
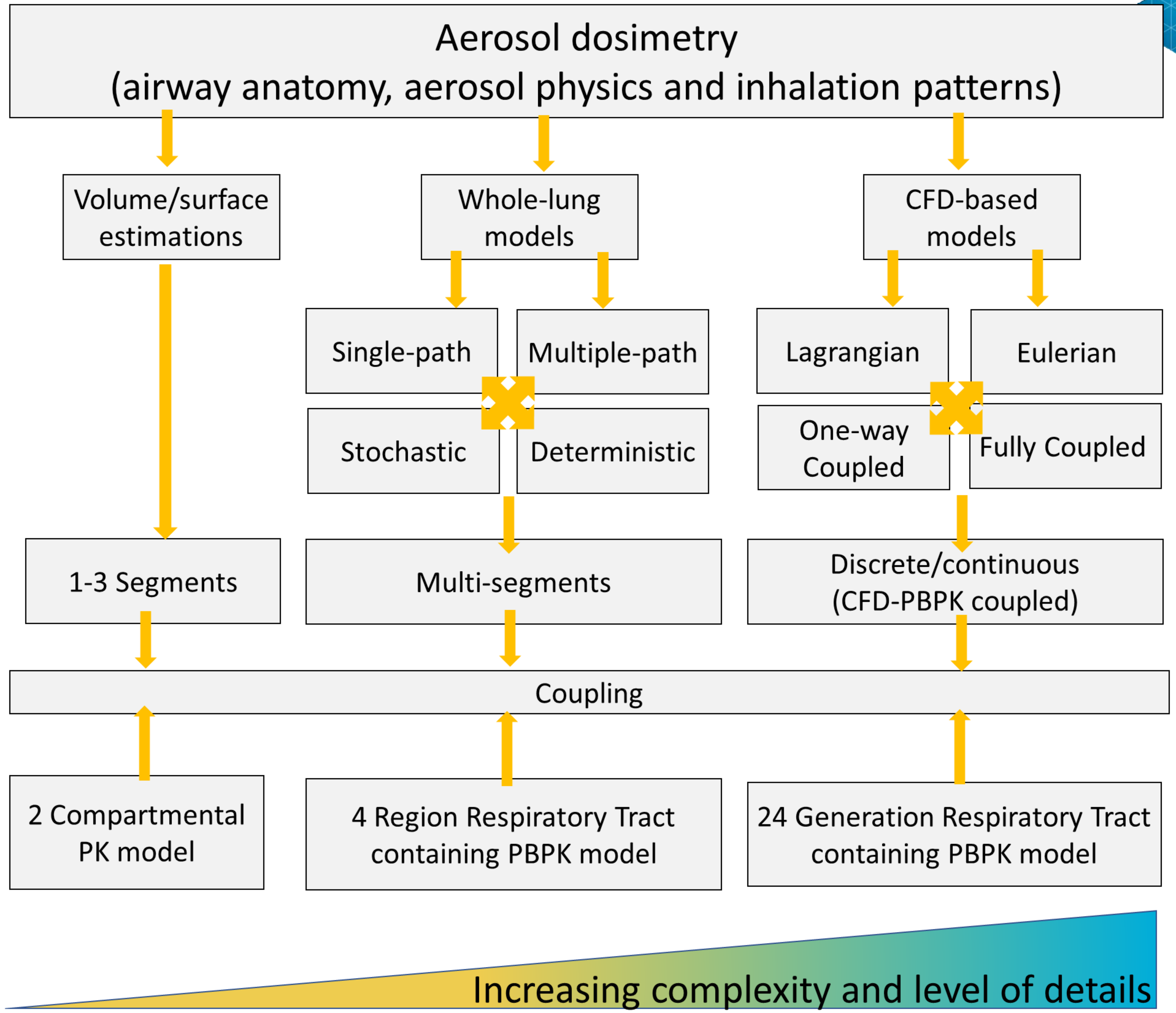
Challenges: Aerosol Dosimetry + PBPK

- 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?



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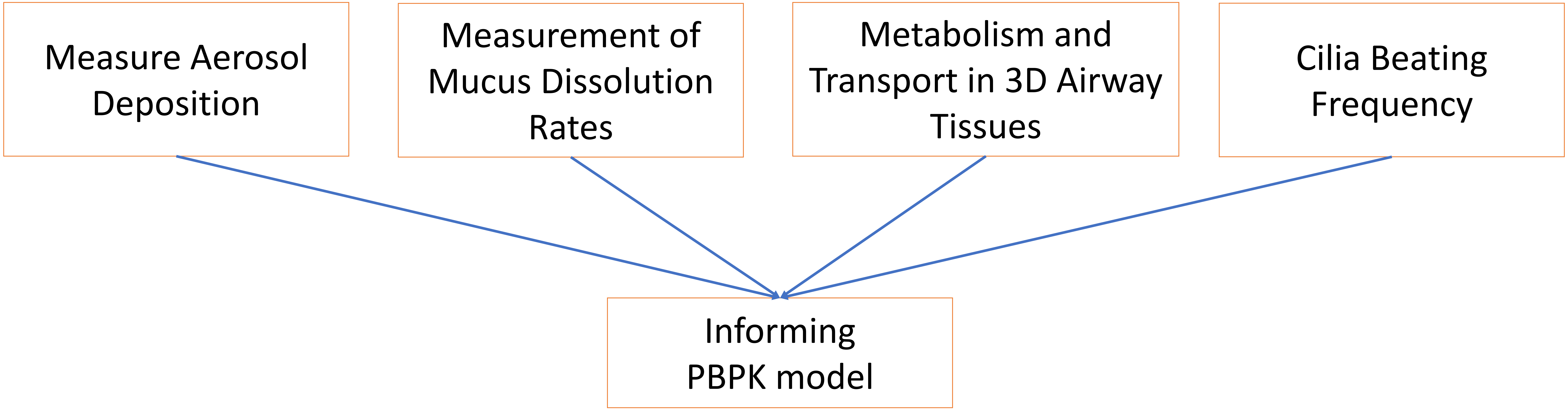
Challenges: ADME+ PBPK

- 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



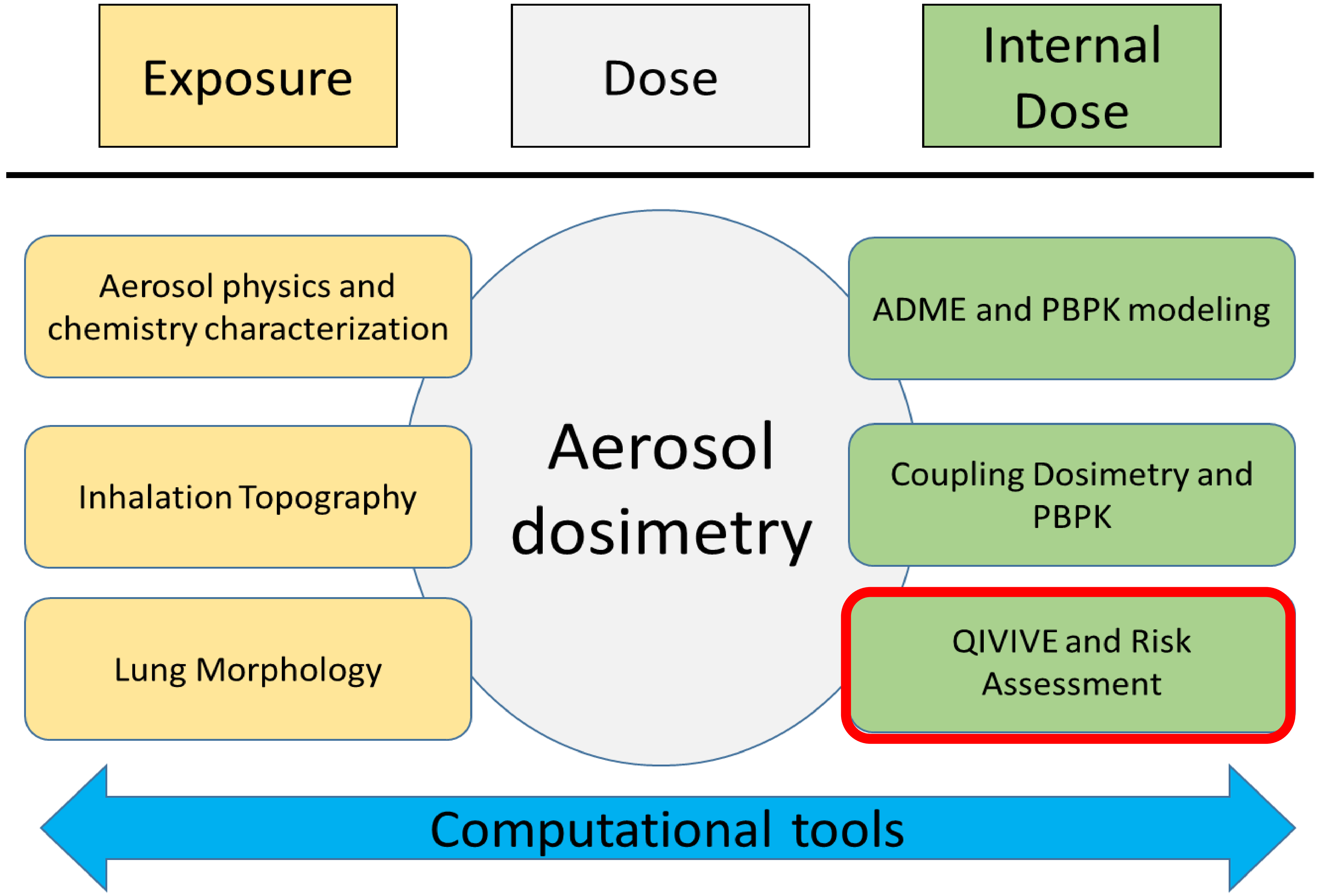
Quantitative in vitro to in vivo Extrapolation (QIVIVE)

- 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?



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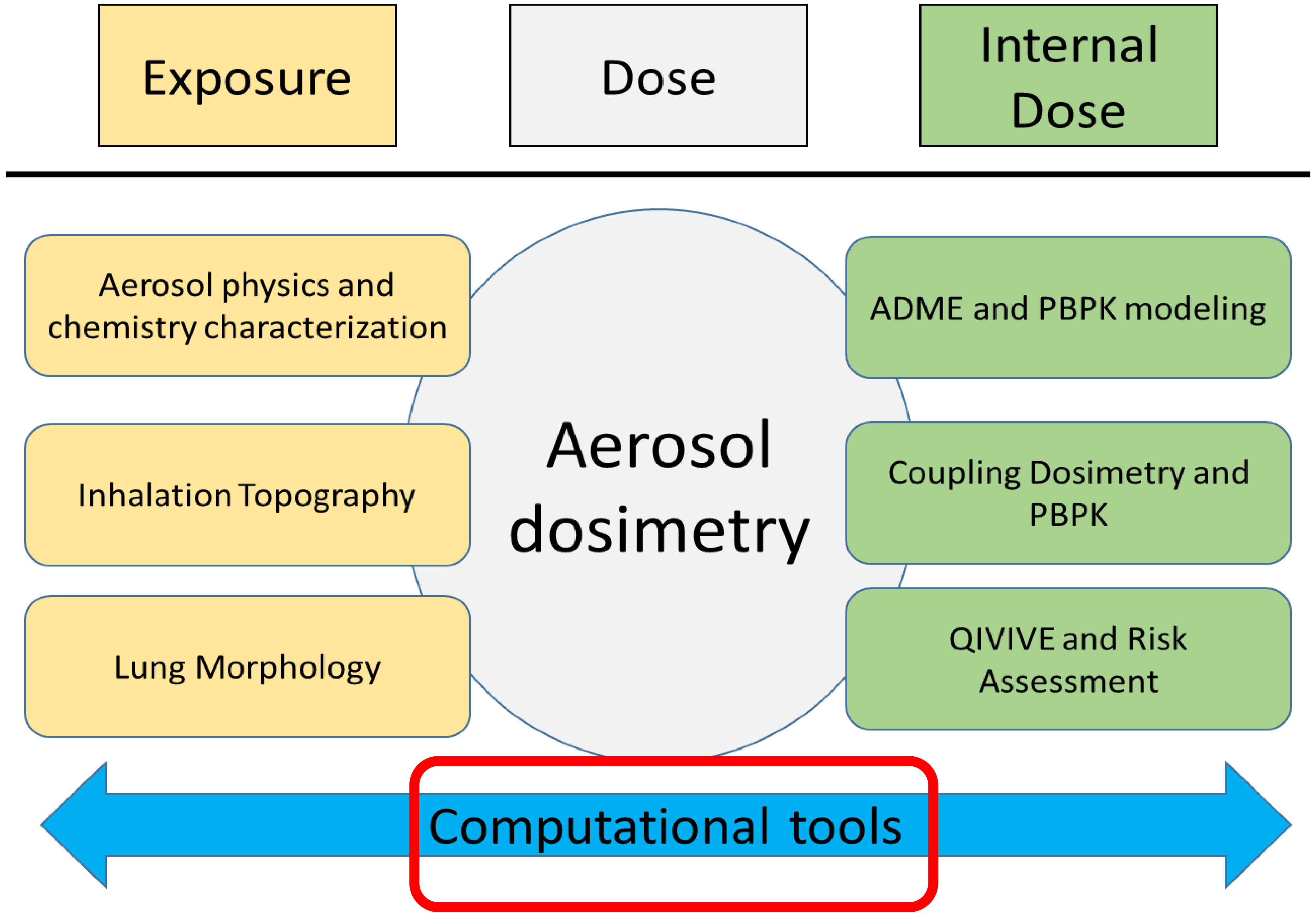
Model Comparison to Identify Best Applicability

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

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



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- Michael Dourson

TERA Workshop Science Panel

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