Assessing bioavailability and systemic delivery of inhaled compounds: current status and future directions

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Workshop on Alternative Approaches for Acute Inhalation Toxicity Testing to Address Global Regulatory and Non-Regulatory Data Requirements
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Washington, DC

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Lung dosimetry for inhalation toxicology and risk assessment

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What matters for lung dosimetry

- how much, where in the airways, and in what form

- Effects at portals of entry
  - Target sites in the respiratory tract
  - Mode of action – metabolic activation or any other transformation
- Systemic effects
  - Bioavailability – parent vs. metabolites

Lung metabolism

- Regional differences
  - CYP450 metabolism only occurs in certain epithelial cells (Type1, Type II and Clara cells)
  - Clara cells comprise the majority of the metabolic activity (Plopper et al. 1980; Plopper 1992)
- Species differences
  - In mice Clara cells are found through out the respiratory tract, but they are only found in the transitional airway of rats and humans (Parent 1992; Plopper et al. 1992; Mercer et al 1994).
- Difficulties in in vitro to in vivo extrapolation
  - Metabolic constants for the lung are typically scaled from measured whole lung homogenate
  - Experimental measurements of metabolic rate constants for metabolically active lung toxicants are not usually measured in Clara cells

Challenges in estimating target tissue dosimetry with metabolic activation

- Examples of a few VoCs with metabolic activation as MoA
  - Butadiene, methylene chloride, trichloroethylene, naphthalene, styrene
  - Clara cells in the bronchio-alveolar region in rodents are responsible for metabolic activation
  - Species differences in the magnitude of the toxicity preceding carcinogenicity or in the incidence of tumors

Limitations of PBPK modeling with a simplified lung description

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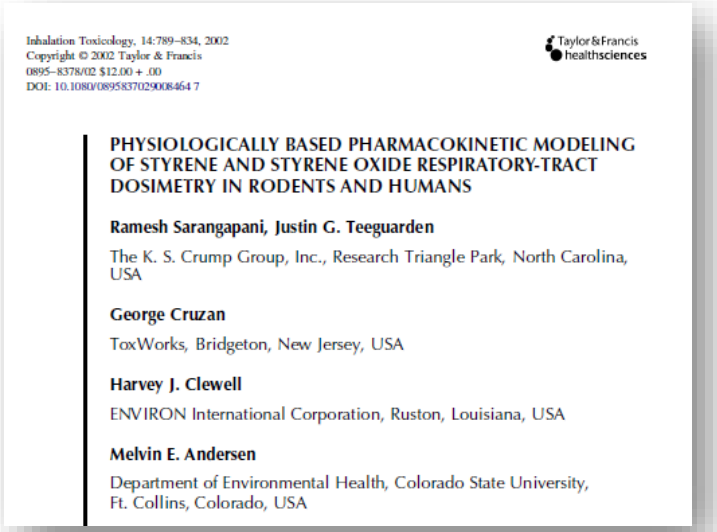
- Typical PBPK models use a single homogeneous tissue in equilibrium with arterial blood for simulating inhalation exposure
- Those simple descriptions do not reflect respiratory tract dosimetry as target tissue
- They do not capture
  - air-phase delivery of the inhaled volatile to the target
  - species differences in the metabolic constants for formation (toxication) and clearance (detoxication) of metabolites by Clara cells
  - regional Clara-cell density

PBPK model with regional lung compartments

- A multi-compartment respiratory tract described in the model
- Both portals of entry and systemic dosimetry can be captured by the model



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PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF STYRENE AND STYRENE OXIDE RESPIRATORY-TRACT DOSIMETRY IN RODENTS AND HUMANS

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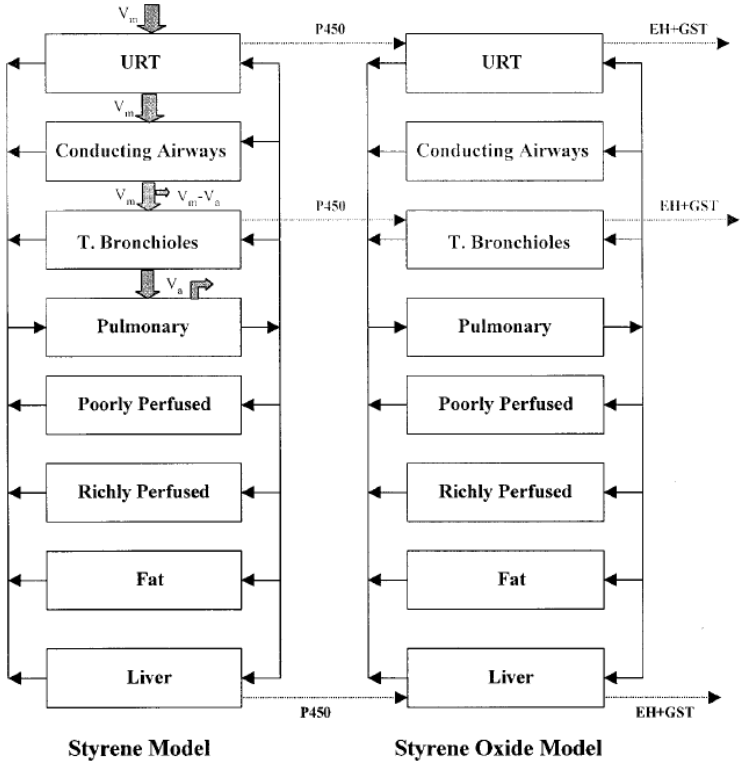
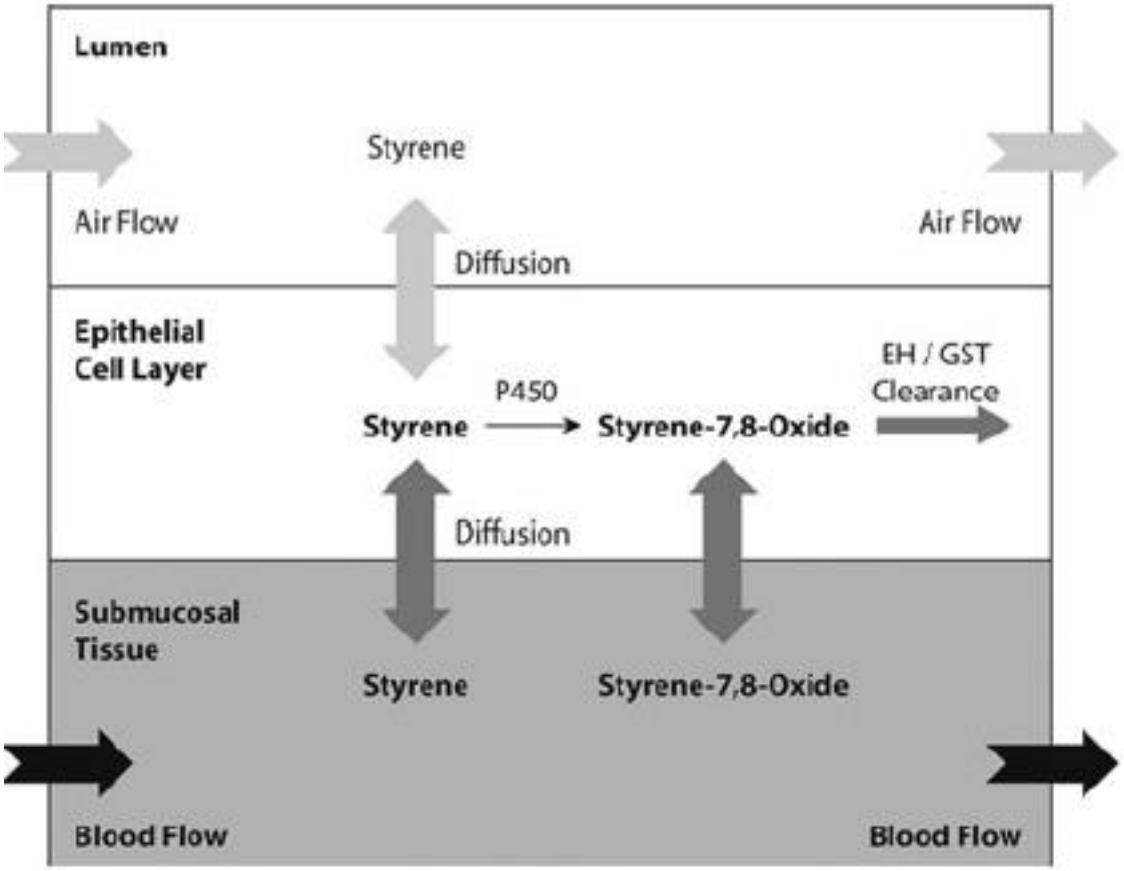


Regional lung compartments in the PBPK model

- Pulmonary metabolism is distributed among four compartment regions with distinct physiological and metabolic features:
  - Oral/nasal passages
  - Conducting airways (tracheas, bronchi and anterior bronchioles)
  - Transitional airways (terminal bronchioles)
  - Alveolar gas exchange regions

Modeling mass transfer at the air:tissue interface



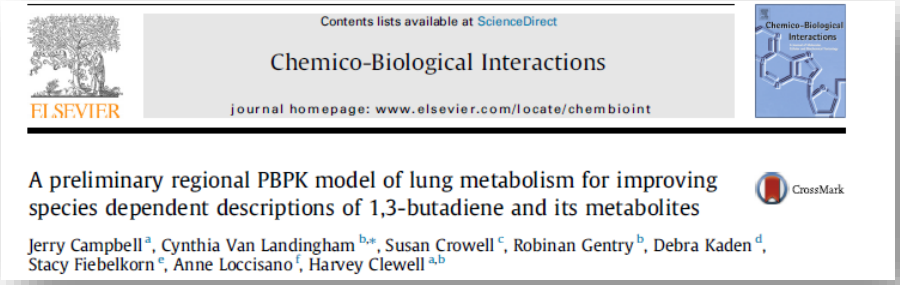
Sarangapani et al., 2002

Hybrid CFD-PBPK modeling

- Computational Fluid Dynamic (CFD) models of the lung airways can be used to predict site-specific deposition of inhaled materials
- CFD models can be linked with PK or PBPK models to address the combined influences of tissue metabolism and airway architecture on region specific lung dosimetry
- CFD models can be time-consuming, complex, and require specialized software but can yield site-specific deposition patterns of different types of inhaled materials

Species extrapolation – current state of the art

- Current practices mainly rely on animal inhalation studies to predict human lung dosimetry
- Regional lung dosimetry model provides a way to properly consider species differences by incorporating species specific regional lung metabolism and transport



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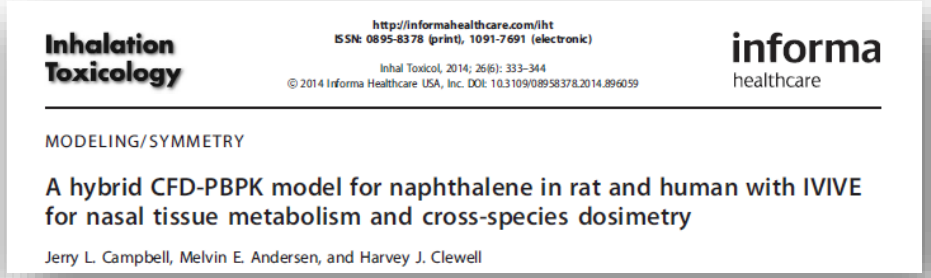
A preliminary regional PBPK model of lung metabolism for improving species dependent descriptions of 1,3-butadiene and its metabolites

Jerry Campbell[a], Cynthia Van Landingham[b,*], Susan Crowell[c], Robinan Gentry[b], Debra Kaden[d], Stacy Fiebelkorn[e], Anne Loccisano[f], Harvey Clewell[a,b]



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MODELING/SYMMETRY

A hybrid CFD-PBPK model for naphthalene in rat and human with IVIVE for nasal tissue metabolism and cross-species dosimetry

Jerry L. Campbell, Melvin E. Andersen, and Harvey J. Clewell

Multiple-path particle dosimetry model (MPPD) for nanoparticles

- Simulates doses deposited, cleared, and retained in specific parts of the lung for particles (available for free at https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304)

- Modeling of nano- and microscale particles disposition (Asgharian et al., 2014)

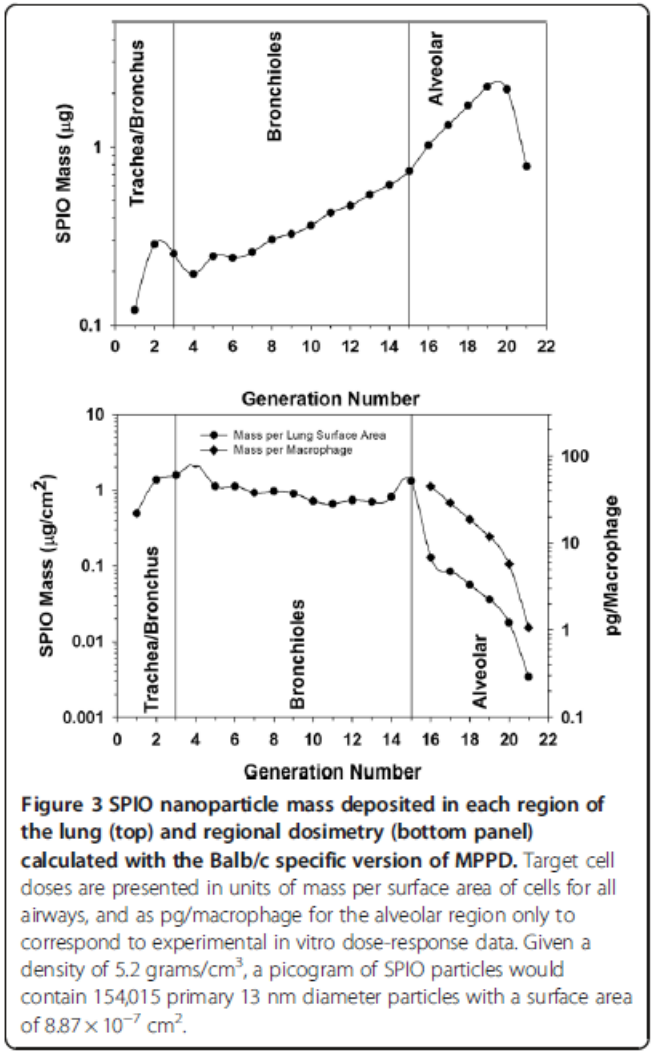
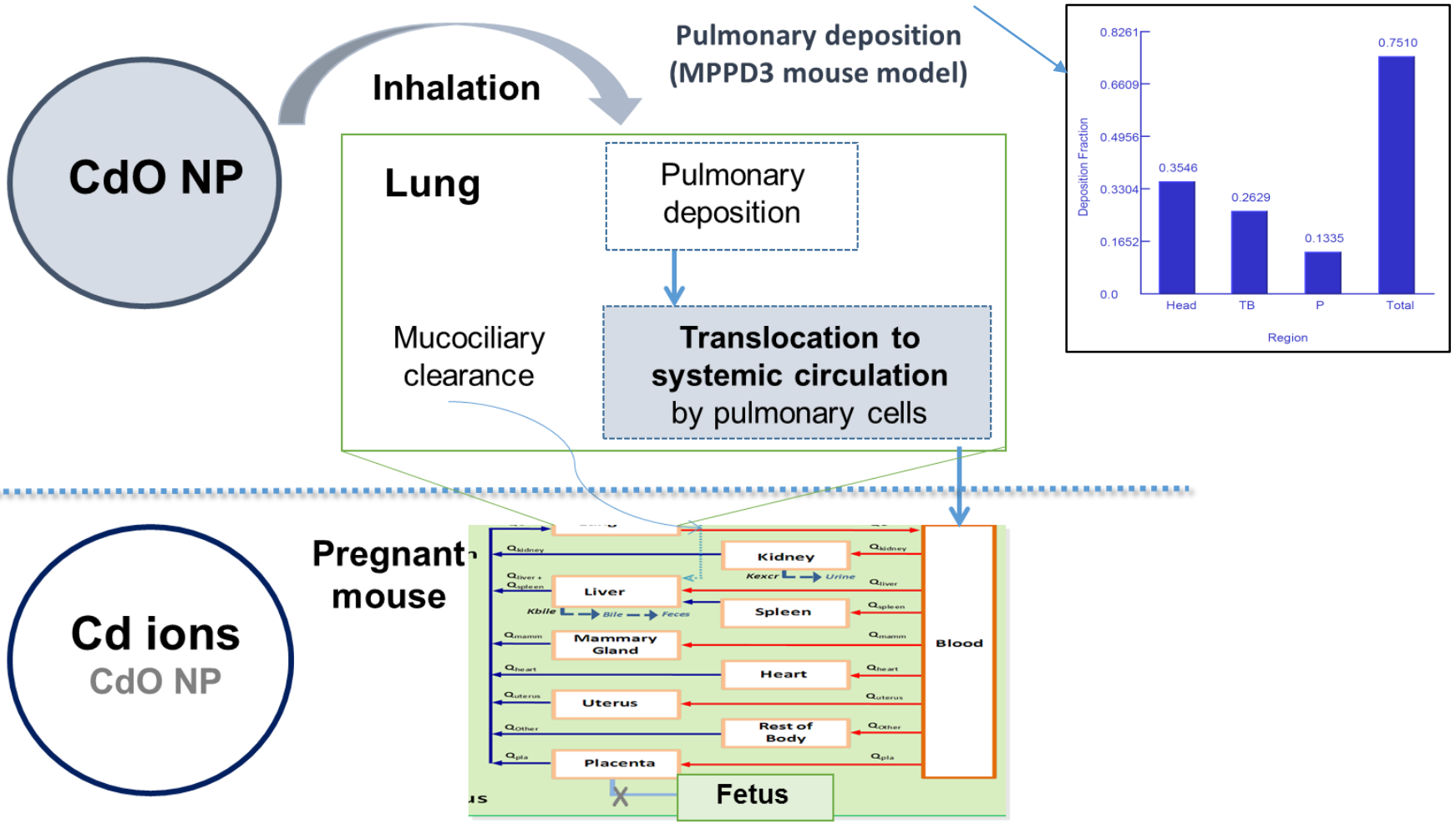


Figure 3 SPIO nanoparticle mass deposited in each region of the lung (top) and regional dosimetry (bottom panel) calculated with the Balb/c specific version of MPPD. Target cell doses are presented in units of mass per surface area of cells for all airways, and as pg/macrophage for the alveolar region only to correspond to experimental in vitro dose-response data. Given a density of 5.2 grams/cm^3, a picogram of SPIO particles would contain 154,015 primary 13 nm diameter particles with a surface area of 8.87×10^{-7} cm^2.

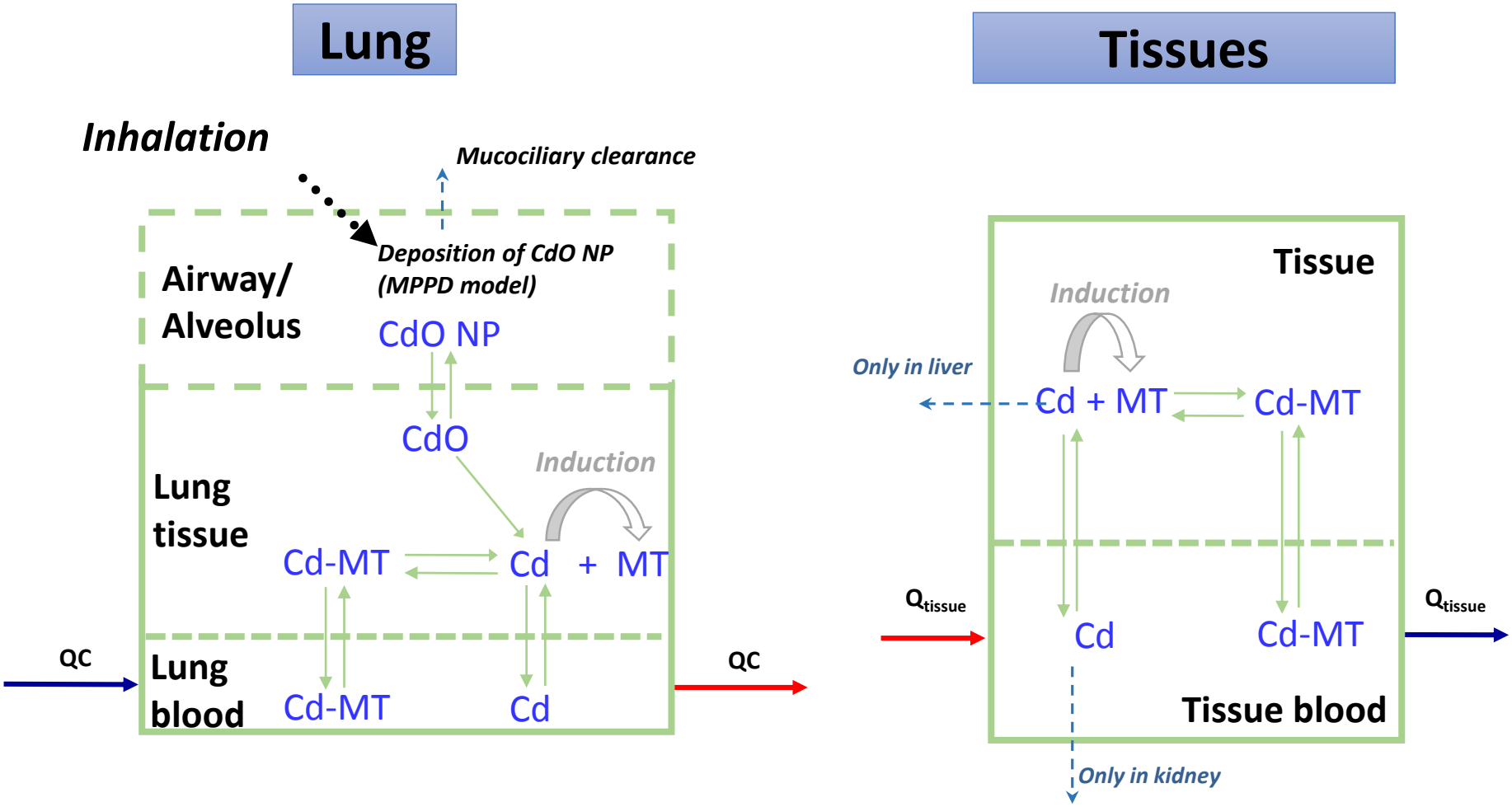
Teeguarden et al., 2014

Nanoparticle dosimetry and bioavailability at portals of entry



MPPD model in Asgharian et al., 2014; CdO PBPK model in Zhao et al., 2014

An example of nanoparticle lung dosimetry



Zhao et al., 2014

IVIVE of nanoparticle dose-response relationships

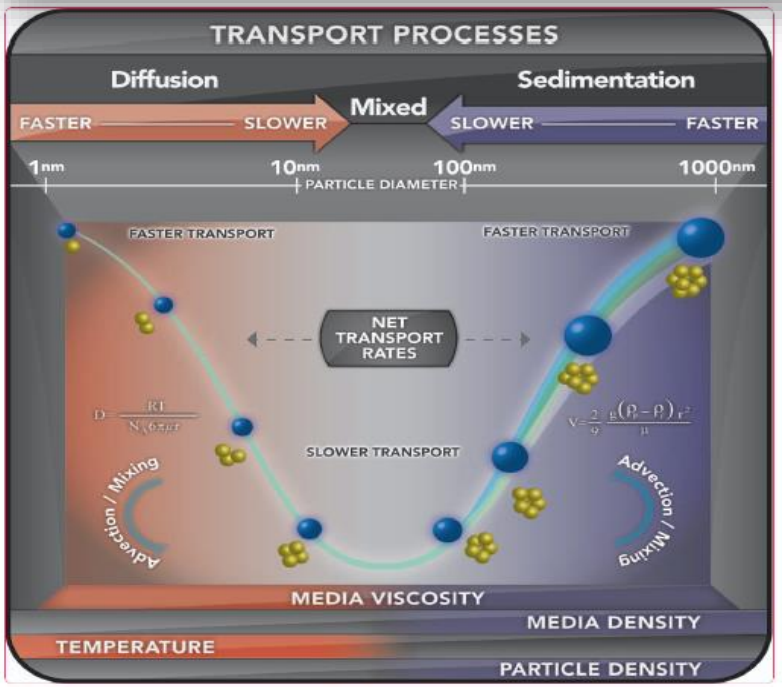
- Particokinetics – key considerations to improve in vitro-in vivo dose response correlations (Teeguarden et al., 2007)
- ISDD model – considerations of nanoparticle behaviors in an in vitro system are critical to determine the cellular dose (Hinderliter et al., 2010)
- In vitro to in vivo extrapolation should be based on the cellular exposure not nominal dose in the culture well and the target region cellular dose in vivo

TOXICOLOGICAL SCIENCES 95(2), 300–312 (2007)
doi:10.1093/toxsci/kfl165
Advance Access publication November 10, 2006

REVIEW

Particokinetics *In Vitro*: Dosimetry Considerations for *In Vitro* Nanoparticle Toxicity Assessments

Justin G. Teeguarden,[1] Paul M. Hinderliter, Galya Orr, Brian D. Thrall, and Joel G. Pounds



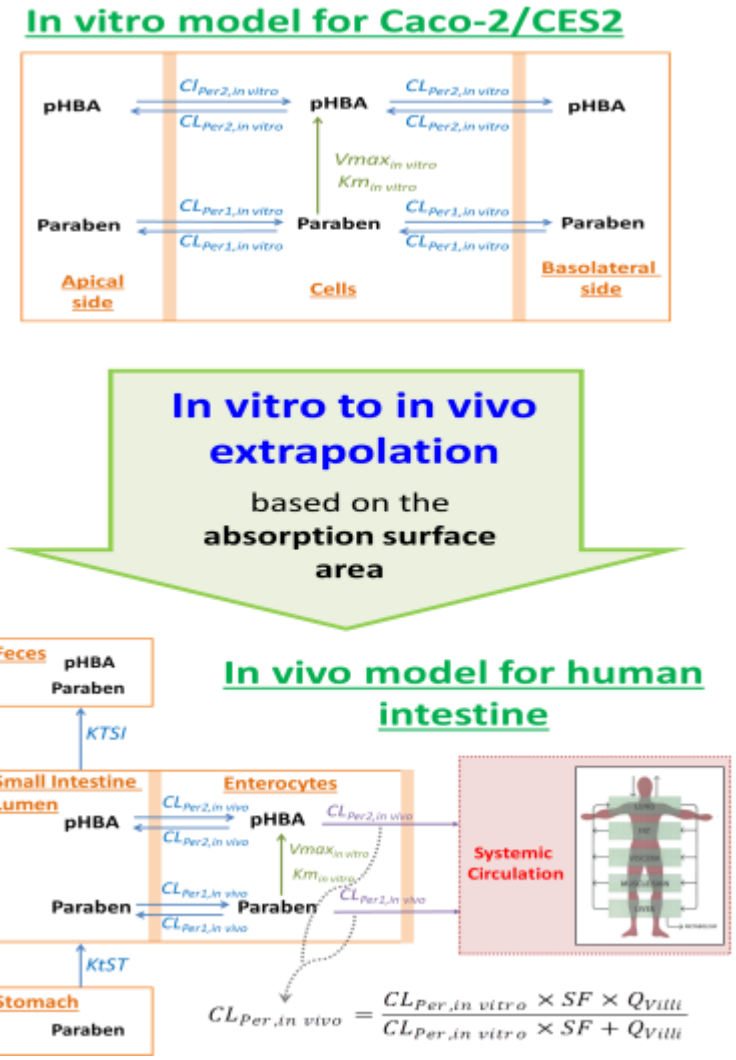
ISDD: A computational model of particle sedimentation, diffusion and target cell dosimetry for *in vitro* toxicity studies

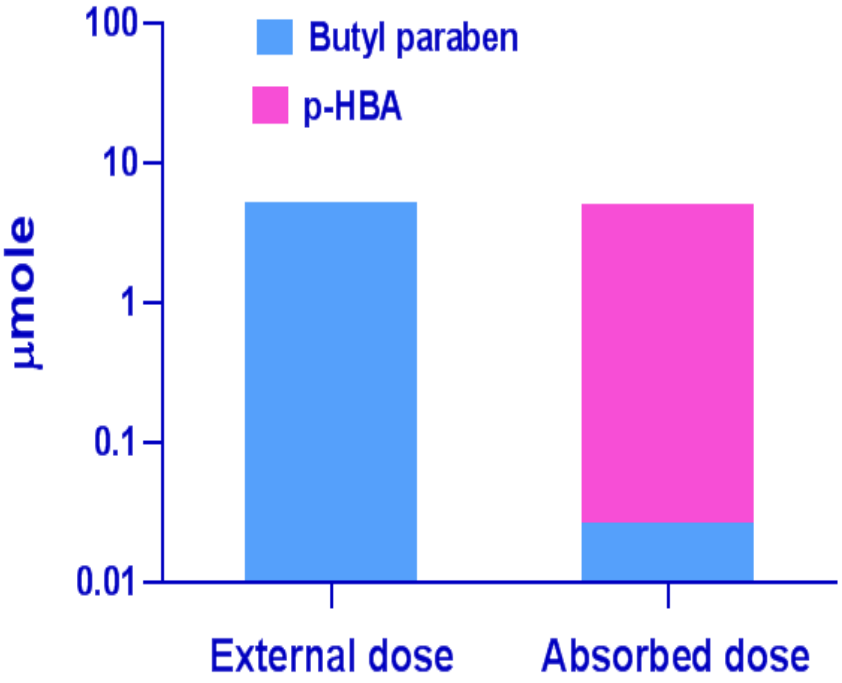
Hinderliter *et al.*

BioMed Central

Hinderliter et al. Particle and Fibre Toxicology 2010, 7:36
http://www.particleandfibretoxicology.com/content/7/1/36 (30 November 2010)

IVIVE of pre-systemic clearance and metabolism – an example of gut





Yoon et al., 2015

Benchmarking points for lung

- Physiologically relevant in vitro models of portals of entry
  - Have to be metabolically competent
- Strategies to incorporate regional differences in metabolism
  - Quantitative and qualitative
- Strategies for in vitro to in vivo extrapolation
  - Basis for extrapolation (e.g., surface area)
- Measurement or simulation of contact time at the sites of absorption along the portals of entry
  - Transit time
- Need to describe kinetics both in vitro and in vivo
  - Estimate metabolism and diffusion parameters
  - For IVIVE
- Uptake into systemic circulation
  - Mechanisms of uptake
  - Bioavailability

Alternative testing methods - key considerations

- Regional distributions in the airways - reasonably mature simulation approaches are available (MPPD, CFD)
- Regional metabolism (as MoA) – alternative (in vitro) approaches can improve currently available lung dosimetry simulation tools
- Bioavailability (metabolic clearance, transformation of material forms)- alternative (in vitro) approaches can improve currently available lung dosimetry simulation tools
- In vitro to in vivo extrapolation strategies are needed – should be considered when developing and optimizing in vitro tools

Discussion points

- How to address lung metabolism in alternative models?
- How to address region specific/cell type specific dosimetry using in vitro models?
- What extrapolation/integration strategies if we combine a number of in vitro models to get a complete picture of in vivo lung dosimetry?
- What specific challenges we expect in developing alternative testing strategies for nanoparticles?

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