



Session 4

Lung absorption

MoBi[®] and PK-Sim[®] interaction

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Acknowledgement & Information

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Pulmonary drug absorption and systemic exposure in human: Predictions using physiologically based biopharmaceutics modeling

Johanna Eriksson ^a, Helena Thörn ^b, Hans Lennernäs ^a, Erik Sjögren ^a

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Drug Absorption Parameters Obtained Using the Isolated Perfused Rat Lung Model Are Predictive of Rat In Vivo Lung Absorption.

Eriksson J, Sjögren E, Lennernäs H, Thörn H.

AAPS J. 2020 May 11;22(3):71. doi: 10.1208/s12248-020-00456-x.

PMID: 32394314 [Free PMC article.](#)

Pulmonary Dissolution of Poorly Soluble Compounds Studied in an ex Vivo Rat Lung Model.

Eriksson J, Thörn H, Sjögren E, Holmstén L, Rubin K, Lennernäs H.

Mol Pharm. 2019 Jul 1;16(7):3053-3064. doi: 10.1021/acs.molpharmaceut.9b00289. Epub 2019 Jun 11.

PMID: 31136181

Pulmonary absorption - estimation of effective pulmonary permeability and tissue retention of ten drugs using an ex vivo rat model and computational analysis.

Eriksson J, Sjögren E, Thörn H, Rubin K, Bäckman P, Lennernäs H.

Eur J Pharm Biopharm. 2018 Mar;124:1-12. doi: 10.1016/j.ejpb.2017.11.013. Epub 2017 Nov 27.

PMID: 29191716

Session 4

Lung absorption: MoBi[®] to PK-Sim[®]

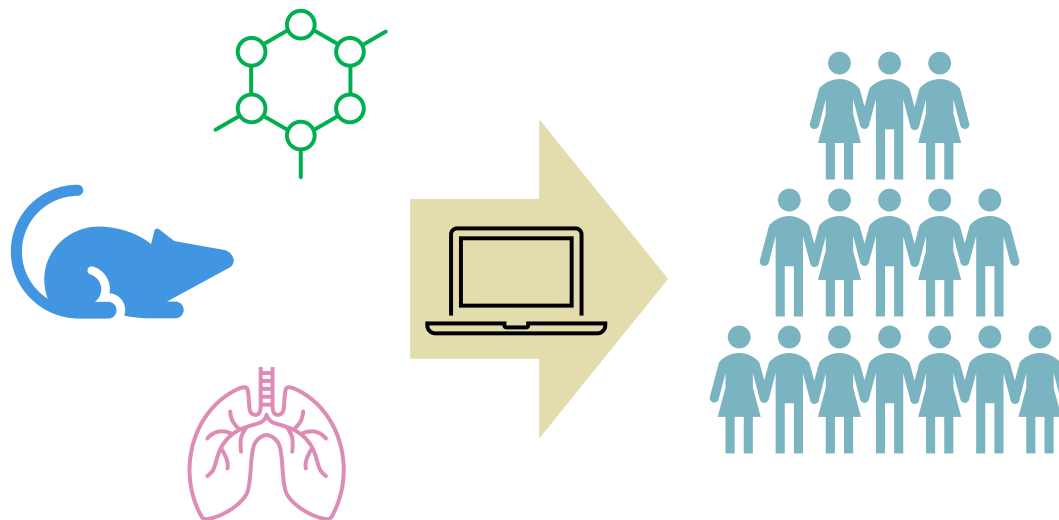
- Aim
- Background
 - Setting of investigation
 - Experimental model
 - Analysis of experimental data
- OSP - Model development
- Application (Showcase MoBi–PK-Sim interaction)

Aim

Show how experimental data and the approach of experimental data analysis can be used to further inform the development of a physiologically based translational model for pulmonary drug delivery.

Application of MoBi and PK-Sim to integrate experimental biopharmaceutics aspects to a PBPK framework.

Application of PK-Sim to evaluate population variability for a model developed in MoBi.



Increased leverage of generated pre-clinical ex-situ information for clinical predictions.

Background – Setting of showcase

Lung administration

- Rapid onset of action
- High concentration at site of target
- Lower risk for systemic adverse effects
- Non-invasive method
- Little first pass effects

Drug delivery complexities

- Narrow and “sensitive” formulation space
- Device and patient dependencies
- Systemic concentrations for assessments

Context of presented work

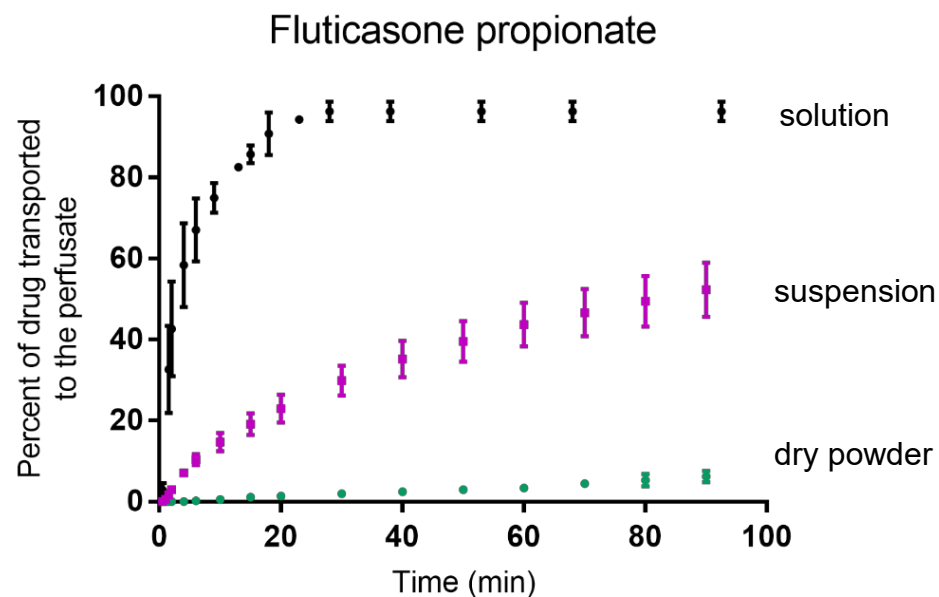
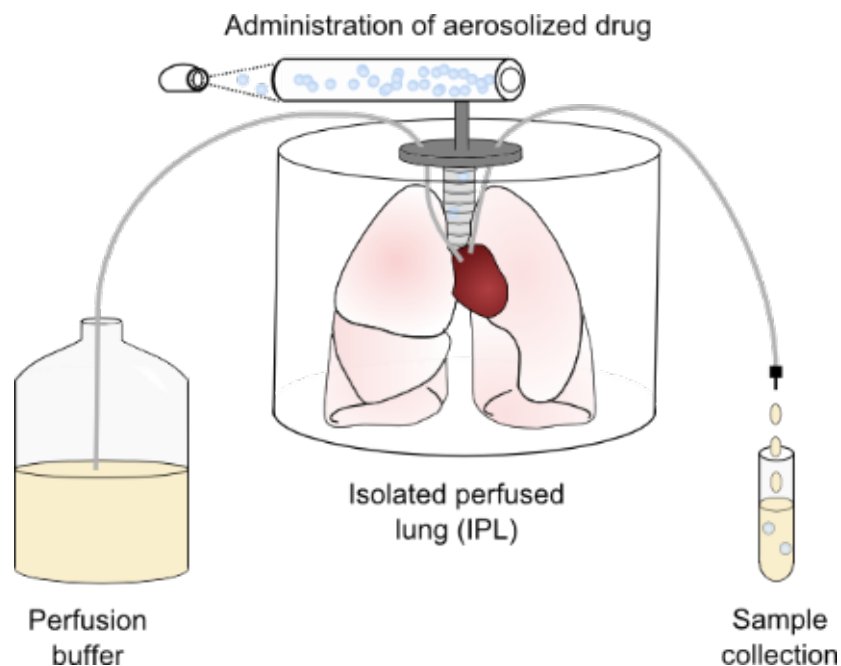
- Formulation evaluation and optimization
- Assessments based on in vitro and pre-clinical data

Background – Experimental model

Isolated Perfused Lung (IPL) experimental setup

1. Lungs and heart removed from rat
2. Pulmonary circulation perfused with a buffer
3. Lungs ventilated with negative pressure
4. Drug administered by tidal breathing

- Intact lung physiology
- No influence of systemic distribution
- Formulations as an aerosol
- Calculate dose



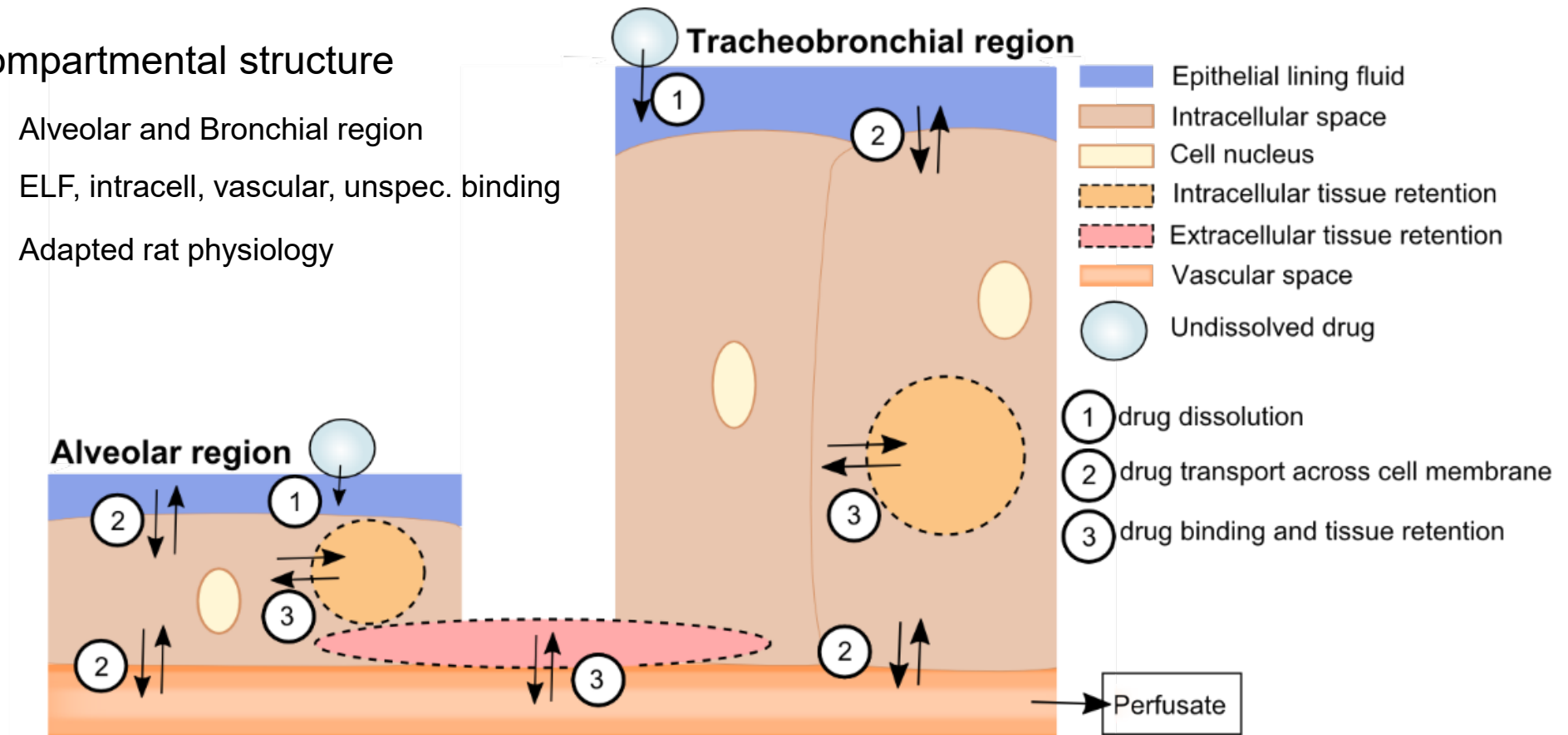
Background – Analysis of experimental data

Compartmental structure

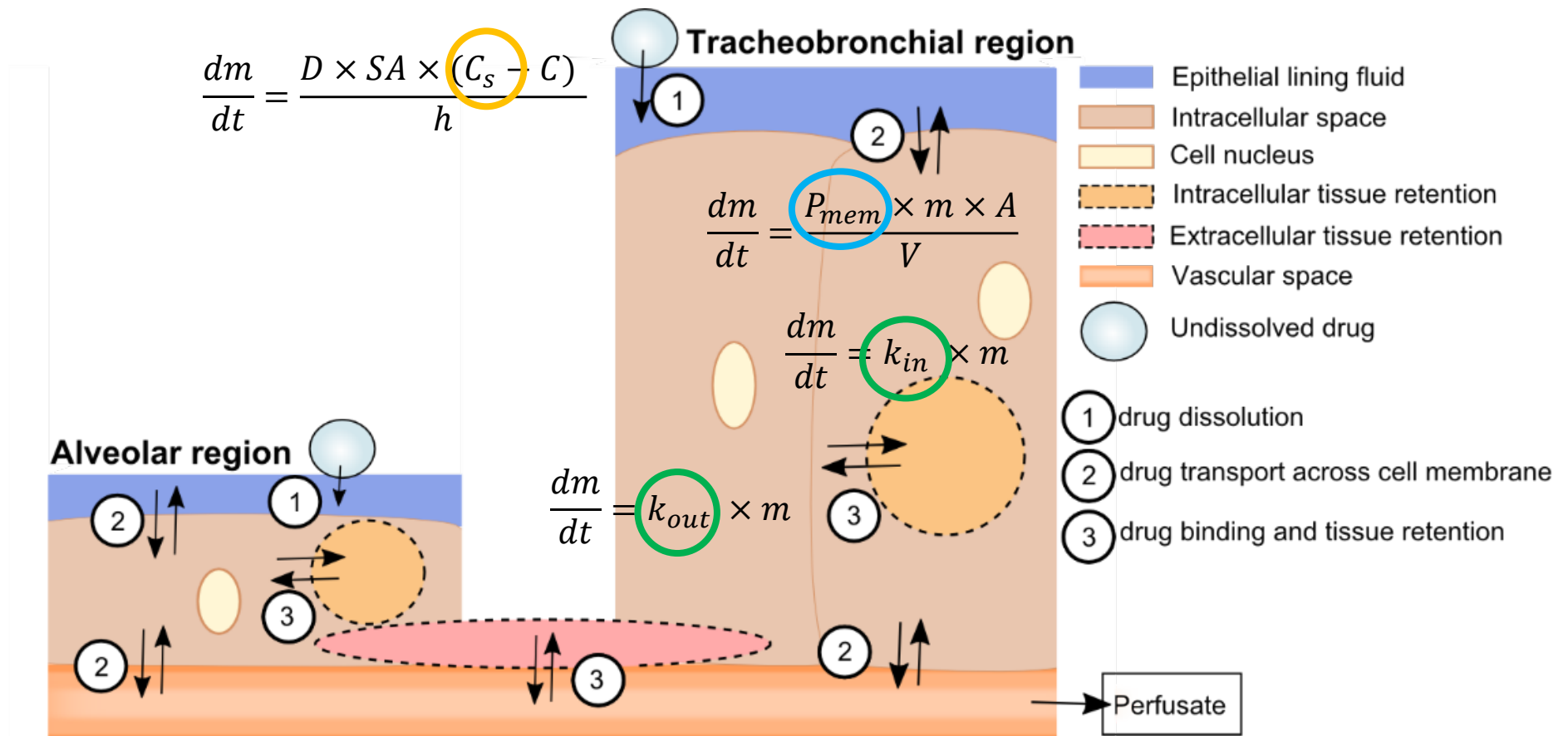
Alveolar and Bronchial region

ELF, intracell, vascular, unspec. binding

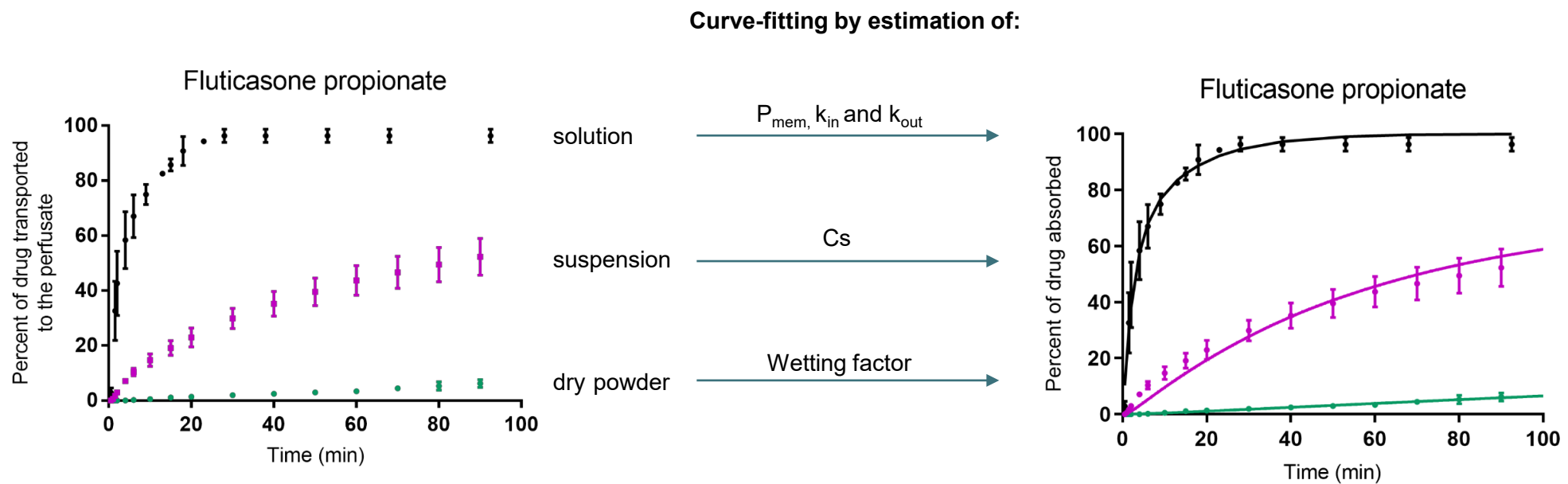
Adapted rat physiology



Background – Analysis of experimental data



Background – Analysis of experimental data



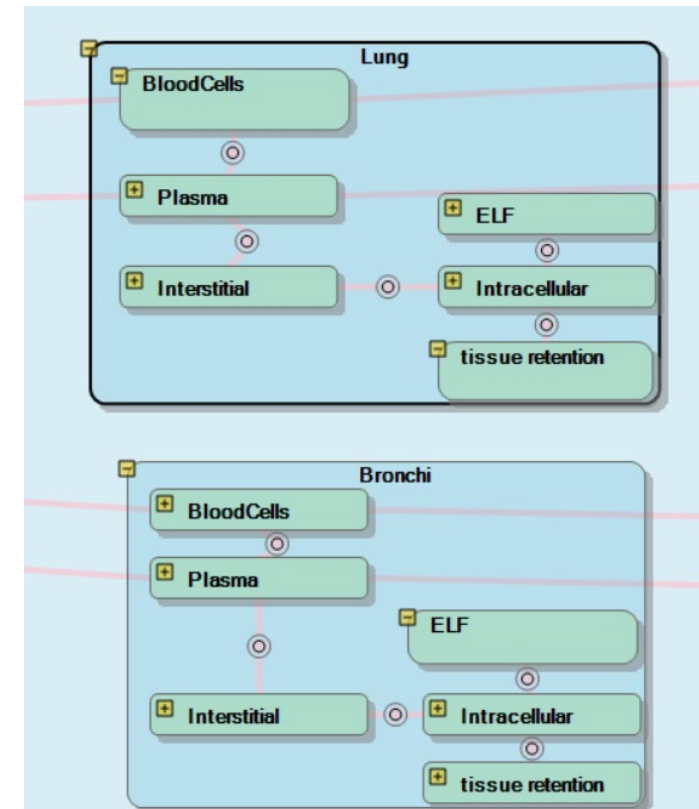
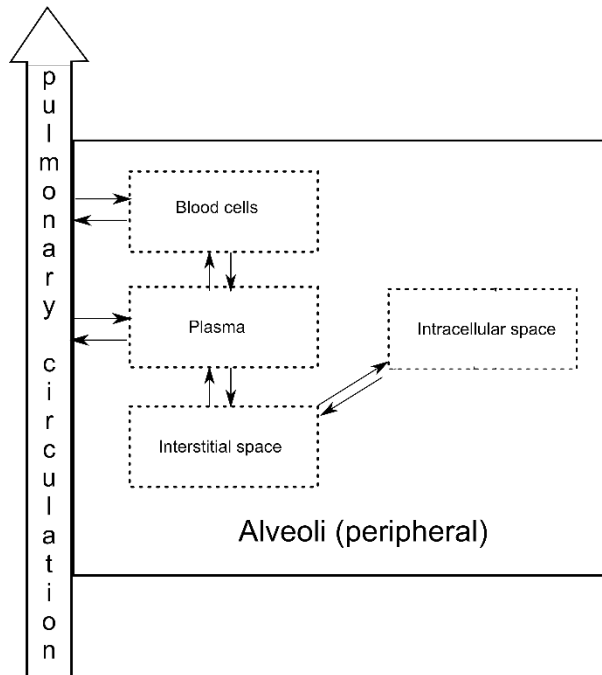
OSP - Model development

Model developed in MoBi using PK-Sim PBPK model structure as back bone

Addition of IPL analysis structure

Human physiology

Addition of extra processes (particle distribution, MCC, trachea etc)



OSP - Model development

- Particle size distribution
 - Input: Median and GSD → output: particle size distribution in 8 bins assuming log-normal distribution
 - Manual input also possible
- Particle dissolution: $\frac{dm}{dt} = \frac{D \times S A_i(t) \times (C_s - C)}{h}$
- Deposition pattern – fraction of dose in bronchial, alveolar and extrathoracic compartment (stomach)
- Mucociliary clearance of undissolved drug from bronchial compartment to stomach:
 - First order process ($k_{mcc} = 0.58 \text{ h}^{-1}$)

OSP - Model evaluation

The performance of the translational approach (input and model) evaluated towards clinical data after administration of solutions, suspensions and particulates.



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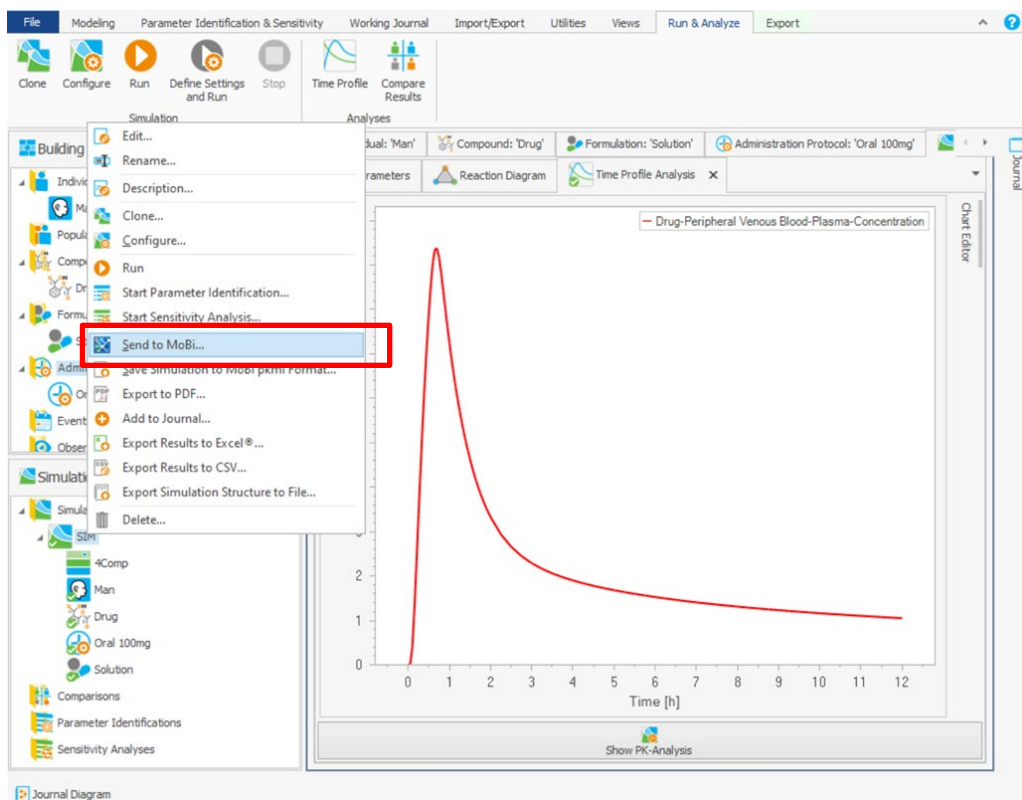
Showcase MoBi – PK-Sim interaction

Showcases

- MoBi ↔ PK-Sim
- Applications
 - Population dependencies
 - Permeability change (*smokers*)
 - Deposition change (*asthmatics*)
 - Drug dependencies
 - Solubility
 - Particle size
 - Local lung vs systemic concentrations for the populations

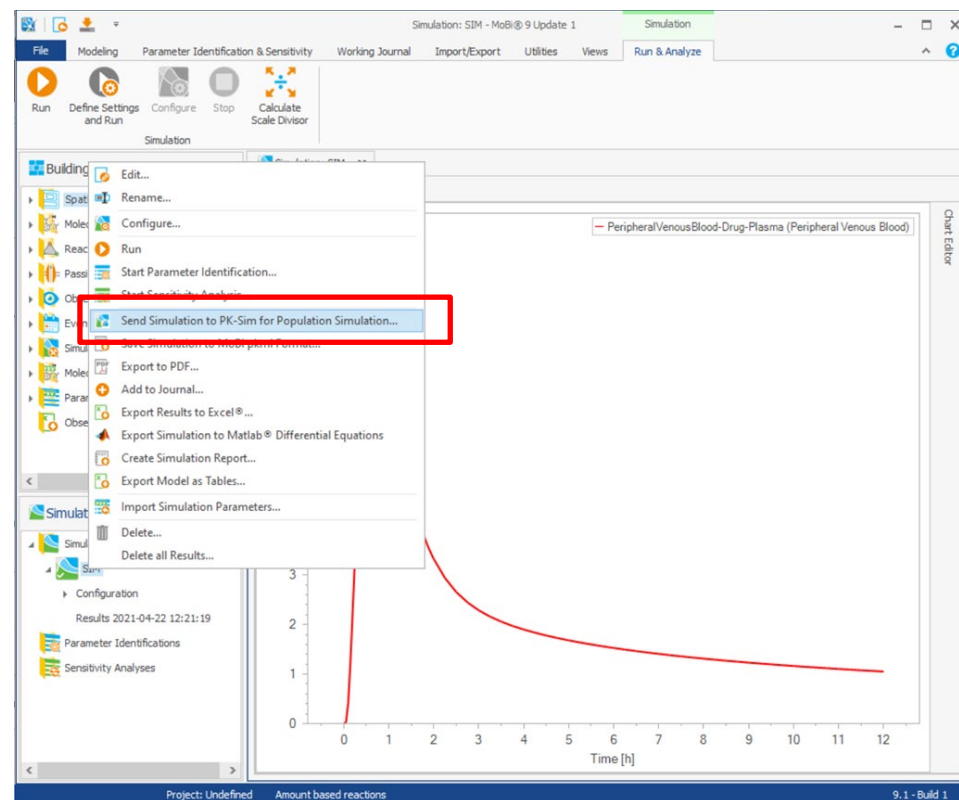
MoBi ↔ PK-Sim

PK-Sim → MoBi



Right click simulation
Send to MoBi...

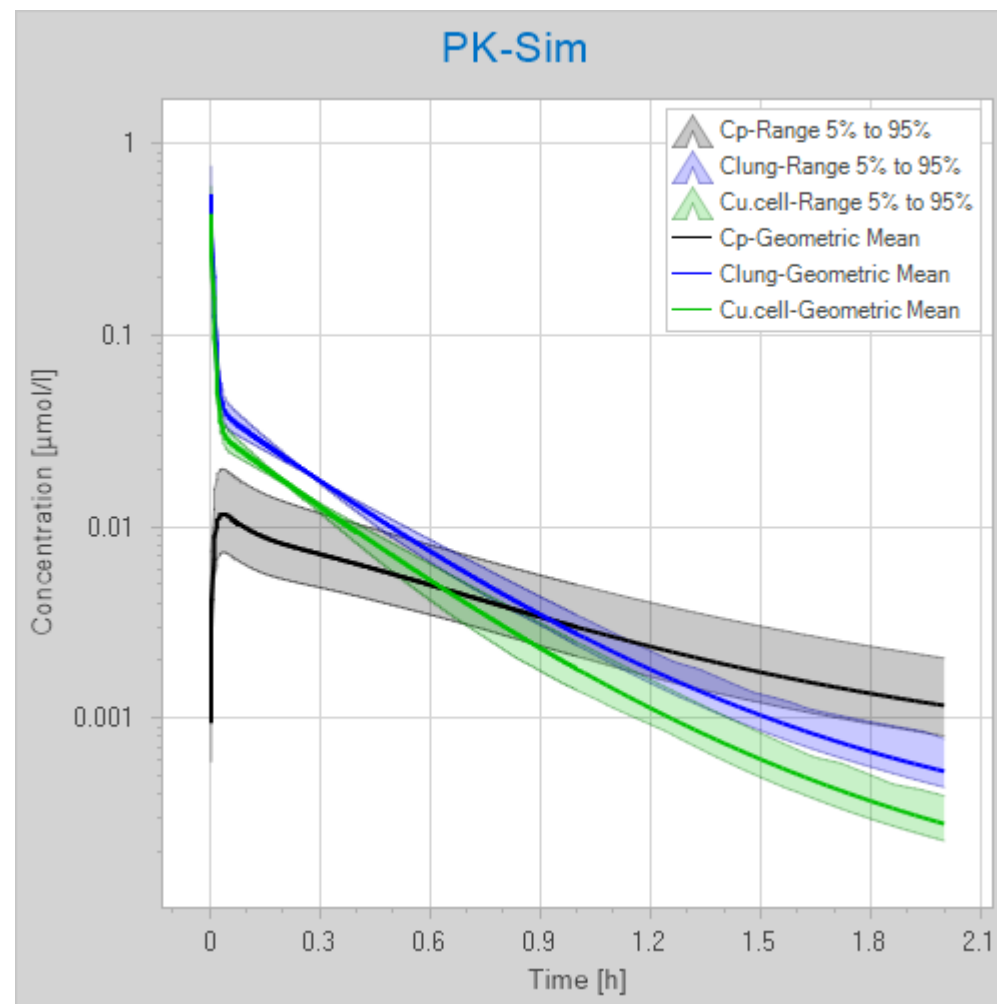
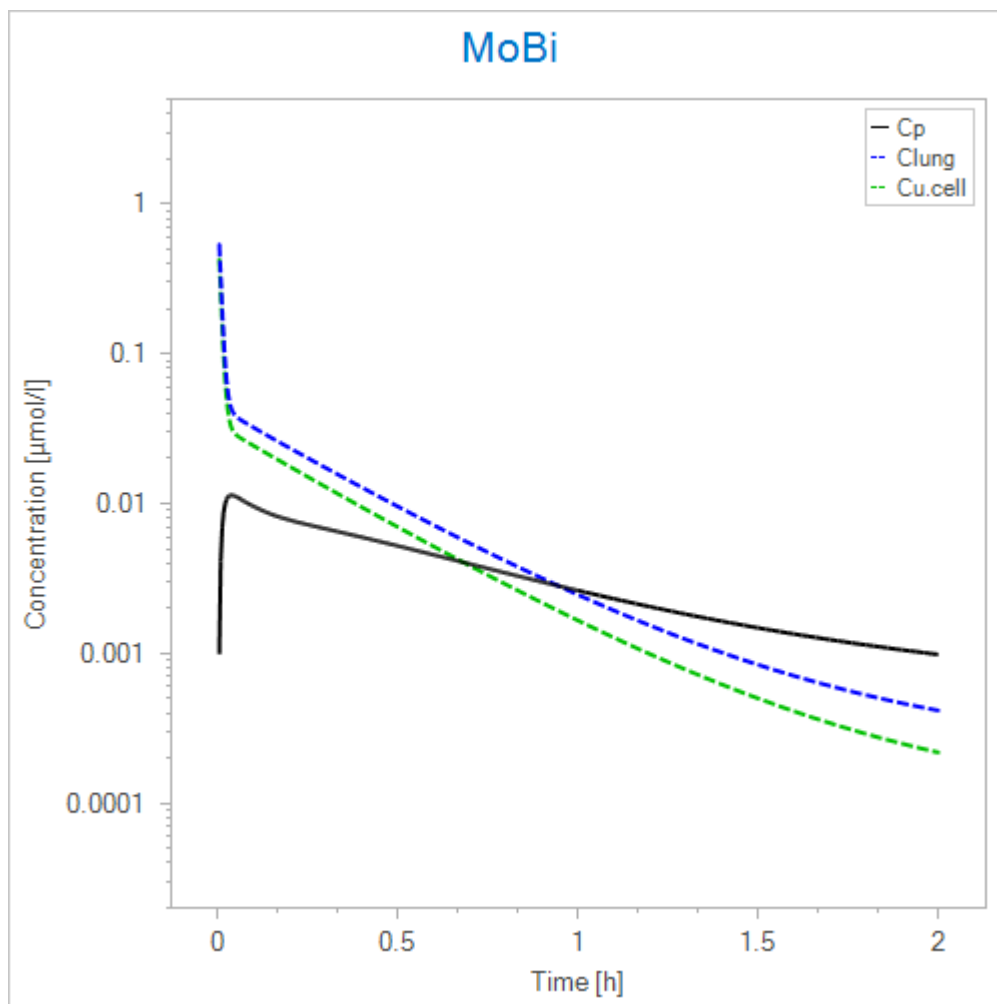
MoBi → PK-Sim



Right click simulation
Send simulation to PK-Sim for Population Simulation...

MoBi \leftrightarrow PK-Sim

MoBi \rightarrow PK-Sim

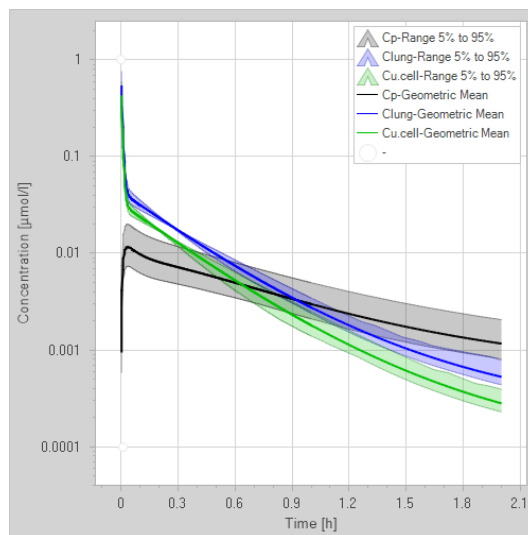


Application

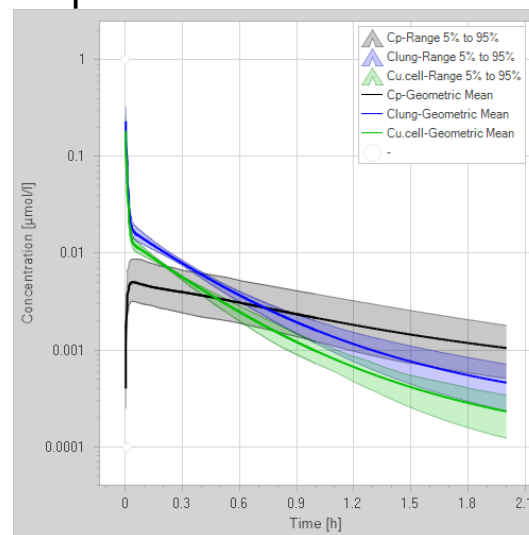
ParticleSize: 1- 5 μm

Solubility = 100 $\mu\text{g/ml}$

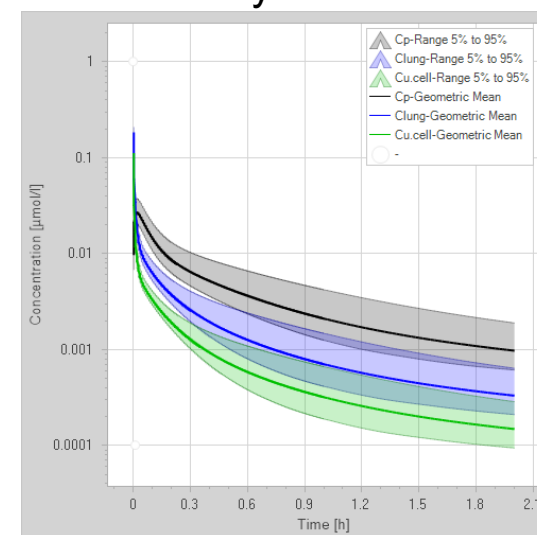
Normal



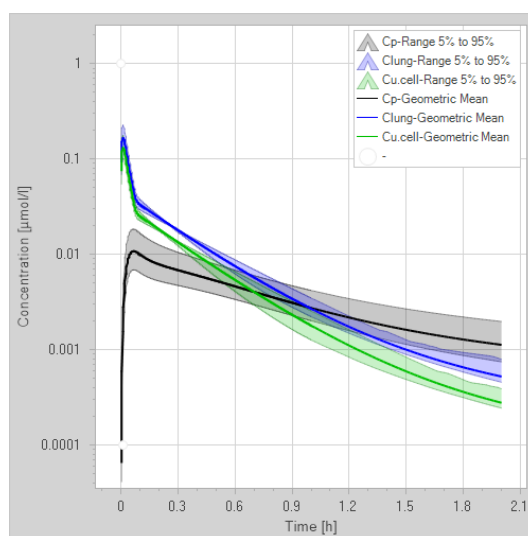
Deposition



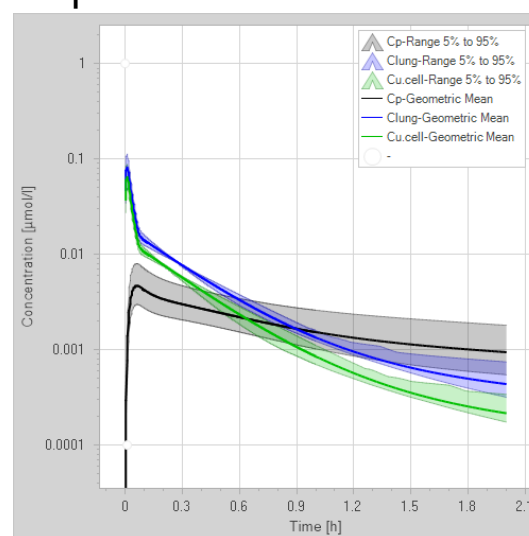
Permeability



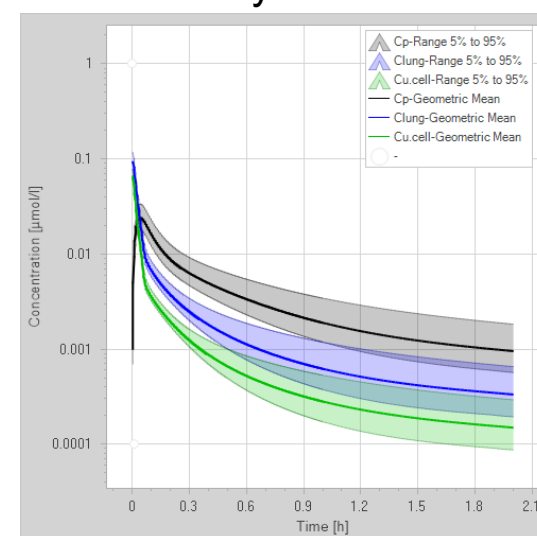
Normal



Deposition



Permeability

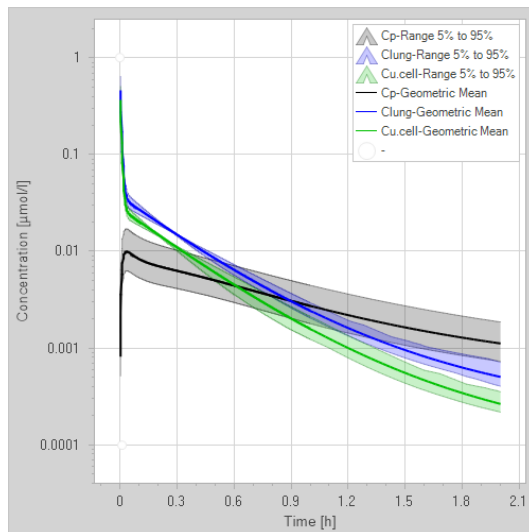


Application

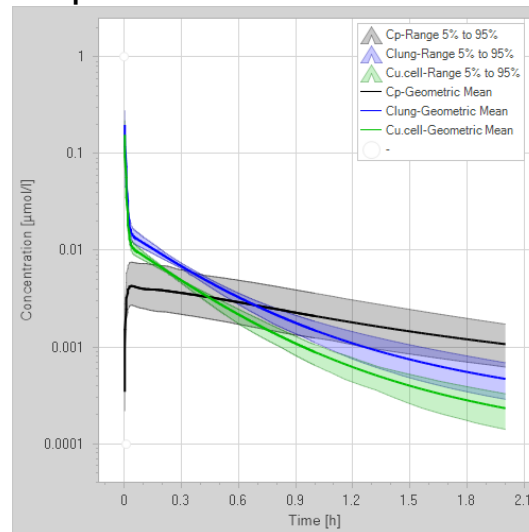
ParticleSize: 2 -10 μm
No change in deposition

Solubility = 100 $\mu\text{g/ml}$

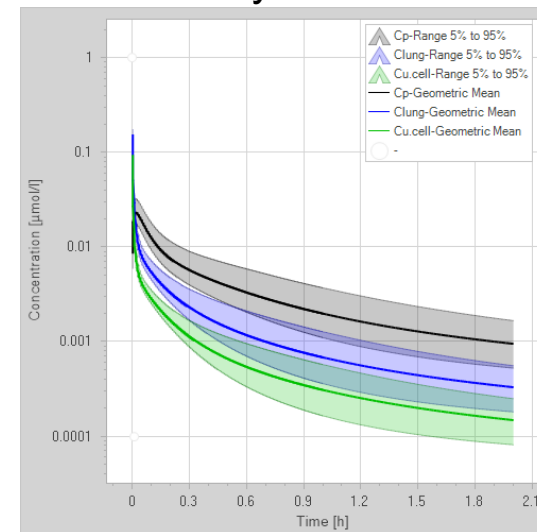
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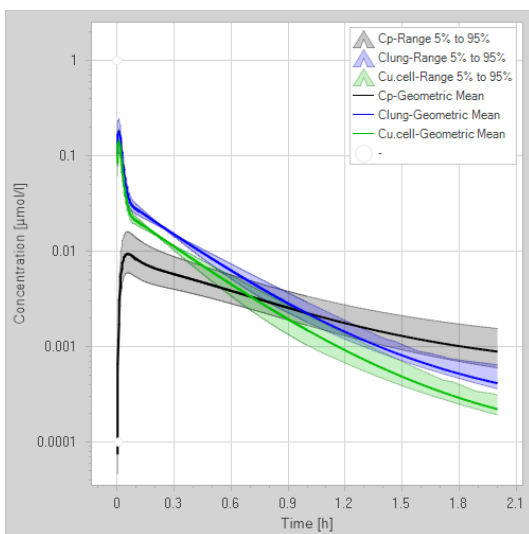
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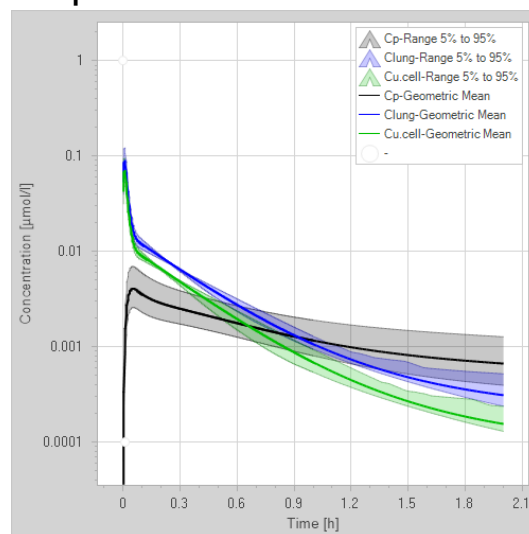
Permeability



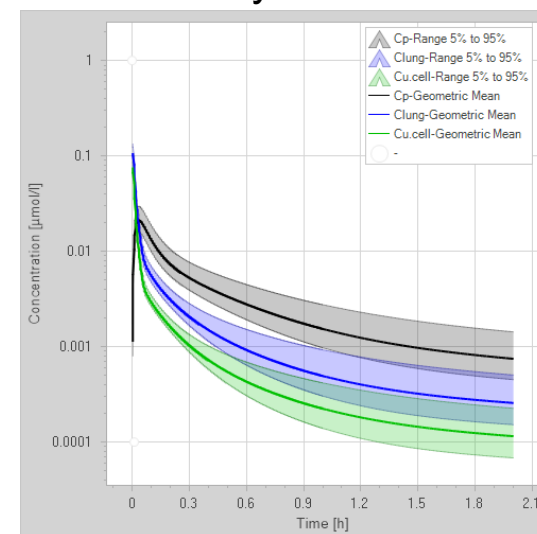
Normal



Deposition



Permeability



Summary:

- Clinical predictions performed via direct physiologically based translation of pre-clinical ex-situ information.
- Integration of data analysis model structure reduces risks of translational errors at use of experimental data.
- Applying the OSP population database to perform virtual population simulations for assessments of pulmonary drug delivery.

