Development of a Mechanistic Model for the PBP/TK Based Prediction of Tissue Exposure Following Inhalation Exposure

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Objectives

The Simcyp physiologically based pharmacokinetic/toxicokinetic (PBP/TK) simulator already contains a multi-compartment, physiologically based lung model for predicting the distribution of compounds within the lung tissue driven from the circulating plasma concentration (Figure 1). Here we describe the expansion of this model to incorporate a mechanistic model of inhalation to allow the prediction of systemic and target organ concentrations following exposure via the inhalation route. The model incorporates respiratory rate, tidal volume, and accounts for the differential deposition of particles along the airway and their solubilisation in the epithelial lining fluid (ELF). From the ELF compound can distribute into the adjacent tissue mass and then into the circulating blood. In addition, the model also incorporates mucocilliary clearance of compound that is escalated back through the airways and ultimately swallowed and delivered to the GI tract.

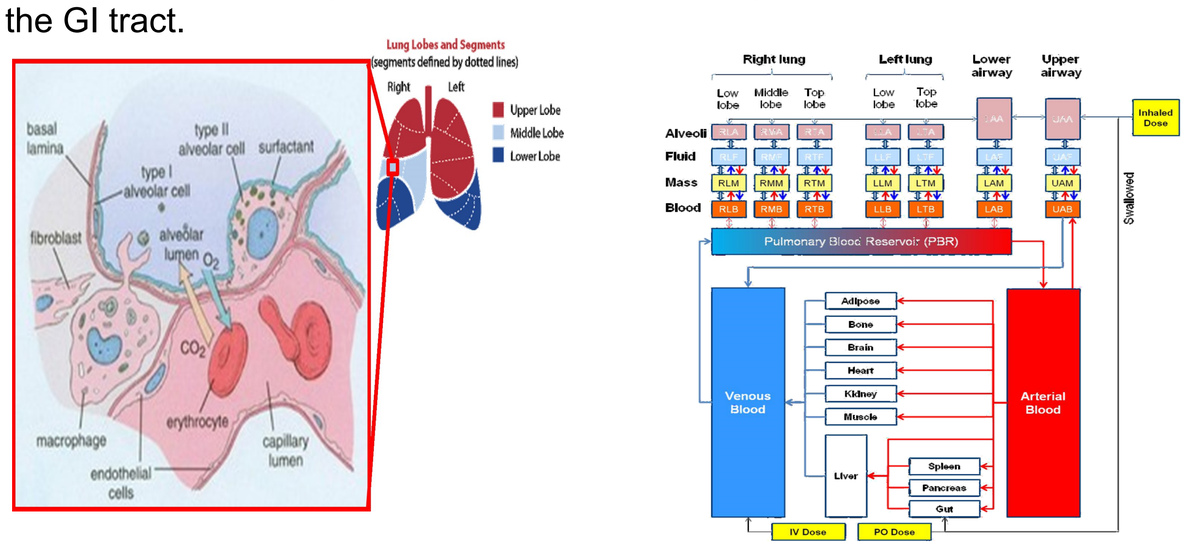


Figure 1 Left panel a representation of the blood air barrier. Right panel the structure of the multi-compartment lung model within the Simcyp PBPK model (Lu et al, CPT-PSP, 2015, 4, 605)

Addition of inhalation exposure route to the lung PBPK model

In developing the PBPK model following inhalation exposure the following factors were considered in the model

- Inhalation exposure could be to either a vapour or an inhalation of particles (Monodisperse or Polydisperse) with a defined size distribution
- Inhalation can be given either through oral or nasal pathway
- A portion of the inhaled drug/chemical could be swallowed and enter the body through the oral route.
- Deposition of particles will be affected by inhalation flow rate modelled using the approaches outlined in the ICRP 66 model
- Inhaled, deposited particles will undergo dissolution and dissolved drug can enter the body through the lung tissue
- Undissolved particles can be cleared via the mucociliary escalator.

The structure of the prototype inhalation model is shown below (figure 2)

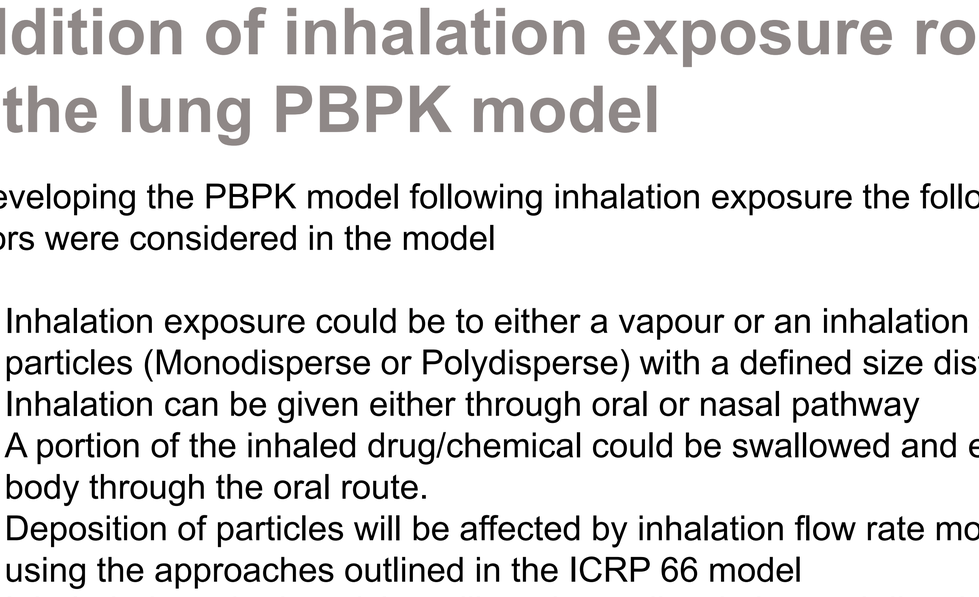


Figure 2 Structure of the prototype inhalation model developed within the EUTOXRISK project. The alveolar regions correspond to generations 16-26, the lower airway corresponds to generation 10-15 and the upper airways correspond to generations 1-8 in the bronchial tree.

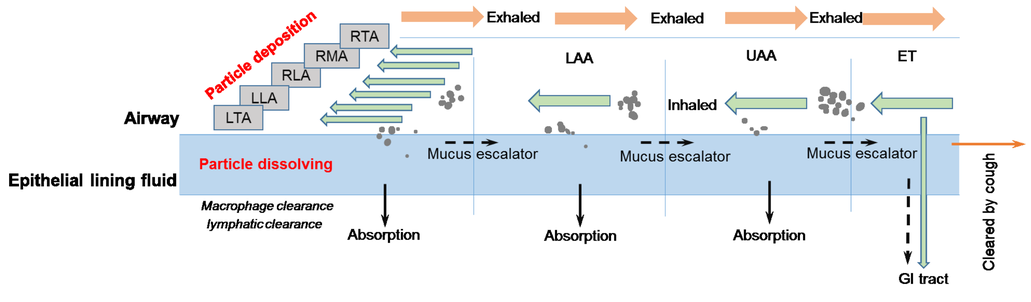


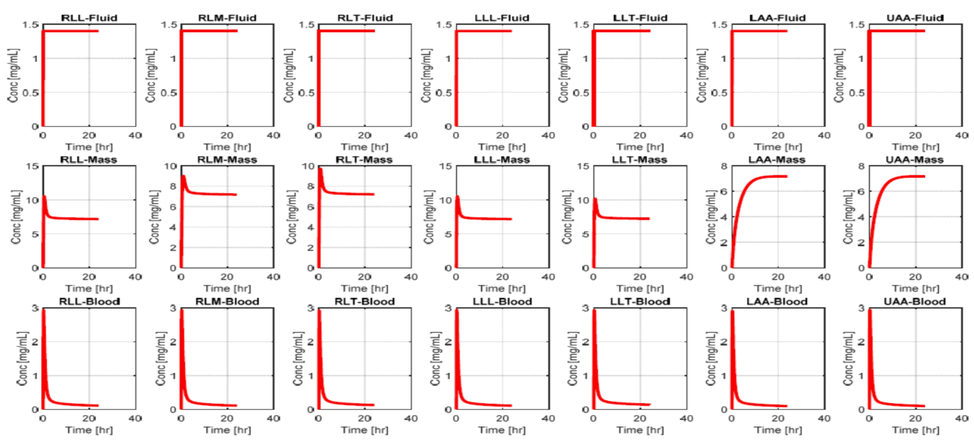
Figure 3 The mechanisms of particle deposition and clearance considered within the inhalation exposure model.

Assumptions of the prototype model

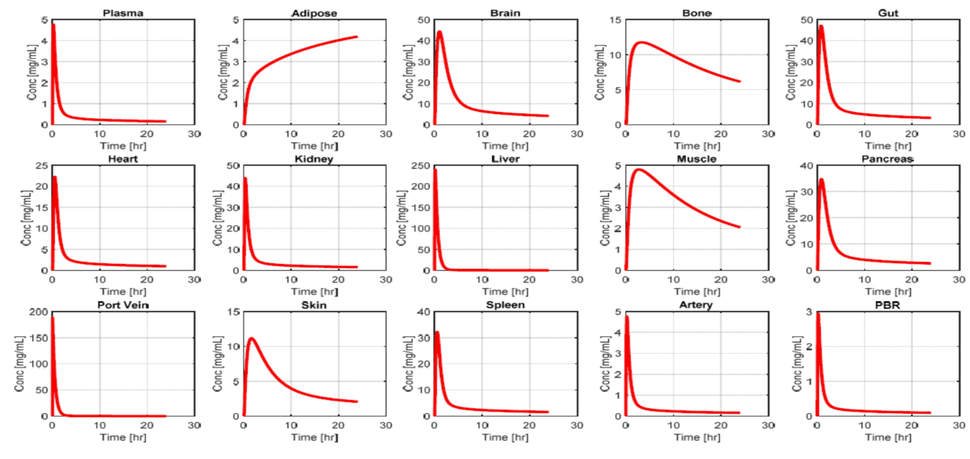
1. No mass lost in the inhalation phase. It has been considered in the deposition model, but set to 0 here.
2. Mucus layer (gel) and Aqueous layer (sol) were combined as one epithelial lining fluid, i.e. there are no relative movement/drug dissolution rate suggesting instantaneous equilibrium in these two layers.
3. Epithelial lining fluid volume was set to constant the same as current lung model. Therefore dynamic change of fluid volume was ignored, i.e. there is no secretion or fluid volume change due to absorption or the secretion-absorption-lost of fluid was assumed to reach steady-state
4. Mucociliary clearance was estimated from ICRP 66 clearance model, which suggests a partition mechanism for particle clearance (both slow & fast). Here a weighted mean clearance was adopted.
5. The macrophage clearance and clearance to local lymphatic system were ignored as they are very slow process and won't have significant impact on the absorption of soluble drug.
6. The portion cleared by cough was set to zero
7. Aerodynamic diameter was assumed to be the same as physical geometric diameter (spherical aerosol particle).
8. Local drug degradation was set to zero

Results

(A)



(B)



(C)

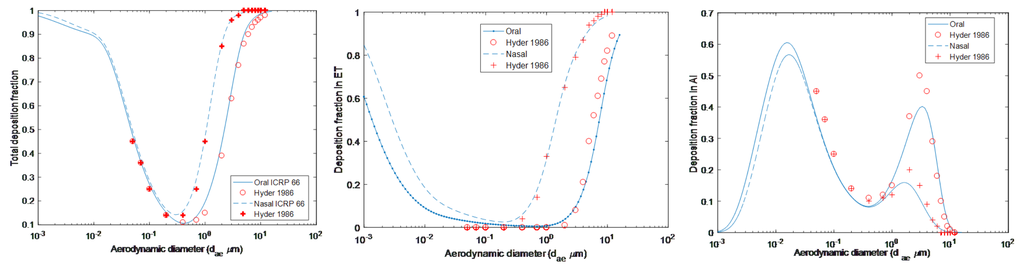


Figure 4 Predicted concentrations in (A) the different lung compartments and (B) the different tissues within the body following inhalation exposure to Rifampicin (used as a model test compound) with particle radius 2.5μm (nasal inhalation). (C) The effect of particle size on particle deposition within the lung in a Male subject with VT = 1000 mL, Q = 750 mL/s. Left panel is the total deposition fraction, middle panel shows deposition in Extrathoracic (ET) region, while right panel shows deposition in the Alveolar interstitial (AI) region . '+' represents observed oral data and 'o' is for nasal data (Heyder 1986). Blue lines are model predictions (solid- oral inhalation, and dot- nasal inhalation).

Conclusions

A prototype model for lung inhalation has been developed. Verification and refinement of the model so that it can be used in CS8 is ongoing.

Heyder et al. Journal of Aerosol Science, 17, 811–825

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