Inhalation model structure evaluation

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Objective

- Demonstrate that the inhalation model can capture the observed behaviour of molecules with varying solubilities
  - Salbutamol: 14,100 mg/L
  - Ciprofloxacin: 38,400 mg/L
  - Budesonide: 10.7 mg/L
  - Fluticasone propionate: <0.15 mg/L
- Main sources of uncertainty:
  - Deposition
  - Solubility in epithelial lining fluid

Model structure

- Inhalation model structure is described in user guide
- Inhalation model is connected to two-compartment model to describe systemic disposition and absorption
- Deposition is either:
  - Calculated using empirical deposition equations (Cheng, 2003; Boger & Wigström, 2018; Yu & Diu, 1982) OR
  - Informed by additional information

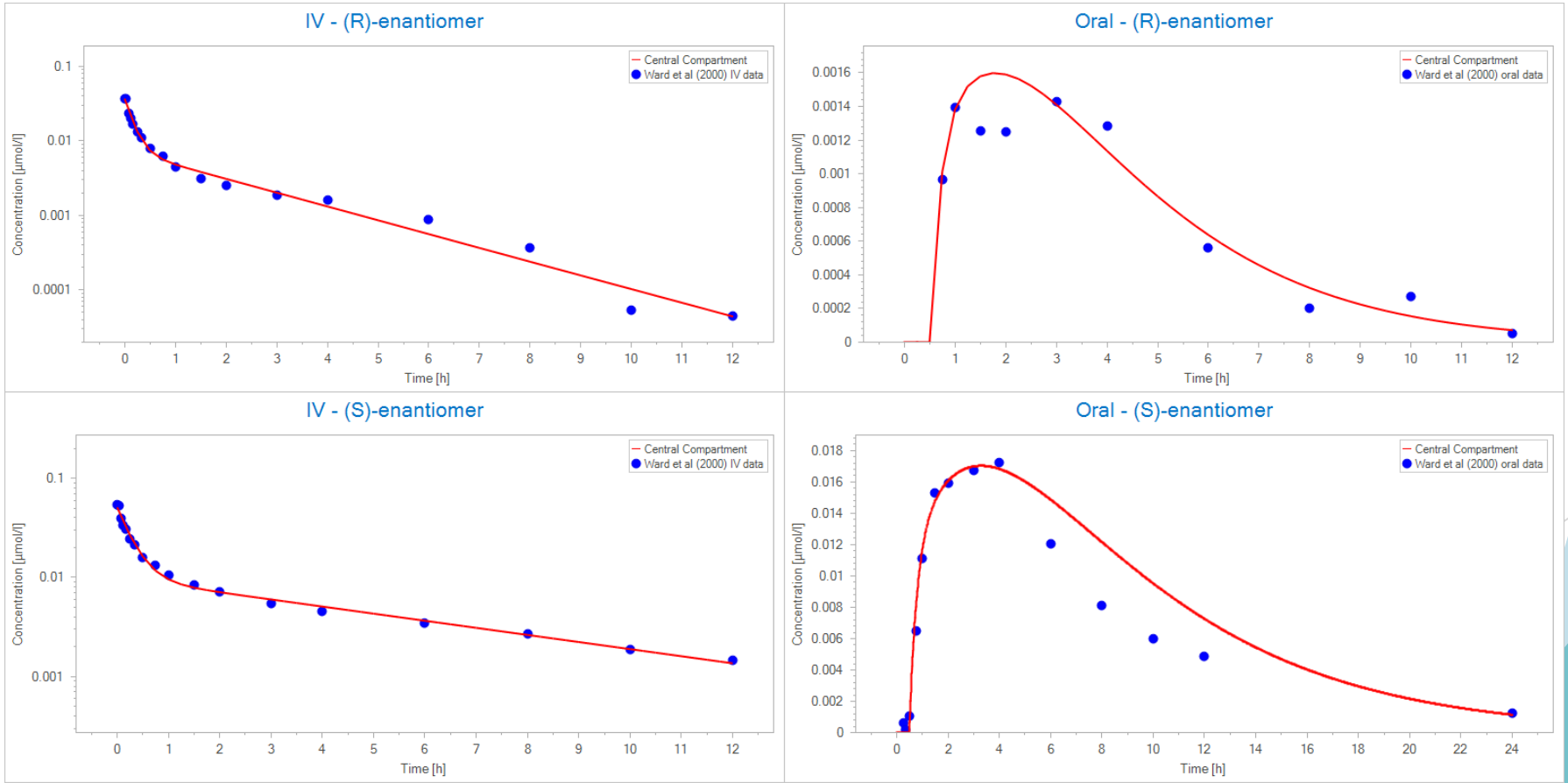
Minimum inhalation model input to get systemic PK

- Physicochemical properties of drug (MW, lipophilicity, fu, solubility)
- Particle size distribution (mean, SD)
- Dose
- Loss due to device (incorporated within $F_{inh,charcoal}$ or F_{inh})

- IV and oral model for systemic disposition and oral absorption
  - Clearance, volume
  - Oral bioavailability (F_{oral}), Time lag of absorption, Absorption rate constant

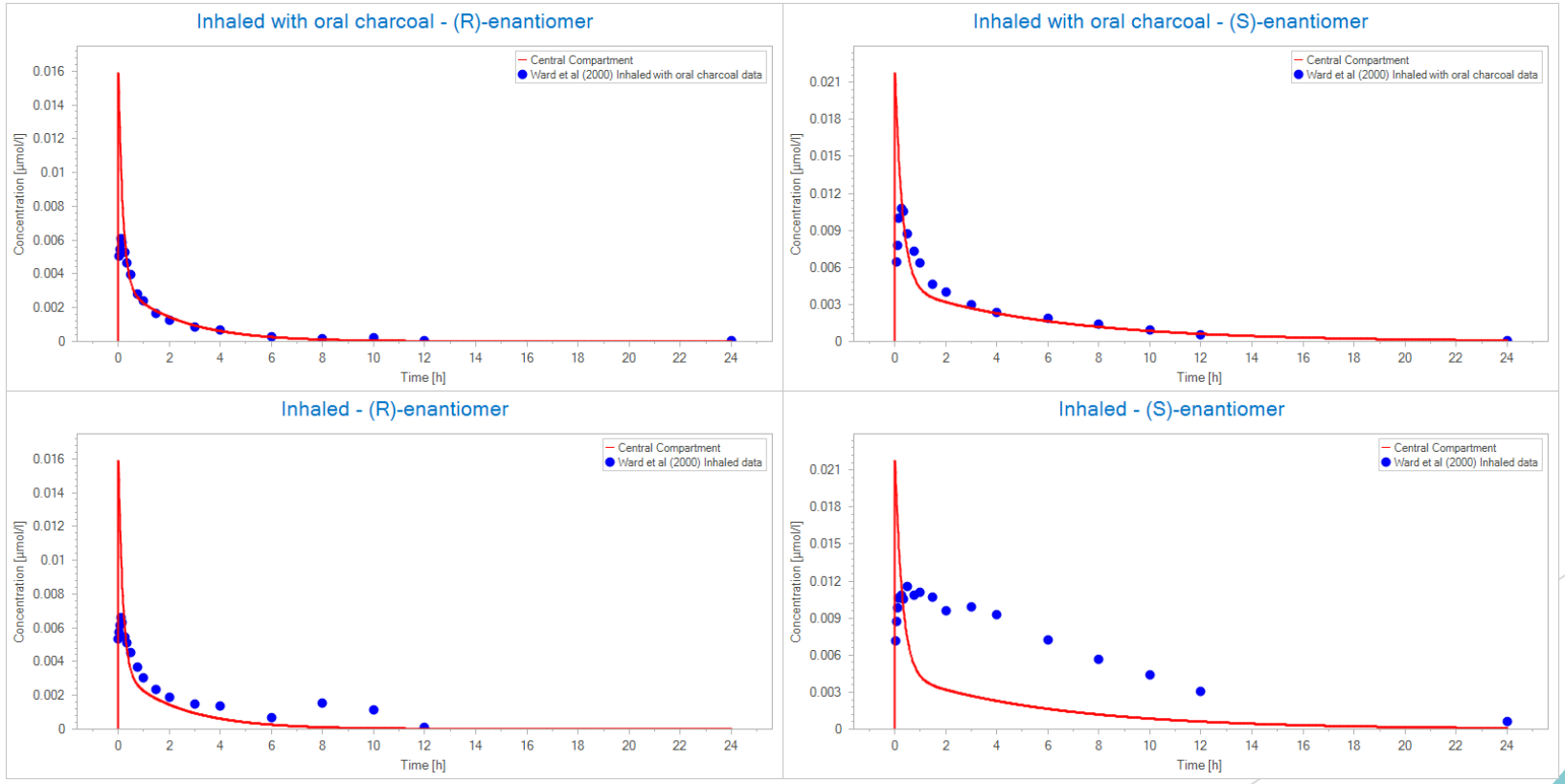
1) Salbutamol – Solubility: 14100 mg/L

- IV and oral models fit to data



1) Salbutamol

- Inhaled with and without oral charcoal simulations using empirical equations
- Cmax is over-estimated and missing effect of extrathoracic proportion for (S) in inhaled simulation

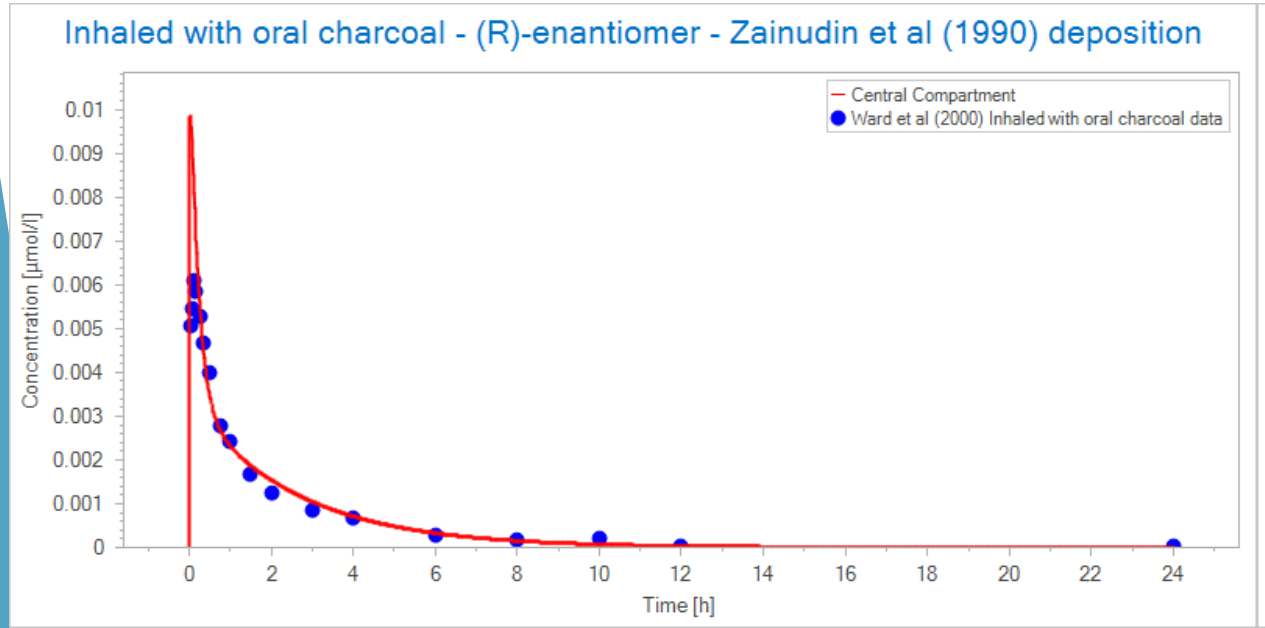


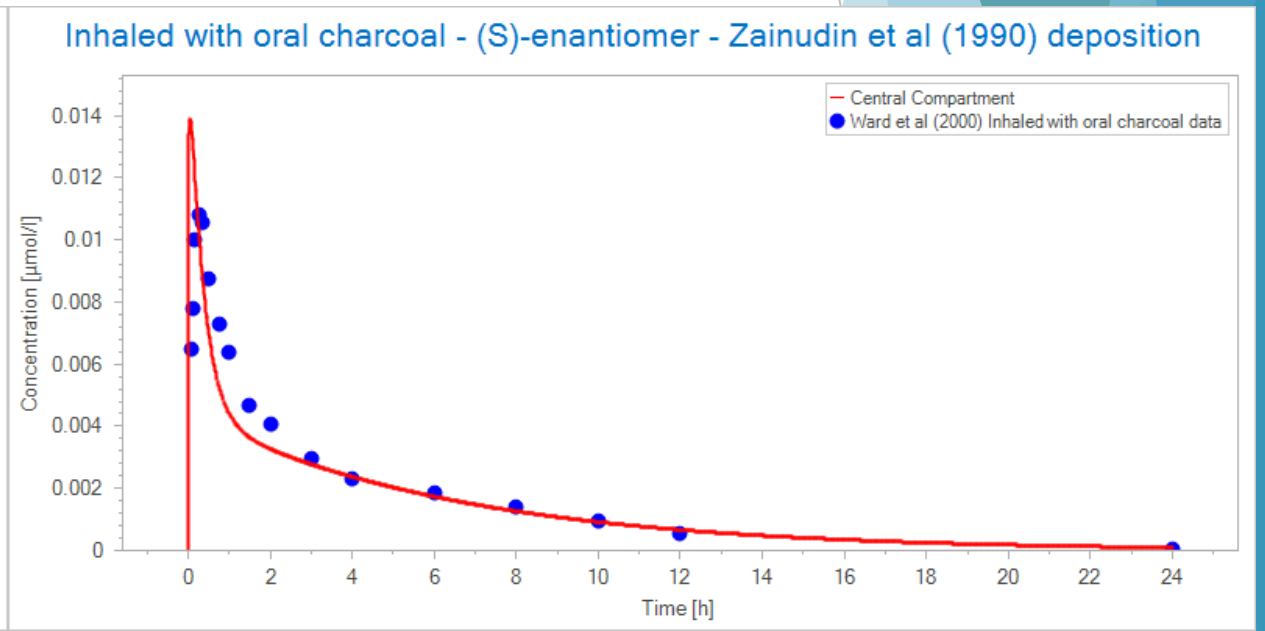
1) Salbutamol

- Inhaled with oral charcoal - additional deposition information (Zainudin et al, 1990; Ward et al, 2000)

	Empirical equations	Zainudin et al (1990)
Tracheobronchial	1.1% (R) / 1.1% (S)	16.4% (R) / 15.7% (S)
Alveolar	18.4% (R) / 17.6% (S)	3.1% (R) / 3% (S)
Total	19.5% (R) / 18.7% (S)	19.5% (R) / 18.7% (S)

- Improved Cmax prediction due to shift in drug from alveolar region to tracheobronchial region



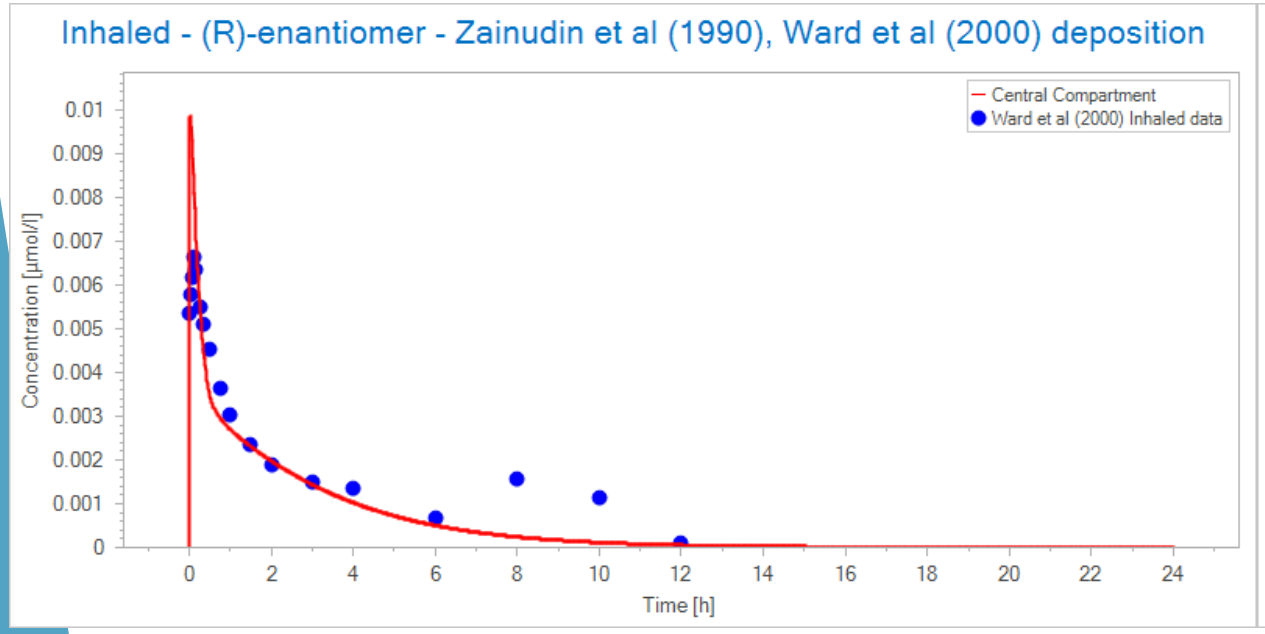


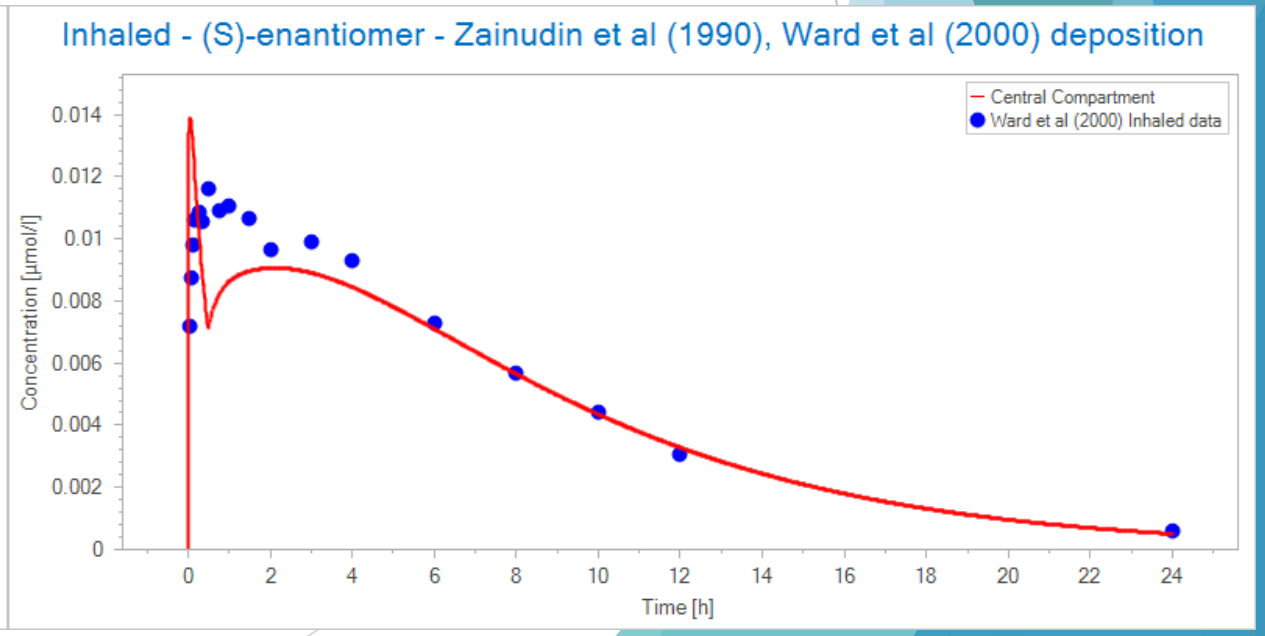
1) Salbutamol

- Inhaled – custom deposition (Zainudin et al, 1990; Ward et al, 2000)
  - Note: F_oral = 9.4% (R), 68.7% (S)

	Empirical	Custom
Extrathoracic	0.05%	45.7% (R) / 60.1% (S)
Lung	19.5% (R) / 18.7% (S)	19.5% (R) / 18.7% (S)

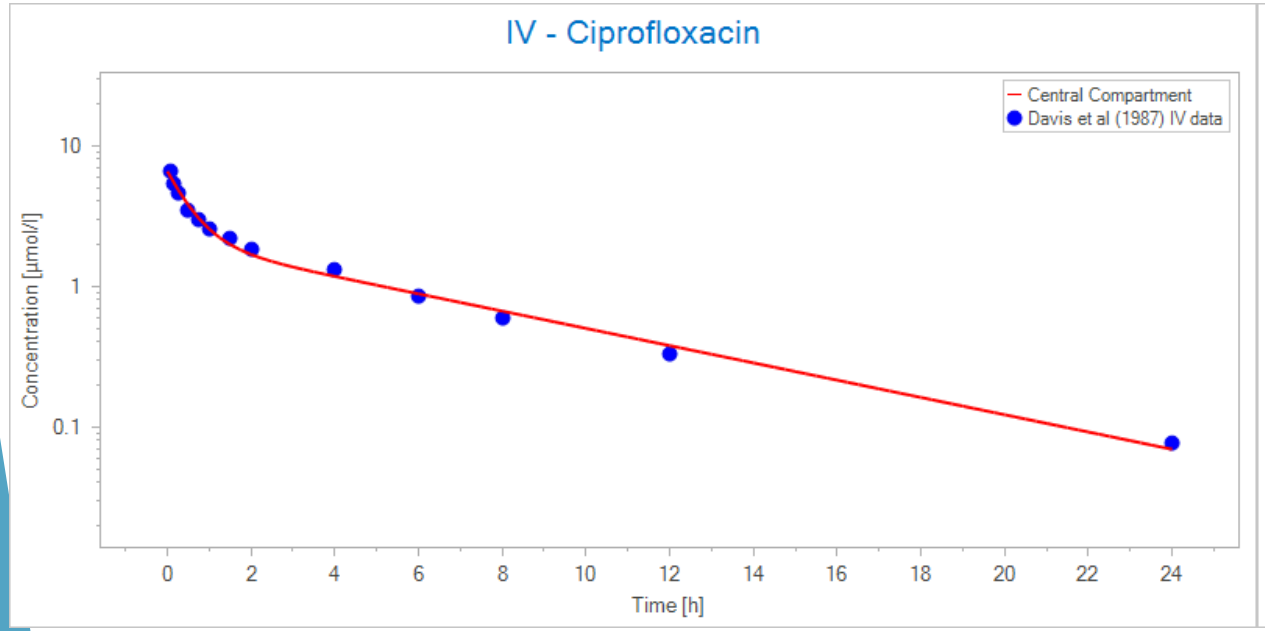
- Larger extrathoracic proportion for (S) due to deposition and oral bioavailability
- Update in deposition was needed to capture observed behaviour

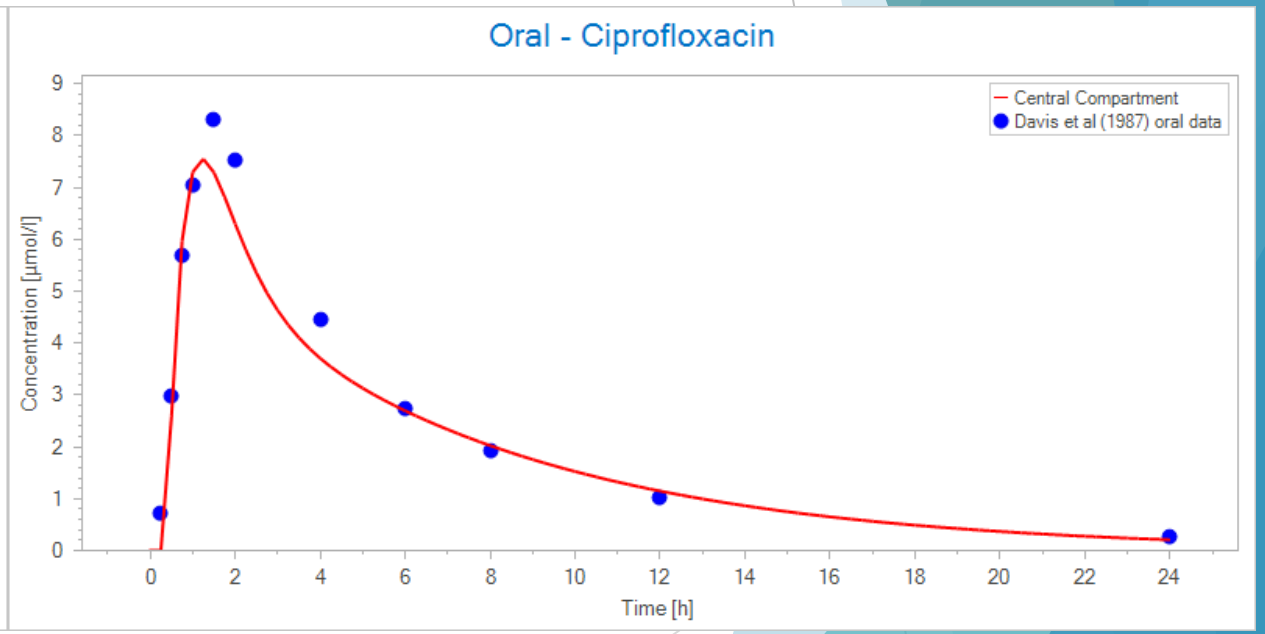




2) Ciprofloxacin – Solubility: 38400 mg/L

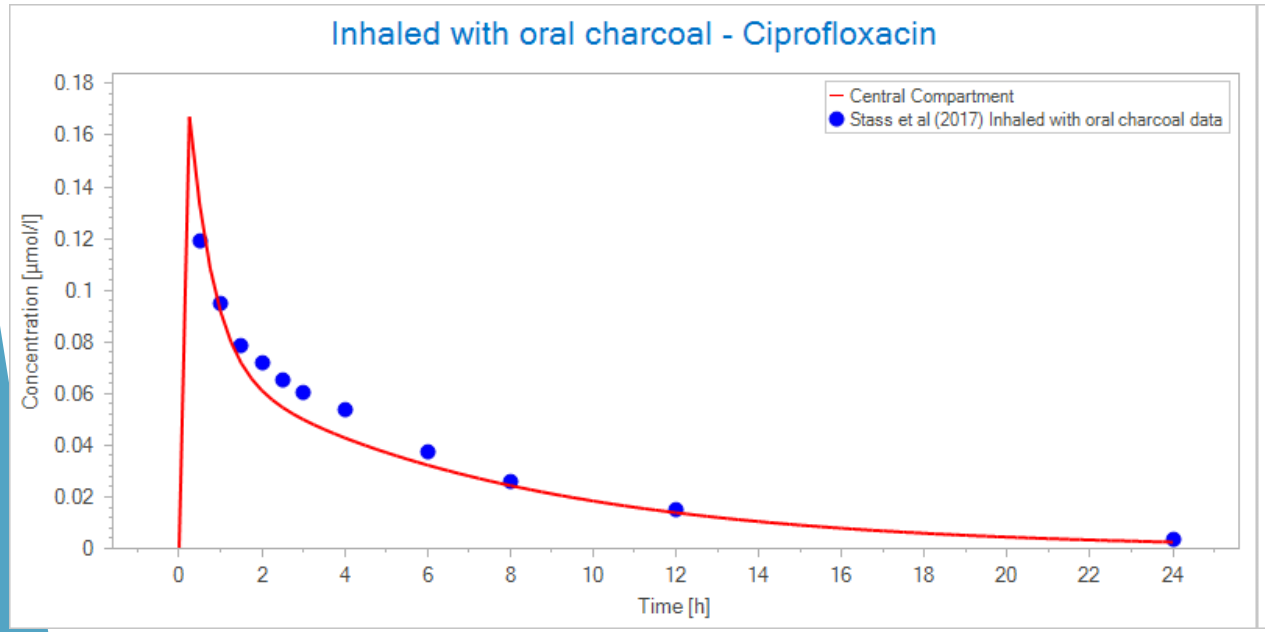
- IV and oral models fit to data

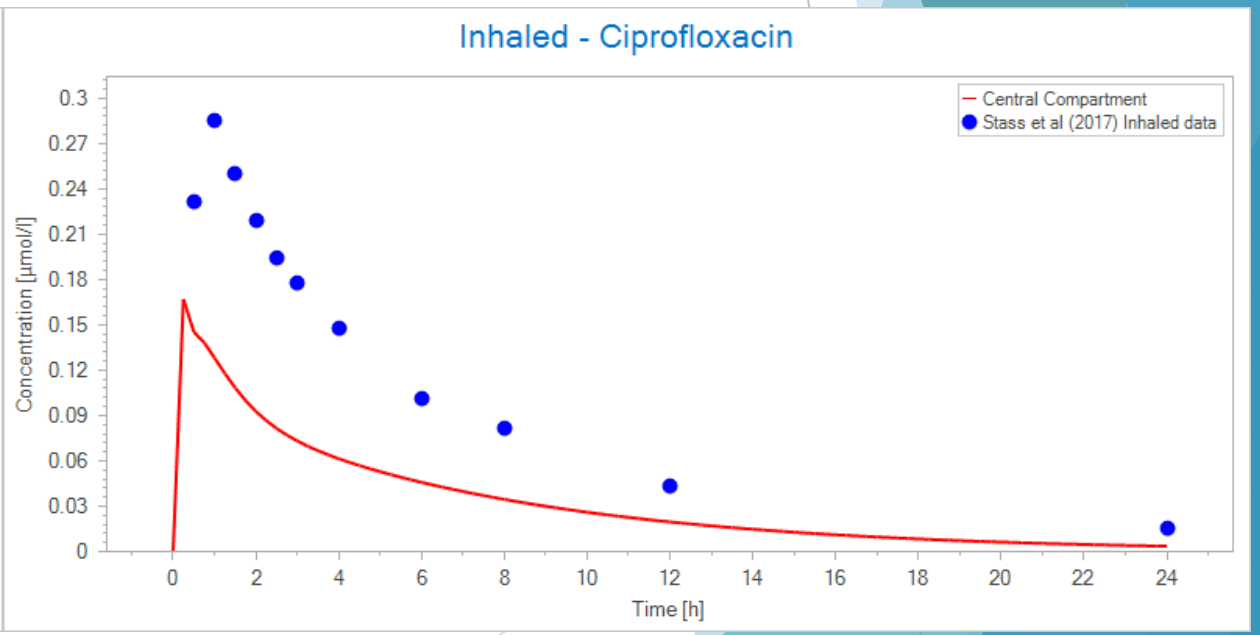




2) Ciprofloxacin – Solubility: 38400 mg/L

- Inhaled with and without oral charcoal – empirical equations
- Inhaled simulation is underestimated due to insufficient deposition



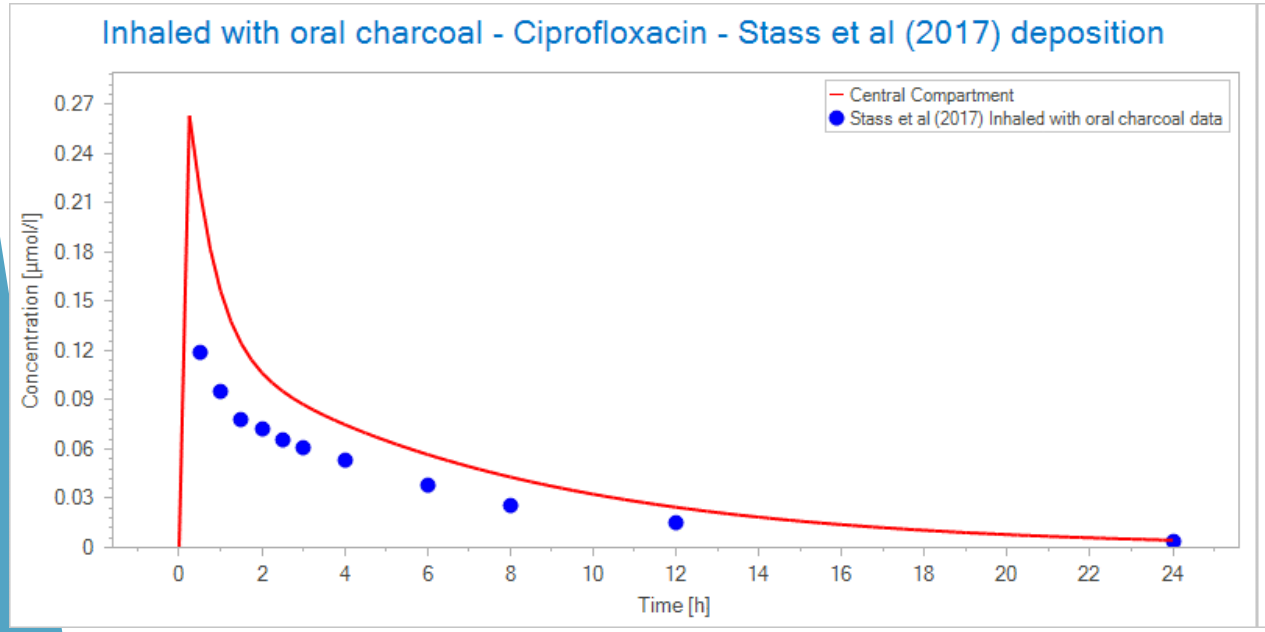


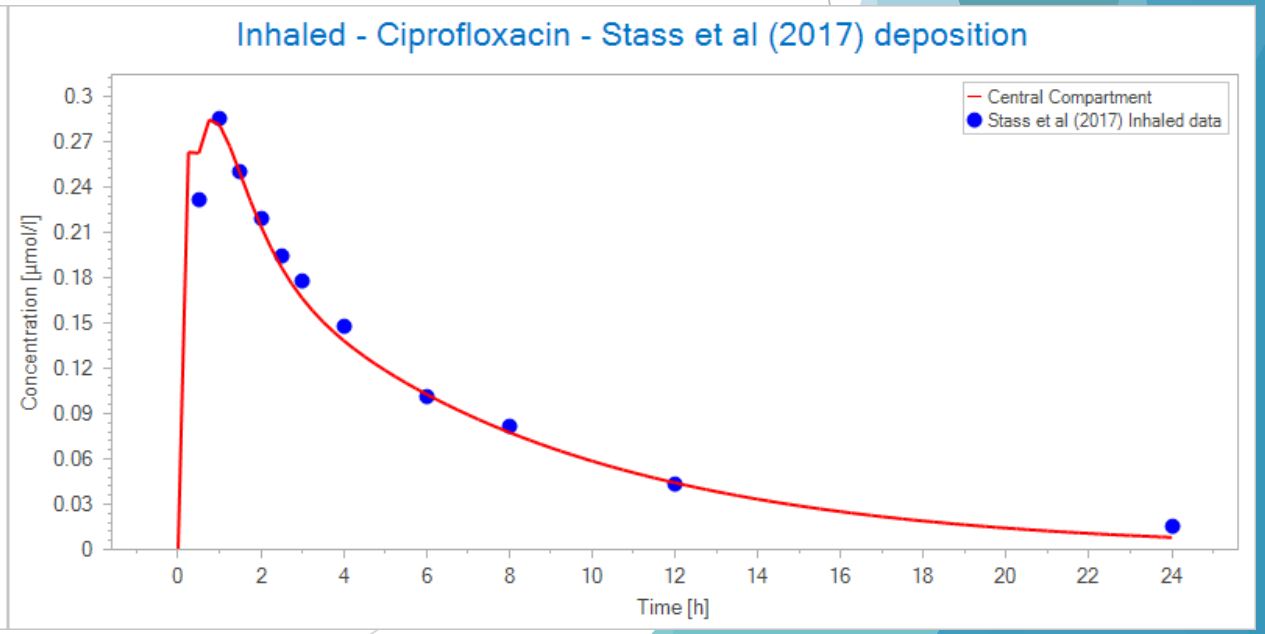
2) Ciprofloxacin

- Inhaled with and without oral charcoal – Stass et al (2017) deposition

	Empirical	Stass et al (2017)
Extrathoracic	11.5%	39.4%
Lung	22.2% (8.5% TB + 13.7% alveolar)	38.1 % (25.4% TB + 12.7% alveolar)

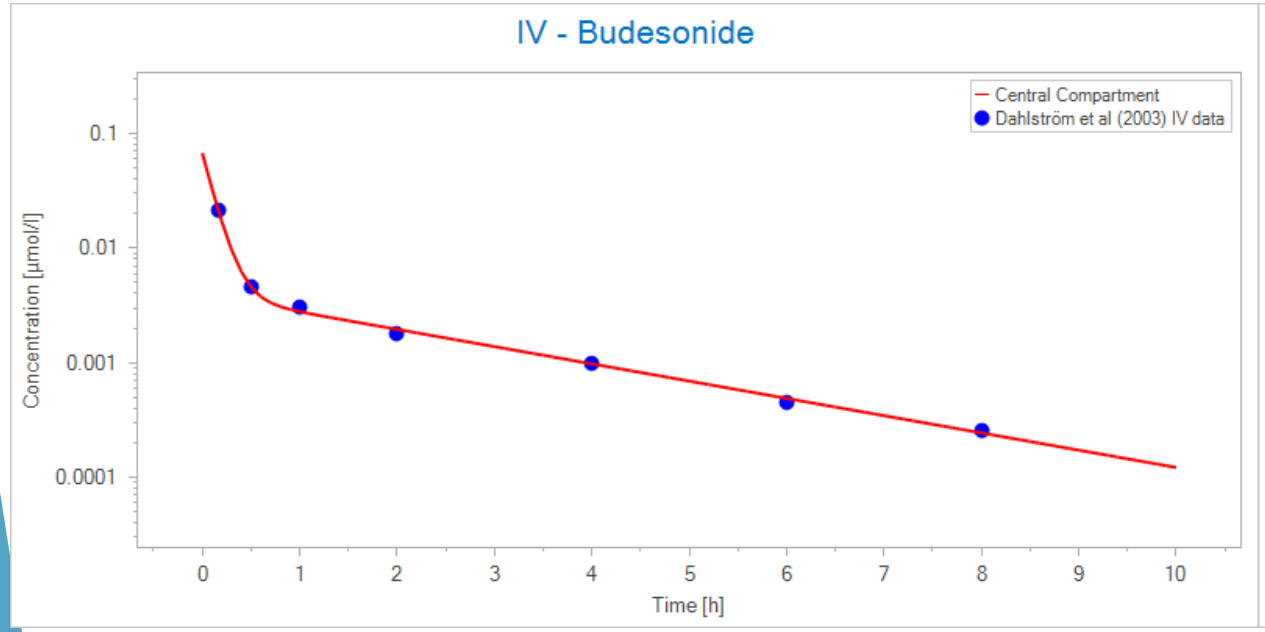
- Update in deposition was needed to capture observed behaviour

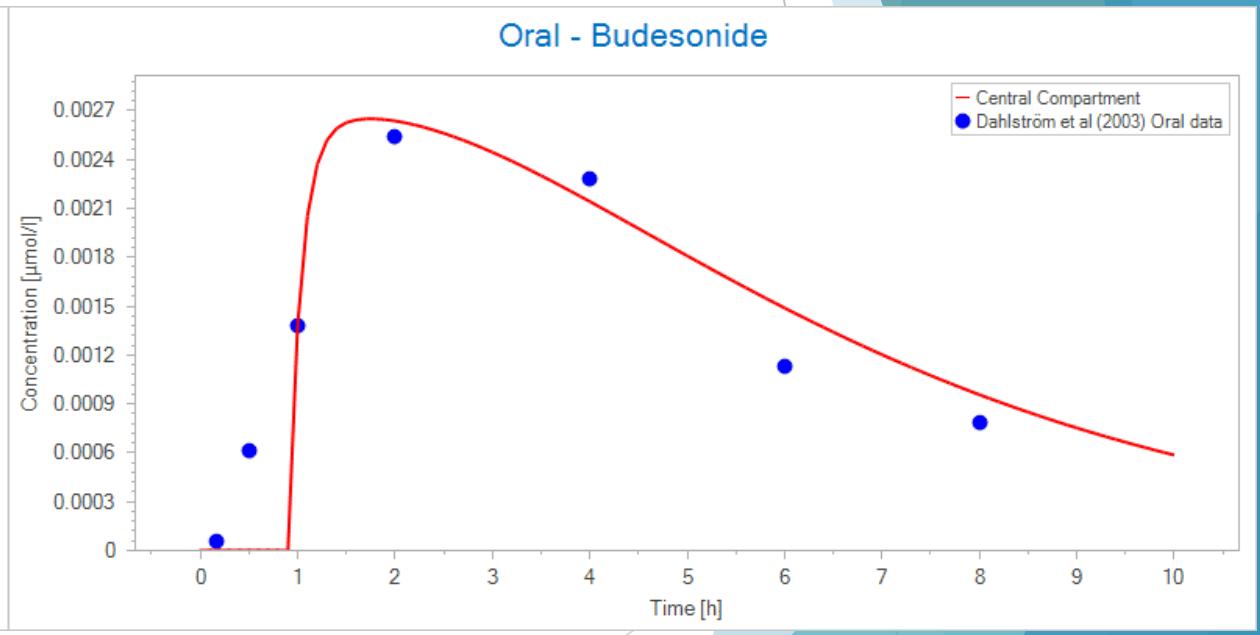




3) Budesonide – Solubility: 10.7 mg/L

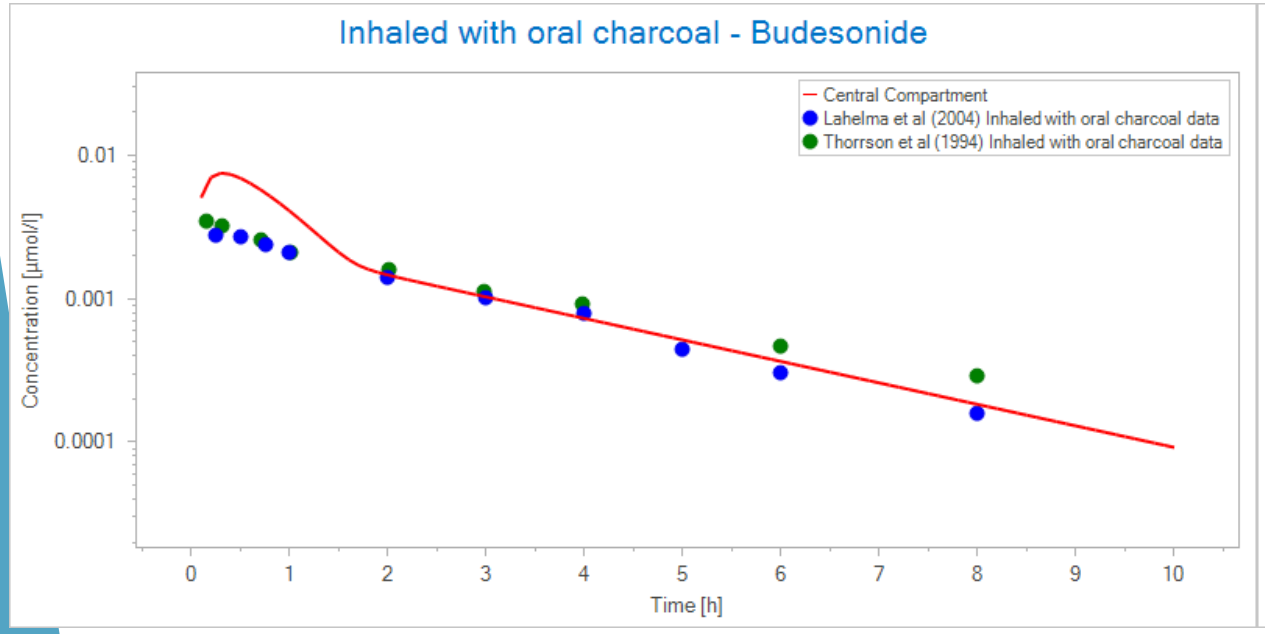
- IV and oral models fit to data

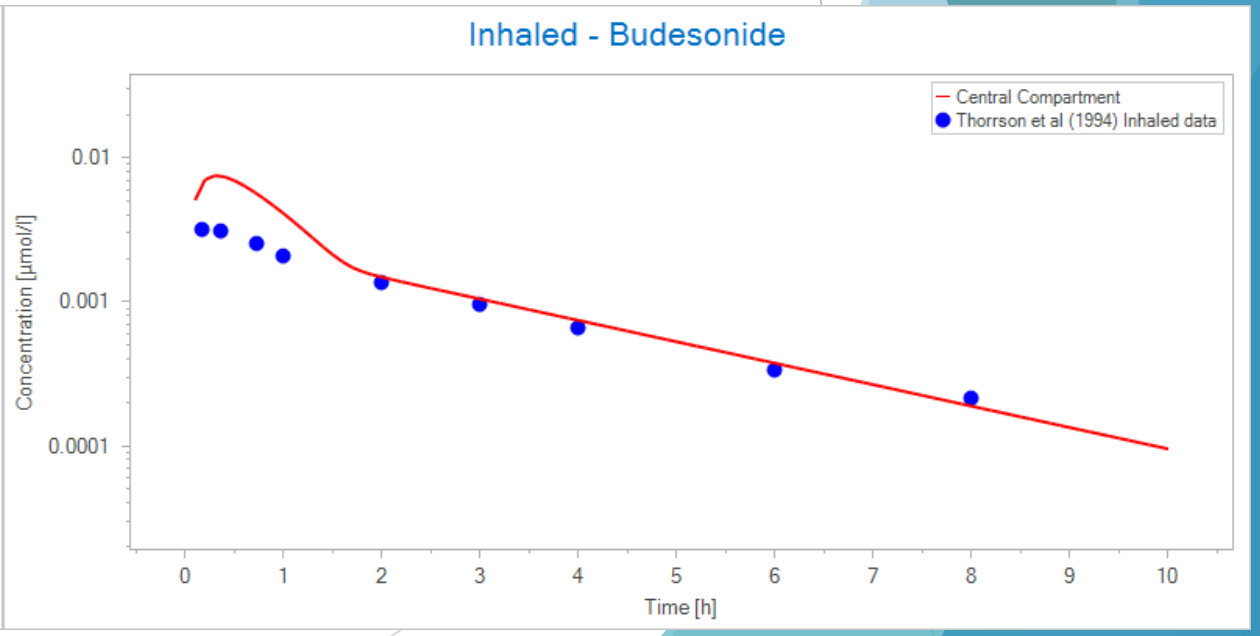




3) Budesonide – Solubility: 10.7 mg/L

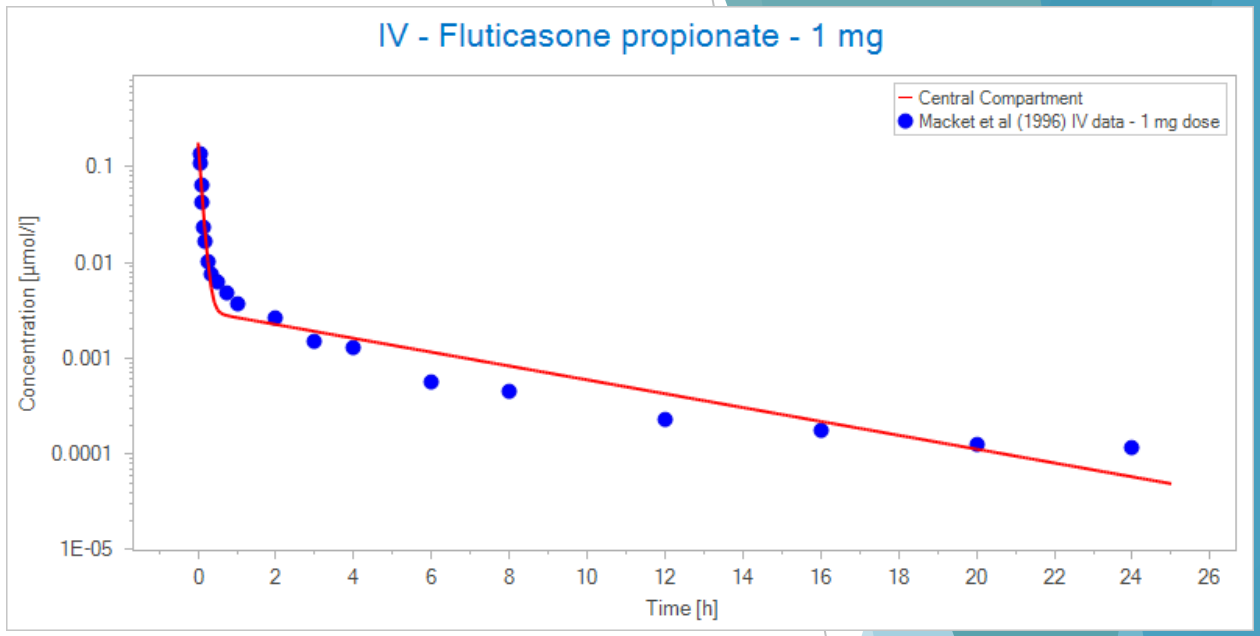
- Inhaled with and without oral charcoal
- No adjustment in deposition or solubility needed to capture observed behaviour

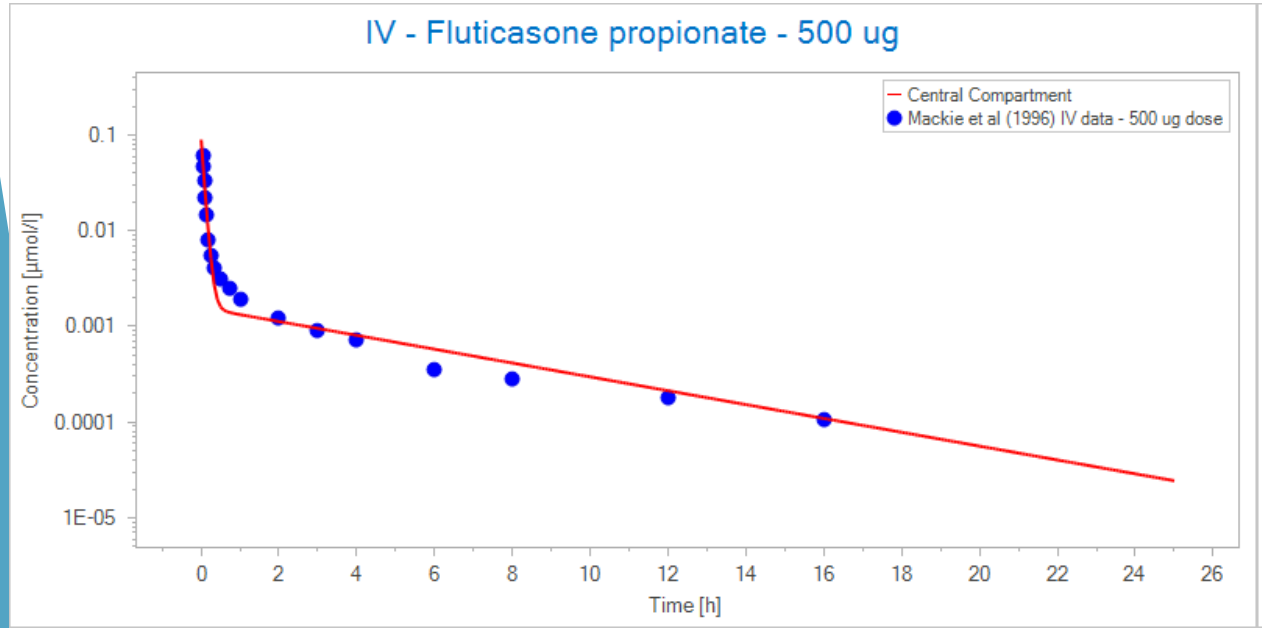


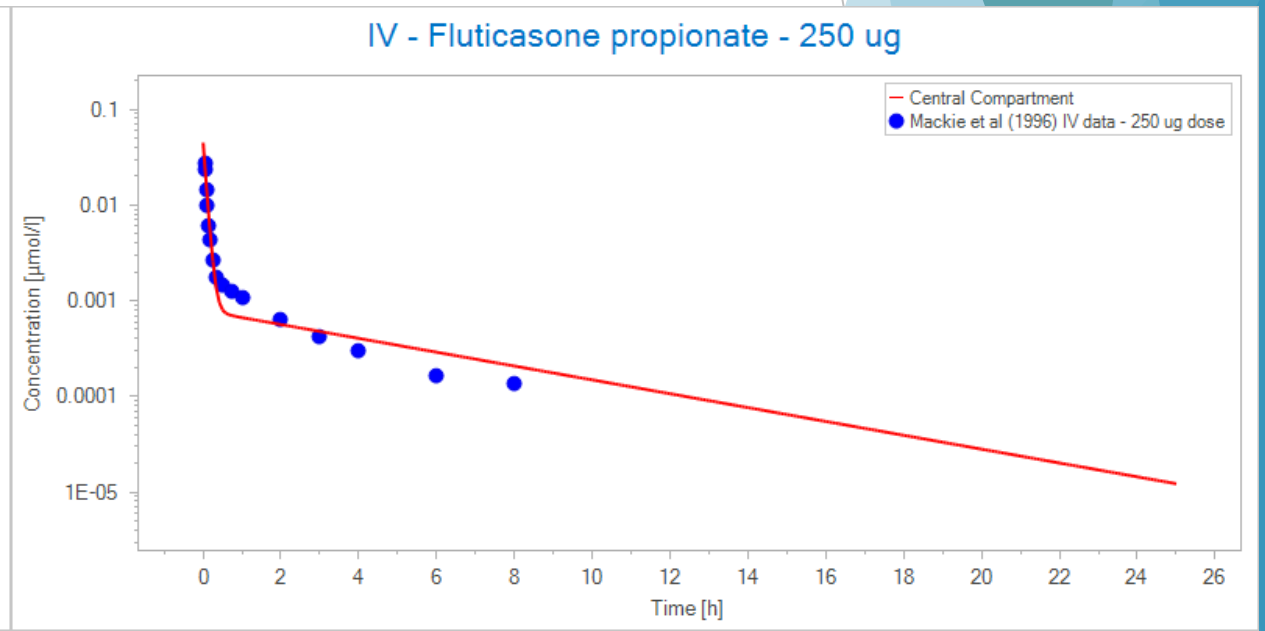


4) Fluticasone propionate – Solubility: <0.15 mg/L

- IV model fit to 1 mg data and evaluated with 500 ug and 250 ug IV data
- Oral model is irrelevant since negligible oral bioavailability for clinically relevant doses (i.e. <10 mg)

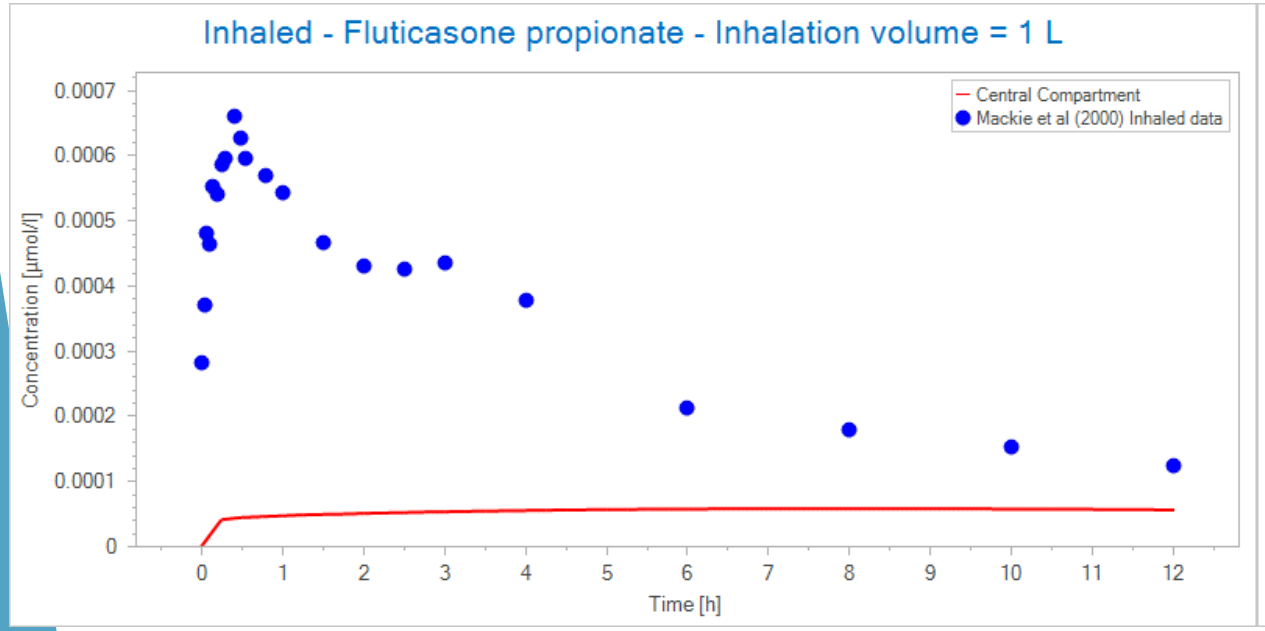


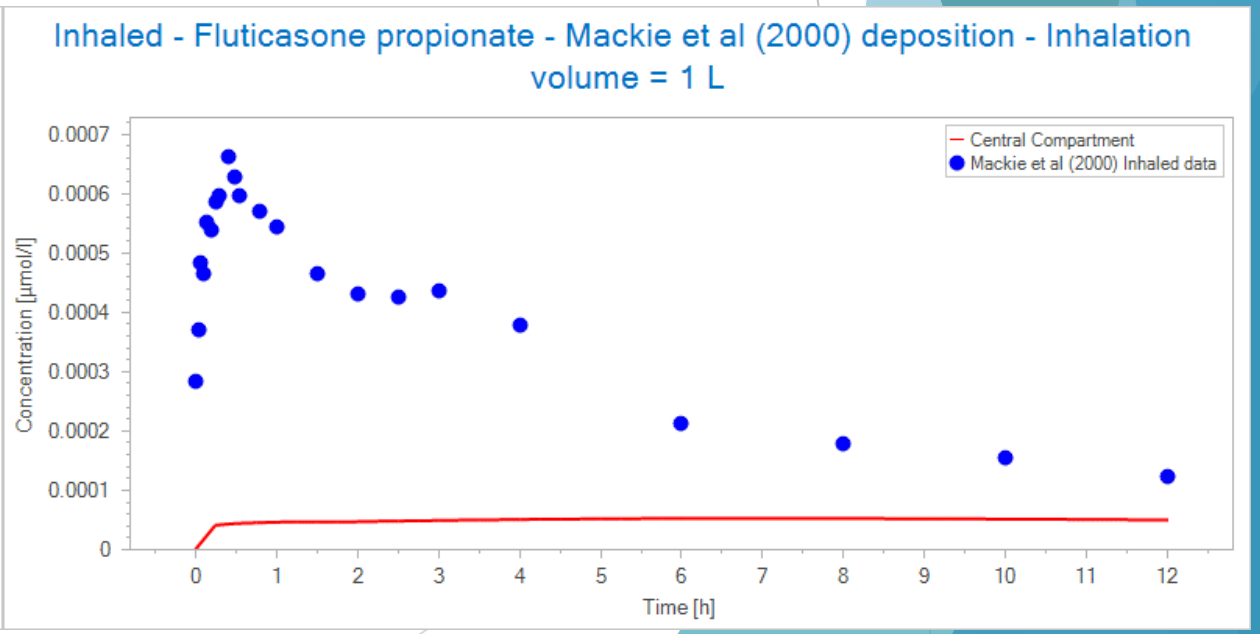




4) Fluticasone propionate

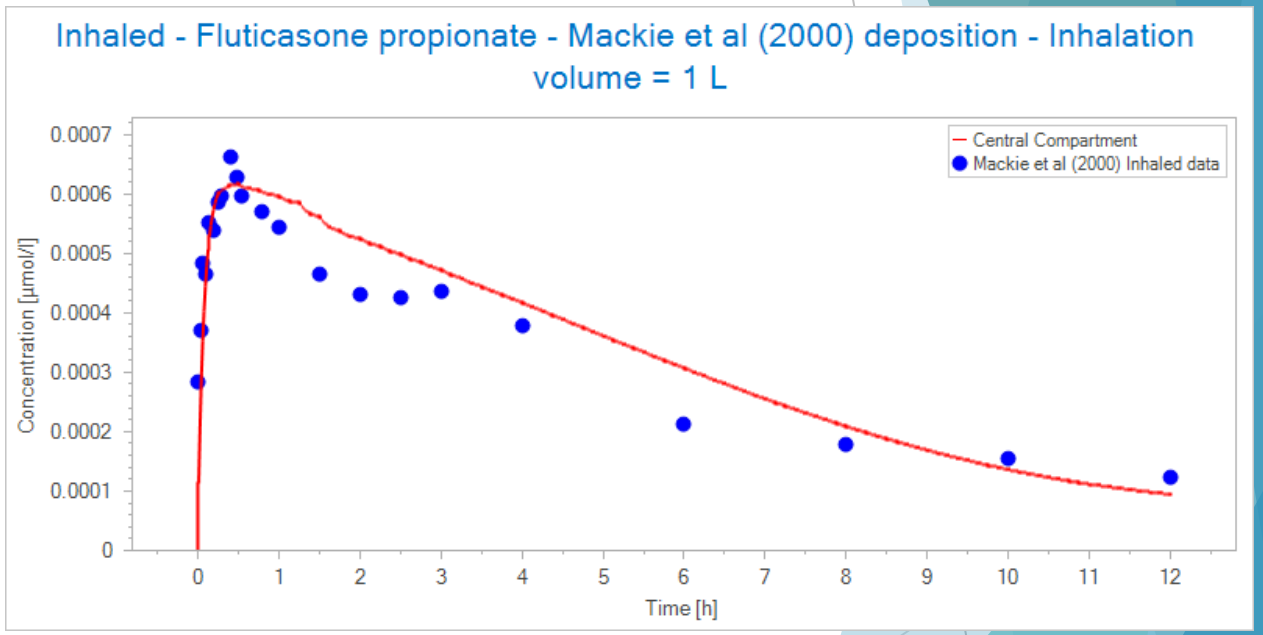
- Inhaled
- Simulation is unable to capture observed behaviour with empirical or with additional deposition information (Mackie et al, 2000)





4) Fluticasone propionate

- Inhaled
- Solubility at reference pH is negligible (<0.15 mg/L) and solubility in epithelial lining fluid is uncertain, so opportunity for parameter optimization
- Solubility in ELF fit: 2.23 mg/L
- Model structure is sufficient to describe observed behaviour with appropriate parameterization



Summary

- The inhalation model can capture the observed behaviour of molecules of varying solubilities (at reference pH)
  - Salbutamol: 14,100 mg/L
  - Ciprofloxacin: 38,400 mg/L
  - Budesonide: 10.7 mg/L
  - Fluticasone propionate: <0.15 mg/L
- Naïve model may over-estimate, under-estimate, or capture observed behaviour
- By understanding model parameter uncertainties and appropriately updating, PK behaviour after inhalation can be captured
- VBE workflow allows for learning from reference product and transfer of learning to test product so that VBE can be completed