Physiologically-based pharmacokinetic (PBPK) models for translation of drug distribution from rat to human

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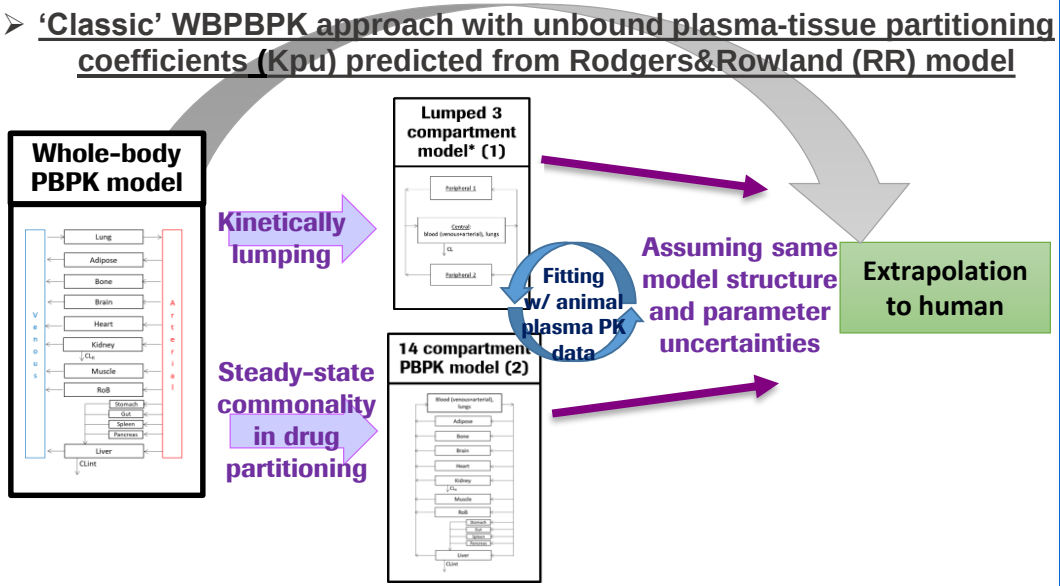
Approaches for predicting human drug distribution

➢ 'Classic' WBPBPK approach with unbound plasma-tissue partitioning coefficients (Kpu) predicted from Rodgers&Rowland (RR) model

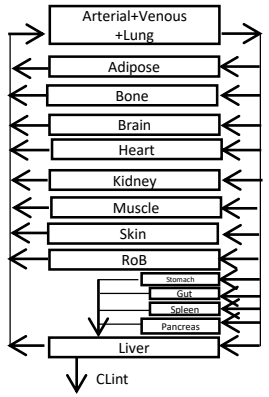


➢ Simplification of PBPK models for fitting and extrapolation

Focus on PBPK models based on steady state commonality in drug partitioning

WBPBPK model (14 comp) with 3 or 4 'common' Kpus or scalars

Assuming lung is instantly equilibrating



Steady-state commonality in drug partitioning

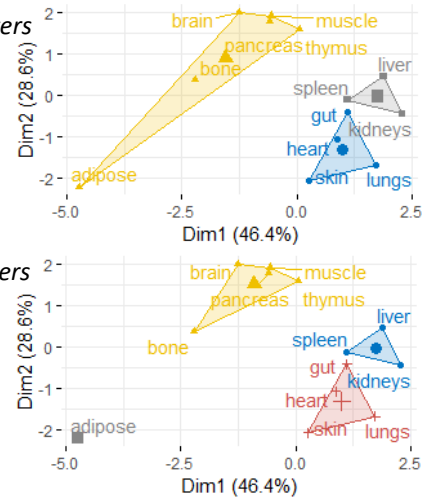
With common Kpus
(assumes same Kpus per species)

With common scalars
(assumes similar bias from RR predicted Kpus values across species)

Commonality assessed by clustering analysis on:
a) similarity in tissue composition (hierarchical or k-means clustering)
b) similarity in normalized rat steady state Kp data

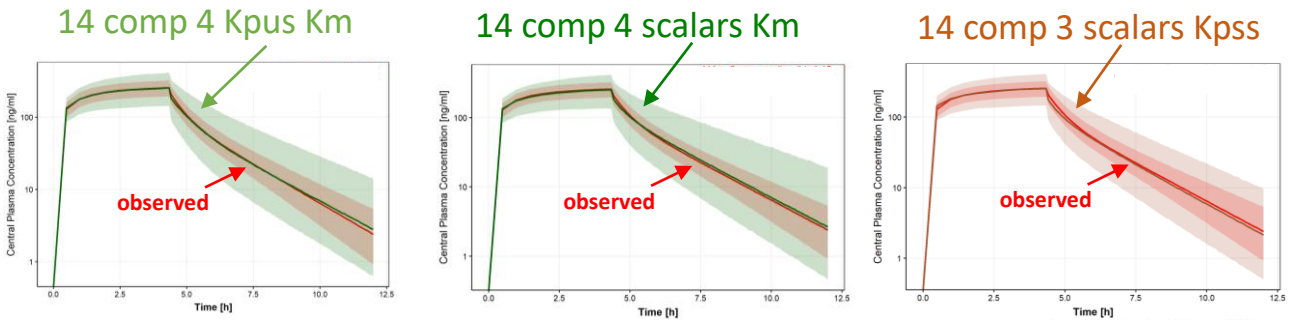
→ **At least 12 combinations of models (With common Kpus and common scalars)**

Illustration of tissue grouping using k-means clustering method on rat tissue composition

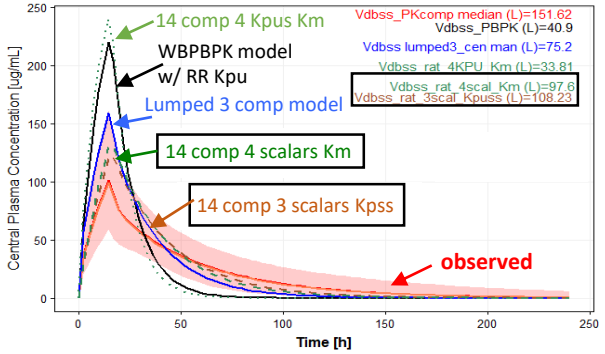


Fitting of PBPK models to rat data and extrapolation to human for diazepam

VPC from the best simplified models when fitting diazepam rat data



Predictions in human : 'classic' WBPBPK approach vs best optimized simplified models



Key points

- The current study provides a **rationale and reproducible assessment of analyzing preclinical** data to aid **translation of drug distribution within a PBPK modelling framework.**
- The work and models proposed may **be extended to other compounds and species**, for a more exhaustive evaluation.