Safety & Environmental Assurance Centre

Utilising membrane partitioning coefficients in physiologically-based kinetic modelling

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Introduction

- Log K_{OW} used as a surrogate to calculate tissue:plasma partitioning
- Tissue:plasma partitioning in turn used to parameterise physiologically-based kinetic (PBK) models [1], which predict the concentration of a compound within an organism
- Log K_{OW} struggles to describe partitioning into biological systems for large and charged molecules
- Here we present an application of log K_{MW} as an input for PBK modelling, and a comparison to use of log K_{OW} as an input.

PBK Modelling

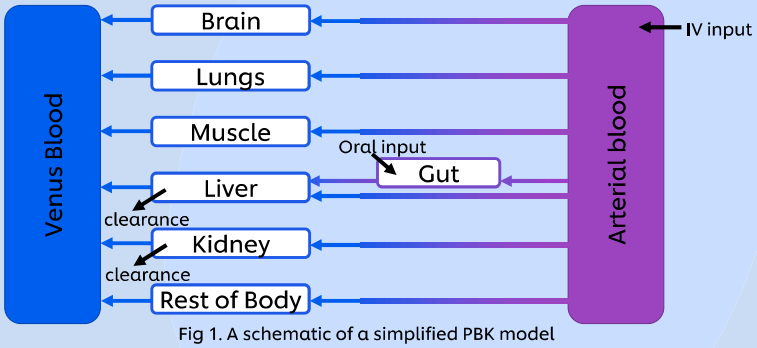


Fig 1. A schematic of a simplified PBK model

Input	Outputs of interest
• Chemical properties (log Kow, pka etc.) • Physiological properties (flow rate, volumes) • ADME properties	• Volume of distribution at steady state (V_{ss}), apparent volume of blood required to give the plasma concentration of a chemical, assuming no chemical is in other tissues • Cmax, maximum plasma concentration after exposure

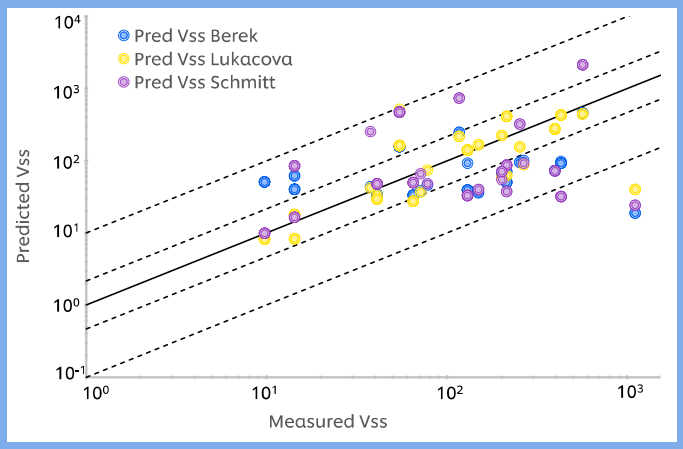
Method

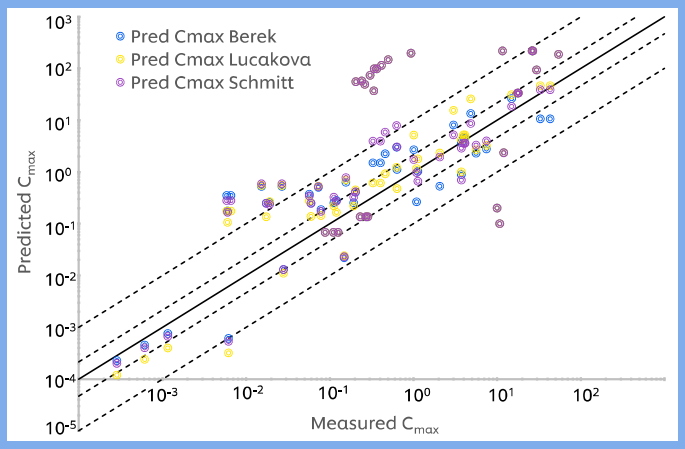
- Literature review carried out to collect V_{ss} and C_{max} for a mixture of neutral and ionisable pharmaceuticals
- log K_{MW} values were calculated using COSMOmic
- Three sets of equations to calculate tissue:plasma partitioning compared:

Method	Description of partitioning
Schmitt [2]	Based on log K_{MW} and accounts for ionization during interactions with tissue constituents
Lukacova [3]	Based on log K_{OW} and accounts for ionisation during interaction with tissue constituents
Berezhkovskiy [4]	Based on log K_{OW} does not consider ionization in albumin binding

- V_{ss}, an intermediate metric based directly on partitioning calculated
- Additionally, C_{max} calculated, as this is the final output used most often in risk assessment

Results and Discussion





Method	R^2 (Vss)	R^2 (C_{max})
Schmitt	-0.48	0.09
Lukacova	0.49	0.15
Berezhkovskiy	-0.02	0.11

- The Lukacova method predicts the Vss better than other methods
- Cmax shows little change, and seems insensitive to the changes in inputs

Conclusions

- Results suggest that varying the equation used to estimate tissue:plasma partitioning does not have a significant impact on C_{max}, although it does affect V_{ss}
- Log K_{MW} could be used as an input for PBK rather than log K_{OW} for surfactants, where log K_{OW} is harder to obtain.

References

[1] L. Kuepfer *et al. CPT Pharmacometrics Syst Pharmacol.* **2016,** 5(10), 516–531.
[2] W. Schmitt, *Toxicol. In Vitro*, **2008**, 22(2), 457–467
[3] V. Lukacova *et al.*, General Approach to Calculation of Tissue:Plasma Partition Coefficients for Physiologically Based Pharmacokinetic (PBPK) Modeling, poster presented in 2008
[4] L. M. Berezhkovskiy, *J. Pharm. Sci.*, 2004, 93(6)