

Application of Physiologically-Based Pharmacokinetics using Simcyp to predict the exposure of Valproic Acid in human breast milk and pediatrics.

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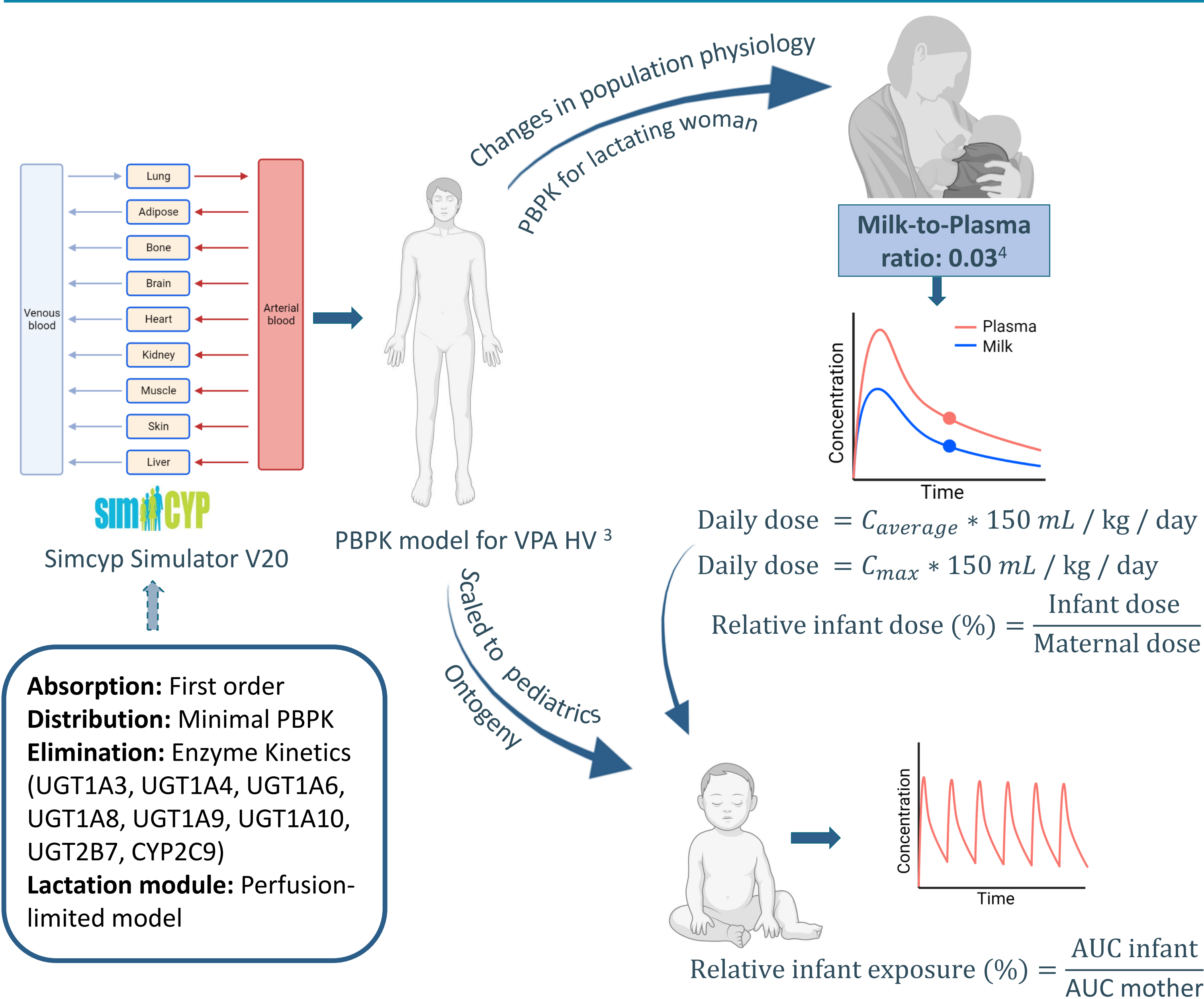
Background

Post-partum women often cease breastfeeding or postpone pharmacotherapy due to scarce data on medication safety in their infant¹. This is a major issue since breastfeeding provides physical and mental benefits to mother and infant². This work is part of the Innovative medicines initiative (IMI) research consortium and project ConcePTION, with the main goal to reduce uncertainty about the use of medication during pregnancy and breastfeeding (e.g., Valproic Acid-VPA).

Objective

Develop a lactation Physiologically-Based Pharmacokinetic (PBPK) model to predict the VPA concentrations in human milk and the systemic exposure in neonates (birth to 28 days) and infants (29 days to 3 months old).

Methods



HV: healthy volunteers; CYP: Cytochrome P450; UGT: UDP-glucuronosyltransferase

Results

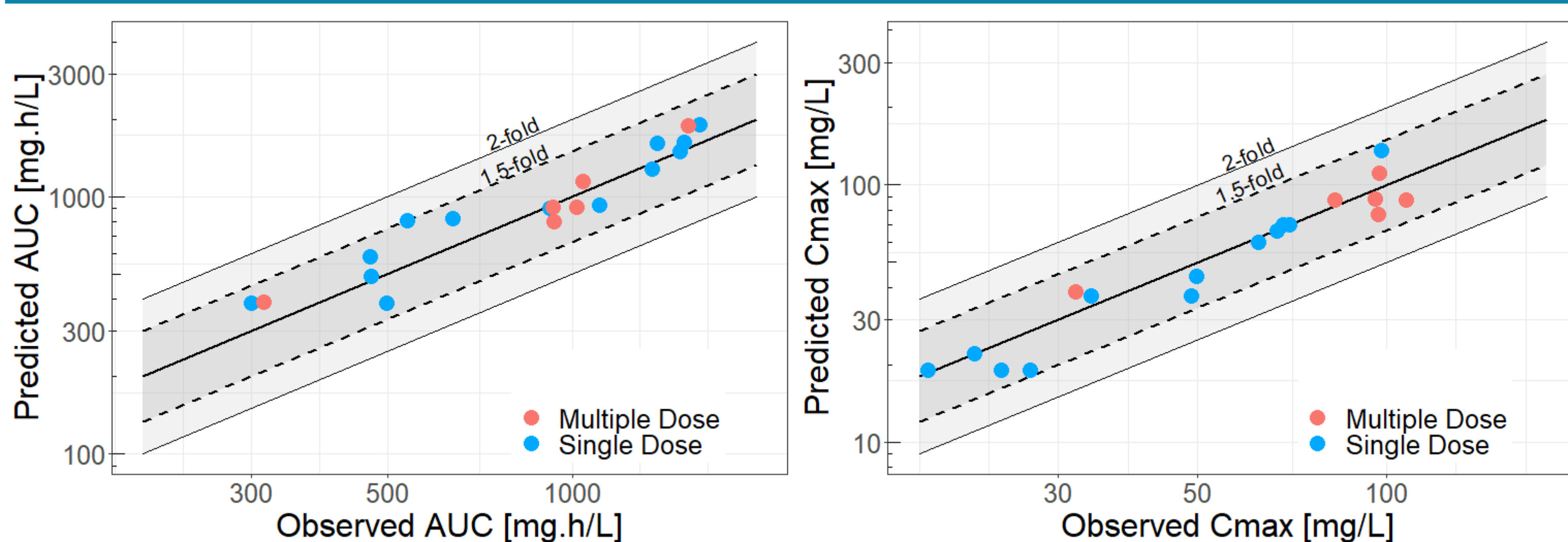


Figure 1. Plots of observed vs simulated AUC and Cmax of VPA (in bold). Geometric mean of Cmax and AUC were predicted within 1.04-fold and 0.96-fold of the actual observed values following single and multiple oral administration.

- ✓ The model qualified as a base model to build the PBPK model for lactating women and to scale to the pediatric population.

References

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Results

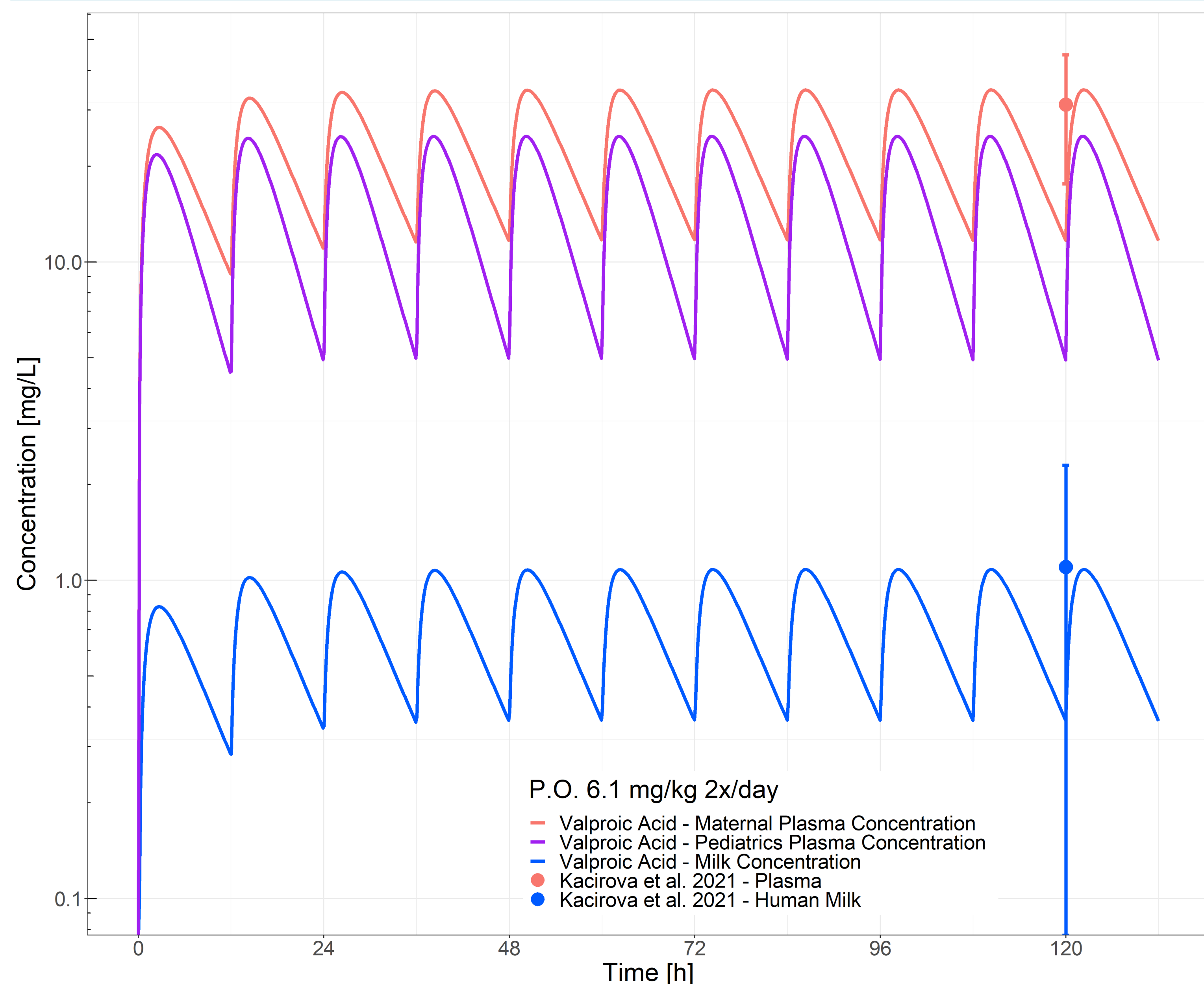


Figure 2. Valproic Acid exposure in human plasma and milk.

- ✓ The lactation PBPK model was able to predict the VPA exposure in plasma and human milk for lactating women.

Table 1 - Infant exposure of Valproic Acid: Simcyp[®] $C_{average}$ and C_{max} methods. PK-Sim[®] $C_{average}$ method.

		Daily Infant dose (mg/kg/day)	Relative Infant dose (%)	Average SS infant plasma concentration (mg/L)	Relative Infant exposure (%)
Simcyp [®]	$C_{average}$ method	0.11	0.96	0.82	1.9
	C_{max} method	0.16	1.44	1.19	1.7
PK-Sim [®]	$C_{average}$	0.16	1.4	0.83	1.2

- ✓ The results obtained using C_{max} and $C_{average}$ are in the reported range of observations (undetectable concentrations up to 41 mg/L)⁴.
- ✓ Similar results were obtained with a lactation PBPK model developed using PK-Sim[®] (v 9.1) (Open Systems Pharmacology)⁵
- ✓ With the PK-Sim[®] model the exposure of VPA in plasma and human milk was successfully predicted relying on an empirical model⁶ (to calculate bidirectional CL values across the blood-milk barrier).

Conclusion

- ✓ The PBPK model was developed to successfully predict plasma concentrations in pediatrics and lactating women.
- ✓ This model will be further verified against clinical VPA plasma and human milk data.
- ✓ Efforts to create a non-clinical workflow for (*in vitro*- and) PBPK-based predictions (using both Simcyp[®] and PK-Sim[®] platforms) of the transfer of medicines into human milk are in progress.
- ✓ **This workflow will be applied to 11 additional medicines selected in the context of the IMI ConcePTION project.**

Acknowledgements

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