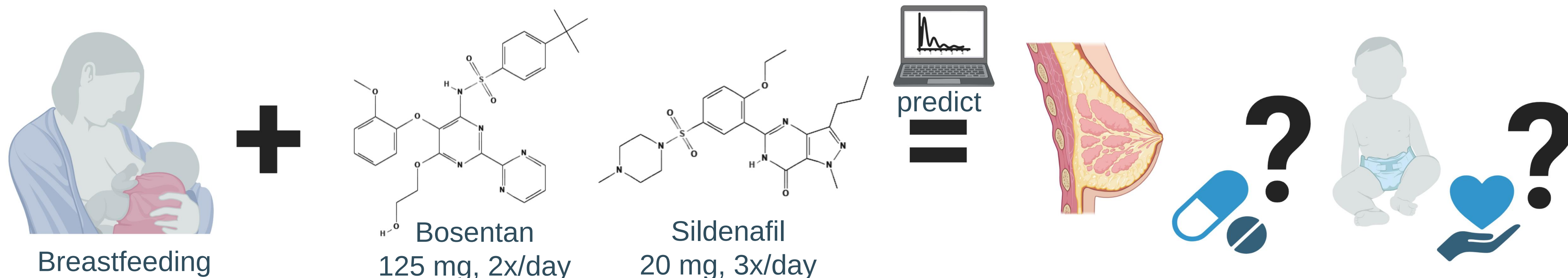


Physiologically-Based Pharmacokinetic (PBPK) Modelling to Predict Human Milk Exposure to Sildenafil and Bosentan: a contribution from the ConcePTION Project

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Introduction



Objective

To explore the utility of Physiologically-Based Pharmacokinetic (PBPK) modelling to predict exposure to sildenafil and bosentan in human milk, and subsequent infant exposure via breastfeeding.

Methods: Physiologically-based pharmacokinetic (PBPK) modelling to predict human milk exposure

PBPK model for healthy reference individual

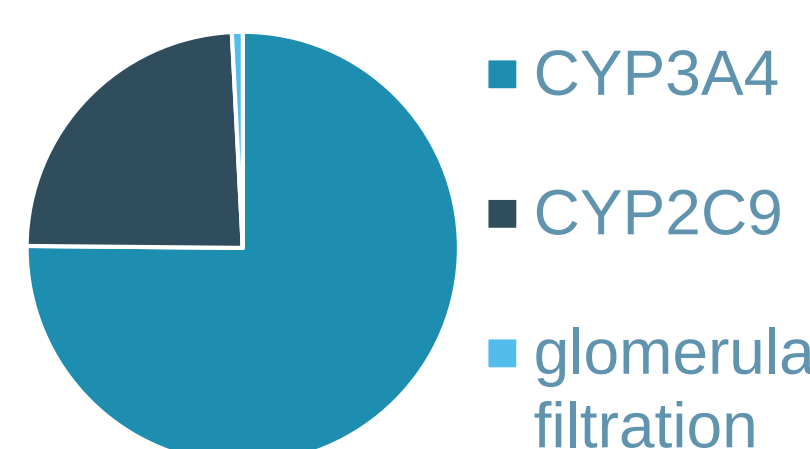
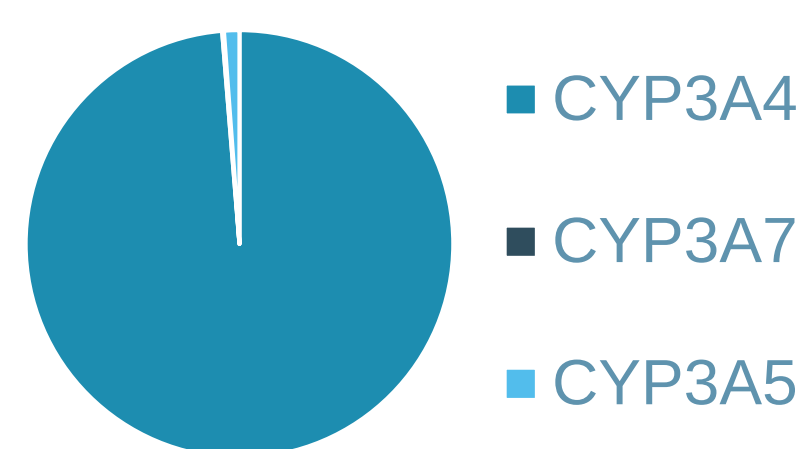
PK-Sim® and MoBi v9.1 (Open Systems Pharmacology) were used to develop the PBPK models for sildenafil [1] and bosentan [unpublished data]. Co-administration results in drug-drug interactions.

Table 1: PBPK models for sildenafil and bosentan

Parameter	Sildenafil	Bosentan
BCS classification	I	II
MW (g/mol)	474.58	569.64
LogP	3.02	2.85
Solubility (mg/mL)	3.50	0.43
pKa	5.97	5.80
F _u	0.04	0.02
P _{int} (cm/min)	1.03E-4	1.67E-4
Partition coefficients	Rodgers & Rowlands	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard	Charge dependent Schmitt

Table 2: CYP3A4 induction by bosentan [2] Table 3: OATP1B1/1B3 inhibition by sildenafil [3]

Enzyme	EC50	E _{max}	Enzyme	K _i
CYP3A4	0.96 μM	9.69	OATP1B1	0.75 μmol/L
			OATP1B3	0.40 μmol/L



PBPK model for lactating women

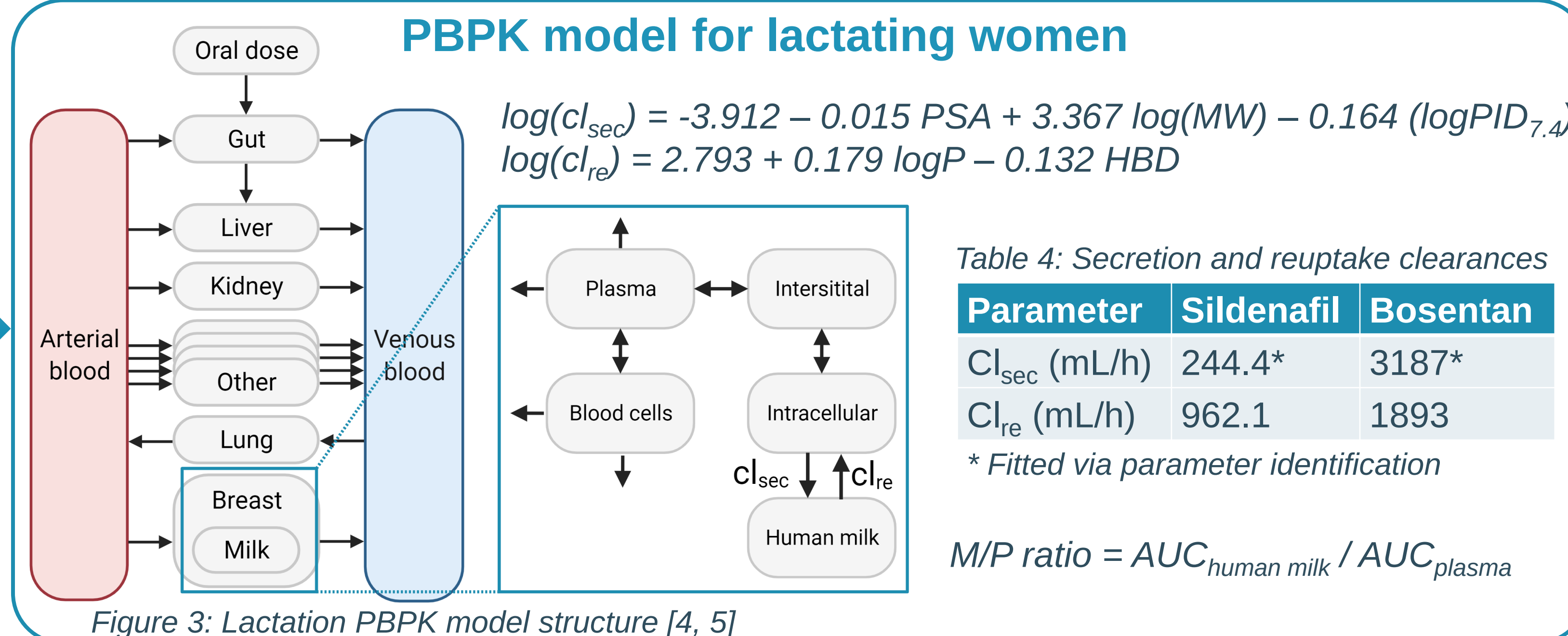


Table 4: Secretion and reuptake clearances

Parameter	Sildenafil	Bosentan
Cl _{sec} (mL/h)	244.4*	3187*
Cl _{re} (mL/h)	962.1	1893

* Fitted via parameter identification

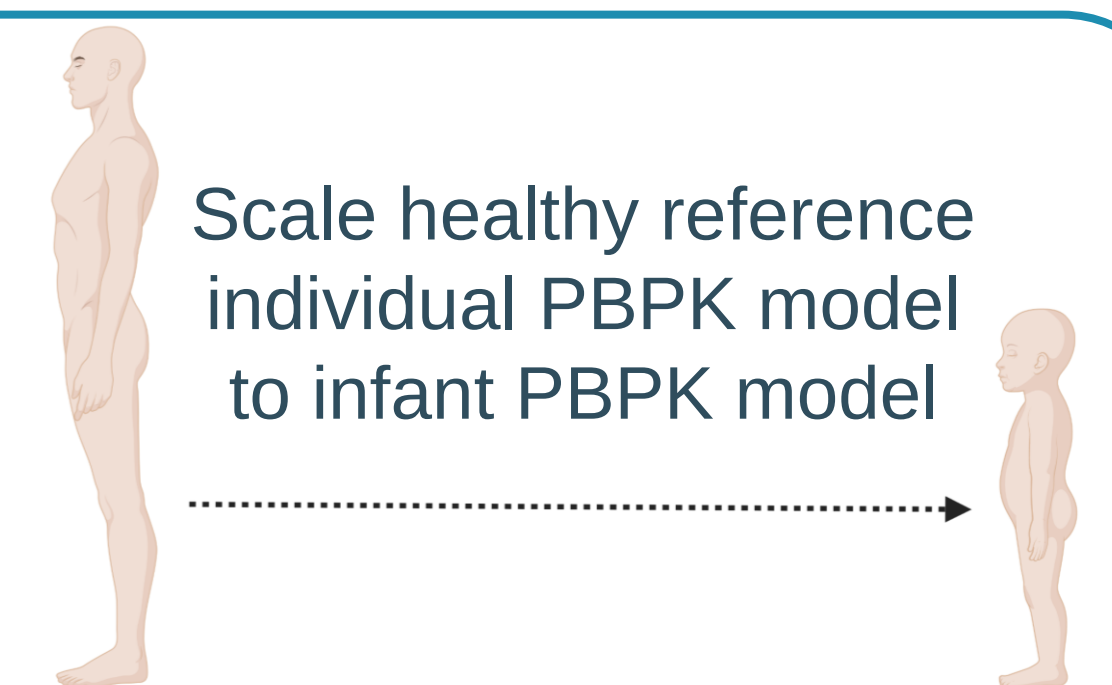
$$M/P \text{ ratio} = AUC_{\text{human milk}} / AUC_{\text{plasma}}$$

Infant PBPK model

$C_{av,ss, \text{human milk}} \text{ (mg/mL)} = AUC_{\text{human milk}} / \tau$

Daily infant dosage (μg/kg/day) = $C_{av,ss, \text{human milk}} \times \text{milk intake}$

Daily infant dosage was compared to the maternal dosage and to common therapeutic infant doses.



Results: Simulation for co-administration sildenafil and bosentan in lactating population

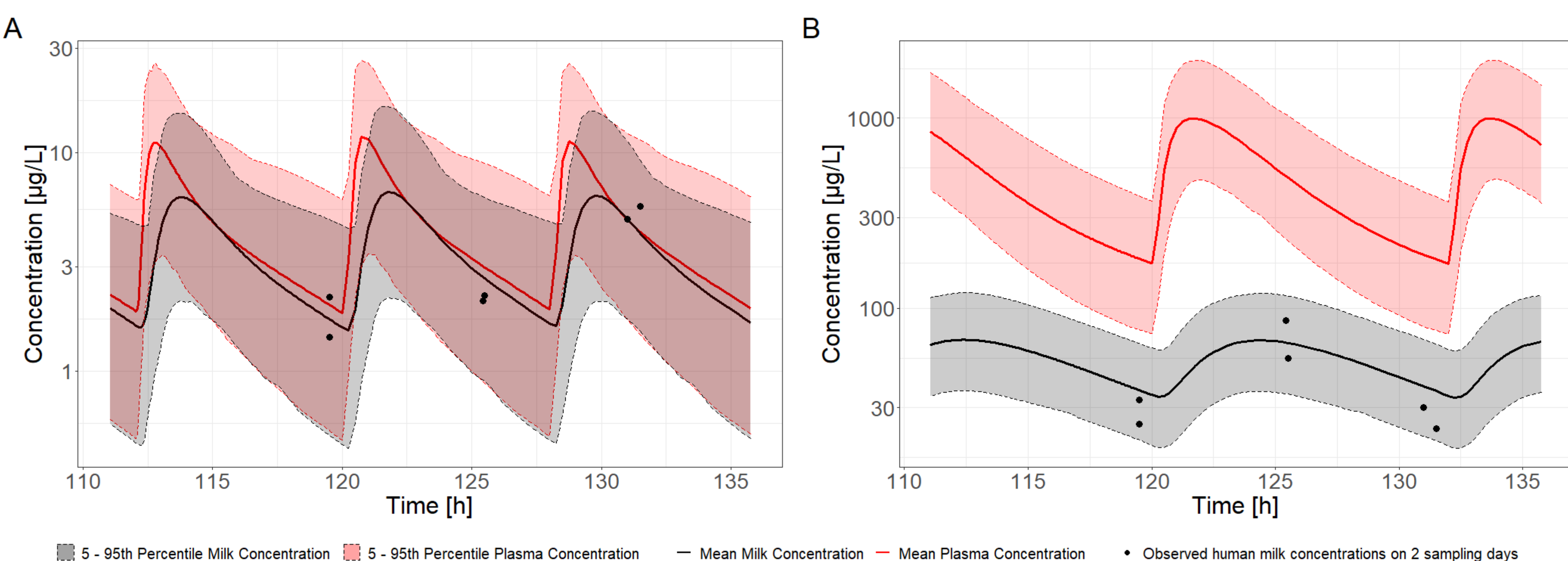


Figure 4: Sildenafil (A) and bosentan (B) in plasma and human milk of lactating women after co-administration of sildenafil (20 mg, 3x/day) and bosentan (125 mg, 2x/day) [6]

Table 5: Human milk, and subsequent infant exposure for sildenafil and bosentan

	Sildenafil	Bosentan
M/P ratio	0.75	0.11
C _{av,ss, human milk}	3.5 μg/L Reported range 1.64 – 4.49 μg/L [7]	53 μg/L
Daily infant dosage	0.53 μg/kg/day 0.07% of maternal dose 0.04% of therapeutic infant dose	7.9 μg/kg/day 0.3% of maternal dose 0.2% of therapeutic infant dose
Infant systemic exposure	1.3% of maternal exposure	7.2% of maternal exposure

Abbreviations: MW: molecular weight; F_u: fraction unbound; P_{int}: Intestinal permeability; CYP: cytochrome P450; OATP: organic anion transporting polypeptides; Cl_{sec}: secretion clearance; Cl_{re}: reuptake clearance; PSA: polar surface area; HBD: hydrogen bond donor; M/P: milk-to-plasma ratio; AUC: area-under-the-curve; C_{av,ss, human milk}: average steady-state human milk concentration; τ: dosing interval

Conclusion

- ✓ PBPK modelling successfully predicts sildenafil and bosentan transfer to human milk, and subsequent infant exposure
- ✓ Further verification of predictive performance recommended when additional observed data becomes available
- ✓ Ongoing efforts aim to determine *in vitro* permeability across the blood-milk barrier
- ✓ Application to other medicines will result in a generic workflow

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