

In Vitro to In Vivo Extrapolation Of Drug Transfer Into Human Milk Using The Simcyp Simulator: A Contribution From The IMI Conception Project.

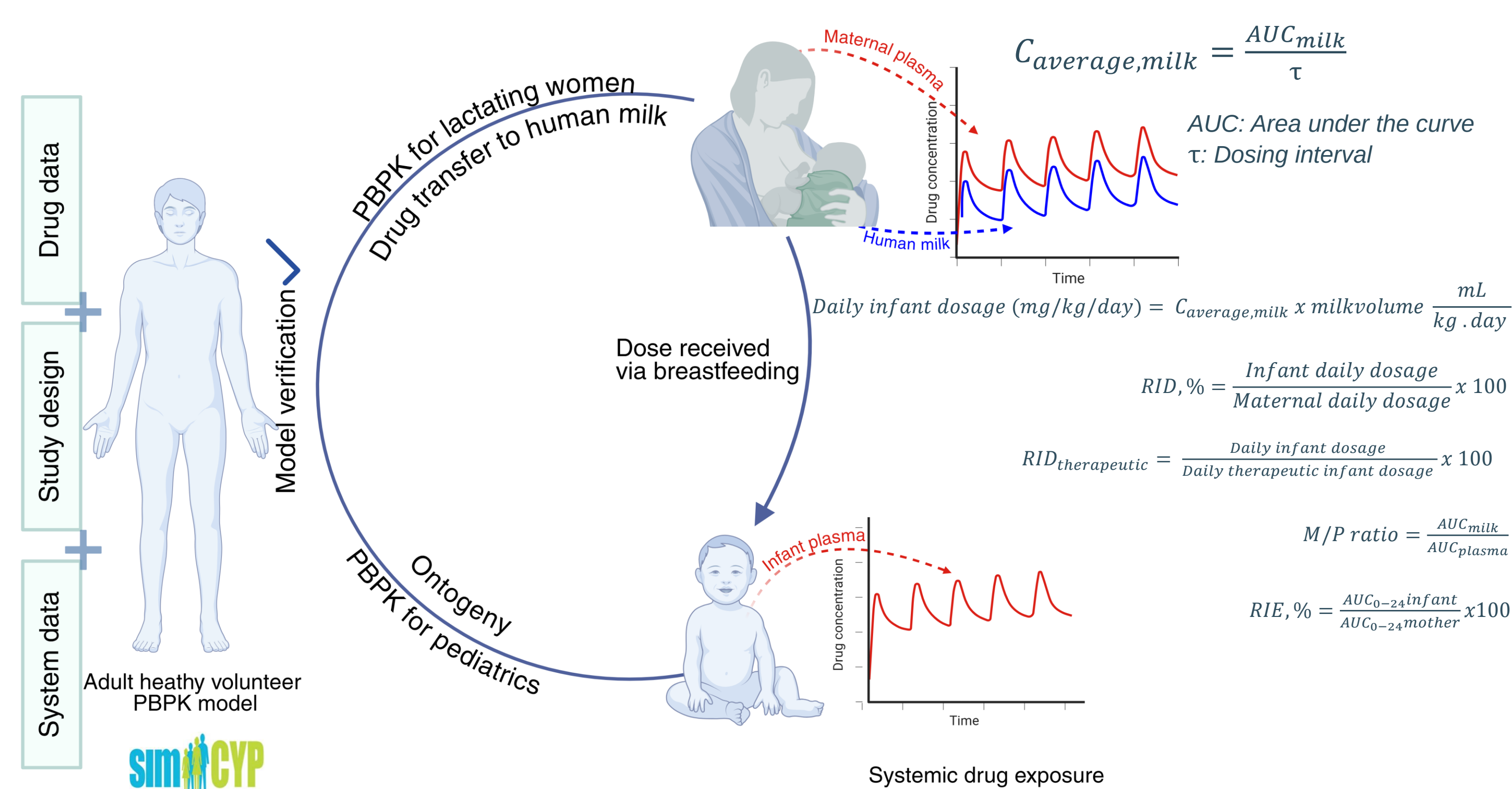
Julia Macente¹ Nina Nauwelaerts¹ Justine Badée² Rodolfo H. Bonan³ Miao-Chan Huang¹ Martje Van Neste^{4,7} Karel Allegaert^{1,6,7} Anne Smits^{5,6,7} Frederico S. Martins¹ Pieter Annaert^{1,3}

Drug delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium¹, Novartis Institutes for BioMedical Research, Novartis, Basel Switzerland² BioNotus CommV, Niel, Belgium³ Clinical Pharmacology and Pharmacotherapy ⁴ Department of Development and Regeneration, KU Leuven⁵, Neonatal intensive care unit, University Hospitals Leuven⁶, KU Leuven Child & Youth Institute, Leuven, Belgium⁷

Background and Objectives

Lactation PBPK models can support risk assessment by providing information on maternal drug exposure during lactation, estimating the milk-to-plasma (M/P) ratio of maternal medication, and predicting the potential systemic exposure of infants to drugs through human milk [1,2]. This work is part of the Innovative Medicines Initiative project Conception, which aims to generate a non-clinical testing platform to determine drug transfer into human milk and subsequent infant systemic exposure. **The aim of the present study was to evaluate the performance of lactation PBPK models, by integrating bidirectional *in vitro* permeability coefficients recently measured from an *in vitro* blood milk barrier model.**

Methods



Five physico-chemically diverse small molecules exhibiting different elimination pathways with available clinical lactation data were selected: amoxicillin, caffeine, cetirizine, levetiracetam and nevirapine.

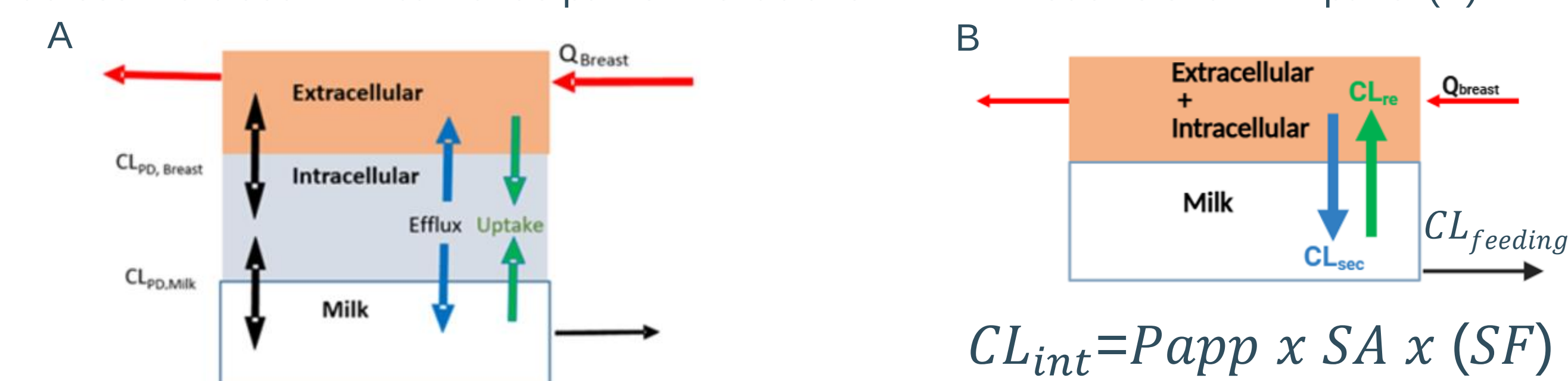
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RID: Relative infant dose, RIE: Relative Infant Exposure

Drug transfer to human milk

Permeability across the blood-milk barrier from *in vitro* model

Figure 1. The default permeability-limited model structure in the Simcyp simulator is shown in panel (A) and the modified structure of the permeability-limited model that was used to describe passage of drugs across the blood-milk barrier as part of the lactation PBPK model is shown in panel (B).



$CL_{int} = Papp \times SA \times (SF)$

CL_{int}: Intrinsic clearance; Papp: Apparent permeability across the blood-milk barrier i.e., basolateral to apical (secretion) and apical to basolateral (reuptake) [3]; SA: Total surface area of mammary glands (1.20 m²) [4]; SF: Scaling factor.

CL_{feeding}: Drug removal from the milk compartment via breast feeding which is defined by the infant daily milk intake.

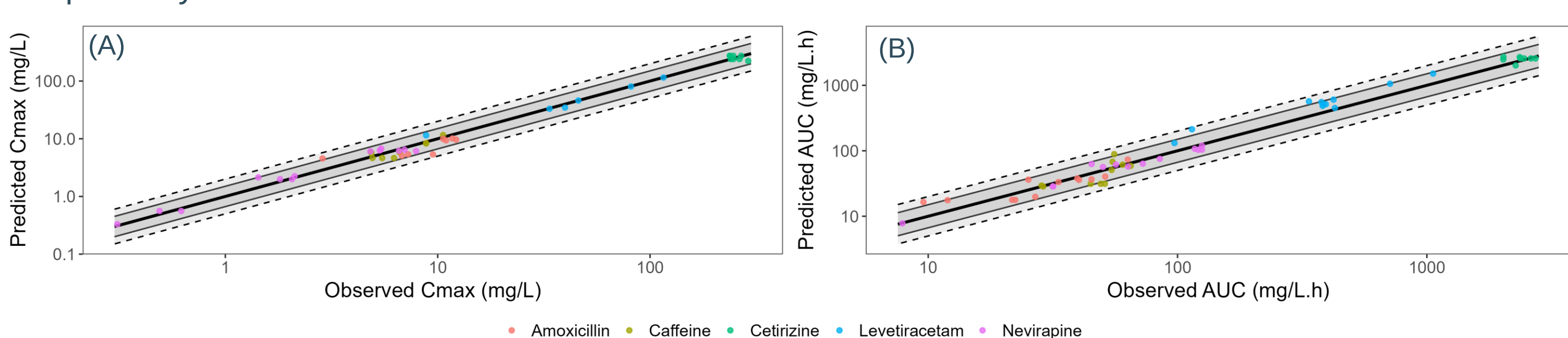
The fraction unbound in human whole milk ($f_{u,milk}$) was calculated using the multiple E_{max} algorithm [5].

$$f_{u,milk} = 1.033 \times \frac{f_{u,plasma}}{0.988 + f_{u,plasma}} + 0.1017 \times \ln(PSA)$$

$f_{u,milk}$: unbound fraction of the drug in the whole milk, $f_{u,plasma}$: fraction unbound in plasma, PSA: polar surface area.

Results

Figure 2. Predictive performance graphs for Cmax (A) and AUC (B) in plasma in adult healthy volunteers. Geometric mean of Cmax and AUC were predicted within 2-fold of the actual observed values. Solid bold line represents the line of unity. Solid and dashed lines represent 1.5- and 2-fold deviation from unity, respectively.



To account for the difference between *in vivo* effective permeability and *in vitro* permeability, a scaling factor was applied for each compound (SF=25 for amoxicillin, cetirizine and levetiracetam and SF=5 for nevirapine and caffeine). The drug removal from the milk compartment was calculated to be 0.03 L/h for all drugs.

Figure 3. A-Comparison of observed and predicted M/P ratio values for the selected drugs. Based on the ratio of AUC_{milk} over AUC_{plasma}. B-F: Predicted and observed human milk concentration time profiles. Symbols represent the clinical observed data obtained from B- Kafetzis et al., (1981) C- Findlay et al., (1988) D- Wilkerson et al., (2021) E- Johannessen et al., (2005) F- Shapiro et al., (2005).

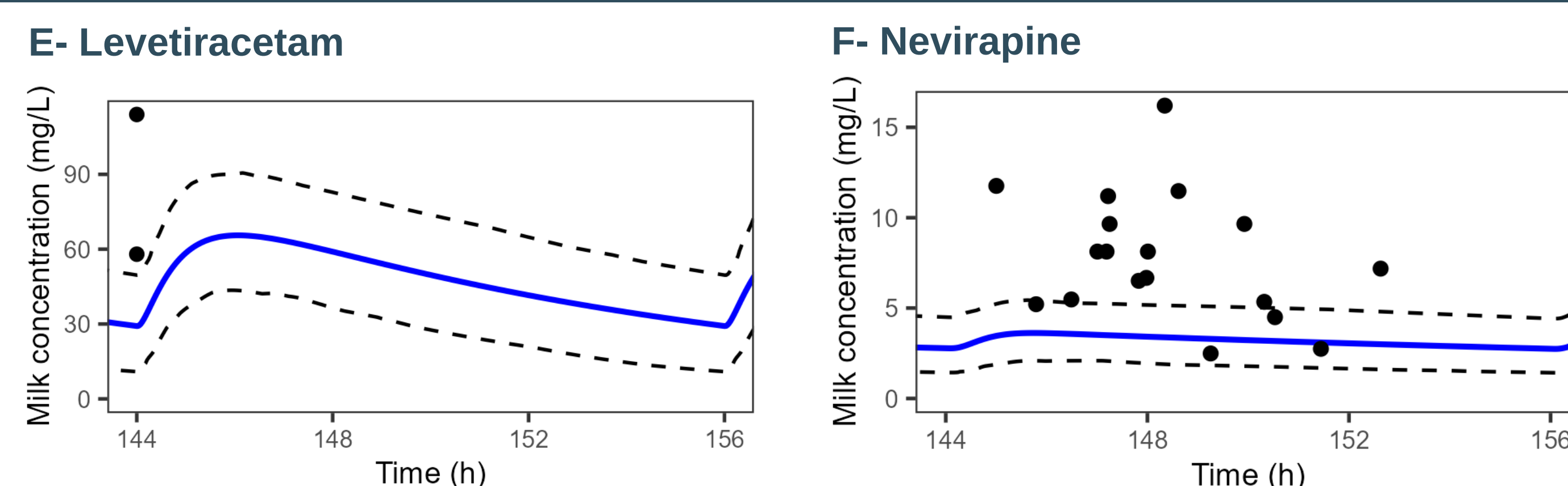
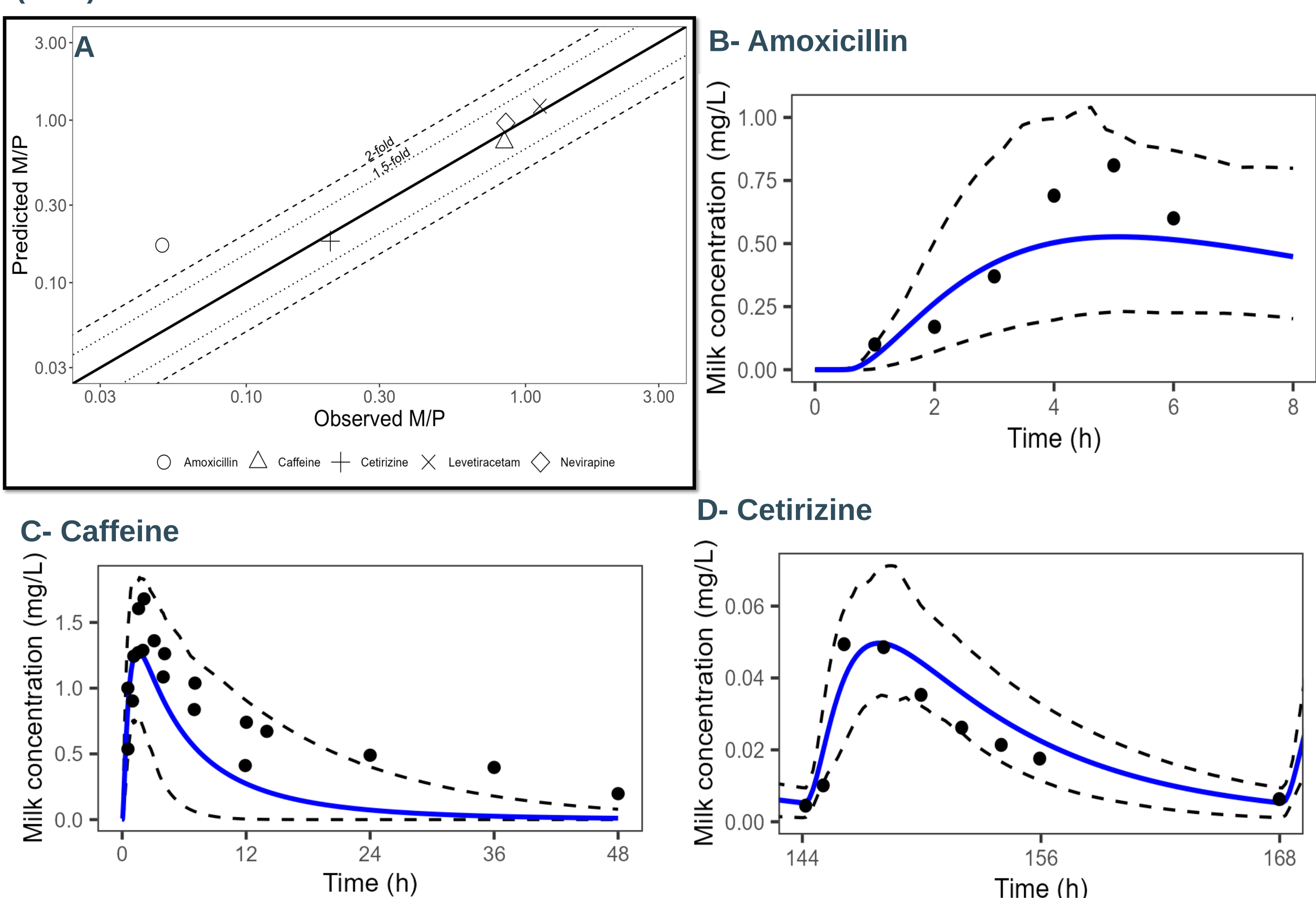
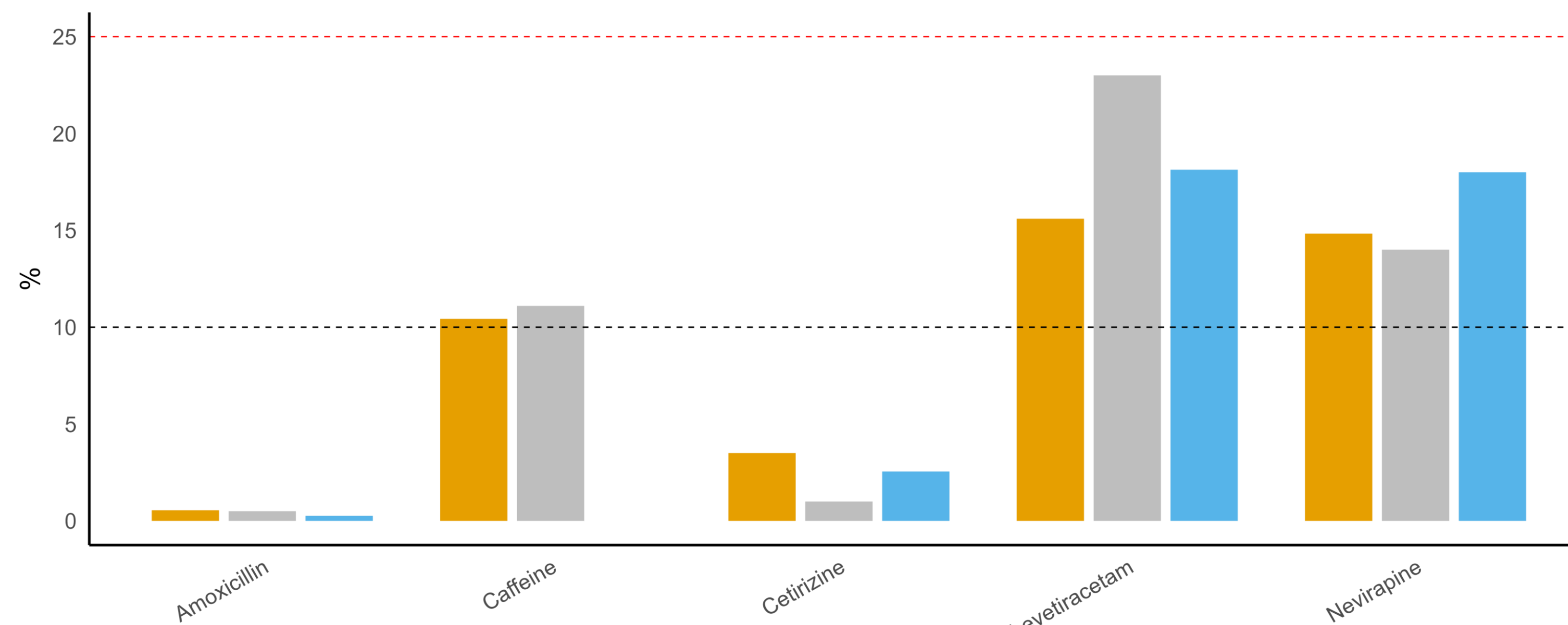


Figure 4. Predicted relative infant dose, relative infant exposure and daily infant dosage as a percentage of the pediatric therapeutic dose (RID_{therapeutic}).

■ RID ■ RID_{therapeutic} ■ RIE



The appropriate threshold to be considered when evaluating these results is still debated. Some authors suggest that RID <10% can be considered a **safety threshold in risk assessment** while ≥25% suggests to be **avoided** by breastfeeding mothers.

Conclusion

- ✓ The PBPK models were developed to successfully predict plasma concentrations in adult HVS, as well as human milk concentration in lactating women.
- ✓ The lactation PBPK models successfully predicted the M/P ratios found in clinical reports, by relying on *in vitro* permeability data across the blood-milk barrier.
- ✓ The estimated RID, RIE and RID_{therapeutic} remained below 25% for all drugs.
- ✓ This workflow will be applied to additional medicines selected in the context of the IMI Conception project.

References

- [1] Nauwelaerts N et al. *Pharmaceutics*. 2023;15(5). doi:10.3390/pharmaceutics15051469 [2] Pansari A et al. *Biopharm Drug Dispos*. 2022;43(5):201–212. doi:10.1002/bdd.2334 [3] La Mantia D et al. *Int J Mol Sci*. 2024;25(21). doi:10.3390/ijms25211454/ [4] Zhang T et al. *Biopharm Drug Dispos*. 2022;43(6):221–232. doi:10.1002/bdd.2335 [5] Yang H et al. *Mol Pharm*. 2022;19(7):2506–2517. doi:10.1021/acs.molpharmaceut.2c00193.

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LinkedIn:

✉ julia.macente@kuleuven.be
macentejulia@gmail.com

