PBPK modelling and simulation on lactation related drug exposure

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The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant no. 821520. The contents reflect the ConcePTION project's view and not that of IMI/EU/EFPIA.

Outline

- Understanding Physiologically-based pharmacokinetic (PBPK) models
- Workflow for developing lactation and infant PBPK models
- PBPK-based simulations of concentrations in human milk for 10 model drugs
- Conclusions and futures perspectives

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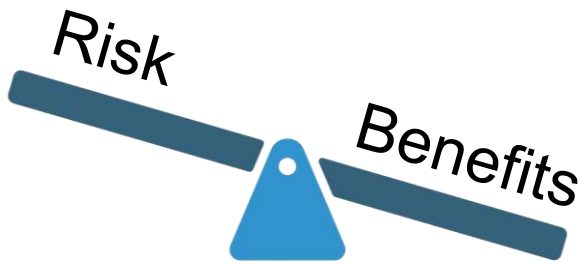
Risk related to medication and breastfeeding

1 in 4 women use medication during breastfeeding

< 5 percent of approved drugs have human lactation data (Wang et al., 2017);

Insufficient information to support the medication safety for pediatrics during lactation



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innovative medicines initiative

ConcePTION is a private and public partnership that aims to generate information about the use of **medicines** during **pregnancy** and **breastfeeding**.

imi.europa.eu/projects-results/project-factsheets/conception

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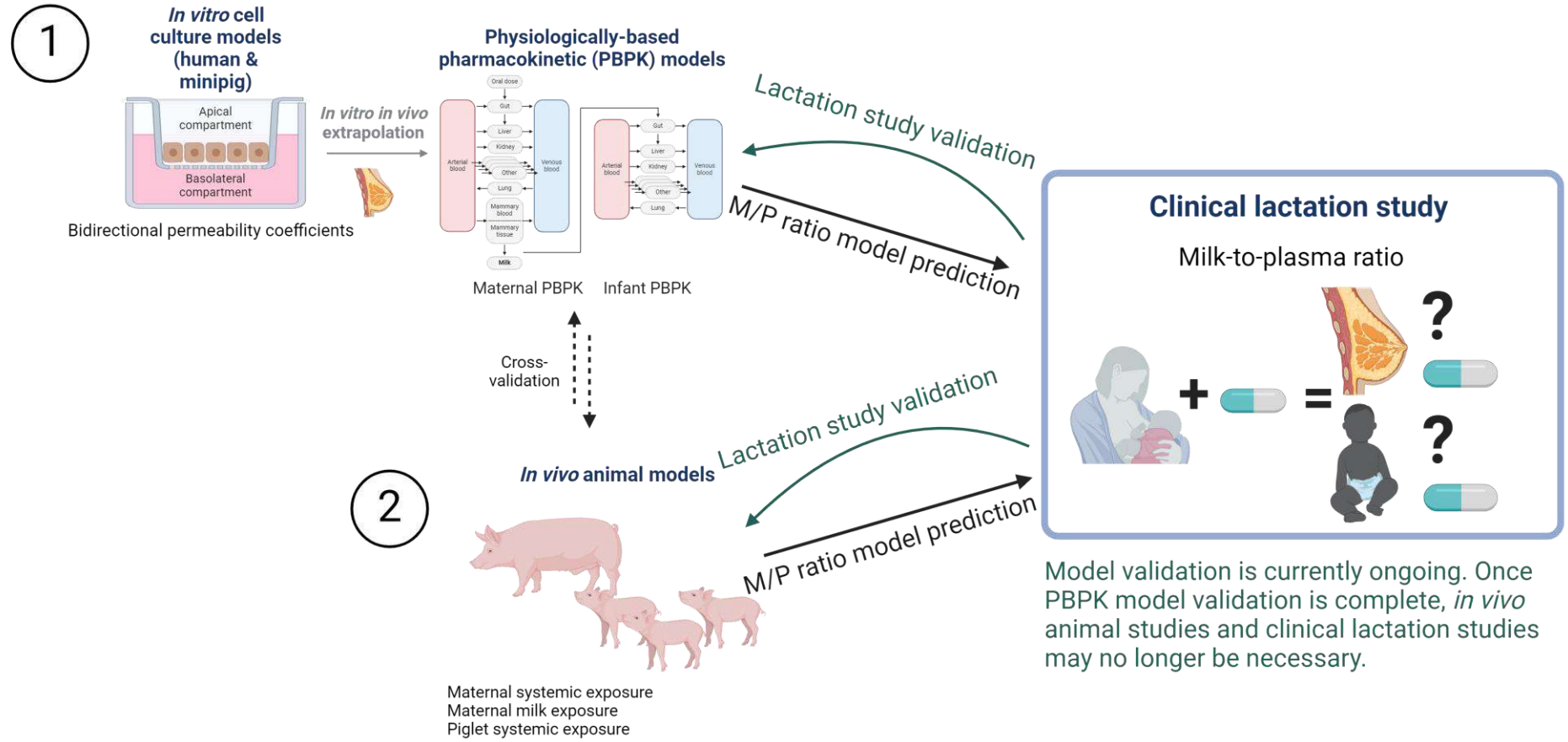
Non-clinical platform for predicting milk and infant exposure to maternal medication



Model validation is currently ongoing. Once PBPK model validation is complete, *in vivo* animal studies and clinical lactation studies may no longer be necessary.

1. *In vitro/in silico* pathway
2. *In vivo* pathway

M/P ratio predictions for either pathway will be compared to available human data (e.g. M/P ratio) to validate the models towards verification.

Most of the figures in this presentation were created with Biorender.com. Adapted from Nauwelaerts N, Deferm N, Smits A et al. A comprehensive review on non-clinical methods to study transfer of medication into breast milk – A contribution from the ConcePTION project. Biomedicine & Pharmacotherapy, volume 136, article 111038, April 2021.

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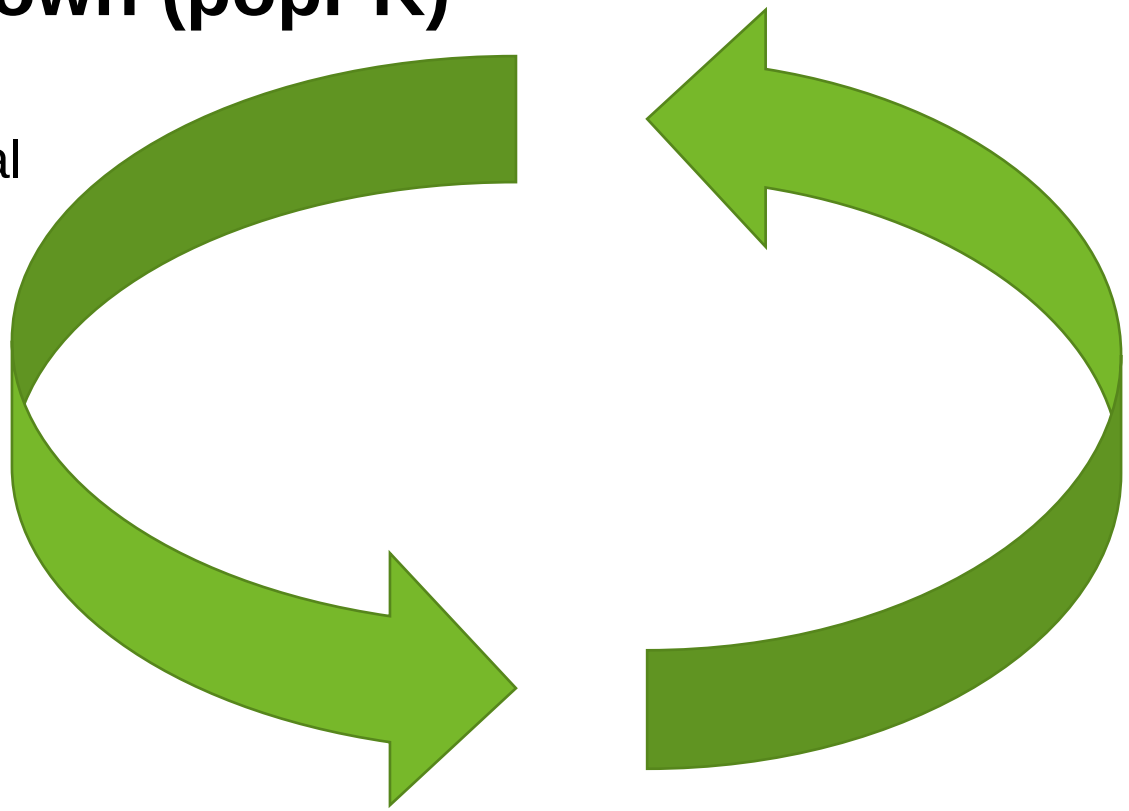
Top-down (popPK)

Observed data (clinical concentration data)

Pharmacokinetic information and builds a model that fits the data.



Physicochemical properties/drug-specific data (e.g., logP, molecular weight, solubility, ADME...); system data/ physiological data (e.g., organ volume, blood flow..)

Bottom-up (PBPK)

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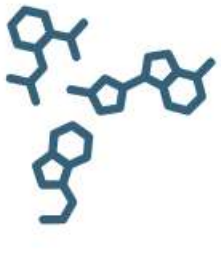
PBPK models can inform safety during lactation

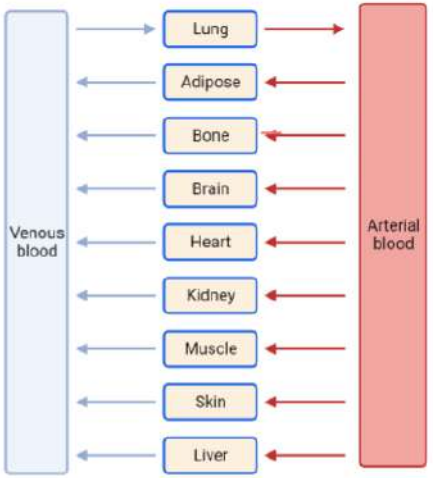
Physiologically-based pharmacokinetic (PBPK) model



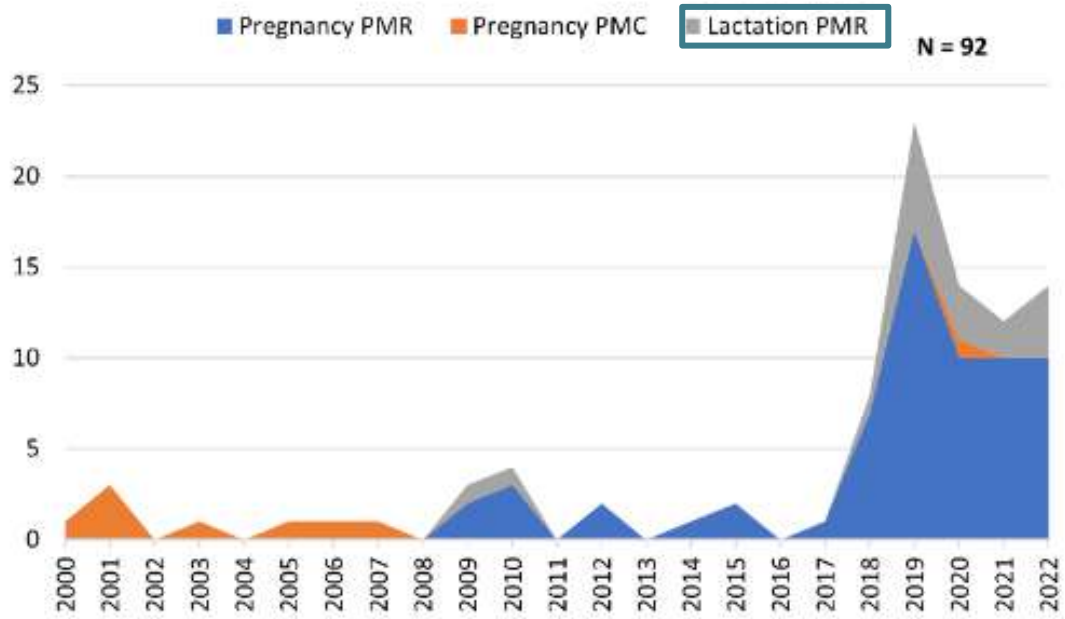
In vitro
In silico

Drug-specific parameters

Clinical trial design-specific parameters

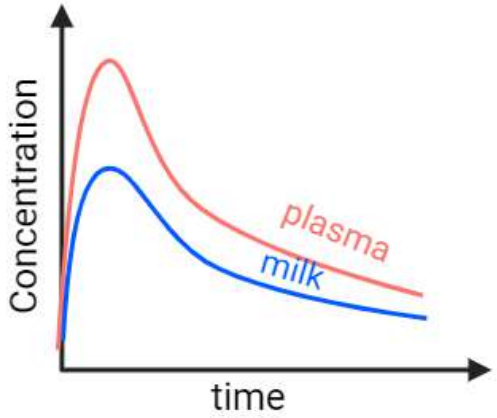


System-specific(physiology) parameters



Avachat et al., 2023

Simulate **A**bsorption **D**istribution **M**etabolism **T**ransporters and **E**xcretion of a drug from the body.



Concept paper on **revision** of the **Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling**

PMR: Postmarketing requirements

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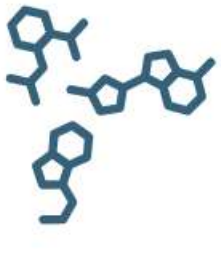
PBPK models can inform safety during lactation

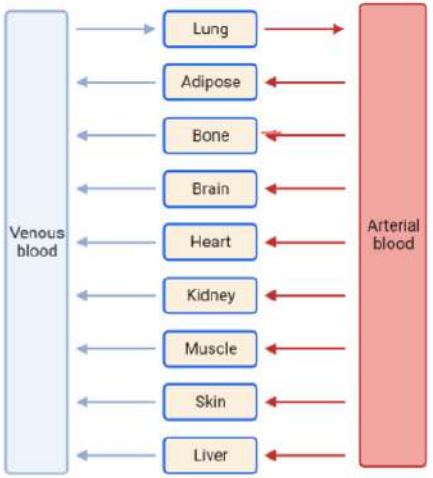
Physiologically-based pharmacokinetic (PBPK) model



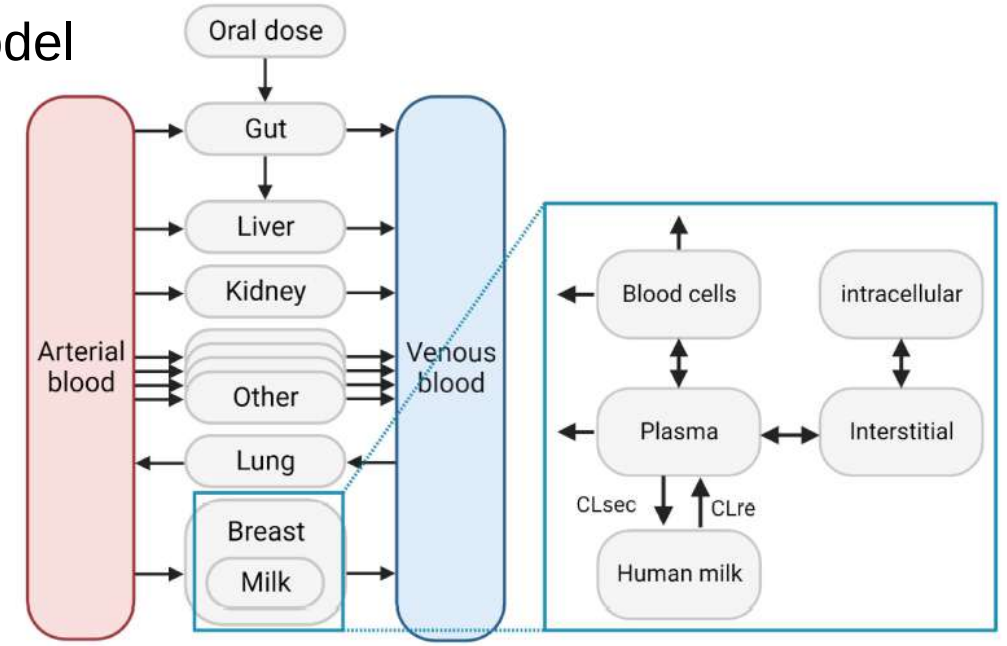
In vitro
In silico

Drug-specific parameters

Clinical trial design-specific parameters

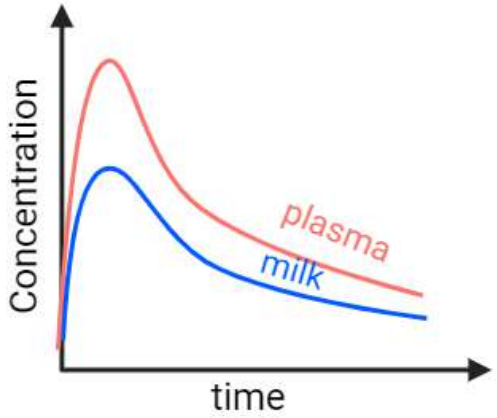


System-specific(physiology) parameters



Nauwelaerts et al., 2023

Simulate **A**bsorption **D**istribution **M**etabolism **T**ransporters and **E**xcretion of a drug from the body.



Lactation PBPK models can **predict** the **drug concentration** in **human milk** and guide **infant risk assessment** in cases of **maternal medication.**

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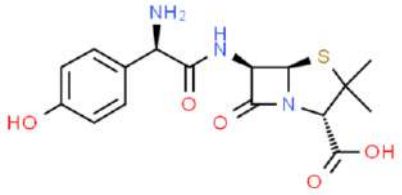
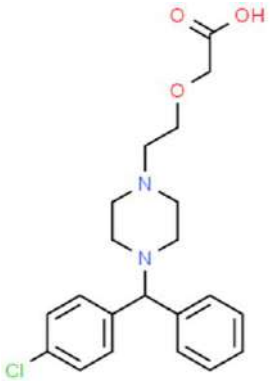
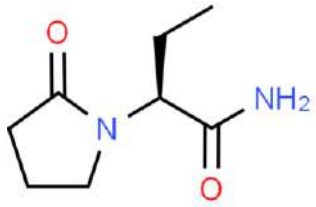
Model compounds



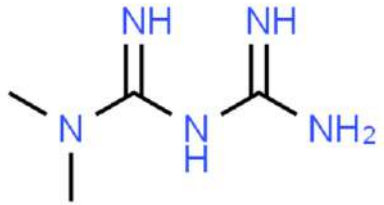
Amoxicillin
(Renal)



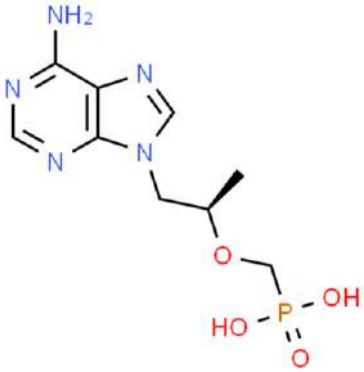
Cetirizine
(Renal)



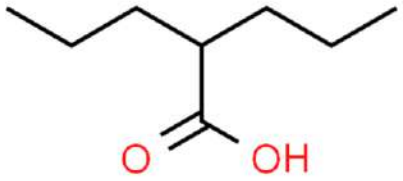
Levetiracetam
(Renal/Esterases)



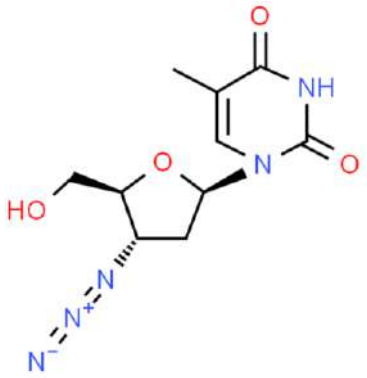
Metformin
(Renal)



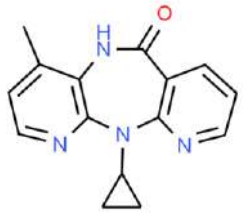
Tenofovir
(Renal)



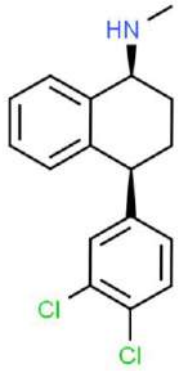
Valproic Acid
(Hepatic UGTs)



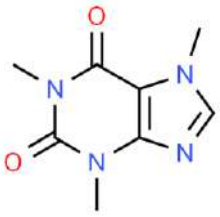
Zidovudine
(Hepatic UGT2B7)



Nevirapine
(Hepatic CYP3A4)



Sertraline
(Hepatic CYPs)



Caffeine
(Hepatic CYP1A2)

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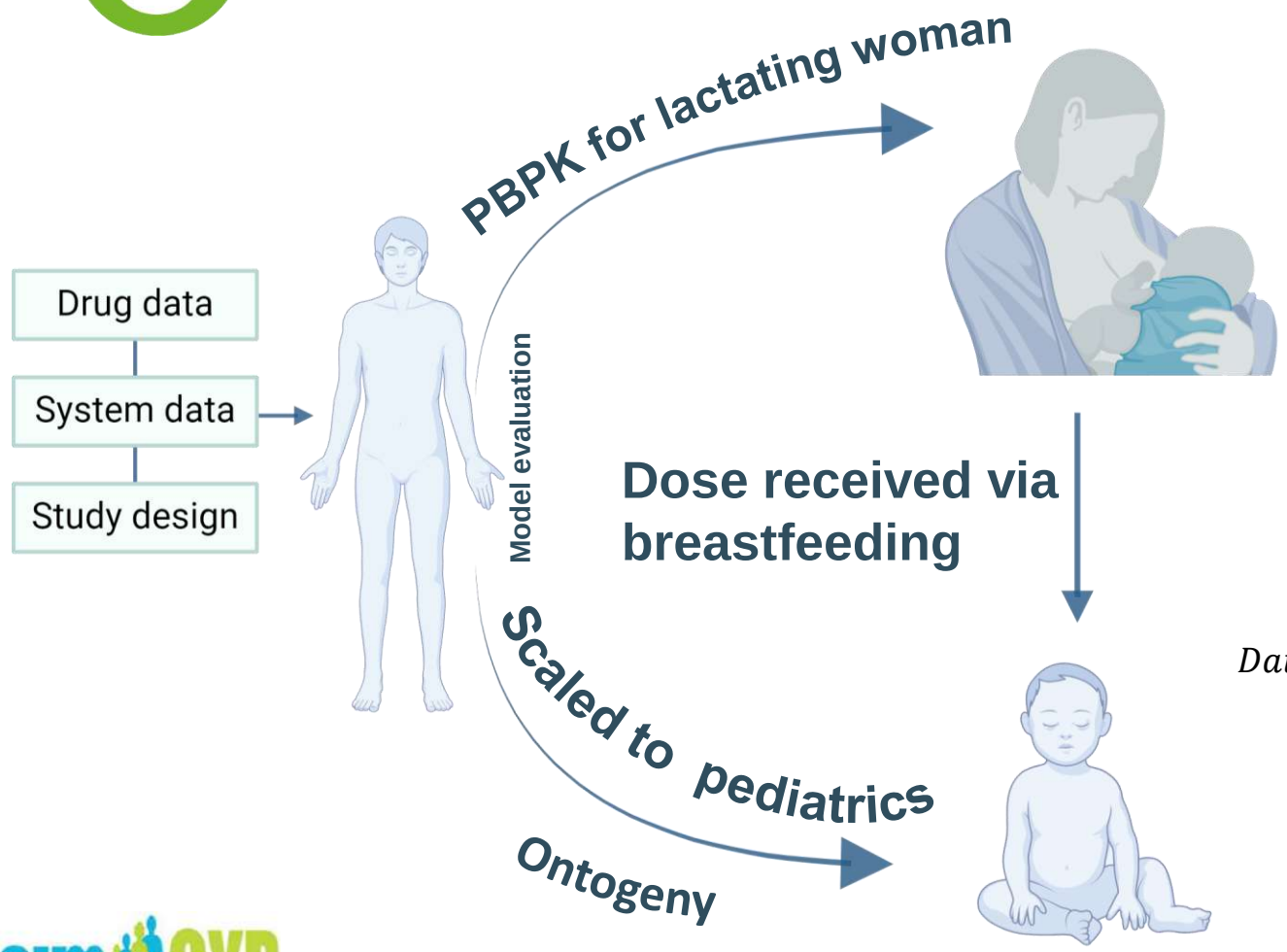
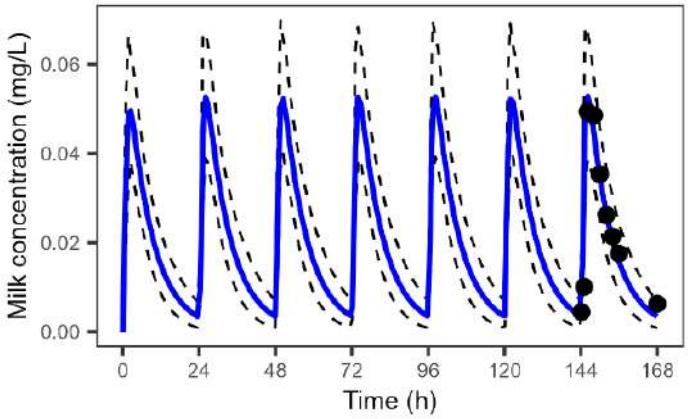
Workflow for lactation PBPK model development





$$C_{average,milk} = \frac{AUC_{milk}}{\tau}$$

$$Daily\ infant\ dosage\ (mg/kg/day) = C_{average,milk}\ x\ milkvolume\ \frac{mL}{kg\ .day}$$

$$\text{Relative infant dose (RID, \%)} = \frac{Infant\ daily\ dosage}{Maternal\ daily\ dosage} \text{ x } 100$$

$$Relative\ Infant\ Exposure\ (RIE, \%) = \frac{AUC\ Infant}{AUC\ maternal}$$

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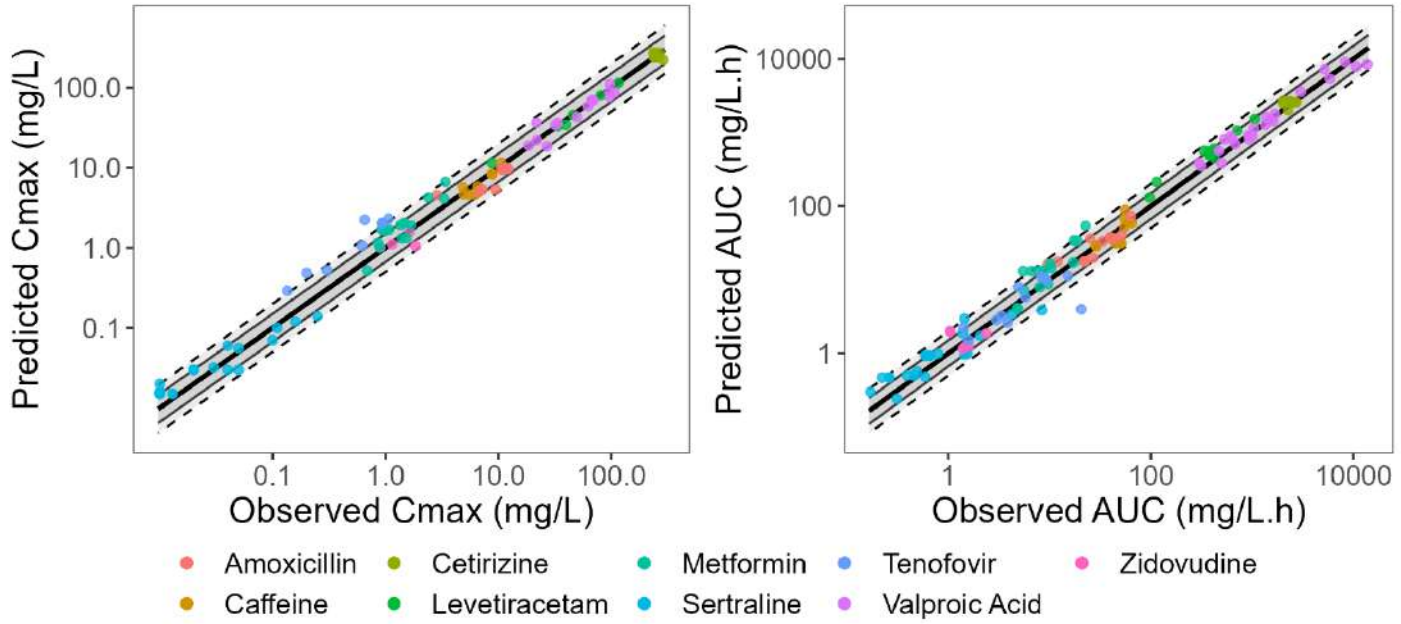
PBPK model performance for adult healthy volunteers

Drug Data

System data

Study design

Sim-Healthy Volunteers



Overall (across all drugs) PBPK model performance for adult healthy volunteers (males and females) was within 2-fold margin for AUC and Cmax.

This qualified as base model for lactation PBPK model

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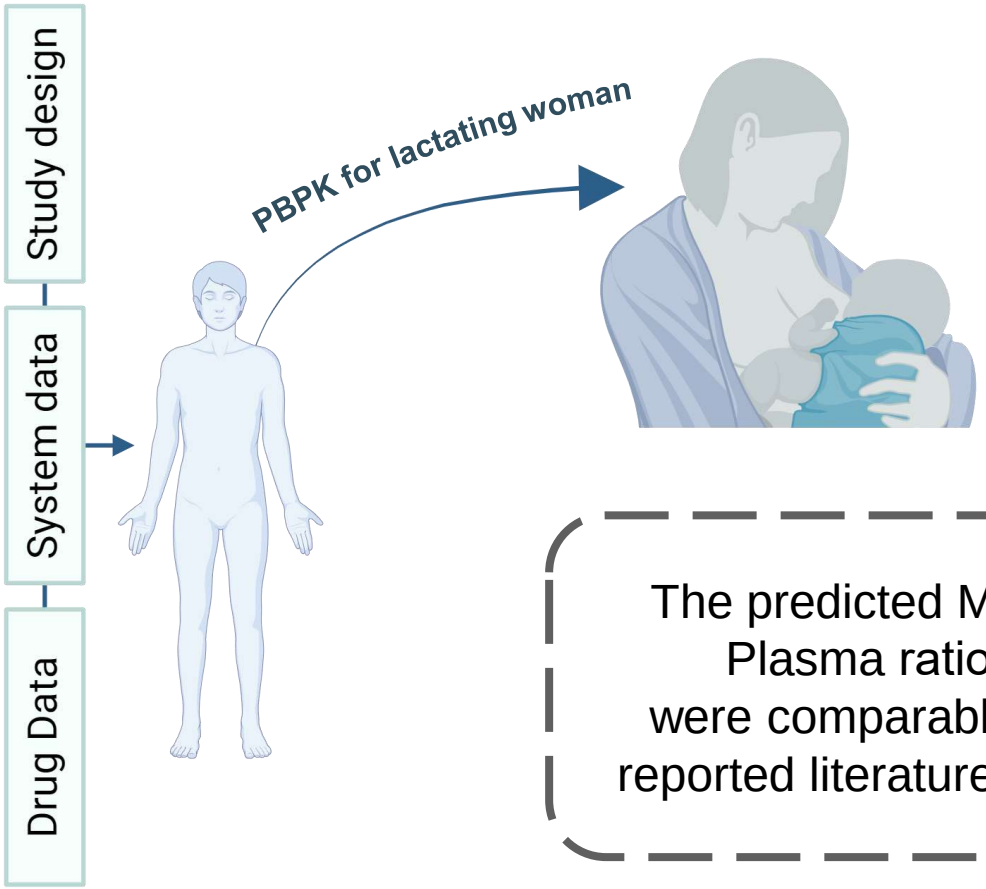
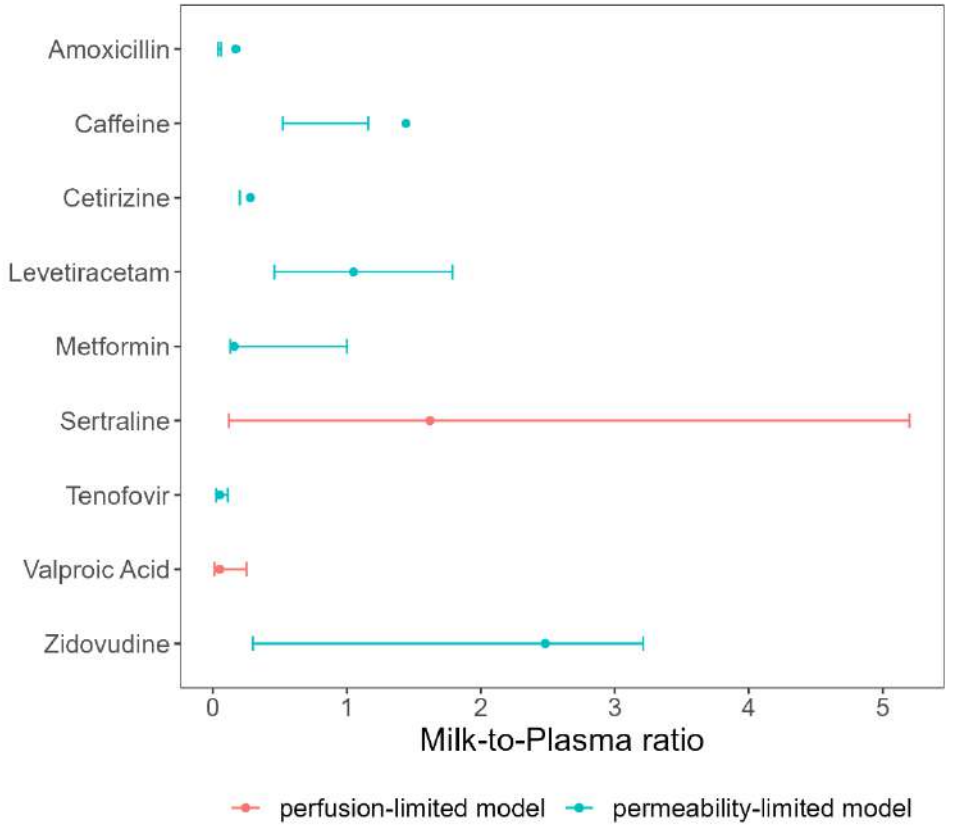
PBPK Prediction of Milk-to-Plasma Ratio



The predicted Milk-to-Plasma ratio's were comparable with reported literature values



The points represent the M/P ratio predicted by the lactation PBPK model and the solid line represents the M/P range reported in the literature.

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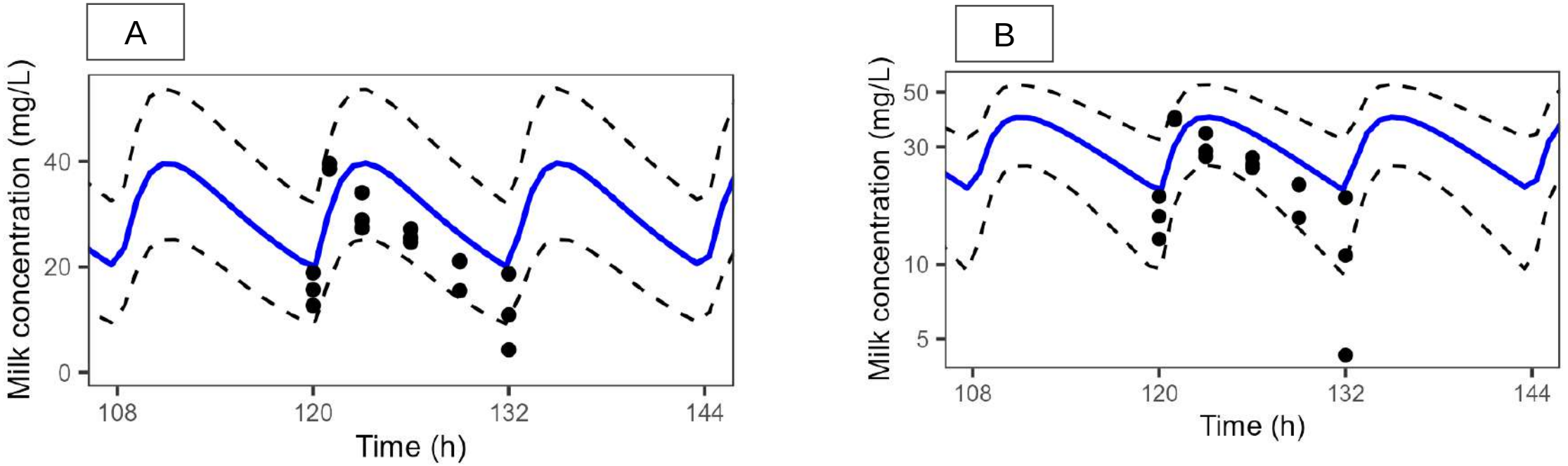
Comparison between prediction and clinical observed data for milk Levetiracetam (Keppra®)



Clinical observed data after maternal oral administration of 1500 mg/day (Dinavitser et al., 2020)
Figure (B) shown the data with the y-axis on a log scale.

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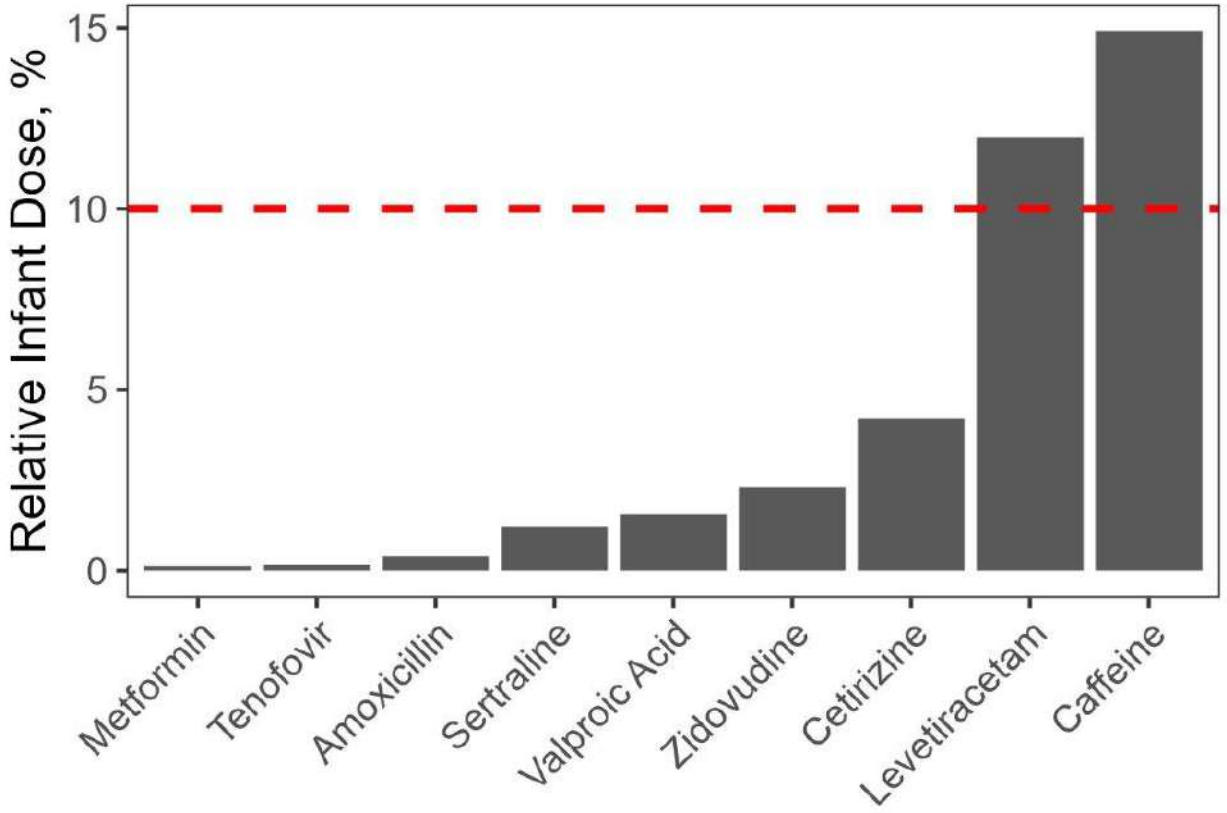
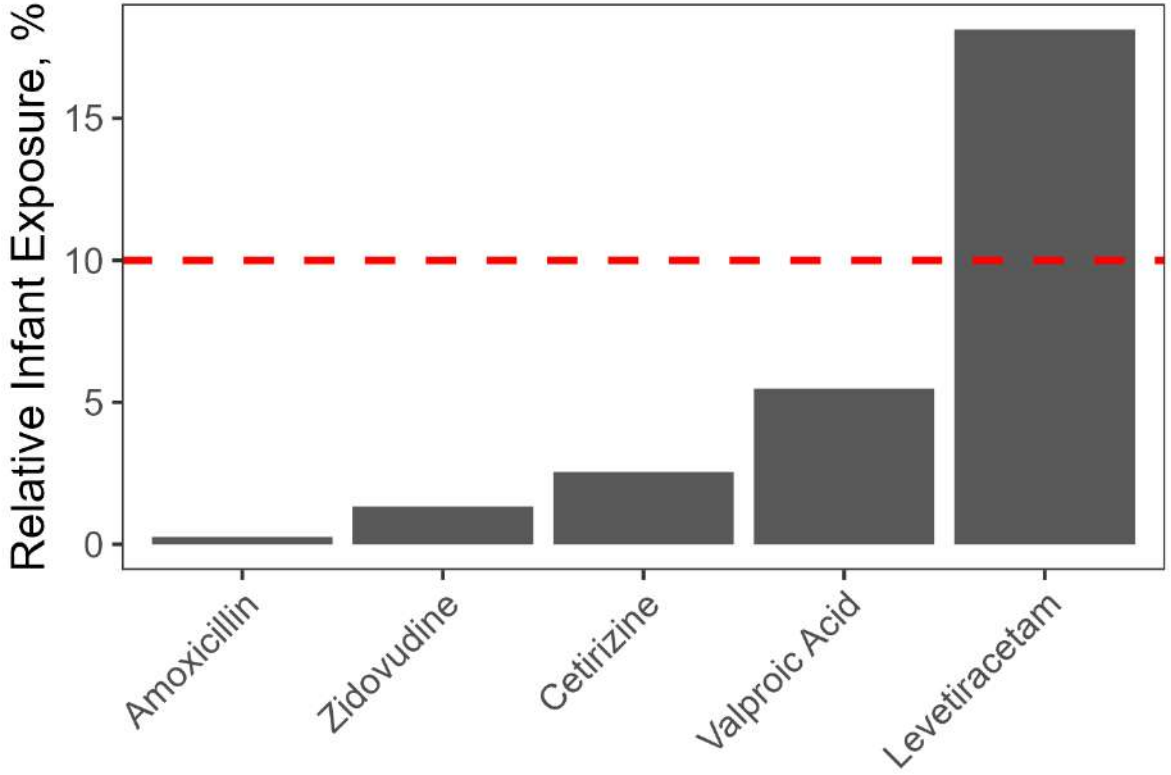
Predicted Relative Infant Dose (%)



Predicted Relative Infant Exposure (%)



$$\text{Relative infant dose (RID, \%)} = \frac{Infant\ daily\ dosage}{Maternal\ daily\ dosage} \text{ x } 100$$

$$Relative\ Infant\ Exposure\ (RIE, \%) = \frac{AUC\ Infant}{AUC\ maternal}$$

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Conclusions and future perspectives

- ✓Lactation PBPK models can **predict** the **drug concentration** in **human milk** and guide infant risk assessment in cases of maternal medication;
- ✓PBPK-based simulations are expected to inform product labelling in medication use during lactation (**applying EMA qualification/opinion**);

"IMI ConcePTION Work Package 3 is seeking European Regulator's support of this innovative non-clinical platform for reliable prediction of medicine concentrations in human milk along with systemic exposure in infants. "

- ✓Future and ongoing efforts will implement *in vitro* permeability coefficients across the blood – milk barrier

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UZ Leuven, Belgium
IMI ConcePTION partners
University of Bologna, Italy
Novartis Institutes for BioMedical Research

Nina Nauwelaerts, Justine Marine Badée, Rodolfo Hernandes Bonan, Martje Van Neste, Miao-Chan Huang, Anne Smits, Karel Allegaert, Pieter Annaert

"The research leading to these Results was conducted as part of the ConcePTION consortium. This presentation only reflects the personal views of the stated authors."

"This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking ConcePTION grant no. 821520."

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Thank you!

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