

Advancing Maternal-Fetal and Lactation PBK Models for Cross-Species Risk Assessment in Toxicology

Sophie Fischer-Holzhausen (1), Raphaëlle Lesage (1), Leonie Lautz (1), Styliani Fragki (1), Pavel Balazki (1), Stephan Schaller (1), Marco Siccardi (1)

(1) ESQlabs GmbH, Saterland, Germany



Presenter:
Sophie Fischer-Holzhausen
sophie.fischer-holzhausen@esqlabs.com
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Introduction

Chemical exposure during pregnancy and postpartum may pose risks to the female and offspring. Yet, in-silico methods offer valuable insights to assess these risks. Physiologically Based Kinetic (PBK) models are well-suited, as they can consider physiological adaptations and substance transfer processes while predicting tissue concentration profiles.

We are expanding the Open Systems Pharmacology (OSP) [1] library to include **pregnancy and lactation models for rats and humans to facilitate comprehensive safety evaluation across species.**

Methods

Data collection

- physiological parameters
- pharmacokinetic data for validation compounds

Model development

- human and rat model structures (Fig.1 and 2) are closely matching → comparability of results
- base models for rat and human available in OSP Suite
- placenta and milk transfer described as permeability-limited processes

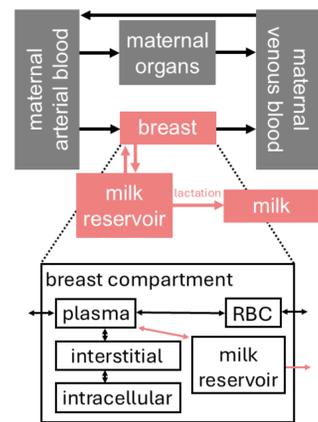


Fig. 1: Simplified representation of lactation PBK model structure for human and rat.
RBD stands for Red Blood Cells.

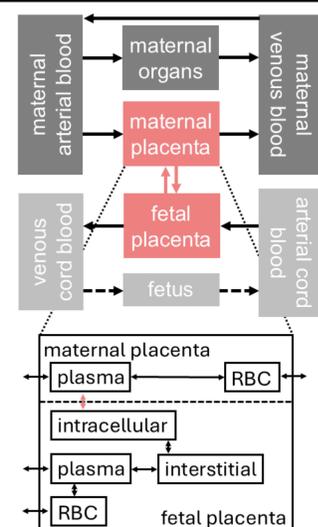


Fig. 2: Simplified pregnancy PBK model for human and rat.
Maternal placenta includes interstitial and intracellular spaces (not shown).

Application example: Prediction of maternal and fetal acyclovir exposure

... in human

Fig. 3: Predicted maternal plasma acyclovir concentration. Oral administration 400mg three times daily during late pregnancy. Data from [2, 3, 4].

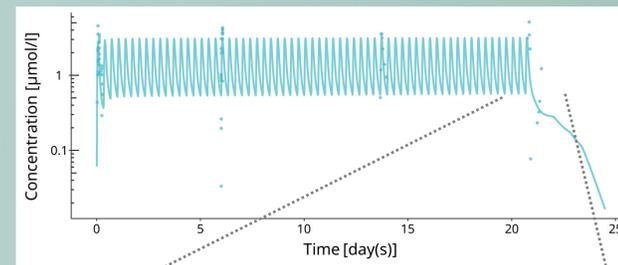


Fig. 4: Predicted maternal plasma and umbilical cord acyclovir concentration at delivery. Data from [3].

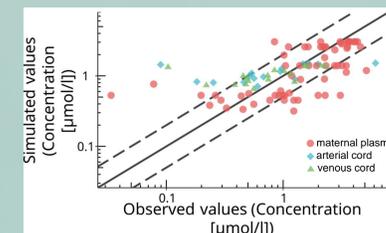
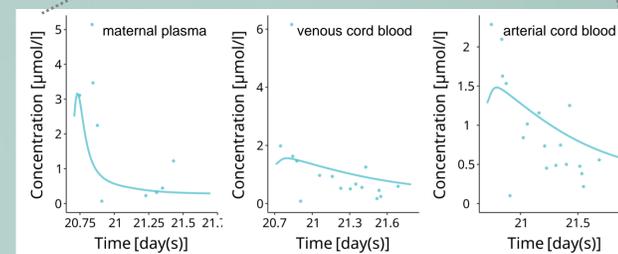


Fig. 5: Predicted vs observed acyclovir concentrations. Dashed lines present the 2-fold deviation.

References

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... in rat

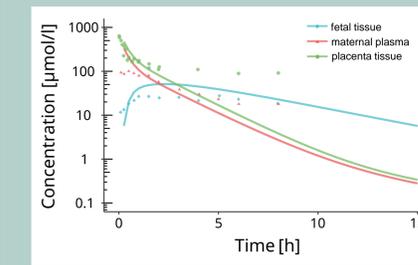


Fig. 6: Predicted acyclovir concentration in maternal plasma, placenta tissue, and fetal tissue. Intravenous administration of 60 mg/kg. Data from [5,6].

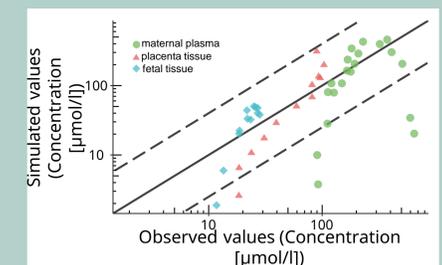


Fig. 7: Predicted vs observed acyclovir concentrations. The dashed line presents the 4-fold deviation.

- placental permeability derived from compound properties underestimates fetal exposure → data-driven optimization improves predictions
- 86% of the predictions fall within the 4-fold change

Conclusion

- model implementation allows for the simulation of long-term exposure during pregnancy and the lactation period
- placenta permeability parameters derived by PK-Sim QSAR for permeability may not be ideal for predicting placenta transfer
 - alternatives for estimating placenta permeability: BeWo cell assay and placenta perfusion experiment
- due to the placenta description model has limited abilities to capture transfer during early pregnancy
- apply models to compounds from a larger chemical space