

Physiologically-based prediction of pharmacokinetics in neonates suffering from perinatal asphyxia and undergoing therapeutic hypothermia - midazolam and its metabolite as case example -

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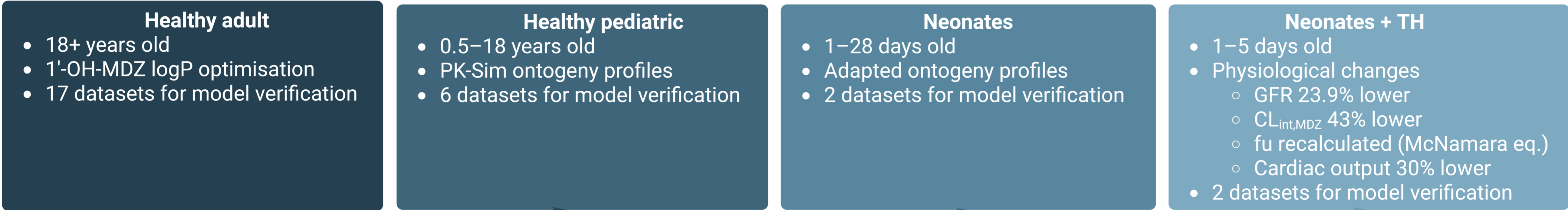
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Background & objective

- ❑ Perinatal asphyxia = 5th most common mortality cause for children < 5 years old [1]
- ❑ Treatment = Therapeutic Hypothermia (TH) → Core body temperature is decreased to 33.5 °C for 72 hours to improve mortality & morbidity outcome
- ❑ TH is associated with a **clinically relevant** impact on the pharmacokinetics (PK), but mechanistic understanding about the impact on **total body clearance**, absorption & volume of distribution is limited [1-2]
- ❑ Accurate & precise prediction of the influence of asphyxia and TH on the PK of a specific drug (in a particular neonate; 0-28 days old) = currently not available
- ❑ Midazolam = clinically relevant drug in this population; it is administered for comfort & to reduce seizures during TH
- ❑ **Goal = PBPK model development of midazolam (MDZ) and 1'-hydroxymidazolam (1'-OH-MDZ) in neonates treated with therapeutic hypothermia (TH)**

Methods

Modelling workflow to achieve a PBPK model for MDZ and 1'-OH-MDZ in neonates with therapeutic hypothermia



McNamara equation:
adapted from [3]
to recalculate fu in neonates

$$f_{u, \text{neonate} + \text{TH}} = \frac{1}{1 + \frac{P_{\text{neonate}} \times (1 - f_{u, \text{adult}})}{P_{\text{neonate}} \times f_{u, \text{adult}}}}$$

With $P_{\text{adult}} = [\text{albumin}]_{\text{plasma, adult}} = 45 \text{ g/L}$
 $P_{\text{neonate} + \text{TH}} = [\text{albumin}]_{\text{plasma, neonate} + \text{TH}} = 23 \text{ g/L}$

$f_{u, \text{adult, MDZ}} = 0.031$
 $f_{u, \text{adult, 1-OH}} = 0.15$

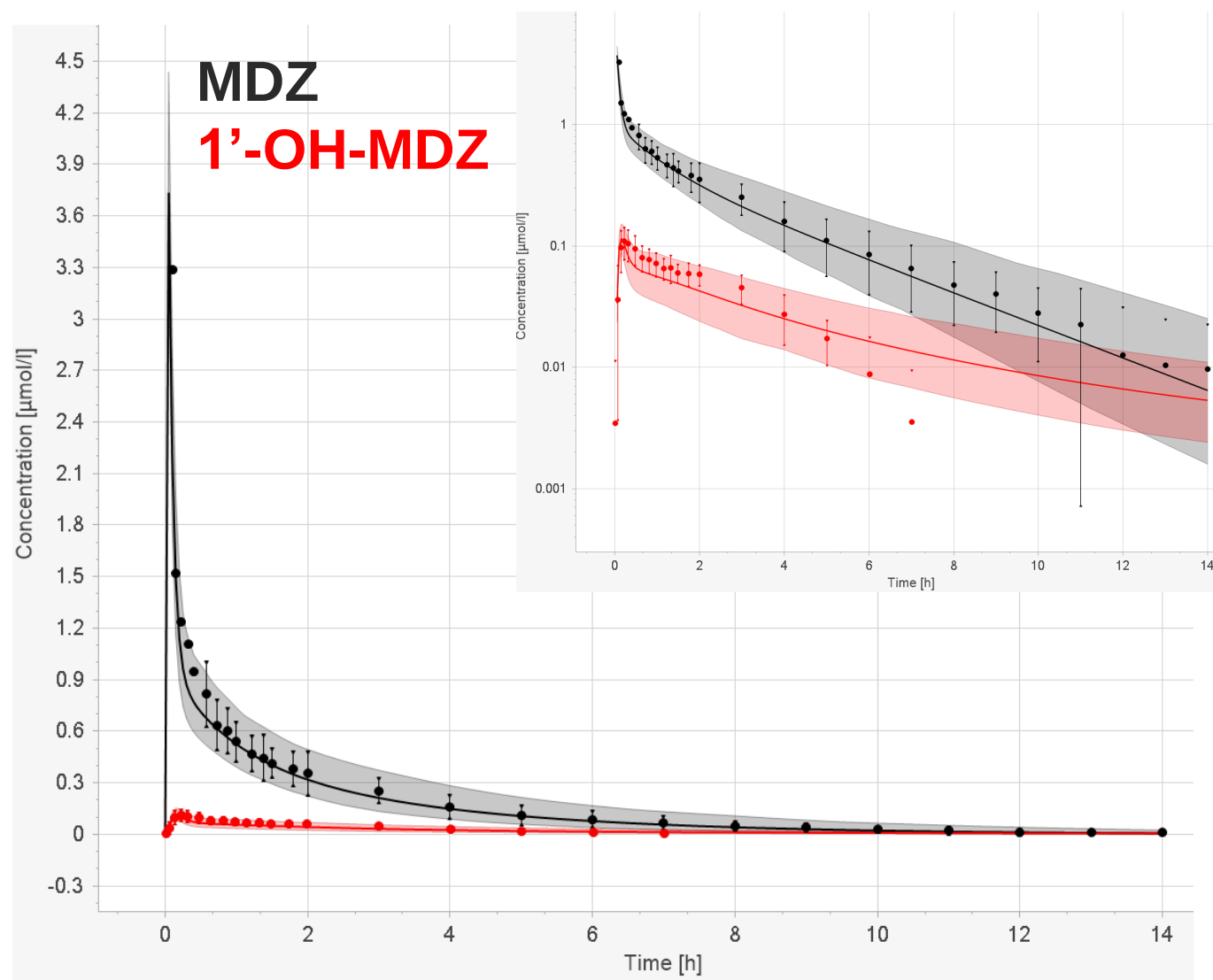
Results and discussion

Healthy adult prediction

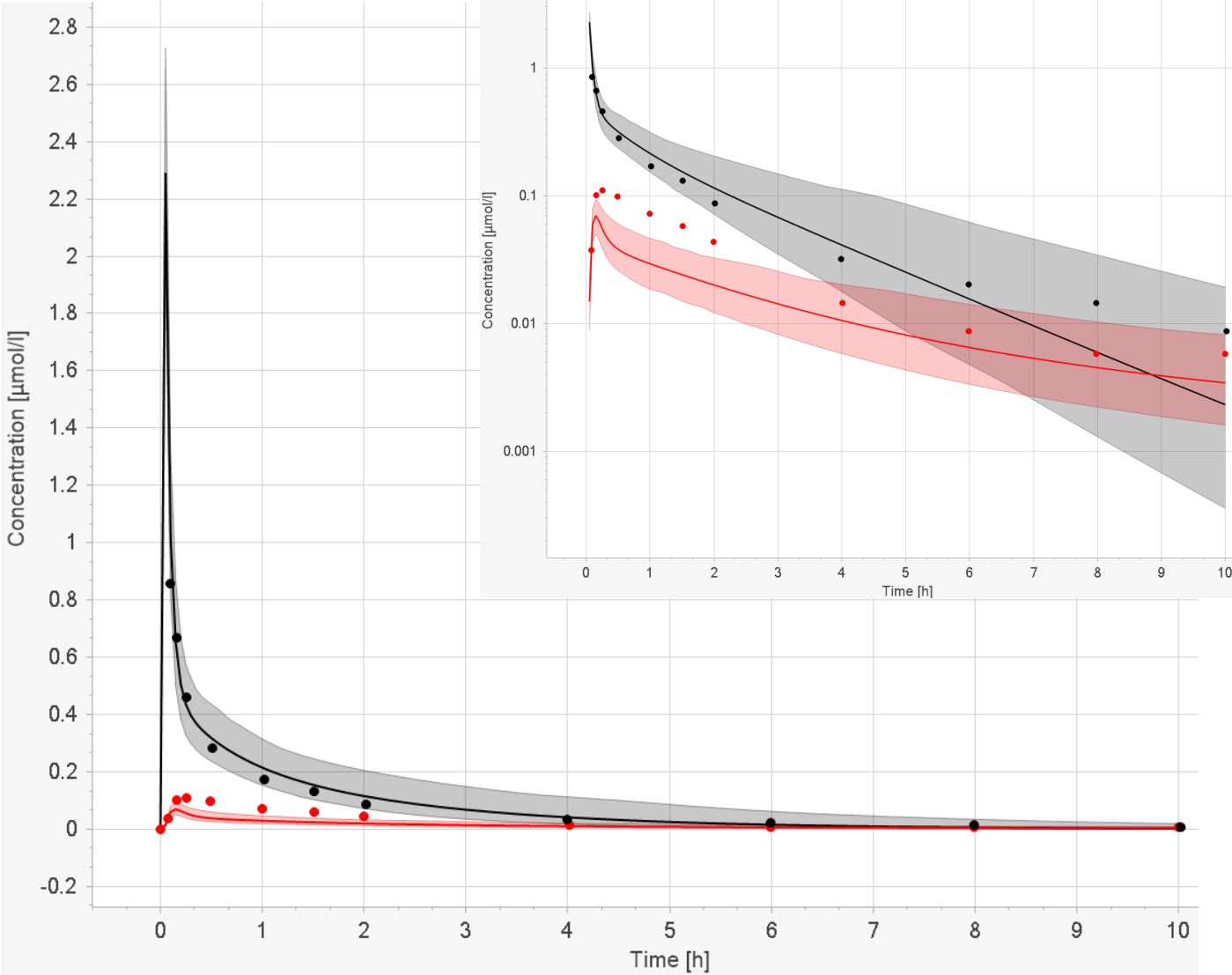
Healthy pediatric prediction

Neonatal prediction
(Preterm NICU patients)

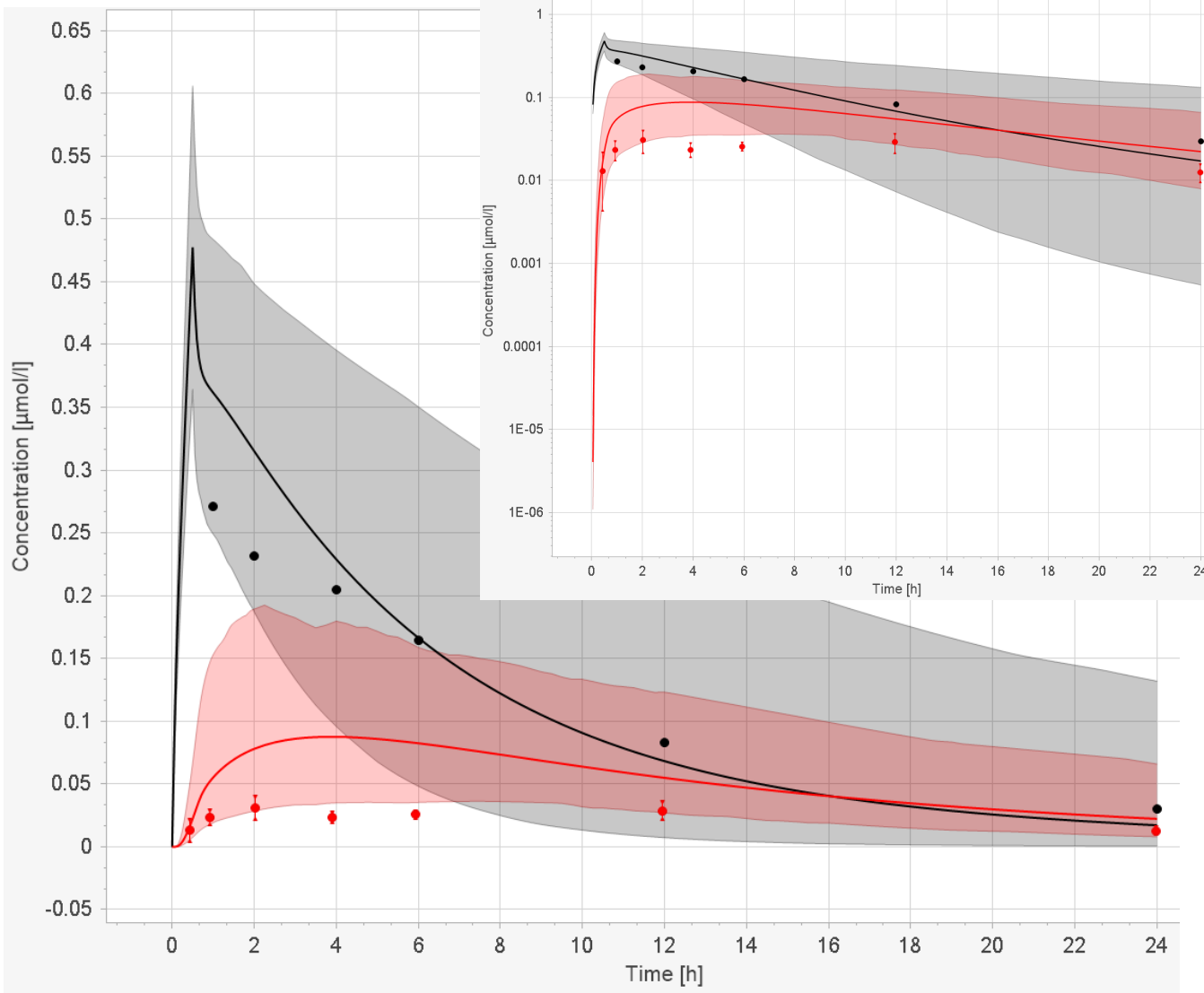
Neonates + TH prediction



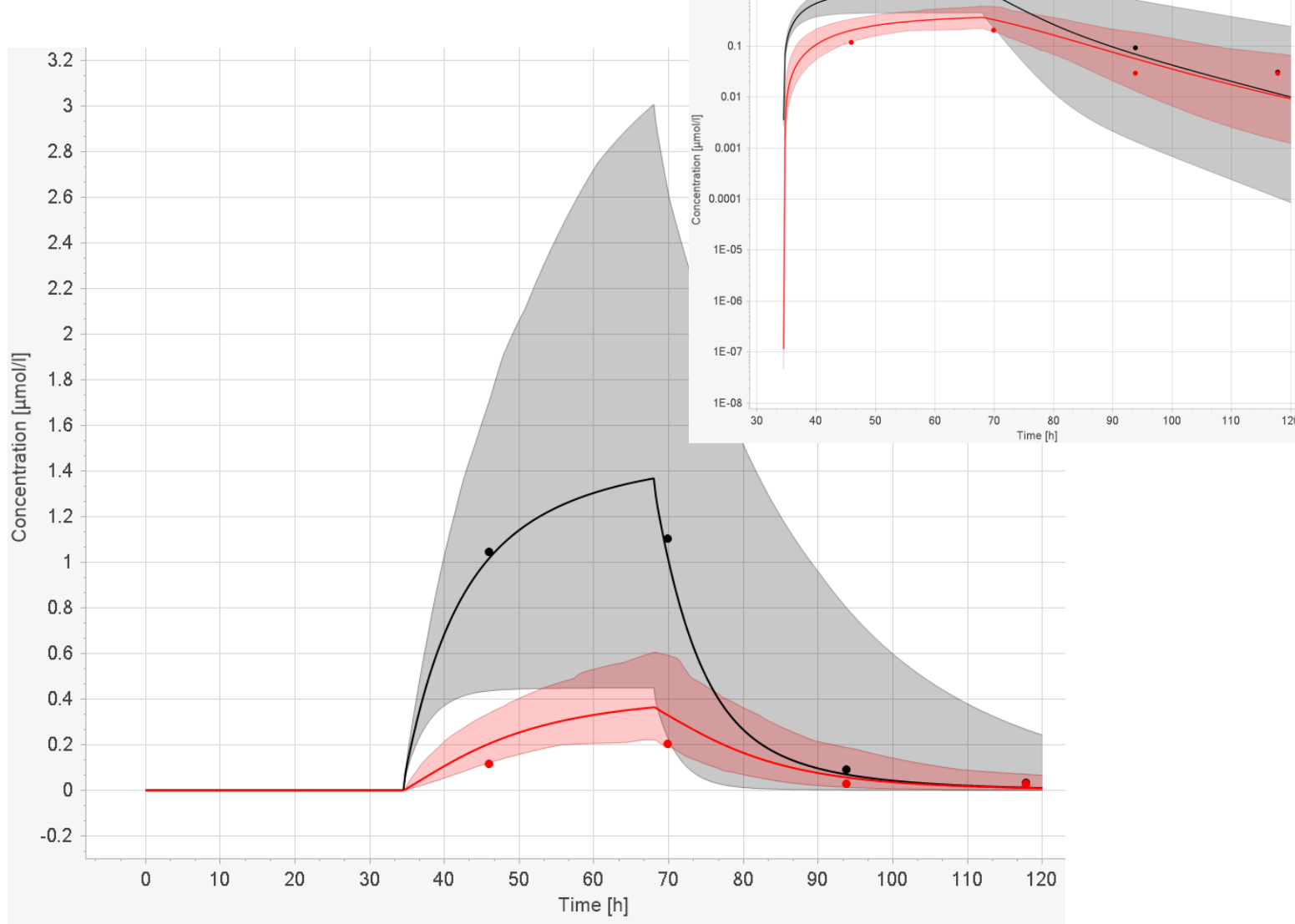
Clausen *et al.* 1988 [4]
0.3 mg/kg IV bolus of MDZ



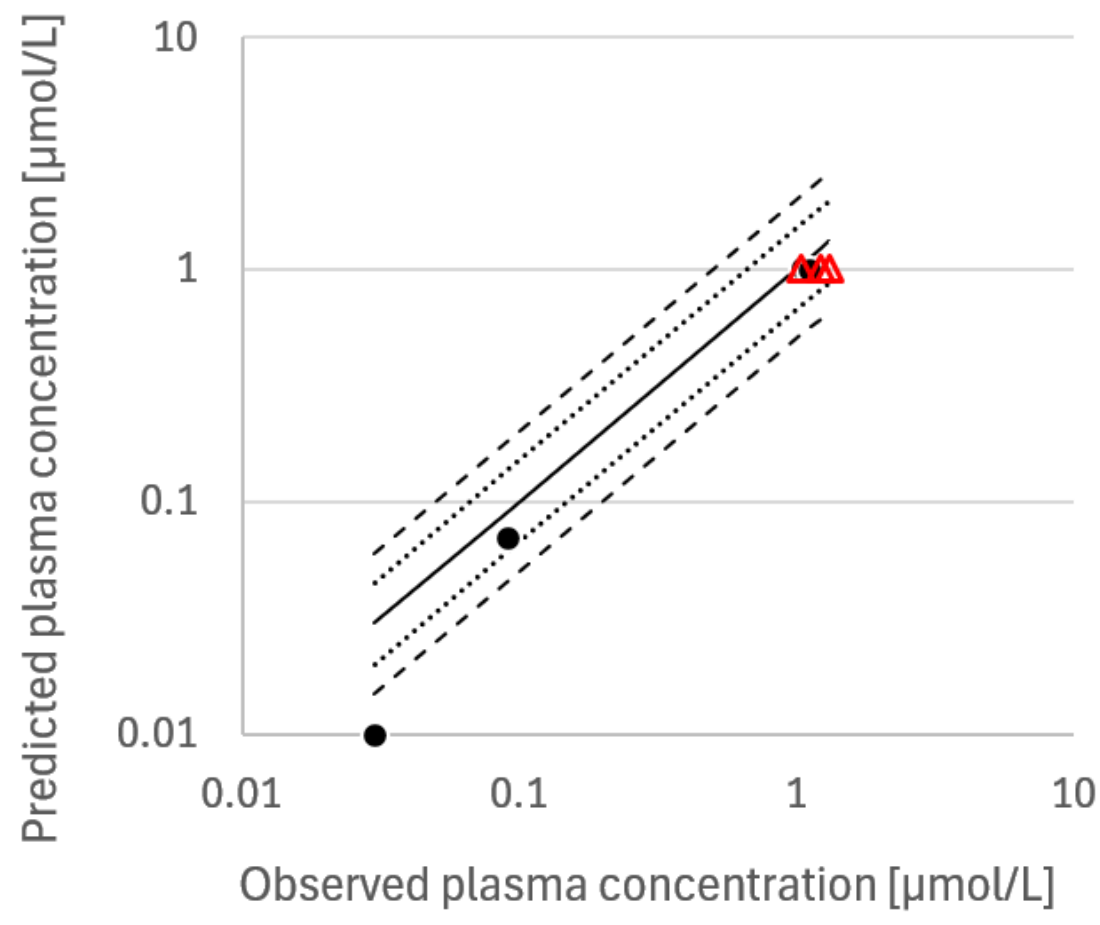
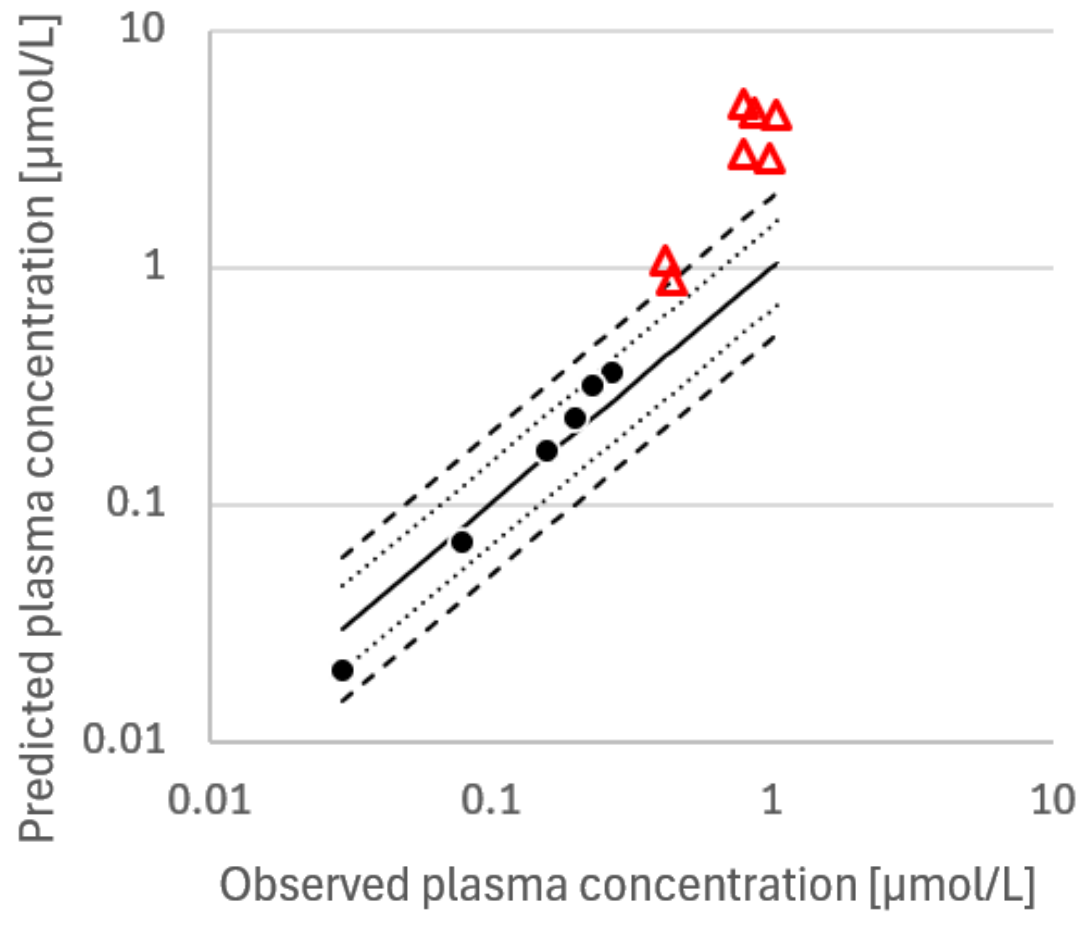
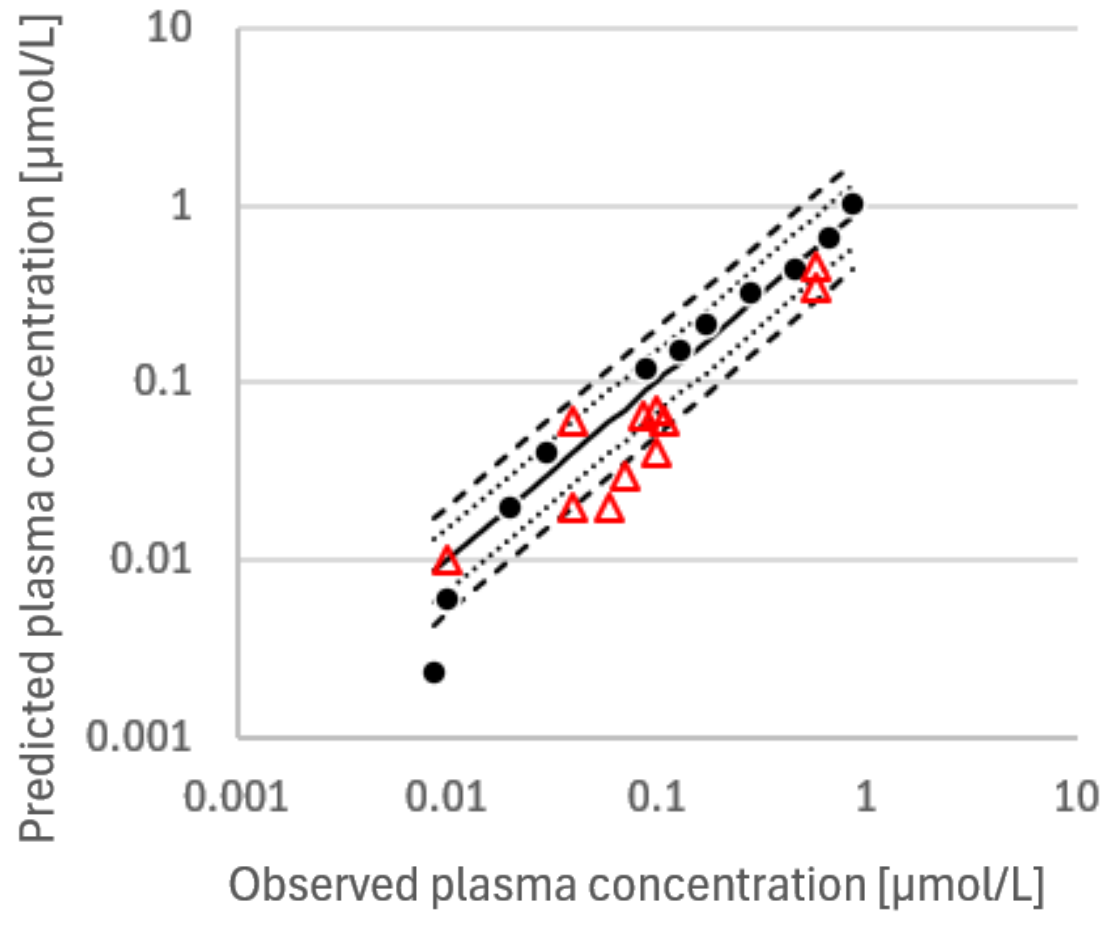
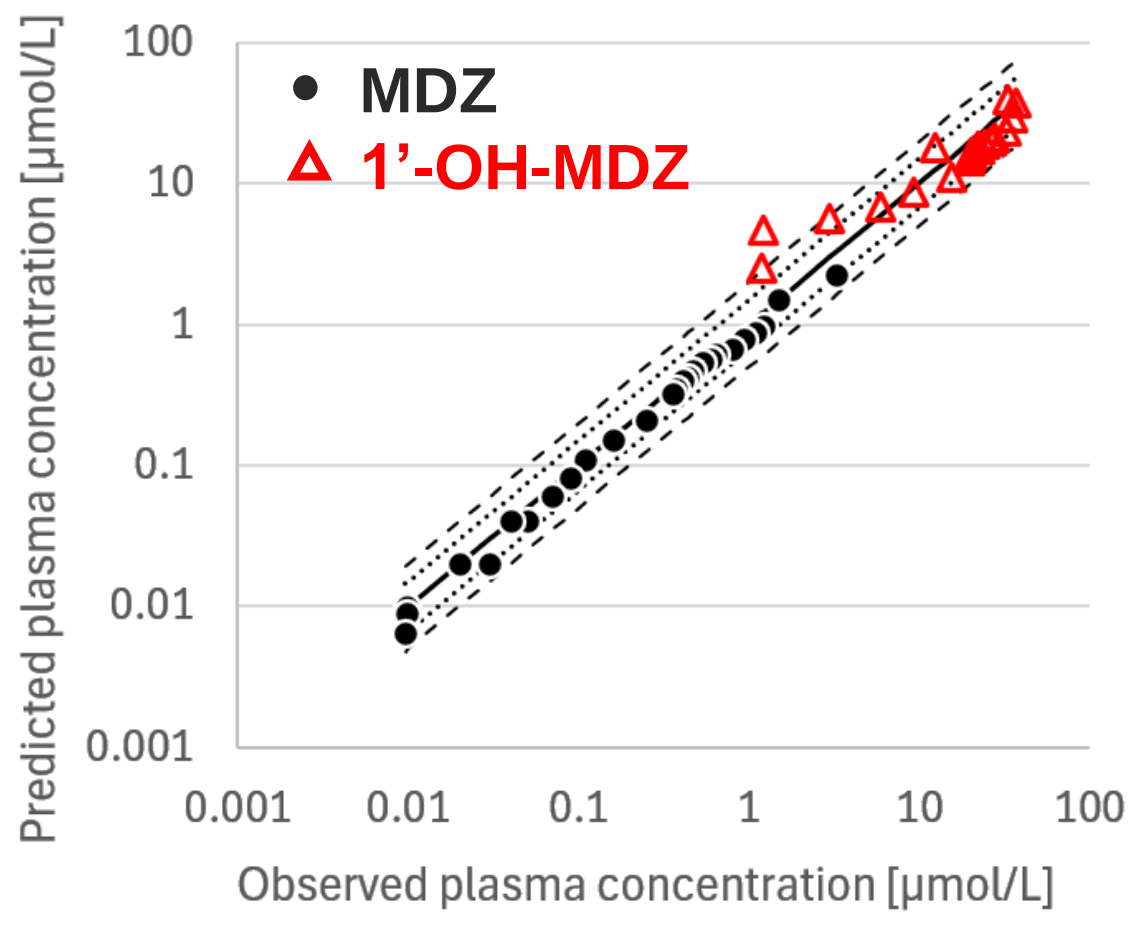
Reed *et al.* 2001 (0.5–12 years old) [5]
0.15 mg/kg IV bolus of MDZ



de Wildt *et al.* 2001 (0–11 days old) [6]
0.1 mg/kg IV 30 min infusion of MDZ



PharmaCool (1d PNA, 38w GA) [7]
0.15 mg/h IV 33.55 h infusion of MDZ



Midazolam prediction accuracy	Healthy adult AUC _{MDZ, plasma}		Healthy pediatric AUC _{MDZ, plasma}		Neonates	Neonates + TH No mechanistic changes	Neonates + TH With mechanistic changes
	AFE	AAFE	AFE	AAFE	Pred./Obs. [MDZ] _{plasma}	Pred./Obs. [MDZ] _{plasma}	Pred./Obs. [MDZ] _{plasma}
	Average Fold Error (AFE) Absolute Average Fold Error (AAFE)						
All datasets	0.8 (n=10)	1.3 (n=10)	1.1 (n=5)	1.1 (n=5)	All datapoints within <u>2-fold</u> (n=2)	All datapoints within <u>15-fold</u> (n=2)	All datapoints within <u>3.9-fold</u> (n=2)

Incorporating the physiological changes occurring during TH, as identified in literature and in vitro experiments, improved the cooled neonatal model, **reducing the deviation from observations from 15-fold to 3.9-fold** compared to using default healthy neonatal parameters. (model updated since submitted abstract)

Conclusion and next steps

- ❑ Results highlight the **potential of PBPK to capture the changes in PK due to cooling to 33.5 °C**
- ❑ **Current understanding** of the impact of TH on physiological parameters **allows for improving the prediction of drug disposition in neonates treated with TH** & to support future dosing of midazolam
- ❑ Next steps:
 - 1) **Further improvement** of MDZ and 1'-OH-MDZ models in non-cooled neonates with **additional clinical data**
 - 2) Incorporation of **additional in vitro data** (to be generated in neonatal hepatocytes)
 - 3) Experimental logP determination of 1'-OH-MDZ
- ❑ Further improvements with **additional in vitro experiments** focused on
 - 1) Proteomics to explore the impact of temperature on the abundance of drug metabolizing enzymes and transporters
 - 2) The impact of temperature on other metabolites

References & Acknowledgements

- [1] LaRosa *et al.* Front. Pediatr. 2017
- [2] Leys *et al.* Expert Opin. Drug Met. 2023
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- [4] Clausen *et al.* Br. J. clin. Pharmac. 1988
- [5] Reed *et al.* Pediatrics 2001
- [6] de Wildt *et al.* Clin. Pharm. Therap. 2001
- [7] Favié *et al.* Neonatology. 2019



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The figure in the methods section was created using BioRender.com

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