ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

Integration of placenta transfer in a physiologically based pharmacokinetic model to characterize acetaminophen exposure and metabolic clearance in the fetus

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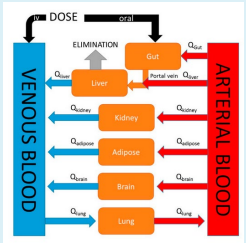
Introduction (1)

80 % of pregnant women use at least 1 drug during pregnancy[1]

Fetus (probably) exposed to any drug taken by mother

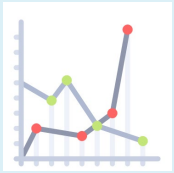


Physiologically-Based Pharmacokinetic modelling (PBPK) valuable tool for predicting fetal drug exposure and metabolism

[1]Pisa FE et al. BMC Pregnancy Childbirth 2015

Introduction (2): Acetaminophen

60% of pregnant women take acetaminophen (paracetamol) at least once during pregnancy[1]



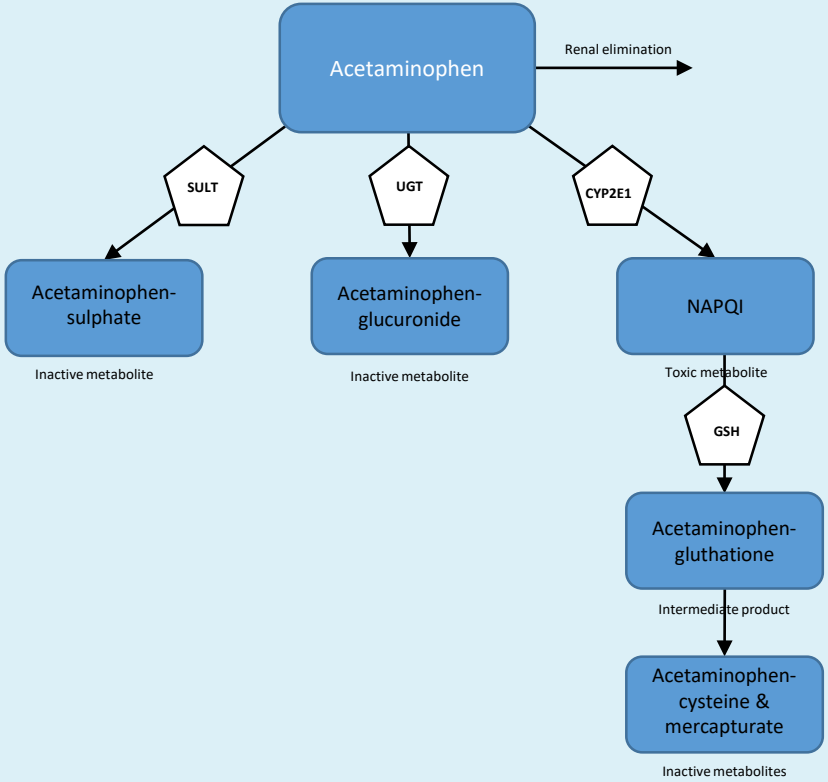
Little is known about acetaminophen PK after therapeutic dosing and potential toxicity in fetus

Safety issues after perinatal acetaminophen exposure [2,3]

- Neurodevelopment
- Pulmonary
- Infertility
- Ductus arteriosus

[1] Nitsche JF et al. Am J Perinatol 2016, [2] McGill MR J of Clin Inves 2012, [3] Allegaert K BJCP 2018

Introduction (2): Acetaminophen[1,2]



[1]Flint RB et al. Ther Drug Monit. 2017, [2] Mian P et al. Drugs& Aging 2018

CYP= cytochrome-P-450, GSH= Glutathion, NAPQI= N-acetyl-p-benzoquinone imine, SULT= Sulfotransferase , UGT= UDP-glucuronosyltransferase

Aims

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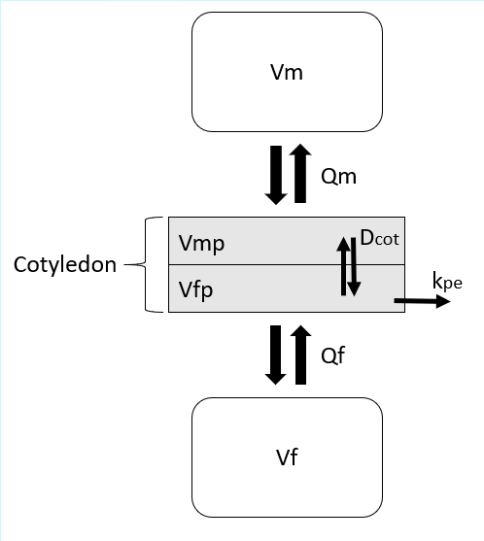
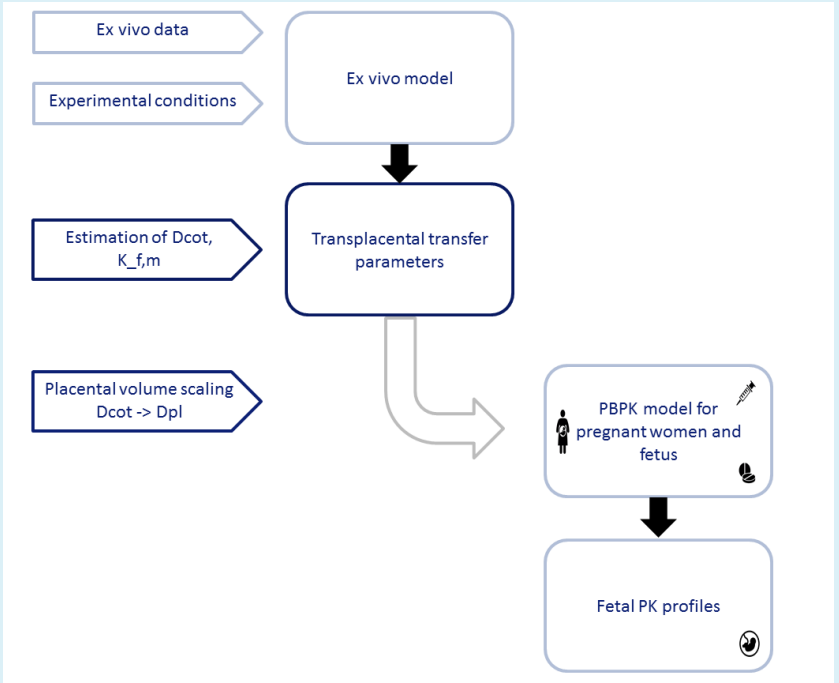
Develop a fetal-maternal physiologically based pharmacokinetic (f-m PBPK) model to:

1. Quantitatively predict and evaluate placenta transfer of acetaminophen in term fetus
   - Ex vivo cotyledon perfusion experiment
   - Caco-2 cell permeability
   - Physicochemical properties [MoBi® default method]

2. Quantitatively predict contribution of different metabolic pathways of acetaminophen in the fetus to total metabolic clearance

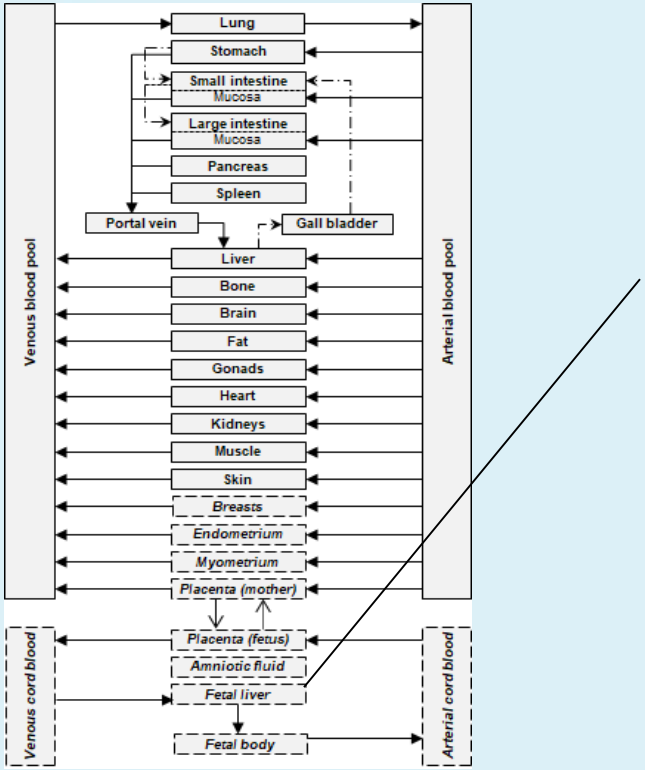
Methods (1): Schematic PBPK & ex vivo cotyledon model





Dcot= diffusion (cotyledon), Dpl= diffusion placenta, f=fetal, K_f,m= partition coefficient, Kpe= placental elimination, IV= intravenous, m=maternal, p= placenta, PBPK= physiologically based pharmacokinetic, PK= pharmacokinetic, phys-chem= physicochemical, Q= flow rate, V= volume

Methods (2): Schematic f-m PBPK model



Enzym expression in the term fetus

SULT1A1/3 [1-5]
6.5 fold adult value

UGT1A1 [6,7]
0 % of adult value

CYP2E1 [8-10]
- 16% of adult value

[1] Adjei AA et al. Birth Defects Res Part A Clin Mol Teratol 2008, [2]Vietri M. et al. Xenobiotica 2008, [3]Richard K et al. J Clin Endocrinol Metab 2001, [4]Duanmu Z et al. Pharmacol Exp Ther 2006, [5]Cappiello M et al. Dev Pharmacol Ther 1991, [6] Kawade N et al. The Biochemical Journal 1981, [7]Felsher BF et al. Pediatr Res 1978, [8] Hines RN et al. Pharmacol Ther 2008, [9] Ring JA et al. Pharmacol Ther. 1999, [10] Johnsrud EK et al. J Pharmacol Exp Ther 2003.

CYP= cytochrome-P-450, f-m PBPK= fetal-maternal physiologically based pharmacokinetic, SULT= sulfotransferase, UGT=Uridine 5'-diphospho-glucuronosyltransferase

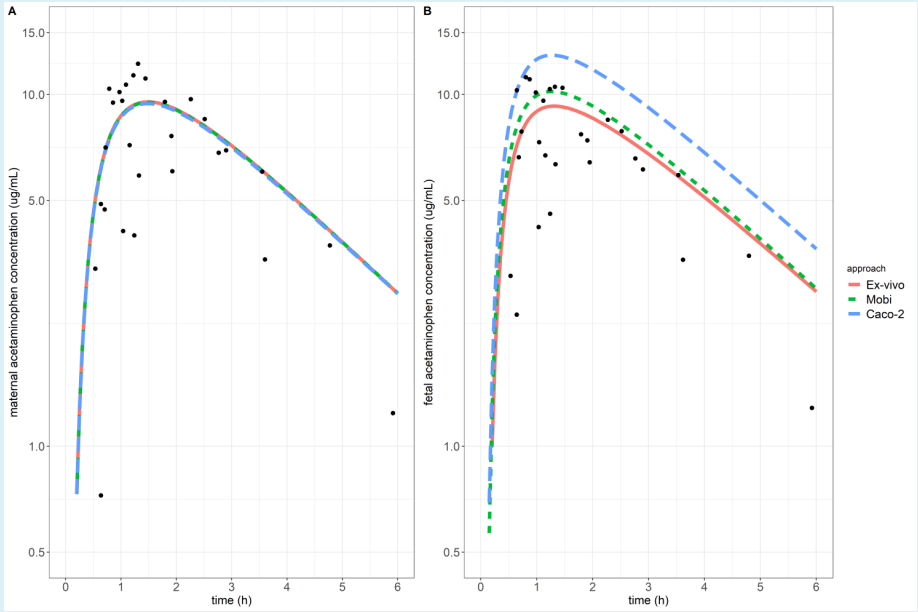
Results (1): Placenta transfer parameters & predicted maternal and fetal acetaminophen profiles

	D_{pl} (mL/min)	$K_{f,m}$
Ex vivo [1]	403	0.737
Caco-2 [2]	4354	1
Mobi® default	3528	1

D_{pl} = placental transfer rate (permeability)
$K_{f,m}$ =partition coefficient

Mother

Fetus



[1] Conings S et al. J Pharmacol Toxicol Methods. 2017, [2] Zhang Z et al. Drug Metab Dispos 2017
Nitsche JF et al. Am J Perinatol 2016

Results (2): Median fractions of metabolite formation from acetaminophen

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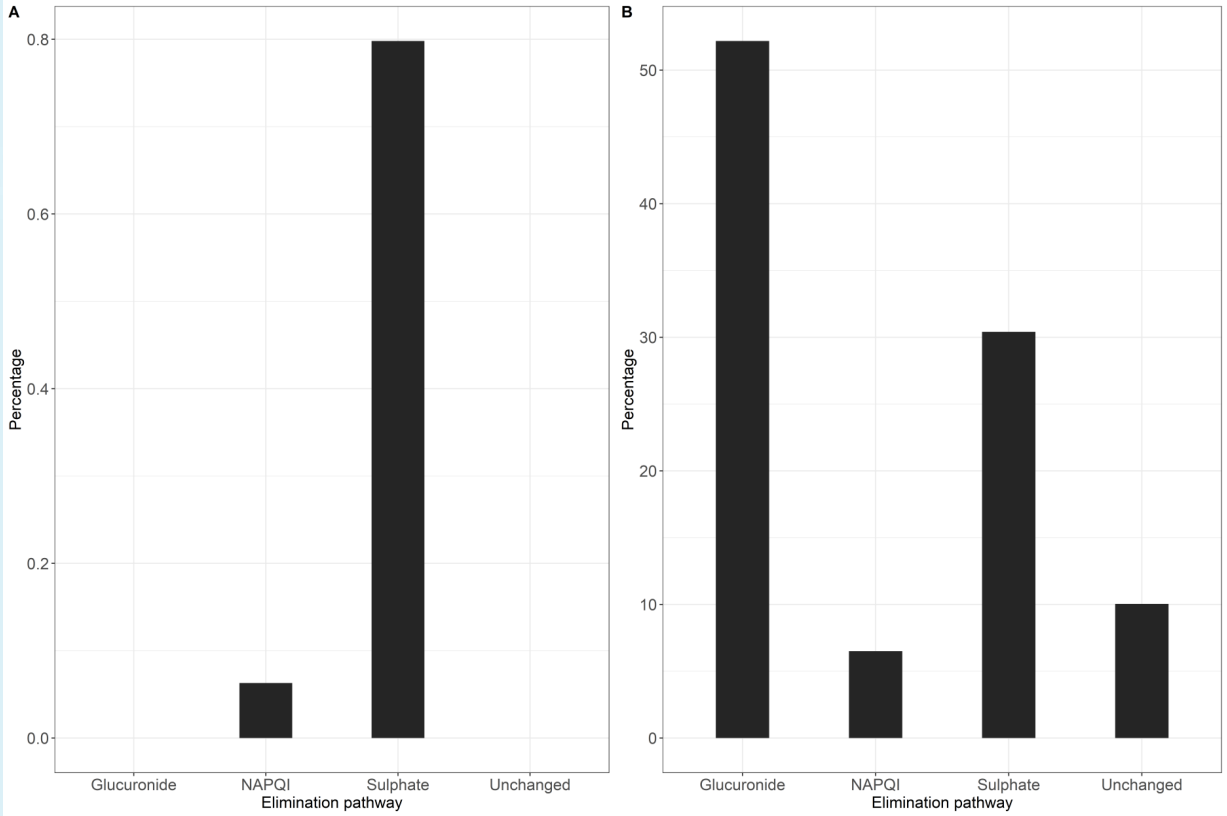
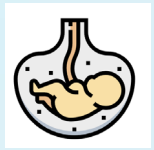
Fetus

Mother



NAPQI = N-acetyl-p-benzochinonimine



Conclusions

- F-m PBPK model adequately predict maternal and fetal PK profiles in term fetus
- Acetaminophen exposure was similar between mother and fetus
- Prediction of formation clearance in fetal liver of sulphate and NAPQI were 0.8% and 0.06% respectively

Limitations

- Contradictory information is known on CYP2E1 expression in fetus at term

Future perspectives

- In vivo validation of metabolite formation clearance predictions

CYP= cytochrome-P-450, f-m PBPK= fetal-maternal physiologically based pharmacokinetic, NAPQI = N-acetyl-p-benzochinonimine