



Session 2: Modeling Pregnancy Pharmacokinetics

# Industry perspective on role of PBPK modeling in pregnancy

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Sr. Directors  
Certara

# The need?



## Healthy Mum, Healthy Baby, Healthy Future

The Case for UK Leadership in  
the Development of Safe, Effective  
and Accessible Medicines for  
Use in Pregnancy

May 2022



### 6. Increasing investment in pregnancy research

Reproduction and childbirth is a 'Cinderella' area of research. It receives neither the funding, attention, nor status that other areas of science and health research garner. Though this area directly affects up to 51% of the population – in truth the entire population, since we are all a product of reproduction – only 2.1% of health research funding in the UK is spent on reproductive health and childbirth.

The UK spends about £51 million a year on pregnancy research, a small fraction of which is relevant to medicines use in pregnancy. For every £1 spent on pregnancy care in the NHS, only 1p is spent on research. For comparison, pregnancy-related litigation costs to the NHS in 2018-19 were £2.5 billion, making up approximately 49% of the total cost of clinical negligence claims.

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making up approximately 49% of the total cost of clinical negligence claims.

This paucity of investment – and subsequent paucity of pregnancy R&D – has serious knock-on effects. One witness noted that the UK remains 'at a 1990s level for progress in this field', where other areas of health science have flourished. This deficit runs through every stage from basic biology to pre-clinical medicines screening, and translation into novel therapies and other interventions which could save lives and relieve suffering for many mothers and babies.

Despite remarkable scientific advances in our understanding of human health and disease in other areas, we know little in comparison about basic human reproductive biology – the early embryo; how medicines affect the workings of the placenta; how medicines cross the placenta from mother to child; the handling of medicines by the fetus; and much of the basic physiology of pregnancy is still poorly understood. Improved understanding of discovery science in reproductive health and embryology is vital. Many of the issues in pregnancy are laid down at the earliest stages – in the first 12 weeks of gestation – so knowing the science of this early stage may be particularly crucial.

Understanding these basics better would help at an earlier stage in the process of designing and developing medicines for use in pregnancy. For example, if researchers could show that a new medicine does not cross the placenta at all, this would provide some reassurance for testing that specific drug in clinical trials with pregnant women.

Better pre-clinical tests would lead to a more secure and safe knowledge base before medicines go into clinical trials with pregnant women. This would mean potentially, that medicines likely to be harmful in pregnancy, would be screened out early. Good *in vitro*, *in vivo* and *in silico* models are needed to screen drug candidates and test the potential effects of medicines given in pregnancy, before the human clinical trial stage.

However, our lack of basic research knowledge and the unique nature of human pregnancy have been barriers.

There are no good animal models to test medicine candidates in pregnancy. Those commonly used have very different placental systems from humans, and do not naturally develop the pregnancy complication pre-eclampsia, for example.

Recent advances bring some hope to the field. A human placental stem cell line was successfully developed by Japanese researchers in 2018. And technological improvements in areas such as 'virtual' clinical studies, better computer modelling, microfluidics and organoids (bioengineered mini organs in the lab) means that we may see effective 'placenta-on-a-chip' models in the next three to five years. The UK could pioneer these technologies, and in turn accelerate pregnancy medicines research faster – provided research investment was prioritised.

The Commission also heard from different sectors that the low status and funding of reproductive science creates difficulties in attracting and retaining researchers. Too often, young scientists are lost to higher-profile and better-resourced areas such as cancer. This is also a challenge on the clinical side of research and care – there are fewer than 10 obstetric physicians in the entire UK, mostly based in London and Oxford.

Together, the Commission was convinced of the need for a clear national strategy related to pregnancy research, to address funding issues across the field: from discovery and translational science to clinical trials and evaluations; and to make the sector more attractive to recruit and retain talented researchers. There was also a compelling rationale to develop better and more efficient pre-clinical screening tools and reproductive toxicology models. Providing clear focal points of public and private investment as 'hubs' for a coherent UK community, well-linked with wider global funders and innovators, will be crucial to accelerating progress.

*'We basically do not understand enough about the physiology of normal pregnancy and certainly about pregnancy complications, in order to know what we should be targeting.'*

Professor Graham Burton, University of Cambridge

## RECOMMENDATIONS

**1. Deliver effective advocacy for medicines in pregnancy** through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

**2. Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy**, unless there are specific safety concerns.

**3. Prioritise updates for existing medicines with the potential to be used in pregnancy**, with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

**4. De-risk insurance processes** for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

**5. Incentivise industry to develop pregnancy-specific medicines**, utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally-collaborative – position to drive drug development for pregnancy-specific conditions.

**6. Establish a UK-wide national network of research centres** encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

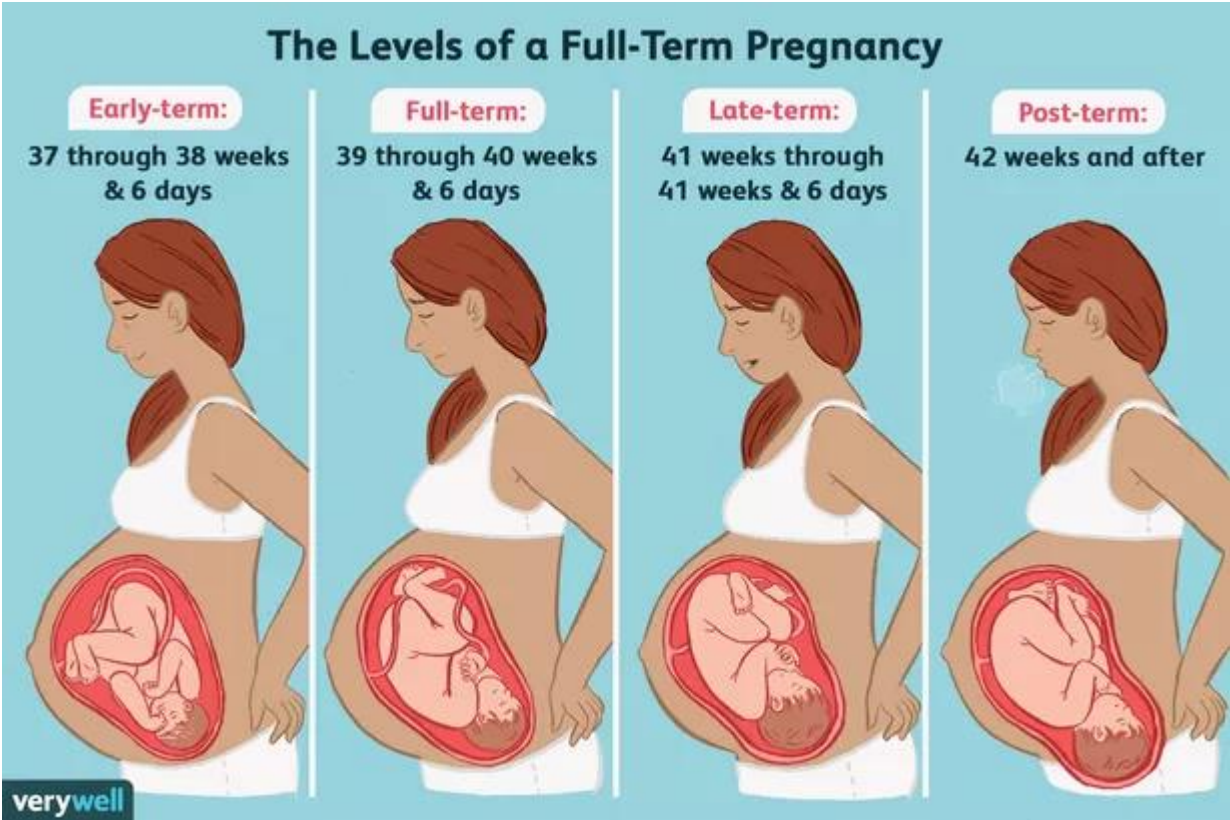
**7. Improve use of routine clinical care maternity data** to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

**8. Appoint a UK Steering Committee** aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

# Gestational stage and terms of pregnancy (consider both pregnant and unborn)

The gestational stage as defined per U.S. Department of Health and Human Services (HHS) recommendations:

- 1-12 weeks for the 1st trimester,
- 13-28 weeks for the 2nd trimester
- 29-40 weeks for the 3rd trimester

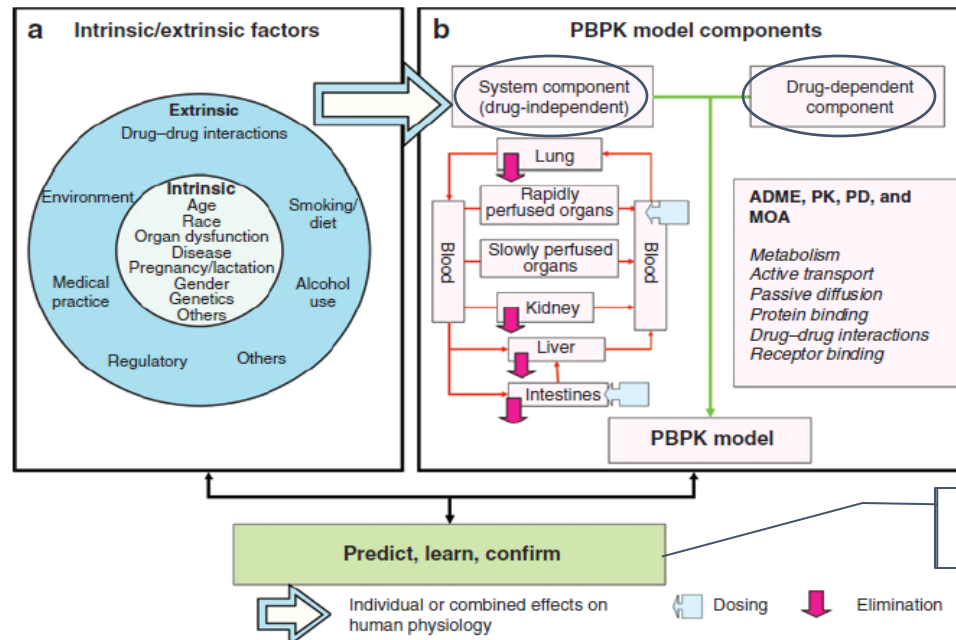


# Physiologically Based Pharmacokinetic Modelling (PBPK)

- Integrate physiological, biochemical and physical chemical information
- Estimate kinetics in a target tissue or organ (effect compartment)
- Evaluate the effect of various intrinsic (age, race, gender, disease, etc.) and extrinsic (DDI, environment, smoking, etc.) factors on drug exposure and response
- Model variability and uncertainty

User friendly software,


- SimCYP
- PK-Sim
- SimulationPlus




Learn, Confirm, Predict Approach!



# PBPK, how often? PubMed

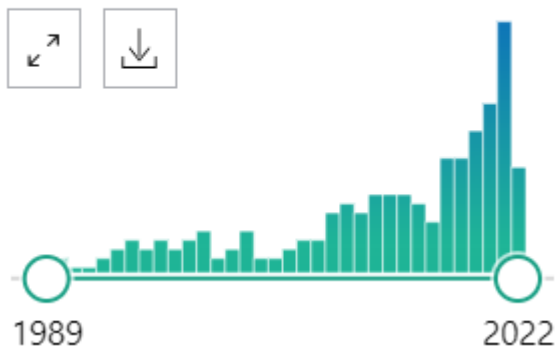
 **National Library of Medicine**  
National Center for Biotechnology Information



[Advanced](#) [Create alert](#) [Create RSS](#) [User Guide](#)

168 results

## RESULTS BY YEAR



### Pharmacometrics in **pregnancy**: An unmet need.

Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD.

Annu Rev Pharmacol Toxicol. 2014;54:53-69. doi: 10.1146/annurev-pharmtox-011613-140009.

PMID: 24392692 [Review](#).

### Model-Informed Dose Optimization in **Pregnancy**.

Chaphekar N, Caritis S, Venkataramanan R.

J Clin Pharmacol. 2020 Oct;60 Suppl 1:S63-S76. doi: 10.1002/jcph.1777.

PMID: 33205432 [Review](#).

### Physiologically Based Pharmacokinetics Model in **Pregnancy**: A Regulatory Perspective on Model Evaluation.

Coppola P, Kerwash E, Cole S.

79 results

*Filters applied: Associated data. [Clear all](#)*

## ARTICLE TYPE

- ☐ Books and Documents
- ☐ Clinical Trial
- ☐ Meta-Analysis
- ☐ Randomized Controlled Trial
- ☐ Review
- ☐ Systematic Review

Found 1 result for *pbpk pregnancy*

*Filters applied: Clinical Trial. [Clear all](#)*

[Clinical Trial](#) > J Subst Abuse Treat. 2021 Nov;130:108521. doi: 10.1016/j.jsat.2021.108521.

Epub 2021 Jun 3.

## Precision dosing of methadone during pregnancy: A pharmacokinetics virtual clinical trials study

Raj K S Badhan <sup>1</sup>, Rosalind Gittins <sup>2</sup>

Affiliations [+ expand](#)

PMID: 34118695 DOI: 10.1016/j.jsat.2021.108521

Found 1 result for *pbpk pregnancy*

*Filters applied: Meta-Analysis. [Clear all](#)*

[Meta-Analysis](#) > Environ Health Perspect. 2015 Dec;123(12):1317-24. doi: 10.1289/ehp.1408837.

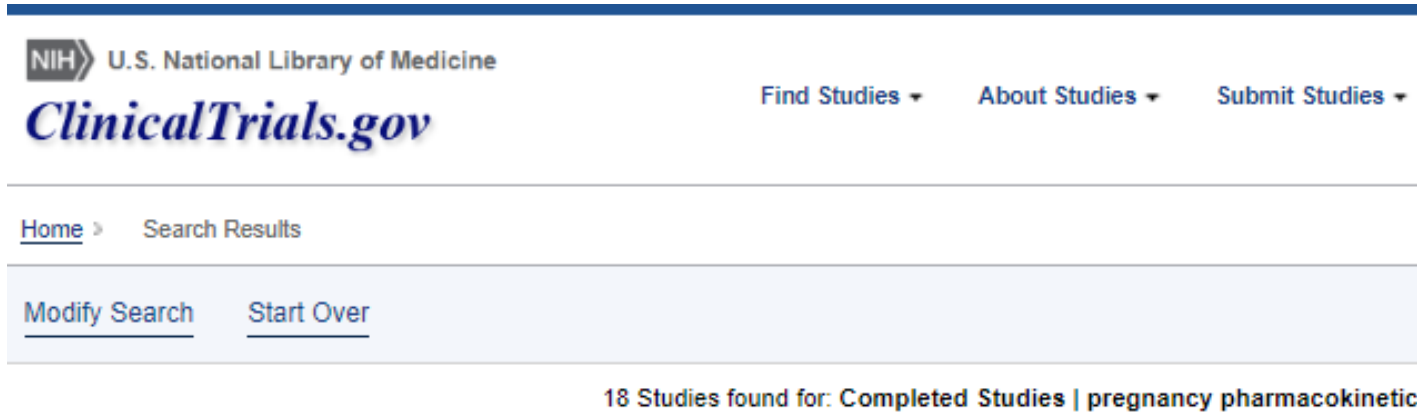
Epub 2015 May 22.

## Associations of Perfluoroalkyl Substances (PFAS) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK)

Marc-André Verner <sup>1</sup>, Anne E Loccisano, Nils-Halvdan Morken, Miyoung Yoon, Huali Wu, Robin McDougall, Mildred Maisonet, Michele Marcus, Reiko Kishi, Chihiro Miyashita, Mei-Huei Chen, Wu-Shiun Hsieh, Melvin E Andersen, Harvey J Clewell 3rd, Matthew P Longnecker

# PBPK, how often? Source of PK Clinicaltrial.gov

Infection, pregnancy related etc, n=35 for ongoing, recruiting and completed



The screenshot shows the ClinicalTrials.gov website interface. At the top, the NIH U.S. National Library of Medicine logo is on the left, and navigation links for 'Find Studies', 'About Studies', and 'Submit Studies' are on the right. Below the logo, the 'ClinicalTrials.gov' name is displayed. A breadcrumb trail shows 'Home' followed by 'Search Results'. Below this, there are links for 'Modify Search' and 'Start Over'. The main content area displays the search results: '18 Studies found for: Completed Studies | pregnancy pharmacokinetic'.

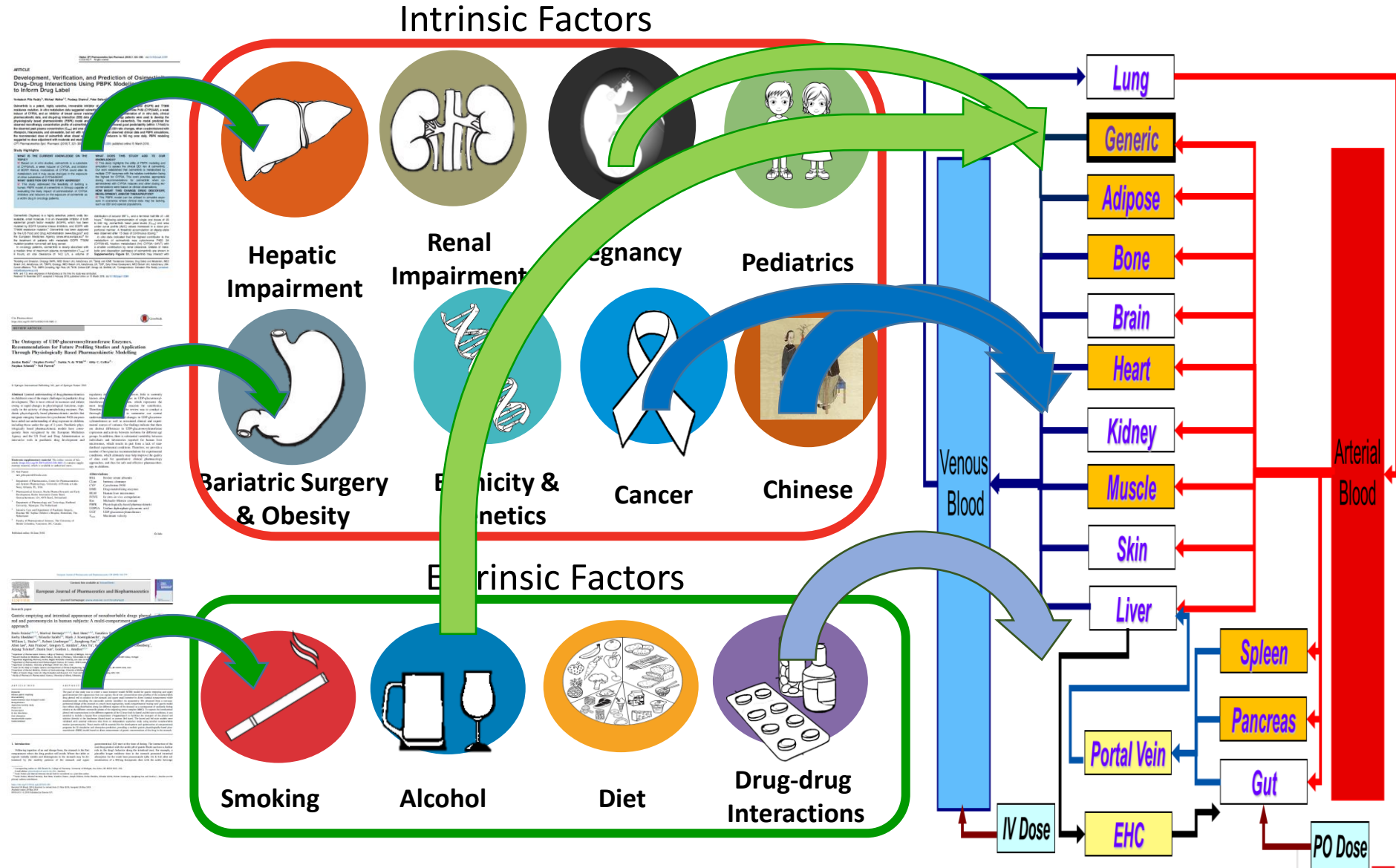
NIH U.S. National Library of Medicine  
*ClinicalTrials.gov*  
Find Studies ▾ About Studies ▾ Submit Studies ▾

[Home](#) > Search Results

[Modify Search](#) [Start Over](#)

18 Studies found for: Completed Studies | pregnancy pharmacokinetic

# Integrating knowledge in PBPK to EXTRAPOLATE!



# Pharmacotherapy during pregnancy/Lactation - status

- Total avoidance of pharmacological treatments is often not feasible during pregnancy.
  - Pregnancy-related conditions (hypertension, gestational diabetes)
  - breastfeeding-related conditions (mastitis, cracks, lesions)
  - Chronic conditions (e.g., asthma, allergy, epilepsy, depression, HIV/infections)
- Fixed non-pregnant dose does not provide the required efficacy.
- Knowledge of proper dosing is required to prevent poor disease control, fetal /neonatal outcomes and teratogenic effects, ..., etc.
- Many drug labels advise not to take many drugs during pregnancy due to the absence of reliable safety data (~ 25% prescribed drugs use during pregnancy are off label and based on safety data from non-pregnant subjects).
- Pregnancy/Lactation studies have been performed in the post-marketing settings
  - delays in drugs availability to pregnant/breastfeeding women



# Regulatory considerations

## Guidance for Industry

Pharmacokinetics in Pregnancy —  
Study Design, Data Analysis,  
and Impact on Dosing and Labeling

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

October 2004  
Clinical Pharmacology

Postapproval  
Pregnancy Safety  
Studies  
Guidance for Industry

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

May 2019  
Clinical/Medical

Pregnant Women:  
Scientific and Ethical  
Considerations for  
Inclusion in Clinical Trials  
Guidance for Industry

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

April 2018  
Clinical/Medical  
Revision 1

Clinical Lactation  
Studies: Considerations  
for Study Design  
Guidance for Industry

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

May 2019  
Clinical/Medical



European Medicines Agency

London, 14 November 2005  
EMA/CHMP/313666/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)

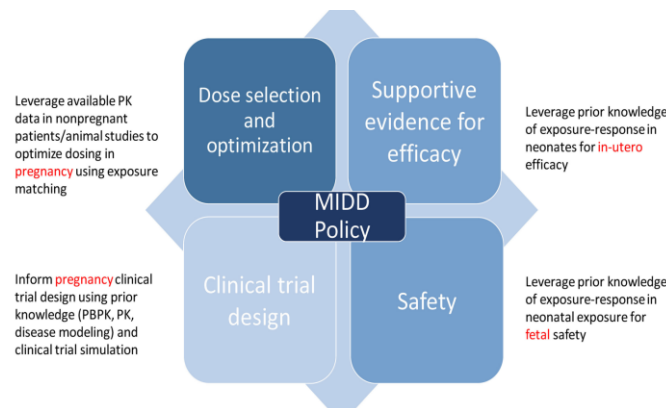
GUIDELINE ON  
THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:  
NEED FOR POST-AUTHORISATION DATA

Regulatory Considerations for the  
Mother, Fetus and Neonate in Fetal  
Pharmacology Modeling



Dionna J. Green<sup>1</sup>, Kyunghun Park<sup>2</sup>, Varsha Bhatt-Mehta<sup>2</sup>, Donna Snyder<sup>1</sup> and  
Gilbert J. Burckart<sup>2\*</sup>

<sup>1</sup> Office of Pediatric Therapeutics, Office of the Commissioner, US Food and Drug Administration, Silver Spring, MD, United States; <sup>2</sup> Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, United States



Physiologically Based  
Pharmacokinetics Model in  
Pregnancy: A Regulatory Perspective  
on Model Evaluation



Paola Coppola\*, Essam Kerwash and Susan Cole

Medicines and Healthcare Products Regulatory Agency, London, United Kingdom

# Challenges in Pregnancy PK/PD Clinical Trial Design

## Physiological Variability

- Change in enzyme/transporters with gestational age
- Return to baseline
- Growth of the feto-placental unit
- Body size metrics

## Enrolment Difficulties

- Usually enrolling ill (target population) pregnancy (HV is unethical unless for vaccine trial)
- Rare disorders: getting enough patients enrolled to satisfy statistical requirements

## Choice of Pharmacodynamic Endpoints

- Sensitive, robust, and clinically relevant biomarkers validated in non-pregnant male adult male subjects can be different in women during perinatal period
- Non-invasive biomarkers only

## Challenges in Determining Dosing Regimen

- Traditional extrapolation from adult? Use WT, BSA or ...?

## Sparse Sampling vs. Intensive Sampling

- often sparse sampling in pregnancy clinical studies

## Safety monitoring

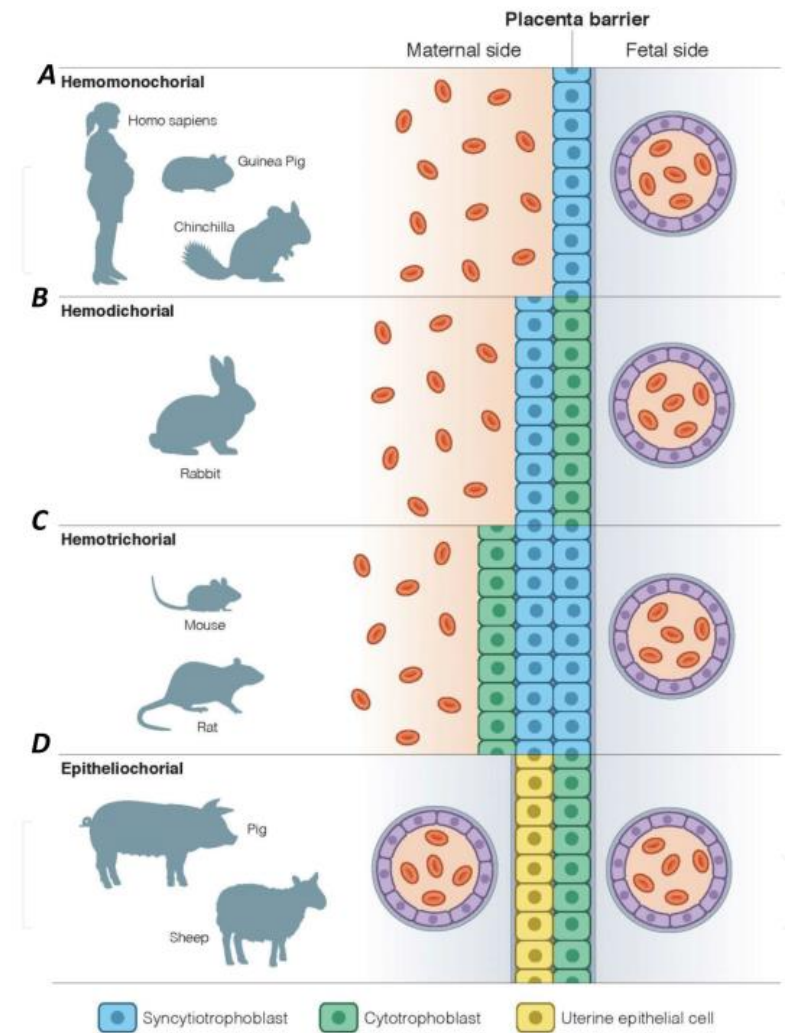
Only in the duration of the pregnancy

# Animal Models of Fetal Medicine and Obstetrics

Table 1 shows the average gestation length, number of fetuses, maternal weight, neonate weight and the placental barrier type in human and relevant species.

Basal gestation parameters of the laboratory animals					
Animal species <i>Latin</i>	Gestation length (days)	Number of fetuses	Maternal pre-pregnancy weight (g)	Neonate weight (g)	Placenta barrier type
Human	266	1	5900	3183	Hemomonochorial villous
<i>Homo sapiens</i>					
Mouse	20	5–6	19	1	Hemotrichorial labyrinth
<i>Mus musculus</i>					
Rat	22	9	283	6	Hemotrichorial labyrinth
<i>Rattus norvegicus</i>					
Guinea pig	67	3–4	728	80	Hemomonochorial labyrinth
<i>Cavia porcellus</i>					
Chinchilla	113	1–2	480	40	Hemomonochorial labyrinth
<i>Chinchilla lanigera</i>					
Rabbit	30	5	1591	39	Hemodichorial labyrinth
<i>Oryctolagus cuniculus</i>					
Sheep	153	1–2	39.100	2376	Epitheliochorial
<i>Ovis aries</i>					
Pig	115	5–14*	84.000*	400–1900*	Epitheliochorial
<i>Sus scrofa</i>					

Data are acquired from the PanTheria database [82].  
Dependent of the breed of pig (domestic pig or mini-pig) [20].



# The role of physiologically-based pharmacokinetic (PBPK) models

- PBPK models combined drug-related data with pregnancy-related physiological changes.
- Impact of inter-individual variability (genotypes, demographics, enzyme activity) of subjects can be addressed.
- PBPK model have been applied recently to\*
  - predict maternal and umbilical drug levels
  - evaluate the requirement of dose adjustment or proposing new dosing regimen during pregnancy

Drugs	Pregnancy PBPK application	Ref
Chloroquine	proposing a dosing regimens for prevention of Zika Virus disease	Olafuyi & Badhan 2019
Darunavir (+ ritonavir)	Dosing optimisation strategy based on predicted umbilical vein concentration	Schalkwijk et al., 2018
Paroxetine	CYP2D6 Genotype-based dose optimization	Almurjan et al., 2020
Piperaquine	Assess the impact of efavirenz or ritonavir on piperaquine in distinct customised HIV infected population (Thailand, Sudan & Papua New Guinea)	Olafuyi et al., 2017
Quetiapine	Dosing optimisation strategy	Badhan & Macfarlane 2020
Efavirenz	CYP2B6 Genotype-based dose optimization	Chetty et al., 2020

# Pregnancy PBPK model- verifications (CYPs)

Journal of Pharmacokinetics and Pharmacodynamics  
<https://doi.org/10.1007/s10928-020-09711-2>

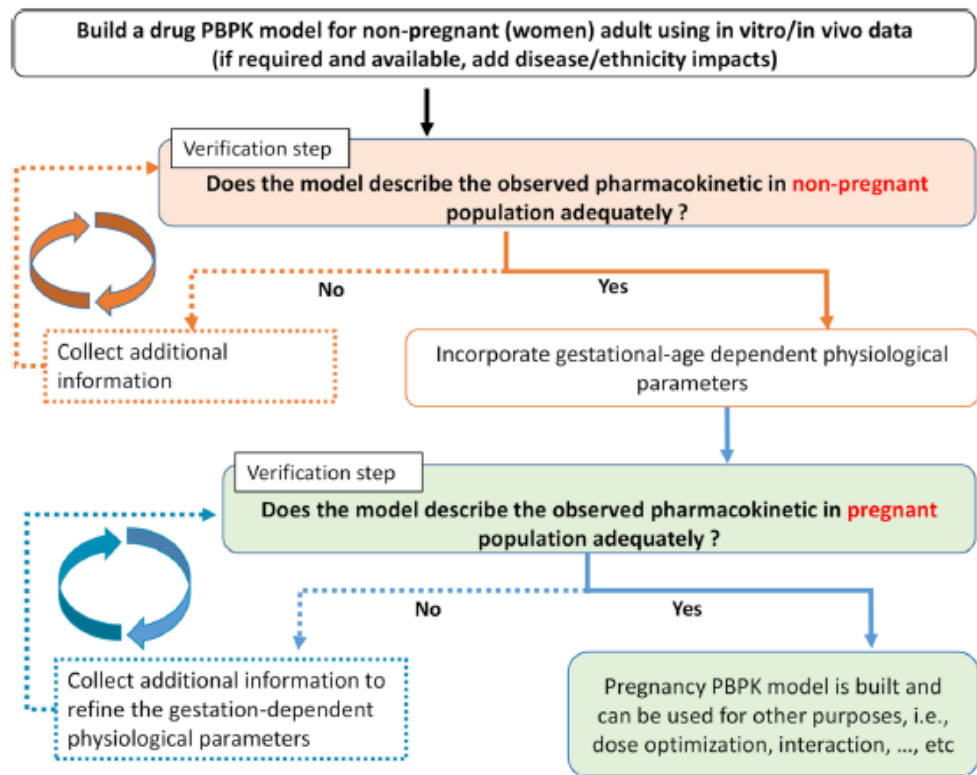
## ORIGINAL PAPER

### Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy

Khaled Abduljalil<sup>1</sup>  · Amita Pansari<sup>1</sup> · Masoud Jamei<sup>1</sup>

Received: 28 July 2020 / Accepted: 11 August 2020  
© Springer Science+Business Media, LLC, part of Springer Nature 2020

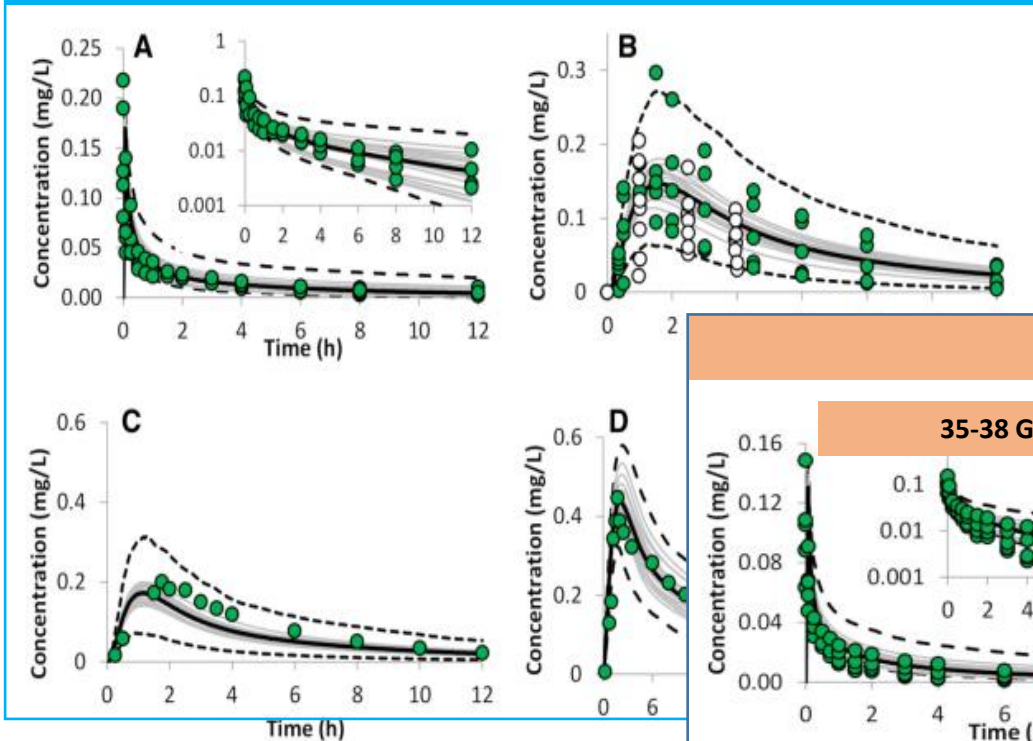
- ✓ Caffeine
- ✓ Theophylline
- ✓ Metoprolol,
- ✓ Propranolol
- ✓ Paroxetine
- ✓ Midazolam
- ✓ Nifedipine
- ✓ Rilpivirine





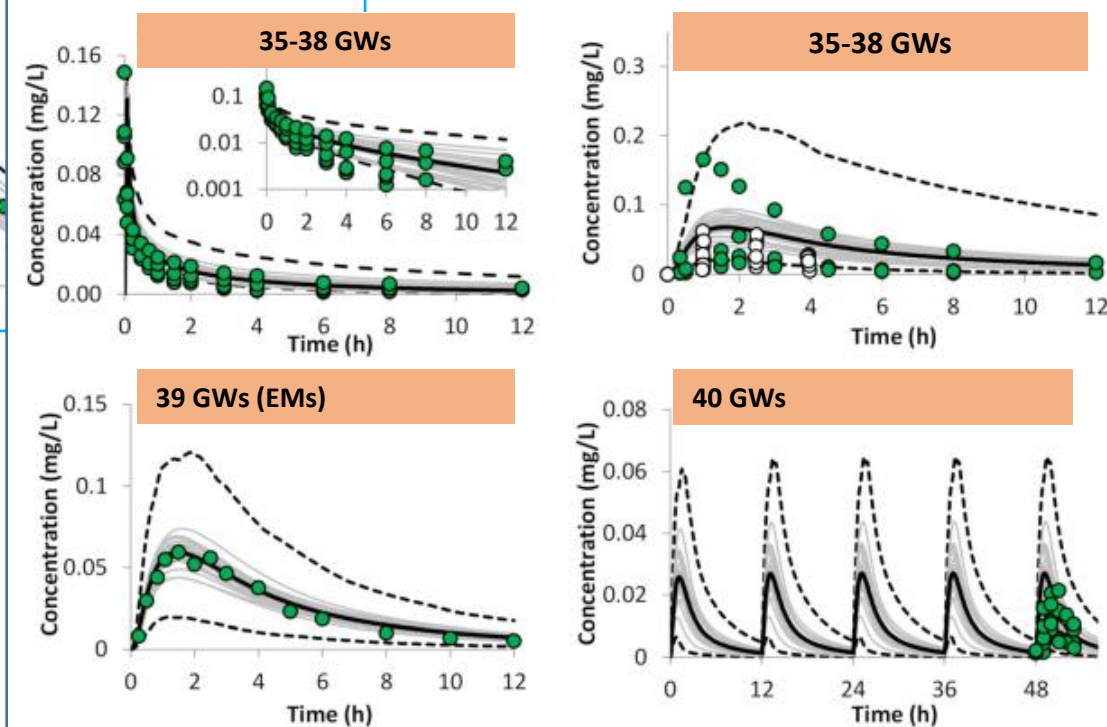
# Metoprolol PK during Pregnancy (CYP2D6)

## Non-pregnant women



Intravenous and oral

## Pregnant women



# Transporter example: Metformin PK during Pregnancy

## Application of physiologically based pharmacokinetic modeling to predict drug disposition in pregnant populations

Vamshi Krishna Jogiraju<sup>1</sup> | Suvarchala

<sup>1</sup> Samuel J. and Joan B. Williamson Institute for Pharmacometrics, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, New York, USA

<sup>2</sup> KinderPharm LLC, Exton, Pennsylvania, USA

### Correspondence

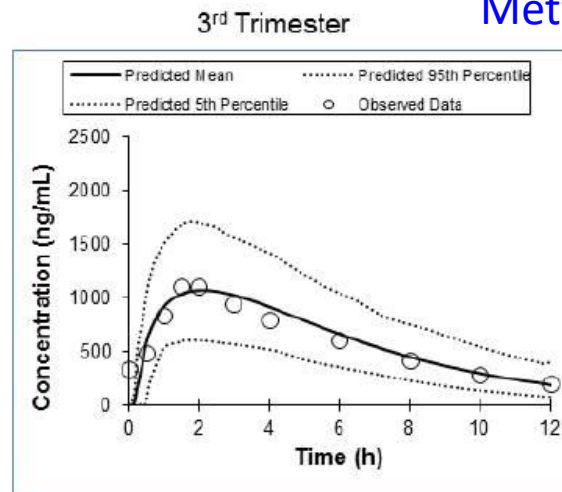
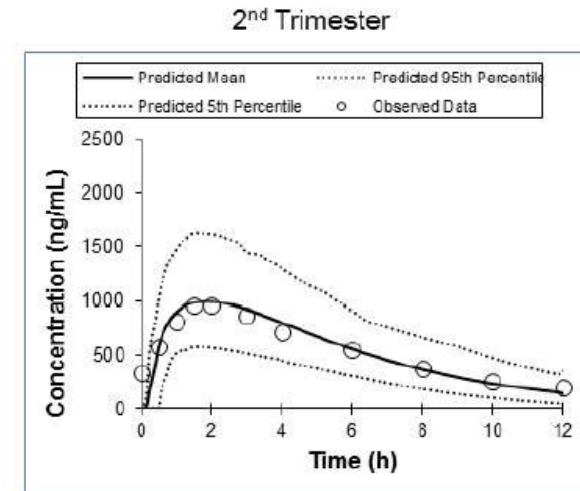
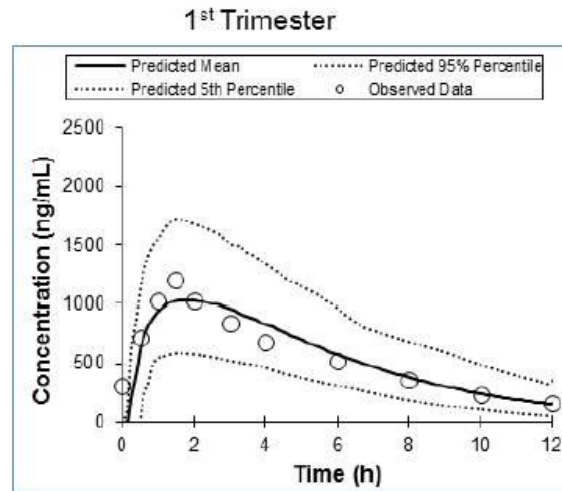
David R. Taft, Professor of Pharmaceutics, Division of Pharmaceutical Sciences, Long Island University, 75 DeKalb Avenue, Brooklyn, NY 11201, USA.  
Email: dtaft@liu.edu

### Abstract

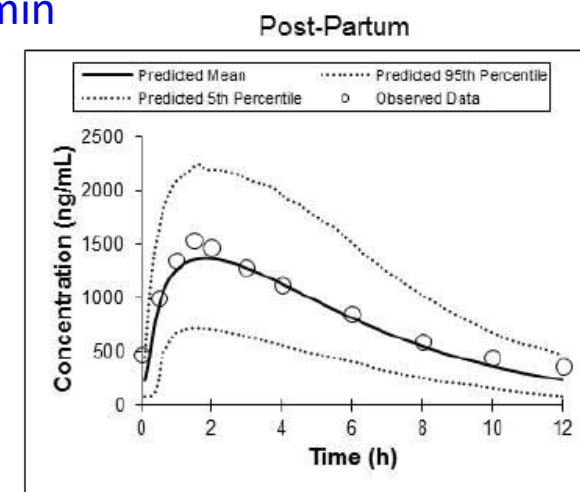
Pregnancy is a time of physiological changes, including alterations in drug disposition. The impact of pregnancy on the pharmacokinetics of metformin is well known. Physiologically based pharmacokinetic modeling is used to predict the concentration-time profile of metformin in pregnant populations.

Metformin is a substrate for several transporters – OCT1, OCT2, MATEs.

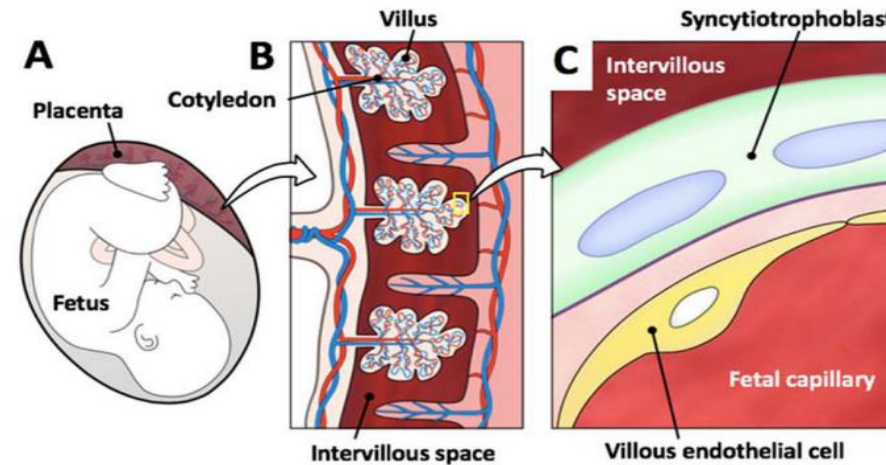
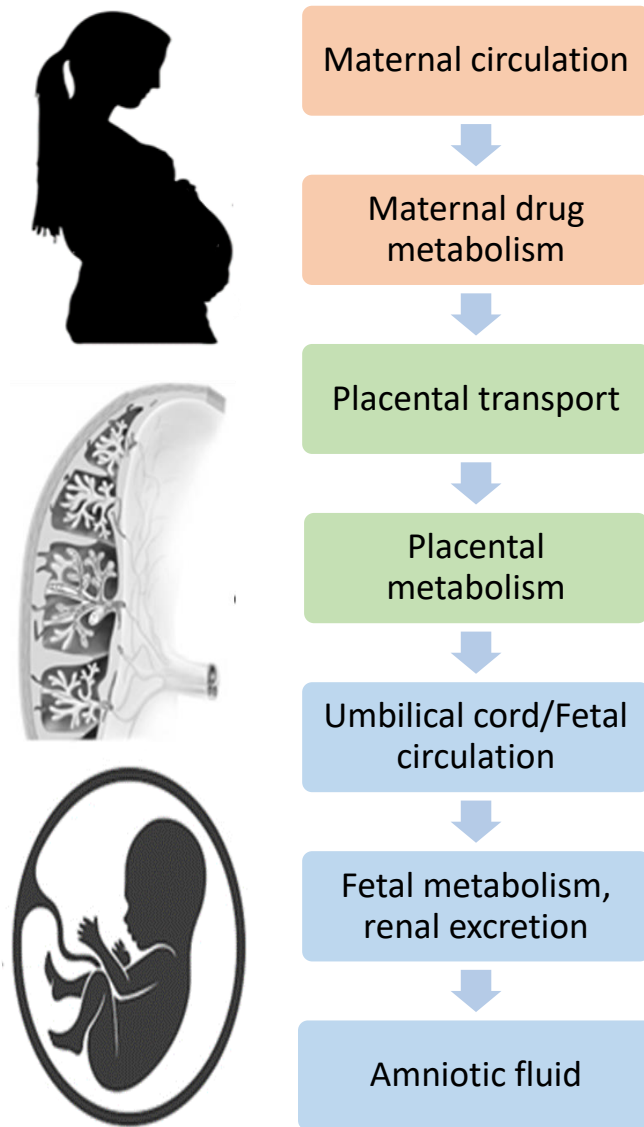
Pregnancy ontogeny for OCT2 considered in model



Metformin



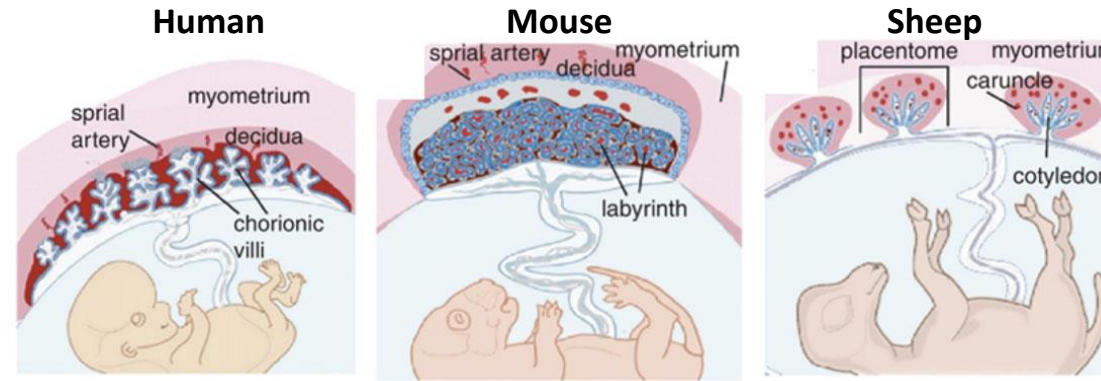
# Maternal-Placental-Fetal drug transfer



Blundell et al. Lab Chip. 2016 August 2; 16(16): 3065–3073.

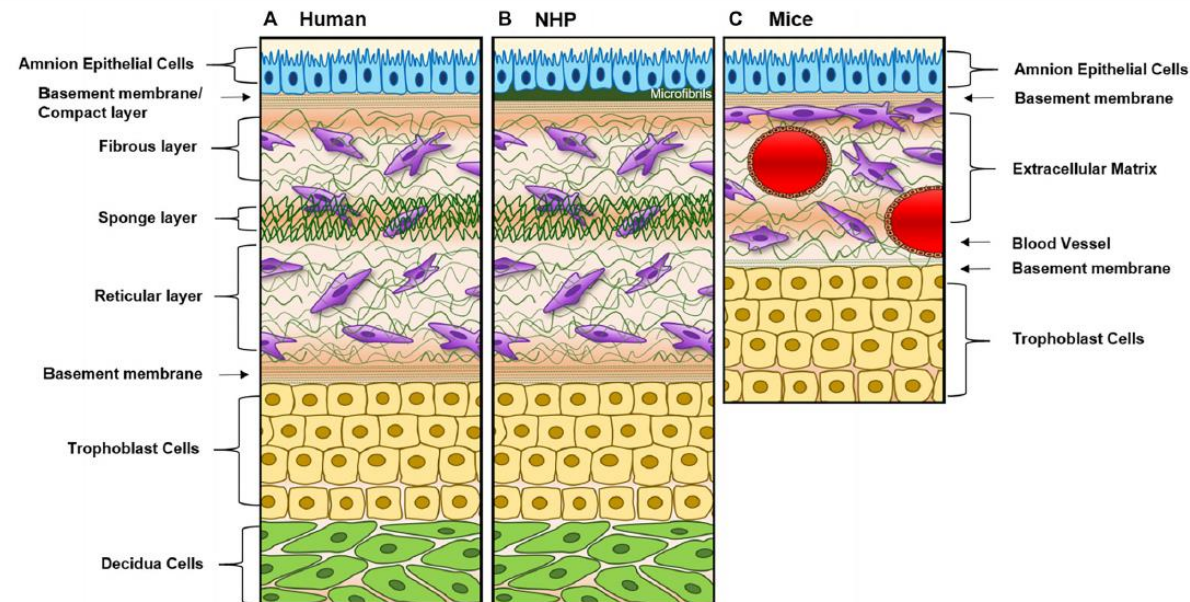
# Animal vs Human: Placenta & Fetus

## Placenta



Pemathilaka et al. 2019.  
Interface Focus 9:  
20190031.

## Fetal membrane

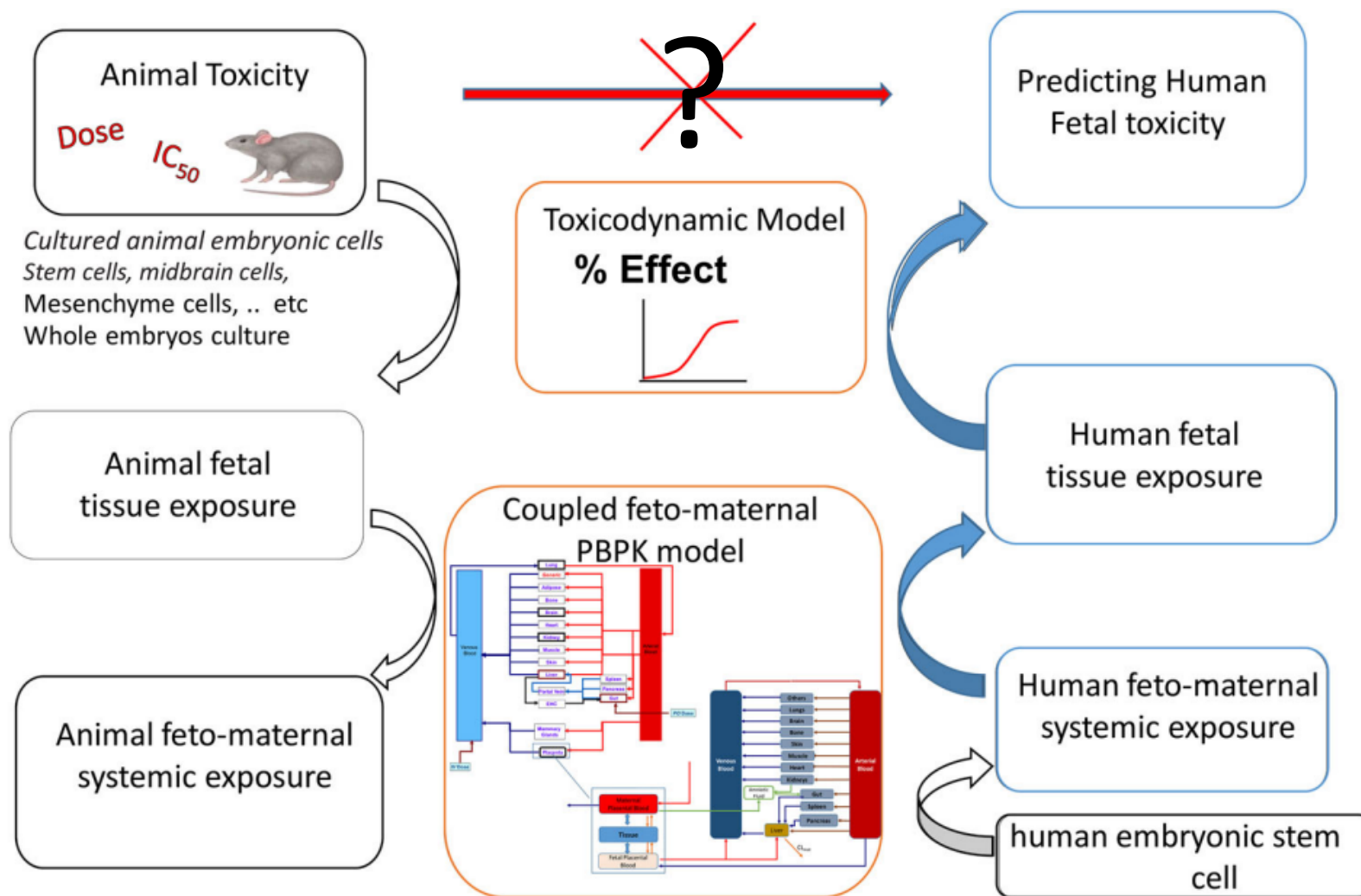


Richardson et al.  
(2020) Front. Physiol.  
11:715.

**Metabolic differences??**: For example, thalidomide is a severe teratogen in humans causing phocomelia, but not in rats.



# PBPK model framework

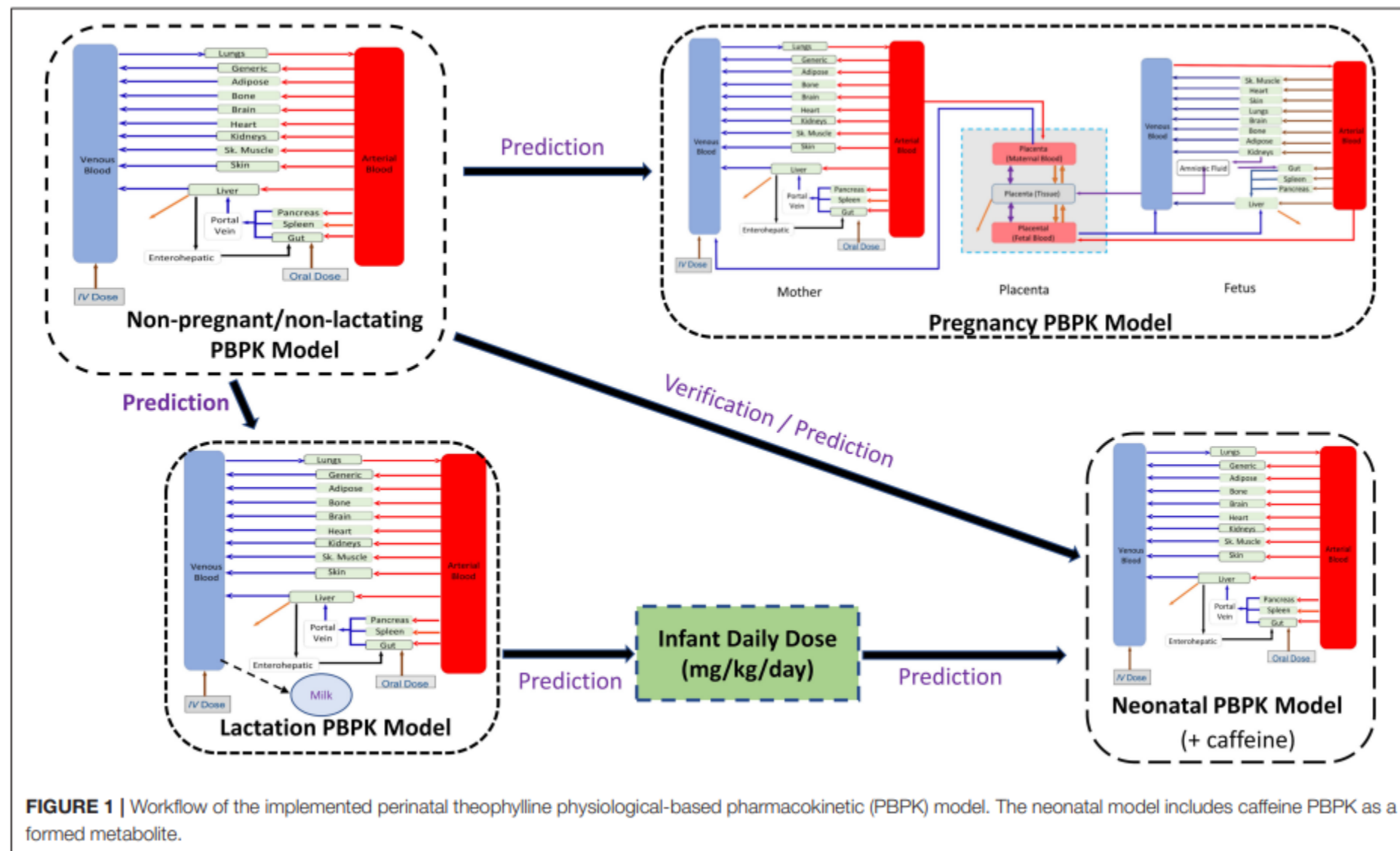




# Model application to assess fetal exposure: vital for safety assessment

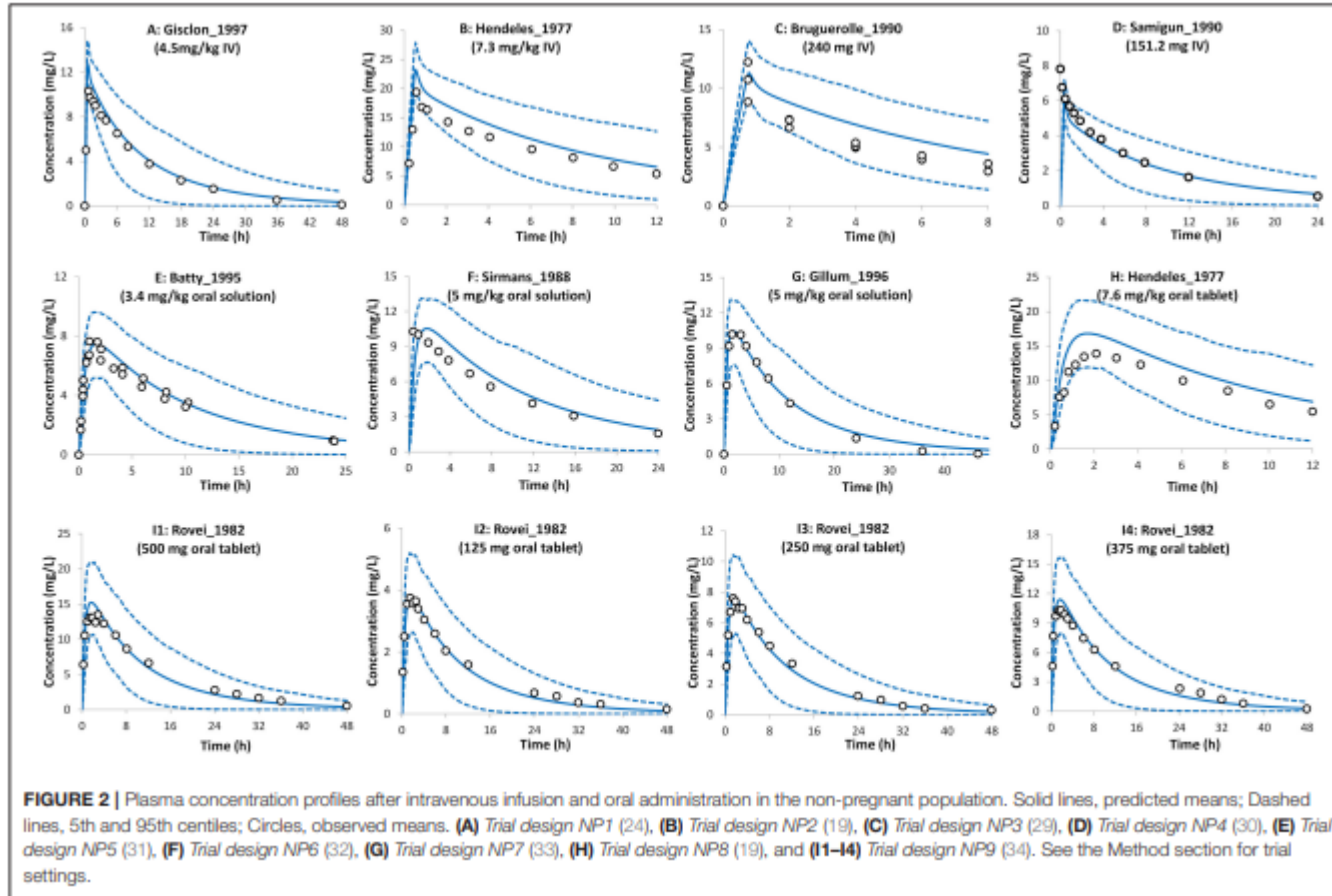
## Application of a Physiologically Based Pharmacokinetic Approach to Predict Theophylline Pharmacokinetics Using Virtual Non-Pregnant, Pregnant, Fetal, Breast-Feeding, and Neonatal Populations

Khaled Abduljalil\*, Iain Gardner and Masoud Jamei

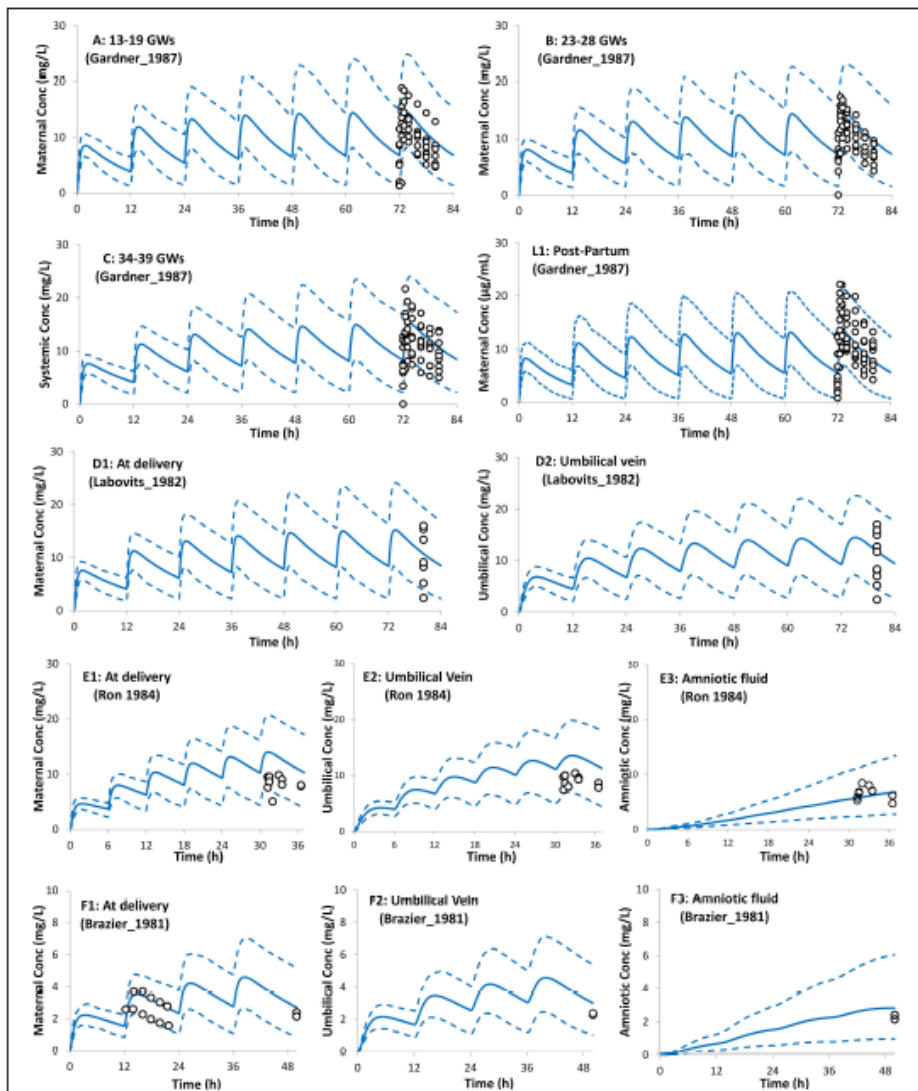


[https://www.frontiersin.org/articles/10.3389/fped.2022.840710/full?utm\\_source=Email\\_to\\_authors&utm\\_medium=Email&utm\\_content=T1\\_11.5e1\\_author&utm\\_campaign=Email\\_publication&field=journalName=Frontiers\\_in\\_Pediatrics&id=840710](https://www.frontiersin.org/articles/10.3389/fped.2022.840710/full?utm_source=Email_to_authors&utm_medium=Email&utm_content=T1_11.5e1_author&utm_campaign=Email_publication&field=journalName=Frontiers_in_Pediatrics&id=840710)

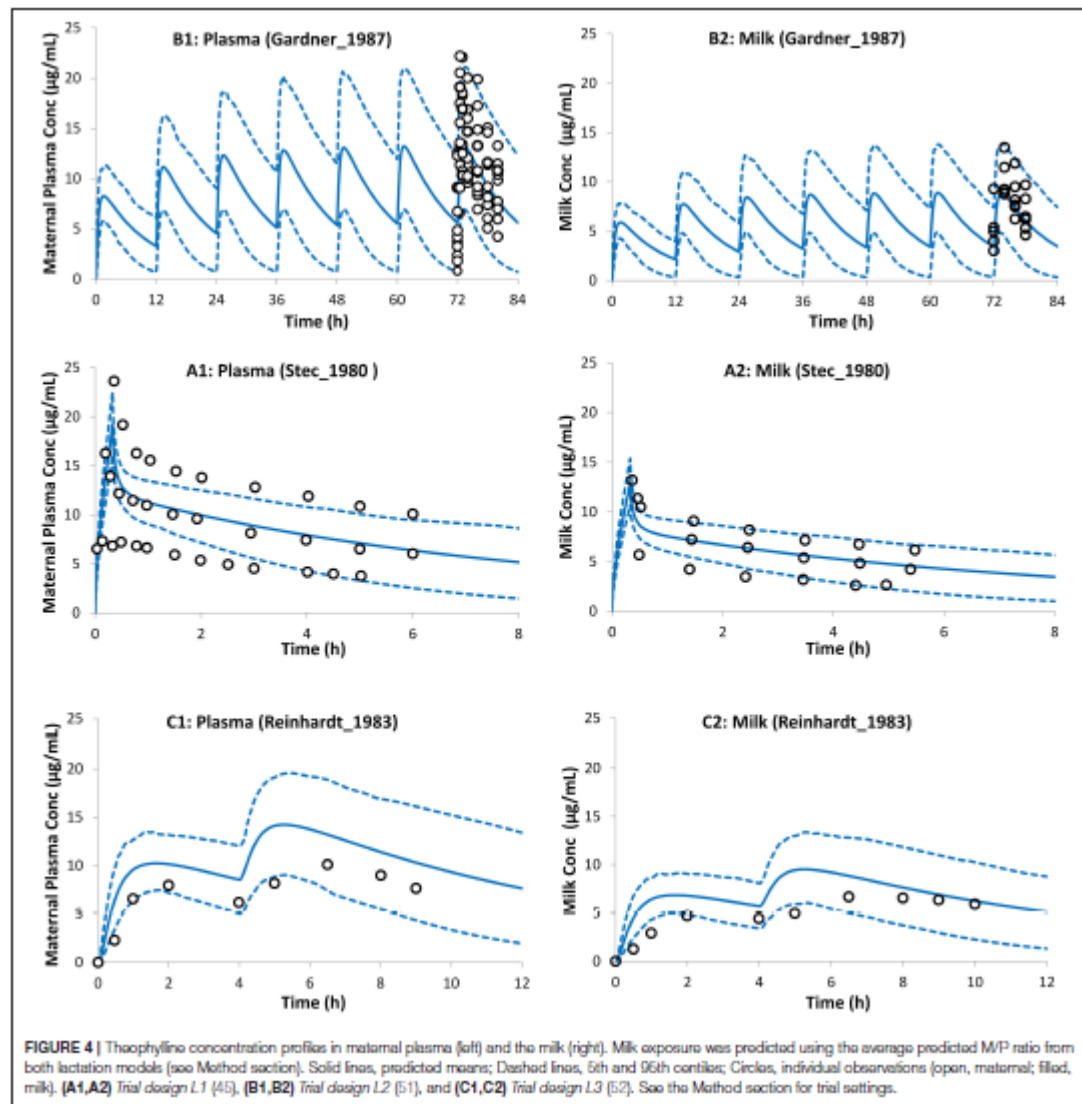
# Non-pregnancy calibration



# Simulation

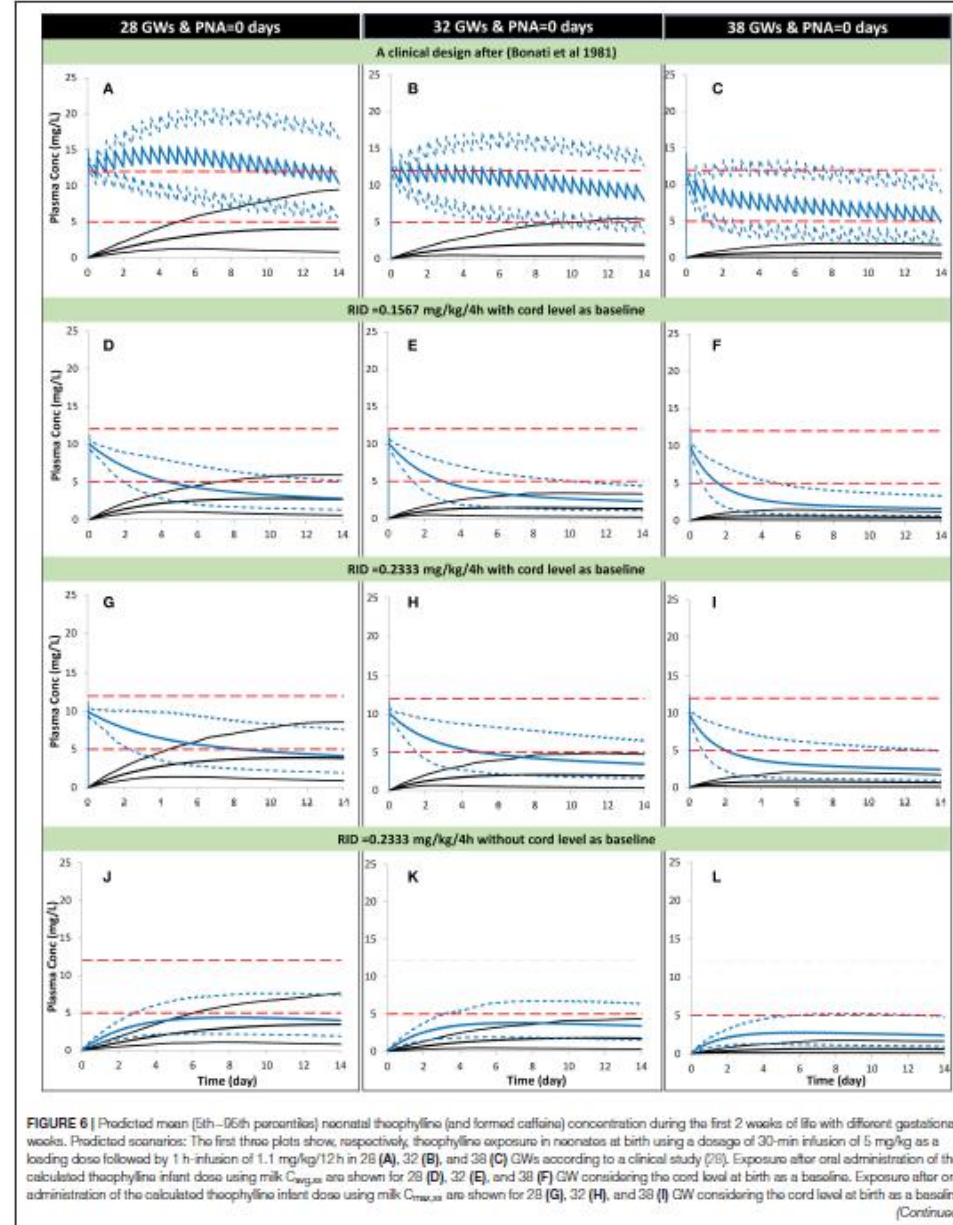
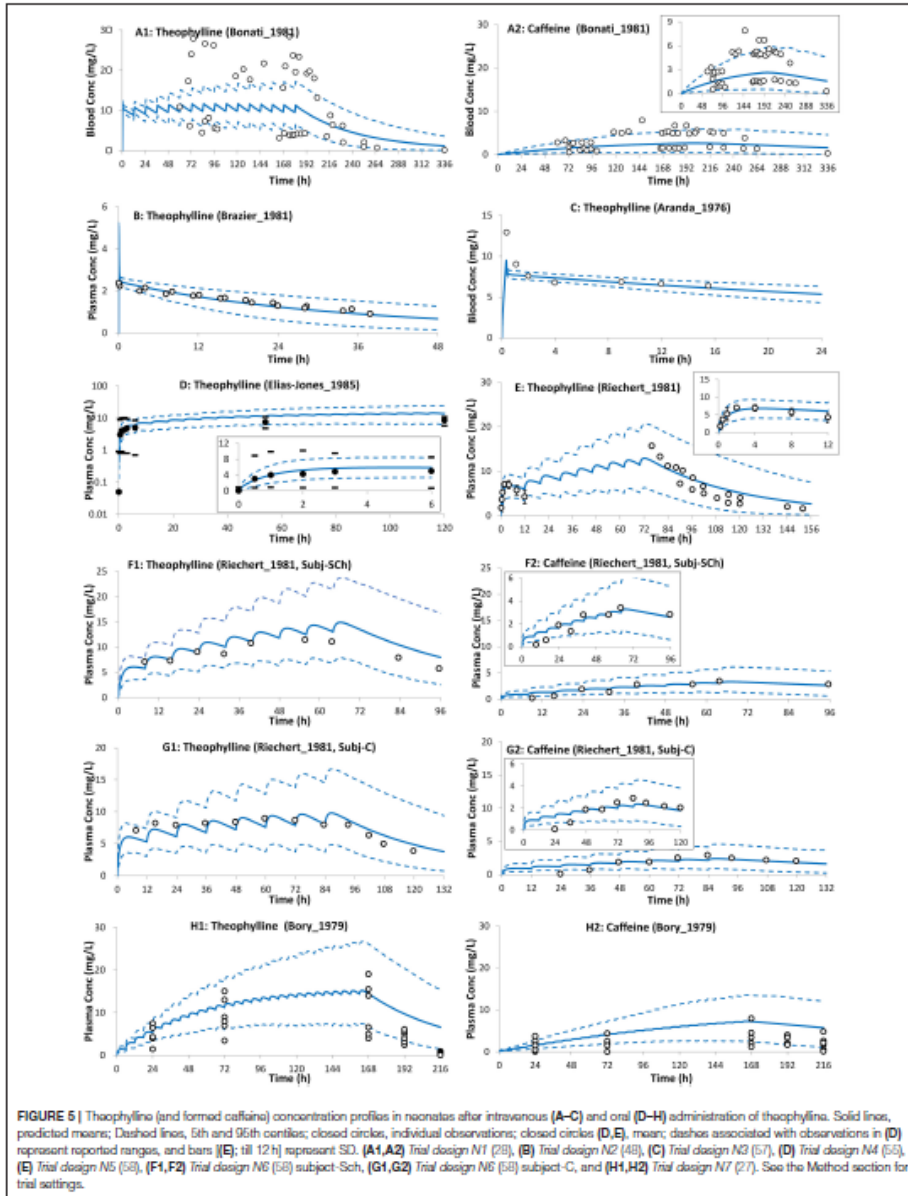


**FIGURE 3 |** Plasma concentration profiles after multiple oral administration in pregnant population during pregnancy and at delivery. Solid lines, predicted means; Dashed lines, 5th and 95th centiles; Circles, individual observations (open, maternal; filled, umbilical cord). Plots representing the following trials: (A) Trial design P1 (45), (B) Trial design P2 (45), (C) Trial design P3 (45), (L1) Trial design L1 (45) added here for comparison (see lactation section), (D1,D2) Trial design P4 (45), (E1-E3) Trial design P5 (47), and (F1-F3) Trial design P6 (45). See the Method section for trial settings.



**FIGURE 4 |** Theophylline concentration profiles in maternal plasma (left) and the milk (right). Milk exposure was predicted using the average predicted M/P ratio from both lactation models (see Method section). Solid lines, predicted means; Dashed lines, 5th and 95th centiles; Circles, individual observations (open, maternal; filled, milk). (A1,A2) Trial design L1 (45), (B1,B2) Trial design L2 (51), and (C1,C2) Trial design L3 (52). See the Method section for trial settings.

# Design evaluations



# Acknowledgement

- IQ CPLG PWG PBPK subgroup colleagues
- James Yates
- Kunal Tasker
- Sue Cole
- Khaled Abduljalil
- Amin Rostami
- Jeff Barrett
- Solange Rohou
- Karen Yeo