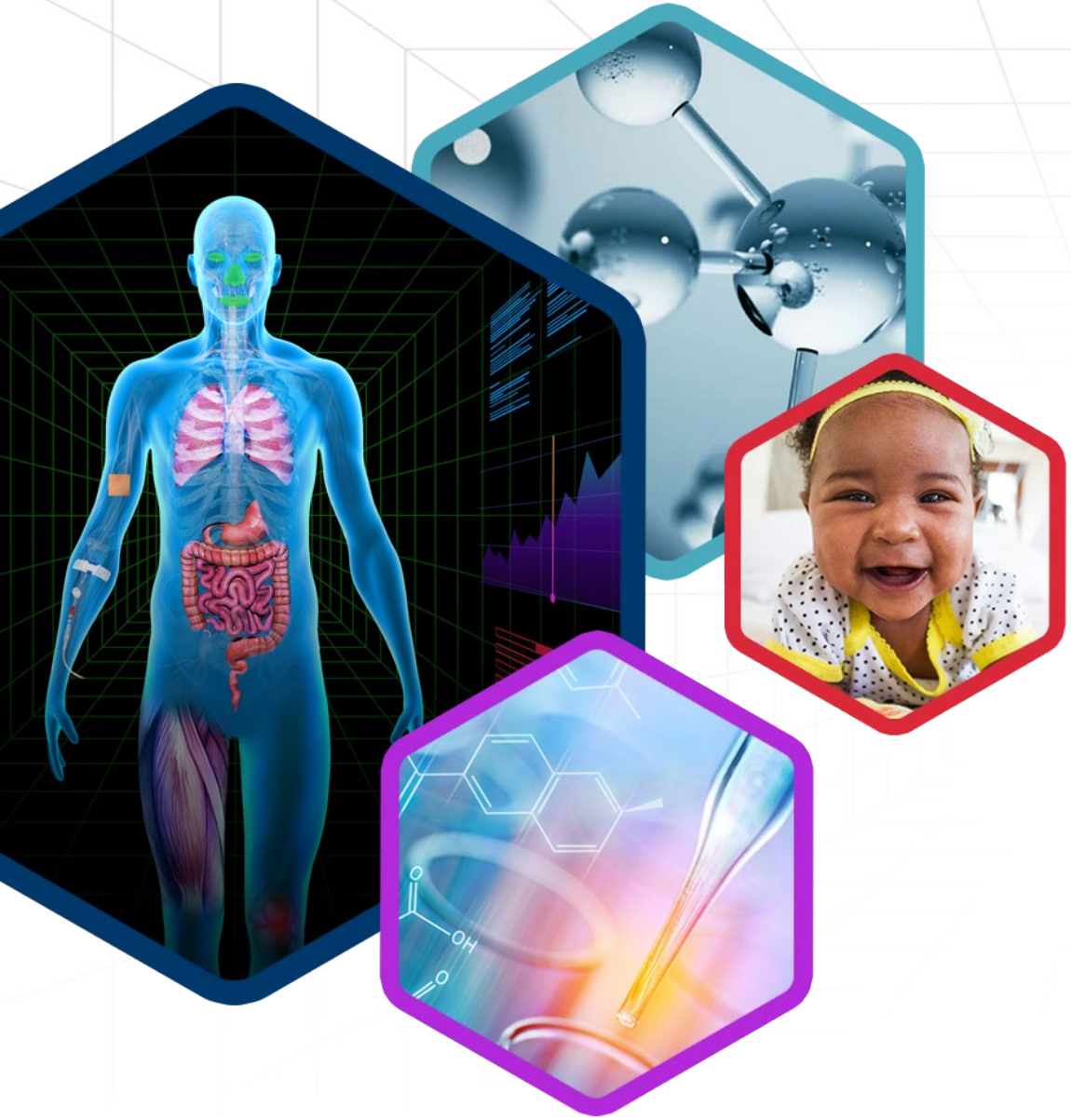

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Application of PBPK Modeling in Pediatric Drug Development (GastroPlus®)

Viera Lukacova

Simulations Plus, Inc.

August 31, 2022

Outline

Why?

- Role of PBPK in pediatric drug development

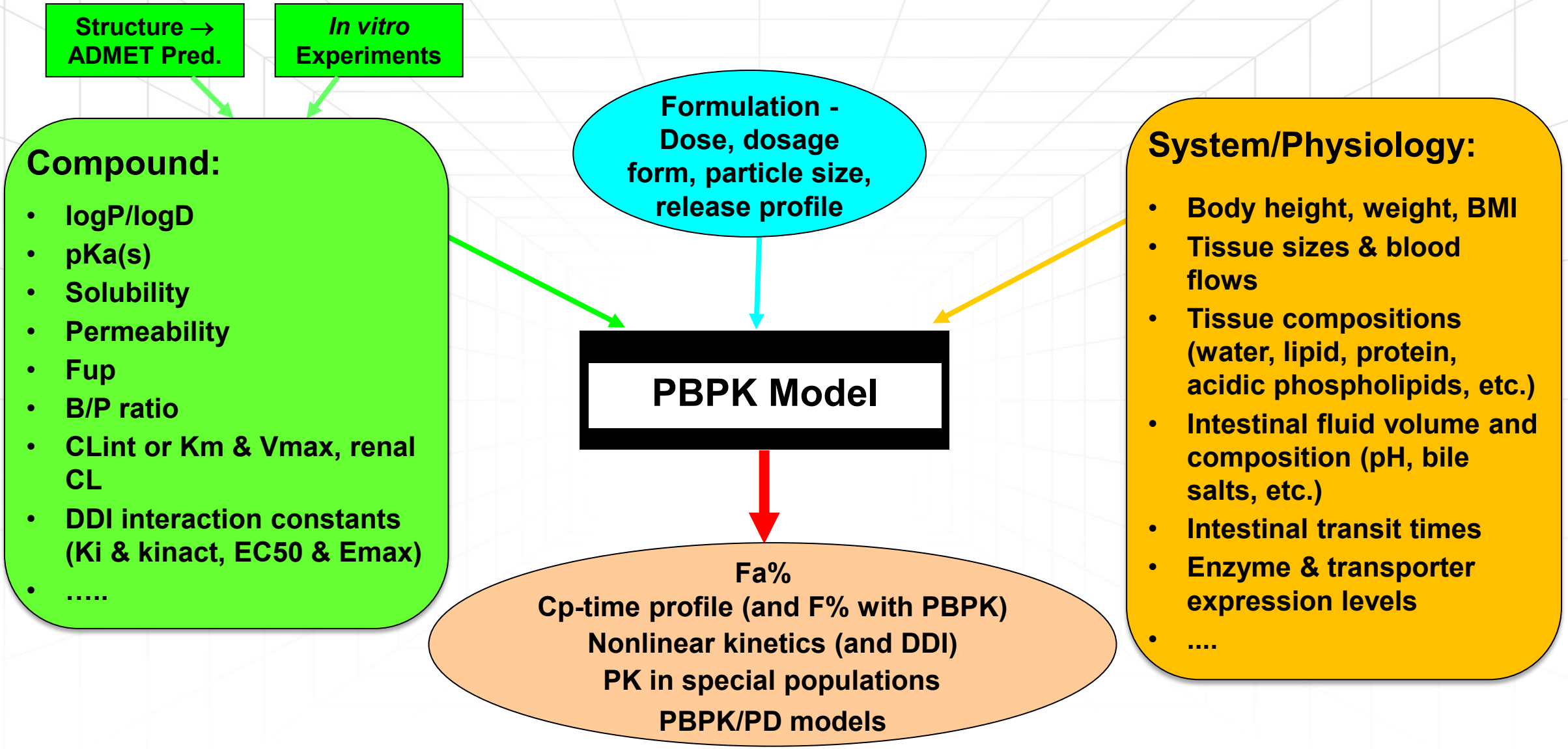
How?

- Pediatric physiology:
  - Tissue growth
  - Tissue and blood composition
  - Intestinal physiology
- Clearance and disposition scaling:
  - Metabolic clearance
  - Glomerular filtration
  - Transporters

What?

- Applications

Why PBPK Model



U.S. FDA

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gilbert J. Burckart at 301-796-2065.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology

applicable, along with any supporting information; and (iii) other information specified in the regulations" promulgated by the FDA.[24,25] When designing the pediatric clinical studies, sponsors should be mindful that modeling and simulation, and pharmacologic considerations, are often critical for the successful completion of a study. Modeling and simulation using all of the information available should therefore be an integral part of all pediatric development programs. The following sections are critically important when developing the clinical pharmacology components of a pediatric study plan.

As science and technology continue to advance, *in silico* and other alternative modeling study methods may be developed that can provide preliminary data to inform the design and conduct of PK/PD studies for investigational drugs in pediatric populations. For example, the development of a physiologically-based PK (PBPK) *in silico* model that integrates drug-dependent parameters (e.g., renal clearance, metabolic pathways) and system-dependent parameters (e.g., non-drug parameters such as blood flow rate, protein binding, and enzyme and transporter activities) is one possible approach. PBPK has been used in pediatric drug development programs for (a) planning for a first-in-pediatric PK study, (b) optimizing the study design, (c) verifying the model in specific age groups, (d) recommending starting doses, (e) informing enzyme ontogeny using a benchmark drug, and (f) facilitating covariate analysis for the effects of organ dysfunction or drug interactions in pediatric patients (Leong, Vieira et al. 2012). The model selected should incorporate *in vivo* PK/PD data obtained in other groups of pediatric and adult patients as well as human volunteer studies, as appropriate.

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

1. Introduction

For the purpose of this guideline, a PBPK model is defined as a mathematical model that simulates the concentration of a drug over time in tissue(s) and blood, by taking into account the rate of the drug's absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of interplay between physiological, physicochemical and biochemical determinants. Presently, the main purposes of PBPK models in regulatory submissions are to qualitatively and quantitatively predict drug-drug interactions (DDIs) and to support initial dose selection in paediatric and first-in-human trials. However, it is expected that the extent of use of PBPK modelling will expand as additional scientific evidence on e.g. physiology parameters in different populations (system knowledge) is gained and confidence in the utility of PBPK models increases.

High regulatory impact analyses

Simulations that are the key source of information to be included in the SmPC are generally considered a high-impact analysis. Whether situations should be considered high impact also depends on the availability of supportive data and on the therapeutic context. High impact simulations could include but are not limited to:

- the use of a PBPK model in place of clinical data (e.g. to waive interaction studies, to simulate non-studied scenarios);
- evaluation of the investigational drug as a victim of DDIs in a pharmacogenetic subpopulation, or in paediatric patients;
- evaluation of complex DDIs where e.g. the combined effect of two inhibitors are simulated;
- prediction of drug-drug interaction assessing other posologies compared to an available DDI study;

PMDA

The following English translation of Japanese Guideline is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and the translation, the former shall prevail.

Provisional Translation

PSEHB/PED Notification No. 1221- 1
December 21, 2020

Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

Throughout the entire process of drug development, prediction using a PBPK model has the potential to provide information useful in decision-making concerning the need and methods for the conducting a particular clinical trial. Furthermore, the simulation results of an appropriately conducted PBPK model analysis may be used for adjustment of dosage and administration of a drug, decisions concerning the requirement for alerts, and the setting of rationale for these measures. PBPK model analyses are considered useful, particularly in qualitative/quantitative prediction of drug interactions and the setting rationale for dosage and administration in clinical trials in pediatric subjects. PBPK model analyses may also be used to investigate the initial dose in first-in-human studies.

CFDA

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

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当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

关于公开征求《生理药代动力学模型在儿科人群药物研发中应用的技术指导原则（征求意见稿）》意见的通知

发布日期：20220817

生理药代动力学模型目前在儿科人群药物研发方面应用广泛，为了合理规范使用该模型，药品审评中心组织起草了《生理药代动力学模型在儿科人群药物研发中应用的技术指导原则（征求意见稿）》。

我们诚挚地欢迎社会各界对征求意见稿提出宝贵意见和建议，以便后续完善。征求意见时限为自发布之日起1个月。

请将您的反馈意见发到以下联系人的邮箱。

联系人：韩鸿璨、潘鹏玉、车津晶

联系方式：panpy@cde.org.cn；chejj@cde.org.cn

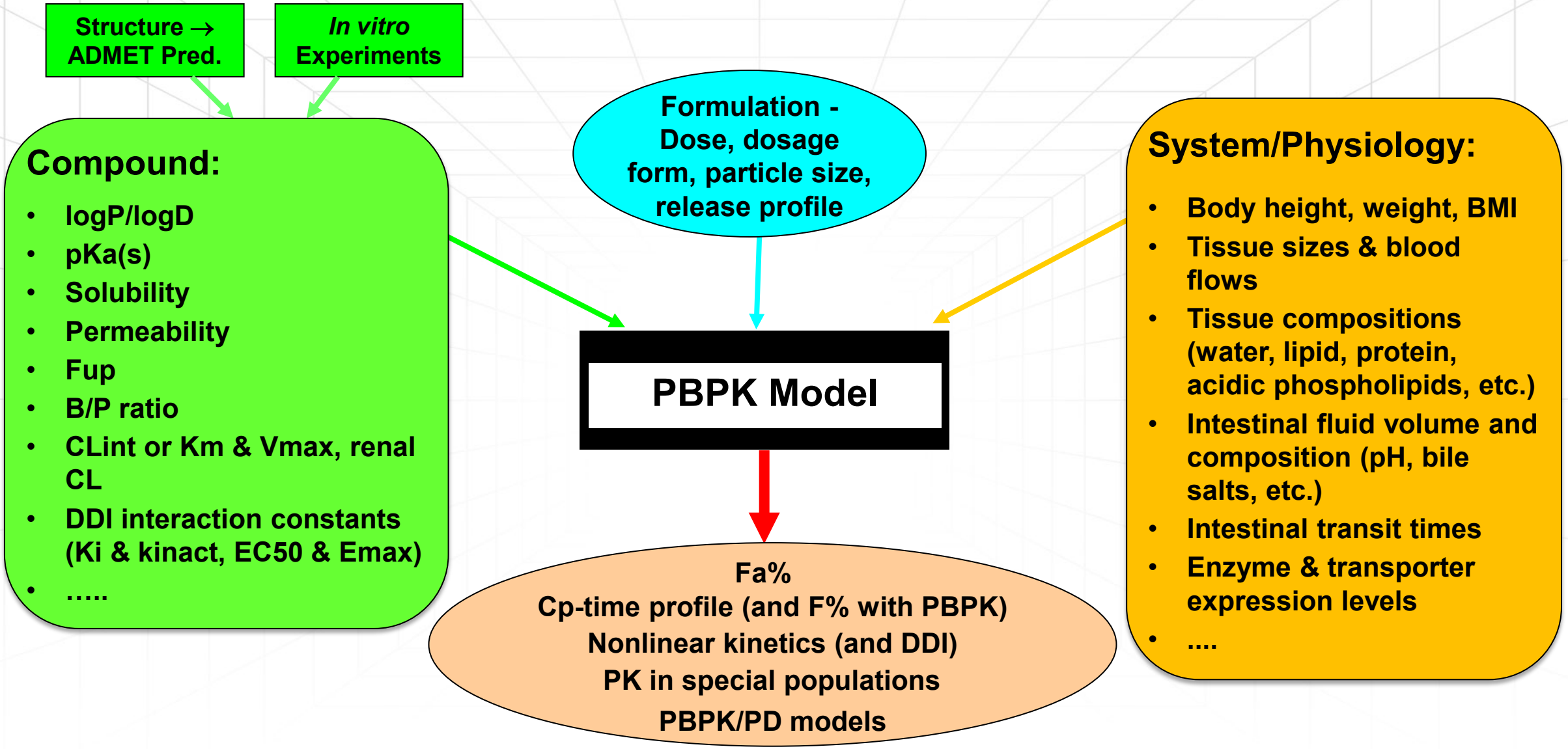
感谢您的参与和大力支持。

国家药品监督管理局药品审评中心

2022年8月17日

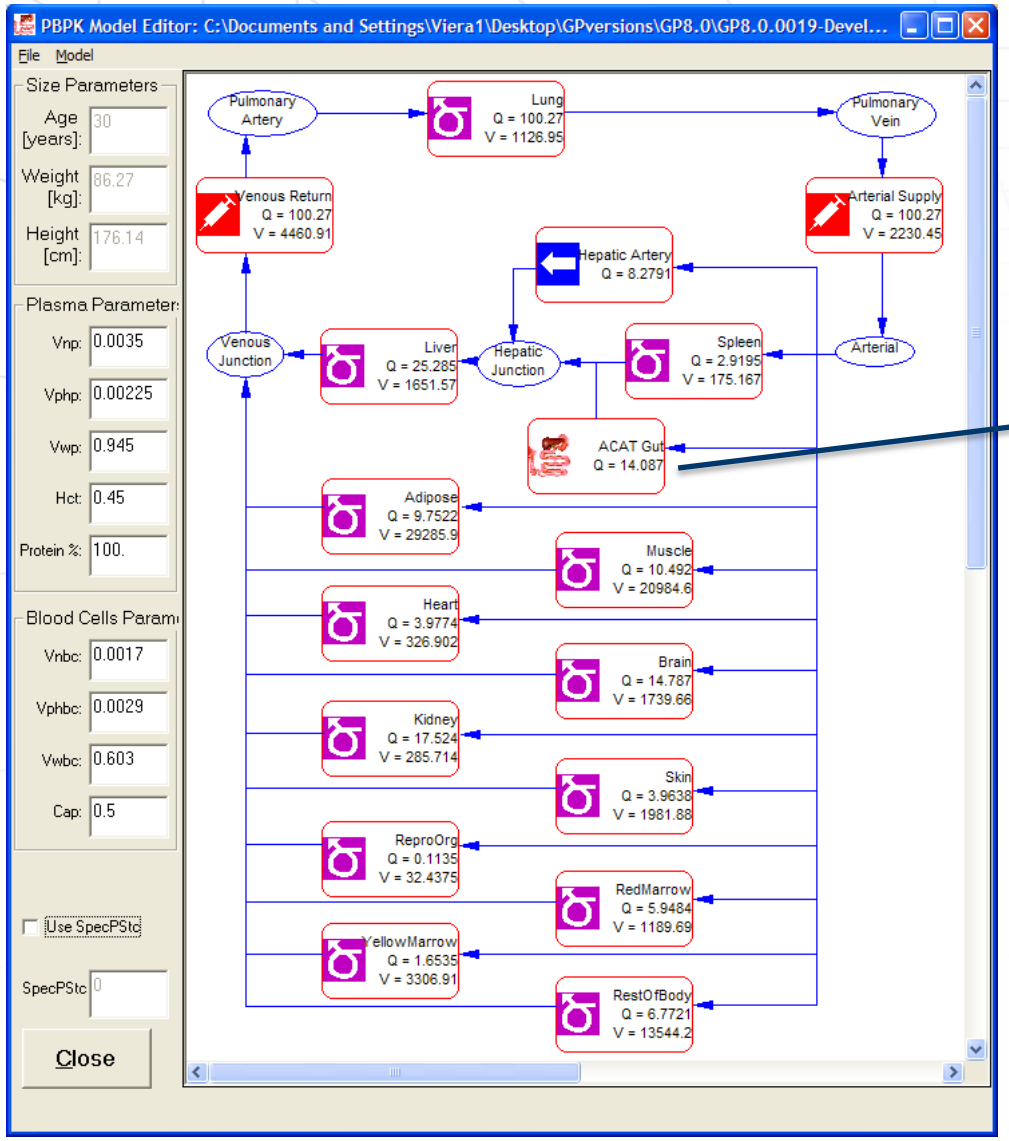
相关附件	
序号	附件名称
1	生理药代动力学模型在儿科人群药物研发中应用的技术指导原则（征求意见稿）.pdf
2	《生理药代动力学模型在儿科人群药物研发中应用的技术指导原则（征求意见稿）》起草说明.pdf

Why PBPK Model



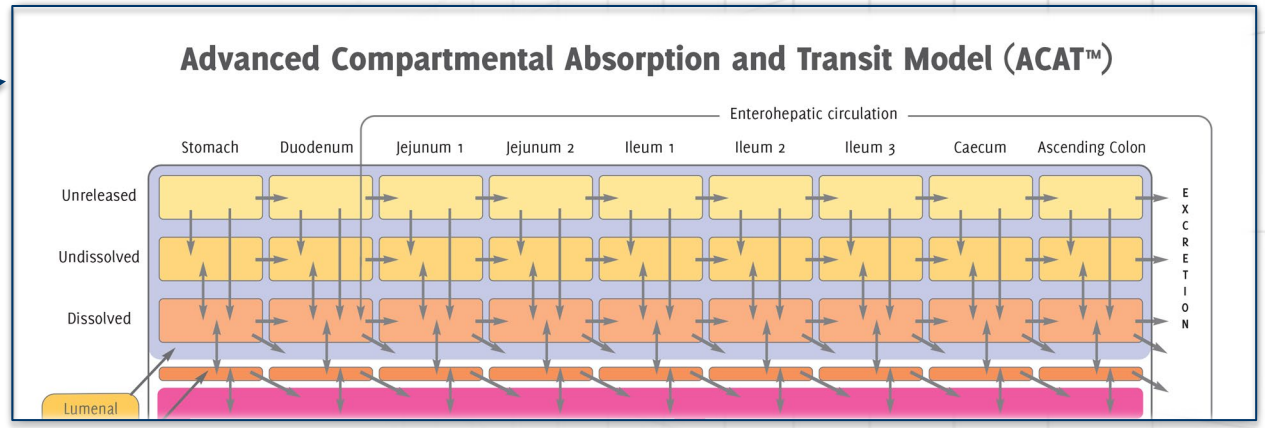
Physiology

Physiologically Based Pharmacokinetics (PBPK)



Each compartment represents a tissue:

- Specific volume(s)
- Blood perfusion rate
- Enzyme/transporter expression levels
- Volume fractions of lipids & proteins
- .....



Each compartment represents intestinal section:

- Length, radius and volume(s)
- Transit time
- Enzyme/transporter expression levels
- Lumen fluid composition
- .....

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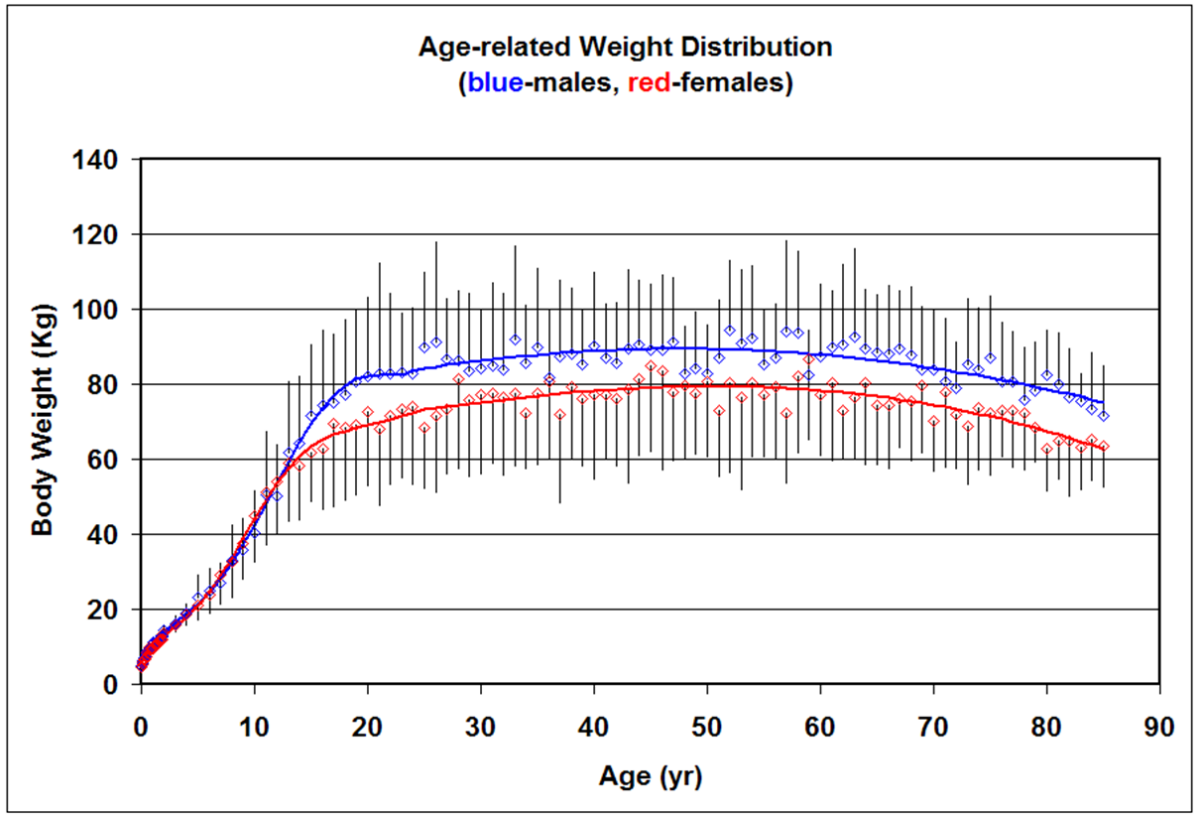
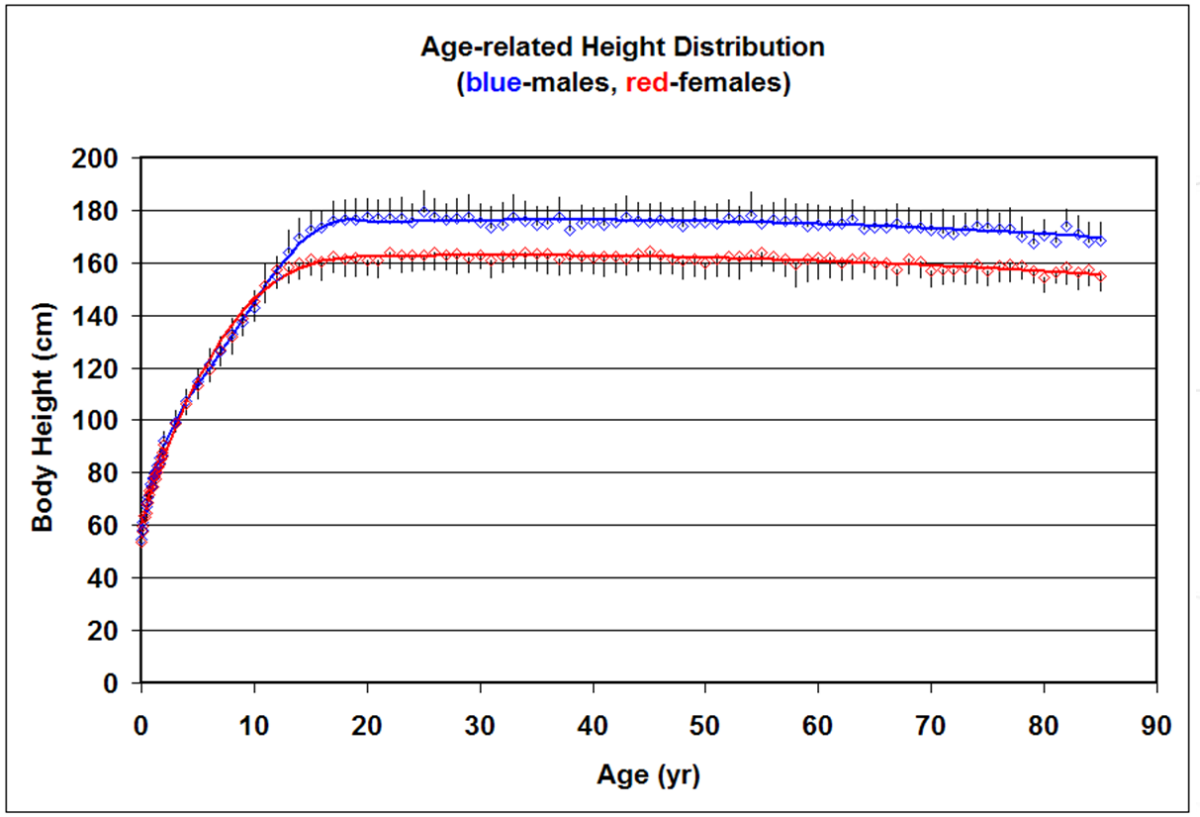
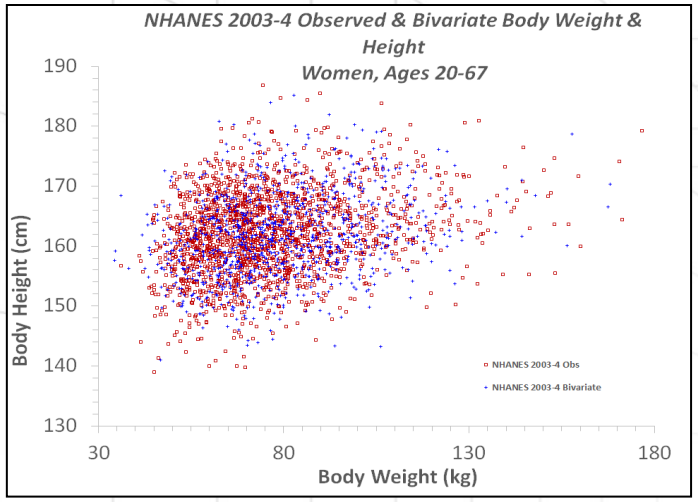
NHANES Average Body Weight & Height (NHANES 2003-2004)

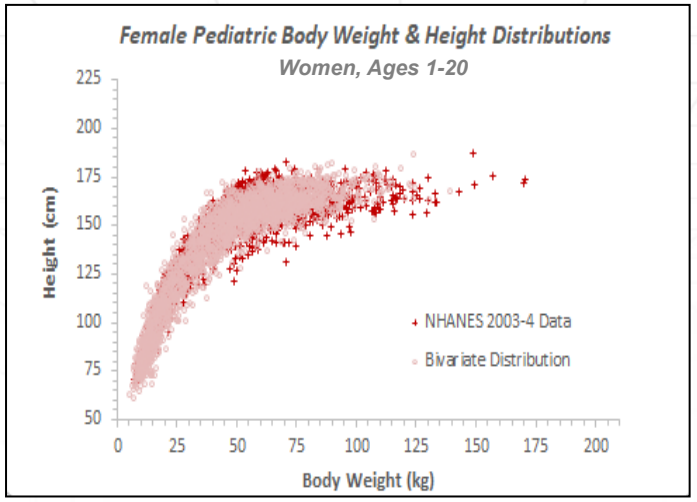


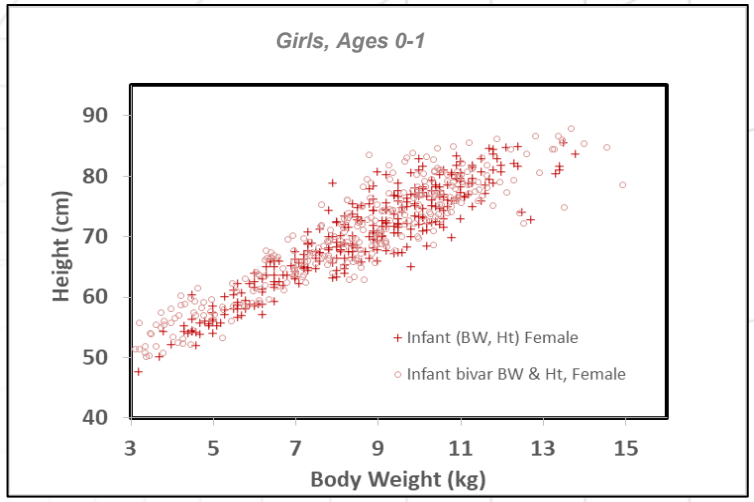


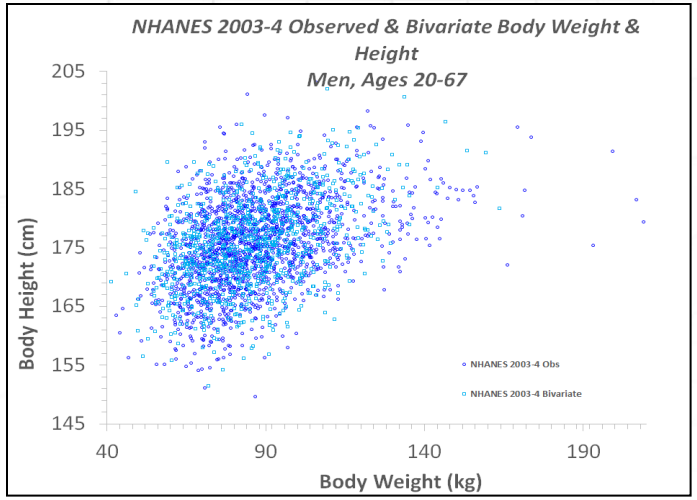
Similar information available from surveys in other countries or regions

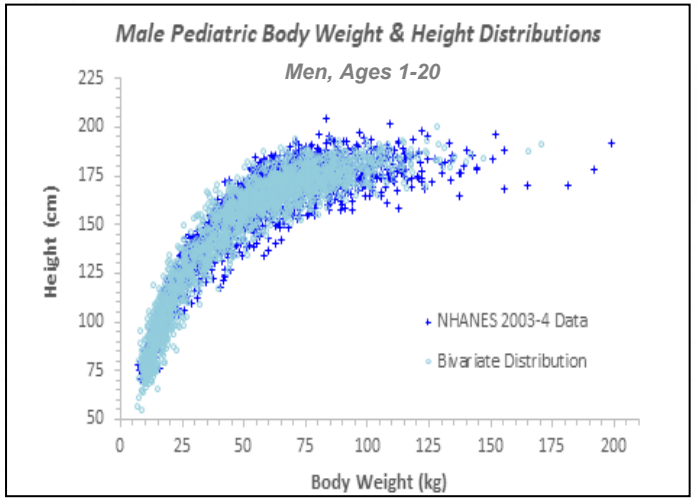
Virtual Subject Populations (NHANES 2003-2004 and other sources)

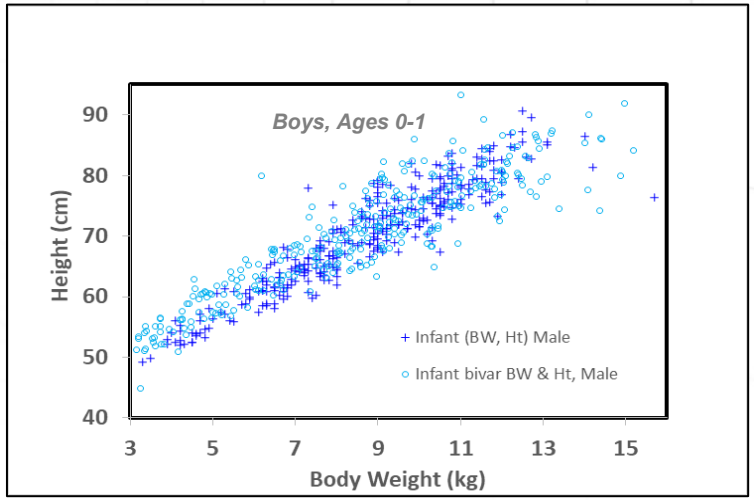






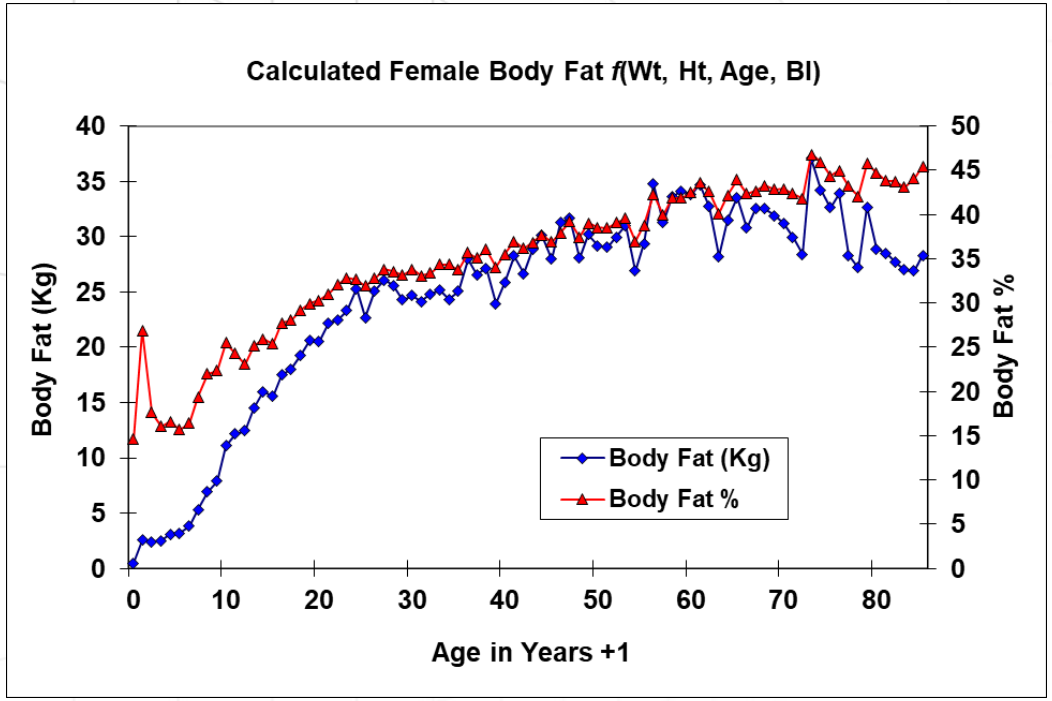




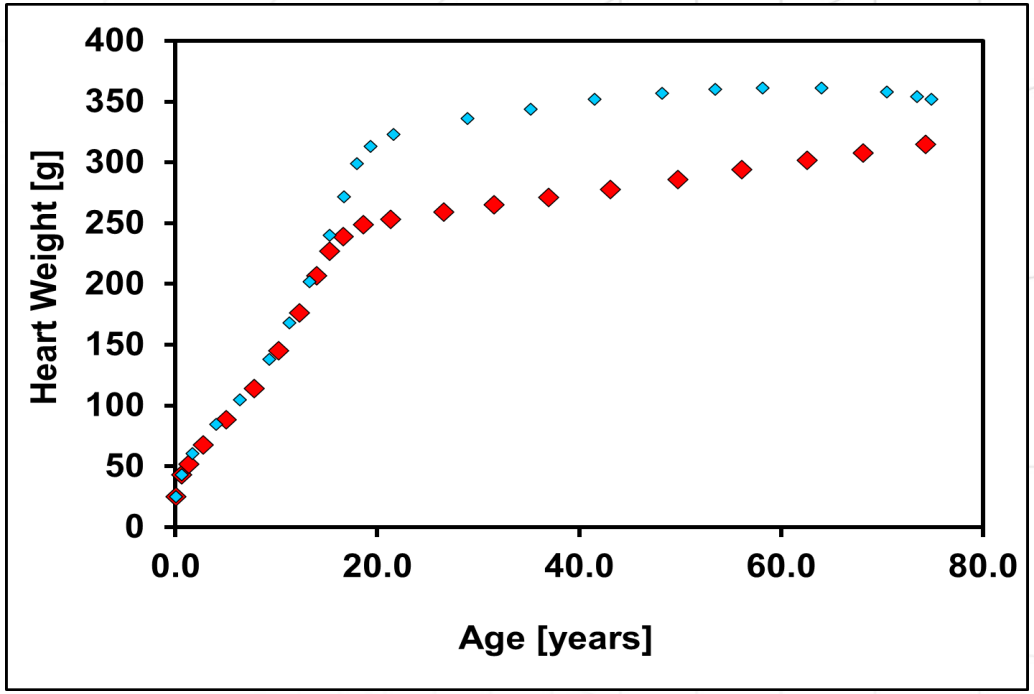


Population information is used to generate realistic virtual populations or algorithms

Individual Tissue Sizes



Houtkooper, LB, J. Appl. Physiol. 72:366 (1992)
Segal, KR, Am. J. Clin. Nutrition 47(1):7 (1988)
NHANES 2003-2004
Price, P.S. Crit. Rev. Toxicol. 33(5):469 (2003)



ICRP23

Organ Flow (mL/s/mL tissue) Data

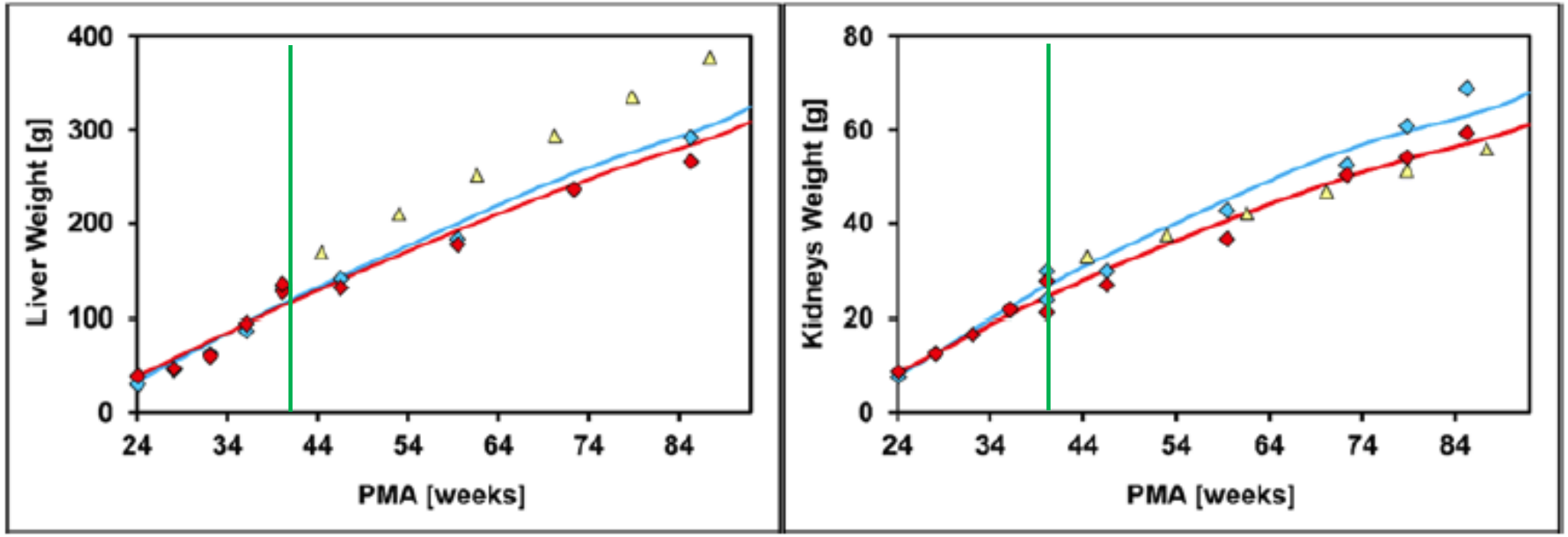
Price, P.S. Crit. Rev. Toxicol. 33(5):469 (2003), Table 16

Table 13. Organ Specific Perfusion Rates (l/min/l)

Organ	Cowles et al., 1971	Fiserova-Bergerova and Hughes (1983)	KAPKR (Williams and Legett, 1989)		Values Used in This Project	
	Male and Female	Male	Male	Female	Male	Female
Thyroid	5.00	3.57	-	-	5.00	5.00
Kidneys	3.96	3.96	3.68	3.22	3.68	3.22
Heart	0.806	0.81	0.73	0.96	0.73	0.96
Brain	0.529	0.53	0.51	0.52	0.51	0.52
Splanchnic Tissues	0.038	-	-	-	-	-
Liver	-	0.58	0.84	1	0.84	1.00
Pancreas	-	-	0.6	0.61	0.60	0.61
Spleen	-	-	1	1.04	1.00	1.04
GI Organs	-	0.37	0.75	0.78	0.75	0.78
Skin	0.057	0.09	0.12	0.15	0.12	0.15
Muscle	0.0212	0.05	0.03	0.03	0.03	0.03
Skeleton	-	-	0.03	0.03		
Red Marrow	0.399	-	-	-	0.30	0.30
Yellow Marrow	0.028	0.03	-	-	0.03	0.03
Bone tissue	-	0.01	-	-	-	-
Adipose Tissue	0.0241	0.03	0.02	0.03	0.02	0.03

Infant Physiologies - Tissue Sizes

For some parameters, the total age (gestational age + postnatal age) is the determining factor. Total body weight, height and tissue sizes for most of the tissues (except adipose) belong to this category. Example plots for two of the tissues, Liver and Kidneys, are shown below

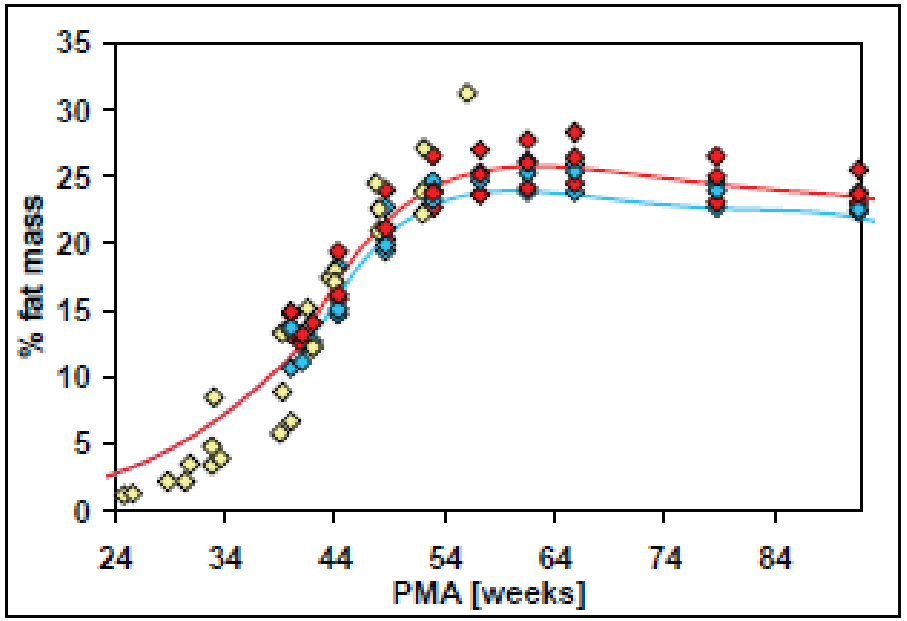


blue – males; red – females; green line shows term birth at 40 weeks of gestation
PMA – postmenstrual age (gestational + postnatal age)

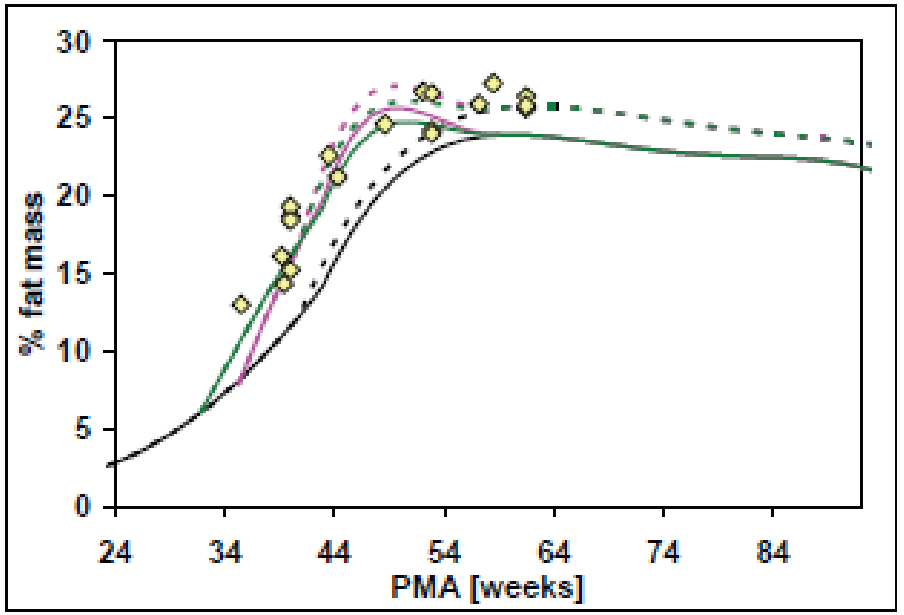
Infant Physiologies - Tissue Sizes

Gestational age is more important factor for % fat mass in infants

born at full term



pre-term

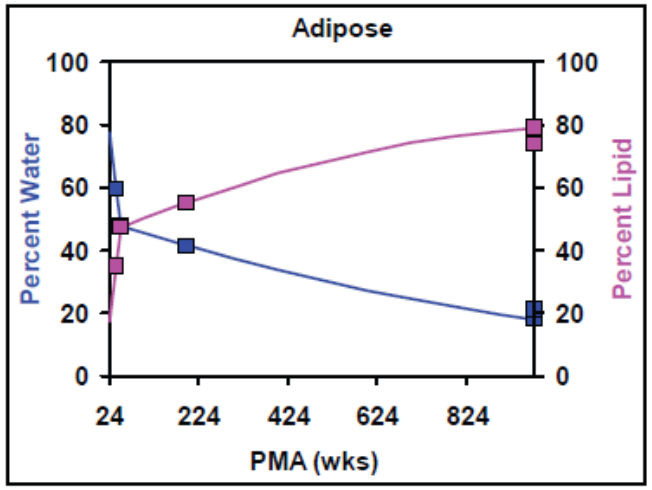


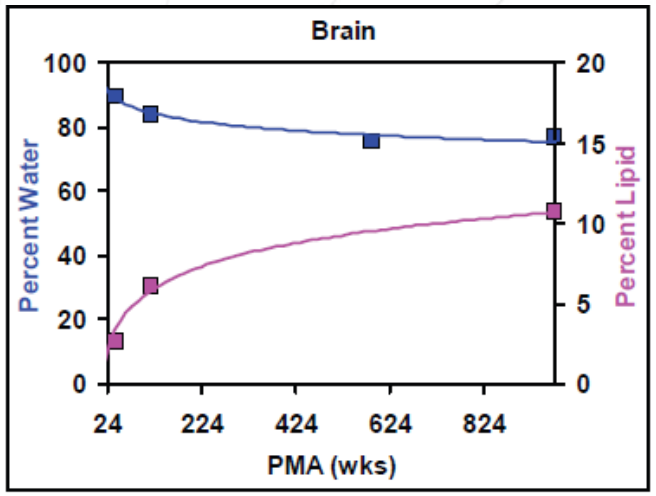
Black lines – representative of term-born infants

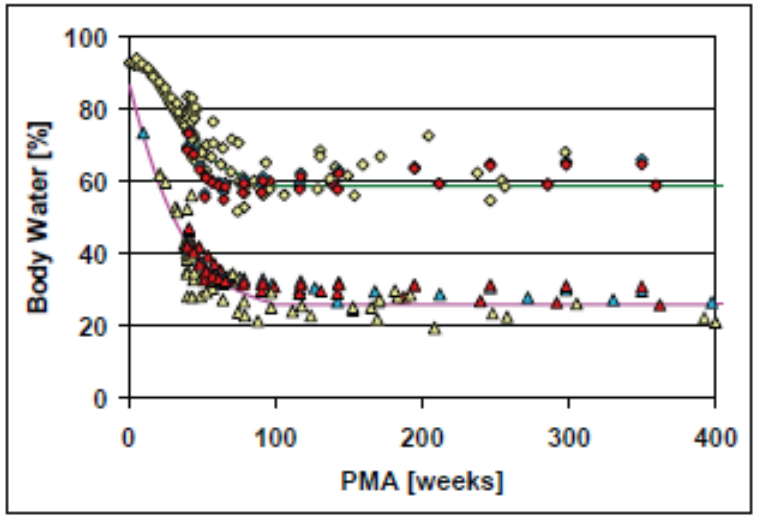
blue – males; red – females; yellow – gender not defined
PMA – postmenstrual age (gestational + postnatal age)

Tissue Composition

Effect of age on tissue compositions needs to be considered for correct prediction of distribution. Example plots for two of the tissues, Adipose and Brain, as well as total body water are shown below

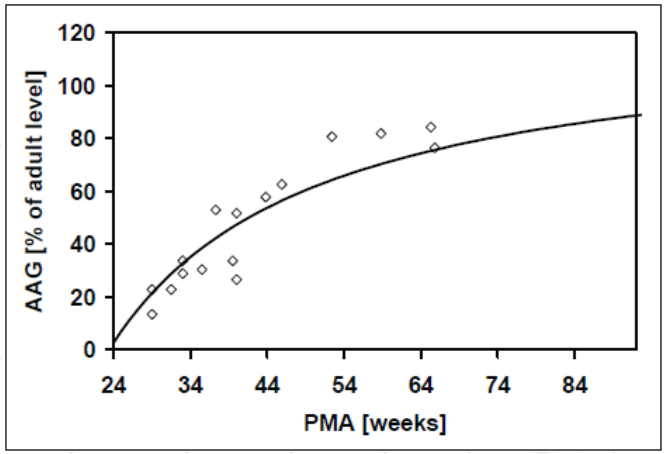


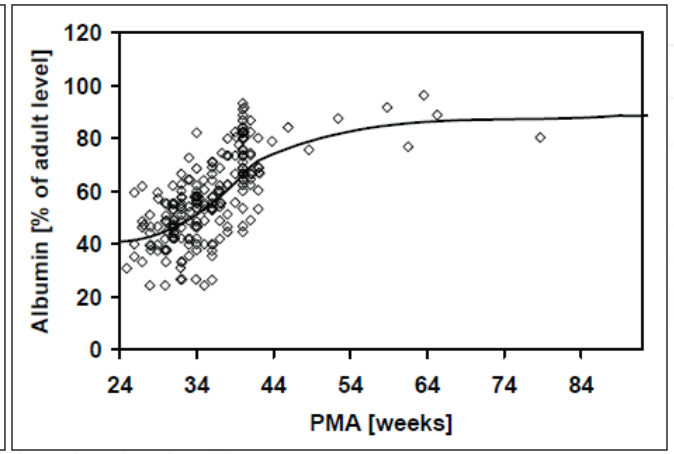


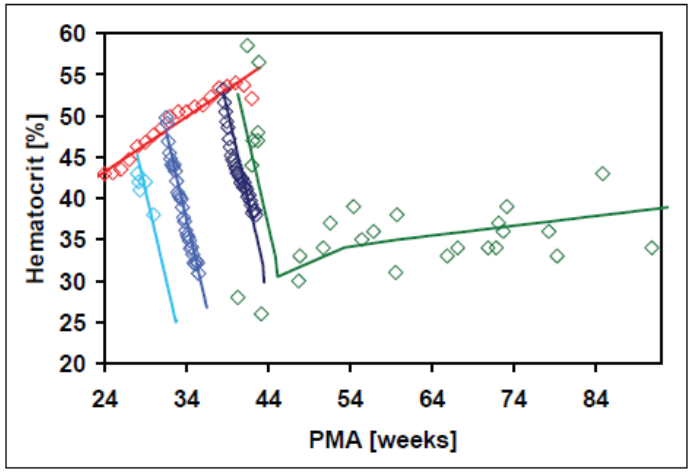


PMA – postmenstrual age (gestational + postnatal age)

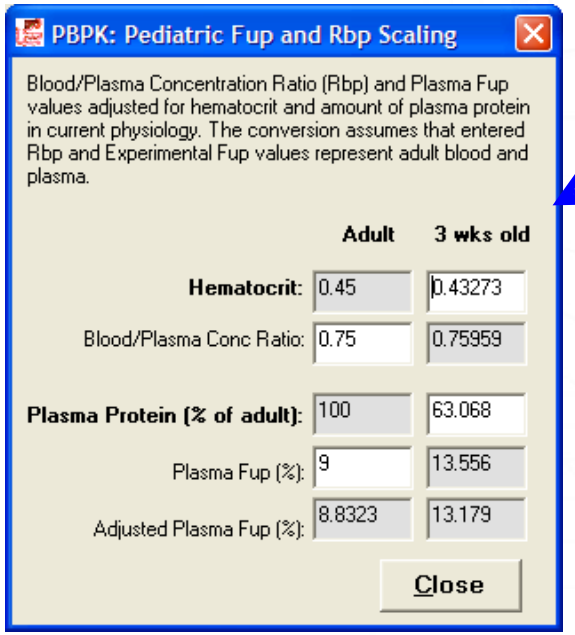
Plasma Protein and Hematocrit

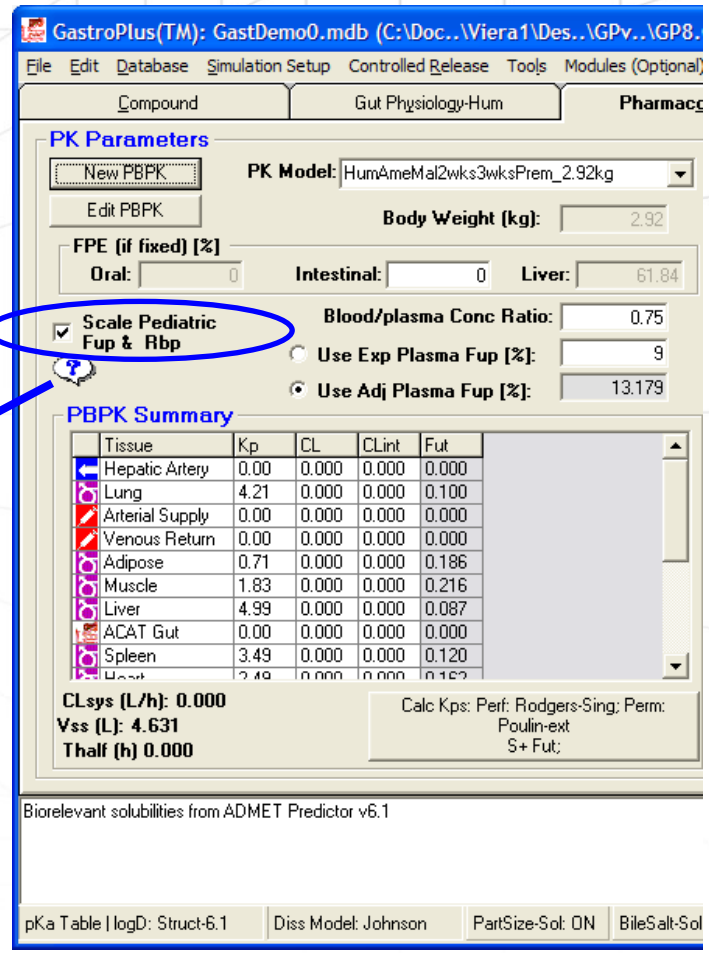






Automatic scaling of Fup and Rbp to account for different hematocrit and plasma protein levels in children than in adults





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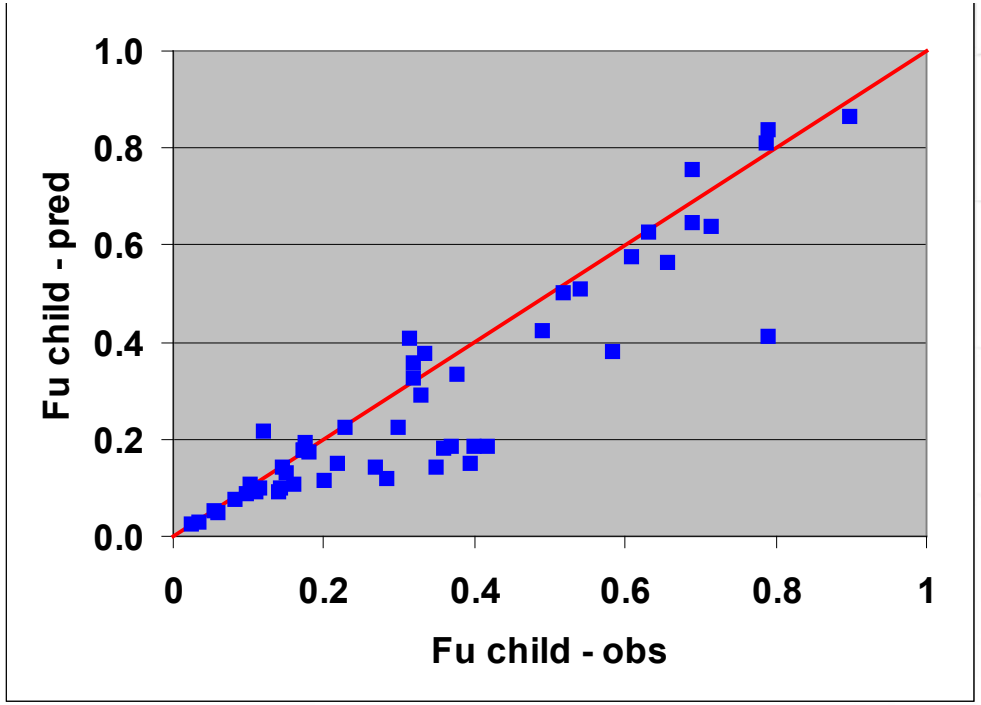
Scaling Pediatric Fup

Fup scaling is based on changes in total plasma protein (albumin and α_1-acid glycoprotein) using previously published equation (McNamara, AAPS PharmSci, 2002, E4)

$$fu_{ped} = \frac{1}{1 + \frac{P_{ped}}{P_{adult}} \frac{(1 - fu_{adult})}{fu_{adult}}}$$

P_{ped} and P_{adult} is binding protein concentration in pediatric and adult subject, respectively; fu_{ped} and fu_{adult} is fraction unbound in plasma in pediatric and adult subject, respectively

Pediatric *fup* observed and predicted from published equation using pediatric plasma protein level as implemented in GastroPlus. Reported values were for ages 1 day to ~ 4 months.



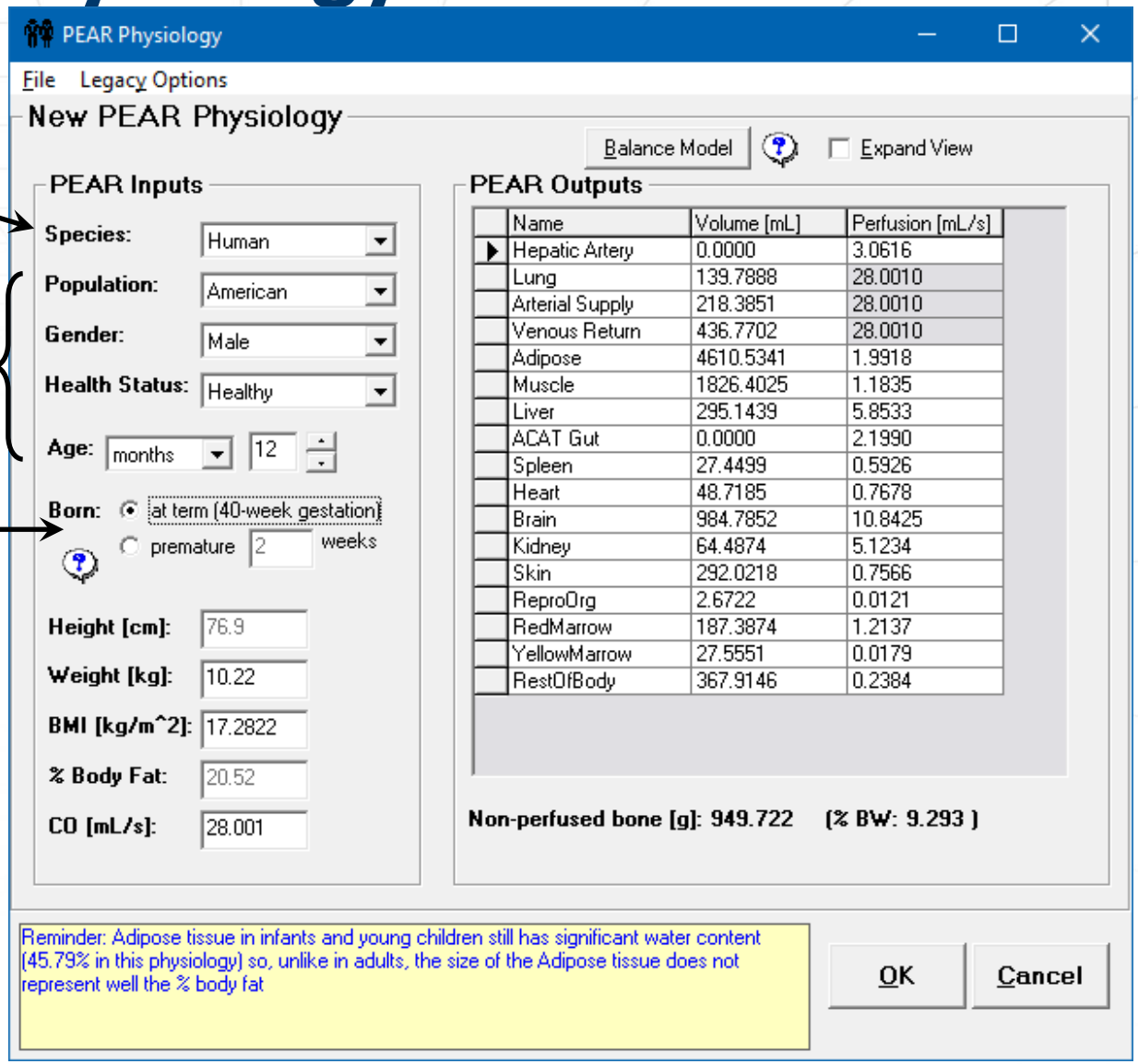
PEAR-Physiology Method

1. Select **Species**

2. For Human physiologies, specify **Population**, **Gender, Health Status** and **Age**
   - **For Health Status:**
   - **Healthy**
   - **Hepatic Impairment**
   - **NEW: NASH, NAFLD**
   - **Renal Impairment**
   - **Obesity**
   - **Pregnancy**

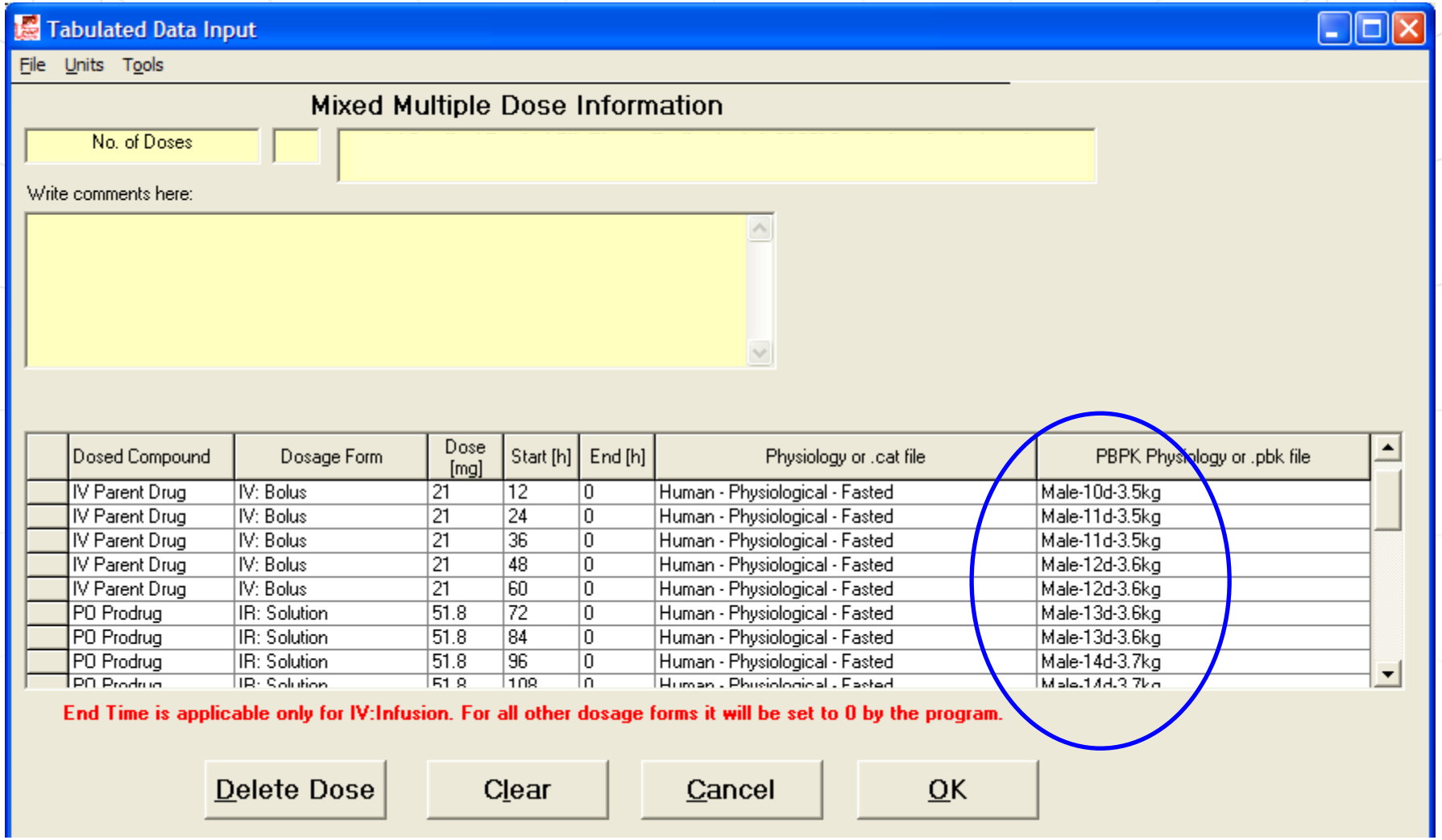
For infants specify born **at term** or **premature** (up to 16 weeks)
(this option appears only when age is set to less than 1 year old)

3. Program creates typical physiology – you can make further adjustments to:
   - Body Weight,
   - Cardiac Output
   - BMI
   - Individual tissues



Child Growth During Study

Account for growth of a child in multi-day study through .mdd file



Intestinal Physiology

- Limited information available for some parameters, i.e. gastric emptying or small intestine transit time (dependent on measurement method)
- For some parameters the information is only qualitative (i.e. underdeveloped villi structure in infants < 3 years old or differences in bile salt composition and site of reabsorption)

Scaling in GastroPlus

- Stomach pH in neonates
- Stomach volume
- Intestinal length and radius (and subsequently volume)
- Transit times
- Enzyme and Transporter Expression Levels:
  - Ontogeny for 3A4 and several others already included
  - Ontogeny is incorporated gradually as it appears in literature (assuming adult density of expression where specific data is lacking)

Estimating PBPK Parameters in GastroPlus

Tissue weights, tissue perfusion rates, tissue densities, and partition coefficients for each tissue for the drug are required for PBPK.

The Population Estimates for Age-Related Physiology™ (PEAR Physiology™) module inside of PBPKPlus™ generates such values. It is based on the NHANES database for American/Western physiologies, a Japanese government database for Japanese physiologies, and CHNS database for Chinese groups. User specifies age and gender.

The PEAR Physiology module also generates tissue parameters for rat, dog, mouse, monkey, rabbit and minipig, but age and gender are fixed.

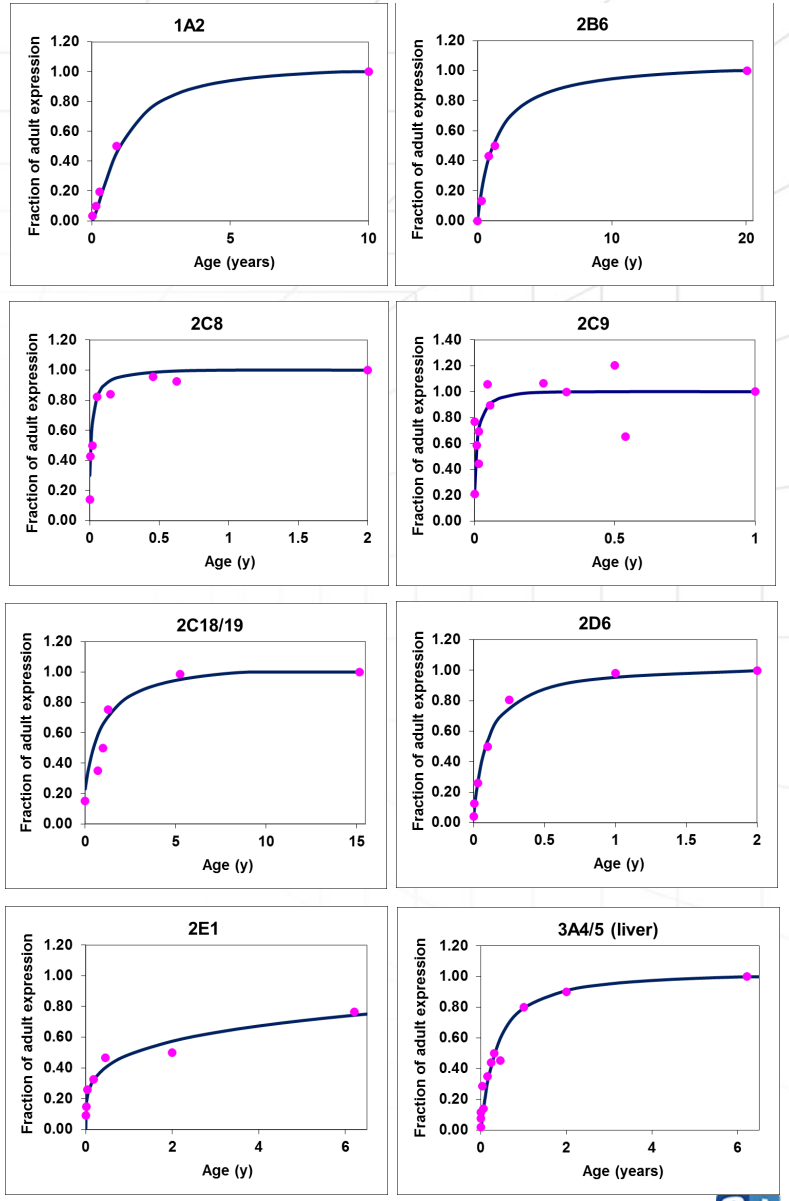
Metabolic clearance

CYP Enzyme Ontogeny

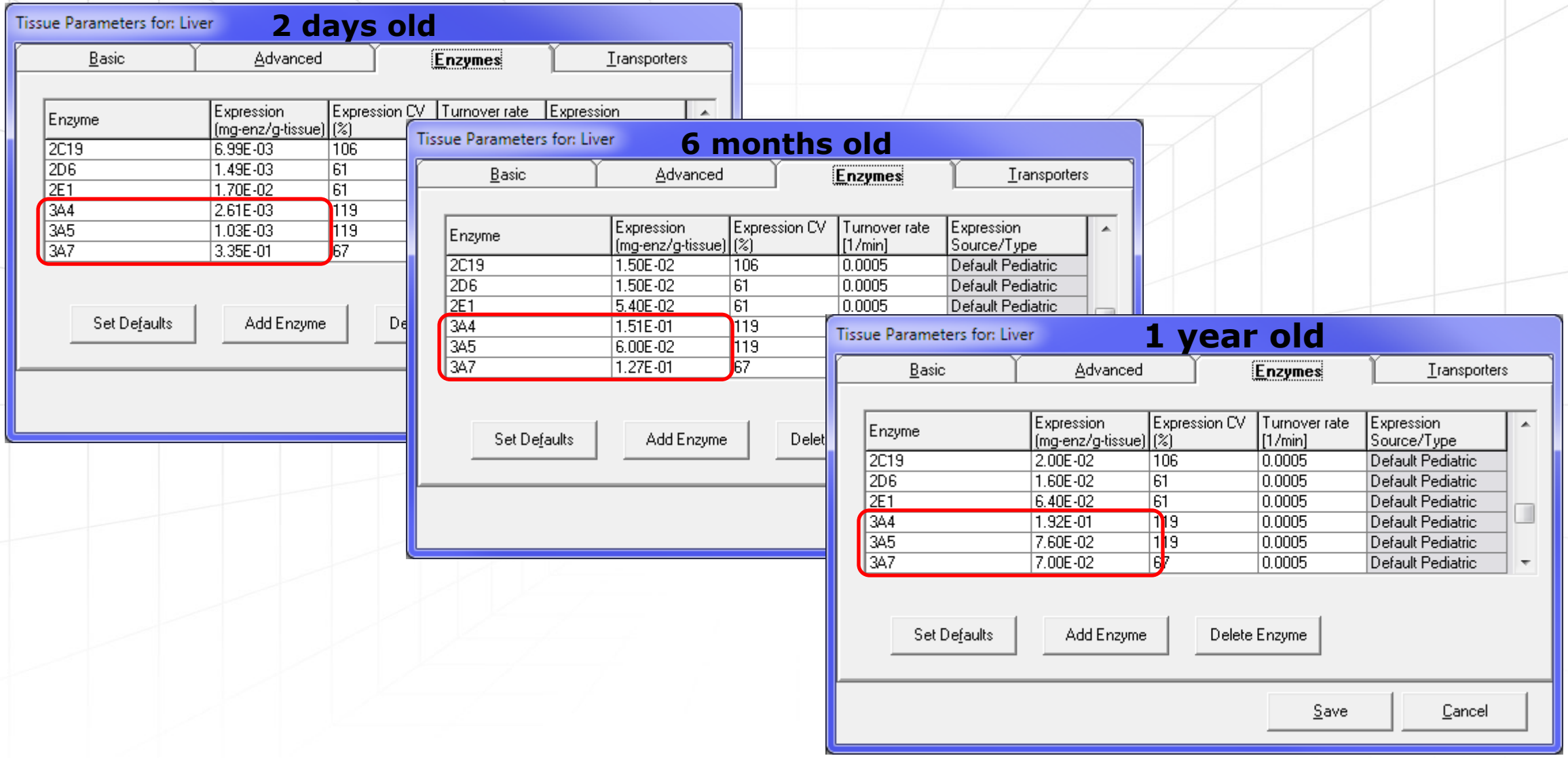
Table I.

Enzyme	Time to half adult expression (y)	Hyperbolic function (fraction of adult CYP abundance)
CYP1A2	0.9	$\frac{1 \times Age^{1.41}}{1.13 + Age^{1.41}}$
CYP2B6	1.31	$\frac{1.07 \times Age}{1.31 + Age}$
CYP2C8	0.02	$\frac{0.716 \times Age}{0.02 + Age} + 0.3$
CYP2C9	0.01	$\frac{0.821 \times Age}{0.01 + Age} + 0.21$
CYP2C18/19	0.99	$\frac{0.857 \times Age}{0.99 + Age} + 0.23$
CYP2D6	0.101	$\frac{1.01 \times Age}{0.101 + Age} + 0.036$
CYP2E1	2	$\frac{4.22 \times Age^{0.27}}{7.66 + Age^{0.27}}$
CYP3A4/5	0.31	$\frac{1 \times Age^{0.83}}{0.31 + Age^{0.83}}$
CYP3A	2.36	$\frac{0.639 \times Age}{2.36 + Age} + 0.42$

Johnson T., Clin Pharmacokinet 45(9):931 (2006)



CYP Enzyme Ontogeny



CYP Enzyme Ontogeny

5 years old

Tissue Parameters for: Liver

Basic | Advanced | **Enzymes** | Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression CV (%)	Turnover rate [1/min]	Expression Source/Type
2C19	2.80E-02	106	0.0005	Default Pediatric
2D6	1.70E-02	61	0.0005	Default Pediatric
2E1	9.30E-02	61	0.0005	Default Pediatric
3A4	2.39E-01	119	0.0005	Default Pediatric
3A5	9.40E-02	119	0.0005	Default Pediatric
3A7	4.11E-03	67	0.0005	Default Pediatric

Set Defaults | Add Enzyme | Delete Enzyme

adult

Tissue Parameters for: Liver

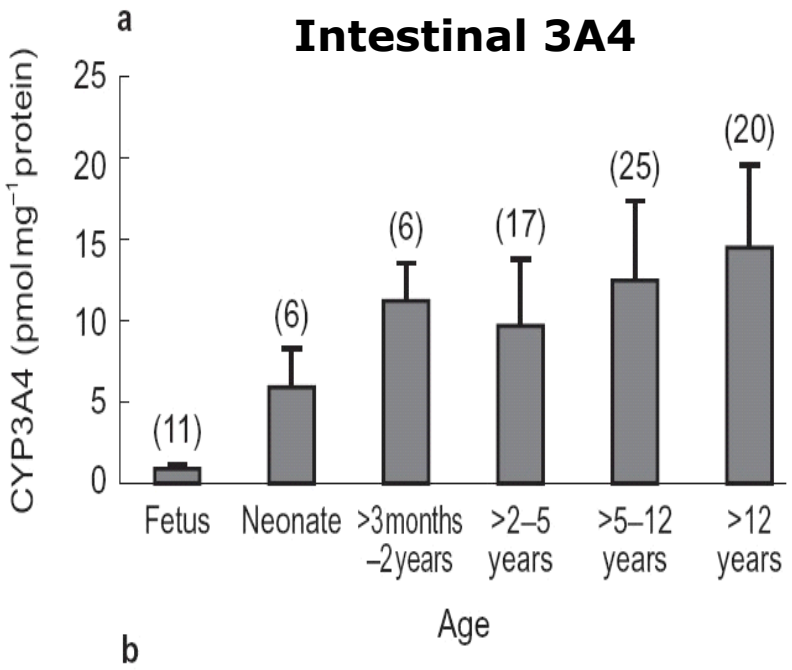
Basic | Advanced | **Enzymes** | Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression CV (%)	Turnover rate [1/min]	Expression Source/Type
2C19	3.00E-02	106	0.0005	Default Adult
2D6	1.70E-02	61	0.0005	Default Adult
2E1	1.32E-01	61	0.0005	Default Adult
3A4	2.42E-01	119	0.0005	Default Adult
3A5	9.50E-02	119	0.0005	Default Adult
3A4/5	3.37E-01	67	0.0005	Default Adult

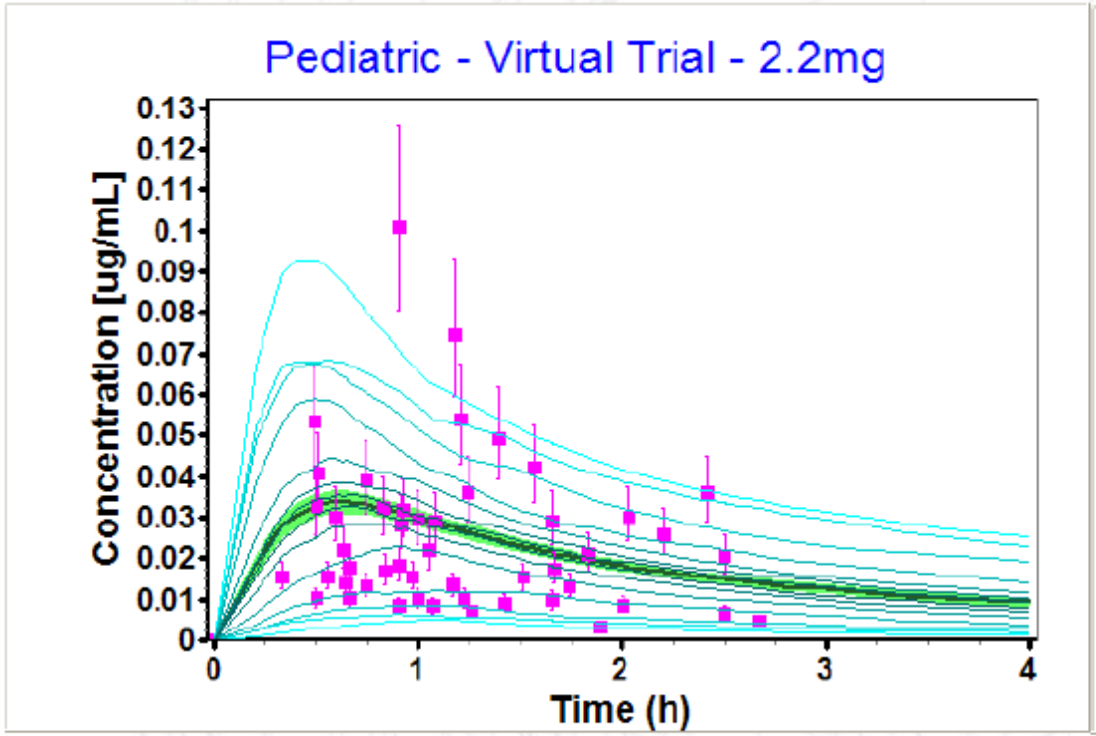
Add Enzyme | Delete Enzyme

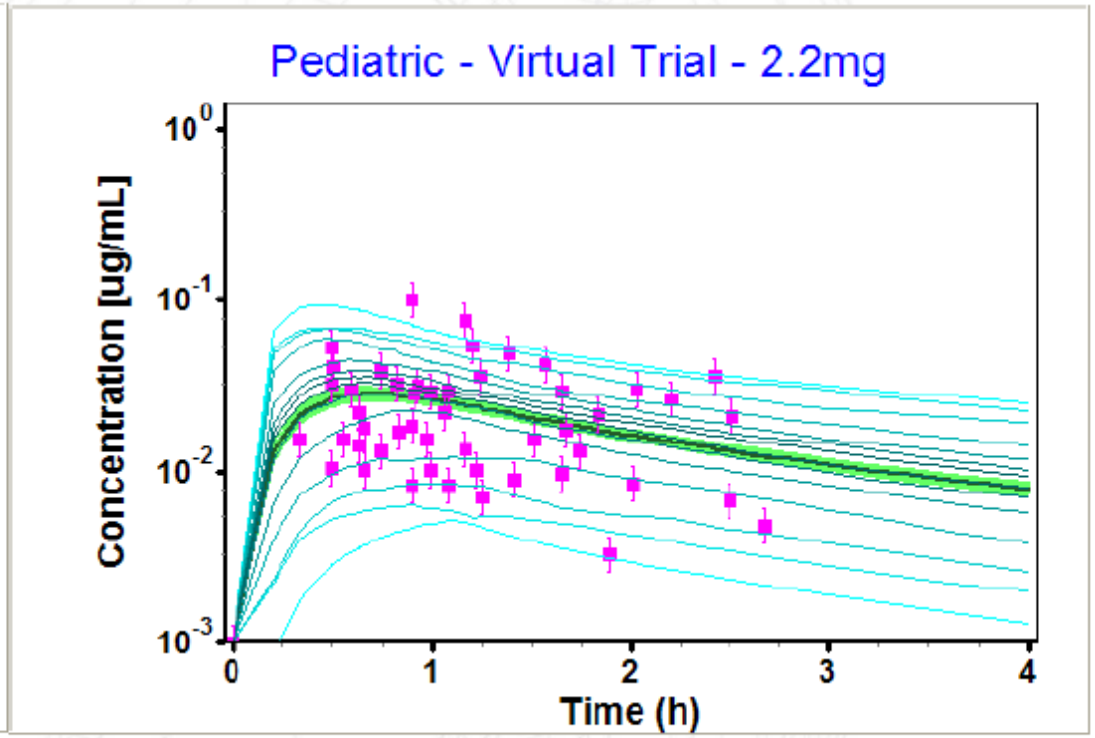
Save | Cancel

Intestinal 3A4



Midazolam

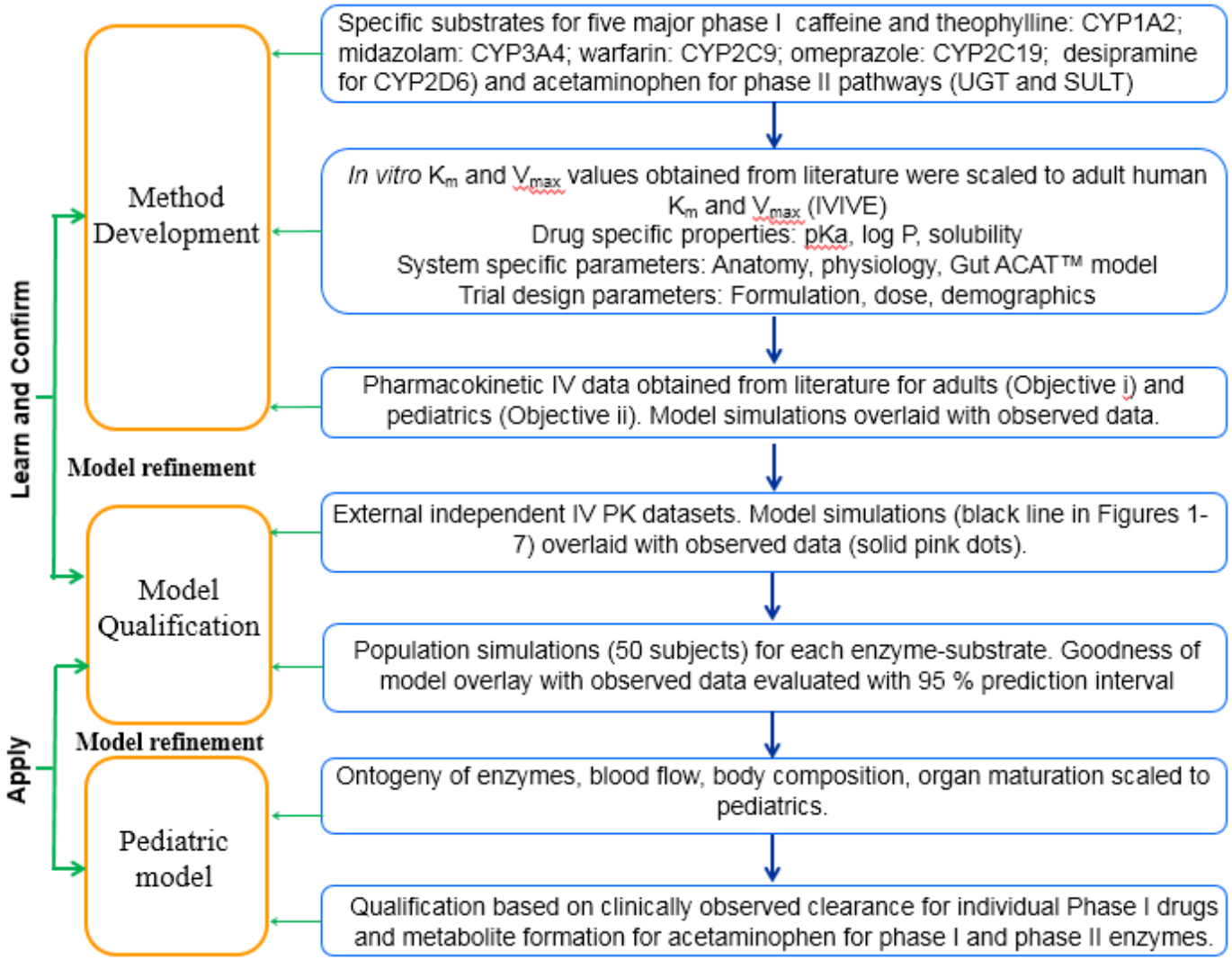




This is a prediction of pediatric population using *in vitro*, *in silico* and adult *in vivo* data and known differences in adult and pediatric physiology. The model was not fitted to pediatric data.

Lukacova – Workshop on Modeling in Pediatric Medicines, 2008

Pediatric CL – metabolism by CYPs

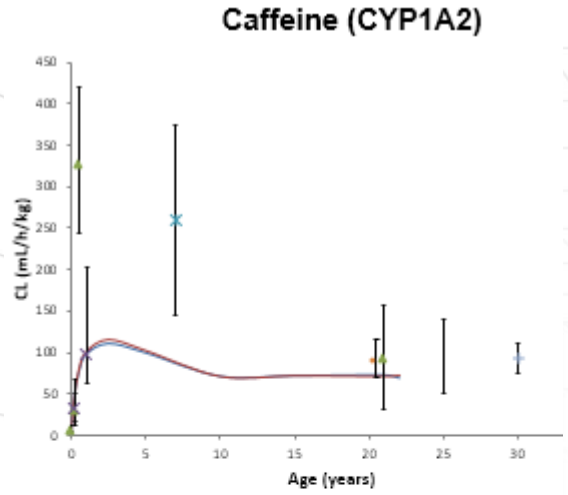


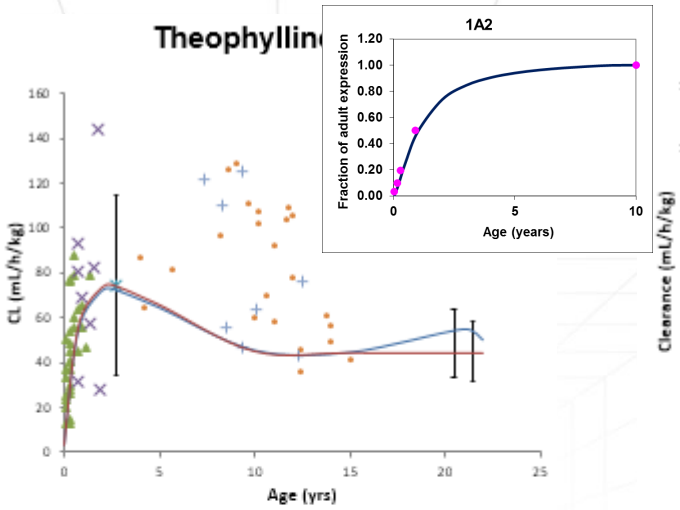
Samant et al. – Poster Presentation (Poster # 111) - ASCPT 2015 also Quantitative Systems Pharmacology pre-conference Poster # QP-16

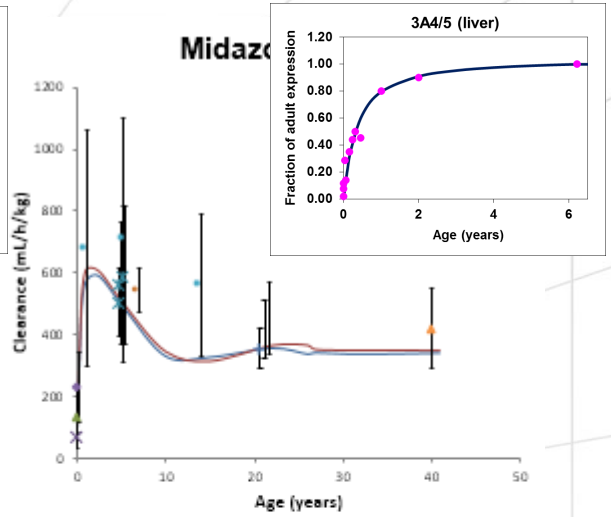
UF College of Pharmacy UNIVERSITY of FLORIDA

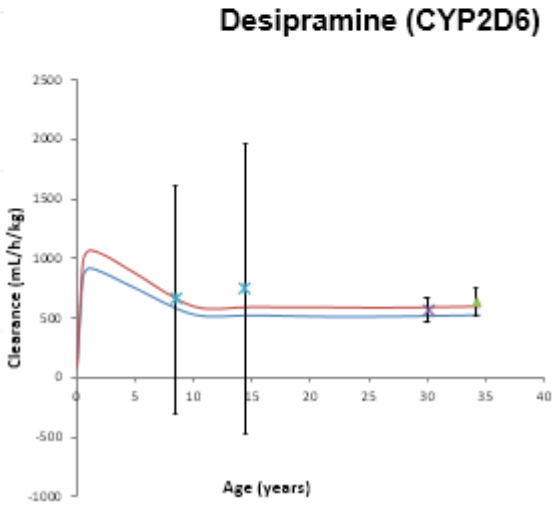
SimulationsPlus
Cognigen | DILIsym Services | Lixoft

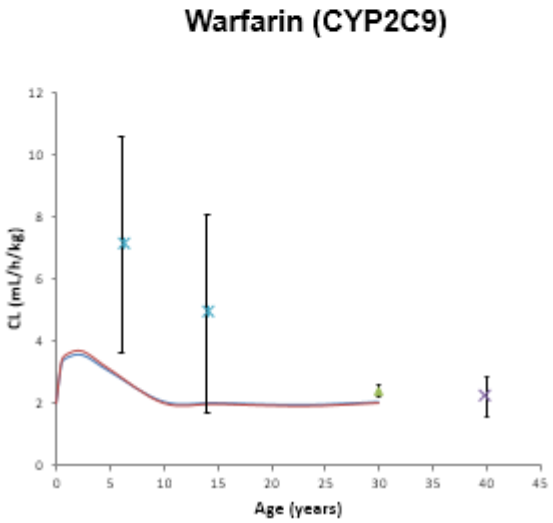
Pediatric CL – metabolism by CYPs

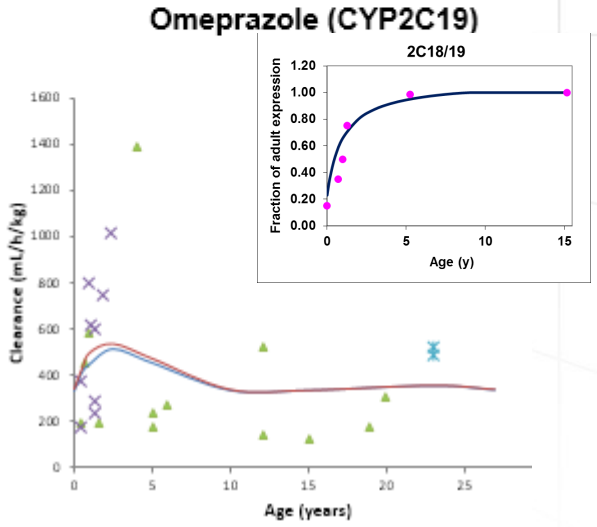












Samant et al. – Poster Presentation (Poster # 111) - ASCPT 2015
also Quantitative Systems Pharmacology pre-conference Poster # QP-16

Pediatric CL – Acetaminophen

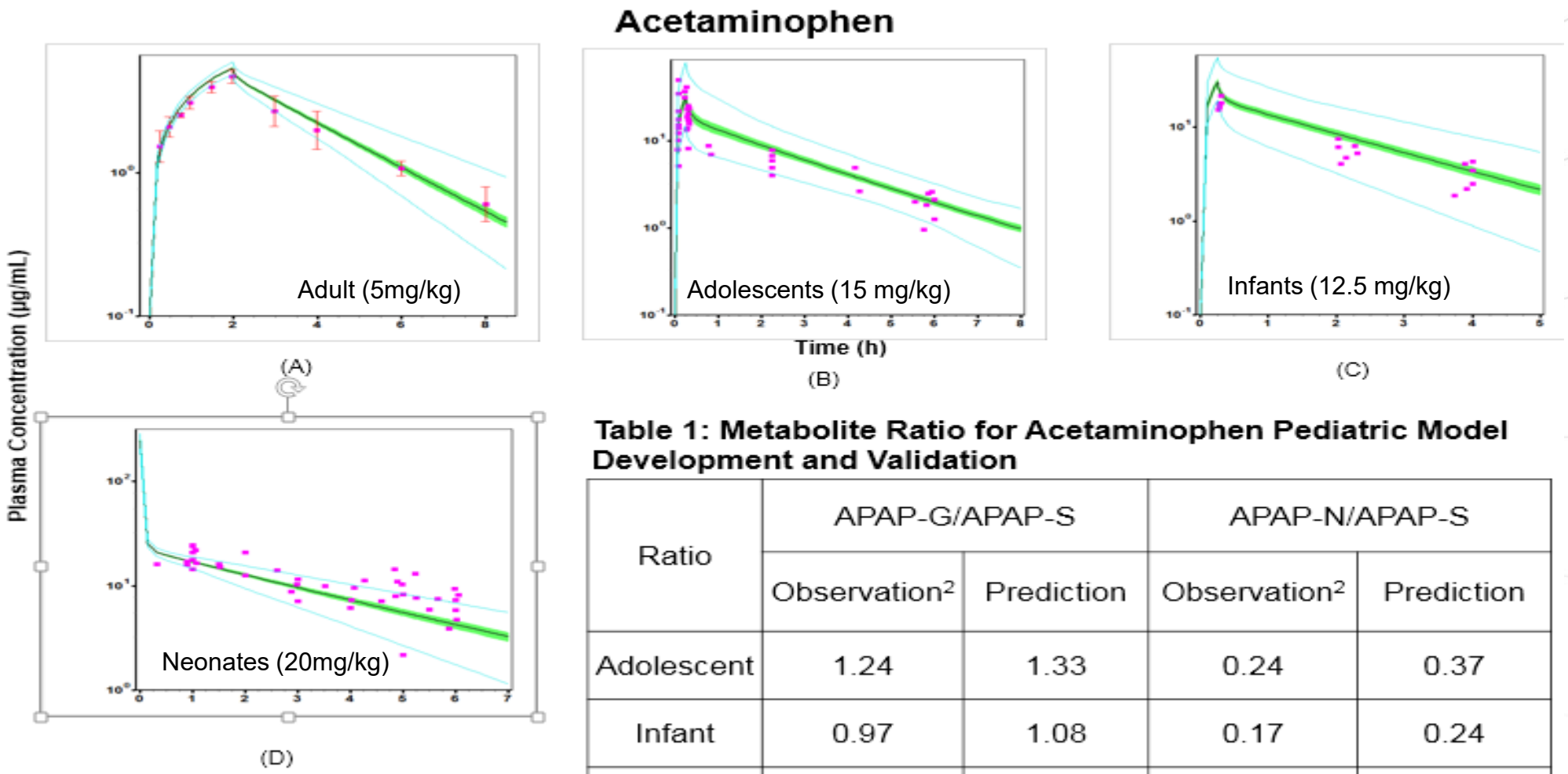


Table 1: Metabolite Ratio for Acetaminophen Pediatric Model Development and Validation

Ratio	APAP-G/APAP-S		APAP-N/APAP-S	
	Observation[2]	Prediction	Observation[2]	Prediction
Adolescent	1.24	1.33	0.24	0.37
Infant	0.97	1.08	0.17	0.24
Neonate	0.60	0.71	0.12	0.08

Samant et al. – Poster Presentation (Poster # 111) - ASCPT 2015
also Quantitative Systems Pharmacology pre-conference Poster # QP-16

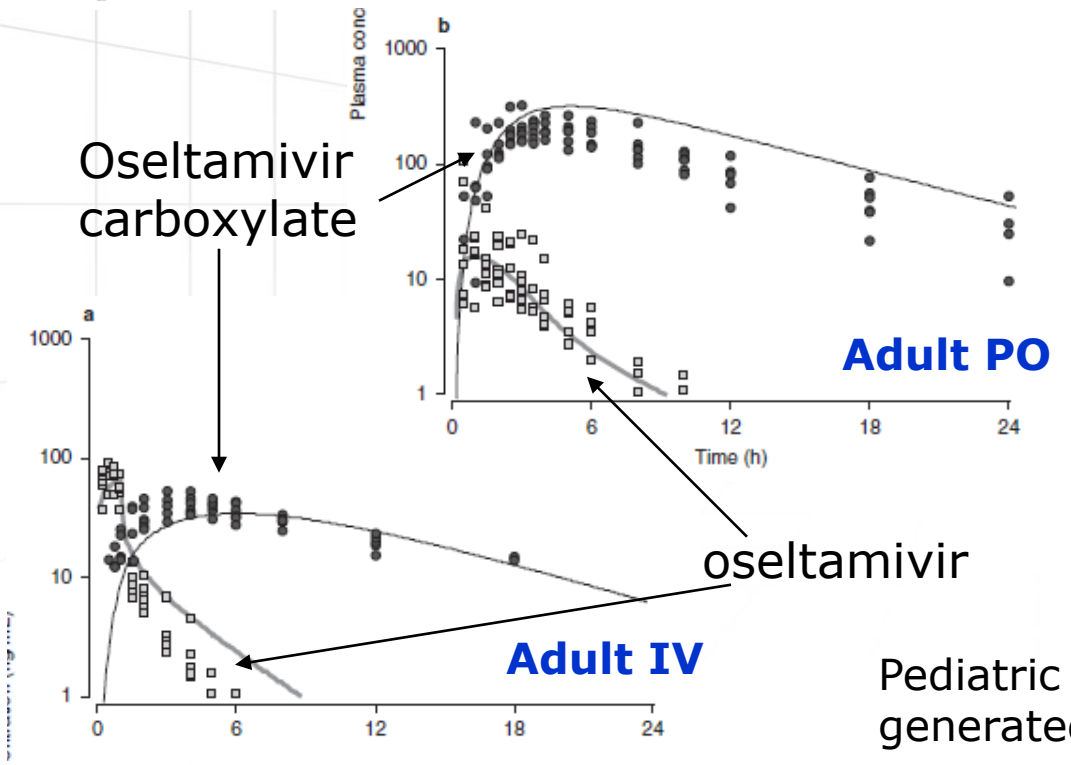
Non-CYP Mediated CL

ORIGINAL RESEARCH ARTICLE

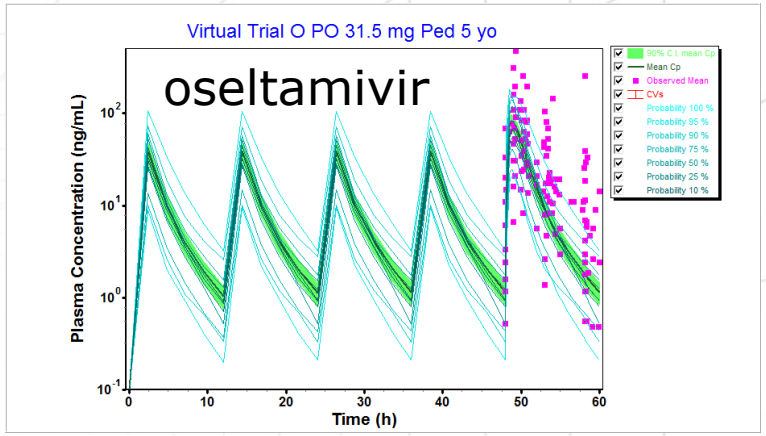
Clin Pharmacokinet 2011; 50 (9): 1-11
0312-5963/11/0009-0001/$49.95/0

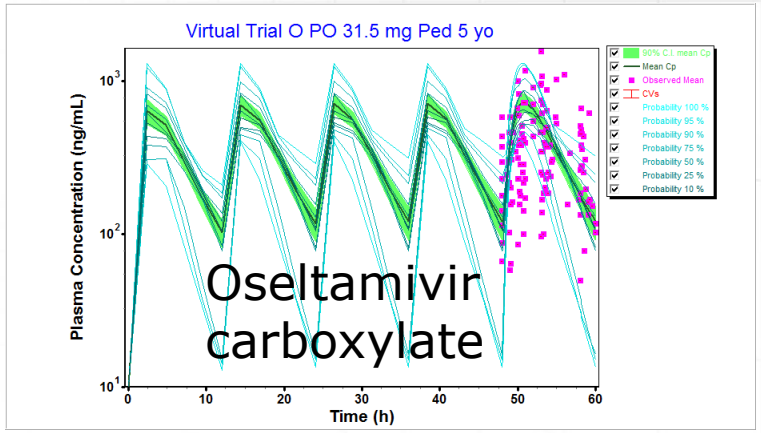
Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants

Neil Parrott,[1] Brian Davies,[2] Gerhard Hoffmann,[1] Annette Koerner,[1] Thierry Lave,[1] Eric Prinssen,[3] Elizabeth Theogaraj[4] and Thomas Singer[1]



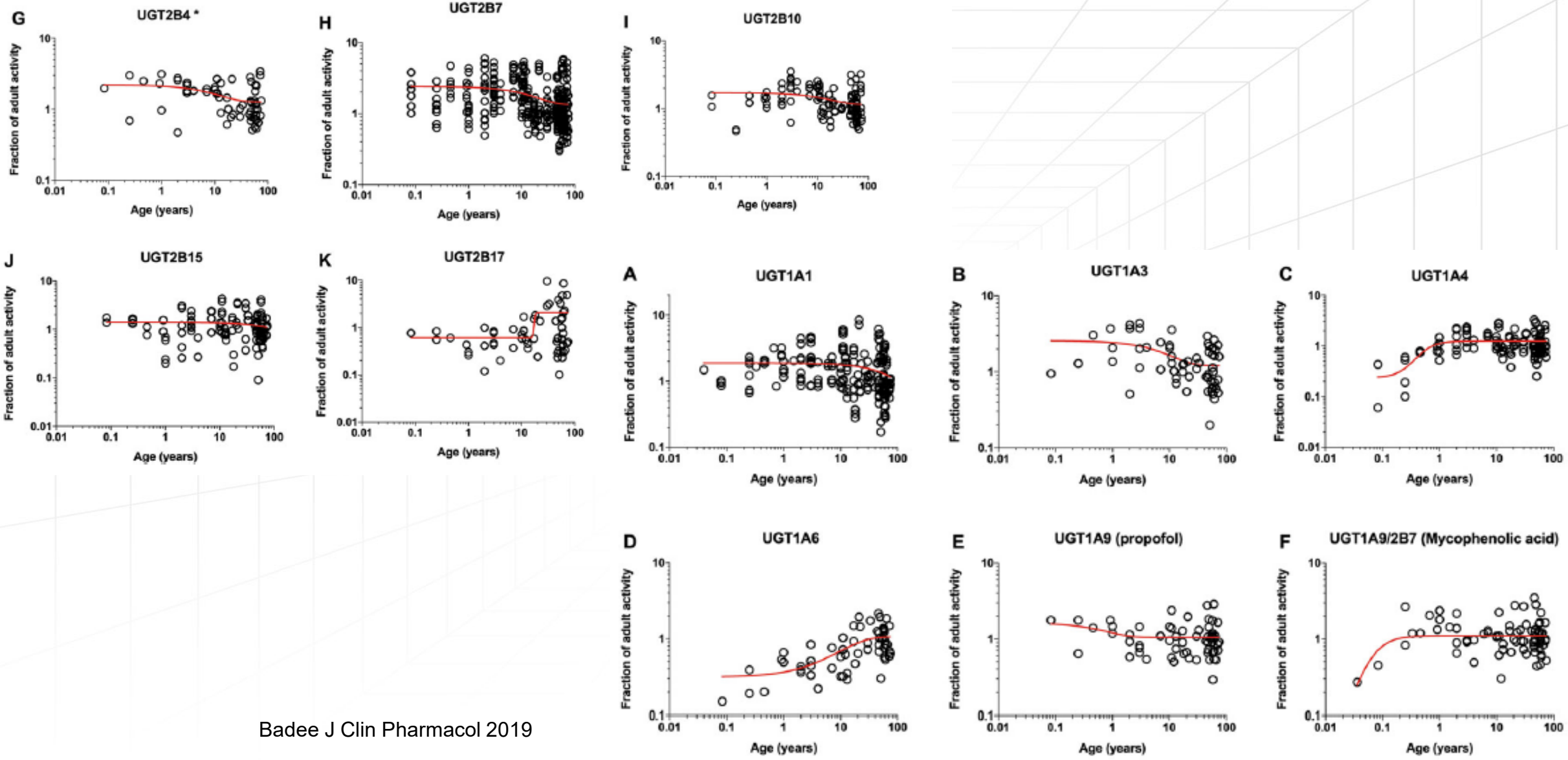
Pediatric PO





Pediatric physiologies are automatically generated by GastroPlus

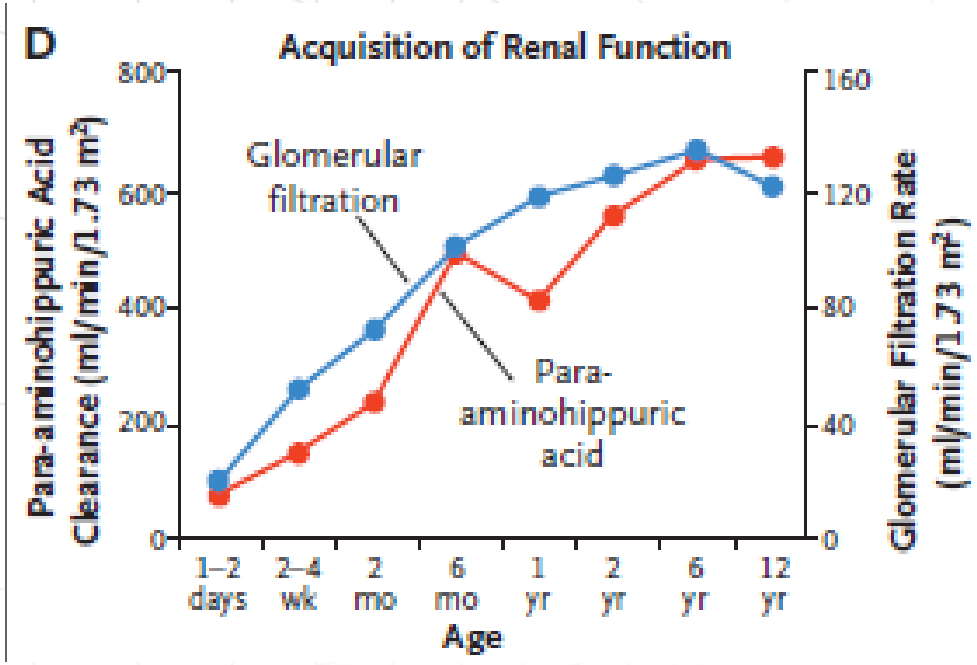
UGT Enzyme Ontogeny



Badee J Clin Pharmacol 2019

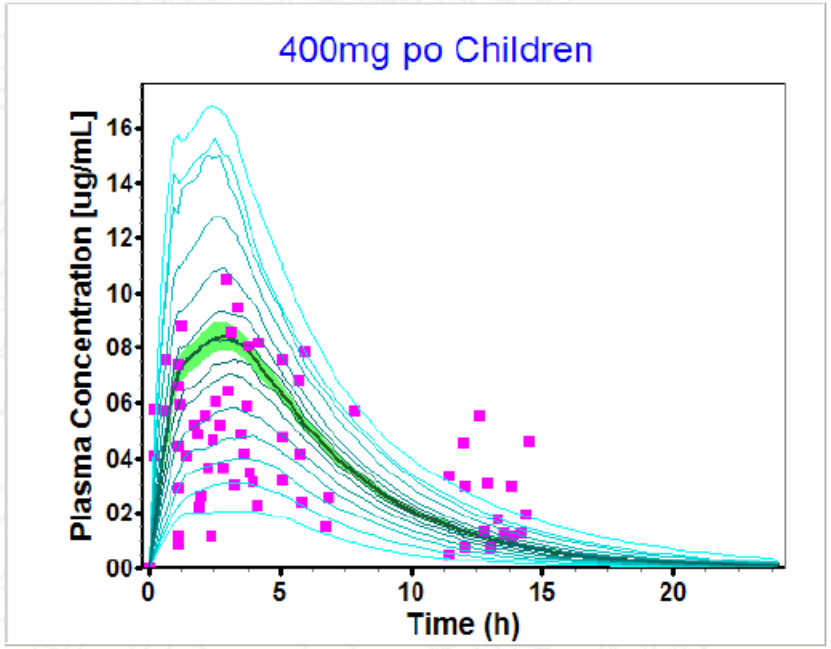
Renal secretion – glomerular filtration

Glomerular Filtration



Kearns – New Engl J Med 2003, 349:1157

Prediction of pediatric population based on fitted adult model and known differences in adult and pediatric physiology



400 mg tablet, 7 yo children

Lukacova – Workshop on Modeling in Pediatric Medicines, 2008

Glomerular Filtration – Neonates

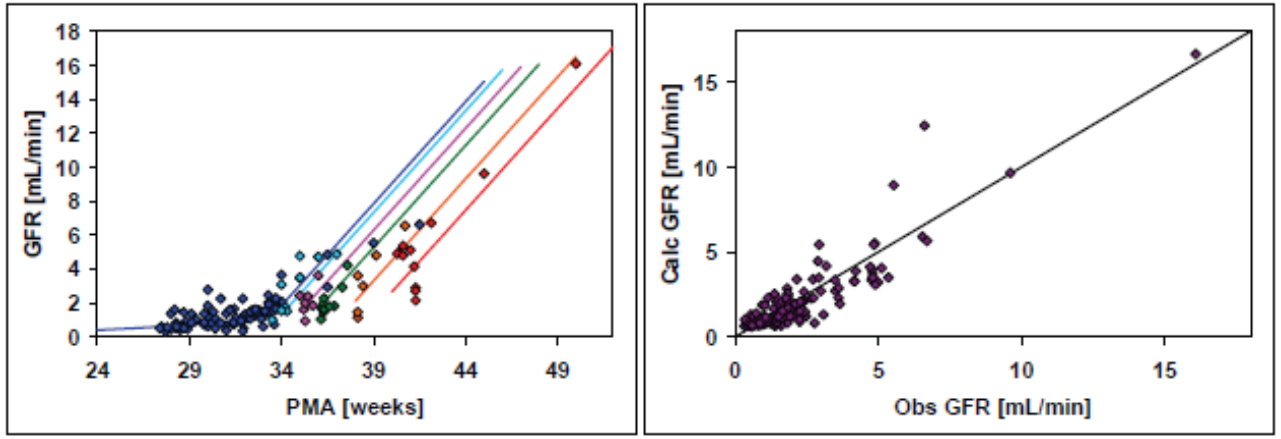
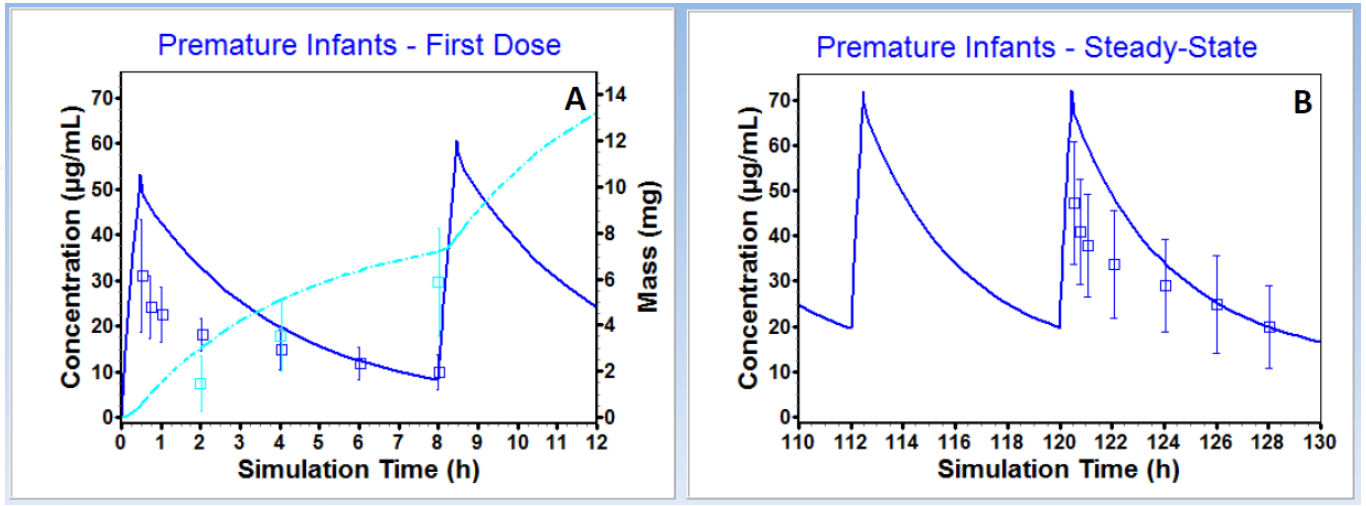


Figure 4-28: Plot of GFR vs post-menstrual age (PMA) for neonates up to 12 weeks old (left) and born after 27-33 (dark blue), 34 (light blue), 35(magenta), 36 (green), 38 (orange) and 40 (red) weeks of gestation (left) and plot of calculated vs observed GFR for the same data (right). Points represent experimental data (Arant 1978, Coulthard 1985, DeWoskin 2008, Fawer 1979) lines show GFR calculated in GastroPlus.



Predicted vancomycin PK in premature infants

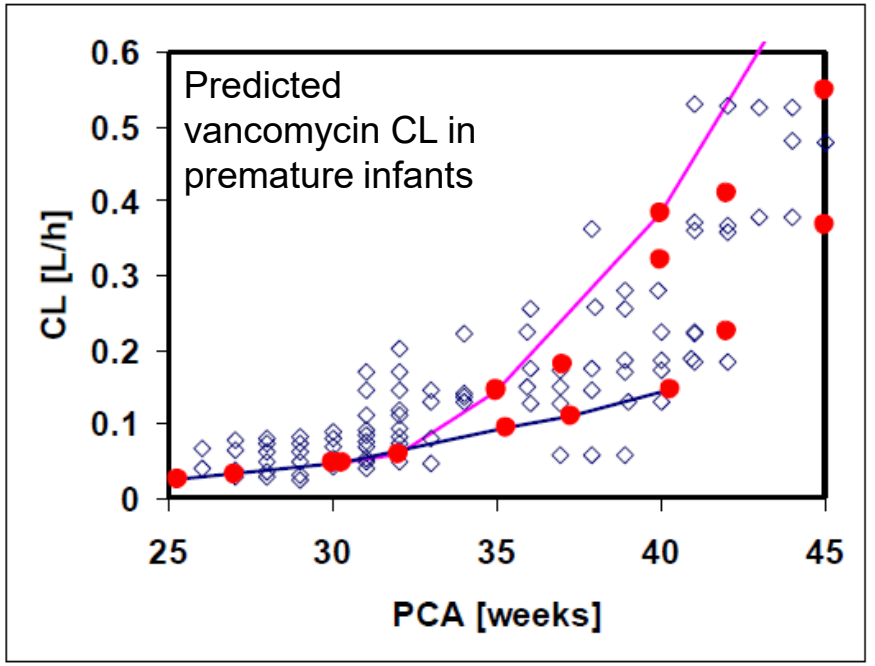
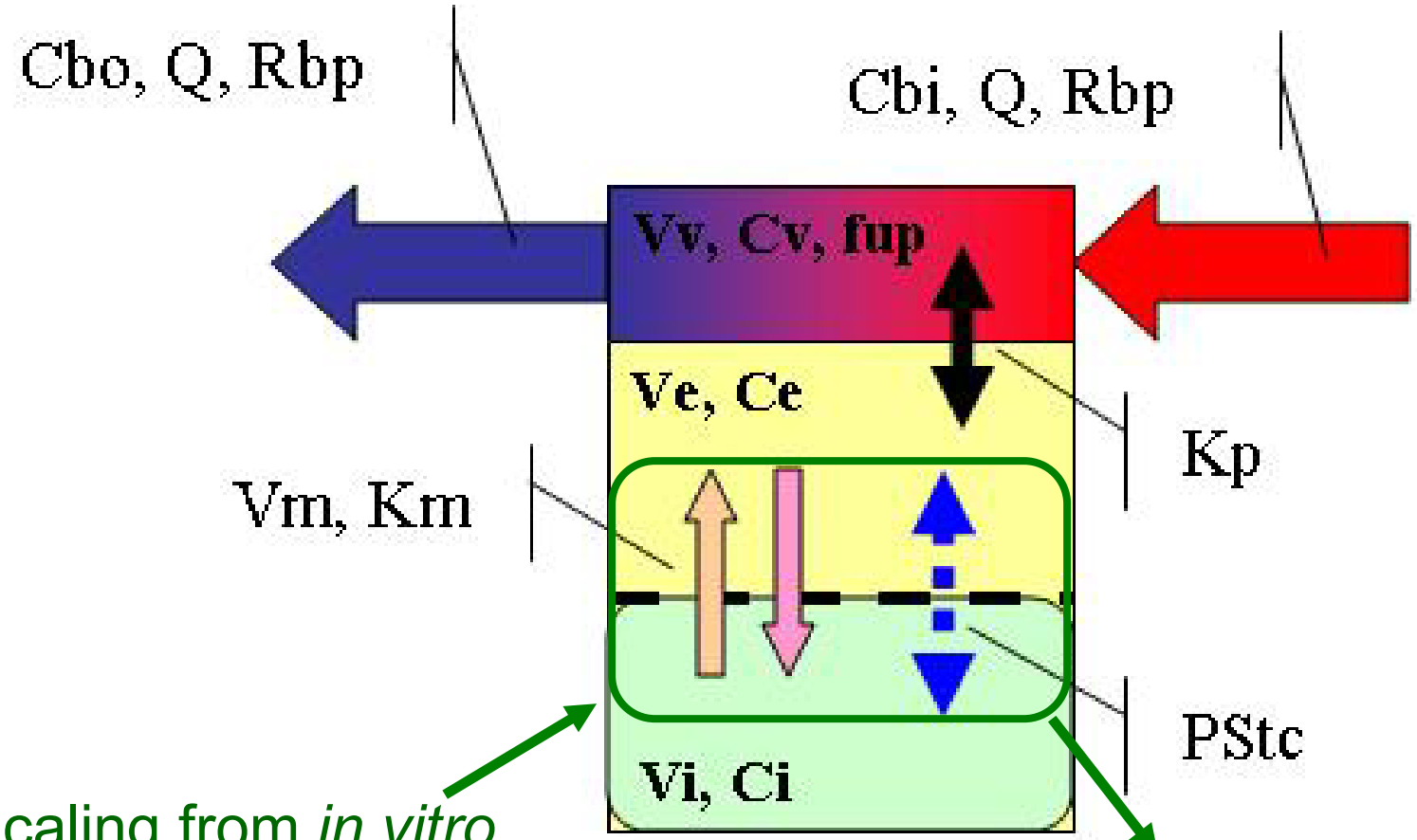


Figure 4: PBPK predicted (red dots) and PopPK fitted (blue dots) VCN renal clearance as a function of post-conceptional age (PCA = GA + PNA). Magenta line shows changes in VCN CL for GA = 30 weeks and varying PNA; blue line shows changes in VCN CL for PNA = 2 days and varying GA as predicted by PBPK model. Simulations were performed using default physiologies and GFR in GastroPlus for

Lukacova – AAPS 2015

Transporters

Tissue Disposition

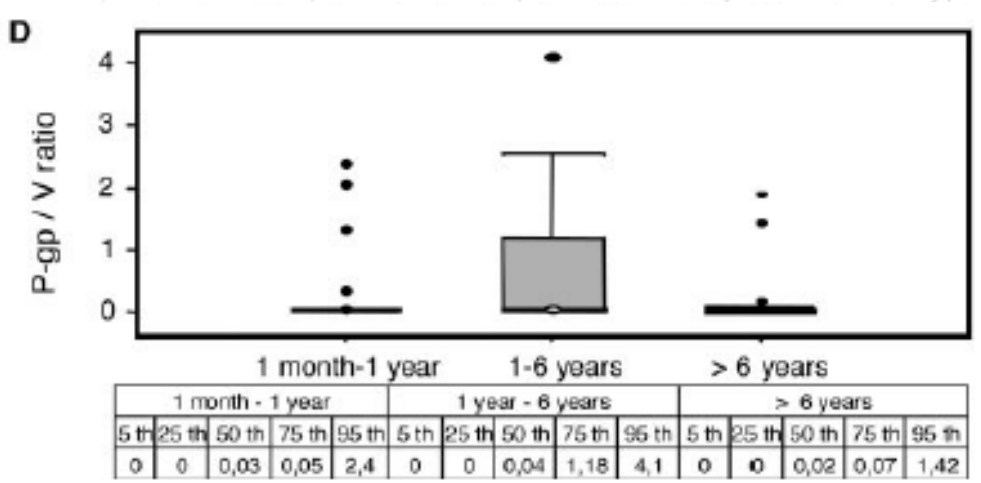


Scaling from *in vitro* and pre-clinical data?

Scaling to different populations?

Transporter Ontogeny

A few studies have evaluated the ontogenic expression of P-glycoprotein in the fetus. P-glycoprotein expression was detected in the 7-week embryo, and differences in tissue distribution between adult and fetus were observed.[40] P-glycoprotein mRNA and protein were detected in the hepatic biliary tract and kidney tubules by weeks 11 to 14 of fetal life, in the gastrointestinal tract at 28 weeks, in the adrenal by 13 weeks and in the brain at 28 weeks gestation.[40] Interestingly, Schumacher and Mollgard[41] demonstrated P-glycoprotein expression in the endothelium of brain microvessels at 8 weeks of development. Expression of this transporter during infant development



1 month - 1 year					1 year - 6 years					> 6 years				
5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th	5 th	25 th	50 th	75 th	95 th
0	0	0,03	0,05	2,4	0	0	0,04	1,18	4,1	0	0	0,02	0,07	1,42

FIG. 2. Ratio box-plots and percentile tables of mRNA copies/villin mRNA copies for A, CYP3A4; B, CYP3A5; C, CYP3A7; and D, P-gp.

[a] Maximum tubular secretion rates (T_m) in early life stages

T_m (mg/min/1.73 m^2) via PAH								
Neonate		Infant				Children	Adult	Reference
1–7 days	8–28 days	1–3 months	4–6 months	7–9 months	10–12 months	>1 year	>18 years	
16		49.6	61	61	61	73.7	79.8	Stewart and Hampton (1987)
13.2 (9.2) 8	14.9 (6.8) 10	16.9 (3.7) 13	41.7 (18.7) 8					Barnett et al. (1948b) Mean(SD) I
11.4	13.8	16.6	39.6					GM (geometric mean)
2.6–51.3	5.5–34.3	11.1–24.7	15.9–98.2					95% Confidence intervals
38.0 (na) 1	21.4 (18.6) 6	51.3 (28.9) 5	51.5 (14.2) 4	53.6 (30.5) 5	45.3 (11.9) 3	69.7 (19.8) 28		Rubin et al. (1949) Mean (SD) *n*
38.0	15.7	43.2	50.0	45.3	44.2	66.4		GM
	2.7	10.5	28.5–87.6	11.7–174.8	25.3–77.3	34.1–129.1		95% Confidence intervals
	91.3	178.2						
20.3	14.9	31.3	46.5	45.3	44.2	66.4		Weighted GM

Alcorn Clin Pharmacokinet 2002; Fakhoury et al. DMD 2005; De Woskin et al. Reg Toxicol Pharmacol 2008

Transporter Ontogeny

- Number of research groups is focused on measuring transporter expression levels
- These few publications show a journey of just one of those groups

1521-009X/42/8/1268–1274$25.00
Drug Metabolism and Disposition

2014 - mRNA

http://dx.doi.org/10.1124/dmd.114.056929
Drug Metab Dispos 42:1268–1274, August 2014

Ontogeny of Human Hepatic and Intestinal Transporter Gene Expression during Childhood: Age Matters[S]

Miriam G. Mooij, Ute I. Schwarz, Barbara A. E. de Koning, J. Steven Leeder, Roger Gaedigk, Janneke N. Samsom, Edwin Spaans, Johannes B. van Goudoever, Dick Tibboel, Richard B. Kim, and Saskia N. de Wildt

1521-009X/44/7/1014–1019$25.00
Drug Metabolism and Disposition

2016 - mRNA

http://dx.doi.org/10.1124/dmd.115.068809
Drug Metab Dispos 44:1014–1019, July 2016

Special Section on Pediatric Drug Disposition and Pharmacokinetics

Human Intestinal PEPT1 Transporter Expression and Localization in Preterm and Term Infants

Miriam G. Mooij, Barbara E. A. de Koning, Dicky J. Lindenbergh-Kortleve, Ytje Simons-Oosterhuis, Bianca D. van Groen, Dick Tibboel, Janneke N. Samsom, and Saskia N. de Wildt

European Journal of Pharmaceutical Sciences 124 (2018) 217–227

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

2018 - Protein

Proteomics of human liver membrane transporters: a focus on fetuses and newborn infants

Bianca D. van Groen[a,*], Evita van de Steeg[b], Miriam G. Mooij[c], Marola M.H. van Lipzig[b], Barbara A.E. de Koning[d], Robert M. Verdijk[e], Heleen M. Wortelboer[b], Roger Gaedigk[f], Chengpeng Bi[f], J. Steven Leeder[f], Ron H.N. van Schaik[g], Joost van Rosmalen[h], Dick Tibboel[a], Wouter H. Vaes[b], Saskia N. de Wildt[a,i]

1521-009X/44/7/1005–1013$25.00
Drug Metabolism and Disposition

2016 - Protein

http://dx.doi.org/10.1124/dmd.115.068577
Drug Metab Dispos 44:1005–1013, July 2016

Special Section on Pediatric Drug Disposition and Pharmacokinetics

Proteomic Analysis of the Developmental Trajectory of Human Hepatic Membrane Transporter Proteins in the First Three Months of Life

Miriam G. Mooij, Evita van de Steeg, Joost van Rosmalen, Jonathan D. Windster, Barbara A.E. de Koning, Wouter H. J. Vaes, Bianca D. van Groen, Dick Tibboel, Heleen M. Wortelboer, and Saskia N. de Wildt

1521-009X/49/12/1038–1046$35.00
Drug Metabolism and Disposition

2021 - Protein

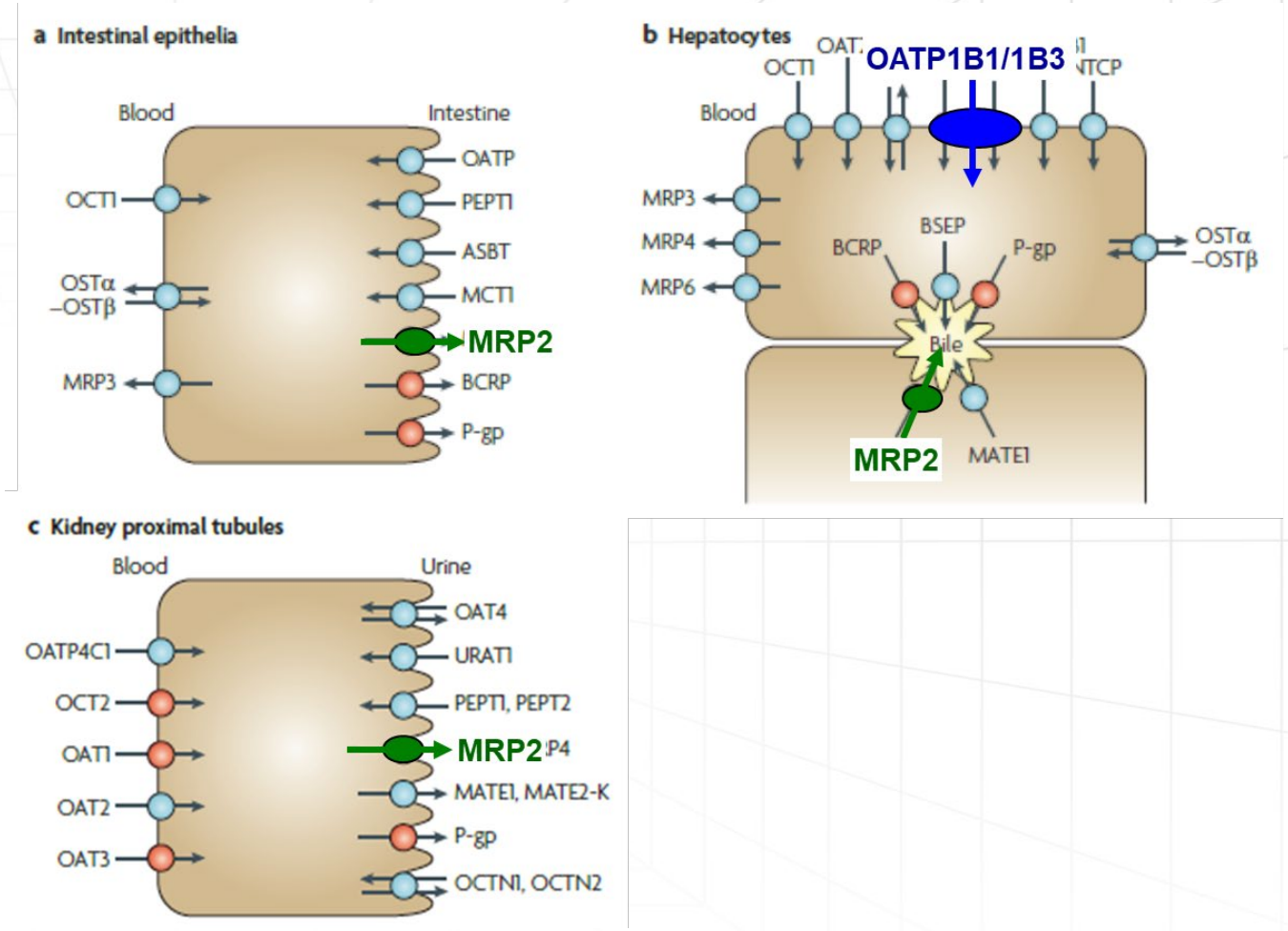
https://doi.org/10.1124/dmd.121.000559
Drug Metab Dispos 49:1038–1046, December 2021

Ontogeny of Small Intestinal Drug Transporters and Metabolizing Enzymes Based on Targeted Quantitative Proteomics[S]

Márton Kiss,[1] Richard Mbasu,[1] Johan Nicolaï, Karin Barnouin, Apoorva Kotian, Miriam G. Mooij, Nico Kist, Rene M. H. Wijnen, Anna-Lena Ungell, Paul Cutler, Frans G. M. Russel, and Saskia N. de Wildt

Example: Valsartan

- Eliminated by biliary secretion
- Substrate for:
  - OATP1B1 and OATP1B3
  - MRP2
- *in vitro* data available from rat and human suspended hepatocytes and human sandwich-cultured hepatocytes
- *in vivo* data available in rat and human (adult and pediatric for 1- to 16-year-old)

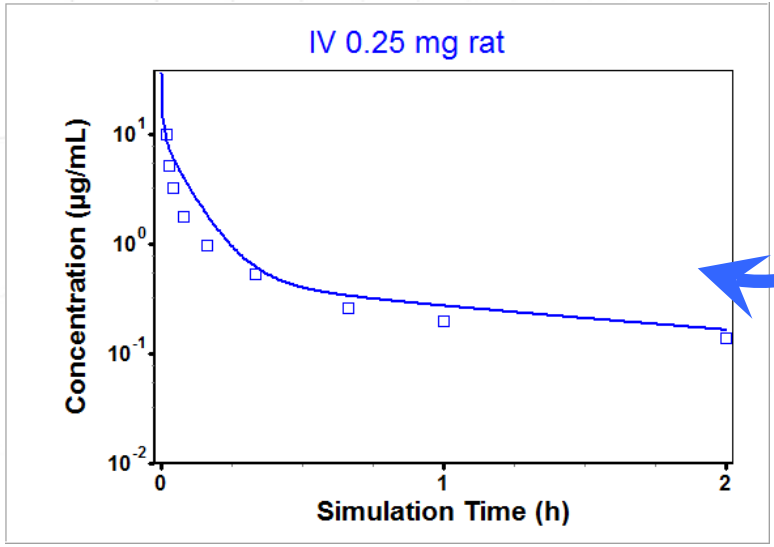


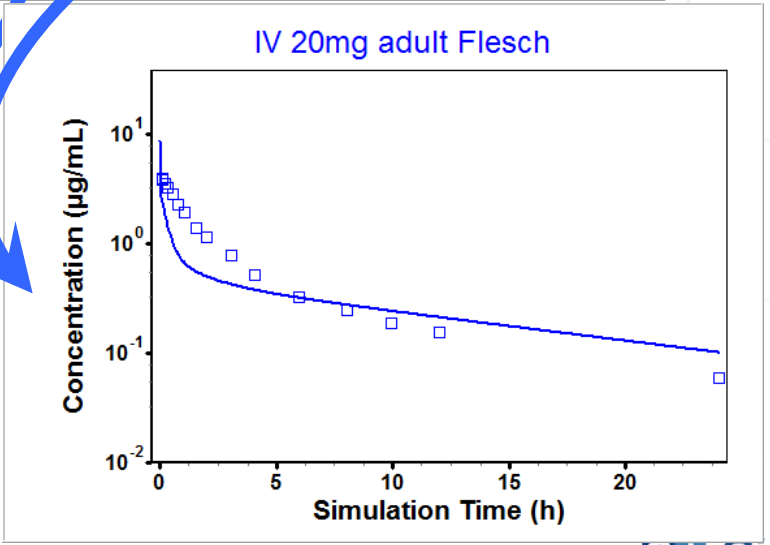
IVIVE with PStc Scaling for ALL Tissues

1. Predicted rat IV using *in vitro* data measured in rat hepatocytes
2. Predicted human IV using *in vitro* data measured in human hepatocytes

Hepatocytes transport data[a]	Wistar rats ($n = 3$) Mean ± SD	Cryopreserved human hepatocytes lot 77 Mean ± SD
Uptake from plasma (in vitro data)		
$K_{mI,u}$		
(μM)	28.4 ± 3.7	44.4 ± 14.6
(mg/l eq. μg/ml)	12.4 ± 1.6	19.3 ± 6.4
V_{maxI} (pmol/mg/min)	1318 ± 176	304 ± 85
J_{maxI} (mg/s)	0.0126 ± 0.0017	0.241 ± 0.067
P_{dif} (μl/mg/min)	1.21 ± 0.42	0.724 ± 0.271
PS_{TC} (ml/s)	0.0266 ± 0.0092	1.32 ± 0.49
f_b (%)	0.394 ± 0.171	0.417 ± 0.226
Excretion from liver to bile		
$K_{mE,u}$ (μg/g eq. mg/l)	12.4	19.3
J_{maxE} (mg/s)	0.01[illegible]6	0.241
PS_{TCAp} (ml/s)	[illegible]	0

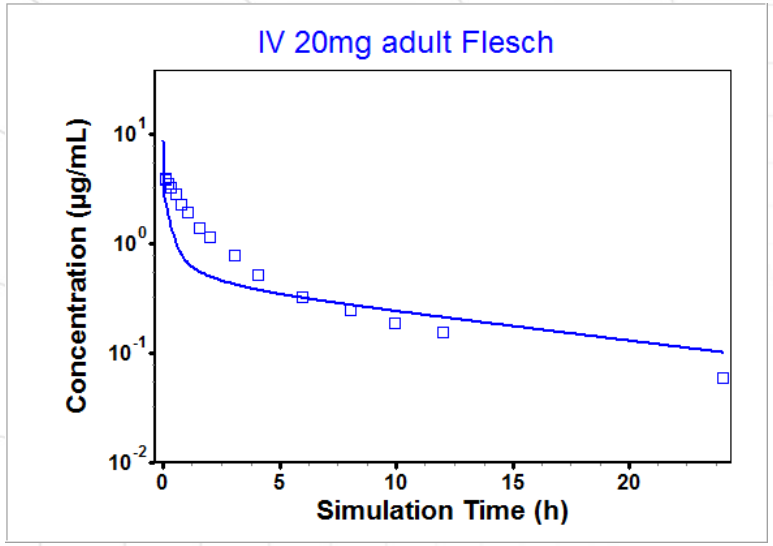
(Poirier – J Pharmacokinet Pharmacodyn 2009, 36:585)

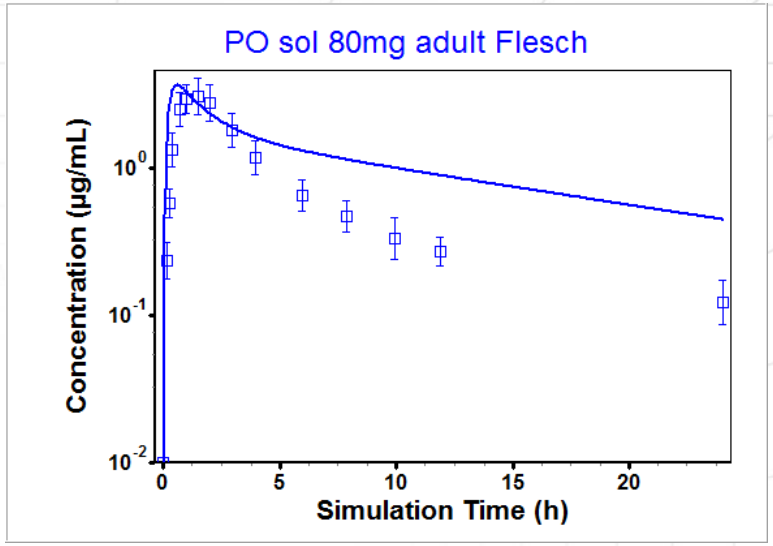




Lukacova – 17th North American ISSX meeting 2011, Atlanta, GA

Refine Adult Model





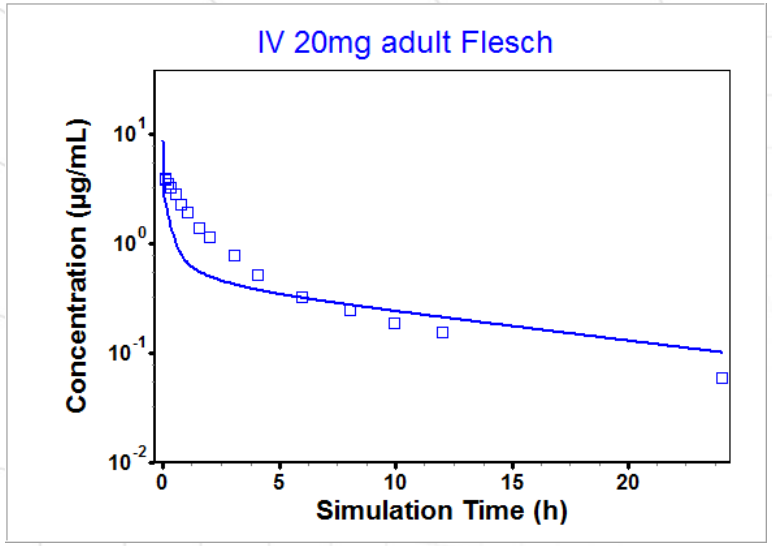
Passive diffusion through tissue membranes in all tissues scaled from liver PStc predicted from *in vitro*

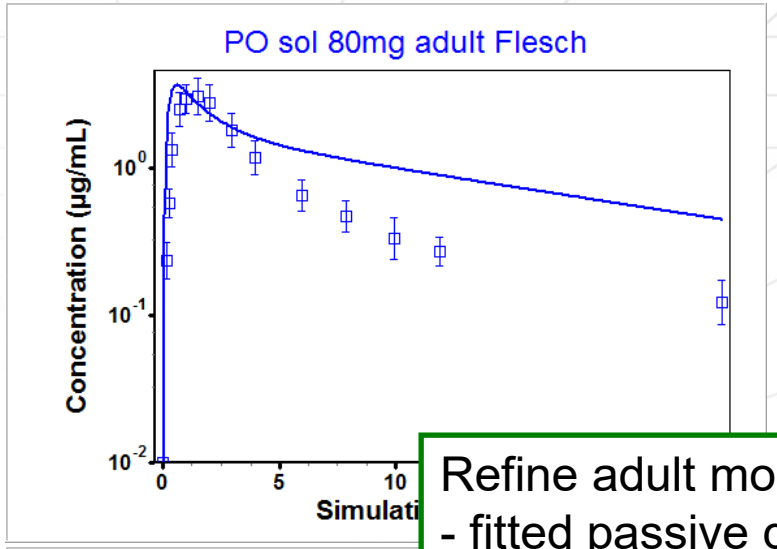
Liver uptake predicted from *in vitro*

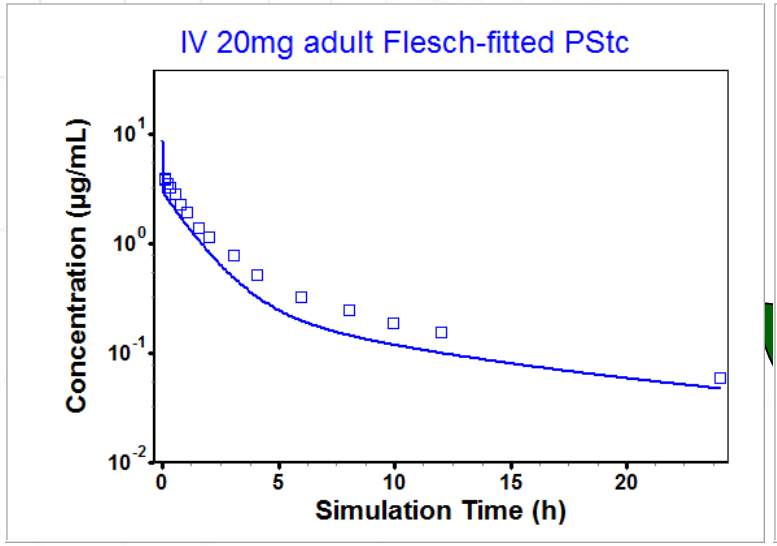
Secretion into bile, urine, and gut lumen via MRP2

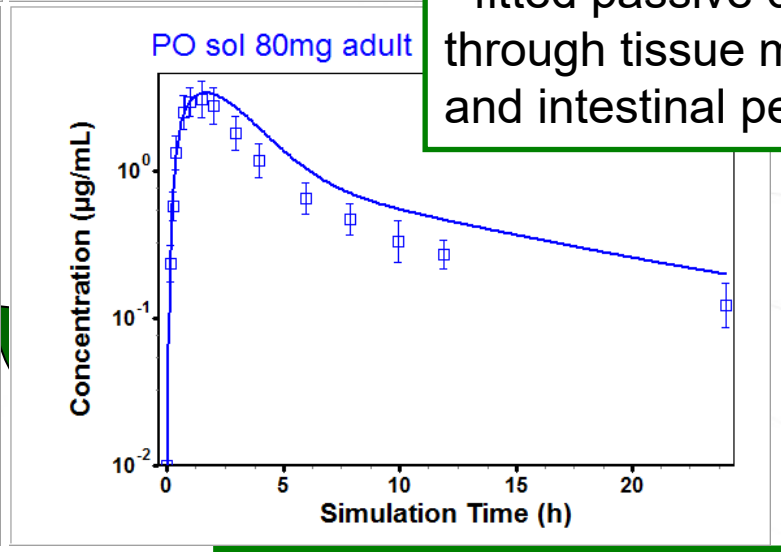
- MRP2 expression in different tissues estimated from reported relative mRNA levels in liver, kidney, small intestine, and colon

Refine Adult Model







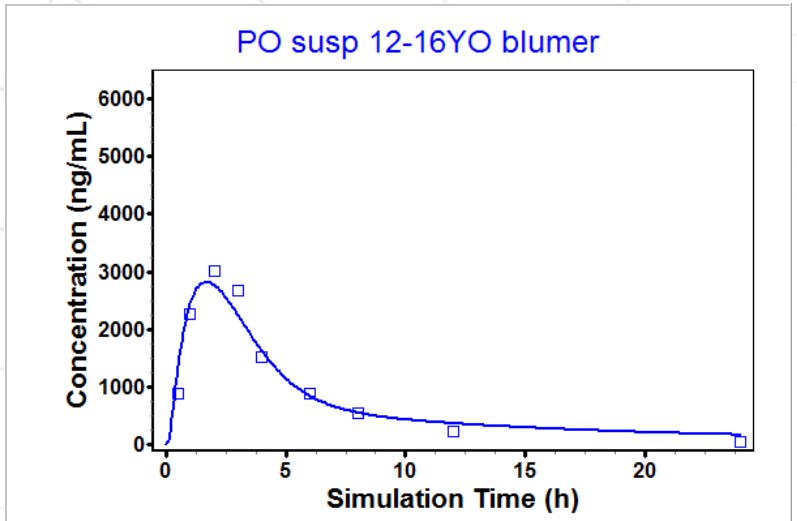


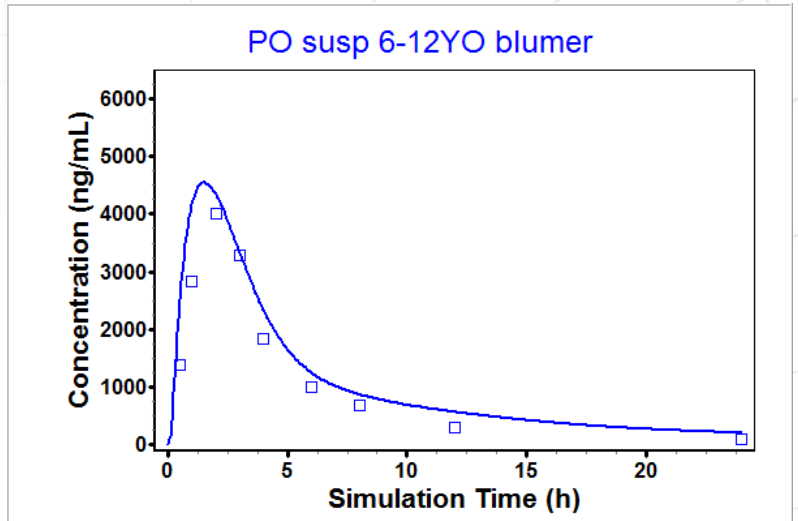
Refine adult model:
- fitted passive diffusion through tissue membranes and intestinal permeability

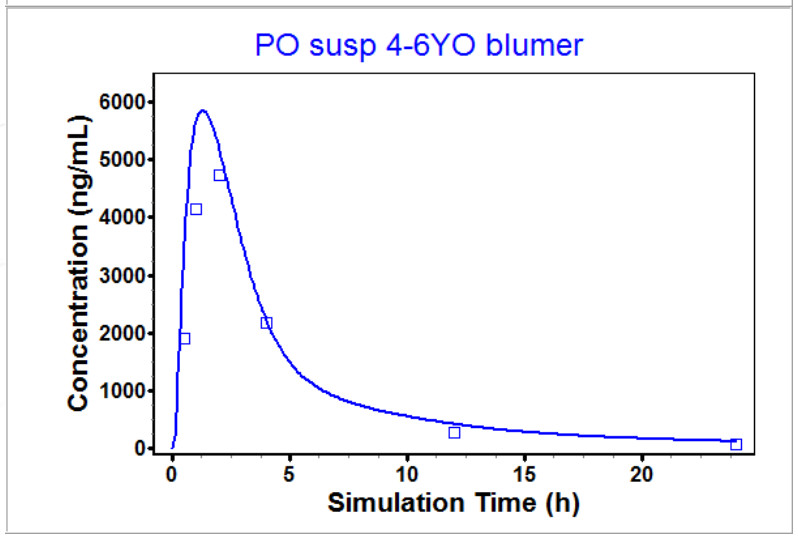
Predict pediatric populations

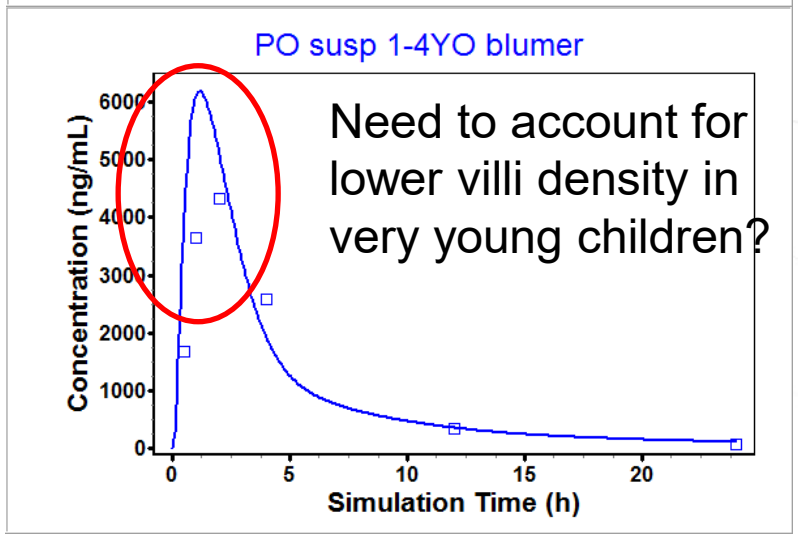
Predict Pediatric Disposition

Dosing 2 mg/kg, experimental profiles are averages of 6-7 individuals
(initial assumption – the same transporter density as in adults)



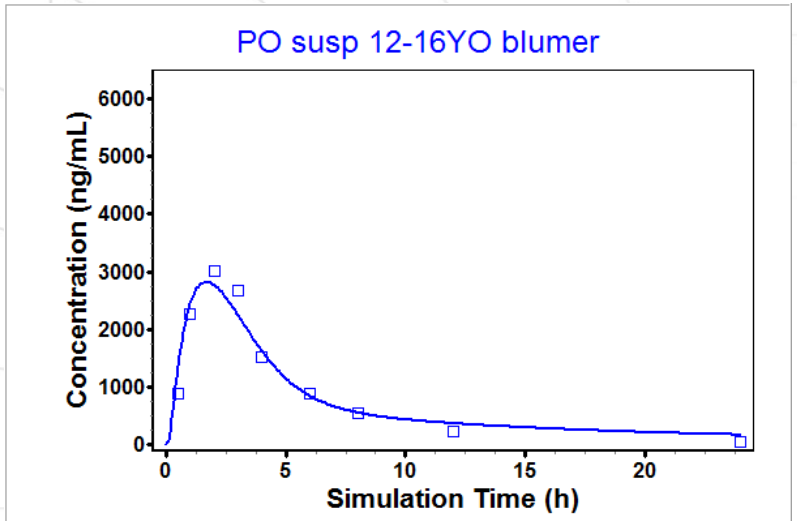


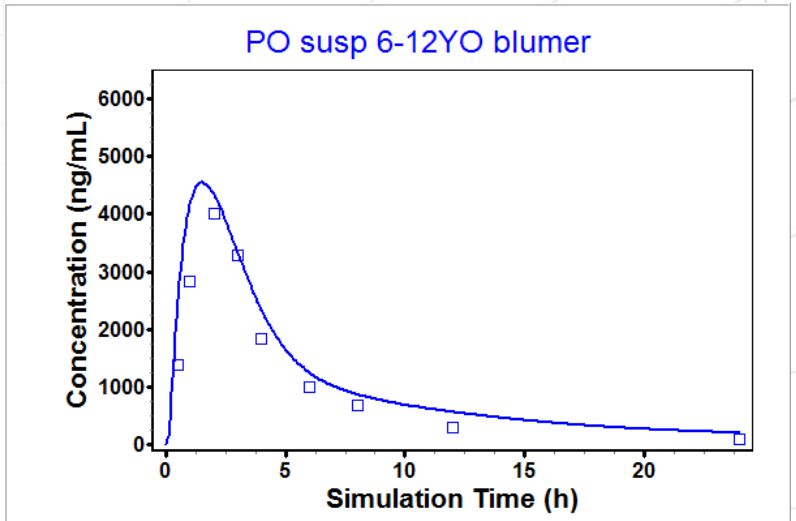


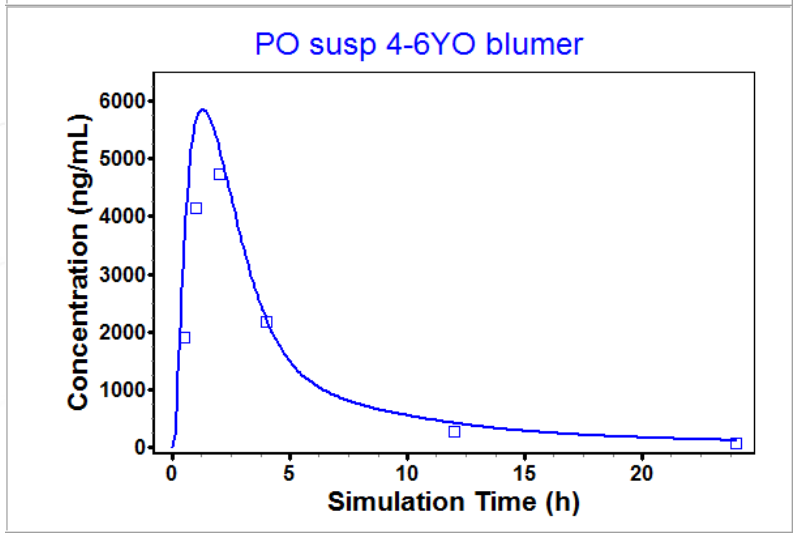


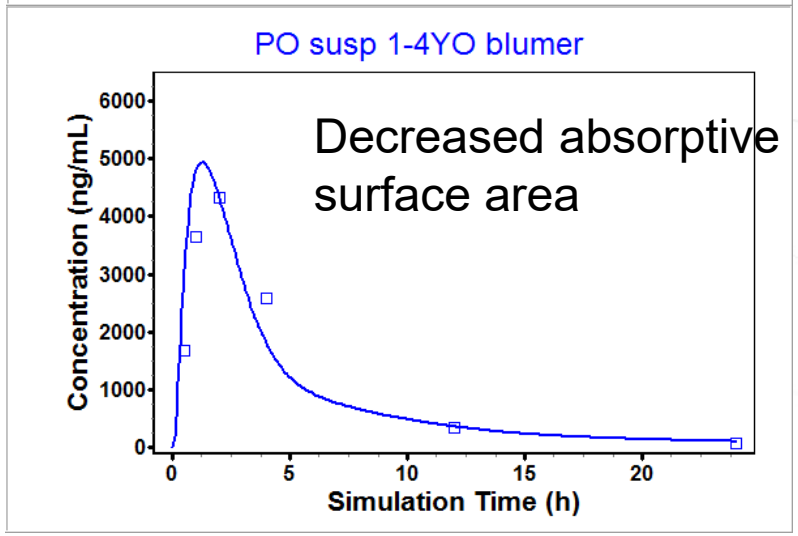
Predict Pediatric Disposition

Dosing 2 mg/kg, experimental profiles are averages of 6-7 individuals
(initial assumption – the same transporter density as in adults)





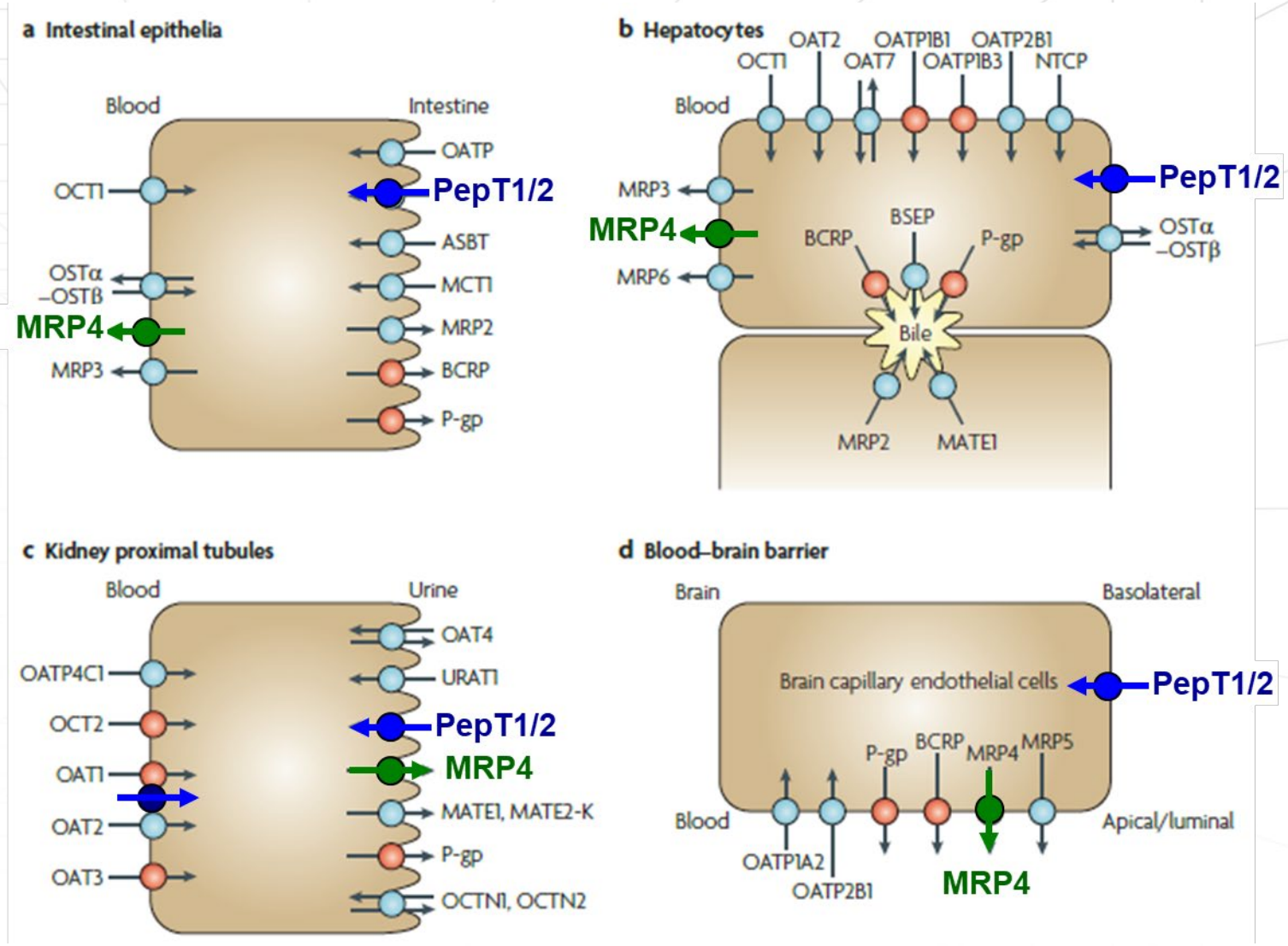




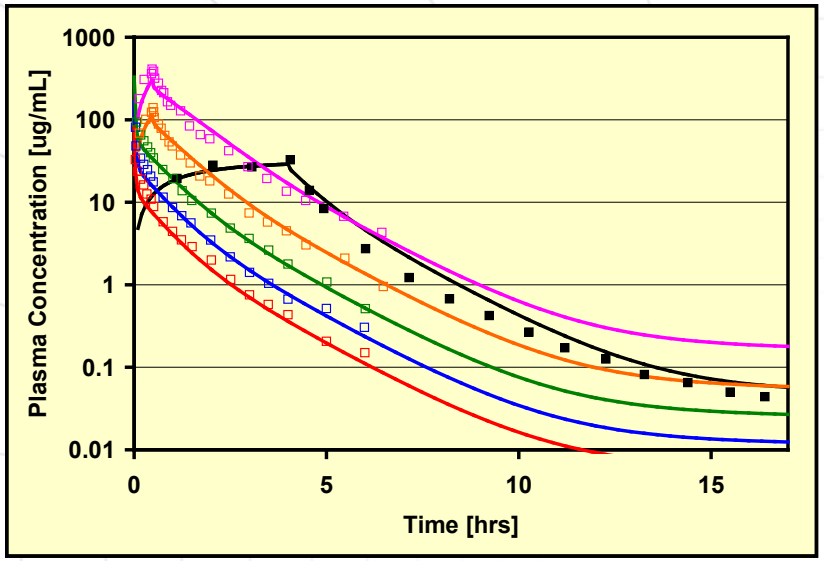
Example: Amoxicillin

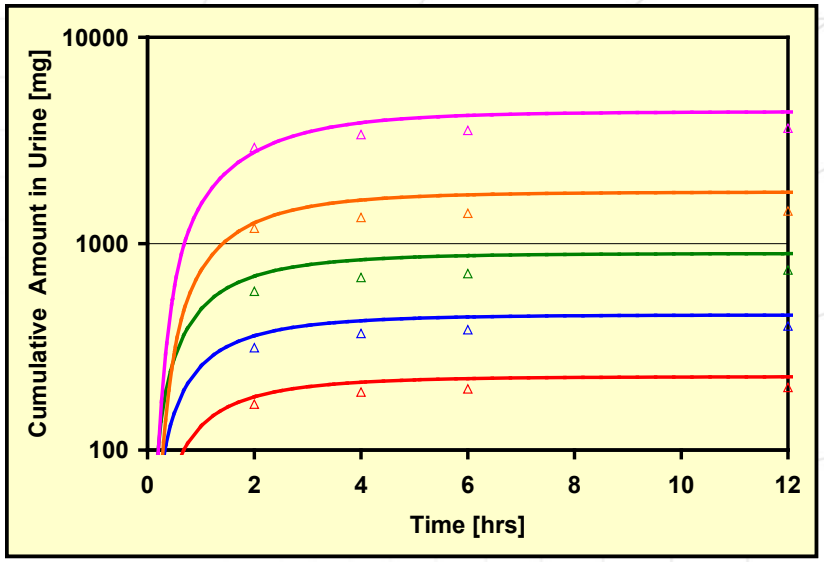
- Eliminated by renal secretion (glomerular filtration and active secretion)
- Substrate for:
  - PepT1/PepT2
  - MRP4
- *in vivo* data available in human (adult and pediatric for infants up to 3 years)

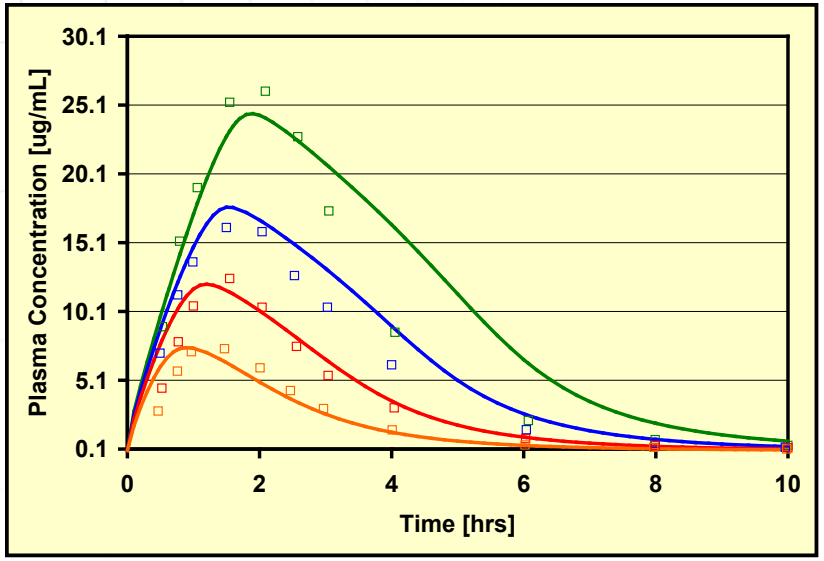
Akanuma et al. DMD 2011

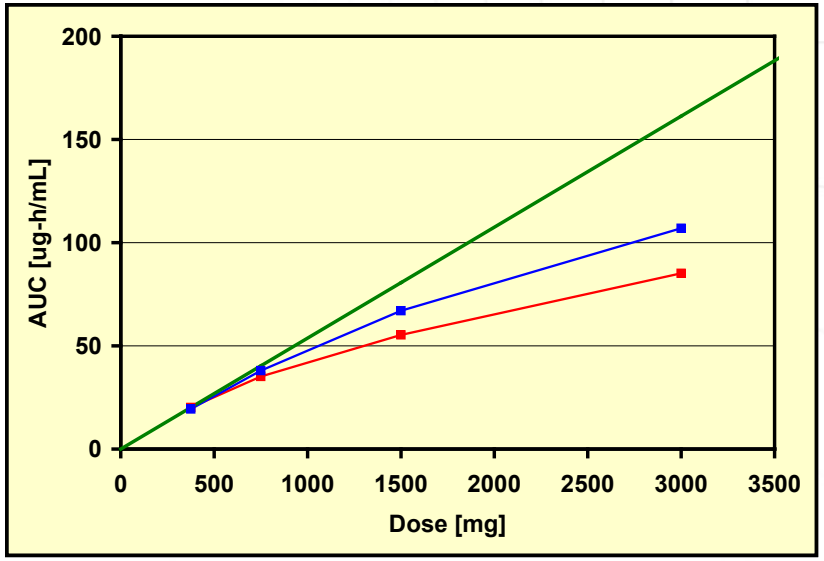


Fit Adult Model



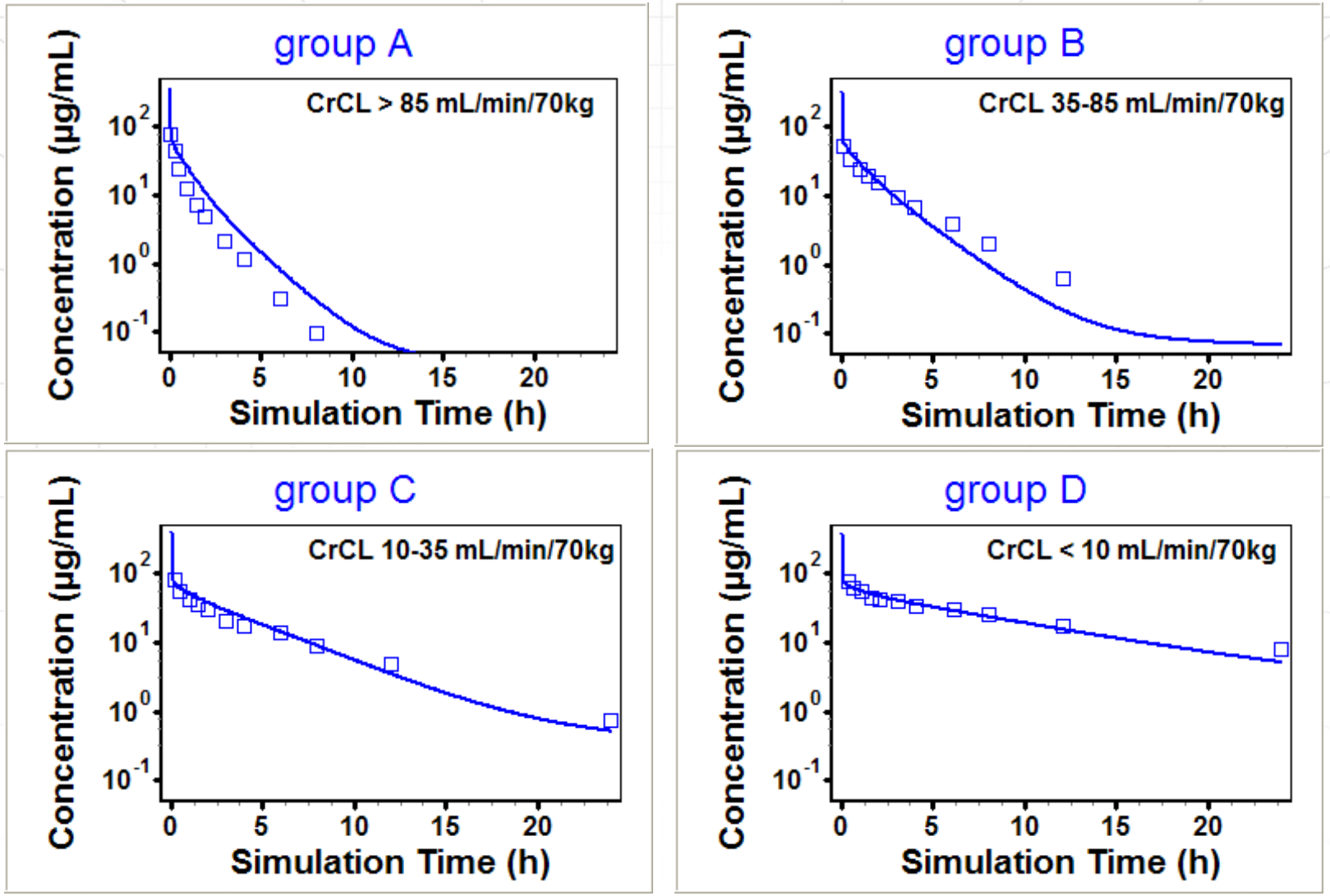






Lukacova – AAPS Annual Meeting 2012, Chicago, IL

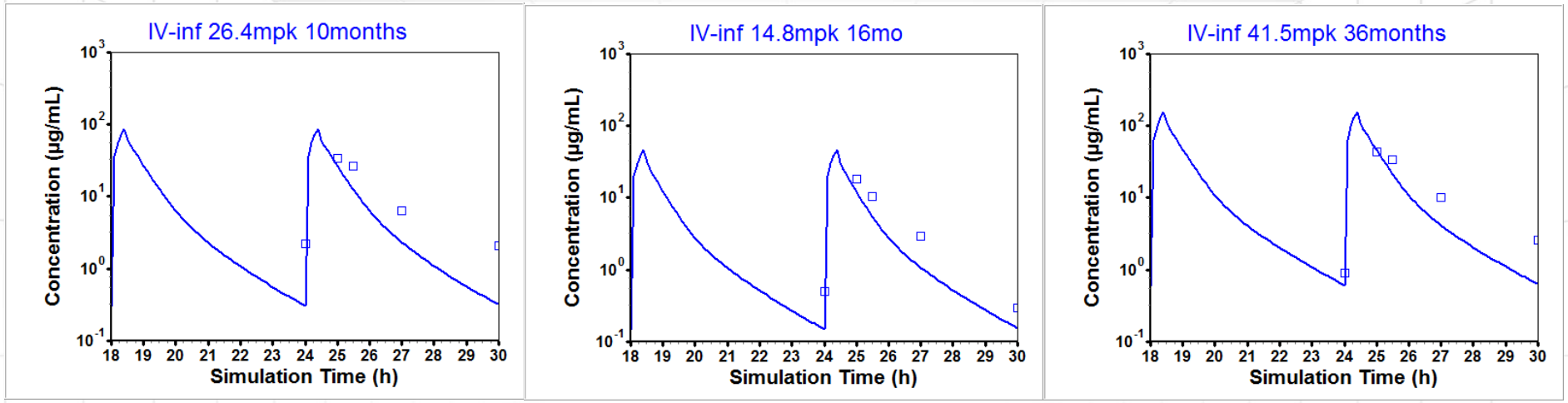
Validate Adult Model



Lukacova – AAPS Annual Meeting 2012, Chicago, IL

Predict Pediatric Disposition

Assumed similar transporter density as in adults



Scaling Renal Transporters from Maximal Tubular Excretory Capacity

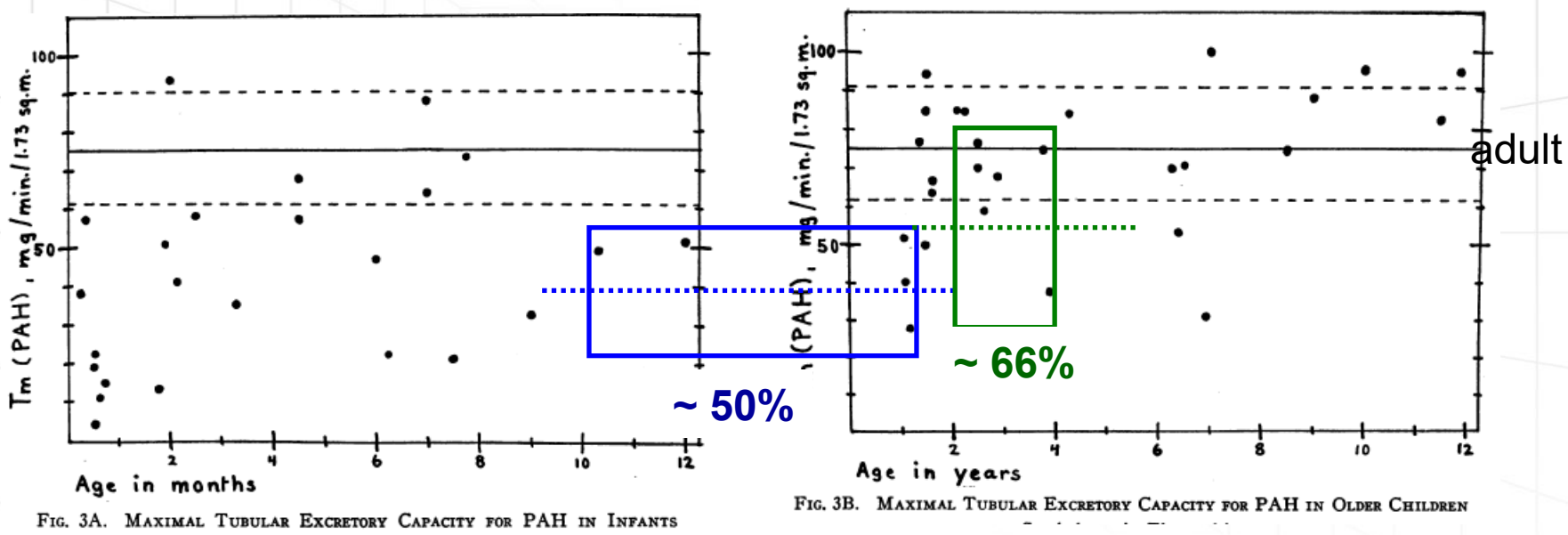


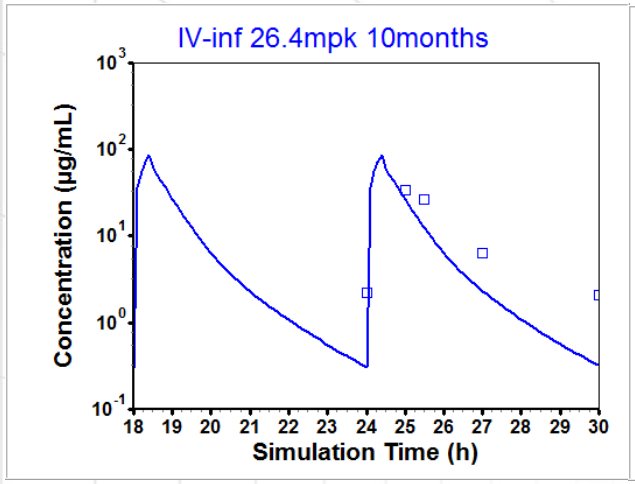
FIG. 3A. MAXIMAL TUBULAR EXCRETORY CAPACITY FOR PAH IN INFANTS

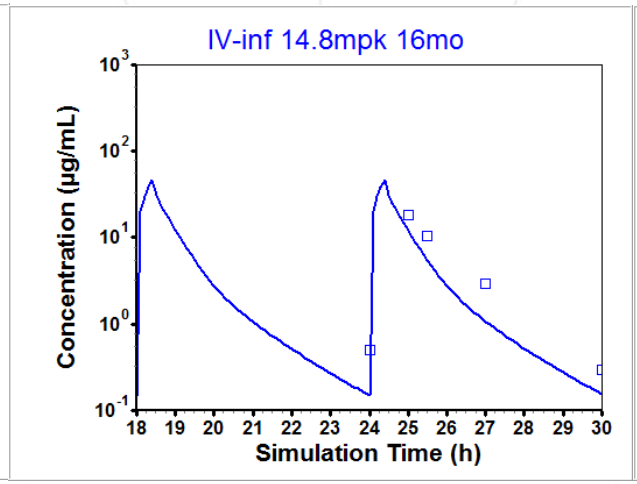
FIG. 3B. MAXIMAL TUBULAR EXCRETORY CAPACITY FOR PAH IN OLDER CHILDREN

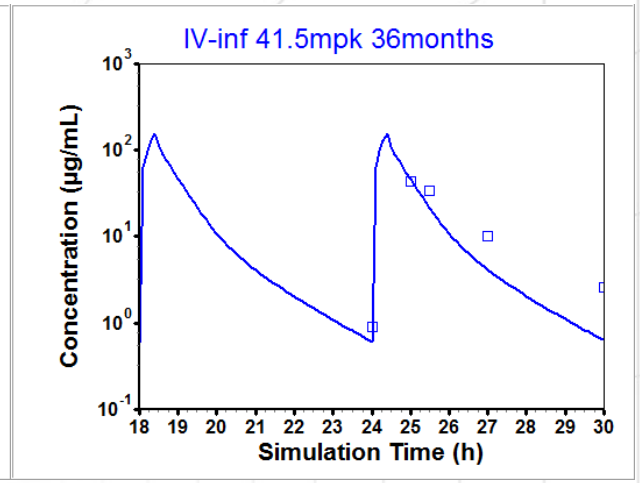
Rubin et al. J Clin Invest 1949

Predict Pediatric Disposition

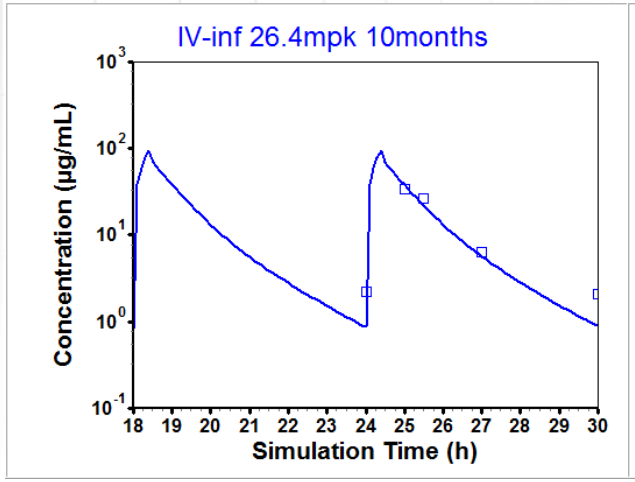
Assuming similar transporter density as in adults

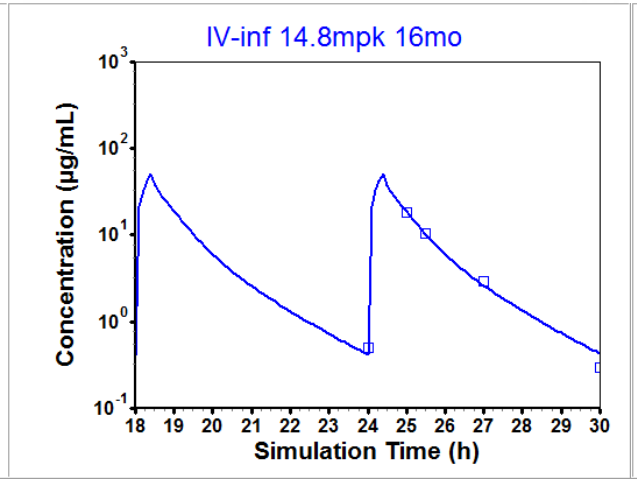


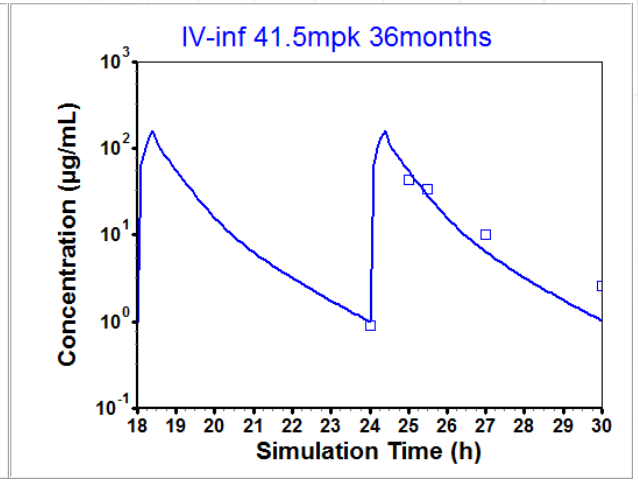




Estimating kidney transporter expression from PAH data

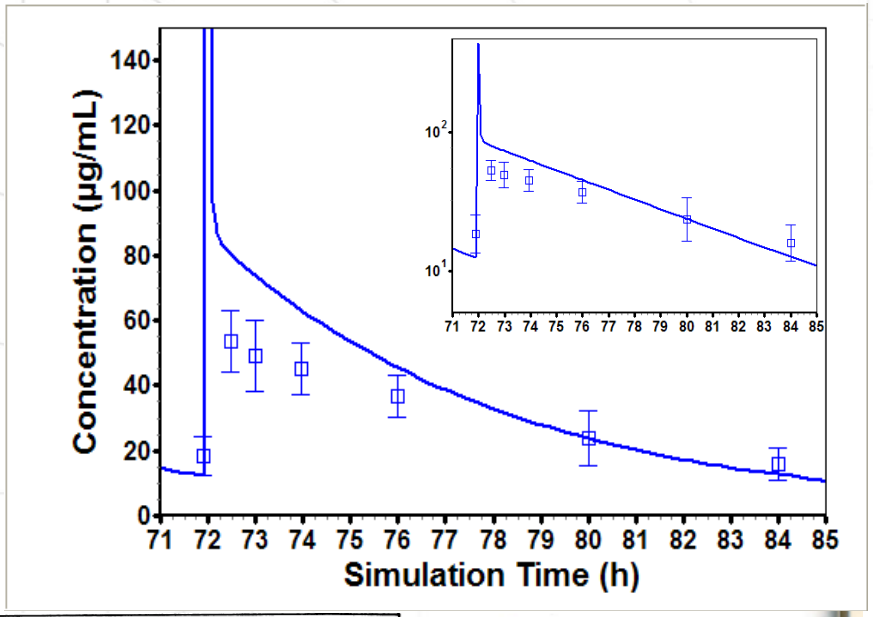




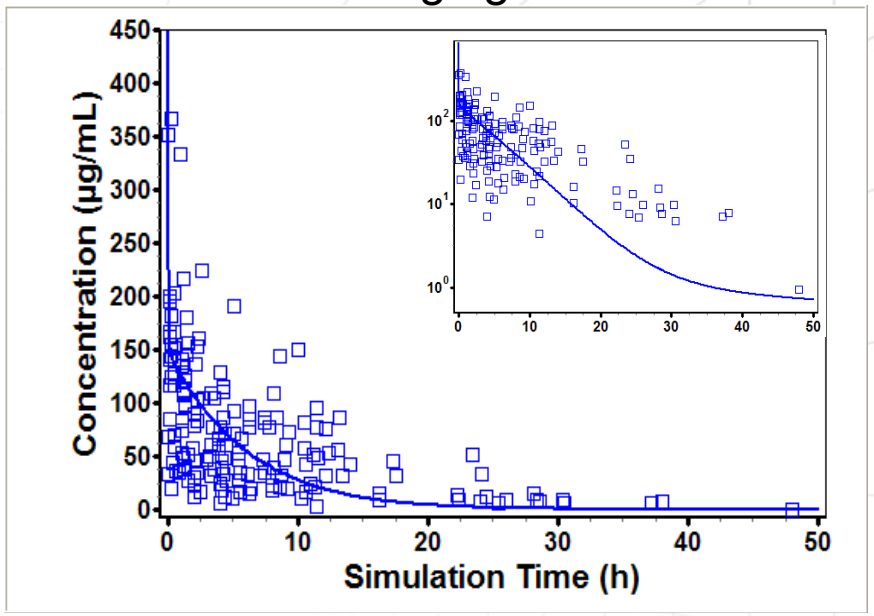


Predict Pediatric Disposition

3 days old, 29 weeks gestation, 25 mg/kg



1-3 days old, 29 weeks gestation, 50 mg/kg



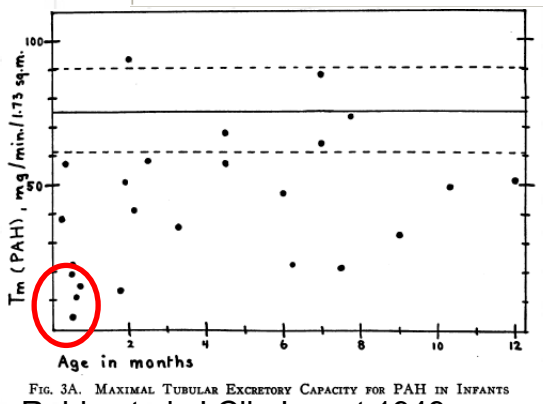
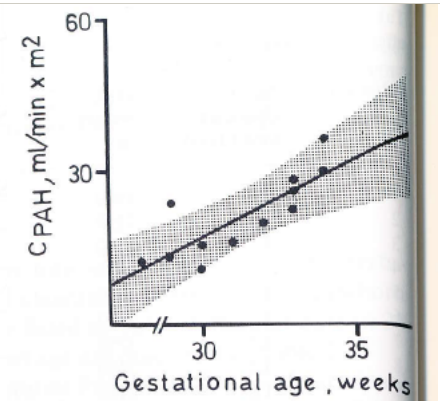


FIG. 3A. MAXIMAL TUBULAR EXCRETORY CAPACITY FOR PAH IN INFANTS

Rubin et al. J Clin Invest 1949



Fawer et al. Helv Paed Acta 1979

Transporter density set to 2% of adult values

Applications

Dosing Recommendations

The AAPS Journal, Vol. 18, No. 6, November 2016 (© 2016)
DOI: 10.1208/s12248-016-9956-4

Research Article

A Physiologically Based Pharmacokinetic Model for Ganciclovir and Its Prodrug Valganciclovir in Adults and Children

V. Lukacova,[1] P. Goelzer,[2] M. Reddy,[3] G. Greig,[4] B. Reigner,[4] and N. Parrott[5,6]

ARTICLES

Bottom-up Meets Top-down: Complementary Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling for Regulatory Approval of a Dosing Algorithm of Valganciclovir in Very Young Children

K Jorga[1], C Chavanne[2], N Frey[2], T Lave[3], V Lukacova[4], N Parrott[3], R Peck[2] and B Reigner[2]

Discussing the strengths and weaknesses of the different approaches with the health authorities and using the existing models for simulations was very useful during the approval process of the VGCV dosing algorithm for children <4 months old. We noticed a slight preference for PopPK simulations with the US Food and Drug Administration and a strong interest by the Australian regulatory authority for PBPK. After consideration of the clinical data as well as the modeling and simulation results, the confidence in the dosing algorithm for VGCV was sufficiently strong and it is now included the drug's prescribing information in several countries, including Europe, Australia, and the United States.

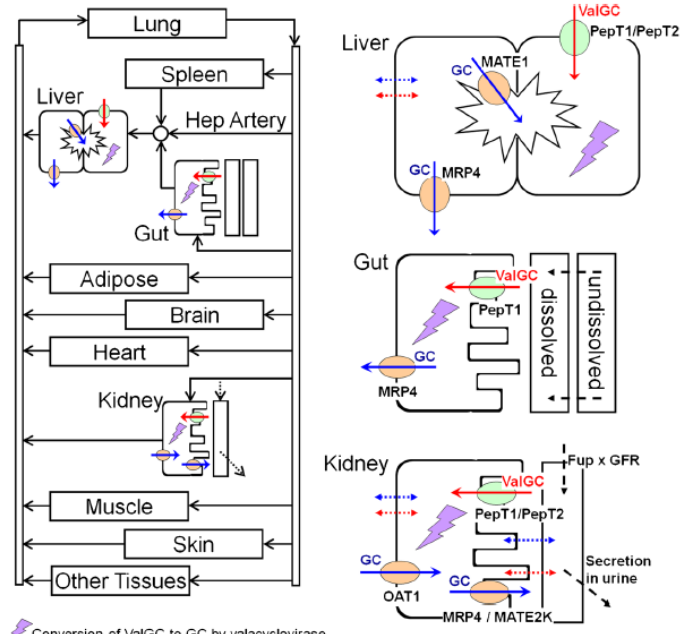
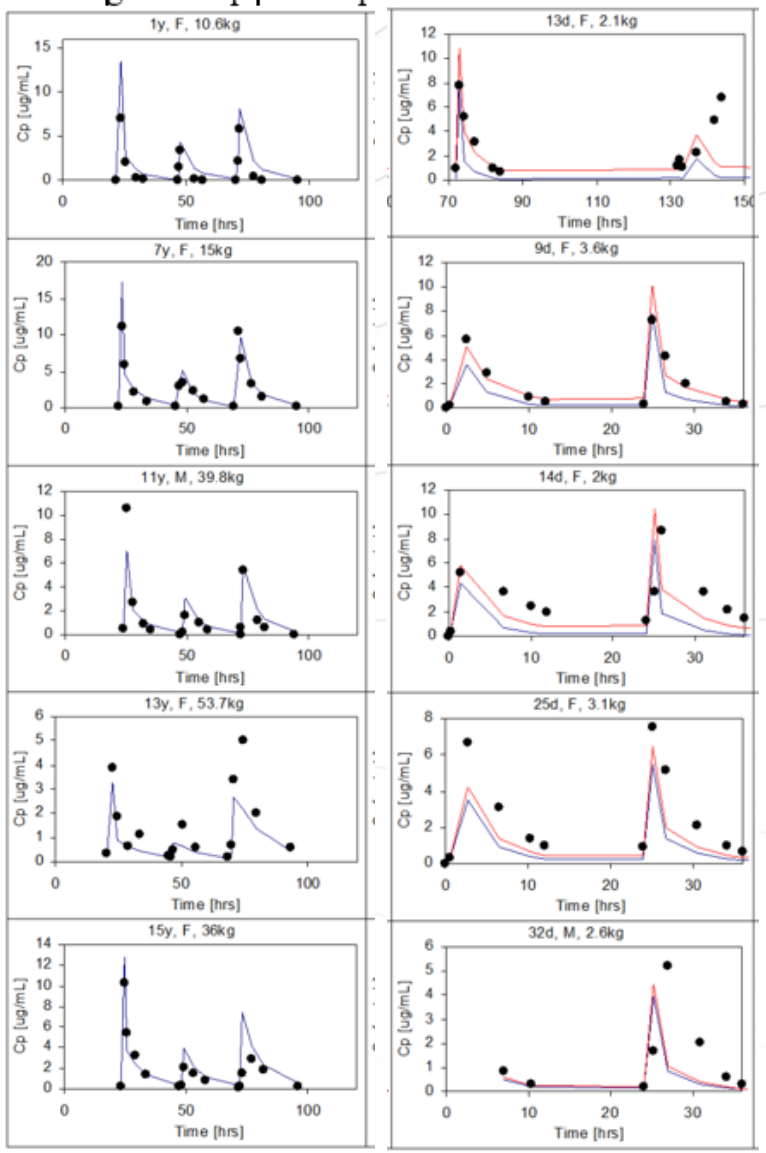


Fig. 1. Schematic diagram of the valganciclovir and ganciclovir PBPK model including more detailed views of three organs with summary of transporters pertinent to the liver, gut, and kidney

- Animal data was used to determine model structure
- Human adult PK data was used to refine parameters
- Model included prodrug and parent drug
- Permeability-limited tissues
- Transporters involved in disposition of both compounds

1-16 yo kidney transplant recipients

Neonates with congenital CMV



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Development of Pediatric Formulation I

The AAPS Journal (2020) 22:126
DOI: 10.1208/s12248-020-00504-6

Research Article

Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

Successful Extrapolation of Paracetamol Exposure from Adults to Infants After Oral Administration of a Pediatric Aqueous Suspension Is Highly Dependent on the Study Dosing Conditions

Marina Statelova,[1] René Holm,[2,3] Nikoletta Fotaki,[4] Christos Reppas,[1] and Maria Vertzoni[1,5]

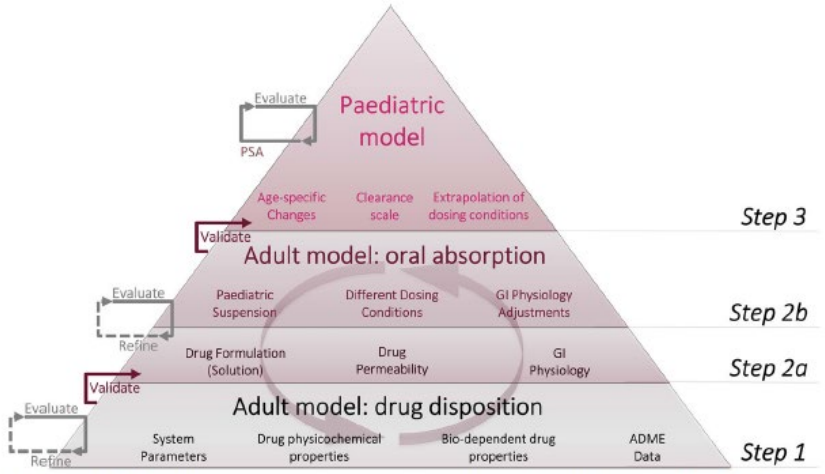

Fig. 1. Model development strategy for the evaluation of food effects in infants based on *in vivo* data in adults. Adapted from (3)

- Model refinement for relevant conditions (pediatric formulation, infant formula) in adults was important for accurate pediatric predictions.
- Formulation itself (excipients) might be the reason for longer gastric emptying in fasted state in both adults and children.
- Mixing of the formulation with the meal (i.e. reference meal vs. infant formula) may also impact gastric emptying.

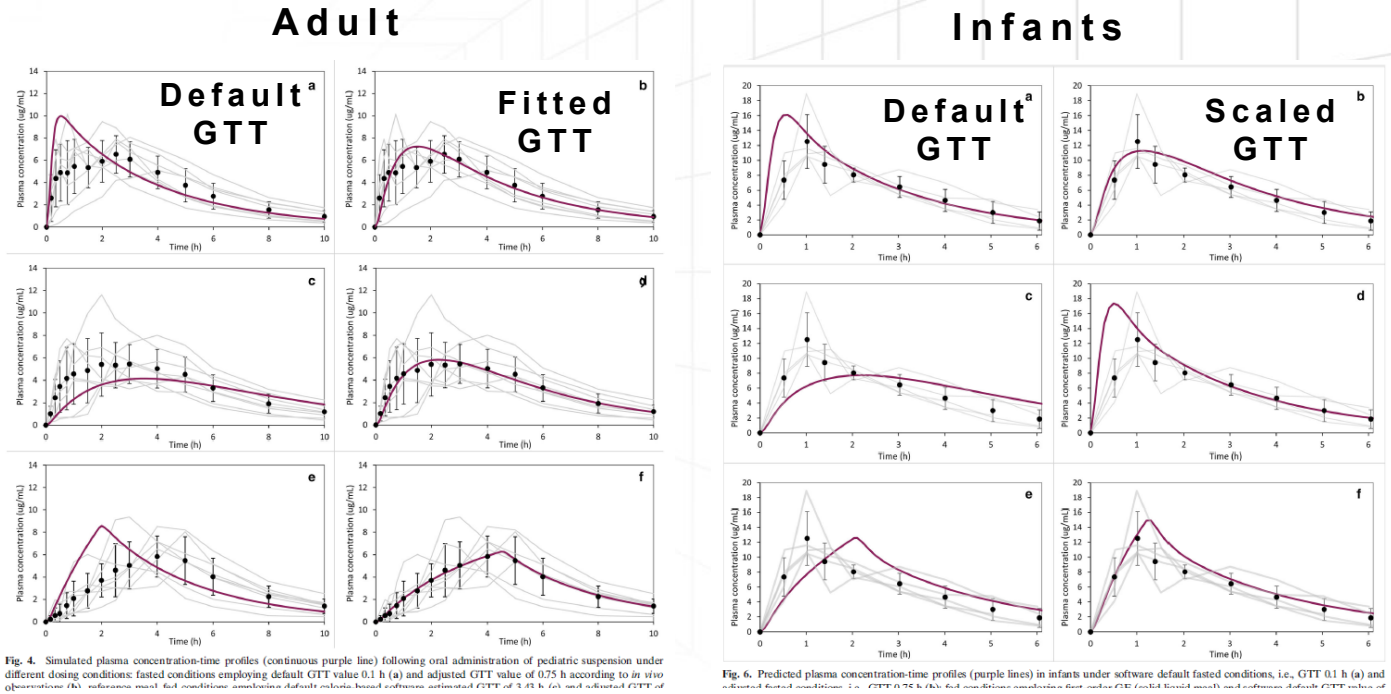

Fig. 4. Simulated plasma concentration-time profiles (continuous purple line) following oral administration of pediatric suspension under different dosing conditions: fasted conditions employing default GTT value 0.1 h (a) and adjusted GTT value of 0.75 h according to *in vivo*

Fig. 6. Predicted plasma concentration-time profiles (purple lines) in infants under software default fasted conditions, i.e., GTT 0.1 h (a) and

GTT - gastric transit time
Scaled GTT – calculated from fitted GTT in adults and caloric needs of each population

Development of Pediatric Formulation I

Journal of Pharmaceutical Sciences 108 (2019) 741-749

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Bioequivalence Comparison of Pediatric Dasatinib Formulations and Elucidation of Absorption Mechanisms Through Integrated PBPK Modeling

Shruthi Vaidhyanathan [1], Xiaoning Wang [2], John Crison [1], Sailesh Varia [3], Julia Z.H. Gao [3], Ajay Saxena [4], David Good [1,*]

Check for updates

These findings and mechanistic understanding have informed regulatory applications in regard to the approval of the pediatric suspension formulation and comparisons made to the adult tablet behavior. The impact of gastric residence time, food intake, and formulation attributes have also been extended to pediatric PBPK modeling to predict pharmacokinetics in different pediatric subjects (age range of 1-21 years), which are the subject of future articles.

Taken together, the observations from *in vitro* assessment of solubility, dissolution behavior, and PBPK modeling lead to the conclusion that that the mechanism that drives the reduced bioavailability is inherent to the *in vivo* gastric behavior of the 2 different dosage forms, that is, shorter gastric transit for suspensions relative to tablet and not related to the formulation composition or other drug product attributes.

- Adult dasatinib (SPRYCEL®) formulation is an immediate release tablet
- Powder for oral suspension formulation was developed for use in pediatric patients
- BE study showed differences in PK between these two formulations in adults
- GastroPlus® modeling was performed to determine the reasons for differences between the formulations:
  - Difference in gastric emptying was determined to be the main cause of the differences in PK
    (Dasatinib is BCS Class II compound, weak base which exhibits strong pH-dependent solubility)

Dissolution Safe Space in Pediatric Population

The AAPS Journal (2020) 22:107
DOI: 10.1208/s12248-020-00493-6

Check for updates

Research Article

Using a Physiologically Based Pharmacokinetic Absorption Model to Establish Dissolution Bioequivalence Safe Space for Oseltamivir in Adult and Pediatric Populations

Lei Miao,[1] Youssef M. Mousa,[1] Liang Zhao,[1] Kimberly Raines,[2] Paul Seo,[2] and Fang Wu[1,3]

verified/validated using intravenous and oral data from multiple generic OP products. The pediatric PBPK AM is extrapolated from the adult PBPK AM. The virtual BE analysis is conducted using simulated PK profiles from the reference products and the generic products with theoretical dissolution profiles as inputs. Results indicate that the generic products with 10% slower dissolution profile than the pivotal reference bio-batch could still maintain BE to the reference in adults. In contrast, a stringent trend of dissolution boundary is observed for pediatrics (6% slower for adolescents, 4% slower for 0–2-month neonates) to maintain BE. This study addresses the important applications of PBPK AM in evaluating BE in different age populations, mitigating risk of formulation/batch changes, and providing a quantitative basis for setting clinically relevant dissolution specifications for OP and OC in both adults and pediatrics.

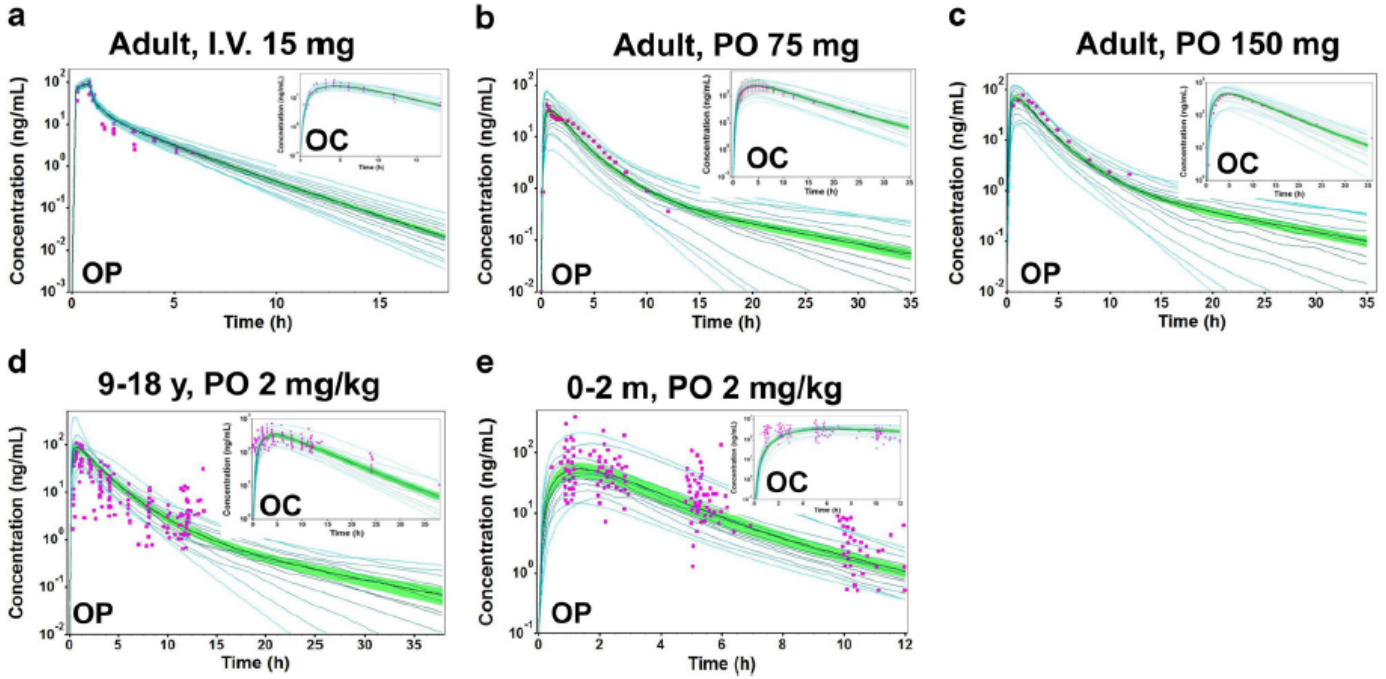

Fig. 2. Predicted and observed plasma concentration-time profiles of OP and OC following the administration of different doses in different age groups. **a** Population simulation of OP and OC in adults ($n = 50$) shows a reasonable capture of clinically observed data obtained after

Table III. GMR and 90% CI for Reference OP Product and OP Products with Lower Dissolution Profiles for Virtual BE Study in Adults, Adolescent, and Neonates (0–2 Months)

GMR% (T/R) (90% CI)		
Low dissolution profiles	C_{max}	AUC
Adults		
10%	91.4 (80.7–103.5)	93.8 (83.8–105.1)
12%	88.2 (78.1–99.7)	90.7 (81.1–101.4)
Adolescent		
6%	93.7 (81.9–107.2)	95.8 (83.1–110.4)
7%	92.1 (75.3–112.6)	94.3 (79.2–112.2)
0–2 months		
4%	98.3 (80.2–120.6)	100.1 (82.4–121.5)
6%	94.9 (75.7–118.9)	96.4 (77.3–120.2)

GMR, geometric mean ration; 90% CI, 90% confidence interval

Summary

- PBPK models are important tool in pediatric drug development: pediatric dose selection, trial design, but also evaluation of pediatric formulations - this has been recognized also by regulatory agencies around the world.

- GastroPlus makes application of PBPK models in pediatric drug development easy through its PEAR Physiology module which includes algorithms for creating physiologies from 16-week premature newborn
  - Mixed Multiple Dose utility allows to account for growth during the course of the study

- Some processes are not well characterized in children (gaps in intestinal physiology characterization, ontogeny of some enzymes and transporters) and we keep updating the physiologies as new information becomes available

- Possibility of filling in the knowledge gaps by utilizing already available clinical data was explored with few compounds. The results so far suggest that this may be a feasible approach, but additional test compounds are needed

Thank you for your kind attention!

Questions?