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A Simulations Plus Companies Workshop

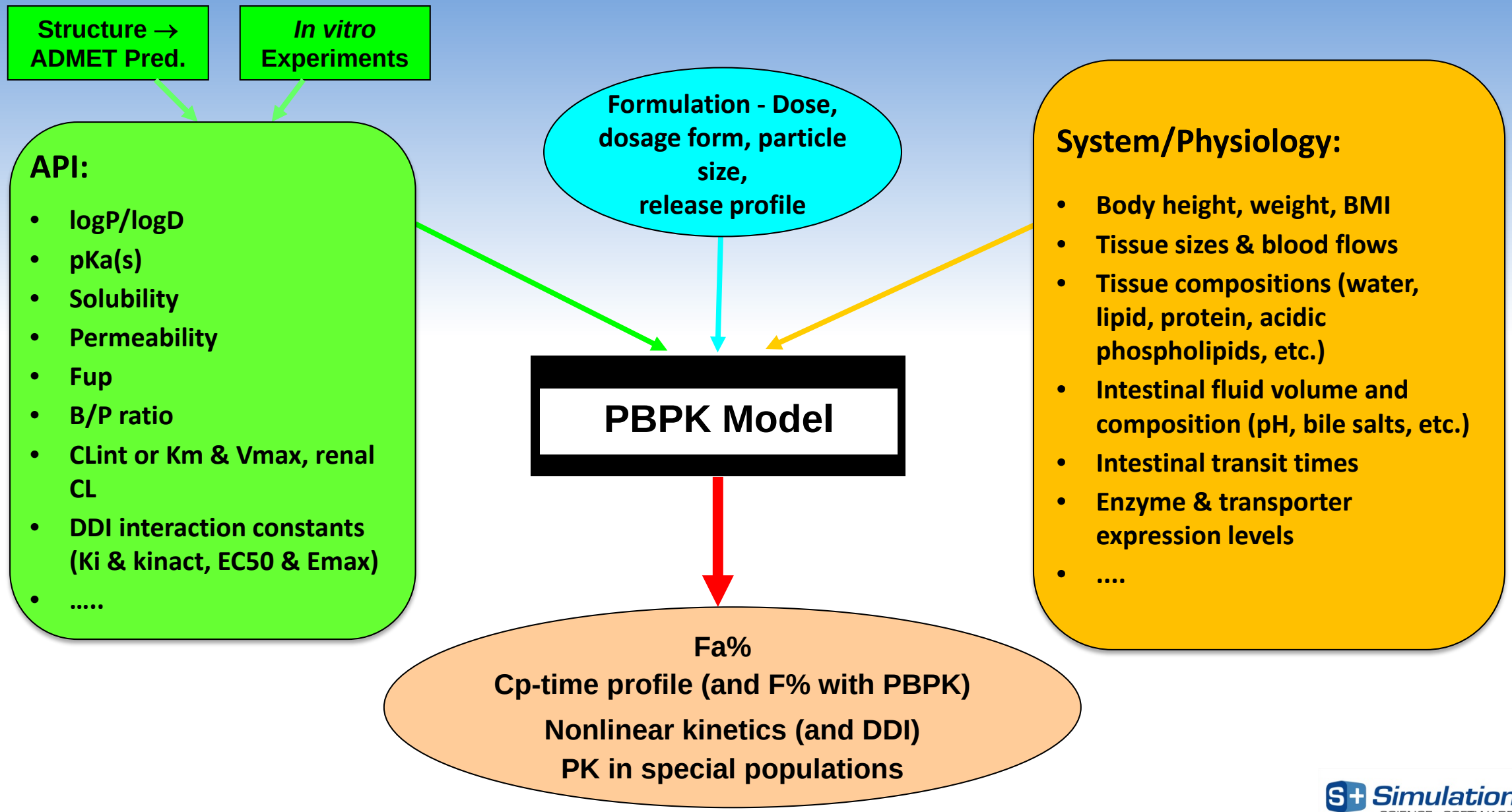
Mechanistic PBPK modeling of special population groups – considerations and opportunities

October 20, 2019

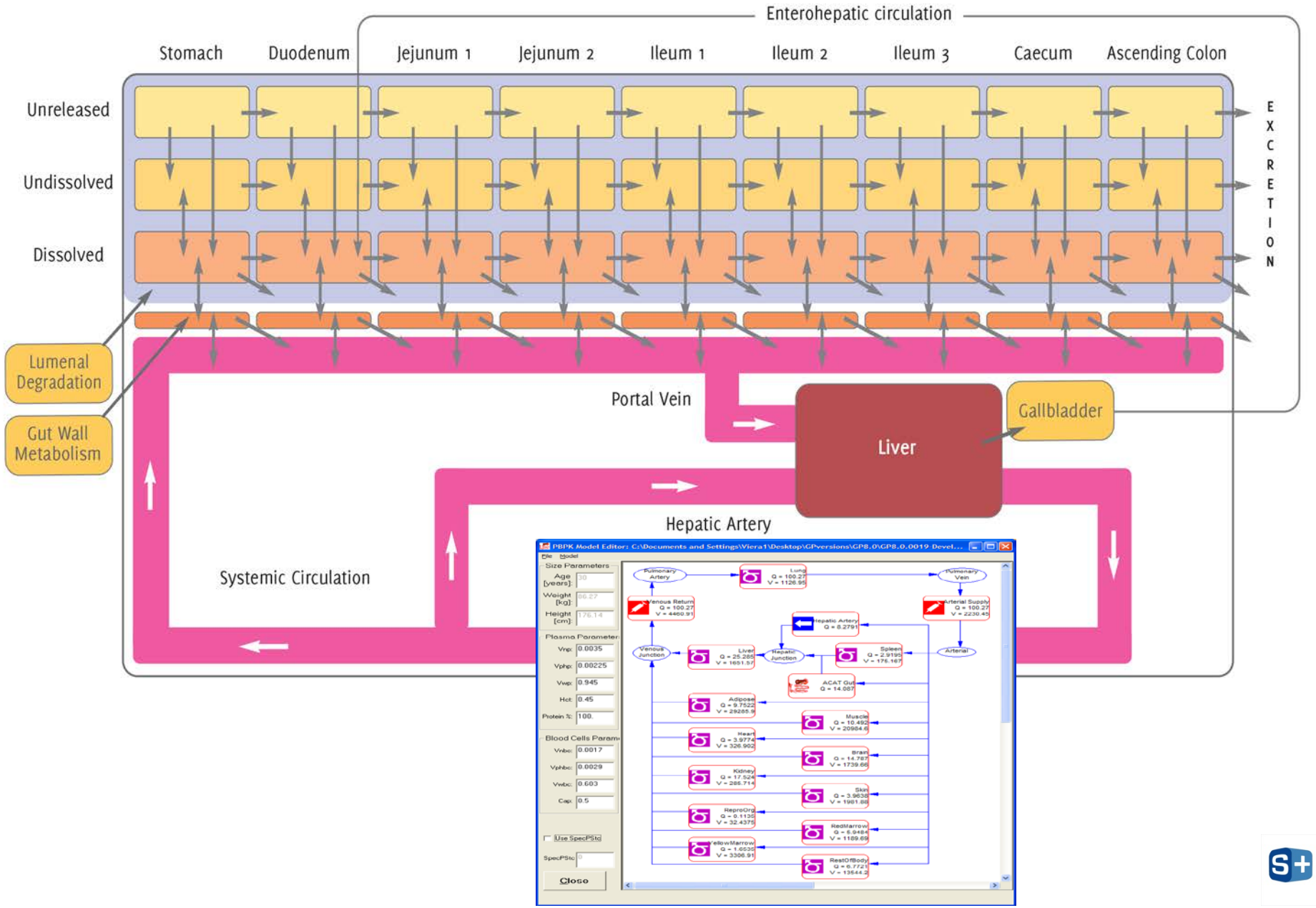
SLP M&S Workshop Agenda

- 8:30 - 8:45 - CEO's Intro and Welcome
- 8:45 - 9:15 - The Big Picture of Integrating Simulation Methods within Drug Development
- 9:15 - 10:30 - Mechanistic PBPK Modeling – Special Populations
- 10:30 - 10:45 - Break
- 10:45 - Noon – Quantitative Systems Toxicology (QST)
- Noon - 1:00 - Lunch
- 1:00 - 2:15 - Quantitative Systems Pharmacology (QSP)
- 2:15 - 2:30 - Break
- 2:30 - 3:45 - Pharmacometrics to Support Regulatory Approval
- 3:45 - 4:00 - Q&A, Wrap-up

The Big Picture



Advanced Compartmental Absorption and Transit Model (ACAT™)



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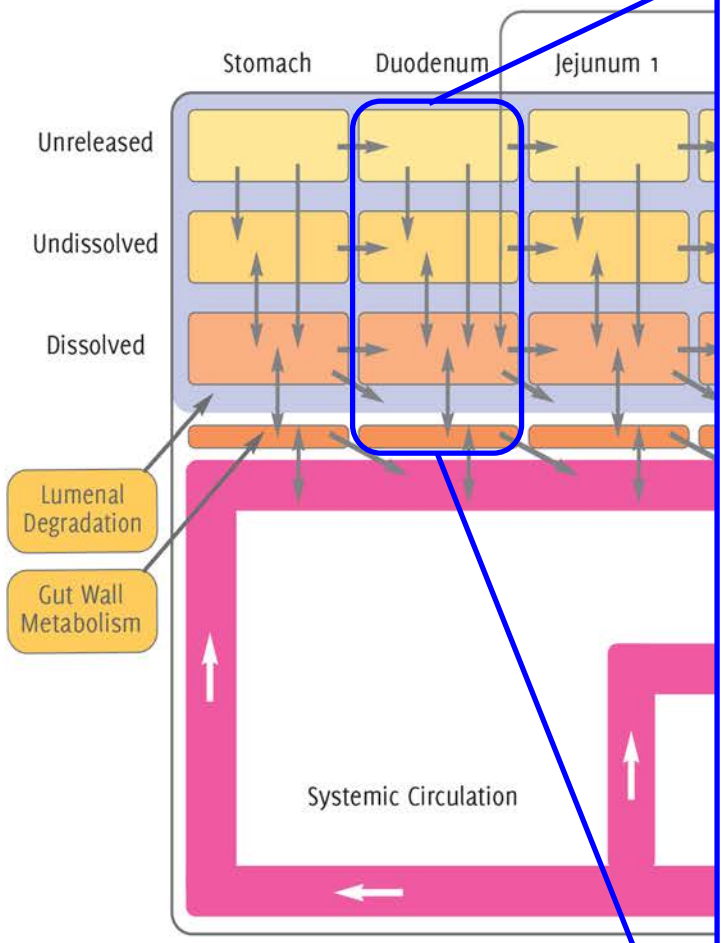
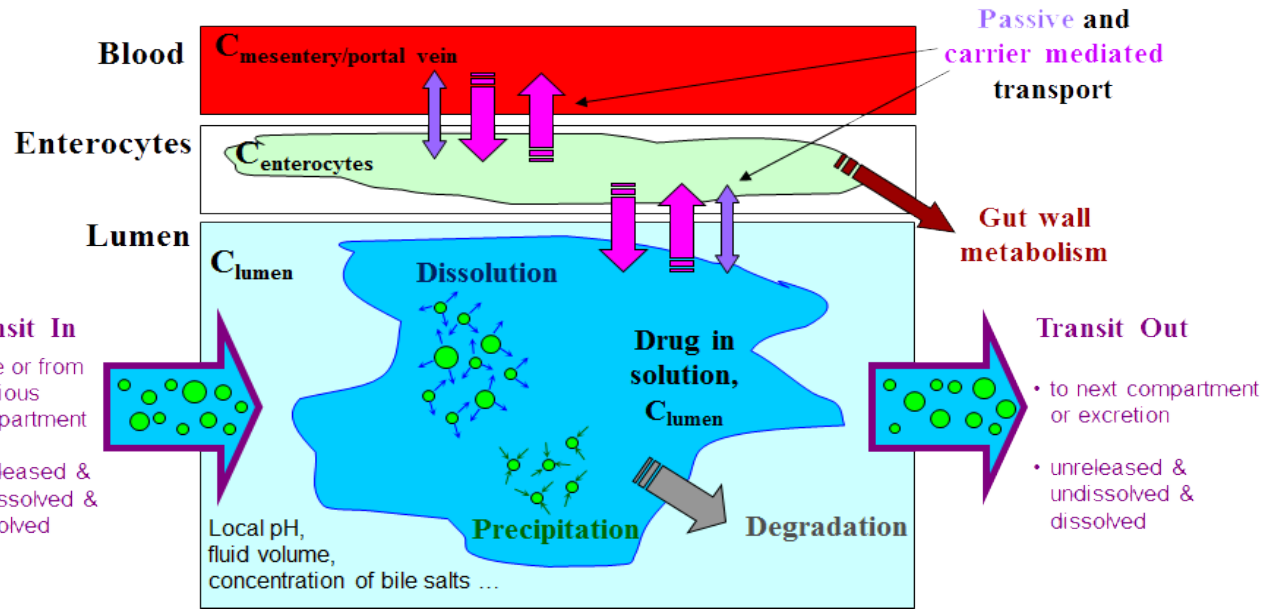
Advanced Compartmental Absorption and Transit Model (ACAT™)



Each compartment represents a region/section of the intestine:

- pH
- Fluid volume
- Bile salt concentration
- Absorptive surface area
- Expression levels of enzymes and transporters
- …..



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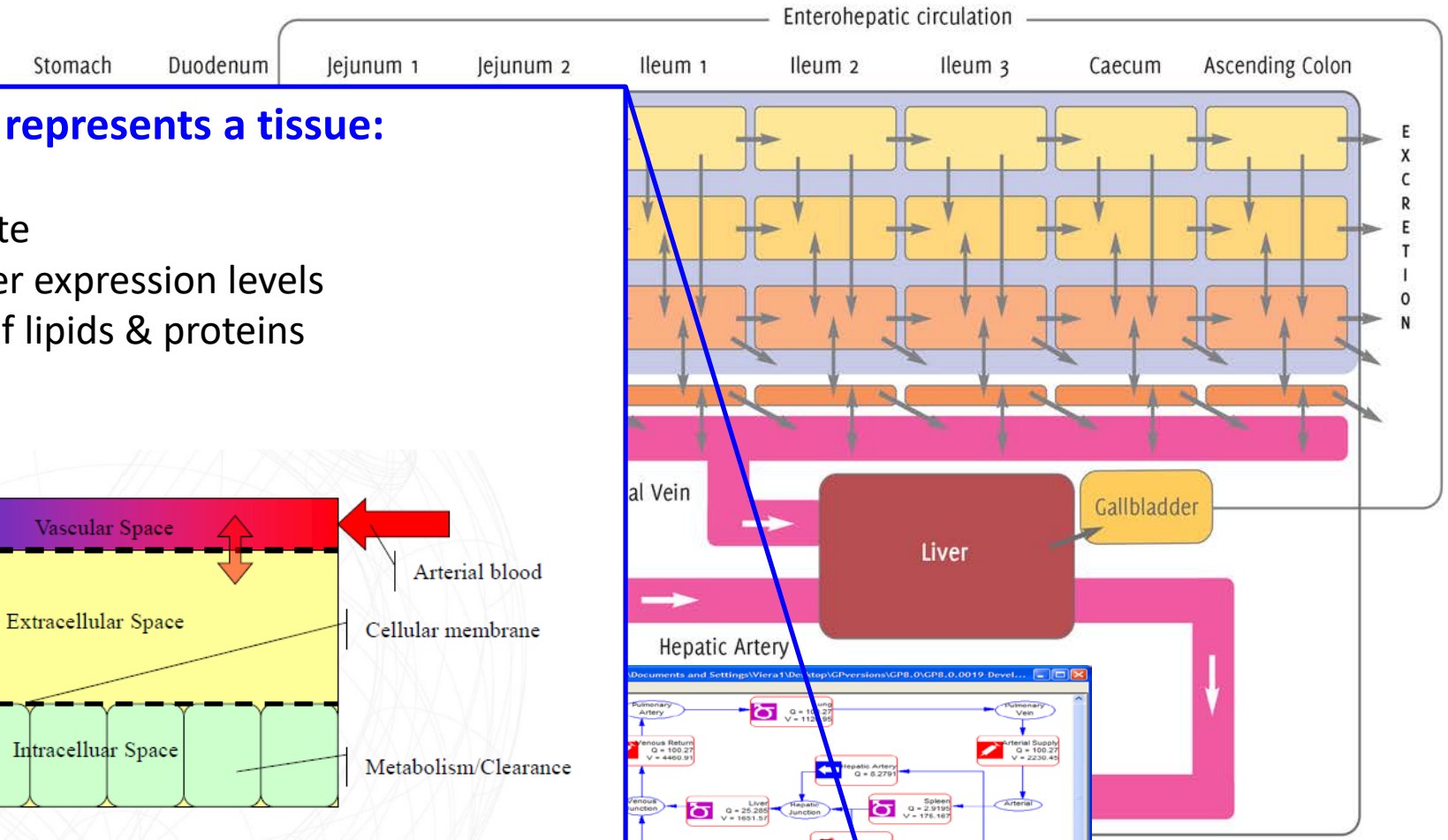
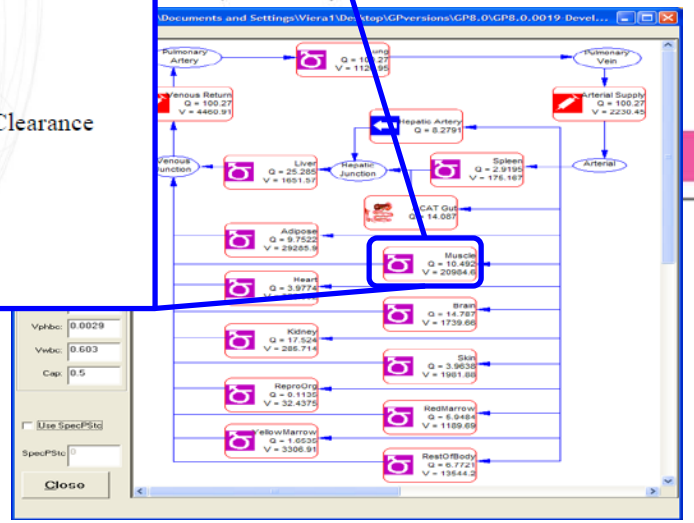
Advanced Compartmental Absorption and Transit Model (ACAT™)



Each compartment represents a tissue:

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



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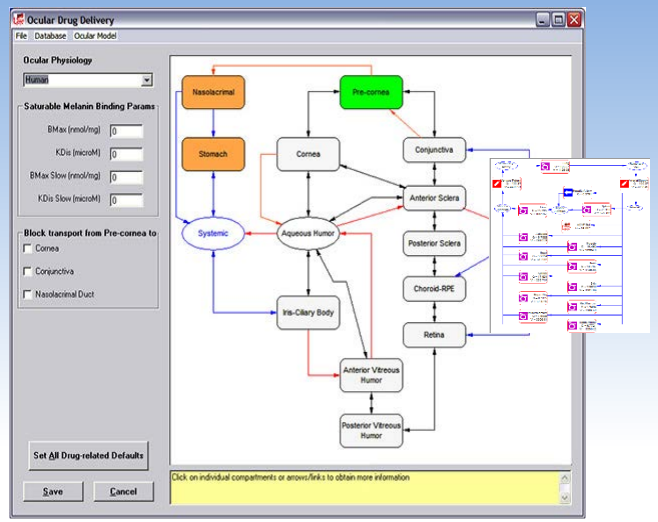
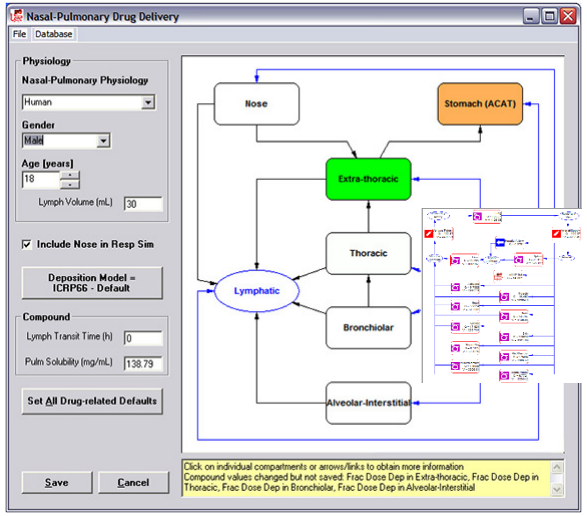
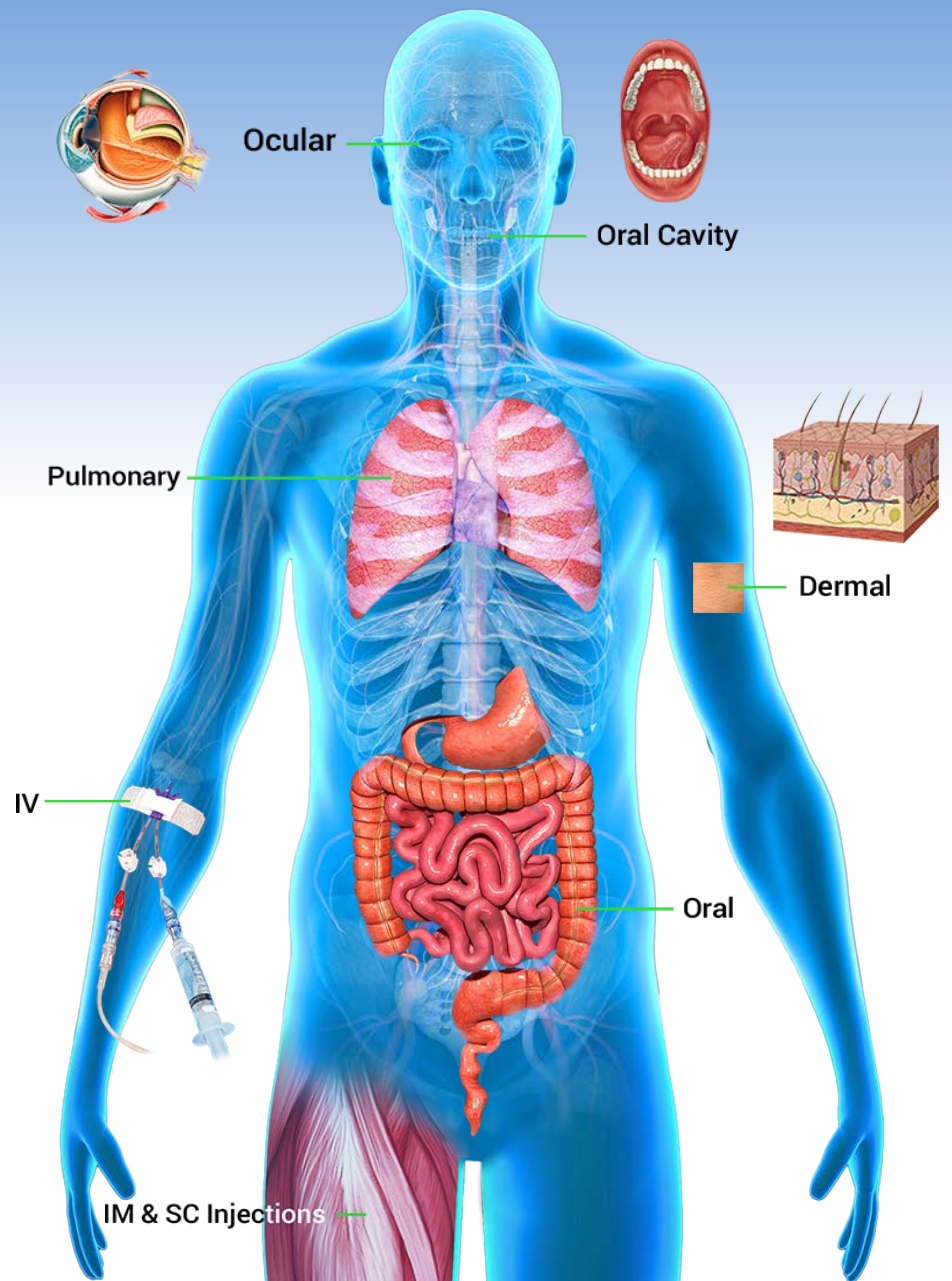
Pathways beyond oral absorption…

Ocular (OCAT™)

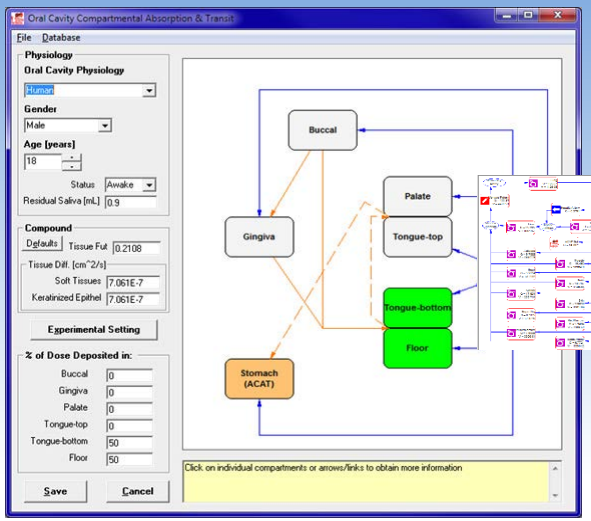


Pulmonary (PCAT™)

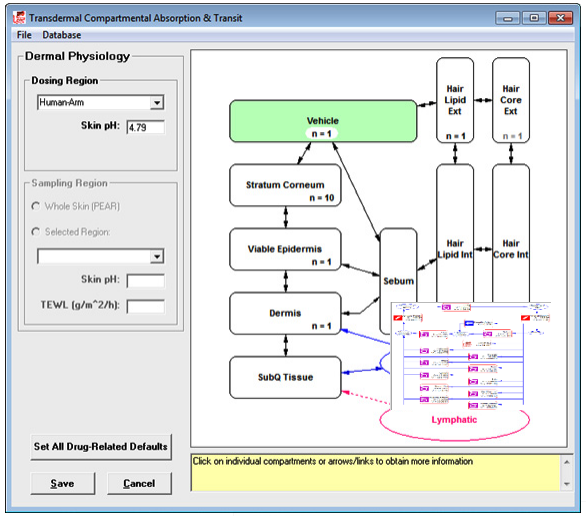




Oral Cavity (OCCAT™)



Dermal (TCAT™)



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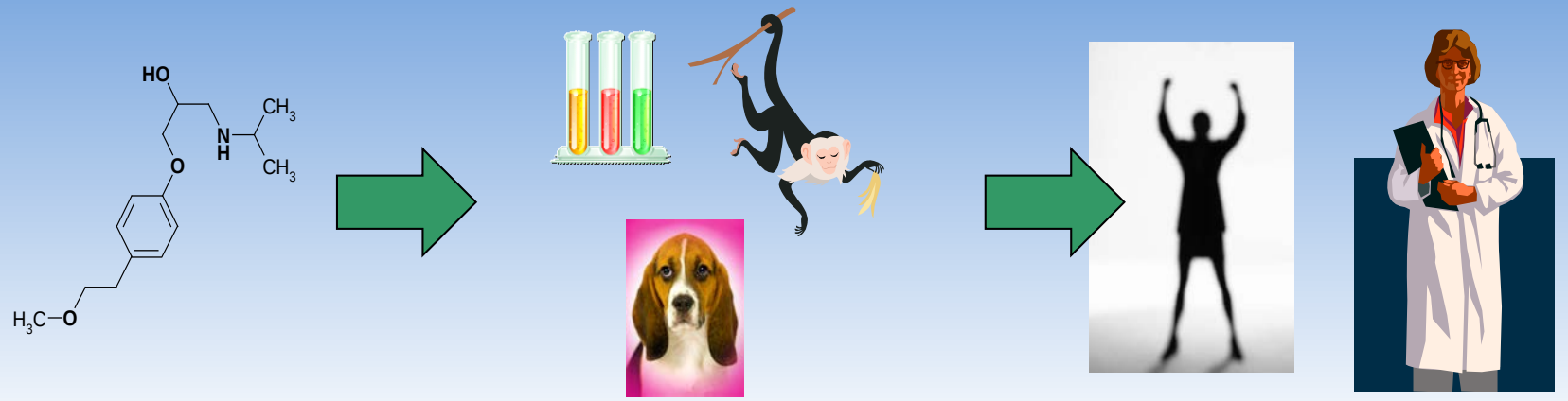
Discovery | Preclinical | Clinical



Discovery PK

Combine *in silico* technologies to screen compound libraries in animals or humans

Incorporate preclinical/*in vitro* data to extend FIH simulations to full *in vivo* outcomes (IVIVE)

Identify toxic dose levels in preclinical species

Clinical PK/Pharmacology

Simulate population behaviors (e.g., pediatrics, disease)

Build PBPK-PD models

Predict DDIs

Pharmaceutical Development

Assess various strategies during formulation development

Assist with Quality by Design (QbD) implementation

Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)

Understand food effects

Human PK Prediction

Comparison of first-in-human prediction accuracy in a 2-year study of 21 compounds
(Cole et al., ISSX 2008)

Summary of IV profile prediction accuracy

APPROACH	PROFILE	Vss		CL	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-11.7 (1)	1.4	90 (100)	1.6	80 (85)
PKSim	-6.4 (2)	1.7	70 (90)	1.6	80 (85)
Current Pfizer Approach	-3.8 (3)	1.6	75 (85)	1.6	80 (85)
SimCYP – hlm	5.6 (4)*	1.5	80 (95)	2.5	58 (74)
SimCYP – rhCYP	7.8 (5)*	1.5	80 (95)	2.4	55 (65)
ChloePK	8.5 (6)*	-	-	1.7	70 (80)

Summary of Oral profile prediction accuracy

AFE→ Average Fold Error

APPROACH	PROFILE	AUC		Cmax	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-9.8 (1)	2.7	50 (72)	2.0	67 (72)
Current Pfizer Approach	-5.3 (2)	3.9	33 (56)	2.5	44 (61)
SimCYP - rhCYP	-3.7 (3)	3.0	56 (67)	2.2	61 (72)
SimCYP - hlm	5.7 (4)*	3.6	41 (53)	2.7	53 (59)
PKSim	6.1 (5)*	4.7	22 (39)	5.0	17 (33)
ChloePK	7.0 (6)*	2.8	39 (50)	2.4	50 (61)

Predicting PK from *in silico* properties
(Hosea et al., 2013)

molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics

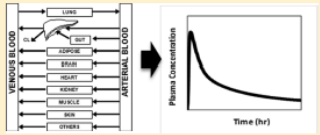
Predicting Pharmacokinetic Profiles Using *in Silico* Derived Parameters

Natalie A. Hosea* and Hannah M. Jones

Department of Pharmacokinetic, Dynamics and Metabolism, Pfizer, Inc., Cambridge, Massachusetts 02140, United States

ABSTRACT: Human pharmacokinetic (PK) predictions play a critical role in assessing the quality of potential clinical candidates where the accurate estimation of clearance, volume of distribution, bioavailability, and the plasma-concentration–time profiles are the desired end points. While many methods for conducting predictions utilize *in vivo* data, predictions can be conducted successfully from *in vitro* or *in silico* data, applying modeling and simulation techniques. This approach can be facilitated using commercially available prediction software such as GastroPlus which has been reported to accurately predict the oral PK profile of small drug-like molecules. Herein, case studies are described where GastroPlus modeling and simulation was employed using *in silico* or *in vitro* data to predict PK profiles in early discovery. The results obtained demonstrate the feasibility of adequately predicting plasma-concentration–time profiles with *in silico* derived as well as *in vitro* measured parameters and hence predicting PK profiles with minimal data. The applicability of this approach can provide key information enabling decisions on either dose selection, chemistry strategy to improve compounds, or clinical protocol design, thus demonstrating the value of modeling and simulation in both early discovery and exploratory development for predicting absorption and disposition profiles.

KEYWORDS: *pharmacokinetic, profiles, prediction, modeling, simulation*



Using *in vitro* data to predict human absorption and gut metabolism
(Heikkinen et al., 2012)

European Journal of Pharmaceutical Sciences 47 (2012) 375–386

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

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

Application of PBPK modeling to predict human intestinal metabolism of CYP3A substrates – An evaluation and case study using GastroPlus™

Aki T. Heikkinen, Guillaume Baneyx, Antonello Caruso, Neil Parrott*

F. Hoffmann-La Roche AG, pRED, Pharma Res

ARTICLE INFO

Article history:
Received 8 February 2012
Received in revised form 11 May 2012
Accepted 23 June 2012
Available online 1 July 2012

Keywords:
Binding in enterocytes
Gut wall metabolism
Monte Carlo simulation
Physiologically based pharmacokinetic modeling
Propagation of error

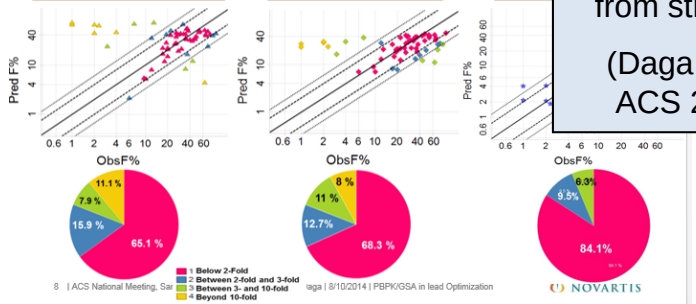
This analysis supports that CYP3A mediated metabolic clearance measured in human liver microsomes can be used to predict gut wall metabolism. Using values scaled from *in vitro* cell permeability as input for effective jejunal permeability resulted in good F_g prediction accuracy (no significant bias and ~95% of predictions within 2 fold from *in vivo* estimated F_g), whereas simulations with *in silico* predicted permeability tended to overestimate gut metabolism (40% of F_g predictions under predicted more than 2 fold) ±2 fold range as an estimate of imprecision in metabolic clearance and permeability inputs propagated to >5 and <2 fold ranges of predicted F_g for compounds with <30% and >75% *in vivo* F_g, respectively, suggesting lower precision of predictions for high extraction compounds. Furthermore, parameter sensitivity analysis suggests that limitations in solubility or dissolution may either decrease F_g by preventing saturation of metabolism or increase F_g by shifting the site of absorption towards the colon where expression of CYP3A is low. The case example illustrates how, when accounting for the associated uncertainty in predicted pharmacokinetics and linking to predictive models for efficacy, PBPK modeling of intestinally metabolized compounds can support decision making in drug Research and Development.

Case Study #2: Internal kinase-"**X**" Inhibitor series

In silico inputs are adequate for GSA

- 61 compounds : Single med-chem series with experi
  - *In vitro* (Solubility, Caco2 permeability, Plasma Protein binding, CL_{int})
  - RAT PK data (%F, AUC, C_{max}, T_{max}, CL_{plasma}, V_{ss})

Measured input properties | In silico input properties | In silico and



Predicting PK profiles using *in silico* estimates from structure
(Daga et al., ACS 2014)

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-019-00741-9

REVIEW ARTICLE

Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

Neil A. Miller[1] · Micaela B. Reddy[2] · Aki T. Heikkinen[3] · Viera Lukacova[4] · Neil Parrott[5]

Abstract

Physiologically based pharmacokinetic modelling is well e
regulatory agencies for the prediction of drug–drug interacti
ling is valuable to address a much wider range of pharmaceu
full power is leveraged. As one example, physiologically base
drug discovery for in-vitro to in-vivo translation and pharmacokinetic modelling in preclinical species, and this leads to the application of verified models for first-in-human pharmacokinetic predictions. A consistent cross-industry strategy in this application area would increase confidence in the approach and facilitate further learning. With this in mind, this article aims to enhance a previously published first-in-human physiologically based pharmacokinetic model-building strategy. Based on the experience of scientists from multiple companies participating in the GastroPlus™ User Group Steering Committee, new Absorption, Distribution, Metabolism and Excretion knowledge is integrated and decision trees proposed for each essential component of a first-in-human prediction. We have reviewed many relevant scientific publications to identify new findings and highlight gaps that need to be addressed. Finally, four industry case studies for more challenging compounds illustrate and highlight key components of the strategy.

FIH predictions: Industry standards
(Miller at al. Clin Pharm 2019)

Parameters for Pyrethroid Insecticide QSAR and PBPK/PD Models for Human Risk Assessment

James B. Knaak, Curtis C. Dary, Xiaofei Zhang, Robert W. Gerlach, R. Tornero-Velez, Daniel T. Chang, Rocky Goldsmith, and Jerry N. Blancato

1 Introduction

This pyrethroid insecticide parameter re
developing quantitative structure–activ
pharmacokinetic/pharmacodynamic (QSA
risks, which interest started with the
insecticides (Knaak et al. 2004, 2008). Th
et al. 2000) are needed for developing py
tion on the metabolic pathways of speci
and humans. Parameters may be obtained by fitting the output from models to experimental data gathered from in vivo studies (Zhang et al. 2007; Nong et al. 2008), in conjunction with using (1) experimental data obtained from in vitro studies, (2) quantitative structure–activity relationships (QSAR) and (3) other mathematical models, such as the mechanistic Poulin-Theil (2000; 2002a; b) algorithms for obtaining blood:tissue partition coefficients.

Applying QSAR & PBPK approaches to assist with human risk assessment
(Knaak et al., 2012)

Pharmaceutical Development

AAPS PharmSciTech, Vol. 16, No. 1, February 2015 (© 2014)
DOI: 10.1208/s12249-014-0194-8

Research Article

Theme: Leveraging BCS Classification and in-silico Modeling for Product Development
Guest Editors: Divyakant Desai, John Crison, and Peter Timmins

Application of Absorption Modeling to Predict Bioequivalence Outcome of Two Batches of Etoricoxib Tablets

Amitava Mitra,[1,3] Filippos Kesisoglou,[1] and Peter Dogterom[2]

Mitra et al., AAPS PharmSciTech 2015, 16(1):76

Virtual Bioequivalence Study Simulations

API Lot	PE/NPE	Dose (mg)	AUC_∞ (ng.h/mL) (N=250) GM	GMR (90% CI)	C_{max} (ng/mL) (N=250) GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142[illegible])
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108[illegible])
Lot 3	NPE	100	8001		395	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	100.0 (97.7, 102.[illegible])
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	95.1 (93.2, 97.0)
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.[illegible])
Lot 4	NPE	300	24525		3171	

API: active pharmaceutical ingredient; AUC_∞: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C_{max}: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ration; NPE: non-particle-engineered; PE: particle-engineered

Tistaert, AAPS Annual Meeting 2015, Orlando, FL

molecular pharmaceutics
Article
pubs.acs.org/molecularpharmaceutics

Justification of Drug Product Dissolution Rate and Drug Substance Particle Size Specifications Based on Absorption PBPK Modeling for Lesinurad Immediate Release Tablets

Xavier J. H. Pepin,*[†] Talia R. Flanagan,[†] David J. Holt,[†] Anna Eidelman,[‡] Don Treacy,[‡] and Colin E. Rowlings[‡]
[†]AstraZeneca, Global Medicines Development, Pharmaceutical Development, Silk Road Business Park, Charter Way, Hurdsfield Industrial Estate, Macclesfi[...]
[‡]Ardea Biosciences, Pharma[...]

Supporting Information

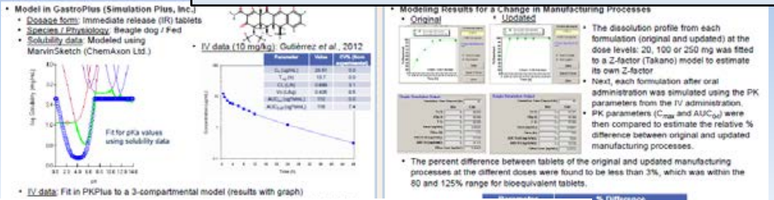
ABSTRACT: In silico [...] performed, to assess the [...] vivo performance for ZU[...] dissolution profiles of lesinurad tablets generated using the quality control method were used as an input to a GastroPlus model to estimate in vivo dissolution in the various parts of the GI tract and predict human exposure. A model was set up, which accounts for differences of dosage form transit, dissolution, local pH in the GI tract, and fluid volumes available for dissolution. The predictive ability of the model was demonstrated by confirming that it can reproduce the C_{max} observed for independent clinical t[...] that drug product batches that pass the proposed dissolution specification of Q = 80% in 3[...] bioequivalent to the clinical reference batch. To further explore the dissolution space, additional[...] using a theoretical dissolution profile below the proposed specification. The GastroPlus modeling i[...] also be bioequivalent to standard clinical batches despite having a dissolution profile, which would[...] specification of Q = 80% in 30 min. This demonstrates that the proposed dissolution specificat[...] region of dissolution performance where bioequivalence is anticipated and is not near an edge of fai[...] additional confidence to the proposed specifications. Finally, simulations were performed using a[...] with a particle size distribution at the limit of the proposed specification for particle size. Based on t[...] is also anticipated to be bioequivalent to clinical reference, demonstrating that the proposed speci[...] distribution would give products bioequivalent to the pivotal clinical batches.
KEYWORDS: biowaiver, PBPK modeling, dissolution, specifications, control strategy

Pepin et al., J. Mol Pharm 2016, 13:3256

In-Silico Modeling: Assessing the Impact of Different Dissolution Profiles in Doxycycline Tablets (Ronaxan®): An Alternative Approach to Replace In Vivo Bioequivalence Studies for Regulatory Product Variations

Jaime A. Yáñez, James Fischer, Laura Letendre and James Gerhart
Merial Inc., a Sanofi company – Drug Safety and Disposition / Pharmacokinetics and Drug Metabolism

Abstract Final ID # 2091



Yanez et al., SOT Annual Meeting 2015, San Diego, CA

Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

The Irrelevance of *In Vitro* Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping

Michael B. Bolger [1,2], Joyce S. Macwan [1], Muhammad Sarfraz [3,4], May Almukainzi [5], Raimar Löbenberg [3,*]
[1] Simulations Plus, Inc., Lancaster, Cal[...]
[2] USC School of Pharmacy, Pharmacol[...]
[3] Faculty of Pharmacy and Pharmace[...]
[4] College of Pharmacy, Al Ain Univers[...]
[5] College of Pharmacy, Princess Noura[...]

Bolger et al., J. Pharm. Sci. 2019

RESEARCH ARTICLE – Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

ANDREW H. BABISKIN, XINYUAN ZHANG
Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland 20993

Received 30 January 2015; revised 8 April 2015; accepted 9 April 2015
Published online in Wiley Online Library (wil[...]

ABSTRACT: Amphetamine (AMP) salts-based ext[...] hyperactivity disorder. We developed physiologic[...] sulfate ER capsules to address specific questions [...] development. The models were verified against se[...] other than normal healthy subjects where BE stu[...] macokinetics (PK) for hypothetical formulations [...] vivo relation. Finally, we demonstrated how to use the models to test sensitivity of PK metrics to the changes in formulation variables. Published 2015. This article is a U.S. Government work and is in the public domain in the USA J Pharm Sci
Keywords: physiological model; absorption; bioequivalence; bioavailability; clinical trial simulation; modified release

Babiskin et al., J. Pharm. Sci. 2015, 104(9):3170

Contents lists available at ScienceDirect
Journal of Pharmaceutical Sciences
journal homepage: www.jpharmsci.org

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies

Christophe Tistaert [1], Tycho Heimbach [2], Binfeng Xia [3], Neil Parrott [4], Tanay S. Samant [2], Filippos Kesisoglou [3,*]
[1] Pharmaceutical Sciences, Discovery and Manufacturing Sciences, Janssen Research and Develop[...]
[2] Department of PK Sciences, Computational and Biopharmaceutics Section, Novartis Institutes [...] 07936
[3] Biopharmaceutics, Pharmaceutical Sciences, Merck & Co., Inc., West Point, Pennsylvania 19486
[4] Pharmaceutical Sciences, Pharmaceutical Research and Early Development, Roche Innovation [...]

Tistaert et al., J. Pharm. Sci. 2018

Virtual population pharmacokinetic using physiologically based pharmacokinetic model for evaluating bioequivalence of oral lacidipine formulations in dogs

Bin Yang[1], Chunnuan Wu[2], Bin Ji[3], Mingrui Wu[1], Zhonggui He[1], Lei Shang[4]* and Jin Sun[1,5]*
Affiliation:
[1]Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, China;
[2]Department of Pharmacy, Tianjin Medical University Cancer Institute and Hospital, China;
[...] Pharmaceutical University, China;

Yang et al., Asian J. Pharm. Sci. 2016; Mar 21

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Recent Services Activities

- Our consulting team is working on 17 projects to support internal review and submissions to regulatory agencies for the following applications:
  - *In silico* safety/exposure screening for new compounds and analogs
  - Preclinical development and First-in-Human predictions
  - Formulation optimization
  - Virtual bioequivalence trial simulations
  - Food effect modeling
  - DDI predictions
  - Special population simulations and dose projections
  - Mechanistic IVIVCs to define product specifications
  - Non-oral delivery product assessment
  - Parent-metabolite and prodrug PBPK modeling

- Recent approved products supported by GastroPlus modeling include:
  - ALECENSA® (absorption/PPI DDI informing drug labeling)
  - BRAFTOVI® (metabolism DDI accepted by regulatory agencies)
  - CALQUENCE® (particle size distributions specifications accepted by regulatory agencies)
  - FARYDAK® (food effect modeling predictions informing drug labeling)
  - INLYTA® (transporter DDI accepted by regulatory agencies)
  - INVOKANA® (product manufacturing changes resulting in waiver of BA/BE study)
  - MEKINIST® (transporter DDI accepted by regulatory agencies)
  - MEKTOVI® (metabolism DDI accepted by regulatory agencies)
  - OPSUMIT® (particle size distributions specifications accepted by regulatory agencies)
  - TAMIFLU® (pediatric PBPK predictions informing dose selection)
  - ZURAMPIC® (wider product specifications accepted by regulatory agencies)
  - … and more!

Discovery | Preclinical | Clinical

Discovery PK

Combine *in silico* technologies to screen compound libraries in animals or humans

Incorporate preclinical/*in vitro* data to extend FIH simulations to full *in vivo* outcomes (IVIVE)

Identify toxic dose levels in preclinical species

Clinical PK/Pharmacology

Simulate population behaviors (e.g., pediatrics, disease)

Build PBPK-PD models

Predict DDIs

Pharmaceutical Development

Assess various strategies during formulation development

Assist with Quality by Design (QbD) implementation

Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)

Understand food effects

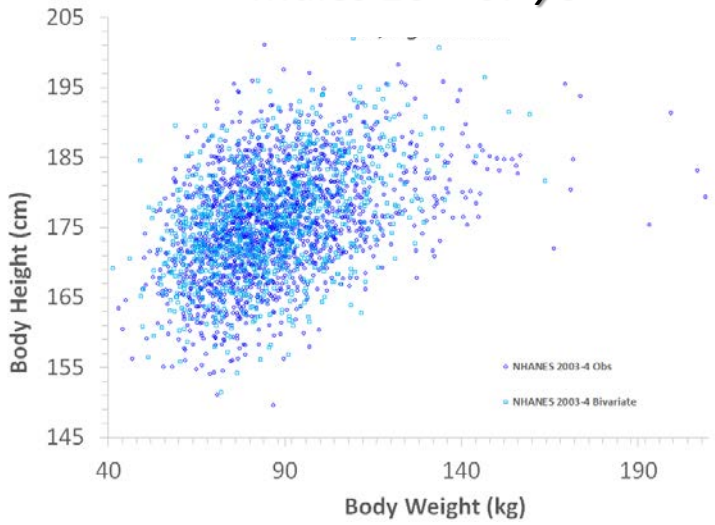
Importance of PBPK Modeling in Special Populations

- Unwarranted studies, due to the general nature of regulatory guidelines, may be avoided.
- Alleviation of the ethical problems and recruitment issues associated with clinical studies in children or subjects with more severe impairment of organs.
- Modeling helps to plan and optimize study design.
- Model simulations help to predict likely outcome in the disease population.
- Current built-in physiologies for special populations include: Pediatric, Liver Cirrhosis, Renal Impairment, Obesity, Pregnancy
- The flexibility of GastroPlus, and access to all physiological parameters, allows the user to create custom physiologies representing many conditions with an understanding of the appropriate changes.
- We're pleased to help users create custom gut (.cat) and the whole body physiology (.pbk) files that incorporate physiological changes relevant for specific population

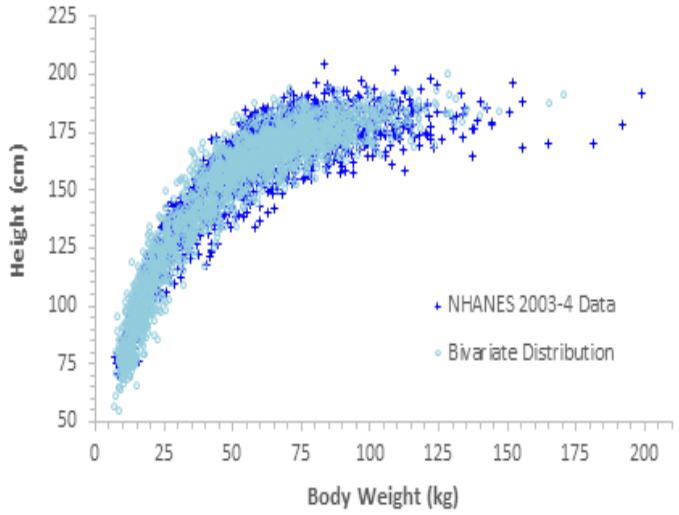
Pediatric

Virtual Population

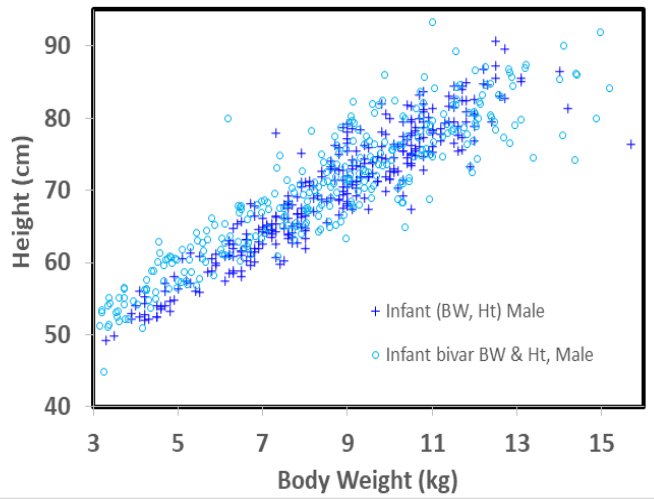
Males 20 – 67 yo



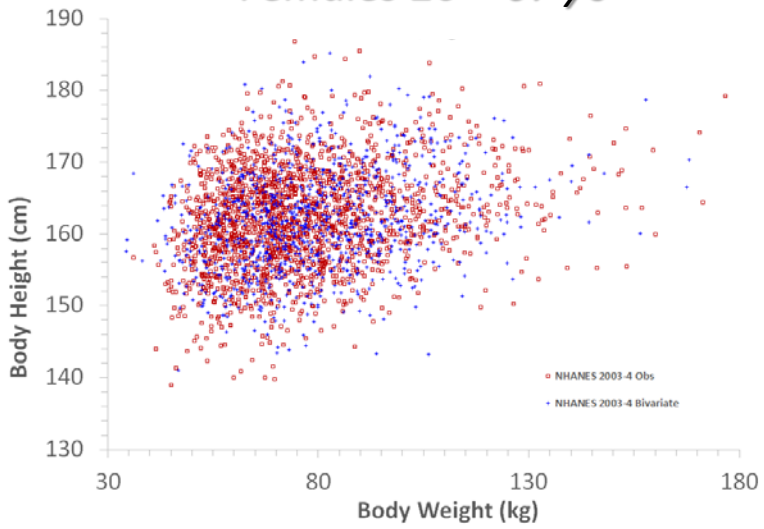
Males 1 – 20 yo



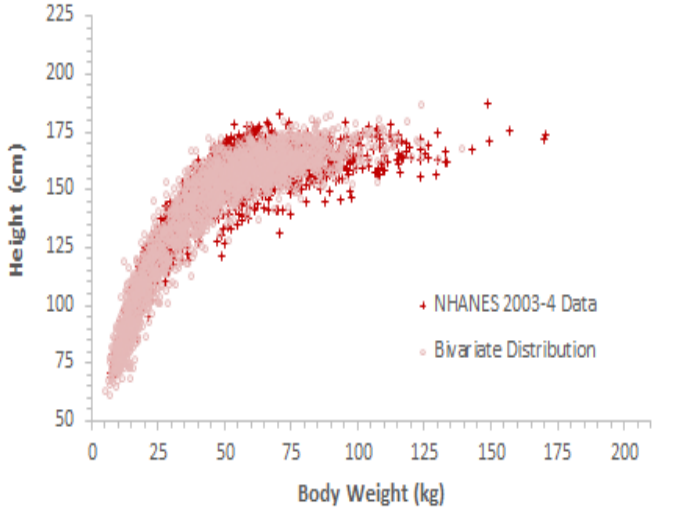
Male infants up to 1 yo



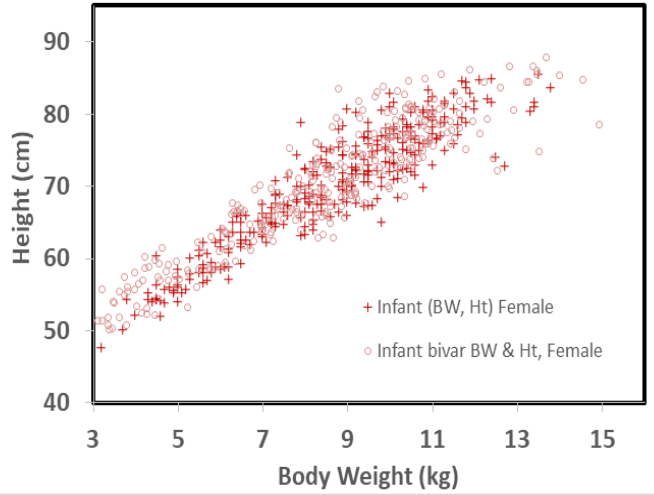
Females 20 – 67 yo



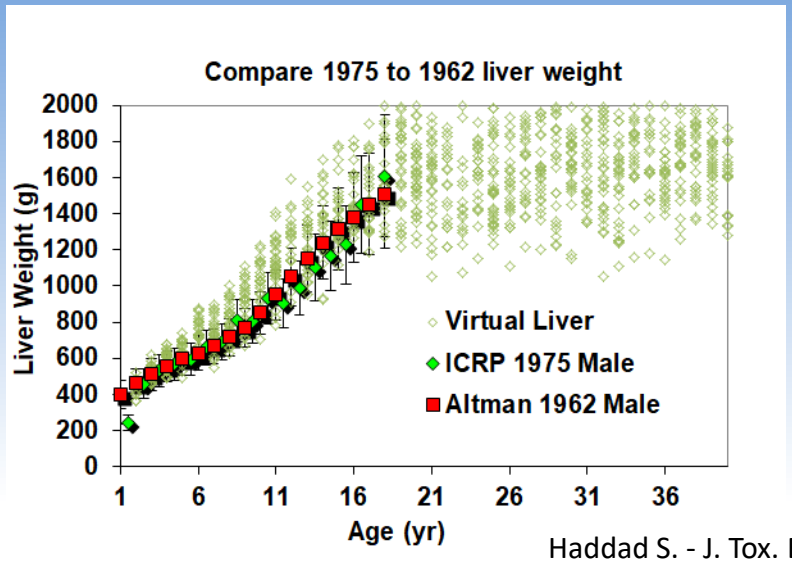
Females 1 – 20 yo



Female infants up to 1 yo



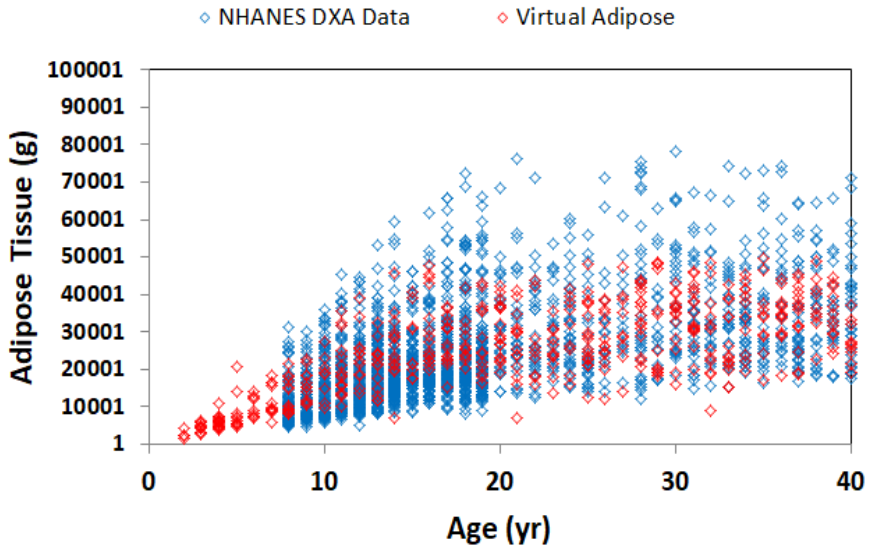
Children & Adults: Tissue Sizes and Blood Flows



Haddad S. - J. Tox. Envir. Health 64:453 (2001)
for ages <= 12

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

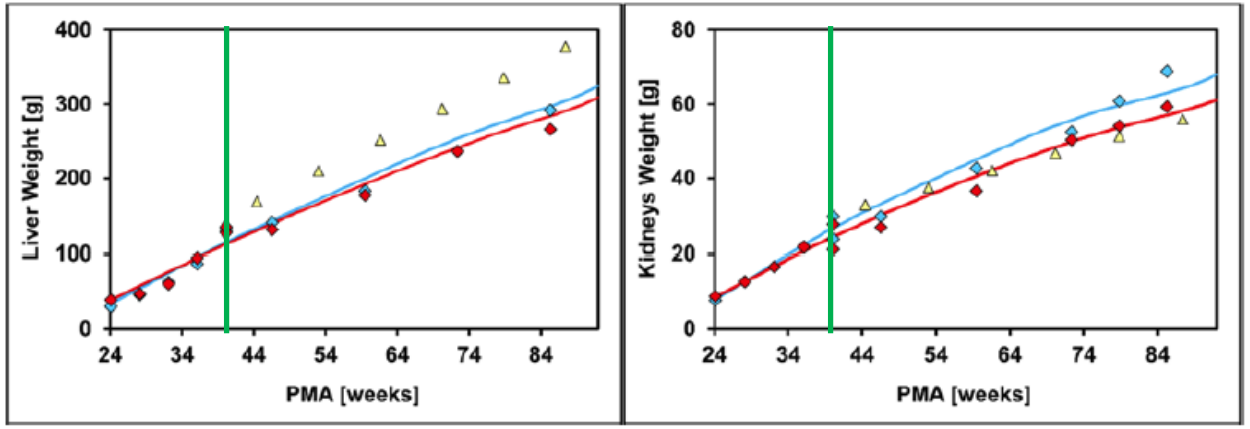
Price, P.S. Crit. Rev. Toxicol. 33(5):469 (2003), Table 16



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)

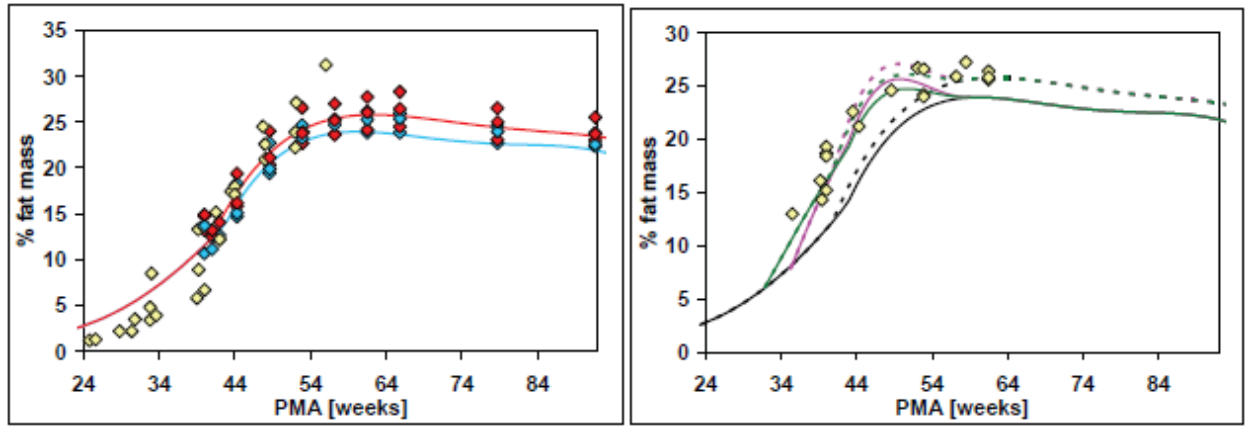
Infants: Tissue Sizes

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 gestation
PMA – postmenstrual age (gestational + postnatal age)

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

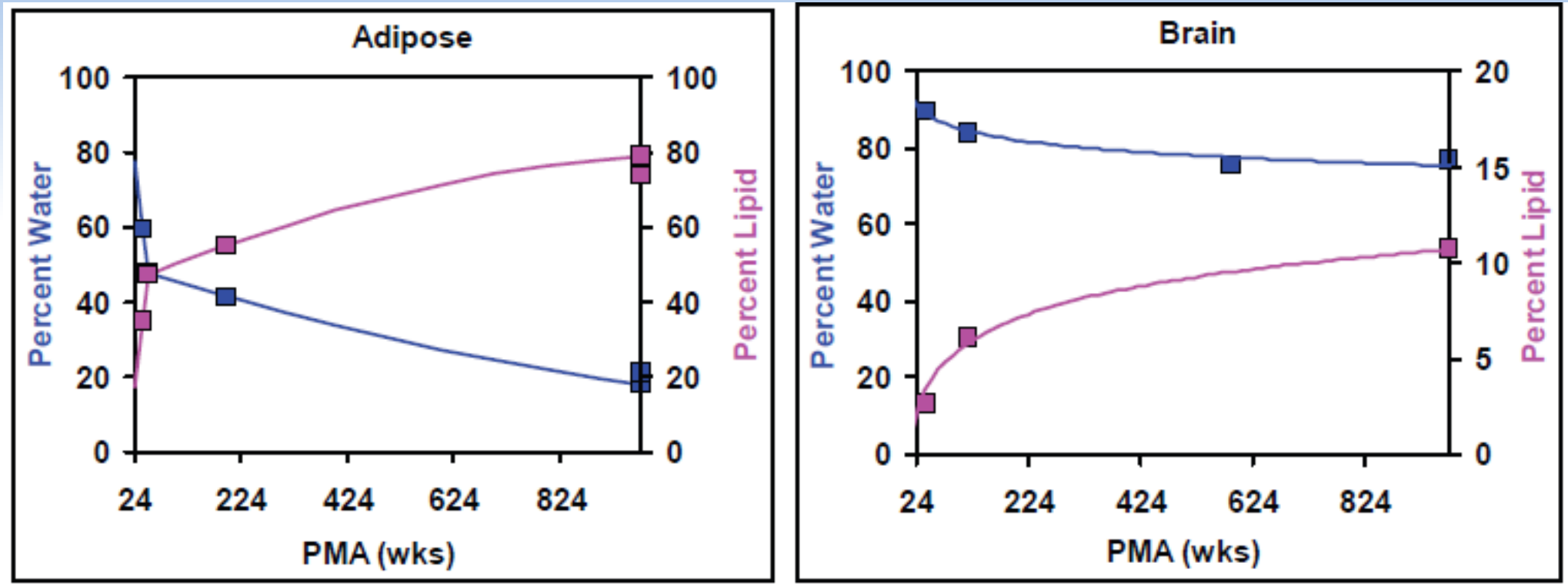


Black lines – representative of term-born infants

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

Age Dependent Tissue Composition

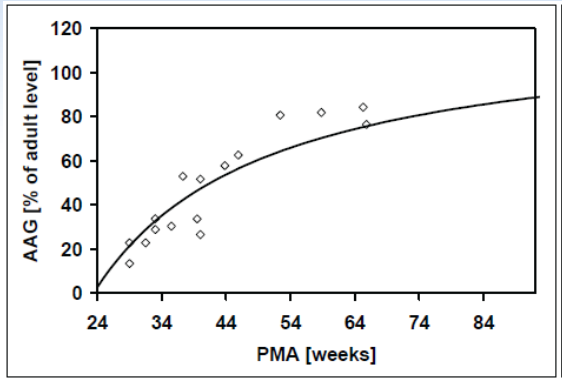
Effect of age on tissue compositions is included. Example plots for two of the tissues, Adipose and Brain, are shown below:

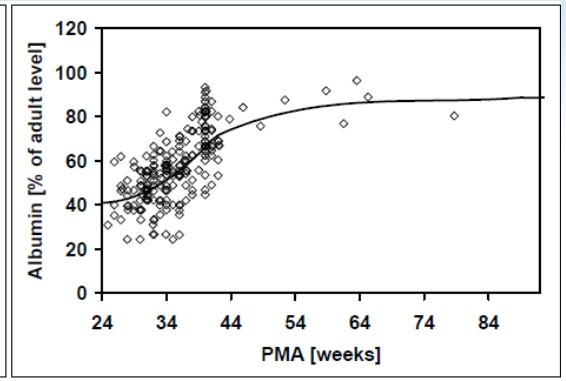


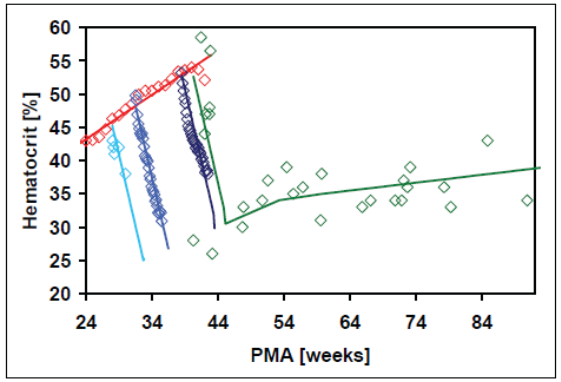
PMA – postmenstrual age (gestational + postnatal age)

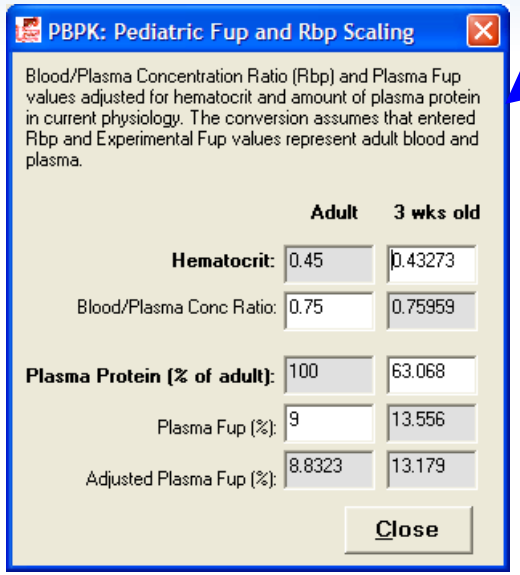
Red Blood Cell and Plasma Protein Binding

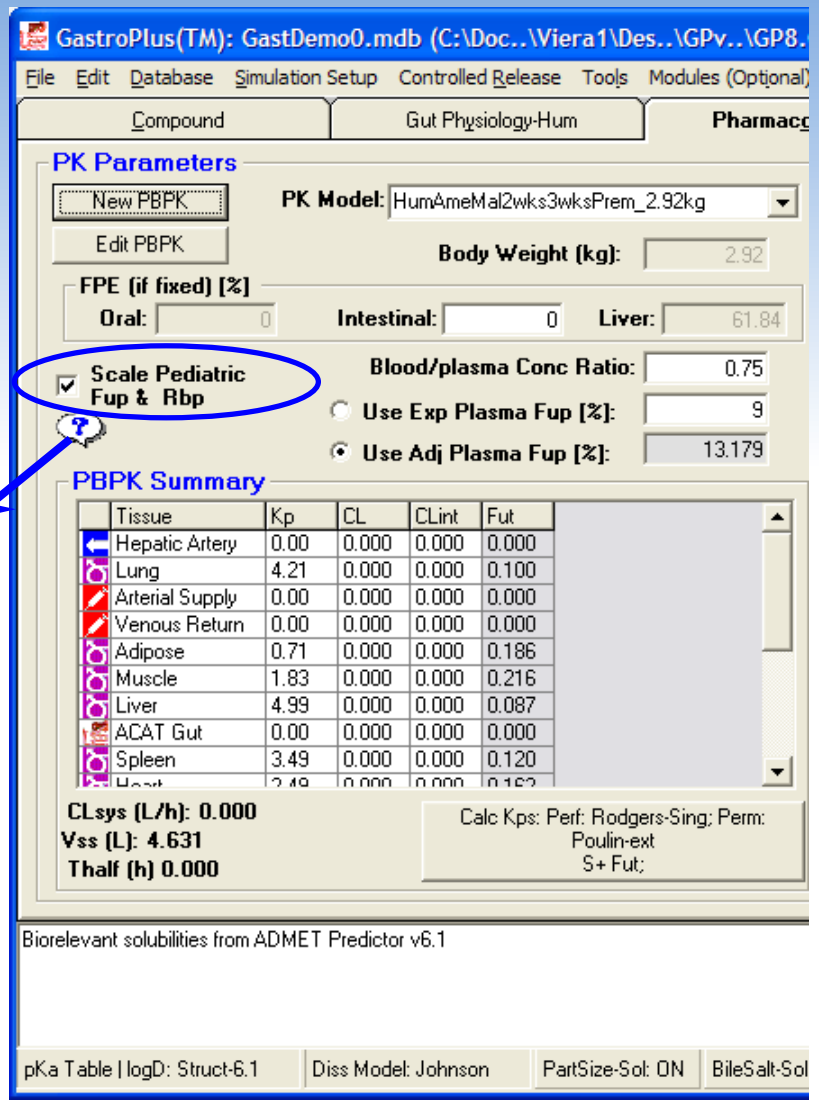
- Includes automatic scaling of Fup and Rbp to account for different hematocrit and plasma protein levels in children than in adults (scaling assumes that entered experimental values represent adult blood and plasma)
- Details of scaling can be reviewed on separate forms











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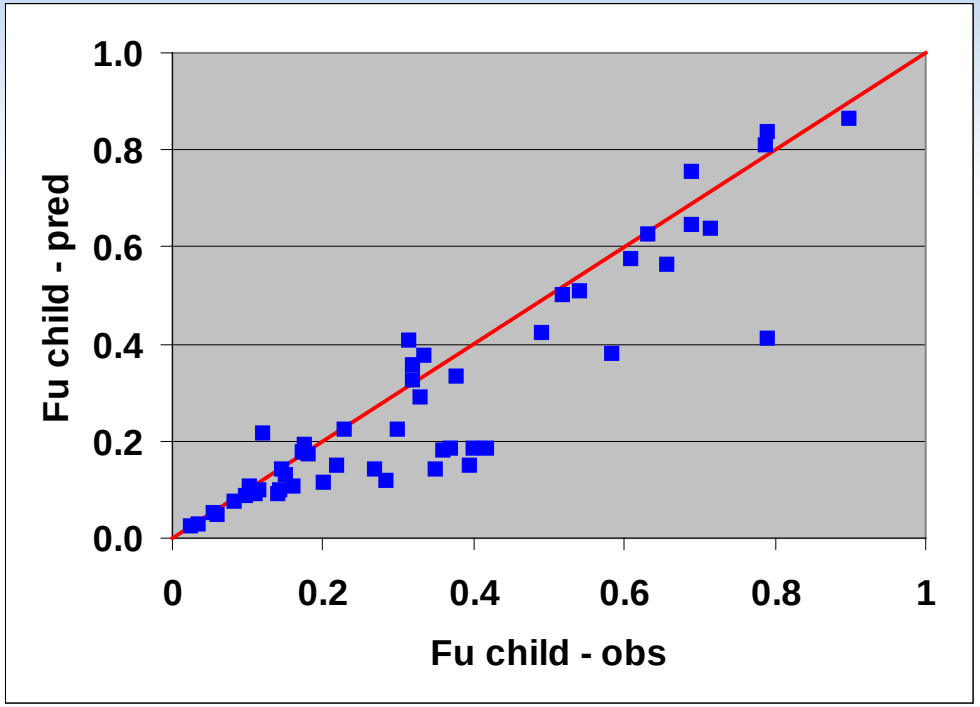
Scaling Pediatric Fup

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)

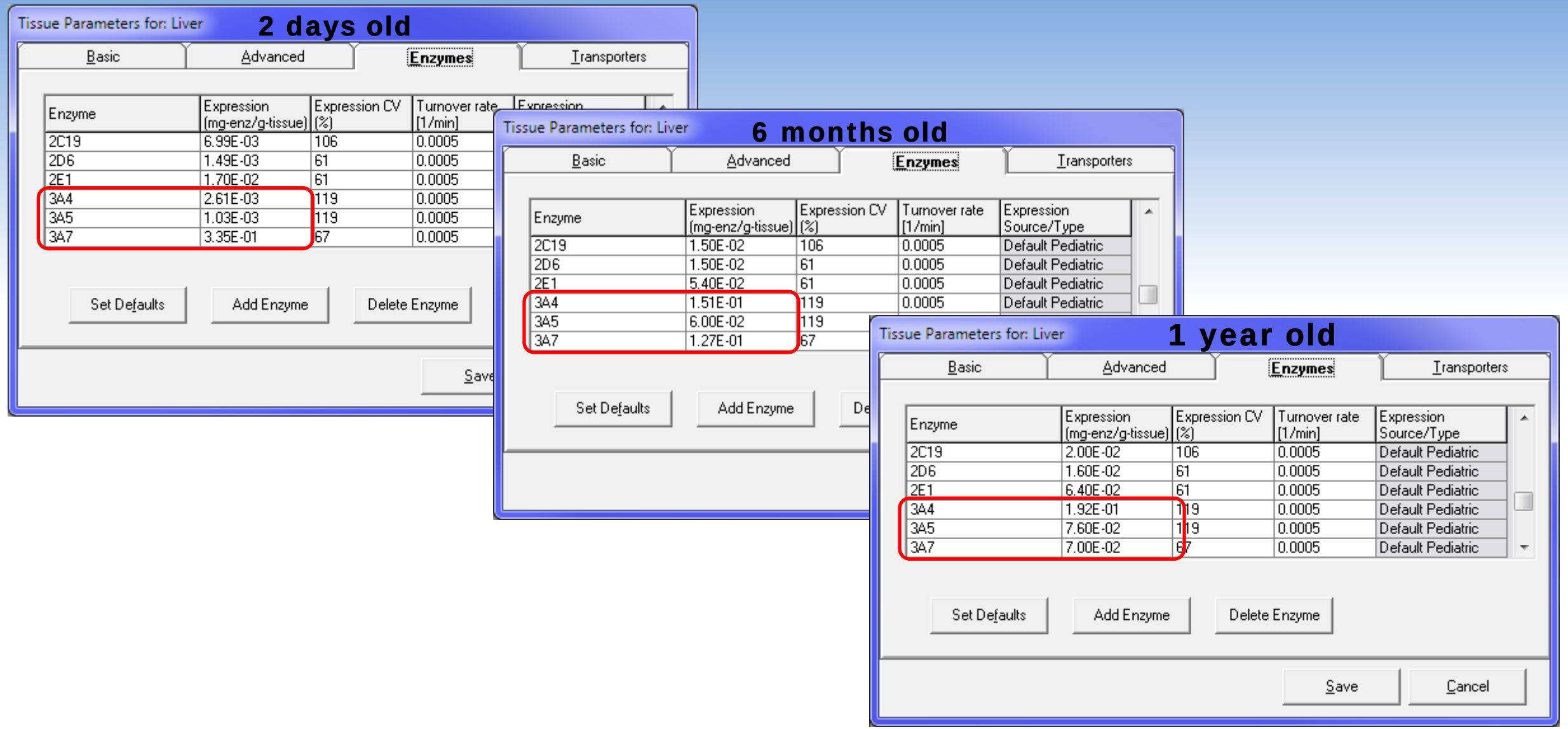
$$fu_{ped} = \frac{1}{1 + \frac{P_{ped}}{P_{adult}} \frac{(1 - fu_{adult})}{fu_{adult}}}$$

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.

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

Save

adult

Tissue Parameters for: Liver

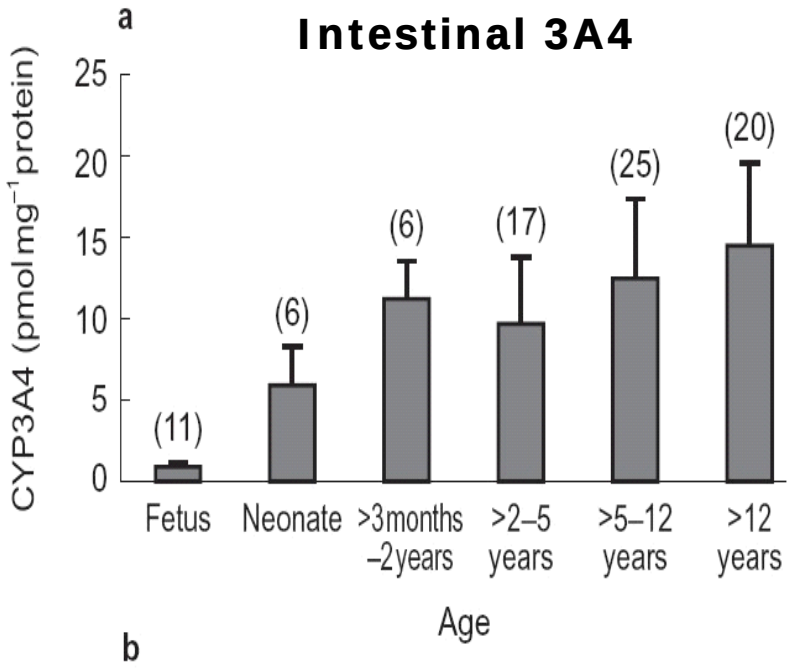
Basic | Advanced | **Enzymes** | Transporters

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

Set Defaults | Add Enzyme | Delete Enzyme

Save | Cancel

Intestinal 3A4



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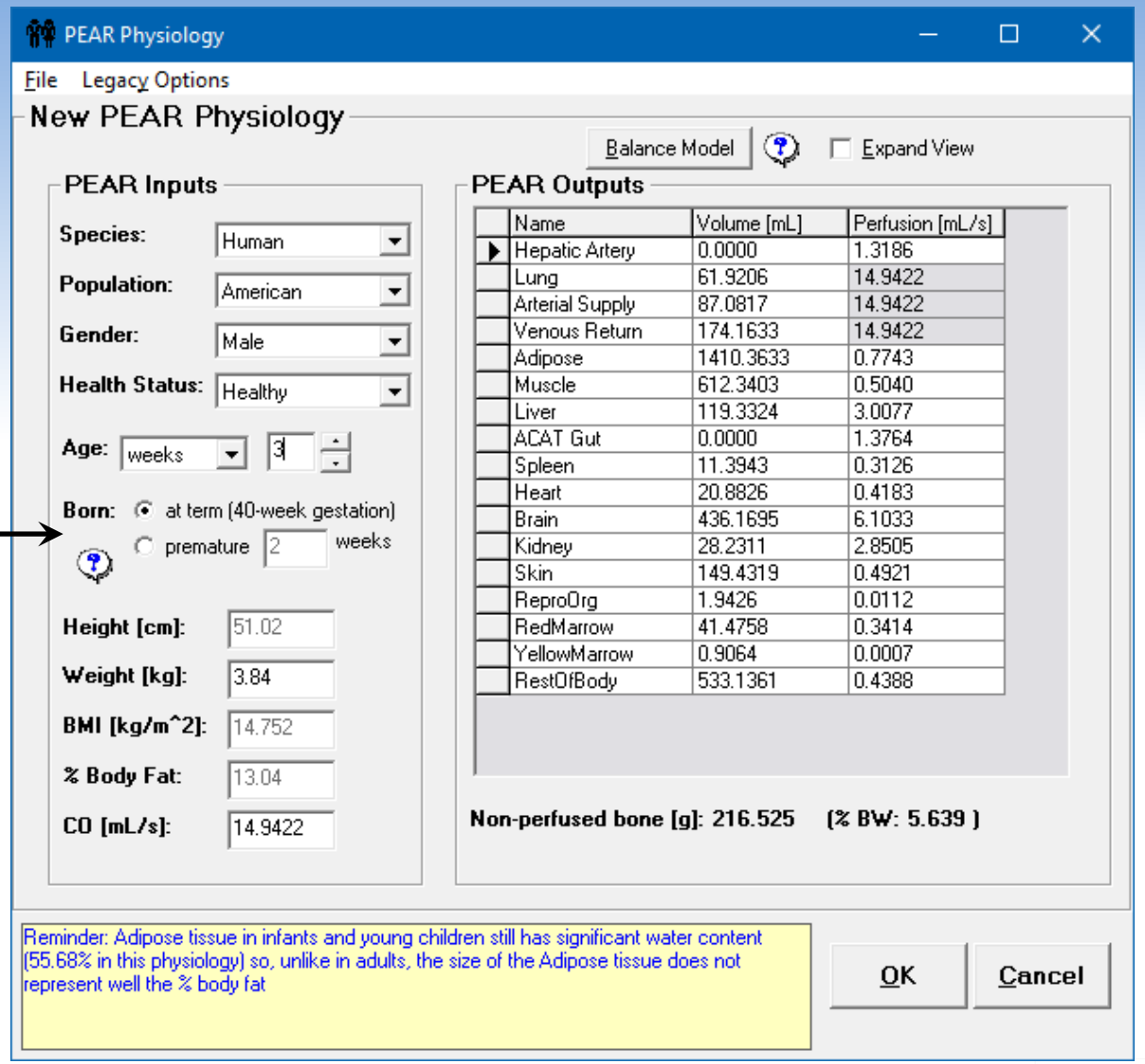
PEAR Physiology: Method

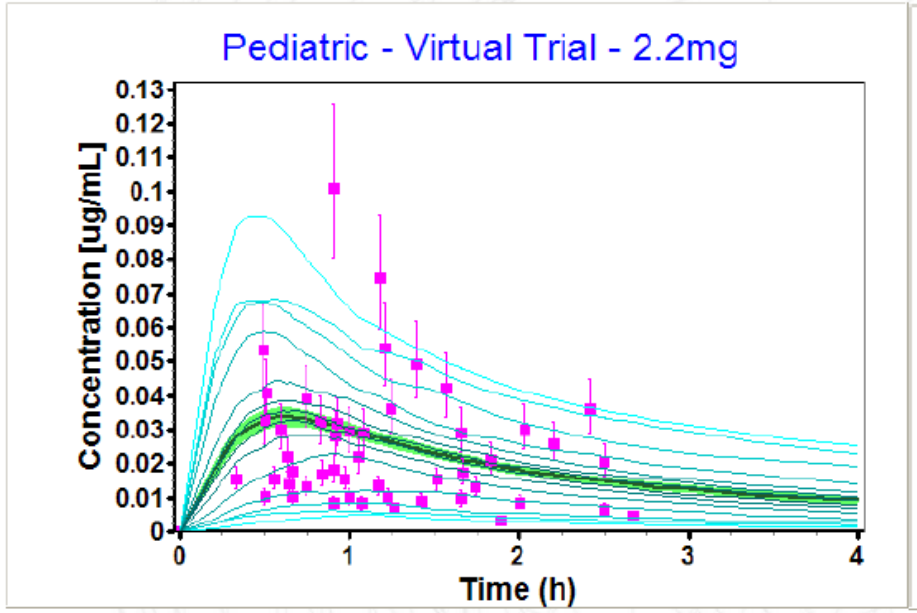
All information is already included in GastroPlus PEAR Physiology module … very easy to create the new pediatric physiologies!

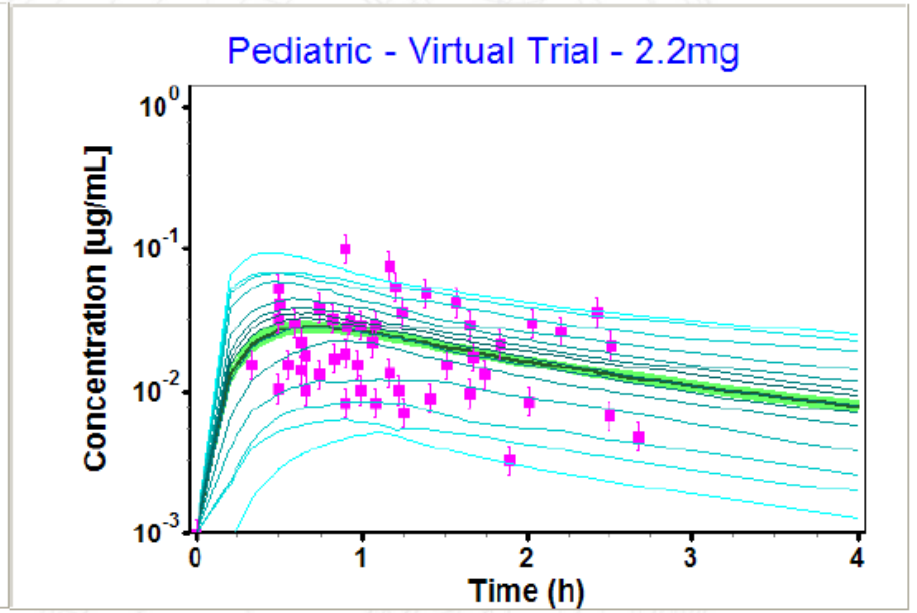
For infants specify born **at term** or **premature** infant (up to 16 weeks premature)
(this option appears only when age is set to less than 1 year old)

Some physiological parameters are dependent on both gestational age and postnatal age (i.e., % body fat, hematocrit, GFR).



Pediatric CL - Midazolam

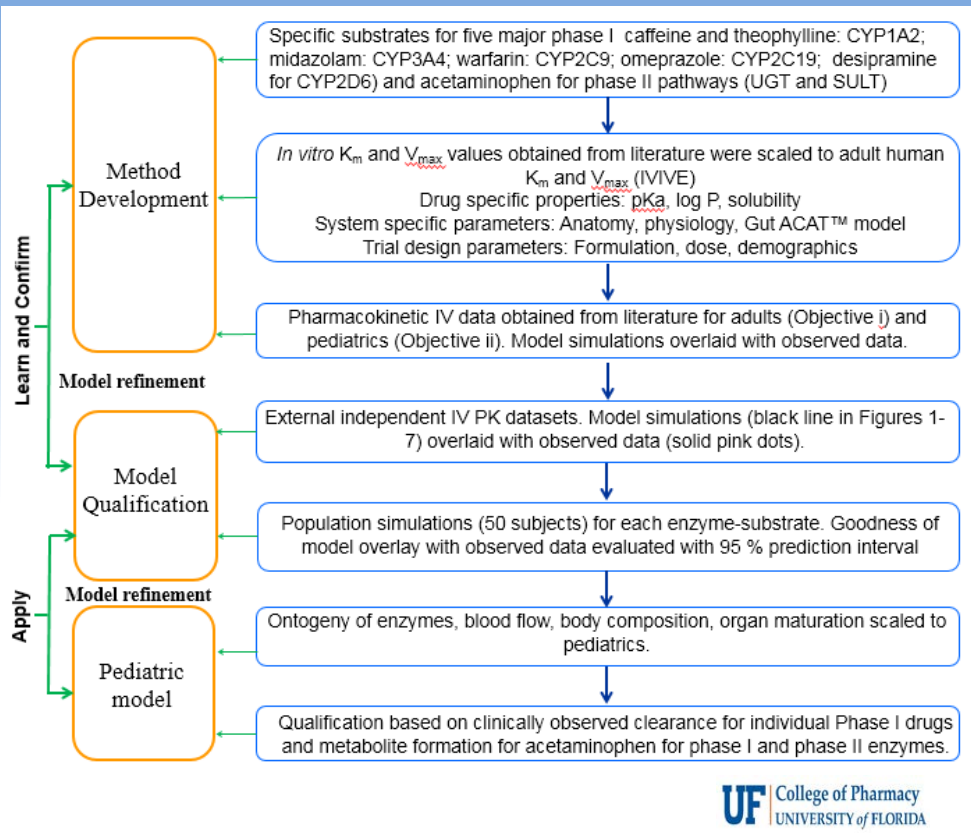


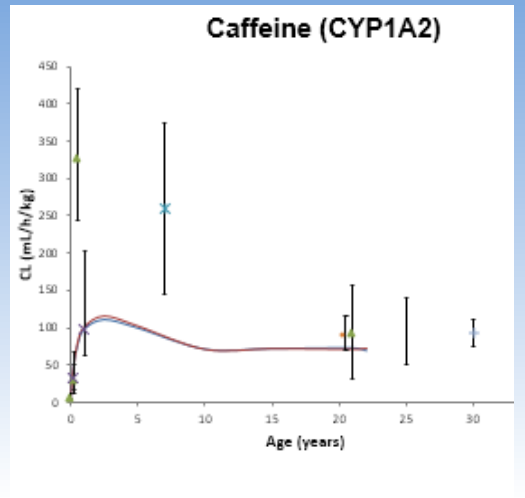


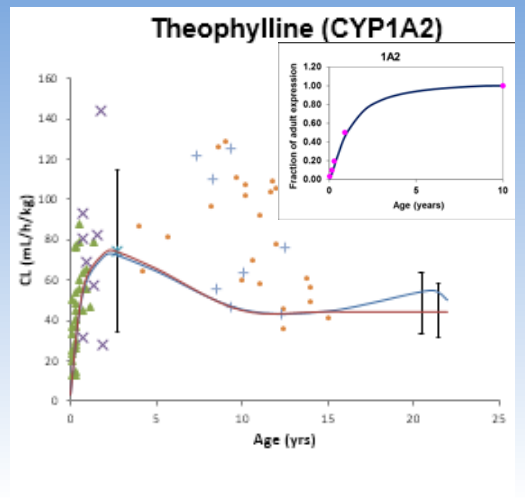
This is a prediction of pediatric population using *in vitro*, *in silico* and adult *in vivo* data and known differences in adult and pediatric physiology. The model was not fitted to pediatric data.

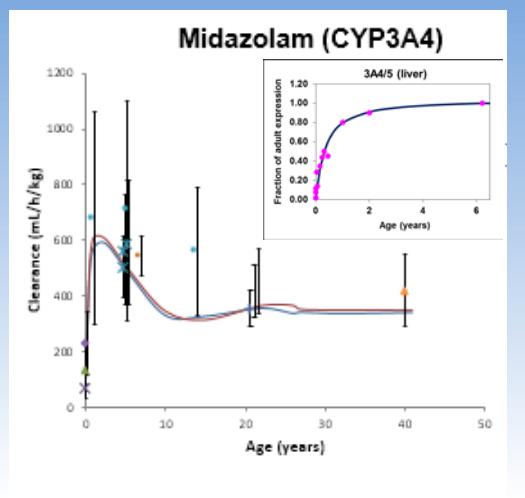
Lukacova – Workshop on Modeling in Pediatric Medicines, 2008

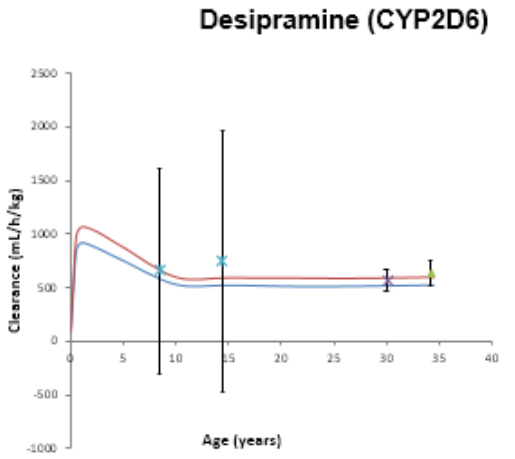
Pediatric CL – metabolism by CYPs

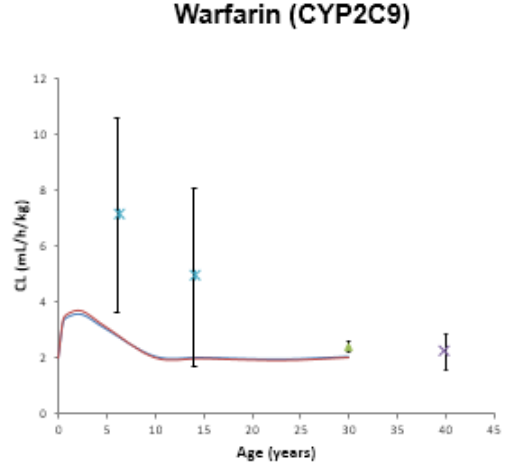


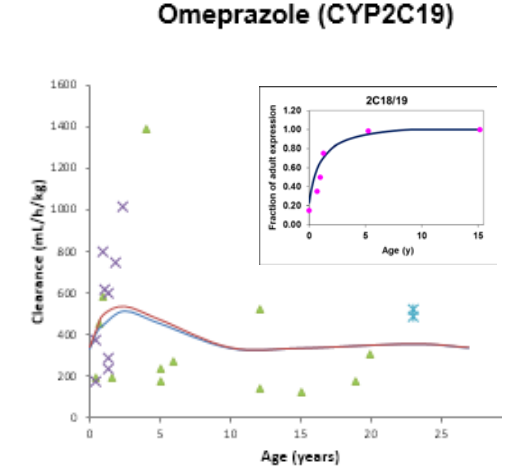












Samant et al. – Poster Presentation (Poster # 111) - ASCPT 2015
also Quantitative Systems Pharmacology pre-conference Poster # QP-16

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Pediatric CL – Acetaminophen

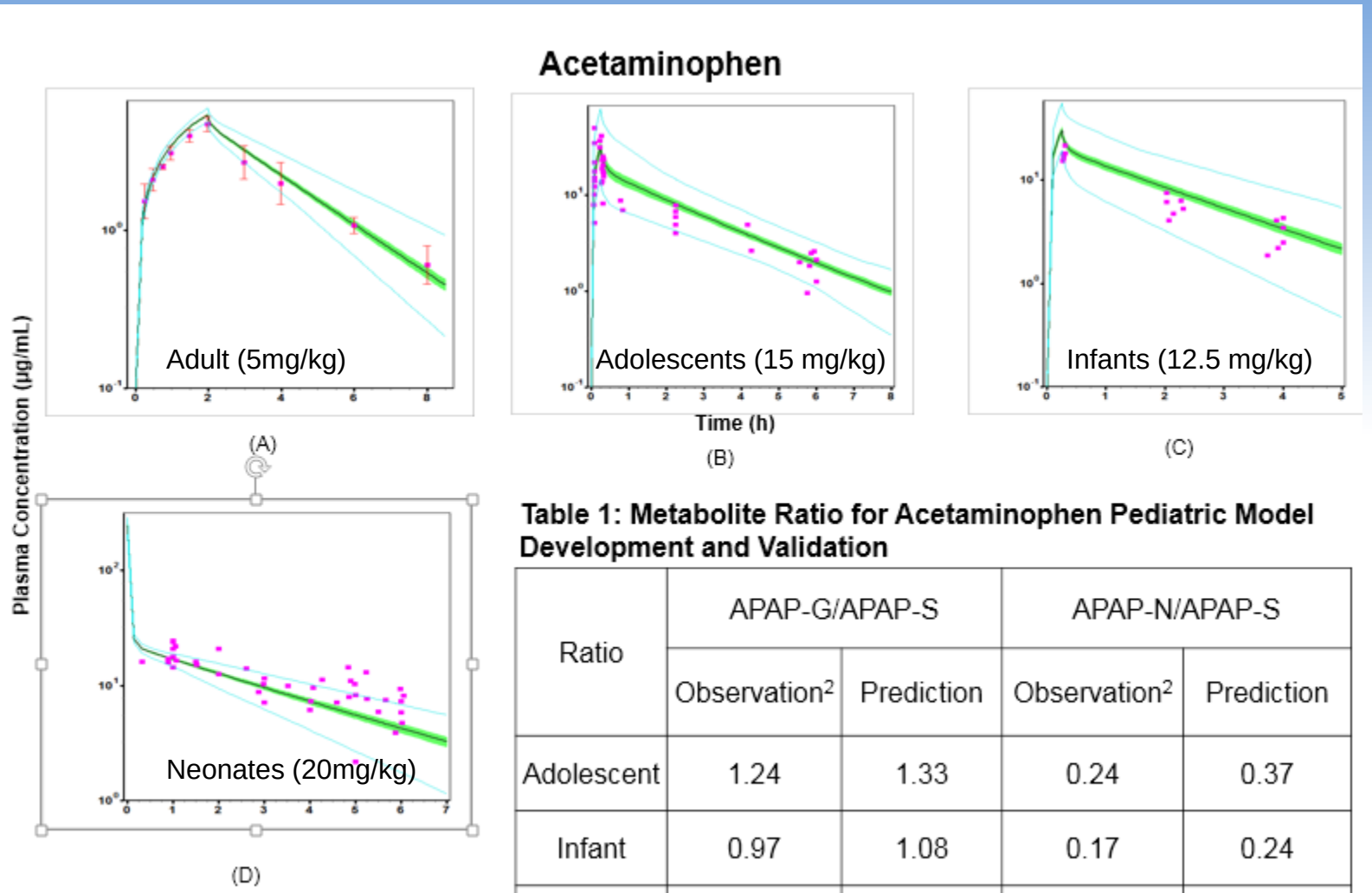

Table 1: Metabolite Ratio for Acetaminophen Pediatric Model Development and Validation

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

UF College of Pharmacy UNIVERSITY of FLORIDA

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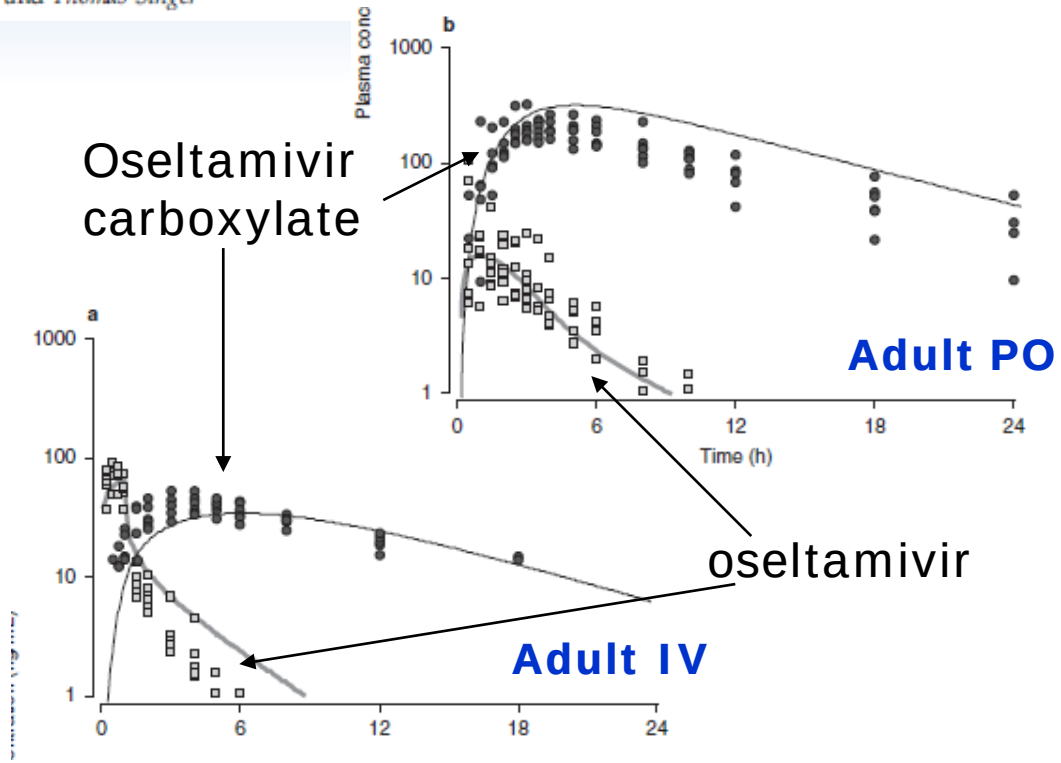
Non-CYP Mediated CL

ORIGINAL RESEARCH ARTICLE

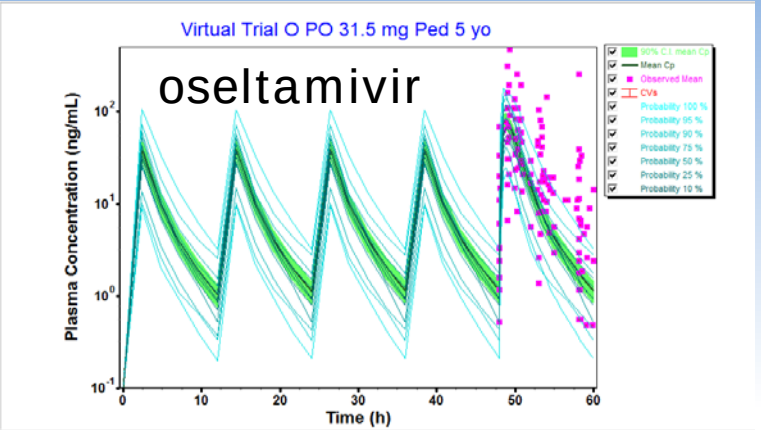
Clin Pharmacokinet 2011; 50 (9): 1-11
0312-5963/11/0009-0001/$49.95/0

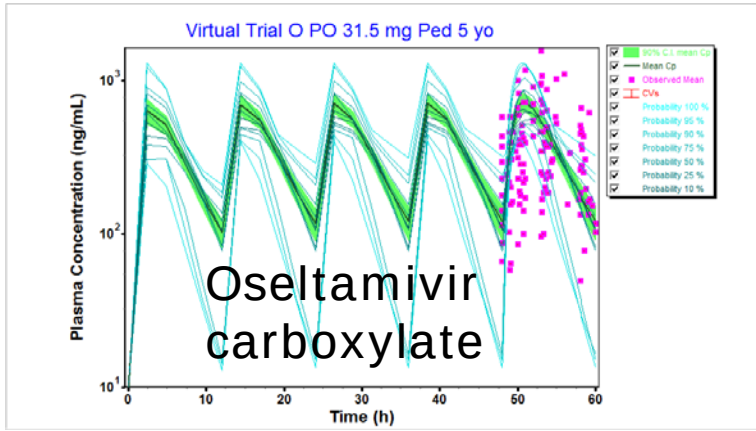
Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants

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





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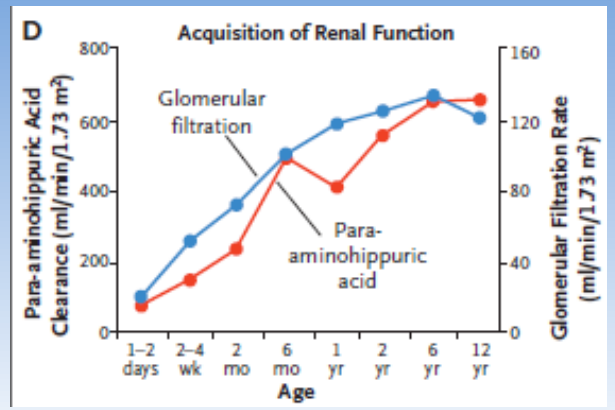
Glomerular Filtration



Kearns – New Engl J Med 2003, 349:1157

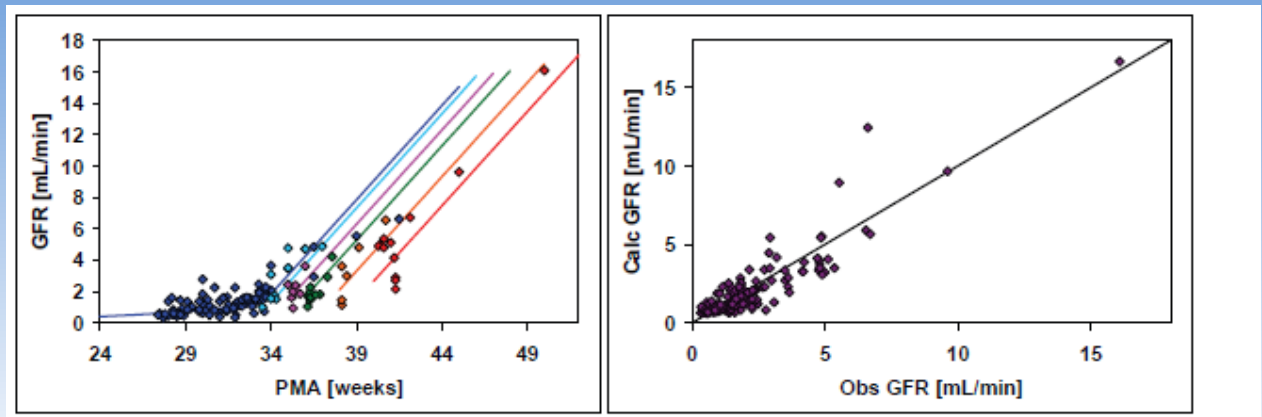
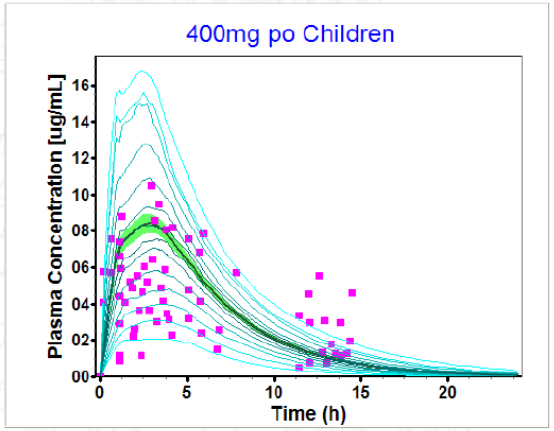


Figure 4-28: Plot of GFR vs post-menstrual age (PMA) for neonates up to 12 weeks old (left) and born after 27-33 (dark blue), 34 (light blue), 35(magenta), 36 (green), 38 (orange) and 40 (red) weeks of gestation (left) and plot of calculated vs observed GFR for the same data (right). Points represent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

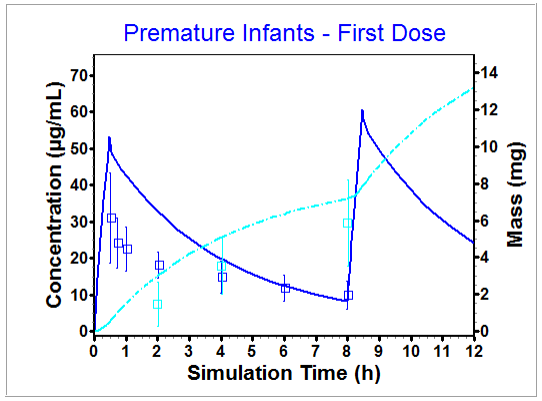
Prediction of gabapentin PK in pediatric population based on fitted adult model and known differences in adult and pediatric physiology

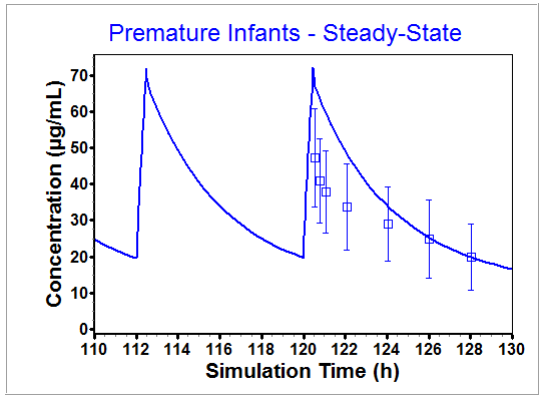


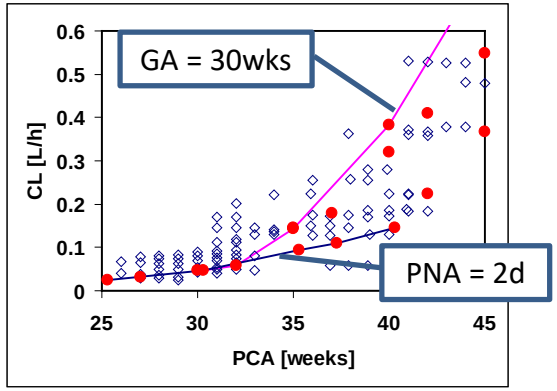
400 mg tablet, 7 yo children

Lukacova – Workshop on Modeling in Pediatric Medicines, 2008

Prediction of vancomycin PK and clearance in infants population based on fitted adult model and known differences in adult and pediatric physiology







20 days old, born 12 weeks premature

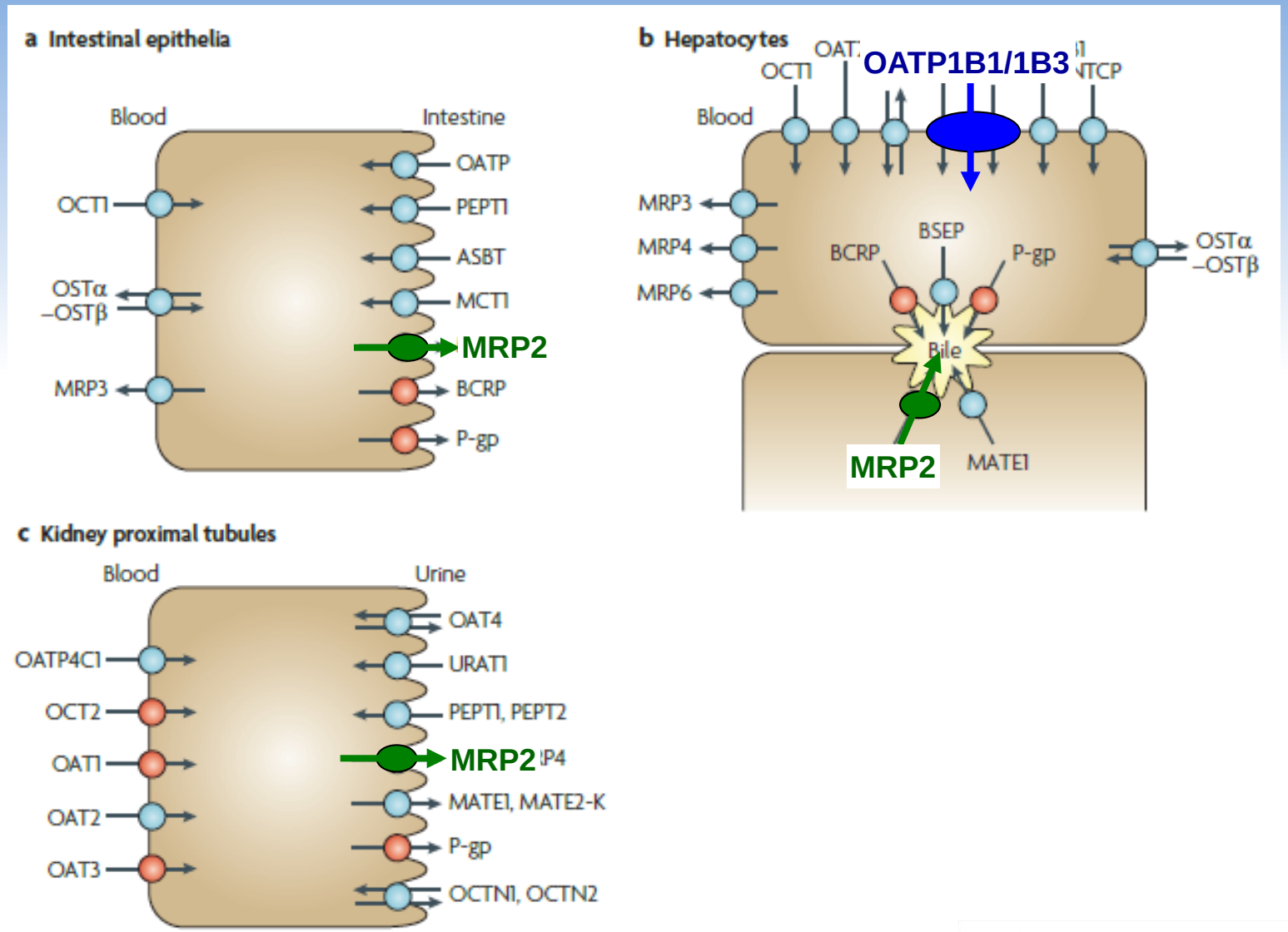
Blue dots – PopPK, red dots - PBPK

Lukacova – Poster presentation, AAPS 2015

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Transporter-Mediated CL: Valsartan

- Transporter-mediated hepatic uptake and biliary secretion
- Substrate for:
  - OATP1B1/1B3 in liver
  - MRP2 – efflux transporter expressed on apical kidney membrane and basolateral membranes in liver, gut and brain
- *in vivo* data available in rat and human (adult and pediatric 1-16 years old)



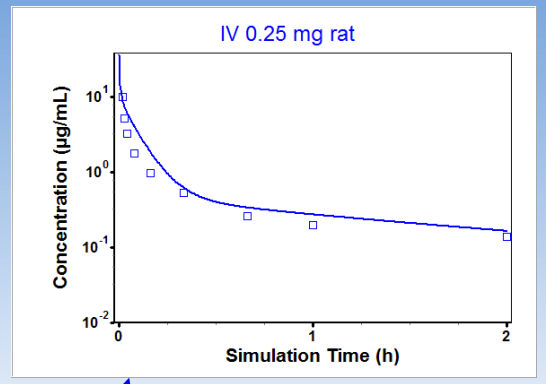
Valsartan : Calibrate Adult PBPK Model

1. Predicted rat IV using *in vitro* data measured in rat hepatocytes
2. Predicted human IV using *in vitro* data measured in human hepatocytes
3. Refined adult PBPK model
4. Used refined adult PBPK model to predict the PK in children

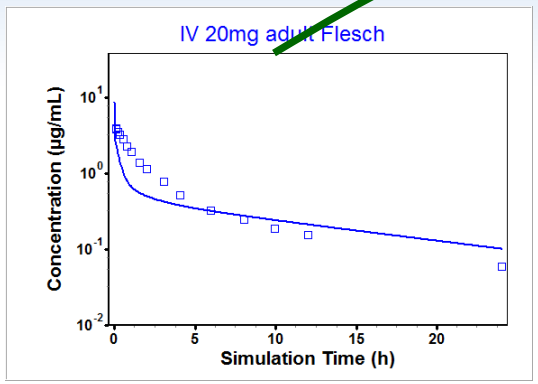
Hepatocytes transport data[a]	Wistar rats ($n = 3$) Mean ± SD	Cryopreserved human hepatocytes lot 77 Mean ± SD
Uptake from plasma (in vitro data)		
$K_{mI,u}$		
(μM)	28.4 ± 3.7	44.4 ± 14.6
(mg/l eq. μg/ml)	12.4 ± 1.6	19.3 ± 6.4
V_{maxI} (pmol/mg/min)	1318 ± 176	394 ± 85
J_{maxI} (mg/s)	0.0126 ± 0.0017	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)	0.0126	0.241
PS_{TCAp} (ml/s)	0	0

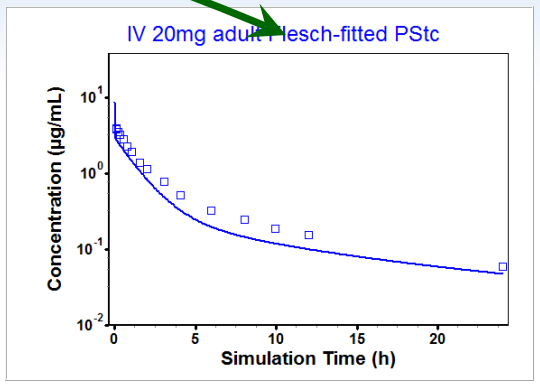
(Poirier – J Pharmacokinet Pharmacodyn 2009, 36:585)

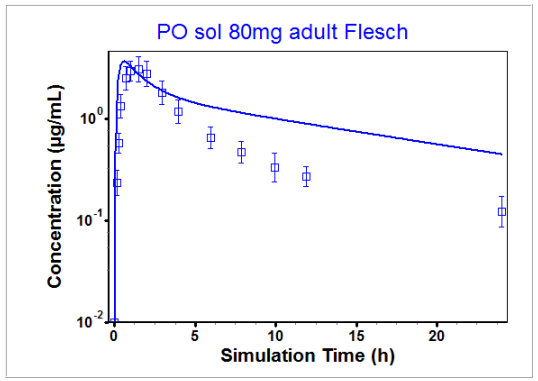
Lukacova – 17th North American ISSX meeting 2011, Atlanta, GA

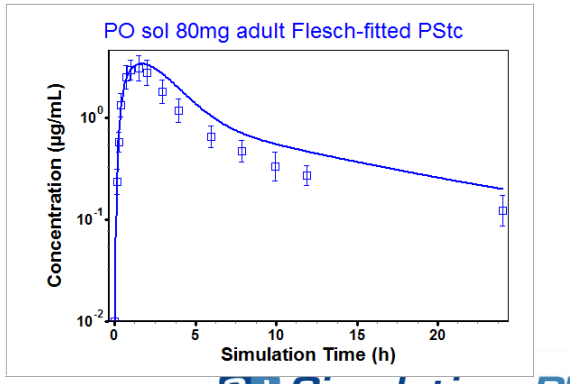


Refine adult model:
- fitted passive diffusion through tissue membranes and intestinal permeability









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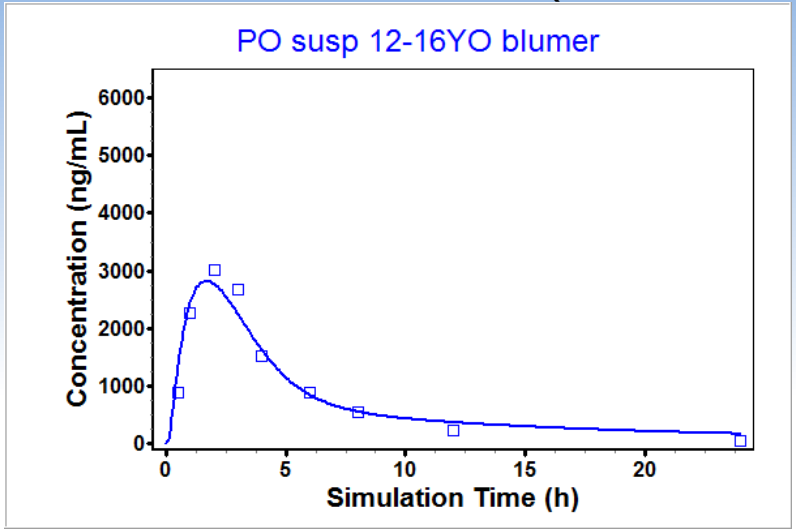
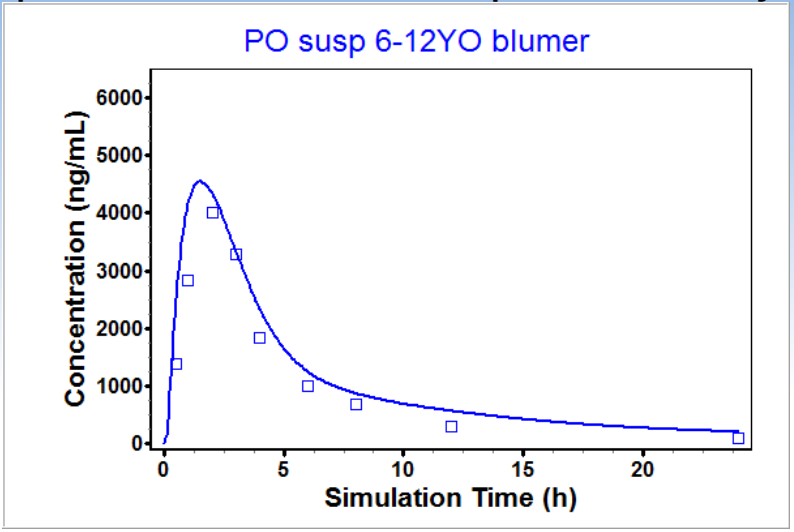
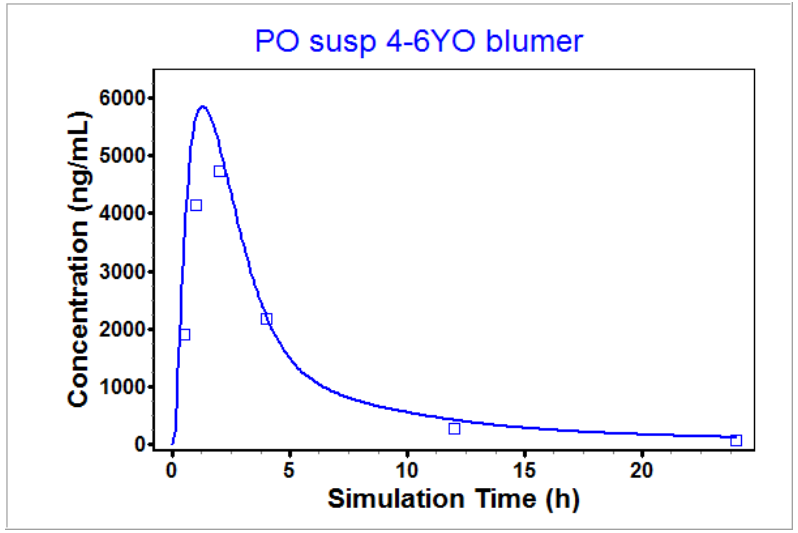
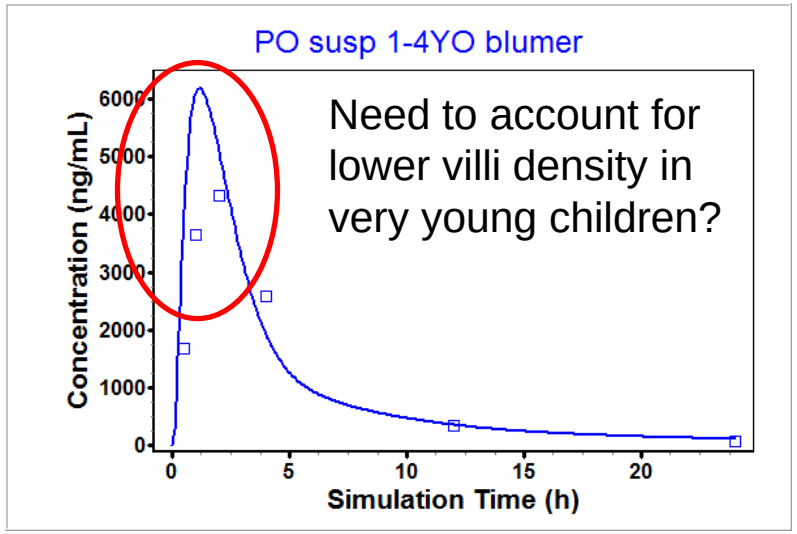
Valsartan: Predict Pediatric Disposition

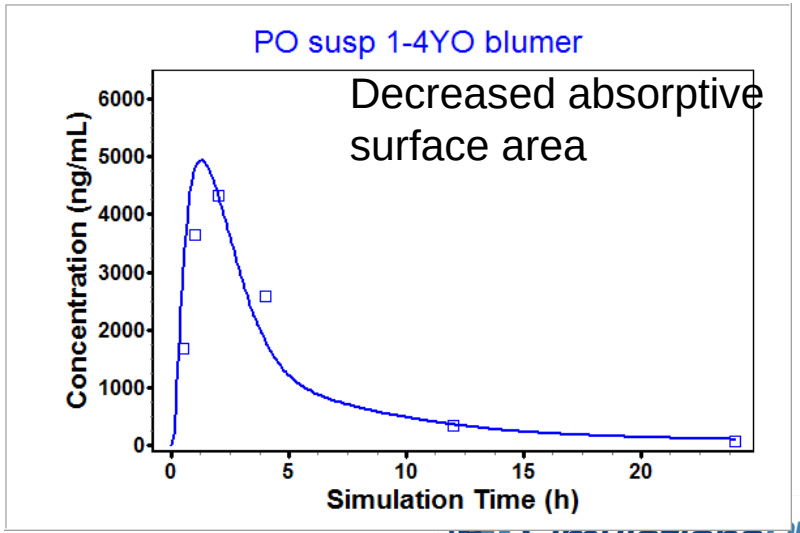
Dosing 2 mg/kg, experimental profiles are averages of 6-7 individuals
(initial assumption – the same transporter density as in adults)







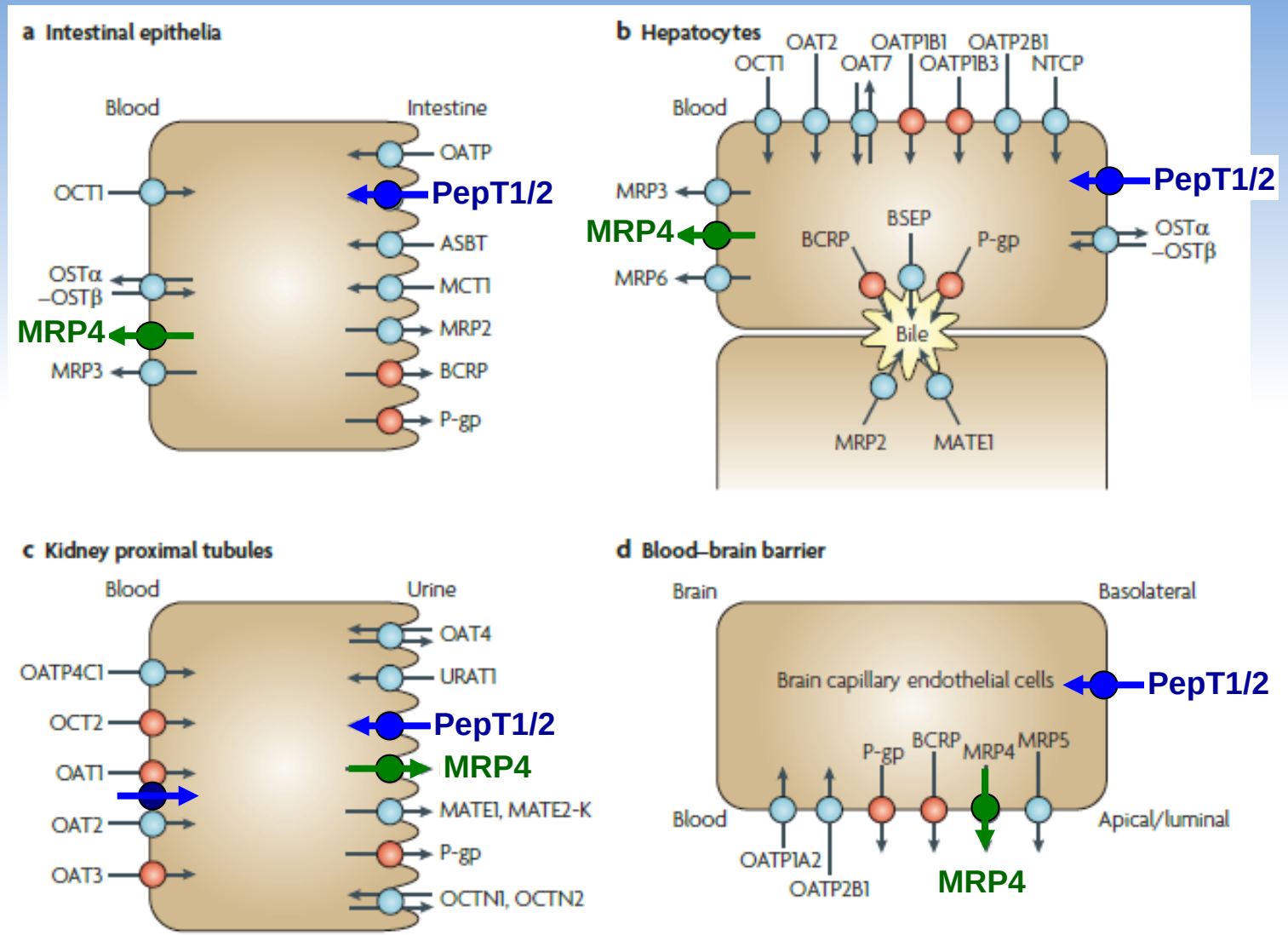




Transporter-Mediated CL: Amoxicillin

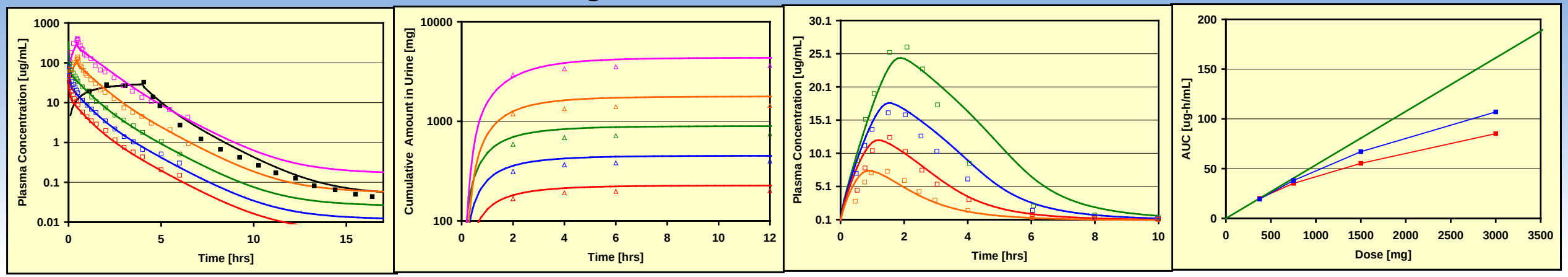
- Eliminated by renal secretion (glomerular filtration and active secretion)
- Substrate for:
  - PepT1/PepT2 – expressed in kidney, liver, brain, gut
  - MRP4 – efflux transporter expressed on apical kidney membrane and basolateral membranes in liver, gut and brain
- *in vivo* data available in human (adult and pediatric for infants up to 3 years)

Akanuma et al. DMD 2011

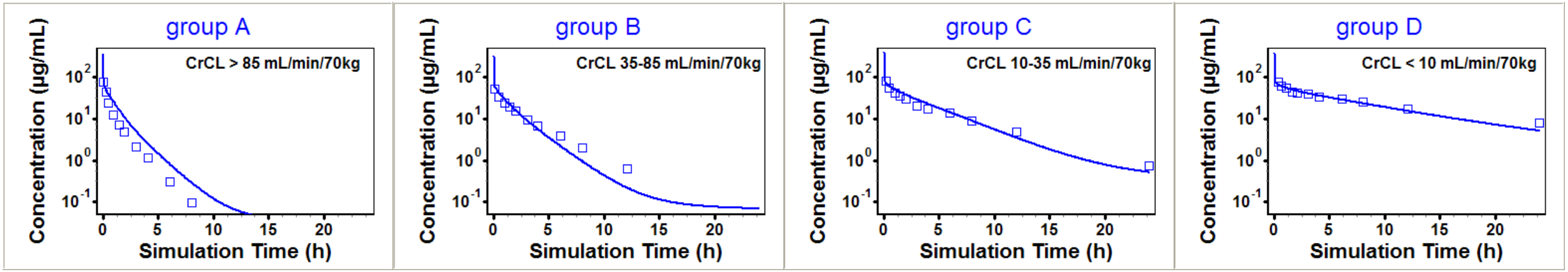


Adult Model Development and Validation

Adult PBPK model was calibrated against in vivo PK data after IV and PO administration in adults



Adult PBPK model was validated by predicting PK in adults with different degrees of renal impairment (manual modifications of GFR and transporter activities based on each groups CrCL)



Lukacova – AAPS Annual Meeting 2012, Chicago, IL

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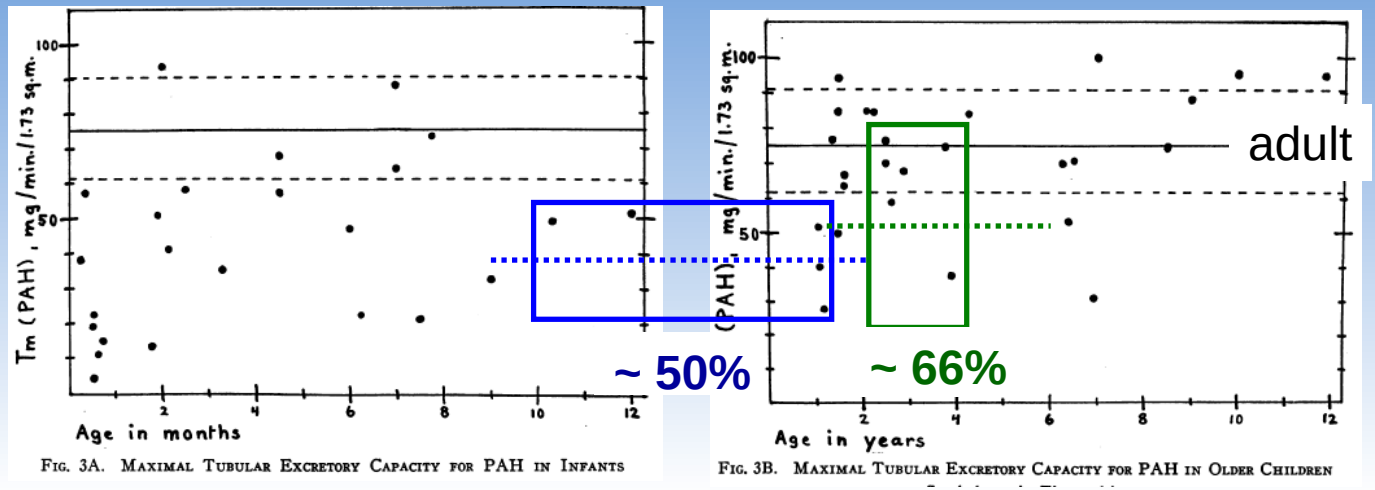
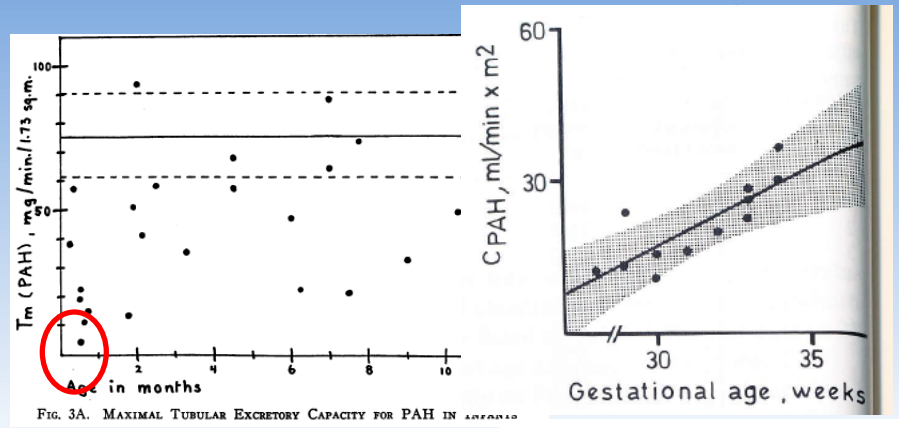
Predict Pediatric Disposition



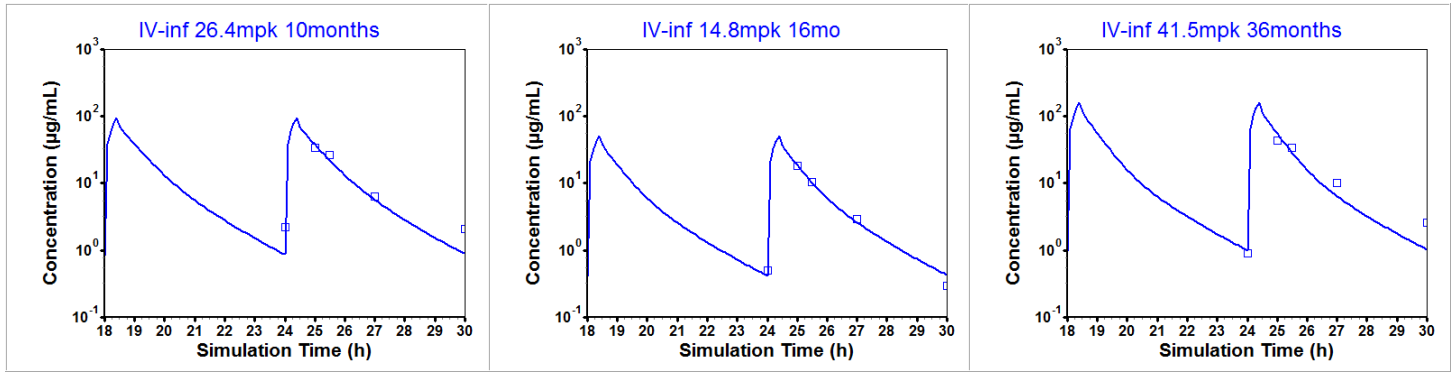
Rubin et al. J Clin Invest 1949



Rubin et al. J Clin Invest 1949

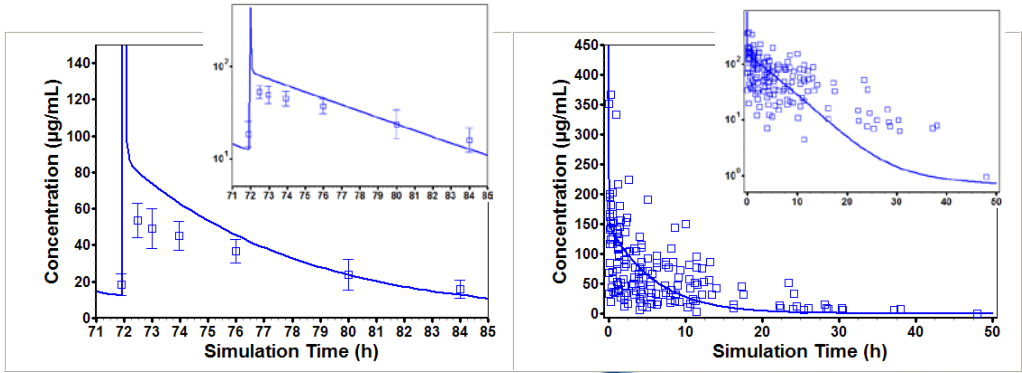
Fawer et al. Helv Paed Acta 1979

Estimating kidney transporter expression from PAH data



3 days, 29 wks GA, 25 mg/kg

1-3 days, 29 wks GA, 50 mg/kg



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Prodrug Administration : Valcyte

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

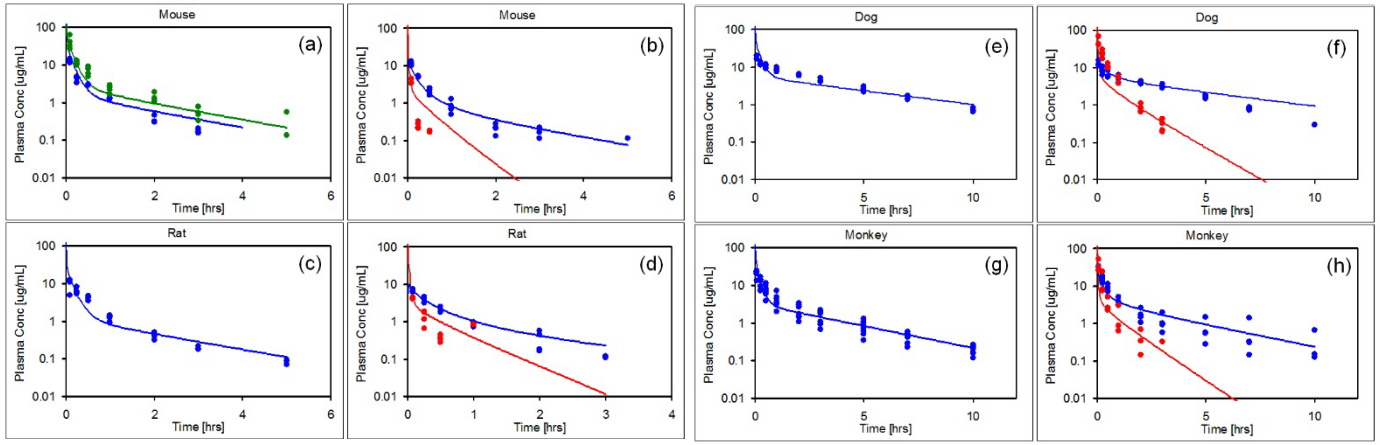
V. Lukacova,[1] P. Goelzer,[2] M. Reddy,[3] G. Greig,[4] B. Reigner,[4] and N. Parrott[5,6]

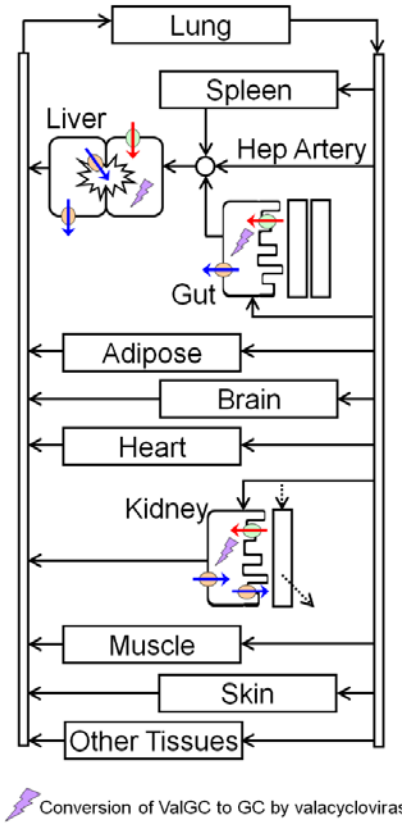
CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 100 NUMBER 6 | DECEMBER 2016

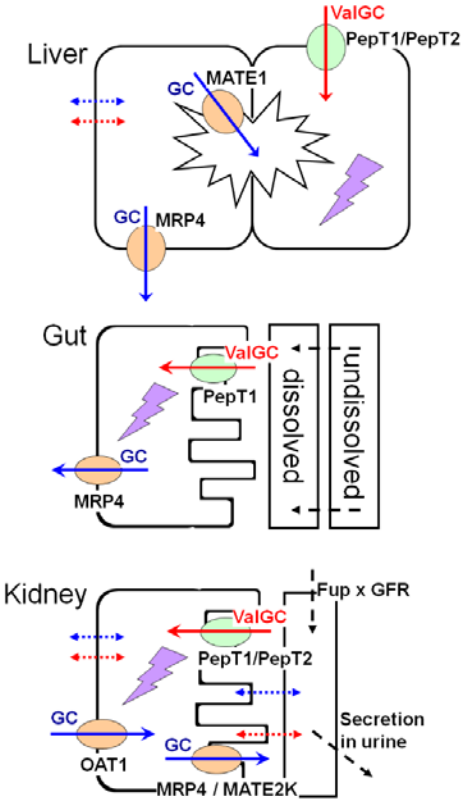
Bottom-up Meets Top-down: Complementary Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling for Regulatory Approval of a Dosing Algorithm of Valganciclovir in Very Young Children

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]

PK data after IV administration in animals was used to determine the systemic disposition mechanisms







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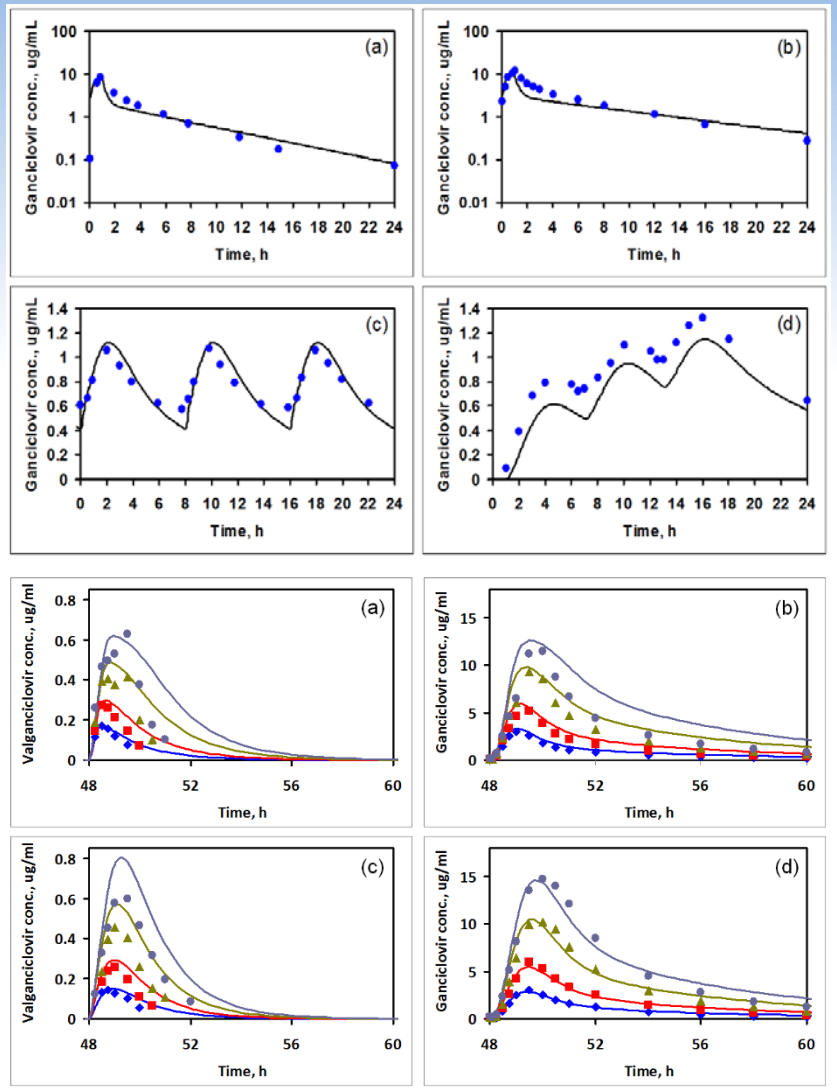
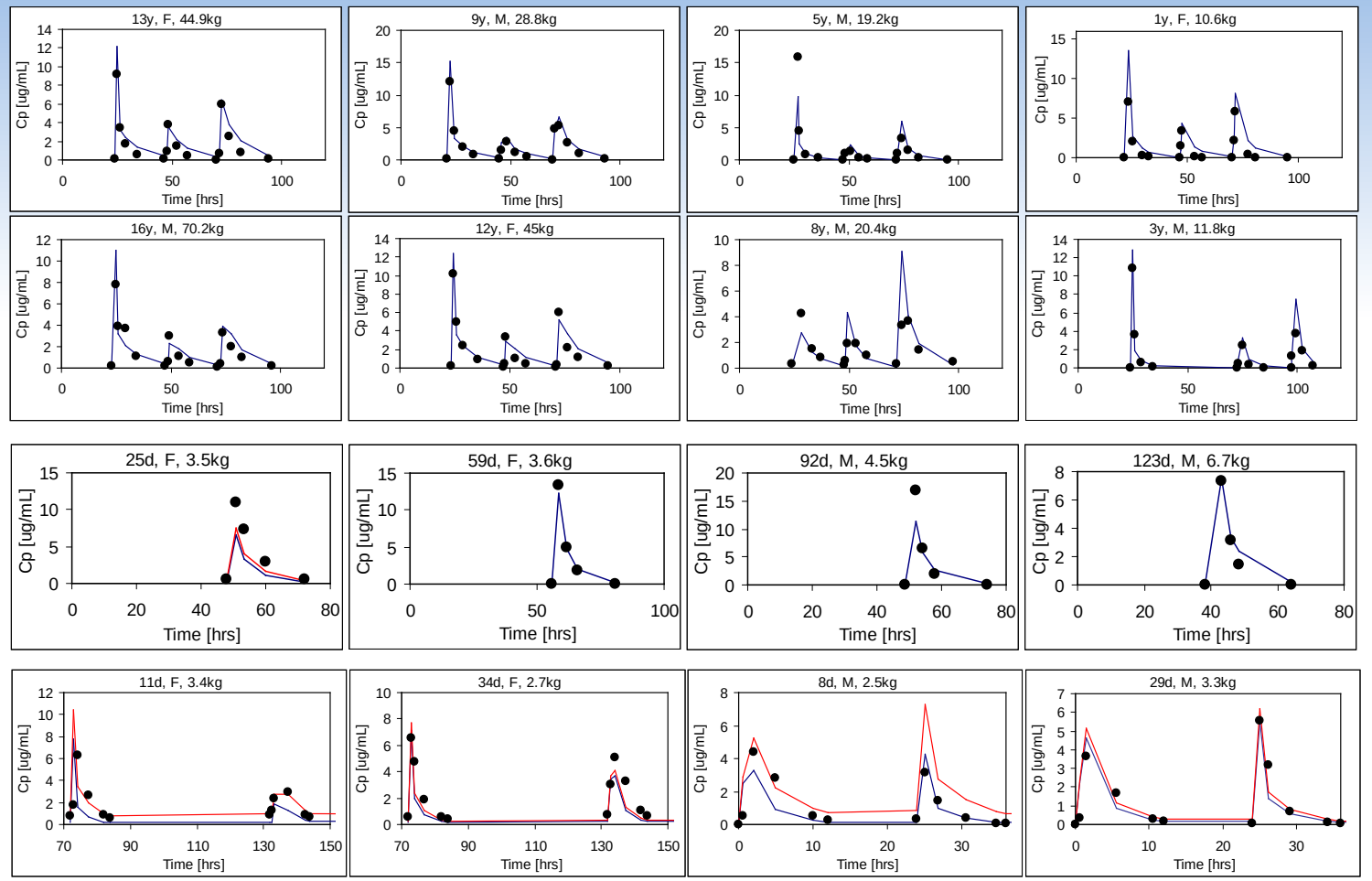
Fit Adult Model and Predict Pediatric PK

Adult PK data after IV and PO administration of ganciclovir and valganciclovir was used to calibrate human PBPK model



Human PBPK model was then used to predict PK in children



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Disease States

Liver Cirrhosis

- Replacement of normal liver tissue with non-functional scar tissue caused by chronic conditions

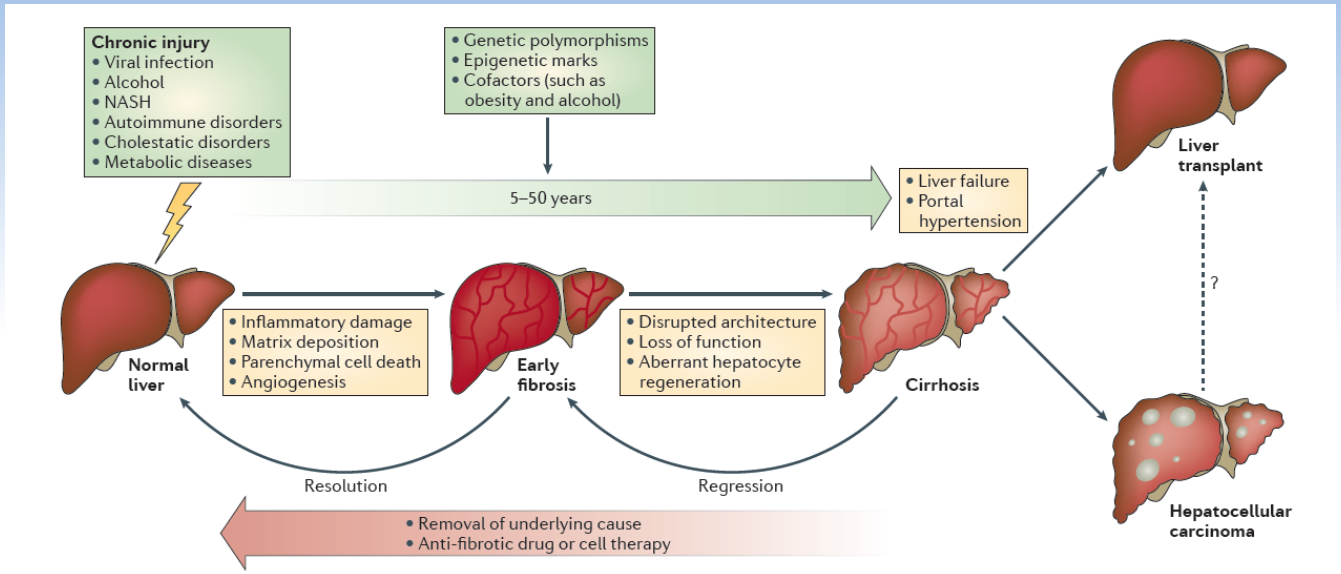


Figure 1: Natural history of chronic liver disease.

From
Liver fibrosis and repair: immune regulation of wound healing in a solid organ
Antonella Pellicoro, Prakash Ramachandran, John P. Iredale & Jonathan A. Fallowfield
Nature Reviews Immunology **14**, 181–194 (2014) | doi:10.1038/nri3623

- Child-Pugh (CP) score is used to classify the degree of disease severity: CP-A (well compensated disease), CP-B (significant functional compromise) & CP-C (decompensated disease)

Physiological Changes In Liver Cirrhosis

Table III. Physiological and biochemical parameter changes associated with liver cirrhosis

Parameter	Control	Child-Pugh score		
		A	B	C
Liver volume fraction	1.0	0.81	0.65	0.53
CYP (ρmol/mg)				
1A2	52	32.9	13.6	6.10
2A6	20	17.7	12.3	6.40
2B6	17	17.0	15.3	13.6
2C8	24	16.6	12.5	7.90
2C9	73	50.4	38.0	24.1
2C18	1.0	0.32	0.26	0.12
2C19	14	4.50	3.60	1.70
2D6	8.0	6.10	2.60	0.84
2E1	61	45.1	29.3	6.71
3A4	137	80.8	53.2	34.2
Gut CYP3A4 (nmol per total gut)	70	59	40	25
Albumin (g/L)	44.7	41.1	33.9	26.3
α_1-acid glycoprotein (g/L)	0.80	0.57	0.52	0.46
Haematocrit (%)	40.9	36.6	32.9	31.9
Cardiac output (L/h)	306	355	403	431
Portal blood flow (L/h)				
males	58.2	52.9	36.9	32.2
females	65.8	59.9	41.7	36.4
Hepatic arterial blood flow (L/h)	19.9	28	32.3	38.1
Q_{villi} (L/h)	18.4	23.7	28.0	36.6
GFR (mL/min)	120	83.7	69.9	66.5

CYP = cytochrome P450; **GFR** = glomerular filtration rate; $\mathbf{Q_{villi}}$ = villous blood flow.

Johnson – Clin Pharmacokinet 2010, 49:189-206

Li – CPT Pharmacometrics Syst. Pharmacol. 2015, 4:338-349

Table 3 Physiological changes associated with liver cirrhosis (fractions of healthy control values ± standard deviation)[a]

Parameter		Child–Pugh Grade A	B	C
Albumin concentration		0.84±0.15	0.69±0.15	0.53±0.15
Hematocrit (%)[b]		38±5.0	34±5.7	34±5.5
Cardiac output		1.1±0.39	1.2±0.34	1.3±0.30
Portal vein blood flow		0.72±0.57	0.60±0.61	0.13±0.57
Splenic vein blood flow		1.2±0.29	1.5±0.52	1.5±0.54
Liver arterial blood flow		1.5±1.1	1.7±1.5	2.1±1.9
Functional liver size		0.91±0.26	0.81±0.26	0.64±0.22
Liver transporter mRNA level[c]	OATP1B1	0.65±0.49	(0.65±0.49)	(0.65±0.49)
	OATP1B3	0.73±0.59	(0.73±0.59)	(0.73±0.59)
	OATP2B1	0.77±0.47	(0.77±0.47)	(0.77±0.47)
	MRP2	0.54±0.48	(0.54±0.48)	(0.54±0.48)
	BCRP	0.58±0.45	(0.58±0.45)	(0.58±0.45)
	BSEP	1.1±0.51	(1.1±0.51)	(1.1±0.51)
	MDR1	1.1±0.49	(1.1±0.49)	(1.1±0.49)
	MDR3	2.3±0.45	(2.3±0.45)	(2.3±0.45)
	MATE1	0.65±0.52	(0.65±0.52)	(0.65±0.52)
Uptake transporter activity[d]		0.78±0.070	0.31±0.033	(0.31±0.033)
Efflux transporter activity[d]		0.69±0.12	2.6±17	(2.6±17)

Table I. Physiological changes associated with liver cirrhosis

Parameter	Child-Pugh class A	B	C
Blood flow			
portal[a]	0.40	0.36	0.04
hepatic arterial[b]	1.3	2.3	3.4
renal[c]	0.88	0.65	0.48
other organs[d]	1.75	2.25	2.75
Cardiac index[e]	1.11	1.27	1.36
Albumin[f]	0.81	0.68	0.50
α_1-Acid glycoprotein[g]	0.60	0.56	0.30
Haematocrit value[h]	0.39	0.37	0.35
Functional liver mass[i]	0.69	0.55	0.28
Hepatic enzymes[j]			
CYP3A4	1	0.4	0.4
CYP1A2	1	0.1	0.1
CYP2E1	1	0.83	0.83
GFR[k]	1	0.70	0.36

Edginton – Clin Pharmacokinet 2008, 47:743-752

Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a condition characterized by a gradual loss of kidney function over time

CKD Classification:

Stage	Description	GFR [ml/min/1.73m^2]
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3a	Moderate ↓ GFR	45-59
3b		30-44
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15

Physiological changes apart from a decrease in GFR:

Table 1. Key physiological and biochemical parameter changes associated with differing degrees of renal impairment.

Parameter	Control	GFR (ml/min/1.73 m²)	
		30–59	<30
CYP1A2 (pmol/mg)	52 [58]	33 [63,129–131]	24 [129–131]
CYP2C8 (pmol/mg)	24 [58]	20 [64]	13 [64]
CYP2C9 (pmol/mg)	73 [58]	63 [65]	29 [65]
CYP2C19 (pmol/mg)	14 [58]	5.5 [66]	2.3 [66]
CYP2D6 (pmol/mg)	8.0 [58]	4.6 [67,132,133]	2.1 [132,133]
CYP3A4 (pmol/mg)	137 [58]	73 [68,134,135]	62 [68,135]
Albumin (g.l^{-1}) M F	44.9 [205] 41.8 [205]	41.6 [136,137,205] 38.8 [136,137,205]	37.6 [136,137,205] 35.0 [136,137,205]
Hematocrit (%) M F	43.0 [43] 38.0 [43]	39.7 [43] 33.2 [43]	36.5 [43] 31.3 [43]
Gastric emptying time (h)	0.40 [35]	0.55 [19]	0.65 [19]

F: Female; GFR: Glomerular filtration rate; M: Male.

Yeo et al., Expert Rev. Clin. Pharmacol. 2010, 4(2):261-274

Decrease in hepatic and renal uptake transporter activity (e.g. OATP, OAT)

Zhao et al., J Clin Pharmacol 2012, 52:91S-108S; Hsu et al., Clin Pharmacokinet 2014, 53:283-293

Obesity

GastroPlus follows WHO (adults) and CDC (children) classifications of obesity

Table 4.3: Classification of overweight and obesity for adults by the body mass index (BMI):

BMI (kg/m^2)	Description	Risk of co-morbidities
<18.5	Underweight	Low
18.5-24.99	Healthy	Average
25-29.99	Overweight	Mildly increased
30-39.99	Obese(combined Obese class I and II)	Moderate-Severe
>40	Morbidly obese(Obese class III)	Very severe

Table 4.4: Classification of overweight and obesity for children by the body mass index (BMI):

Description	Percentile Range
Underweight	$< 5^{th}$ percentile
Healthy	$5^{th} – 85^{th}$ percentile
Overweight	$85^{th} – 95^{th}$ percentile
Obese	$>95^{th}$ percentile

Physiological changes in:

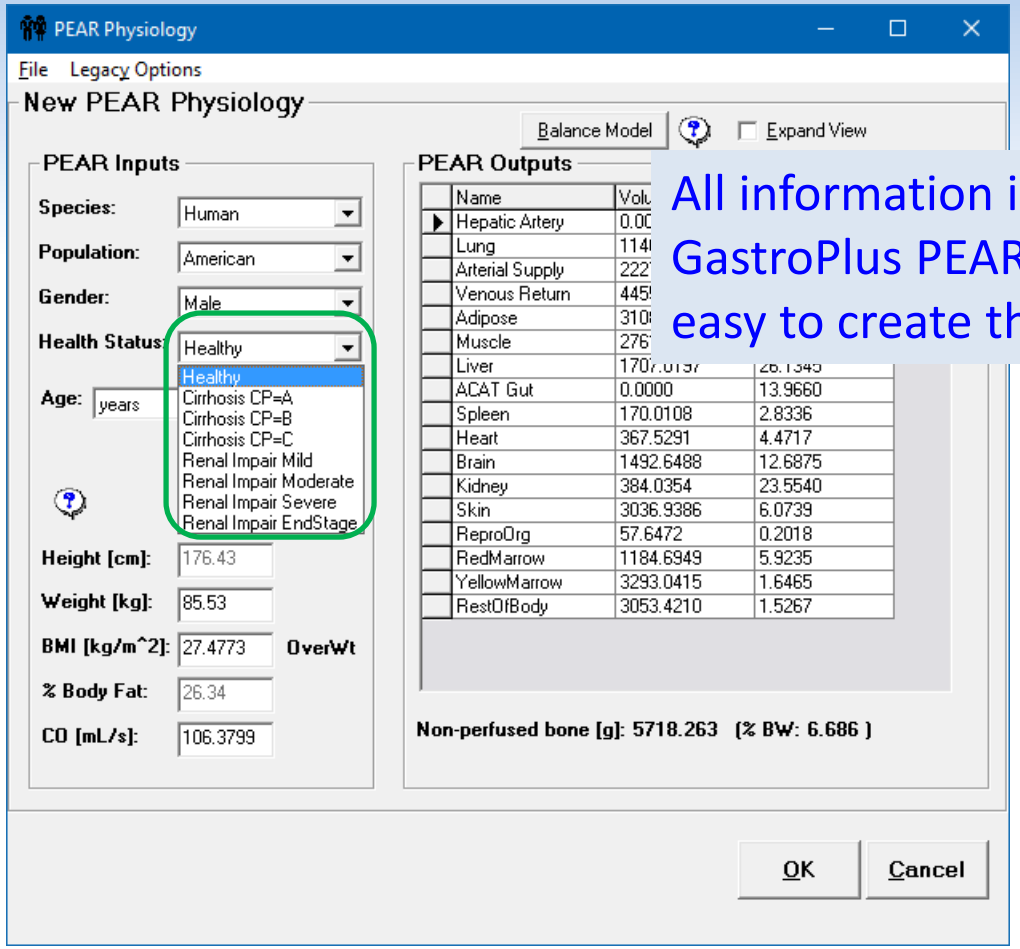
- Body and tissue composition
- Cardiac output and tissue blood flows
- GFR
- Hepatic CYP450 expressions

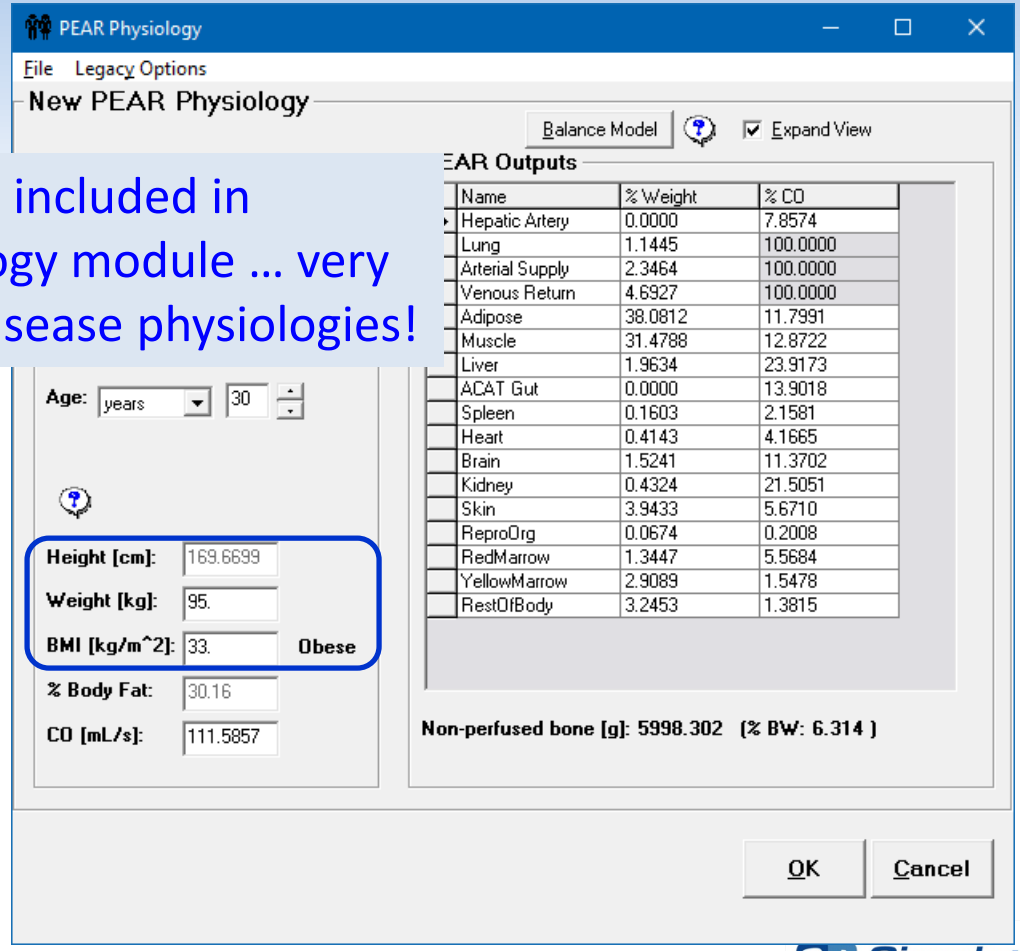
PEAR – Disease Conditions

For hepatic and renal impairment, user has an option to select a group of patients depending on severity of the disease

Based on combination of Height, Weight and BMI, algorithms account for normal, overweight and obese subjects when creating physiologies

All information is already included in GastroPlus PEAR Physiology module … very easy to create the new disease physiologies!





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Example: Buspirone

Absorption:

- Rapidly and almost complete absorption
- Mean absolute oral bioavailability is approximately 4%, ranging from 1.5-13%.
- C_{max} of 1-6 ng/mL and T_{max} of 0.13-1.5

Distribution:

- Mean volume of distribution of 5.3 L/kg
- 95% bound to plasma proteins

Metabolism:

- Extensive first pass metabolism
- Mainly metabolized by CYP3A4

Elimination:

- Less than 1% of an administered dose was recovered as unchanged drug in urine
- Mean elimination half-life = 2-3 hrs

Ref: Mahmood et al., Clin Pharmacokinet 1999 Apr; 36 (4): 277-287

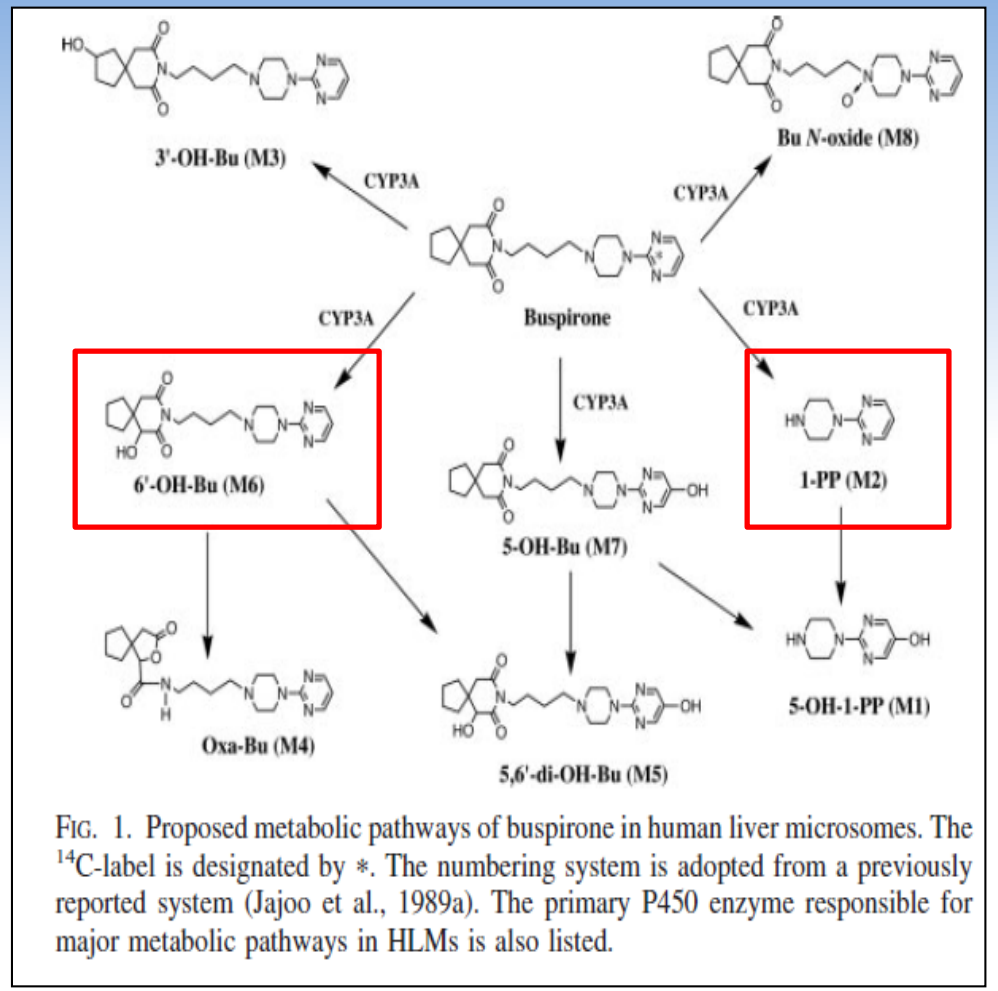


FIG. 1. Proposed metabolic pathways of buspirone in human liver microsomes. The ^{14}C-label is designated by *. The numbering system is adopted from a previously reported system (Jajoo et al., 1989a). The primary P450 enzyme responsible for major metabolic pathways in HLMs is also listed.

Ref: Zhu et al., DMD 33; 500–507, 2005

Available *in vivo* Data: Healthy Subjects

Baseline model for healthy subjects was built using *in silico, in vitro* and fitted (where *in silico* and *in vitro* estimates were not available) parameter values to describe PK of buspirone and two major metabolites after different PO doses

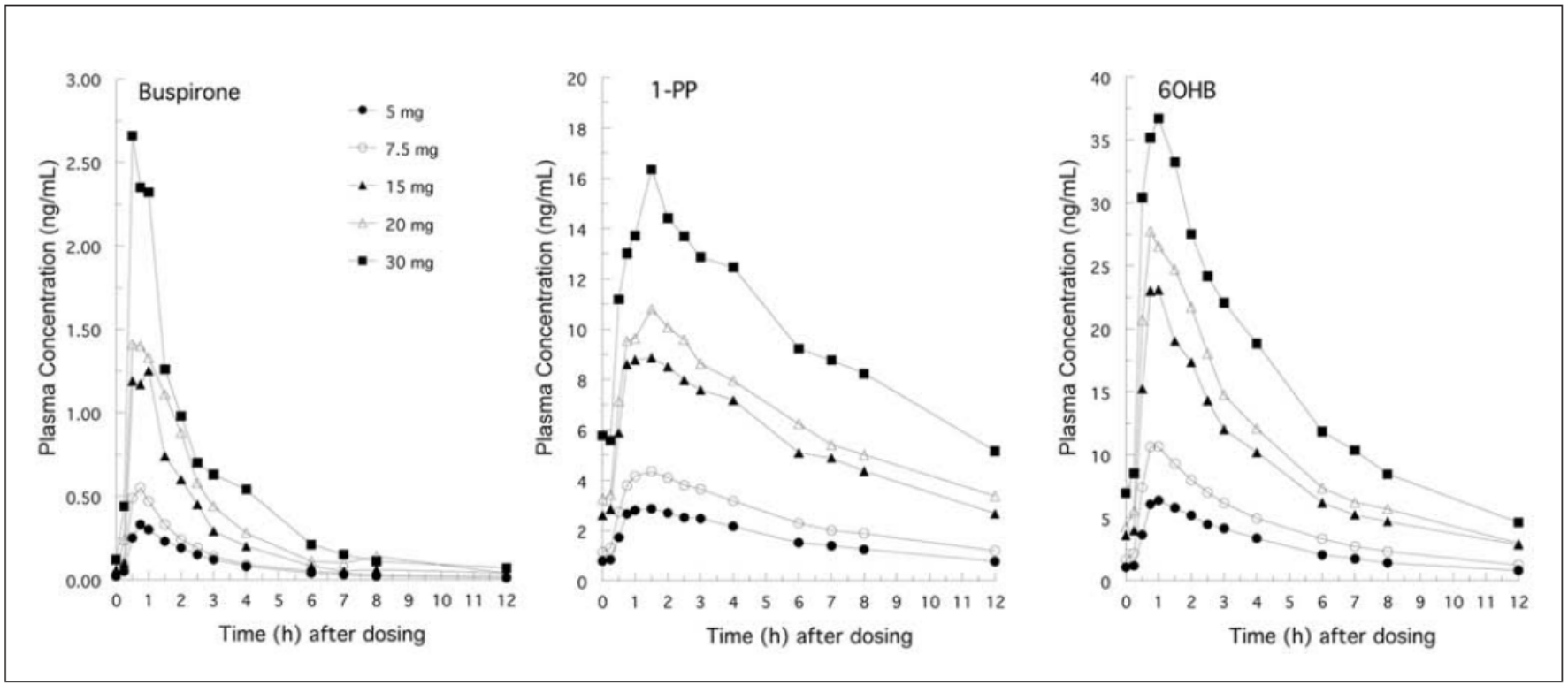
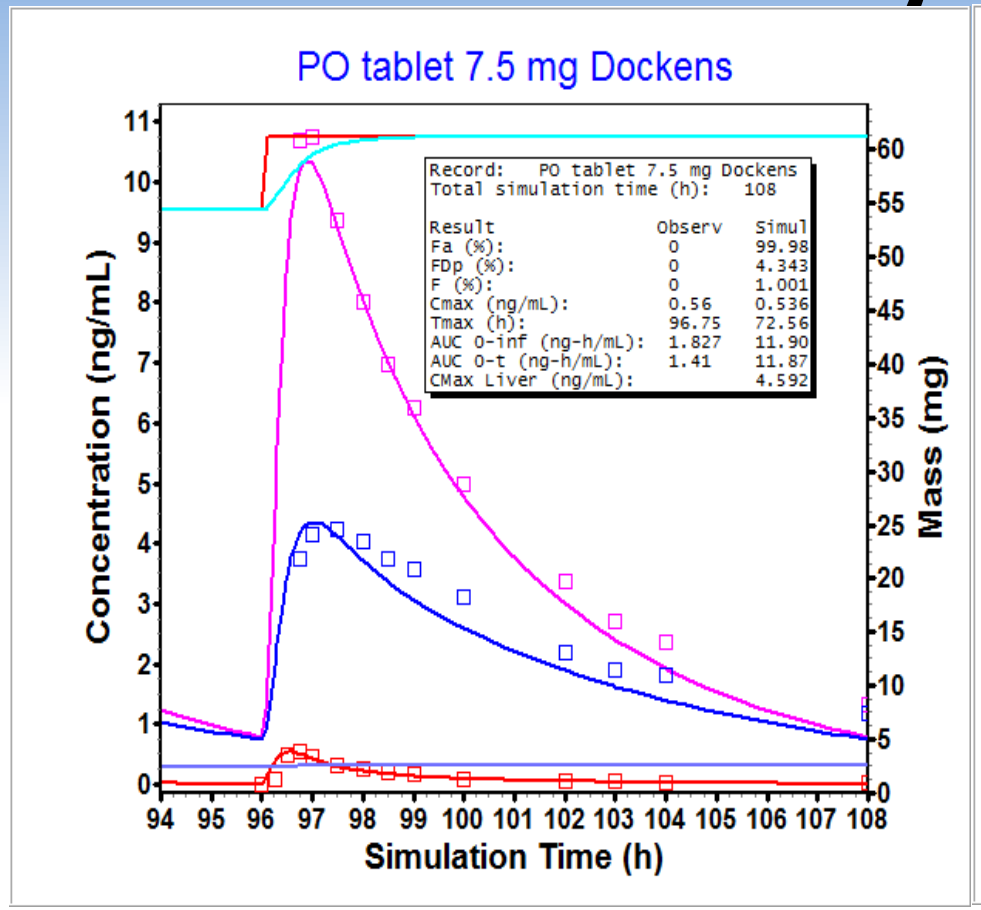
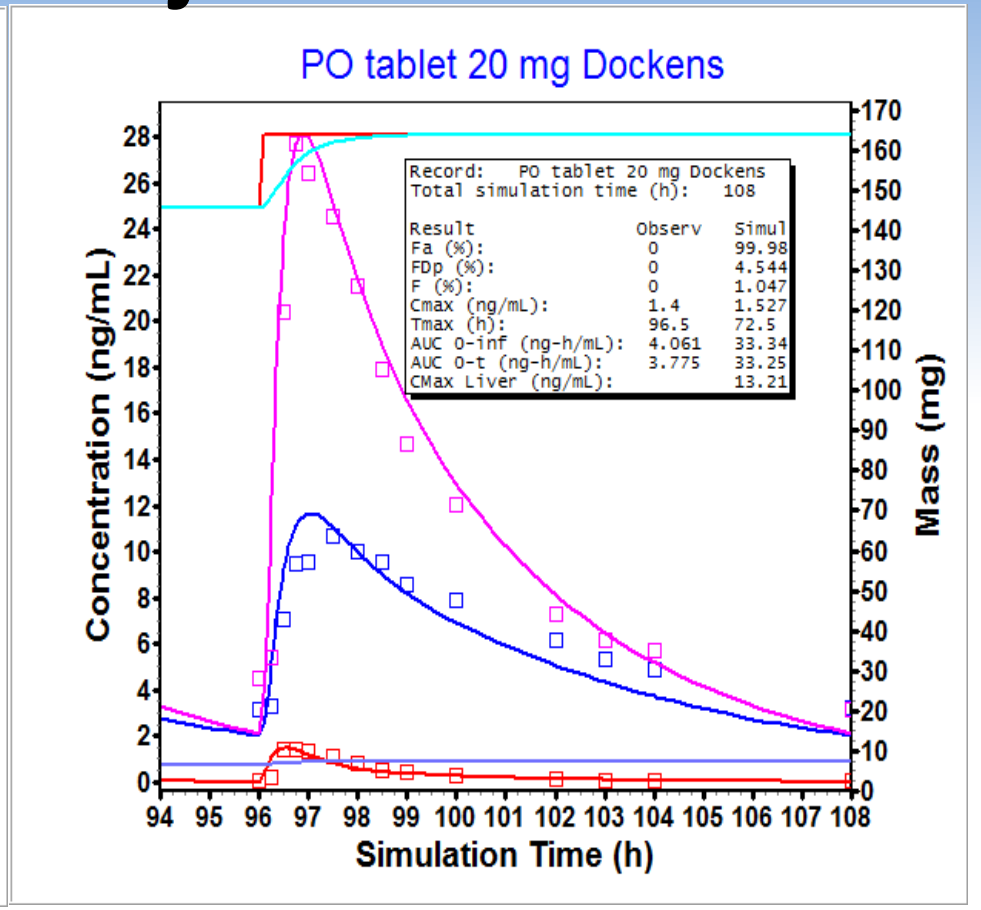


Figure 1. Mean plasma concentration versus time profiles of buspirone, 1-(2-pyrimidinyl)-piperazine (1-PP), and 6-hydroxybuspirone (6OHB) after a 5-day oral administration of 5, 7.5, 15, 20, and 30 mg buspirone HCl on a twice-daily dosing reimen.

Dockens et al., J Clin Pharm 46; 1308-1312, 2006

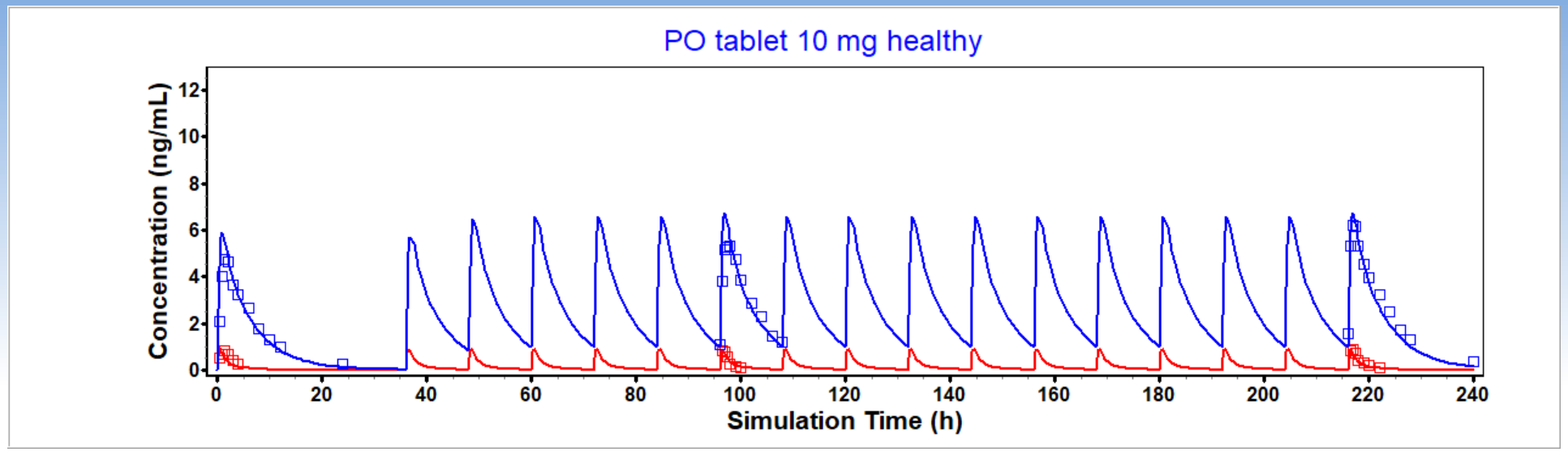
PO IR Tablet 7.5 and 20 mg BID on Day 5 Healthy Subjects

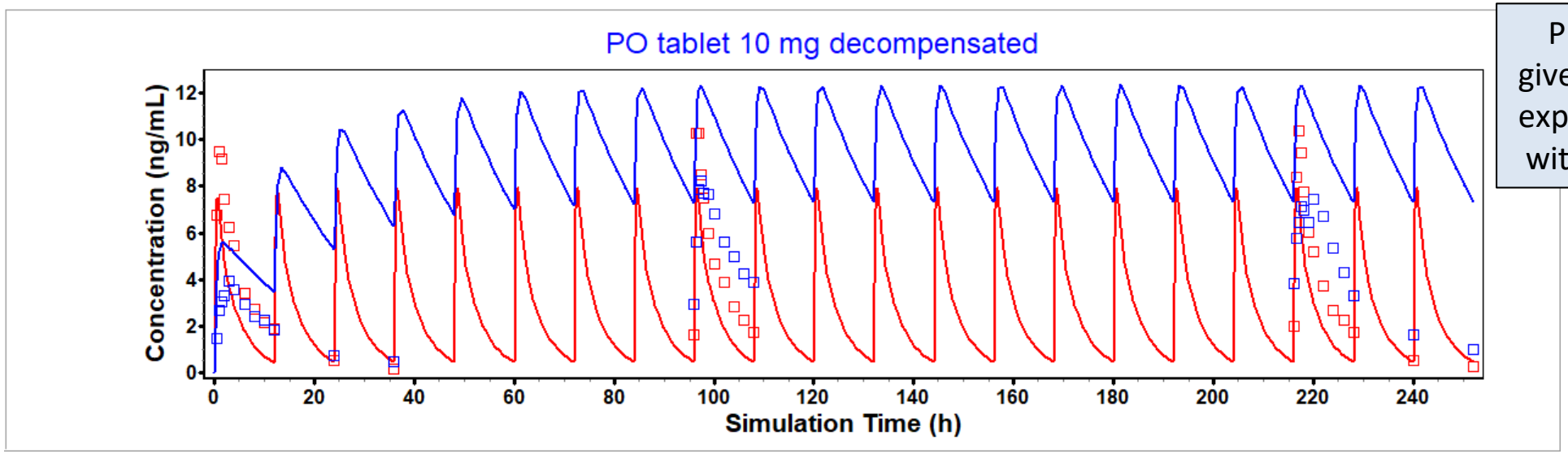




Predicted (lines) and observed (points) Cp-time profiles of buspirone (red), 1-pyrimidinylpiperazine metabolite (blue) and 6-hydroxybuspirone metabolite (pink) in healthy adult volunteers after 9 doses of 7.5 mg and 20 mg buspirone hydrochloride administered once a day.

PO IR Tablet 10 mg BID: Healthy & Hepatic Impairment

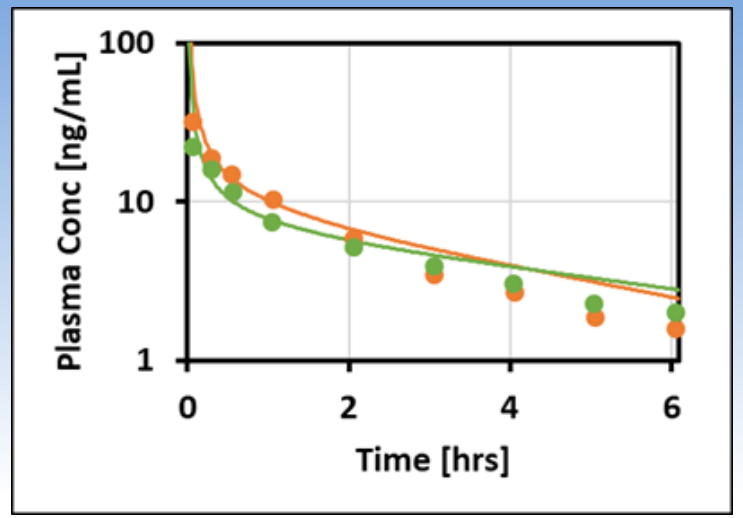


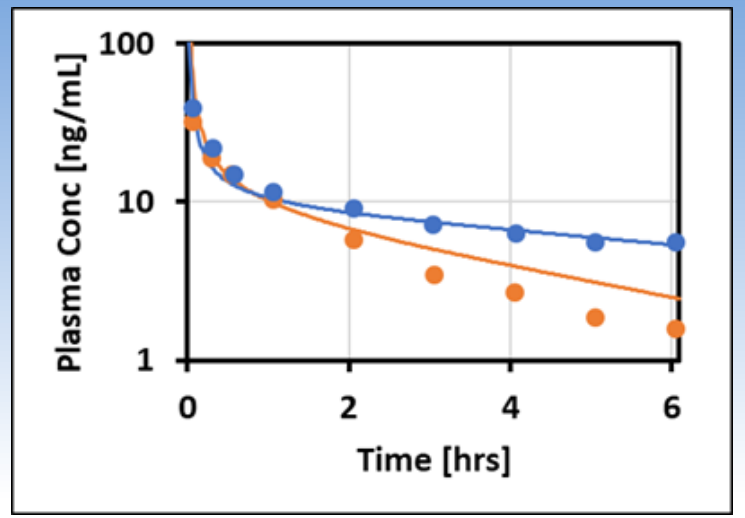


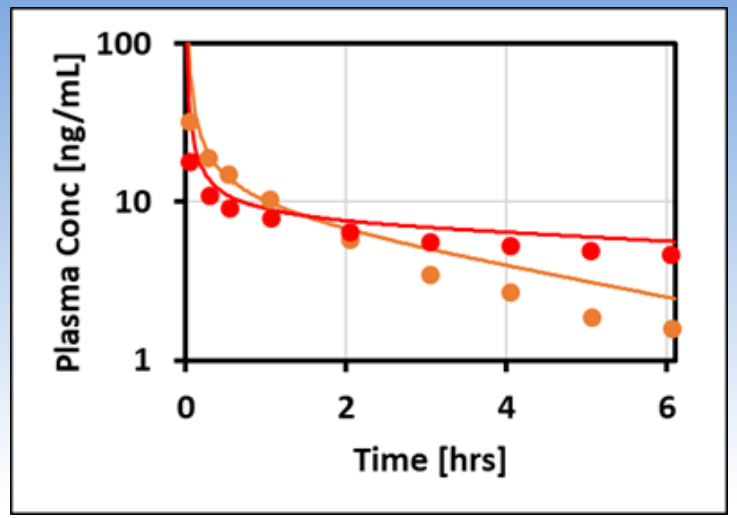
Prediction is not perfect, but gives a good insight into how the exposure may change in patients with severe hepatic impairment

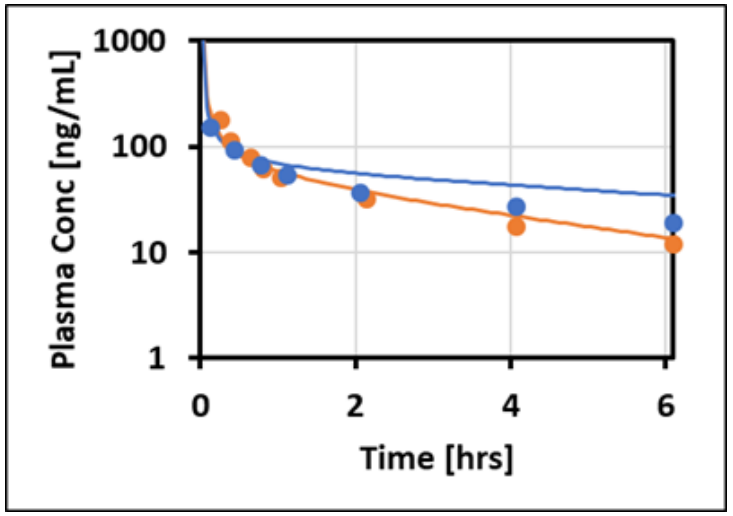
Observed data from Barbhaiya et al., Eur J Clin Pharmacol (1994) 46-41-47

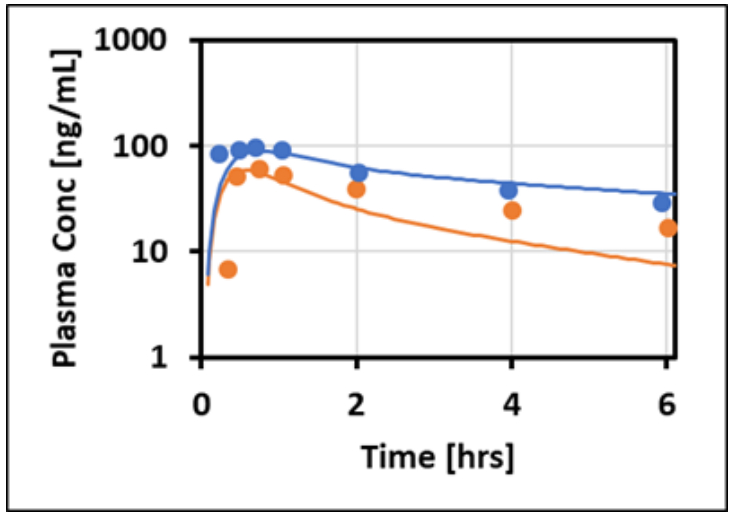
Liver Cirrhosis - Midazolam











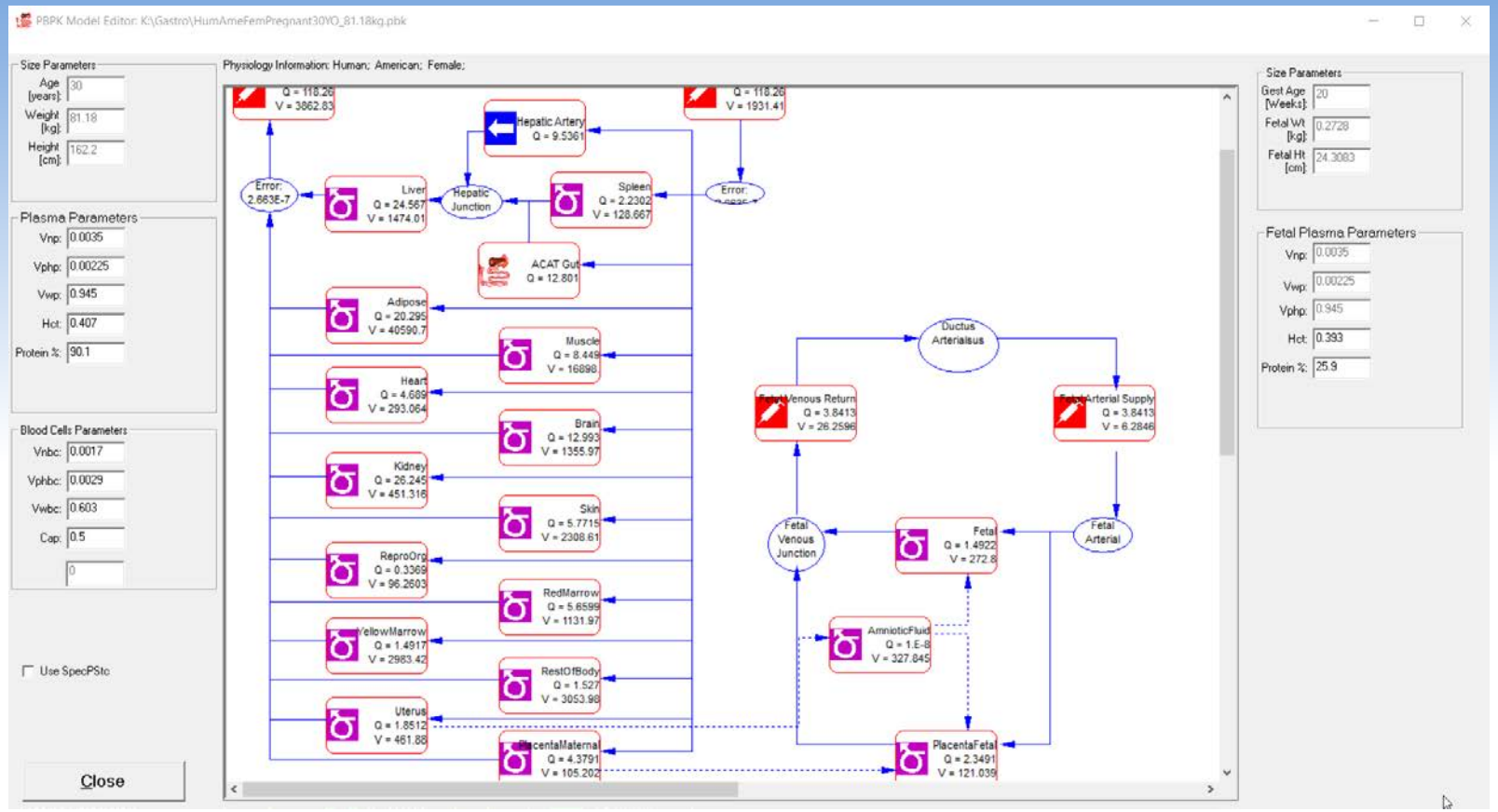
orange – healthy
green – Cirrhosis CP = A
blue – Cirrhosis CP = B
red – Cirrhosis CP = C

Top: 1mg IV bolus

Bottom: 7.5 mg IV bolus and 15 mg PO
(assumed degree of hepatic impairment for second study)

Pregnancy

Pregnancy Model

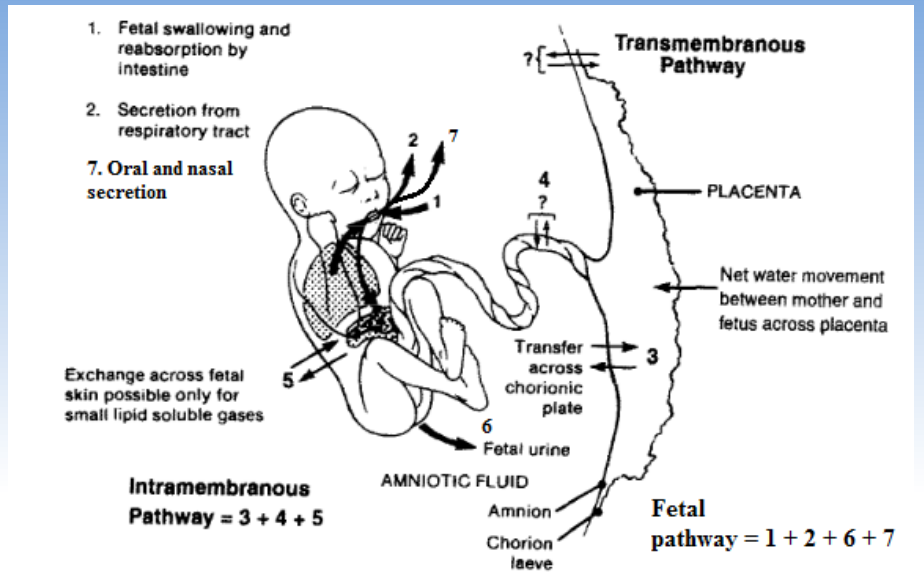


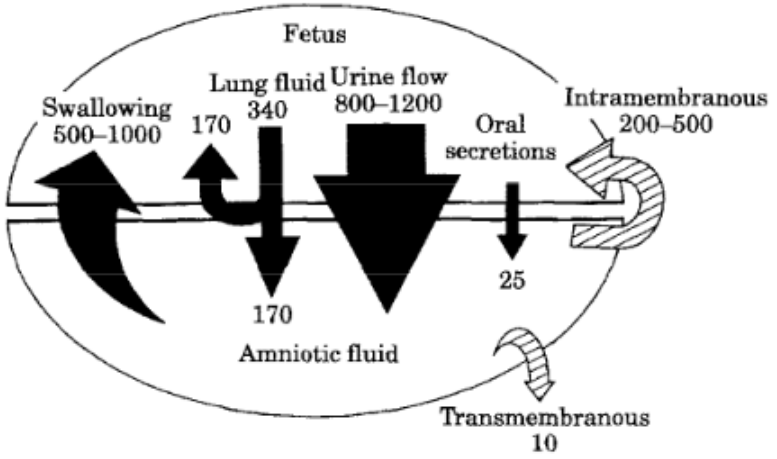
Relevant mechanisms:

1. Intramembranous pathway (between amniotic fluid and fetal blood within the placenta and membranes)
2. Transmembranous pathway (between amniotic fluid and uterus)
3. Fetal pathway (swallowing, secretion, urination etc.)
4. Trans-placenta pathway

Regulation of Amniotic Fluid Volume

- **Poorly understood:**
  - Complex mechanisms: multiple pathways and exchange occurs simultaneously
  - Mechanisms for volume regulatory vary with gestational age
  - Most data are derived from sheep experiment
- **3 principals mechanisms:**
  - Intramembranous pathway
  - Transmembranous pathway
  - Fetal pathway



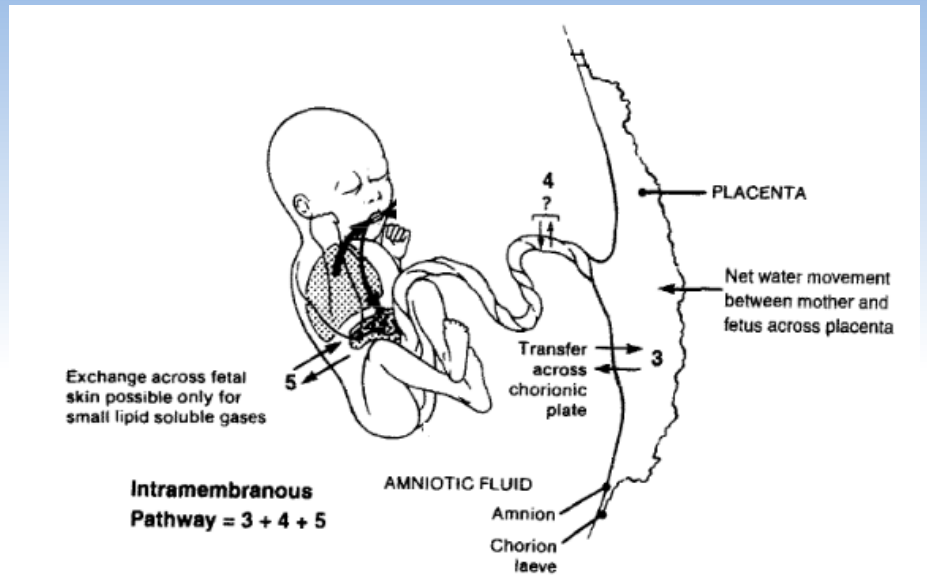


Adapted from R. Brace - 1995

Regulation of Amniotic Fluid Volume

Intramembranous pathway

- rapid movement of water and solute that occurs between amniotic fluid and fetal blood within the placenta and membranes.
- Transcutaneous exchange between fetal blood and amniotic fluid disappears after skin keratinization
  - Keratinization begins between 19 to 20 weeks of gestation
  - Usually, keratinization is completed at 25 weeks of gestation
- Intramembranous pathway could be split into 2 components(Brace et al – 2014):
  - **Passive pathway** where rate depends on the osmolality
  - **Active pathway**(presumed to be a vesicular transcytotic pathway) that moves amniotic fluid in bulk together with dissolved solutes from the amniotic fluid outward across the amnion into fetal blood

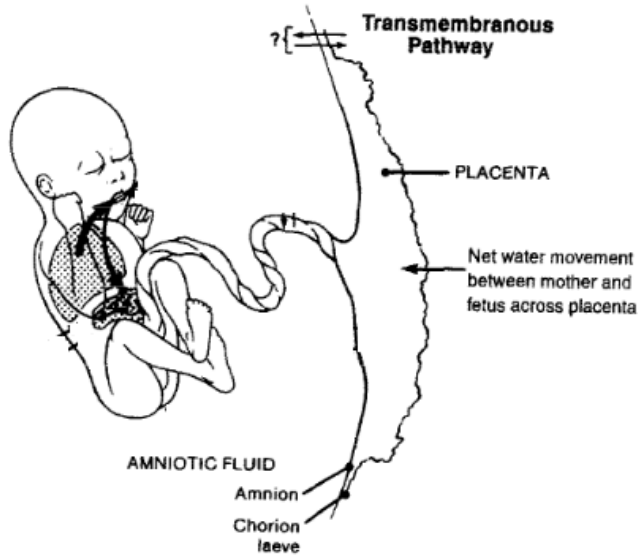


Adapted from R. Brace - 1995

Regulation of Amniotic Fluid Volume

Transmembranous pathway

- Movement of water and solute between amniotic fluid and maternal blood within the wall of the uterus
- Appears to make little if any contribution to net amniotic fluid volume or the concentration of the major solutes during the second half of gestation
- In early gestation, this pathway should be important (as other main pathway are not mature)

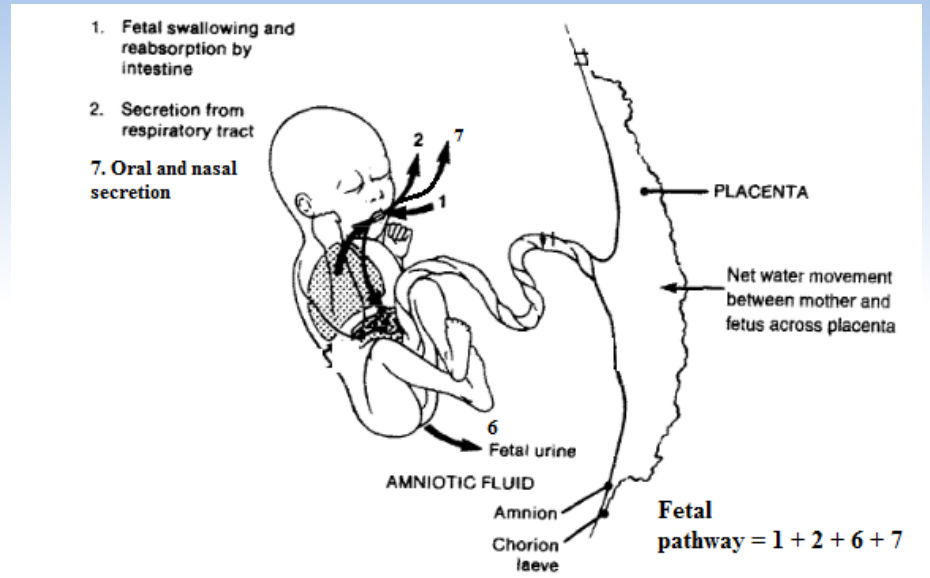


Adapted from R. Brace - 1995

Regulation of Amniotic Fluid Volume

Fetal pathway

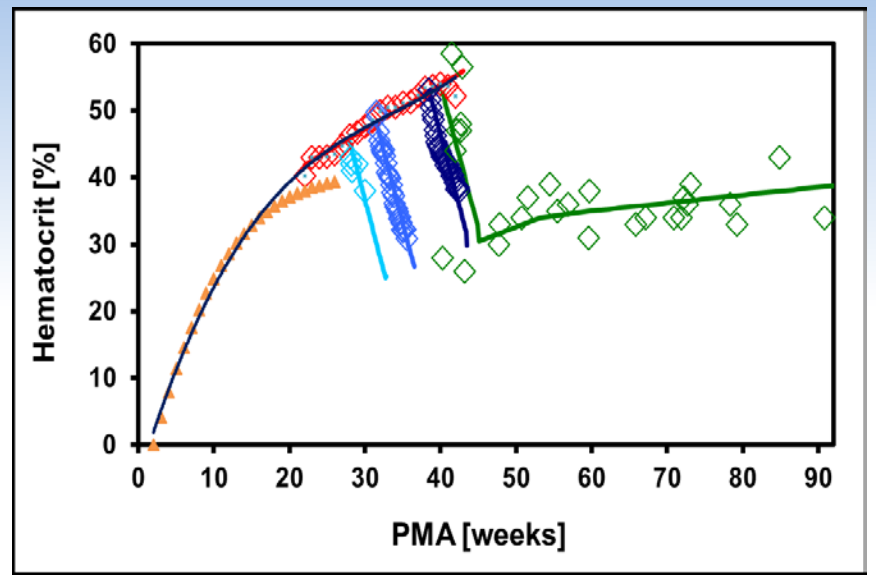
- Movement of water and solute between amniotic fluid and fetal organs
- Represents the major flux of amniotic fluid during the second half of pregnancy
- The formation of urine by the fetal kidney begins with the appearance of the definitive kidney, between 9th and 12th week of gestation.
- The human fetus begins to swallow at the same time that fetal urine begins to enter the amniotic cavity.
- Around the 25th weeks of gestation, a substantial portion of the amniotic fluid is produced by the pulmonary epithelium.



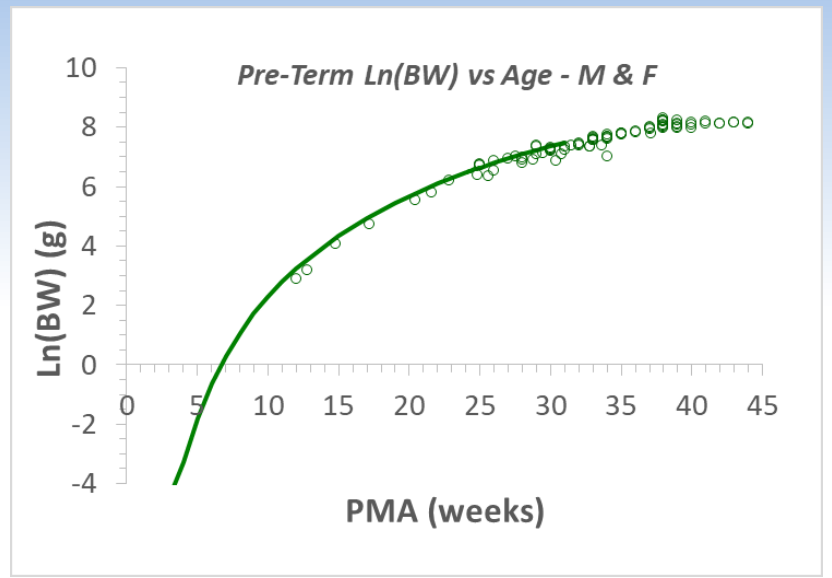
Adapted from R. Brace - 1995

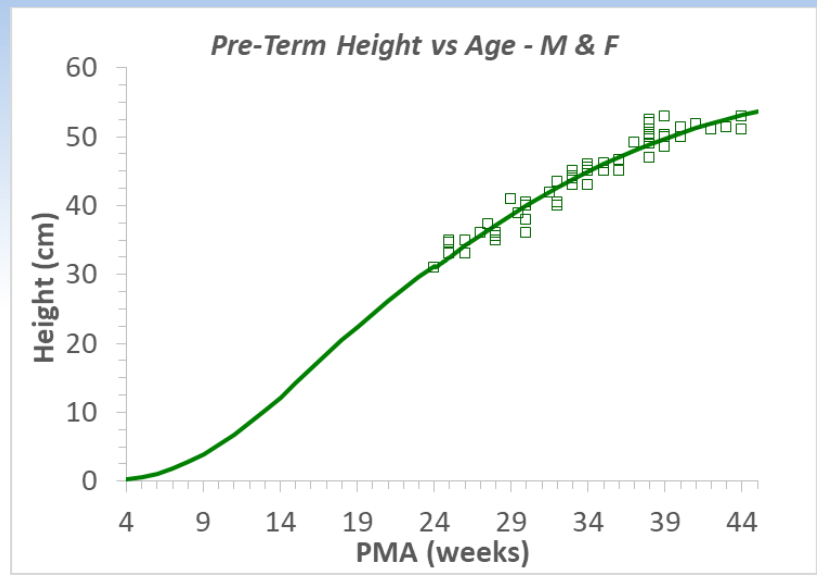
Fetal Physiology

Fetal growth is consistent with infant physiology



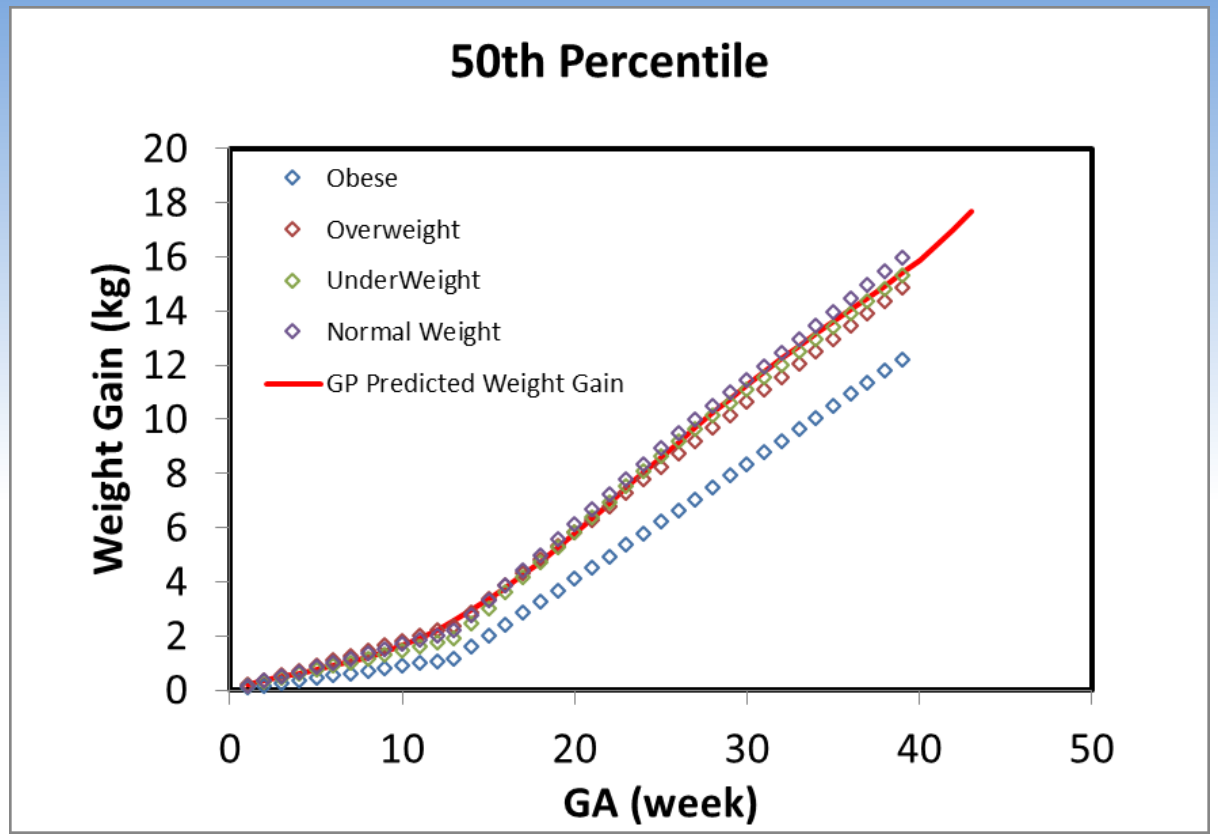
Plot of hematocrit vs post-menstrual age (PMA) for infants up to 1 year old or gestational age for fetus. The yellow triangles were calculated by the equation provided in Dallmann (Dallmann 2017). The final hematocrit equation for fetus was fitted with the Dallmann equation and rest of the observed data (black line).





Fetal weight and height prediction in GastroPlus vs. observed data. Solid line represents the current GP predicted value for fetal weights and the green circles are the observed values from multiple publications (refer to the Infant PBPK section).

Weight Gain During Pregnancy

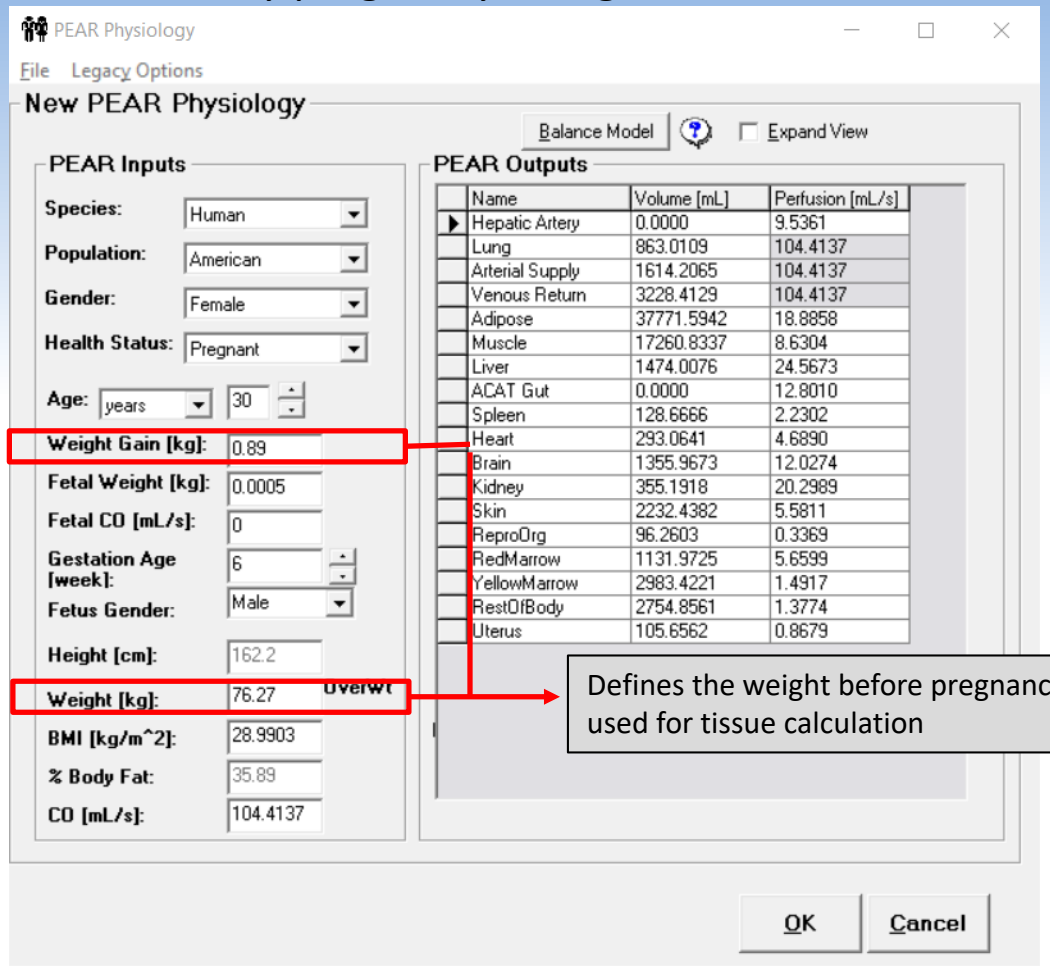


Weight gain during pregnancy. Red solid line represents the calculation in GastroPlus, the color coded diamonds are the observed weight gain for obese, overweight, normal weight and underweight subjects (Carmichael 1997)

Pre-pregnancy weight is important: will be used for calculation of all the tissue weights. Gestation age (in weeks) and pregnant weight will be used for calculating certain tissues' change during pregnancy such as uterus, kidney, fetal, adipose etc.

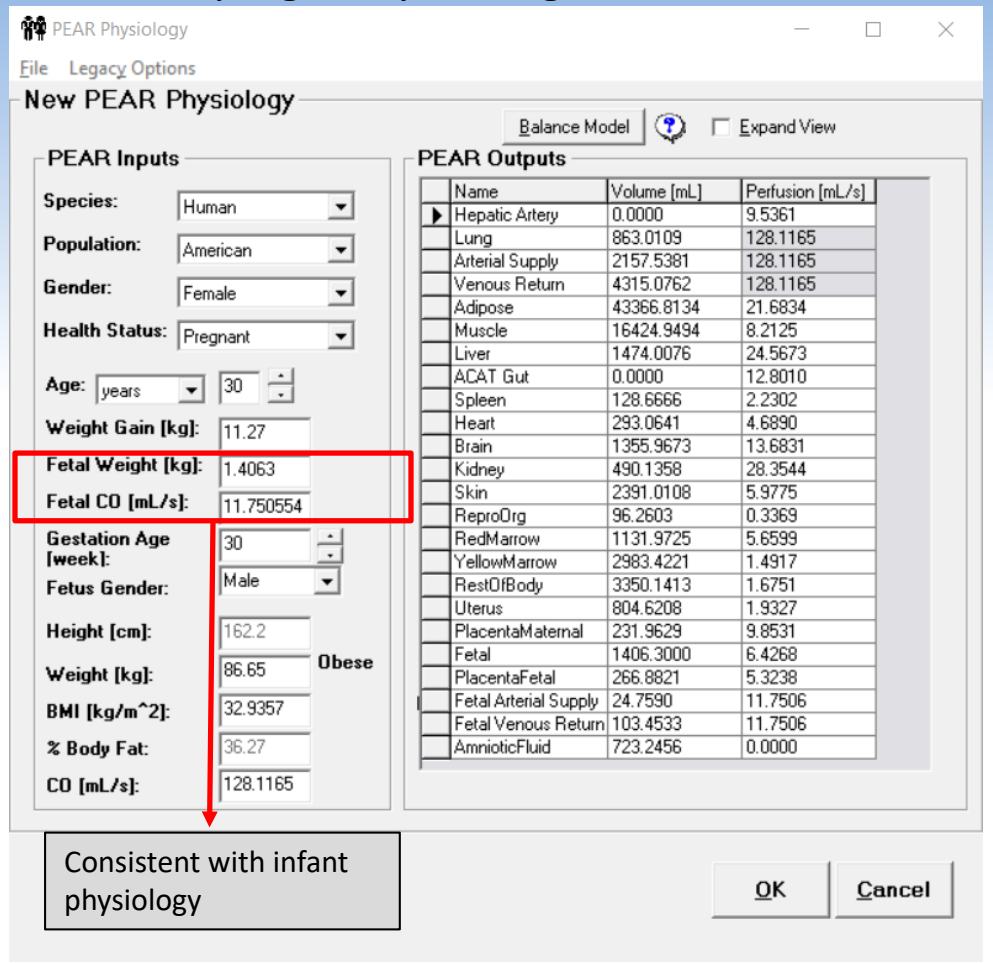
Pregnancy Model

For early pregnancy: 0-6 gestation weeks



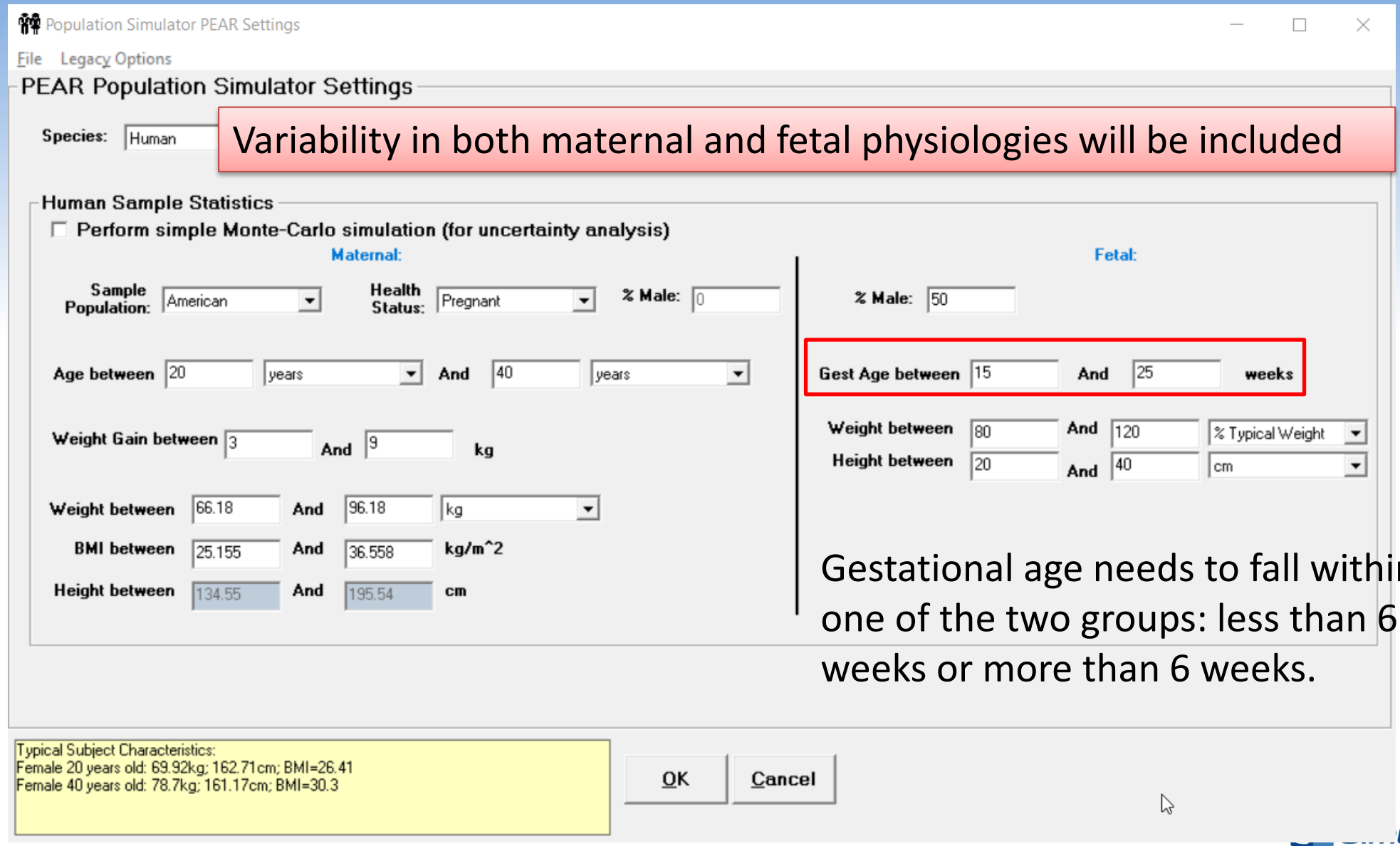
Defines the weight before pregnancy and used for tissue calculation

For pregnancy: 7-43 gestation weeks



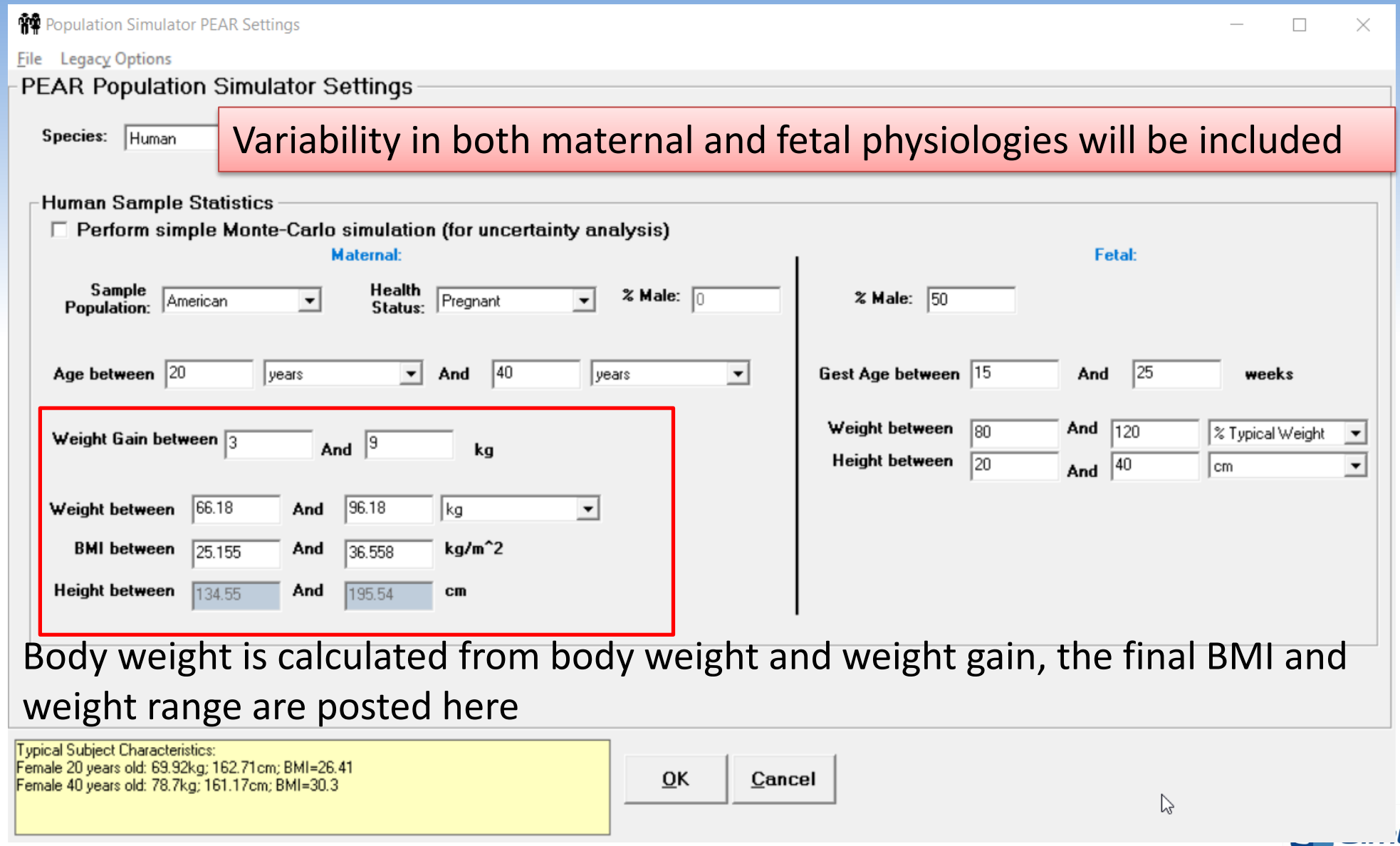
Consistent with infant physiology

Population Simulator: Pregnancy



Gestational age needs to fall within one of the two groups: less than 6 weeks or more than 6 weeks.

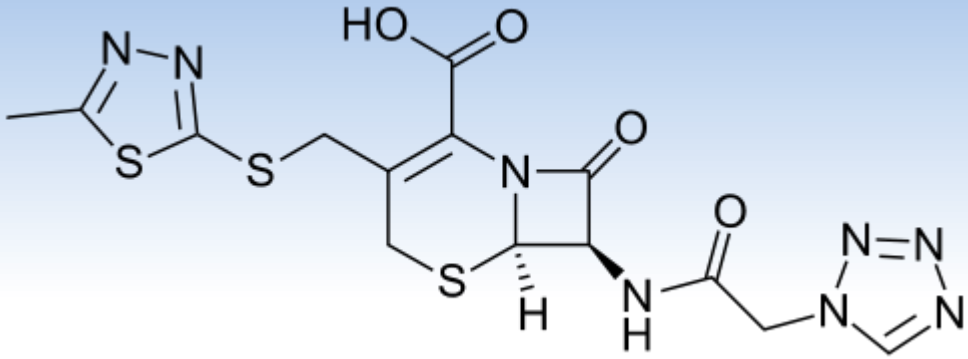
Population Simulator: Pregnancy



Body weight is calculated from body weight and weight gain, the final BMI and weight range are posted here

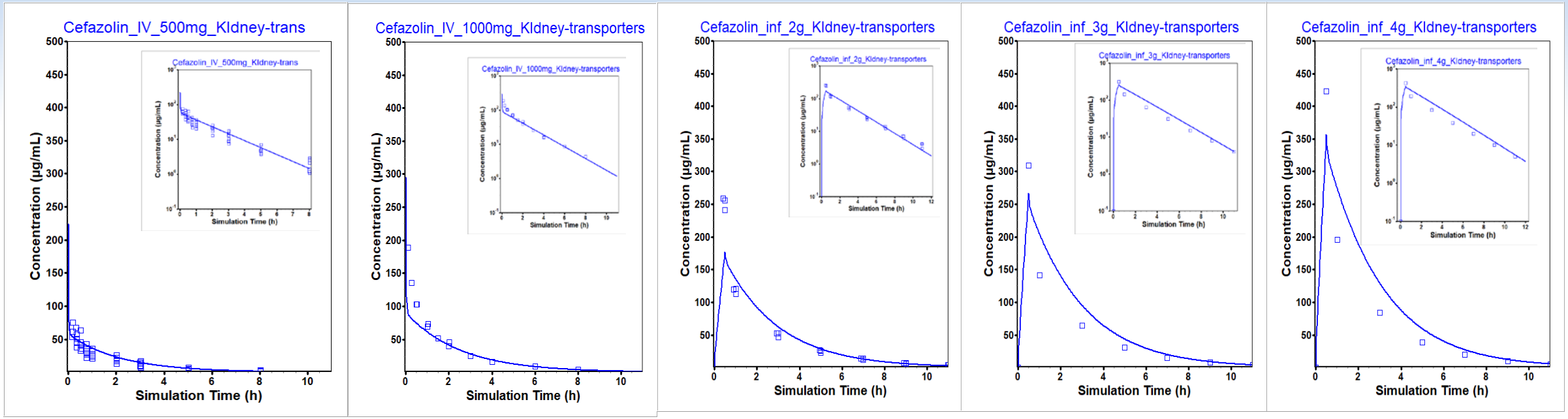
Example: Cefazolin

- Widely used for antibacterial prophylaxis during several surgical procedures in pregnant women
- Urinary recovery of unchanged cefazolin constitutes 100% of the administered dose
- Renal elimination of cefazolin involves glomerular filtration and tubular secretion mediated by influx OATs 1/3 and efflux transporter MRP 4 (Km and Vmax values were fitted for healthy subjects). For Kidney filtration, the default fup*GFR is used.



Example: Cefazolin

Baseline model was calibrated/validated against in vivo data from literature (healthy males)



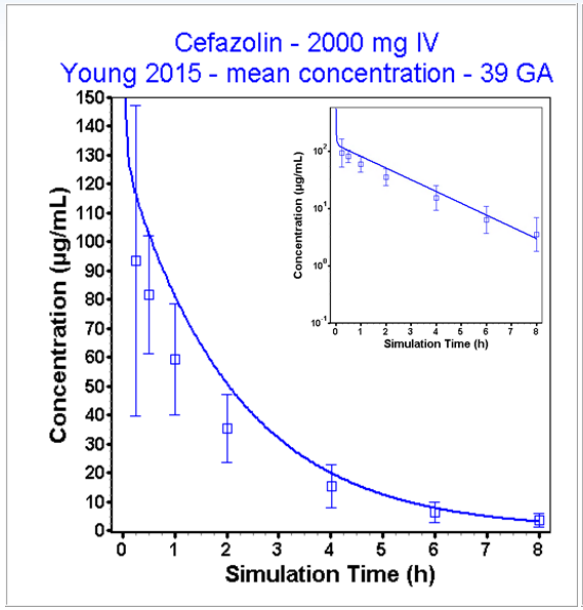
Observed Data: Philipson 1987 → 0.5 g IV; Rattie 1974→ 1 g IV; Smyth 1979→ 2; 3; 4 g IV

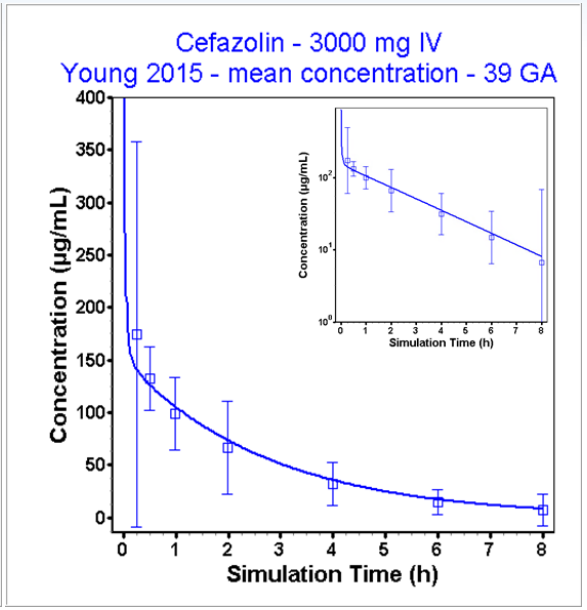
Example: Cefazolin

Validated model was then used to predict maternal and fetal PK

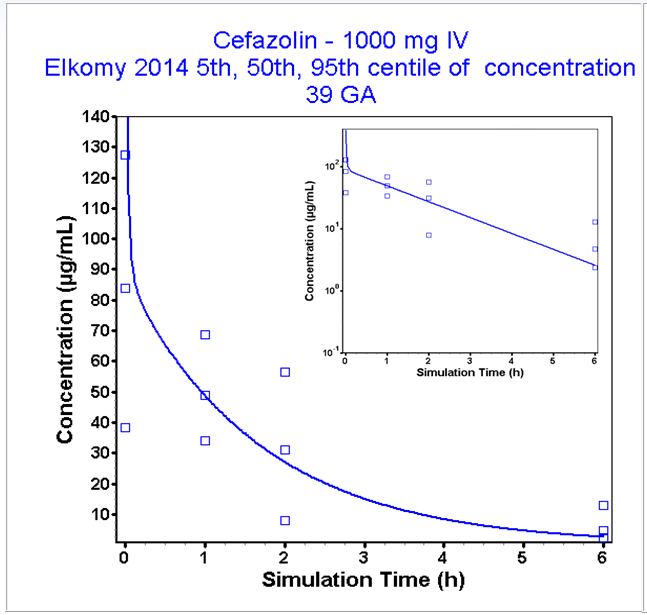
Cefazolin was administered to pregnant women before undergoing cesarean delivery

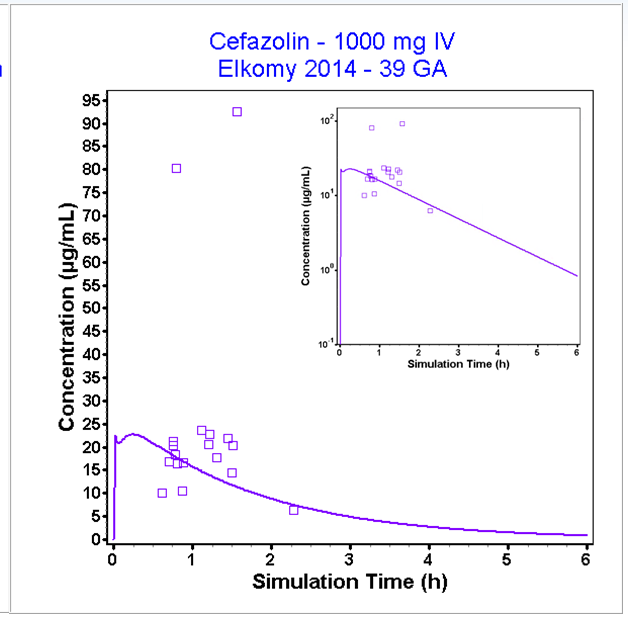
Maternal plasma





Maternal (left) and neonatal (right) plasma



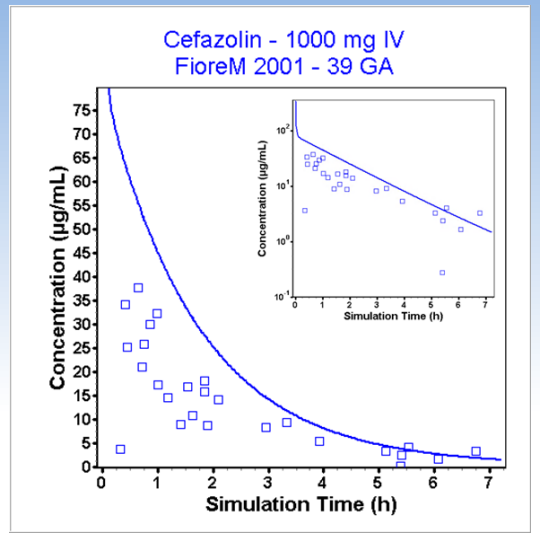


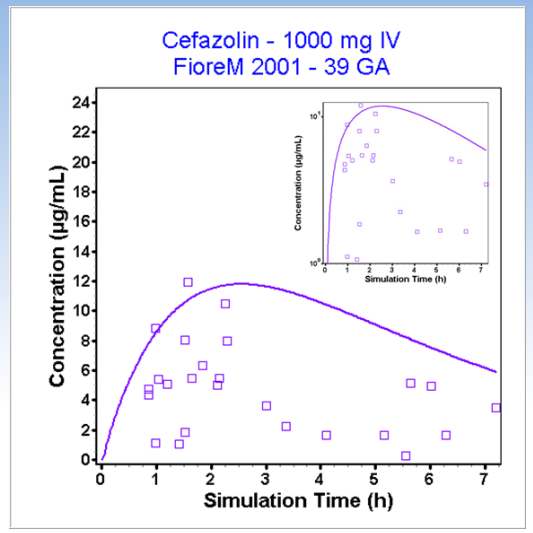
Observed Data: Young 2015; Elkomy 2014

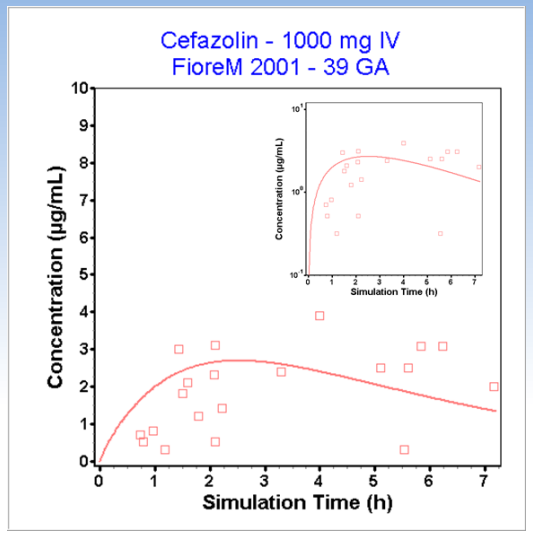
Example: Cefazolin

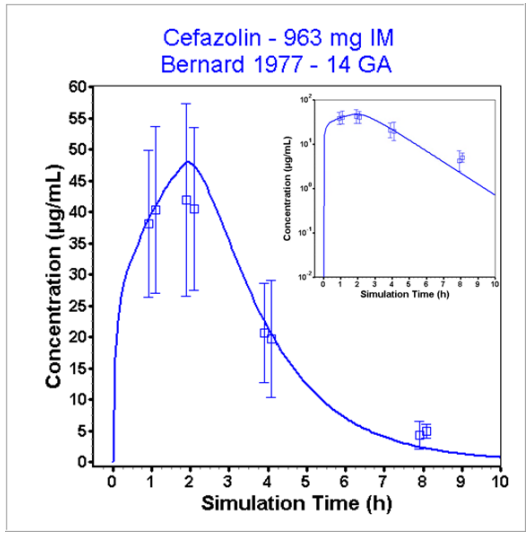
Maternal plasma (left), neonatal plasma (middle), amniotic fluid (right)

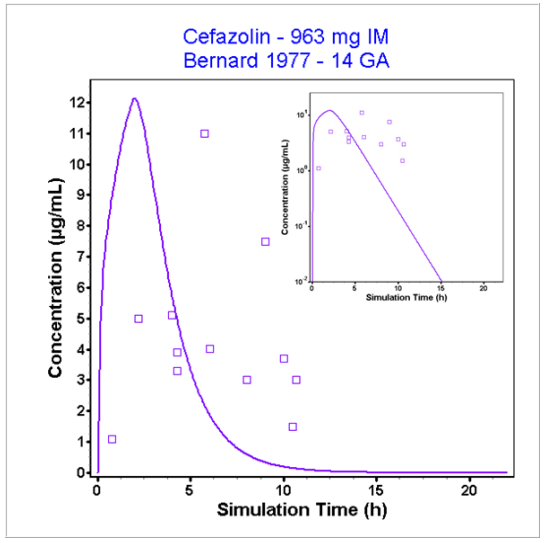
- Validated model was then used to predict maternal and fetal PK
- Cefazolin was administered to pregnant women (IV or IM) before undergoing elective cesarean delivery or hysterectomy

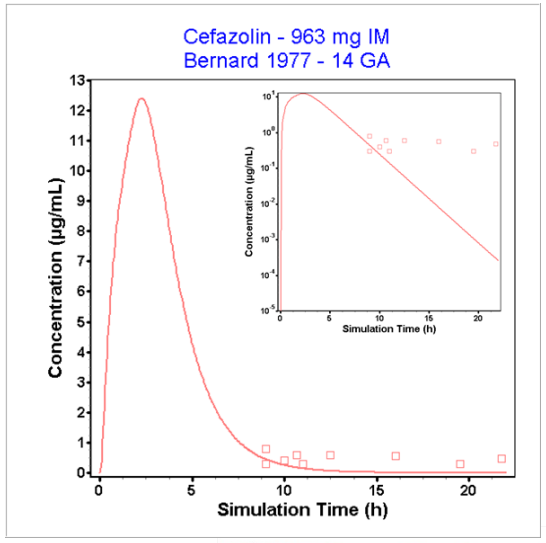












Observed Data: Fiore Mitchell 2001; Bernard 1977

Summary

PBPK models are here to stay

- PBPK modeling is already being used routinely for first-in-human predictions, pharmaceutical development and drug-drug interaction evaluations
- PBPK models also provide a platform for predictions of exposure in special populations and have a potential to go beyond the major groups in focus today (pediatric, hepatic and renal impairment)

PBPK models play well with others

- PBPK can be used as complimentary approach to PopPK modeling, especially for groups where it is difficult to obtain PK data in large cohort
- With predictions of individual tissue concentrations, the simulated profiles can be linked with QSP/QST models to simulate the local effects of administered drug.

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Dechuan Zhuang

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Kevin Cooper

>1000 members on the LinkedIn group page – membership is free!

http://www.linkedin.com/groups/GastroPlus-User-Group-5025927/about

Mission & Goals:

Discuss best practices, Q&A and FAQs

Share knowledge of software functionality and applications

Publish journal articles to show validation for different applications

Present and advance M&S science via social media, webinars and face-to-face meetings

Feedback on improvements and software functionality requests to Simulations Plus

Understand and influence regulatory expectations for M&S submissions