Science For A Better Life

Use of PBPK in Drug Development and Application to the Pediatric Setting

Innovative Approaches to Pediatric Drug Development and Pediatric Medical Countermeasures: A Role for Physiologically-Based PK?

FDA White Oak Campus – May 5, 2014

Dr. Jörg Lippert
Vice President, Head Clinical Pharmacometrics

Agenda

- Why do we use PBPK?
- How much biology can we capture with PBPK?
- How do we apply it?
- What is still missing?

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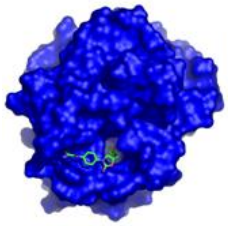
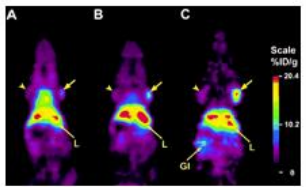
The pharmaceutical R&D paradigm relies on indirect assessments





PNAS July 18, 2000 vol. 97 no. 15 8495-8500



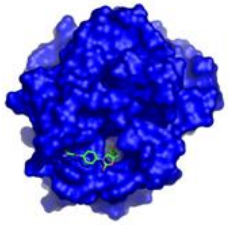
http://www.damtp.cam.ac.uk/group/apde/people.html

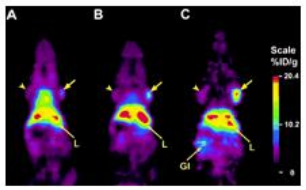
http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472_468x313.jpg

Pathway? Target? Molecule? Dose? Patient?

Integration and holistic interpretation of information is a major challenge

- Based on models and extrapolation







PNAS July 18, 2000 vol. 97 no. 15 8495-8500

http://www.damtp.cam.ac.uk/group/apde/people.html

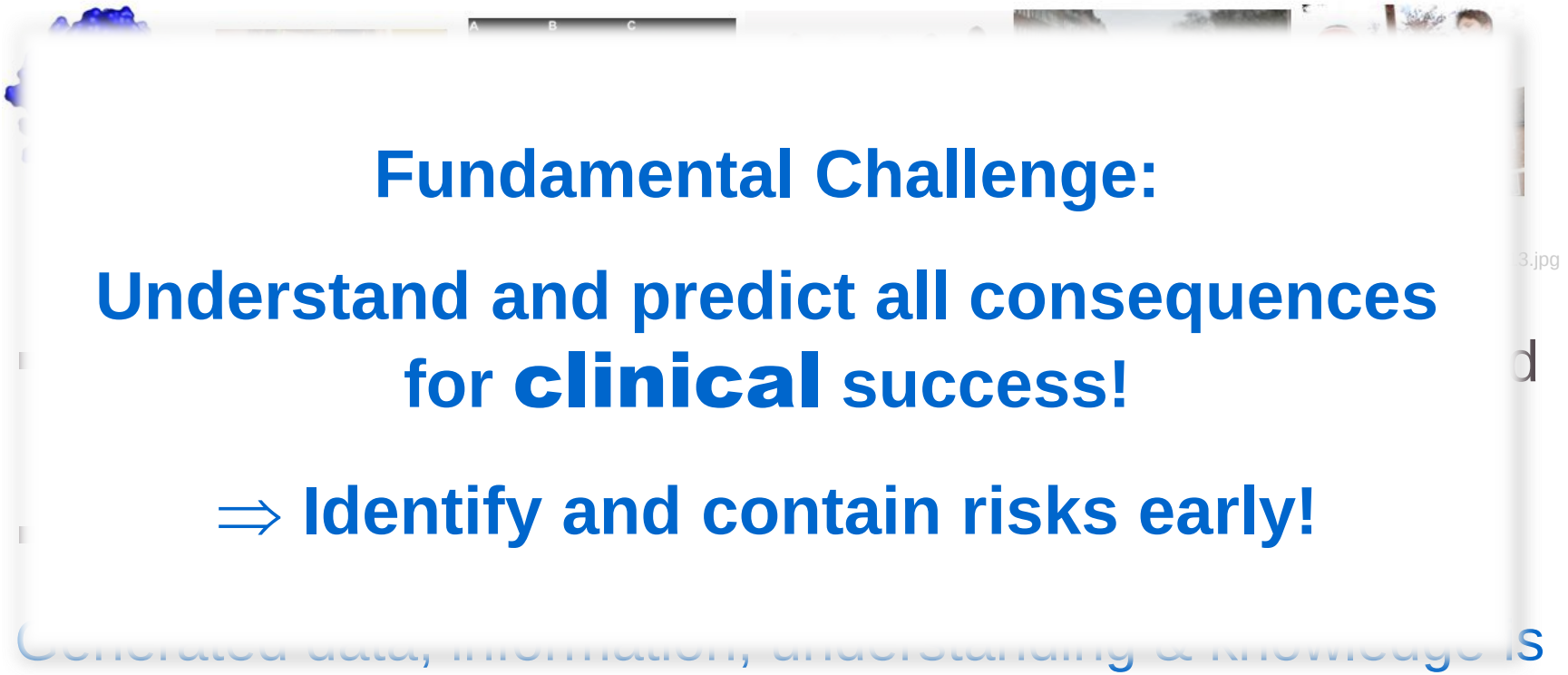
http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472_468x313.jpg

- Distributed in a complex organization of highly specialized experts (time & space)
- Analytical and reductionist

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

Output of Pharma R&D is a matter of debate for more than a decade

- Based on models and extrapolation



Fundamental Challenge:

Understand and predict all consequences for clinical success!

⇒ Identify and contain risks early!

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

Output of Pharma R&D is a matter of debate for more than a decade

- Based on models and extrapolation

Lack of understanding (explicit & implicit) and uncertainty translate into high development risks!

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

Output of Pharma R&D is a matter of debate for more than a decade

- Based on models and extrapolation

How can PBPK modeling help?

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

Why do we use PBPK?

1. **PBPK provides the method for stringent integration of pharmacology relevant knowledge, assumptions and data – along the whole R&D process**
2. **PBPK enables the identification of risks by revealing inconsistencies between different sources of information**
3. Based on a consistent representation of all information, directly drug related as well as independent prior information, PBPK allows prediction of most likely outcomes of future experiments and enables decision making and optimization of development strategies and study designs

Agenda

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- **How much biology can we capture with PBPK?**
- How do we apply it?
- What is still missing?

Metabolism

ORIGINAL RESEARCH ARTICLE

Mol Diagn Ther 2012; 16 (1): 43-53
1177-1062/12/0001-0043/$49.95/0

Pharmacogenomics of Codeine, Morphine, and Morphine-6-Glucuronide

Model-Based Analysis of the Influence of CYP2D6 Activity, UGT2B7 Activity, Renal Impairment, and CYP3A4 Inhibition

Thomas Eissing, *Jörg Lippert* and *Stefan Willmann*

Competence Center Systems Biology and Computational Solutions, Bayer Technology Services GmbH, Leverkusen, Germany

ARTICLES

nature publishing group

Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study

[1]Competence Center Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany; [2]School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada; [3]Clinical Pharmacokinetics, Bayer HealthCare AG, Wuppertal, Germany. Correspondence: S Willmann (stefan.willmann@bayertechnology.com)

Received 30 April 2009; accepted 19 June 2009; advance online publication 26 August 2009. doi:10.1038/clpt.2009.151

VOLUME 86 NUMBER 6 | DECEMBER 2009 | www.nature.com/cpt

The use of codeine by breastfeeding mothers has been a matter of debate due to the risk of opioid intoxication of the child

NATIONAL REVIEW of MEDICINE
JUNE 15, 2007 | VOLUME 4 NO. 11
PATIENTS & PRACTICE

Codeine linked to breastfeeding danger

Warnings and class action suit follow Toronto neonate's poisoning death

BY OWEN DYER

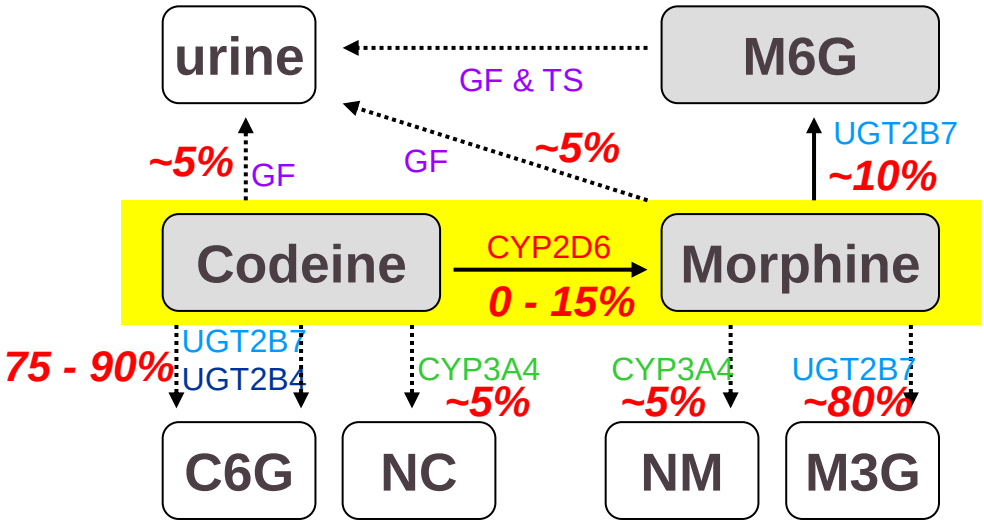
A class action suit over the death of an apparently healthy Toronto newborn, who died last year from opiate toxicity from breast milk, has renewed the debate over prescribing Tylenol 3 to breastfeeding mothers. After the baby's death, doctors at Toronto's Hospital for Sick Children issued a warning that codeine given for postnatal pain can produce deadly concentrations of morphine in breast milk.

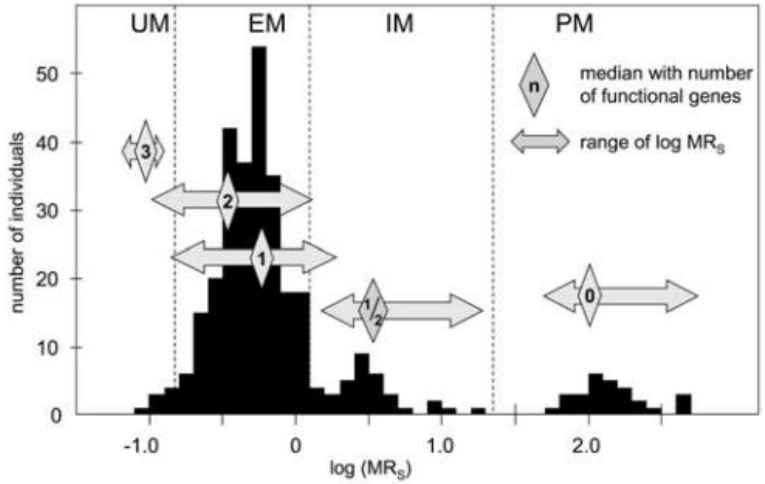
Asian and African babies are at greater risk of rapidly metabolizing codeine

Tariq Jamieson was delivered vaginally at full term and healthy weight — everything appeared normal. His mother Rani suffered some lingering pain from an episiotomy so she was prescribed two tablets of Tylenol 3 twice daily — a common pain treatment for mothers who have just given birth. Doctors halved that dose after two days due to constipation and somnolence.

Tariq developed increasing lethargy from the seven-day mark, and at 11 days was

Explicit representation of all mass-balance information is a strength of PBPK and key to robust models





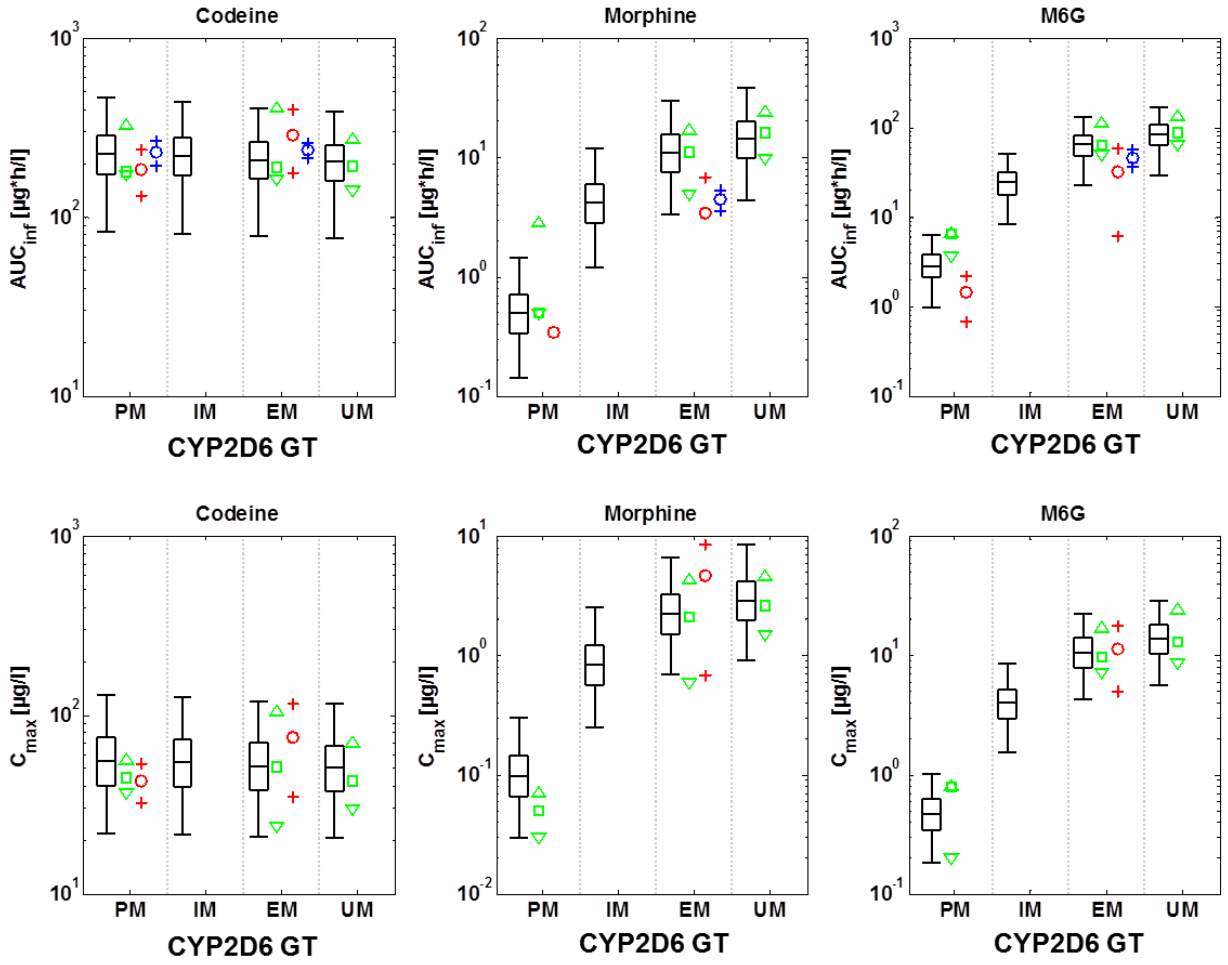
Naunyn-Schmiedeberg's Arch Pharmacol (2004) 369 : 23–37
DOI 10.1007/s00210-003-0832-2

REVIEW

Ulrich M. Zanger · Sebastian Raimundo
Michel Eichelbaum

Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry

A systematic model validation requires comparison with all available data



Simulation Results
Box-Whisker Plots
Median, IQR, and
95% C.I.

Clinical Data
Kirchheiner et al.
Pharmacogen. 2007

△ median
□ min./max

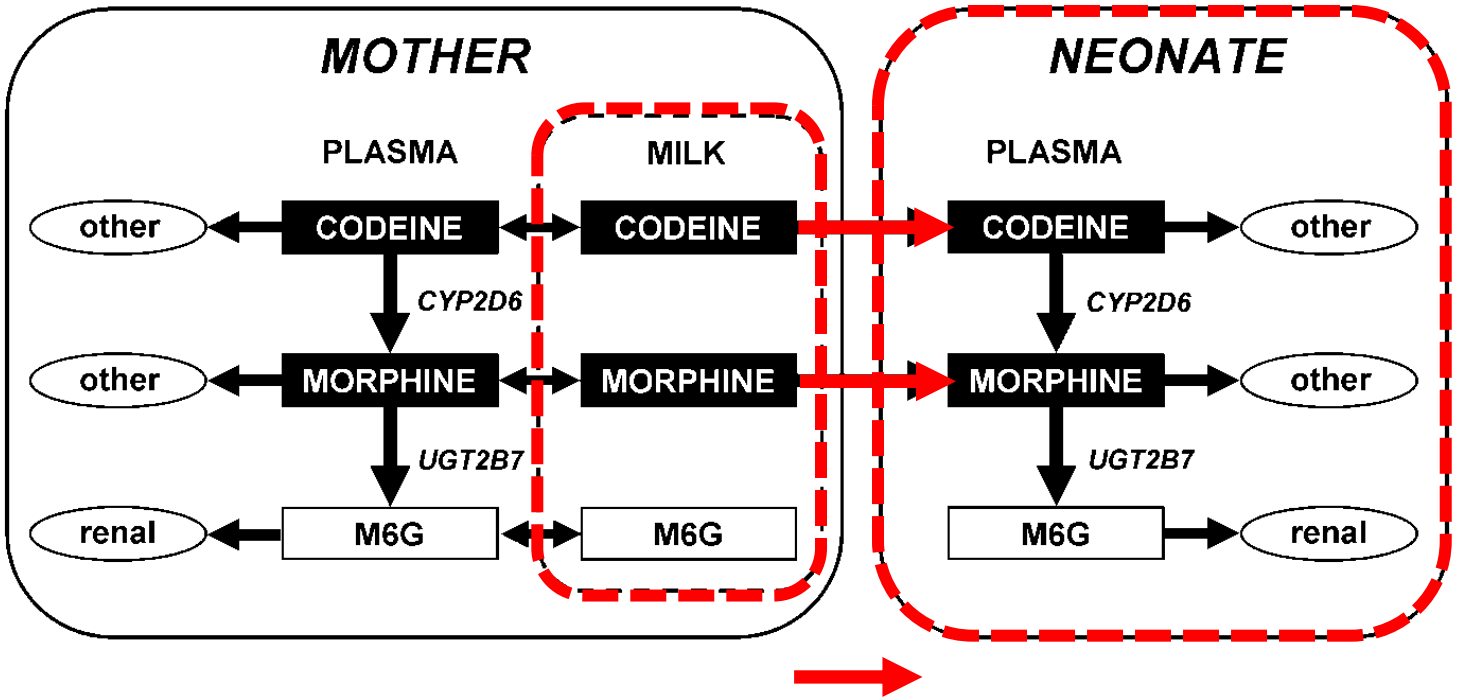
Yue et al.
Br. J. Clin. Pharmacol. 1991

○ mean
\+ std.dev.

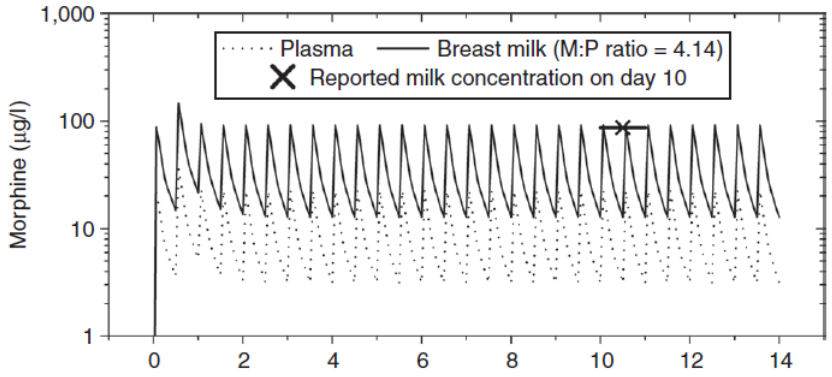
Caraco et al.
J. Pharm. Exp. Therap. 1996

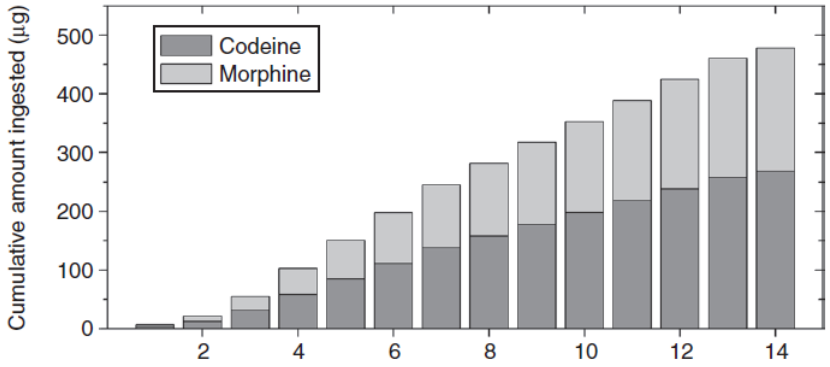
○ mean
\+ std.dev.

Coupled models of codeine-morphine-M6G can be established to represent mother and child in a breastfeeding situation



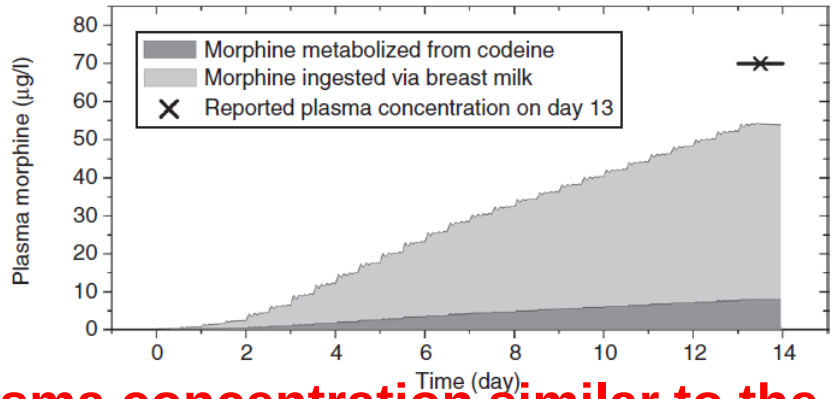
The Toronto case – coupled PBPK models can be applied to simulate arbitrary scenario





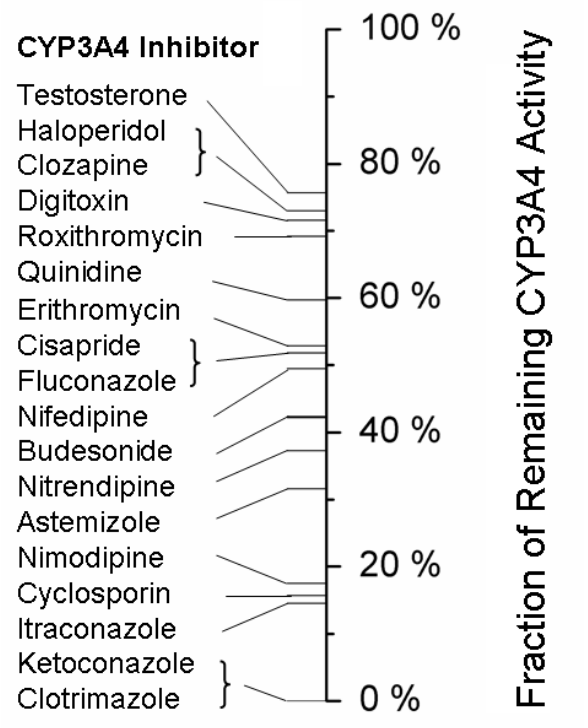
Maternal codeine dose: initially 120 mg/d, 60 mg/d from day 2 on

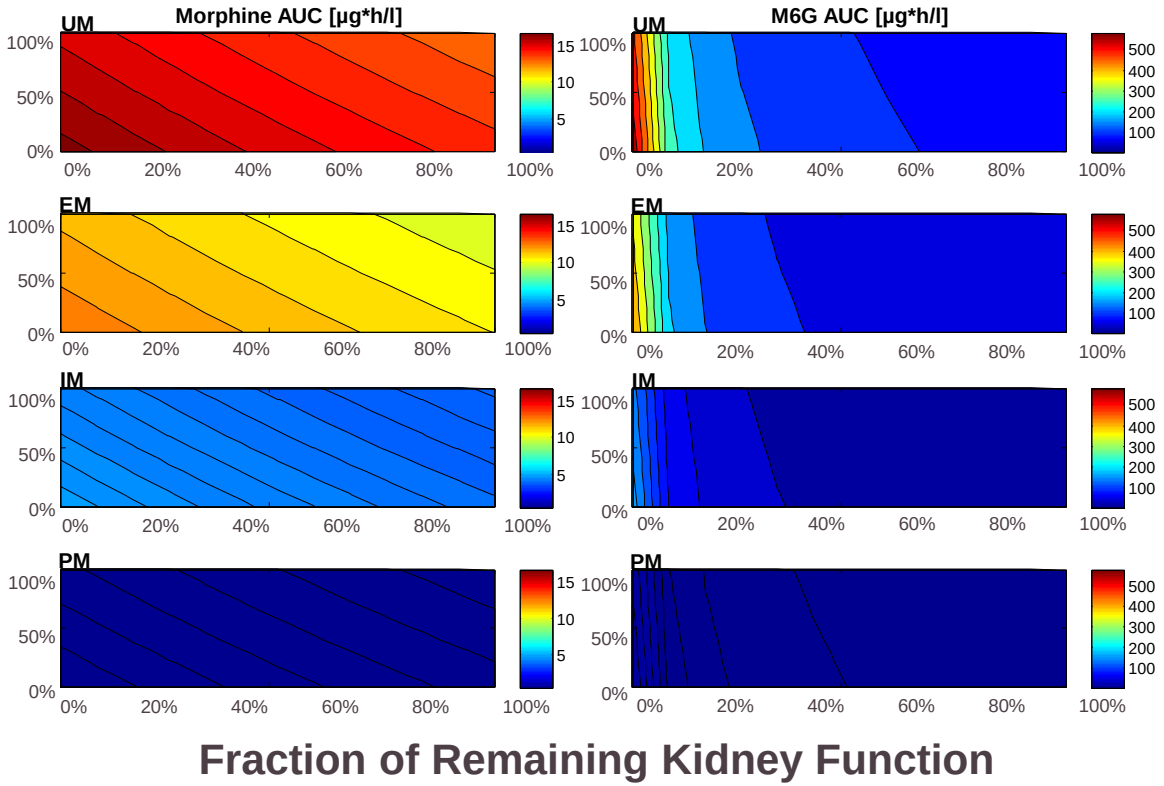
Neonatal codeine and morphine dose: calculated assuming a typical breast-feeding scenario



Model shows neonatal morphine plasma concentration similar to the reported *post-mortem* level on day 13.

The systematic analysis of CYP3A4 related DDI and renal impairment are more common applications





Study of combined influence of CYP3A4 inhibition, renal impairment and CYP2D6 genotype reveals strongest influence of kidney function on active opioid exposure after codeine administration

Active Transport

1521-009X/12/4005-892–901$25.00
DRUG METABOLISM AND DISPOSITION
Vol. 40, No. 5
43174/3761775
DMD 40:892–901, 2012

Using Expression Data for Quantification of Active Processes in Physiologically Based Pharmacokinetic Modeling

Michaela Meyer, Sebastian Schneckener, Bernd Ludewig, Lars Kuepfer, and Joerg Lippert

Systems Biology and Computational Solutions, Bayer Technology Services, Leverkusen, Germany

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e13; doi:10.1038/psp.2012.14

www.nature.com/psp

ORIGINAL ARTICLE

A Mechanistic, Model-Based Approach to Safety Assessment in Clinical Development

J Lippert[1], M Brosch[2], O von Kampen[2], M Meyer[1], H.-U Siegmund[1], C Schafmayer[3], T Becker[3], B Laffert[4], L Görlitz[1], S Schreiber[2], PJ Neuvonen[5,6], M Niemi[5,6], J Hampe[2] and L Kuepfer[1]

OATP1B1 (SLCO1B1) genotype drives statin exposure and myopathy risk

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

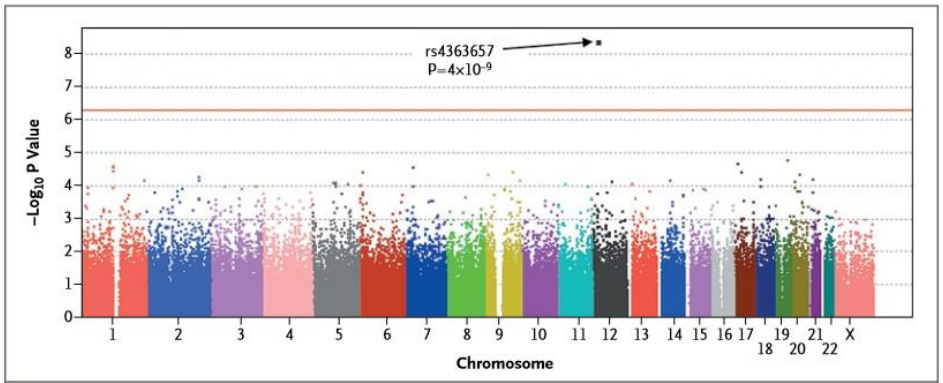
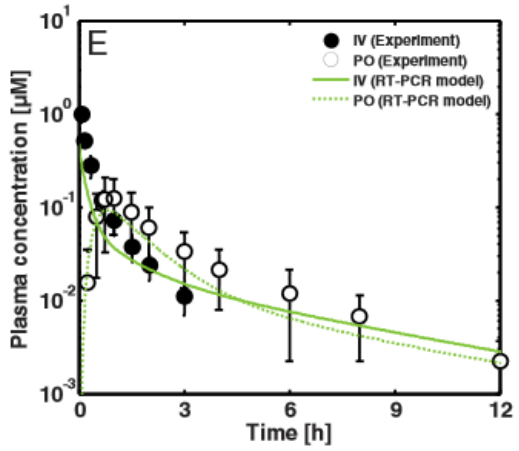


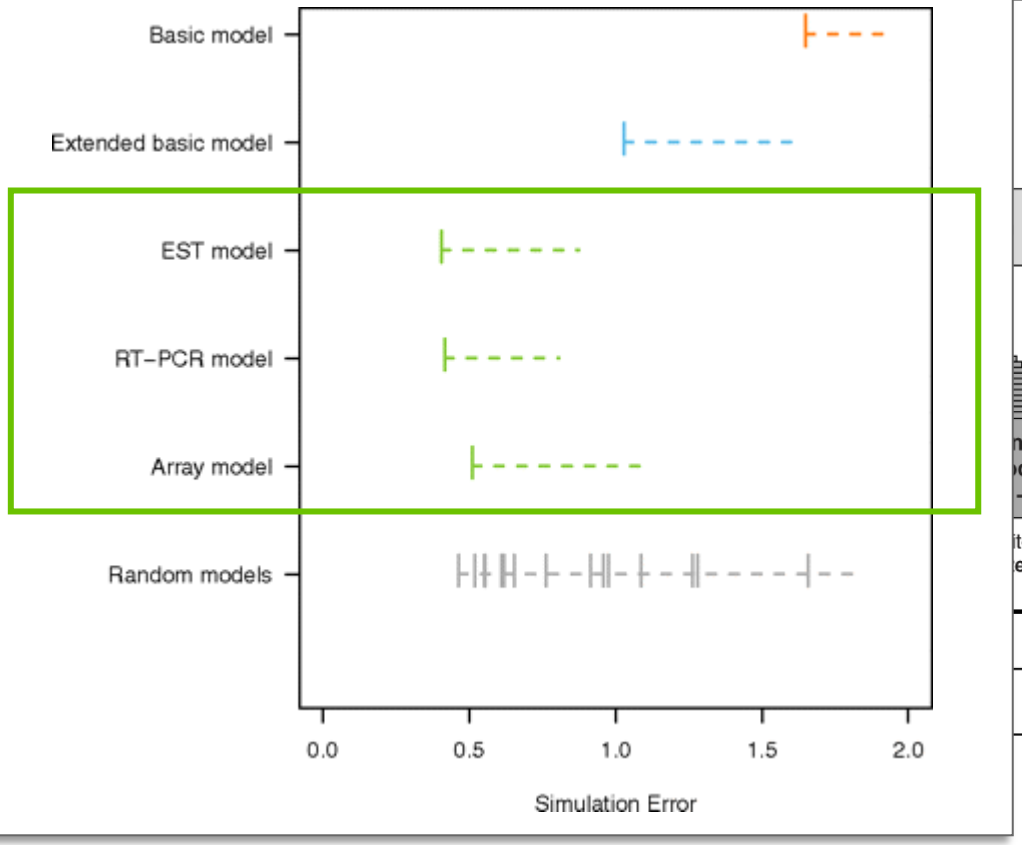
Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

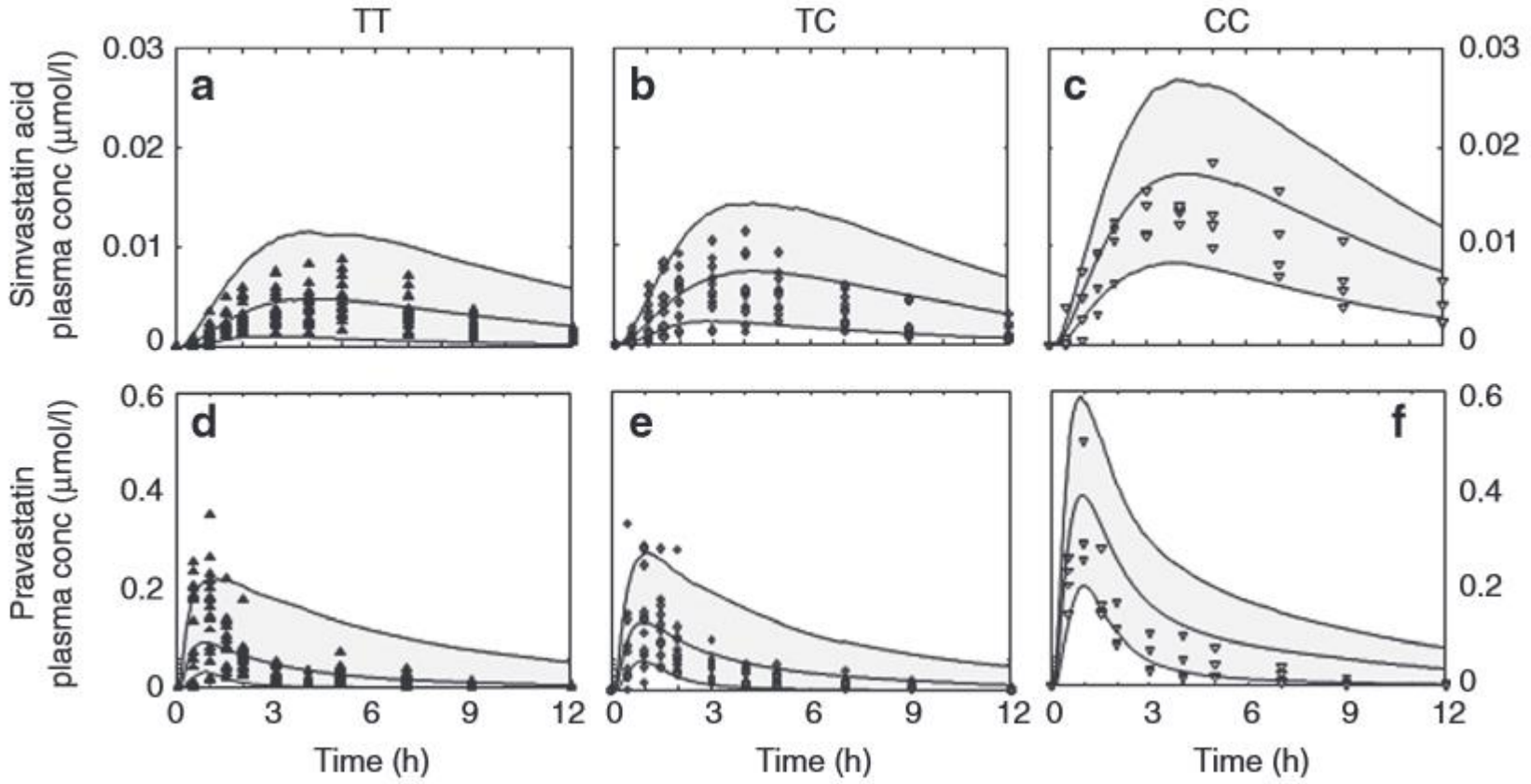
Transporters and their tissue-specific expression once integrated into PBPK models improve performance

Models representing transporter information show optimal performance

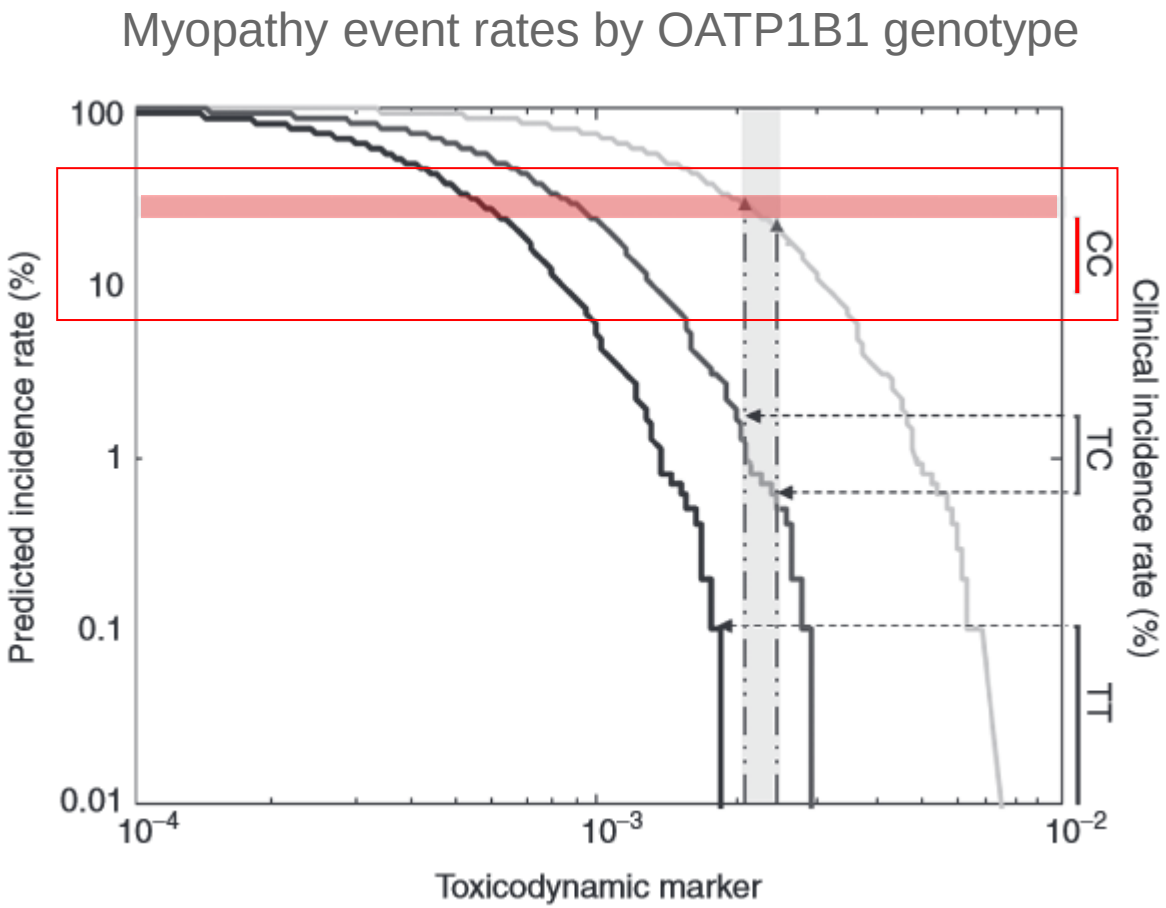




The pharmacogenomics of transporter can be simulated accurately



Event rates of relevant side effects in a small high risk subpopulations can be quantitatively predicted



(Off-)Target Interaction

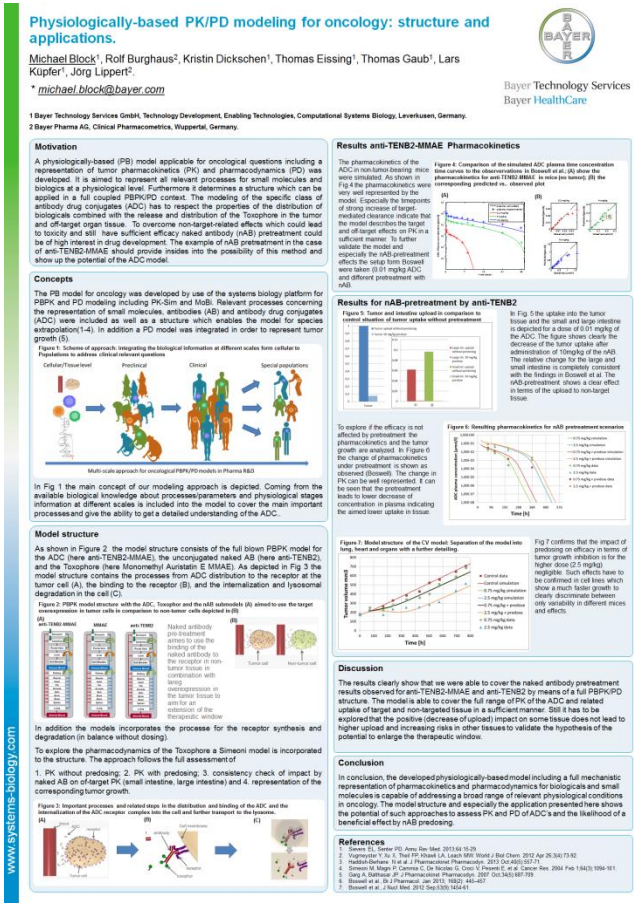
Physiologically-based PK/PD modeling for oncology: structure and applications.

Michael Block[1], Rolf Burghaus[2], Kristin Dickschen[1], Thomas Eissing[1], Thomas Gaub[1], Lars Küpfer[1], Jörg Lippert[2].

* michael.block@bayer.com

1 Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany.

2 Bayer Pharma AG, Clinical Pharmacometrics, Wuppertal, Germany.



Bayer HealthCare

Protein PK, target binding and target mediated processes are available in commercial standard PBPK models

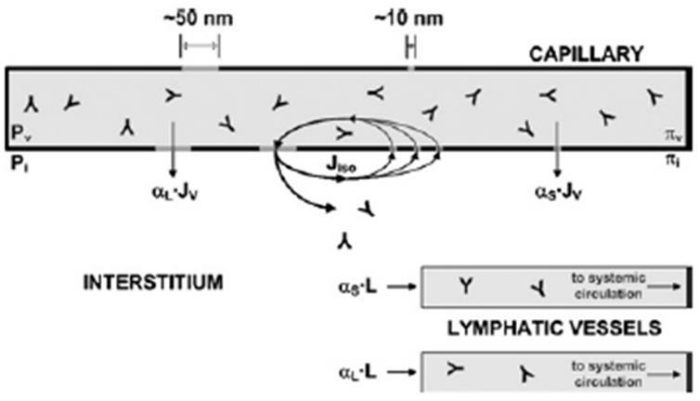


figure taken from Ferl et al., *Ann. Biomed. Eng.* 33, 1640 (2005)

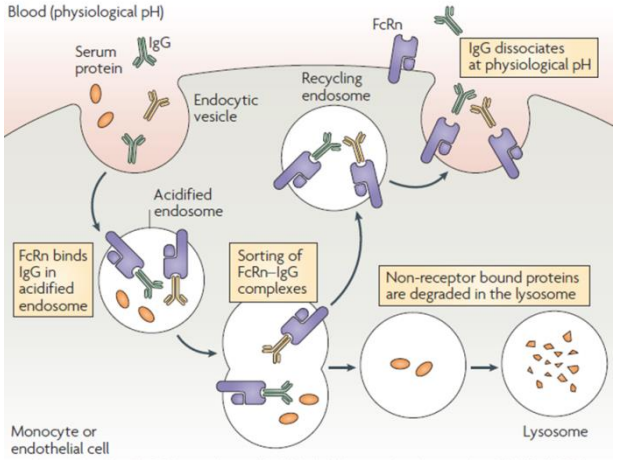
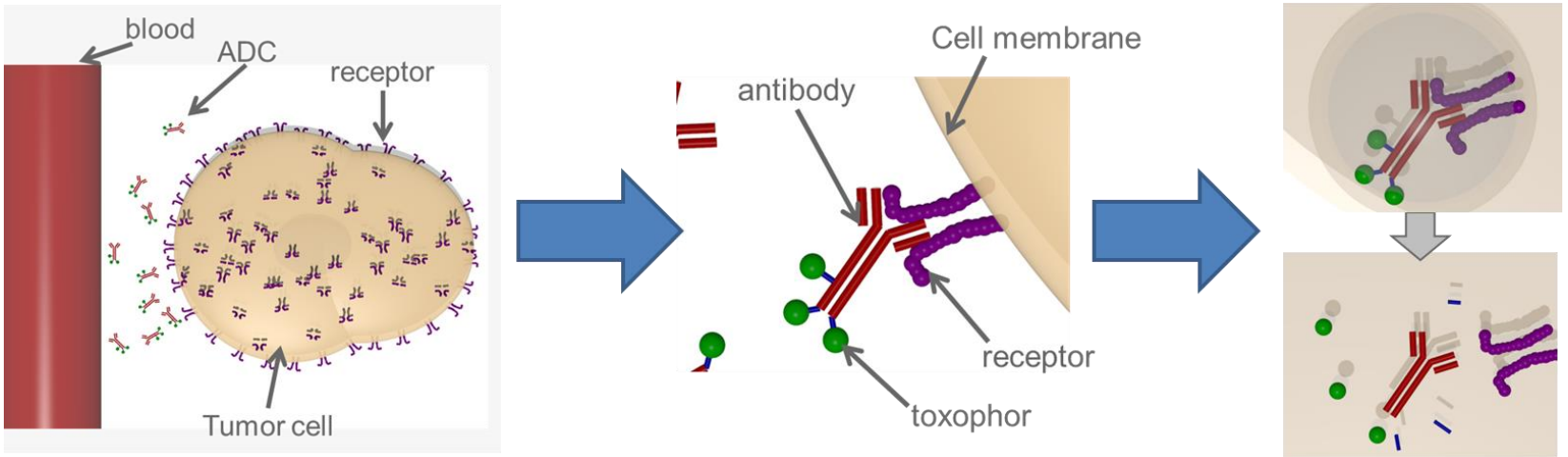
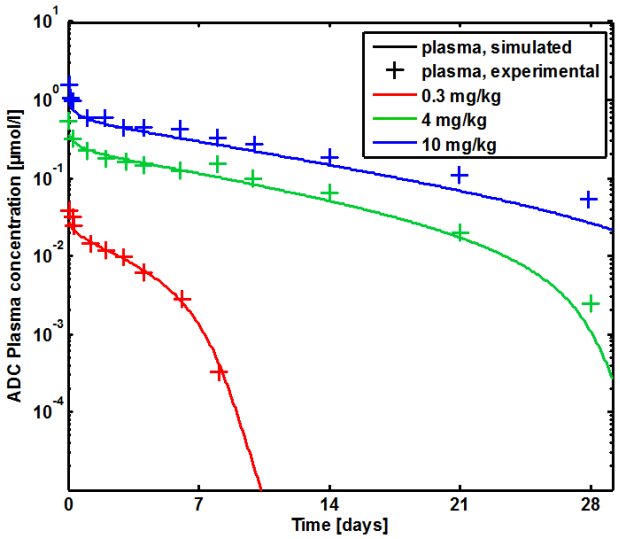


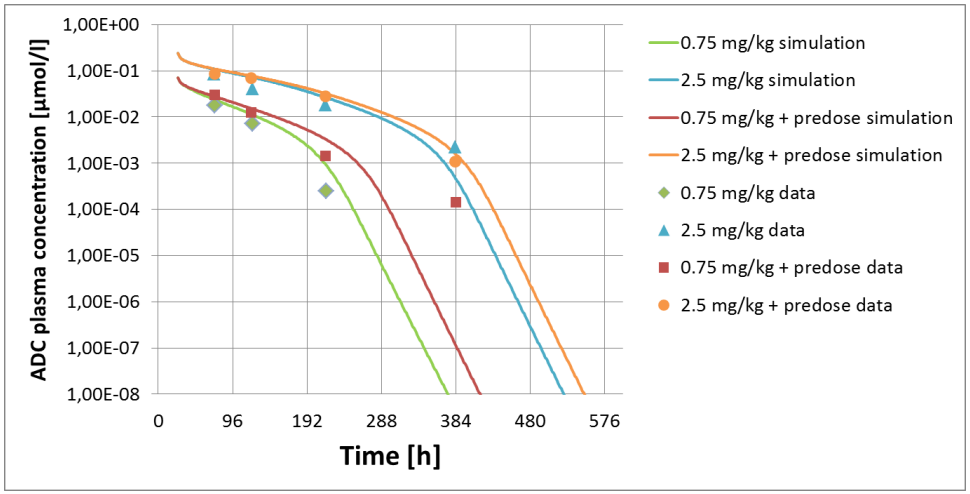
figure taken from D. C. Roopenian and S. Akilesh, Nature reviews immunology, 7, 715, (2007)

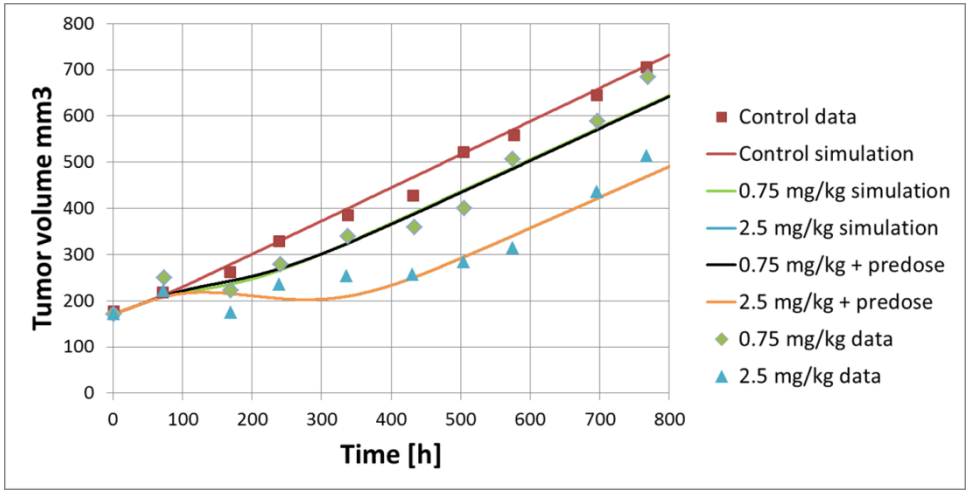


Models for ADCs reflect all relevant properties and allow the simulation of complex scenarios such as nAb predosing

PBPK-PD predictions for TENB2 - MMAE ADC PK and tumor growth







TENB2 - MMAE ADC data taken from
Boswell et al., Br J Pharmacol. Jan 2013; 168(2): 445–457.
Boswell et al., J Nucl Med. 2012 Sep;53(9):1454-61.

Organ Physiology

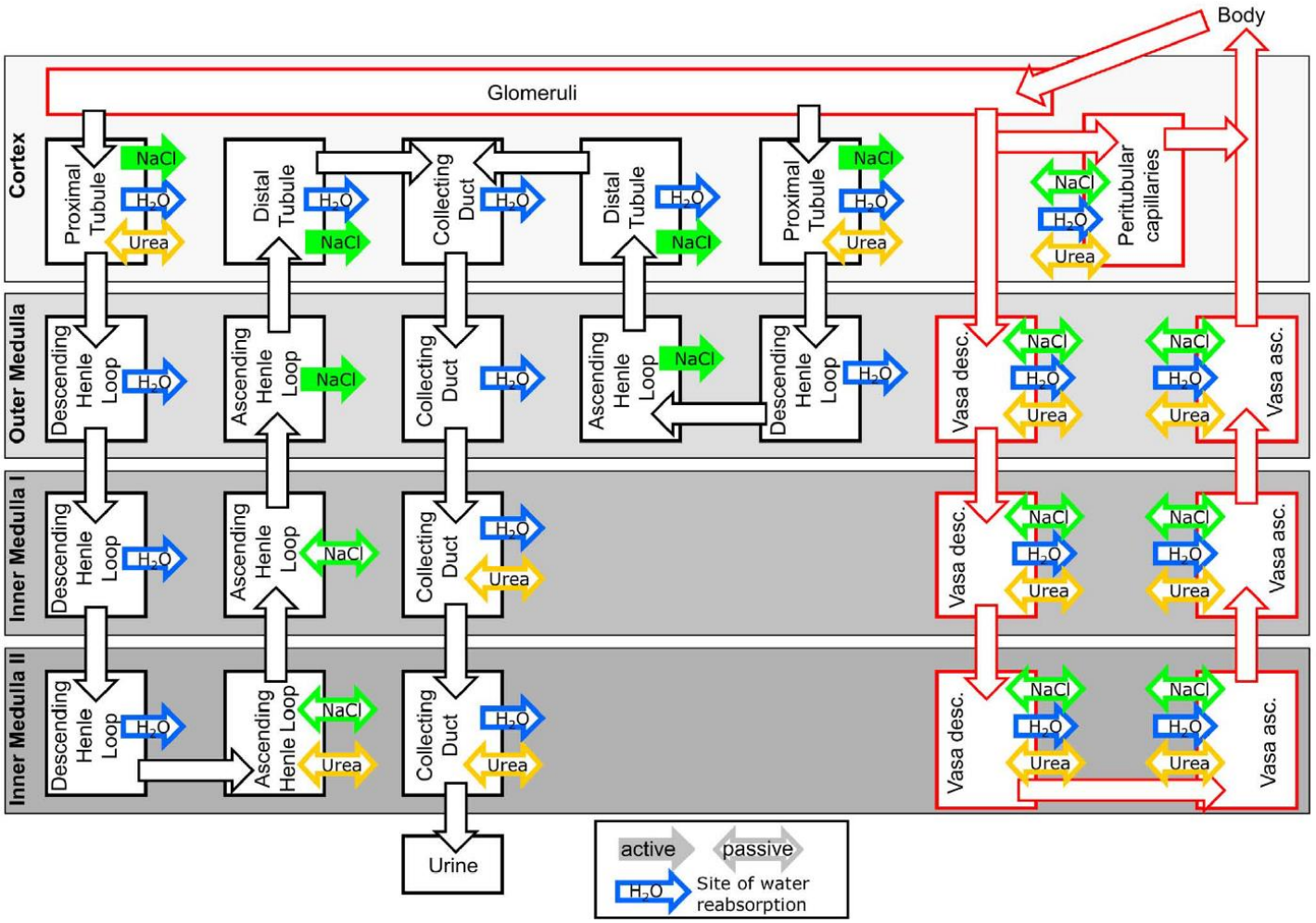
frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 24 January 2013
doi: 10.3389/fphys.2012.00494

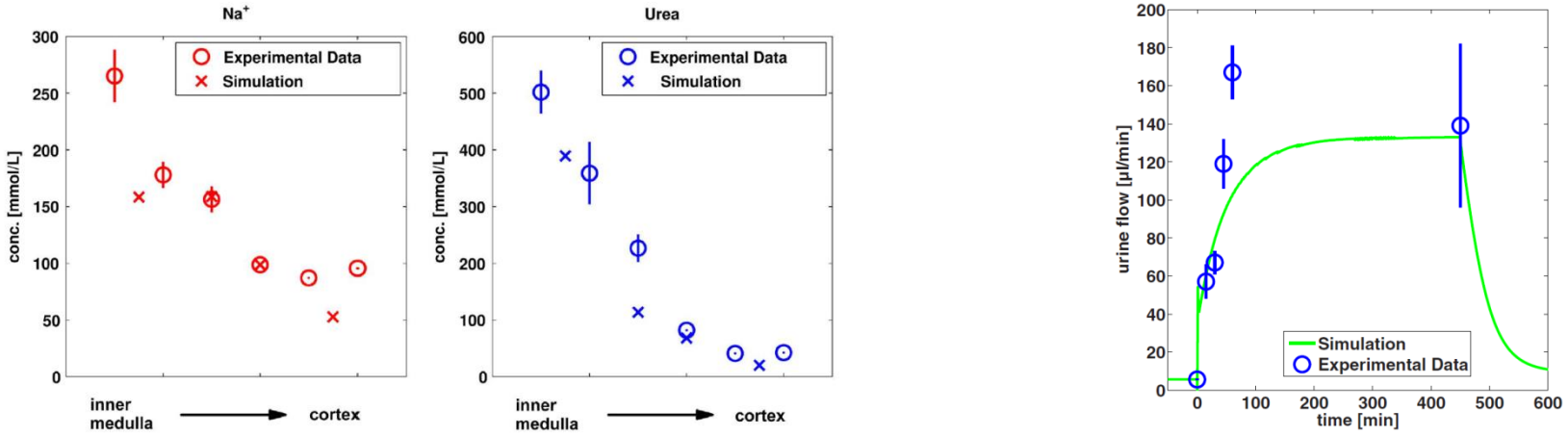
Development of a physiologically based computational kidney model to describe the renal excretion of hydrophilic agents in rats

Christoph Niederalt[1], Thomas Wendl[1], Lars Kuepfer[1], Karina Claassen[2], Roland Loosen[1], Stefan Willmann[1], Joerg Lippert[1], Marcus Schultze-Mosgau[3], Julia Winkler[1], Rolf Burghaus[4], Matthias Bräutigam[5], Hubertus Pietsch[6] and Philipp Lengsfeld[7]*

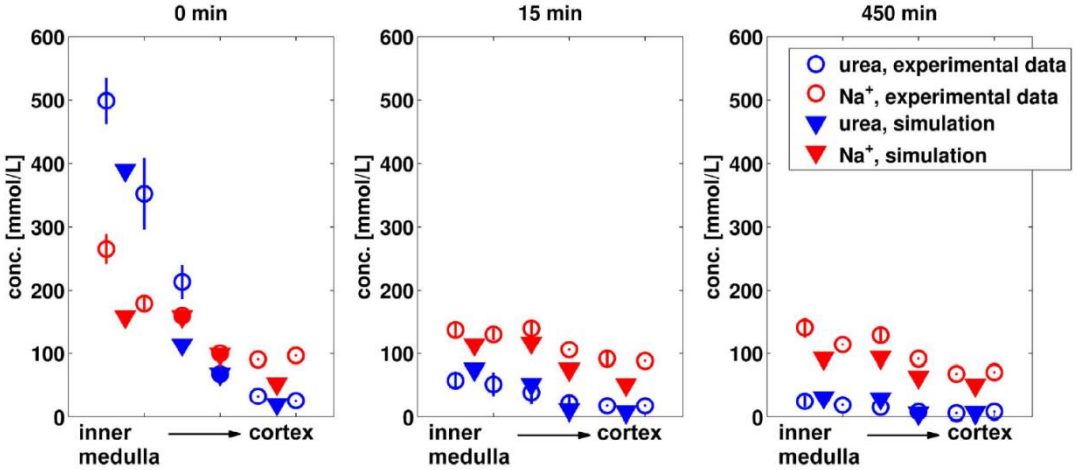
Standard PBPK models can be enhanced to represent organ function



The interaction between organ function and drugs can be studied mechanistically



The impact of mannitol on urine flow and concentration profile



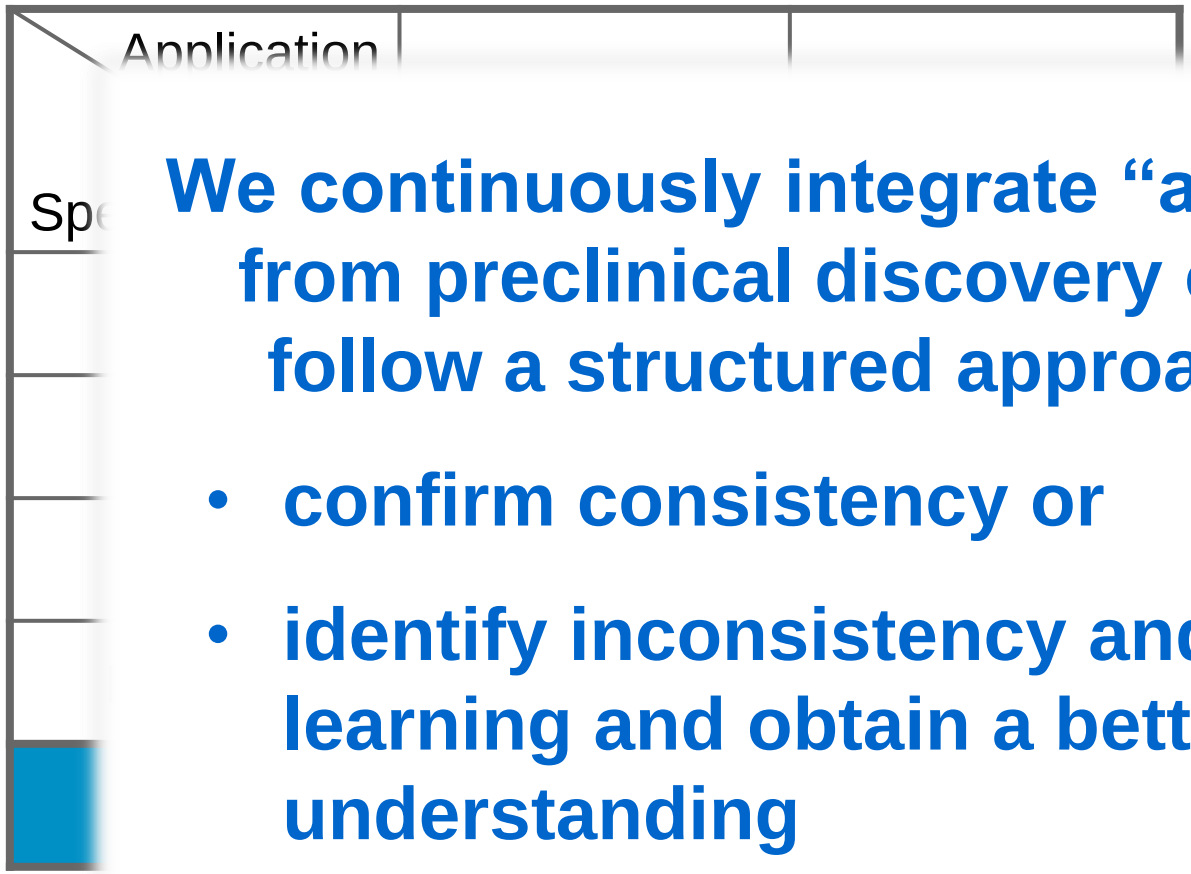
How much biology can we capture with PBPK?

- Commercial state-of-the-art PBPK modeling platforms PK-Sim® already provide implementations for all classical aspects of ADME, pharmacokinetics and pharmacogenomics
- Within these platforms models can be extended to MoBi® customized PBPK-PD-physiology models to represent specific aspects relevant for a project / application
- PBPK is not constrained by modeling technology or feature lists of modeling tools but only by limits to our pharmacological understanding
- When applied systematically, PBPK can provide clinically relevant insights clearly beyond the limits of PK

Agenda

- Why do we use PBPK?
- How much biology can we capture with PBPK?
- **How do we apply it?**
- What is still missing?

As a representation of information, data, and assumptions the PBPK model enables continuous explicit check of consistency

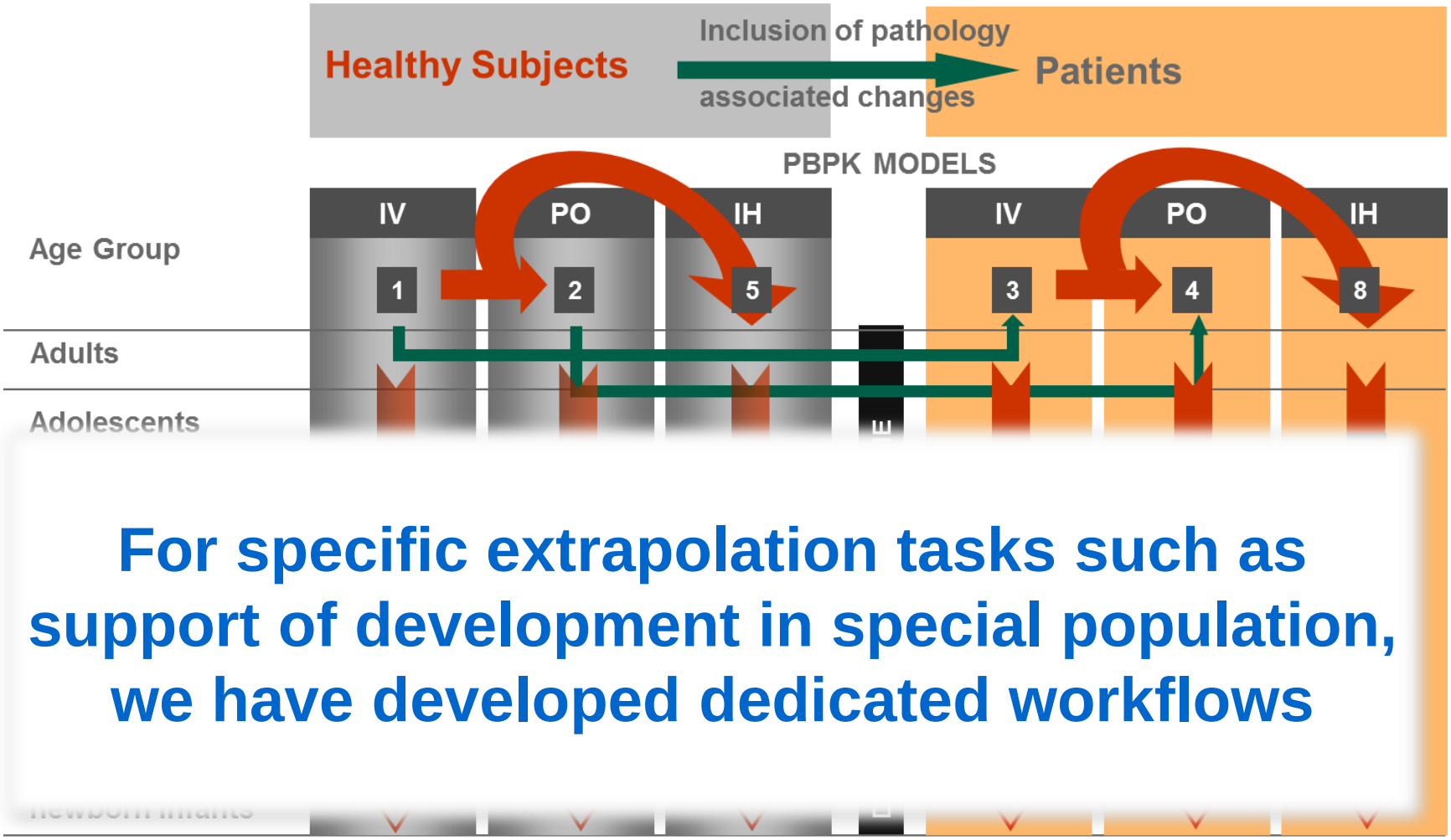


We continuously integrate "all" information from preclinical discovery on and try to follow a structured approach to either

- **confirm consistency or**
- **identify inconsistency and guide active learning and obtain a better understanding**

in each step

A systematic staggered approach minimizes uncertainty and risk



For specific extrapolation tasks such as support of development in special population, we have developed dedicated workflows

Pediatric Scaling

Clin Pharmacokinet (2014) 53:89–102
DOI 10.1007/s40262-013-0090-5

ORIGINAL RESEARCH ARTICLE

Development of a Paediatric Population-Based Model of the Pharmacokinetics of Rivaroxaban

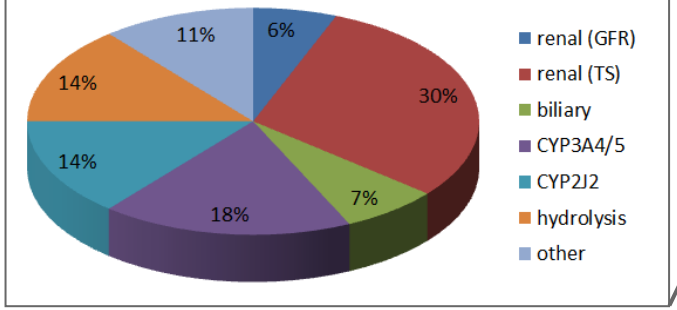
Stefan Willmann · Corina Becker · Rolf Burghaus · Katrin Coboeken · Andrea Edginton · Jörg Lippert · Hans-Ulrich Siegmund · Kirstin Thelen · Wolfgang Mück

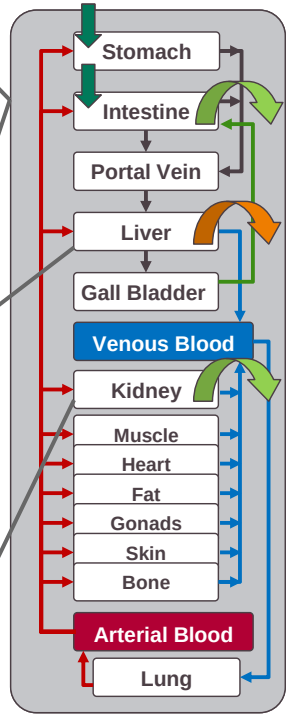
The PBPK model for rivaroxaban integrates all existing ADME information

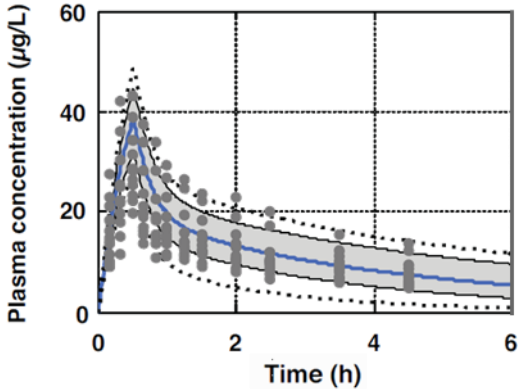
Step 1: Development and validation of a Rivaroxaban PBPK Model for Adults

Development using physico-chemical data, preclinical and clinical IV/PO data:

Lipophilicity	2.275
Plasma Protein Binding	5.1%
Solubility	
solubility in FaSSIF	20 mg/L
solubility in FeSSIF	80 mg/L
Molecular Weight	435.89 g/mol
Intestinal Permeability	
in the small intestine	4.74 x 10^{-6} cm/s
in the large intestine	9.48 x 10^{-6} cm/s





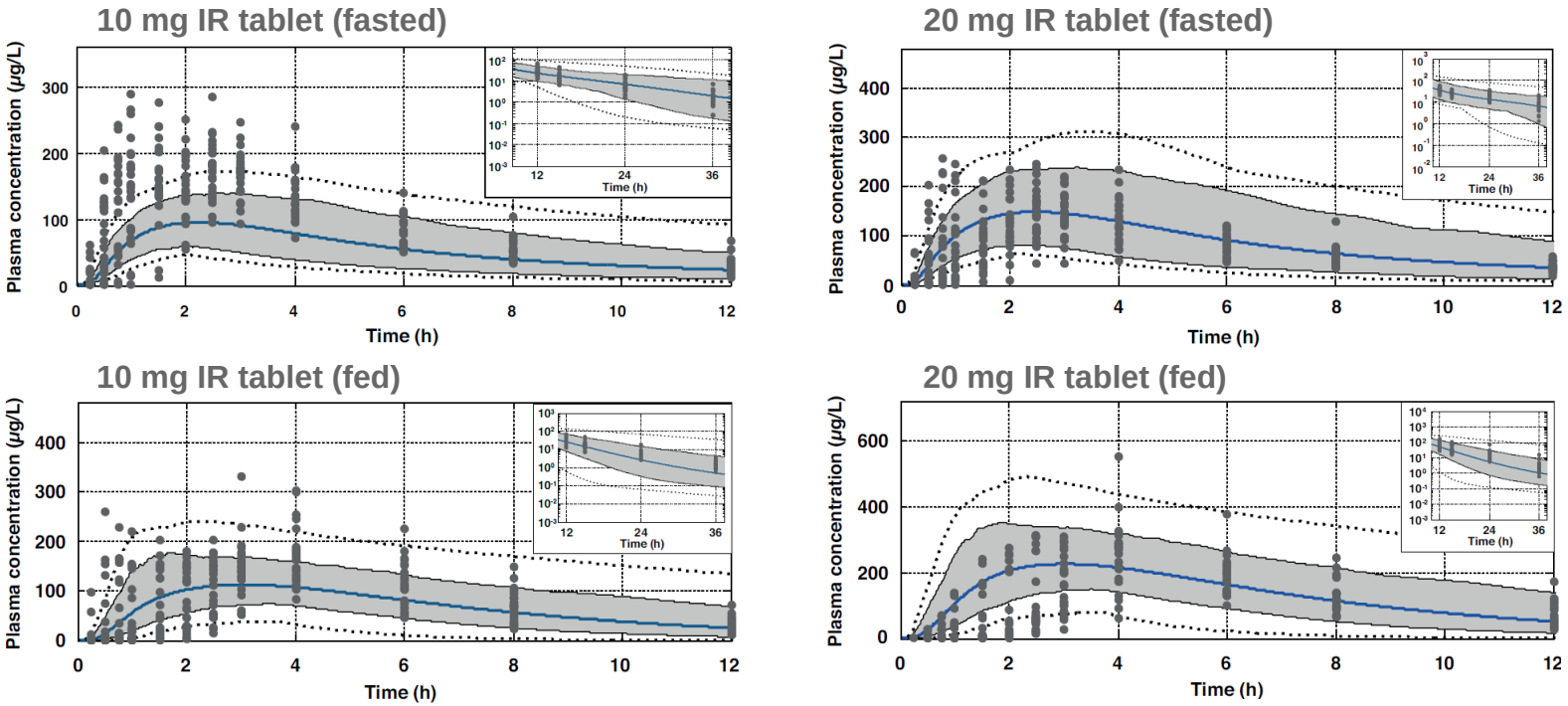


Willmann et al., Clin. Pharmacokin. 2014

The model represents PK in adults

Step 1: Validation of a Rivaroxaban PBPK Model for Adults

Validation: Comparison of PBPK model predictions with phase I study data

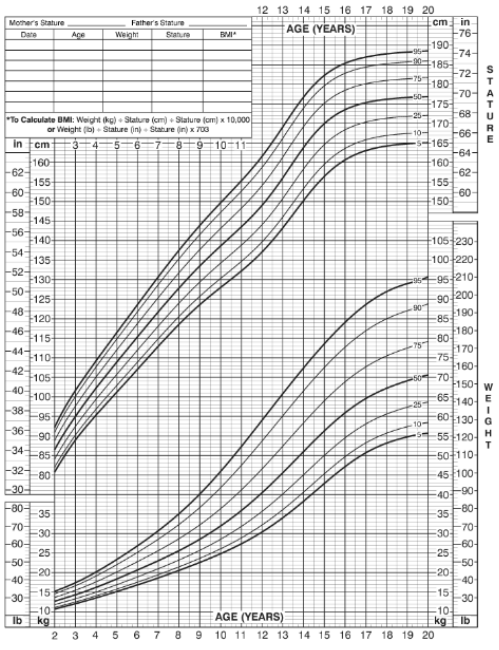


Willmann et al., Clin. Pharmacokin. 2014

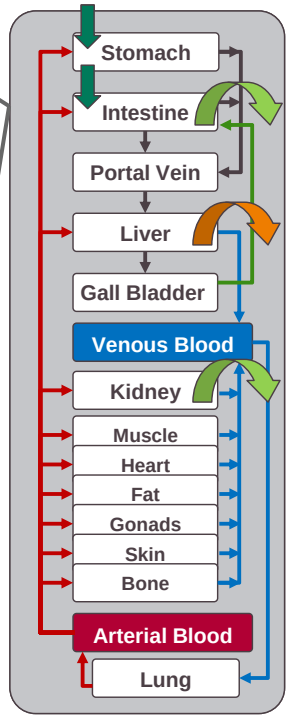
The scaling to children is based on prior knowledge about 1. growth

Step 2: Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age



*www.**cdc**.gov/**growthcharts***



Edginton et al., Clin. Pharmacokin. 2006

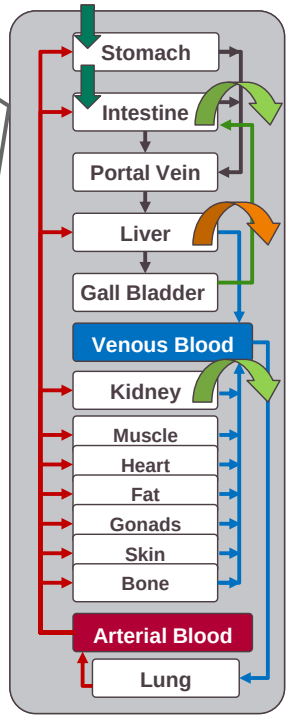
The scaling to children is based on prior knowledge about 2. maturation

Step 2: Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age

Parameter	Newborn	1y	5y	10y	15y	Adult (30y)
Organ blood flow (mL/min)						
adipose	30	12	171	250	315/484[a]	325/502[a]
brain	180	700	900	840/750[a]	805/708[a]	780/708[a]
gonads	0.3	0.6	1.7/0.7[a]	2.5/1.0[a]	3.2/1.1[a]	3.3/1.2[a]
heart	24	48	136	200	252/285[a]	260/295[a]
kidneys	110	230	577	854	1335/950[a]	1325/1120[a]
large intestine	24	48	136	200	251/285[a]	260/295[a]
liver	39	78	221	325	409/370[a]	423/383[a]
muscle	31	72	212	429	941/646[a]	1105/665[a]
pancreas	6	12	34	50	63/57[a]	65/59[a]
skeleton	30	60	170	250	315/285[a]	325/295[a]
skin	30	60	170	250	315/285[a]	325/295[a]
small intestine	60	120	340	500	630/627[a]	650/649[a]
spleen	18	36	102	150	189/171[a]	195/177[a]
stomach	6.0	12	34	50	63/57[a]	65/59[a]
Portal blood flow (mL/min)	114	228	646	950/950[a]	1197/1197[a]	1235/1239[a]
Q_H (mL/min)	153	306	867	1275/1273[a]	1600/1566[a]	1660/1620[a]
Bodyweight (kg)	3.5	10	19	32	56/53[a]	73/60[a]
Height (cm)	51	76	109	138	167/161[a]	176/163[a]

a Male/female.

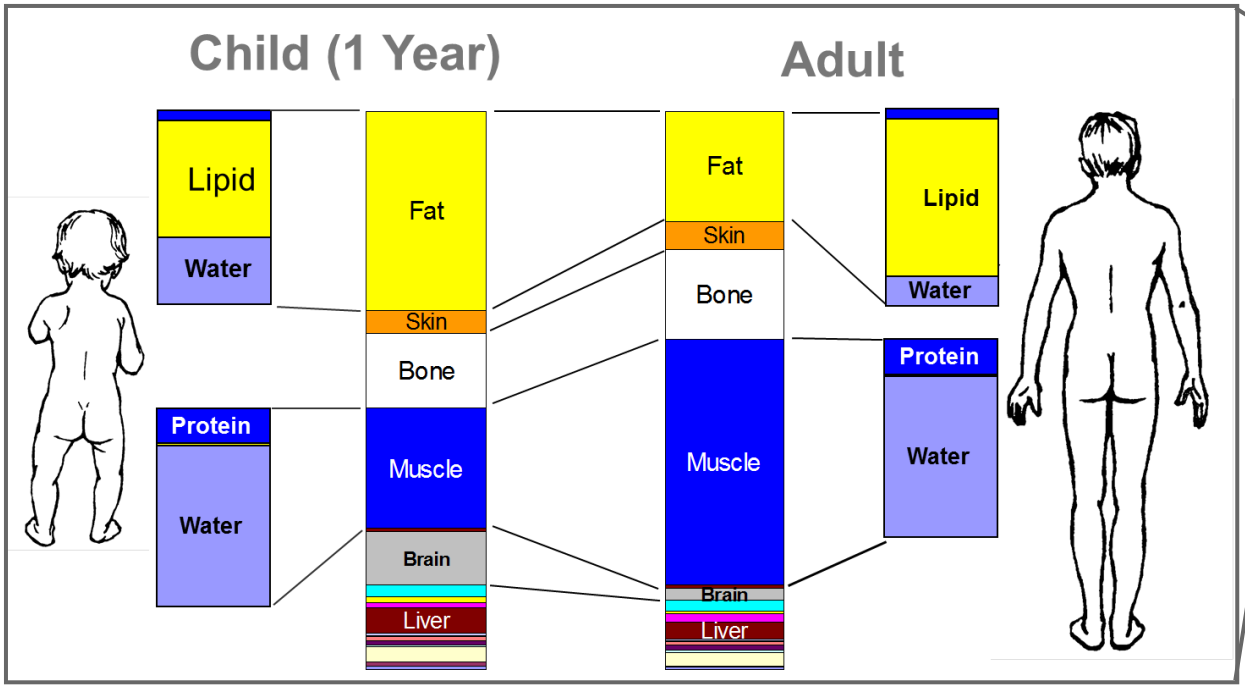


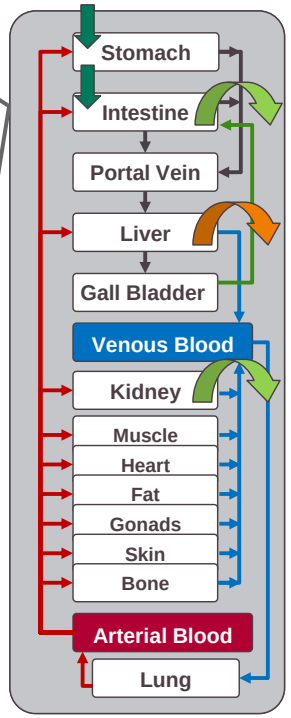
Edginton et al., Clin. Pharmacokin. 2006

The scaling to children is based on prior knowledge about 2. maturation

Step 2: Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age



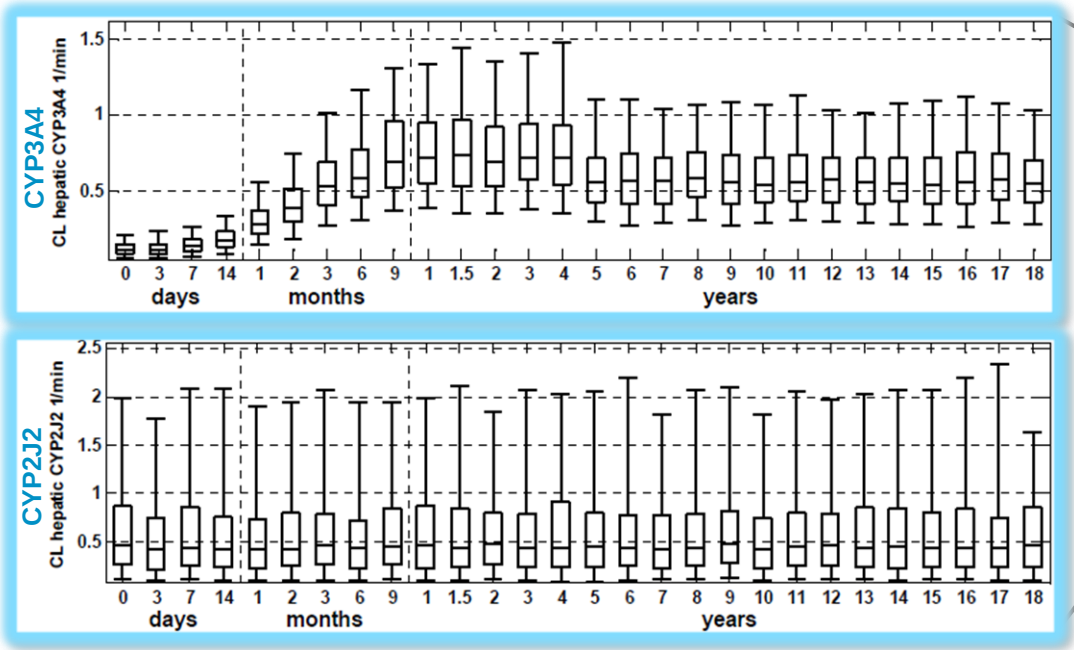


Edginton et al., Clin. Pharmacokin. 2006

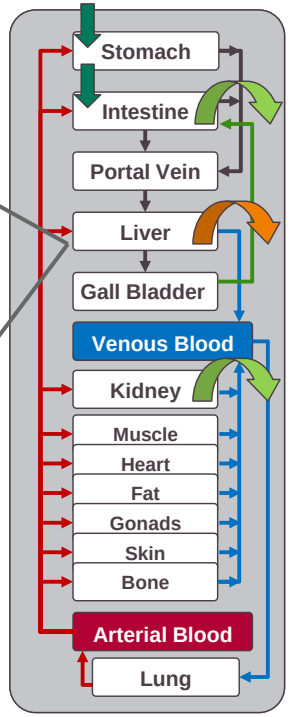
The scaling to children is based on prior knowledge about 2. maturation

Step 2: Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of ontogeny information for relevant processes



*** CYP3A4/5**
*** CYP2J2**



Willmann et al., Clin. Pharmacokin. 2014

Population simulations provide expectations about exposure in children

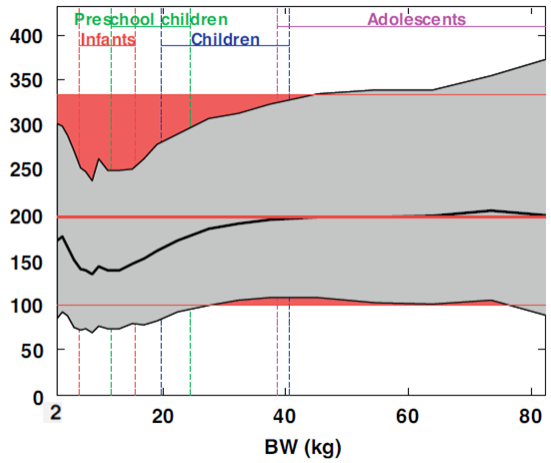
Step 3: Prediction of Rivaroxaban pharmacokinetics in pediatric populations

Simulations of virtual pediatric populations according to study proposal

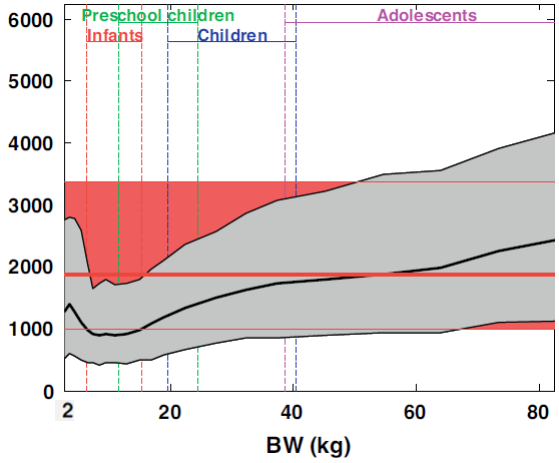
- mixed gender (male:female = 50:50), fasted:fed state = 50:50
- Rivaroxaban doses: 10 mg/70 kg and 20 mg/70 kg
- influence of formulation needs to be considered (tablet vs. suspension)

Results (dose = 20 mg/70 kg, pooled for gender and fasted/fed):

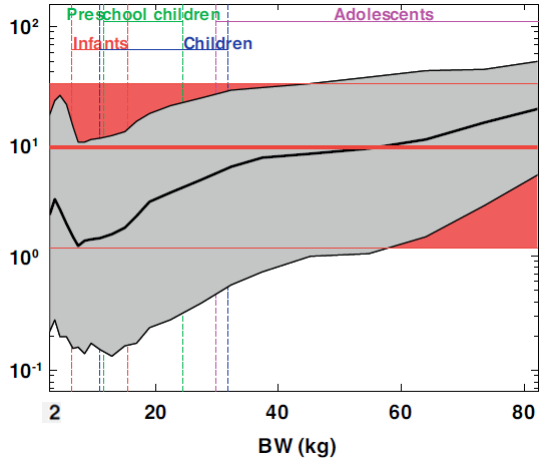
C_{max} [µg/L]



AUC_{inf} [µg h/L]



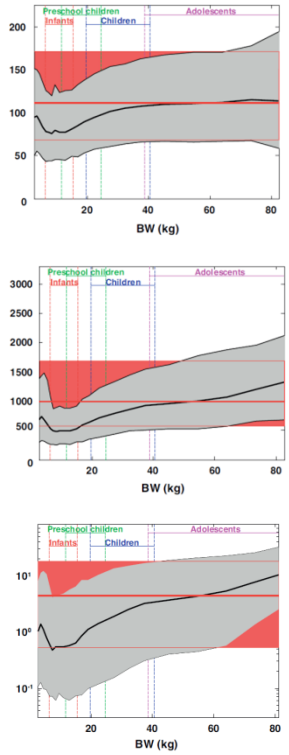
C_{24h} [µg/L]



Willmann et al., Clin. Pharmacokin. 2014

To match exposure to levels known to be efficacious and safe in adults dose adjusted are calculated

Step 3: Prediction of Rivaroxaban pharmacokinetics in pediatric populations



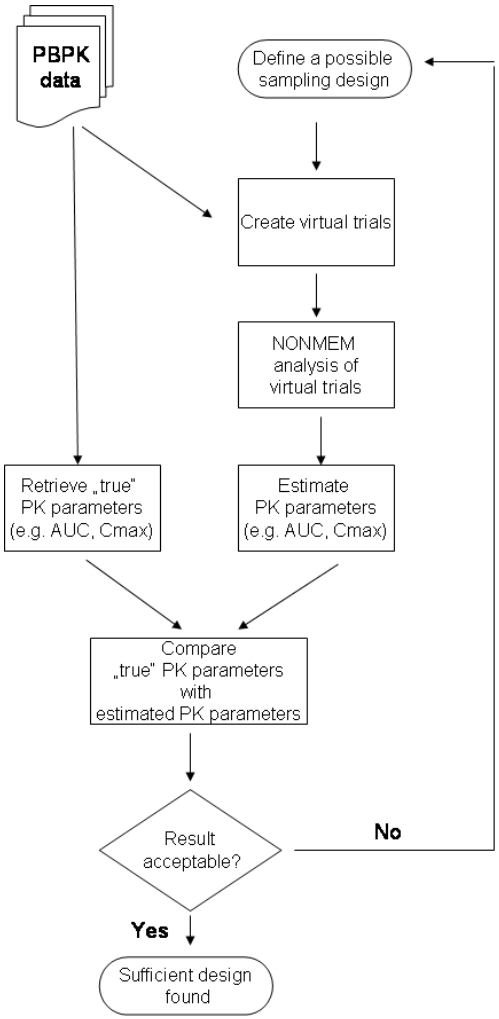
Result: Age and body weight adapted dosing table

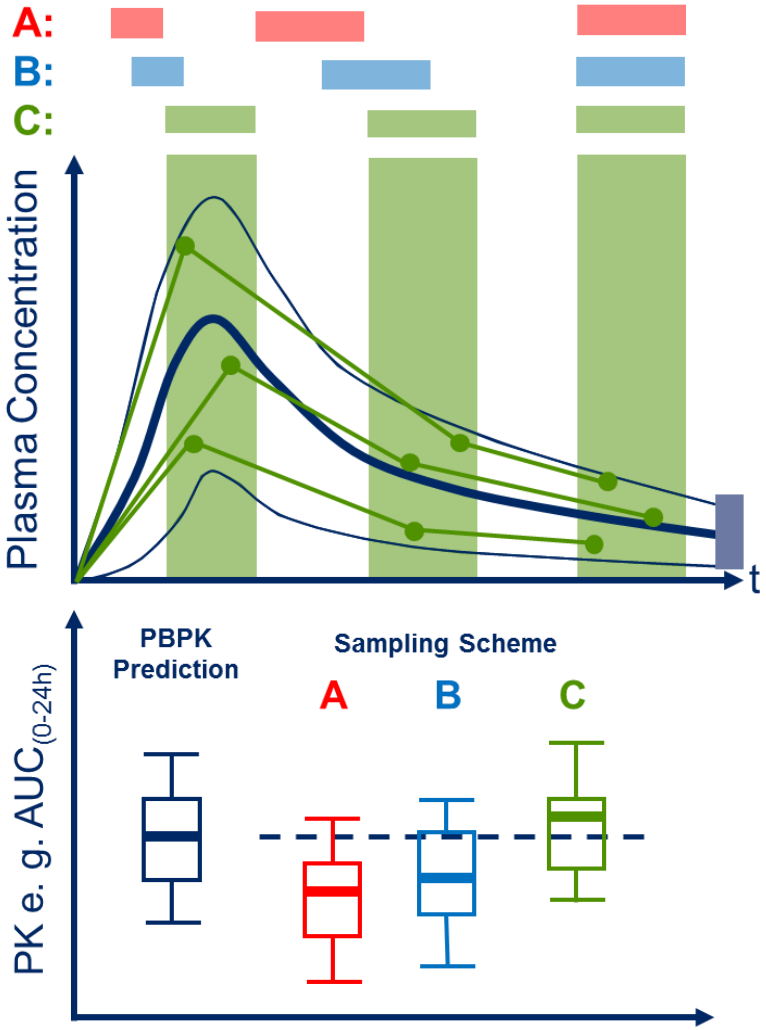
Age group	Body weight [kg]	Dose	
		Tablet	Suspension
Body weight			

Clinical Trial Simulations with PopPK based on PBPK simulations help to optimize sampling design in pediatric trials

Step 4:

Sampling schemes are optimized for accurate determination of PK parameters with a minimum of samples



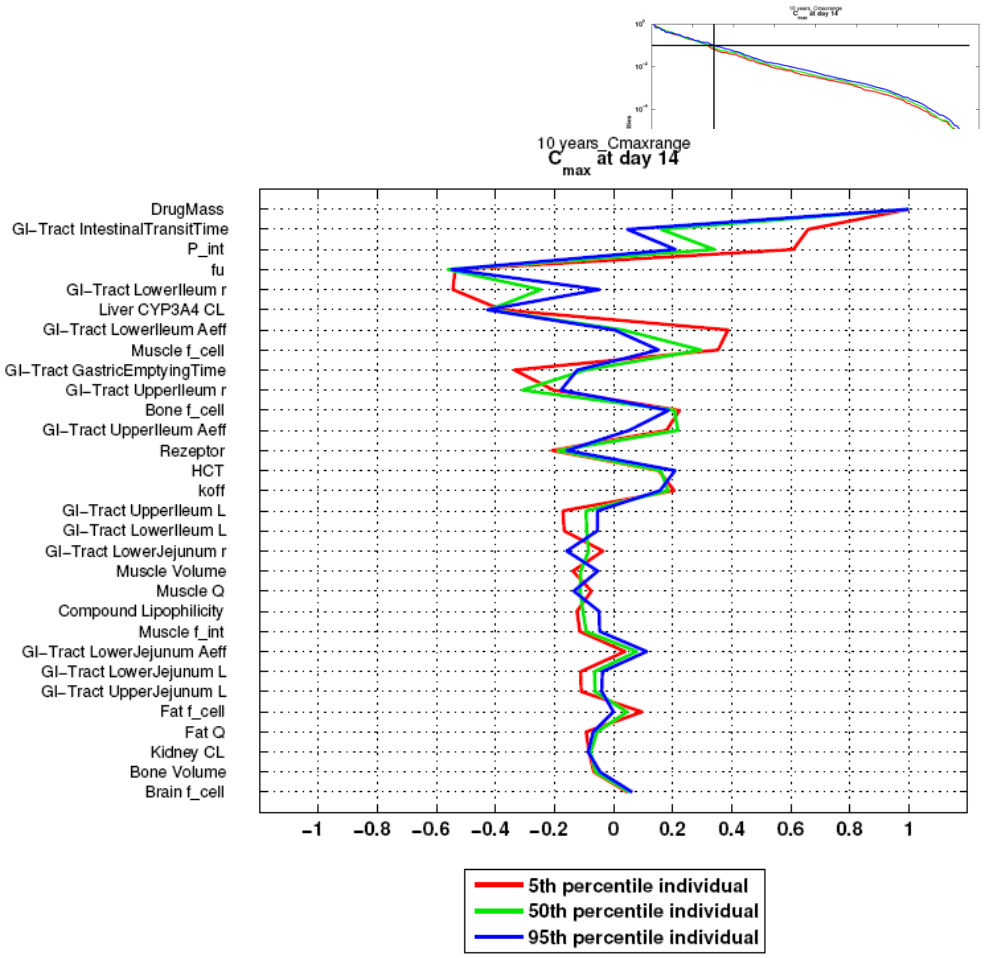


Evaluation of the sensitivities of simulated outcomes to model parameters is a mandatory risk assessment measure

1. Determination of globally normalized sensitivities of all (independent) parameters
2. Determination of cut-off using integral sensitivity threshold
3. Detailed analysis and discussion of dominant “factors” using standard report format

Check of understanding!

Discussion of sensitivities is the natural step for an assessment of uncertainty, lack of understanding and resulting risks!



How do we apply it?

1. Continuous integration of all information and on-going check of consistency at each development (project) step
2. Consistent use of the same fully transparent base PBPK model across all therapeutic areas, projects and development stages from discovery to clinic
3. Explicit formulation and documentation of all assumptions and evaluation of sensitivities of predictions to these

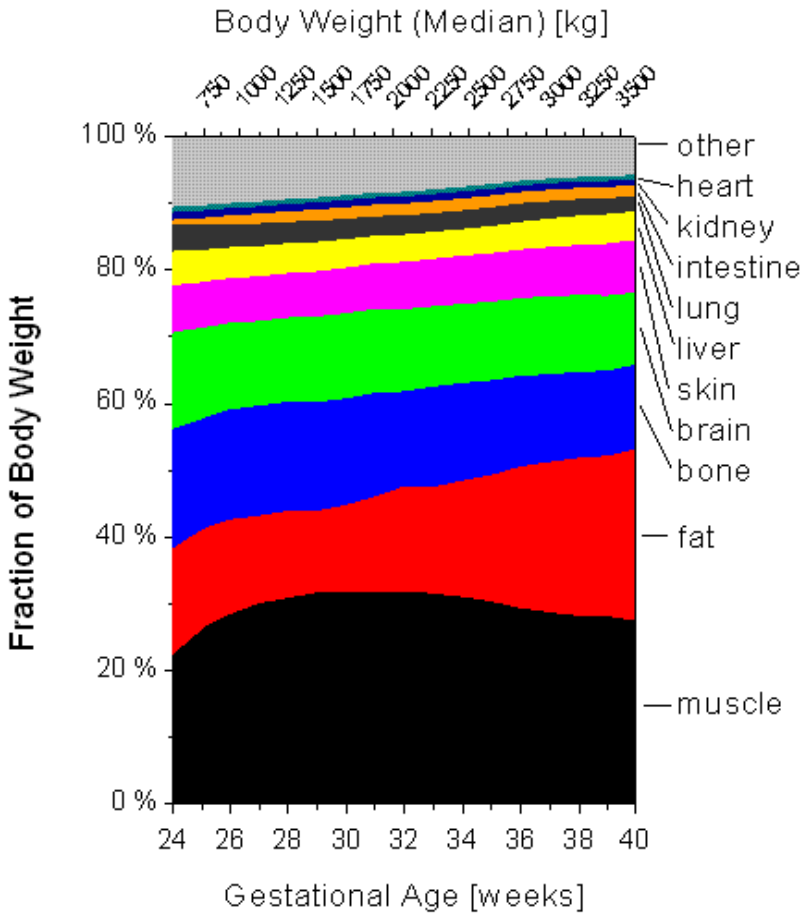
PK-Sim®

Full transparency and explicit formulation of assumptions is key to identify non-characterized development risks!

Agenda

- Why do we use PBPK?
- How much biology can we capture with PBPK?
- How do we apply it?
- **What is still missing?**

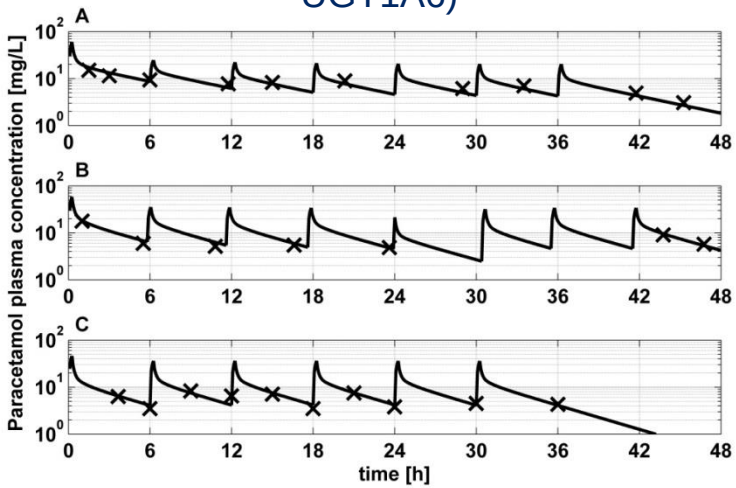
Existing information about anatomy and physiology of **preterm neonates** allows establishment of dedicated PBPK models

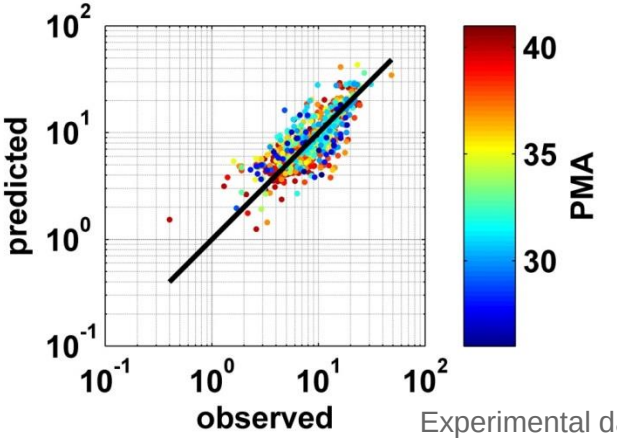


PK-Sim® Database	Early gestation	Mid gestation	Late gestation	postnatal
Oxidative enzymes				
Alcoholdehydrogenase				
ADH		31%*		45%
Cytochrome P450 system				
CYP 1A1		low or no expression*		
CYP 1A2		5%*		10%
CYP 1B1		undetectable*		
CYP 2A6		low or no expression*		
CYP 2A13		undetectable*		
CYP 2B6		50%		
CYP 2C		0%*		3%
CYP 2C9	0%	4-5%	10%	25%
CYP 2C18		undetectable*		
CYP 2C19	0%	1%	10-20%	50%
CYP 2D6	5%	5%	6%	9%
CYP 2E1	0%	0%	0%	10%
CYP 3A4		3%		13%
CYP 3A5		is present, no change as function of age*		
CYP 3A7		500%*		130%
FMO system				
FMO1	100%	50%	25%	0%
FMO3	0%	0%	0%	50%
Conjugation enzymes				
Epoxide hydrolase				
EPHX1	6%	10%	32%	50%
Glutathione S-transferases				
GSTM (GST1)		22%*		93%
GSTA (GST2)		25%*		62%
GSTP (GST3)		5300%*		2100%

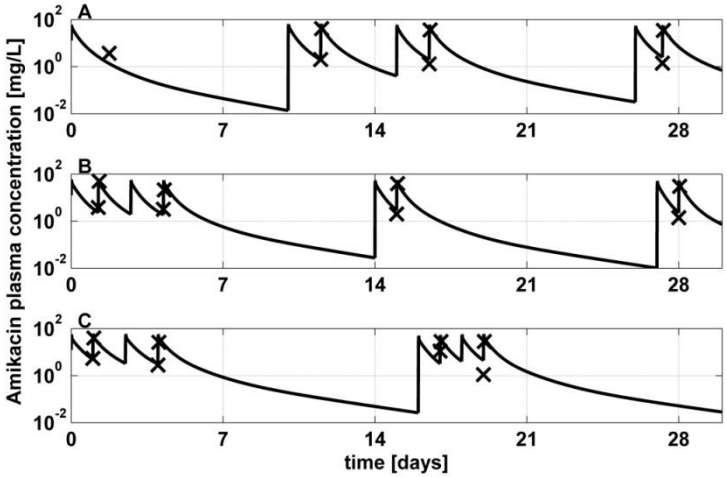
Prediction of Therapeutic Drug Monitoring (TDM) data already shows promising performance but reveals current limitations

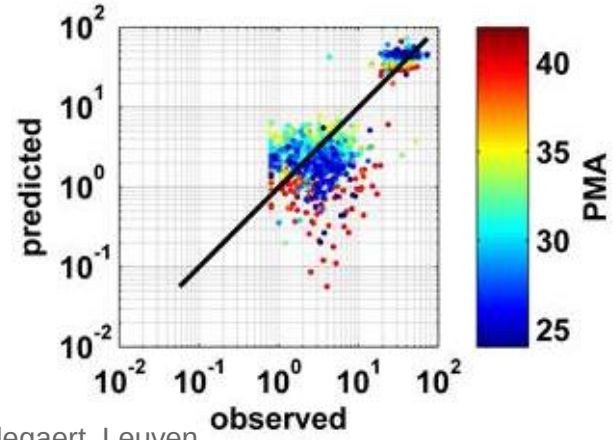
Paracetamol TDM (CYP2E1, SULT1A1, and UGT1A6)





Amikacin TDM (glomerular filtration)



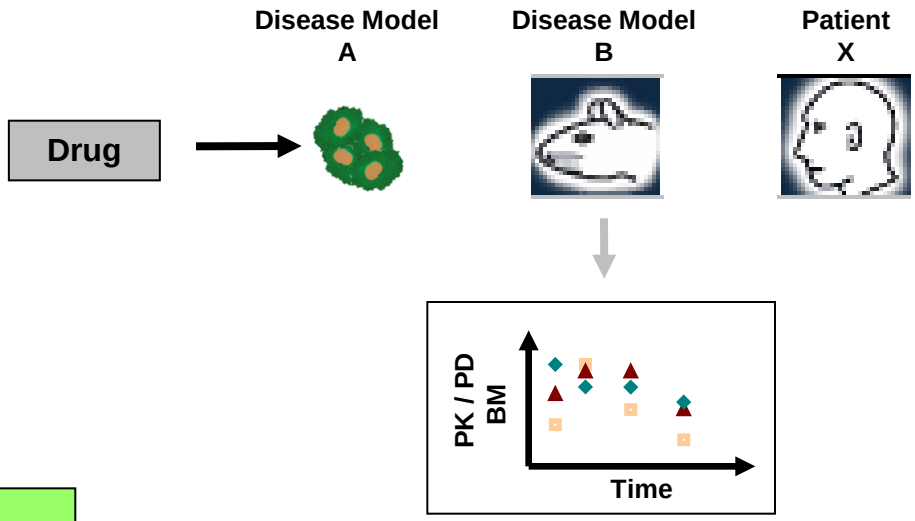


Experimental data provided by Dr. Karel Allegaert, Leuven

The knowledge base is broad, our knowledge gaps are significant

- Knowledge about anatomy, physiology and liver enzymes is already considerable
- In other highly relevant areas (**target**, **transporter proteins** etc.) we often rely on assumptions such as
  - constant specific expression level is assumed
  - target protein maturation is assumed to be similar to

PBPK provides a means to systematically implement the Probe Study Concept to all trials in order to learn continuously and generalize knowledge



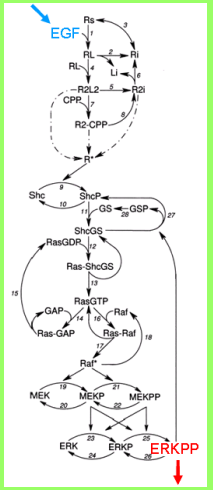
Drug Property Knowledge

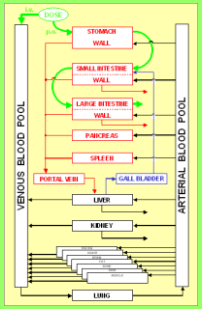
Use of prior information

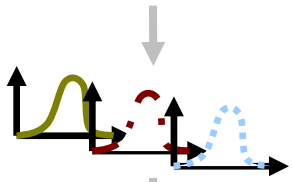
MCMC-based Bayesian Analysis

Use of prior information

Model-Based Representation of Biological Knowledge





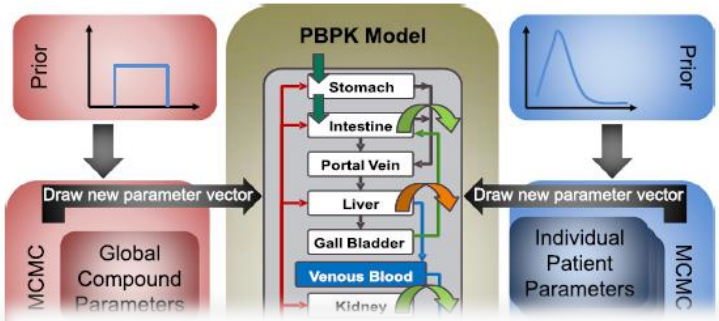


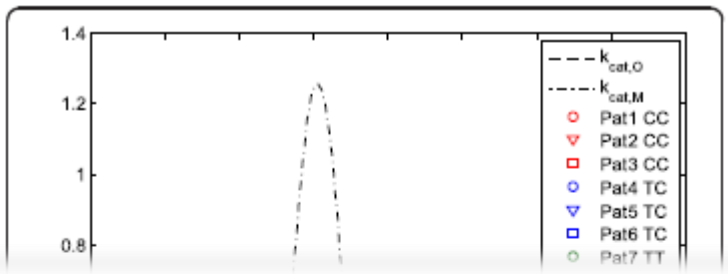
Extraction of posterior information

De-convolution & Identification of Systems Parameters, MoA & Drug Parameters

Extraction of posterior information

Application of Bayesian MCMC with PBPK to clinical data is feasible





PBPK-MCMC platform allows companies the continuous build-up of proprietary knowledge bases.

Agencies could develop an across-industry knowledge base of priors for future data interpretation and predictions!

What is still missing?

Coordinated, state-of-the-art (Bayesian) exploitation of rapidly growing database of pediatric trial data and continuous improvement of all priors (anatomy, physiology,…) for PBPK modeling and simulation

Science For A Better Life

Thank you!