Statens legemiddelverk
Norwegian Medicines Agency

A modeling and simulation perspective on extrapolation

EMA Workshop on extrapolation of efficacy and safety in medicine development across age groups, 17 – 18 May 2016, European Medicines Agency, London

Ine Skottheim Rusten

on behalf of the Modeling and Simulation Working Group (MSWG)

What facilitates informed extrapolation?

Decision making

Expert opinion
= estimation or prediction

Warning of past events:
A change in paradigm!

Modeling and simulation

The philosophy of M&S

and why should clinicians and regulators encourage explicit quantitative modeling?

A method to test our understanding of a particular system or process

- useful to describe a set of data
- can integrate different sources of data

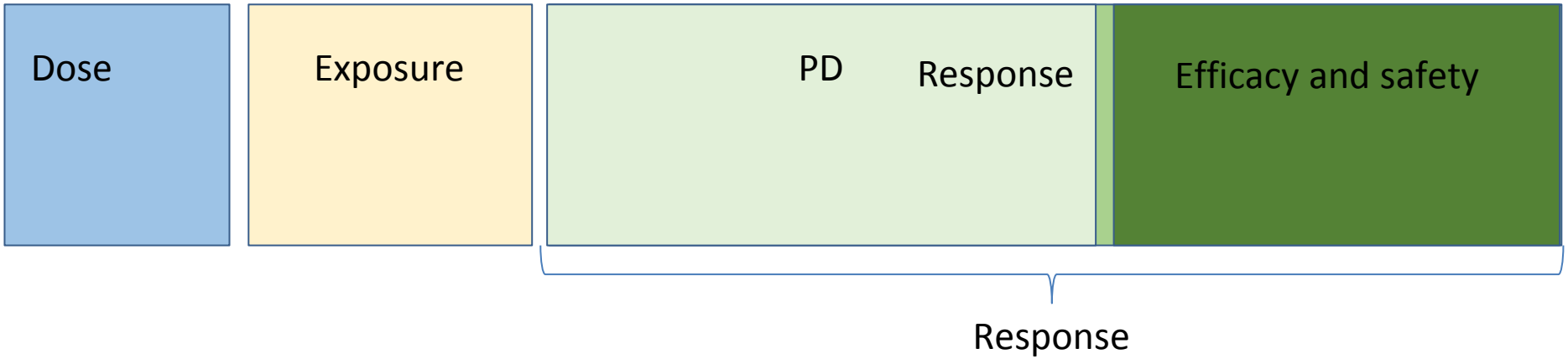
- helps making assumptions explicit
- helps identify uncertainty and can help explore impact of uncertainty

- leads way to predictions to inform transitions

The sign of a mature science

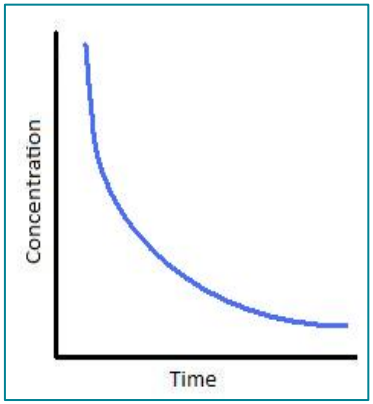
- > not only describe, but able to predict

Dose Exposure Response (DER)



Paediatric models

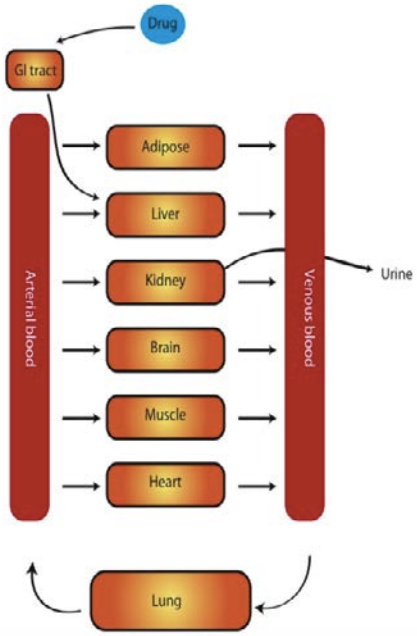
- Size models (weight, BSA, allometry)
- Maturation models
- Organ function models
- Co-variate models
- Exposure response models
- Disease models



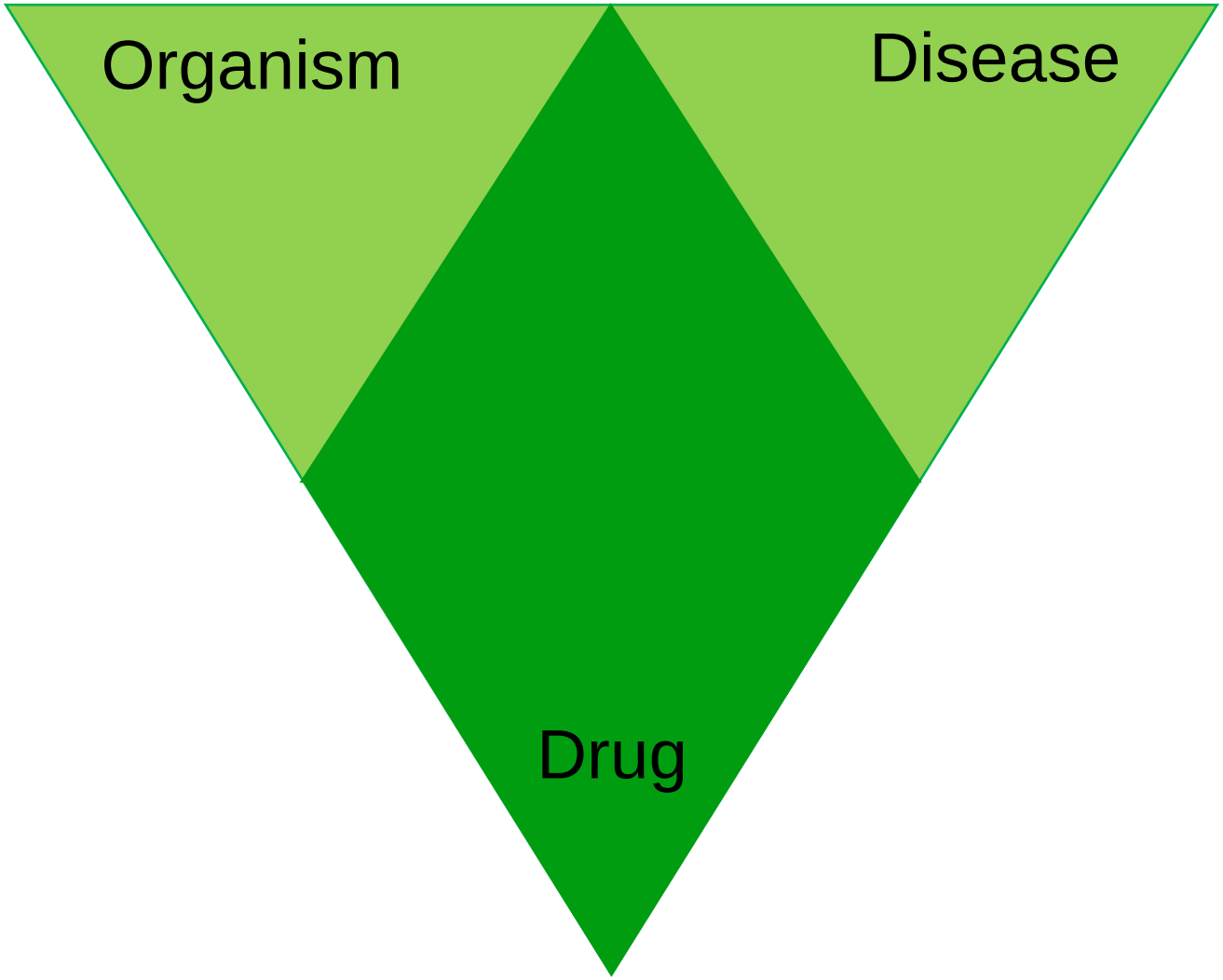
$C = C(0)*e^{(t*k)}$

$C = C(0)*e^{(t*CL/V)}$

$CL_{child} = CL_{adult} * (BW_{child}/BW_{adult})^{0.75}$

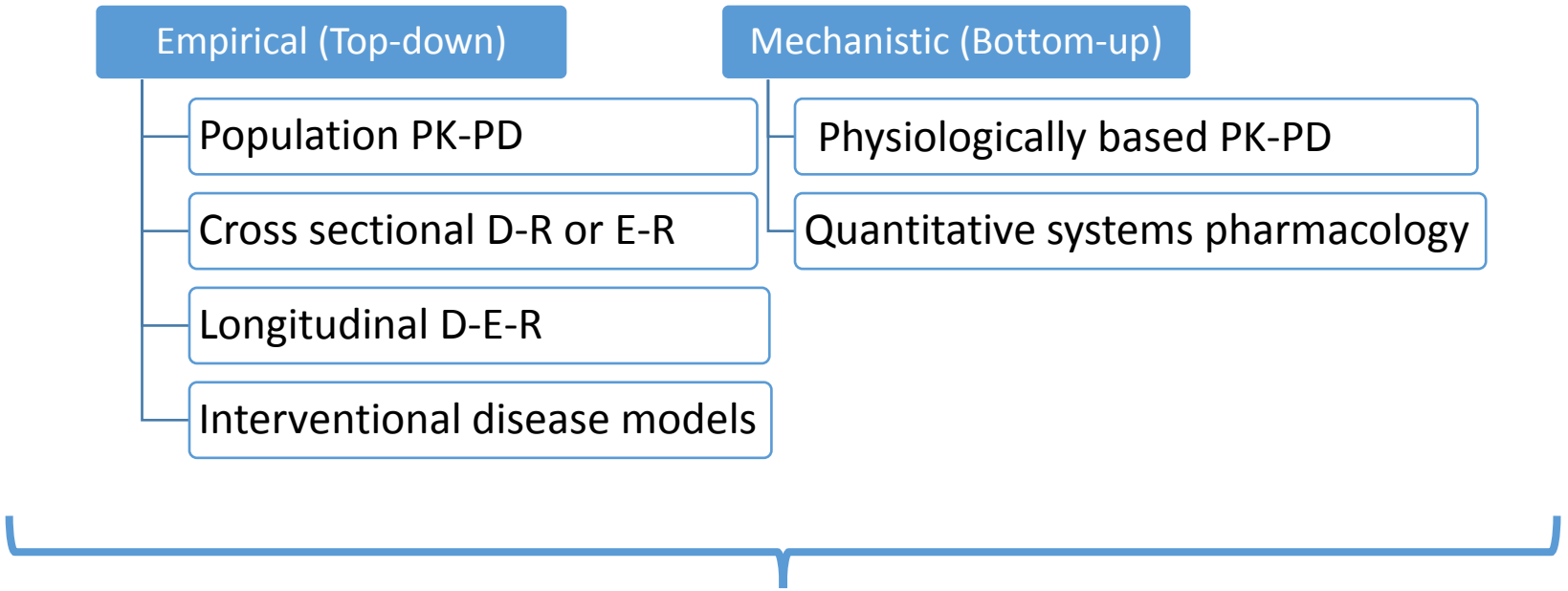


System data



The value of modelling system data extends beyond product specific product development questions and can facilitate drug development as a whole.

Tool box for pharmacological M&S



Combine methods to use all existing knowledge

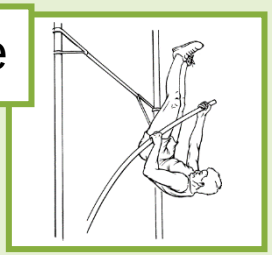
Optimal design and clinical trial simulations to optimize trial design

Framework for M&S in Regulatory Review

High impact

Replace

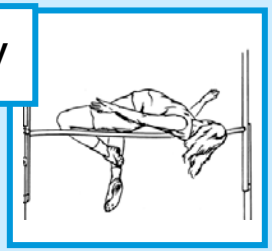
Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++



Medium impact

Justify

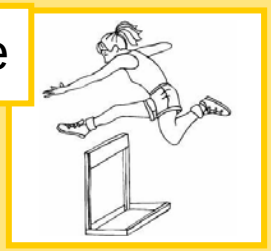
Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++



Low impact

Describe

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +



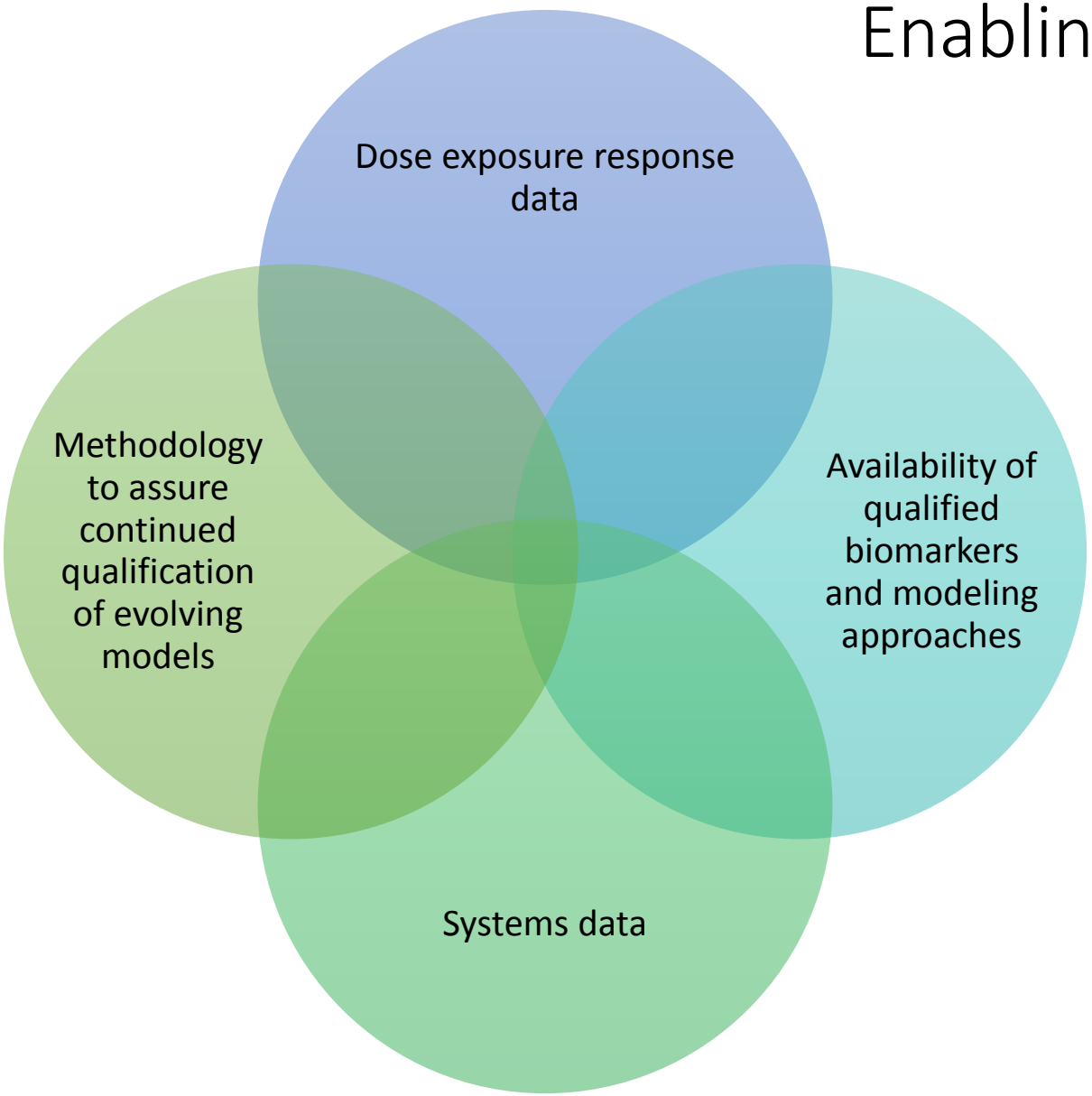
Impact on regulatory decision

From EMA-EFPIA Modelling and Simulation Workshop, December 2011

Challenges and opportunities

- Generate the data
  - Optimize the individual adult developments on formulations, dosing rationale, validation of endpoints
  - Optimize the individual pediatric developments (extrapolation concept planning, powering, inclusion of PD endpoints, addressing the clinically important gaps with appropriate methodologies)
  - Agree PIPs with learning objectives on the systems knowledge
  - Expand HTA models for relative effectiveness to be appropriate also for benefit-risk evaluations and extrapolation purposes?
  - Initiatives to address pediatric issues at the academic and public/private level at the disease level?
- Share the data and qualify the evidence and models
  - Precompetitive collaborative initiatives across companies
  - Regulatory databases to look across developments. *A role for EMA?*
  - Crowdsourcing the validation of models?

Enabling approaches



Thank you!

Modelling and Simulation principles and tools for extrapolation

EMA Workshop on extrapolation of efficacy and safety in medicine development across age groups

17 – 18 May 2016, European Medicines Agency, London

Piet van der Graaf

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall[1]*, R Burghaus[2], V Cosson[3], SYA Cheung[4], M Chenel[5], O DellaPasqua[6], N Frey[3], B Hamrén[7], L Harnisch[1], F Ivanow[8], T Kerbusch[9], J Lippert[2], PA Milligan[1], S Rohou[10], A Staab[11], JL Steimer[12], C Tornøe[13] and SAG Visser[14]

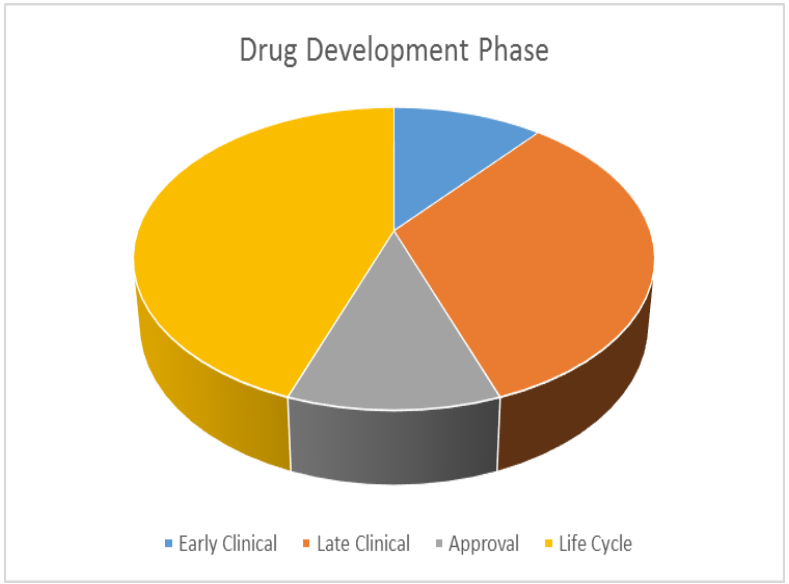
This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of "good practice" recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.

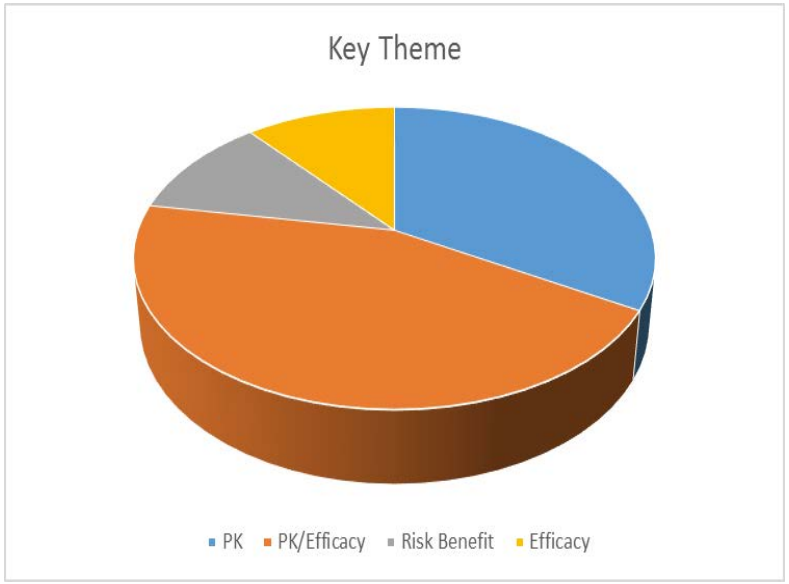
CPT Pharmacometrics Syst. Pharmacol. (2016) **5**, 93–122; doi:10.1002/psp4.12049; published online 14 March 2016.

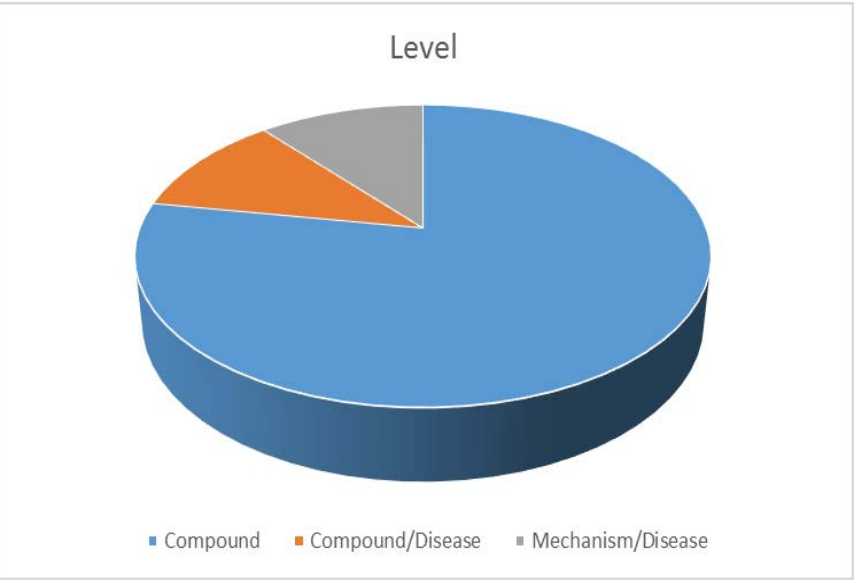
Appendix Table 1 Summary of number of papers for each of eight identified application types across the drug development phases

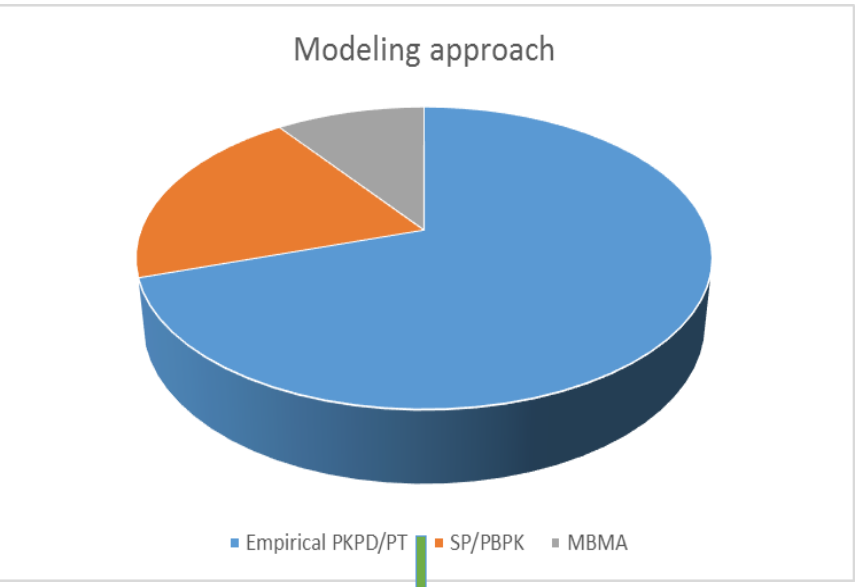
	Application Type (below) / Development Phase (right)	A Target selection and validation	B Lead Generation and Optimization	C Preclinical Development	D Early Clinical Development	E Late Clinical Development	F Approval Phase	G Life Cycle Management & Therapeutic use	Total
1	Target authorization and mechanistic understanding	3	2		3	1			9
2	Candidate comparison, selection, human PK and dose prediction		7	6					13
3	Study design optimization		2		4	4			10
4	Predicting and characterizing ADME including intrinsic and extrinsic factors impacting PK variability		3	2	2	9			16
5	Risk/Benefit characterization, and outcome prediction from early clinical responses		2	3	8	2			15
6	Dose and schedule selection and label recommendations (including drug combinations)			1	3	3	3	6	16
7	Comparator / Standard-of-Care differentiation and commercialization strategies		2	1	1	7		1	12
8	Patient population selection and bridging between populations (pediatrics, elderly, obese)				1	5	1	5	12
Total		3	18	13	22	31	4	12	103

N=9 paediatric









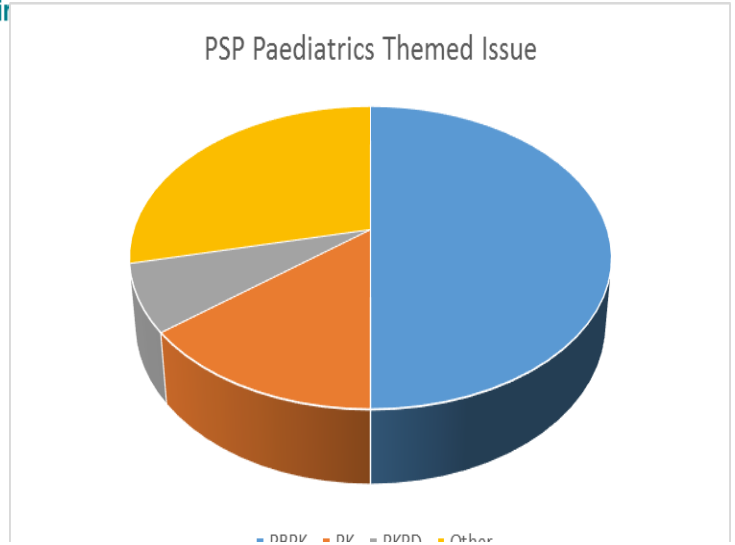
100% PK

Virtual Issues

Virtual issues are collections of articles on a particular subject, published in *CPT: Pharmacometrics & Systems Pharmacology*. They will be updated on a regular basis by the Editor-in-Chief.

The following virtual issues are available:

- Cancer
- Diabetes
- Infectious Diseases
- PBPK Modelir
- Pediatrics
- Reviews
- Tutorials



ORIGINAL ARTICLE

Model-Based Assessment of Dosing Strategies in Children for Monoclonal Antibodies Exhibiting Target-Mediated Drug Disposition

S Zheng[1], P Gaitonde[1], MA Andrew[2], MA Gibbs[3], LJ Lesko[1] and S Schmidt[1]

Body weight/body surface area–based and/or tiered fixed dosing strategies are widely utilized for monoclonal antibodies with linear clearance to scale adult clinical doses to children. However, there is limited knowledge on whether or not body weight–based dosing strategies also yield comparable dose-concentration-response relationships in adults and children for monoclonal antibodies that exhibit target-mediated drug disposition. Our findings indicate that it is important to interpret pharmacokinetics information in a pharmacokinetics/pharmacodynamics context as similar systemic drug exposure in adults and children may not be reflective of the corresponding target occupancy. They further indicate that BW-based dosing is superior to fixed dosing for the same target concentration, whereas the opposite holds true for the same target amount in adults and children. Michaelis-Menten approximations yielded similar profiles compared to the full target-mediated drug disposition model for all simulation scenarios and may be used to guide the selection of appropriate dosing regimens in children.

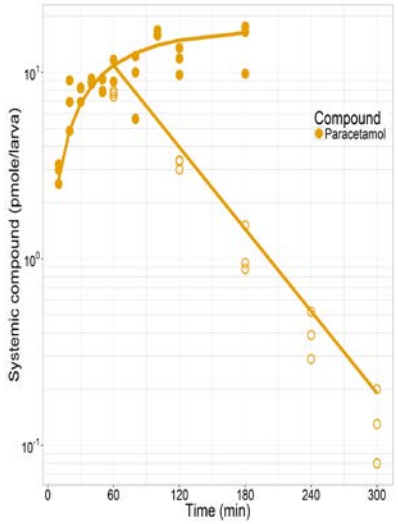
CPT Pharmacometrics Syst. Pharmacol. (2014) **3**, e138; doi:10.1038/psp.2014.38; published online 1 October 2014

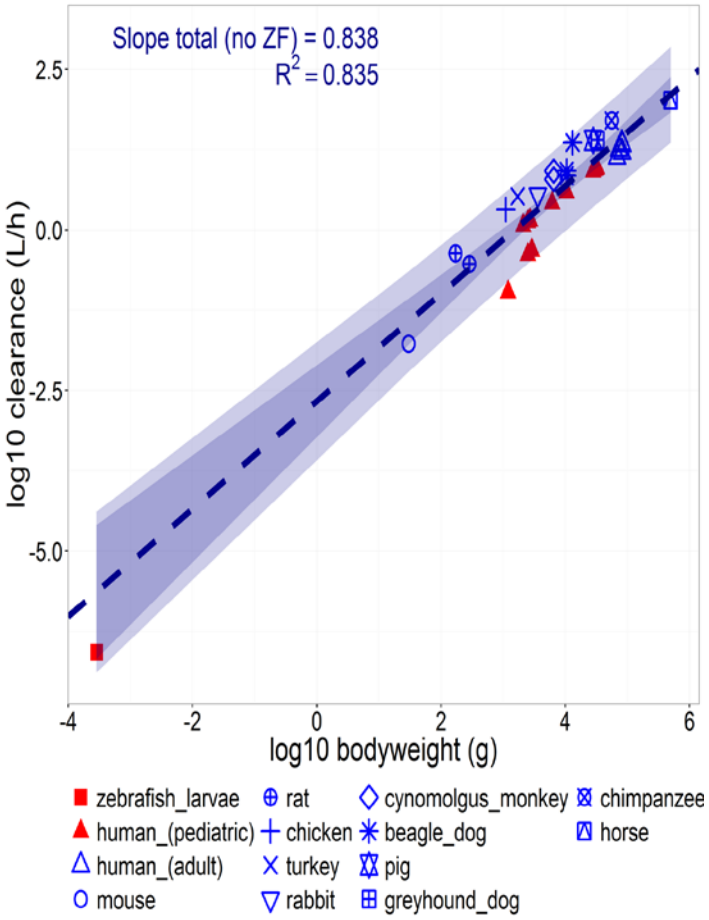
THE ZEBRAFISH AS MODEL FOR TRANSLATIONAL SYSTEMS PHARMACOLOGY:

EXPANDING THE ALLOMETRIC SCALE IN VERTEBRATES WITH FIVE ORDERS OF MAGNITUDE

R.C. van Wijk[1], E.H.J. Krekels[1], V. Kantae[2], A.C. Harms[2], Y. Guo[3], W.J. Veneman[4], F.J. Verbeek[3], T. Hankemeier[2], H.P. Spaink[4], and P.H. van der Graaf[1]

Systems Pharmacology Cluster, [1]Division of Pharmacology & [2]Division of Analytical Biosciences, Leiden Academic Centre for Drug Research (LACDR), Leiden

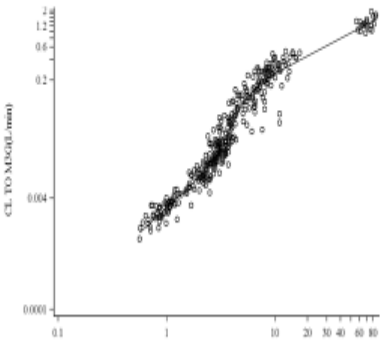


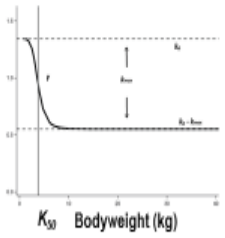


Quantification of morphine glucuronidation from neonates to adults

$$CL_{ind} = CL_{pop} * BW^{k}$$

$$k = 1.44 - \frac{0.57 * BW^{5}}{4.2^{5} + BW^{5}}$$





Wang C et al., Clin Drug Invest 2013

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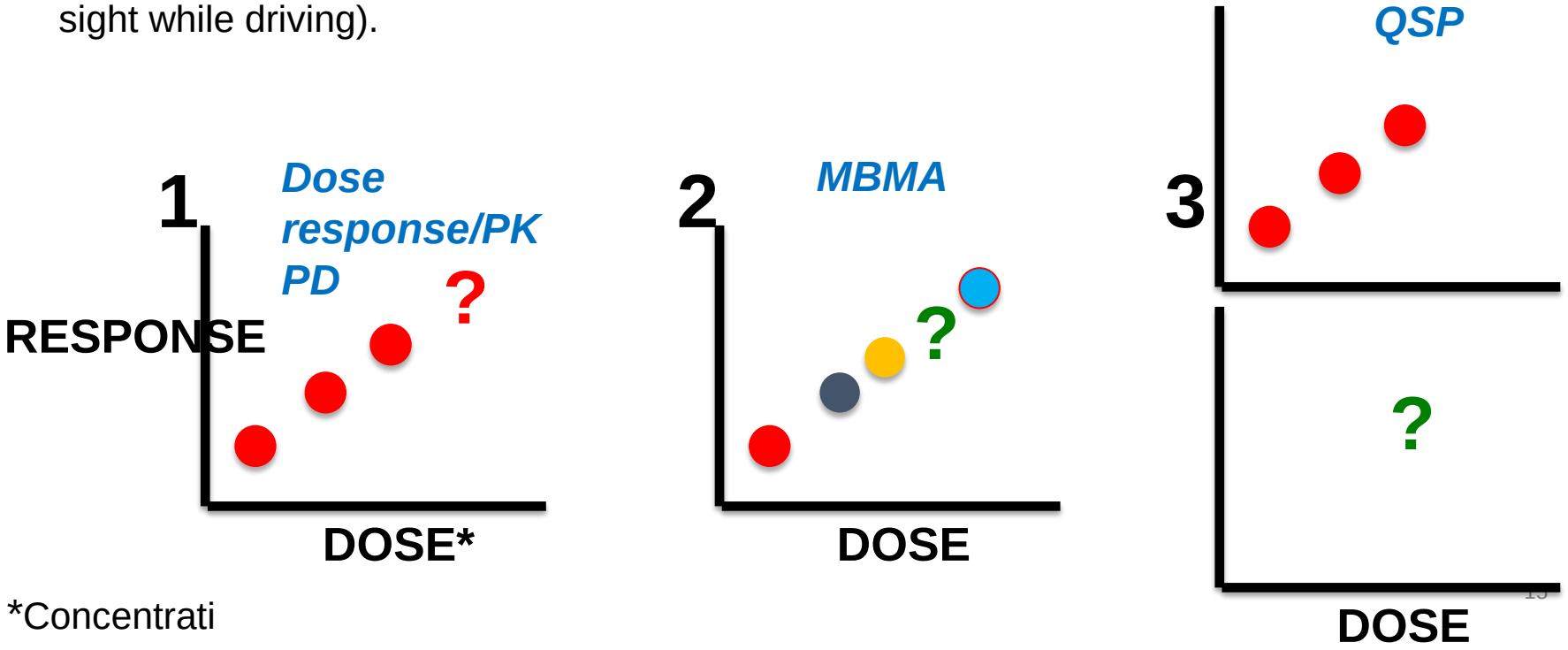
Extrapolation versus Interpolation

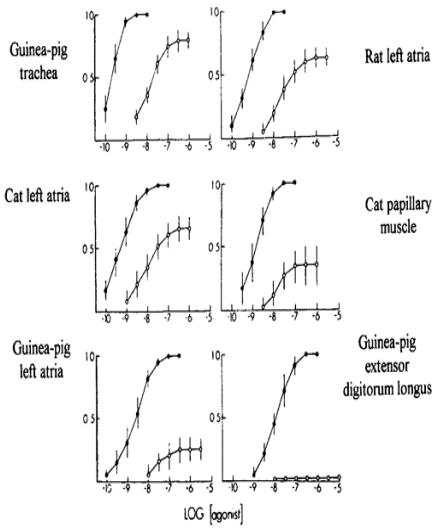
1. In mathematics, extrapolation is the process of estimating, beyond the original observation range, the value of a variable on the basis of its relationship with another variable. It is similar to interpolation, which produces estimates between known observations, but extrapolation is subject to greater uncertainty and a higher risk of producing meaningless results.
2. Extrapolation may also mean extension of a method, assuming similar methods will be applicable.
3. Extrapolation may also apply to human experience to project, extend, or expand known experience into an area not known or previously experienced so as to arrive at a (usually conjectural) knowledge of the unknown (e.g. a driver extrapolates road conditions beyond his sight while driving).

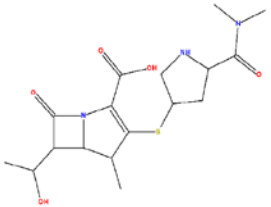


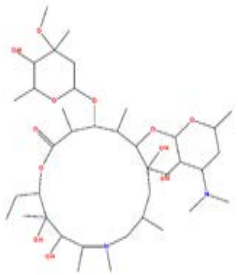
*Concentrati

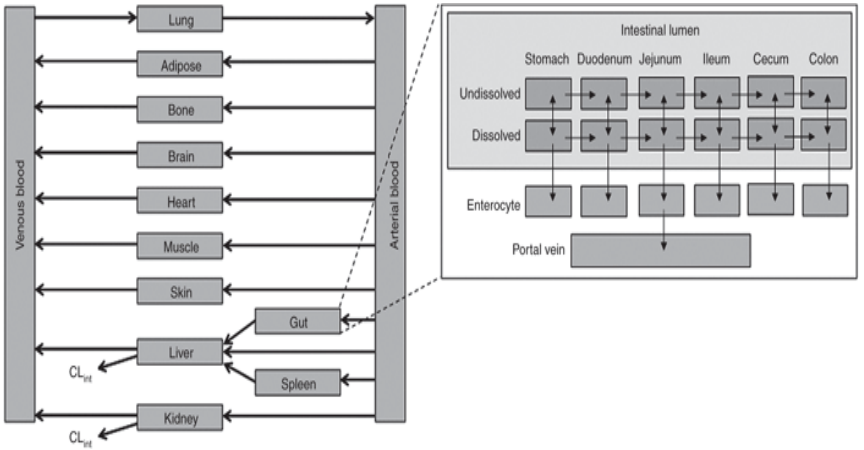
Extrapolation using Quantitative Systems Pharmacology (QSP)

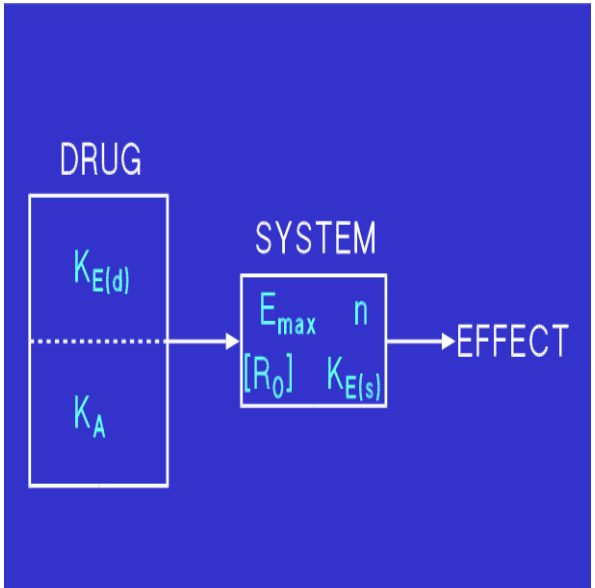
- Isoprenaline
- Prenalterol

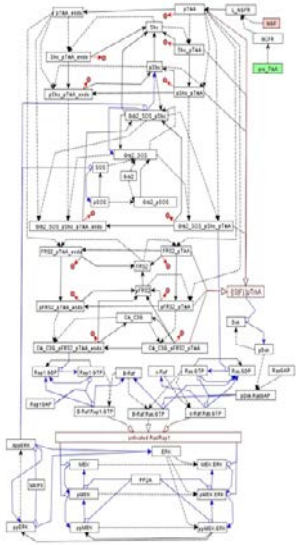












Universiteit Leiden
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A systems pharmacology model to explain developmental differences in sensitivity to drug-induced QT prolongation

Verena Gotta, Marc Pfister, John van den Anker, Piet H. van der Graaf

[1]*Systems Pharmacology, Leiden Academic Center of Drug Research (LACDR), Leiden University, Leiden, The Netherlands.*

[2]*University Children's Hospital Basel, University of Basel, Basel, Switzerland*

European Society for Developmental Perinatal and Pediatric Pharmacology (ESDPPP), Belgrade, 23-26th June 2015

1.1. Estimation of system-specific transduction parameters for translational preclinical–clinical scaling *(dofetilide)*

- maximal $\Delta QTc_{\%}$ via hERG-block: $E_{m,human} = E_{m,dog} = 28\%$ **from baseline**
- transducer ratio τ: $\tau_{human} = 2.4 \cdot \tau_{dog}$

Interpretation of τ: τ ~ hERG-channel/I_{kr}-density, and
$1/\tau$ ~ %hERG/I_{kr}-block leading to half-maximal ΔQTc

→ Equal $\Delta QTc_{\%}$ achieved in human at 60% lower hERG-block than in dog ($1/\tau = 26\%$ in human vs 62% in dog), explained by a **2.4 x higher hERG-channel density in human and/or I_{kr}-net contribution to cardiac repolarization**.

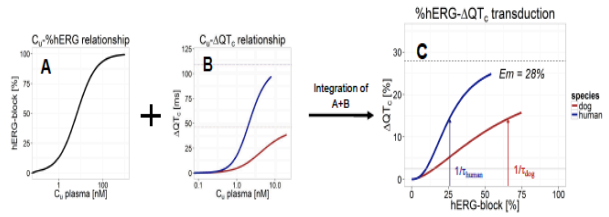

Fig.1: Pharmacodynamics of dofetilide in preclinical (consious dog[4]) and clinical setting (healthy men[5]). **A**: %hERG-block (from *in vitro* binding kinetic experiments) and **B:** ΔQTc (from *in vivo* studies). **C**: estimated transduction of hERG-block. C_u: unbound plasma concentration.

1.2. External evaluation of translational predictions *(sotalol & moxifloxacin)*

Good clinical predictions in adults and children were obtained (*<5-10 ms prediction discrepancy from clinical regression model until ΔQTc of 35 ms*). However, QTc- effects in neonates were under-predicted (*>20 ms prediction discrepancy*).

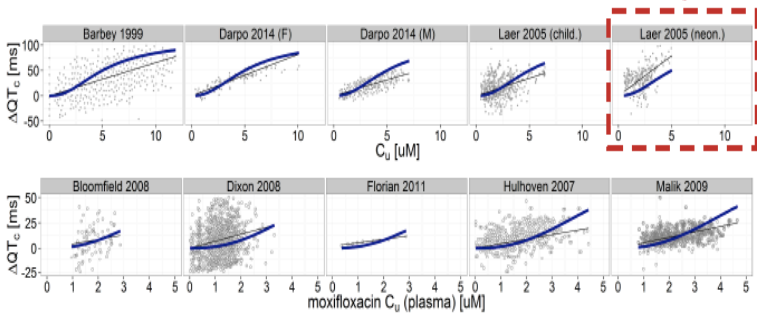

Fig.2: Translational predictions from preclinical data and system-specific scaling parameters only *(blue lines)* are contrasted with reported clinical ΔQTc from indicated references (*grey dots:* digitized observations. *black lines:* predictions from respective clinical regression model).

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2. Refinement of system-specific transduction parameters for neonates

Re-estimated transducer ratio: $\tau_{neonates} = 1.77 \cdot \tau_{children}$

→ Higher sensitivity of neonates to drug-induced ΔQTc explained by a **1.77 x higher hERG-channel density and/or I_{kr}-net contribution to cardiac repolarization** than in older children (≈ adults), resulting in equal $\Delta QTc_{\%}$ at 43% lower hERG-block.

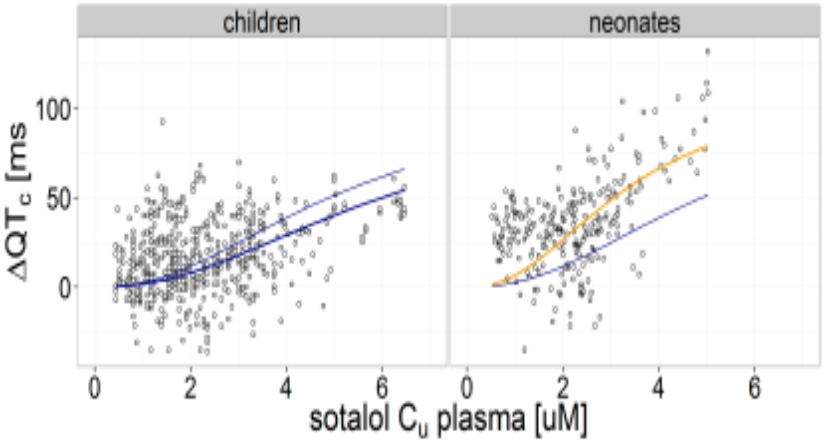


Fig.3: Observed pediatric ΔQTc (*dots*, digitized from Läer et al.[6]) after sotalol administration, contrasted with translational predictions for adults (*thin blue lines*) and refined predictions for children (*thick blue line*) and neonates (*orange line*). ΔQTc-pharmacodynamics in children and adults was very similar.

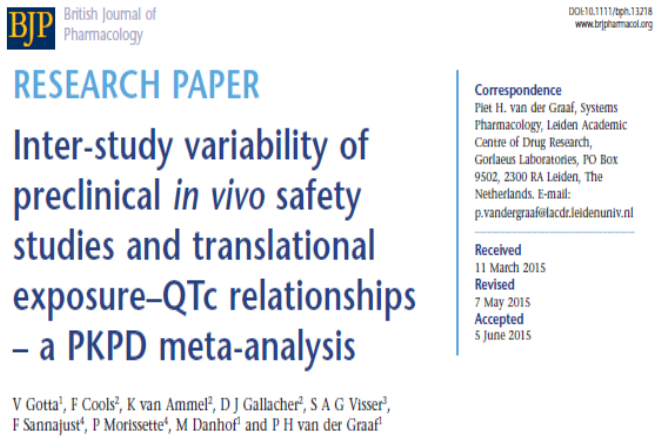

Contents lists available at ScienceDirect
Journal of Pharmacological and Toxicological Methods
journal homepage: www.elsevier.com/locate/jpharmtox
ELSEVIER

Original article

Sensitivity of pharmacokinetic–pharmacodynamic analysis for detecting small magnitudes of QTc prolongation in preclinical safety testing

Verena Gotta [a], Frank Cools [b], Karel van Ammel [b], David J. Gallacher [b], Sandra A.G. Visser [c], Frederick Sannajust [d], Pierre Morissette [d], Meindert Danhof [a], Piet H. van der Graaf [a,*]

[a] Systems Pharmacology, Leiden Academic Centre of Drug Research (LACDR), Leiden University, Leiden, The Netherlands


BJP British Journal of Pharmacology
DOI:10.1111/bph.13218
www.brjpharmacol.org

RESEARCH PAPER

Inter-study variability of preclinical *in vivo* safety studies and translational exposure–QTc relationships – a PKPD meta-analysis

V Gotta[1], F Cools[2], K van Ammel[2], D J Gallacher[2], S A G Visser[3], F Sannajust[4], P Morissette[4], M Danhof[1] and P H van der Graaf[1]

Correspondence
Piet H. van der Graaf, Systems Pharmacology, Leiden Academic Centre of Drug Research, Gorlaeus Laboratories, PO Box 9502, 2300 RA Leiden, The Netherlands. E-mail: p.vandergraaf@lacdr.leidenuniv.nl

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7 May 2015
Accepted
5 June 2015

What it took to extrapolate a compound class:

- 3 Compounds
- 2 *In vitro* studies
- 14 Preclinical *in vivo* studies
- 28 Clinical studies
- 2+ FTE Years

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Summary and Take Home

- **Within-population extrapolation (WPE; i.e. predicting a higher-than-tested dose) is fundamentally different from between-population extrapolation (BPE; i.e. predicting paediatric PKPD from adults):**
  - Statistical approach may work for WPE; no rational basis to decide why it could or could not work in BPE
  - **Quantitative frameworks for predicting system-dependency of pharmacological responses have been:**
    - Developed and adopted by the scientific community since the 1950's
    - Boosted by recent interest in QSP
    - But (with the exception of PBPK) there is little evidence of adaptation in paediatric drug development

- **A shift is required from an individual study-study oriented extrapolation paradigm to a systems one:**
  - Scientifically, ethically, economically, logistically
  - Requires a joined-up approach moving away from a compound-centric focus
  - PBPK serves as an example of feasibility and demonstrable impact

KNOWN KNOWNS & KNOWN UNKNOWNS in USING VIRTUAL POPULATIONS for EXTRAPOLATION

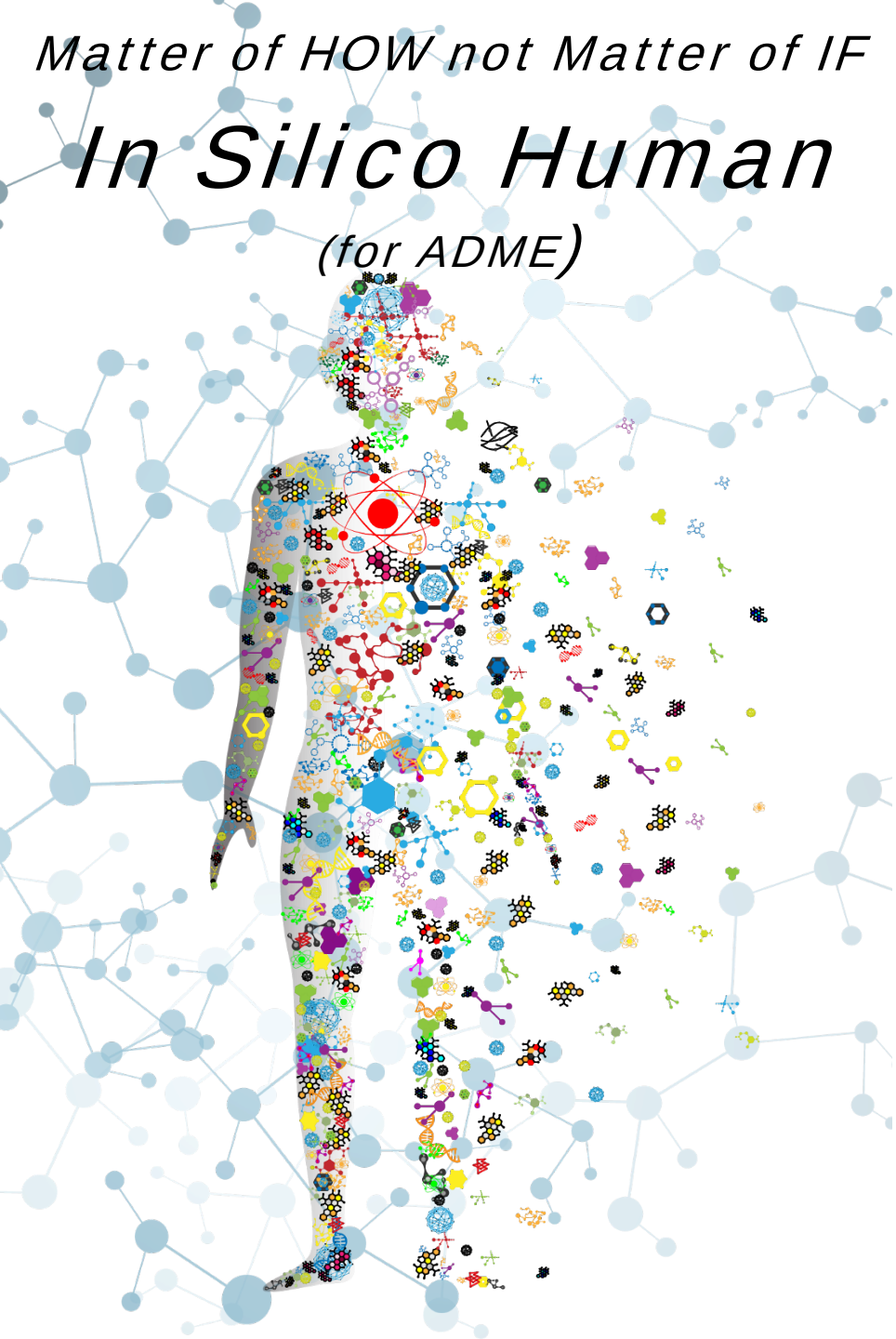
Amin Rostami

Professor of Systems Pharmacology
University of Manchester, Manchester, UK

Matter of HOW not Matter of IF

In Silico Human

(for ADME)



ASCPT 2016 ANNUAL MEETING

MARCH 8–12, 2016 | HILTON BAYFRONT, SAN DIEGO, CA

ADVANCING THERAPEUTIC HORIZONS THROUGH GLOBAL COLLABORATIONS

ROUNDTABLE

How Should Simulated DDI Results be Communicated in the Label?

D D R U

COMMUNITIES

Regulatory Science (RS), Pharmacometrics & Pharmacokinetics (PMK)

CHAIRS

Ping Zhao, PhD
US Food and Drug Administration, Silver Spring, MD

Vikram Sinha, PhD
US Food and Drug Administration, Silver Spring, MD

PANELISTS

Lawrence Lesko, PhD, FCP
University of Florida at Lake Nona, Orlando, FL

Joseph Grillo, PharmD
US Food and Drug Administration, Silver Spring, MD

Anna Nordmark, PhD
Swedish Medical Product Agency, Huddinge, Sweden

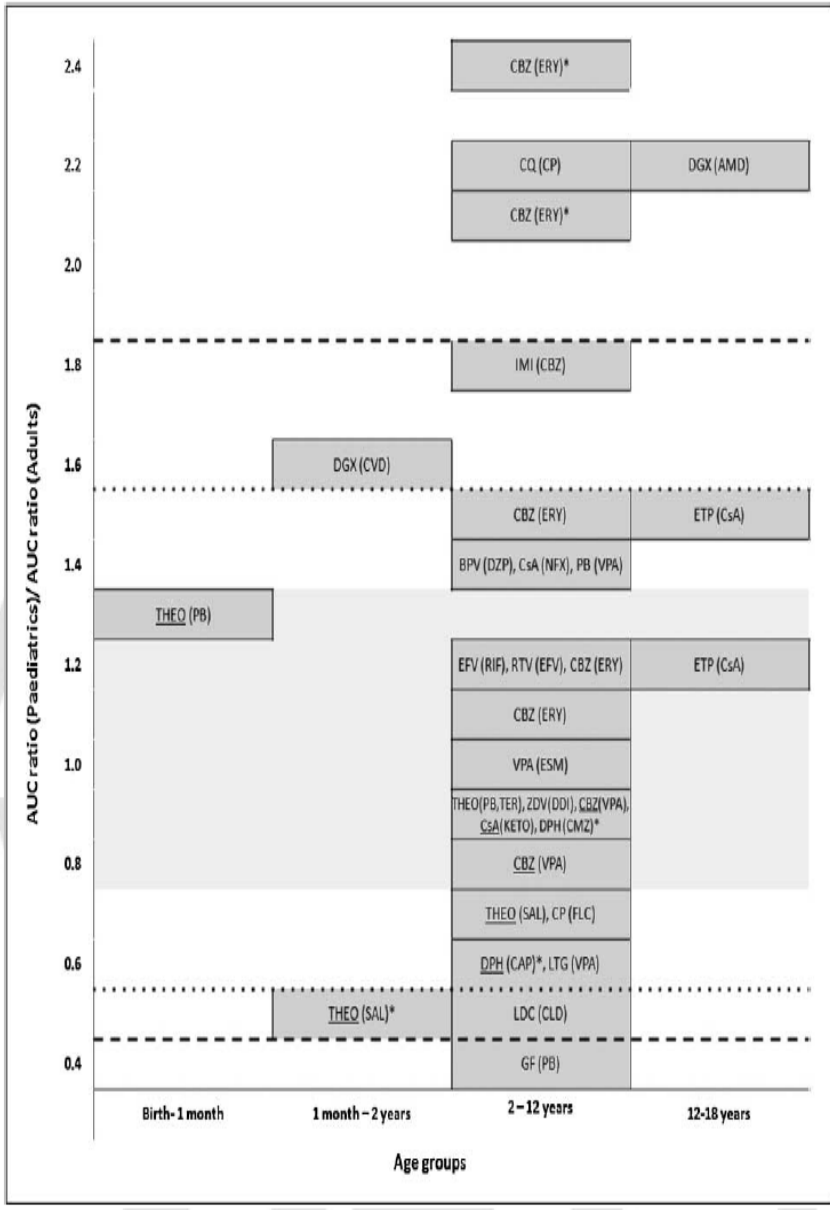
Jack Cook, PhD
Pfizer, Groton, CT

Why the trend? Latest fad? Or a true need?

Do Children Have the Same Vulnerability to Metabolic Drug–Drug Interactions as Adults? A Critical Analysis of the Literature

Farzaneh Salem, PharmD[1], Amin Rostami-Hodjegan, PharmD, PhD and Trevor N. Johnson, PhD[2]

An age-related trend in the magnitude of DDIs could not be established. However, the study highlighted the clear paucity of the data in children younger than 2 years. Care should be exercised when applying the knowledge of DDIs from adults to children younger than 2 years of age.



Public Interest: Answer to an Unmet Need

News Site of the Year | The 2008 Newspaper Awards

TIMESONLINE

Filling the void
Stopping guess-work

News Comment Business Money Sport Life & Style Travel Driving Arts & Ents Archiv

Career & Jobs Education Food & Drink Health Property Court & Social Women Men Related Feat

From The Times July 28, 2008

Virtual children will take guesswork out of making the medicine go down

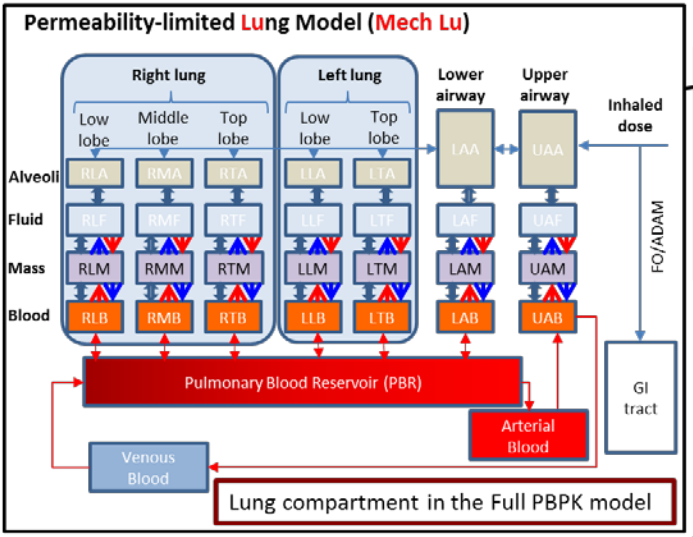
David Rose

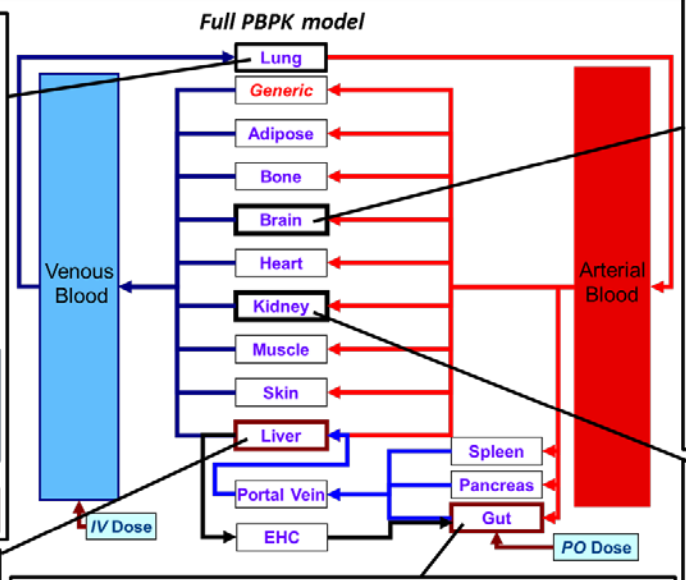
Using computers to test medicines could soon become routine, after the introduction of European Union regulations that require stricter testing for drugs intended for children.

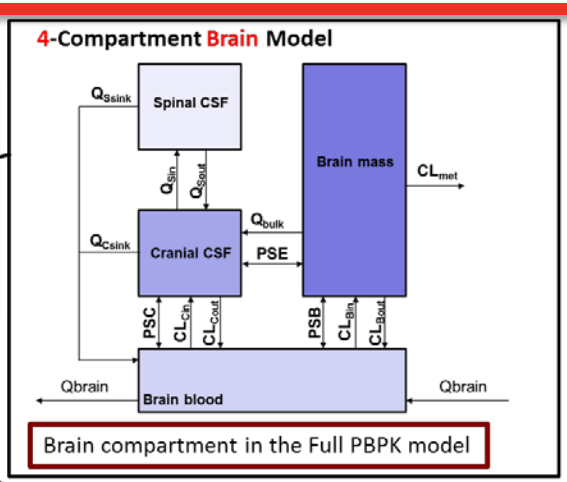
Computer models that simulate the action of a drug on the body could hasten the development of new

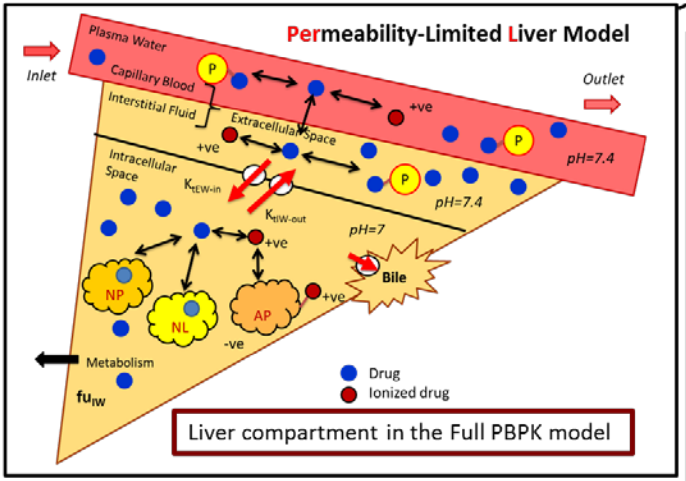
Blog

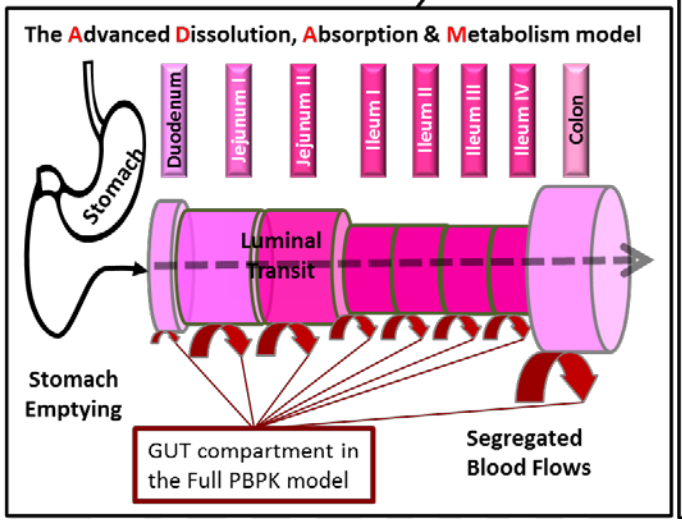
How it is done? Integrating system information

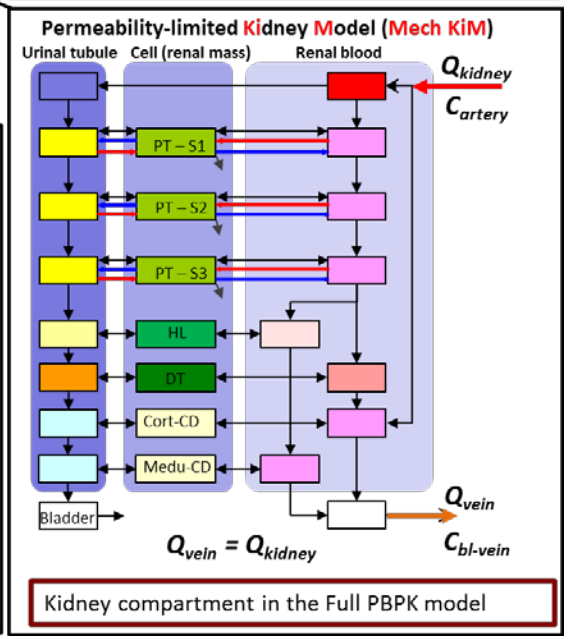










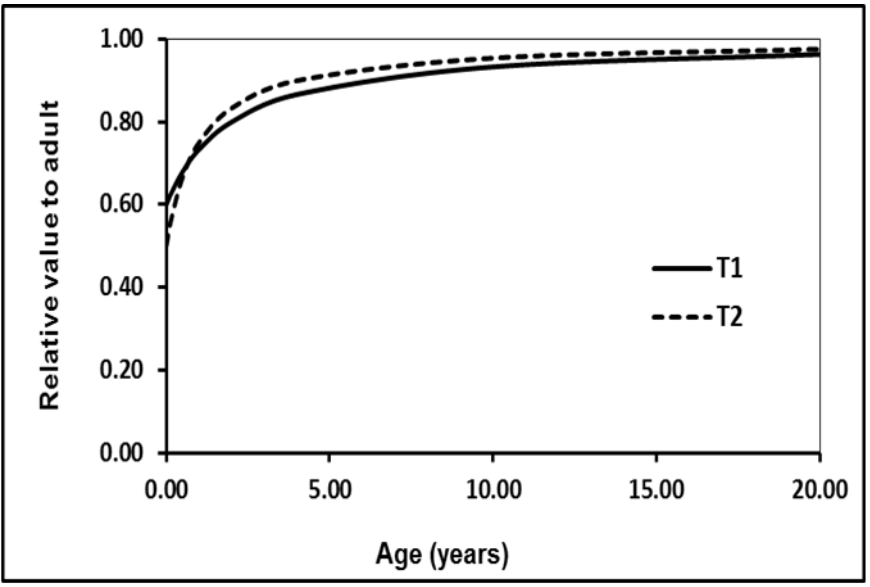


- Replacement and additional organ

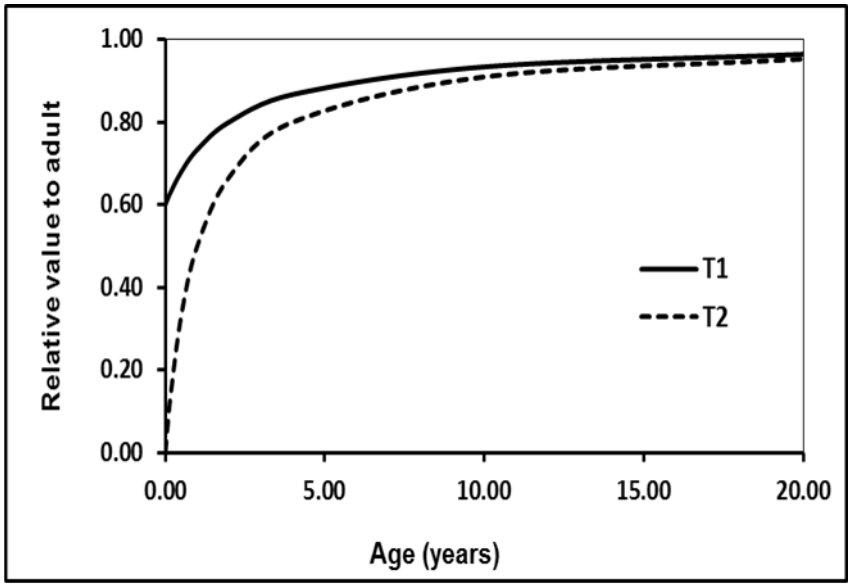
Permeability-limited model are available for the intestine, liver, kidney, brain and lung.

- Transport across a membrane is often defined as Perfusion Limited
- But we now define uptake/efflux into/out of selected organs as Permeability Limited

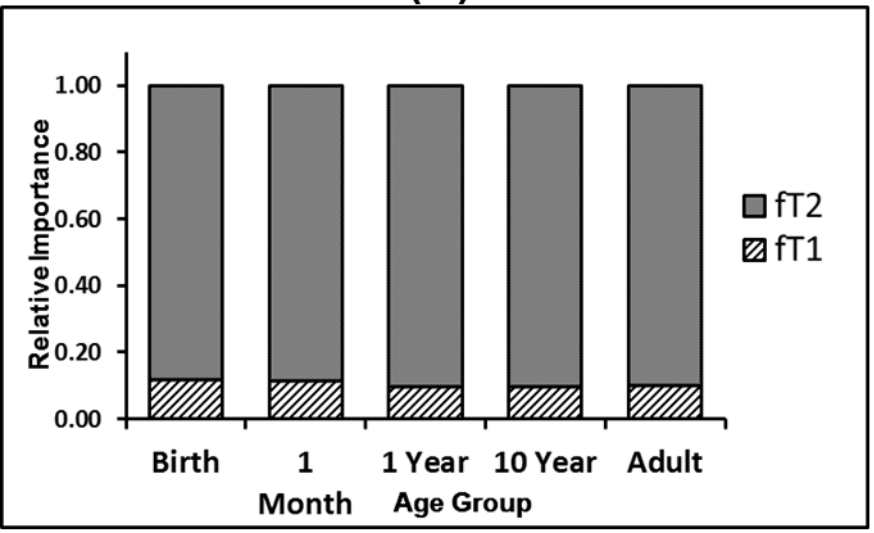
What are the challenges? Variable ontogeny (enzymes/transporters)



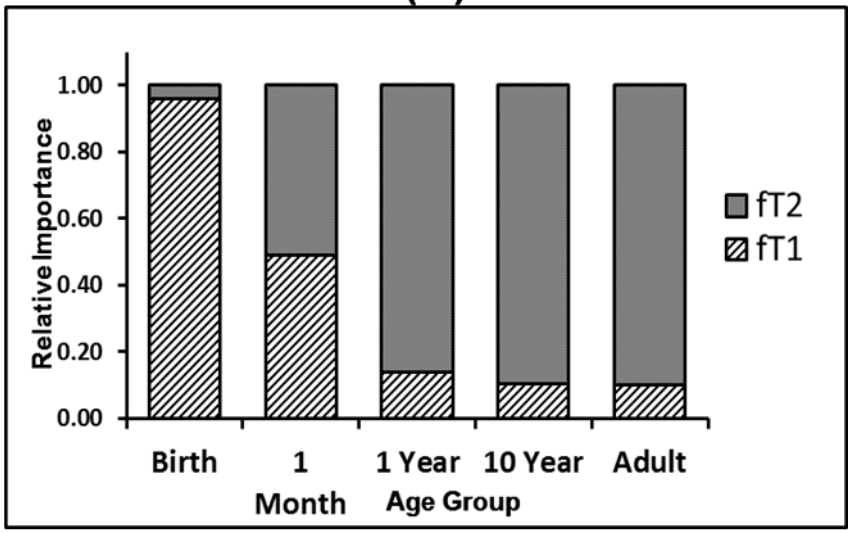
(A)



(B)



(C)



(D)

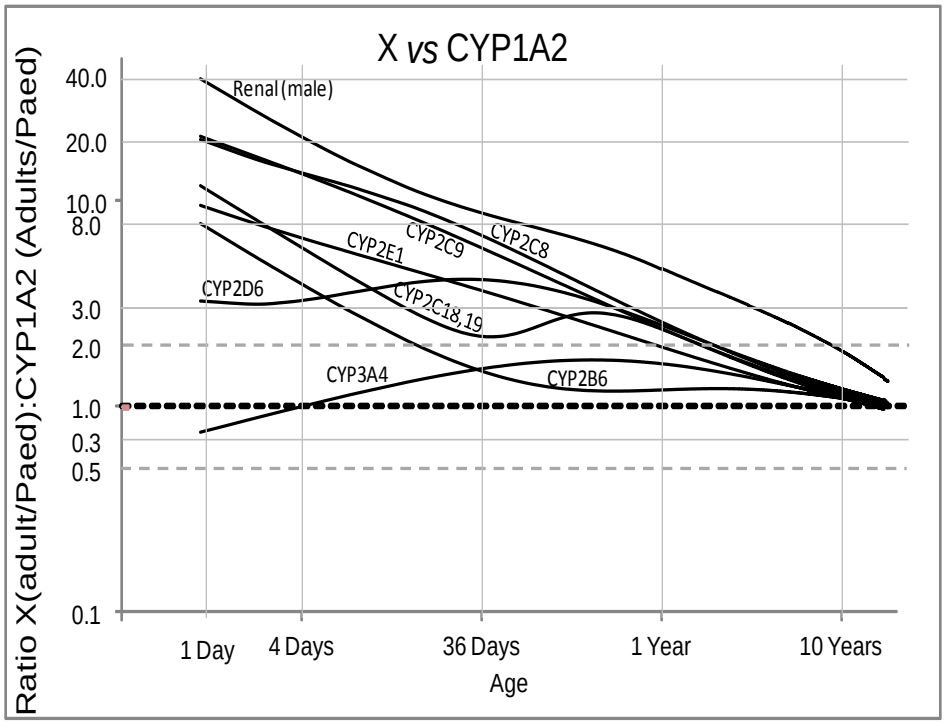
Relative Importance of Pathways: "Ratio of Ratios"!

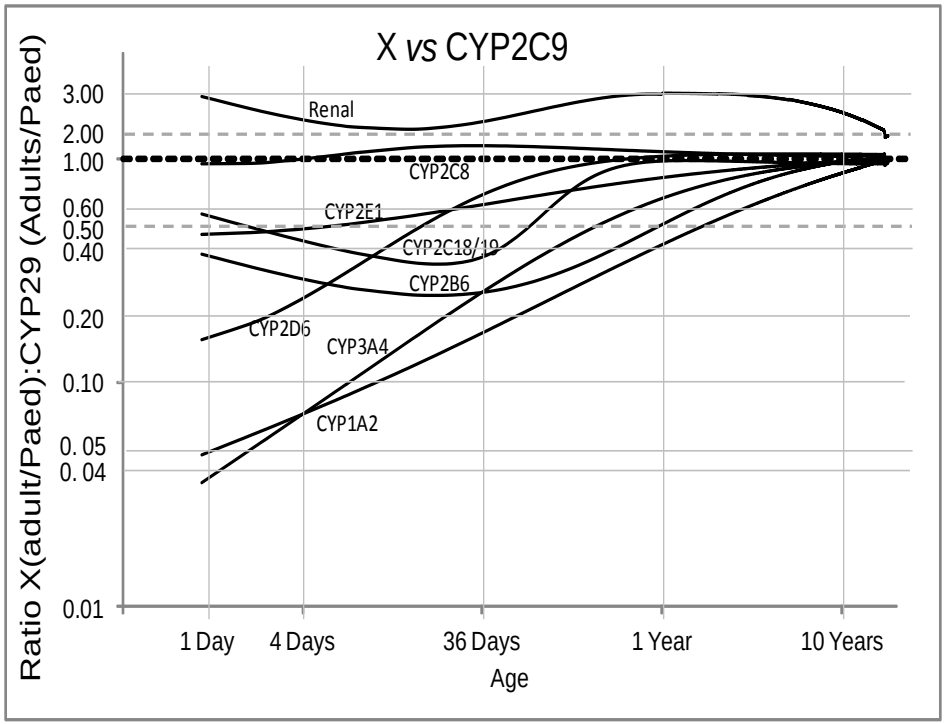
Age Related Changes in Fractional Elimination Pathways for Drugs: Assessing the Impact of Variable Ontogeny on Metabolic Drug–Drug Interactions

J Clin Pharmacol
2013; 53: 857–865

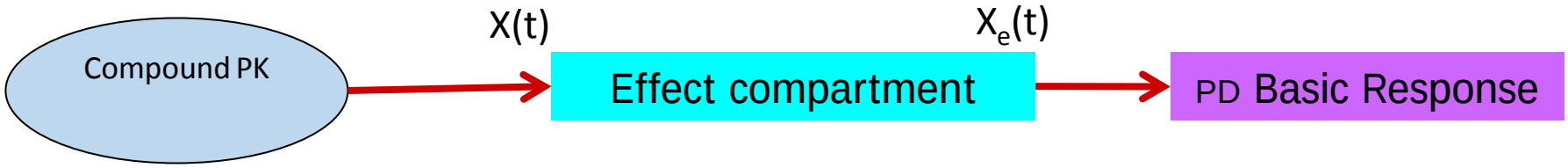
Farzaneh Salem, PharmD[1], Trevor N. Johnson, PhD[2], Zoe E. Barter, PhD[2], J. Steven Leeder, PharmD, PhD[3,4,5], and Amin Rostami-Hodjegan, PharmD, PhD, FCP[1,2]

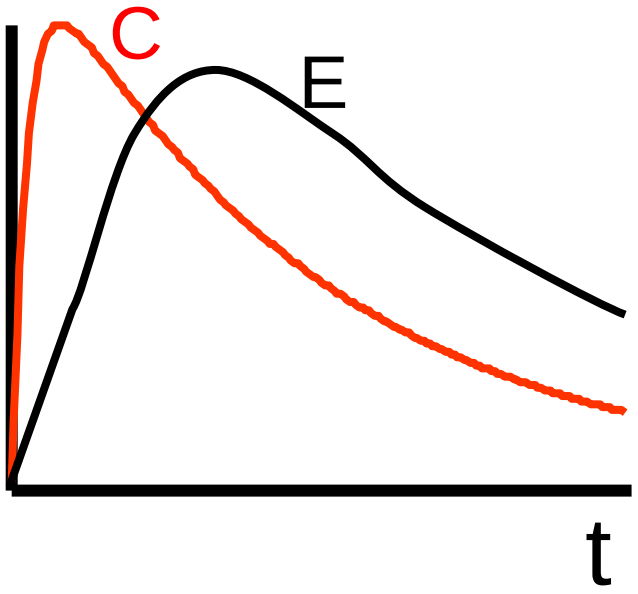
$$\text{Relative Ontogeny} = \frac{\dfrac{\text{Pathway A in Paediatrics}}{\text{Pathway A in Adults}}}{\dfrac{\text{Pathway B in Paediatrics}}{\text{Pathway B in Adults}}}$$

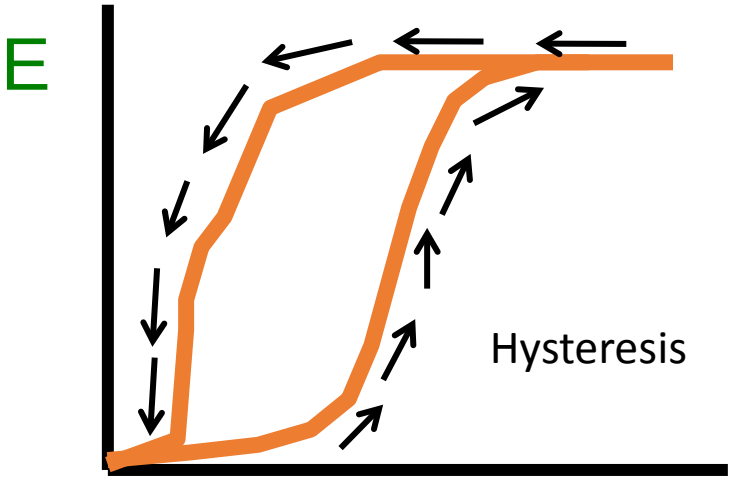




What are the challenges? Reference point (systemic vs organ)







$$\uparrow\!\!\leftrightarrow AUC_{tissue} = \frac{\uparrow AUC_{sys} \cdot CL_{in}\downarrow}{CL_{out}\downarrow}$$

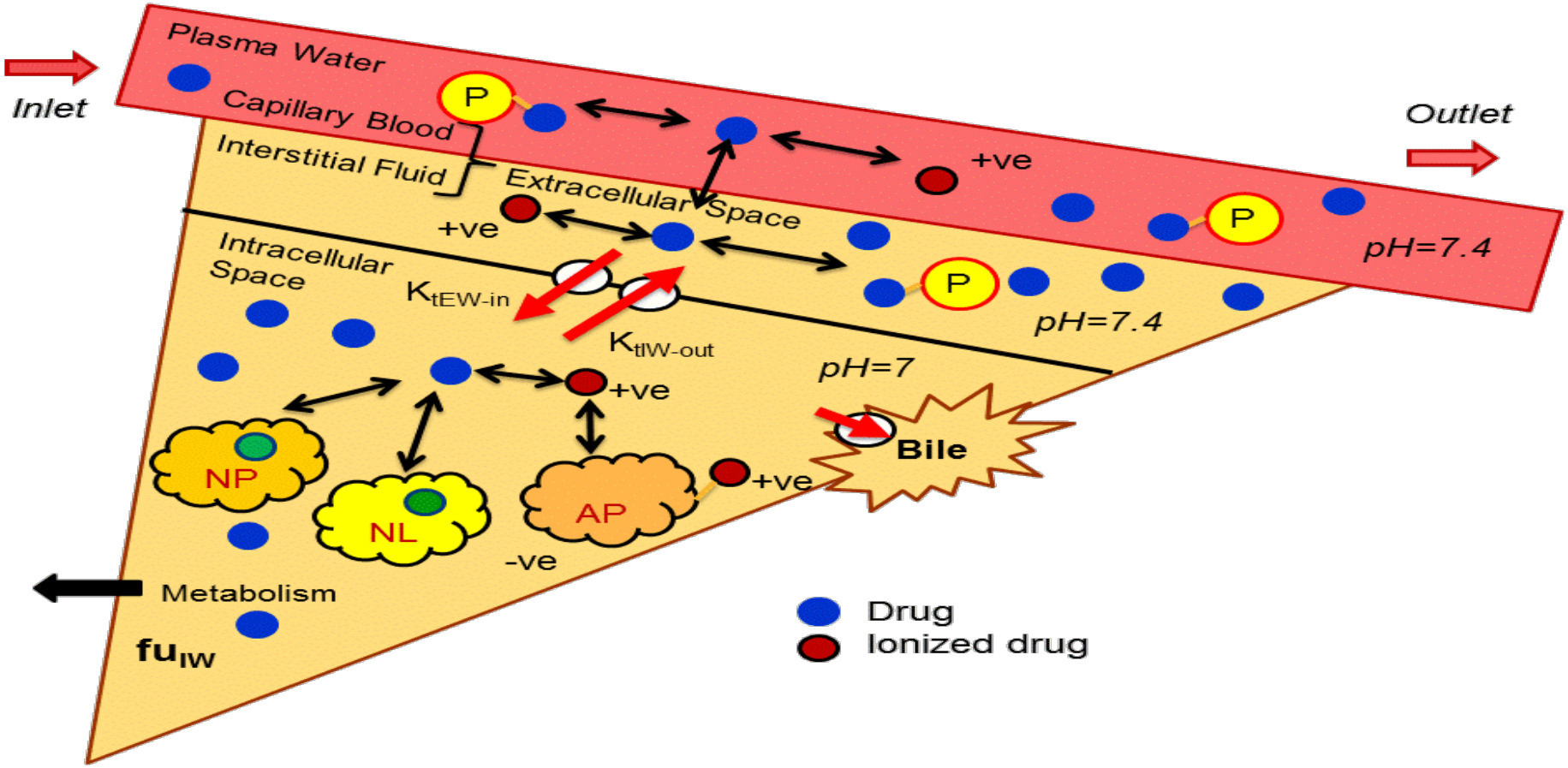
C

Clin Pharmacokinet
DOI 10.1007/s40262-013-0097-y

ORIGINAL RESEARCH ARTICLE

A Mechanistic Framework for In Vitro–In Vivo Extrapolation of Liver Membrane Transporters: Prediction of Drug–Drug Interaction Between Rosuvastatin and Cyclosporine

M. Jamei · F. Bajot · S. Neuhoff · Z. Barter · J. Yang · A. Rostami-Hodjegan · K. Rowland-Yeo



Drugs with Paediatric Application

Drugs known to be affected by liver transporters

175

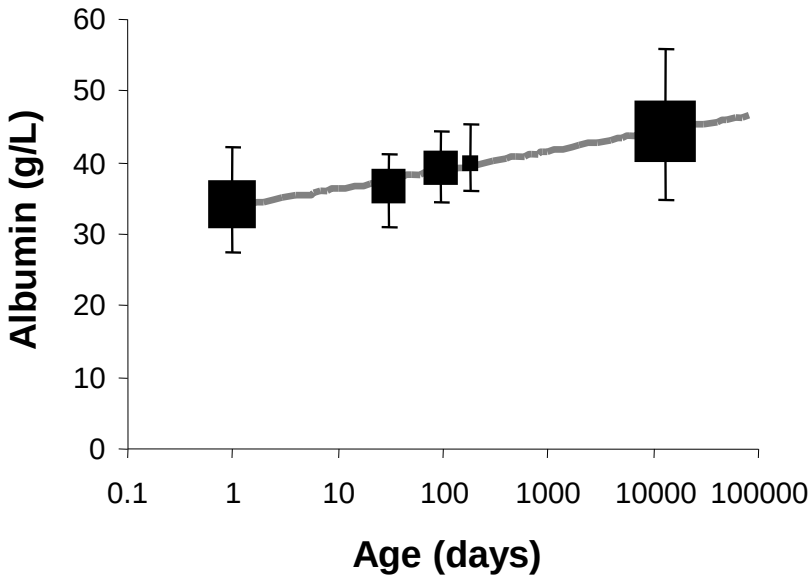
?

104

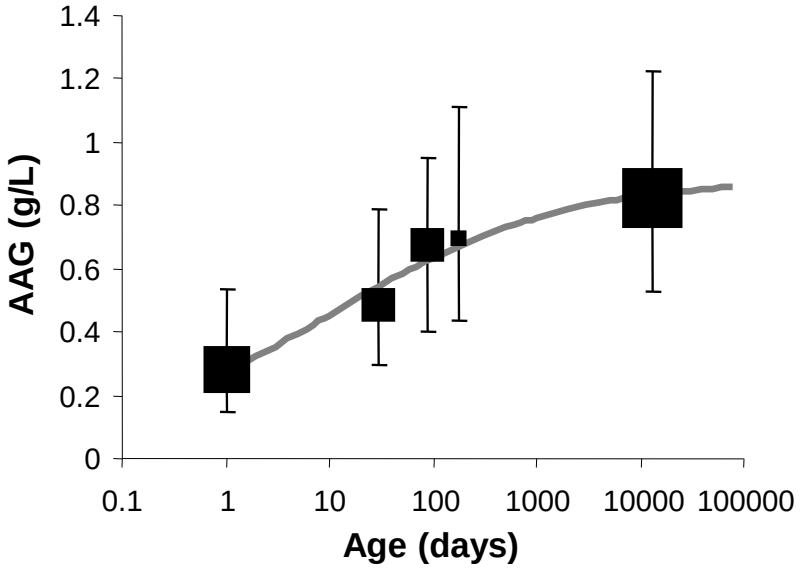
Drugs of Paediatric Use

What are the challenges? Reference point (free vs bound)

Serum Albumin & Age



Serum AAG & Age



In the absence of changes in dynamics of binding:

$$fu_{neonate} = \frac{1}{1 + \left[\frac{[P]_{neonate}}{[P]_{adult}} \times \frac{(1 - fu_{adult})}{fu_{adult}} \right]}$$

Absence of info on free local concentrations: Sensitivity???

Ontogeny of Plasma Proteins, Albumin and Binding of Diazepam, Cyclosporine and Deltamethrin

Sethi; et al

Pediatric Research accepted article preview online 16 November 2015;

Fig. 1

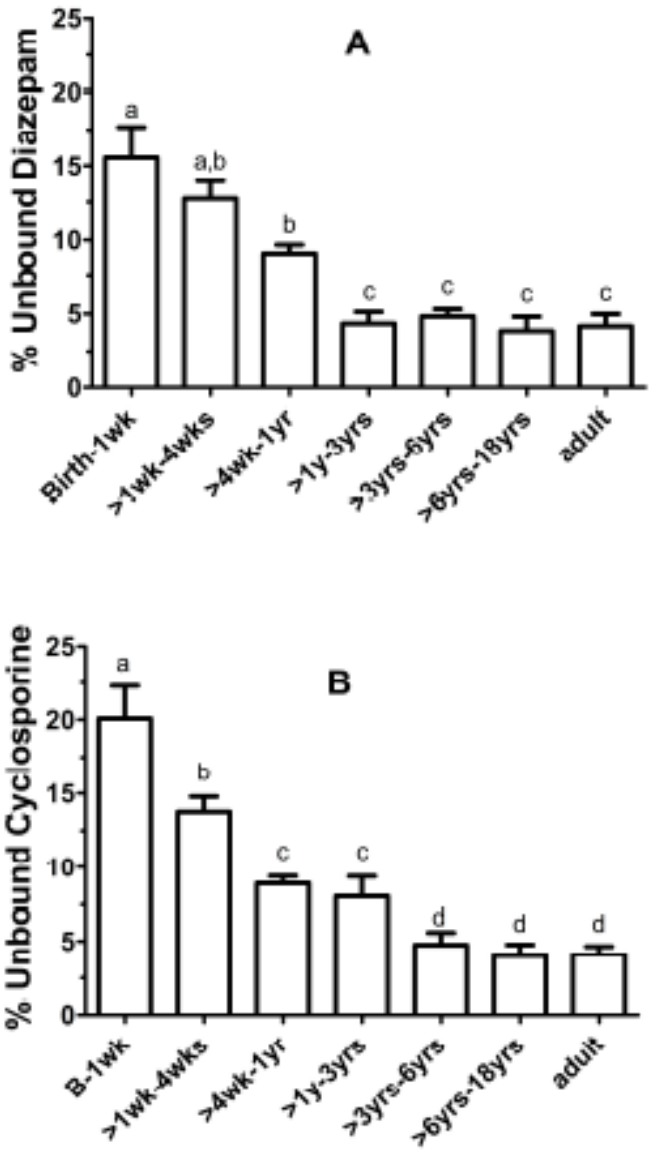
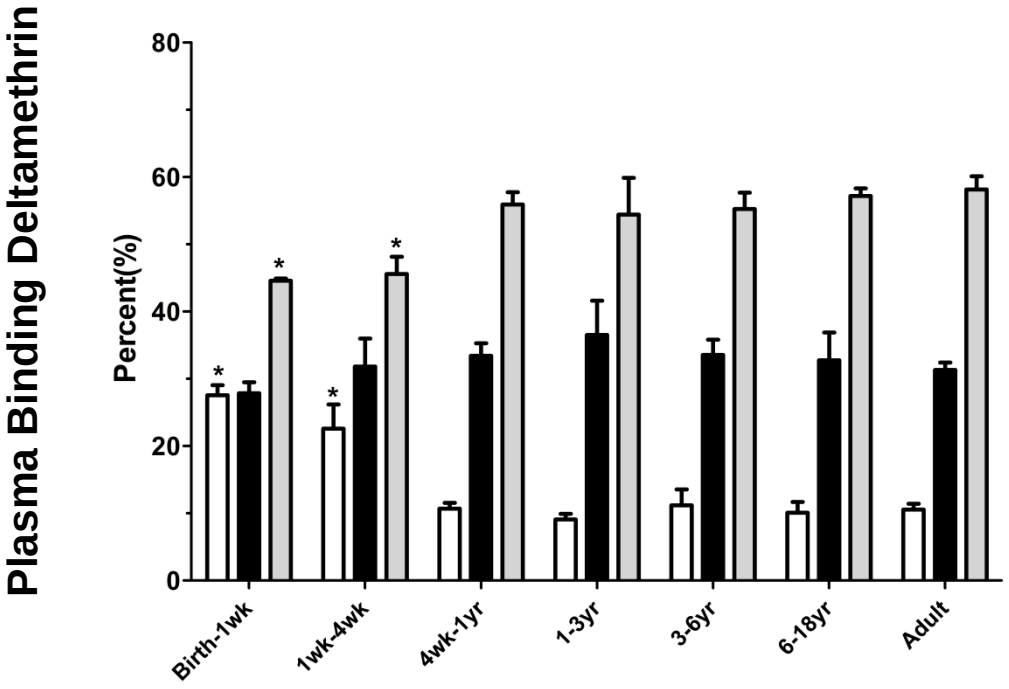
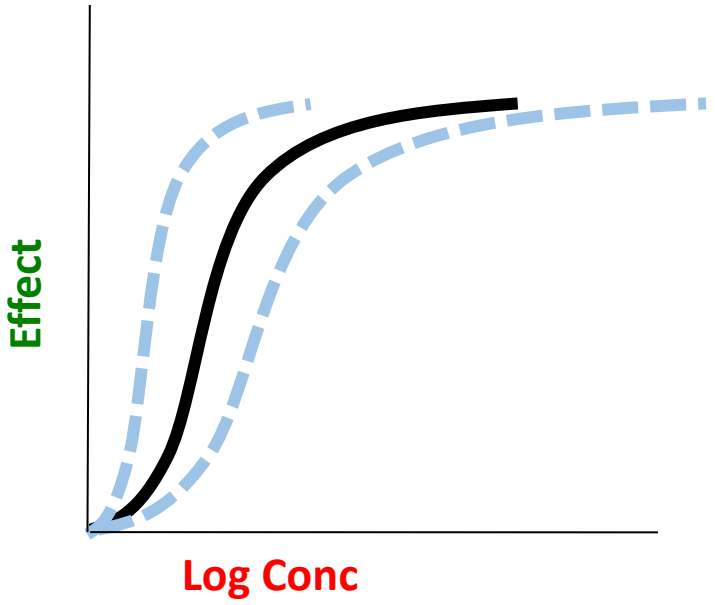
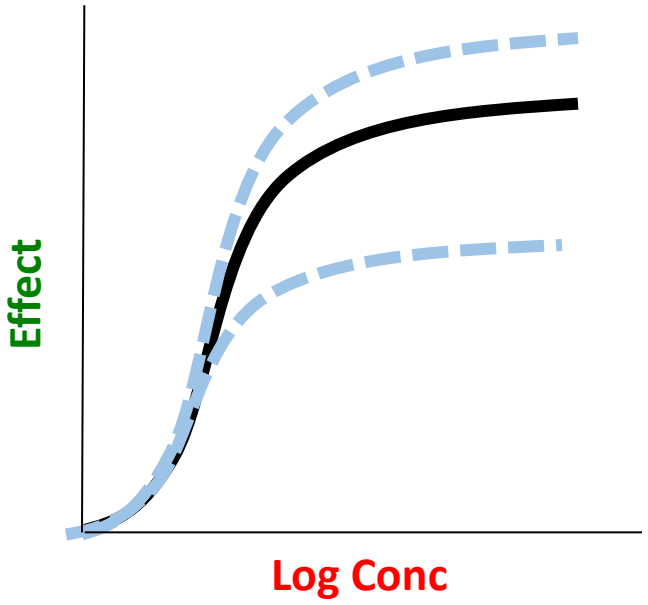


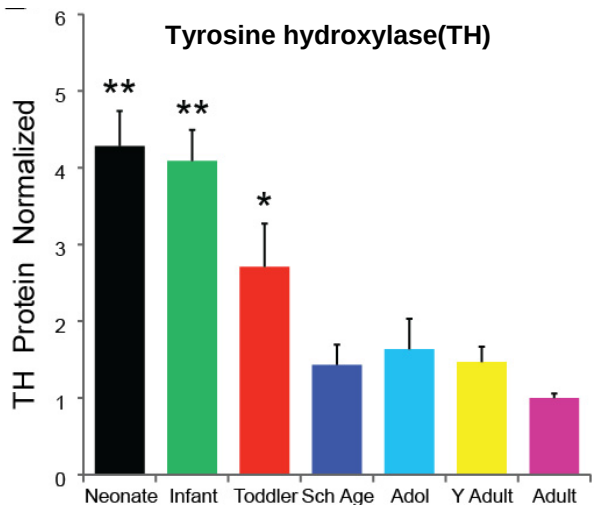
Fig. 2

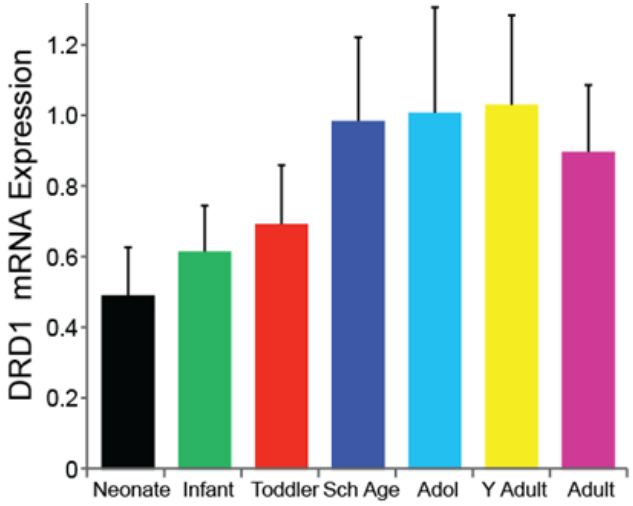


True vs Apparent PD Differences in Paediatrics









Rothmond et al., 2012