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Simulating Oral Absorption with PK-Sim® Methodology and Application Examples

Stefan Willmann, Andrea N. Edginton, Walter Schmitt,
Marcus Kleine-Besten, and Jennifer B. Dressman

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Presentation Overview

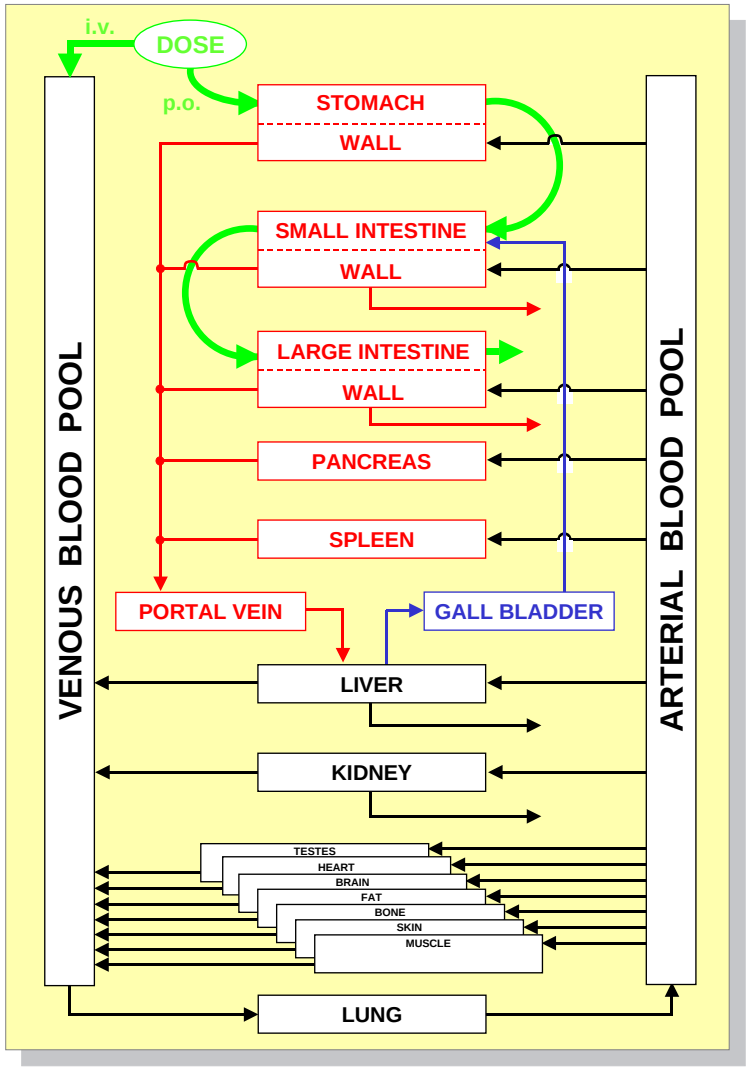
- **PK-Sim®'s Absorption Model**
- Application Examples
  - Example 1
  - Example 2
  - Example 3

PK-Sim® Model-Structure

Real ***Integrated Whole Body Model*** comprising:

- ⇨ Fully integrated GI-tract
- ⇨ Biliary tract, enables enterohepatic cycling
- ⇨ Most important organs
- ⇨ For each organ:
  - metabolizing pathways
  - different active transporter types (influx, efflux, Pgp-like)

Capability for treating even very sophisticated problems.



Willmann et al., *Biosilico* **1(4)**, 121-124 (2003)

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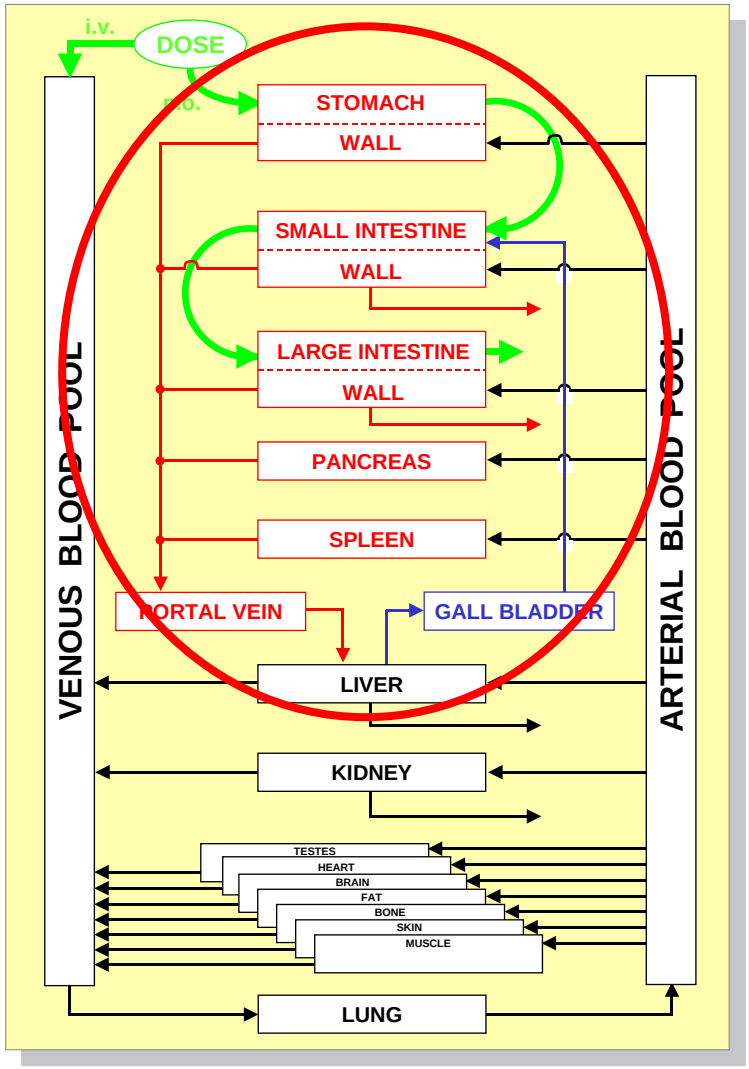

Willmann et al., *Biosilico* **1(4)**, 121-124 (2003)

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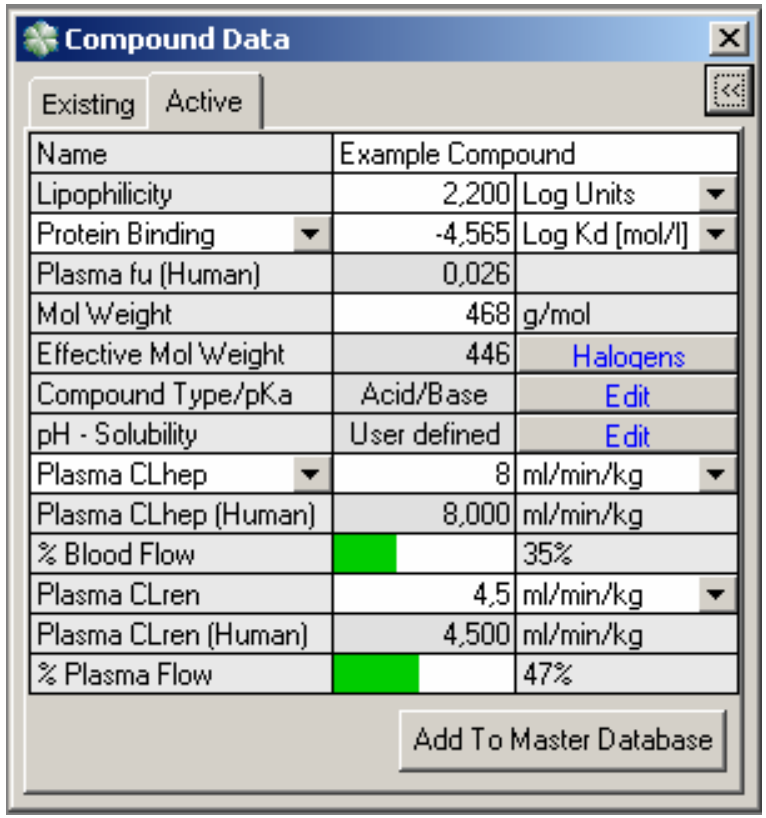
PK-Sim®'s Input Parameters

- Lipophilicity (LogMA preferred)
- Plasma Protein Binding (alternatively unbound fraction)
- (effective) Molweight
- pKa values for acids/bases
- Solubility vs. pH table
- Plasma Clearance hepatic/renal (alternatively in vitro metabolisation rates, K_m & V_{max}, …)



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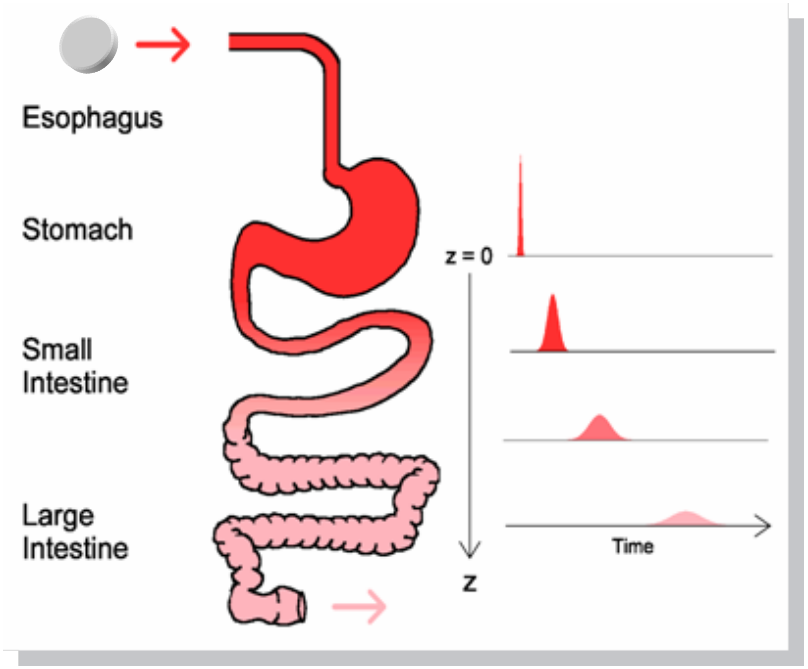
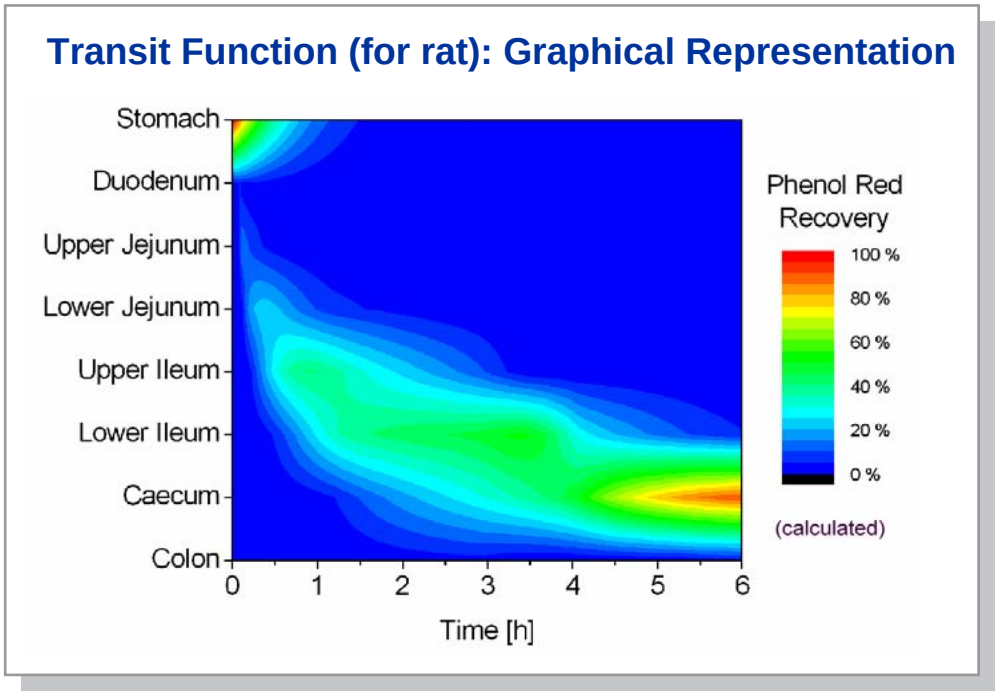
Simulation of Intestinal Transit & Absorption

Principle

Continuous one-compartment model for small intestine:

- Spatially varying properties (effective surface area, pH)
- GI transit described as *plug-flow with dispersion*





Willmann et al., *Pharm. Res.* **20**, 1766-1771 (2003)

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Model for Passive Absorption

- Intestinal permeability is based on an empirical equation*:

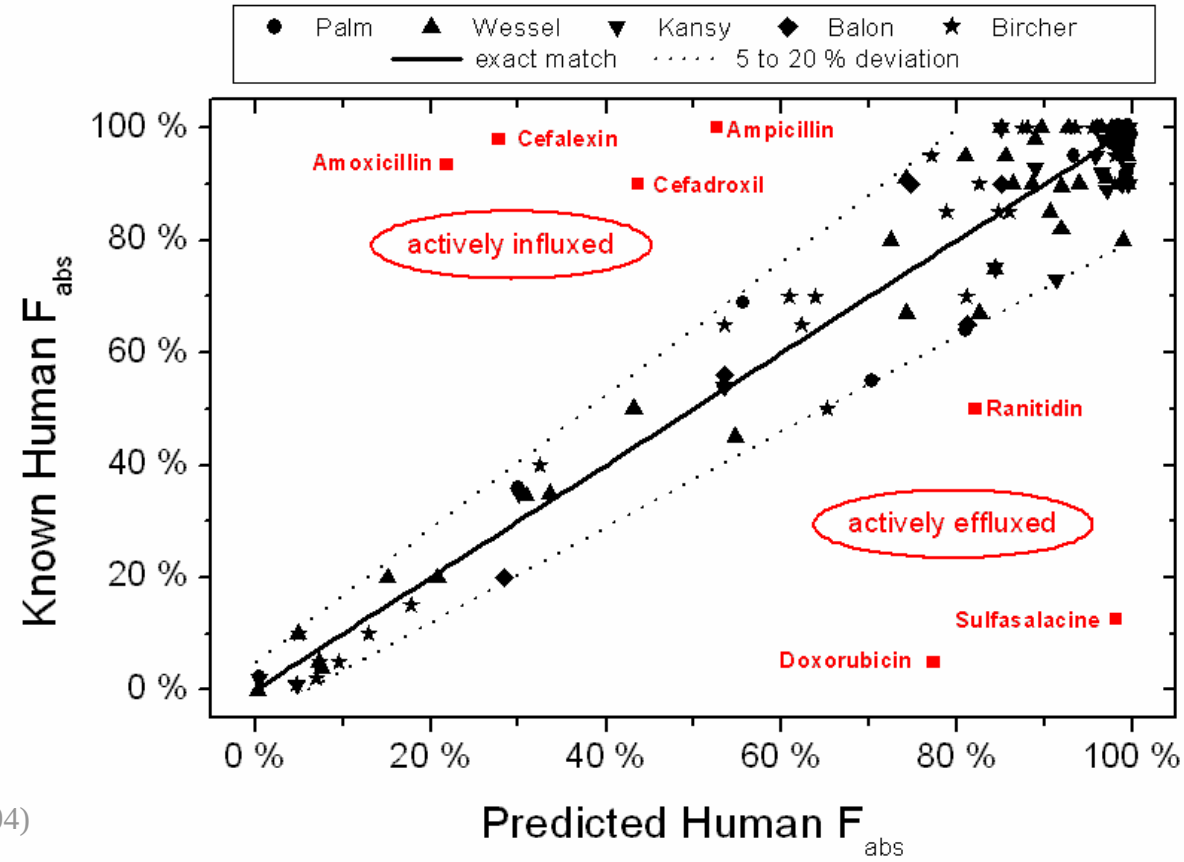
$$P_{int}(MW, MA) = \underbrace{A \frac{MW^{-\alpha-\beta}\, MA}{MW^{-\alpha} + B\, MW^{-\beta}\, MA}}_{\text{transcellular}} + \underbrace{C \frac{MW^{-\gamma}}{D^{-\gamma} + MW^{-\gamma}}}_{\text{paracellular}} \quad [cm/s]$$

•D. Leahy et al. in *Novel Drug Delivery and Its Therapeuthic Application* (1989)

Model for the intestinal permeability coefficient was build using a data set of 126 marketed compounds with no solubility limitation at thera-peutic doses.

An excellent fit was obtained.

All outliers are known to be substrates active transporters.



Willmann et al., *J. Med. Chem.* **47**, 4022-4031 (2004)

Presentation Overview

- PK-Sim®'s Absorption Model
- **Application Examples**
  - **Example 1: Dissolution Limited Absorption**
  - Example 2
  - Example 3

Compound X (from ongoing BHC development project)

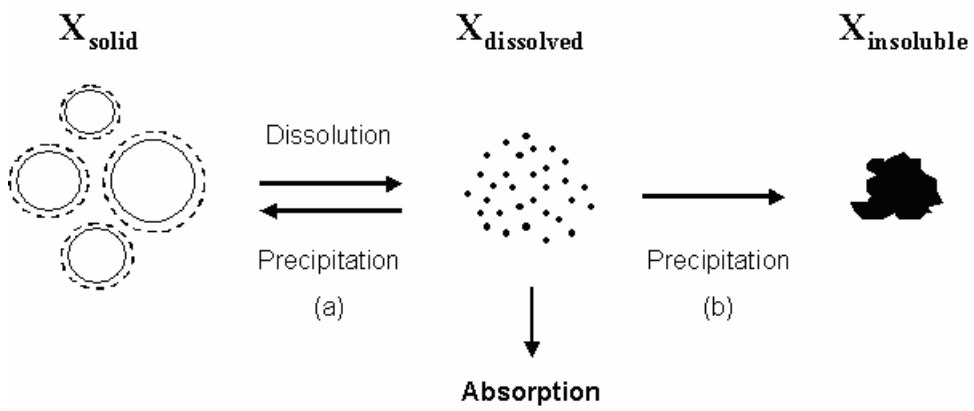
Properties

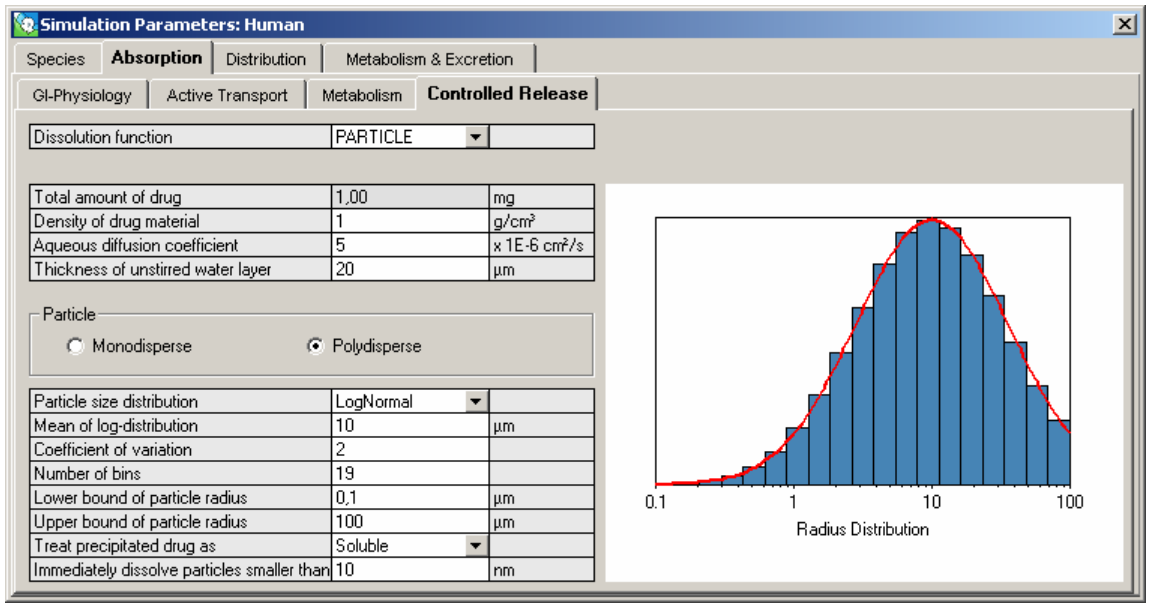
- neutral
- medium lipophilicity (LogMA = 2.2)
- MW ~ 450 g/mol
- high permeability (Caco2, animal models)
- low aqueous solubility

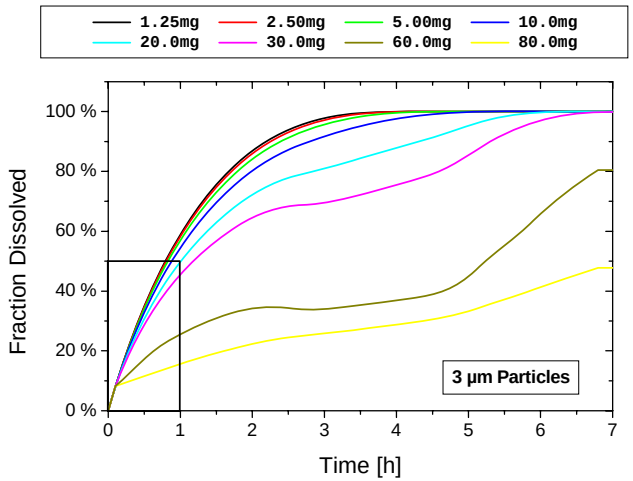
- Human study data:
  - single dose under fasted conditions
  - solution: 5 and 10 mg
  - IR tablet: 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg
    (mean particle diameter of IR tablet formulation: 3 µm)

Model for Dissolution-Limited Absorption

- Add-on module to dynamically simulate dissolution of poly-disperse spherical particles







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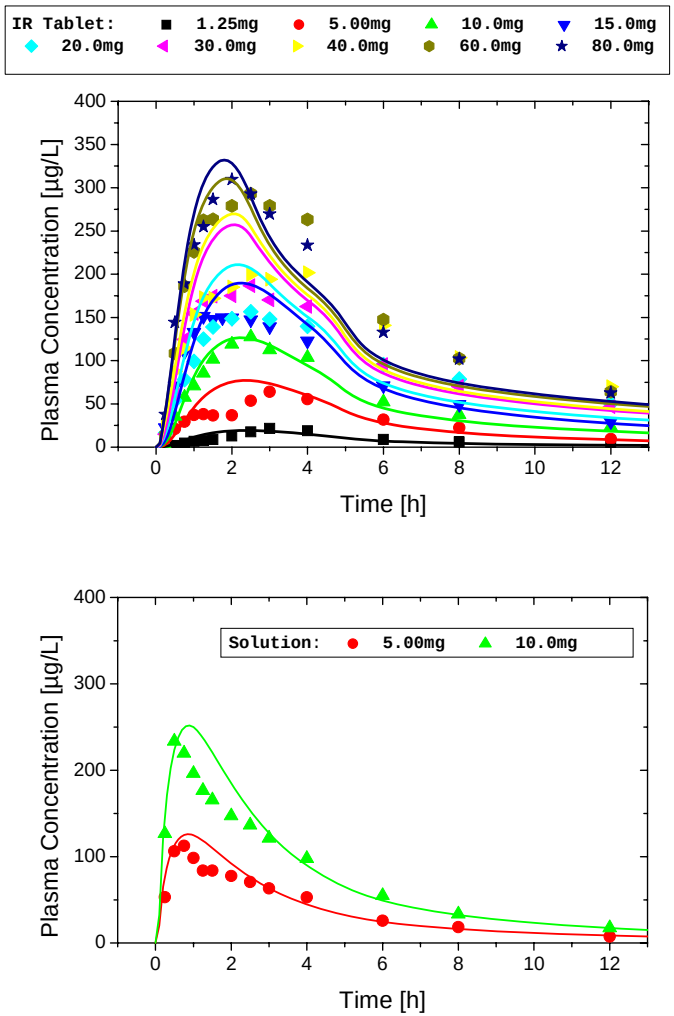
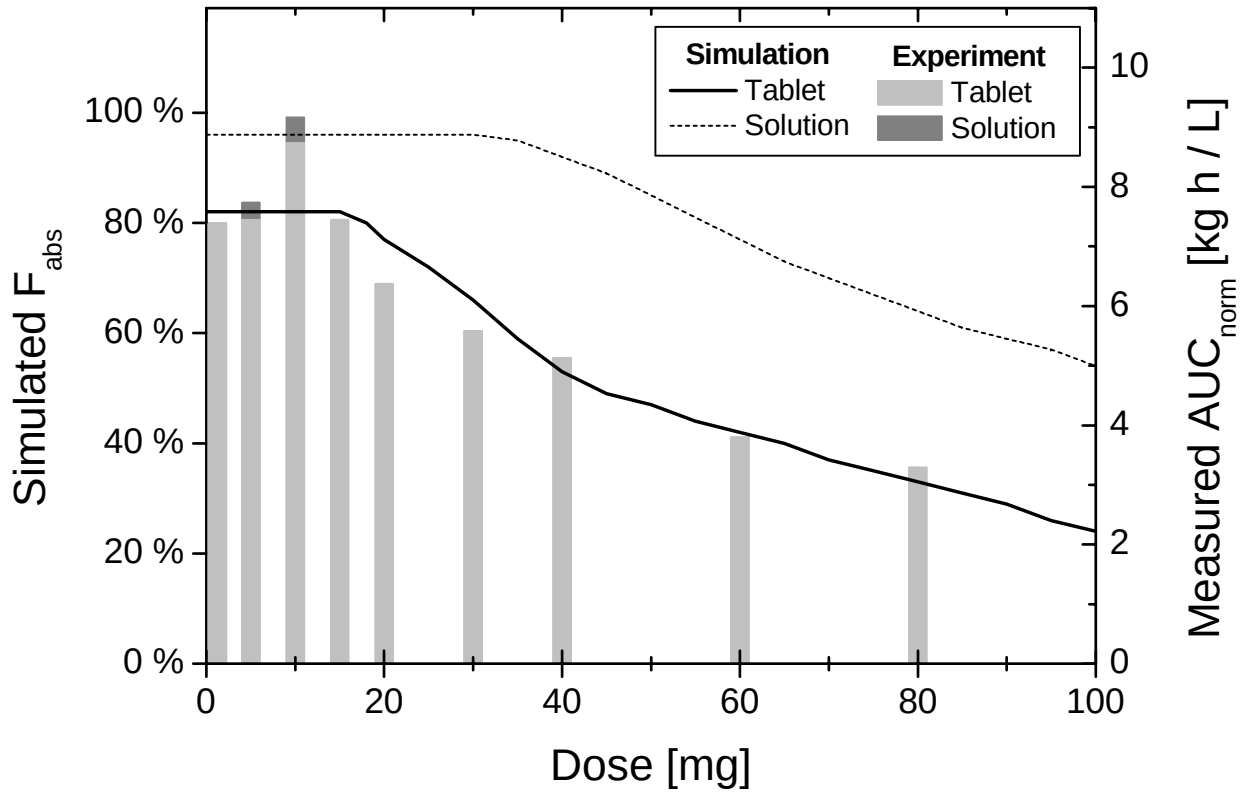
Simulation of Dose Dependent Exposure





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Presentation Overview

- PK-Sim®'s Absorption Model
- **Application Examples**
  - Example 1
  - **Example 2: Cimetidine PK Variability**
  - Example 3

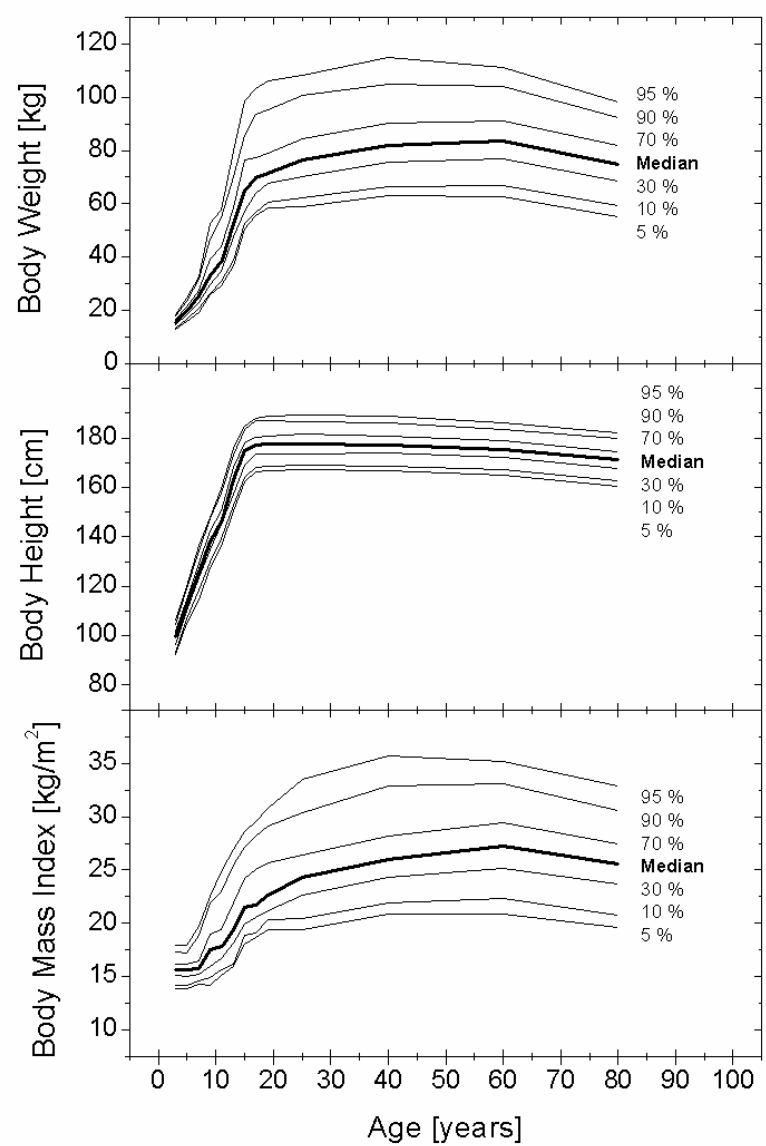
What About Inter-Individual Variability ?

?

What About Inter-Individual Variability ?

?

Age Dependence and Variability of Physiological and Anatomical Parameters



Data for the age dependence of physiological parameters relevant for PBPK modelling such as

- body weight, body height, body mass index,
- organ weights, blood flow rates,
- tissue composition (water, lipid, and protein content)
- fractions vascular, interstitial and intracellular

and their variability and cross-correlation were collected in a comprehensive literature search.

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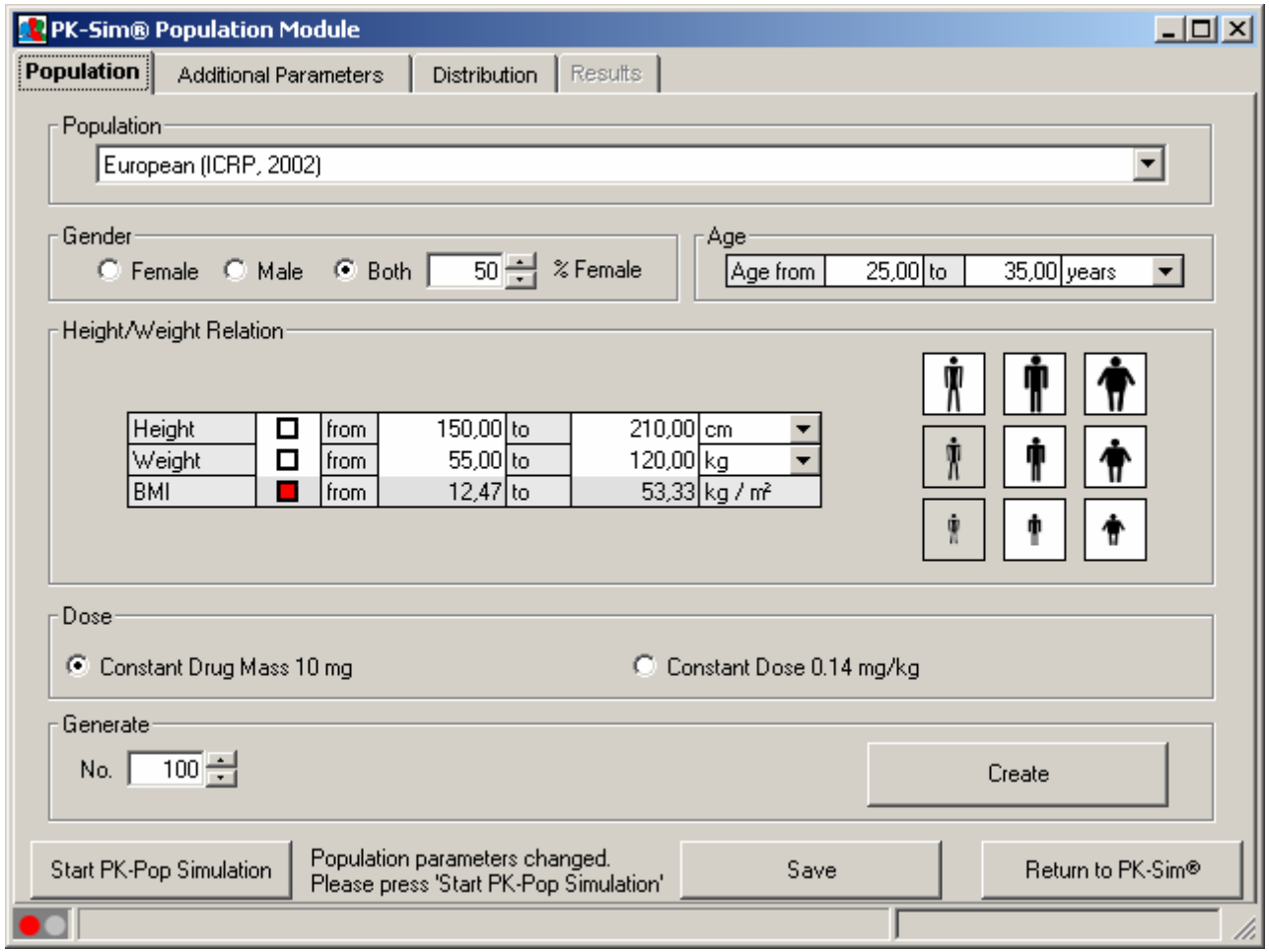
Modelling Inter-Individual Variability in PK-Sim® with the add-on module “PK-Pop“



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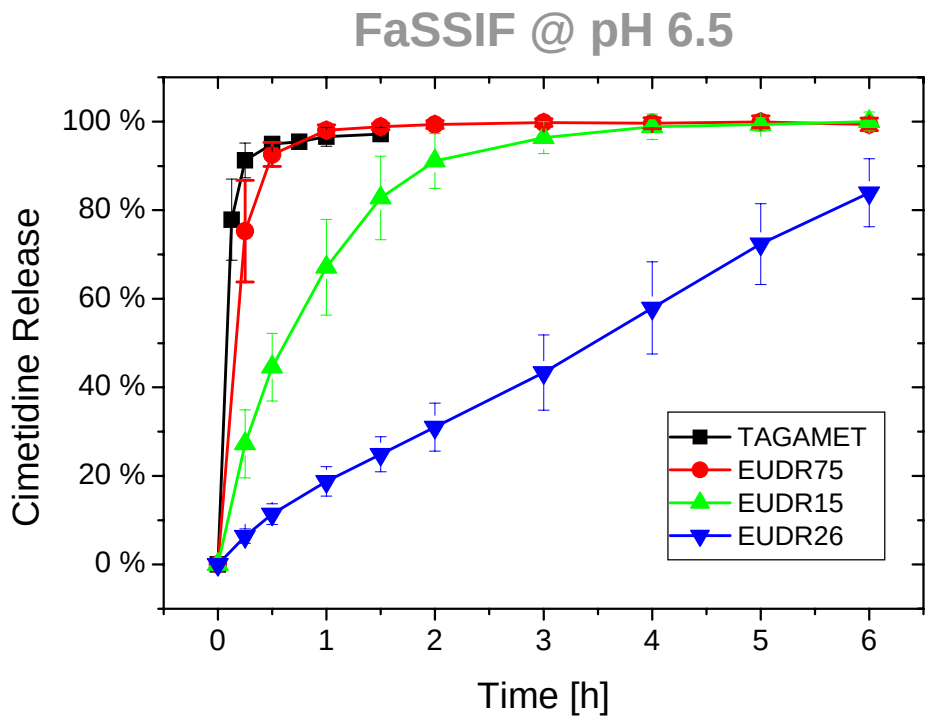
Example: Cimetidine

- Available Information:
  - *in vitro* dissolution profiles of IR Tagamet® tablets plus three experimental CR formulations (400 mg cimetidine)
  - *in vivo* data from 12 male volunteers
  - PK profiles after iv admin. in same individuals (clearance distribution !)



Exp. Data from: Jantratid et al., *Clin. Pharmacokin.* (2006;45(4):385-99)

- Population Simulation:
  - 100 virtual individuals (age, weight and height matched) with varying gastric emptying time (***15–45 min.***) and small intestinal transit time (***2,5–5,5 h***)

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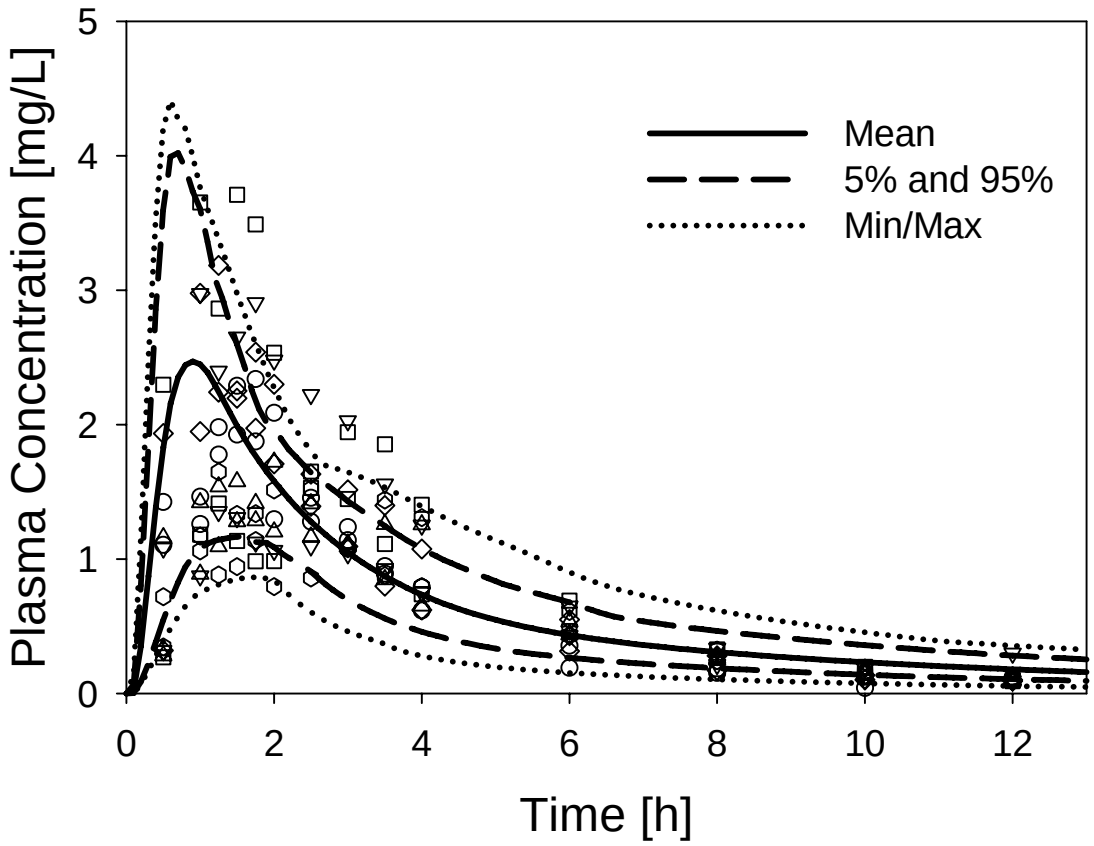
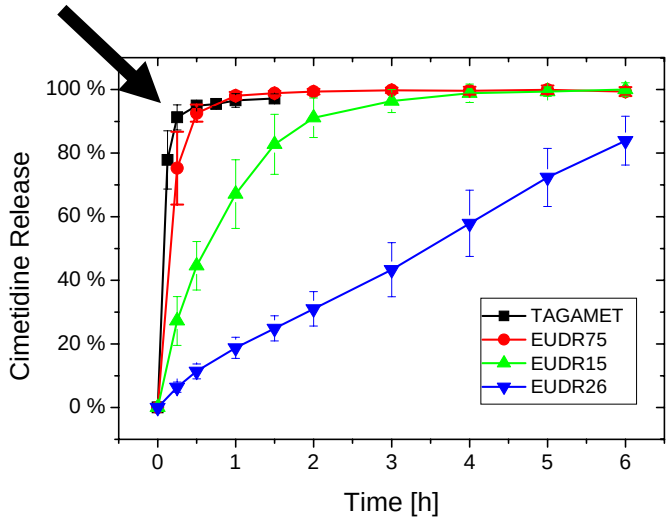
Example: Cimetidine

Tagamet® tablets



In vitro release profile:



(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)

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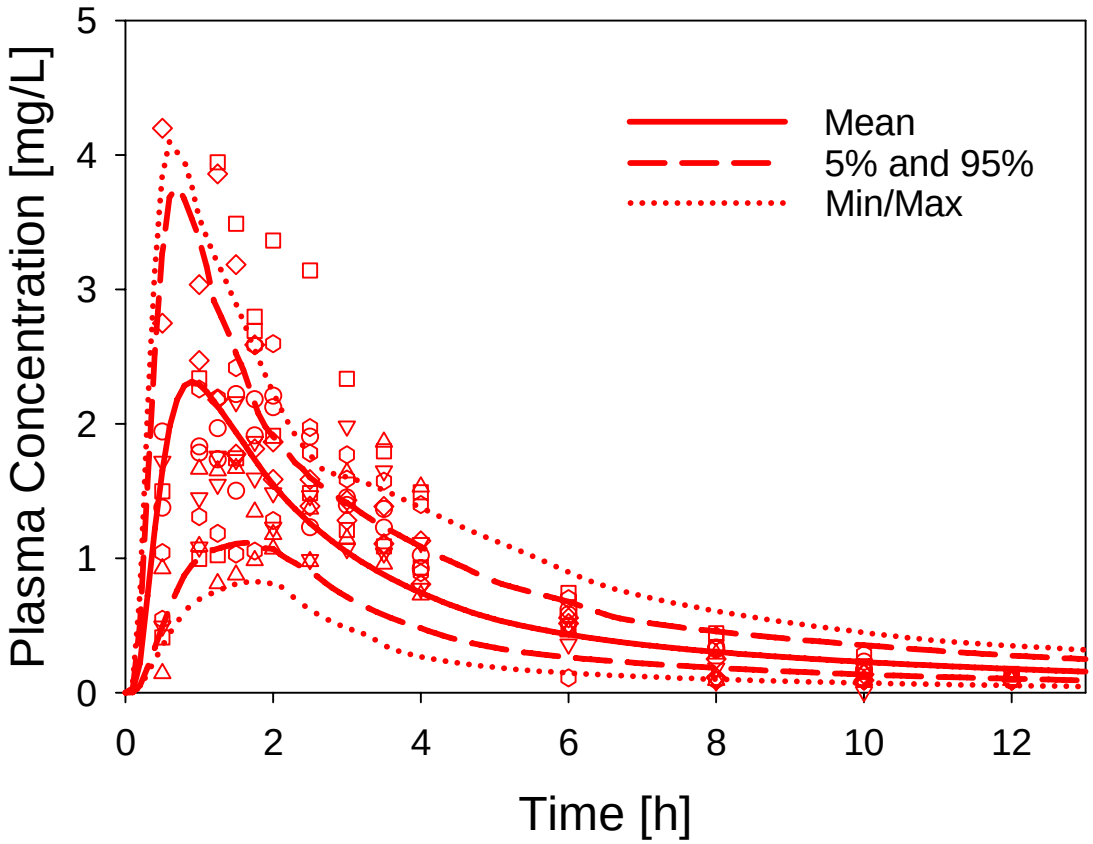
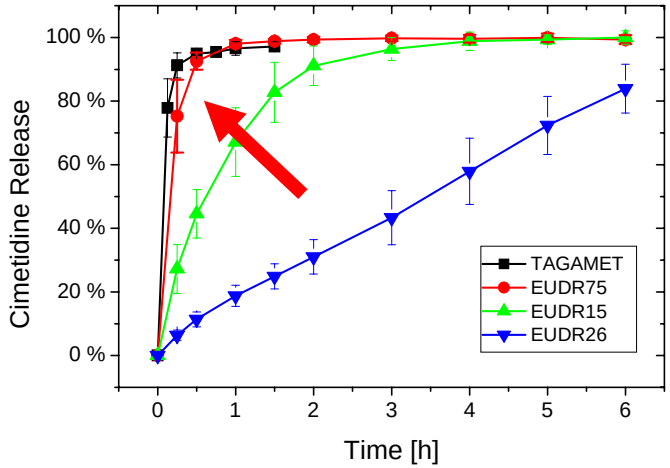
Example: Cimetidine

Eudragit 7,5 %



In vitro release profile:



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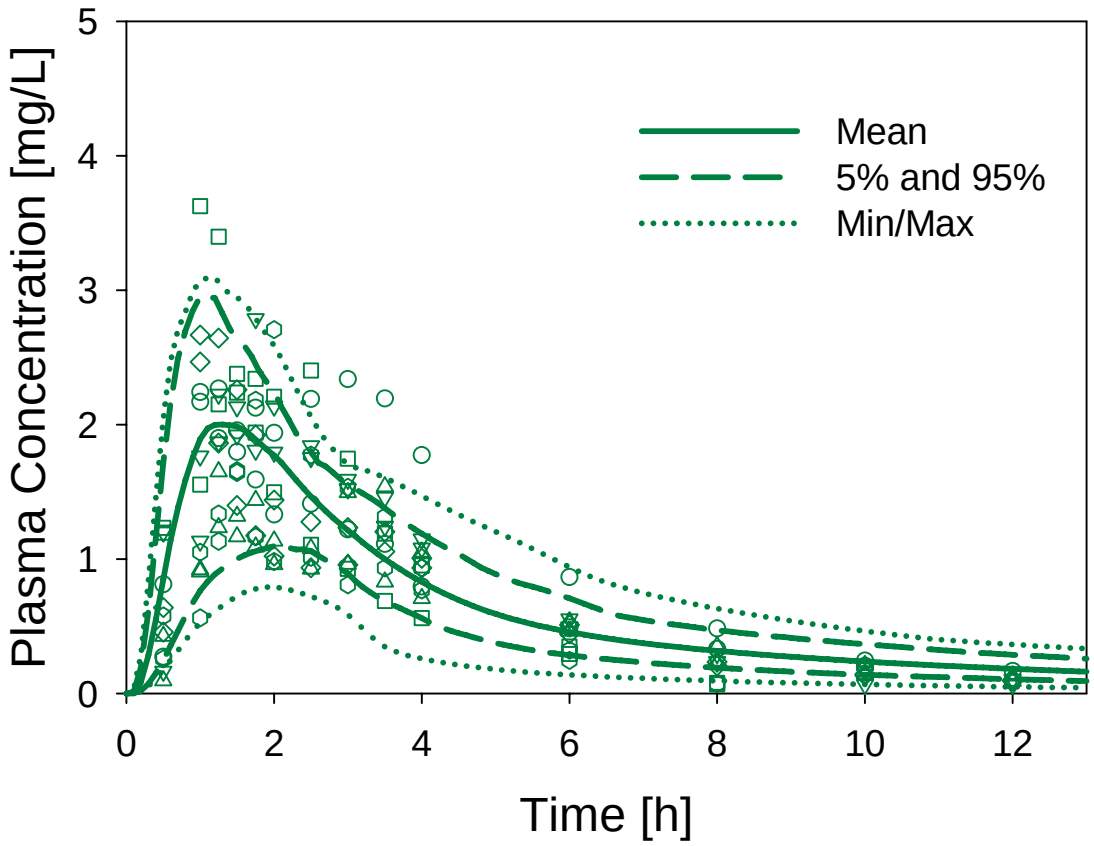
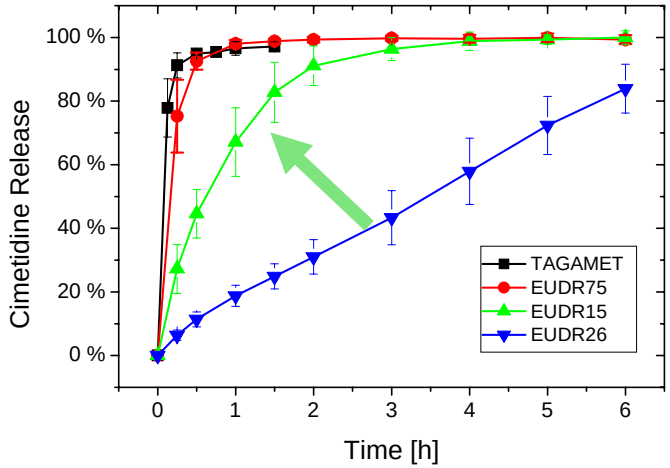
Example: Cimetidine

Eudragit 15 %



In vitro release profile:



(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)

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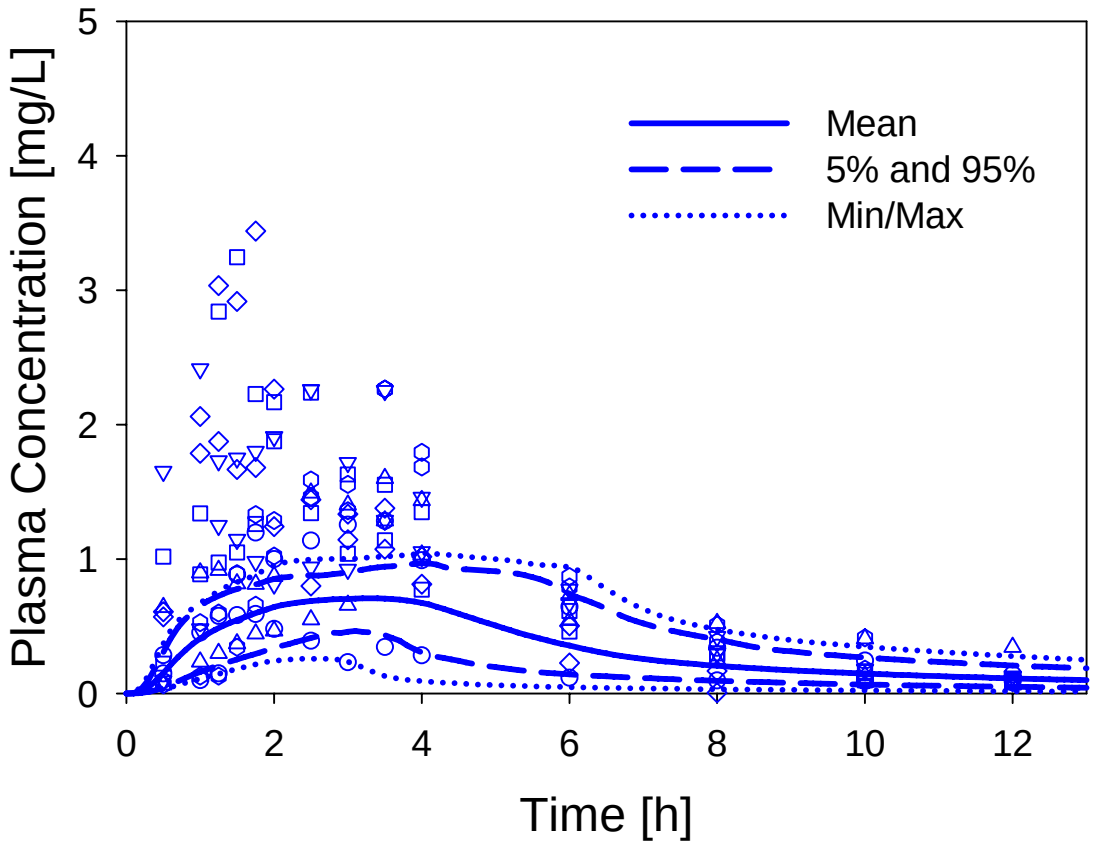
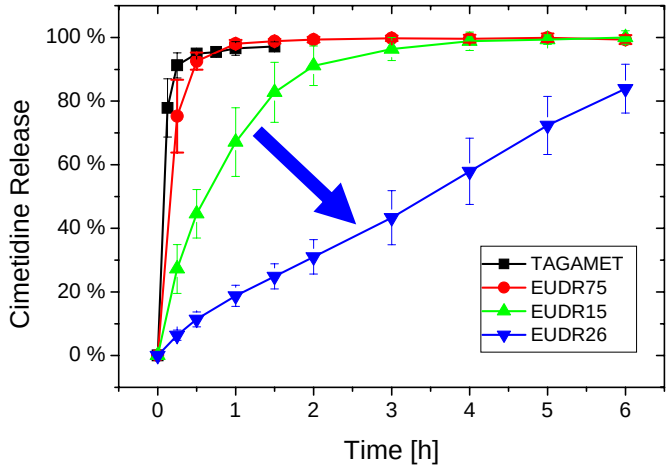
Example: Cimetidine

Eudragit 26 %



In vitro release profile:



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- PK-Sim®'s Absorption Model
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  - Example 1
  - Example 2
  - **Example 3: Simulations in Children**

Special Populations: Children

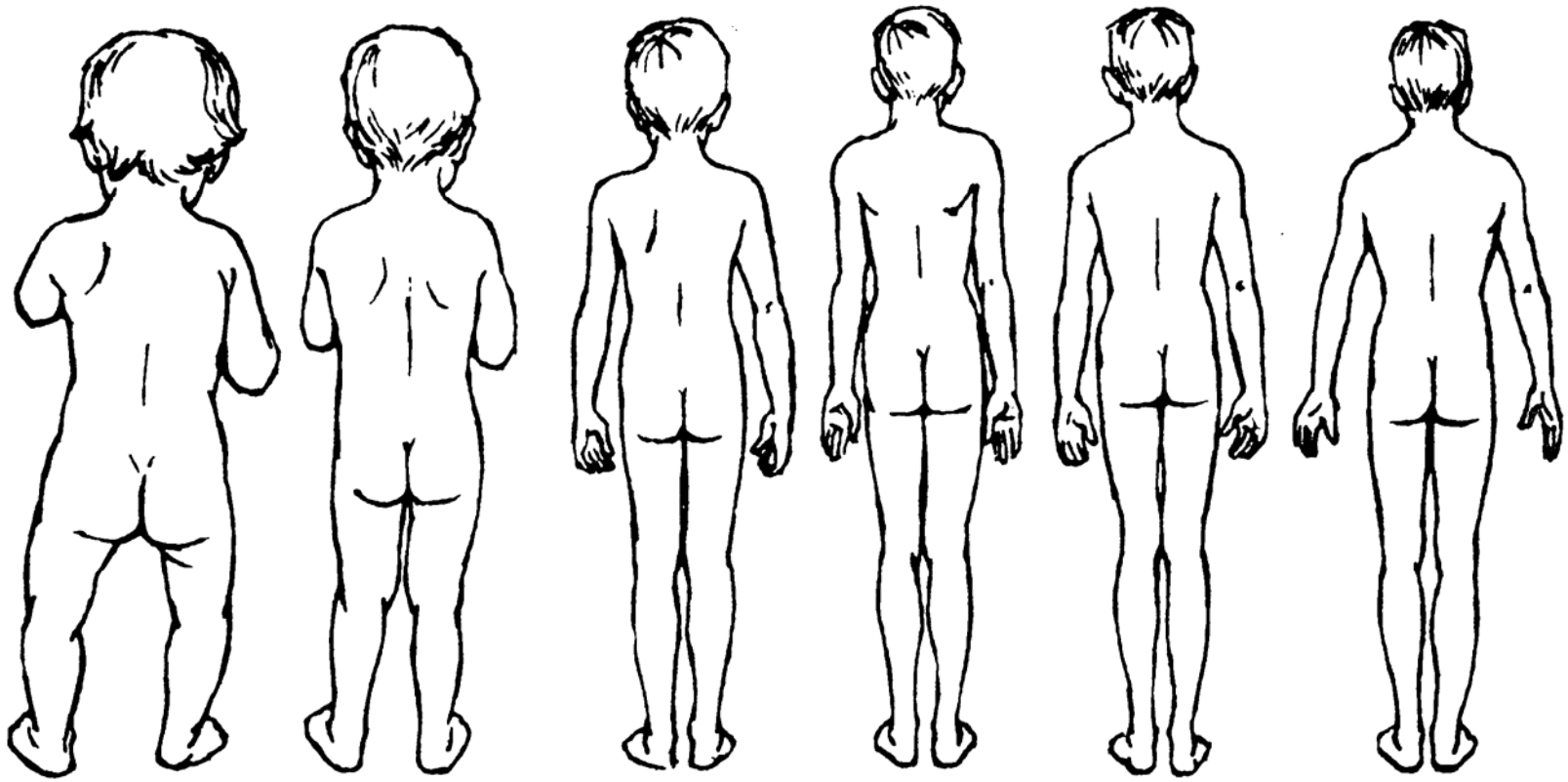
- Food & Drug Administration (FDA) and European authorities pressuring industry to perform clinical trials in paediatric patients
- Increase access to treatments for children and reduce off-label, unlicensed treatment
- 50% of all drugs administered in hospitals are not properly licensed for use in children*
- Adverse drug reactions due to dosing errors and use in non-labeled ages - from Dec 2001-2004, 820 serious ADRs occurred due to off label use with 130 being fatal (reported)**

* Conroy et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. British Medical Journal 320:79-82. (2000)

** European Medicines Agency. Evidence of harm from off label or unlicensed medicines in children. EMEA/11207/04. (2004)

Scaling PBPK Models to Children

- PBPK Modelling in children requires knowledge about the ***physiological*** and ***clearance*** differences relative to adults.



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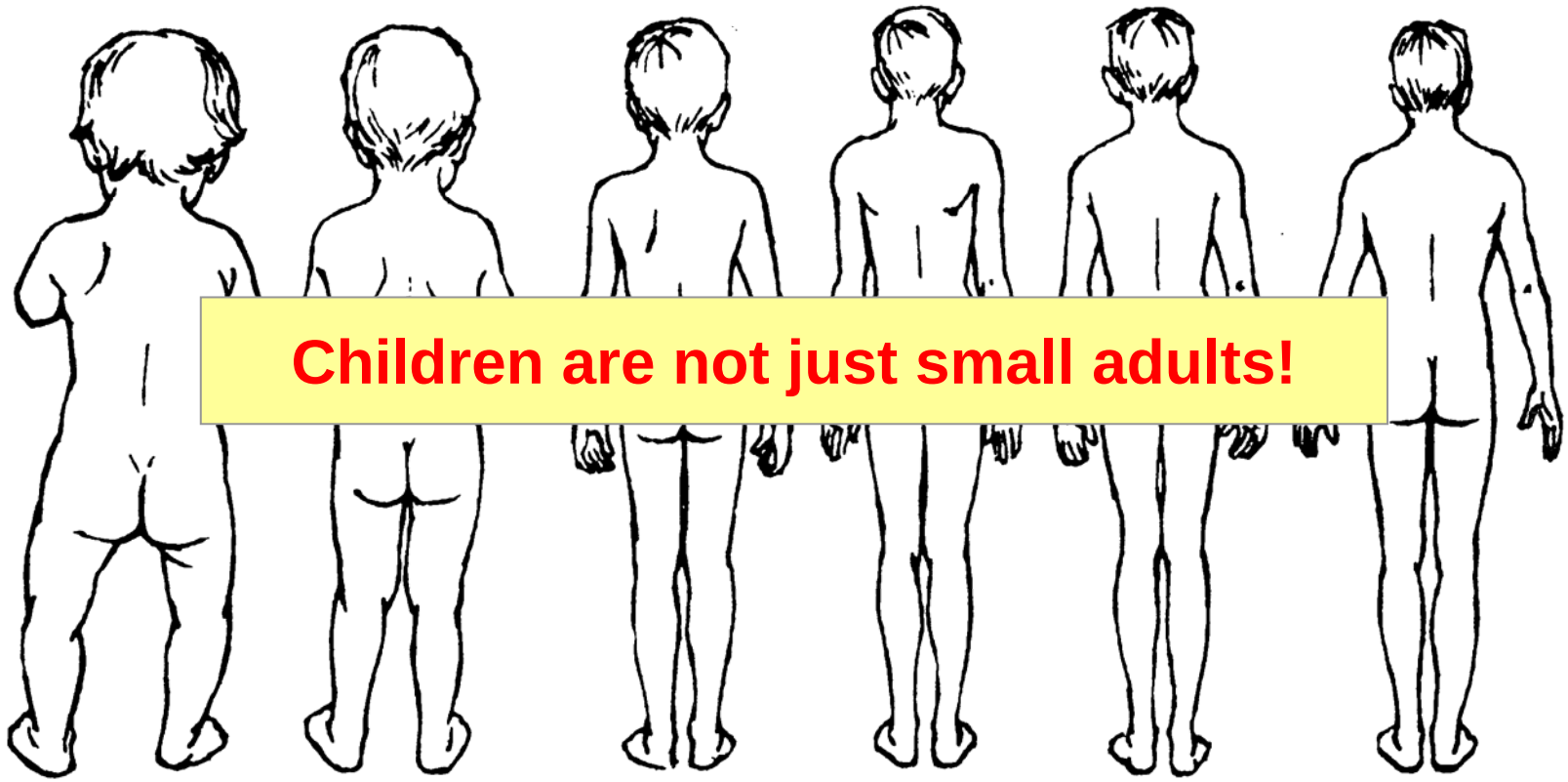

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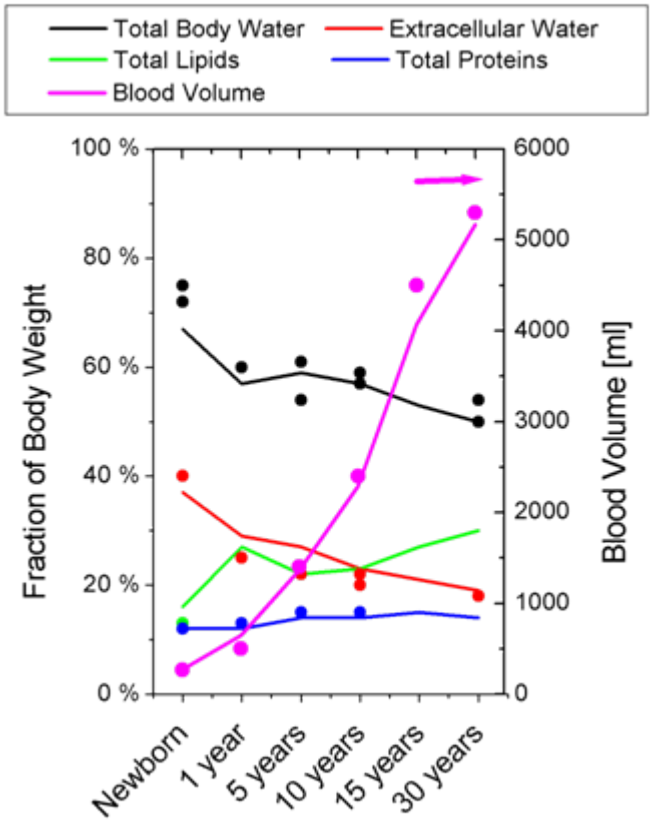
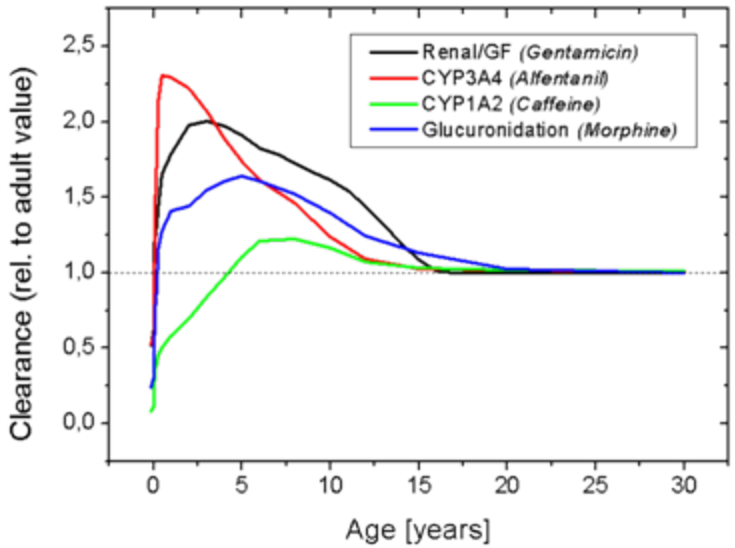


-> mechanistic model for clearance scaling



(Edginton et al., *Clin. Pharmacokin. (in press 2006)*)

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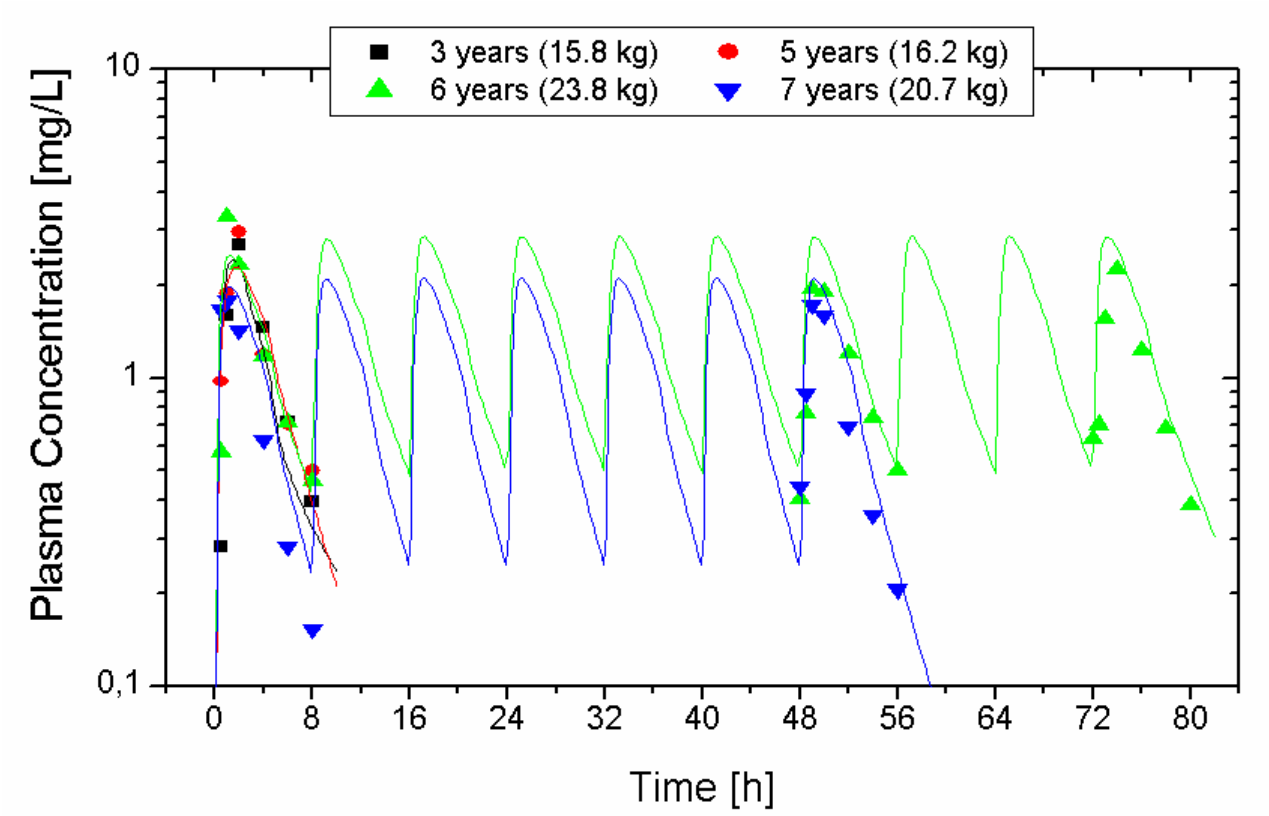
Simulating Oral Absorption in Children

- **Example:** Oral administration of 10 mg/kg Ciprofloxacin in children



Simulating Drug Absorption: Summary

- The rate and extent of oral drug absorption can be well simulated based on simple physico-chemical input parameters and a detailed description of the GI physiology

- Physiology-based simulations of drug absorption can be used
  - to make predictions in the early development phase
  - for hypothesis testing in later development stages
  - to aid formulation development
  - to study sub-populations (e.g. children, elderly, diseases)

The PK-Sim®-Team

- BTS-Systems Biology & Computational Solutions
  - Dr. Andrea Edginton
  - Karsten Höhn
  - Marcus Kleine-Besten
  - Dr. Jörg Lippert
  - Dr. Walter Schmitt
  - Michael Sevestre
  - Juri Solodenko
  - Wolfgang Weiss
  - Dr. Stefan Willmann

- Bayer-internal Cooperations
  - PK groups of BHC-Pharma
    (Dr. G. Ahr, Dr. W. Mück, Dr.H.Stass and colleagues)

- External Cooperations
  - Prof. Jenny Dressman, Uni Frankfurt
  - NIMBUS Biotechnology, Leipzig
  - Physiomics plc, UK

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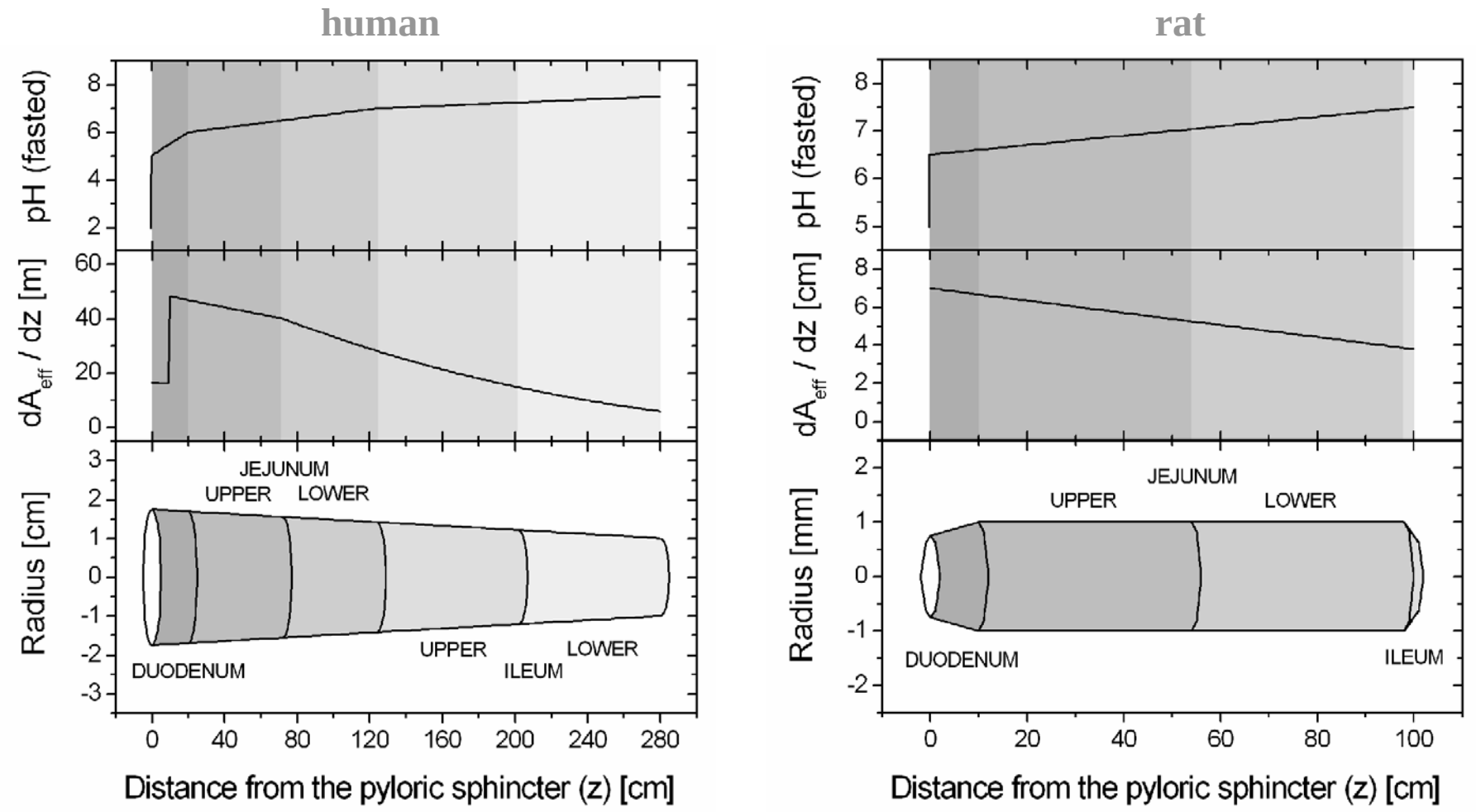
BACKUP SLIDES

Relevant Physiological Parameters: Summary



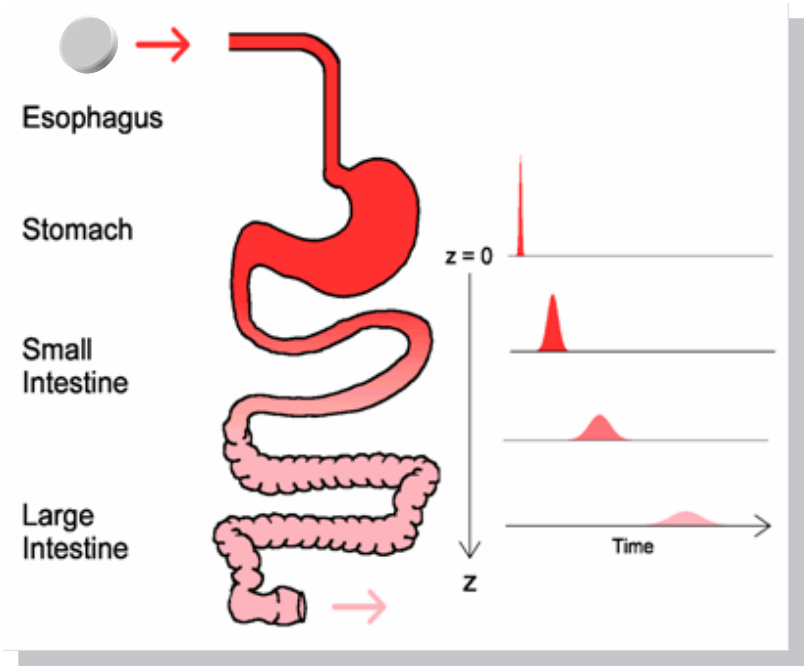
(Physiological data collected in collaboration with Prof. Dressman, Frankfurt, data for dogs and mice not shown)

Simulation of Intestinal Transit & Absorption

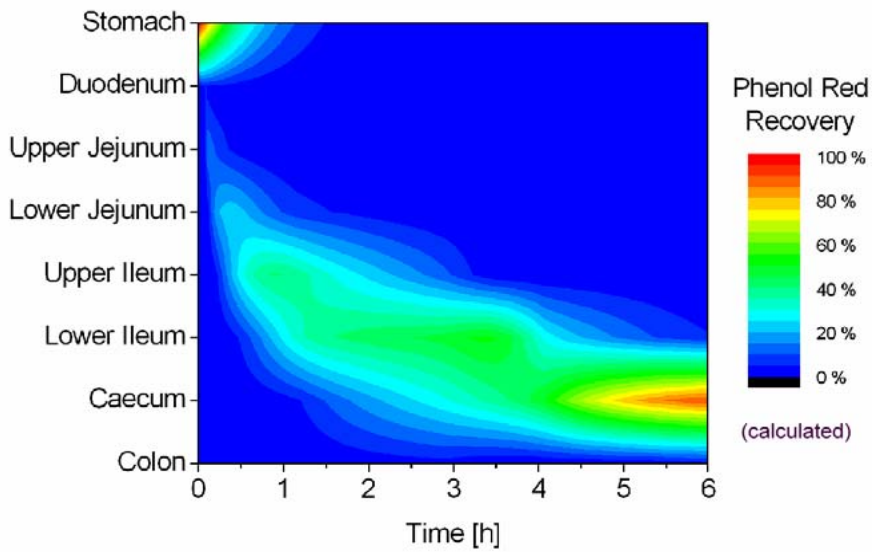
$$\frac{d^2 M_{pv}(z,t)}{dz\,dt} = \frac{d}{dz}\left(P_{int}\,[C_{lumen}(z,t) - C_{pv}(t)]\,A_{eff}(z)\right) \qquad (C_{lumen}(z,t) \le S_{int}\ !)$$

substance-specific properties

physiological properties



Transit Function (for rat): Graphical Representation



Willmann et al., *Pharm. Res.* **20**, 1766-1771 (2003)

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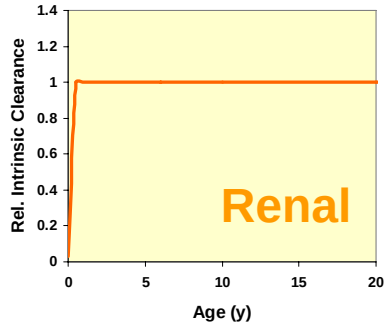
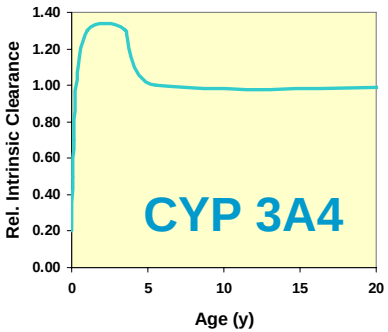
Scaling of Intrinsic Clearances

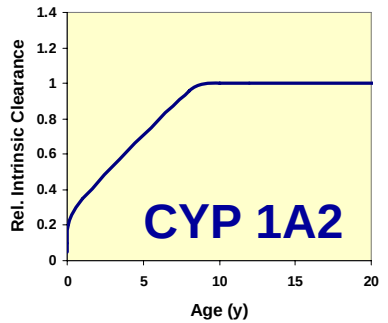
Hypothetical Compound



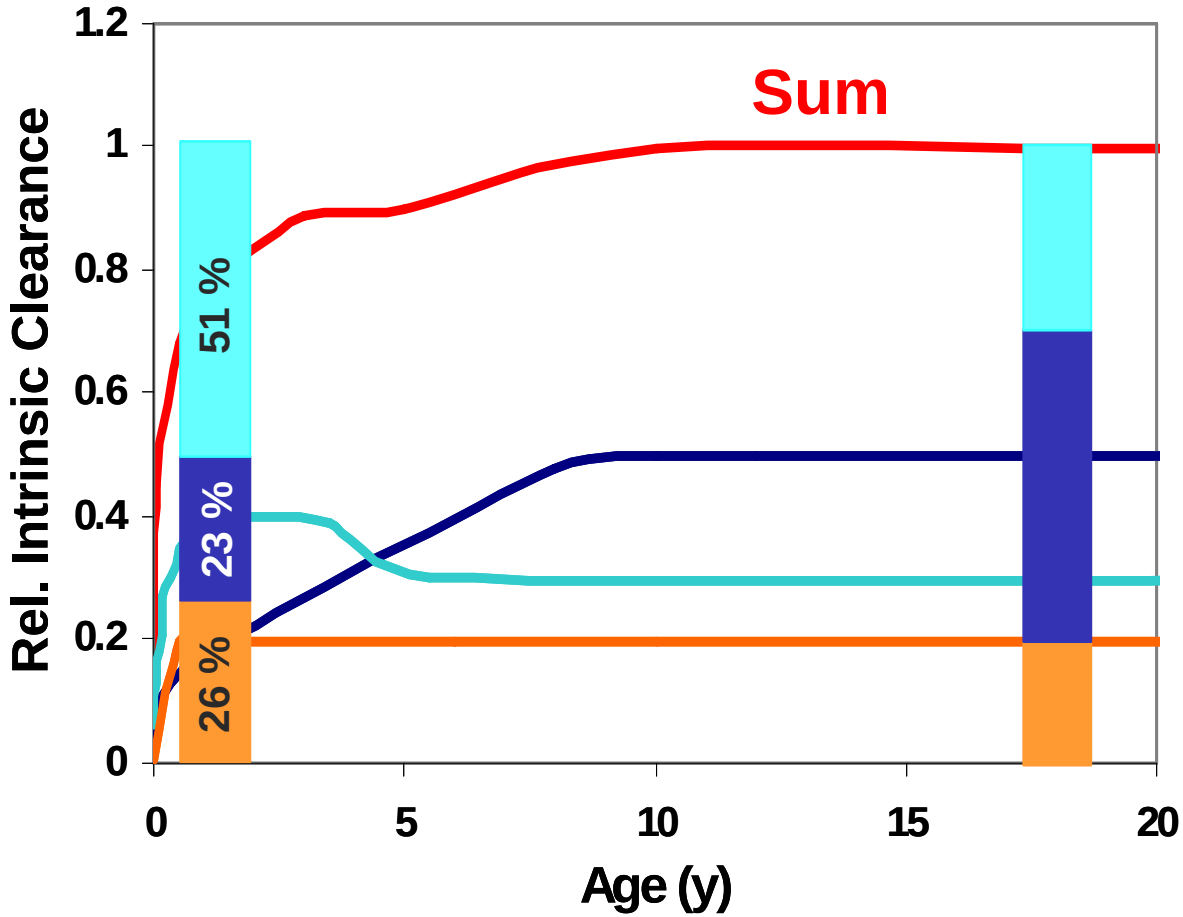
20 %



30 %



50 %



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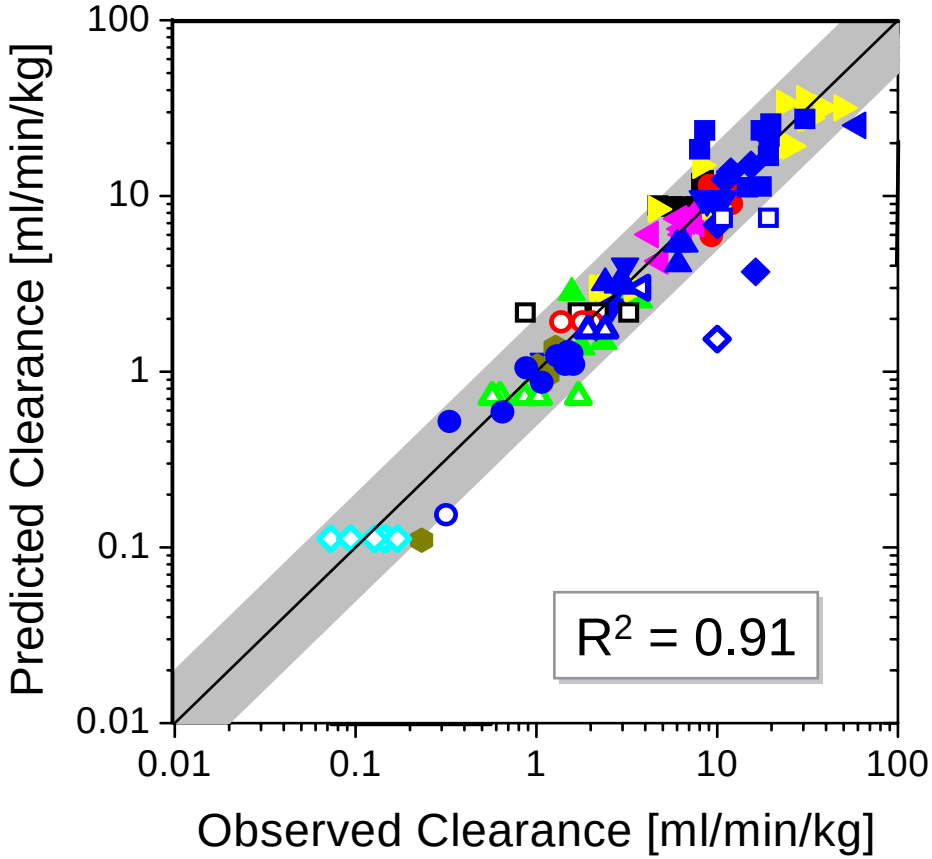
Validation of Clearance Scaling

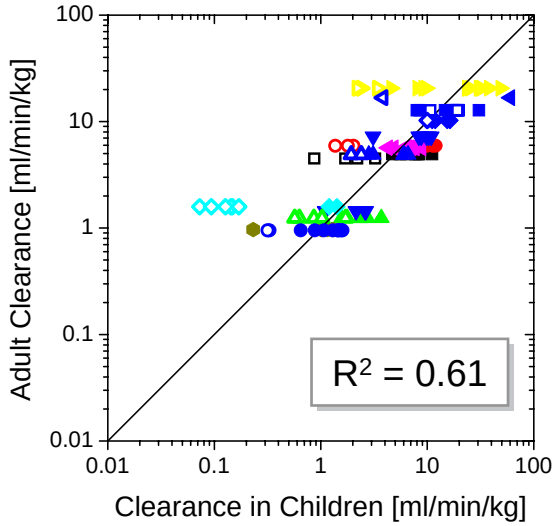


One Pathway

- Alfentanil
- Midazolam
- Gentamicin
- Isepamicin
- Caffeine
- Ropivacaine
- Morphine
- Lorazepam

Multiple Pathways

- Buprenorphine
- Lidocaine
- Ciprofloxacin
- Paracetamol
- Theophylline
- Fentanyl



Using adult clearances would lead to much worse prediction!

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Calculation of Partition Coefficients

Steady state organ/plasma partition coefficients

$$K_{tissue\,/\,water} = f_{lipid}^{tissue} * K_{lipid\,/\,water} + f_{protein}^{tissue} * K_{protein\,/\,water} + f_{water}^{tissue}$$

K = Partition Coefficient ($K_{protein/water}$ = HSA binding in case of plasma and calculated from Lipophilicity in all other cases)

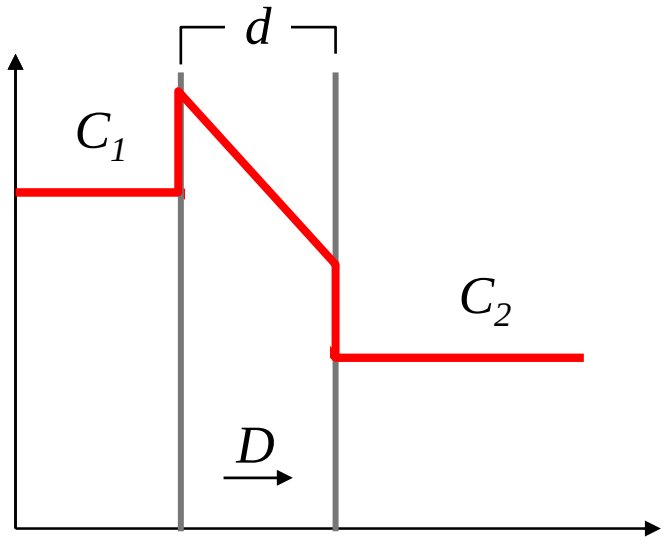
f = Volume fraction

$$K_{tissue\,/\,plasma} = \frac{C_{tissue}}{C_{plasma}} = \frac{K_{tissue\,/\,water}}{K_{plasma\,/\,water}} = K_{tissue\,/\,water} \cdot f_u$$

Calculation of Distribution Dynamic

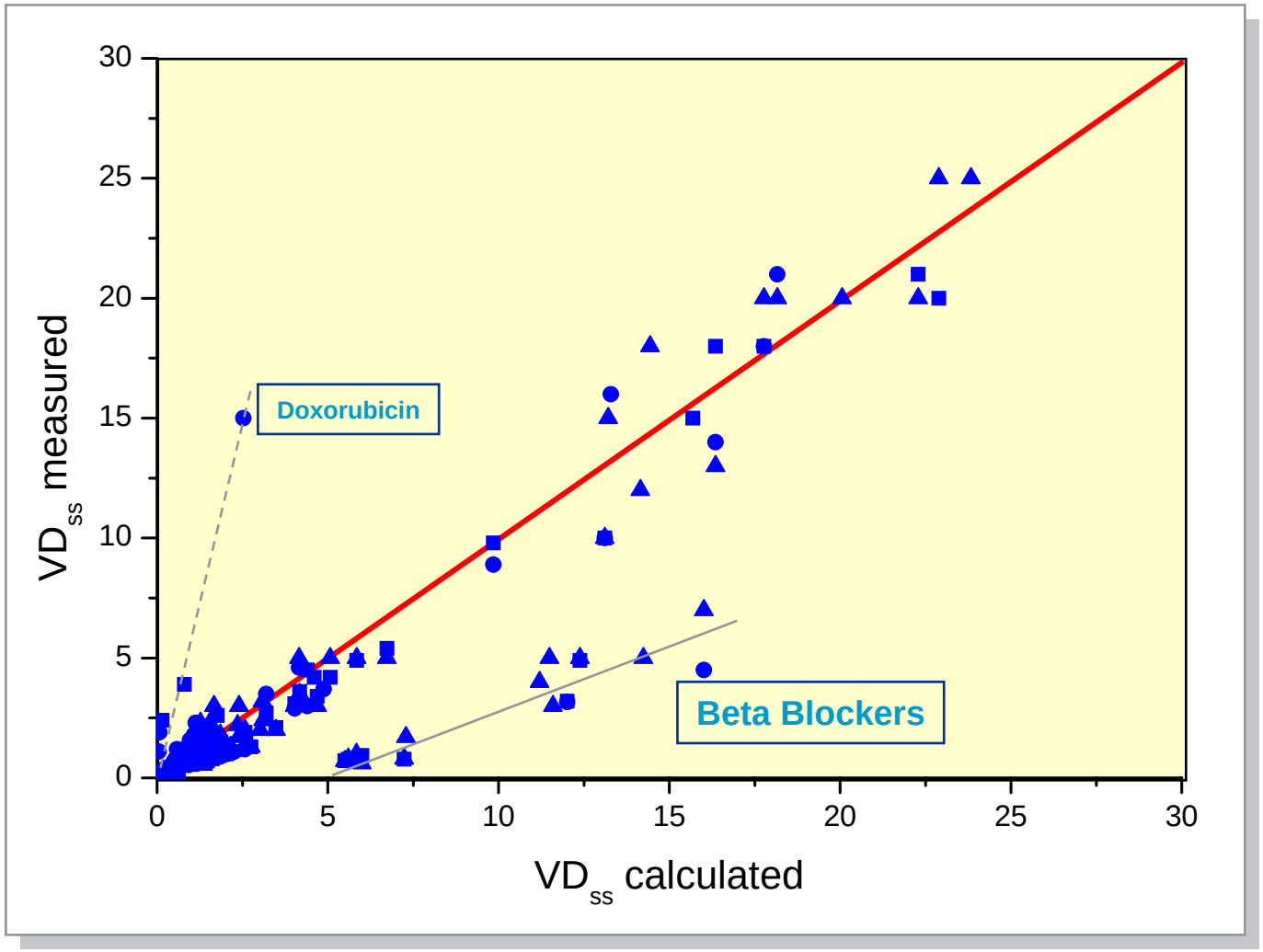
Permeability x Surface-Area Products

Fick's First Law: $J = K\frac{D}{d} \cdot A \cdot (C_1 - C_2)$



PA_{tissue} ~ Lipophilicity · $MW^{-\alpha}$ · A_{tissue}

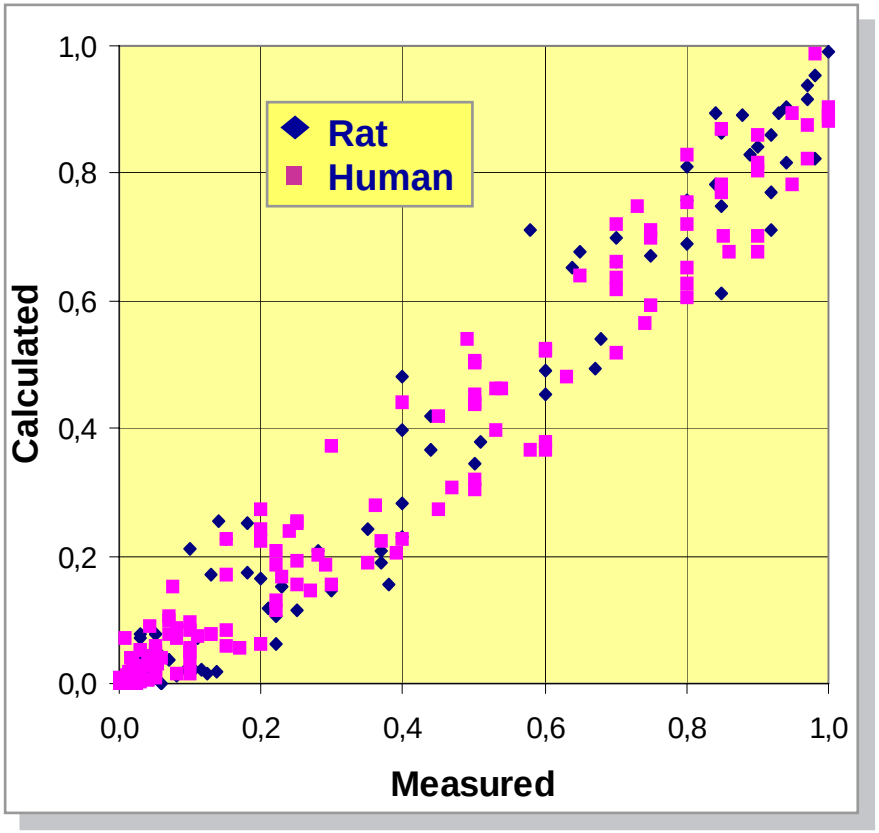
Volume of Distribution



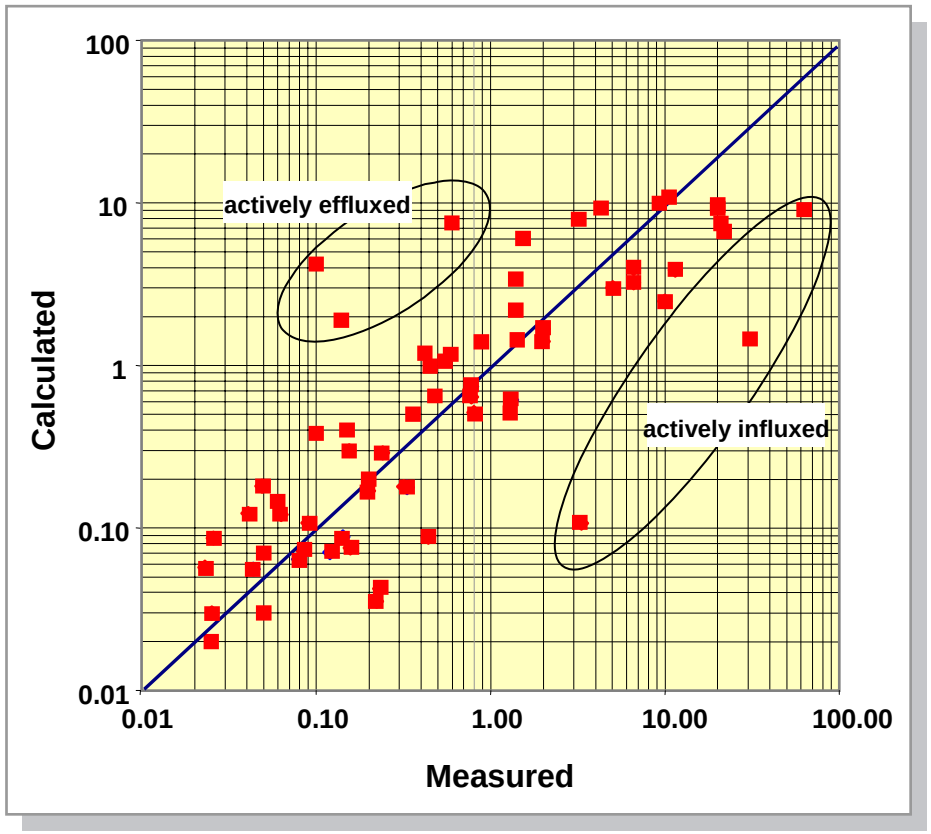
Prediction of Partition Parameters

Validation

Fraction Unbound in Plasma



Brain/Plasma Partition-Coefficient



Keldenich et al., oral presentation at *LogP2004 Symposium*, Zürich (2004)

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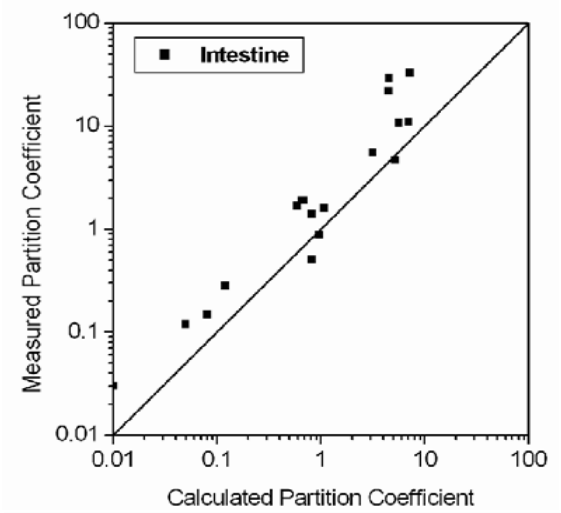
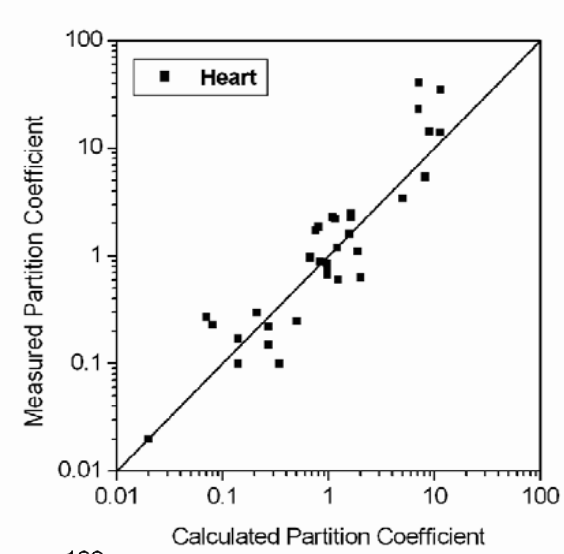
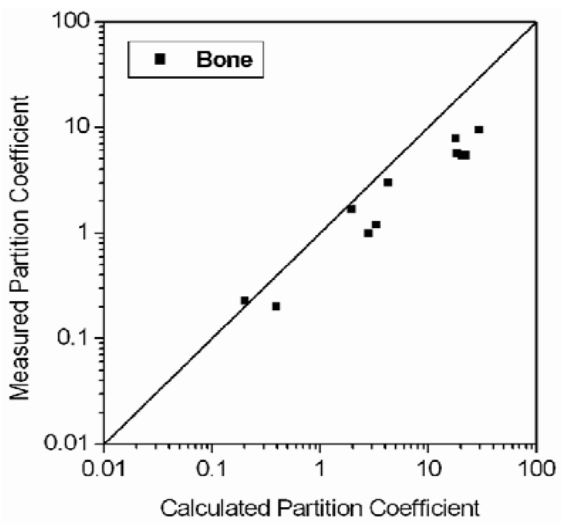
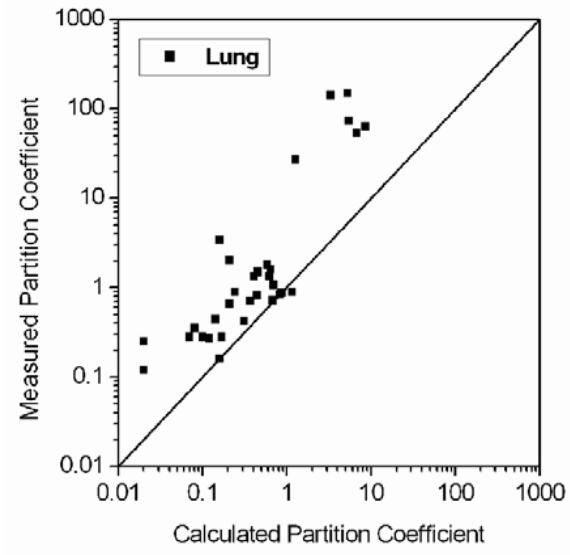
Organ/Plasma Partition Coefficients

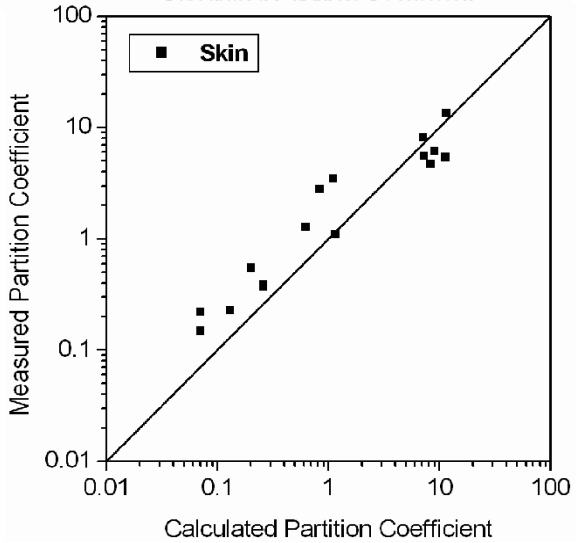
More Examples

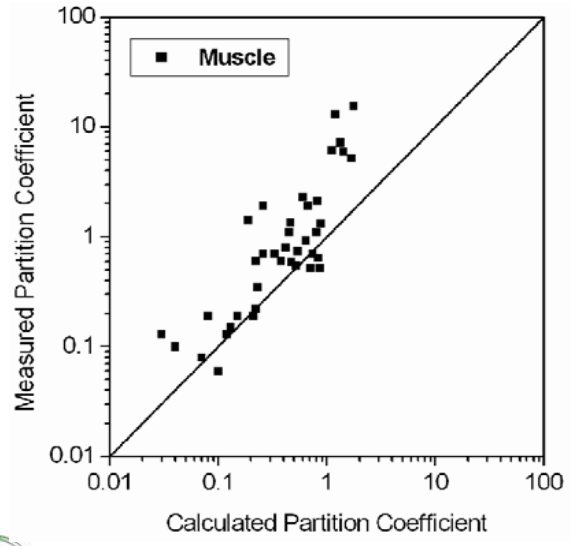












Willmann et al., Poster presentation at *LogP2004 Symposium*, Zürich (2004)

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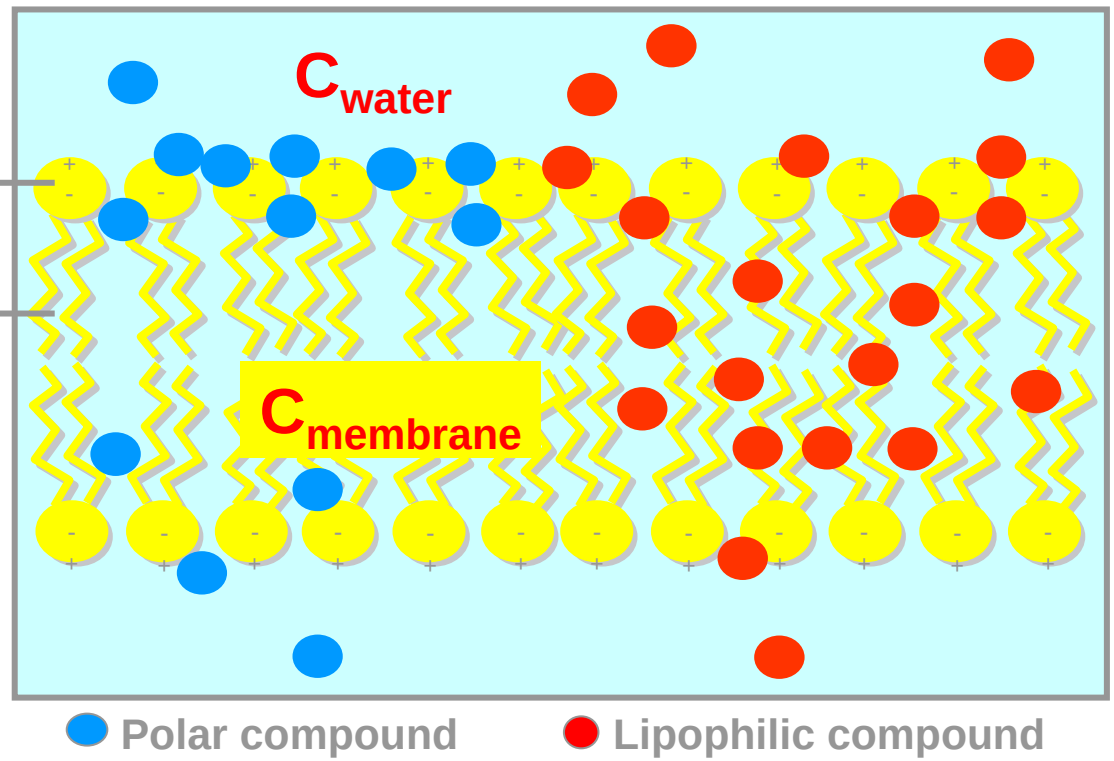
Membrane Affinity

$$MA = C_{membrane} / C_{water}$$

Partitioning into Phospholipid-Membrane



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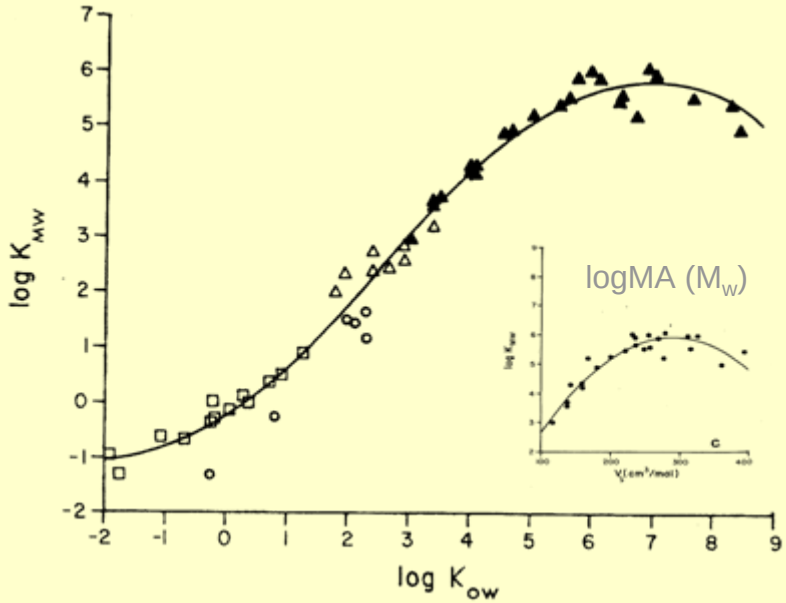
Membrane Affinity vs. $logK_{ow}$

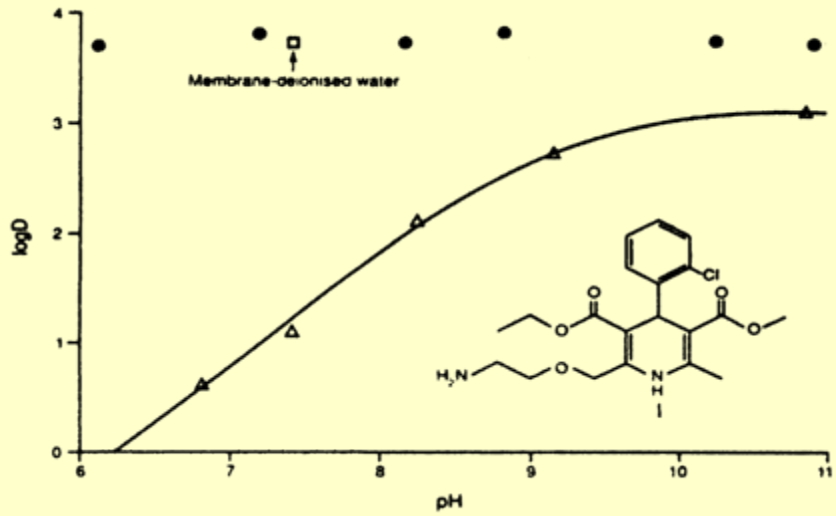
Relationship $logK_{ow}$ / logMA nonlinear



Gobas et al. , J. Pharm. Sci 77, 265 (1988)

pH-Dependence different from $logK_{ow}$

Example: Basic compound



Austin et al. , Fisons Pharmaceuticals
I. logP Symposium, Lausanne 1995

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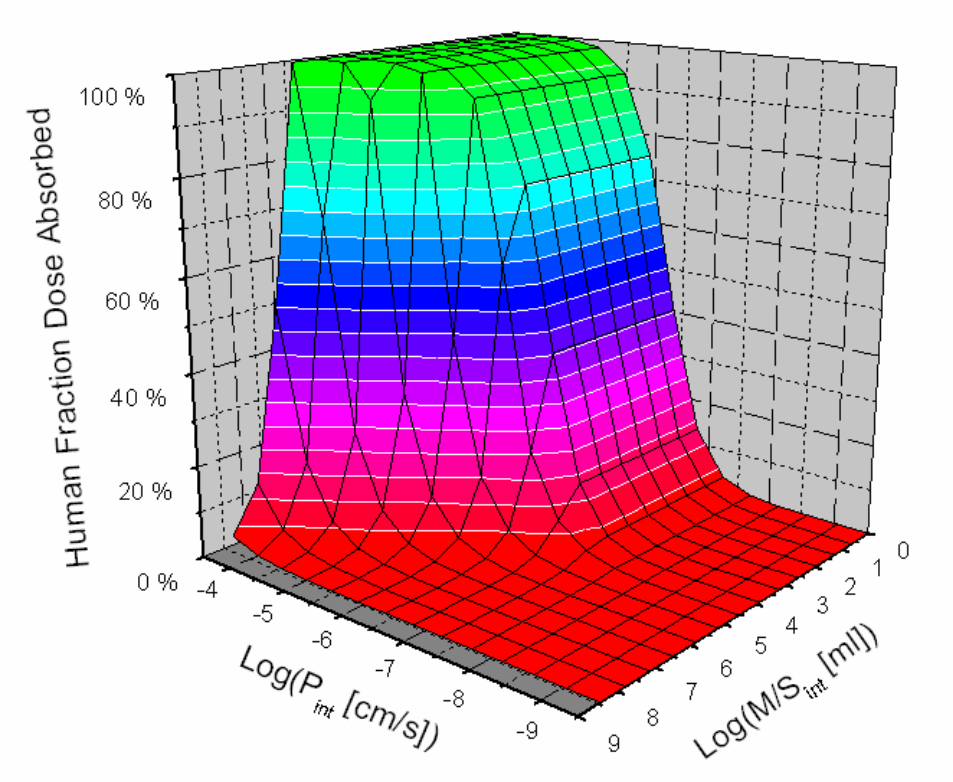
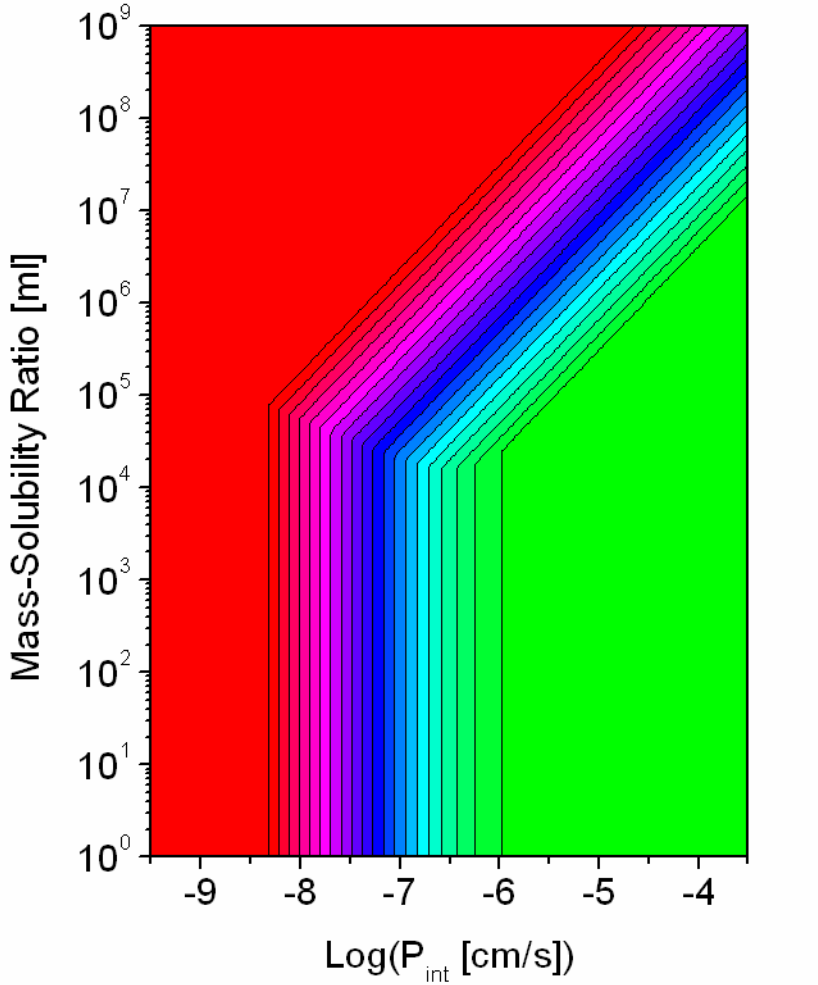
General Model Results

Assumption: Dissolution is not the rate limiting step for absorption





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General Model Results

Region A: no solubility limitation

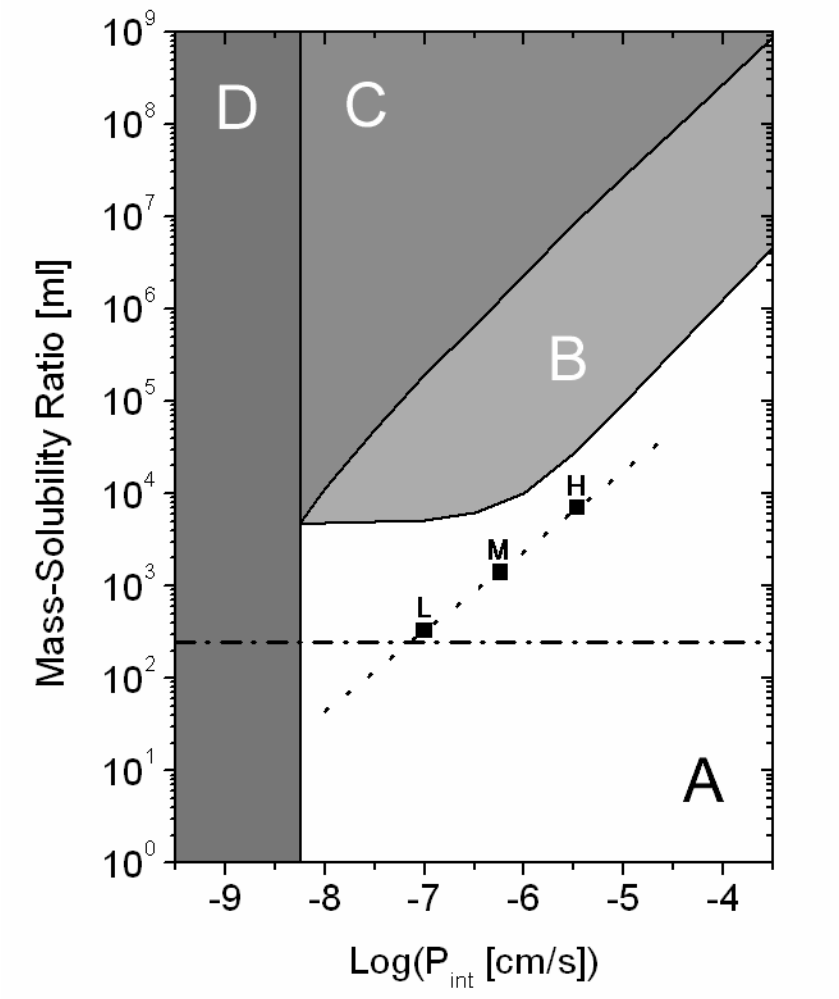
Region B: dose-dependent absorption

Region C: F_{abs} < 1 % (solubility-limited)

Region D: F_{abs} < 1 % (permeability-limited)

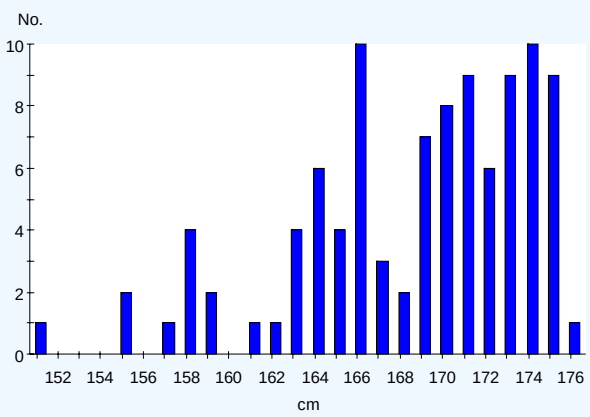
FDA-Suggestion: (M/S) = 250 ml

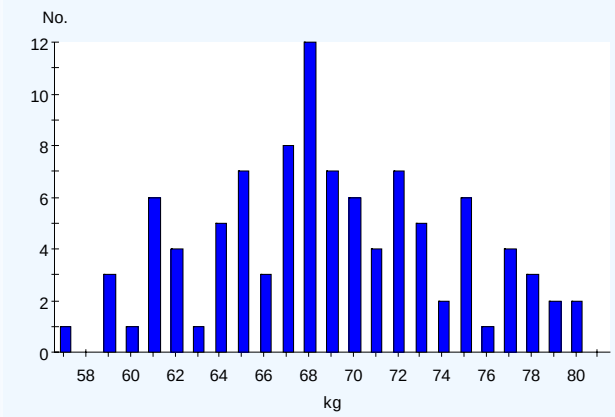
"Minimum Acceptable Solubility" *)

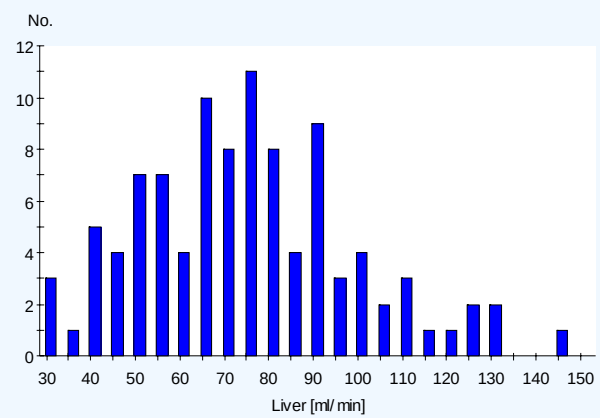


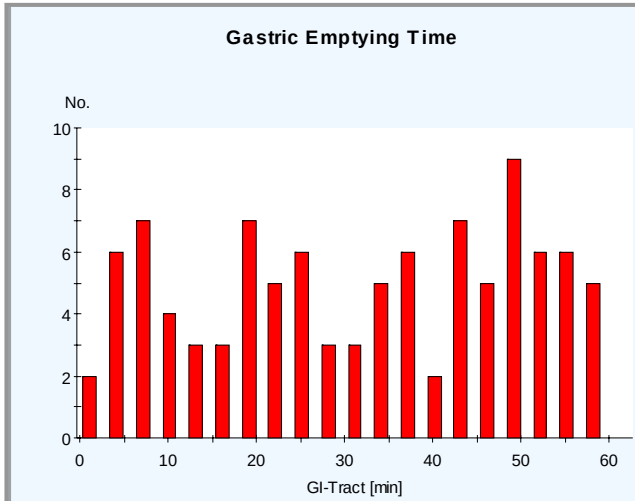
*) W. Curatolo (Pfizer)
Pharm. Sci. Technol. Today **1(9)**, 387-393 (1998)

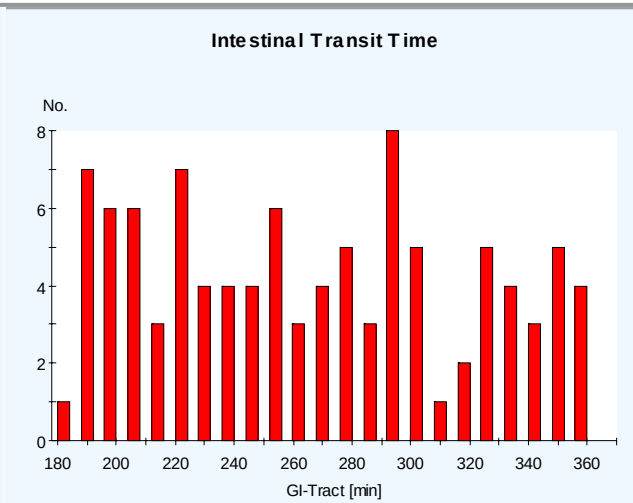
Example: Cimetidine





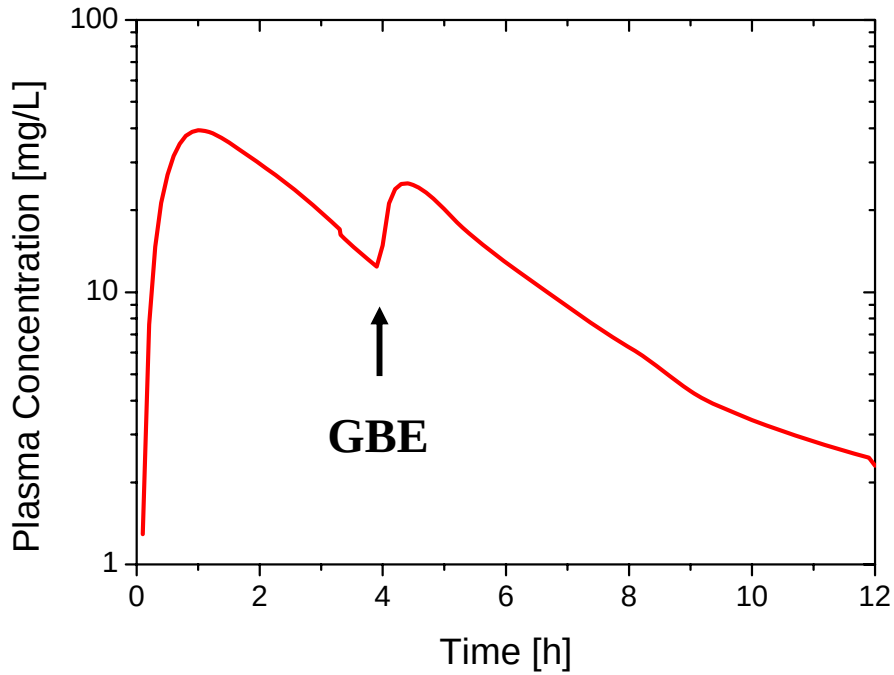






Model Application: Assessment of EHC

- **Example:** Model compound: weak base with pKa = 8.5, LogMA = 4,2, MW = 520, Solubility = 250 mg/L at pH 6.5, dose = 25 mg, subject to EHC



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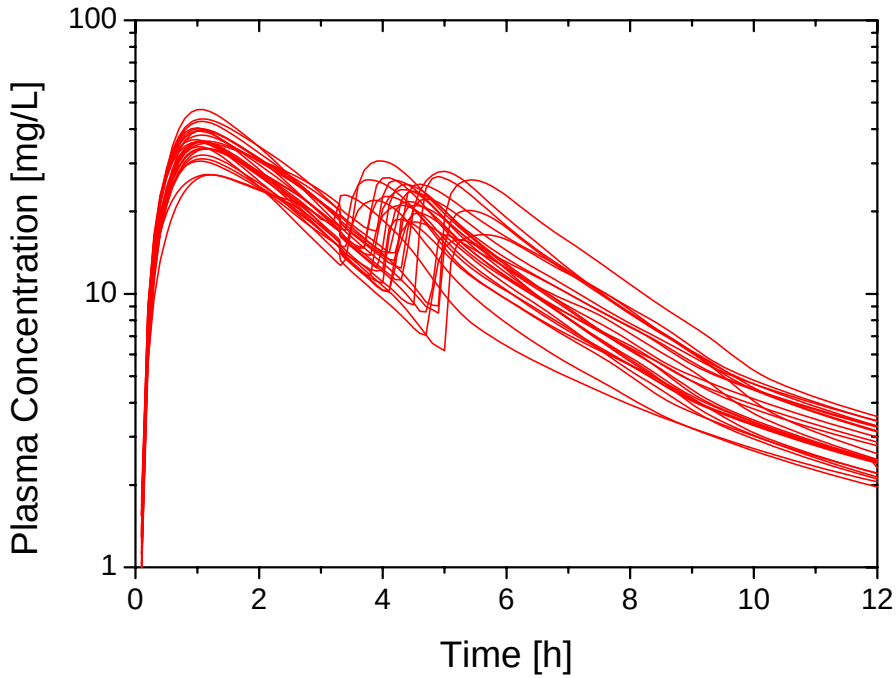
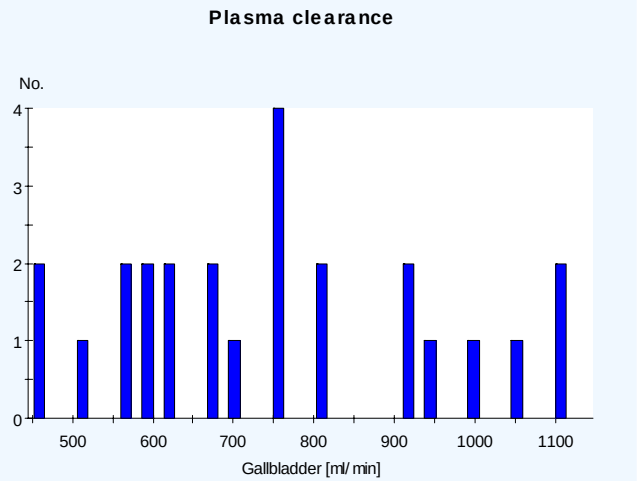
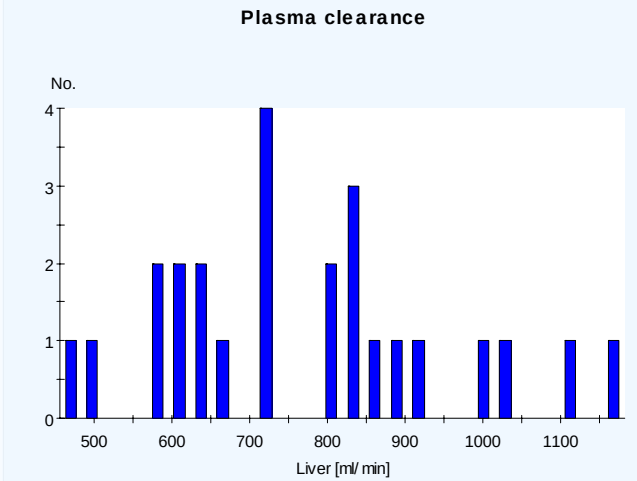
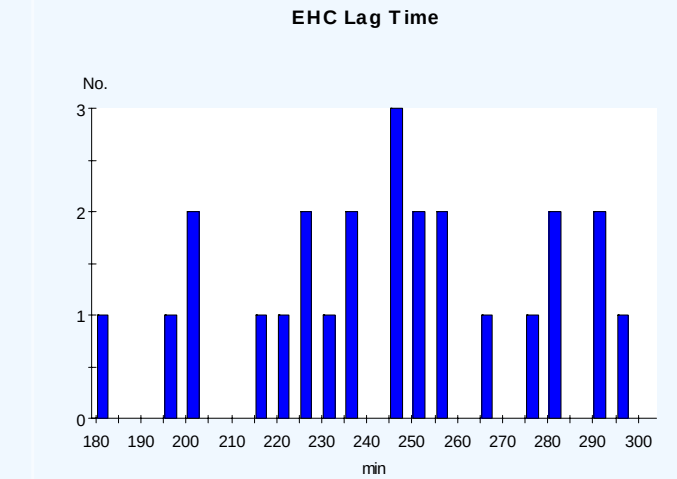


- **Population Simulation (N=25)**







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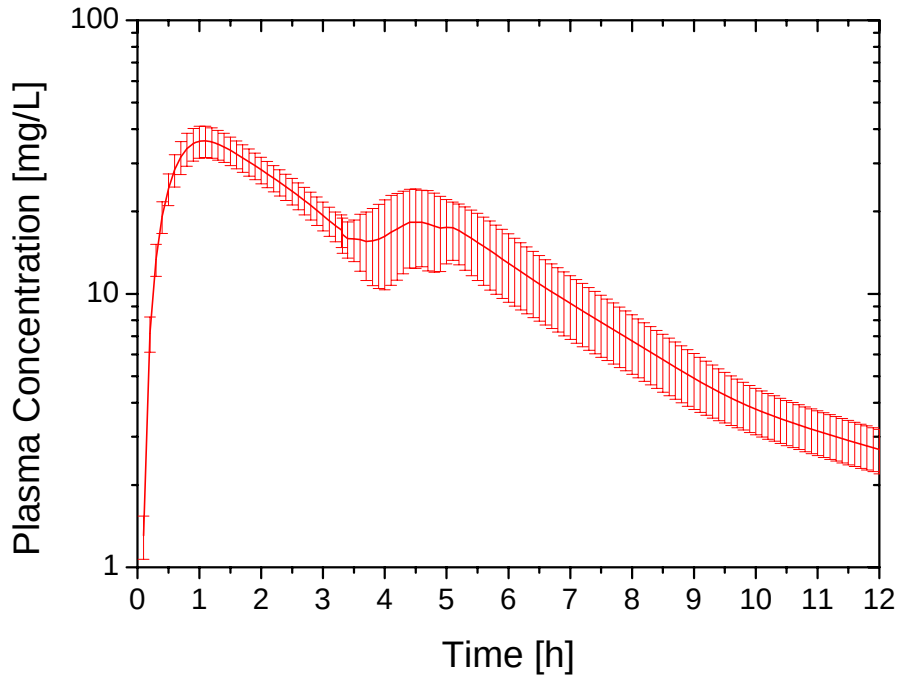

- **Population Simulation (N=25)**