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Pharmacokinetic Modeling & Simulation in Discovery and non-clinical Development

Where do we stand?

P. Theil, Non-clinical Safety, Roche

Disclaimer

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- I am not a bioinformatician, mathematician or biomedical engineer.
- I am a simple minded pharmacist, who enjoys the challenge of pharmacokinetics and pharmacodynamics.

Pharmacokinetic M&S in Discovery and non-clinical Development

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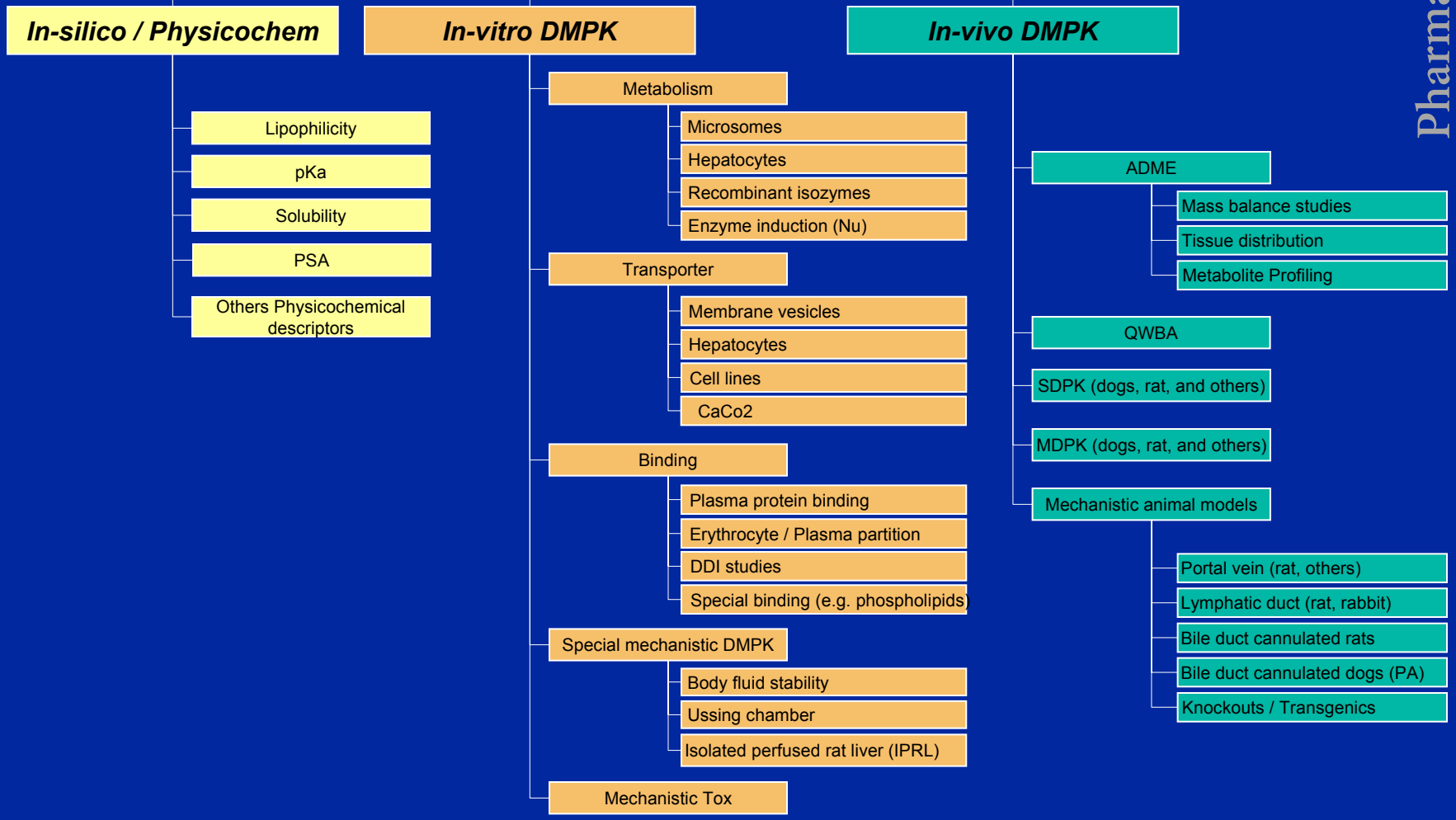
Desktop Drug Discovery – Pharma companies turn to computer simulations to complement experimentation and trial design. A. Constans

in Scientist 18 (2004) 4, 33

"Imagine being able to discover the latest blockbuster drug using nothing but a PC and some highly sophisticated software. It is not as far-fetched as it sounds. ….." ????

Non-clinical DMPK Technologies



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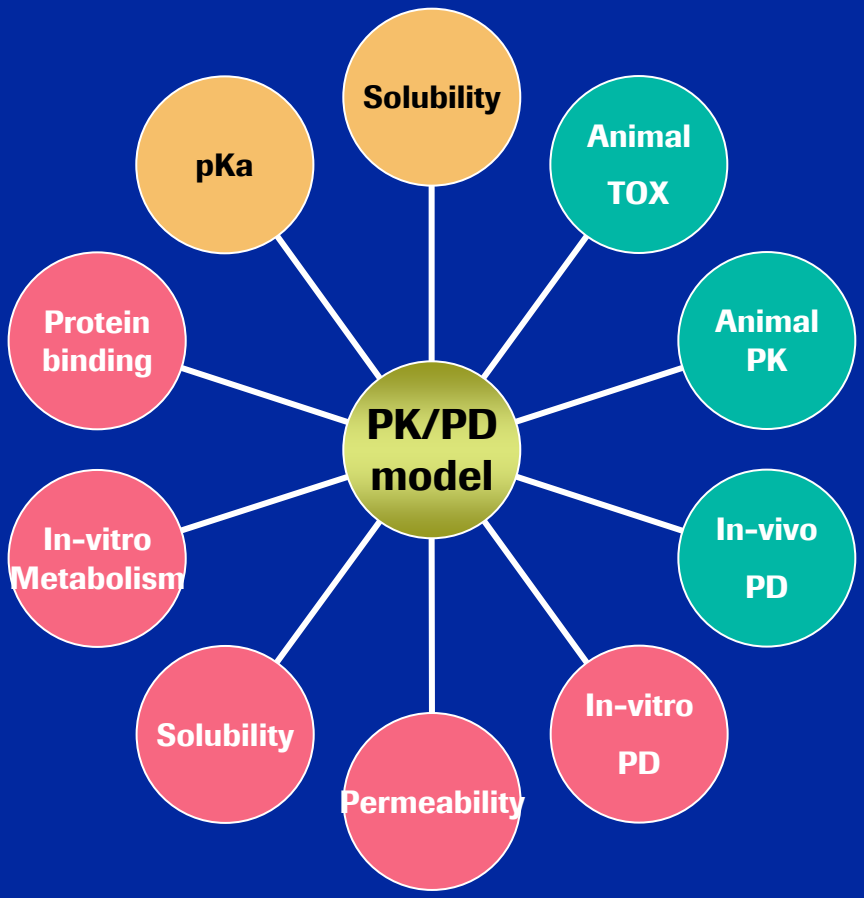
Potential DMPK data – in-silico, in-vitro, in-vivo data



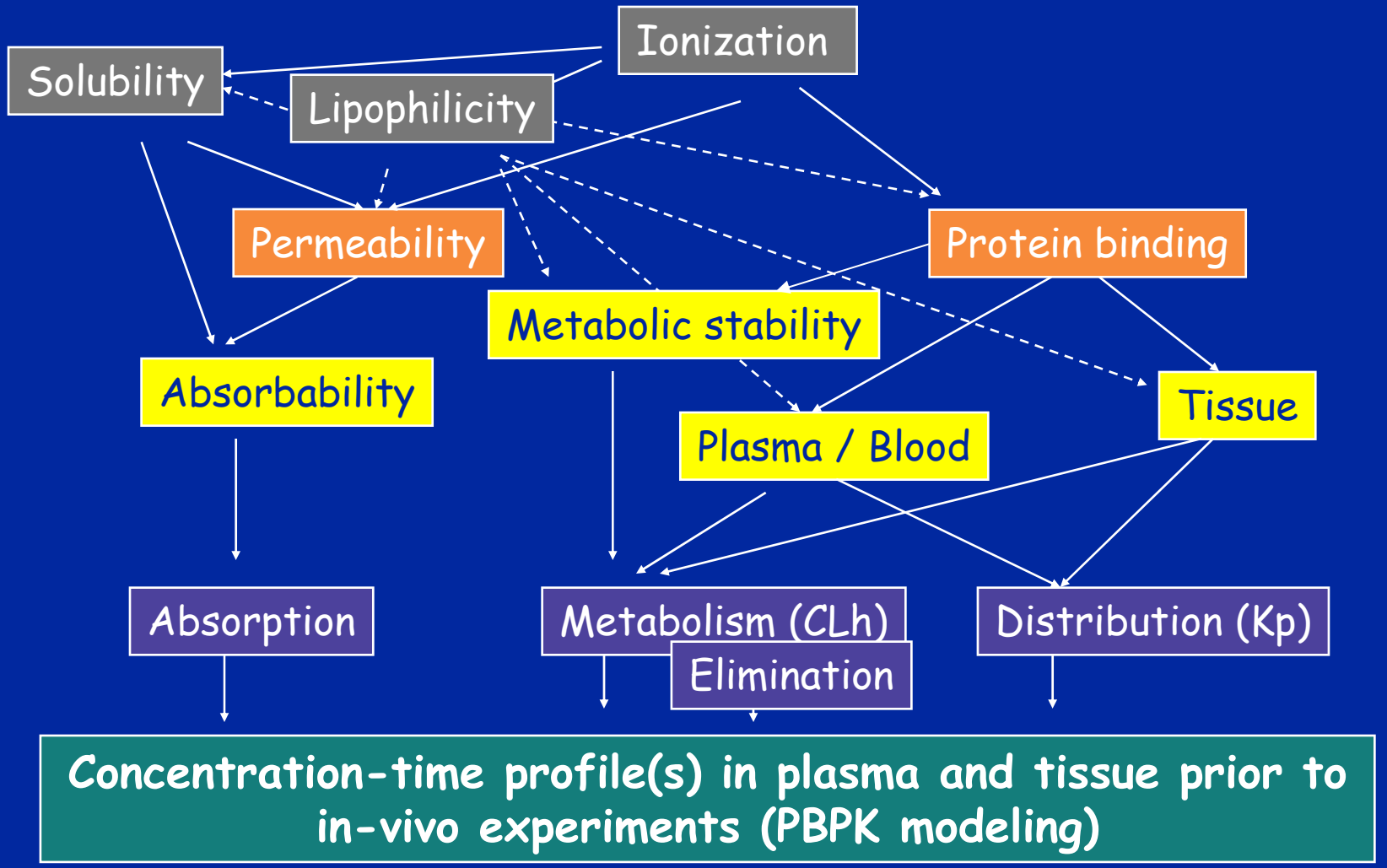
Ultimate Goal:

To predict the concentration-effect-relationship(s) in man,

Ideally in the target population

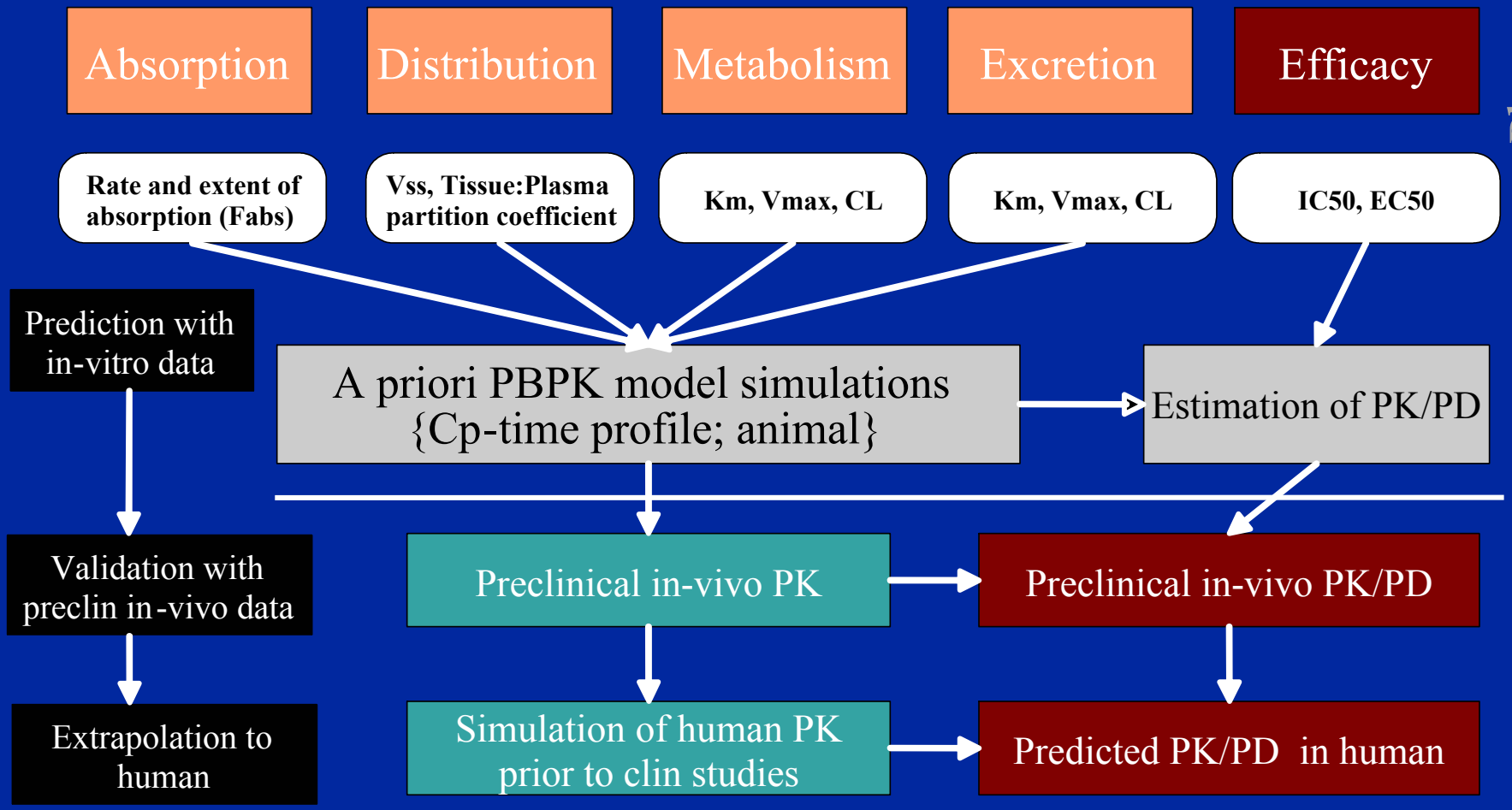
Suggested integrated PBPK modeling

(Theil et. al. Toxicol. Letters 138 (2003) 29-49)



Suggested integrated PBPK modeling

(Theil et. al. Toxicol. Letters 138 (2003) 29-49)



Partition coefficients of volatile organic chemicals

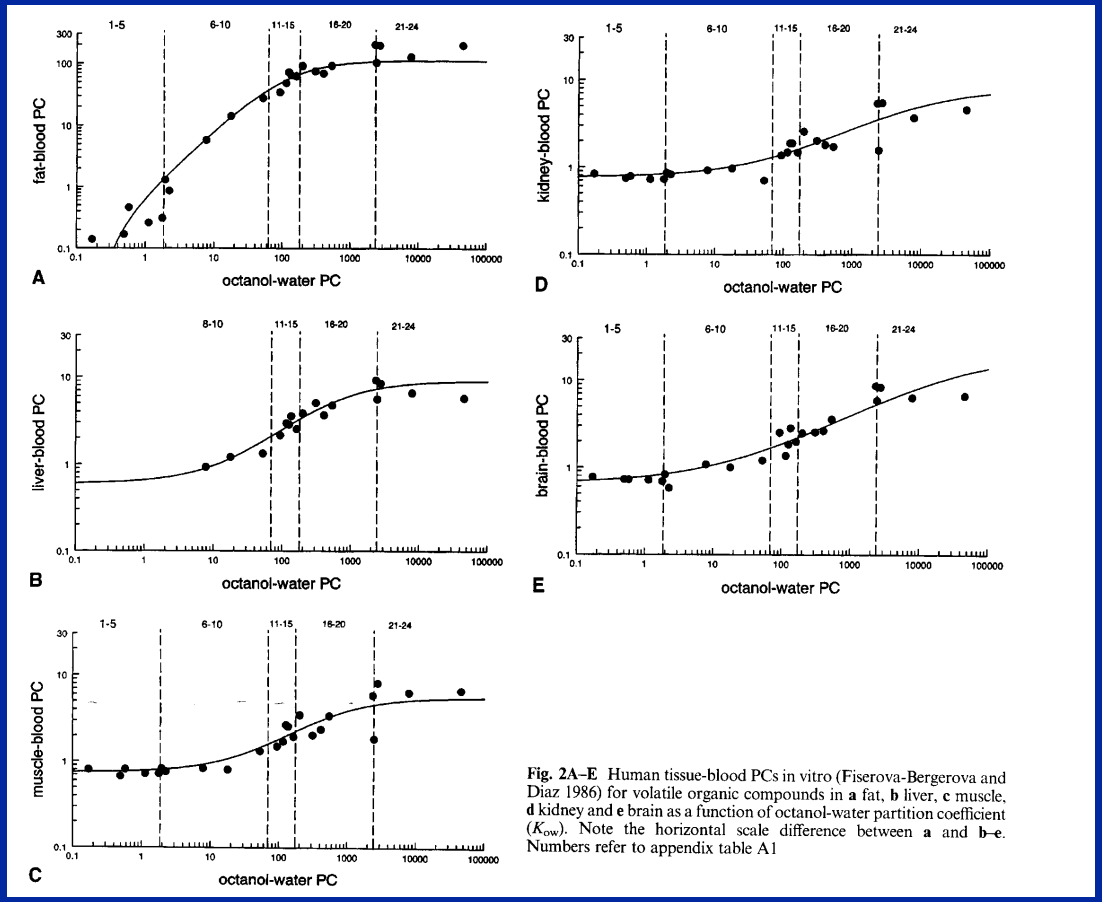


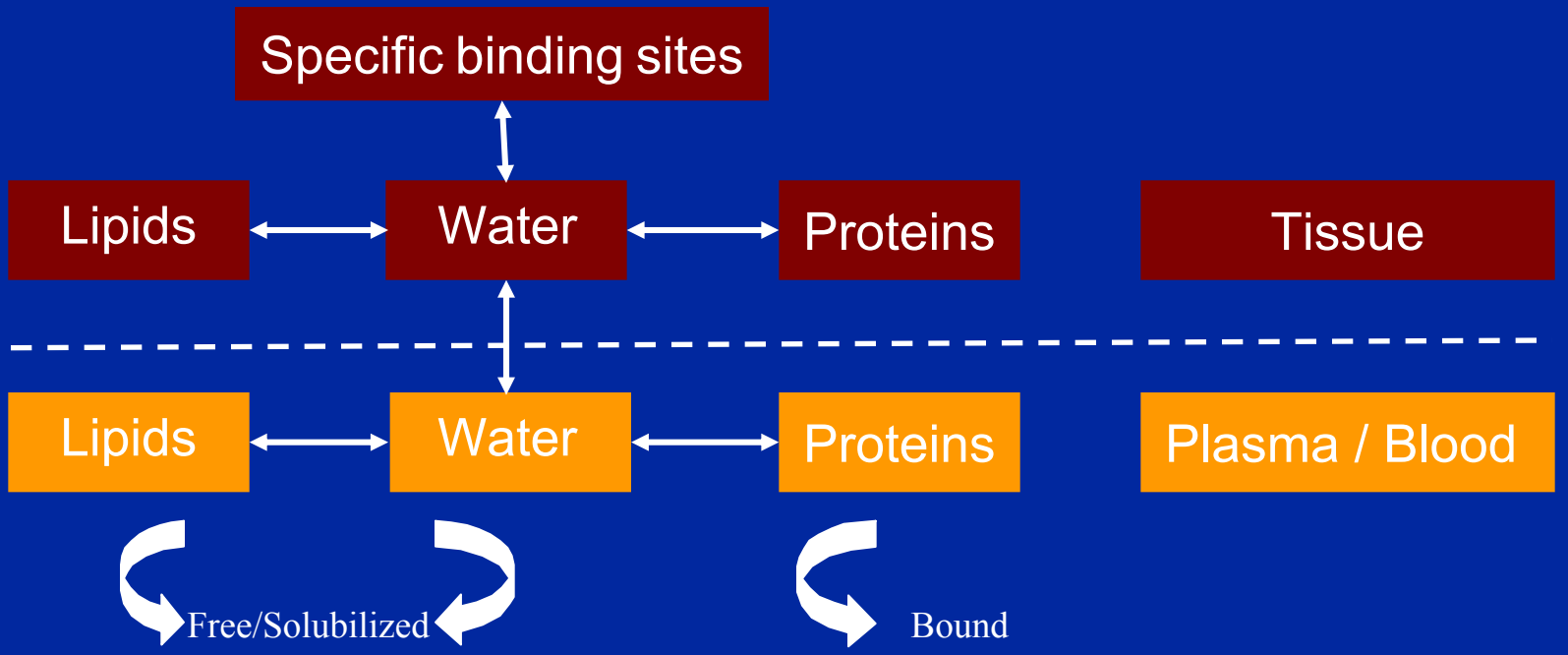
Fig. 2A–E Human tissue-blood PCs in vitro (Fiserova-Bergerova and Diaz 1986) for volatile organic compounds in **a** fat, **b** liver, **c** muscle, **d** kidney and **e** brain as a function of octanol-water partition coefficient (K_{ow}). Note the horizontal scale difference between **a** and **b–e**. Numbers refer to appendix table A1

J. deJongh et al. Arch. Toxicol. 72 (1997) 17

The left Plateau:
Water_fraction in tissue / Water_fraction in plasma

The right Plateau:
Lipid_fraction in tissue / Lipid_fraction in plasma

Distribution – Tissue composition models

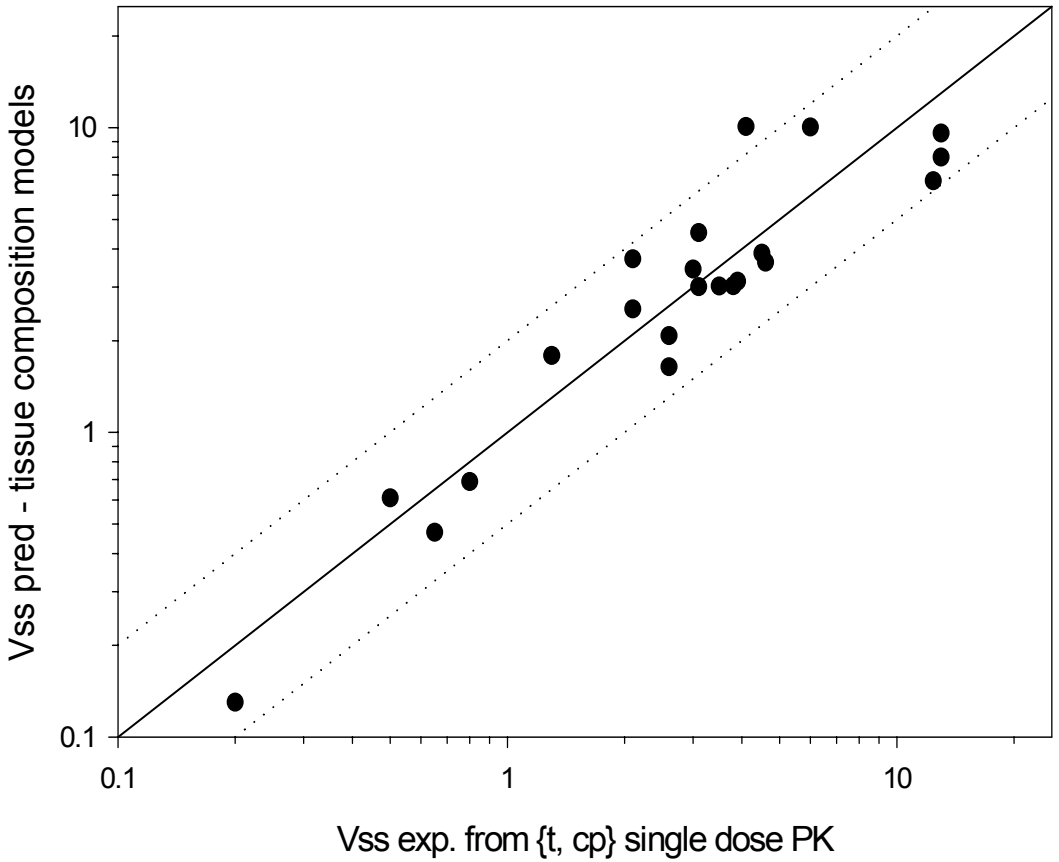


$$P_{T:P} = \frac{K_{vo:w} \bullet (V_{nt} + 0.3V_{pht}) + 1 \bullet (V_{wt} + 0.7V_{pht})}{K_{vo:w} \bullet (V_{np} + 0.3V_{php}) + 1 \bullet (V_{wp} + 0.7V_{php})} \bullet \frac{fu_p}{fu_t}$$

$$Vss = V_p + \sum P_{T_i:P} \bullet V_{T_i}$$

Poulin and Theil. J. Pharm. Sci. 89 (2000) 16

Vss Modeling and Validation with an internal data set (n=21)



Input:

Physiology: Tissue composition data

Compound information: Lipophilicity, protein binding, pKa

Output:

$P_{T:P}$, Volume of distribution (Vss)

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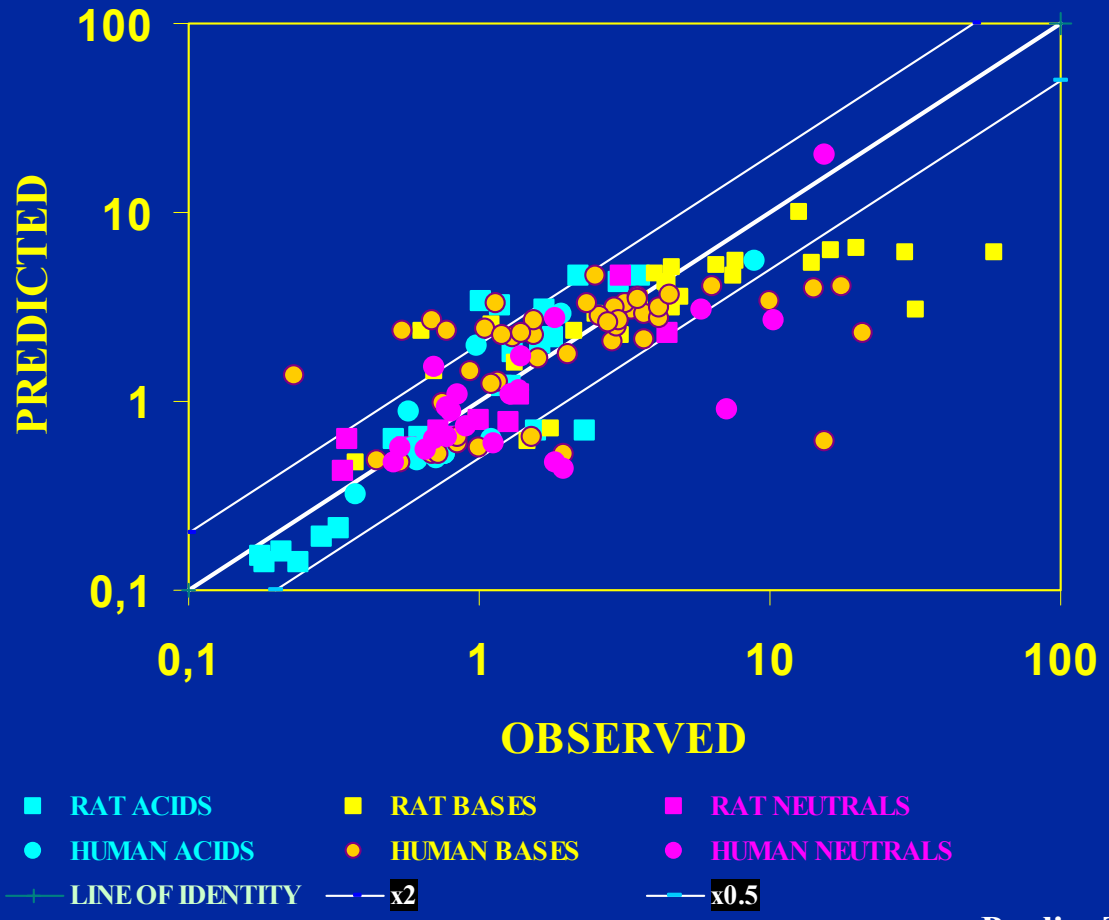
Vss Modeling and Validation with an external data set (n=123)



Input:

Physiology: Tissue composition data

Compound information: Lipophilicity, protein binding, pKa

Output:

$P_{T:P}$, Volume of distribution (Vss)

Poulin, Theil J. Pharm. Sci. 2002

Distribution – Mechanism based modeling

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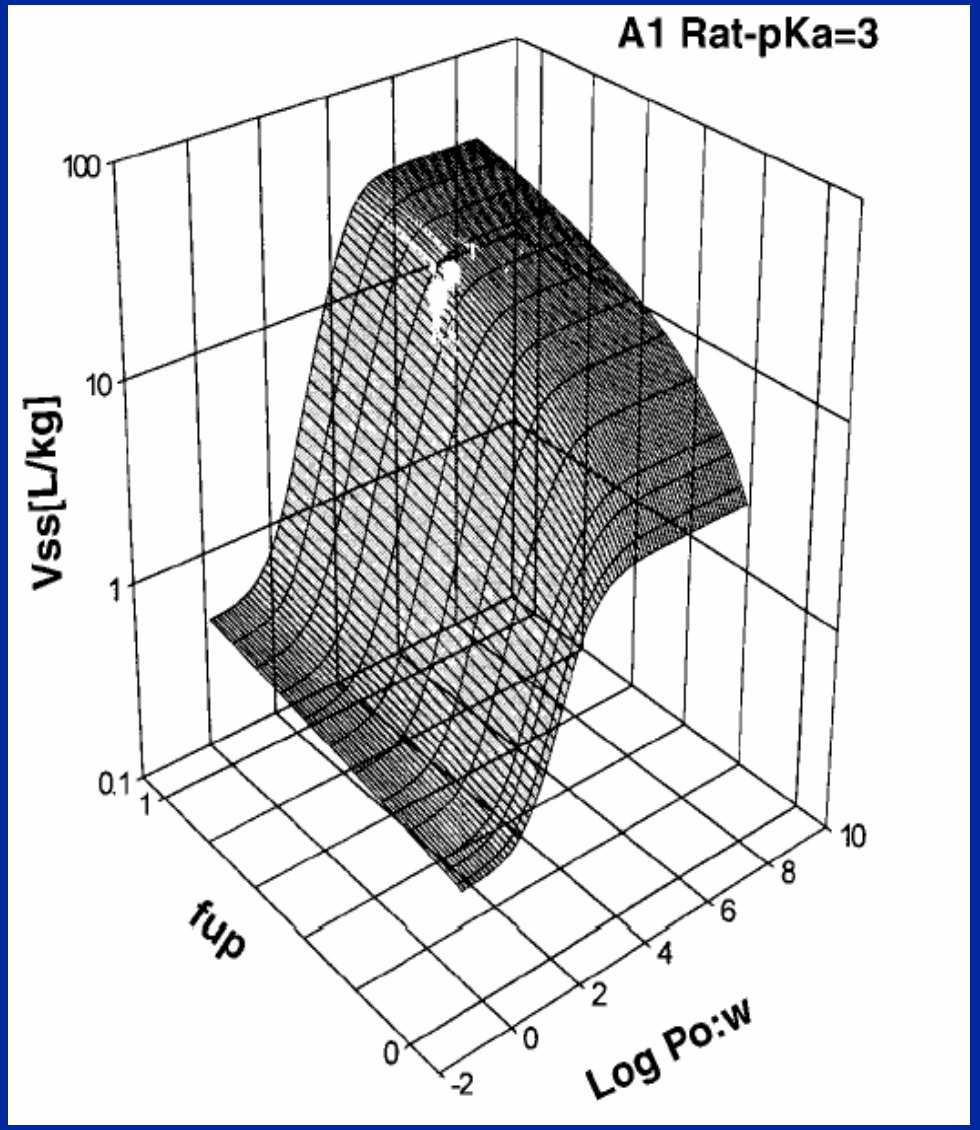
Vp - Plasma volume
Vt - Tissue volume

Kp - Tissue:Plasma partition coeff

fup - unbound fraction in plasma
LogP - Octanol:buffer partition coefficient

Poulin, Theil, J Pharm Sci Feb 2002



Available physiologically based ADME Modules

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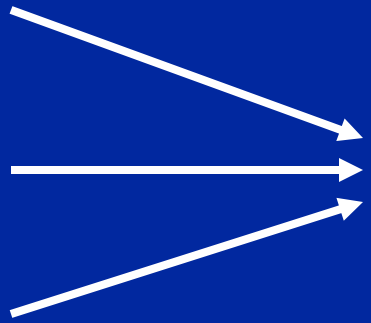
- Absorption
- Distribution
- Metabolism



PBPK Model to predict
Concentration-time profiles
prior to in-vivo experiments

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Generic PBPK modeling

To describe ADME (Pharmacokinetics)
in animals (validation) and
in humans (prediction)

Modeling – Input information (data)

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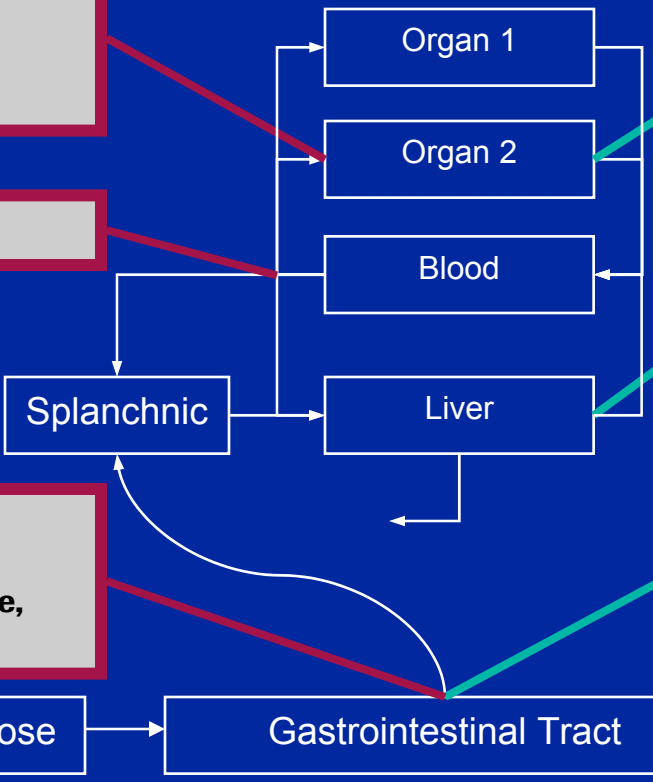
Physiology

Tissue composition (water, proteins, lipids, neutral lipids, phospholipids), Tissue volumes,

Organ Blood Flows

GIT compartmental volumes; Surface, pH, motility, transit time, Transporter activity



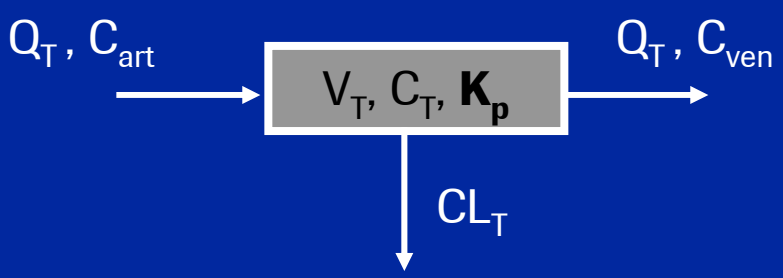
Drug-specific input

Distribution
Organ distribution governed by e.g.:Hydrophobicity, LogD
Phospholipid binding
Protein binding
Blood cell distribution

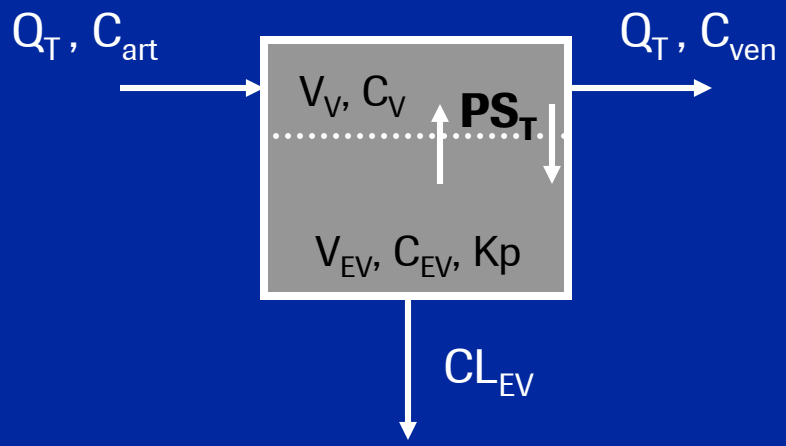
Hepatic clearance
Intrinsic clearance: km and Vmax,
Protein binding

Absorption
LogD, Permeability,
Transporter affinity
Solubility, pKa, particle size, dissolution rates, excipients

PBPK Modeling – Conventional mass balance ODEs



$$\frac{dC_T(t)}{dt} = -\frac{Q_T}{V_T \bullet K_p} \bullet C_T(t) + \frac{Q_T}{V_T} \bullet C_{art}(t)$$



$$\frac{dC_V(t)}{dt} = -\frac{Q_T + CL_V + PS_T}{V_V} \bullet C_V(t) + \frac{PS_T}{V_V \bullet K_p} \bullet C_{EV}(t) + \frac{Q_T}{V_T} \bullet C_{Art}(t)$$

Absorption – physiological advanced

PBPK model with ACAT model (GastroPlus®) as input

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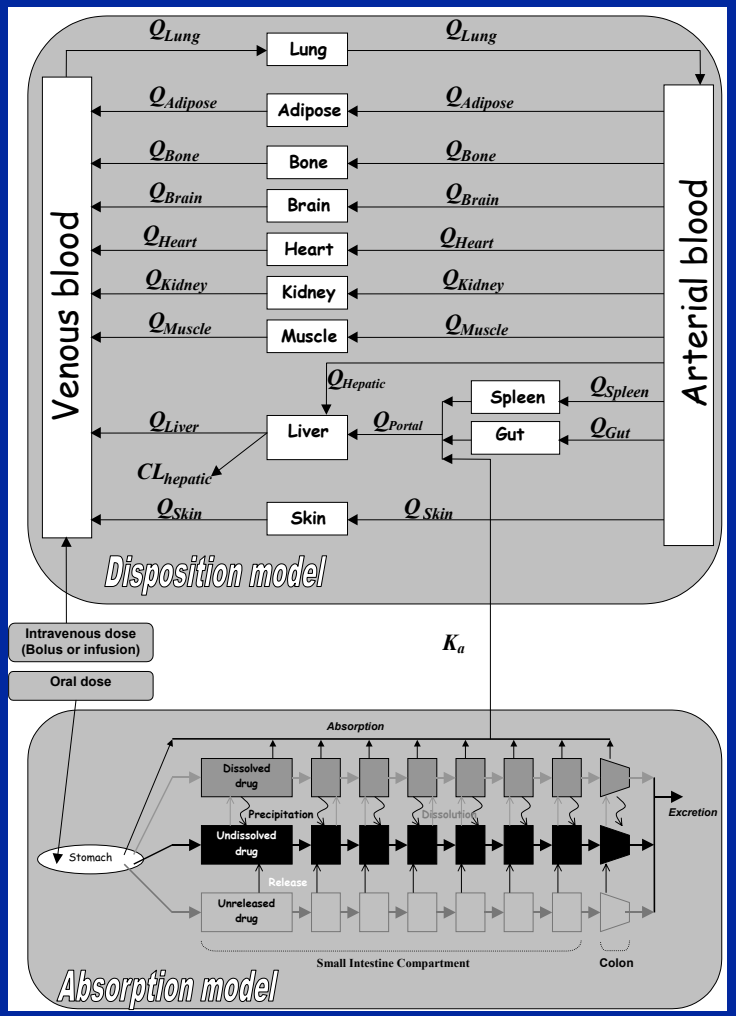
Physiological Disposition Model

Physiological Absorption Model

GastroPlus®



Input:

Physiology (tissue flows, tissue volumes)

Compound information: Lipophilicity, pKa, molecular weight, protein binding, in-vitro clearance

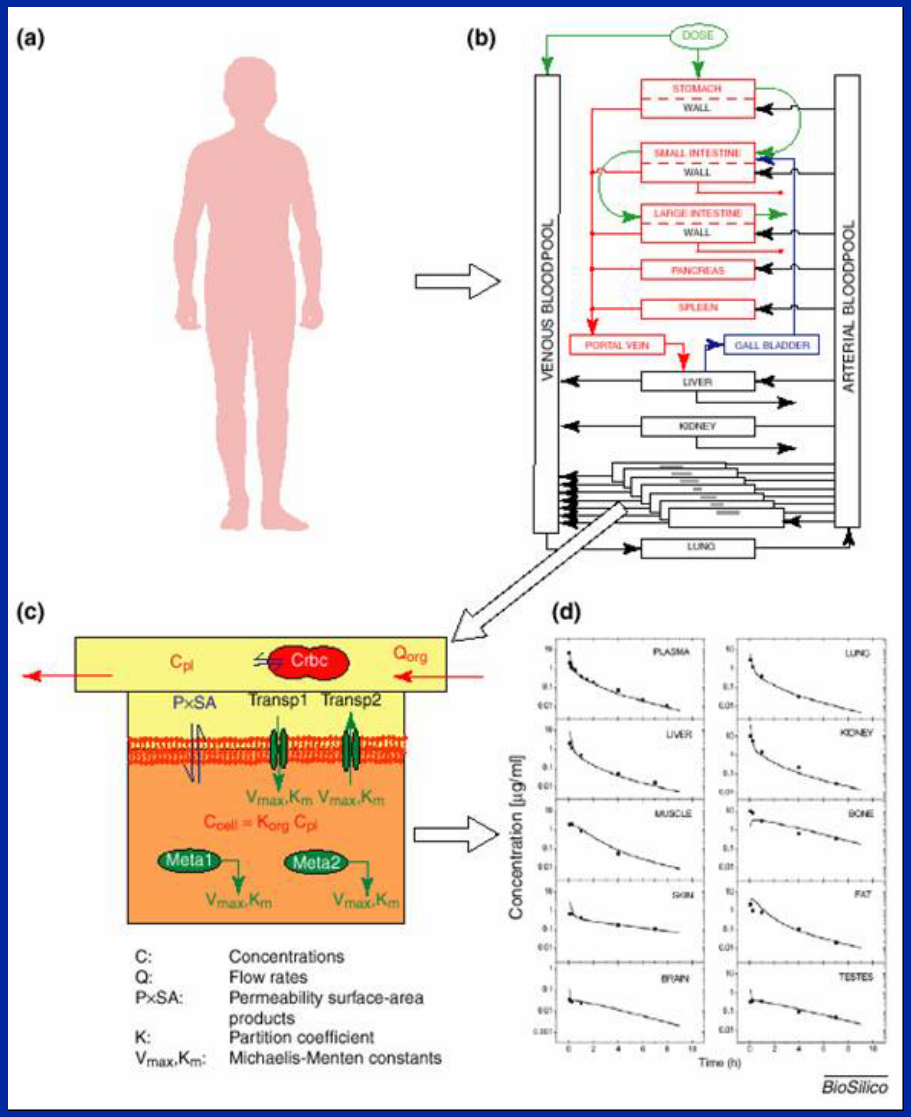
Output:

Blood, Plasma and Tissue concentrations

Disadvantages:

no enterohepatic circulation
only perfusion limited PK
no permeability limited PK
no transporter functionality

PK-Sim® – whole body PBPK simulation tool



Input:

Physiology (tissue flows, tissue volumes)

Compound information: Lipophilicity, molecular weight, protein binding, in-vitro clearance

Output:
Blood, Plasma and Tissue concentrations

Merits:
Distinguishes between permeability and perfusion-limited PK based upon

Current status of PK M&S in discovery and non-clinical development

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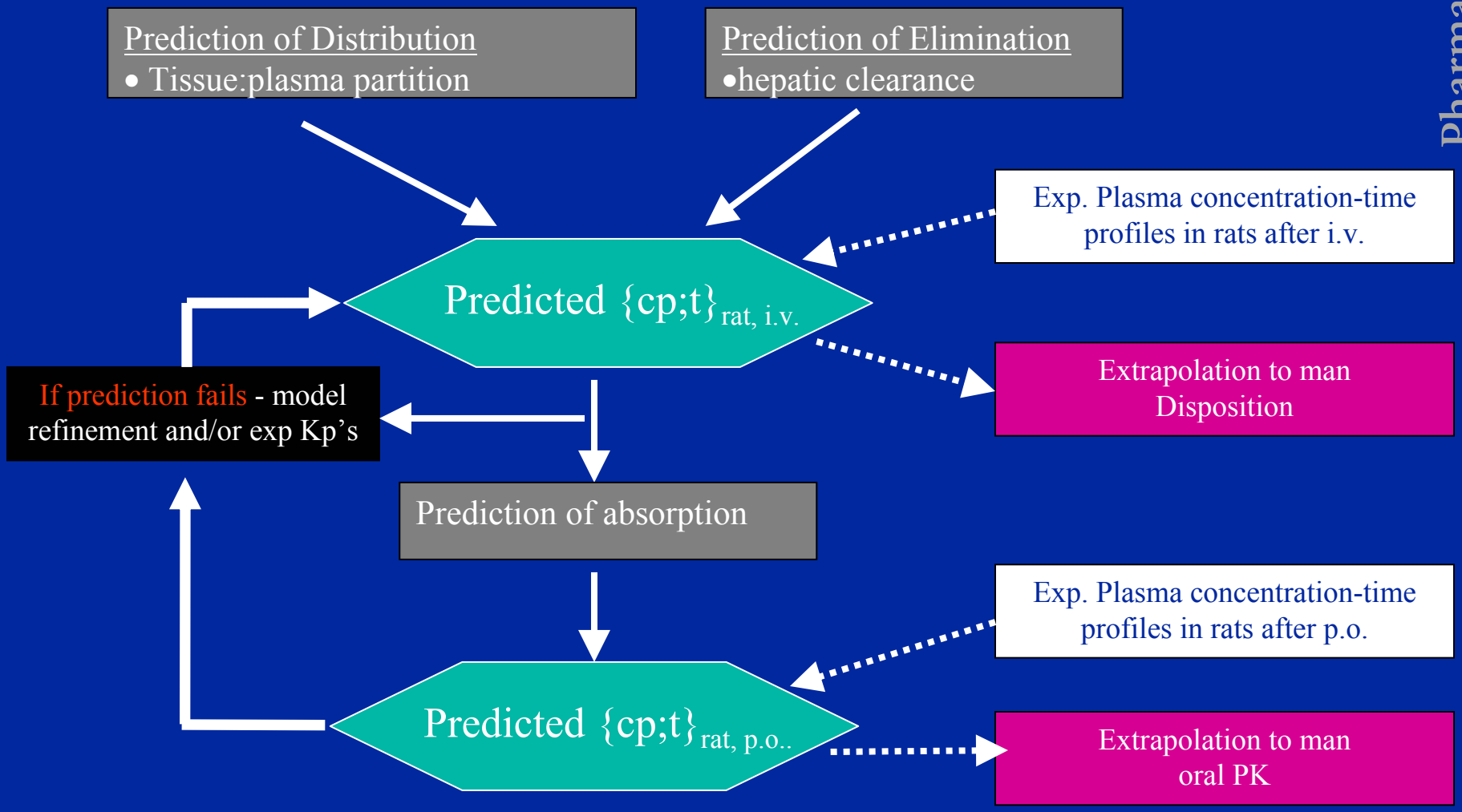
- In silico tools developed, validated and implemented to predict passive absorption and distribution processes
- Prediction of hepatic clearance requires in-vitro data
- Generic PBPK tools are available to predict primarily based on in-silico and some in-vitro data plasma and tissue kinetics
- Quantitative prediction of contributions of active transport for the disposition remains still a challenge
- First attempts attempt are made to incorporate variability and uncertainty information into the predictions

Modeling Strategy

(Theil et. al. Toxicol. Letters 138 (2003) 29-49)



Iteration – Modeling & Experimentation

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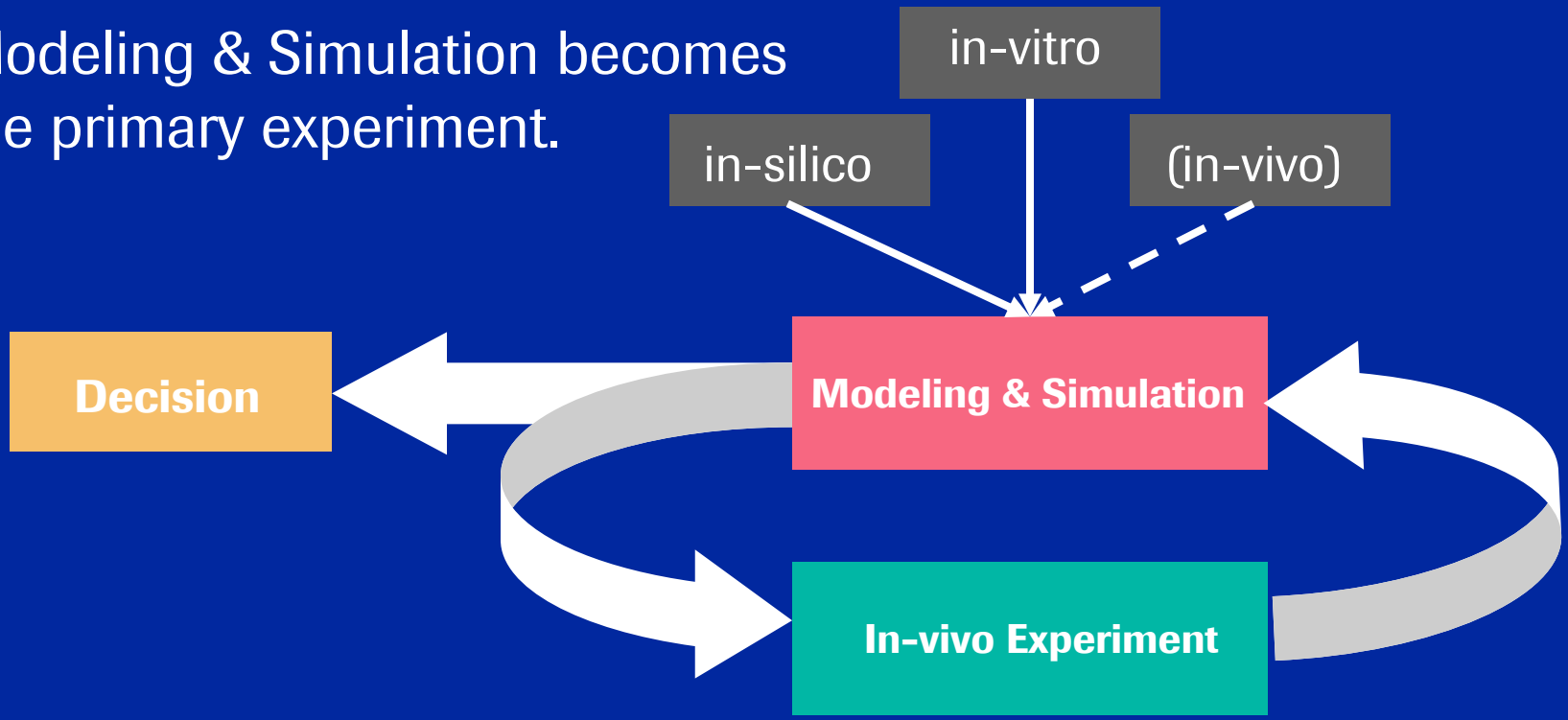
Modeling & Simulation becomes the primary experiment.



The in-vivo experiment can be considered as confirmatory trial

Challenges in the field of PK M&S

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- Prediction of sub-populations e.g. children, elderly, obese patients
- Prediction of regional distribution
- Incorporation of variability and uncertainty
- More relevant contribution with regards to modeling of dynamics (safety and efficacy information)

Acknowledgement

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