

State-of-the-art on tissue partitioning and volume of distribution predictions

Viera Lukacova, PhD, FAAPS

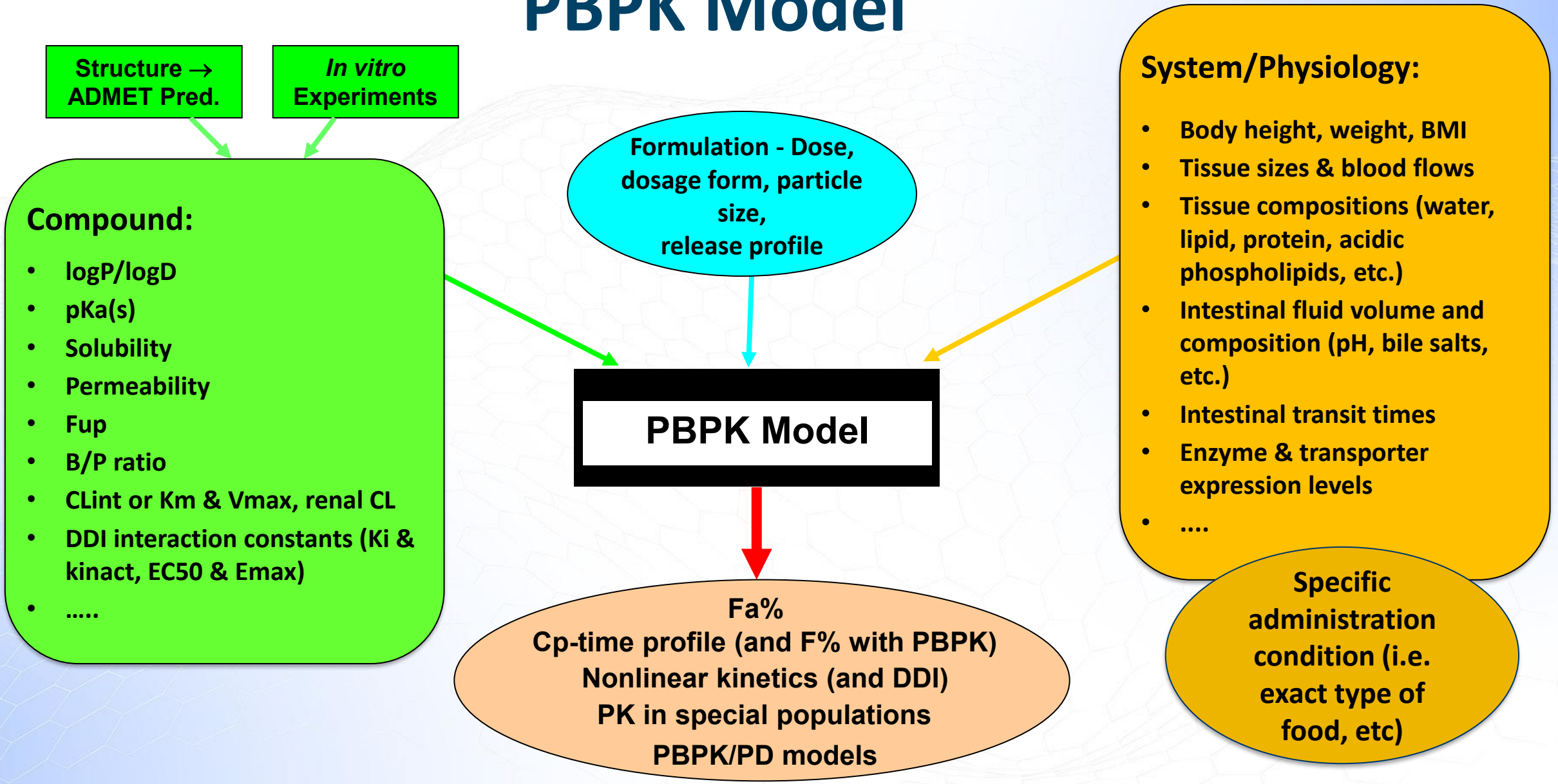
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October 11, 2026

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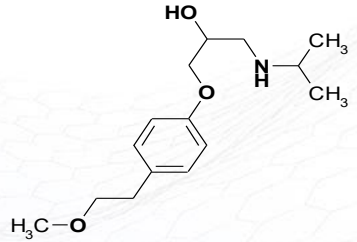
PBPK Model



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PBPK model applications in MIDD

Discovery



Preclinical



Clinical





Discovery PK

- Combine *in silico* technologies to screen compound libraries in animals or humans
- Incorporate preclinical/*in vitro* data for First In Human (FIH) predictions/IVIVE
- Identify toxic dose levels in preclinical species

Clinical PK/Pharmacology

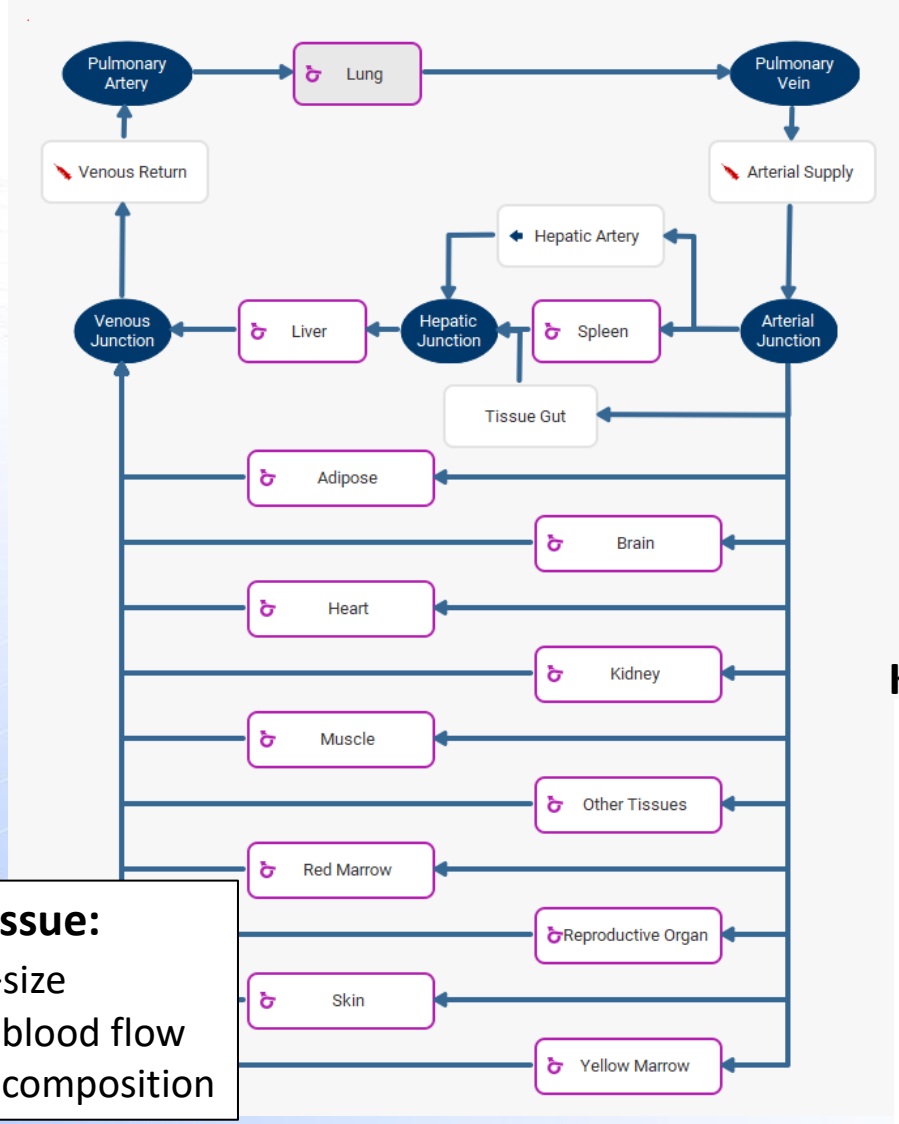
- Simulate population behaviors (e.g., pediatrics, disease)
- Build PBPK-PD models
- Predict Drug Drug Interactions (DDIs)

Pharmaceutical Development

- Assess various strategies during formulation development
- Assist with Quality by Design (QbD) implementation
- Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)
- Understand food effects
- Establish drug product specifications and safe spaces

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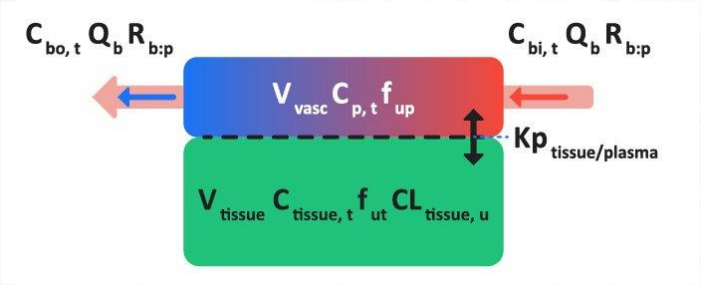
PBPK Model



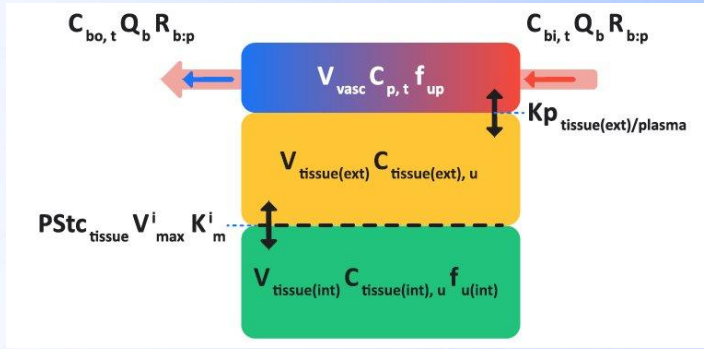
Tissue:
- -size
- -blood flow
- -composition

General Tissue Models

Perfusion-Limited Tissues

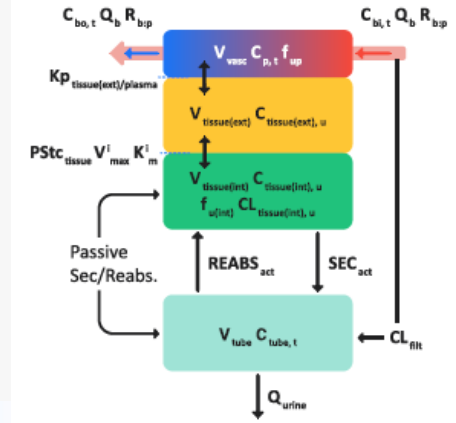


Permeability-Limited Tissues

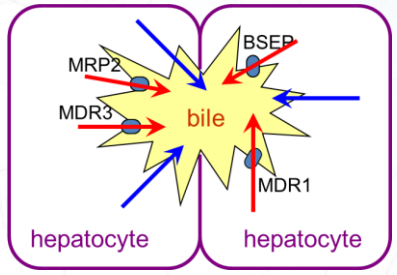


Additional Tissue-Specific Mechanisms

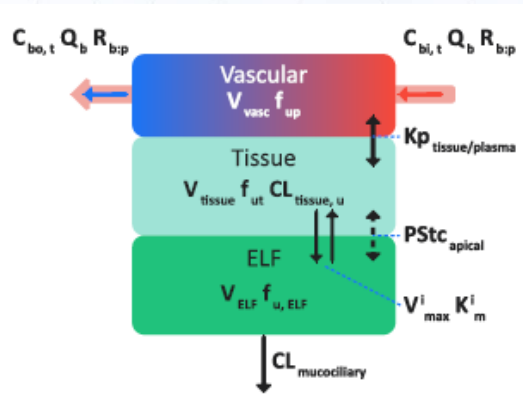
Kidney – Renal Secretion



Liver – Biliary Secretion



Lung – Mucociliary CL



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Mechanisms: Distribution

- Partitioning into tissues
  - binding
  - lipid partitioning
  - transport
  - other??
- Measurable quantity
  - $Kp_{app} = Ct_{tot} / Cp_{tot}$ at steady state
    - non-eliminating tissue

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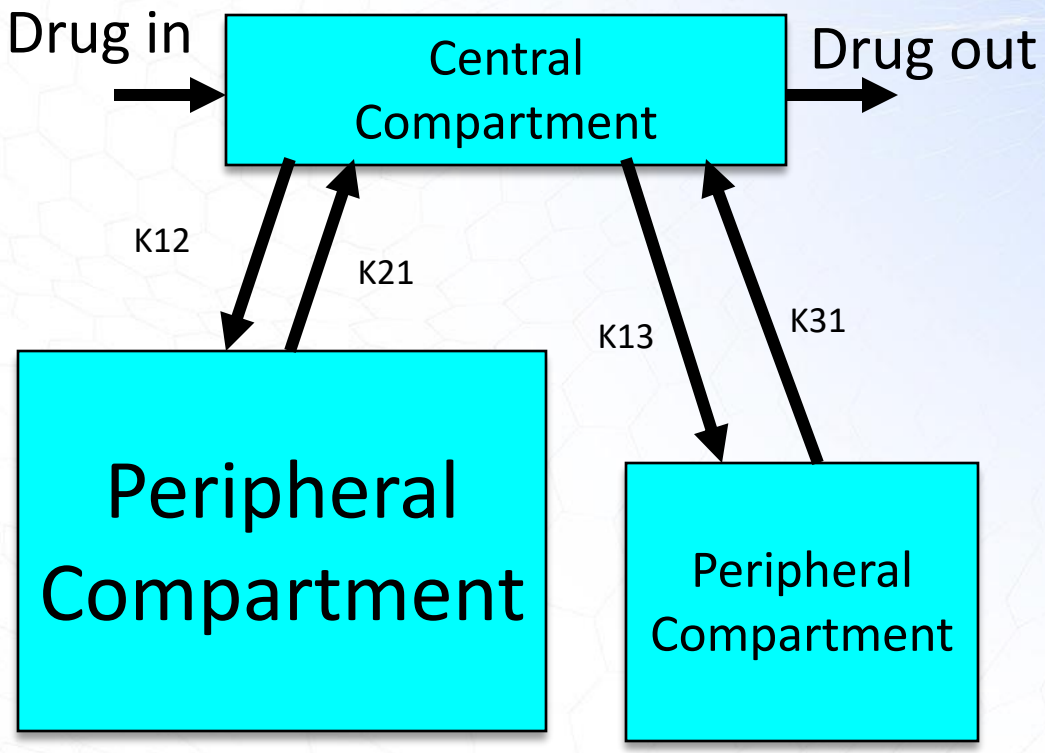
Traditional (Top-down) Compartmental PK

Traditional compartmental PK employs empirical models for one or more mathematical compartments.

Peripheral compartments serve as reservoirs with different volumes and different rates of exchange of drug with the central compartment.

The data defines the model – the model is not defined from physiology.

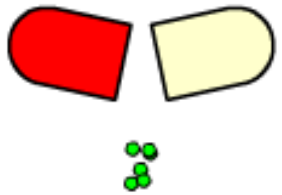
The model is used to describe and interpolate the data rather than to predict or conduct what-if simulations.

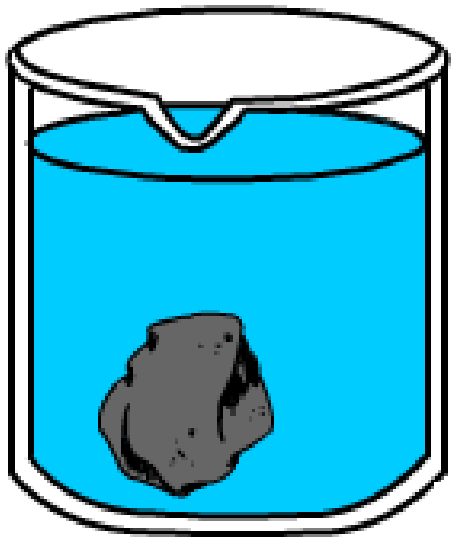


Rowland, Balant, & Peck, AAPS Pharm Sci 2004 6 (1)

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“Top Down” Volume of Distribution



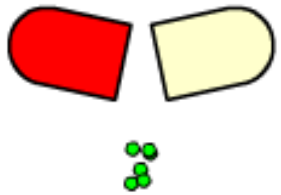


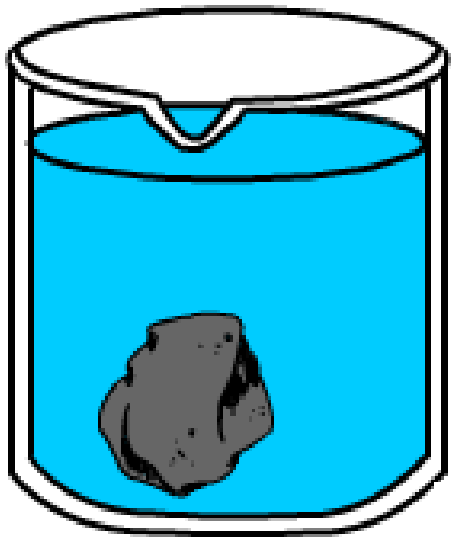
1 L Beaker

- What is the volume of fluid and rock in the beaker?
- Add 10 mg of Drug
- Measure Conc. = 12 mg/L
- V_d = Dose / C_0
- V_d = 10 mg/ 12 mg/L = 0.83 L
- V_{rock} = 1 - 0.83 = 170 mL

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“Top Down” Volume of Distribution





1 L Beaker

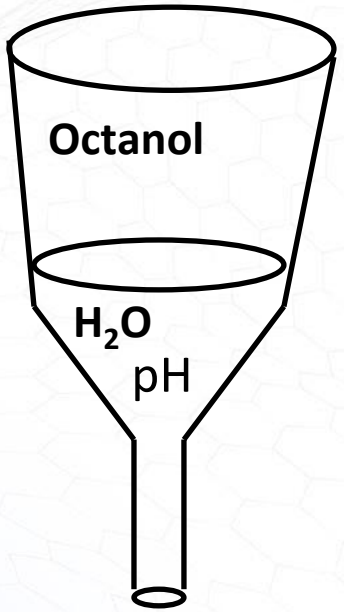
- What is the volume of fluid and **lump of charcoal** in the beaker?
- Add 10 mg of Drug
- Measure Concn. = 0.12 mg/L
- V_d = Dose / C_0
- V_d = 10 mg/ 0.12 mg/L = 83 L
- V_{rock} = 1 - 83 = -82 L
- Thus, the calculated V_d is not a real volume but rather an apparent Vol.

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Distribution vs. Partition Coefficient

Hydrophobic phase

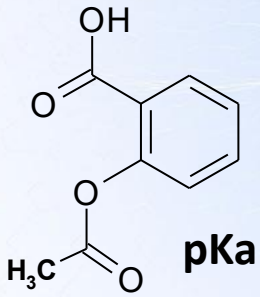
Hydrophilic phase





pH = 2

log D ~ log P = 2

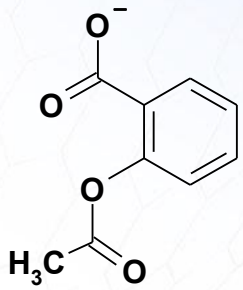


pKa = 3.5



pH = 8

Log D = -1.5



$$LogD_{oct/water} = \log \frac{C_{oct}^{aspirin}}{C_{water}^{aspirin}} = \log \frac{[HA]_{oct} + [A^-]_{oct}}{[HA]_{water} + [A^-]_{water}}$$

$$LogP_{oct/water} = \log \frac{[HA]_{oct}}{[HA]_{water}}$$

Log P is defined for the unionized species **only**

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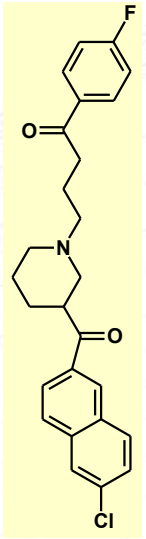
“Bottom-up” Volume of Distribution

$$Vd_{ss} = \sum V_t K_p * (1 - ER) + V_e(E:P) + V_P$$

$$E:P = (R_B - (1 - H_t)) / H_t$$

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Combining *In Silico* Technologies



QSPR

log P/logD(7.4)
pKa(s)
Aqueous and biorelevant solubility
Human permeability
Volume of distribution
Plasma protein binding
Blood:plasma concentration ratio
. . . etc.

Structure-property predictions provide estimates for:
pKa(s), logP, solubility, permeability, plasma protein binding, etc…

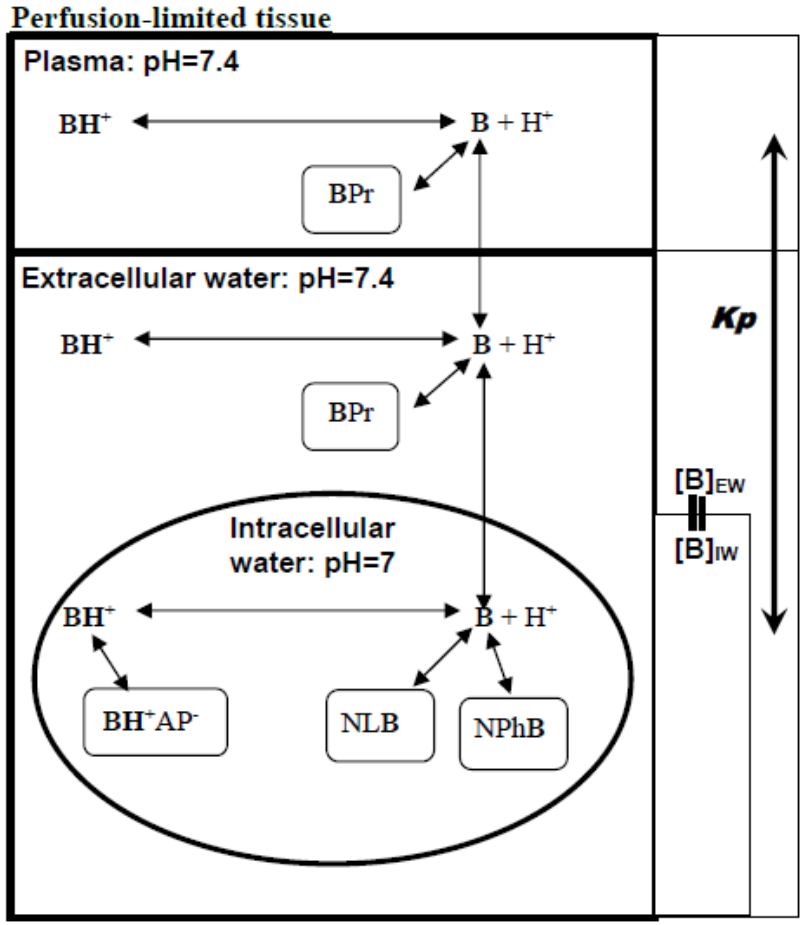
K_p's estimated from:

1. logP/logD(7.4)
2. pKa(s)
3. Plasma protein binding (fup)
4. Blood:plasma concentration ratio (Rbp)
5. and tissue properties

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“Bottom-up” Volume of Distribution

Tissue/Plasma partition coefficient (K_p) depends on drug interaction with tissue components



B – neutral unbound form of drug

BH^+ - ionized unbound form of drug

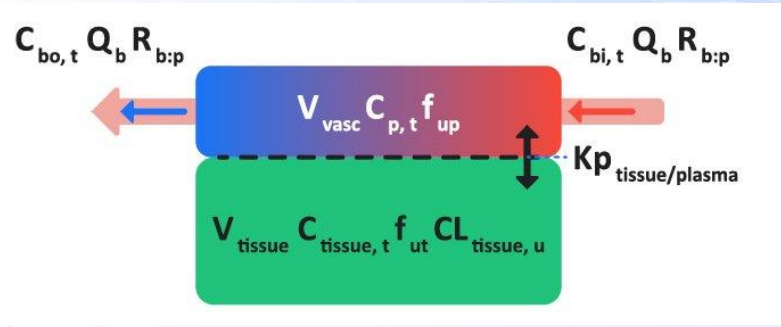
BPr – neutral (or anionic) drug bound to plasma or tissue protein (albumin)

BH^+AP^- - cationic form of drug bound to acidic phospholipids

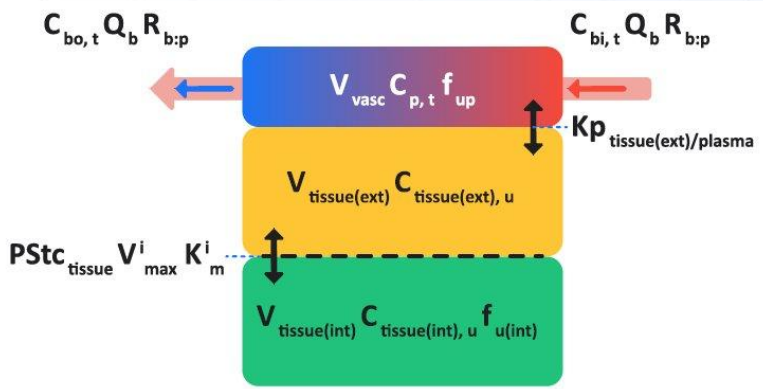
NLB – neutral (or anionic) form of drug bound to neutral lipids

NPhB – neutral (or anionic) form of drug bound to neutral phospholipids

Perfusion-Limited Tissues



Permeability-Limited Tissues



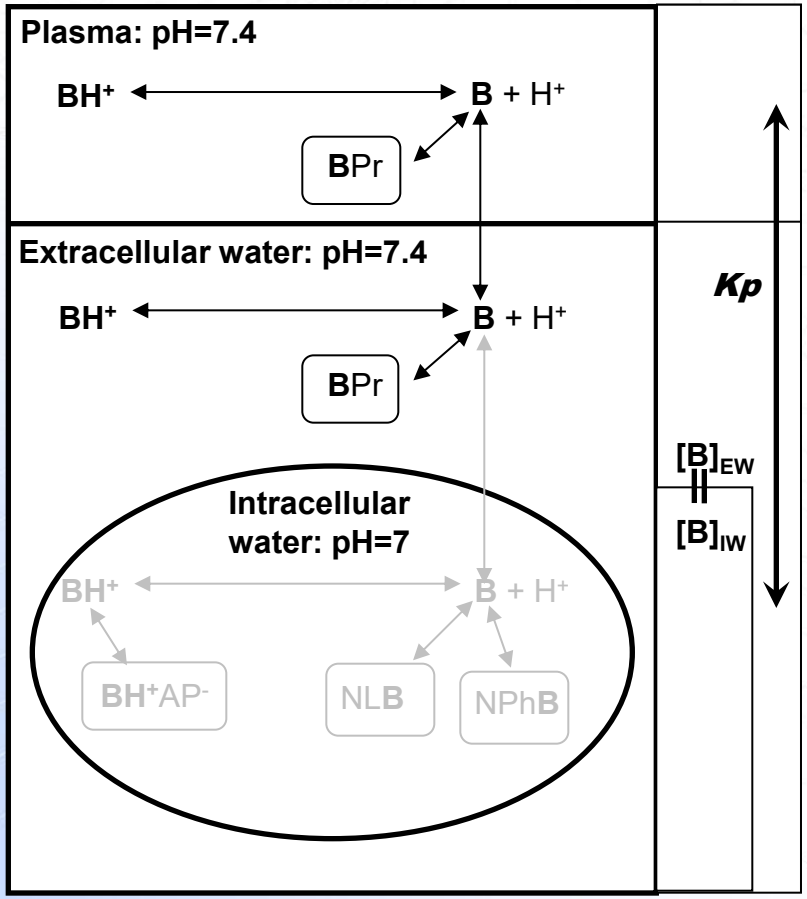
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Predicting Kps

Poulin - Extracellular

To describe partitioning only to extracellular space:



For permeability-limited tissues, Kp is used to calculate partitioning between plasma and extracellular space:

$$Kp = \frac{C_t^{ext}}{C_p} = \frac{C_{t,u}^{ext}}{fut} \times \frac{fup}{C_{p,u}} = \frac{fup}{fut}$$

For perfusion-limited tissues, Kp is used to calculate partitioning between plasma and entire tissue:

$$Kp = \frac{C_t}{C_p} = \frac{C_{t,u}}{fut} \times \frac{fup}{C_{p,u}} = \frac{fup}{fut} \times f_{vec}$$

$$C_{t,u} = C_{t,u}^{ext} \times \frac{V_t^{ext}}{V_t} = C_{t,u}^{ext} \times f_{vec}$$

$$fu_t = \left[\left(1 + \left(1 - fu_p\right)/fu_p\right) \cdot RA_{tp}\right]$$

RA_{tp}: Albumin ratio tissue:plasma

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Predicting Kps

Poulin & Theil method

$$Kp = \frac{\left[K \cdot \left(V_{nlt} + 0.3V_{pht}\right)\right] + \left[\left(V_{wt} + 0.7V_{pht}\right)\right]}{\left[K \cdot \left(V_{nlp} + 0.3V_{php}\right)\right] + \left[\left(V_{wp} + 0.7V_{php}\right)\right]} \cdot \frac{fu_p}{fu_t}$$

Berezhkovskiy method

$$Kp = \frac{\left[K \cdot \left(V_{nlt} + 0.3V_{pht}\right)\right] + \left[\left(V_{wt}/fu_t + 0.7V_{pht}\right)\right]}{\left[K \cdot \left(V_{nlp} + 0.3V_{php}\right)\right] + \left[\left(V_{wp}/fu_p + 0.7V_{php}\right)\right]}$$

adipose: $K = D^*_{vo:w}$
other: $K = P_{o:w}$

$fu_t = \left[\left(1 + \left(1 - fu_p\right)/fu_p\right) \cdot RA_{tp}\right]$
V_{nlt}, V_{pht}, V_{wt}: Volume fraction of neutral lipids, phospholipids, water
RA_{tp}: Albumin ratio tissue:plasma

1. Poulin, P. and Theil, F.P. (2002). "Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution." J Pharm Sci 91(1): 129-56.
2. Poulin, P. and Theil, F.P. (2002). "Prediction of pharmacokinetics prior to in vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition." J Pharm Sci 91(5): 1358-70.
3. Berezhkovskiy, L.M. (2004). "Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination." J Pharm Sci 93(6): 1628-40.

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Predicting Kps

Rodgers and Rowland method

$$Kp = Kpu * fup$$

Unbound tissue plasma partition coefficient, *Kpu*, is calculated differently for strong bases than for other drugs:

1. **Strong bases and zwitterions with at least one base pKa ≥ 7** – takes into consideration the unique interaction of bases with acidic phospolipids

$$Kpu = V_{ewt} + \left(\frac{(1/X_{[D],IW})}{(1/X_{[D],P})} V_{iwt} \right) + \left(\frac{K \cdot V_{nlt} + (0.3K + 0.7)V_{pht}}{(1/X_{[D],P})} \right) + \left(\frac{Ka[AP]_T((1/X_{[D],IW}) - 1)}{(1/X_{[D],P})} \right)$$

2. **Acids, Neutrals, and weak bases** – takes into account binding to lipoproteins (neutral drugs) or tissue albumin (acids and weak bases – ionized fractions)

$$Kpu = V_{ewt} + \left(\frac{(1/X_{[D],IW})}{(1/X_{[D],P})} V_{iwt} \right) + \left(\frac{K \cdot V_{nlt} + (0.3K + 0.7)V_{pht}}{(1/X_{[D],P})} \right) + \left[\left(\frac{1}{fup} - 1 - \frac{K \cdot V_{nlp} + (0.3K + 0.7)V_{php}}{(1/X_{[D],P})} \right) \times RA_t \right]$$

***X*$_{[D]}$** – fraction of neutral drug species in intracellular water (IW, pH=7) and plasma (P, pH=7.4)
K – vegetable oil/water partition coefficient for adipose tissue and 1-octanol/water partition coefficient for remaining tissues
fup-fraction unbound of drug in plasma, ***Ka*** – association constant of base with acidic phospholipids, ***[AP]*$_T$** – tissue concentration of acidic phospholipids
RA$_t$ – tissue/plasma lipoprotein or albumin ratio

1. Rodgers, T. and Rowland, M. (2005). "Physiologically based pharmacokinetic modelling 1: predicting the tissue distribution of moderate-to-strong bases" J Pharm Sci 94:1259-1276
2. Rodgers, T. and Rowland, M. (2006). "Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions." J Pharm Sci 95(6): 1238-57

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Predicting Kps

Lukacova (i.e., Rodgers and Rowland – Single)

Simulations Plus developed an alternative approach to calculating Kps according to Rodgers and Rowland:

$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \left(\frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[\frac{1}{fup} - 1 - \left(\frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

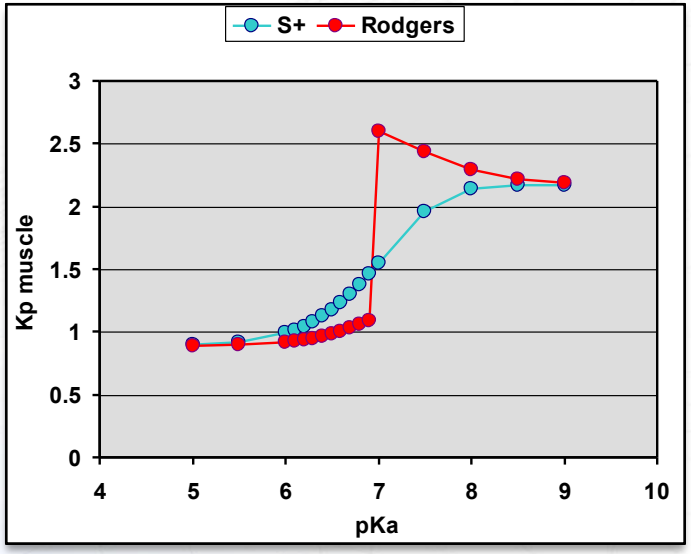
$$(Fc) \cdot \left(\frac{Ka \cdot [AP]_T ((1/X_{[D],IW}) - 1)}{(1/X_{[D],P})} \right)$$

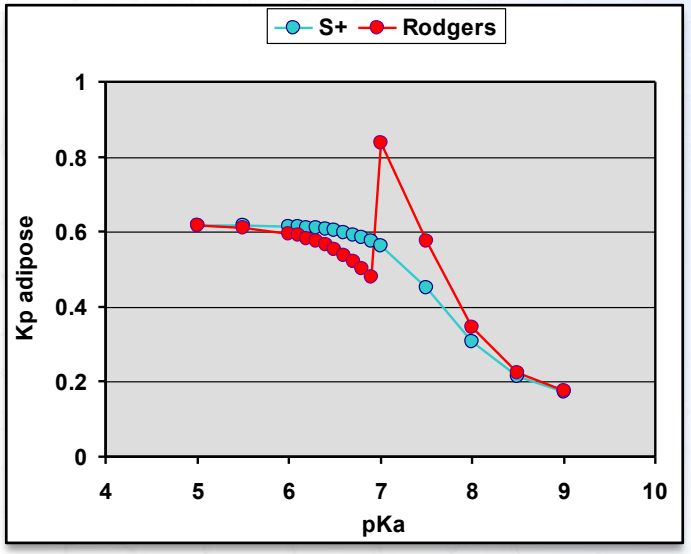
- Single equation is being used for all compounds
- The binding of drug to acidic phospholipids or plasma proteins is given by actual ionization of each drug at physiological pH

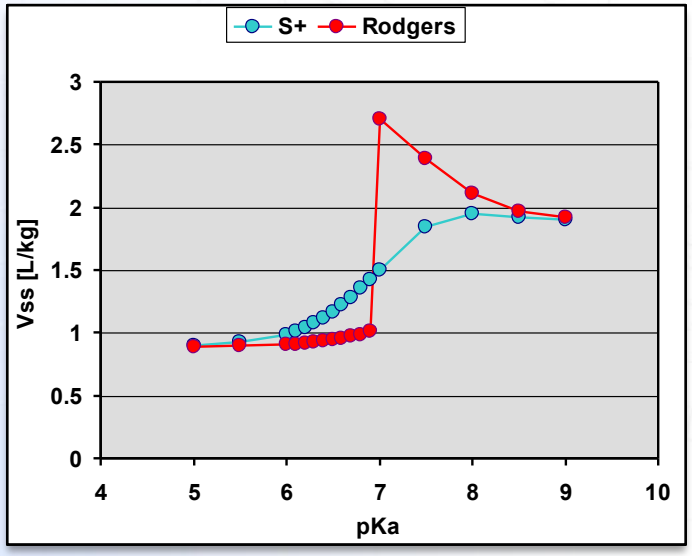
V. Lukacova, N. Parrott, T. Lave, G. Fraczkiewicz, M. Bolger, W. Woltosz. Role of fraction unbound in plasma in calculation of tissue:plasma partition coefficients, AAPS National meeting, Atlanta, November 15-20, 2008

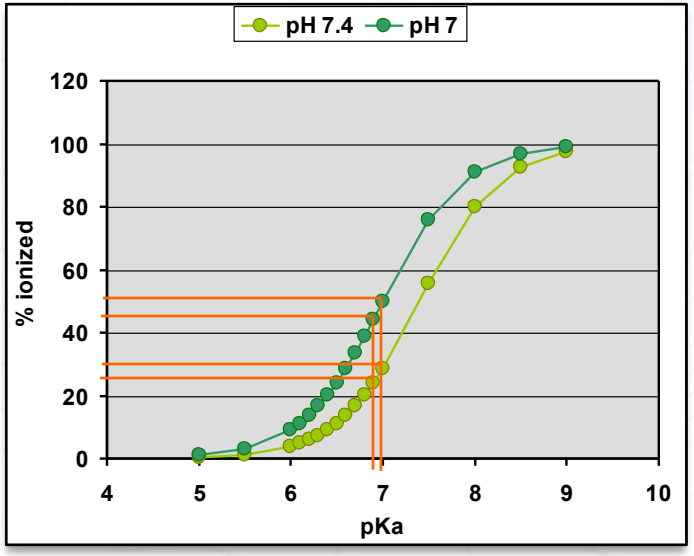
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Predicting Kps:
Rodgers vs. Lukacova (S+ Method)









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Predicting Kps

Schmitt Equation

$$K_{t:p} = \frac{C_t}{C_p} = \frac{C_t}{C_u}\frac{C_u}{C_p}$$
$$= \frac{F_{int}C_{int} + F_{cell}C_{cell}}{C_u}\frac{C_u}{C_p} = \left(\frac{F_{int}}{f_u^{int}} + \frac{F_{cell}}{f_u^{cell}}\right)f_u^p$$

Unbound fraction in cells accounts for binding to membrane neutral lipids, neutral phospholipids, acidic phospholipids, and cellular protein

$$\frac{C_{total}}{C_u} = \frac{1}{f_u^{cell}} = F_W + K_{n_L}F_{n_L} + K_{n_PL}F_{n_PL} + K_{a_PL}F_{a_PL} + K_PF_P$$

Unbound fraction in interstitium estimated from fup assuming the same protein fraction in interstitium and plasma ratio in all tissues

$$\frac{1}{f_u^{int}} = F_W^{int} + F_P^{int}K_P^{pl} = F_W^{int} + \frac{F_P^{int}}{F_P^{pl}}\left(\frac{1}{f_u^{pl}} - F_W^{pl}\right)$$

Affinity to acidic phospholipids is estimated from membrane affinity using empirically derived scaling factors

for acids:

$$K_{a_PL} = K_{n_PL}\cdot\left[f_{neutral} + 20\cdot f_{charged}\right]$$
$$= K_{n_PL}\cdot\left[\frac{1}{1+10^{pH-pK_a}} + 20\cdot\left(1 - \frac{1}{1+10^{pH-pK_a}}\right)\right] \quad (17)$$

for bases, respectively:

$$K_{a_PL} = K_{n_PL}\cdot\left[\frac{1}{1+10^{pK_a-pH}} + 0.05\cdot\left(1 - \frac{1}{1+10^{pK_a-pH}}\right)\right]$$

Includes additional mechanism for binding to cellular proteins

$$K_P = 0.163 + 0.0221K_{n_PL}$$

Schmitt W. (2008) General approach for the calculation of tissue plasma partition coefficients. Toxicol in vitro 22: 457-467

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Predicting Kps

Assmus

Assmus et al. extended Rodgers and Rowland equation for strong bases to account for lysosomal trapping:

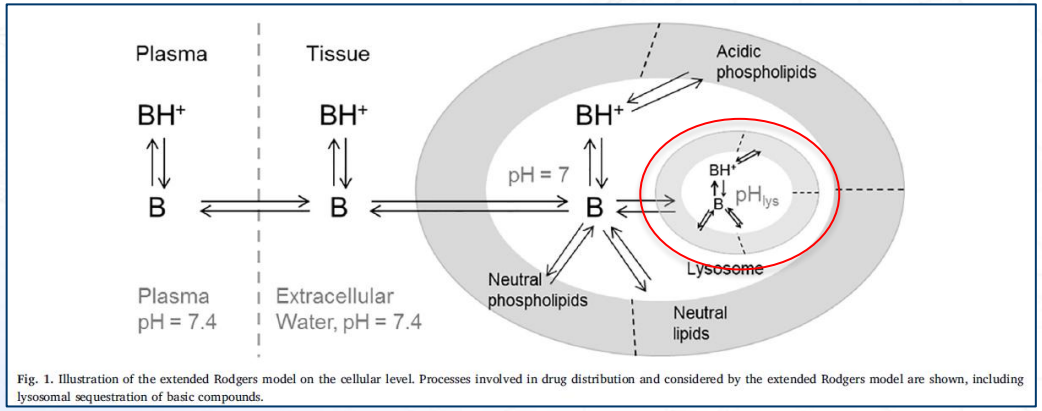


Fig. 1. Illustration of the extended Rodgers model on the cellular level. Processes involved in drug distribution and considered by the extended Rodgers model are shown, including lysosomal sequestration of basic compounds.

Equation extended for lysosomal trapping

$$Kpu_R^* = Kpu_R + \sum_{Cell\ \ Type\ \ 1}^{Cell\ \ Type\ \ n} \left(\frac{1 + 10^{pK_a - pH_{IW}}}{1 + 10^{pK_a - pH_p}} \right) \cdot Kpu^{Lys} \cdot f_{Lys} \cdot f_{Cell\ \ Type}$$

Original R&R equation

$$C_{Tissue,R} = \frac{A_{Tissue,R}}{V_{Tissue}} = Cu_P \cdot \left[\begin{array}{l} f_{EW} + \left(\frac{1 + 10^{pK_a - pH_{IW}}}{1 + 10^{pK_a - pH_p}} \cdot f_{IW} \right) \\ + \left(\frac{K_a \cdot |AP^-|_T \cdot 10^{pK_a - pH_{IW}}}{1 + 10^{pK_a - pH_P}} \right) \\ + \left(\frac{P \cdot f_{NL} + ((0.3P + 0.7) \cdot f_{NP})}{1 + 10^{pK_a - pH_p}} \right) \end{array} \right]$$

$$Kpu_{Lys} = \frac{C_{Lys}}{Cu_{IW}} = \left[\begin{array}{l} \left(\frac{1 + 10^{pK_a - pH_{Lys}}}{1 + 10^{pK_a - pH_{IW}}} \cdot f_{IW} \right) \\ + \left(\frac{K_a \cdot |AP^-|_T \cdot 10^{pK_a - pH_{Lys}}}{1 + 10^{pK_a - pH_{IW}}} \right) \\ + \left(\frac{P \cdot f_{NL} + ((0.3P + 0.7) \cdot f_{NP})}{1 + 10^{pK_a - pH_{IW}}} \right) \end{array} \right]$$

Assmus F, Houston JB, Galetin A. (2017) “Incorpration of lysosomal sequestration in the mechanistic model for prediction of tissue distribution of basic drugs. Eur J Pharm Sci 109: 419-430

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Predicting Kps

Lukacova with Lysosomal Trapping

Lukacova Kp method was extended to include lysosomal compartment

Accumulation in lysosomal water compartment

$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \frac{1/X_{[D],Lys}}{1/X_{[D],p}} V_{Lys} + \left(\frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[\frac{1}{fup} - 1 - \left(\frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

$$(Fc) \cdot \frac{Ka \cdot [AP]_T}{(1/X_{[D],P})} \cdot \left[(1 - V_{Lys}) \cdot \frac{X_{[D^+],iw}}{X_{[D],iw}} + V_{Lys} \cdot \frac{X_{[D^+],Lys}}{X_{[D],Lys}} \right]$$

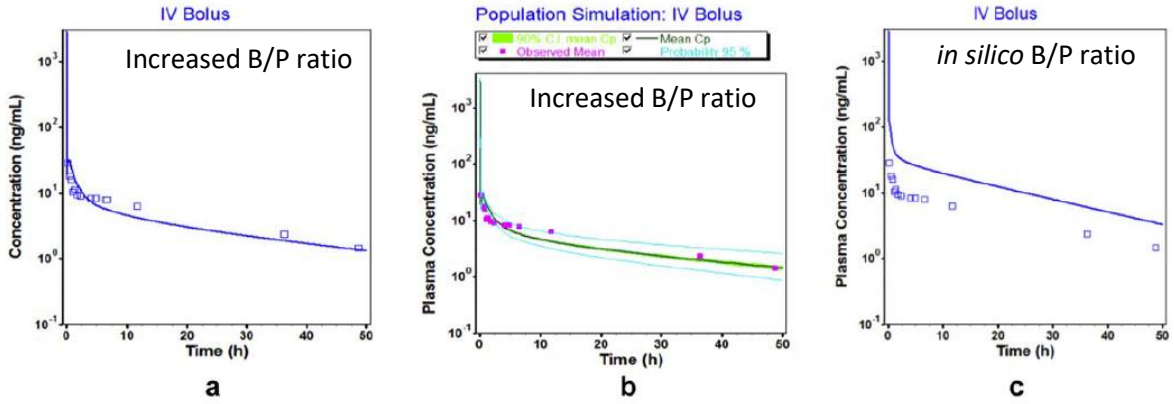
Binding to acidic phospholipids in lysosomes

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Predicting Kps: Effect of Lysosomal Trapping on Vss

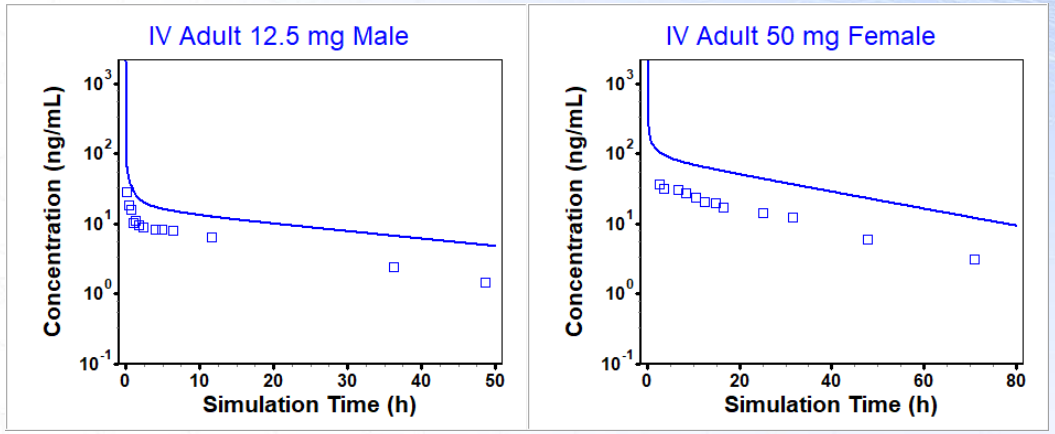
Desipramine example (GastroPlus)

Previously published model – accurate Vss was obtained by artificially increasing B/P ratio for Kp calculation

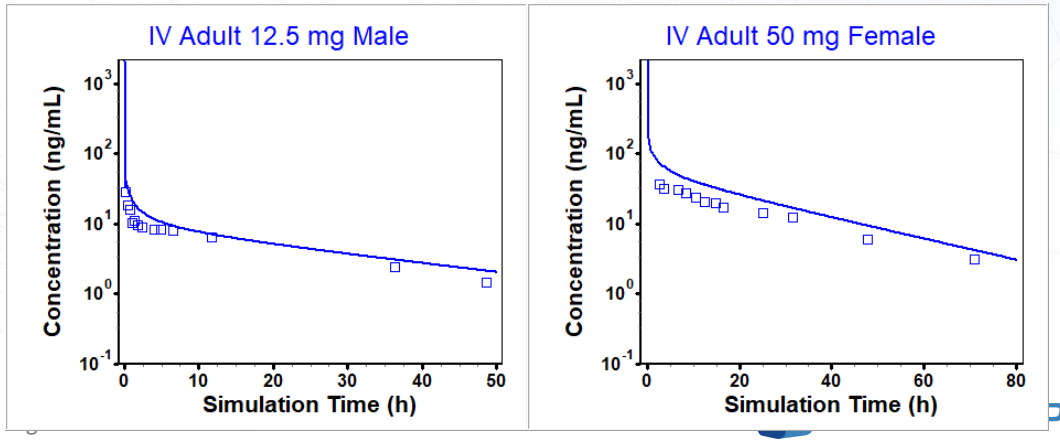


Samant – CPT: PSP 2017, 6, 315-321

Experimental B/P values are little bit higher than previously used *in silico* prediction, but still don't capture the Vss accurately without the lysosomal trapping consideration



New equation with lysosomal trapping predicts distribution more accurately



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Predicting Kps:

Adjusted Fup

- Highly lipophilic drugs can exhibit significant binding to plasma lipids
- Binding to plasma lipids may not be captured by standard equilibrium dialysis measurement of Fup

$$f_{up} = \frac{1}{10^{\log D_{o/w}\left(\frac{V_{lipid}}{V_{water}}\right)} + 1 + \frac{1 - F_{up,\exp}}{F_{up,\exp}}}$$

Assumptions:

1. $\log D_{o/w}$ can be used as an estimate for the drug partitioning into plasma lipids
2. Experimental F_{up} is a measure of drug binding ONLY to plasma albumin

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Highly Lipophilic Compounds

Role of Fraction Unbound in Plasma in Calculations of Tissue:Plasma Partition Coefficients

Roche

Pharmaceuticals

Lukacova,

(1) Simulations Plus, Inc. La

Abstract:

Purpose: Previous investigations have shown that the Rodgers and Rowland method [Rodgers 2007] for prediction of tissue:plasma partition coefficients (Kps) provides good prediction for compounds with low to moderate lipophilicity, but it often fails when applied to highly lipophilic compounds. The reasons for the unreasonably high Kp predictions for lipophilic compounds were investigated.

Methods: The effects on errors in predictions of experimental measurements of logP, pKa, Fup and Rbp on the accuracy of Kp prediction were evaluated. The main focus was on prediction of Kps, and the resultant volume of distribution, using the Rodgers & Rowland method for highly lipophilic compounds. The study revealed that this method tends to overpredict Kps especially for lipophilic compounds which also have fairly high measured fraction unbound in plasma (Fup). This could be due to the inability of current experimental techniques to capture the possible binding of drug to plasma lipids in Fup measurements. We have derived an equation which corrects the experimental Fup for binding to plasma lipids, assuming that the experimental Fup is

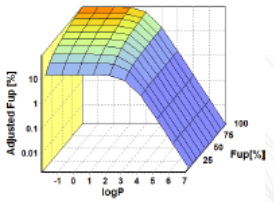
Assuming that:

(1) experimental F_{up} (by equilibrium dialysis) is a measure of drug binding only to protein

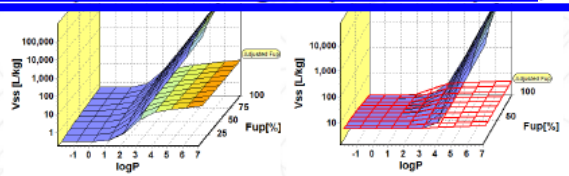
(2) logP can be used as an estimate for the drug partitioning to plasma lipids, the "corrected" fraction unbound in plasma can be calculated as:

$$f_{up} = \frac{1}{10^{logP_{o/w}} \left(\frac{V_{lipid}}{V_{water}} \right) + 1 + \frac{1 - F_{up,exp}}{F_{up,exp}}}$$

where V_{lipid} is the volume fraction of total neutral lipid and phospholipid in plasma, V_{water} is the volume fraction of water in plasma, $logP_{o/w}$ is octanol/water partition coefficient, $F_{up,exp}$ is the experimentally measured value of fraction unbound in plasma, and f_{up} is the adjusted fraction unbound in plasma which will be used in Kp calculations.



Dependency of adjusted fup on logP and experimental fup



Dependency of volume of distribution (Vss) on Fup and logP using the "experimental" F_{up} directly in Kp calculations and with adjusting the Fup for binding to plasma lipids. F_{up} [%] on the Y-axis shows the "experimental" F_{up} in all graphs. The V_{ss} values were calculated for model compounds (neutral with blood-to-plasma-ratio = 1 on the left and strong base with pKa = 8.5 and blood-to-plasma-ratio = 1 on the right) using adult male physiology.

For neutral compound, the V_{ss} is increasing with increasing experimental F_{up} and increasing $logP_i$ with logP having larger impact. Adjusting F_{up} for possible binding to plasma lipids results in lower V_{ss} values reaching plateau and not increasing significantly with further increase in logP.

However, the F_{up} adjustment does not automatically result in lower V_{ss} for all compounds. For a strong base (base pKa = 8.5 and blood-to-plasma-ratio = 1), V_{ss} is increasing with increasing logP but shows much less uniform dependency on F_{up}: V_{ss} decreases with increasing F_{up} for compounds with low lipophilicity but increases with increasing F_{up} for highly lipophilic compounds. Adjustment of F_{up} for binding to plasma lipids again results in plateau in V_{ss} for highly lipophilic compounds, but for moderately lipophilic compounds, the F_{up} adjustment may result in increase in predicted Kps and subsequently V_{ss}.

Kp prediction with experimental and adjusted F_{up} for specific compounds. For Mofarotene and Glycyrrhetinic acid, the F_{up} adjustment resulted in significant decreases in calculated Kps. Azithromycin represents compounds where the F_{up} adjustment results in increases of calculated Kps.

	Mofarotene*		Glycyrrhetinic Acid*		Azithromycin		
	Fold error of Kp prediction		Fold error of Kp prediction		Kp		
	with Exp Fup	with Adjusted Fup	with Exp Fup	with Adjusted Fup	Experimental [Shepard 1990]	Calc with Exp Fup	Calc with Adjusted Fup
Adipose	>1000	4	>10000	>10			
Brain	500	2	>10000	5			
Gut	500	2	>5000	5			
Heart	100	3	>1000	3			
Kidney	>100	3	>1000	2	317.5	2.58	26.48
Liver	>100	3	>1000	2	442.5	3.05	24.03
Lung	>100	>5	>1000	2	205	2.19	20.59
Muscle	>100	2	>1000	2			
Repro Org	>500	3					
Skin	>100	3	>1000	3			
Spleen	100	>5	>1000	3	1897.5	2.80	16.78

* Experimental Kp values are from unpublished Roche measurements

References:

Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3151-3152

Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3153-3154

Shepard, R. M. Falkner, F. C.; J Antimicrob Chemother 1990, 25 (suppl. A): 49-60

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Highly Lipophilic Compounds

Pharmacokinetics, Pharmacodynamics and Drug Metabolism

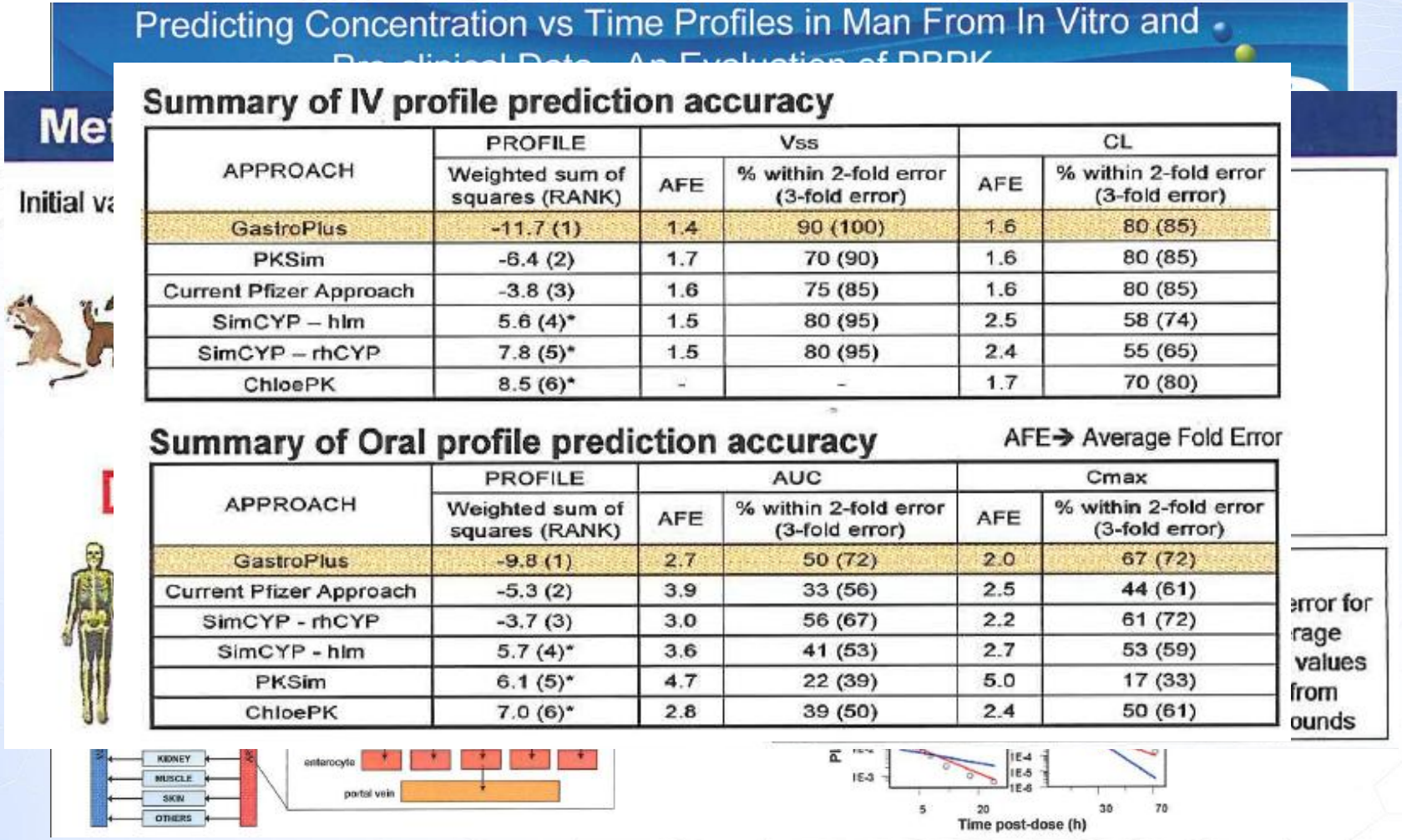
Advancing Prediction of Tissue Distribution and Volume of Distribution of Highly Lipophilic Compounds from a Simplified

ABSTRACT: It has been reported that values of tissue–plasma ratios (K_p) and resulting volume of distribution at steady state (V_{ss}) are substantially overpredicted for several highly lipophilic drugs. This effect was observed particularly with the published version of the tissue-composition-based model, which used experimentally determined unbound fraction in plasma (fu_p) as input for drugs. The reasons for the unreasonably high V_{ss} predictions were investigated in this study for 14 highly lipophilic compounds with a log *n*-octanol–water partition coefficient (log P_{ow}) of at least 5.8. Here, we argue that the experimentally determined fu_p is inaccurate for these compounds, which affected the prediction of K_p and V_{ss}. Alternatively, the tissue-

ABSTRACT: It has been reported that values of tissue–plasma ratios (K_p) and resulting volume of distribution at steady state (V_{ss}) are substantially overpredicted for several highly lipophilic drugs. This effect was observed particularly with the published version of the tissue-composition-based model, which used experimentally determined unbound fraction in plasma (fu_p) as input for drugs. The reasons for the unreasonably high V_{ss} predictions were investigated in this study for 14 highly lipophilic compounds with a log *n*-octanol–water partition coefficient (log P_{ow}) of at least 5.8. Here, we argue that the experimentally determined fu_p is inaccurate for these compounds, which affected the prediction of K_p and V_{ss}. Alternatively, the tissue-
plasma ratio of neutral lipids (nl) equivalent was used as the main factor governing K_p, and hence V_{ss}, in addition to log P_{ow}. The average fold error of deviation between the predicted and observed human V_{ss} is 124 for the published model, whereas it significantly decreased to 1.5 for the proposed model. The sensitivity analysis confirmed the importance of nl content and drug lipophilicity. Overall, this study proposes a generic and simplified tissue-composition-based model for highly lipophilic drugs and chemicals, which is a step forward toward improving prediction of V_{ss} into physiologically based pharmacokinetic (PBPK) models. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2250–2261, 2012
Keywords: animal alternative; ADME; disposition; distribution; volume of distribution; pharmacokinetics; protein binding; unbound fraction; PBPK; first-time-in-human

Poulin – J Pharm Sci 2012

Allometric Scaling vs. PBPK:
in vitro-in vivo extrapolation (IVIVE)



Summary of IV profile prediction accuracy

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

Summary of Oral profile prediction accuracy

AFE➔ Average Fold Error

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

Cole et al., 2008 – Asian ISSX Meeting
Jones et al. 2011. Clin. Pharmacokinet. 50(5): 331

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Vss is Not Predicted Well – Now What?

Missing Mechanism?

- Tissue specific binding?
- Impact of transporters?
- Membrane Permeability limitation?
- Other?

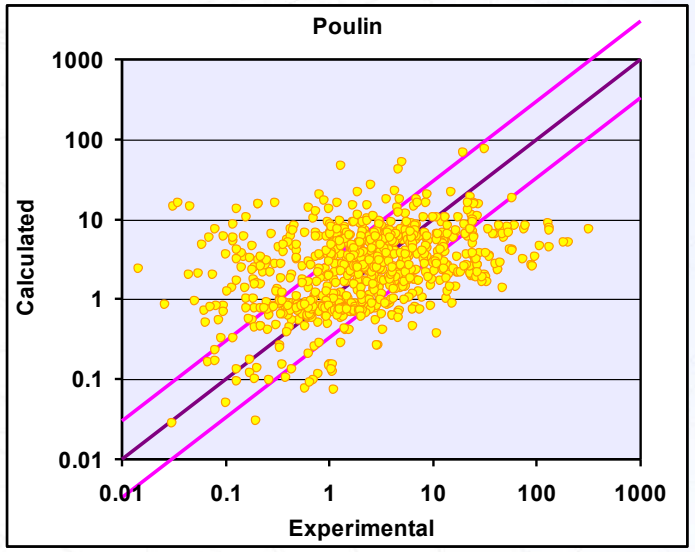
Input error/uncertainty?

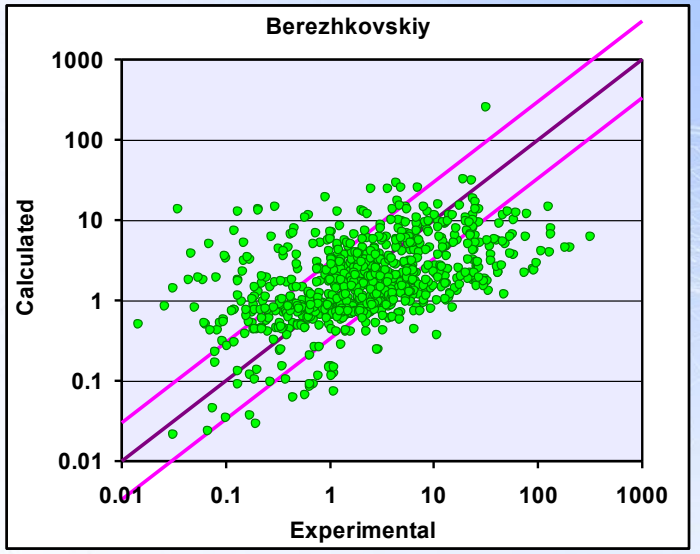
Compound specific properties typically used as inputs (method-specific):

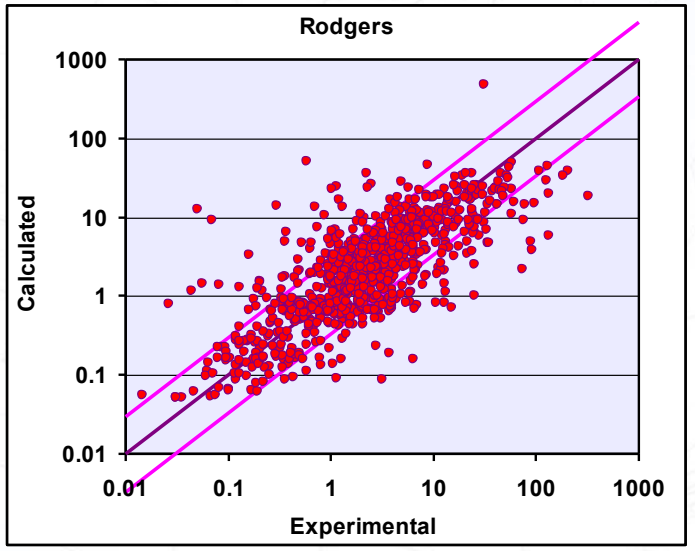
- pKa(s)
- logP or logD
- Fup
- B/P ratio
- Membrane affinity

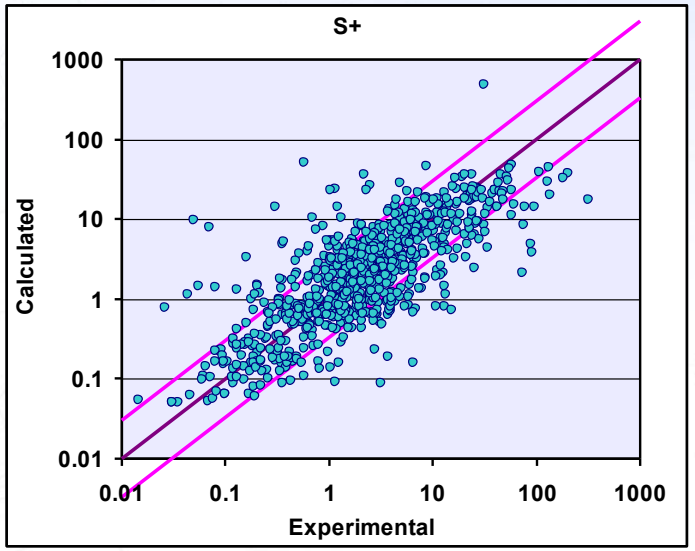
Method Selection?

- Methods consider different mechanisms
- All methods make assumptions







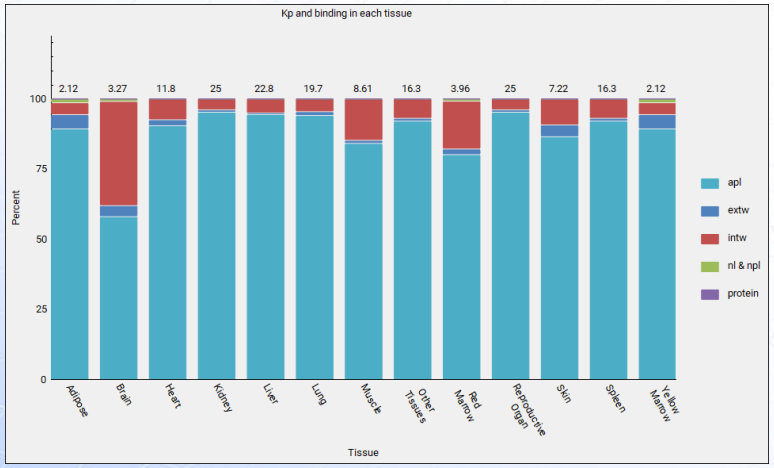


Lukacova – AAPS Annual Meeting 2008

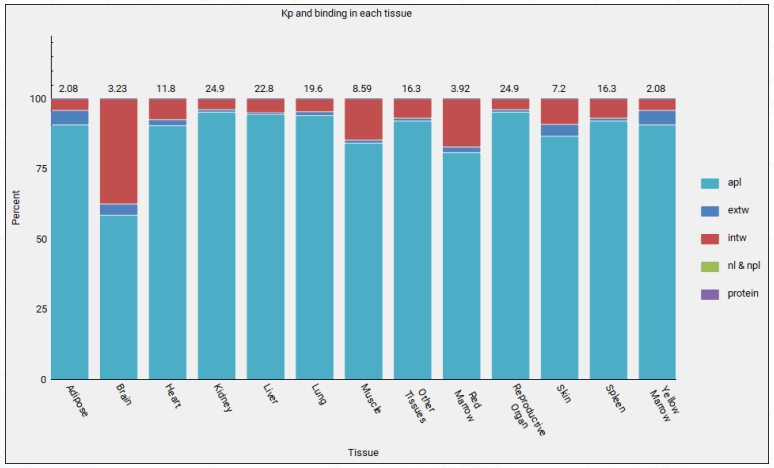
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What Impacts Tissue Partitioning for My Compound?

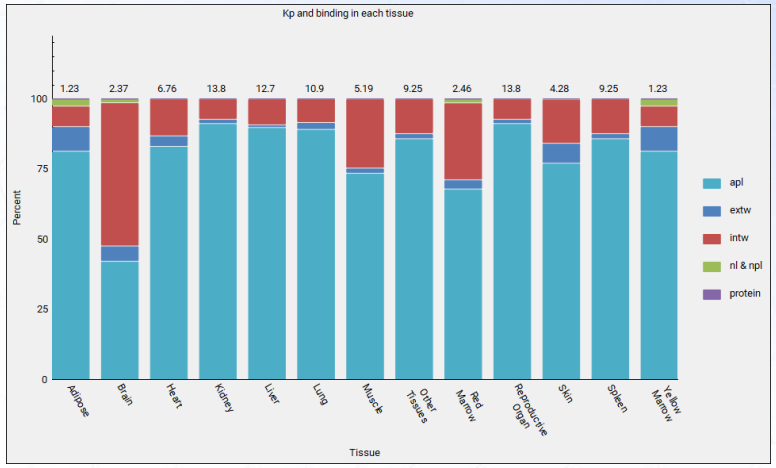
pKa = 9.7 (B)
logP = 2.15
B/P ratio = 1.52
Fup = 80%
Predicted Vss = 474.4L

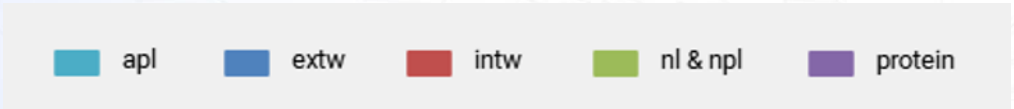


pKa = 9.7 (B)
logP = 2.15 x 0.1
B/P ratio = 1.52
Fup = 80%
Predicted Vss = 472.2L



pKa = 9.7 (B)
logP = 2.15
B/P ratio = 1.52 x 0.8
Fup = 80%
Predicted Vss = 283.6L

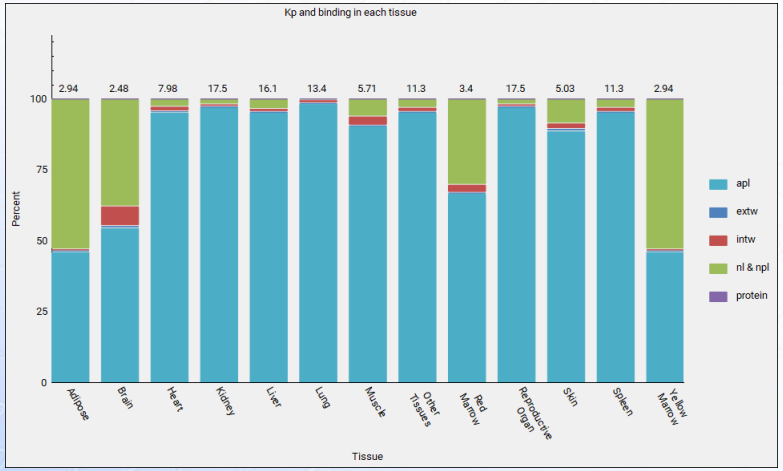




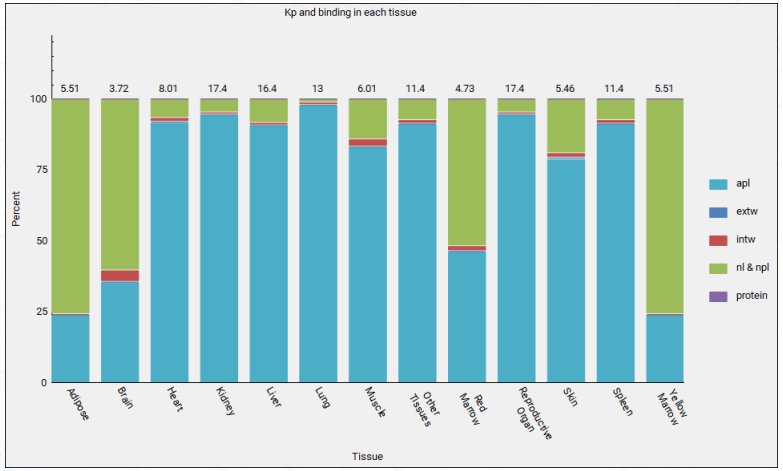
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What Impacts Tissue Partitioning for My Compound?

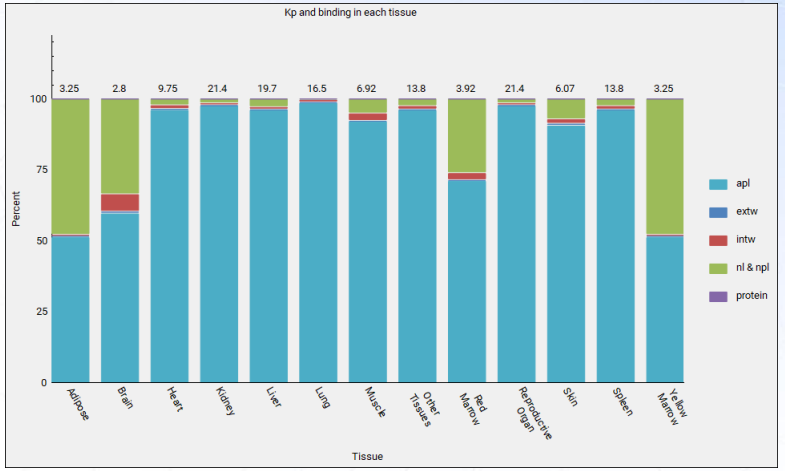
pKa = 9.687 (B)
logP = 4.379
B/P ratio = 1.072
Fup = 12.33%
Predicted Vss = 378L

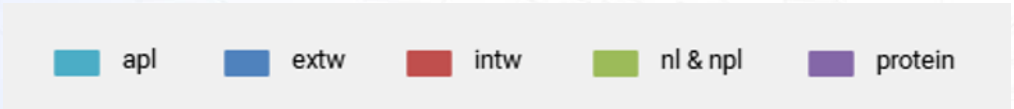


pKa = 9.687 (B)
logP = 4.379 x 1.1
B/P ratio = 1.072
Fup = 12.33%
Predicted Vss = 479L



pKa = 9.687 (B)
logP = 4.379
B/P ratio = 1.072 x 1.1
Fup = 12.33%
Predicted Vss = 446.2L

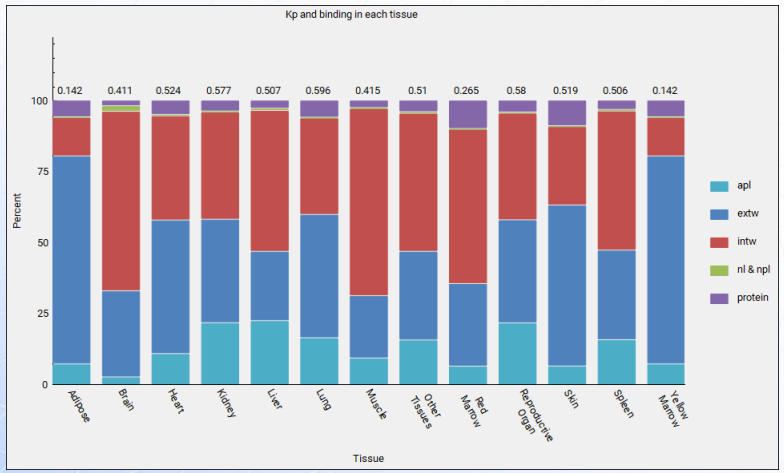




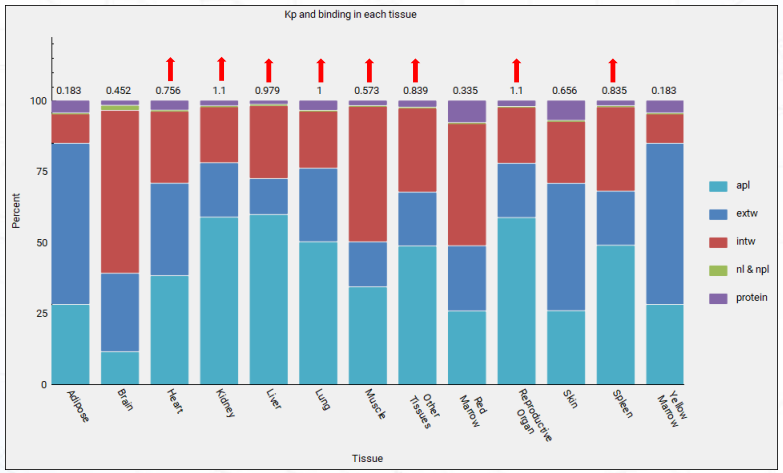
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What Impacts Tissue Partitioning for My Compound?

pKa = 6.95 (B), 3.01 (A)
logP = -1.935
B/P ratio = 0.7424
Fup = 77%
Predicted Vss = 27.29L

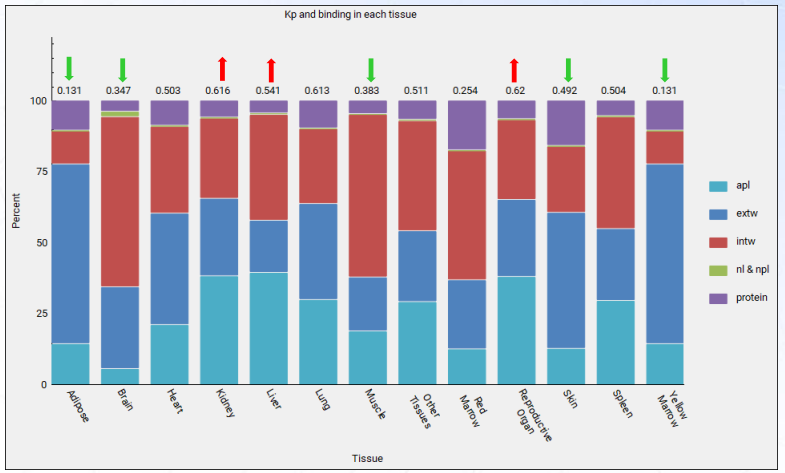


pKa = 6.95 (B), 3.01 (A)
logP = -1.935
B/P ratio = 0.7424 x 1.2
Fup = 77%
Predicted Vss = 36.13L

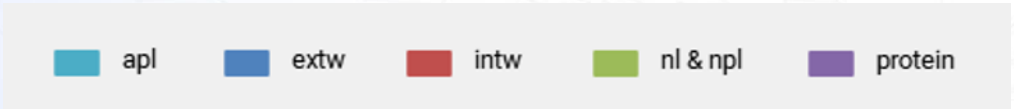


arrows mark Kps with >30% change
(range +10 to +93%)

pKa = 6.95 (B), 3.01 (A)
logP = -1.935
B/P ratio = 0.7424
Fup = 77% x 0.8
Predicted Vss = 25.92L

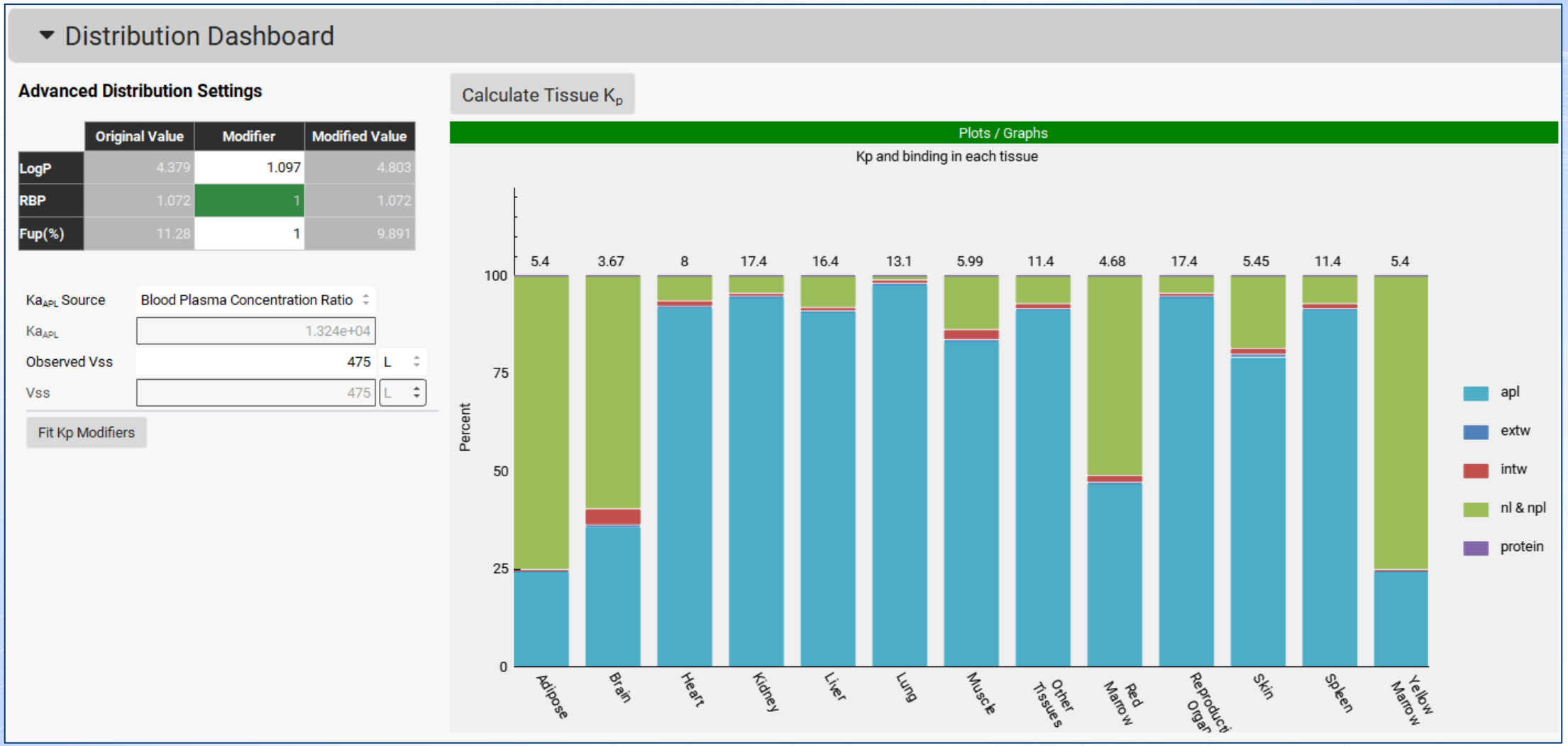


arrows mark Kps with >5% change
(range -16% to +7%)



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Fitting Observed Vss

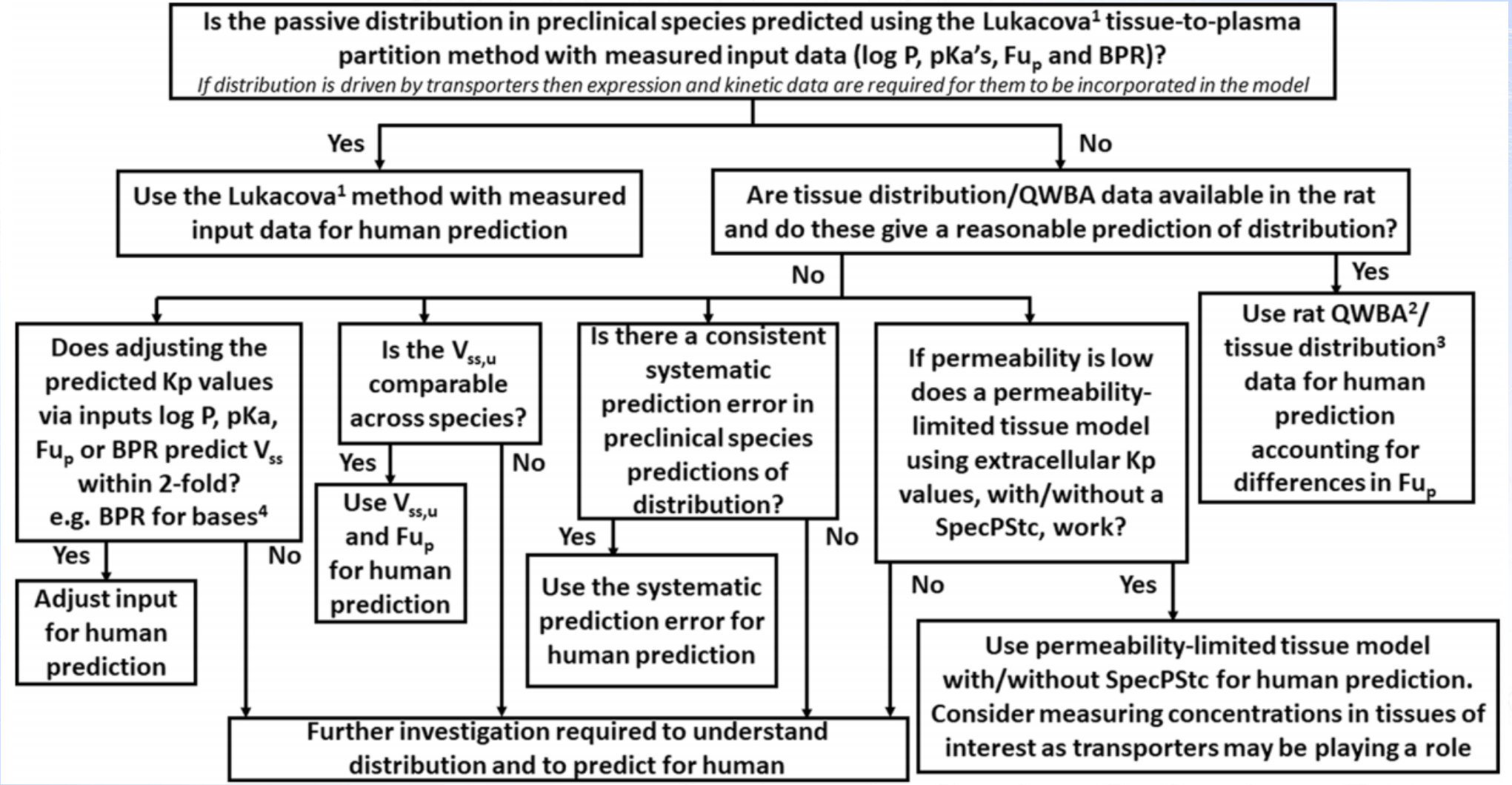


Distribution Dashboard in GastroPlus

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SimulationsPlus

Industrial decision tree for PBPK before FIH: Distribution



Miller et al. (2019) Clinical Pharmacokinetics.

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An Industry Defined FIH PBPK Strategy

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

REVIEW ARTICLE

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

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

Case study 2: Assessment of Vss – impact of B/P ratio

Table 3 Measured blood/plasma ratio (BPR), fraction unbound in plasma (Fu_p) and intravenous volume of distribution at steady state (V_{ss}) [observed and predicted] for Compound 2

Species	BPR	Fu_p (%)	Observed V_{ss} (L/kg) [blood]	Observed V_{ss} (L/kg) [plasma]	GastroPlus™ predicted V_{ss} (L/kg) [plasma]	Fold error V_{ss}
Rat	1.8	37	9.1	16.4	14.7	− 1.1
Rabbit	1.3	34	8.0	10.4	7.2	− 1.4
Dog	1.1	31	8.5	9.4	5.7	− 1.6
Monkey	0.8	4	7.3	5.8	2.0	− 2.9
Minipig	0.9	20	5.0	4.5	4.9	+ 1.1
Human	0.6	17	–	2.6	3.0	+ 1.2

Note: Human pharmacokinetics were measured in plasma and GastroPlus predicts plasma pharmacokinetics; only for preclinical species where observed pharmacokinetics were measured for blood was it necessary to convert blood V_{ss} to plasma V_{ss} using species-specific BPR for comparison to GastroPlus outputs

Fold error V_{ss} = − Observed V_{ss}/Predicted V_{ss} if Observed V_{ss} > Predicted V_{ss}

Fold error V_{ss} = + Predicted V_{ss}/Observed V_{ss} if Predicted V_{ss} > Observed V_{ss}

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SimulationsPlus

An Industry Defined FIH PBPK Strategy

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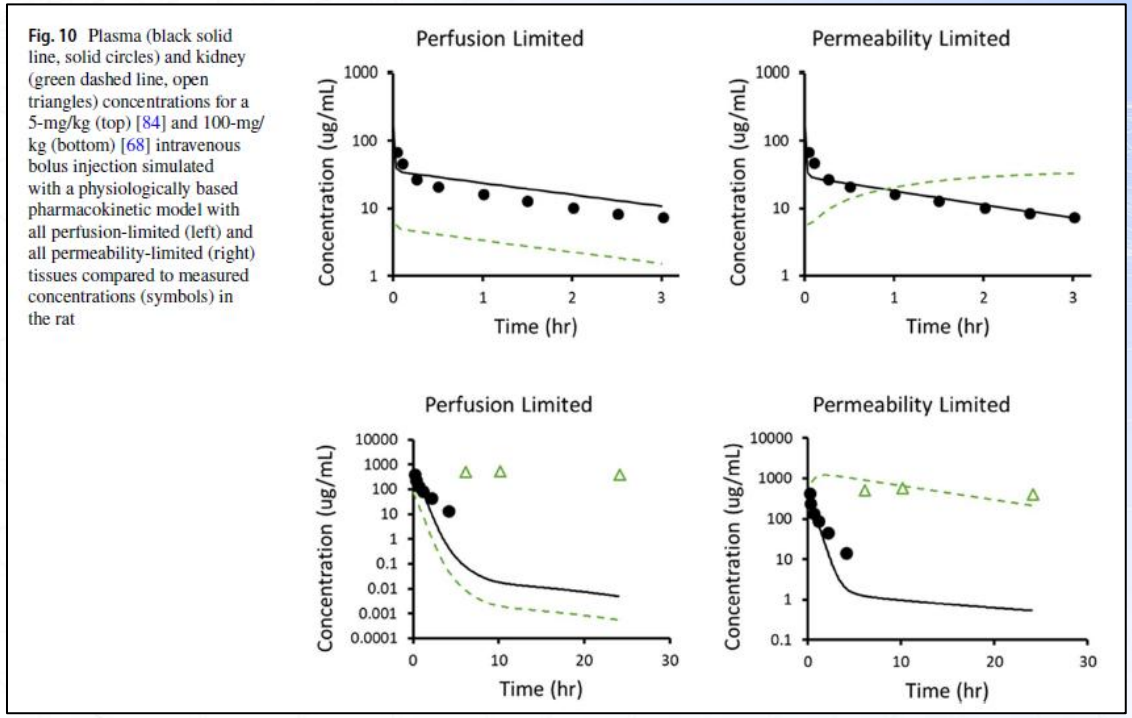


Fig. 10 Plasma (black solid line, solid circles) and kidney (green dashed line, open triangles) concentrations for a 5-mg/kg (top) [84] and 100-mg/kg (bottom) [68] intravenous bolus injection simulated with a physiologically based pharmacokinetic model with all perfusion-limited (left) and all permeability-limited (right) tissues compared to measured concentrations (symbols) in the rat

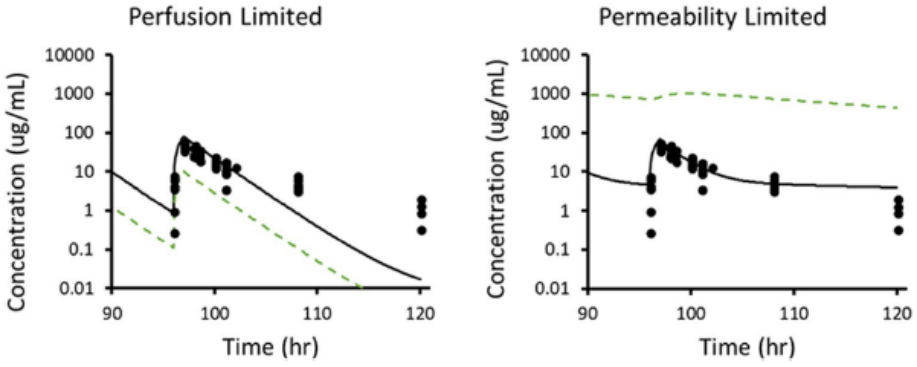


Fig. 11 Plasma (black solid line, solid circles) and kidney (green dashed line) concentrations for a 1000-mg dose administered as 1-h intravenous infusion every 12 h [85] predicted with physiologically based pharmacokinetic models with all perfusion-limited (left) and all permeability-limited (right) tissues compared to measured plasma concentrations in healthy volunteers

Case study 3: Impact of Distribution Mechanism

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Summary

- Mechanistic (semi-mechanistic) methods are available to predict tissue partitioning (Kp) and Vss from compound properties and tissue physiology.
- Prediction accuracy depends on reliable inputs and method assumptions that match the compound's distribution mechanisms.
- When predictions miss observed Vss, investigate input uncertainty and missing mechanisms before making empirical adjustments.
- Sensitivity analysis can be used to evaluate which inputs drive Kp and Vss uncertainty for each compound.

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