

# Pharmacokinetics Modelling Course:

## 5. Pharmacodynamics, PBPK

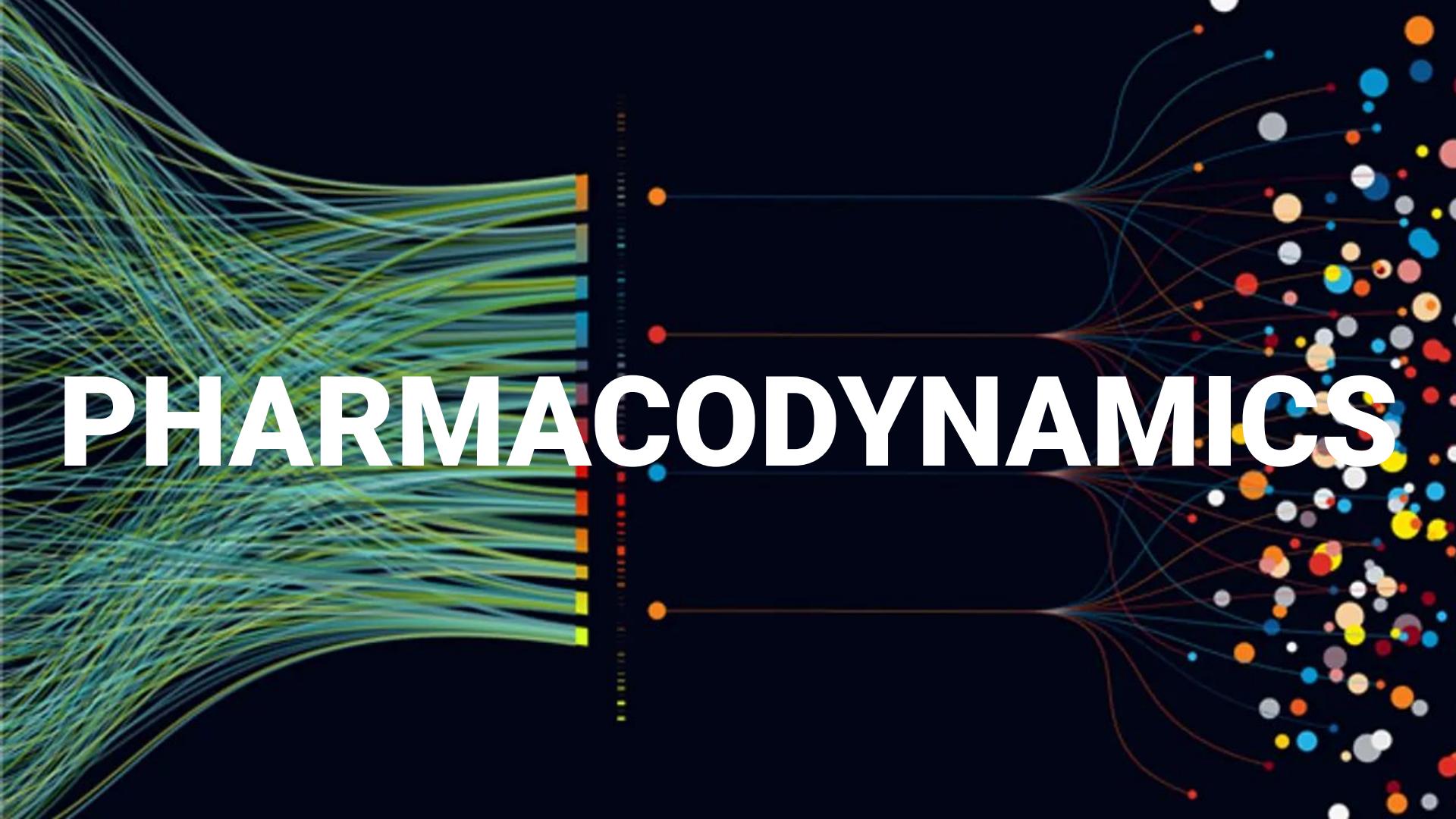
Matthias König, MB19, SS2023

Humboldt-University Berlin, Systems Medicine of the Liver Lab

<https://livermetabolism.com>

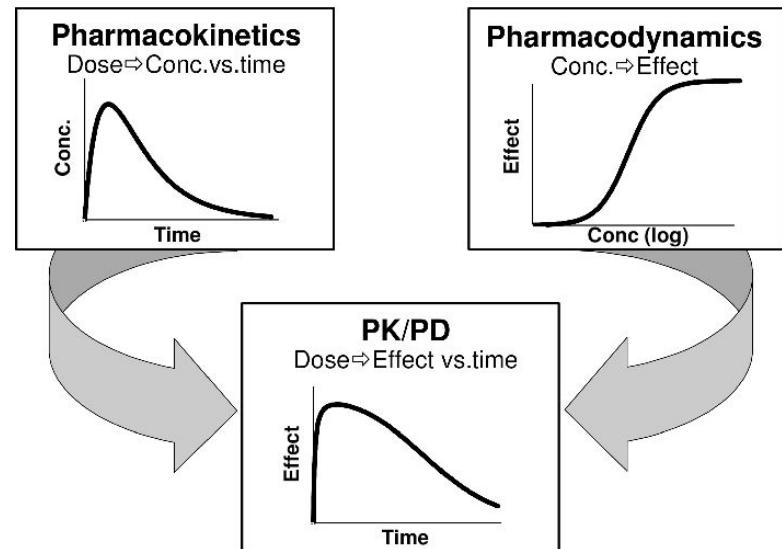


# PHARMACODYNAMICS

The background features a complex network of colored lines and dots against a dark blue gradient. On the left, several thick, curved lines in shades of green, yellow, and blue converge towards a central vertical axis. From this axis, thin lines branch out to a cluster of colorful dots (orange, red, blue, yellow) on the right. The overall effect is a dynamic, interconnected system.

# Pharmacokinetics (PK) & pharmacodynamics (PD)

- **Pharmacokinetics is what the body does to the drug**
  - study of the time course of drug absorption, distribution, metabolism, and excretion
  - **drug disposition**
- **Pharmacodynamics is what the drug does to the body**
  - **desired (and adverse) effects**

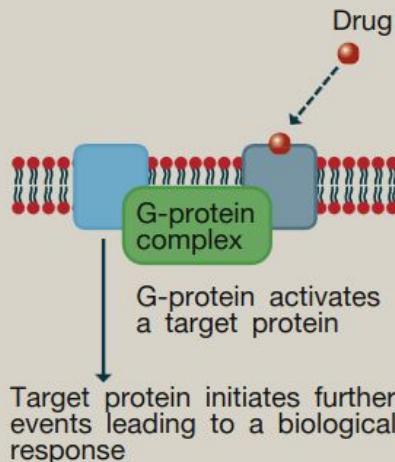


# Drug targets

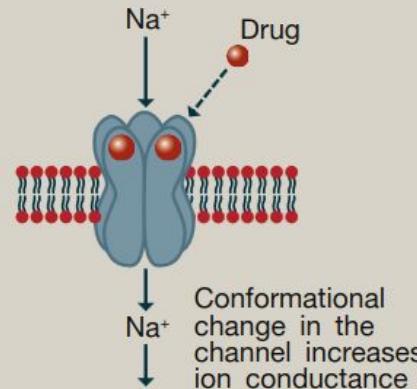
- Drugs interact with components within the body to produce a response.
  - proteins (receptors, enzymes)
  - DNA, genes

## Receptors and other drug targets

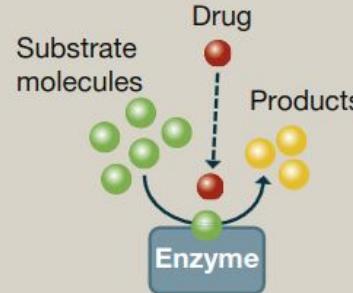
a. A G-protein-coupled receptor (GPCR)



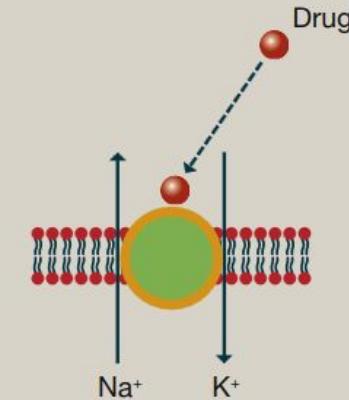
b. A channel-linked receptor



c. An enzyme drug target



d. A transport protein drug target



# Agonists & Antagonists

- **agonists:** increase functional response (e.g. receptor)
- **antagonists:** diminish functional response
  - **full agonists or full antagonists:** produce the maximum possible effect
  - **partial agonists or partial antagonists:** compounds that fail to achieve the greatest effect, even at very high concentrations
- **inducers:** increase synthesis (amount)
- **activators:** increase activity
- **inhibitors:** decreasing activity

## Agonists and Antagonists

Agonists - Drugs that occupy receptors and activate them.

Antagonists - Drugs that occupy receptors but do not activate them

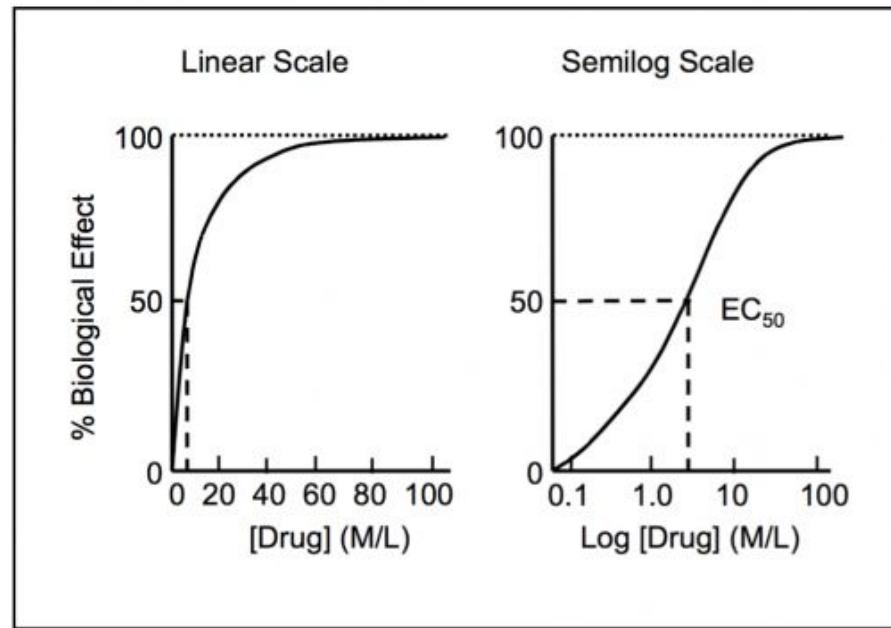
Antagonists block receptor activation by agonists.



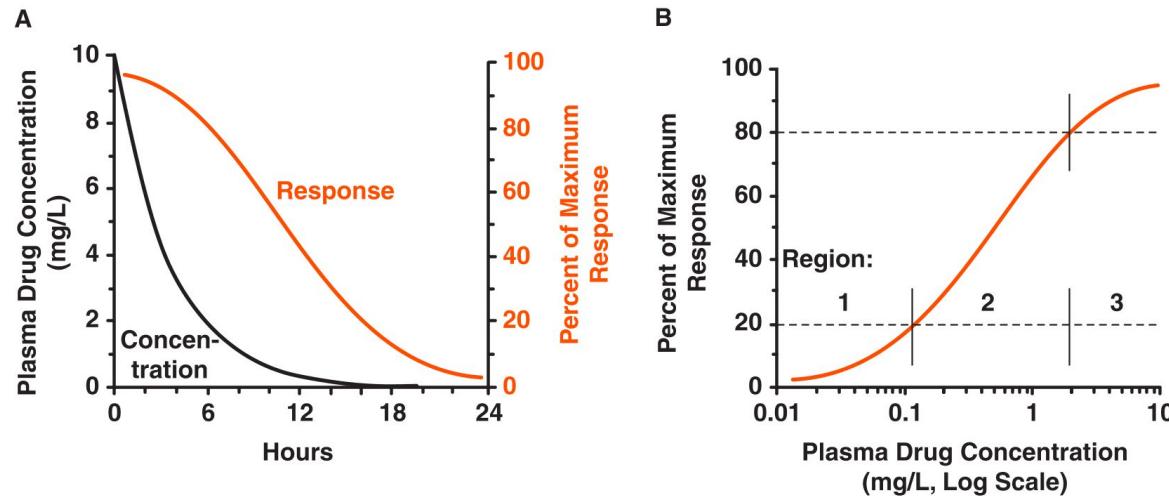
<https://psychonautwiki.org/wiki/Antagonist>

# Dose-response curve

- relationship between drug dose and biological response
- normally plotted on a logarithmic dose scale, appearing as a sigmoid curve
- Dose-response curve can be influenced by patient factors (e.g. age, disease) and by the presence of other drugs that compete for binding at the same receptor (e.g. receptor antagonists)



# From time-response to dose response



**FIGURE 9-6** The decline in the intensity of pharmacologic effect with time (colored line, A) after a single large intravenous bolus dose of a drug displaying monoexponential decline (black line, graph A) depends on the region of the concentration-response curve (B). Initially, in Region 3, the response remains almost maximal despite a 75% fall in concentration. Thereafter, as long as the concentration is within Region 2, intensity of response declines approximately linearly with time. Only when concentration falls into Region 1 does decline in response parallel that of drug in plasma. The concentration-response relationship is defined by:  $E = E_{\max} \cdot C^{\gamma} / (C_{50}^{\gamma} + C^{\gamma})$  with  $E_{\max} = 100\%$ ,  $C_{50} = 0.5 \mu\text{g}/\text{L}$ , and  $\gamma = 1$ .

Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics**. Second edition

# Potency & Efficacy

- **potency:** The potency of a drug is an expression of the amount of a drug required to produce biological effects (normally expressed as the ED<sub>50</sub>, the dose required to produce 50% of E<sub>max</sub>)
- **efficacy:** E<sub>max</sub>, i.e., maximum effect of the drug. Efficacy of a drug is a measure of its capacity to produce a biological effect.
- **desensitization** to drugs is a common phenomenon; when it occurs rapidly it is known as **tachyphylaxis**, and when it occurs more slowly it is known as **tolerance**.

Dose-response curves for drugs with high, medium and low potency acting on the same target

Note that the drug with the highest potency has the lowest efficacy and vice versa

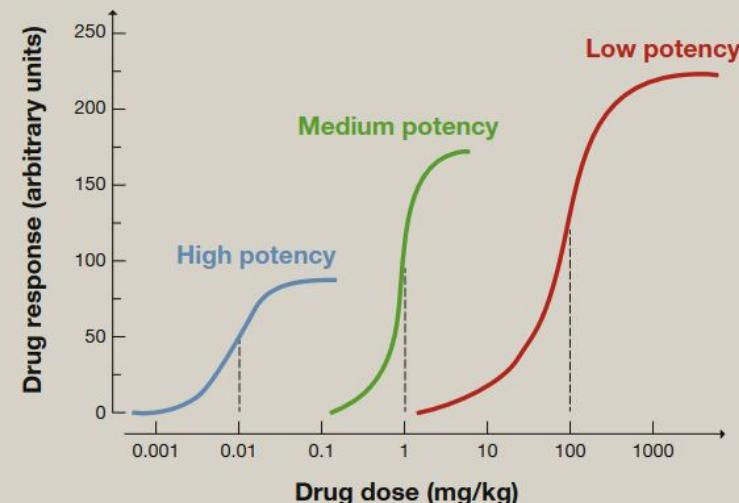


Figure 3

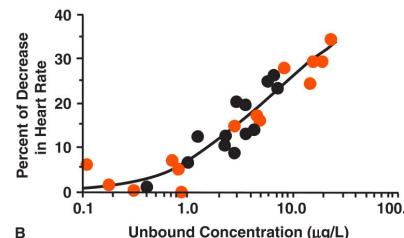
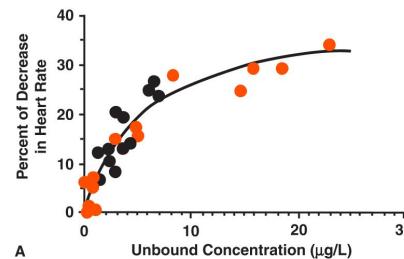
Maxwell S. **Pharmacodynamics for the prescriber**. Medicine Volume 48, Issue 7, July 2020, Pages 427-432

# Dose-dependency drug response

- An equation for describing the response is

$$E = \frac{E_{\max} \cdot C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$$

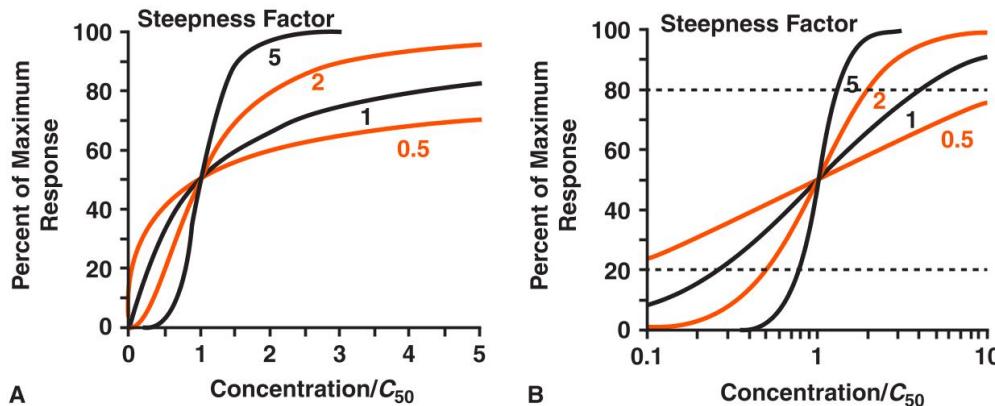
- $E_{\max}$ : maximum response
- $C_{50}$ : concentration to achieve 50% effect
- $\gamma$ : steepness factor (for drugs normally 1-3)



**FIGURE 3-6** **A.** Response, measured by the percent decrease in exercise-induced tachycardia, to propranolol increases with an increase in the unbound concentration of the drug in plasma. **B.** The same data as in **(A)**, except that now concentration is plotted on a logarithmic scale. The data points represent measurements after single and multiple (daily) oral doses of two 80-mg tablets of propranolol (black circle) or a 160-mg modified-release capsule (color) in an individual subject. The solid line is the fit of Equation 3-2 to the data. The response appears to follow the  $E_{\max}$  model with a  $\gamma$  of 1, an  $E_{\max}$  of 40%, and a  $C_{50}$  of 5.3 µg/L. (Redrawn from Lalonde RL, Straka RJ, Pieper JA, et al. Propranolol pharmacodynamic modeling using unbound and total concentrations in healthy volunteers. *J Pharmacokinet Pharmacodyn* 1987;15:569-582.)

# Steepness factor

$$E = \frac{E_{\max} \cdot C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}$$



**FIGURE 3-5** Linear (A) and semilogarithmic (B) concentration-response plots, predicted according to Equation 3-2, for three hypothetical drugs that have the same  $C_{50}$ , the concentration at which the response is one-half the maximum value, but different values of the steepness factor,  $\gamma$ . At low concentrations, the effect increases almost linearly with concentration (A), when  $\gamma=1$ , approaching a maximal value at high concentrations. The greater the value of  $\gamma$ , the steeper is the change in response around the  $C_{50}$  value. Between 20% and 80% of maximal effect, the response appears to be proportional to the logarithm of the concentration (B) for all values of  $\gamma$ . Concentrations are expressed relative to  $C_{50}$ .

# Beneficial and adverse effects

- The **therapeutic index** is the ratio between the dose of a drug that causes adverse effects and the dose that achieves therapeutic benefits
- **selectivity** of the drug, that is, a greater therapeutic response relative to its adverse responses.

## Dose-response curves for the beneficial and adverse effects of a drug

Prescribers will aim to prescribe doses that maximize benefits and minimize harms. That is easier for drugs where the ratio between the dose causing harm and that causing benefit (the 'therapeutic index') is high

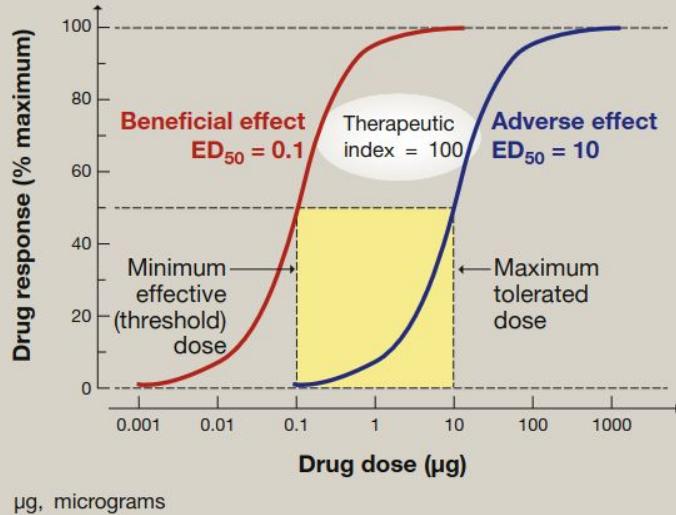


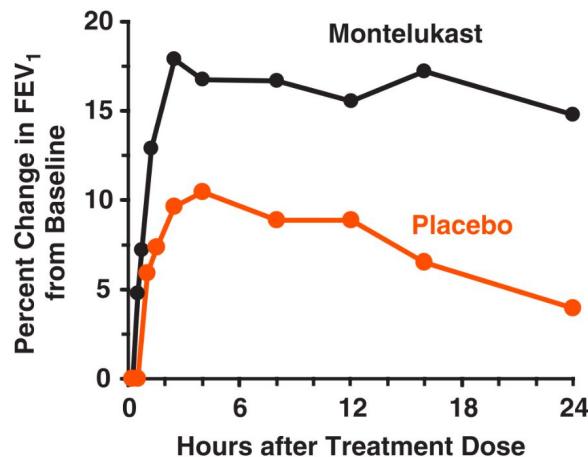
Figure 4

# Drug response & placebo effect

- **placebo effect** is a deviation from the baseline value produced when the patient takes or receives what has all the appearances of drug treatment but lacks the active principle

$$\text{Measured response} = \text{Drug response} + \text{Placebo response} + \text{Baseline}$$

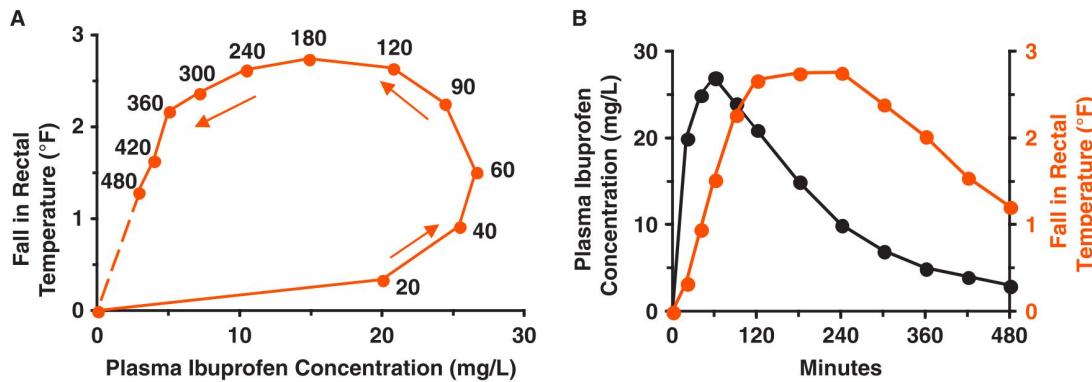
Eq. 3-1



**FIGURE 3-2** Figure showing changes in FEV<sub>1</sub>, a measure of respiratory function, with time following administration of a single dose of a placebo (color) or montelukast (10 mg, black), a specific leukotriene receptor antagonist, in asthmatic patients. Notice both the appreciable difference in FEV<sub>1</sub> from baseline between the two treatments, which is sustained over the 24-hour period response and also the positive effect of montelukast seen as the difference in FEV<sub>1</sub> between the two treatments, which is sustained over the 24-hour period of study. (Redrawn from Dockendorf RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000;55:260-265.)

# Time-dependency of response (time delays)

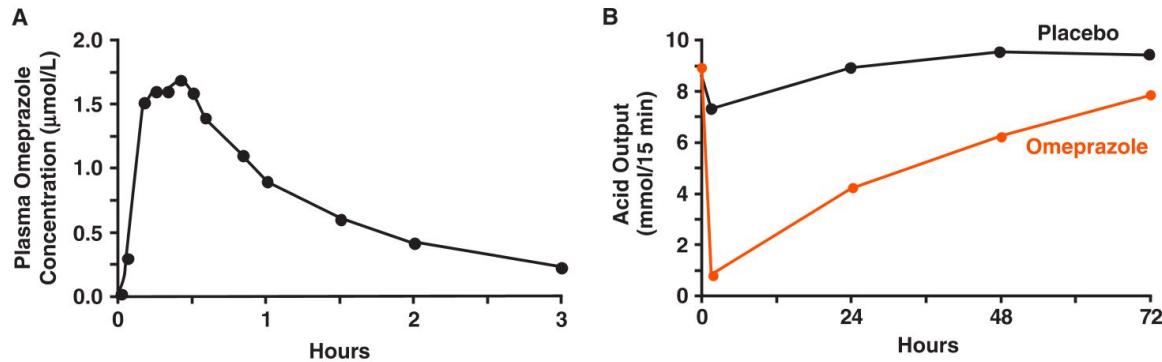
- drug response often lags behind its plasma concentration
- causes
  - delayed distribution to the site of action
  - underlying dynamics of affected system
- **pharmacokinetic rate-limited response**  
(instantaneous response)
- **pharmacodynamic rate-limited response**  
(pharmacodynamics slower than pharmacokinetics)



**FIGURE 9-3** The fall in rectal temperature (observation minus baseline in degrees Fahrenheit,  $1.8^{\circ}\text{F} = 1.0^{\circ}\text{C}$ ) in 36 febrile children from 6 months through 11 years of age after a 6-mg/kg oral dose of ibuprofen. **A.** Relationship between the fall in temperature and plasma ibuprofen concentration. Note the large degree of hysteresis present. The time of sampling (minutes) is indicated next to each point. **B.** Plasma ibuprofen concentration (black line) and fall in temperature (colored line) as a function of time after dosing. (Redrawn from Kelley MT, Walson PD, Edge JH, et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clin Pharmacol Ther* 1992;52:181–189.)

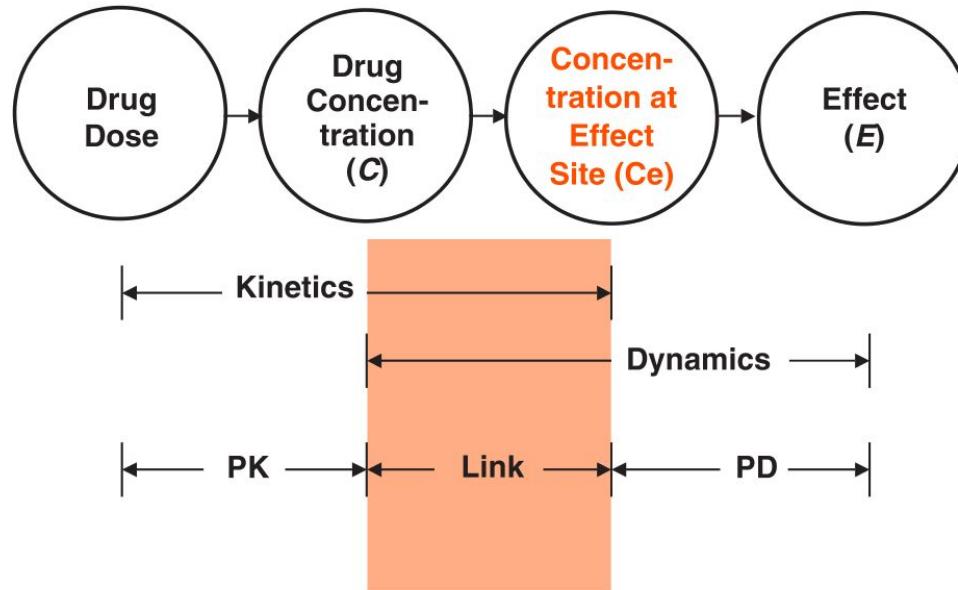
# Pharmacodynamic rate-limiting

- Omeprazole, an inhibitor of the proton pump within the acid-secreting parietal cells of the stomach
- **Gastric acid production** promptly falls, but the **return to baseline is very slow**, over days
- omeprazole **covalently binds and inactivates its receptor**—in this case the proton pump—which takes time to be resynthesized

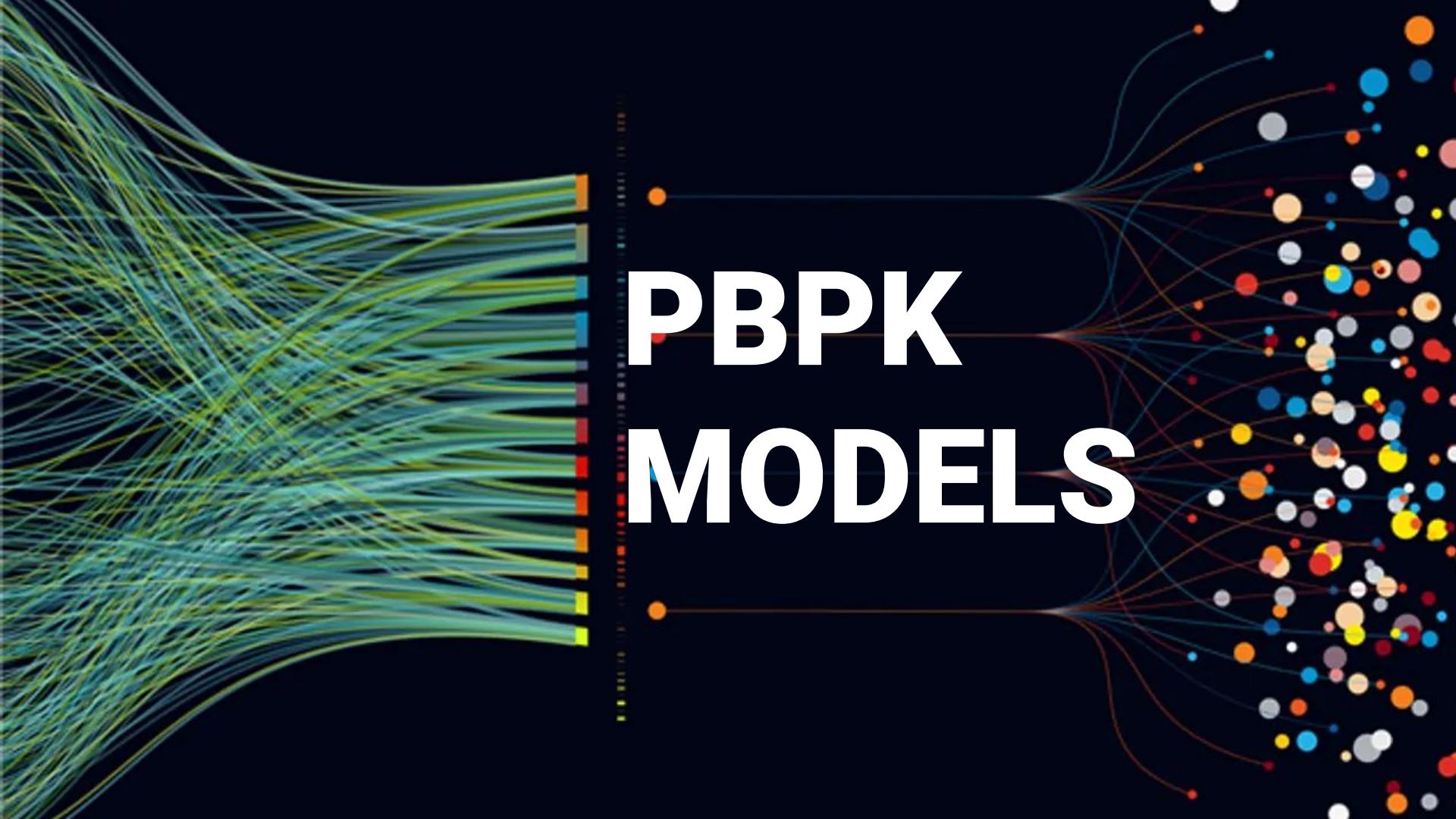


**FIGURE 9-9** Despite being very rapidly metabolized within the body, such that little remains in plasma after 3 hours following a 40-mg oral dose of omeprazole (A), the inhibition of gastric acid secretion (colored line) continues for several days (B). Also shown is the response after a placebo dose (black line). The response (expressed as a decrease in acid output over 15 minutes following a 1-hour infusion of intravenous pentagastrin, which maximally induces gastric acid secretion) was assessed before administration of drug or placebo at 2 hours postadministration, and again at 1, 2, and 3 days. This slow restoration of gastric acid secretion after omeprazole administration is due to a combination of very slow dissociation of tightly bound omeprazole-derived compounds to the proton pump receptor within the parietal cells of the stomach, together with the covalent binding and inactivating by omeprazole of this receptor, requiring synthesis of new receptor, which takes time. (A composite figure taken from data provided in Lind T, Cederberg C, Ekenved G, et al. Effect of omeprazole—a gastric proton pump inhibitor on the pentagastrin simulated secretion in man. *Gut* 1983;24:270–276.)

# Accounting for delays via effect compartments



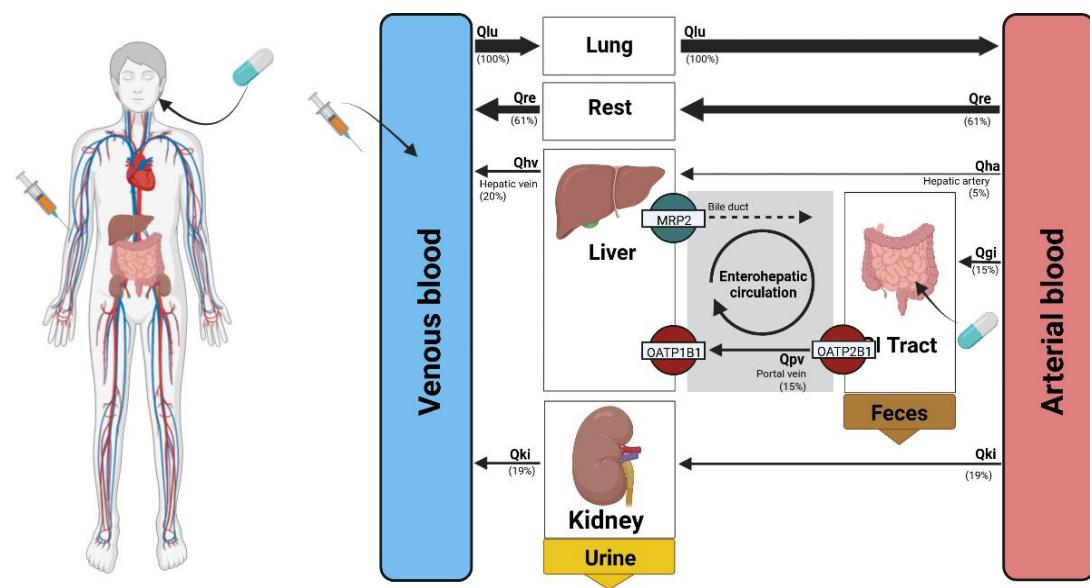
**FIGURE 9-10** The concept of an effect compartment linking plasma concentration (PK) with response (PD) helps to accommodate the frequently observed delay in time between plasma concentration and response. The delay is due to the time needed to distribute into the site of action. By accommodating for and thus effectively removing this delay, it is possible to reveal the underlying direct relation between effect site concentration ( $C_e$ ) and response.

A complex network visualization on a dark background. On the left, a dense cluster of green and yellow lines forms a fan-like pattern. A vertical column of small colored dots (orange, red, blue, yellow) serves as hubs, from which numerous thin lines radiate outwards. On the right, these lines converge into a large, scattered cluster of colorful circular nodes in shades of orange, red, yellow, blue, and white.

# PBPK MODELS

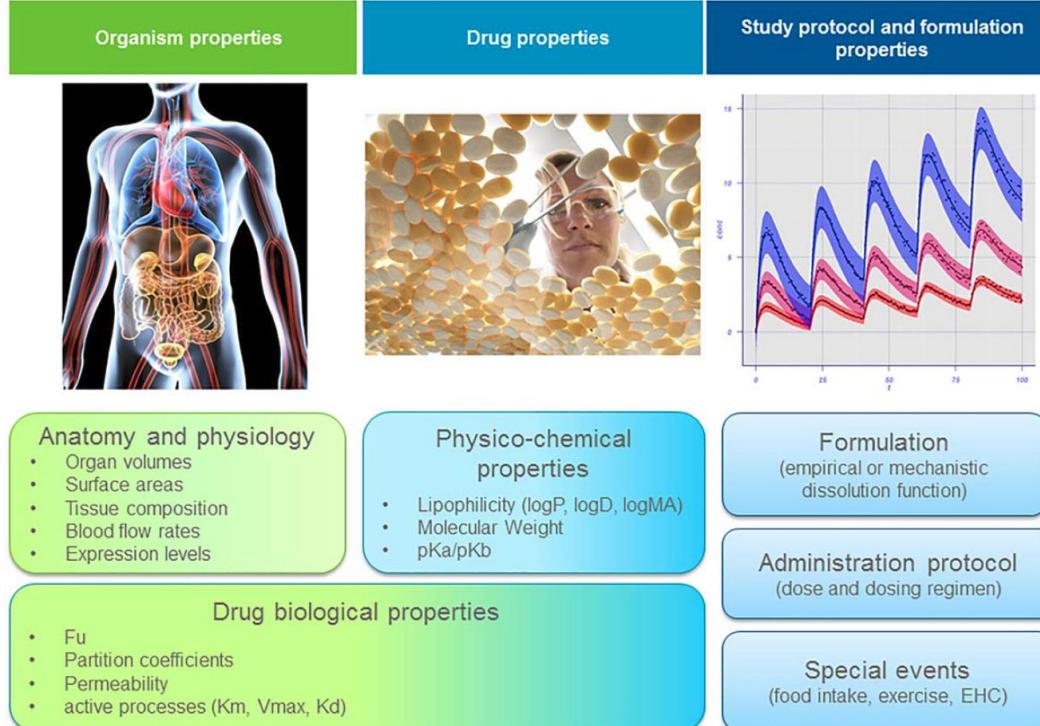
# Physiologically based pharmacokinetics (PBPK) models

- **Human physiology *in silico***  
Combine test substance information with physiology
- **Multi-scale Body-Organ**
- **High pharmacological & clinical relevance**  
Individualization



# PBPK Models

## Building blocks of a PBPK model



### Compartments

- organs

### State variables

- drug & metabolite amounts

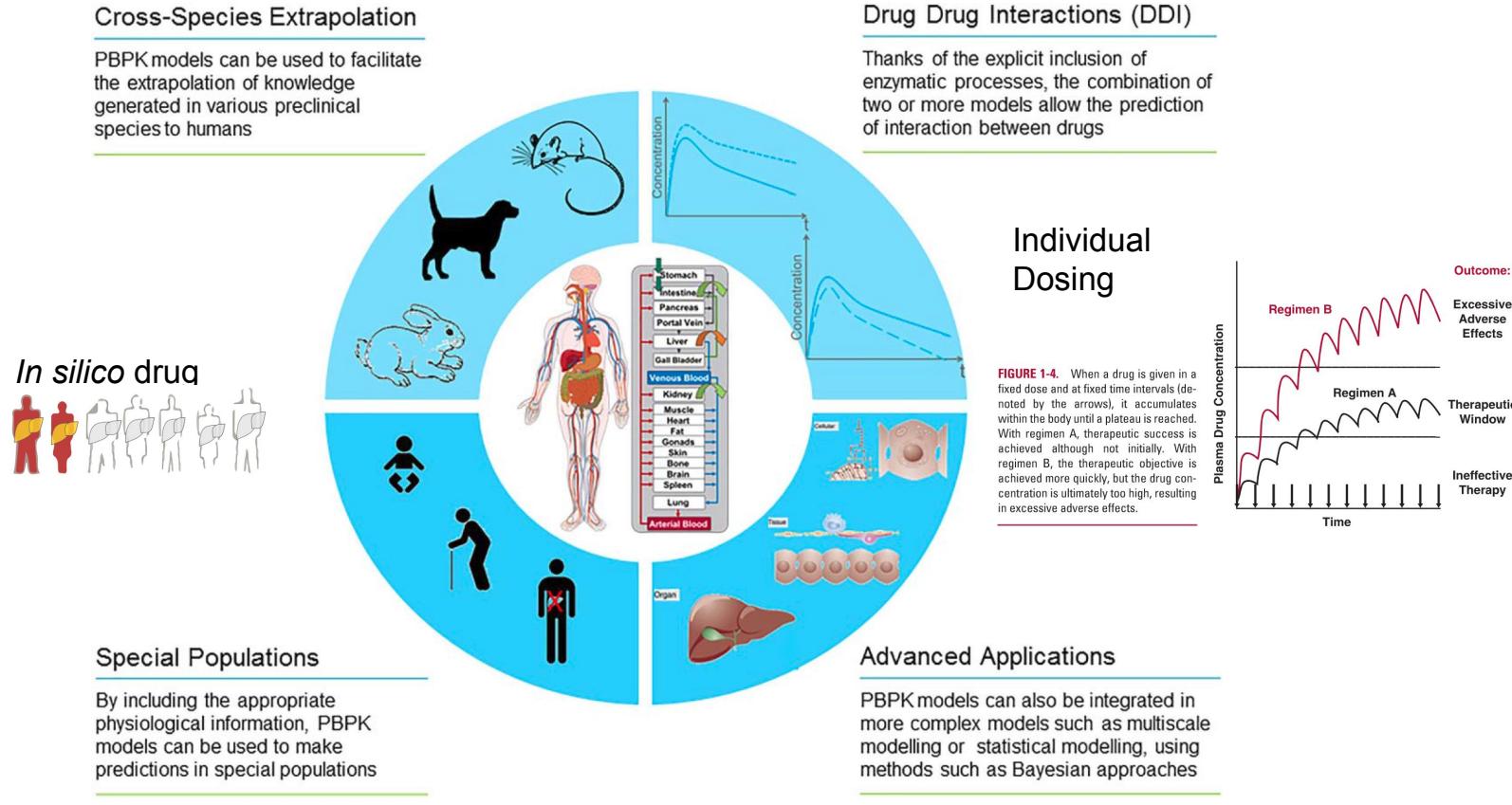
### Ordinary Differential equations (ODE) & rules

- Blood flows, Transport, Disposition
- Metabolism, Elimination
- Absorption

### Parameters

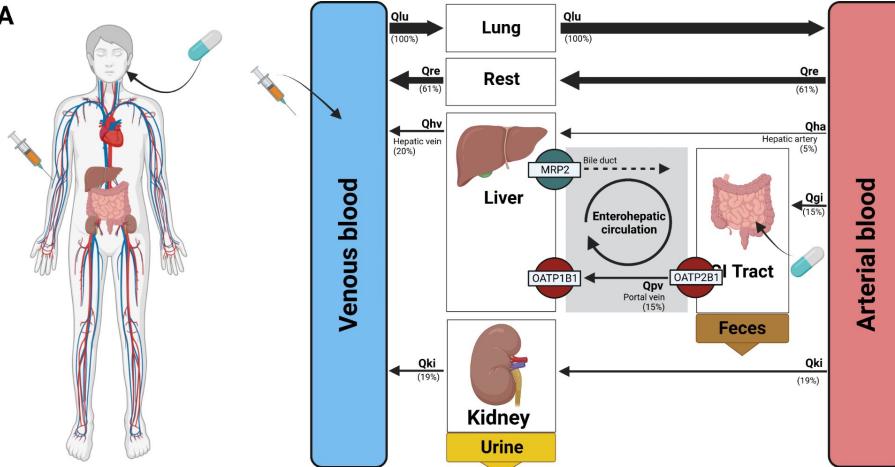
- Tissue partition coefficients
- Protein binding
- Kinetic parameter (transport & elimination)
- Blood flows, organ volumes, ...

# PBPK Applications

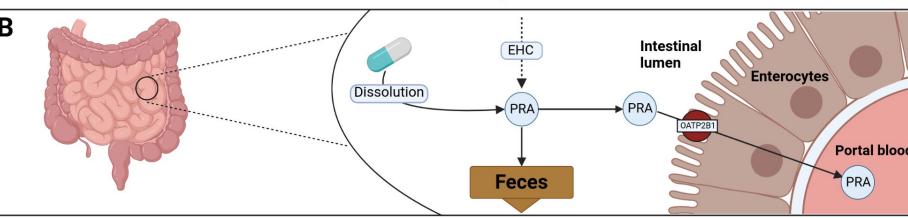


# Pravastatin - Hepatorenal impairment

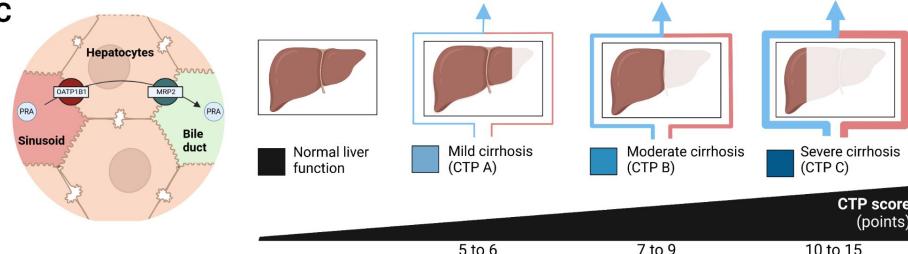
A



B



C

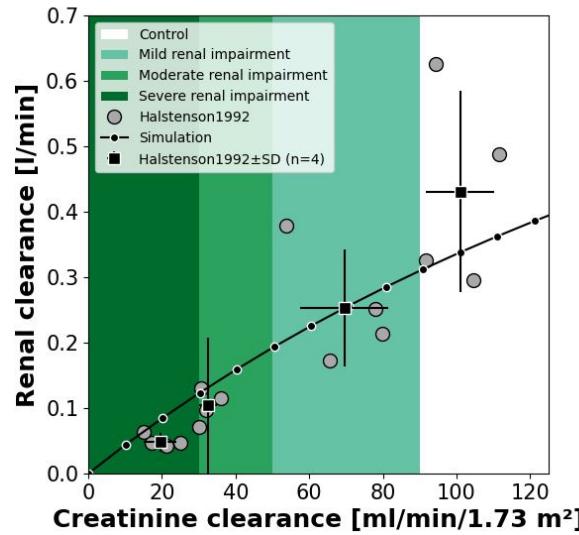
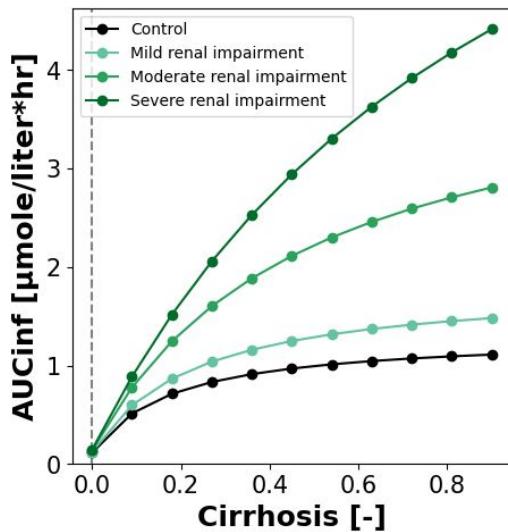
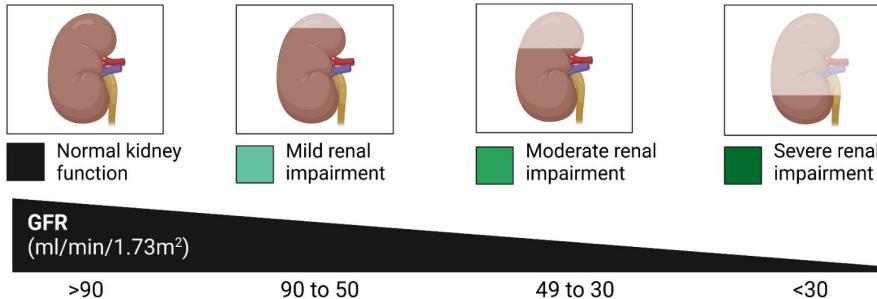
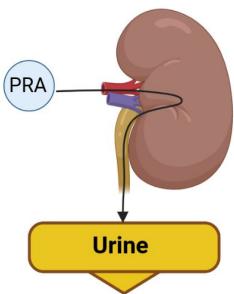


HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn,  
M.König

**A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2**

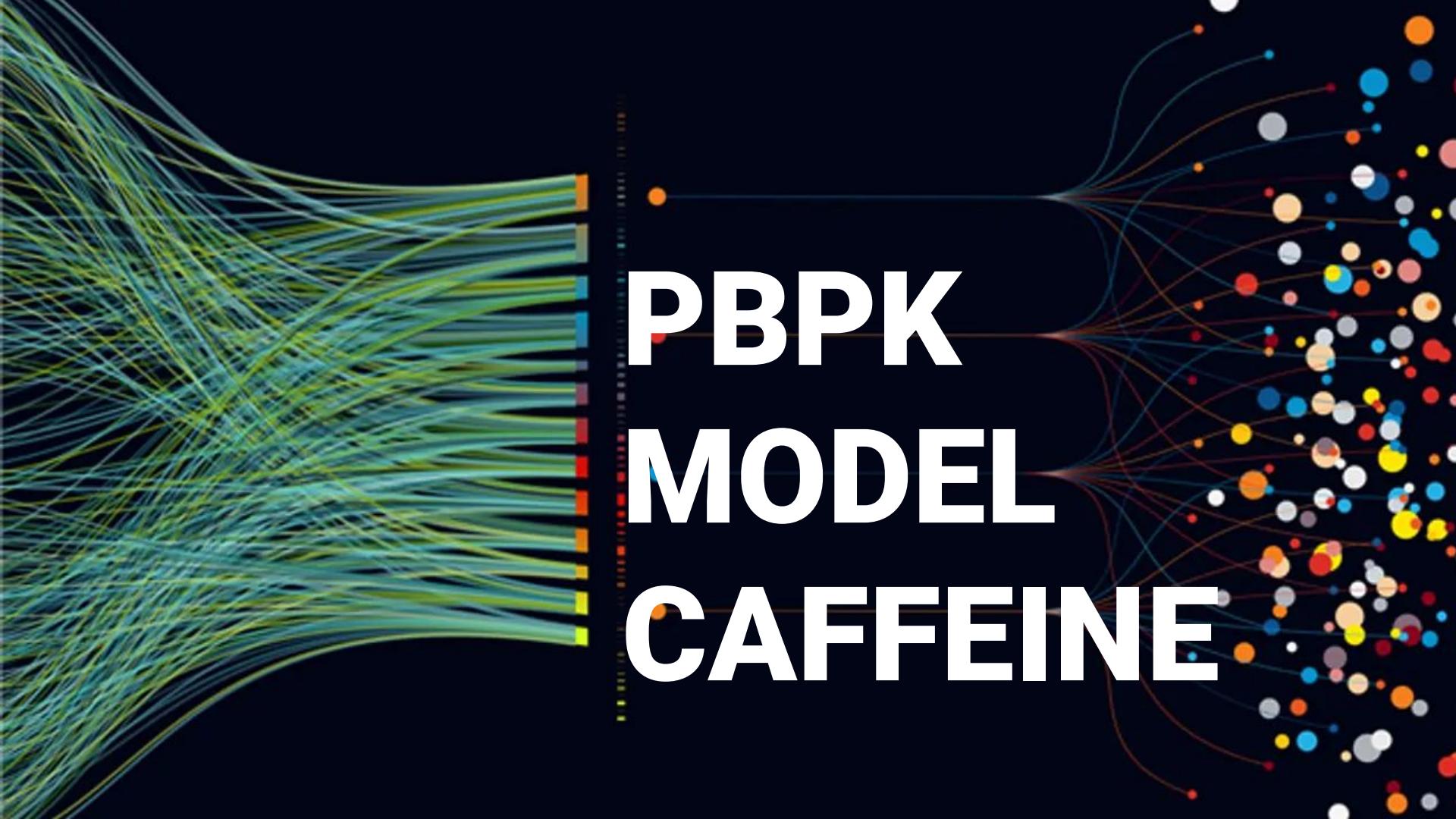
<https://www.youtube.com/watch?v=ddQYx4fGgRE>

# Pravastatin - Renal impairment



HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn,  
M.König  
**A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2**

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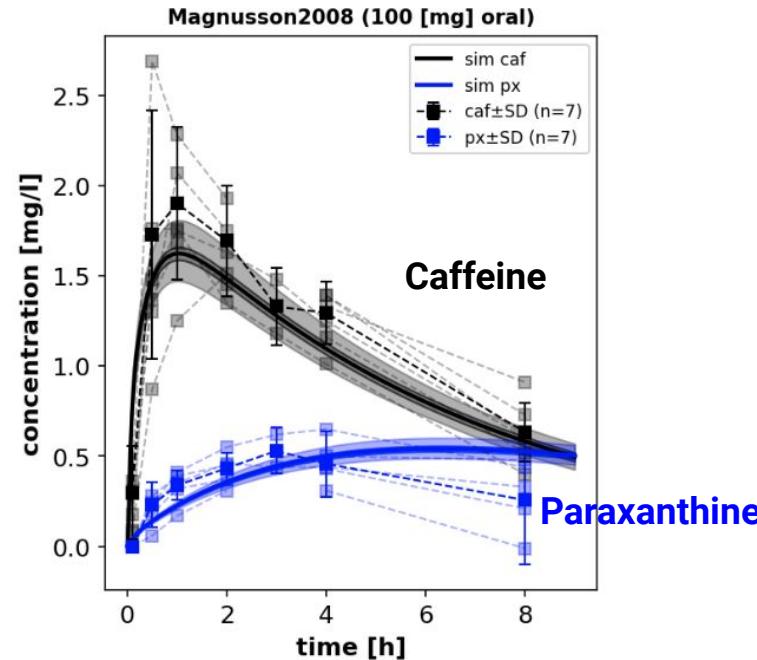
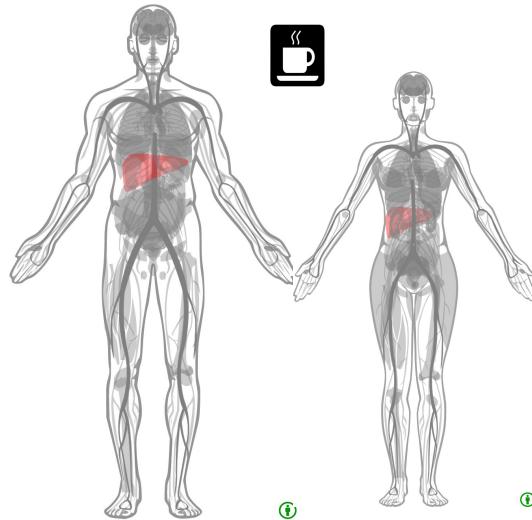


# PBPK MODEL CAFFEINE

# Pharmacokinetics of caffeine

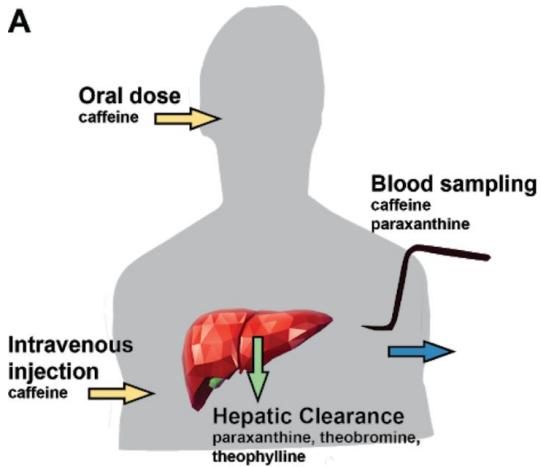
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100 mg oral caffeine

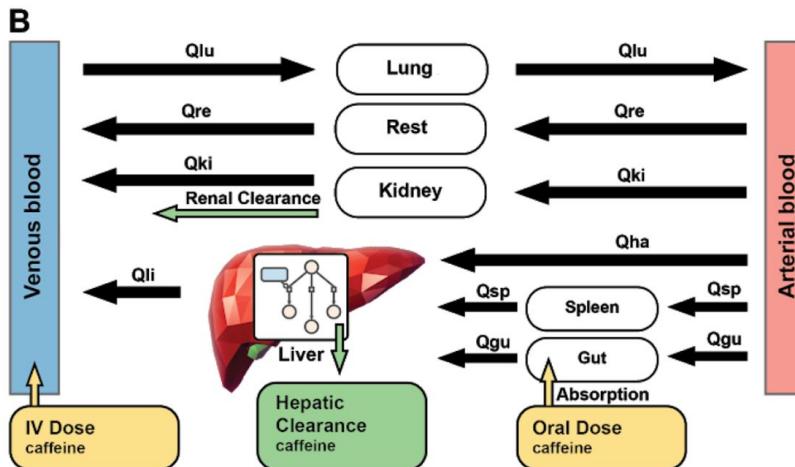


# Physiologically based caffeine model

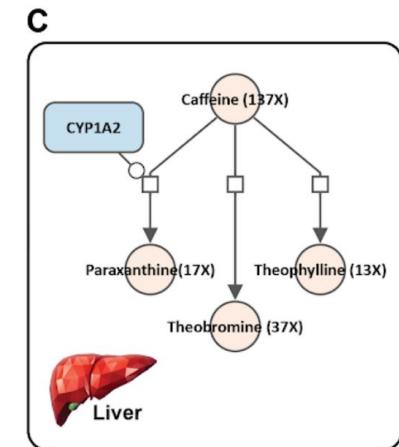
A



B



C

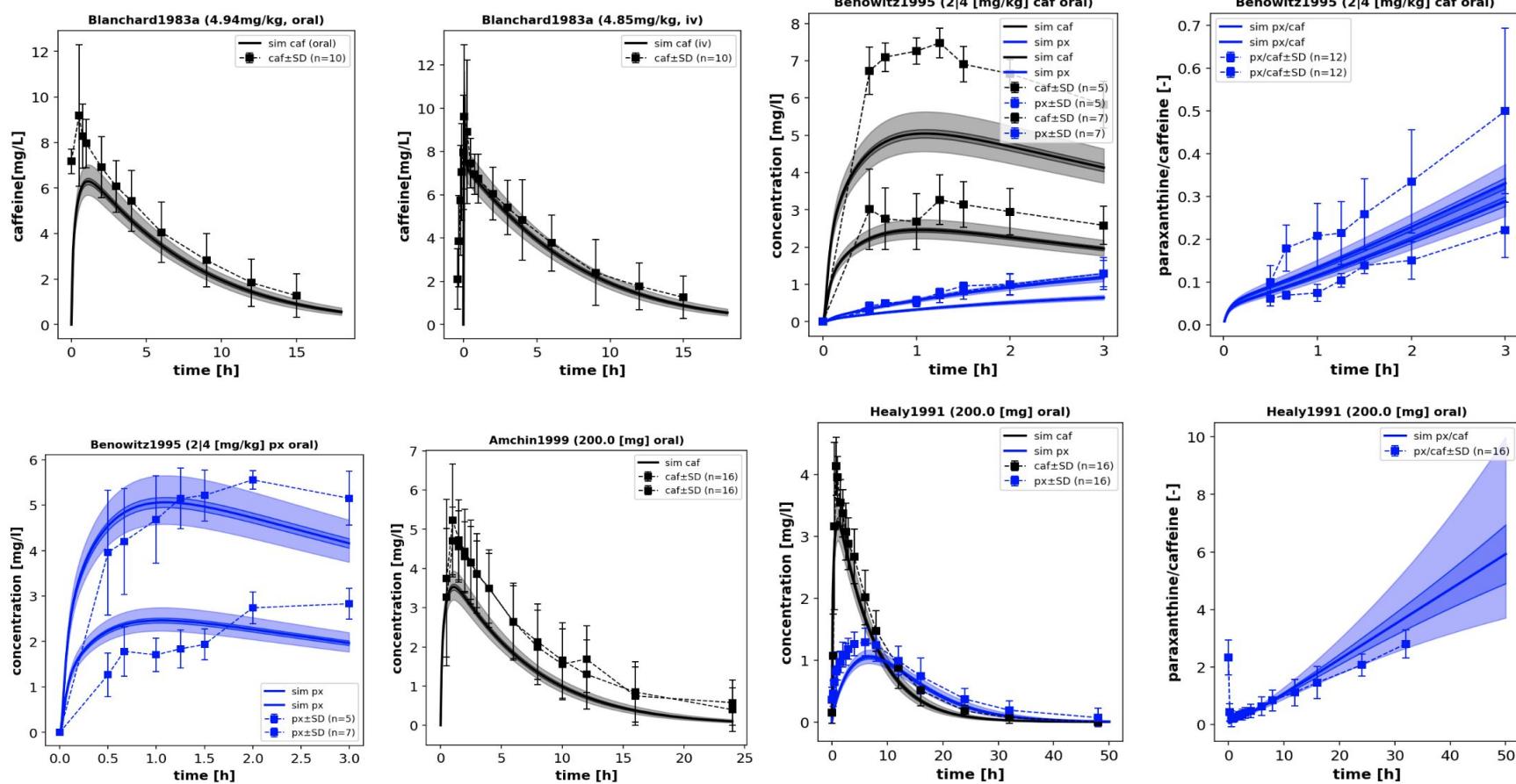


- Caffeine metabolized by **CYP1A2** to paraxanthine,
- Classical liver function test
  - Time course of caffeine
  - Caffeine/paraxanthine ratio

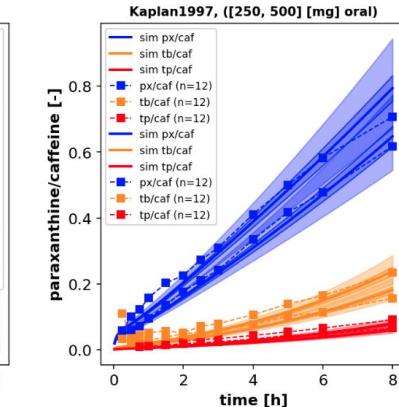
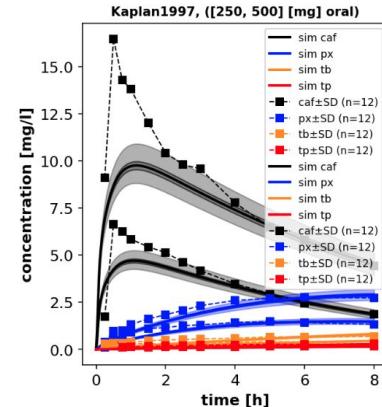
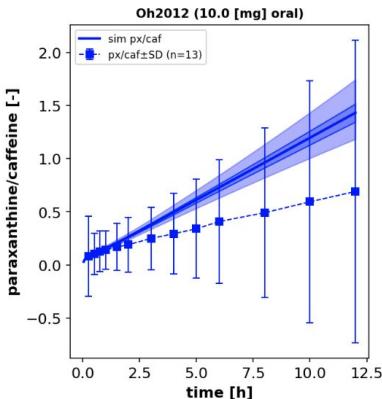
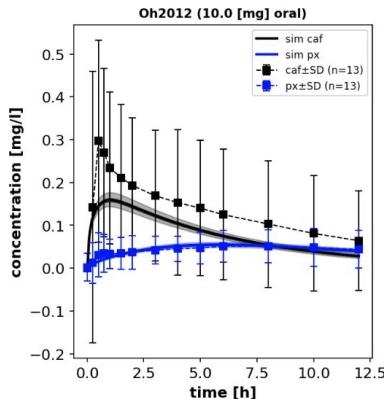
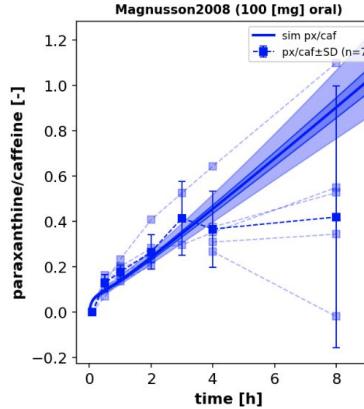
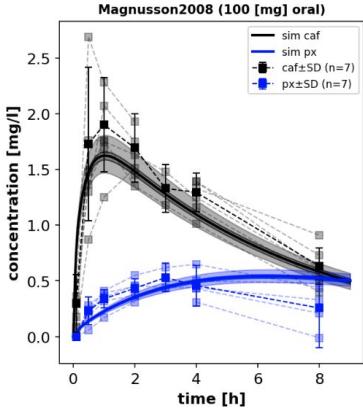
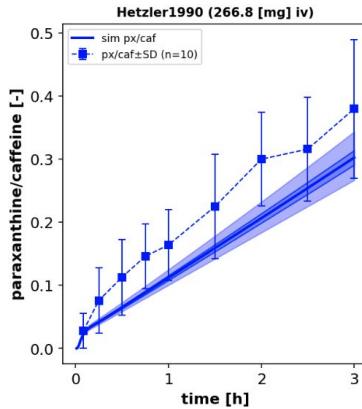
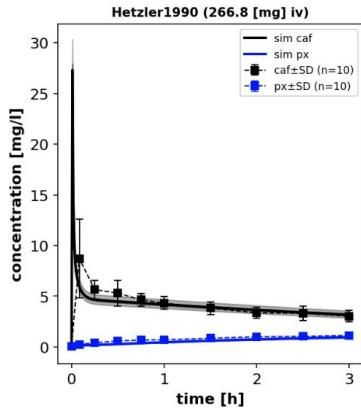
## Challenges

- Large inter-subject variability
  - Effects of lifestyle on expression (induction smoking)
  - Effects of medication (oral contraceptives)
- Dose dependency

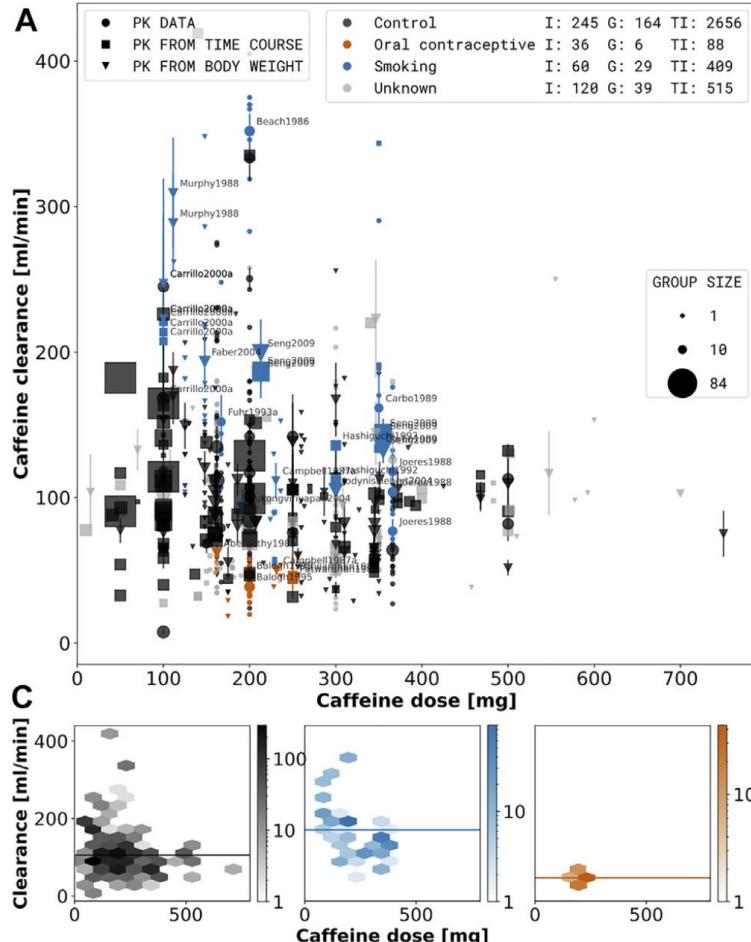
# Model performance (training)



# Model performance II (training)



# **Effect of smoking and oral contraceptives**



- Smoking induces caffeine clearance
  - oral contraceptives inhibit caffeine clearance

**control**  
**smoking**  
**oral**  
**contraceptives**

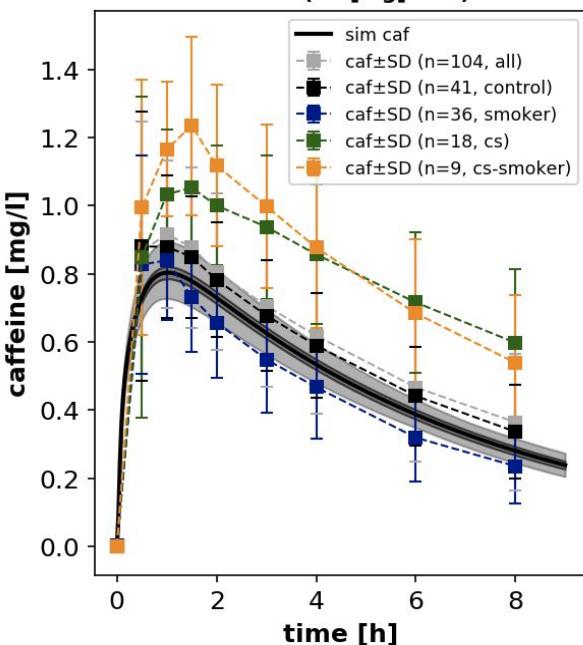
J.Grzegorzewski, F.Bartsch, A.Köller, and M.König  
***Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing***

Frontiers in Pharmacology 2022, Vol12; doi:  
[10.3389/fphar.2021.752826](https://doi.org/10.3389/fphar.2021.752826)

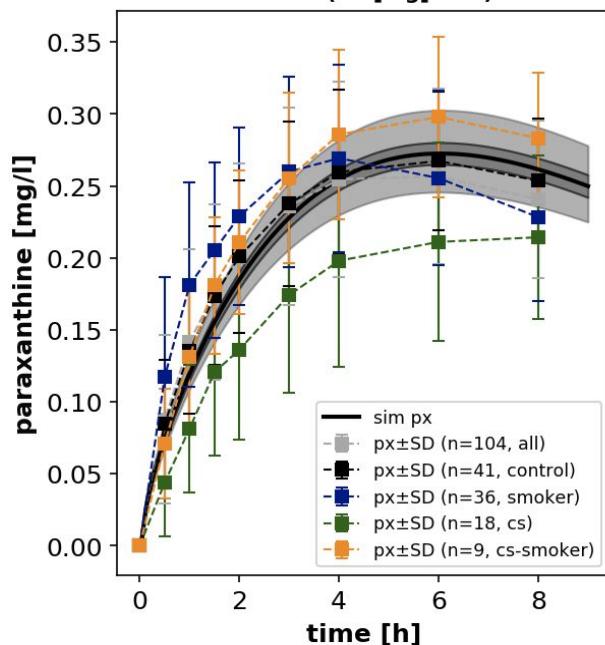
Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorsch F, Köller A, Ke DYJ, De Angelis S, König M. **PK-DB: pharmacokinetics database for individualized and stratified computational modeling**. Nucleic Acids Res. 2020 Nov; 5:gkaa990. doi: 10.1093/nar/gkaa990.

# Stratification by smoking & contraceptives

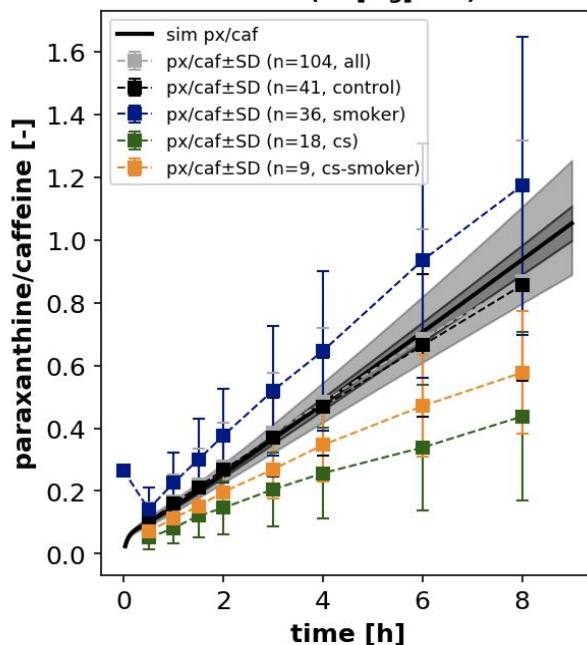
IKP243 (50 [mg] oral)



IKP243 (50 [mg] oral)



IKP243 (50 [mg] oral)



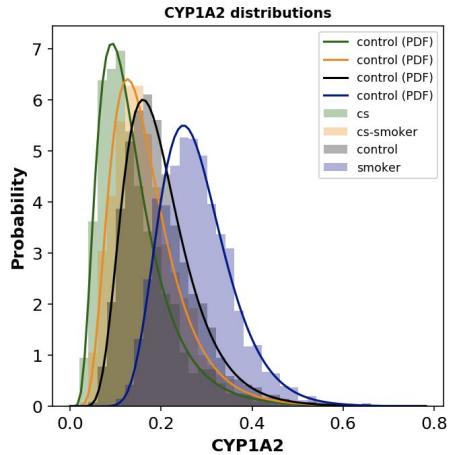
contraceptives (cs)

contraceptives-smoker (cs-smoker)

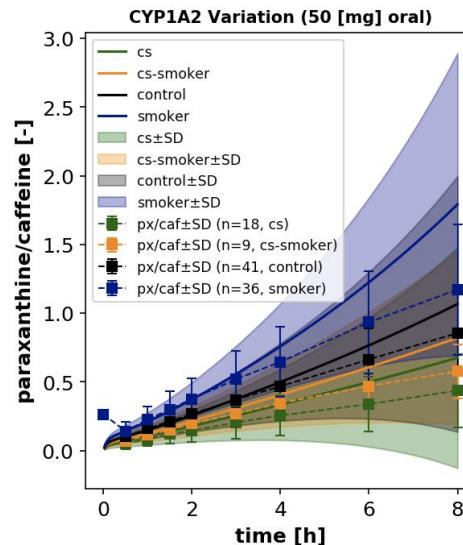
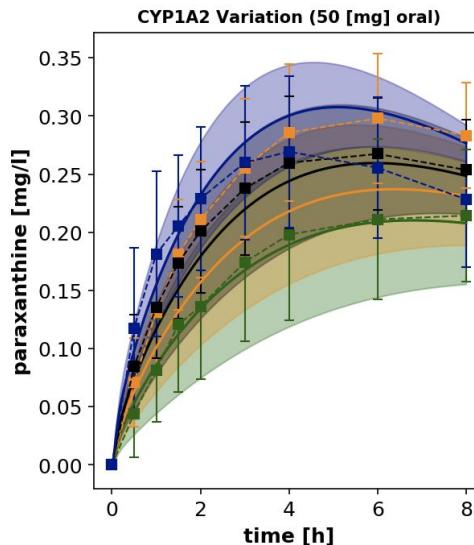
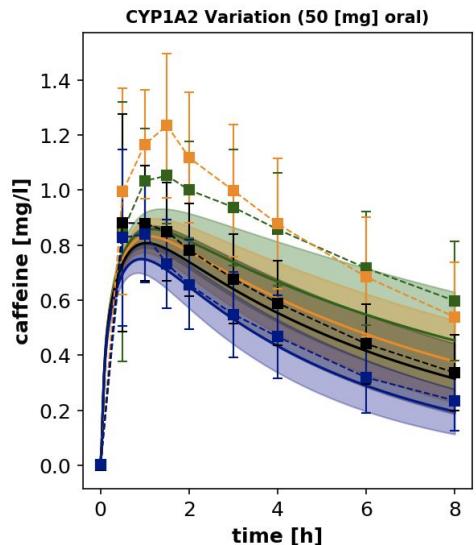
control

smoker

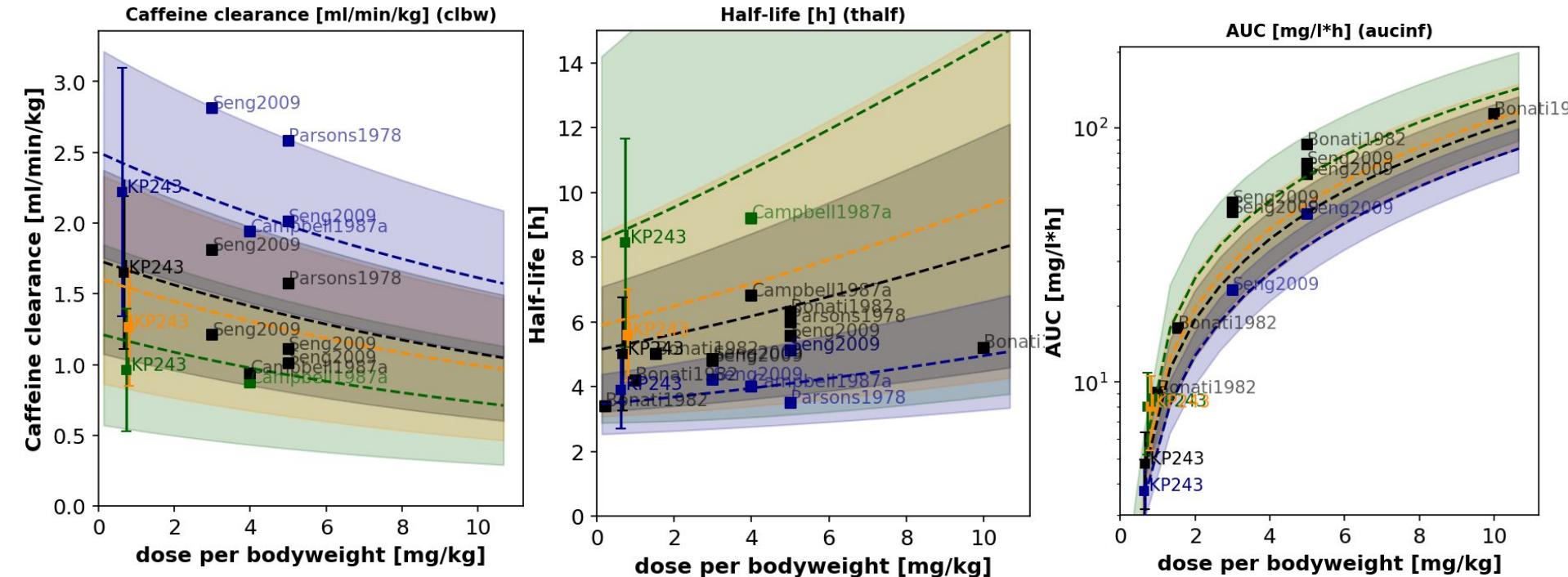
# CYP1A2 distributions



- contraceptives (cs)
- contraceptives-smoker (cs-smoker)
- control
- smoker

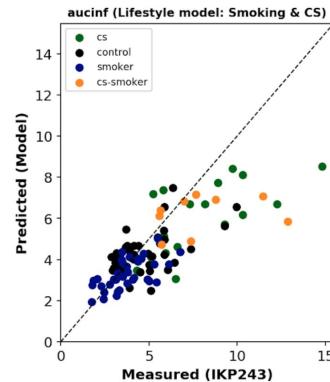
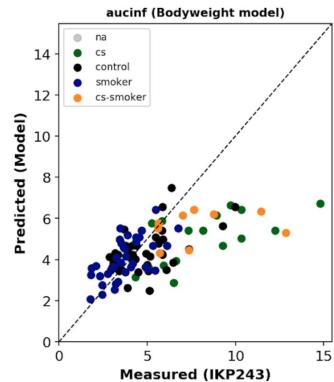
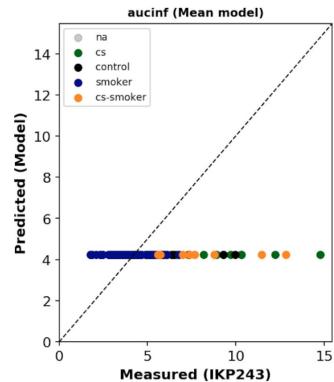
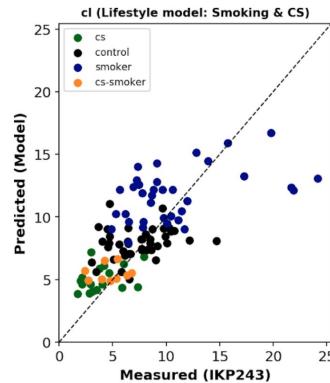
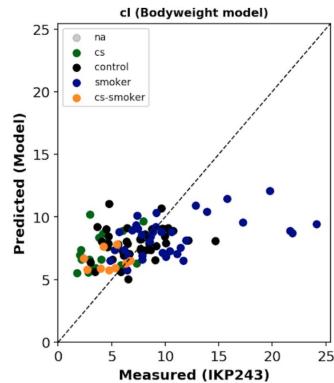
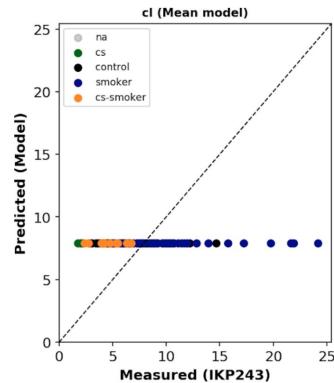


# Stratified dose-dependent pharmacokinetics (validation)



# Individualized predictions

## Clearance



mean

anthropometric

lifestyle

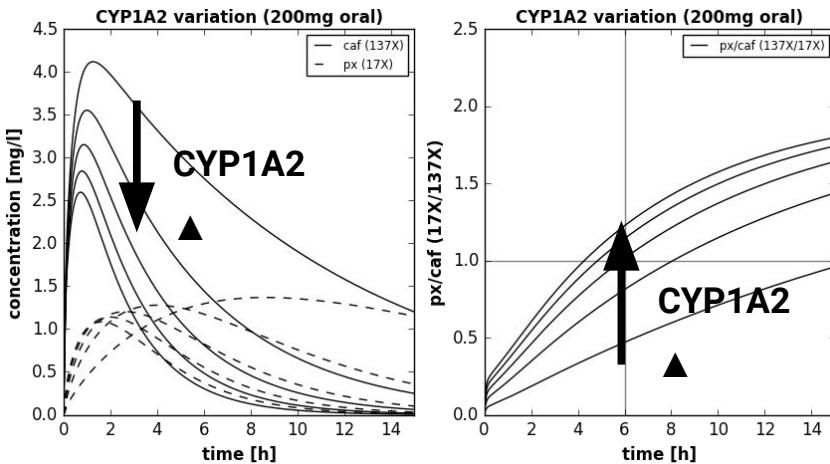
contraceptives (cs)  
contraceptives-smoker (cs-smoker)  
control  
smoker

- Improved predictions of pharmacokinetic parameters by account for individual lifestyle factors (smoking)

- Results directly transfer to all drugs metabolized via CYP1A2

# CYP1A2 & caffeine pharmacokinetics

- CYP1A2 expression altered by many lifestyle factors
- Strong effect: **Smoking**
- Altered function test results



**Table 4.** Parameter estimates of covariates obtained for logarithmic clearance values using the paraxanthine/caffeine ratio method (equation 1)

Covariate	Symbol used in equation 5	Estimate	95% Confidence interval		Mean resulting change of clearance (factor)
			Lower bound	Upper bound	
—	Intercept	0.264	-0.015	0.542	—
Coffee intake (litre day <sup>-1</sup> )	Slope <sub>coffee</sub>	0.368	0.287	0.449	1.445
Body mass index (kg m <sup>-2</sup> )	Slope <sub>BMI</sub>	-0.010	-0.018	-0.002	0.990
Cigarettes/day					
Non-smokers	$V_{smoking\ habit\ index}$	0	—	—	Reference
1–5		0.195	0.065	0.324	1.215
6–10		0.383	0.253	0.509	1.467
11–20		0.504	0.386	0.621	1.655
>20		0.543	0.430	0.655	1.721
Oral contraceptives					
No	$V_{oral\ contraceptive\ index}$	0	—	—	Reference
Yes		-0.332	-0.236	-0.428	0.717
Country					
Germany	$V_{country\ of\ residence\ index}$	0	—	—	Reference
Bulgaria		-0.209	-0.356	-0.061	0.811
Slovakia		-0.303	-0.450	-0.156	0.739
Sex					
Male	$V_{sex\ index}$	0	—	—	Reference
Female		-0.111	-0.178	-0.044	0.895

## CYP1A2 induction ▲

- Clearance ▲
- kel ▲
- T<sub>1/2</sub> ▼
- T<sub>max</sub> ▼
- px(17X)/caf(137X) ▲