Dissertation Defense
Jan Grzegorzewski

Physiologically based pharmacokinetic modeling (PBPK) for dynamical liver function tests and Cytochrome P450 (CYP) phenotyping

Chairman
Prof. Dr. Richard Kempter

Reviewer
Dr. Matthias König **(Supervisor)**
Prof. Dr. Hanspeter Herzel
Prof. Dr. Wilhelm Huisinga

Further member
Prof. Dr. Dagmar Waltemath

Date
07.07.2023

KÖNIG LAB

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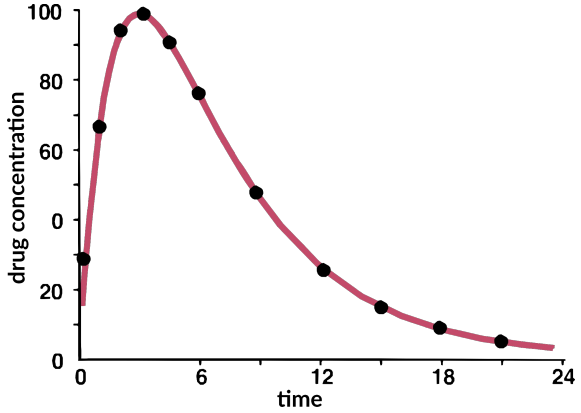
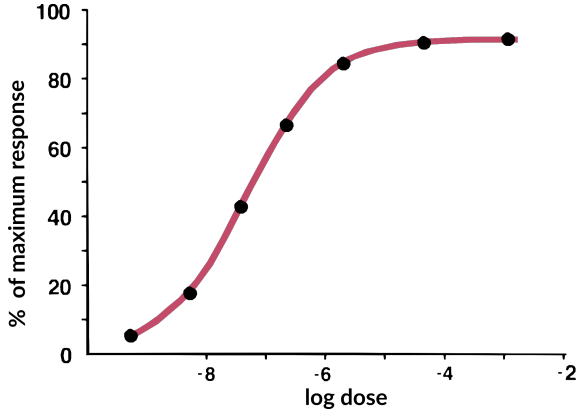
Part 1

Introduction

Pharmacokinetics (PK) & Pharmacodynamics (PD)



Pharmacokinetics is the field in which the fate of substances applied to the human body is studied.



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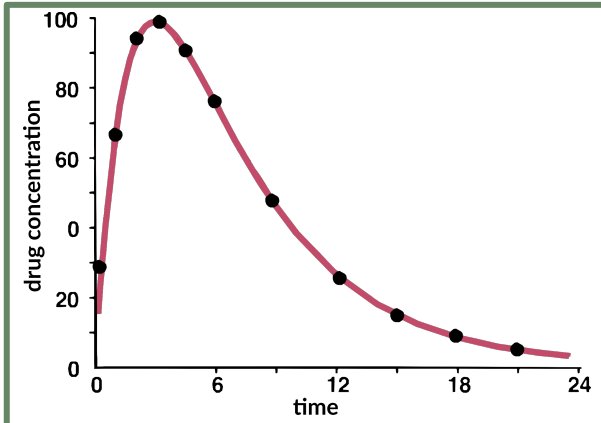
Pharmacokinetics (PK) & Pharmacodynamics (PD)



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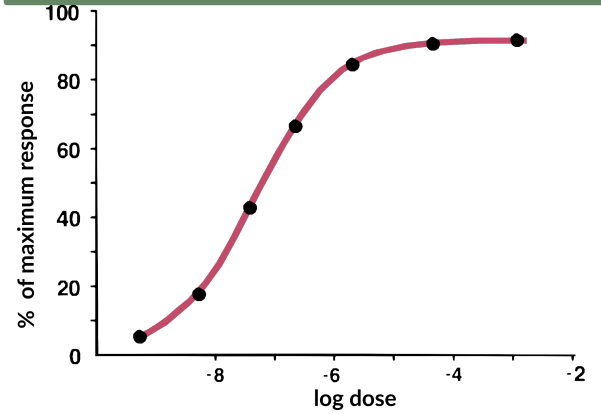
focus of the talk



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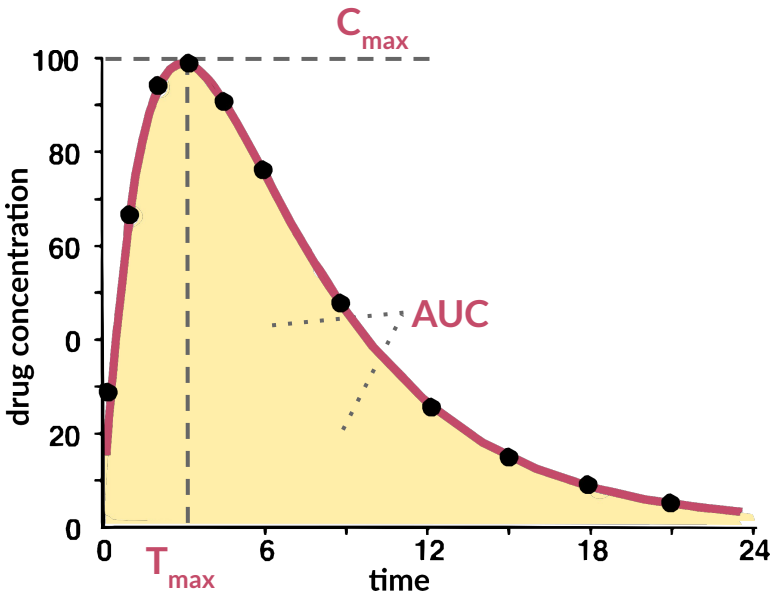
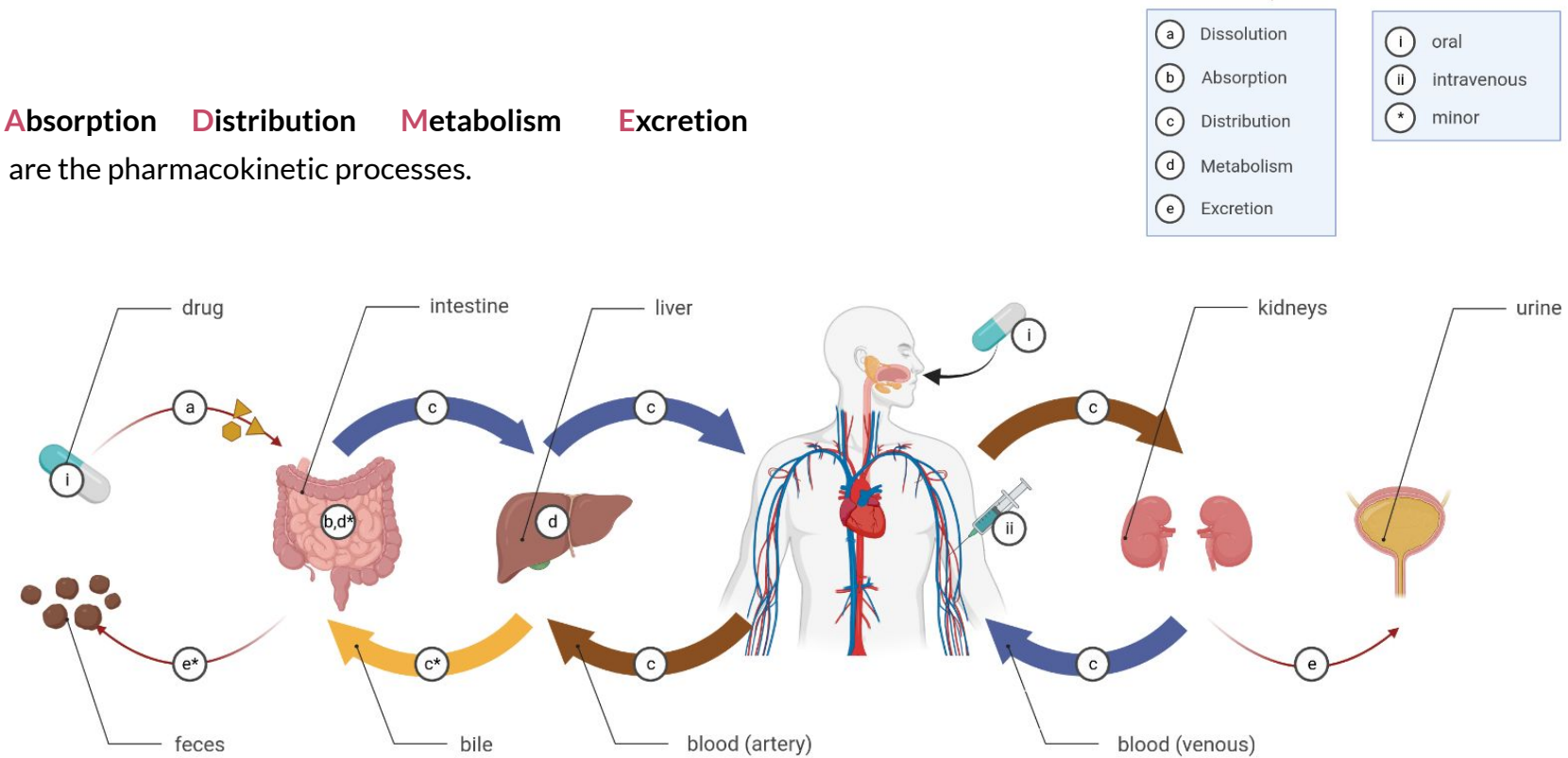
Pharmacokinetic Parameter



C_{max}	maximum concentration
T_{max}	time of maximum concentration
AUC	area under the curve
CL	clearance (=Dose/AUC, =Dose/C(0)extrapolated)
Vd	volume of distribution (= CL/k), dilution space
k_{el}	elimination rate, fitting linear part of terminal phase (log)
t_{half}	half-life (= ln2/kel) time for concentration to fall to half

ADME

Absorption **D**istribution **M**etabolism **E**xcretion
are the pharmacokinetic processes.

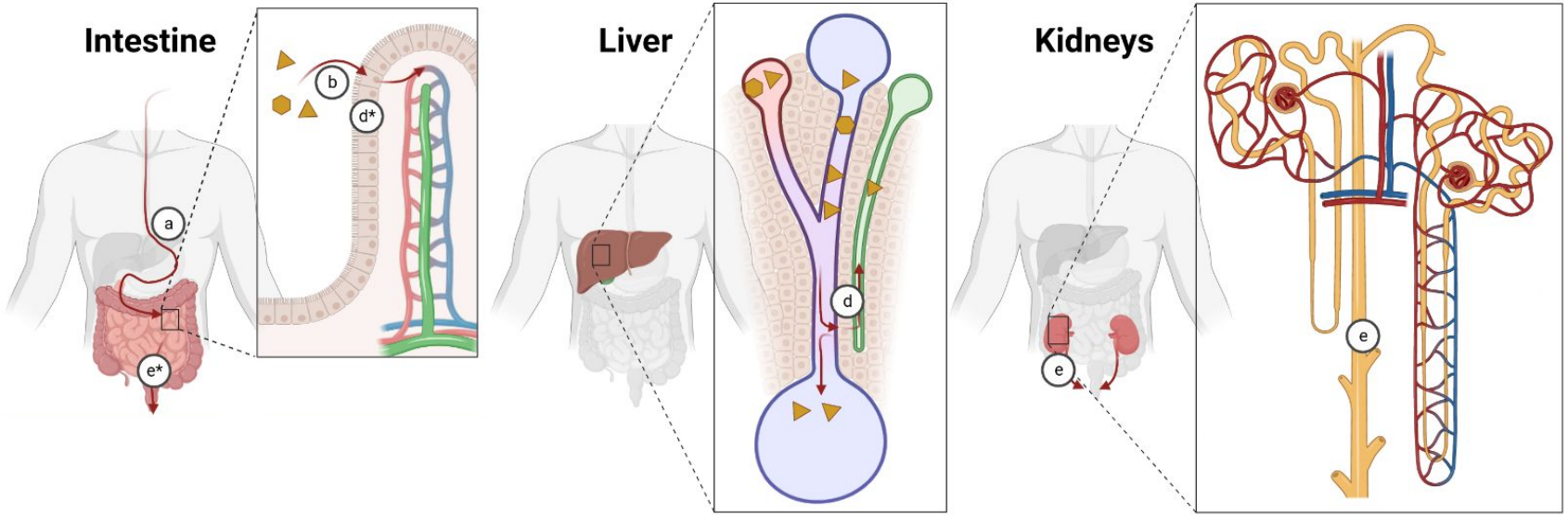


Intestine, Liver & Kidneys

The role of the three central organs which are involved in the ADME process and a schematic representation of their “functional units”.

- (a) Dissolution
- (b) Absorption
- (c) Distribution
- (d) Metabolism
- (e) Excretion

- (i) oral
- (ii) intravenous
- (*) minor



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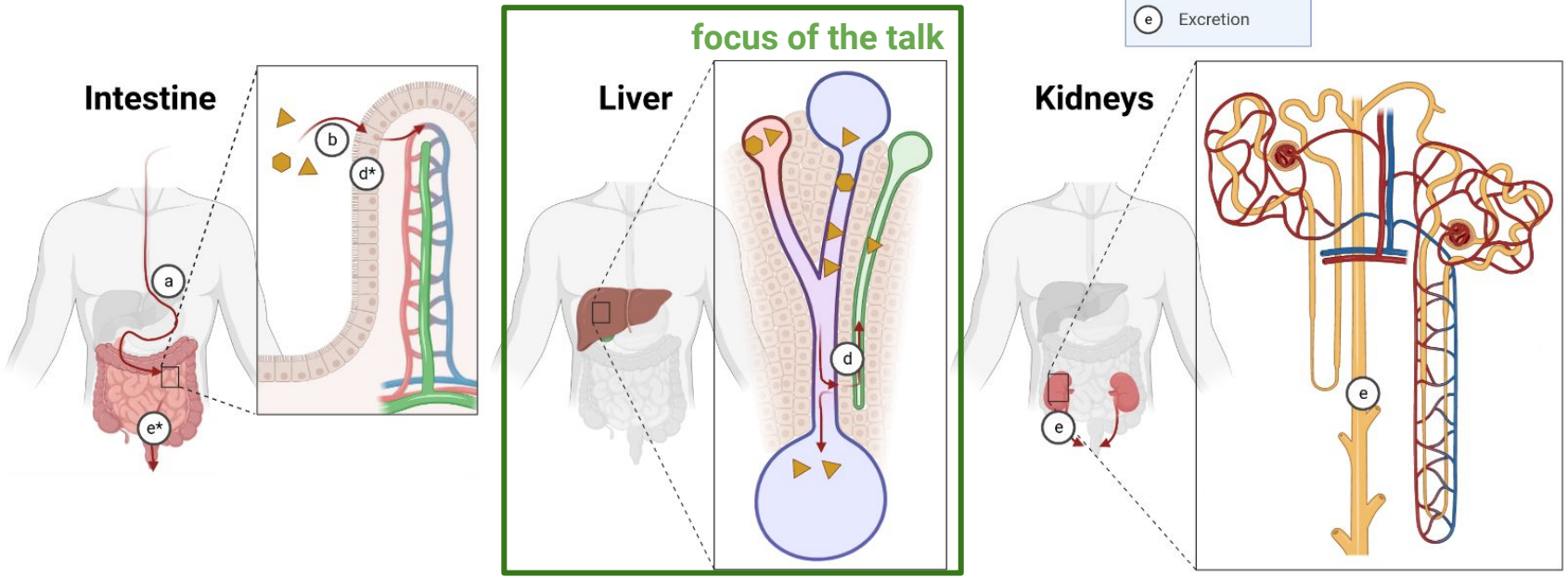
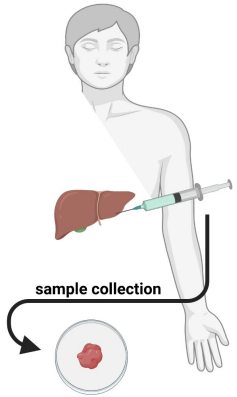
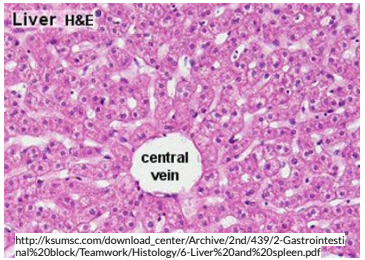


Liver Function & Health Diagnostics

Liver biopsy





- Histology (not function)
- Highly invasive
- Sampling & interobserver variability

Liver Function & Health Diagnostics

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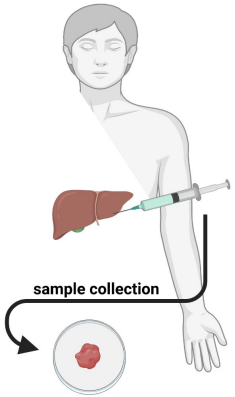

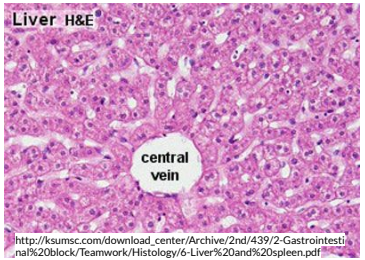

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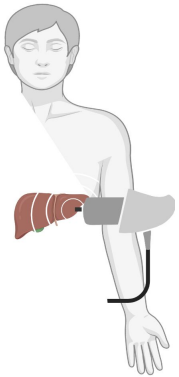
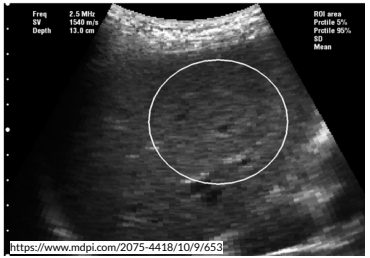
Liver elastography

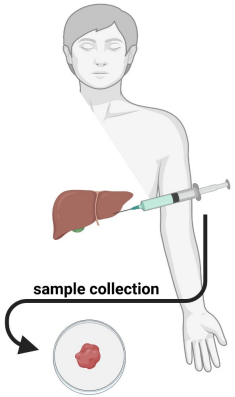


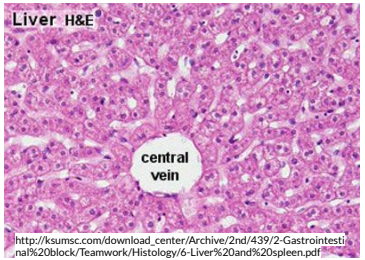


- Liver stiffness and fatty changes in your liver
- Simple and non-invasive

Liver Function & Health Diagnostics

Liver biopsy





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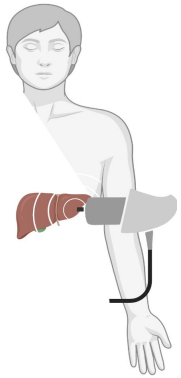

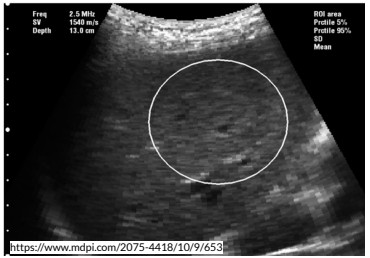

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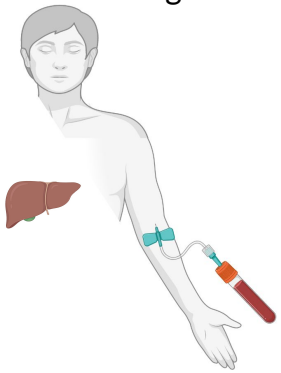
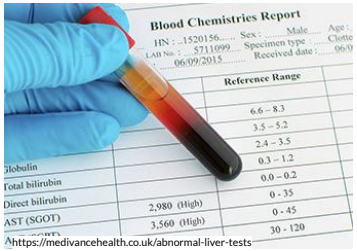
Static liver function testing



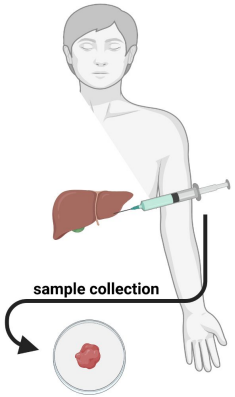


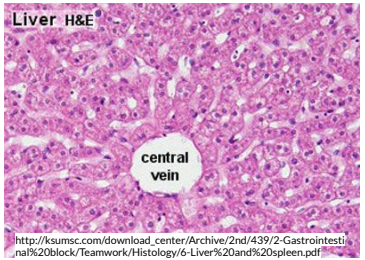
- Static biochemical parameters
- Albumin, AST, ALT, …
- Not reliable marker to quantify liver function

Liver Function & Health Diagnostics

focus of the talk

Liver biopsy





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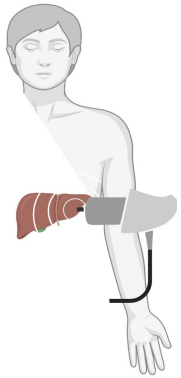

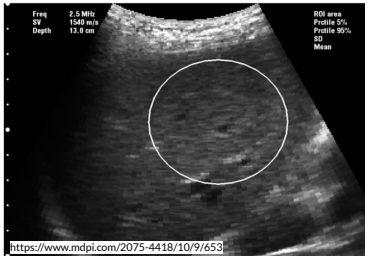

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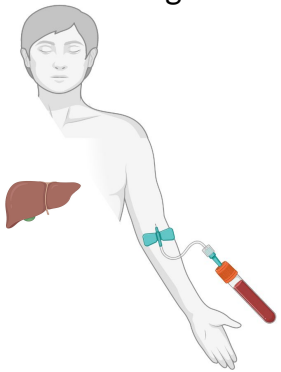

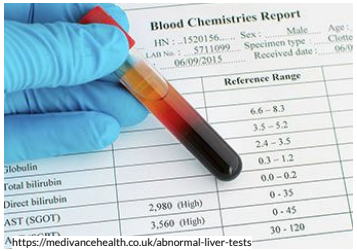

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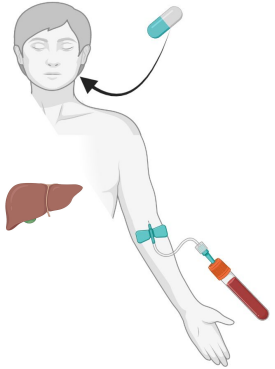
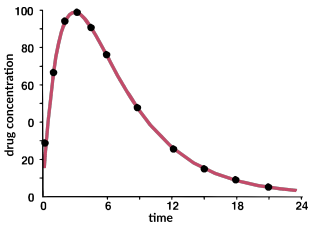
Dynamic liver function testing



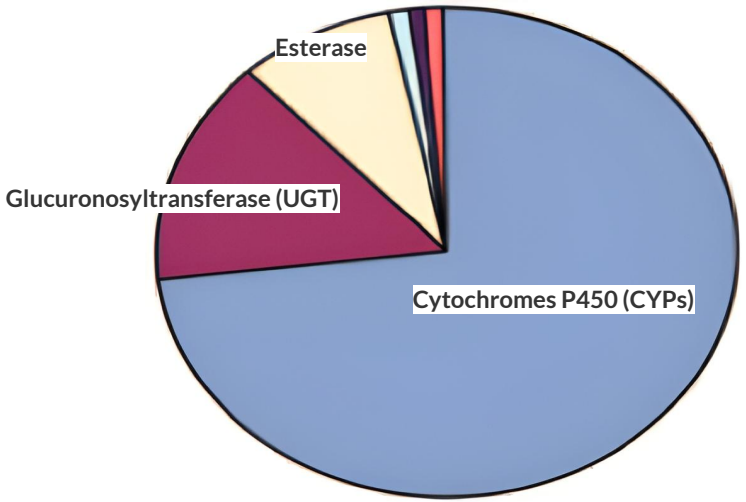


- Rate of disappearance is proxy for liver function
- Caffeine, ICG, galactose, ...
- High inter-individual variability

Cytochromes P450 (CYPs)

- CYPs located in the liver metabolize 70-80 percent of prescribed drugs
- High interindividual variation
- Highly involved in drug-drug interactions
- Important in personalized drug dosing

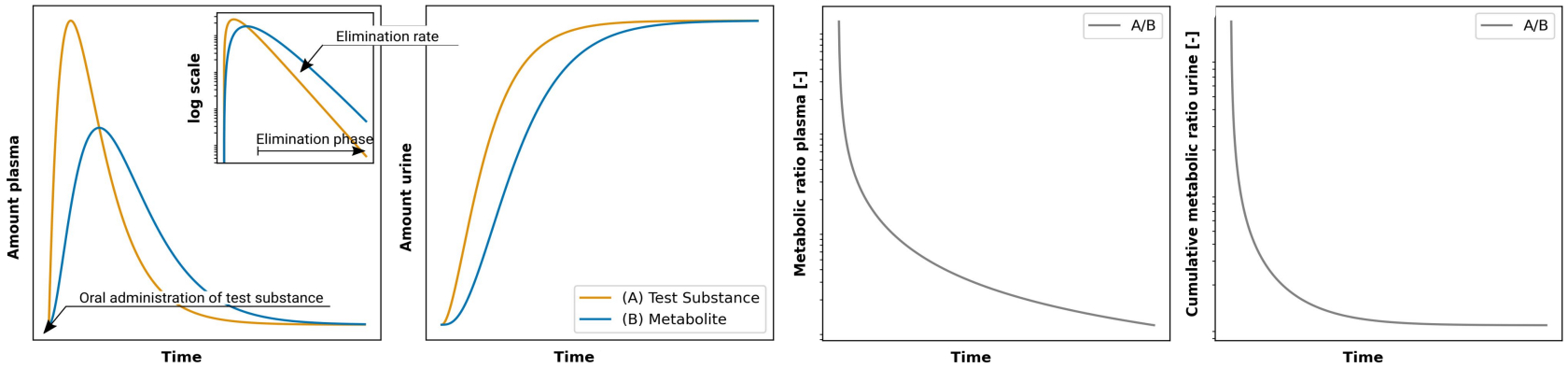
Enzymes involved in the metabolism of most drugs



Williams, J. A. (2004). *DRUG-DRUG INTERACTIONS FOR UDP-GLUCURONOSYLTRANSFERASE SUBSTRATES: A PHARMACOKINETIC EXPLANATION FOR TYPICALLY OBSERVED LOW EXPOSURE (AUCI/AUC) RATIOS. Drug Metabolism and Disposition, 32(11), 1201–1208.* doi:10.1124/dmd.104.000794

Phenotyping of CYPs

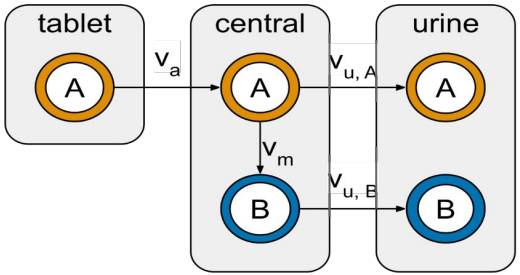
CYPs	CYP1A2	CYP3A4	CYP2C19	CYP2D6	CYP2E1
Test substance	caffeine	midazolam	omeprazol	dextromethorphan	chlorzoxazone
Metabolic ratio	caffeine / paraxanthine	1-hydroxymidazolam / midazolam	omeprazol / 5-hydroxyomeprazole	dextromethorphan / dextrorphan	6-hydroxychlorzoxazone / chlorzoxazone



Basic pharmacokinetics model

- 2 substances (A, B)
- 3 compartments (tablet, central, urine)
- Transport and reaction kinetics - irreversible mass-action

Model



System of ordinary differential equations

$$
\begin{aligned}
\frac{dA_{tablet}}{dt} &= -v_a \\
\frac{dA_{central}}{dt} &= v_a - v_m - v_{u,A} \\
\frac{dB_{central}}{dt} &= v_m - v_{u,B} \\
\frac{dA_{urine}}{dt} &= v_{u,A} \\
\frac{dB_{urine}}{dt} &= v_{u,B}
\end{aligned}
$$

$$
\begin{aligned}
v_a &= k_a \cdot A_{tablet} \\
v_m &= k_m \cdot A_{central} \\
v_{u,A} &= k_e \cdot A_{central} \\
v_{u,B} &= k_e \cdot B_{central}
\end{aligned}
$$

Rate of absorption

Rate of metabolism (A → B)

Rate of excretion of A

Rate of excretion of B

Basic pharmacokinetics model

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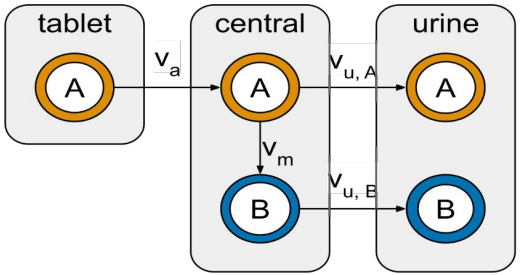

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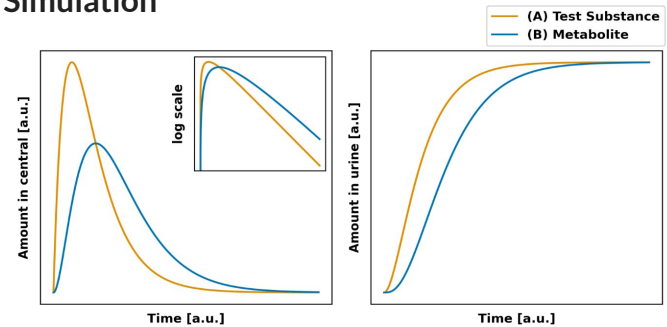
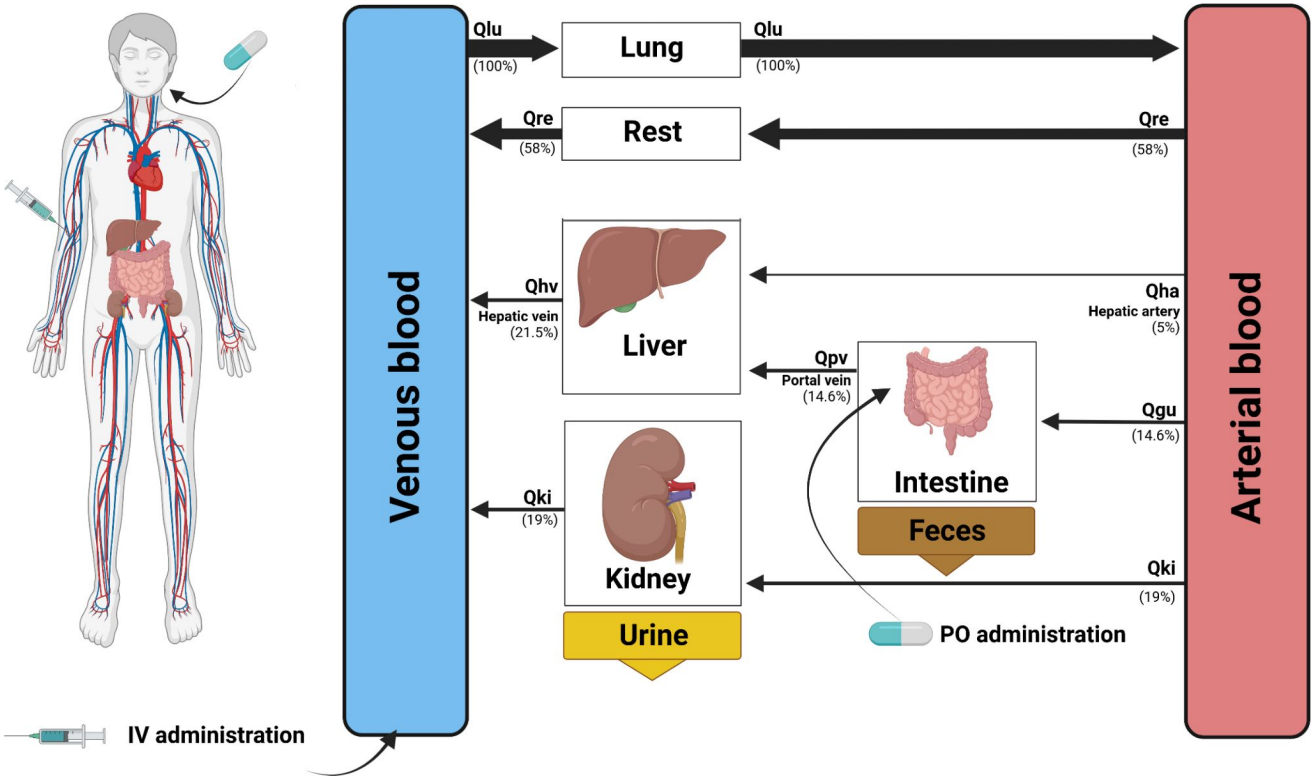
Simulation



Physiologically Based Pharmacokinetics (PBPK) Modeling



Part 2

Results and Publications

Big Picture

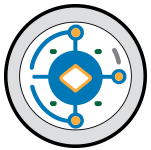
Main goal

Establish reusable workflows for physiological based pharmacokinetic (PBPK) modeling of liver function tests and CYP phenotyping.

Challenges

Standardized data

Data integration



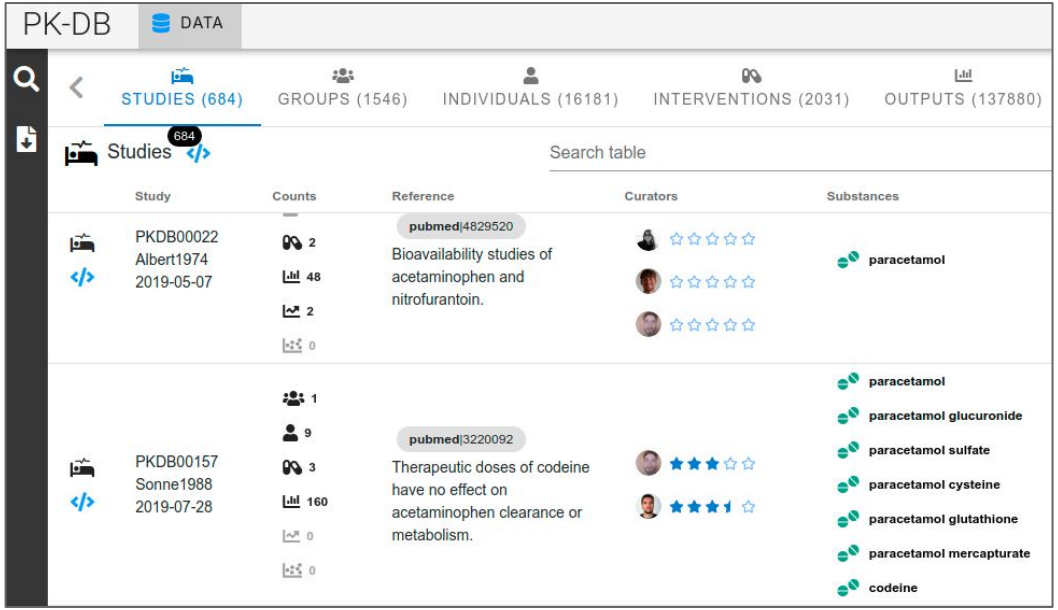
Reusable models

Standardized Data

Objectives

- A standardized format for PK data as reported in literature.
- Establish a large high-quality PK dataset on liver function testing and CYP phenotyping.

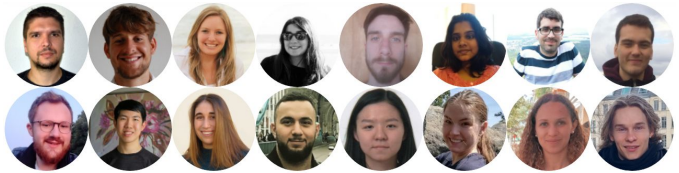
2.1 PK-DB: A Pharmacokinetics Database for Individualized and Stratified Computational Modeling (https://pk-db.com/)



Publication

Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorscht F, Köller A, Ke DYJ, De Angelis S, König M.
PK-DB: pharmacokinetics database for individualized and stratified computational modeling.
Nucleic Acids Res. 2021 Jan 8;49(D1):D1358-D1364. doi: 10.1093/nar/gkaa990. PMID: 33151297; PMCID: PMC7779054.

Curators



Funded By

Bundesministerium für Bildung und Forschung
LiSyM Liver Systems Medicine

Typical PK Publication

Our subjects were 13 normal males (age range 18 to 71 years; mean weight ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA_{12}) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

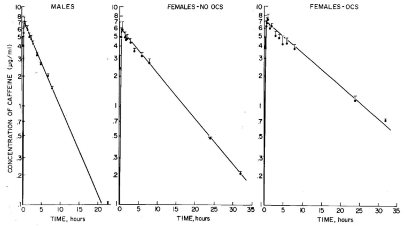
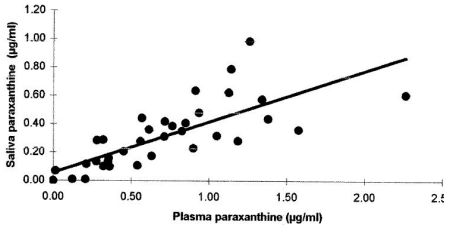


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	*Normal females taking no OCS* (n = 9)	*Normal females on OCS* (n = 9)
$t_{½(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (L/kg)	0.54 ± 0.18	0.69 ± 0.16*	0.72 ± 0.24
$Vd_{(extrap)}$ (L/kg)	0.54 ± 0.13	0.70 ± 0.14*	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 0.57	1.12 ± 0.28†

Values are mean ± S.D.
*$p < 0.05$ for normal males vs females taking no OCS.
†$p < 0.001$ for females taking no OCS vs. females on OCS.



R V Patwardhan, P V Desmond, R F Johnson, S Schenker, *The Journal of laboratory and clinical medicine, 1980-05-30*

Curated as: https:/.pk-db.com/data/PKDB00057

Typical PK Publication

Individuals

Groups

Our subjects were 13 normal males (age range 18 to 71 years; mean weight ± S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight ± S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight ± S.D. 58.4 ± 9.6 kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA_{12}) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

Intervention

After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

Time courses

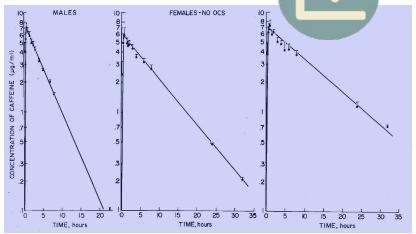


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

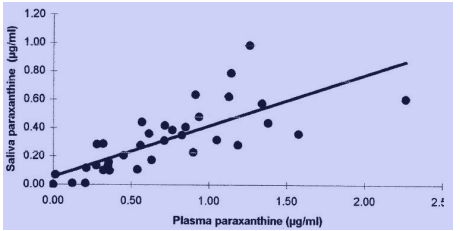
Outputs

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, [illegible] and females on OCS

	Normal males (n = 13)	*Normal females taking no OCS* (n = 9)	*Normal females on OCS* (n = 9)
$t_{½(\beta)}$ (hr)	5.5 ± 2.6	6.2 ± 1.6	10.7 ± 3.0†
$Vd_{(\beta)}$ (L/kg)	0.54 ± 0.18	0.69 ± 0.16*	0.72 ± 0.24
$Vd_{(extrap)}$ (L/kg)	0.54 ± 0.13	0.70 ± 0.14*	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	0.79 ± 0.21†
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 0.57	1.12 ± 0.28†

Values are mean ± S.D.
*$p < 0.05$ for normal males vs females taking no OCS.
†$p < 0.001$ for females taking no OCS vs. females on OCS.

Scatters

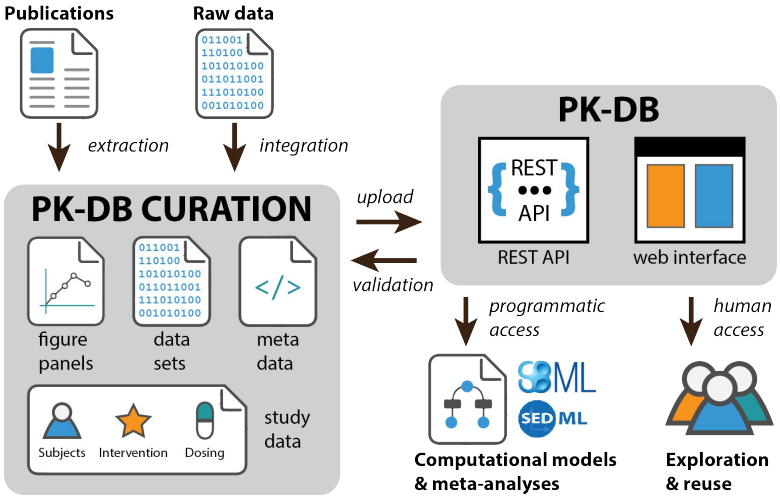


R V Patwardhan, P V Desmond, R F Johnson, S Schenker, *The Journal of laboratory and clinical medicine, 1980-05-30*

Curated as: https:/.pk-db.com/data/PKDB00057 Live demonstration

PK-DB

Overview



Content

- PK data from literature
- Enriched with metadata

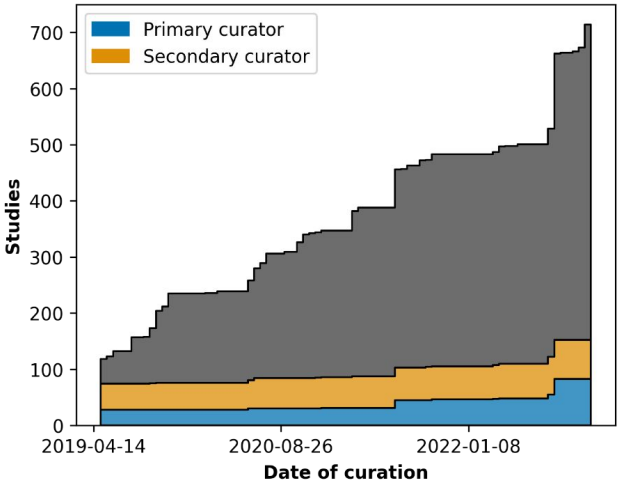
Features

- Validation of curation quality
- Automatic PK parameter calculation
- FAIR, ontologies, REST API, …

PK-DB

- Largest openly available high quality dataset on in vivo pharmacokinetics 🎉
- >10 substances for liver function and CYP phenotyping 🎉
- 22 citations 🎉

Studies in PK-DB



Studies related to liver function and phenotyping

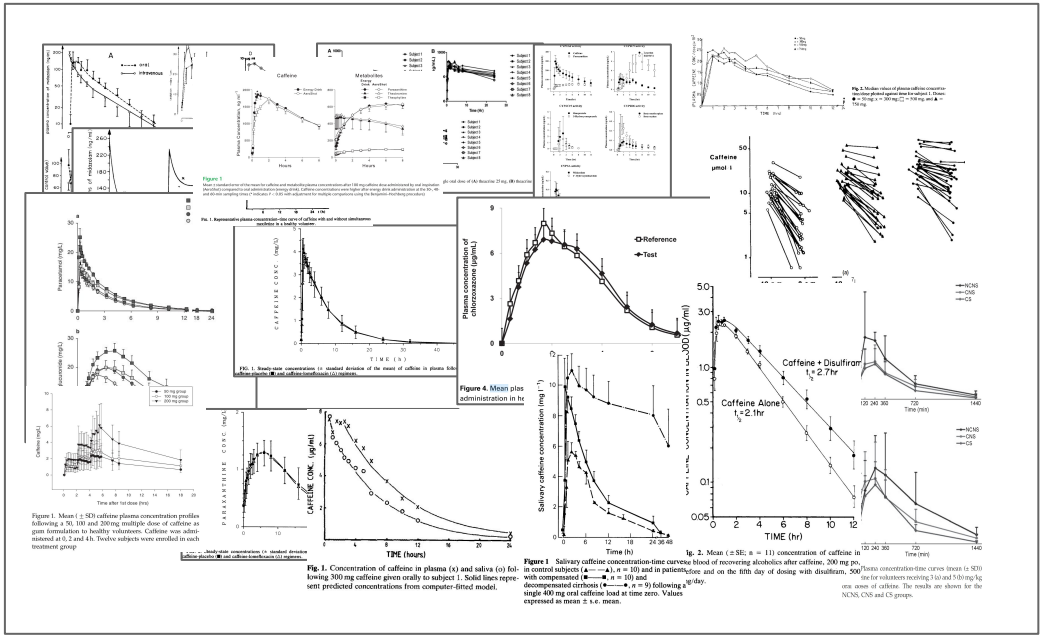
Test substance	Primary proteins	PK-DB studies
caffeine	CYP1A2 (P05177)	147
chlorzoxazone	CYP2E1 (P05181)	23
codeine / morphine	CYP2D6 (P10635)	42/12
dextromethorphan	CYP2D6 (P10635) CYP3A4/5 (P08684, P20815)	51
diazepam	CYP3A4/5 (P08684, P20815)	28
galactose	galactokinase (P51570)	3
indocyanine green (ICG)	OATP1B3 (Q9NPD5)	51
metoprolol	CYP2D6 (P10635)	13
midazolam	CYP3A4/5 (P08684, P20815)	65
omeprazole	CYP2C19 (P33261)	16
pravastatin	OATP1B1 (Q9Y6L6)	33
simvastatin	CYP3A4/5 (P08684, P20815) OATP1B1 (Q9Y6L6)	48
talinolol	P-glycoprotein (P08183)	13
torasemide	CYP2C8 (P10632) CYP2C9 (P11712)	18

Data Integration

Objectives

- Integrate PK-DB data on CYP phenotyping and liver function.
- Analyse reporting quality of CYP phenotyping and liver function.

2.2 Pharmacokinetics of Caffeine: A Systematic Analysis of Reported Data for Application in Metabolic Phenotyping and Liver Function Testing



Publication

Grzegorzewski, J., Bartsch, F., Köller, A., & König, M. (2022). Pharmacokinetics of Caffeine: A Systematic Analysis of Reported Data for Application in Metabolic Phenotyping and Liver Function Testing.
Frontiers in Pharmacology, 12, 752826., doi: 10.3389/fphar.2021.752826

Authors

Funded By

Bundesministerium für Bildung und Forschung

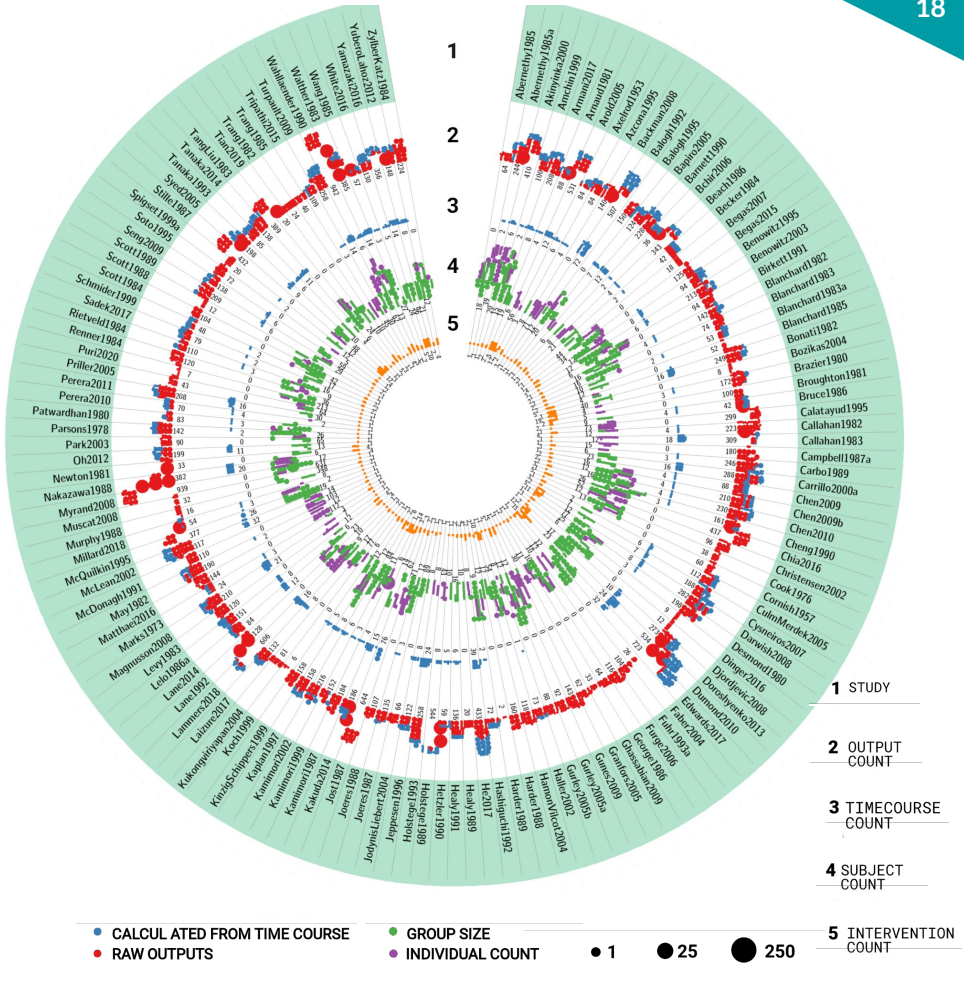
QuaLi PerF

Dataset & Reporting

- 141 studies

- Main study designs:
  a. Case-control (64 out of 141).
  b. Crossover (33 out of 141).
  c. Screening Studies (42 out of 141).

- Low quality individual participant data (78 out of 141)
- High quality individual participant data (6 out of 141)
- Group level data (57 out of 141)



Meta-Analysis

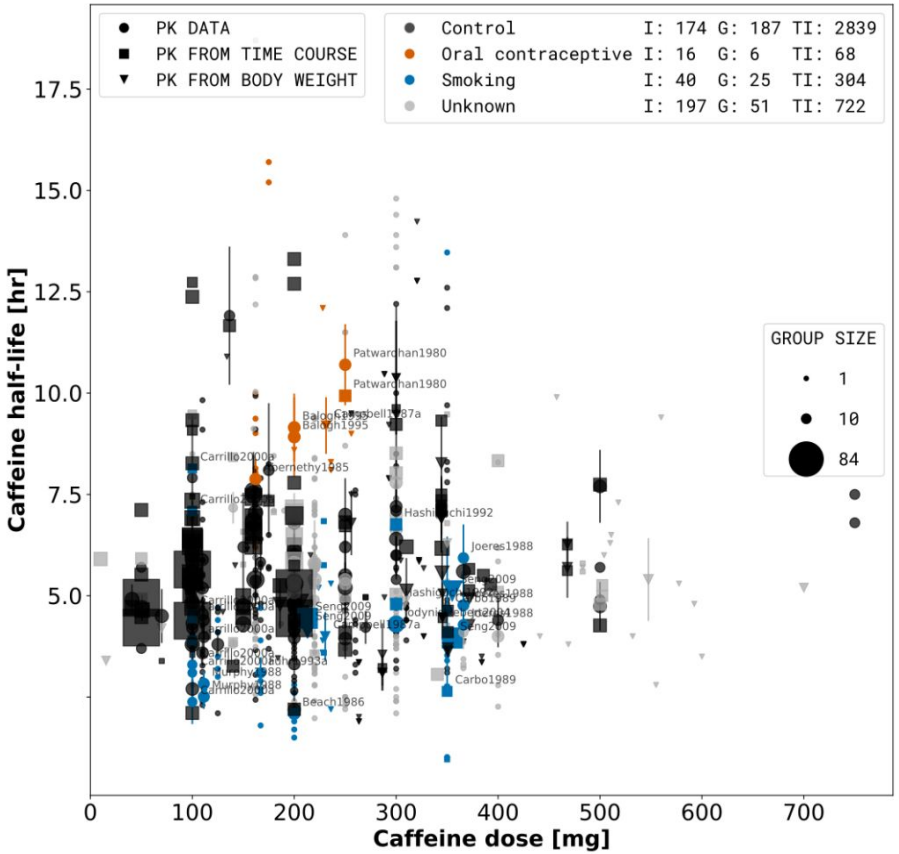
Smoking and oral contraceptives

- Range of caffeine half-lifes [2-15] hr
- Average caffeine half-lifes:

  smoking 4.1hr,

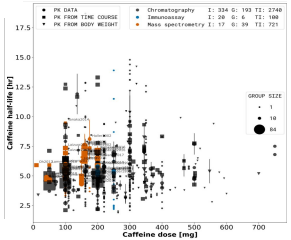
  control 5.7hr,

  oral contraceptives 9.3hr



Further Meta-Analyses on Caffeine PK

- Impact of quantification method



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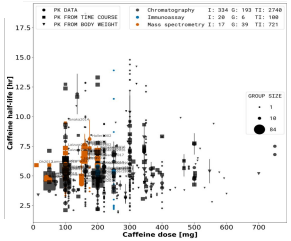
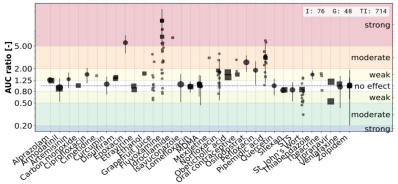


- Drug-drug interactions:

  ↔ most substances

  ↓ enoxacin, fluvoxamine, Idrocilamide*, norfloxacin, osilodrostat, pipemidic acid

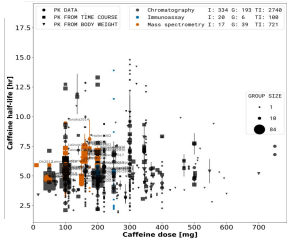
  ↑ tipranavir*



*interaction missing in go.drugbank.com

Further Meta-Analyses on Caffeine PK

- Impact of quantification method



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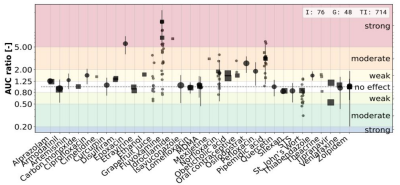
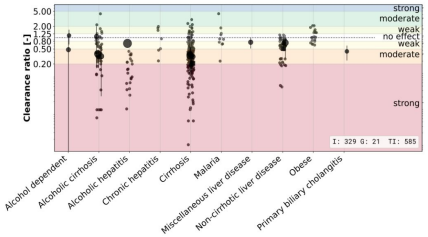


*interaction missing in go.drugbank.com

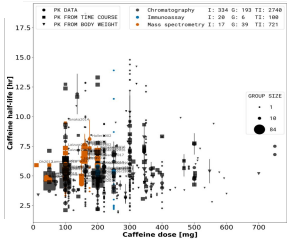
- Drug-disease interactions:

  ↓ disease of liver



Further Meta-Analyses on Caffeine PK

- Impact of quantification method



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  ↔ most substances

  ↓ enoxacin, fluvoxamine, Idrocilamide*, norfloxacin, osilodrostat, pipemidic acid

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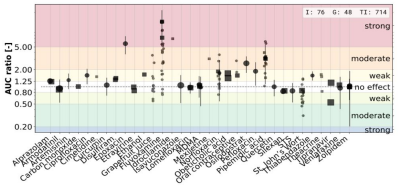
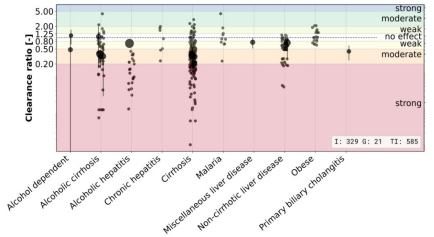
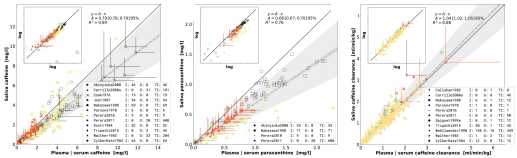




- Drug-disease interactions:

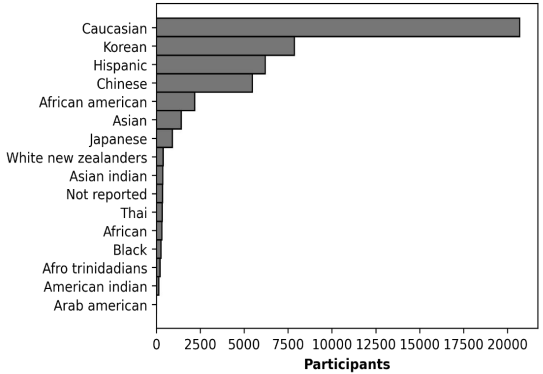
  ↓ disease of liver

- Saliva as sampling side



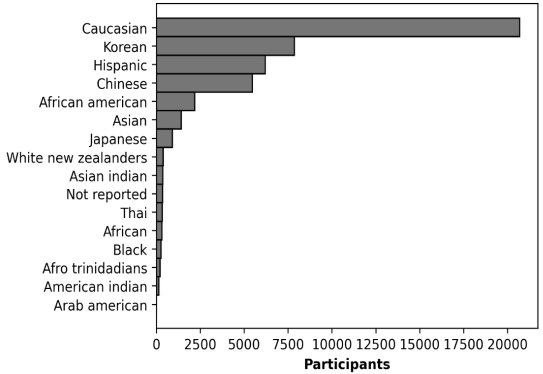
Bias in PK literature

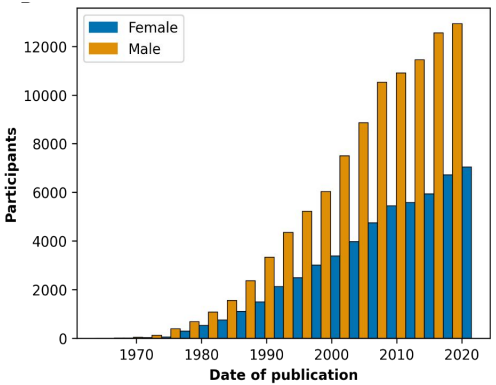
- Caucasians overrepresented



Bias in PK literature

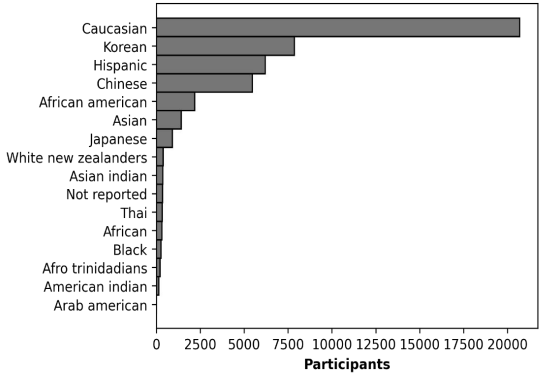
- Caucasians overrepresented
- Males overrepresented

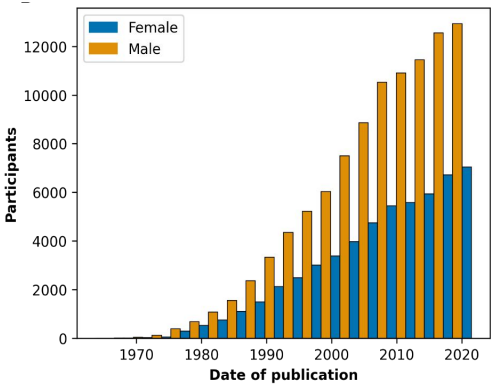


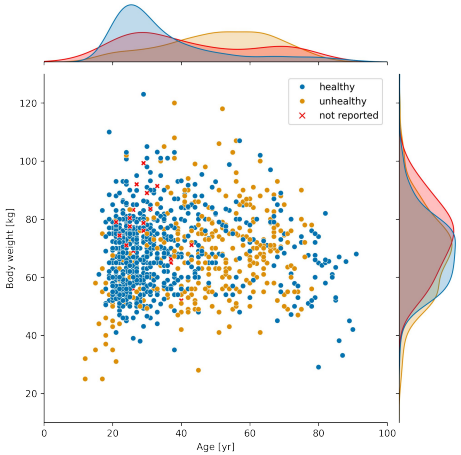


Bias in PK literature

- Caucasians overrepresented
- Males overrepresented
- Healthy ≈ 20 years younger than non-healthy







Outcome

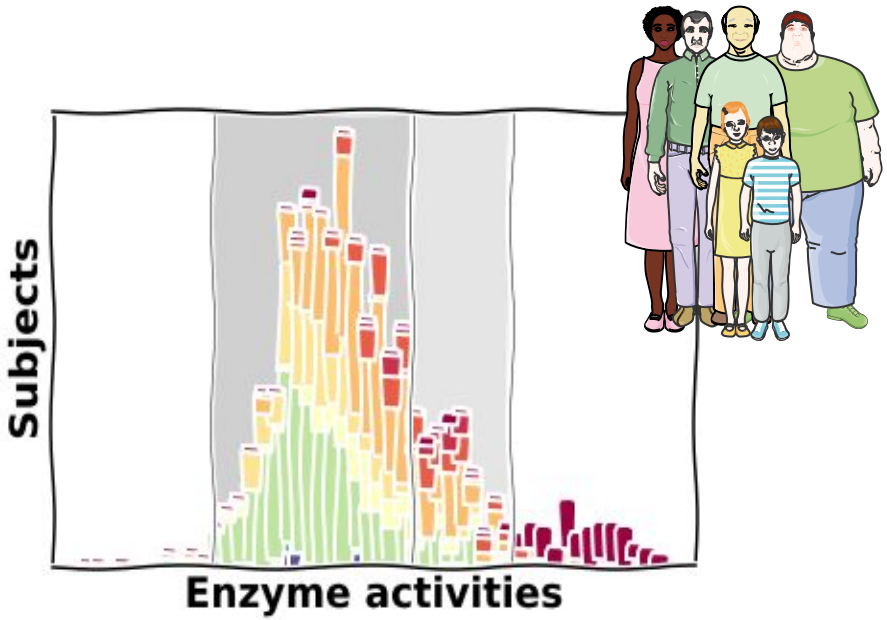
- Largest openly available PK dataset on in vivo caffeine 🎉
- Analysis of a wide set of PK related scientific questions 🎉
- 14 citations 🎉

Reusable models

Objective

- Calibration & validation of PBPK models for phenotyping and liver function testing.

Physiologically Based Pharmacokinetic (PBPK) Modeling of the Role of CYP2D6 Polymorphism for Metabolic Phenotyping with Dextromethorphan



Publication

Grzegorzewski, J., Brandhorst, J., & König, M. (2022). Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan. Frontiers in Pharmacology, 13, 1029073. ; DOI: 10.3389/fphar.2022 ; PMID: 1029073

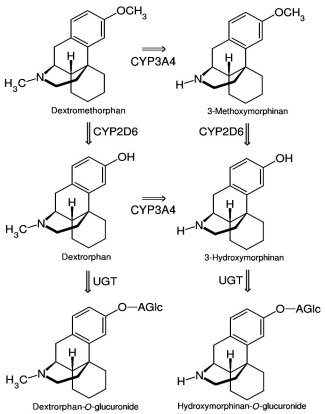
Authors

Funded By

Bundesministerium für Bildung und Forschung
QuaLi PerF
DFG Deutsche Forschungsgemeinschaft German Research Foundation

Literature Research

Metabolic pathway of dextromethorphan



Strauch K, Lutz U, Bittner N, Lutz WK (August 2009). "Dose-response relationship for the pharmacokinetic interaction of grapefruit juice with dextromethorphan investigated by human urinary metabolite profiles". *Food and Chemical Toxicology*. **47** (8): 1928–35. doi:10.1016/j.fct.2009.05.004. PMID 19445995.

Literature Research

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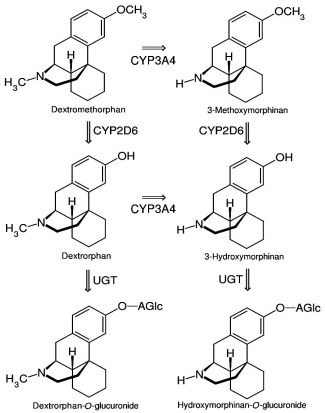

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CYP2D6 Polymorphism

Activity Value	Allele
0	*3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, …
0.25	*10
0.5	*9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59
1	*1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53,
>1	*1x2, *1x>2, *2x2, *1x>3, …

[M. Whirl-Carrillo[1], R. Huddart[1], L. Gong, K. Sangkuhl, C.F. Thorn, R. Whaley and T.E. Klein. "An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine" *Clinical Pharmacology & Therapeutics* (2021) online ahead of print.

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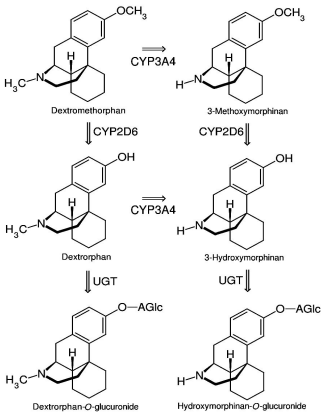

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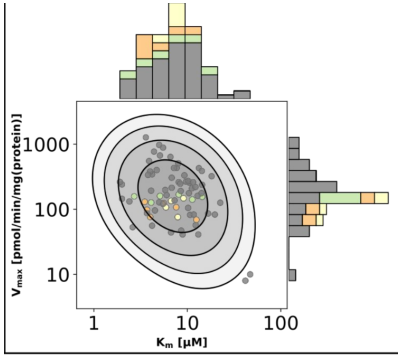
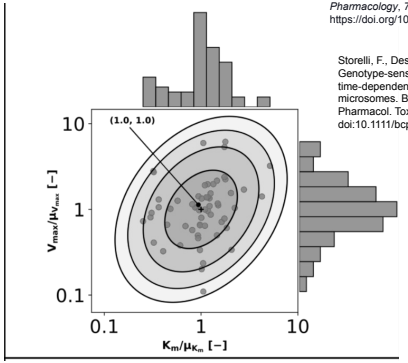
Reaction kinetics

CYP2D6



CYP3A4



Yang, J., He, M. M., Niu, W., Wrighton, S. A., Li, L., Liu, Y., & Li, C. (2012). Metabolic capabilities of cytochrome P450 enzymes in Chinese liver microsomes compared with those in Caucasian liver microsomes. *British Journal of Clinical Pharmacology*, *73*(2), 268-284. https://doi.org/10.1111/j.1365-2125.2011.04076.x

Storelli, F., Desmeules, J., and Daali, Y. (2019a). Genotype-sensitive reversible and time-dependent CYP2D6 inhibition in human liver microsomes. Basic Clin. Pharmacol. Toxicol. 124, 170–180. doi:10.1111/bcpt.13124

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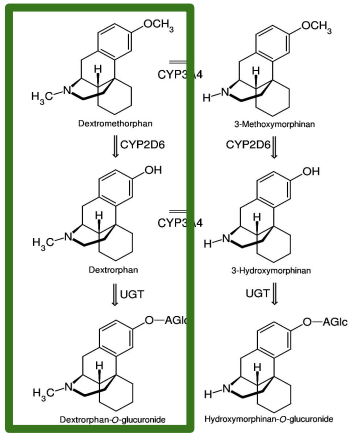

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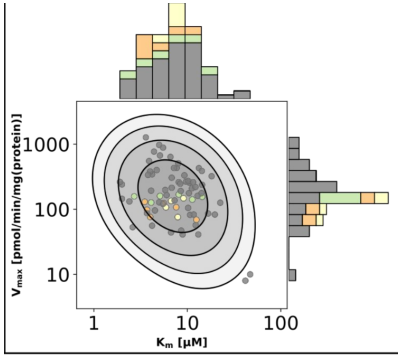
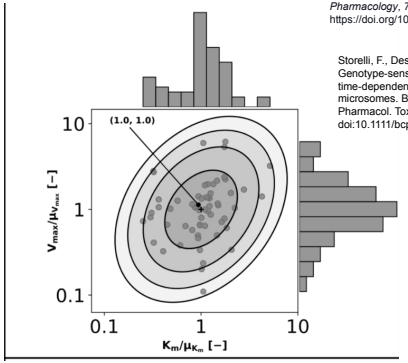
Reaction kinetics

CYP2D6



CYP3A4



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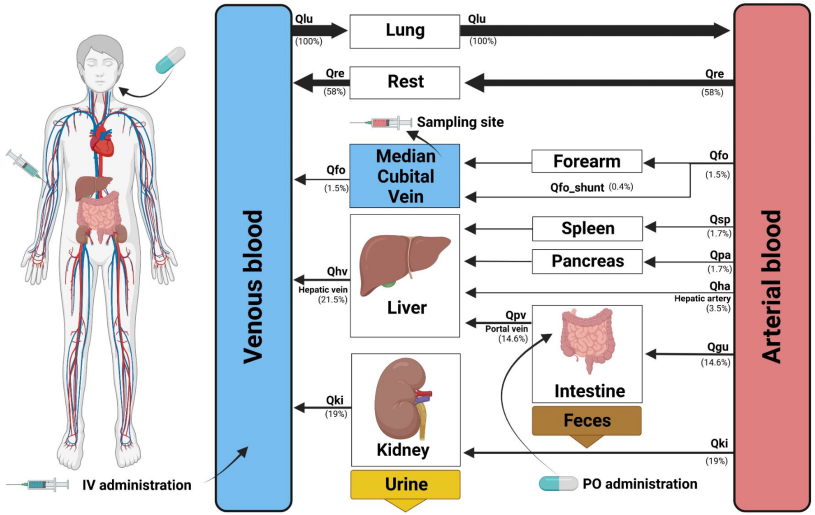
Pharmacokinetics

32 Clinical studies

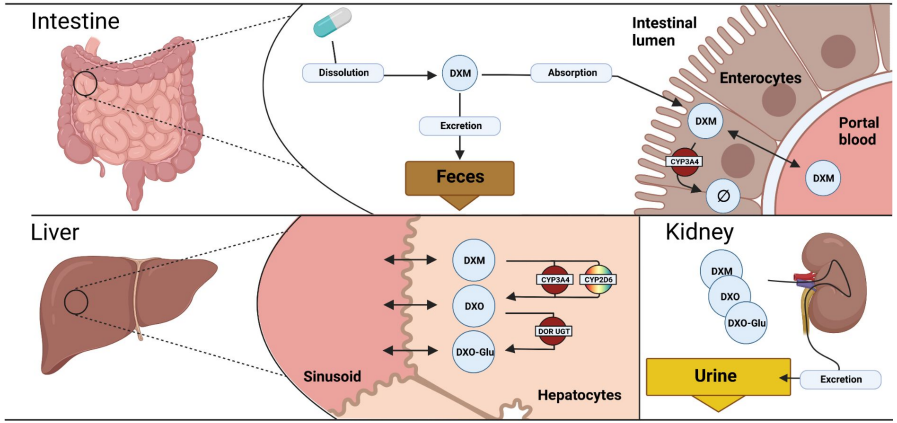
- Plasma concentration
- Urinary amounts
- Metabolic ratios

Physiological-based pharmacokinetics model of Dextromethorphan

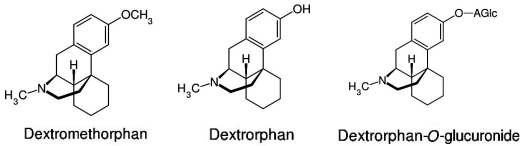
Whole-body model



Tissue models



Substance/Metabolites

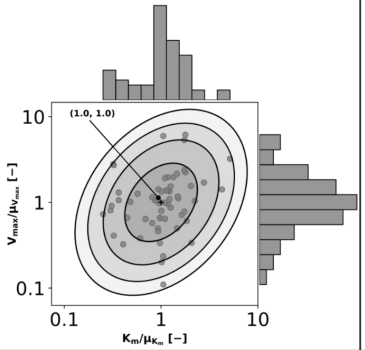
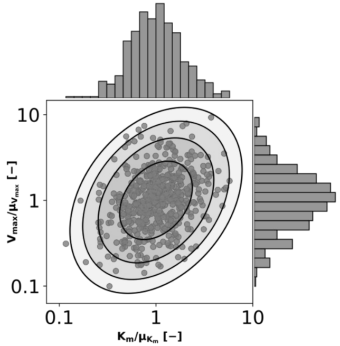
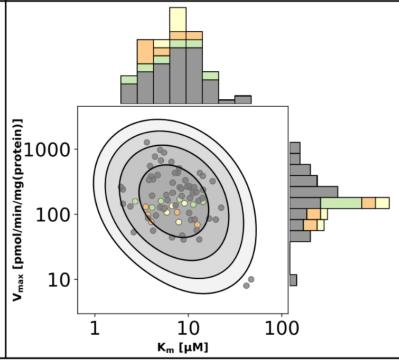
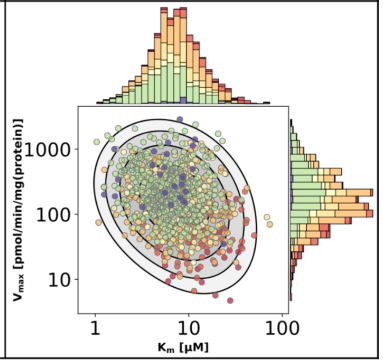


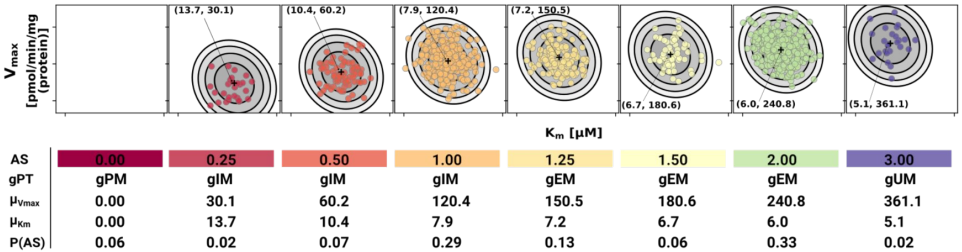
Enzyme model

- CYP2D6
- CYP3A4
- UGT

Michaelis Menten: $v = \frac{V_{\max}[S]}{K_M + [S]}$

Model of CYP2D6 and CYP3A4 variability

Enzyme	Data	Model
CYP3A4		
CYP2D6		

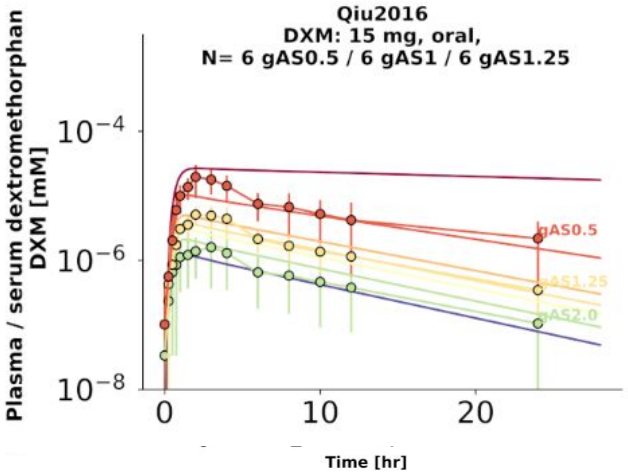


AS	0.00	0.25	0.50	1.00	1.25	1.50	2.00	3.00
gPT	gPM	gIM	gIM	gIM	gEM	gEM	gEM	gUM
μ_{Vmax}	0.00	30.1	60.2	120.4	150.5	180.6	240.8	361.1
μ_{Km}	0.00	13.7	10.4	7.9	7.2	6.7	6.0	5.1
P(AS)	0.06	0.02	0.07	0.29	0.13	0.06	0.33	0.02

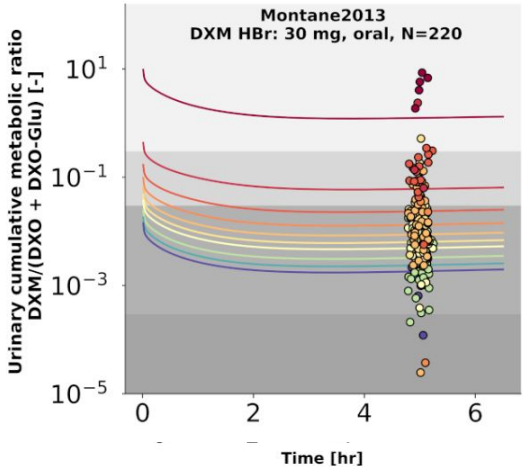
Simulations

AS: 0.0 AS: 0.25 AS: 0.5 AS: 1.0 AS: 1.25 AS: 1.5 AS: 2.0 AS: 3.0

Dextromethorphan plasma concentrations

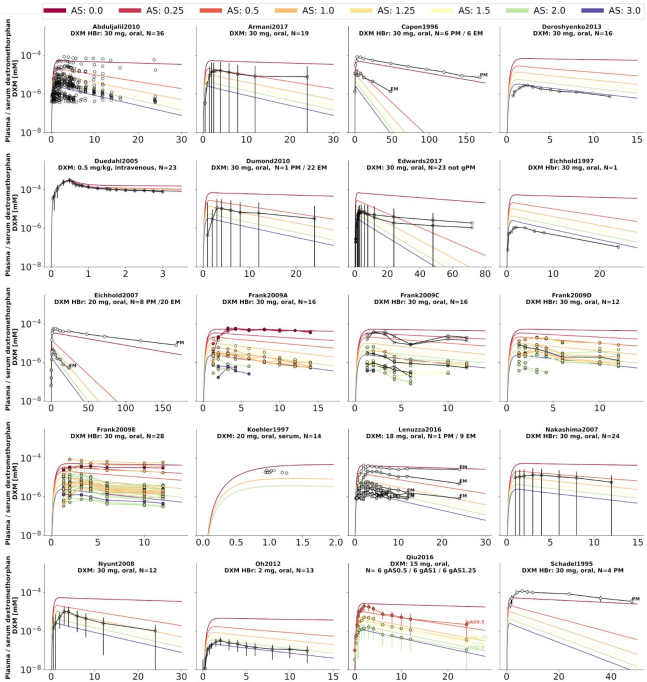


Urinary cumulative metabolic ratio

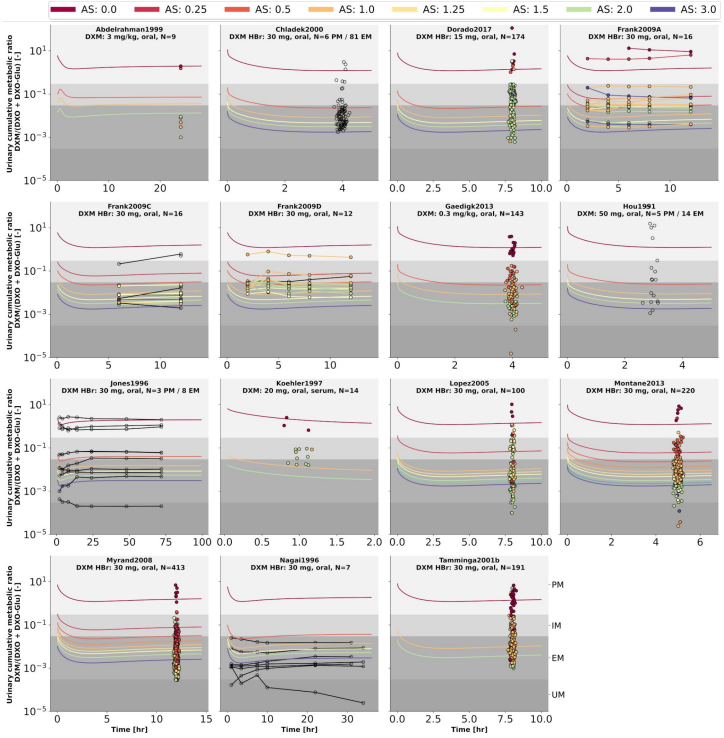


Simulations

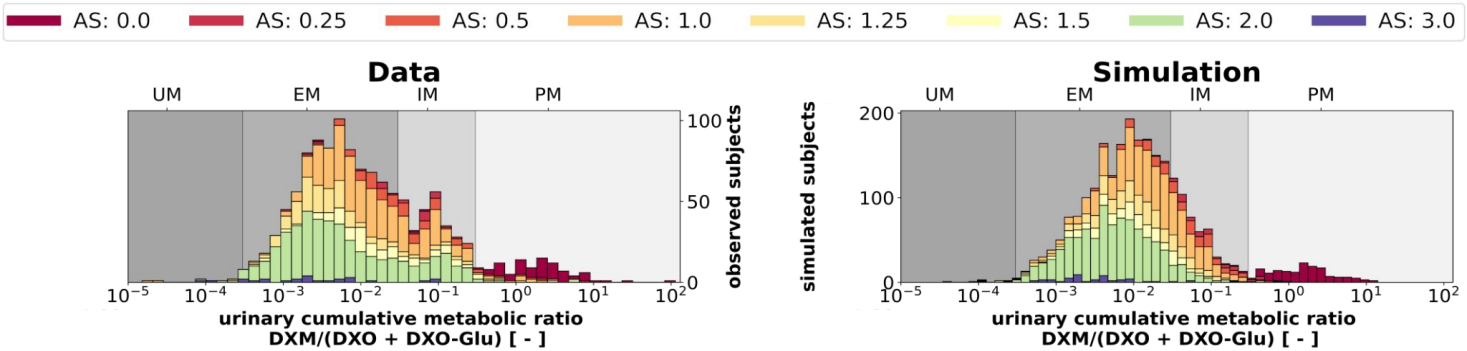
Dextromethorphan plasma concentrations



Urinary cumulative metabolic ratio

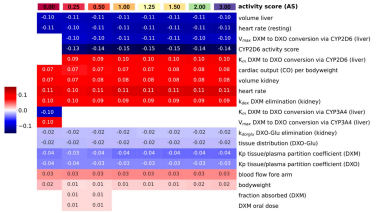


Effect of genotype on CYP2D6 phenotyping



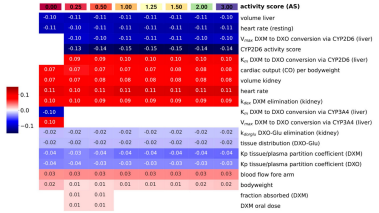
Further work

- Local sensitivity analysis

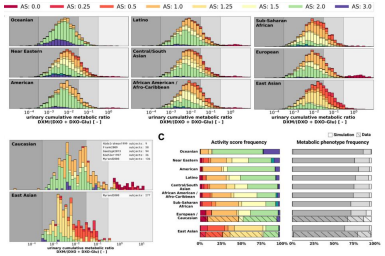


Further work

- Local sensitivity analysis

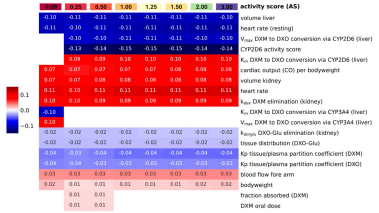


- Biogeographical population based on reported CYP2D6 genotype frequencies



Further work

- Local sensitivity analysis



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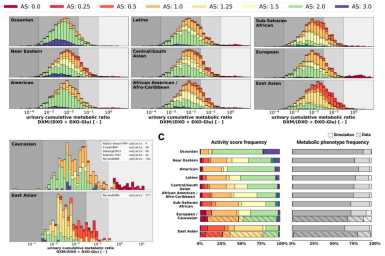
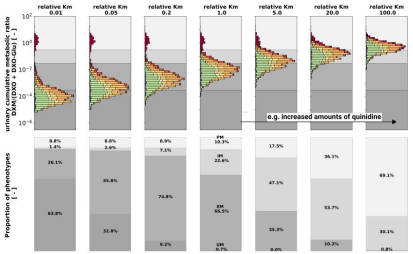


- Inhibition and induction of CYP3A4 and CYP2D6



Outcome

- Largest openly available PK dataset on dextromethorphan 🎉
- Openly available PBPK dextromethorphan model (https://github.com/matthiaskoenig/dextromethorphan-model) 🎉
- Established workflow applied in König group 🎉

Test substance	Primary proteins	Reference publication	PK-DB studies	Primary PKPB modeler
caffeine	CYP1A2 (P05177)	[Grz+22]	147	M. König
chlorzoxazone	CYP2E1 (P05181)		23	J. Küttner
codeine / morphine	CYP2D6 (P10635)		42/12	J. Grzegorzewski
dextromethorphan	CYP2D6 (P10635) CYP3A4/5 (P08684, P20815)	[GBK22]	51	J. Grzegorzewski
diazepam	CYP3A4/5 (P08684, P20815)		28	D. Ke
galactose	galactokinase (P51570)		3	M. König
indocyanine green (ICG)	OATP1B3 (Q9NPD5)	[Köl21; KGK21; Köl+21]	51	A. Köller
metoprolol	CYP2D6 (P10635)		13	P. Ogata
midazolam	CYP3A4/5 (P08684, P20815)	[Dup20]	65	Y. Duport
omeprazole	CYP2C19 (P33261)	[Bal21]	16	S. Balci
pravastatin	OATP1B1 (Q9Y6L6)	[LP22]	33	H. Leal Pujol
simvastatin	CYP3A4/5 (P08684, P20815) OATP1B1 (Q9Y6L6)	[Bar20]	48	F. Bartsch
talinolol	P-glycoprotein (P08183)		13	B. S. Mallol
torasemide	CYP2C8 (P10632) CYP2C9 (P11712)		18	S. De Angelis

- Reused CYP2D6 model 🎉

Part 3

Summary and Outlook

Summary

- First open pharmacokinetics database
- Meta-analysis of caffeine pharmacokinetics
- PBPK model of dextromethorphan
- Infrastructure for data-driven PBPK modeling

Title	Authors	Type	Date	Pubmed
PK-DB: pharmacokinetics database for individualized and stratified computational modeling	**Grzegorzewski J**, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Bartsch	Publication	2021	33151297
Pharmacokinetics of Caffeine: A Systematic Analysis of Reported Data for Application in Metabolic Phenotyping and Liver Function Testing	**Grzegorzewski J**, Bartsch F, Köller A, Eleftheriadou D, König M	Publication	2022	35280254
Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan	**Grzegorzewski J**, Brandhorst J, König M.	Publication	2022	36353484
Physiologically Based Modeling of the Effect of Physiological and Anthropometric Variability on Indocyanine Green Based Liver Function Tests	Köller A, **Grzegorzewski J**, König M	Publication	2021	34880776
Prediction of Survival After Partial Hepatectomy Using a Physiologically Based Pharmacokinetic Model of Indocyanine Green Liver Function Tests	Köller A, **Grzegorzewski J**, Tautenhahn H-M, König M	Publication	2021	34880771
Ten Simple Rules for FAIR Sharing of Experimental and Clinical Data with the Modeling Community	König M., **Grzegorzewski J.**, Golebiewski M., Hermjakob H., Hucka M., Olivier B.; Keating S., Nickerson D., Schreiber F., Sheriff R., Waltemath D.	Preprint	2021	
A physiologically based pharmacokinetic model for CYP2E1 phenotyping via chlorzoxazone	Küttner J, **Grzegorzewski J**, Tautenhahn H-M, König M	Preprint	2023	
Simvastatin therapy in different subtypes of hypercholesterolemia - a physiologically based modelling approach	Bartsch F. , **Grzegorzewski J.** , Pujol H, Tautenhahn H-M, König M	Preprint	2023	
Computational Modelling of Simvastatin - Effects on HMG-CoA Reductase Activity and Cholesterol	Florian Bartsch	Bachelor Thesis	2020	
Computational Modelling of Omeprazole - Pharmacokinetics and Pharmacodynamics	Sükrü Balci	Bachelor's Thesis	2021	
Computational Modelling of Midazolam Clearance: Effect of Inhibitors and Inducers	Yannick Duport	Bachelor's Thesis	2020	
A Physiologically Based Model of Indocyanine Green Liver Function Tests - Effects of Physiological Factors, Hepatic Disease and Hepatic Surgery Bachelor Thesis	Adrian Köller	Bachelor's Thesis	2021	
A Physiologically Based Model of Pravastatin - The Role of Genotypes and Hepatic or Renal Impairment on the Pharmacokinetics of Pravastatin	Helena Leal Pujol	Bachelor's Thesis	2022	

Outlook

- Experimental validation of the PBPK model of dextromethorphan:
  - in vitro reaction kinetics
  - CYP2D6 genotyping
  - pharmacokinetic measurements
- “Digital pharmacokinetic twin” based on CYP activities
- (Semi-) automatic data curation by LLMs (GPT4, LAMA) or multimodal models (SPAE)

Outlook

- Experimental validation of the PBPK model of dextromethorphan:
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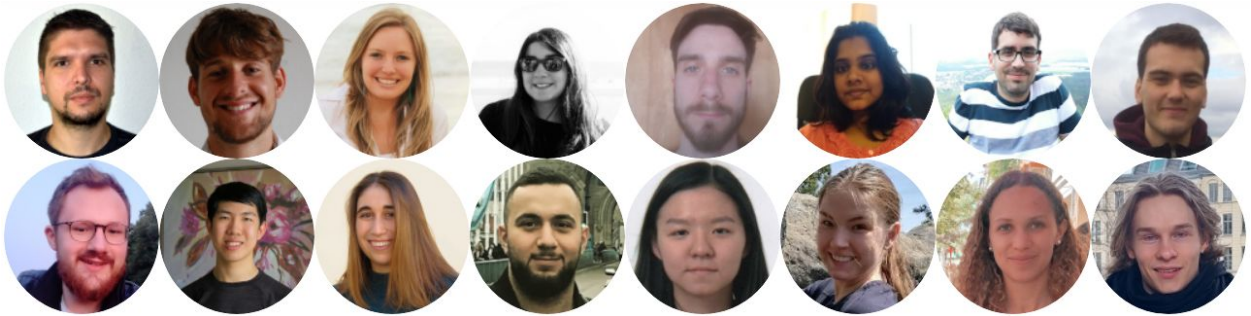
Thank you for your attention

Collaborators and Colleagues

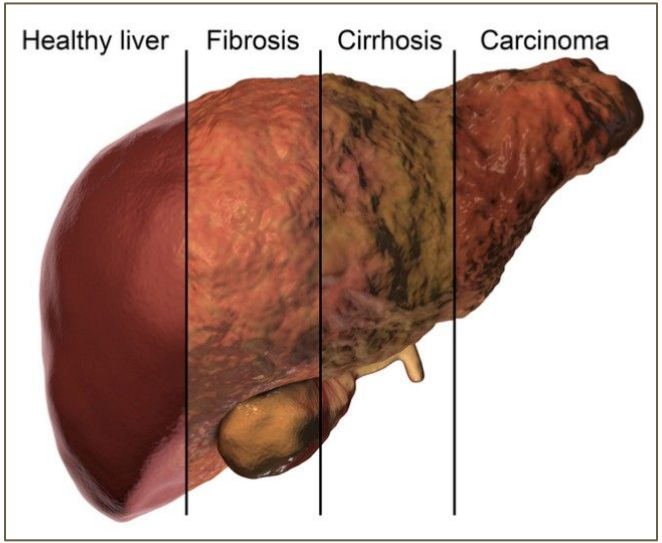


Liver Function & Disease

The liver is the heaviest solid internal organ, accounting for about 2% of body weight and 18% contribution to the total resting energy consumption.

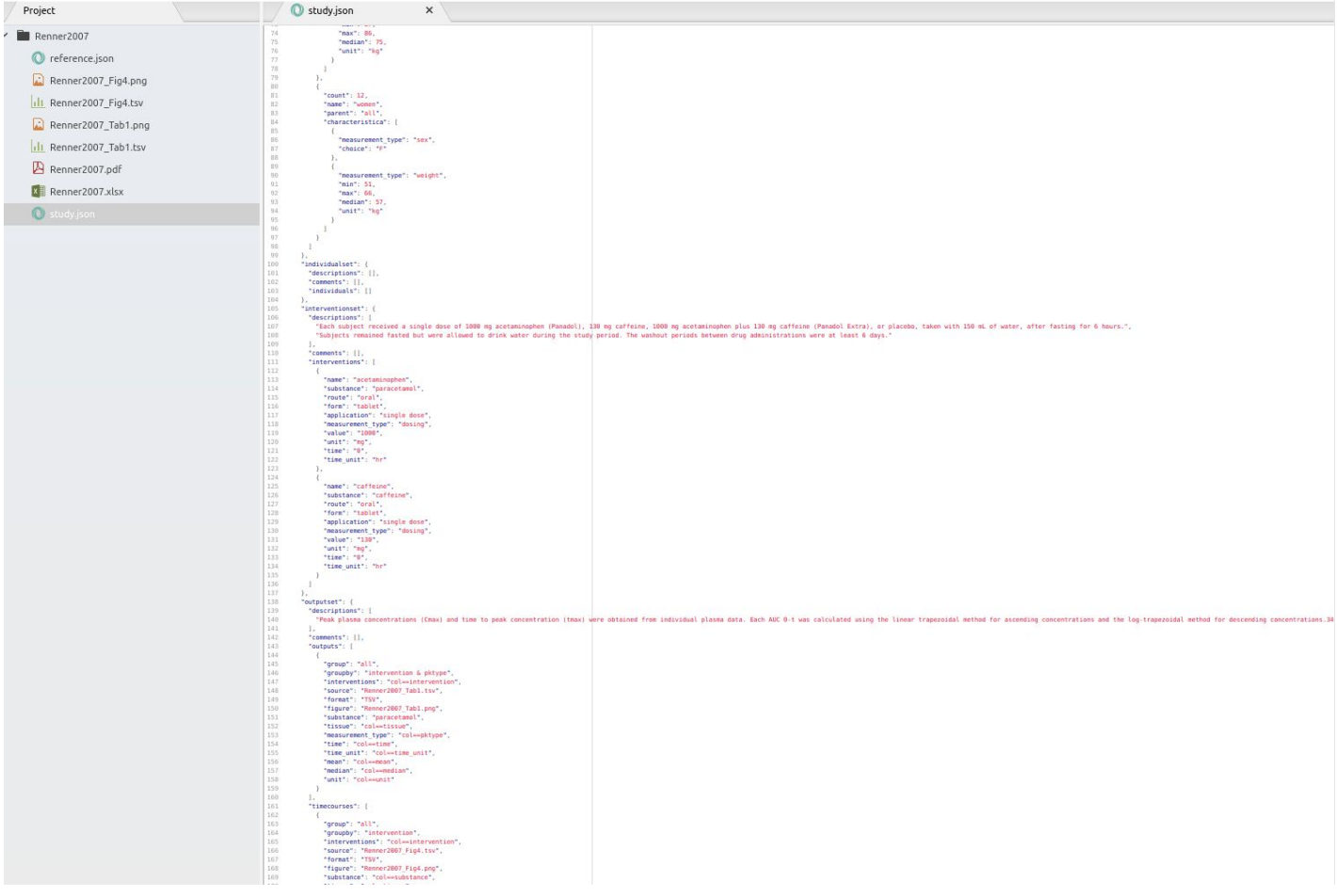
Function

- drug metabolism
- detoxification
- synthesis of plasma proteins and biochemicals (e.g. albumin, bile)
- …



Liver Cirrhosis and **Liver cancer** are the 11th and 16th leading causes of death worldwide.

Upload Format



Interactive Data Curation

```
(pkdb_data) mkoenig@prime1:~/git/pkdb_data$ watch_study -s ./studies/acetaminophen/Renner2007/
INFO ------------------------------------------------------------------------------
INFO Watching [Renner2007]
INFO    /home/mkoenig/git/pkdb_data/studies/acetaminophen/Renner2007
INFO ------------------------------------------------------------------------------
INFO - 0.11 [s] : Upload references
INFO - 0.13 [s] : Upload files
INFO - 0.08 [s] : Upload core study
INFO - 0.05 [s] : Upload groups
INFO - 0.00 [s] : Upload individuals
INFO - 0.00 [s] : Upload study
INFO - 0.05 [s] : Index study
INFO ------------------------------------------------------------------------------
INFO http://0.0.0.0:8000/api/v1/studies/17442681/
INFO UPLOAD SUCCESSFUL ( http://0.0.0.0:8080/#/studies/17442681 )
INFO ------------------------------------------------------------------------------
```

```
INFO ------------------------------------------------------------------------------
INFO Updating [Renner2007]
INFO ------------------------------------------------------------------------------
INFO - 0.13 [s] : Upload references
INFO - 0.26 [s] : Upload files
INFO - 0.12 [s] : Upload core study
WARNING
{
  "groupset": {
    "group_exs": [
      {},
      {},
      {
        "groups": [
          {
            "characteristica": [
              {},
              {
                "non_field_errors": [
                  "{'unit': 'For measurement type `weight` the unit [mol] with dimension [substance] is not allowed.', 'Only units with the following dimensions are allowed:': ['[mass]'], 'Units are allowed which can be converted to the following normalized units:': <QuerySet ['kg']>}"
                ]
              }
            ]
          }
        ]
      }
    ]
  }
}
INFO - 0.16 [s] : Upload groups
INFO - 0.08 [s] : Upload individuals
INFO - 0.08 [s] : Upload study
INFO - 0.10 [s] : Index study
INFO ------------------------------------------------------------------------------
ERROR UPLOAD ERROR (check error and warnings above)
INFO ------------------------------------------------------------------------------
```

Dextromethorphan: A probe drug for CYP2D6 activity

- Cytochrome P450 2D6 (CYP2D6) is involved in the clearance of ~20%

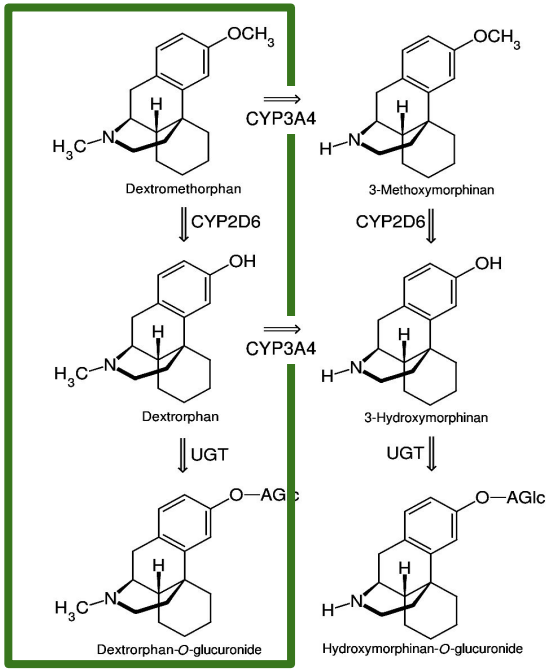
- Dextromethorphan is in vivo probe
  - CYP2D6 metabolizes Dextromethorphan (DMT) to Dextrorphan (DXO)

- Substance for CYP2D6 phenotyping.
  - Urinary metabolic ratio
  - DMT/(DXO + DXO-Glu)

- CYP2D6-mediated drug response exhibits a large inter-individual variability due to genetic polymorphism

- Genetic polymorphism is related to
  - risk of adverse effects
  - non-response during treatment
  - death by drug intoxication

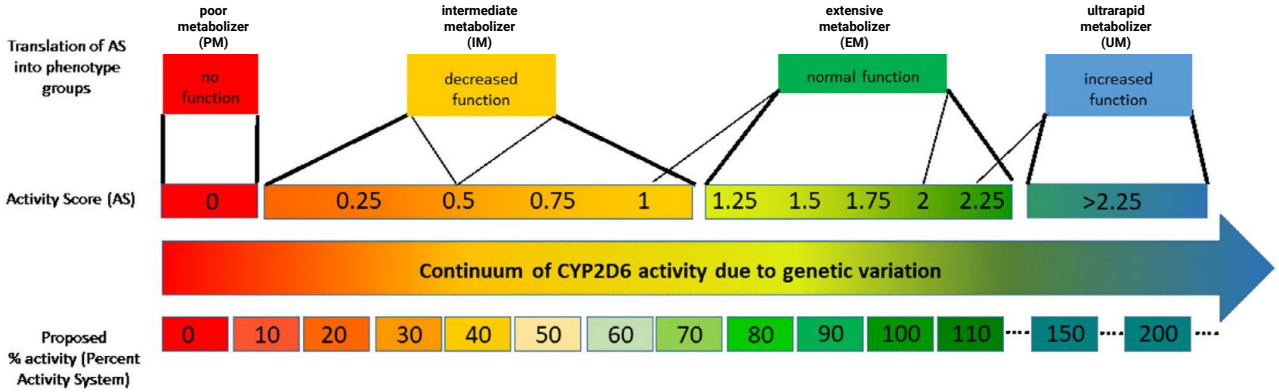
Metabolic pathway of dextromethorphan



Strauch K, Lutz U, Bittner N, Lutz WK (August 2009). "Dose-response relationship for the pharmacokinetic interaction of grapefruit juice with dextromethorphan investigated by human urinary metabolite profiles". *Food and Chemical Toxicology*. **47** (8): 1928–35. doi:10.1016/j.fct.2009.05.004. PMID 19445995.

CYP2D6 Polymorphism

- genetic variants have different activities values
- subjects carry combinations of these variants
- sum of individual activity values is the activity score (AS)

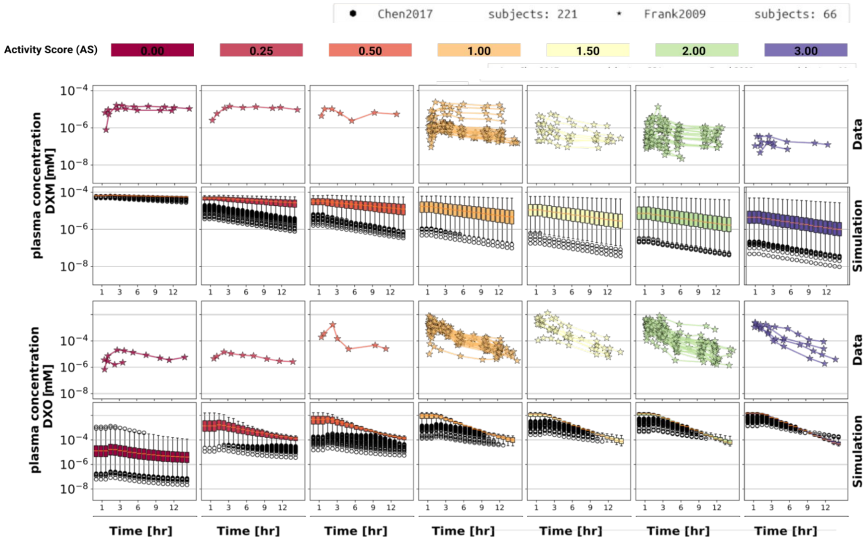


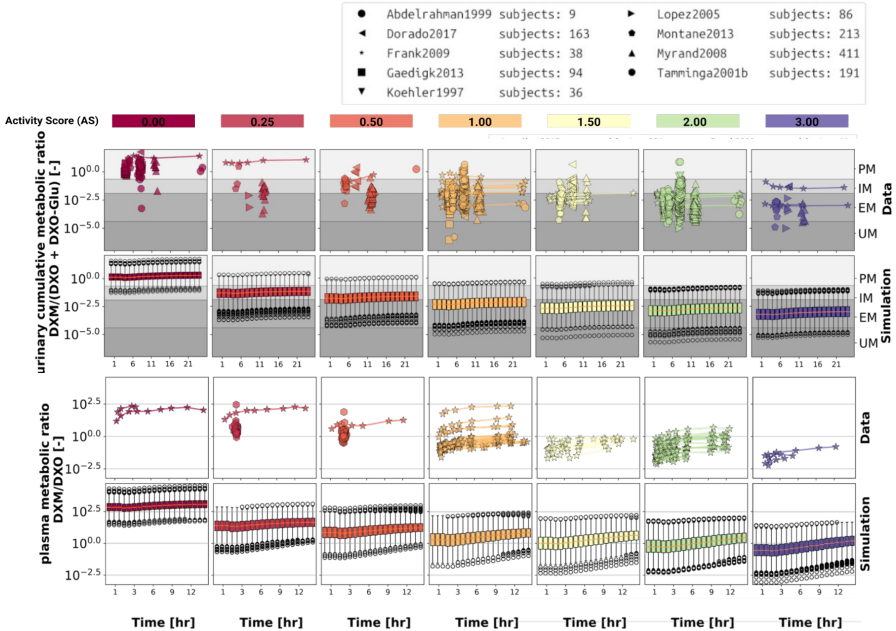
K. E. Caudle et al., "Standardizing CYP 2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group," Clin Transl Sci, vol. 13, no. 1, pp. 116–124, Jan. 2020, doi: 10.1111/cts.12692.

Activity Score (AS): $AS = \sum ActivityValue$

Activity Value	Allele
0	*3,*4, *5, *6, *7, *8,*11,*12,*13,*15,*42,*44, …
0.25	*10
0.5	*9,*10x2,*14,*17,*29,*41,*49,*50,*54,*55,*59
1	*1,*2,*9x2, *17x2, *33,*34,*35,*45,*46,*53,
>1	*1x2, *1x>2, *2x2, *1x>3, …

Effect of polymorphism on dextromethorphan metabolic ratios

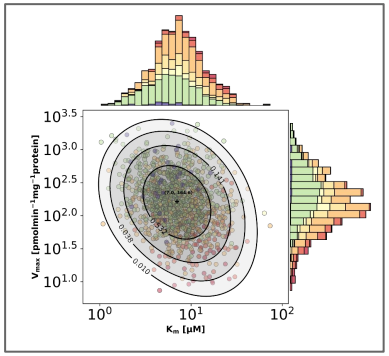


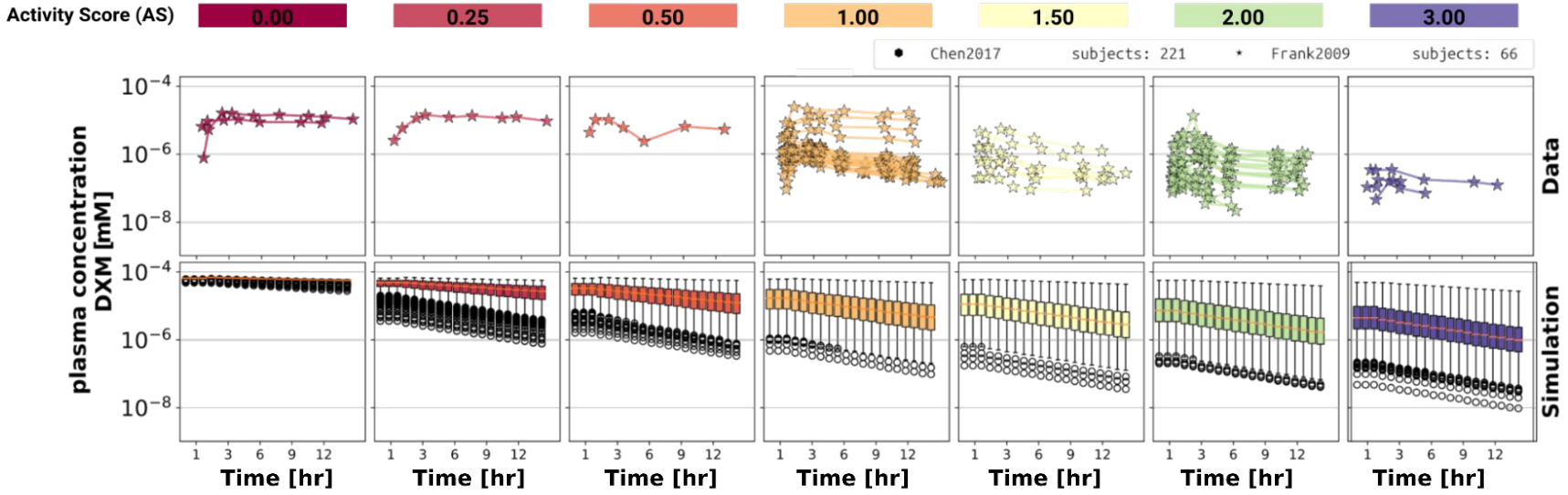


Effect of polymorphism on dextromethorphan pharmacokinetics

Model can predict timecourse data

32 clinical studies





Parameter Fitting

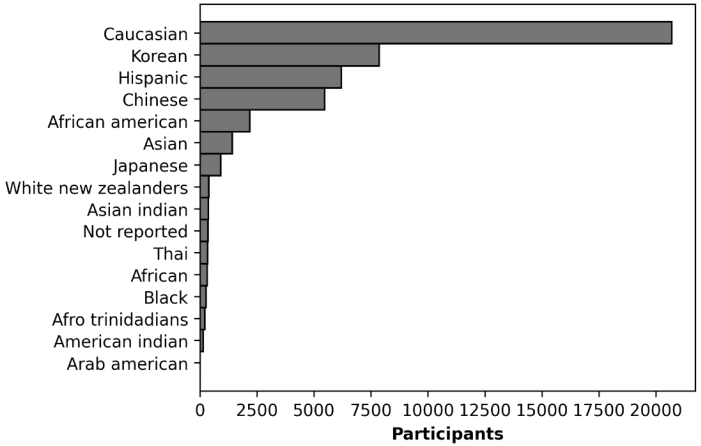
- 12 PBPK model parameter were fitted with time course data from the studies by weighted mean square error.

Parameter	Description	References	Value	Unit	F
BW	Body weight	ICRP (2002) (male)	75	kg	
HEIGHT	Height	ICRP (2002) (male)	170	cm	
HR	Heart rate		70	1/min	
HRrest	Heart rate (resting)		70	1/min	
COBW	Cardiac output per bodyweight	ICRP (2002); de Simone et al. (1997)	1.548	ml/s/kg	
HCT	Hematocrit	Vander (2001); Herman (2016) (upper range male)	0.51	-	
Kp_fo_dxm	Tissue/plasma partition coefficient DXM forearm		10	-	✓
f_shunting_forearm	Shunting in forearm		0.2795	-	✓
FVgu	Gut fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0171	l/kg	
FVki	Kidney fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0044	l/kg	
FVli	Liver fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.021	l/kg	
FVlu	Lung fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0076	l/kg	
FVsp	Spleen fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0026	l/kg	
FVpa	Pancreas fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.01	l/kg	
FVfo	Fore arm fractional tissue volume		0.0048	l/kg	✓
FVve	Venous fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0514	l/kg	
FVar	Arterial fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.0257	l/kg	
FVpo	Portal fractional tissue volume	Jones and Rowland-Yeo (2013); ICRP (2002)	0.001	l/kg	

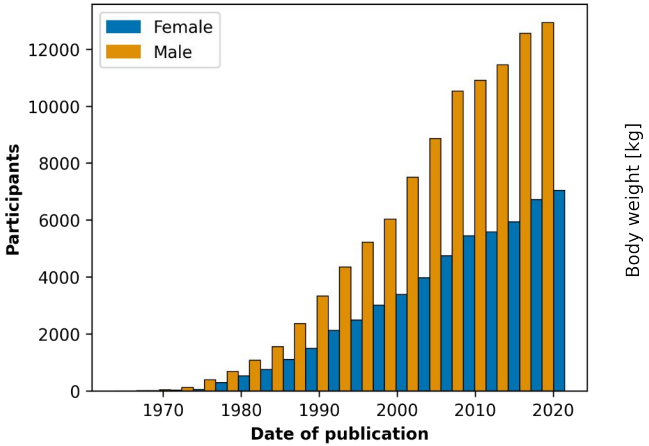
Parameter	Description	References	Value	Unit	F
FQgu	Gut fractional tissue blood flow	Jones and Rowland-Yeo (2013)	0.146	-	
FQki	Kidney fractional tissue blood flow	Jones and Rowland-Yeo (2013)	0.19	-	
FQh	Hepatic (venous side) fractional tissue blood flow	Jones and Rowland-Yeo (2013)	0.215	-	
FQlu	Lung fractional tissue blood flow	Jones and Rowland-Yeo (2013)	1	-	
FQsp	Spleen fractional tissue blood flow	Jones and Rowland-Yeo (2013)	0.017	-	
FQfo	Fore arm fractional tissue blood flow	RNAO (2022)	0.0146	-	
FQpa	Pancreas fractional tissue blood flow	ICRP (2002)	0.017	-	
ftissue_dxm	Vmax tissue distribution DXM		1000	l/min	✓
Kp_dxm	Tissue/plasma partition coefficient DXM		8.7346	-	✓
Ka_dis_dxm	DXM rate of dissolution and stomach passage		0.0217	1/hr	✓
Mr_dxo	Molecular weight DXO	CHEBI:29133	257.3707	g/mole	
ftissue_dxo	Vmax tissue distribution DXO		100	l/min	✓
Kp_dxo	Tissue/plasma partition coefficient DXO		4	-	✓
Mr_dxo_glu	Molecular weight DXO_glu	CHEBI:32645	433.4948	g/mole	
ftissue_dxo_glu	Vmax tissue distribution DXO_glu		3	l/min	✓
Kp_dxo_glu	Tissue/plasma partition coefficient DXO_glu		0.08	-	✓
KI__DXMEX_k	DXM urinary excretion rate		0.017	1/min	✓
KI__DXOEX_k	DXO urinary excretion rate		0.3	1/min	✓
KI__DXOGLUEX_k	DXO glucuronide urinary excretion rate		10	1/min	✓
LI__DXMCYP2D6_Vmax	DXM CYP2D6 Vmax		0.003	mmol/	✓
LI__DXMCYP2D6_Km	DXM CYP2D6 Km	Storelli et al. (2019a); Yang et al. (2012)	0.0079	mM	
LI__cyp2d6_ac	CYP2D6 activity score		0.0–3.0	-	
LI__lambda_1	Slope of Km by principal component regression of (Km, Vmax) in log space	Storelli et al. (2019a); Yang et al. (2012)	-0.4	-	✓
LI__DXMCYP3A4_Vmax	Vmax of DXO formation by CYP3A4		0.0004	mmol/ min/l	✓
LI__DXMCYP3A4_Km	Km of DXO formation by CYP3A4	Yu and Haining (2001)	0.157	mM	
LI__DXOUGT_Vmax	DXO UGT Vmax (glucuronidation)		0.8953	mmol/ min/l	✓
LI__DXOUGT_Km	DXO UGT Km (glucuronidation)	Lutz and Isoherranen (2012)	0.69	mM	
GU__F_dxm	Fraction absorbed DXM	Schadel et al. (1995)	0.55	-	
GU__Ka_abs_dxm	Ka_abs absorption DXM		3.4285	1/hr	✓
GU__DXMCYP3A4_Vmax	DXM CYP3A4 Vmax		0.0002	mmol/ min/l	✓
GU__DXMCYP3A4_Km	DXM CYP3A4 Km	Kerry et al. (1994); Yu and Haining (2001)	0.7	mM	
PODOSE	DXM oral dose			mg	

Biases in Literature

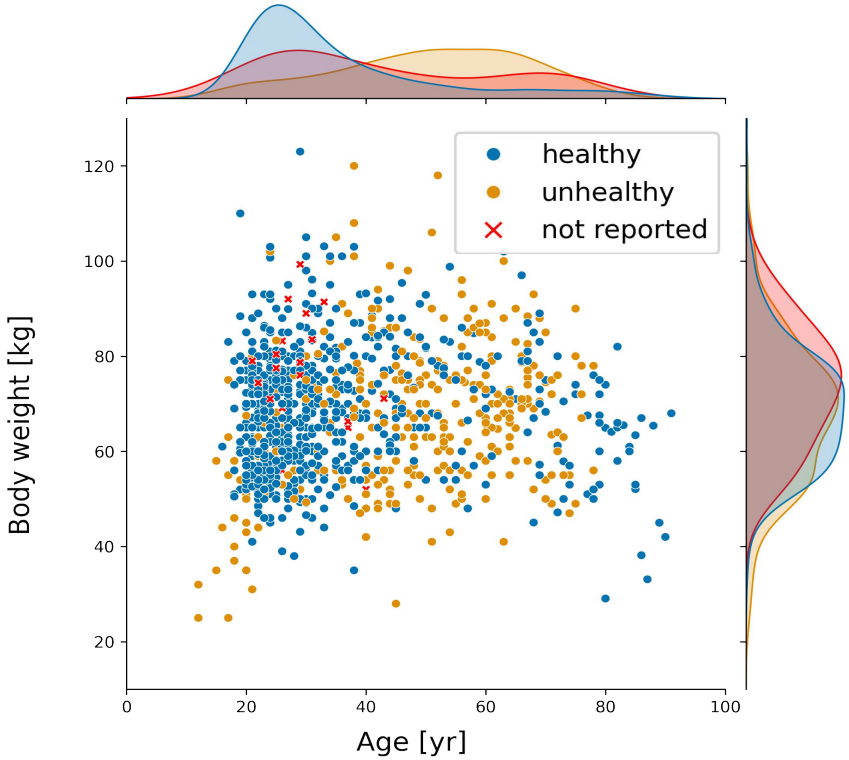
Ethnicity



Sex



Age-Health


healthy
unhealthy
not reported
Body weight [kg]
Age [yr]
20
40
60
80
100
120
0
20
40
60
80
100

Tools for reproducible model implementation

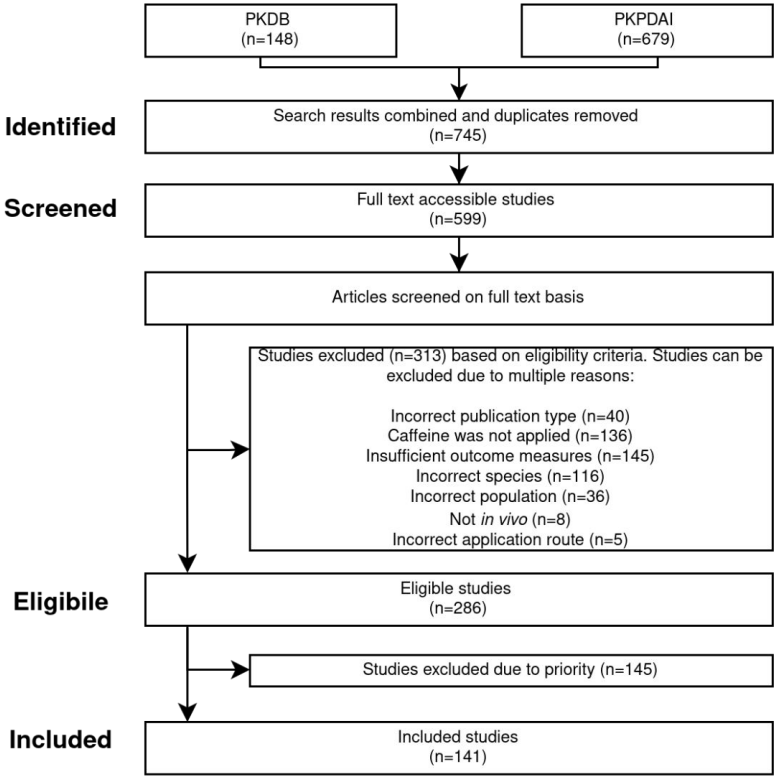
parameter estimation

AMICI

libRoadRunner

PEtab

Preferred Reporting Items for Systematic reviews and Meta-Analysis for Scoping Reviews (PRISMA-ScR)

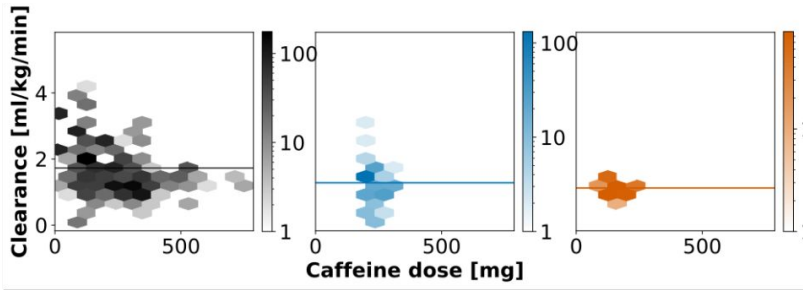


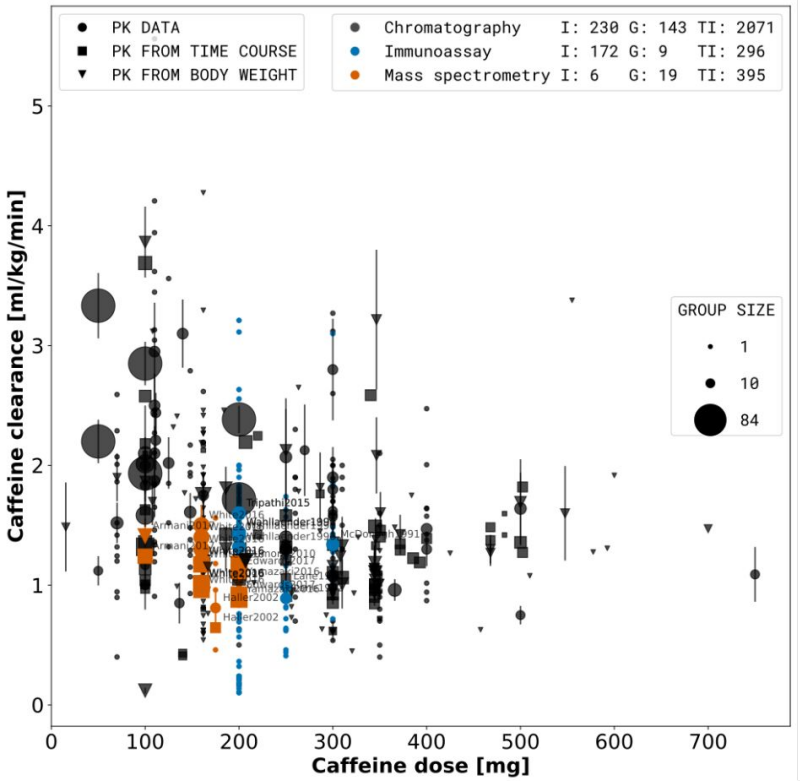
Eligibility Criteria

- Original studies (no reviews, no computational studies)
- Homo Sapiens
- Age >=18 years
- In vivo
- Application of caffeine
- Application route (oral, intravenous)
- Reported pharmacokinetics data for caffeine of its metabolites (time courses or pharmacokinetic parameters)

Meta-analysis: Methods

- Probably no influence of quantification method on caffeine clearance





Meta-analysis: Caffeine-Drug Interactions

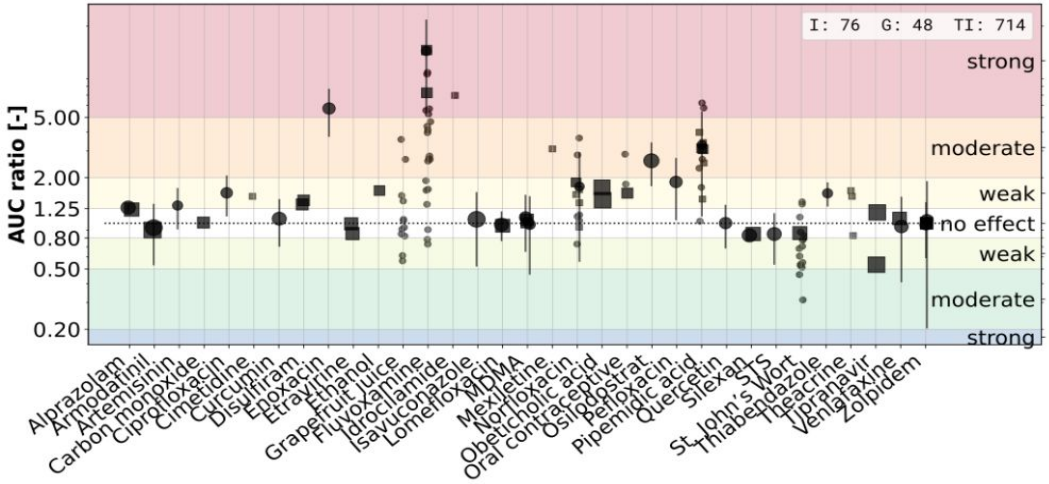
- Drug-drug interactions by AUC of Caffeine:

  ↔ most substances

  ↓ enoxacin, fluvoxamine, Idrocilamide*, norfloxacin, osilodrostat, pipemidic acid

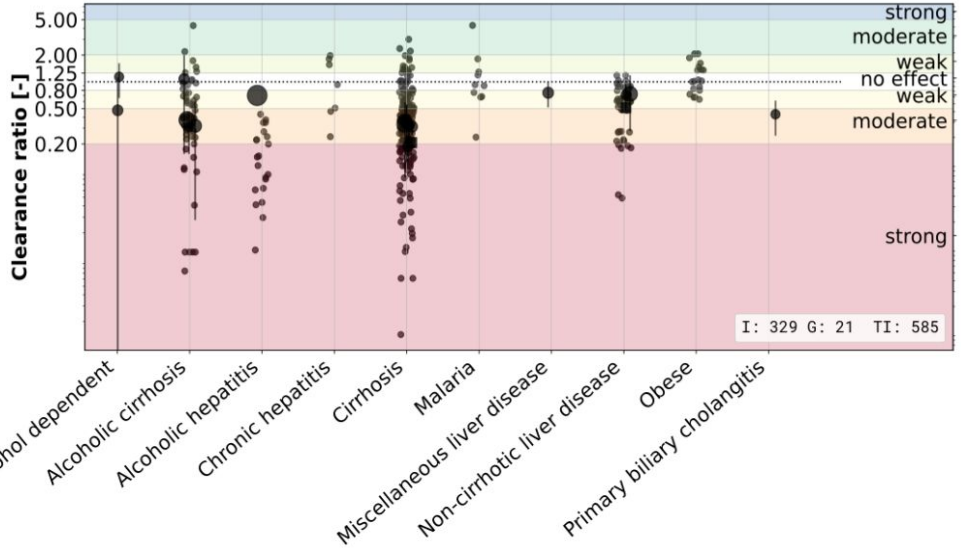
  ↑ tipranavir*

*interaction missing in go.drugbank.com



Meta-analysis: Caffeine-Disease Interactions

- Cirrhotic liver disease had moderate to strong effects on the caffeine clearance
- None of the reported diseases increased the clearance rate of caffeine.
- Difficult to combine aggregated data with IPD. Sometimes on mean is reported. Not possible to create a distribution for sampling.

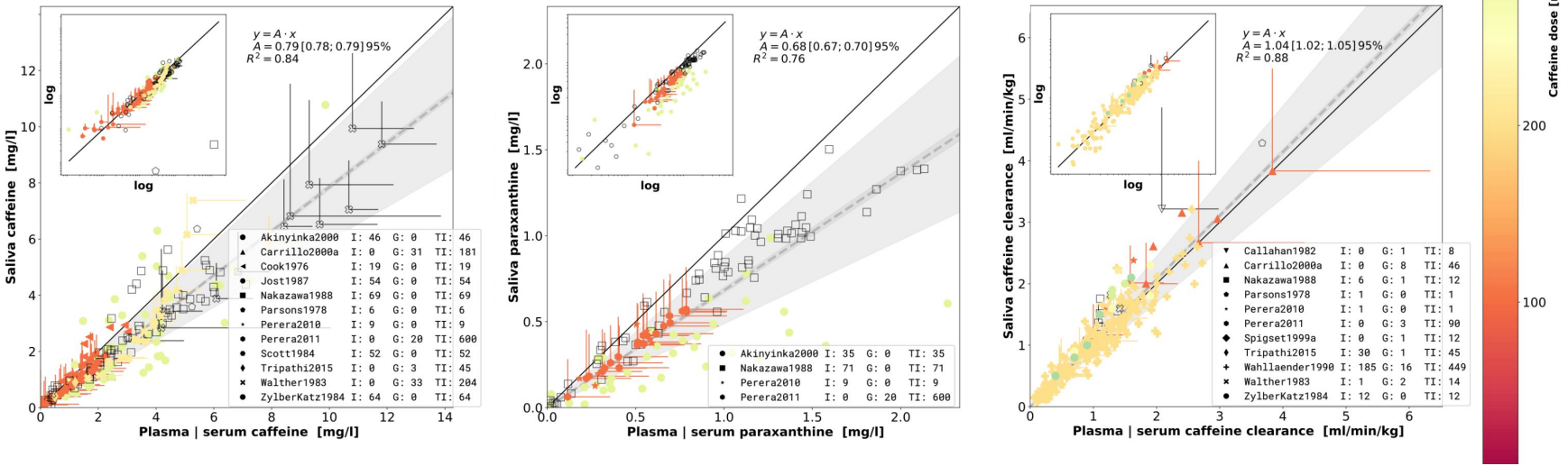


Hypotheses:

- lower liver function due to worse perfusion and shunting, …
- Proinflammatory cytokines down regulating CYP expression.

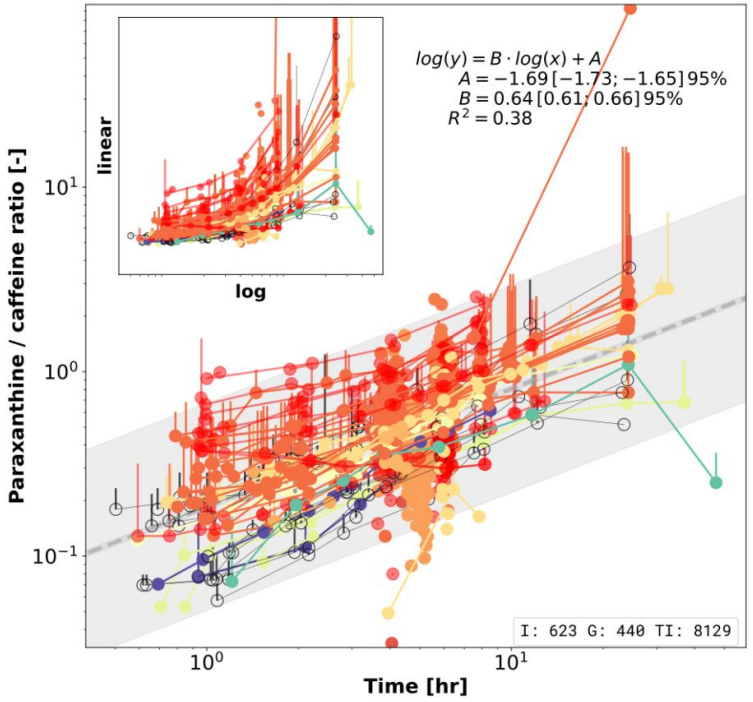
Meta-analysis: Plasma vs. Saliva

- Concentrations of caffeine and paraxanthine are 21% and 32%, respectively, lower in saliva in comparison to plasma.
- Strong correlation (R^2=0.88) between clearance in saliva and plasma.

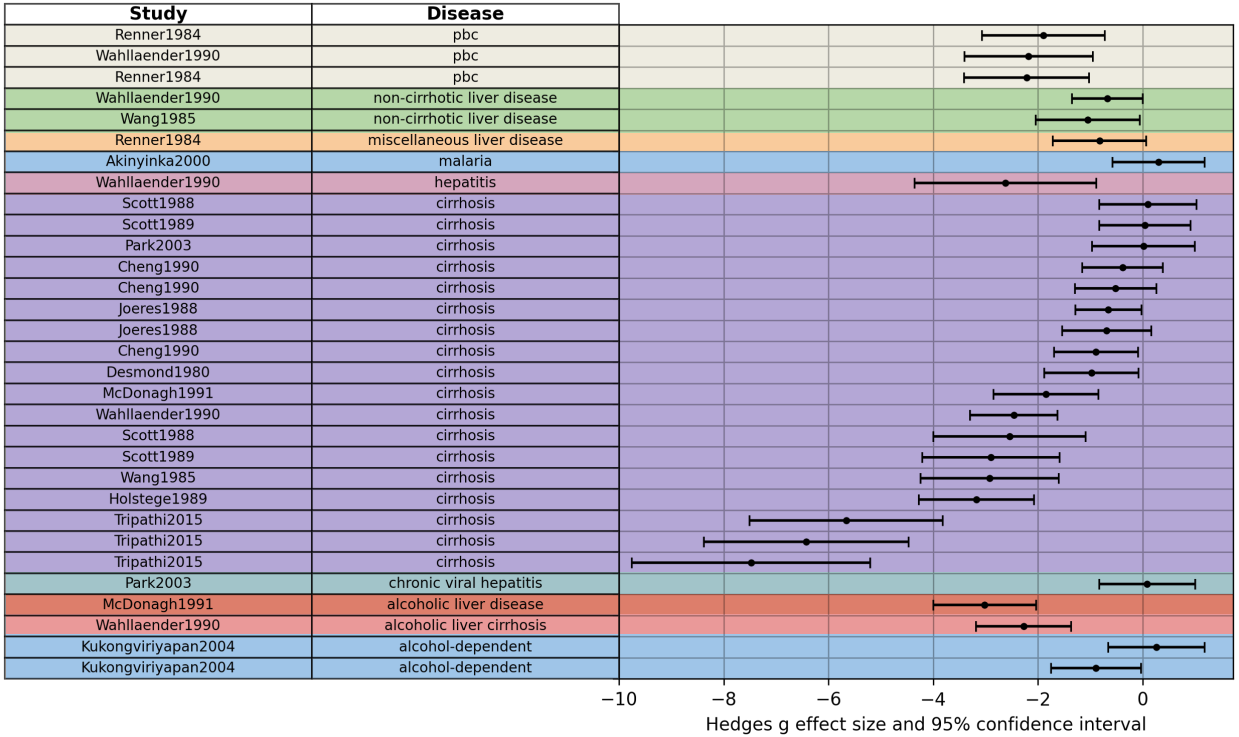


Meta-analysis: Metabolic ratio in plasma over time

- Sampling timing of the metabolic ratio (MR) (paraxanthine / caffeine) in plasma matters. MR increases over time.



Effect size analysis of caffeine clearance for various diseases



$$g = (x_1 - x_2) / \sqrt{((n_1-1)*s_{12} + (n_2-1)*s_{22}) / (n_1+n_2-2)}$$

Rule of thumb:

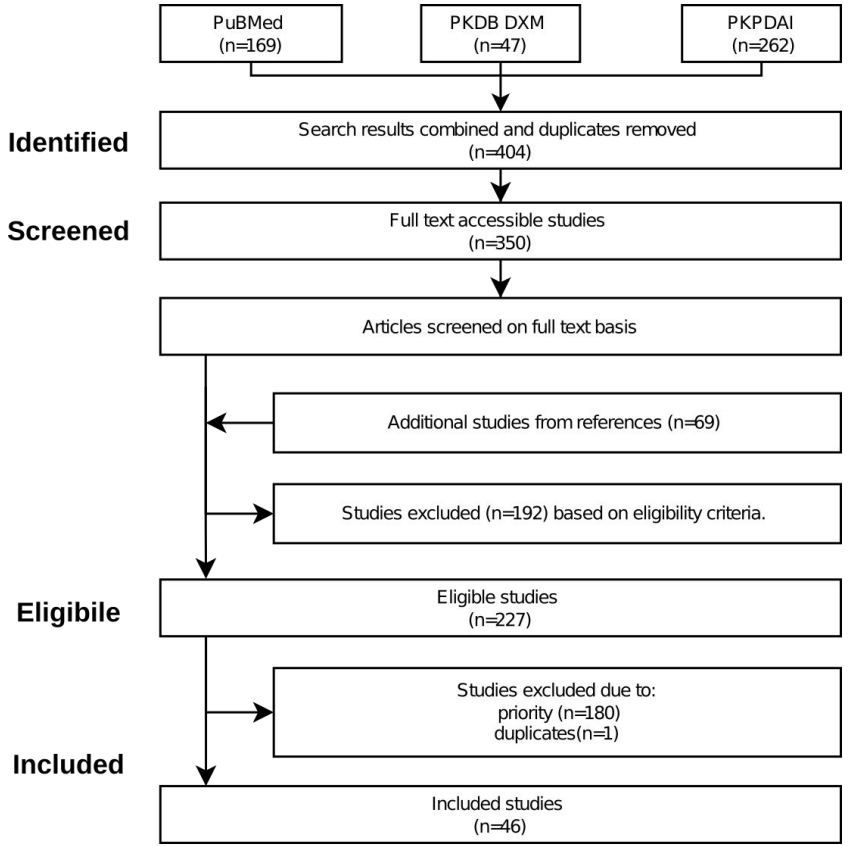
Hedges g < 0.2 small effect

Hedges g ≈ 0.5 medium effect

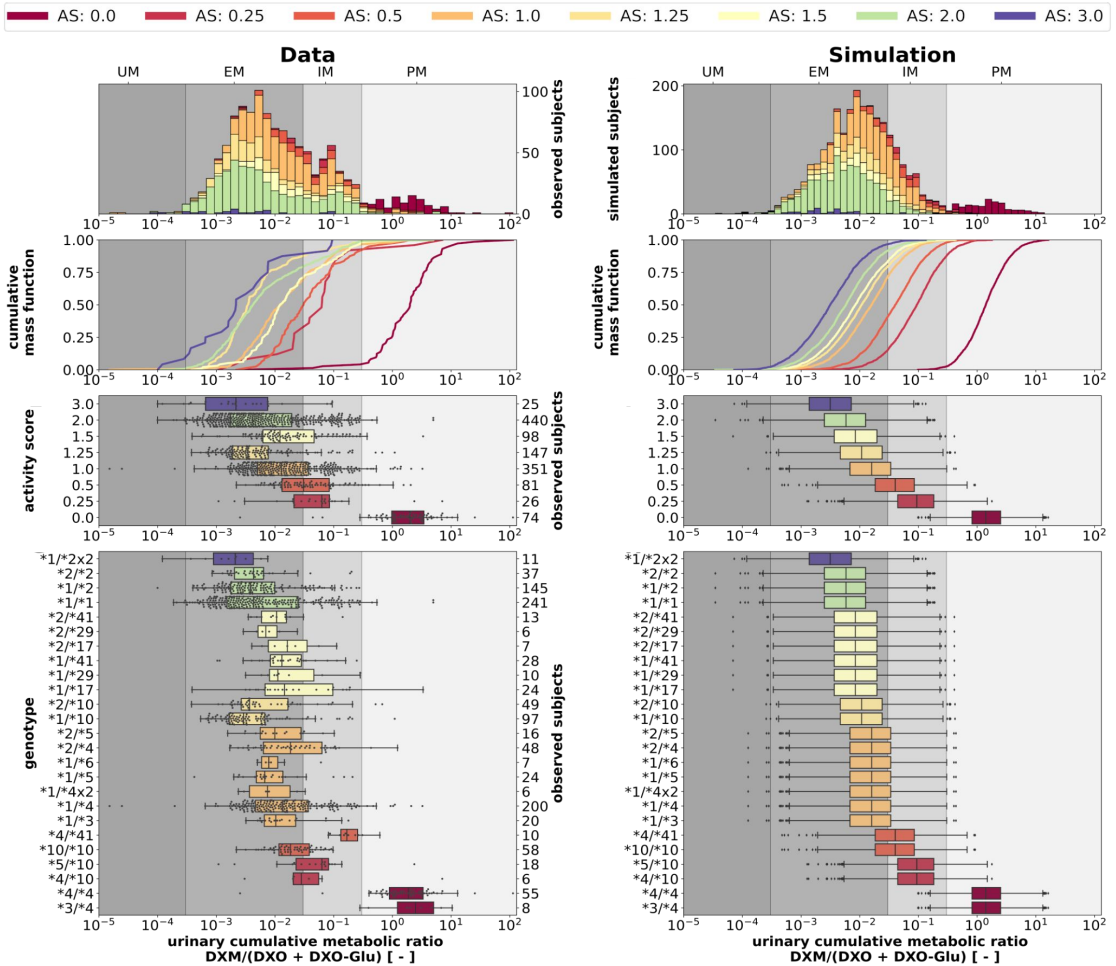
Hedges g > 0.8 large effect

PRISMA flow diagram for Dextromethorphan

Overview of the data selection for the pharmacokinetics dataset used in this work. PuBMed, PKDB, and PKPDAI were utilized for the literature search on DXM pharmacokinetics. Applied eligibility criteria resulted in 227 studies of which 46 were curated for this work.



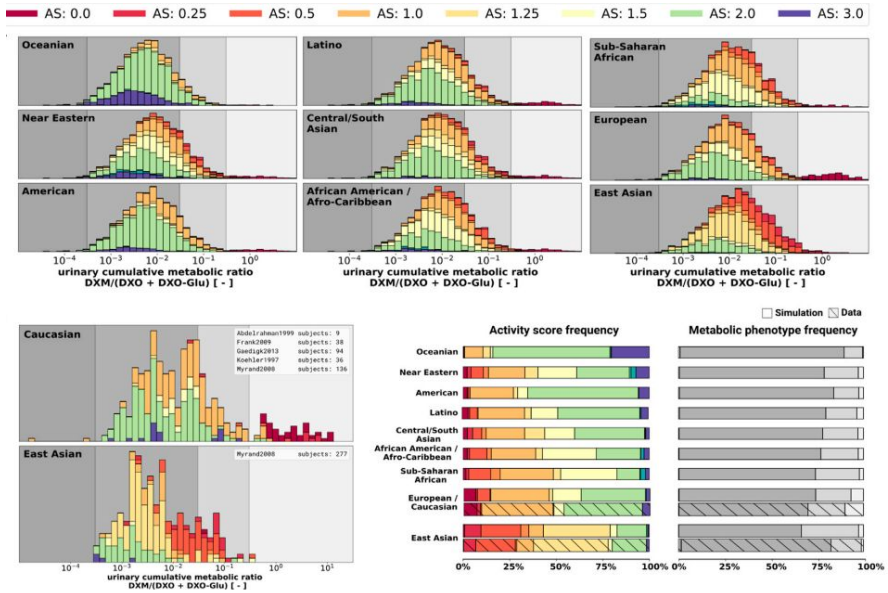
Effect of genotype on CYP2D6 phenotyping



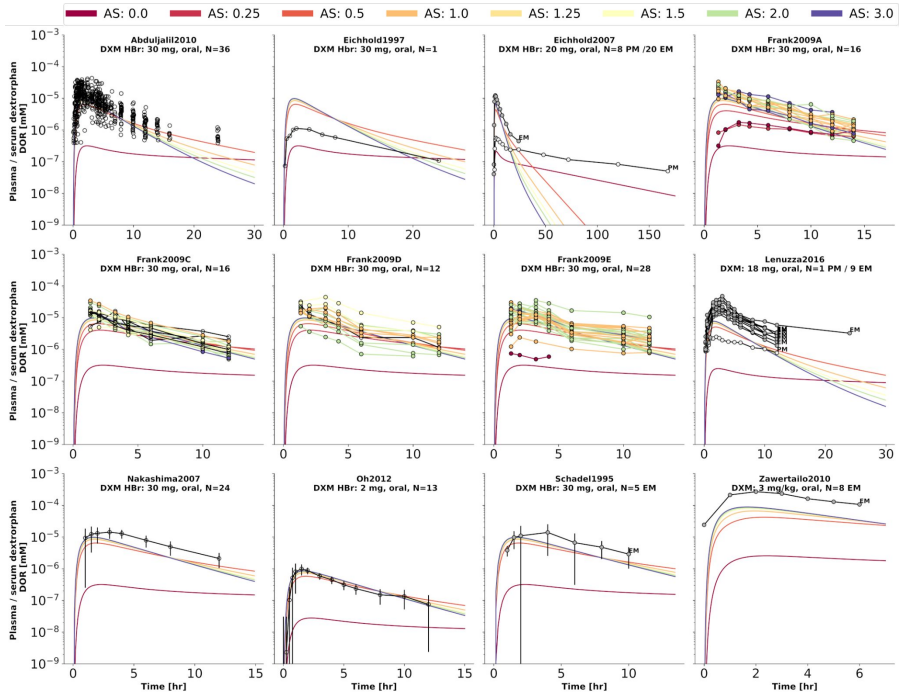
Biogeographical Population

Activity Score	Sub-Saharan African	African American & Afro-Caribbean	European	Near Eastern	East Asian	Central & South Asian	American	Latino	Oceanian
0	1.53	2.33	6.47	2.20	0.86	2.34	2.18	3.12	0.38
0.25	1.38	1.17	0.80	2.01	8.10	2.65	0.42	0.93	0.31
0.5	10.90	9.29	6.72	6.34	19.82	4.71	1.03	3.84	0.17
0.75	4.77	2.29	0.41	2.69	3.94	2.24	0.10	0.56	0.04
1	26.45	23.46	31.01	18.82	7.28	19.94	22.04	23.76	9.57
1.25	3.64	3.62	1.81	6.80	33.15	10.35	2.14	3.37	3.90
1.5	28.04	28.43	15.16	19.93	3.45	15.44	5.10	13.67	1.32
2	11.40	23.38	34.03	27.14	14.62	36.09	56.27	42.02	61.14
2.25	0.32	0.22	0.05	0.88	0.69	0.26	0.10	0.15	0.60
2.5	2.44	1.69	0.46	2.56	0.07	0.39	0.24	0.59	0.20
3	1.86	2.68	1.99	6.49	0.60	1.81	5.15	3.57	18.37
4	0.08	0.08	0.03	0.42	0.01	0.02	0.12	0.08	1.41
Phenotype									
UM	0.4	0.4	0.5	0.7	0.3	0.5	0.7	0.7	1.1
EM	73.7	76.6	73.8	78.2	66.3	77.5	83.3	79.1	88.5
IM	23.7	20.2	19.1	18.5	30.9	19.0	13.5	16.8	9.9
PM	2.2	2.7	6.7	2.7	2.6	2.9	2.4	3.5	0.5

Table S2. Proportion [%] of CYP2D6 activity scores and simulated metabolic phenotypes by biogeographical group.

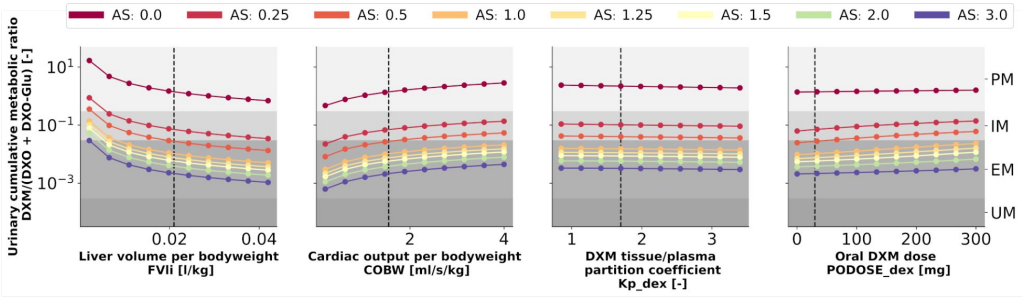


Dextrorphan Plasma Concentration Simulation



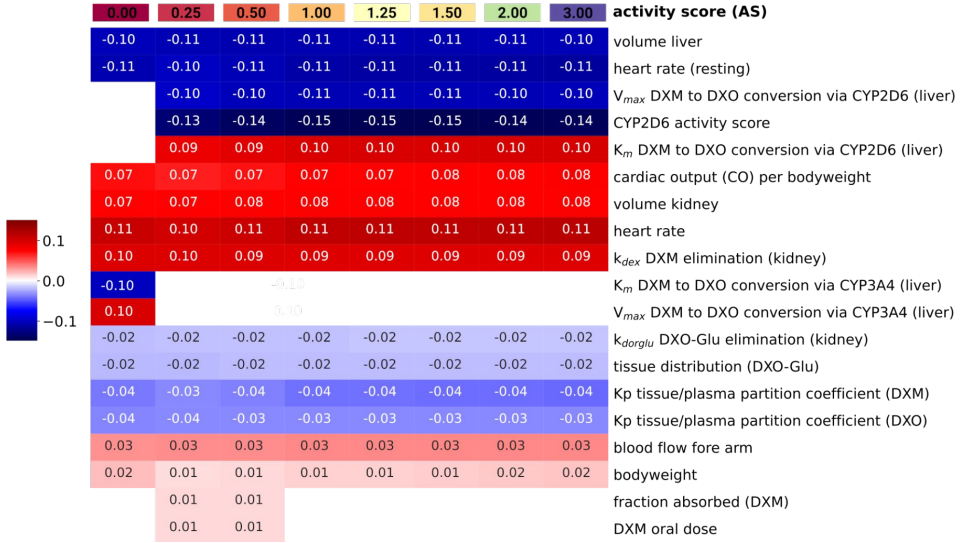
Parameter Scans

- Dependency of UCMR (urinary cumulative ratio of DXM/(DXO-Glu) after 8 hr and 30 mg oral DXM) on selected physiological parameters and the DXM dose. Parameter scans were performed for all activity scores.



Local Sensitivity Analysis

- Sensitivity analysis of model parameters. To systematically study the effect of parameter changes the local sensitivity of UCMR were calculated for all activity scores. Parameters were varied 10% in both direction around the reference parameter value and the relative change of UCMR was calculated (insensitive parameters with relative change of UCMR smaller than 1% were omitted).



model: dextromethorphan_body

Autogenerated ODE System from SBML file with sbmlutils. `time: [min] substance: [mmol] extent: [mmol] volume: [l] area: [m^2] length: [m]`

Parameters p

```
BW = 75.0  # [kg]
COBW = 1.548  # [ml/s/kg]
COHRI = 150.0  # [ml]
FQfo = 0.01461538461538461538  # [-]
FQgu = 0.146  # [-]
FQh = 0.215  # [-]
FQki = 0.19  # [-]
FQlu = 1.0  # [-]
FQpa = 0.017  # [-]
FQsp = 0.017  # [-]
FVar = 0.0257  # [l/kg]
FVfo = 0.00482857142857143  # [l/kg]
FVfov = 0.001  # [l/kg]
FVgu = 0.0171  # [l/kg]
FVhv = 0.001  # [l/kg]
FVki = 0.0044  # [l/kg]
FVkiv = 0.001  # [l/kg]
FVli = 0.021  # [l/kg]
FVlu = 0.0076  # [l/kg]
FVpa = 0.01  # [l/kg]
FVpo = 0.001  # [l/kg]
FVrev = 0.001  # [l/kg]
FVsp = 0.0026  # [l/kg]
FVve = 0.0514  # [l/kg]
Fblood = 0.02  # [-]
GU__DXMCYP3A4_Km = 0.7  # [mmol/l]
GU__DXMCYP3A4_Vmax = 0.0002  # [mmol/min/l]
GU__DXMCYP3A4_activity = 1.0  # [-]
GU__F_dxm = 0.55  # [-]
GU__Ka_abs_dxm = 3.42854395495006  # [1/hr]
GU__Vmem = nan  # [m^2]
HCT = 0.51  # [-]
HEIGHT = 170.0  # [cm]
HR = 70.0  # [1/min]
HRrest = 70.0  # [1/min]
KI__DXMEX_k = 0.017  # [1/min]
KI__DXOEX_k = 0.3  # [1/min]
KI__DXOGLUEX_k = 10.0  # [1/min]
KI__Vmem = nan  # [m^2]
Ka_dis_dxm = 0.0217391304347826  # [1/hr]
Kp_dxm = 8.73461301162365  # [-]
Kp_dxo = 4.0  # [-]
Kp_dxo_glu = 0.08  # [-]
Kp_fo_dxm = 10.0  # [-]
LI__DXMCYP2D6_Ki_qui = 1e-06  # [mmol/l]
LI__DXMCYP2D6_Km = 0.0079  # [mmol/l]
LI__DXMCYP2D6_Vmax = 0.003  # [mmol/min/l]
LI__DXMCYP3A4_Km = 0.157  # [mmol/l]
LI__DXMCYP3A4_Vmax = 0.0004  # [mmol/min/l]
LI__DXOUGT_Km = 0.69  # [mmol/l]
LI__DXOUGT_Vmax = 0.0952850262649854  # [mmol/min/l]
LI__Vmem = nan  # [m^2]
LI___activity_score = nan  # [-]
LI__cyp2d6_a0 = 1.0  # [-]
LI__cyp2d6_a1 = 0.25  # [-]
LI__cyp2d6_a10 = 0.0  # [-]
LI__cyp2d6_a11 = 0.0  # [-]
LI__cyp2d6_a12 = 0.5  # [-]
LI__cyp2d6_a13 = 0.0  # [-]
LI__cyp2d6_a14 = 0.5  # [-]
LI__cyp2d6_a15 = 1.0  # [-]
LI__cyp2d6_a16 = 0.0  # [-]
LI__cyp2d6_a17 = 0.0  # [-]
LI__cyp2d6_a18 = 2.0  # [-]
LI__cyp2d6_a19 = 3.0  # [-]
LI__cyp2d6_a2 = 0.0  # [-]
LI__cyp2d6_a20 = 4.0  # [-]
LI__cyp2d6_a21 = 5.0  # [-]
LI__cyp2d6_a22 = 6.0  # [-]
LI__cyp2d6_a23 = 1.0  # [-]
LI__cyp2d6_a24 = 0.0  # [-]
LI__cyp2d6_a25 = 0.0  # [-]
LI__cyp2d6_a26 = 1.0  # [-]
LI__cyp2d6_a27 = 0.5  # [-]
LI__cyp2d6_a28 = 1.0  # [-]
LI__cyp2d6_a29 = 2.0  # [-]
LI__cyp2d6_a3 = 0.0  # [-]
LI__cyp2d6_a30 = 3.0  # [-]
LI__cyp2d6_a31 = 4.0  # [-]
LI__cyp2d6_a32 = 5.0  # [-]
LI__cyp2d6_a33 = 6.0  # [-]
LI__cyp2d6_a34 = 0.0  # [-]
LI__cyp2d6_a35 = 0.0  # [-]
LI__cyp2d6_a36 = 1.0  # [-]
LI__cyp2d6_a37 = 1.0  # [-]
LI__cyp2d6_a38 = 1.0  # [-]
LI__cyp2d6_a39 = 2.0  # [-]
LI__cyp2d6_a4 = 0.5  # [-]
LI__cyp2d6_a40 = 0.0  # [-]
LI__cyp2d6_a41 = 0.0  # [-]
LI__cyp2d6_a42 = 0.0  # [-]
LI__cyp2d6_a43 = 1.0  # [-]
LI__cyp2d6_a44 = 0.0  # [-]
LI__cyp2d6_a45 = 0.0  # [-]
LI__cyp2d6_a46 = 0.0  # [-]
LI__cyp2d6_a47 = 0.5  # [-]
LI__cyp2d6_a48 = 1.0  # [-]
LI__cyp2d6_a49 = 1.5  # [-]
LI__cyp2d6_a5 = 0.0  # [-]
LI__cyp2d6_a50 = 0.0  # [-]
LI__cyp2d6_a51 = 0.0  # [-]
LI__cyp2d6_a52 = 1.0  # [-]
LI__cyp2d6_a53 = 2.0  # [-]
LI__cyp2d6_a54 = 1.0  # [-]
LI__cyp2d6_a55 = 0.0  # [-]
LI__cyp2d6_a56 = 1.0  # [-]
LI__cyp2d6_a57 = 0.5  # [-]
LI__cyp2d6_a58 = 0.0  # [-]
LI__cyp2d6_a59 = 0.0  # [-]
LI__cyp2d6_a6 = 0.0  # [-]
LI__cyp2d6_a60 = 0.0  # [-]
LI__cyp2d6_a61 = 0.0  # [-]
LI__cyp2d6_a62 = 0.0  # [-]
LI__cyp2d6_a63 = 0.5  # [-]
LI__cyp2d6_a64 = 0.0  # [-]
LI__cyp2d6_a65 = 1.0  # [-]
LI__cyp2d6_a66 = 0.5  # [-]
LI__cyp2d6_a67 = 0.5  # [-]
LI__cyp2d6_a68 = 0.0  # [-]
LI__cyp2d6_a69 = 0.0  # [-]
LI__cyp2d6_a7 = 0.0  # [-]
LI__cyp2d6_a70 = 0.5  # [-]
LI__cyp2d6_a71 = 0.0  # [-]
LI__cyp2d6_a72 = 0.0  # [-]
LI__cyp2d6_a73 = 0.0  # [-]
LI__cyp2d6_a74 = 0.0  # [-]
LI__cyp2d6_a75 = 0.0  # [-]
LI__cyp2d6_a76 = 0.0  # [-]
LI__cyp2d6_a77 = 0.0  # [-]
LI__cyp2d6_a78 = 0.0  # [-]
LI__cyp2d6_a79 = 0.0  # [-]
LI__cyp2d6_a8 = 0.0  # [-]
LI__cyp2d6_a80 = 0.5  # [-]
LI__cyp2d6_a81 = 0.0  # [-]
LI__cyp2d6_a82 = 0.0  # [-]
LI__cyp2d6_a83 = 0.0  # [-]
LI__cyp2d6_a84 = 1.0  # [-]
LI__cyp2d6_a9 = 0.0  # [-]
LI__cyp2d6_ac = 1.0  # [-]
LI__cyp2d6_allele1 = 0.0  # [-]
LI__cyp2d6_allele2 = 0.0  # [-]
LI__f_DXMCYP2D6_Km = 1.0  # [-]
LI__f_DXMCYP3A4_Km = 1.0  # [-]
LI__lambda_1 = -0.4  # [-]
Mr_dxm = 271.404  # [g/mol]
Mr_dxo = 257.37066  # [g/mol]
Mr_dxo_glu = 433.49478  # [g/mol]
Ri_dxm = 0.0  # [mg/min]
Vfeces = 1.0  # [l]
Vfo = 1.0  # [l]
Vfov = 1.0  # [l]
Vgulumen = 1.0  # [l]
Vstomach = 1.0  # [l]
Vurine = 1.0  # [l]
conversion_min_per_day = 1440.0  # [min/day]
f_shunting_forearm = 0.279517545017716  # [-]
ftissue_dxm = 1000.0  # [l/min]
ftissue_dxo = 100.0  # [l/min]
ftissue_dxo_glu = 3.0  # [l/min]
ti_dxm = 10.0  # [s]
```

Initial conditions x0

```
Afeces_dxm = 0.0  # [mmol] Vfeces
Astomach_dxm = 0.0  # [mmol] Vstomach
Aurine_dxm = 0.0  # [mmol] Vurine
Aurine_dxo = 0.0  # [mmol] Vurine
Aurine_dxo_glu = 0.0  # [mmol] Vurine
Car_dxm = 0.0  # [mmol/l] Var
Car_dxo = 0.0  # [mmol/l] Var
Car_dxo_glu = 0.0  # [mmol/l] Var
Cfo_dxm = 0.0  # [mmol/l] Vfo_tissue
Cfo_dxo = 0.0  # [mmol/l] Vfo_tissue
Cfo_dxo_glu = 0.0  # [mmol/l] Vfo_tissue
Cfo_plasma_dxm = 0.0  # [mmol/l] Vfo_plasma
Cfo_plasma_dxo = 0.0  # [mmol/l] Vfo_plasma
Cfo_plasma_dxo_glu = 0.0  # [mmol/l] Vfo_plasma
Cfov_dxm = 0.0  # [mmol/l] Vfov
Cfov_dxo = 0.0  # [mmol/l] Vfov
Cfov_dxo_glu = 0.0  # [mmol/l] Vfov
Cgu_dxm = 0.0  # [mmol/l] Vgu_tissue
Cgu_dxo = 0.0  # [mmol/l] Vgu_tissue
Cgu_dxo_glu = 0.0  # [mmol/l] Vgu_tissue
Cgu_plasma_dxm = 0.0  # [mmol/l] Vgu_plasma
Cgu_plasma_dxo = 0.0  # [mmol/l] Vgu_plasma
Cgu_plasma_dxo_glu = 0.0  # [mmol/l] Vgu_plasma
Cgulumen_dxm = 0.0  # [mmol/l] Vgulumen
Chv_dxm = 0.0  # [mmol/l] Vhv
Chv_dxo = 0.0  # [mmol/l] Vhv
Chv_dxo_glu = 0.0  # [mmol/l] Vhv
Cki_dxm = 0.0  # [mmol/l] Vki_tissue
Cki_dxo = 0.0  # [mmol/l] Vki_tissue
Cki_dxo_glu = 0.0  # [mmol/l] Vki_tissue
Cki_plasma_dxm = 0.0  # [mmol/l] Vki_plasma
Cki_plasma_dxo = 0.0  # [mmol/l] Vki_plasma
Cki_plasma_dxo_glu = 0.0  # [mmol/l] Vki_plasma
Ckiv_dxm = 0.0  # [mmol/l] Vkiv
Ckiv_dxo = 0.0  # [mmol/l] Vkiv
Ckiv_dxo_glu = 0.0  # [mmol/l] Vkiv
Cli_dxm = 0.0  # [mmol/l] Vli_tissue
Cli_dxo = 0.0  # [mmol/l] Vli_tissue
Cli_dxo_glu = 0.0  # [mmol/l] Vli_tissue
Cli_plasma_dxm = 0.0  # [mmol/l] Vli_plasma
Cli_plasma_dxo = 0.0  # [mmol/l] Vli_plasma
Cli_plasma_dxo_glu = 0.0  # [mmol/l] Vli_plasma
Clu_dxm = 0.0  # [mmol/l] Vlu_tissue
Clu_dxo = 0.0  # [mmol/l] Vlu_tissue
Clu_dxo_glu = 0.0  # [mmol/l] Vlu_tissue
Clu_plasma_dxm = 0.0  # [mmol/l] Vlu_plasma
Clu_plasma_dxo = 0.0  # [mmol/l] Vlu_plasma
Clu_plasma_dxo_glu = 0.0  # [mmol/l] Vlu_plasma
Cpa_dxm = 0.0  # [mmol/l] Vpa_tissue
Cpa_dxo = 0.0  # [mmol/l] Vpa_tissue
Cpa_dxo_glu = 0.0  # [mmol/l] Vpa_tissue
Cpa_plasma_dxm = 0.0  # [mmol/l] Vpa_plasma
Cpa_plasma_dxo = 0.0  # [mmol/l] Vpa_plasma
Cpa_plasma_dxo_glu = 0.0  # [mmol/l] Vpa_plasma
Cpo_dxm = 0.0  # [mmol/l] Vpo
Cpo_dxo = 0.0  # [mmol/l] Vpo
Cpo_dxo_glu = 0.0  # [mmol/l] Vpo
Cre_dxm = 0.0  # [mmol/l] Vre_tissue
Cre_dxo = 0.0  # [mmol/l] Vre_tissue
Cre_dxo_glu = 0.0  # [mmol/l] Vre_tissue
Cre_plasma_dxm = 0.0  # [mmol/l] Vre_plasma
Cre_plasma_dxo = 0.0  # [mmol/l] Vre_plasma
Cre_plasma_dxo_glu = 0.0  # [mmol/l] Vre_plasma
Crev_dxm = 0.0  # [mmol/l] Vrev
Crev_dxo = 0.0  # [mmol/l] Vrev
Crev_dxo_glu = 0.0  # [mmol/l] Vrev
Csp_dxm = 0.0  # [mmol/l] Vsp_tissue
Csp_dxo = 0.0  # [mmol/l] Vsp_tissue
Csp_dxo_glu = 0.0  # [mmol/l] Vsp_tissue
Csp_plasma_dxm = 0.0  # [mmol/l] Vsp_plasma
Csp_plasma_dxo = 0.0  # [mmol/l] Vsp_plasma
Csp_plasma_dxo_glu = 0.0  # [mmol/l] Vsp_plasma
Cve_dxm = 0.0  # [mmol/l] Vve
Cve_dxo = 0.0  # [mmol/l] Vve
Cve_dxo_glu = 0.0  # [mmol/l] Vve
GU__dxmmet = 0.0  # [mmol/l] Vgu_tissue
IVDOSE_dxm = 0.0  # [mg]
LI__qui = 0.0  # [mmol/l] Vli_tissue
PODOSE_dxm = 0.0  # [mg]
cum_dose_dxm = 0.0  # [mg]
```

ODE system

```
# y
Afov_dxm = Cfov_dxm * Vfov  # [mmol]
Afov_dxo = Cfov_dxo * Vfov  # [mmol]
Afov_dxo_glu = Cfov_dxo_glu * Vfov  # [mmol]
Aurine_dxo_total = Aurine_dxo + Aurine_dxo_glu  # [mmol]
BSA = 0.024265 * (BW / 1)**0.5378 * (HEIGHT / 1)**0.3964  # [m^2]
CO = BW * COBW + (HR - HRrest) * COHRI / 60  # [ml/s]
FQre = 1 - (FQki + FQh + FQfo)  # [-]
FVre = 1 - (FVgu + FVki + FVli + FVlu + FVsp + FVpa + FVve + FVar + FVfo)  # [l/kg]
Ki_dxm = (0.693 / ti_dxm) * 60  # [1/min]
LI__cyp2d6_activity1 = piecewise(LI__cyp2d6_ac / 2, LI__cyp2d6_allele1 == -1, LI__cyp2d6_a0, LI__cyp2d6
LI__cyp2d6_activity2 = piecewise(LI__cyp2d6_ac / 2, LI__cyp2d6_allele2 == -1, LI__cyp2d6_a0, LI__cyp2d6
Var = BW * FVar - (FVar / (FVar + FVve)) * BW * Fblood * (1 - FVve - FVar)  # [l]
```

model: dextromethorphan_body

Autogenerated ODE System from SBML file with sbmlutils. time: [min] substance: [mmol] extent: [mmol] volume: [l] area: [m^2] length: [m]

```
Vfo_plasma = Vfo * Fblood * (1 - HCT)  # [l]
Vfo_tissue = Vfo * (1 - Fblood)  # [l]
Vgu = BW * FVgu  # [l]
Vhv = (1 - HCT) * (BW * FVhv - (FVhv / (FVar + FVve + FVpo + FVhv + FVkiv + FVrev + FVfov)) * BW * Fbloo
Vki = BW * FVki  # [l]
Vkiv = BW * FVkiv - (FVkiv / (FVar + FVve)) * BW * Fblood * (1 - FVve - FVar)  # [l]
Vli = BW * FVli  # [l]
Vlu = BW * FVlu  # [l]
Vpa = BW * FVpa  # [l]
Vpo = (1 - HCT) * (BW * FVpo - (FVpo / (FVar + FVve + FVpo + FVhv + FVkiv + FVrev + FVfov)) * BW * Fbloo
Vrev = BW * FVrev - (FVrev / (FVar + FVve)) * BW * Fblood * (1 - FVve - FVar)  # [l]
Vsp = BW * FVsp  # [l]
Vve = BW * FVve - (FVve / (FVar + FVve)) * BW * Fblood * (1 - FVve - FVar)  # [l]
Xfeces_dxm = Afeces_dxm * Mr_dxm  # [mg]
Xurine_dxm = Aurine_dxm * Mr_dxm  # [mg]
Xurine_dxo = Aurine_dxo * Mr_dxo  # [mg]
Xurine_dxo_glu = Aurine_dxo_glu * Mr_dxo_glu  # [mg]
dissolution_dxm = (Ka_dis_dxm / 60) * PODOSE_dxm / Mr_dxm  # [mmol/min]
dxm_dxo_fov = Cfov_dxm / Cfov_dxo  # [-]
dxm_dxo_plasma = Cve_dxm / Cve_dxo  # [-]
dxm_dxo_rev = Crev_dxm / Crev_dxo  # [-]
dxm_dxo_total_fov = Cfov_dxm / (Cfov_dxo + Cfov_dxo_glu)  # [-]
dxm_dxo_total_plasma = Cve_dxm / (Cve_dxo + Cve_dxo_glu)  # [-]
dxm_dxo_total_rev = Crev_dxm / (Crev_dxo + Crev_dxo_glu)  # [-]
dxm_dxo_total_urine = Aurine_dxm / (Aurine_dxo + Aurine_dxo_glu)  # [-]
dxm_dxo_urine = Aurine_dxm / Aurine_dxo  # [-]
dxo_total_fov = Cfov_dxo + Cfov_dxo_glu  # [mmol/l]
dxo_total_plasma = Cve_dxo + Cve_dxo_glu  # [mmol/l]
dxo_total_rev = Crev_dxo + Crev_dxo_glu  # [mmol/l]
transport_fo_dxm = ftissue_dxm * (Cfo_plasma_dxm * Kp_fo_dxm - Cfo_dxm)  # [mmol/min]
transport_fo_dxo = ftissue_dxo * (Cfo_plasma_dxo * Kp_dxo - Cfo_dxo)  # [mmol/min]
transport_fo_dxo_glu = ftissue_dxo_glu * (Cfo_plasma_dxo_glu * Kp_dxo_glu - Cfo_dxo_glu)  # [mmol/min]
transport_gu_dxm = ftissue_dxm * (Cgu_plasma_dxm * Kp_dxm - Cgu_dxm)  # [mmol/min]
transport_gu_dxo = ftissue_dxo * (Cgu_plasma_dxo * Kp_dxo - Cgu_dxo)  # [mmol/min]
transport_gu_dxo_glu = ftissue_dxo_glu * (Cgu_plasma_dxo_glu * Kp_dxo_glu - Cgu_dxo_glu)  # [mmol/min]
transport_ki_dxm = ftissue_dxm * (Cki_plasma_dxm * Kp_dxm - Cki_dxm)  # [mmol/min]
transport_ki_dxo = ftissue_dxo * (Cki_plasma_dxo * Kp_dxo - Cki_dxo)  # [mmol/min]
transport_ki_dxo_glu = ftissue_dxo_glu * (Cki_plasma_dxo_glu * Kp_dxo_glu - Cki_dxo_glu)  # [mmol/min]
transport_li_dxm = ftissue_dxm * (Cli_plasma_dxm * Kp_dxm - Cli_dxm)  # [mmol/min]
transport_li_dxo = ftissue_dxo * (Cli_plasma_dxo * Kp_dxo - Cli_dxo)  # [mmol/min]
transport_li_dxo_glu = ftissue_dxo_glu * (Cli_plasma_dxo_glu * Kp_dxo_glu - Cli_dxo_glu)  # [mmol/min]
transport_lu_dxm = ftissue_dxm * (Clu_plasma_dxm * Kp_dxm - Clu_dxm)  # [mmol/min]
transport_lu_dxo = ftissue_dxo * (Clu_plasma_dxo * Kp_dxo - Clu_dxo)  # [mmol/min]
transport_lu_dxo_glu = ftissue_dxo_glu * (Clu_plasma_dxo_glu * Kp_dxo_glu - Clu_dxo_glu)  # [mmol/min]
transport_pa_dxm = ftissue_dxm * (Cpa_plasma_dxm * Kp_dxm - Cpa_dxm)  # [mmol/min]
transport_pa_dxo = ftissue_dxo * (Cpa_plasma_dxo * Kp_dxo - Cpa_dxo)  # [mmol/min]
transport_pa_dxo_glu = ftissue_dxo_glu * (Cpa_plasma_dxo_glu * Kp_dxo_glu - Cpa_dxo_glu)  # [mmol/min]
transport_re_dxm = ftissue_dxm * (Cre_plasma_dxm * Kp_dxm - Cre_dxm)  # [mmol/min]
transport_re_dxo = ftissue_dxo * (Cre_plasma_dxo * Kp_dxo - Cre_dxo)  # [mmol/min]
transport_re_dxo_glu = ftissue_dxo_glu * (Cre_plasma_dxo_glu * Kp_dxo_glu - Cre_dxo_glu)  # [mmol/min]
transport_sp_dxm = ftissue_dxm * (Csp_plasma_dxm * Kp_dxm - Csp_dxm)  # [mmol/min]
transport_sp_dxo = ftissue_dxo * (Csp_plasma_dxo * Kp_dxo - Csp_dxo)  # [mmol/min]
transport_sp_dxo_glu = ftissue_dxo_glu * (Csp_plasma_dxo_glu * Kp_dxo_glu - Csp_dxo_glu)  # [mmol/min]
Aar_dxm = Car_dxm * Var  # [mmol]
Aar_dxo = Car_dxo * Var  # [mmol]
Aar_dxo_glu = Car_dxo_glu * Var  # [mmol]
Afo_plasma_dxm = Cfo_plasma_dxm * Vfo_plasma  # [mmol]
Afo_plasma_dxo = Cfo_plasma_dxo * Vfo_plasma  # [mmol]
Afo_plasma_dxo_glu = Cfo_plasma_dxo_glu * Vfo_plasma  # [mmol]
Ahv_dxm = Chv_dxm * Vhv  # [mmol]
Ahv_dxo = Chv_dxo * Vhv  # [mmol]
Ahv_dxo_glu = Chv_dxo_glu * Vhv  # [mmol]
Akiv_dxm = Ckiv_dxm * Vkiv  # [mmol]
Akiv_dxo = Ckiv_dxo * Vkiv  # [mmol]
Akiv_dxo_glu = Ckiv_dxo_glu * Vkiv  # [mmol]
Apo_dxm = Cpo_dxm * Vpo  # [mmol]
Apo_dxo = Cpo_dxo * Vpo  # [mmol]
Apo_dxo_glu = Cpo_dxo_glu * Vpo  # [mmol]
Arev_dxm = Crev_dxm * Vrev  # [mmol]
Arev_dxo = Crev_dxo * Vrev  # [mmol]
Arev_dxo_glu = Crev_dxo_glu * Vrev  # [mmol]
Ave_dxm = Cve_dxm * Vve  # [mmol]
Ave_dxo = Cve_dxo * Vve  # [mmol]
Ave_dxo_glu = Cve_dxo_glu * Vve  # [mmol]
LI__cyp2d6_activity = LI__cyp2d6_activity1 + LI__cyp2d6_activity2  # [-]
Mfov_dxm = (Afov_dxm / Vfov) * Mr_dxm  # [mg/l]
Mfov_dxo = (Afov_dxo / Vfov) * Mr_dxo  # [mg/l]
Mfov_dxo_glu = (Afov_dxo_glu / Vfov) * Mr_dxo_glu  # [mg/l]
QC = (CO / 1000) * 60  # [l/min]
Vgu_plasma = Vgu * Fblood * (1 - HCT)  # [l]
Vgu_tissue = Vgu * (1 - Fblood)  # [l]
Vki_plasma = Vki * Fblood * (1 - HCT)  # [l]
Vki_tissue = Vki * (1 - Fblood)  # [l]
Vli_plasma = Vli * Fblood * (1 - HCT)  # [l]
Vli_tissue = Vli * (1 - Fblood)  # [l]
Vlu_plasma = Vlu * Fblood * (1 - HCT)  # [l]
Vlu_tissue = Vlu * (1 - Fblood)  # [l]
Vpa_plasma = Vpa * Fblood * (1 - HCT)  # [l]
Vpa_tissue = Vpa * (1 - Fblood)  # [l]
Vre = BW * FVre  # [l]
Vsp_plasma = Vsp * Fblood * (1 - HCT)  # [l]
Vsp_tissue = Vsp * (1 - Fblood)  # [l]
Xfov_dxm = Afov_dxm * Mr_dxm  # [mg]
Xfov_dxo = Afov_dxo * Mr_dxo  # [mg]
Xfov_dxo_glu = Afov_dxo_glu * Mr_dxo_glu  # [mg]
iv_dxm = Ki_dxm * IVDOSE_dxm / Mr_dxm  # [mmol/min]
Agu_plasma_dxm = Cgu_plasma_dxm * Vgu_plasma  # [mmol]
Agu_plasma_dxo = Cgu_plasma_dxo * Vgu_plasma  # [mmol]
Agu_plasma_dxo_glu = Cgu_plasma_dxo_glu * Vgu_plasma  # [mmol]
Aki_plasma_dxm = Cki_plasma_dxm * Vki_plasma  # [mmol]
Aki_plasma_dxo = Cki_plasma_dxo * Vki_plasma  # [mmol]
Aki_plasma_dxo_glu = Cki_plasma_dxo_glu * Vki_plasma  # [mmol]
Ali_plasma_dxm = Cli_plasma_dxm * Vli_plasma  # [mmol]
Ali_plasma_dxo = Cli_plasma_dxo * Vli_plasma  # [mmol]
Ali_plasma_dxo_glu = Cli_plasma_dxo_glu * Vli_plasma  # [mmol]
Alu_plasma_dxm = Clu_plasma_dxm * Vlu_plasma  # [mmol]
Alu_plasma_dxo = Clu_plasma_dxo * Vlu_plasma  # [mmol]
Alu_plasma_dxo_glu = Clu_plasma_dxo_glu * Vlu_plasma  # [mmol]
Apa_plasma_dxm = Cpa_plasma_dxm * Vpa_plasma  # [mmol]
Apa_plasma_dxo = Cpa_plasma_dxo * Vpa_plasma  # [mmol]
Apa_plasma_dxo_glu = Cpa_plasma_dxo_glu * Vpa_plasma  # [mmol]
Asp_plasma_dxm = Csp_plasma_dxm * Vsp_plasma  # [mmol]
Asp_plasma_dxo = Csp_plasma_dxo * Vsp_plasma  # [mmol]
Asp_plasma_dxo_glu = Csp_plasma_dxo_glu * Vsp_plasma  # [mmol]
GU__DXMCYP3A4 = GU__DXMCYP3A4_Vmax * GU__DXMCYP3A4_activity * Vgu_tissue * Cgu_dxm / (Cgu_dxm + GU__DXMC
GU__absorption = (Vgu_tissue * GU__Ka_abs_dxm / 60) * Cgulumen_dxm  # [mmol/min]
KI__DXMEX = KI__DXMEX_k * Vki_tissue * Cki_dxm  # [mmol/min]
KI__DXOEX = KI__DXOEX_k * Vki_tissue * Cki_dxo  # [mmol/min]
KI__DXOGLUEX = KI__DXOGLUEX_k * Vki_tissue * Cki_dxo_glu  # [mmol/min]
LI__DXMCYP2D6 = LI__DXMCYP2D6_Vmax * Vli_tissue * LI__cyp2d6_activity * Cli_dxm / ((1 + LI__qui / LI__DX
LI__DXMCYP3A4 = LI__DXMCYP3A4_Vmax * Vli_tissue * Cli_dxm / (LI__f_DXMCYP3A4_Km * LI__DXMCYP3A4_Km + Cli
LI__DXOUGT = LI__DXOUGT_Vmax * Vli_tissue * Cli_dxo / (LI__DXOUGT_Km + Cli_dxo)  # [mmol/min]
Mar_dxm = (Aar_dxm / Var) * Mr_dxm  # [mg/l]
Mar_dxo = (Aar_dxo / Var) * Mr_dxo  # [mg/l]
Mar_dxo_glu = (Aar_dxo_glu / Var) * Mr_dxo_glu  # [mg/l]
Mfo_plasma_dxm = (Afo_plasma_dxm / Vfo_plasma) * Mr_dxm  # [mg/l]
Mfo_plasma_dxo = (Afo_plasma_dxo / Vfo_plasma) * Mr_dxo  # [mg/l]
Mfo_plasma_dxo_glu = (Afo_plasma_dxo_glu / Vfo_plasma) * Mr_dxo_glu  # [mg/l]
Mhv_dxm = (Ahv_dxm / Vhv) * Mr_dxm  # [mg/l]
Mhv_dxo = (Ahv_dxo / Vhv) * Mr_dxo  # [mg/l]
Mhv_dxo_glu = (Ahv_dxo_glu / Vhv) * Mr_dxo_glu  # [mg/l]
Mkiv_dxm = (Akiv_dxm / Vkiv) * Mr_dxm  # [mg/l]
Mkiv_dxo = (Akiv_dxo / Vkiv) * Mr_dxo  # [mg/l]
Mkiv_dxo_glu = (Akiv_dxo_glu / Vkiv) * Mr_dxo_glu  # [mg/l]
Mpo_dxm = (Apo_dxm / Vpo) * Mr_dxm  # [mg/l]
Mpo_dxo = (Apo_dxo / Vpo) * Mr_dxo  # [mg/l]
Mpo_dxo_glu = (Apo_dxo_glu / Vpo) * Mr_dxo_glu  # [mg/l]
Mrev_dxm = (Arev_dxm / Vrev) * Mr_dxm  # [mg/l]
Mrev_dxo = (Arev_dxo / Vrev) * Mr_dxo  # [mg/l]
Mrev_dxo_glu = (Arev_dxo_glu / Vrev) * Mr_dxo_glu  # [mg/l]
Mve_dxm = (Ave_dxm / Vve) * Mr_dxm  # [mg/l]
Mve_dxo = (Ave_dxo / Vve) * Mr_dxo  # [mg/l]
Mve_dxo_glu = (Ave_dxo_glu / Vve) * Mr_dxo_glu  # [mg/l]
Qfo = QC * FQfo  # [l/min]
Qgu = QC * FQgu  # [l/min]
Qh = QC * FQh  # [l/min]
Qki = QC * FQki  # [l/min]
Qlu = QC * FQlu  # [l/min]
Qpa = QC * FQpa  # [l/min]
Qre = QC * FQre  # [l/min]
Qsp = QC * FQsp  # [l/min]
Vre_plasma = Vre * Fblood * (1 - HCT)  # [l]
Vre_tissue = Vre * (1 - Fblood)  # [l]
Xar_dxm = Aar_dxm * Mr_dxm  # [mg]
Xar_dxo = Aar_dxo * Mr_dxo  # [mg]
Xar_dxo_glu = Aar_dxo_glu * Mr_dxo_glu  # [mg]
Xfo_plasma_dxm = Afo_plasma_dxm * Mr_dxm  # [mg]
Xfo_plasma_dxo = Afo_plasma_dxo * Mr_dxo  # [mg]
Xfo_plasma_dxo_glu = Afo_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xhv_dxm = Ahv_dxm * Mr_dxm  # [mg]
Xhv_dxo = Ahv_dxo * Mr_dxo  # [mg]
Xhv_dxo_glu = Ahv_dxo_glu * Mr_dxo_glu  # [mg]
Xkiv_dxm = Akiv_dxm * Mr_dxm  # [mg]
Xkiv_dxo = Akiv_dxo * Mr_dxo  # [mg]
Xkiv_dxo_glu = Akiv_dxo_glu * Mr_dxo_glu  # [mg]
Xpo_dxm = Apo_dxm * Mr_dxm  # [mg]
Xpo_dxo = Apo_dxo * Mr_dxo  # [mg]
Xpo_dxo_glu = Apo_dxo_glu * Mr_dxo_glu  # [mg]
Xrev_dxm = Arev_dxm * Mr_dxm  # [mg]
Xrev_dxo = Arev_dxo * Mr_dxo  # [mg]
Xrev_dxo_glu = Arev_dxo_glu * Mr_dxo_glu  # [mg]
Xve_dxm = Ave_dxm * Mr_dxm  # [mg]
Xve_dxo = Ave_dxo * Mr_dxo  # [mg]
Xve_dxo_glu = Ave_dxo_glu * Mr_dxo_glu  # [mg]
Are_plasma_dxm = Cre_plasma_dxm * Vre_plasma  # [mmol]
Are_plasma_dxo = Cre_plasma_dxo * Vre_plasma  # [mmol]
Are_plasma_dxo_glu = Cre_plasma_dxo_glu * Vre_plasma  # [mmol]
Flow_ar_fo_dxm = Car_dxm * Qfo * (1 - f_shunting_forearm)  # [mmol/min]
Flow_ar_fo_dxo = Car_dxo * Qfo * (1 - f_shunting_forearm)  # [mmol/min]
Flow_ar_fo_dxo_glu = Car_dxo_glu * Qfo * (1 - f_shunting_forearm)  # [mmol/min]
Flow_ar_gu_dxm = Qgu * Car_dxm  # [mmol/min]
Flow_ar_gu_dxo = Qgu * Car_dxo  # [mmol/min]
Flow_ar_gu_dxo_glu = Qgu * Car_dxo_glu  # [mmol/min]
Flow_ar_ki_dxm = Qki * Car_dxm  # [mmol/min]
Flow_ar_ki_dxo = Qki * Car_dxo  # [mmol/min]
Flow_ar_ki_dxo_glu = Qki * Car_dxo_glu  # [mmol/min]
Flow_ar_pa_dxm = Qpa * Car_dxm  # [mmol/min]
Flow_ar_pa_dxo = Qpa * Car_dxo  # [mmol/min]
Flow_ar_pa_dxo_glu = Qpa * Car_dxo_glu  # [mmol/min]
Flow_ar_re_dxm = Qre * Car_dxm  # [mmol/min]
Flow_ar_re_dxo = Qre * Car_dxo  # [mmol/min]
Flow_ar_re_dxo_glu = Qre * Car_dxo_glu  # [mmol/min]
Flow_ar_sp_dxm = Qsp * Car_dxm  # [mmol/min]
Flow_ar_sp_dxo = Qsp * Car_dxo  # [mmol/min]
Flow_ar_sp_dxo_glu = Qsp * Car_dxo_glu  # [mmol/min]
Flow_fo_fov_dxm = Qfo * (1 - f_shunting_forearm) * Cfo_plasma_dxm + Qfo * f_shunting_forearm * Car_dxm
Flow_fo_fov_dxo = Qfo * (1 - f_shunting_forearm) * Cfo_plasma_dxo + Qfo * f_shunting_forearm * Car_dxo
Flow_fo_fov_dxo_glu = Qfo * (1 - f_shunting_forearm) * Cfo_plasma_dxo_glu + Qfo * f_shunting_forearm *
Flow_fov_ve_dxm = Qfo * Cfov_dxm  # [mmol/min]
Flow_fov_ve_dxo = Qfo * Cfov_dxo  # [mmol/min]
Flow_fov_ve_dxo_glu = Qfo * Cfov_dxo_glu  # [mmol/min]
Flow_gu_po_dxm = Qgu * Cgu_plasma_dxm  # [mmol/min]
Flow_gu_po_dxo = Qgu * Cgu_plasma_dxo  # [mmol/min]
Flow_gu_po_dxo_glu = Qgu * Cgu_plasma_dxo_glu  # [mmol/min]
Flow_hv_ve_dxm = Qh * Chv_dxm  # [mmol/min]
Flow_hv_ve_dxo = Qh * Chv_dxo  # [mmol/min]
Flow_hv_ve_dxo_glu = Qh * Chv_dxo_glu  # [mmol/min]
Flow_ki_kiv_dxm = Qki * Cki_plasma_dxm  # [mmol/min]
Flow_ki_kiv_dxo = Qki * Cki_plasma_dxo  # [mmol/min]
Flow_ki_kiv_dxo_glu = Qki * Cki_plasma_dxo_glu  # [mmol/min]
Flow_kiv_ve_dxm = Qki * Ckiv_dxm  # [mmol/min]
Flow_kiv_ve_dxo = Qki * Ckiv_dxo  # [mmol/min]
Flow_kiv_ve_dxo_glu = Qki * Ckiv_dxo_glu  # [mmol/min]
Flow_li_hv_dxm = Qh * Cli_plasma_dxm  # [mmol/min]
Flow_li_hv_dxo = Qh * Cli_plasma_dxo  # [mmol/min]
Flow_li_hv_dxo_glu = Qh * Cli_plasma_dxo_glu  # [mmol/min]
Flow_lu_ar_dxm = Qlu * Clu_plasma_dxm  # [mmol/min]
Flow_lu_ar_dxo = Qlu * Clu_plasma_dxo  # [mmol/min]
Flow_lu_ar_dxo_glu = Qlu * Clu_plasma_dxo_glu  # [mmol/min]
Flow_pa_po_dxm = Qpa * Cpa_plasma_dxm  # [mmol/min]
Flow_pa_po_dxo = Qpa * Cpa_plasma_dxo  # [mmol/min]
Flow_pa_po_dxo_glu = Qpa * Cpa_plasma_dxo_glu  # [mmol/min]
Flow_re_rev_dxm = Qre * Cre_plasma_dxm  # [mmol/min]
Flow_re_rev_dxo = Qre * Cre_plasma_dxo  # [mmol/min]
Flow_re_rev_dxo_glu = Qre * Cre_plasma_dxo_glu  # [mmol/min]
Flow_rev_ve_dxm = Qre * Crev_dxm  # [mmol/min]
Flow_rev_ve_dxo = Qre * Crev_dxo  # [mmol/min]
Flow_rev_ve_dxo_glu = Qre * Crev_dxo_glu  # [mmol/min]
Flow_sp_po_dxm = Qsp * Csp_plasma_dxm  # [mmol/min]
Flow_sp_po_dxo = Qsp * Csp_plasma_dxo  # [mmol/min]
Flow_sp_po_dxo_glu = Qsp * Csp_plasma_dxo_glu  # [mmol/min]
Flow_ve_lu_dxm = Qlu * Cve_dxm  # [mmol/min]
Flow_ve_lu_dxo = Qlu * Cve_dxo  # [mmol/min]
Flow_ve_lu_dxo_glu = Qlu * Cve_dxo_glu  # [mmol/min]
GU__absorption_dxm = GU__F_dxm * GU__absorption  # [mmol/min]
GU__excretion_dxm = (1 - GU__F_dxm) * GU__absorption  # [mmol/min]
Mgu_plasma_dxm = (Agu_plasma_dxm / Vgu_plasma) * Mr_dxm  # [mg/l]
Mgu_plasma_dxo = (Agu_plasma_dxo / Vgu_plasma) * Mr_dxo  # [mg/l]
Mgu_plasma_dxo_glu = (Agu_plasma_dxo_glu / Vgu_plasma) * Mr_dxo_glu  # [mg/l]
Mki_plasma_dxm = (Aki_plasma_dxm / Vki_plasma) * Mr_dxm  # [mg/l]
Mki_plasma_dxo = (Aki_plasma_dxo / Vki_plasma) * Mr_dxo  # [mg/l]
Mki_plasma_dxo_glu = (Aki_plasma_dxo_glu / Vki_plasma) * Mr_dxo_glu  # [mg/l]
Mli_plasma_dxm = (Ali_plasma_dxm / Vli_plasma) * Mr_dxm  # [mg/l]
Mli_plasma_dxo = (Ali_plasma_dxo / Vli_plasma) * Mr_dxo  # [mg/l]
Mli_plasma_dxo_glu = (Ali_plasma_dxo_glu / Vli_plasma) * Mr_dxo_glu  # [mg/l]
Mlu_plasma_dxm = (Alu_plasma_dxm / Vlu_plasma) * Mr_dxm  # [mg/l]
Mlu_plasma_dxo = (Alu_plasma_dxo / Vlu_plasma) * Mr_dxo  # [mg/l]
Mlu_plasma_dxo_glu = (Alu_plasma_dxo_glu / Vlu_plasma) * Mr_dxo_glu  # [mg/l]
Mpa_plasma_dxm = (Apa_plasma_dxm / Vpa_plasma) * Mr_dxm  # [mg/l]
Mpa_plasma_dxo = (Apa_plasma_dxo / Vpa_plasma) * Mr_dxo  # [mg/l]
Mpa_plasma_dxo_glu = (Apa_plasma_dxo_glu / Vpa_plasma) * Mr_dxo_glu  # [mg/l]
Msp_plasma_dxm = (Asp_plasma_dxm / Vsp_plasma) * Mr_dxm  # [mg/l]
Msp_plasma_dxo = (Asp_plasma_dxo / Vsp_plasma) * Mr_dxo  # [mg/l]
Msp_plasma_dxo_glu = (Asp_plasma_dxo_glu / Vsp_plasma) * Mr_dxo_glu  # [mg/l]
Qha = Qh - Qgu - Qsp - Qpa  # [l/min]
Qpo = Qsp + Qpa + Qgu  # [l/min]
Xgu_plasma_dxm = Agu_plasma_dxm * Mr_dxm  # [mg]
Xgu_plasma_dxo = Agu_plasma_dxo * Mr_dxo  # [mg]
Xgu_plasma_dxo_glu = Agu_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xki_plasma_dxm = Aki_plasma_dxm * Mr_dxm  # [mg]
Xki_plasma_dxo = Aki_plasma_dxo * Mr_dxo  # [mg]
Xki_plasma_dxo_glu = Aki_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xli_plasma_dxm = Ali_plasma_dxm * Mr_dxm  # [mg]
Xli_plasma_dxo = Ali_plasma_dxo * Mr_dxo  # [mg]
Xli_plasma_dxo_glu = Ali_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xlu_plasma_dxm = Alu_plasma_dxm * Mr_dxm  # [mg]
Xlu_plasma_dxo = Alu_plasma_dxo * Mr_dxo  # [mg]
Xlu_plasma_dxo_glu = Alu_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xpa_plasma_dxm = Apa_plasma_dxm * Mr_dxm  # [mg]
Xpa_plasma_dxo = Apa_plasma_dxo * Mr_dxo  # [mg]
Xpa_plasma_dxo_glu = Apa_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Xsp_plasma_dxm = Asp_plasma_dxm * Mr_dxm  # [mg]
Xsp_plasma_dxo = Asp_plasma_dxo * Mr_dxo  # [mg]
Xsp_plasma_dxo_glu = Asp_plasma_dxo_glu * Mr_dxo_glu  # [mg]
Flow_ar_li_dxm = Qha * Car_dxm  # [mmol/min]
Flow_ar_li_dxo = Qha * Car_dxo  # [mmol/min]
Flow_ar_li_dxo_glu = Qha * Car_dxo_glu  # [mmol/min]
Flow_po_li_dxm = Qpo * Cpo_dxm  # [mmol/min]
Flow_po_li_dxo = Qpo * Cpo_dxo  # [mmol/min]
Flow_po_li_dxo_glu = Qpo * Cpo_dxo_glu  # [mmol/min]
Mre_plasma_dxm = (Are_plasma_dxm / Vre_plasma) * Mr_dxm  # [mg/l]
Mre_plasma_dxo = (Are_plasma_dxo / Vre_plasma) * Mr_dxo  # [mg/l]
Mre_plasma_dxo_glu = (Are_plasma_dxo_glu / Vre_plasma) * Mr_dxo_glu  # [mg/l]
Xre_plasma_dxm = Are_plasma_dxm * Mr_dxm  # [mg]
Xre_plasma_dxo = Are_plasma_dxo * Mr_dxo  # [mg]
Xre_plasma_dxo_glu = Are_plasma_dxo_glu * Mr_dxo_glu  # [mg]

# odes
d Afeces_dxm/dt = GU__excretion_dxm  # [mmol/min]
d Astomach_dxm/dt = 0  # [mmol/min]
d Aurine_dxm/dt = KI__DXMEX  # [mmol/min]
d Aurine_dxo/dt = KI__DXOEX  # [mmol/min]
d Aurine_dxo_glu/dt = KI__DXOGLUEX  # [mmol/min]
d Car_dxm/dt = (-Flow_ar_gu_dxm / Var - Flow_ar_ki_dxm / Var - Flow_ar_li_dxm / Var) + Flow_lu_ar_dxm /
d Car_dxo/dt = (-Flow_ar_gu_dxo / Var - Flow_ar_ki_dxo / Var - Flow_ar_li_dxo / Var) + Flow_lu_ar_dxo /
d Car_dxo_glu/dt = (-Flow_ar_gu_dxo_glu / Var - Flow_ar_ki_dxo_glu / Var - Flow_ar_li_dxo_glu / Var) +
d Cfo_dxm/dt = transport_fo_dxm / Vfo_tissue  # [mmol/l/min]
d Cfo_dxo/dt = transport_fo_dxo / Vfo_tissue  # [mmol/l/min]
d Cfo_dxo_glu/dt = transport_fo_dxo_glu / Vfo_tissue  # [mmol/l/min]
d Cfo_plasma_dxm/dt = -transport_fo_dxm / Vfo_plasma + Flow_ar_fo_dxm / Vfo_plasma - Flow_fo_fov_dxm /
d Cfo_plasma_dxo/dt = -transport_fo_dxo / Vfo_plasma + Flow_ar_fo_dxo / Vfo_plasma - Flow_fo_fov_dxo /
d Cfo_plasma_dxo_glu/dt = -transport_fo_dxo_glu / Vfo_plasma + Flow_ar_fo_dxo_glu / Vfo_plasma - Flow_f
d Cfov_dxm/dt = Flow_fo_fov_dxm / Vfov - Flow_fov_ve_dxm / Vfov  # [mmol/l/min]
d Cfov_dxo/dt = Flow_fo_fov_dxo / Vfov - Flow_fov_ve_dxo / Vfov  # [mmol/l/min]
d Cfov_dxo_glu/dt = Flow_fo_fov_dxo_glu / Vfov - Flow_fov_ve_dxo_glu / Vfov  # [mmol/l/min]
d Cgu_dxm/dt = transport_gu_dxm / Vgu_tissue + GU__absorption_dxm / Vgu_tissue - GU__DXMCYP3A4 / Vgu_ti
d Cgu_dxo/dt = transport_gu_dxo / Vgu_tissue  # [mmol/l/min]
d Cgu_dxo_glu/dt = transport_gu_dxo_glu / Vgu_tissue  # [mmol/l/min]
d Cgu_plasma_dxm/dt = -transport_gu_dxm / Vgu_plasma + Flow_ar_gu_dxm / Vgu_plasma - Flow_gu_po_dxm / V
d Cgu_plasma_dxo/dt = -transport_gu_dxo / Vgu_plasma + Flow_ar_gu_dxo / Vgu_plasma - Flow_gu_po_dxo / V
d Cgu_plasma_dxo_glu/dt = -transport_gu_dxo_glu / Vgu_plasma + Flow_ar_gu_dxo_glu / Vgu_plasma - Flow_g
d Cgulumen_dxm/dt = dissolution_dxm / Vgulumen - GU__absorption_dxm / Vgulumen - GU__excretion_dxm / Vg
d Chv_dxm/dt = Flow_li_hv_dxm / Vhv - Flow_hv_ve_dxm / Vhv  # [mmol/l/min]
d Chv_dxo/dt = Flow_li_hv_dxo / Vhv - Flow_hv_ve_dxo / Vhv  # [mmol/l/min]
d Chv_dxo_glu/dt = Flow_li_hv_dxo_glu / Vhv - Flow_hv_ve_dxo_glu / Vhv  # [mmol/l/min]
d Cki_dxm/dt = transport_ki_dxm / Vki_tissue - KI__DXMEX / Vki_tissue  # [mmol/l/min]
d Cki_dxo/dt = transport_ki_dxo / Vki_tissue - KI__DXOEX / Vki_tissue  # [mmol/l/min]
d Cki_dxo_glu/dt = transport_ki_dxo_glu / Vki_tissue - KI__DXOGLUEX / Vki_tissue  # [mmol/l/min]
d Cki_plasma_dxm/dt = -transport_ki_dxm / Vki_plasma + Flow_ar_ki_dxm / Vki_plasma - Flow_ki_kiv_dxm /
d Cki_plasma_dxo/dt = -transport_ki_dxo / Vki_plasma + Flow_ar_ki_dxo / Vki_plasma - Flow_ki_kiv_dxo /
d Cki_plasma_dxo_glu/dt = -transport_ki_dxo_glu / Vki_plasma + Flow_ar_ki_dxo_glu / Vki_plasma - Flow_k
d Ckiv_dxm/dt = Flow_ki_kiv_dxm / Vkiv - Flow_kiv_ve_dxm / Vkiv  # [mmol/l/min]
d Ckiv_dxo/dt = Flow_ki_kiv_dxo / Vkiv - Flow_kiv_ve_dxo / Vkiv  # [mmol/l/min]
d Ckiv_dxo_glu/dt = Flow_ki_kiv_dxo_glu / Vkiv - Flow_kiv_ve_dxo_glu / Vkiv  # [mmol/l/min]
d Cli_dxm/dt = transport_li_dxm / Vli_tissue - LI__DXMCYP2D6 / Vli_tissue - LI__DXMCYP3A4 / Vli_tissue
d Cli_dxo/dt = transport_li_dxo / Vli_tissue + LI__DXMCYP2D6 / Vli_tissue + LI__DXMCYP3A4 / Vli_tissue
d Cli_dxo_glu/dt = transport_li_dxo_glu / Vli_tissue + LI__DXOUGT / Vli_tissue  # [mmol/l/min]
d Cli_plasma_dxm/dt = -transport_li_dxm / Vli_plasma + Flow_ar_li_dxm / Vli_plasma + Flow_po_li_dxm / V
d Cli_plasma_dxo/dt = -transport_li_dxo / Vli_plasma + Flow_ar_li_dxo / Vli_plasma + Flow_po_li_dxo / V
d Cli_plasma_dxo_glu/dt = -transport_li_dxo_glu / Vli_plasma + Flow_ar_li_dxo_glu / Vli_plasma + Flow_p
d Clu_dxm/dt = transport_lu_dxm / Vlu_tissue  # [mmol/l/min]
d Clu_dxo/dt = transport_lu_dxo / Vlu_tissue  # [mmol/l/min]
d Clu_dxo_glu/dt = transport_lu_dxo_glu / Vlu_tissue  # [mmol/l/min]
d Clu_plasma_dxm/dt = -transport_lu_dxm / Vlu_plasma + Flow_ve_lu_dxm / Vlu_plasma - Flow_lu_ar_dxm / V
d Clu_plasma_dxo/dt = -transport_lu_dxo / Vlu_plasma + Flow_ve_lu_dxo / Vlu_plasma - Flow_lu_ar_dxo / V
d Clu_plasma_dxo_glu/dt = -transport_lu_dxo_glu / Vlu_plasma + Flow_ve_lu_dxo_glu / Vlu_plasma - Flow_lu
d Cpa_dxm/dt = transport_pa_dxm / Vpa_tissue  # [mmol/l/min]
d Cpa_dxo/dt = transport_pa_dxo / Vpa_tissue  # [mmol/l/min]
d Cpa_dxo_glu/dt = transport_pa_dxo_glu / Vpa_tissue  # [mmol/l/min]
d Cpa_plasma_dxm/dt = -transport_pa_dxm / Vpa_plasma + Flow_ar_pa_dxm / Vpa_plasma - Flow_pa_po_dxm / Vp
d Cpa_plasma_dxo/dt = -transport_pa_dxo / Vpa_plasma + Flow_ar_pa_dxo / Vpa_plasma - Flow_pa_po_dxo / Vp
d Cpa_plasma_dxo_glu/dt = -transport_pa_dxo_glu / Vpa_plasma + Flow_ar_pa_dxo_glu / Vpa_plasma - Flow_pa
d Cpo_dxm/dt = (Flow_gu_po_dxm / Vpo - Flow_po_li_dxm / Vpo) + Flow_pa_po_dxm / Vpo + Flow_sp_po_dxm / V
d Cpo_dxo/dt = (Flow_gu_po_dxo / Vpo - Flow_po_li_dxo / Vpo) + Flow_pa_po_dxo / Vpo + Flow_sp_po_dxo / V
d Cpo_dxo_glu/dt = (Flow_gu_po_dxo_glu / Vpo - Flow_po_li_dxo_glu / Vpo) + Flow_pa_po_dxo_glu / Vpo + Fl
d Cre_dxm/dt = transport_re_dxm / Vre_tissue  # [mmol/l/min]
d Cre_dxo/dt = transport_re_dxo / Vre_tissue  # [mmol/l/min]
d Cre_dxo_glu/dt = transport_re_dxo_glu / Vre_tissue  # [mmol/l/min]
d Cre_plasma_dxm/dt = -transport_re_dxm / Vre_plasma + Flow_ar_re_dxm / Vre_plasma - Flow_re_rev_dxm / V
d Cre_plasma_dxo/dt = -transport_re_dxo / Vre_plasma + Flow_ar_re_dxo / Vre_plasma - Flow_re_rev_dxo / V
d Cre_plasma_dxo_glu/dt = -transport_re_dxo_glu / Vre_plasma + Flow_ar_re_dxo_glu / Vre_plasma - Flow_re
d Crev_dxm/dt = Flow_re_rev_dxm / Vrev - Flow_rev_ve_dxm / Vrev  # [mmol/l/min]
d Crev_dxo/dt = Flow_re_rev_dxo / Vrev - Flow_rev_ve_dxo / Vrev  # [mmol/l/min]
d Crev_dxo_glu/dt = Flow_re_rev_dxo_glu / Vrev - Flow_rev_ve_dxo_glu / Vrev  # [mmol/l/min]
d Csp_dxm/dt = transport_sp_dxm / Vsp_tissue  # [mmol/l/min]
d Csp_dxo/dt = transport_sp_dxo / Vsp_tissue  # [mmol/l/min]
d Csp_dxo_glu/dt = transport_sp_dxo_glu / Vsp_tissue  # [mmol/l/min]
d Csp_plasma_dxm/dt = -transport_sp_dxm / Vsp_plasma + Flow_ar_sp_dxm / Vsp_plasma - Flow_sp_po_dxm / Vs
d Csp_plasma_dxo/dt = -transport_sp_dxo / Vsp_plasma + Flow_ar_sp_dxo / Vsp_plasma - Flow_sp_po_dxo / Vs
d Csp_plasma_dxo_glu/dt = -transport_sp_dxo_glu / Vsp_plasma + Flow_ar_sp_dxo_glu / Vsp_plasma - Flow_sp
d Cve_dxm/dt = (iv_dxm / Vve + Flow_kiv_ve_dxm / Vve + Flow_hv_ve_dxm / Vve - Flow_ve_lu_dxm / Vve) + Fl
d Cve_dxo/dt = (Flow_kiv_ve_dxo / Vve + Flow_hv_ve_dxo / Vve - Flow_ve_lu_dxo / Vve) + Flow_rev_ve_dxo /
d Cve_dxo_glu/dt = (Flow_kiv_ve_dxo_glu / Vve + Flow_hv_ve_dxo_glu / Vve - Flow_ve_lu_dxo_glu / Vve) + F
d GU__dxmmet/dt = GU__DXMCYP3A4 / Vgu_tissue  # [mmol/l/min]
d IVDOSE_dxm/dt = -iv_dxm * Mr_dxm + Ri_dxm  # [mg/min]
d LI__qui/dt = 0  # [mmol/l/min]
d PODOSE_dxm/dt = -dissolution_dxm * Mr_dxm  # [mg/min]
d cum_dose_dxm/dt = Ri_dxm  # [mg/min]
```