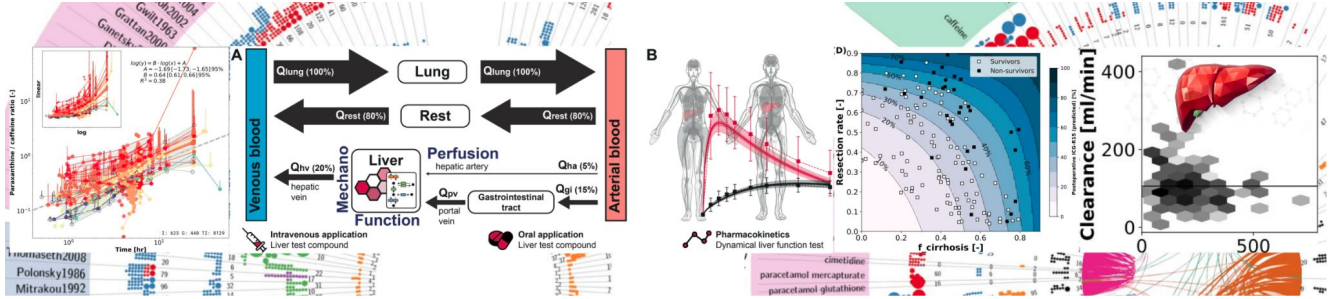


Pharmacokinetics Modeling Course

Pharmacokinetic Parameters & Pharmacokinetics Data

Dr. Matthias König
Humboldt-University Berlin
Systems Medicine of the Liver
koenigmx@hu-berlin.de
https://livermetabolism.com

🎯 Teaching Goals

By the end of this section, you should be able to:

1. Understand key **pharmacokinetic parameters**: **clearance (CL)**, **volume of distribution (Vd)**, **half-life ($t_{1/2}$)**, **bioavailability (F)**, and **AUC**.
2. Learn how these parameters are **derived** from concentration-time data.
3. Understand the relationship between **dose**, **exposure**, and **elimination**.
4. Get an overview of the **PK database** (e.g., **PK-DB**) and their role in **model development** and **data integration**.
5. Understand the importance of **data quality**, **standardization**, and **metadata** in PK modeling.
6. Explore **interindividual variability** in pharmacokinetic parameters.

Pharmacokinetic Parameters

- **C_{max}** : Maximal concentration
- **T_{max}** : time of maximal concentration
- **AUC** : area under the curve
- **k_{el}**: elimination rate
  fitting linear part of terminal phase (log)
- **$t_{1/2}$** : half-life (= ln2/k_{el})
  time for concentration to fall to half
- **Vd**: volume of distribution
  (= CL/k), dilution space
- **CL**: clearance (=Dose/AUC, =Dose/$C(0)_{extrapolated}$)

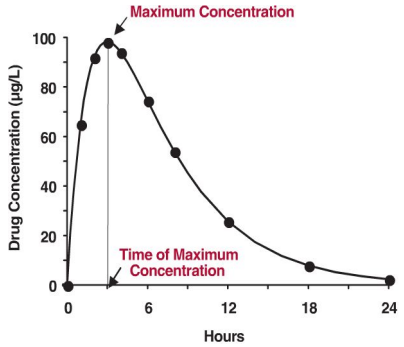


FIGURE 2-1. Drug concentration–time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

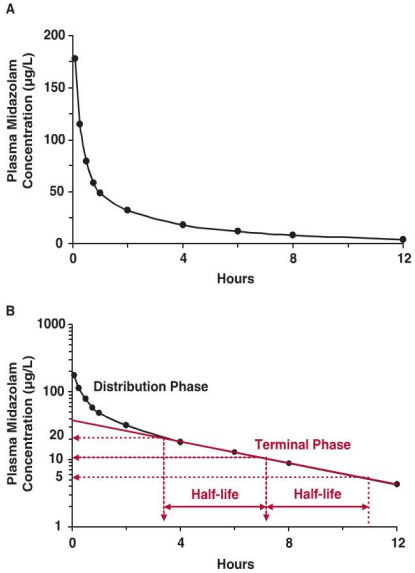


FIGURE 3-4. **A.** Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. **B.** The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Välisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29: 272–277.)

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

Pharmacokinetic Parameters

Pharmacokinetic parameters are numerical values that describe how a drug behaves in the body. They play a vital role in determining the dosage and frequency of drug administration.

1. **Absorption**: This parameter involves how the drug is absorbed into the bloodstream from the site of administration. The rate and extent of absorption can influence the onset, intensity, and duration of a drug's effect.
2. **Distribution**: This refers to how the drug spreads throughout the body. The volume of distribution (Vd) is a key parameter that quantifies the extent to which a drug is distributed in the body's tissues compared to its concentration in the blood.
3. **Metabolism (Biotransformation)**: Metabolism is how the drug is chemically modified or broken down in the body, primarily by liver enzymes. This can change the drug's activity and affects how quickly it's cleared from the body.
4. **Elimination (Excretion)**: This parameter refers to the removal of the drug from the body, primarily through the kidneys (urine) or liver (bile). The rate of elimination is usually expressed as the drug's half-life (t1/2), which is the time it takes for the concentration of the drug in the body to be reduced by half.
5. **Clearance (Cl)**: This is a measure of the body's efficiency in eliminating the drug, expressed as volume/time (like mL/min). It's a crucial parameter that determines the steady-state concentration of the drug for a given dosage regimen.
6. **Bioavailability (F)**: This is the fraction of the administered dose of a drug that reaches the systemic circulation in an unchanged form. It's a crucial parameter, especially for oral medications.
7. **Area Under the Curve (AUC)**: This is a measure of the total exposure of the body to the drug. It's calculated as the integral of the concentration-time curve, from administration to elimination.
8. **Peak Concentration (Cmax) and Time to Reach Peak Concentration (Tmax)**: Cmax is the highest concentration a drug achieves in the body after administration, and Tmax is the time it takes to reach this peak concentration.

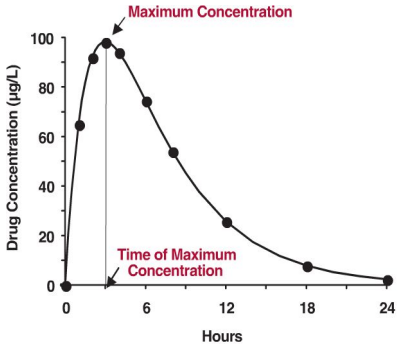


FIGURE 2-1. Drug concentration–time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

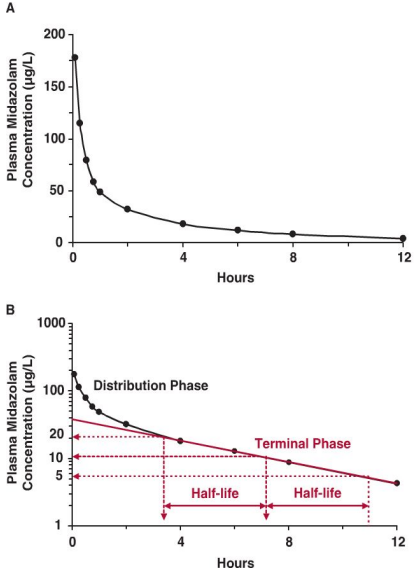


FIGURE 3-4. **A.** Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. **B.** The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Välisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29: 272–277.)

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

Area Under the Curve (AUC)

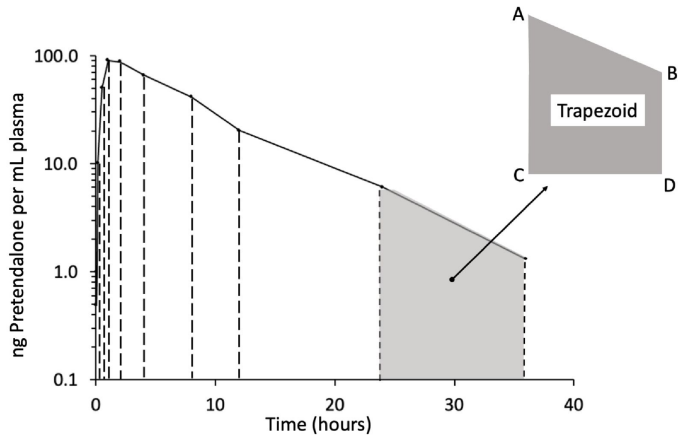


Figure 22: illustration of calculation of area of each trapezoid across the drug-concentration time plot using the linear trapezoidal rule.

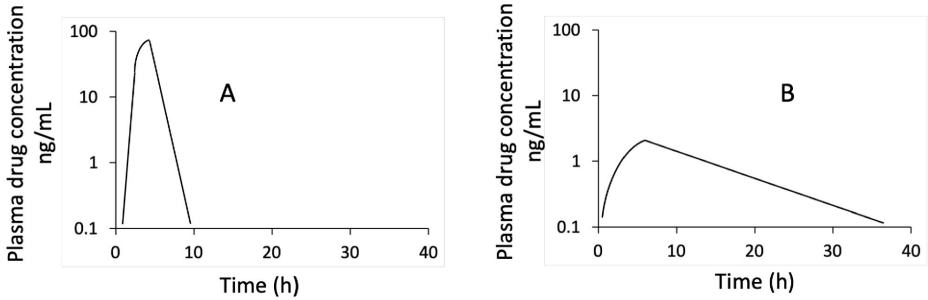


Figure 20: two pharmacokinetic curves of different shape but with the same AUC.

AUC Extrapolation

Area Under the Curve (AUC):

- It's a pharmacokinetic parameter that represents the total exposure of the body to a drug.
- AUC is calculated as the integral of the drug concentration-time curve, from the time of administration until the drug is eliminated from the body.
- The AUC provides valuable information about the drug's bioavailability and clearance rate.
- It's widely used in therapeutic drug monitoring, dose adjustment, and comparison of generic drugs with original brands (bioequivalence studies).

AUC Interpolated to Infinity (AUC0-∞):

- This is an extension of the AUC that accounts for the drug amount that remains in the body and has not yet been eliminated at the last measured time point.
- It's calculated by adding the AUC from time zero to the last measurable concentration (AUC0-t) and the extrapolated AUC from the last measurable concentration to infinity (Clast/elimination rate constant).
- AUC0-∞ provides a more complete picture of the body's exposure to the drug over an infinite period.
- It is particularly useful when determining the bioavailability of a drug, as it accounts for the total drug exposure from the time of administration onwards.

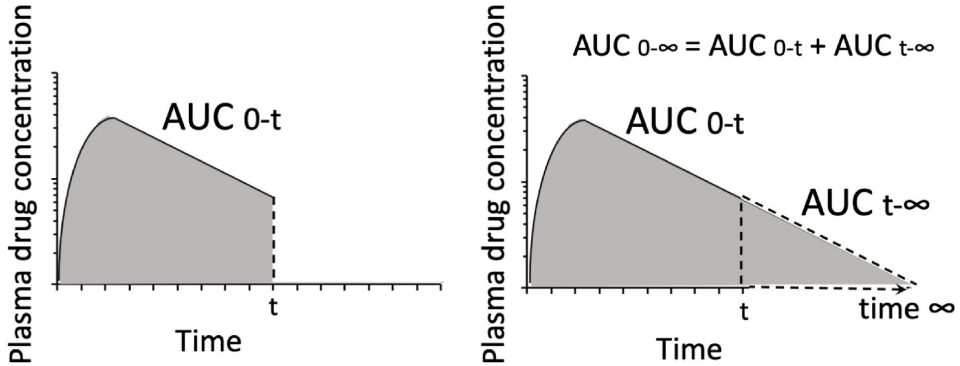
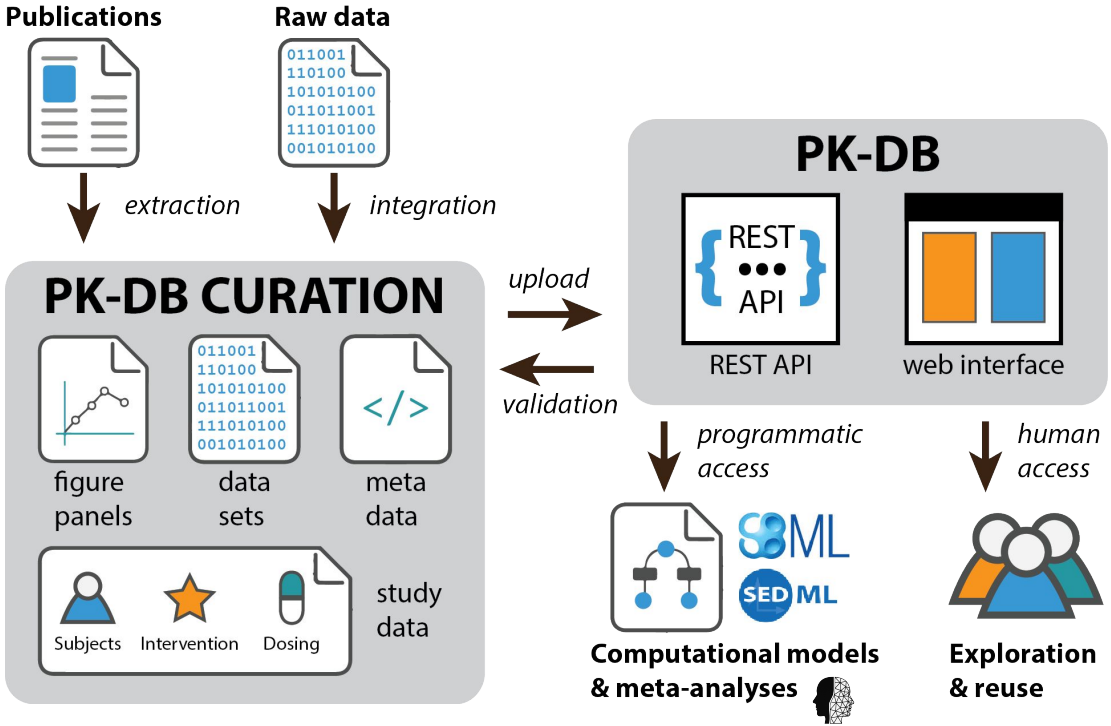


Figure 19: grey areas underneath the drug-concentration versus time curve are diagrammatic representations of areas under the curve with AUC_{0-t} (on the left) and $AUC_{0-\infty}$ (on the right) for a typical oral administration. Dotted lines on the right-hand plot represent extrapolation of AUC_{0-t} to $AUC_{0-\infty}$.

Pharmacokinetic Database (PK-DB)



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

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.

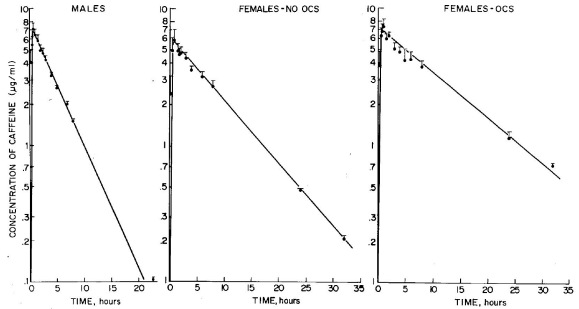


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

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)
$t½_{(\beta)}$ (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.

Groups

Individuals

Intervention

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.

Time courses

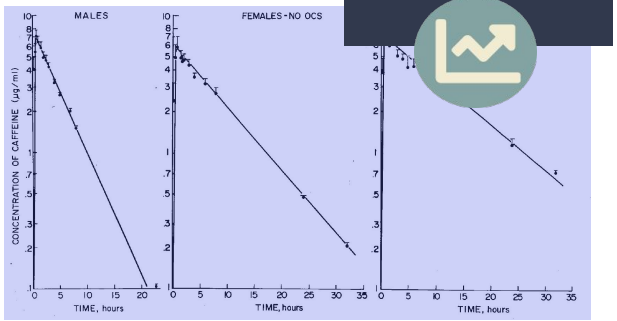


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean ± S.E.).

Outputs

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

	Normal males (n = 13)	*Normal females taking no OCS* (n = 9)	*Normal females on OCS* (n = 9)
$t½_{(\beta)}$ (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.

Live Demonstration

Pharmakokinetik Datenbank (PK-DB)

1071	**Studies**	Clinical or experimental study measuring data in groups and/or individuals.
3425	**Groups**	Group of individuals for which data was reported, e.g., the control group and the group which received an intervention. A group is described by certain characteristica, e.g., bodyweight, health status, smoking status or medication.
20065	**Individuals**	A single subject in the study. A subject is characterized by the group it belongs to as well as individual characteristica like age, body weight or sex. Individuals are only created if outputs or timecourses have been reported on the subject level (not group level).
3168	**Interventions**	Intervention which was performed in the study. Often interventions consist of application of a substance, e.g. caffeine or codeine. Other examples are changes in lifestyle like smoking cessation.
200160	**Outputs**	Clinical or experimental output. These can be single parameters or variables, e.g. pharmacokinetic parameters like AUC, clearance or half-life of the applied substances. An output is always linked to the respective intervention and group or individual.
10094	**Timecourses**	Clinical or experimental time course measurements. Often timecourses are concentration measurements. A timecourse is always linked to the respective intervention and group or individual.
199	**Scatters**	Correlations between outputs are often provided as scatter plots (e.g. age ~ clearance).

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

Pharmakokinetik Datenbank (PK-DB)

1071	**Studies**	Clinical or experimental study measuring data in groups and/or individuals.
3425	**Groups**	Group of individuals for which data was reported, e.g., the control group and the group which received an intervention. A group is described by certain characteristica, e.g., bodyweight, health status, smoking status or medication.
20065	**Individuals**	A single subject in the study. A subject is characterized by the group it belongs to as well as individual characteristica like age, body weight or sex. Individuals are only created if outputs or timecourses have been reported on the subject level (not group level).
3168	**Interventions**	Intervention which was performed in the study. Often interventions consist of application of a substance, e.g. caffeine or codeine. Other examples are changes in lifestyle like smoking cessation.
200160	**Outputs**	Clinical or experimental output. These can be single parameters or variables, e.g. pharmacokinetic parameters like AUC, clearance or half-life of the applied substances. An output is always linked to the respective intervention and group or individual.
10094	**Timecourses**	Clinical or experimental time course measurements. Often timecourses are concentration measurements. A timecourse is always linked to the respective intervention and group or individual.
199	**Scatters**	Correlations between outputs are often provided as scatter plots (e.g. age ~ clearance).

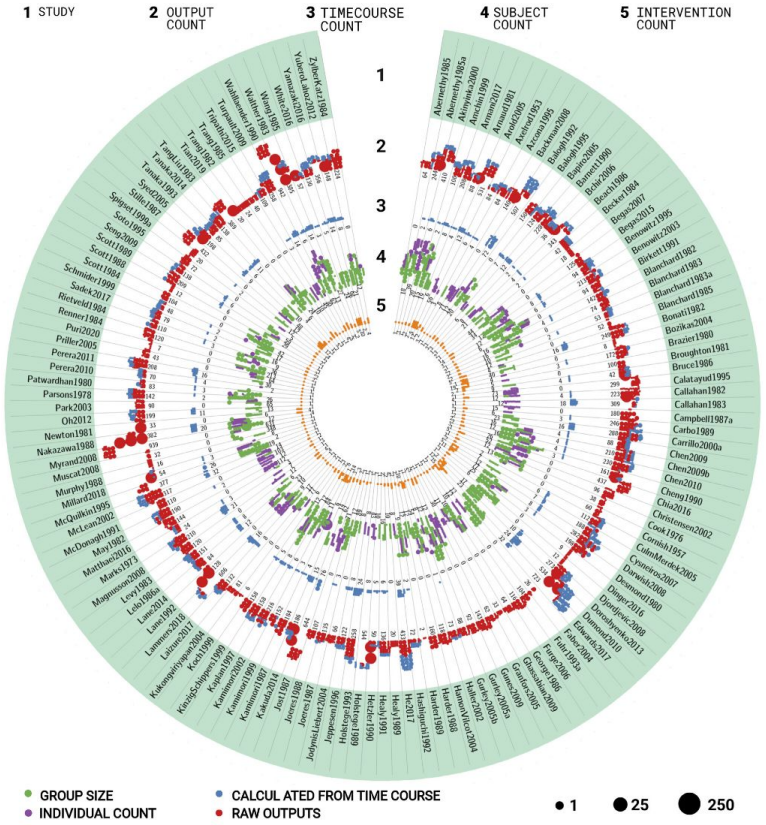


FIGURE 2 | Overview of studies in the caffeine pharmacokinetics data set. The data set consists of 141 studies containing 500 groups, 4,714 individuals, 387 interventions, 24 ,571 outputs, and 846 time-courses. The circular plot is structured in stripes and rings. Each stripe represents a different study, each ring the amount of different data types for the respective study. The dots represent the respective amount of data with the dot size corresponding to the number of entries per dot. The rings contain the following information for the respective study **(A)** name of the study; **(B)** number of outputs (pharmacokinetics parameters and other measurements). Red dots represent reported data, blue dots data calculated from time-courses reported in the study; **(C)** number of time-courses; **(D)** number of participants. Purple dots represent participants with individual data, green dots represent collectively reported participants; **(E)** number of interventions applied to the participants in the study. For additional information see **Table 1**.

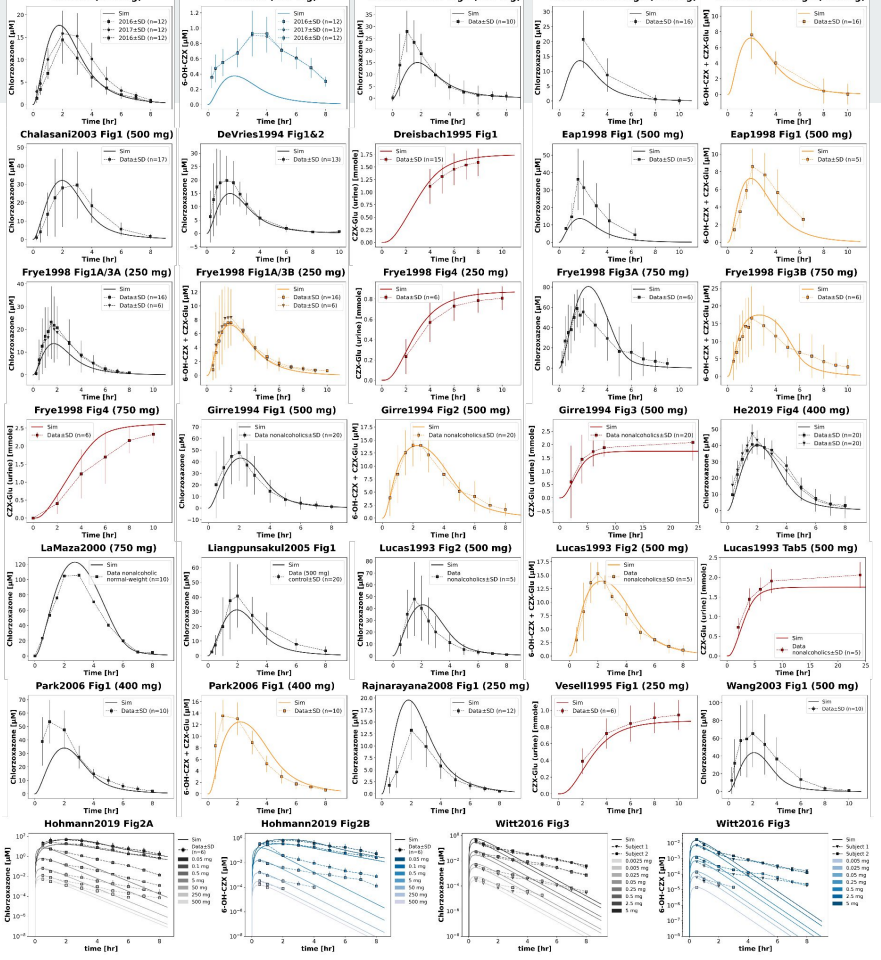
PK-DB: pharmacokinetics database for individualized and stratified computational modeling. Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorscht F, Köller A, Ke DYJ, De Angelis S, **König M.** Nucleic Acids Res. 2020 Nov 5:gkaa990. doi: 10.1093/nar/gkaa990.

Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing. J.Grzegorzewski, F.Bartsch, A.Köller, and **M.König**. Frontiers in Pharmacology 2022, Vol12; doi: 10.3389/fphar.2021.752826

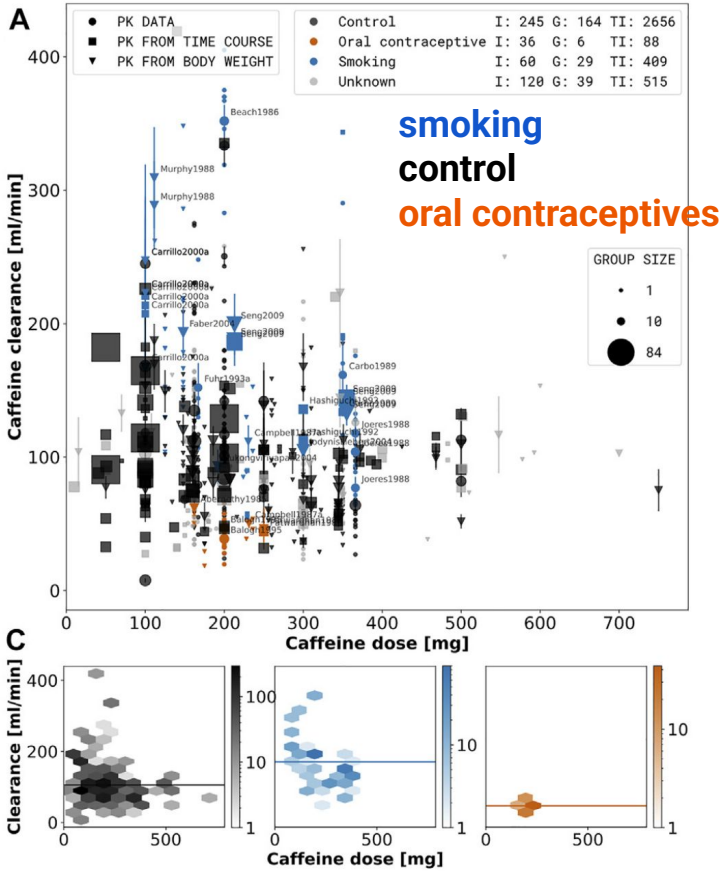
Table 1: Overview of curated clinical studies.

References	PK-DB	PMID	Dosing protocol	Health status	Data	Fit	Validation
Bedada and Neerati (2016)	PKDB00621	26680654	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Bedada and Boga (2017)	PKDB00622	27670974	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Bedada and Neerati (2018)	PKDB00623	28983678	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓*	
Benowitz et al. (2003)	PKDB00623	14586387	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Chalasani et al. (2003)	PKDB00623	12601351	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Burckart et al. (1998)	PKDB00624	9542473	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
de Vries et al. (1994)	PKDB00626	7849234	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Dreisbach et al. (1995)	PKDB00627	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time-course (6-OH-CZX)	✓	
Ernstgard et al. (2004)	PKDB00699	15255802	250, 500, 750 mg, oral, multiple dose, tablet	healthy	metabolic ratios, urinary recovery		✓
Frye et al. (1998)	PKDB00629	9597564	250, 750 mg, oral, multiple dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time-course (6-OH-CZX)	✓	
Girre et al. (1994)	PKDB00631	7910460	500 mg, oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX,6-OH-CZX), urine time-course (6-OH-CZX)	✓	✓
He et al. (2019)	PKDB00632	31363741	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Hohmann et al. (2019)	PKDB00633	31222796	0.005, 0.01, 0.05, 0.5, 5, 50 mg as solution, 250, 500 mg as tablet, oral, multiple dose	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Hukkanen et al. (2010)	PKDB00698	20233178	250 mg, oral, single dose, tablet	healthy	urinary recovery	✓	
Kharasch et al. (1993)	PKDB00623	8513656	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
de la Maza et al. (2000)	PKDB00634	10832901	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Liangpunsakul et al. (2005)	PKDB00636	15841467	500 mg, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Lucas et al. (1993)	PKDB00637	8120116	500 mg oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX, 6-OH-CZX), urine time course (6-OH-CZX)	✓	✓
Lucas et al. (1995)	PKDB00688	7625570	500 mg oral, single dose, tablet	alcoholics	metabolic ratios		✓
Mishin et al. (1998)	PKDB00638	9820389	750 mg, oral, single dose, tablet	alcoholics	plasma time-course (CZX, 6-OH-CZX)		✓
Oneta et al. (2002)	PKDB00689	7955797	500 mg, 250 mg, oral, multiple dose, tablet	alcoholics	metabolic ratios		✓
Orellana et al. (2006)		16321567	500 mg, oral, single dose, tablet	healthy, steatosis, steatohepatitis	metabolic ratios		✓
O'Shea et al. (1994)	PKDB00697	11804663	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
Park et al. (2006)	PKDB00641	16397290	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX)	✓	
Rajnarayana et al. (2008)	PKDB00643	19326774	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Vesell et al. (1995)	PKDB00644	7773304	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urine time-course (6-OH-CZX)	✓	
Wang et al. (2003)	PKDB00639	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Witt et al. (2016)	PKDB00640	27300008	5, 2.5, 0.5, 0.25, 0.05, 0.025, 0.005, 0.0025mg, oral, single dose, solution	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Wilkinson et al. (1977)	PKDB00700	881642	ethanol: 11.2, 22.5, 33.7, 45.0 g, oral, single dose, solution	healthy	plasma time-course (ethanol)	✓	

* 6-OH-CZX was measured without the chlorzoxazone-O-glucuronide.



Lifestyle: Smoking & Oral Contraceptives

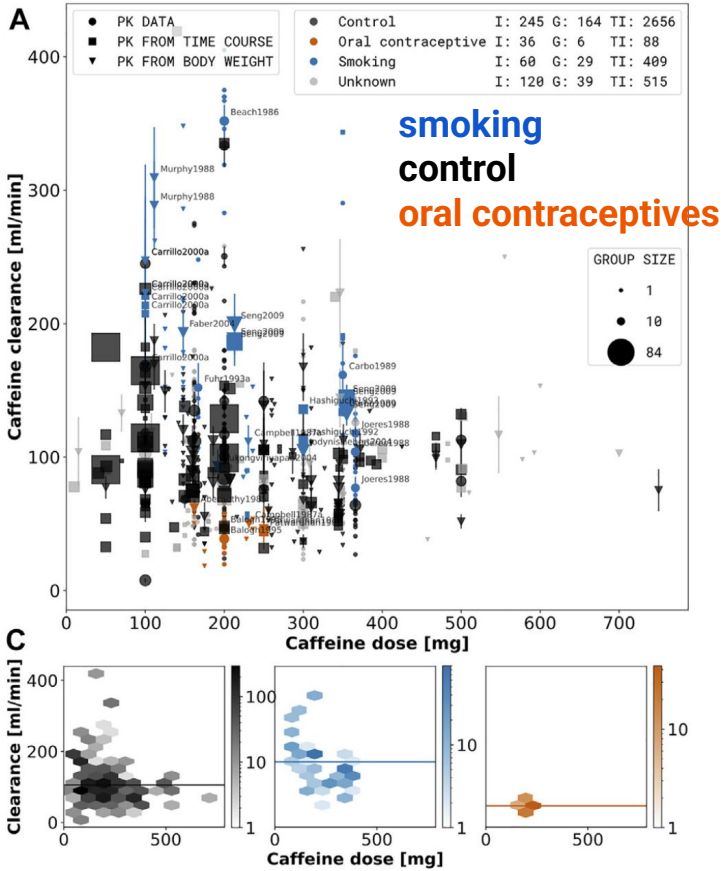


- Smoking induces caffeine clearance
- Oral contraceptives reduce

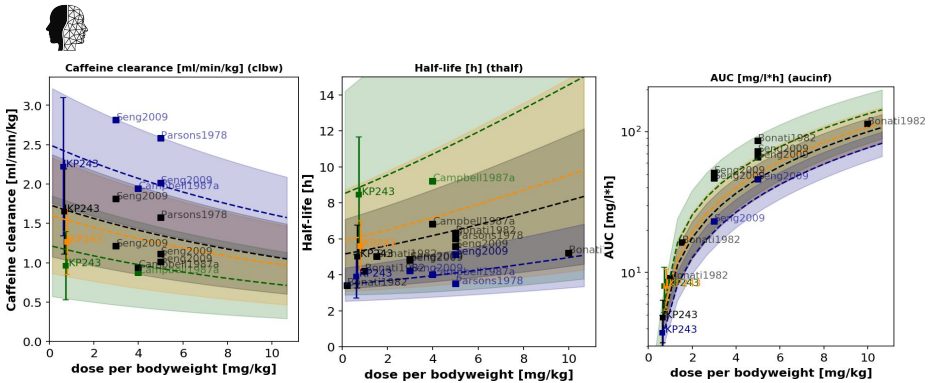
J.Grzegorzewski, F.Bartsch, A.Köller, and **M.König**
Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing
Frontiers in Pharmacology 2022, Vol12; doi: 10.3389/fphar.2021.752826

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. 2020 Nov 5:gkaa990. doi: 10.1093/nar/gkaa990.

Lifestyle: Smoking & Oral Contraceptives



- Smoking induces caffeine clearance
- Oral contraceptives reduce



J.Grzegorzewski, F.Bartsch, A.Köller, and **M.König**
Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing
Frontiers in Pharmacology 2022, Vol12; doi: 10.3389/fphar.2021.752826

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. 2020 Nov 5:gkaa990. doi: 10.1093/nar/gkaa990.