Characterising uncertainty in intrinsic clearance rates to support transparent and robust exposure assessment in Next Generation Risk Assessment

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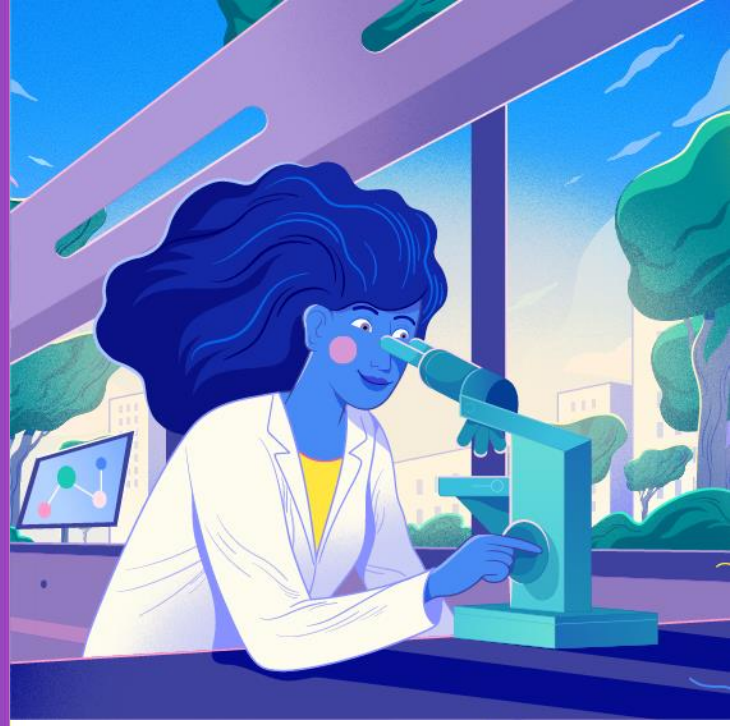

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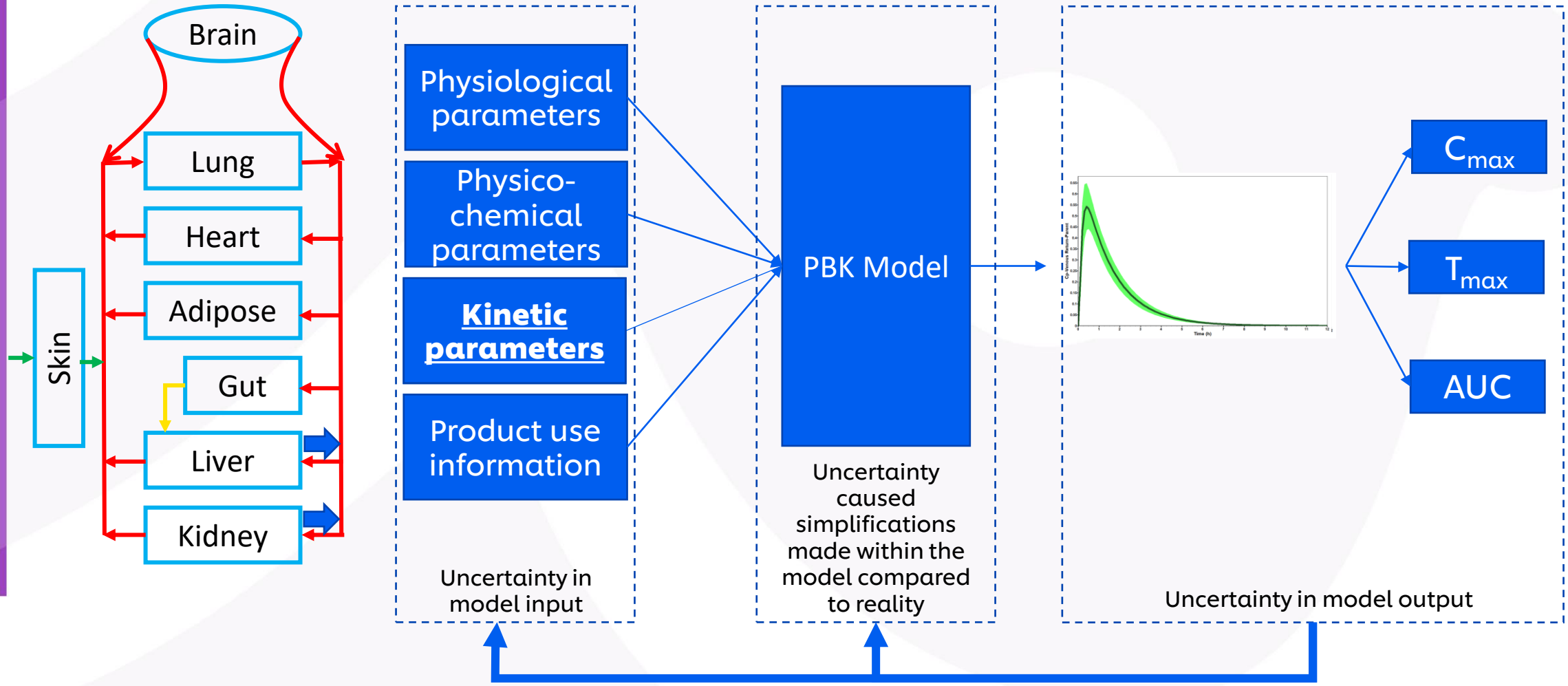
Physiological Based Kinetics (PBK) modelling

- ADME properties of a chemical can be used to predict its concentration time course in different organs/tissues in the human body after exposure to the chemical via different exposure routes, e.g., oral, skin and inhalation. The outcome of PBK modelling, e.g., the maximum concentration of the chemical in an organ (C_{max}), can be compared with Point of Departure from in vitro bioactivity assays to support NGRA decision



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Clearance rate – what it is and why it is important

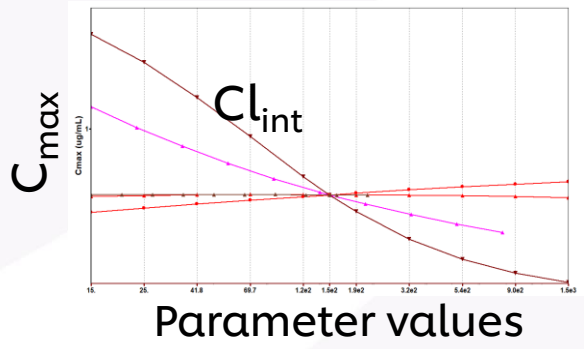
Clearance: The volume of plasma from which a substance is completely removed per unit time (ml/min, L/h)

- Hepatic Clearance
- Renal Clearance

Influenced by

- Blood flow through the liver, reflecting drug delivery to the liver
- Fraction of drug in the blood that is not bound to plasma proteins
- Intrinsic clearance (Cl_{int}): Intrinsic ability of hepatic enzymes to metabolize the drug
- One of the most sensitive parameters to C_{max} (Moxon, 2020; Punt, 2022; van Tongeren, 2022)
- Understanding the uncertainty of Cl_{int} estimation is critical to characterisation of the uncertainty of C_{max} predictions
- **Support a transparent exposure assessment in NGRA**

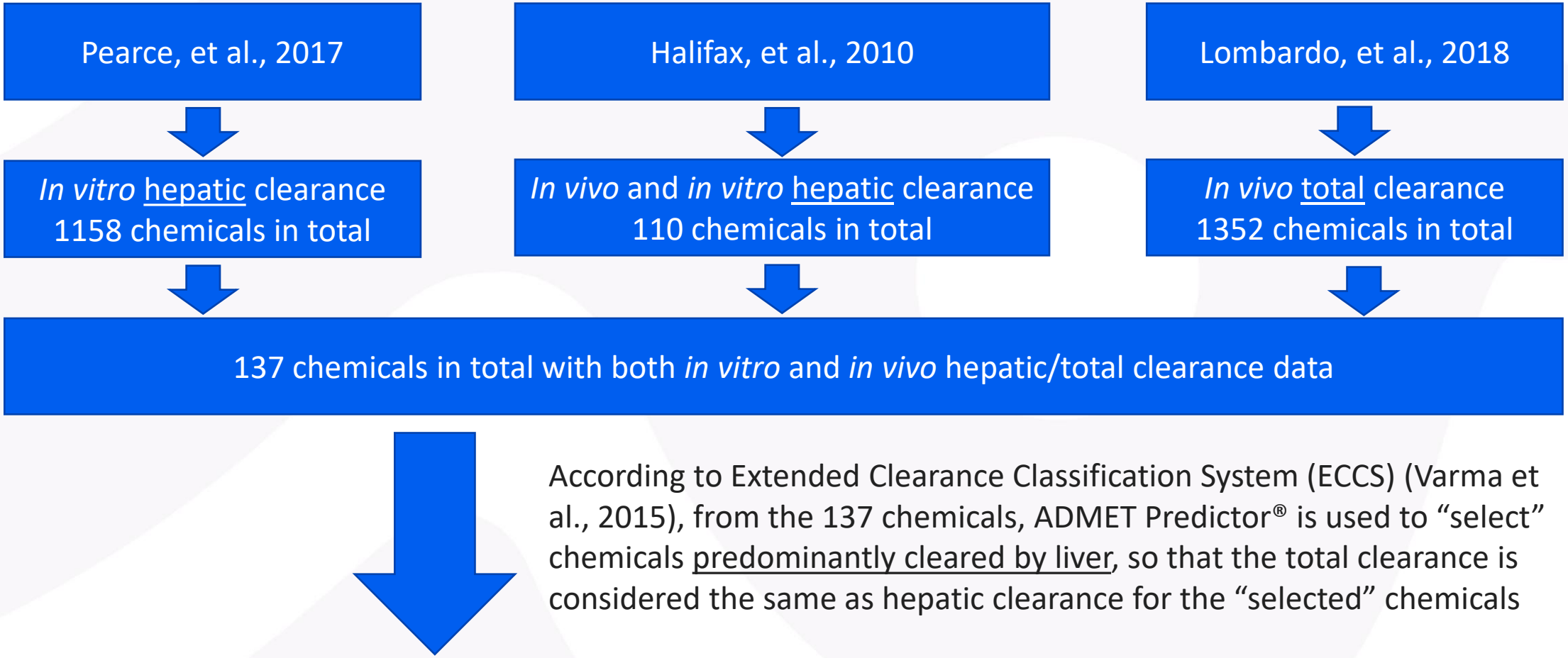
e.g.,



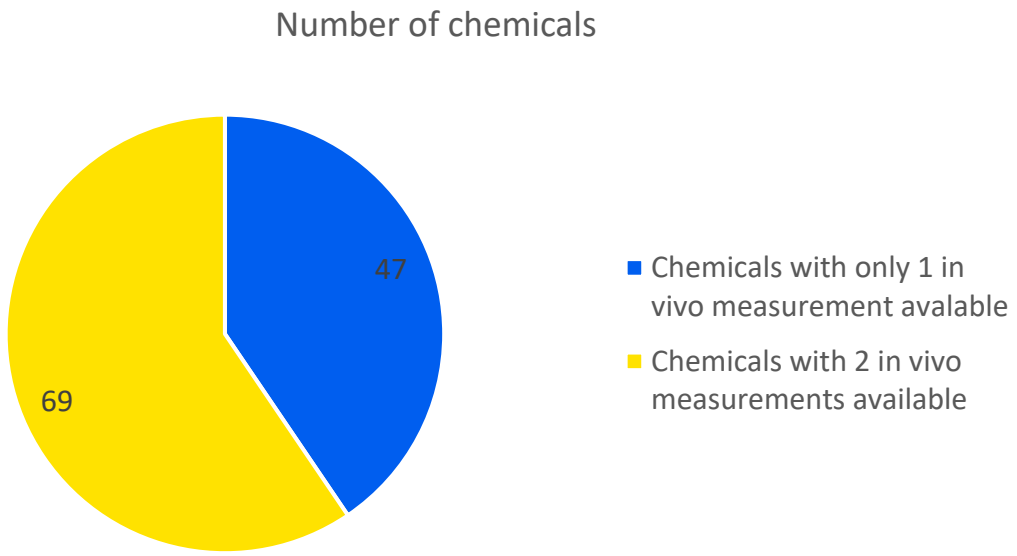
This work aims to characterise the uncertainty for Clint from the in vitro and/or in vivo clinical measurements so that its impact on the uncertainty on C_{max} could be analysed to support a transparent exposure assessment in NGRA

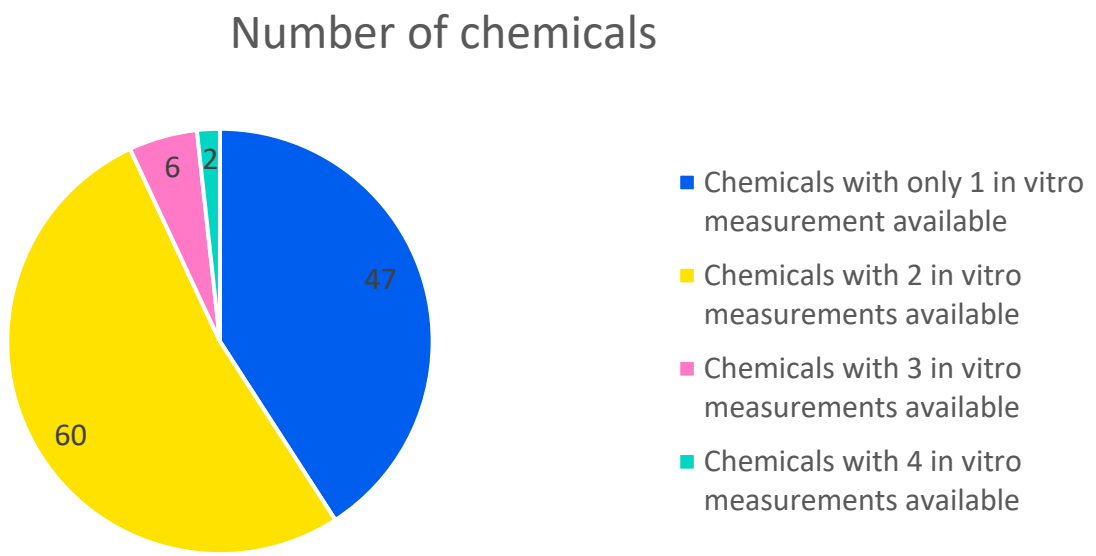
Data collation

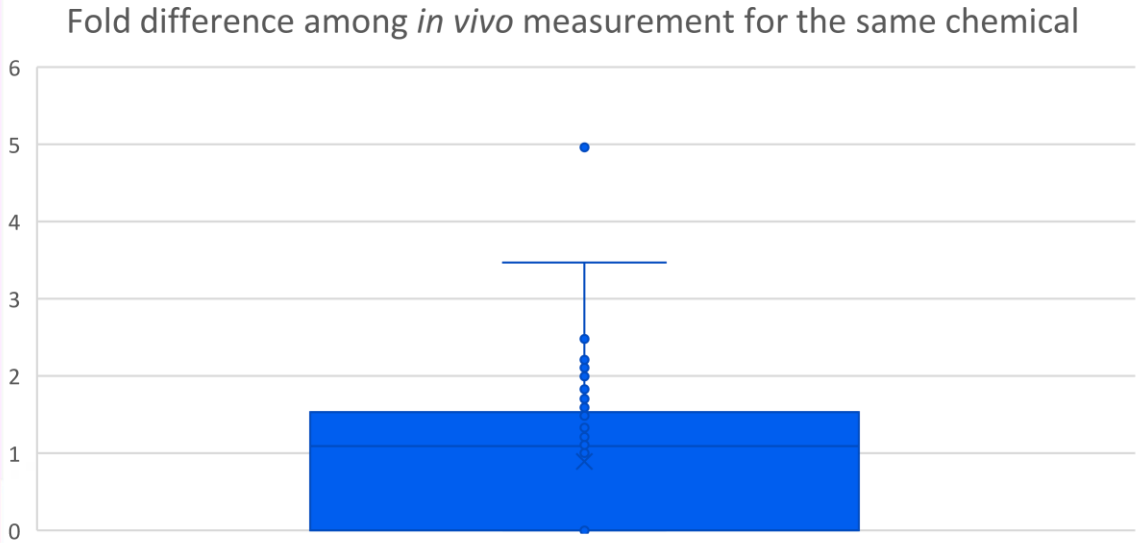
Aim: find chemicals with both in vitro and in vivo clinical clearance measurement data, so that the relationship between the measurements and Cl_{int} including the uncertainty associated can be analysed.

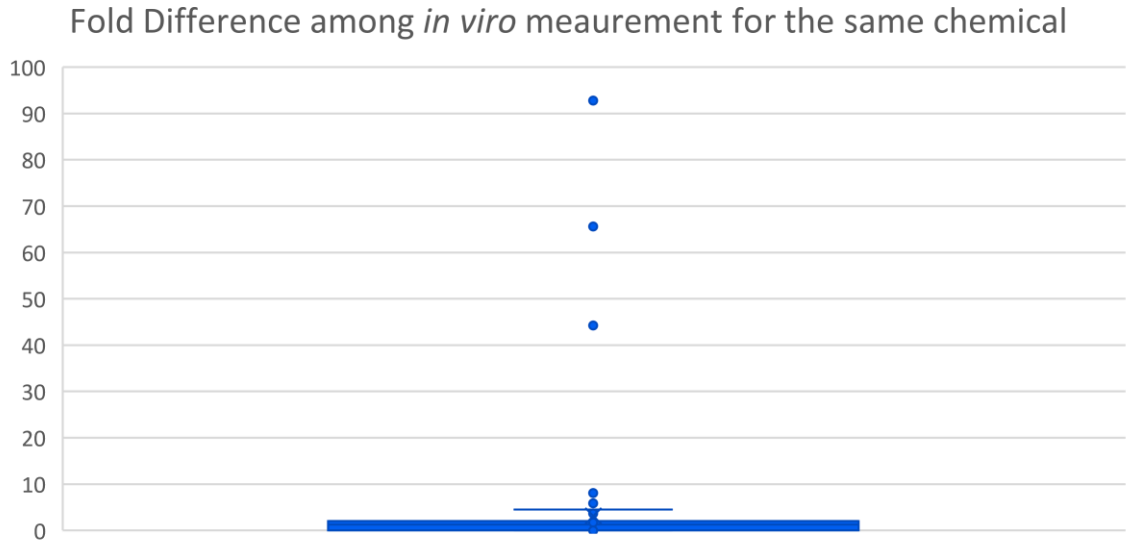


Data insight



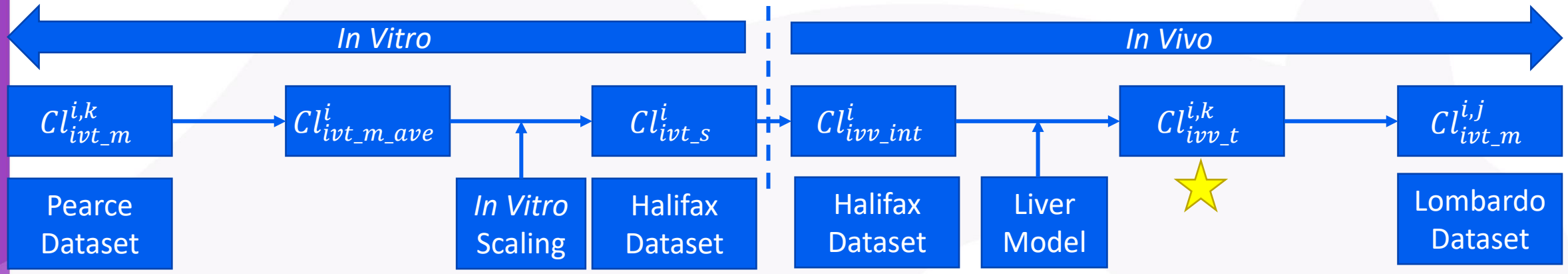






For the same chemical, *in vitro* measurements are in general is less consistent compared to *in vivo* measurements (thus create more uncertainty)

Bayesian model (1) – Structure



$Cl^{i,k}_{ivt\_m}$: the kth measurement of hepatocyte based *in vitro* clearance rate for chemical i

$Cl^{i}_{ivt\_m\_ave}$: the average measured value of hepatocyte based *in vitro* clearance rate for chemical i

$Cl^{i}_{ivt\_s}$: the scaled *in vitro* clearance rate for chemical i, considering the fraction unbound of chemical i (fu_i), hepatocellularity (SF) and human liver weight (HLW)

$Cl^{i}_{ivv\_int}$: the *in vivo* intrinsic clearance rate ★

$Cl^{i}_{ivv\_t}$: the total *in vivo* hepatic clearance rate, relation between $Cl^{i}_{ivv\_t}$ and $Cl^{i}_{ivv\_int}$ is determined by **liver models** accounting for the impact of blood flow through liver and the fraction of chemicals that are unbound to plasma protein

$Cl^{i,j}_{ivv\_m}$: the jth measurement *in vivo* clearance rate for chemical i

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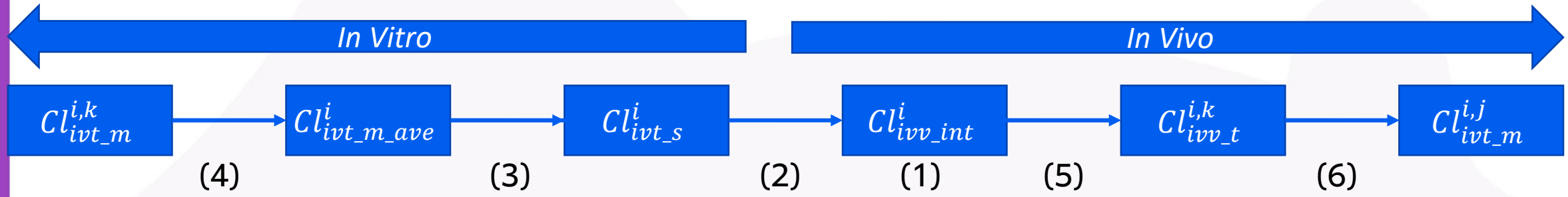
Bayesian model (2) - Equations



$$\log\left(Cl^{i}_{ivv\_int}\right) \sim N\left(log\left(\mu_{ivv\_int}\right), \sigma_{ivv\_int}\right) \quad (1)$$

$$\log\left(Cl^{i}_{ivt\_s}\right) \sim N\left(\mathrm{a} * \log\left(Cl^{i}_{ivv\_int}\right) + b, \sigma_{ivive}\right) \quad (2)$$

$$Cl^{i}_{ivt\_m\_ave} = \frac{Cl^{i}_{ivt\_s} \times fu^{i}_{inc}}{SF \times HLW}, fu^{i}_{inc} = f\left(\log P^{i} \; or \; \log D^{i}\right) \quad (3)$$

$$log\left(Cl^{i,k}_{ivt\_m}\right) \sim N\left(log\left(Cl^{i}_{ivt\_m\_ave}\right), \sigma_{ivt\_m}\right) \quad (4)$$

$$Cl^{i}_{ivv\_t} = Q_H \frac{fu * Cl_{ivv\_int}}{Q_H + fu * Cl_{ivv\_int}} \quad (5)$$

$$log\left(Cl^{i,j}_{ivv\_m}\right) \sim N\left(log\left(Cl^{i}_{ivv\_t}\right), \sigma_{ivv\_m}\right) \quad (6)$$

(1): Capture uncertainty in estimation of Cl_{ivv_int} across all chemicals in the dataset

(2): Assume linear relation between Cl_{ivt_s} and Cl_{ivv_int} (Halifax, 2010) with uncertainty

(3): *In vitro* clearance scaling (Halifax, 2010), considering

- The fraction unbound of chemical (fu_{inc}), a regression function based on $logP$ or $logD$
- Hepatocellularity (SF, 120 million/g liver)
- Human liver weight (HLW, 21.4 g liver/kg body weight)

(4): Capture uncertainty in measurement of Cl_{ivt_m}

(5): Well Stirred liver model (Halifax, 2010) capturing the impact of

- Blood flow through liver (Q_H, 20.7 ml/min/kg for an average adult)
- The fraction of chemicals that are unbound to plasma protein (f_u)

(6): Capture uncertainty in measurement of Cl_{ivv_m}

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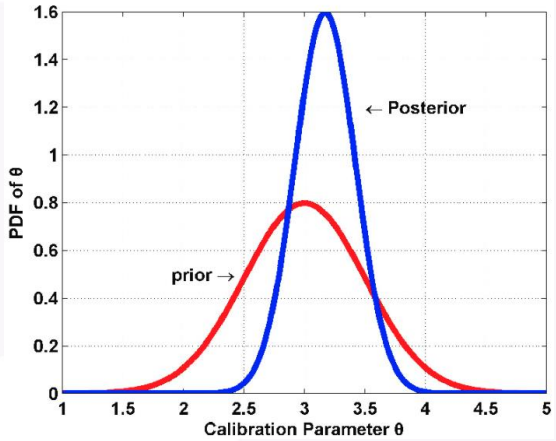
Bayesian model (3) – Bayesian Idea in clearance data analysis

Data

$$P(\Theta|data) \propto P(data|\Theta) \times P(\Theta)$$

Collection of unknown parameters



$$\log\left(Cl^{i}_{ivv\_int}\right) \sim N\left(log\left(\mu_{ivv\_int}\right), \sigma_{ivv\_int}\right)$$

$$\log\left(Cl^{i}_{ivt\_s}\right) \sim N\left(a * \log\left(Cl^{i}_{ivv\_int}\right) + b, \sigma_{ivive}\right)$$

$$Cl^{i}_{ivt\_m\_ave} = \frac{Cl^{i}_{ivt\_s} \times fu^{i}_{inc}}{SF \times HLW}, \quad fu^{i}_{inc} = f\left(\log P^{i} \text{ or } \log D^{i}\right)$$

$$log\left(Cl^{i,k}_{ivt\_m}\right) \sim N\left(log\left(Cl^{i}_{ivt\_m\_ave}\right), \sigma_{ivt\_m}\right)$$

$$Cl^{i}_{ivv\_t} = Q_H \frac{fu * Cl_{ivv\_int}}{Q_H + fu * Cl_{ivv\_int}}$$

$$log\left(Cl^{i,j}_{ivv\_m}\right) \sim N\left(log\left(Cl^{i}_{ivv\_t}\right), \sigma_{ivv\_m}\right)$$

- Unknown parameters
- Chemical specific constants
- Physiological related constants
- Data

Bayesian model (4) – Prior

$$\log\left(Cl^{i}_{ivv\_int}\right) \sim N\left(\log\left(\mu_{ivv\_int}\right), \sigma_{ivv\_int}\right) \quad (1)$$

$$\log\left(Cl^{i}_{ivt\_s}\right) \sim N\left(a * \log\left(Cl^{i}_{ivv\_int}\right) + b, \sigma_{ivive}\right) \quad (2)$$

$$Cl^{i}_{ivt\_m\_ave} = \frac{Cl^{i}_{ivt\_s} \times fu^{i}_{inc}}{SF \times HLW}, fu^{i}_{inc} = f\left(\log P^{i} \; or \; \log D^{i}\right) \quad (3)$$

$$log\left(Cl^{i,k}_{ivt\_m}\right) \sim N\left(log\left(Cl^{i}_{ivt\_m\_ave}\right), \sigma_{ivt\_m}\right) \quad (4)$$

$$Cl^{i}_{ivv\_t} = Q_H \frac{fu * Cl_{ivv\_int}}{Q_H + fu * Cl_{ivv\_int}} \quad (5)$$

$$log\left(Cl^{i,j}_{ivv\_m}\right) \sim N\left(log\left(Cl^{i}_{ivv\_t}\right), \sigma_{ivv\_m}\right) \quad (6)$$

$\sigma_{ivt\_int} \sim normal(0,1), \sigma_{ivt\_int} > 0$

$\sigma_{ivive} \sim normal(0,1), \sigma_{ivive} > 0$

$\sigma_{ivt\_m} \sim normal(0,1), \sigma_{ivt\_m} > 0$

$\sigma_{ivv\_m} \sim normal(0,1), \sigma_{ivv\_m} > 0$

Non negative, non informative prior

$a \sim N(0,1)$

$b \sim N(0,1)$

Non informative prior

$\mu_{ivv\_int} \sim N(1.73, 0.9)$

Data informed prior

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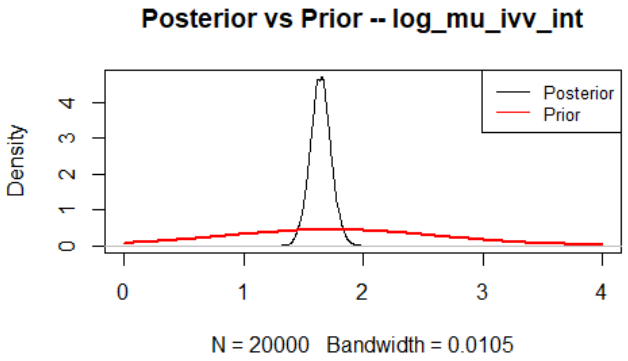
Result - parameter posterior VS prior

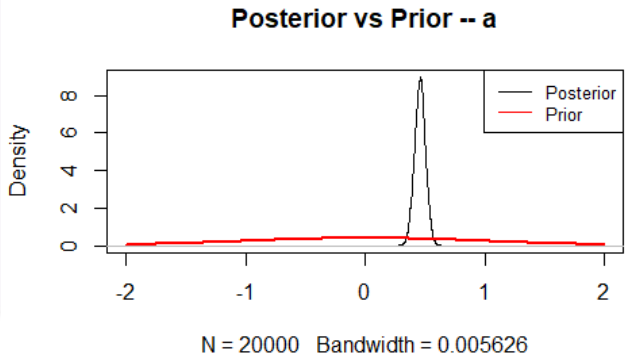
The Bayesian model is built using R 4.3.0 and rstan 2.21.8.

After running the model using all *in vitro* and *in vivo* measured clearance data, the posterior distribution of the parameters are plotted against their prior distributions, as below:



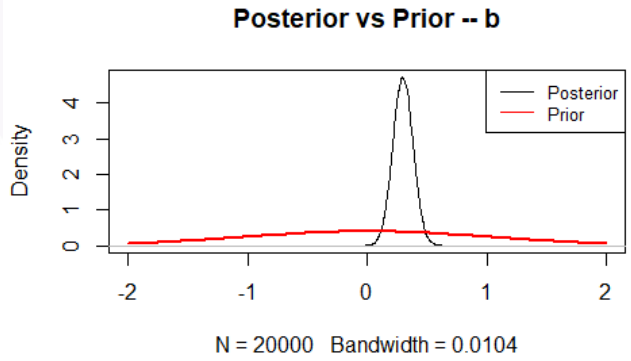
Prior Mean = 1.73, SD = 0.9

Posterior Mean = 1.64, SD =0.09



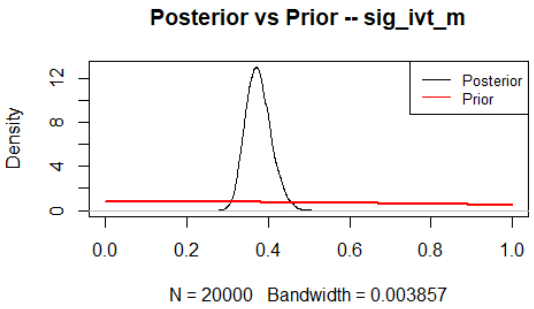
Prior Mean = 0, SD = 1

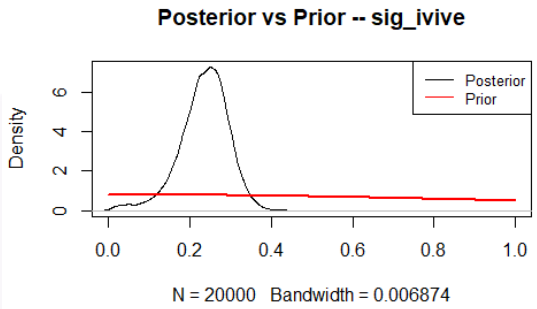
Posterior Mean = 0.46, SD =0.05

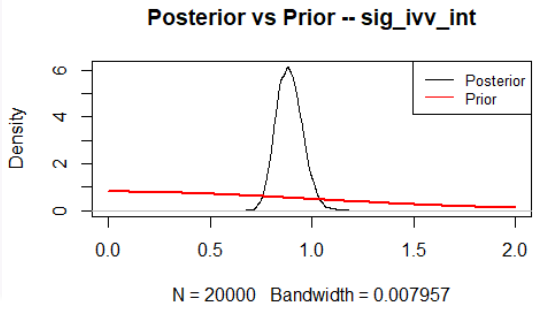


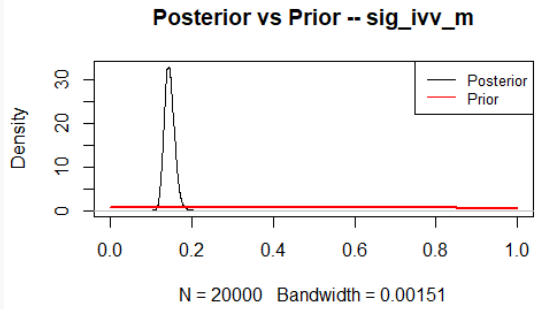
Prior Mean = 0, SD = 1

Posterior Mean = 0.30, SD =0.08





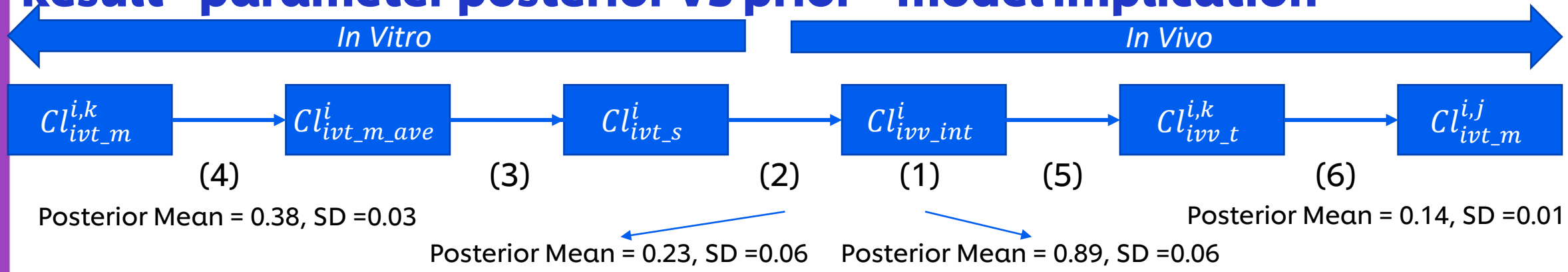




Prior: half normal distribution (non-negative) half with mean = 0 and standard deviation = 1

Posterior Mean = 0.38, SD =0.03 Posterior Mean = 0.23, SD =0.06 Posterior Mean = 0.89, SD =0.06 Posterior Mean = 0.14, SD =0.01

Result - parameter posterior VS prior – model implication



(1): Capture uncertainty in estimation of Cl_{ivv_int} across all chemicals in the dataset

(2): Assume linear relation between Cl_{ivt_s} and Cl_{ivv_int} (Halifax, 2010) with uncertainty

(3): *In vitro* clearance scaling (Halifax, 2010), deterministic

(4): Capture uncertainty in measurement of Cl_{ivt_m}

(5): Well Stirred liver model (Halifax, 2010), deterministic

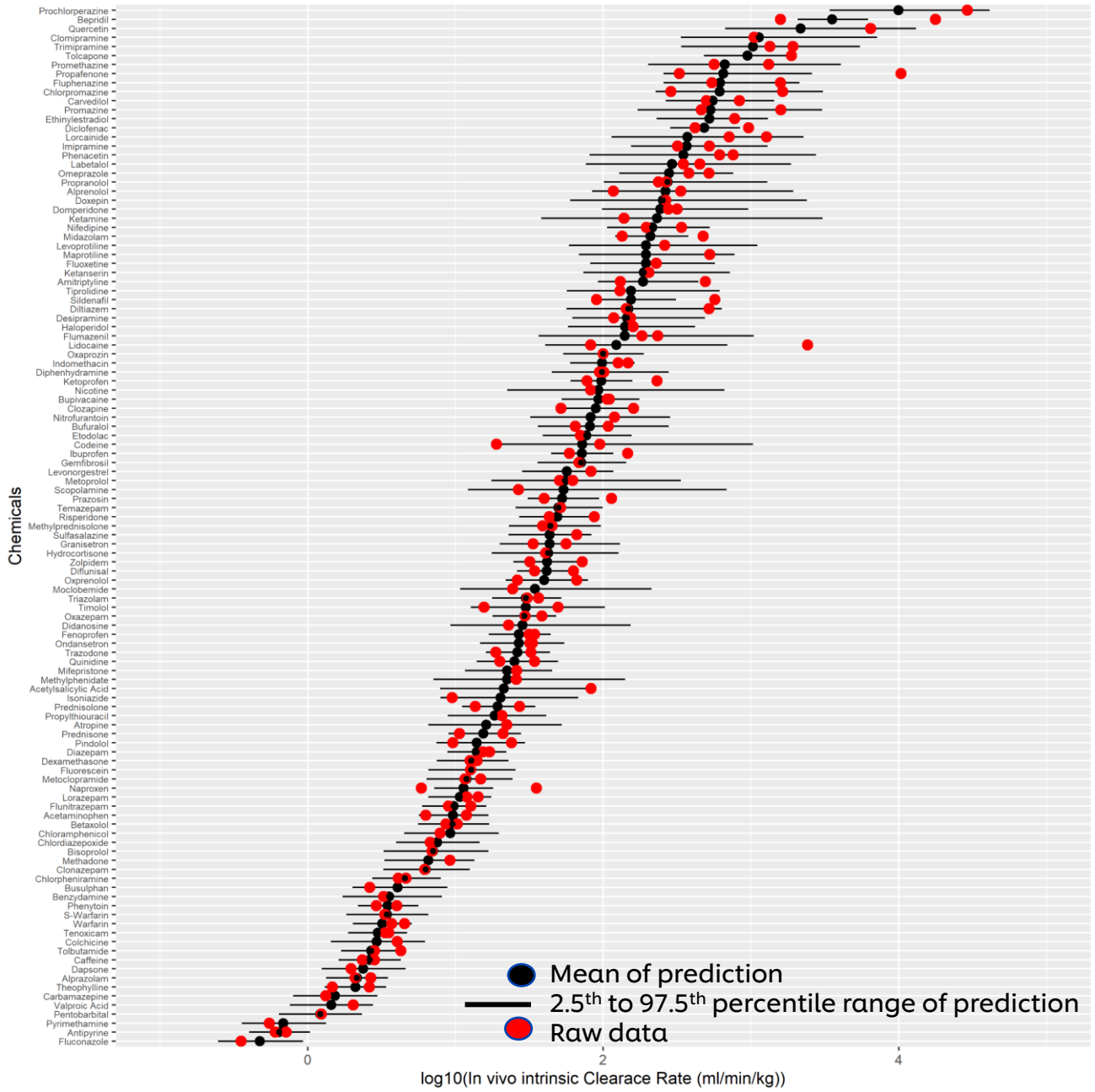
(6): Capture uncertainty in measurement of Cl_{ivv_m}

- From posterior mean of σ_{ivt_m} in (4) and σ_{ivv_m} in (6), it can be seen the posterior uncertainty of *in vitro* measurement is higher than that of *in vivo* measurement – consistent with the data collated
- The uncertainty of Cl_{ivv_int} (reflected by posterior mean of σ_{ivt_int} in (1)) is larger than that of Cl_{ivt_m} as the uncertainty of Cl_{ivt_m} is enlarged by the deterministic relation in (5)
- The relation between *in vitro* clearance and *in vivo* clearance in (2) based on posterior parameter distribution is in general agree with the same relation specified deterministically in (Halifax, 2010)

$$\log\left(Cl^{i}_{ivt\_s}\right) \sim N\left(0.46 * \log\left(Cl^{i}_{ivv\_int}\right) + 0.30, 0.23\right)$$ Relation based on posterior distribution and dataset collated

$$\log CL_{\text{int, hepatocytes}} = 0.512 \log CL_{\text{int, in vivo}} + 0.293$$ Deterministic relation in (Halifax, 2010) based on its data

Result– predicted VS raw data for *in vivo* intrinsic clearance



The figure on the left is a comparison between model prediction on Cl_{ivv_int} based on the posterior distributions of the parameters and the raw data in the literature for 115 chemicals

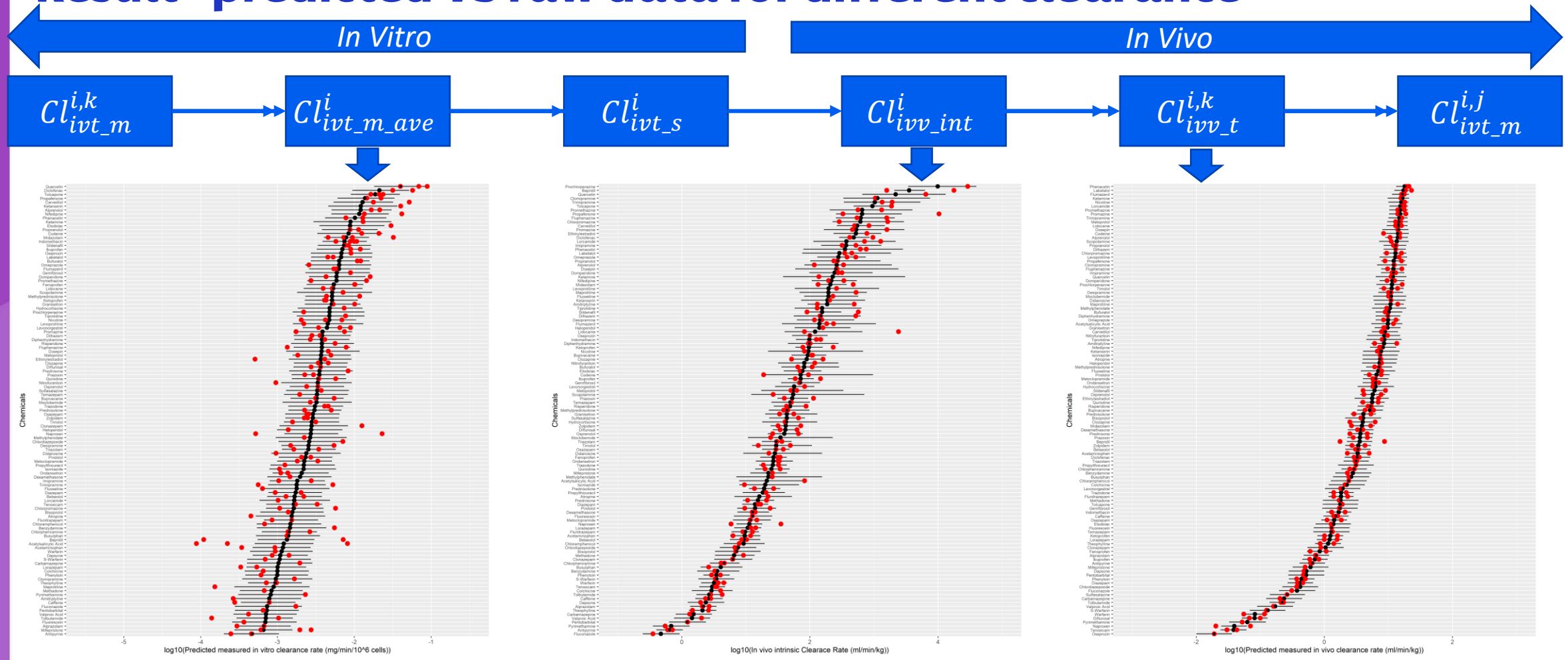
From the figure, it can be seen that

- Almost all raw data lies in 2.5 to 97.5 percentile range of the prediction except a few chemicals, e.g., Naproxen, Lidocaine, Propafenone and Bepridil
- This could be explained by the big difference between the value in the raw data from different literature, e.g., the value of Cl_{ivv_int} for the above 4 chemicals are (unit: ml/min/kg):

	Lombardo, et al., 2018	Halifax 2010
Naproxen	35	5.86
Lidocaine	2422	82
Propafenone	10348	328
Bepridil	17699	1583

Based on the measured clearance (either *in vitro* or *in vivo* or both), the model can predict the Cl_{ivv_int} for each chemical and characterise the uncertainty associated with the prediction

Result– predicted VS raw data for different clearance



Using the posterior distribution of the parameters derived from the Bayesian model, the uncertainty in the measurement of both *in vitro* and *in vivo* clearance for each chemical can also be inferred.

In general, the uncertainty of prediction of $Cl_{ivt\_m\_ave}$ is the largest while the uncertainty of prediction of Cl_{ivv_t} is the smallest, this is consistent with the uncertainty associated in the raw data

(In all 3 figures, the x-axis is spanning across 6 order of magnitude, so that the uncertainty in prediction and in raw data can be visually compared)

Summary

- Based on the measurements of *in vitro and in vivo clinical clearance rate* for 115 chemicals, a Bayesian model was built to
  - Understand the relationship between different clearance rates
  - Estimate the *in vivo* intrinsic clearance rate, one of the most sensitive parameters of a PBK model, with corresponding uncertainty being characterised,

- Understanding uncertainty of *in vivo* intrinsic clearance rate can help us to have more understanding of the source and extend of uncertainty in PBK outcome, contributing to a transparent exposure assessment for NGRA

- The model can also be used to estimate the uncertainty in the *in vitro* and *in vivo* measurement of the clearance rate.

- When there is a new (predominantly liver cleared) chemical with either in vitro or in vivo clinical measurements of clearance rate or both, this model can be used to estimate the corresponding *in vivo* intrinsic clearance rate, and the corresponding uncertainty.

- The extent of uncertainty of estimation is based on the extent of uncertainty in the corresponding measurement data.

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Reference

Hallifax D, Foster JA, Houston JB. Prediction of human metabolic clearance from in vitro systems: retrospective analysis and prospective view. Pharm Res. 2010 Oct;27(10):2150-61. doi: 10.1007/s11095-010-0218-3.

Li, H., Reynolds, J., Sorrell, I. et al. (2022). PBK modelling of topical application and characterisation of the uncertainty of Cmax estimate: A case study approach. Toxicol Appl Pharmacol442, 115992. doi: 10.1016/j.taap.2022.115992

Lombardo F, Berellini G, Obach RS. Trend Analysis of a Database of Intravenous Pharmacokinetic Parameters in Humans for 1352 Drug Compounds. Drug Metab Dispos. 2018 Nov;46(11):1466-1477. doi: 10.1124/dmd.118.082966.

Moxon TE, Li H, Lee MY, Piechota P, Nicol B, Pickles J, Pendlington R, Sorrell I, Baltazar MT. Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products. Toxicol In Vitro. 2020 Mar;63:104746. doi: 10.1016/j.tiv.2019.104746.

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS. httk: R Package for High-Throughput Toxicokinetics. J Stat Softw. 2017 Jul 17;79(4):1-26. doi: 10.18637/jss.v079.i04

Punt A, Louisse J, Pinckaers N, Fabian E, van Ravenzwaay B. Predictive Performance of Next Generation Physiologically Based Kinetic (PBK) Model Predictions in Rats Based on In Vitro and In Silico Input Data. Toxicol Sci. 2022 Feb 28;186(1):18-28. doi: 10.1093/toxsci/kfab150.

van Tongeren TCA, Carmichael PL, Rietjens IMCM, Li H. Next Generation Risk Assessment of the Anti-Androgen Flutamide Including the Contribution of Its Active Metabolite Hydroxyflutamide. Front Toxicol. 2022 Jun 2;4:881235. doi: 10.3389/ftox.2022.881235.

Varma MV, Steyn SJ, Allerton C, El-Kattan AF. Predicting Clearance Mechanism in Drug Discovery: Extended Clearance Classification System (ECCS). Pharm Res. 2015 Dec;32(12):3785-802. doi: 10.1007/s11095-015-1749-4.

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