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REVERSE DOSIMETRY IN TKPLATE TO RECONSTRUCT EXPOSURE DISTRIBUTIONS USING BIOMONITORING DATA

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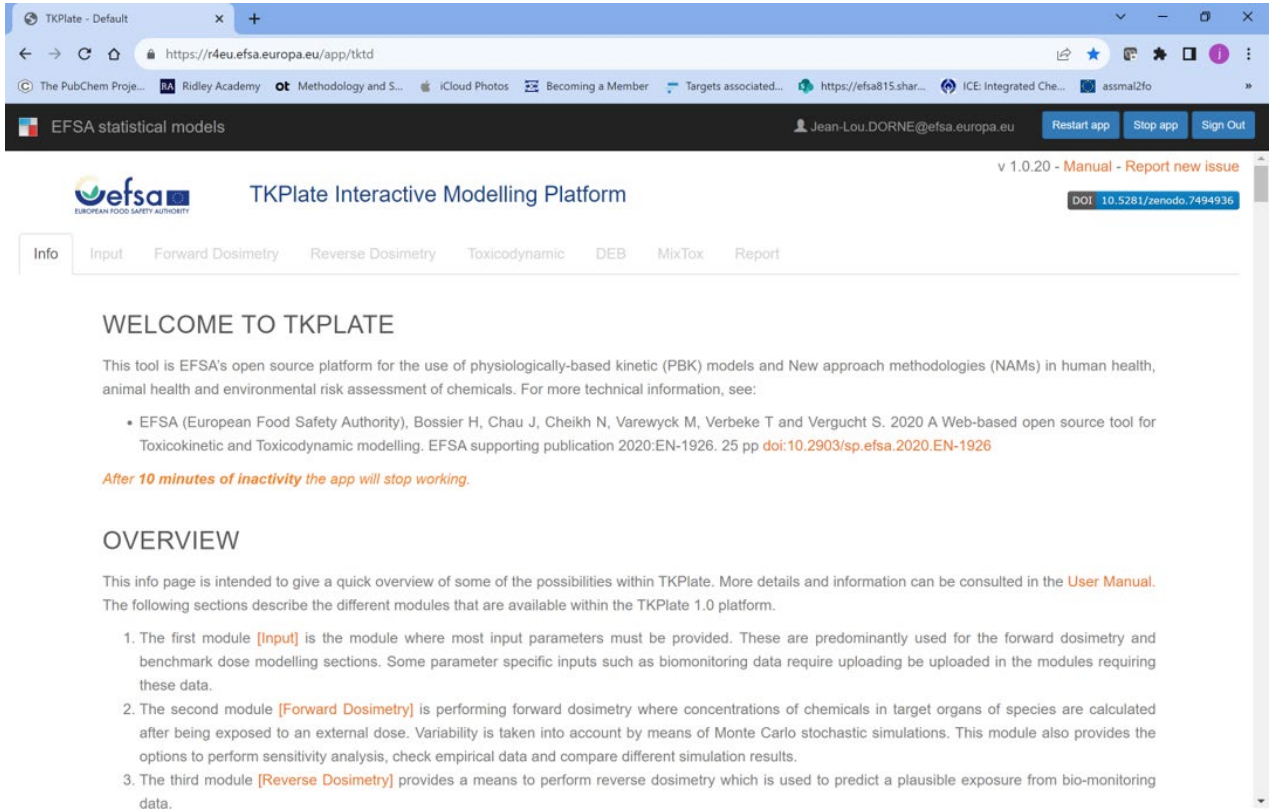
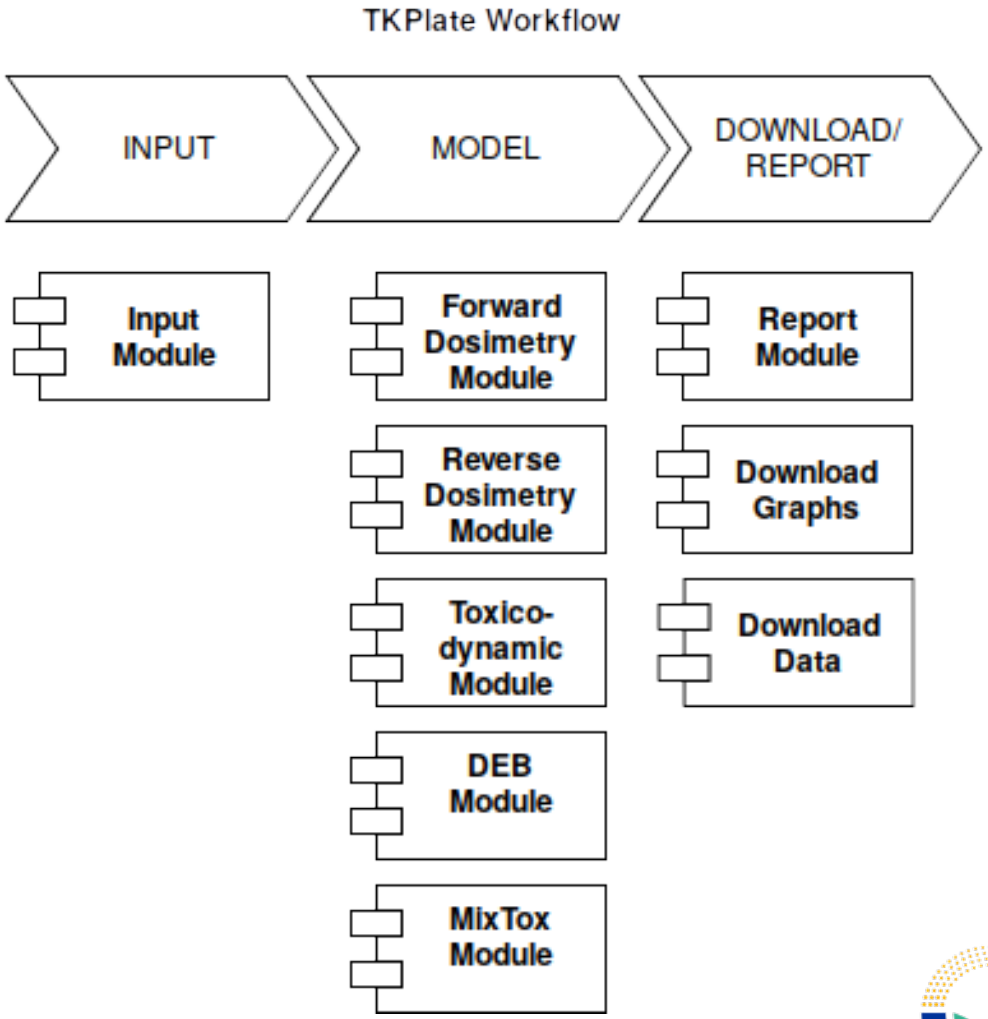
OUTLINE

- TKPlate 1.0 : Introduction and General Workflow
- TKPlate : Reverse Dosimetry
- Caffeine Case Study
- Current and Future perspectives

TKPlate General Workflow and Reverse Dosimetry

TKPLATE 1.0: INFO PAGE AND GENERAL WORKFLOW





RELEVANCE OF TKPLATE 1.0 TO EFSA'S REMIT

❖ Relevance to EFSA

- All Units dealing with chemicals at EFSA
- Supports use of NAMs@EFSA without testing: generate TK TD profiles, Id data gaps etc..
- Pesticides, food and feed additives, contaminants, novel foods etc.
- PBK/QIVIVE particularly relevant to pesticides (e.g. Developmental Neurotoxicity).

❖ Input parameters

- Data from regulatory dossiers (i.e. kinetic data/dose response data for regulated products
- Data from literature
- Previous assessments
- Public databases such as EFSA'sOpenFoodTox, US-EPA CompToxChemicals dashboard, ECHA's REACH Database

WHAT CAN TKPLATE 1.0 DO FOR RISK ASSESSMENT AS A NAM TOOL ?

❖ **Human and animal PBK models in Annex of 2021 OECD guidance, described/validated with reporting template**

❖ **Forward Dosimetry (From exposure to internal dose) for humans and animals (test/farm)**

- Predict through simulations elimination and residues of chemicals in blood/target organs:

✓ In vivo data (oral route as well as multiple route (oral, dermal, inhalation))

✓ In vitro data through QIVIVE models

- Comparison predictions/ experimental data for kinetic profiles/ residues in fluids/organs
- Inter-species comparisons

❖ **Reverse Dosimetry (From internal to external dose)**

- Recalculate exposure based on biomonitoring data
- Can be used to derive human biomonitoring guidance values (HBM-GVs) i.e. assess chemical exposure levels measured in HBM studies in a health risk assessment context.

TK PLATE 1.0 : PUBLICATION AND ASSOCIATED OUTPUTS

Further development of a web-based open-source platform for Toxicokinetic and Toxicodynamic modelling: TKPlate 1.0

Han Bossier, Joris Chau, Machteld Varewyck, Stephanie Vergucht and Tobias Verbeke

Open Analytics NV

Technical Report

APPROVED: 8 November 2023
doi: 10.2903/sp.efsa.2023.EN-8441

efsa SUPPORTING PUBLICATIONS

User Guide for TKPlate 1.0: An open access platform for implementing new approach methodologies in chemical risk assessment through toxicokinetic and toxicodynamic modelling

European Food Safety Authority (EFSA),
Han Bossier, José Cortiñas-Abrahantes, Keyvin Darney, Fotis Spyropoulos, Leonie S Lautz, Pierre André Billat, Rémy Beaudouin, Florence Zeman, Cléo Bodin, Jean Lou CM Dorne

Approved: 12 October 2023
DOI: 10.2903/j.efsa.2023.e211101

EDITORIAL

efsa JOURNAL

TKPlate 1.0: An Open-access platform for toxicokinetic and toxicodynamic modelling of chemicals to implement new approach methodologies in chemical risk assessment

Technical Report

APPROVED: 8 November 2023
doi: 10.2903/sp.efsa.2023.EN-8440

efsa SUPPORTING PUBLICATIONS

Applications of TKPlate 1.0 for toxicokinetic and toxicodynamic modelling of chemicals: Case Studies

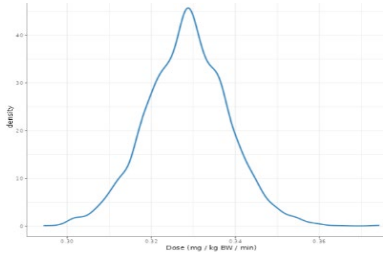
European Food Safety Authority (EFSA),
Han Bossier, Fotis Spyropoulos, Keyvin Darney, Leonie S Lautz, Pierre André Billat, Rémy Beaudouin, Florence Zeman, Cléo Bodin, José Cortiñas-Abrahantes, Jean Lou CM Dorne

TKPlate: Reverse Dosimetry

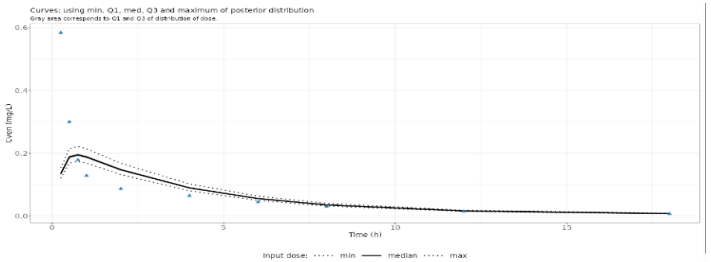
REVERSE DOSIMETRY MODULE : WHAT THE BODY DOES TO THE CHEMICAL : FROM THE INSIDE TO THE OUTSIDE

Prior Distributions

Posterior Distributions



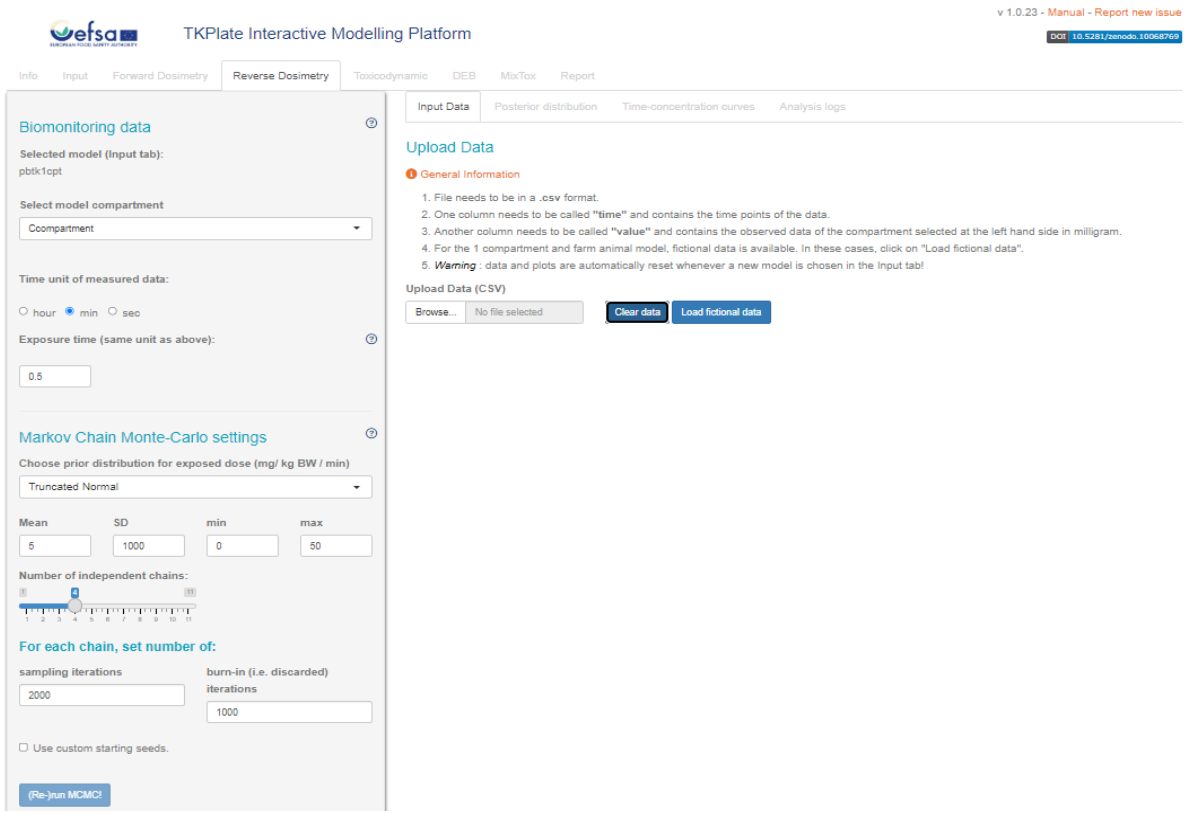
Exposure Distribution



Predicting human exposure from concentrations inside the body (blood or urine levels): Biomonitoring

INTRODUCTION TO REVERSE DOSIMETRY

- **Definition: R**econstruct exposure distribution from internal measured concentrations
- **Key Purpose:** Allows more accurate interpretation HBM data identifying external exposure sources.
- **Example:** Select kinetic/PBK model to simulate external dose for a given exposure scenario

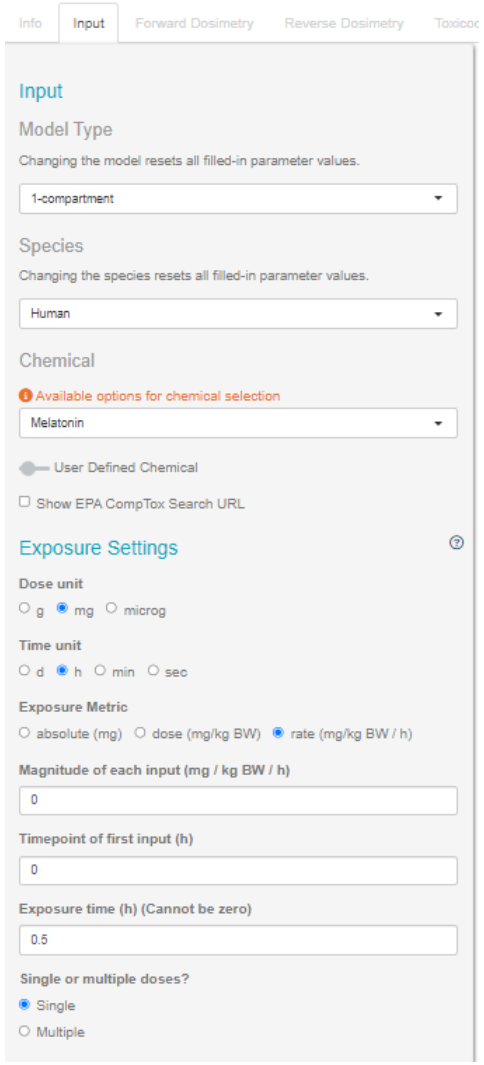


STEPS IN REVERSE DOSIMETRY

1. **Select PBK Model:** Define set of input parameters (chemical-specific and physiological parameters) to simulate kinetic processes (select model)
2. **Biomonitoring Input:** Biomonitoring data (e.g., blood) measuring concentrations of chemicals, compartment of interest, exposure scenario and MCMC settings.
3. **Output:** Run simulations, diagnostic of model are presented, checking convergence and other metrics to support model evaluation. In addition, posterior distribution of the attributable external dose based on previous inputs as well as a plot of observed vs fitted biomonitoring data are provided.

STEPS IN REVERSE DOSIMETRY: PBPK MODEL AND PARAMETERS

1.1. PBPK Model inputs: Defining model type, species, chemical and exposure setting



1.2. Chemical Specific and Physiological inputs:

Chemical Specific Parameters

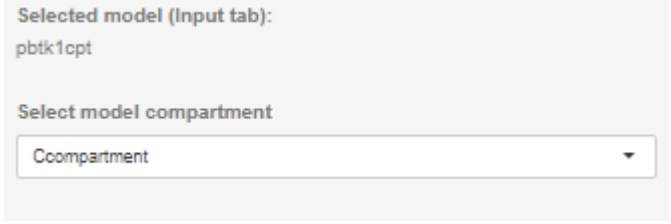
	Parameter	Value	Unit	Descript
1	k_abs	2.18	min^-1	Absorption rate constant
2	ke	0.23	min^-1	Elimination rate constant
3	MW	232.3	g/mol	Molecular weight
4	vdist	1.1	L/kg	Volume of distribution

Physiological Parameters

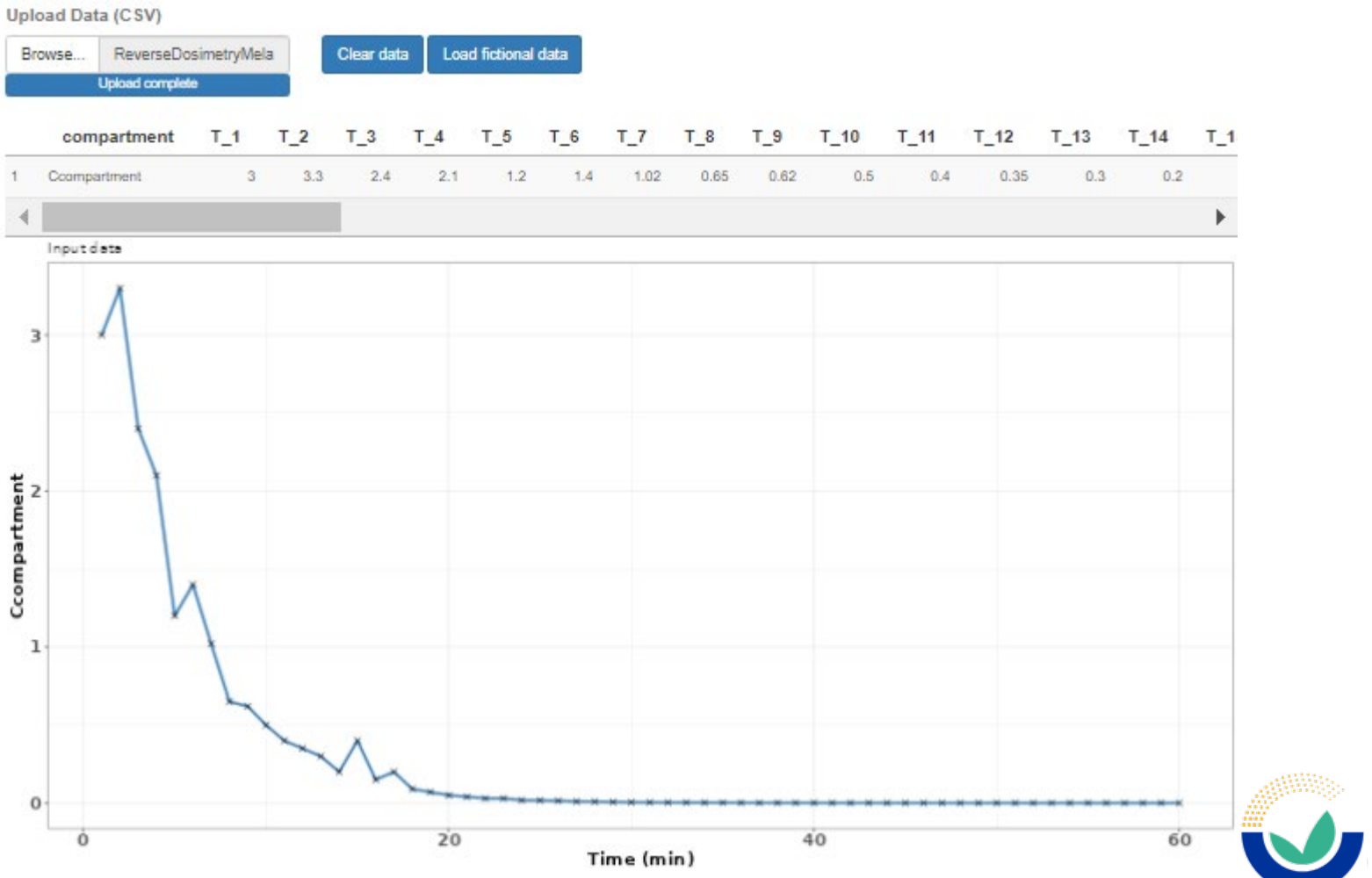
	Parameter	Value	Unit	Descript
1	BW	70	kg	Body weight

STEPS IN REVERSE DOSIMETRY: BIOMONITORING INPUT

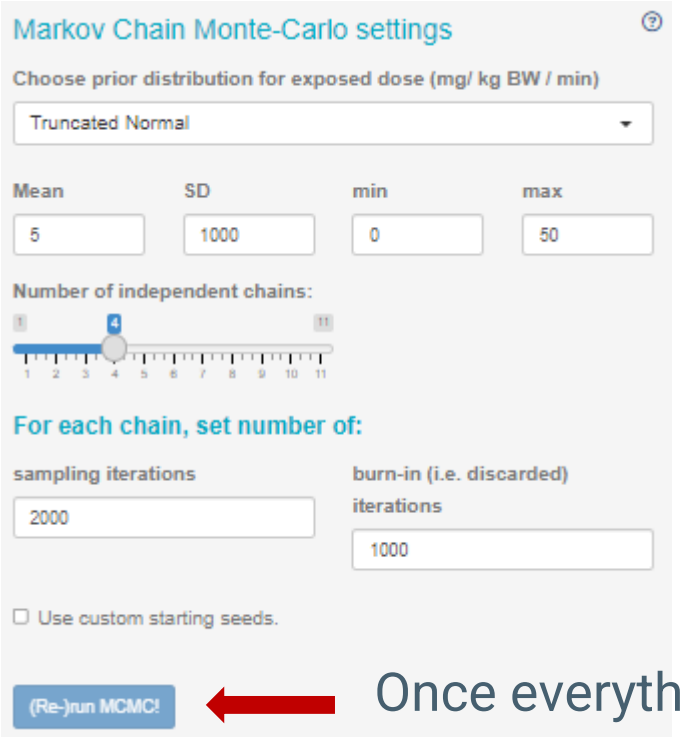
2.1. Model and Compartment



2.2. Upload Biomonitoring data



2.3. MCMC setting



Once everything is uploaded and select, run the MCMC procedure

STEPS IN REVERSE DOSIMETRY: OUTPUT

3.1. Model diagnostic

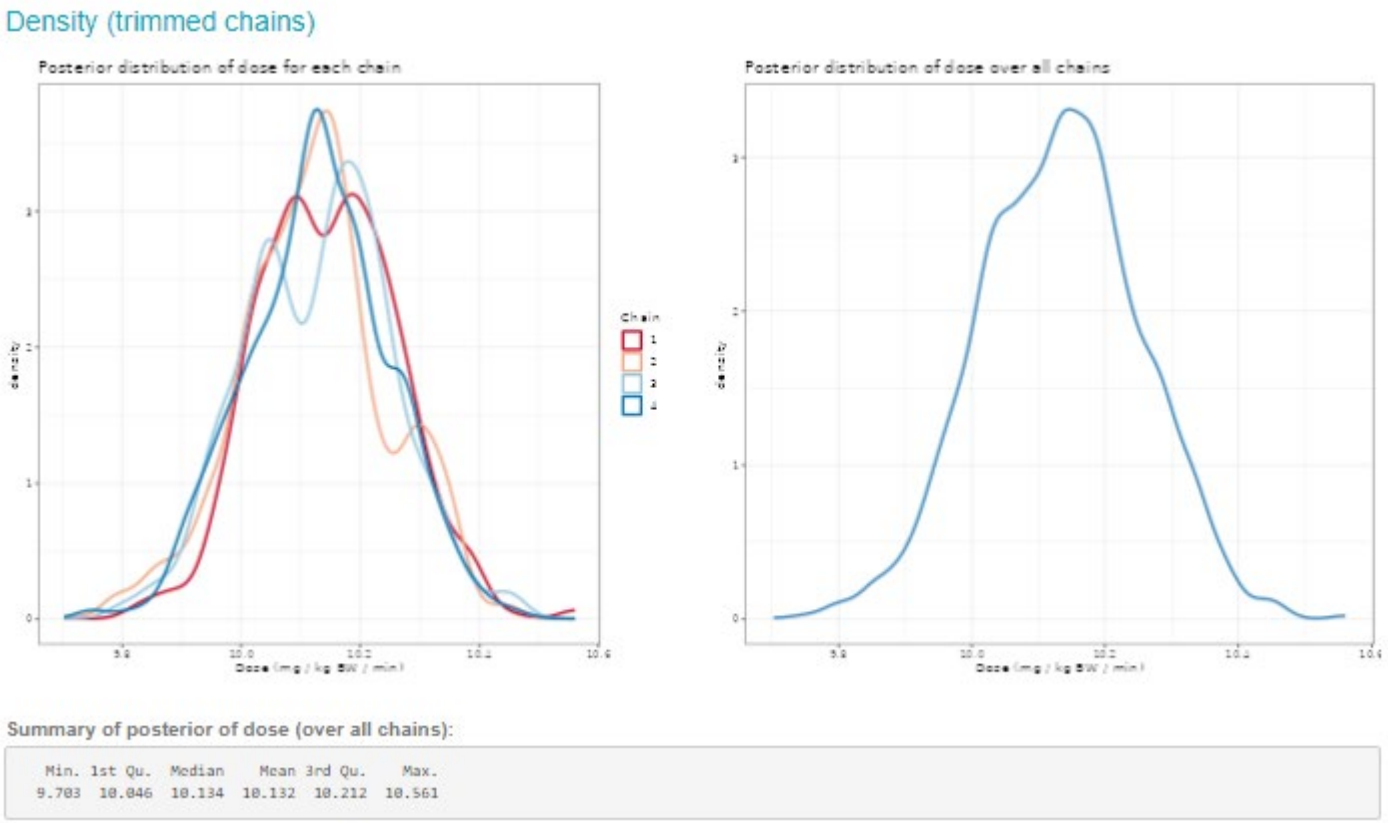
Complete MCMC runs for 4 chains representing different starting points

Trimmed MCMC runs after burn-in is discarded for the 4 chains, providing information about convergence and mixing of each chain

Autocorrelation plot showing how well the chains are mixing, with low autocorrelation indicating good mixing and convergence is achieved

STEPS IN REVERSE DOSIMETRY: OUTPUT

3.2. Posterior distribution of external dose



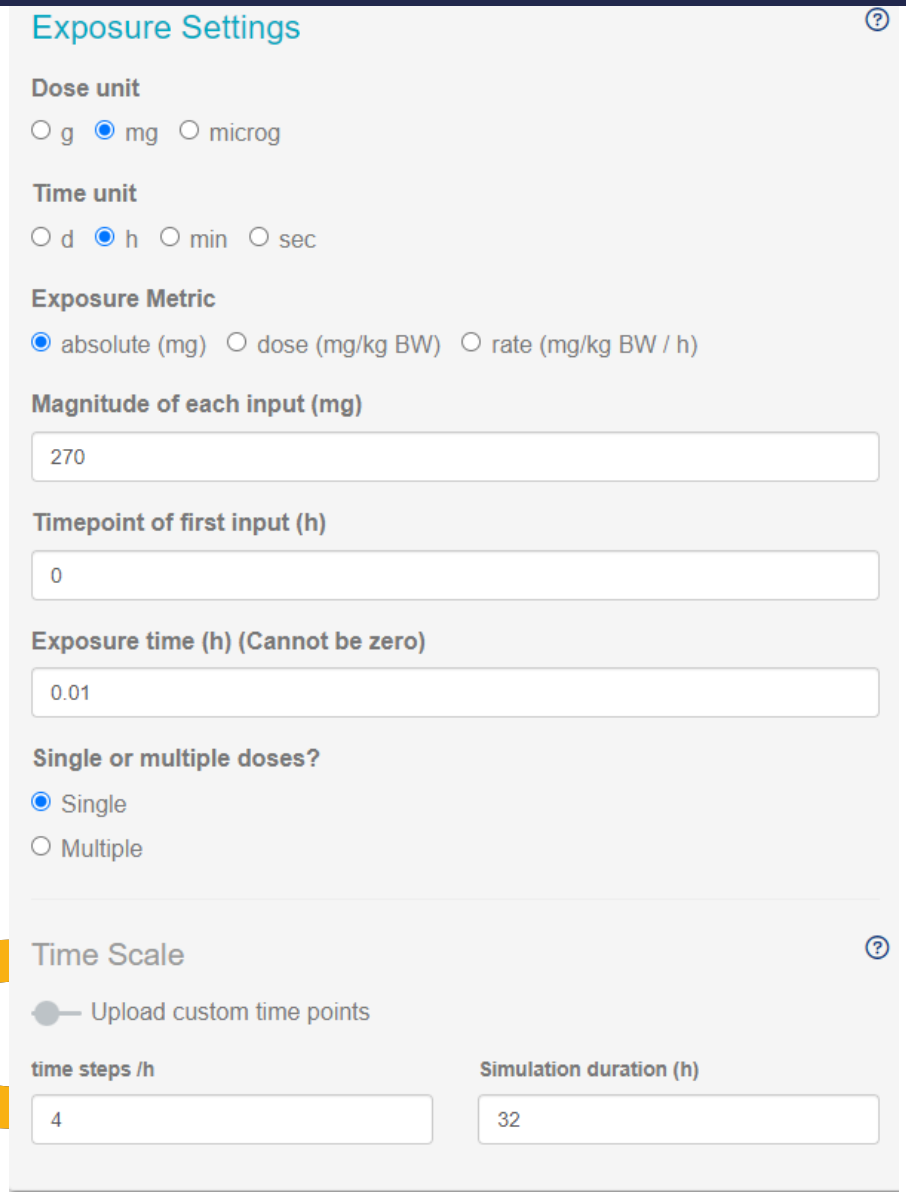
Summary of posterior of dose (over all chains):

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  9.703  10.046  10.134  10.132  10.212  10.561
```

- Two plots are shown, one showing the posterior distributions for each chain separately and the second one with all chains combined.
- Summary statistics of posterior distribution indicating that in this case the potential external dose is around 10.1, with a minimum of 9.7 and maximum of 10.6

Caffeine Case Study

CAFFEINE PARAMETERS



In vitro/QIVIVE US-EPA Comptox data

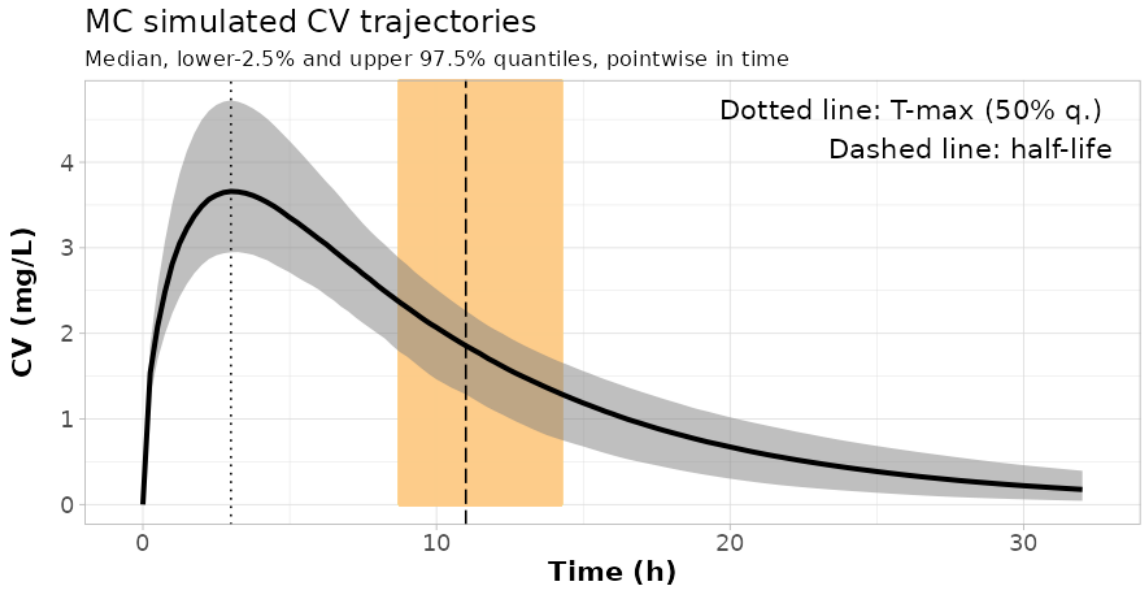
CLint = 0.2855 µL/min/million hepatocytes

- $CL_{in\ vivo}$ = 0.2855 x 140 (million hepatocytes/g liver) x 2000 (g liver) = 0,08 L/min metabolism via CYP1A2
- Exposure **270 mg oral**
- Simulation with variability in CYP1A2 35% (Dorne et al., 2001)

Chemical Specific Parameters

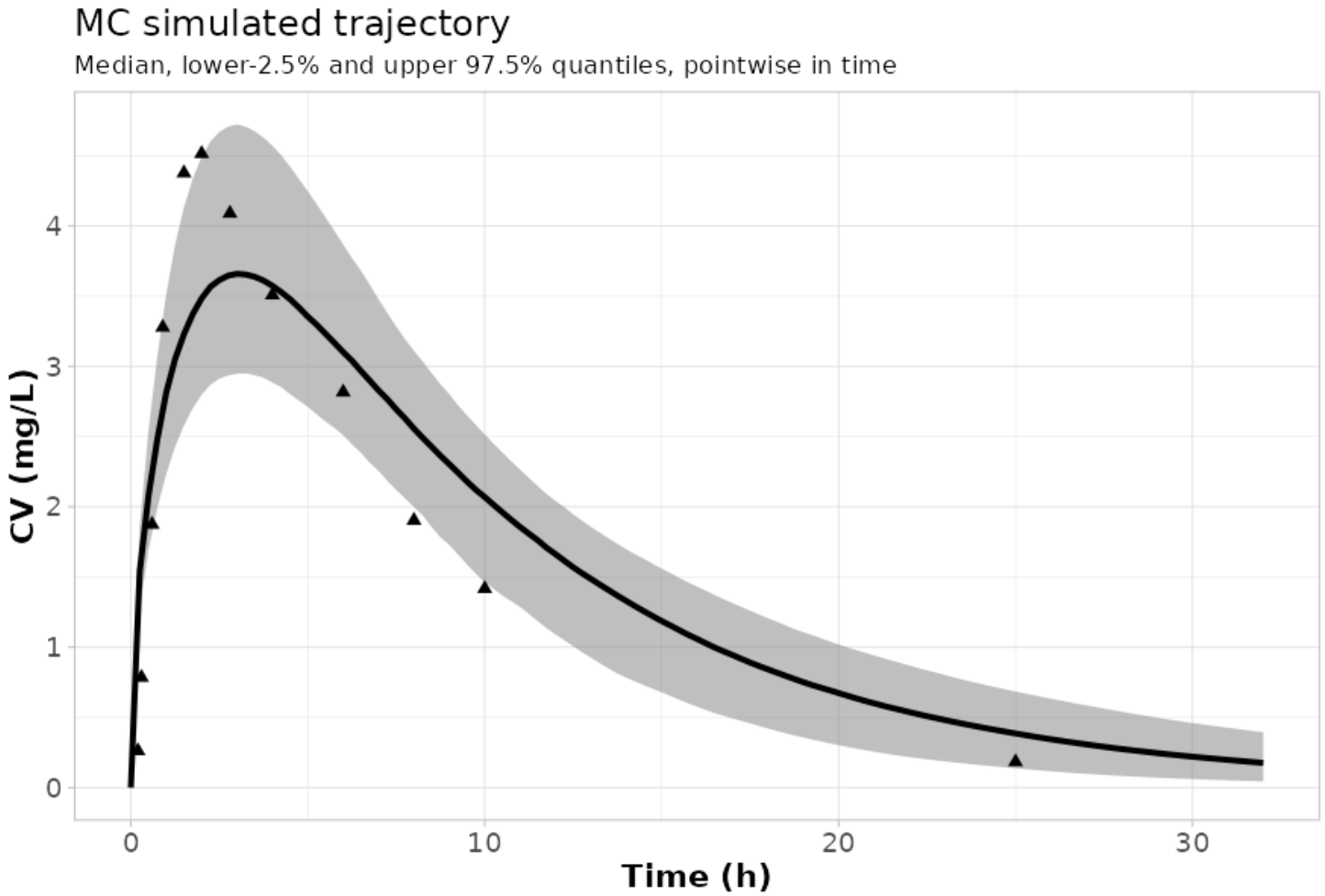
	Parameter	Value	Unit	Description
1	BP	1		Blood plasma ratio
2	cl_hepatic	0.08	L/min	Hepatic clearance
3	frac_abs_gut	0.8		Fractional absorption gut
4	FUP	1		Fraction unbound in plasma
5	GFR	0.06	L/min	Glomerular filtration rate
6	k_abs	0.01	min^-1	Absorption rate constant (1st order)
7	MW	194.2	g/mol	Molecular Weight
8	P_adipose	0.263825		Blood tissue partition coefficient in the adipose
9	P_gut	0.943705		Blood tissue partition coefficient in the gut
10	P_kidney	1.025077		Blood tissue partition coefficient in the kidney
11	P_liver	1.013832		Blood tissue partition coefficient in the liver
12	P_rapid	1.002098		Blood tissue partition coefficient in the rapid compartment
13	P_slow	0.984071		Blood tissue partition coefficient in the slow compartment

Caffeine Forward Dosimetry



	0%-quantile	2.5%-quantile	50%-quantile	97.5%-quantile	100%-quantile
T-max (h)	2.50E+00	2.74E+00	3.00E+00	3.50E+00	3.75E+00
C-max (mg/L)	2.67E+00	2.95E+00	3.66E+00	4.73E+00	5.19E+00
Half-life (h)	5.00E+00	6.00E+00	8.00E+00	1.08E+01	1.20E+01
AUC (h * mg/L)	2.90E+01	3.49E+01	4.44E+01	5.36E+01	5.78E+01

Caffeine : Model Evaluation
Predictions vs Experimental Data

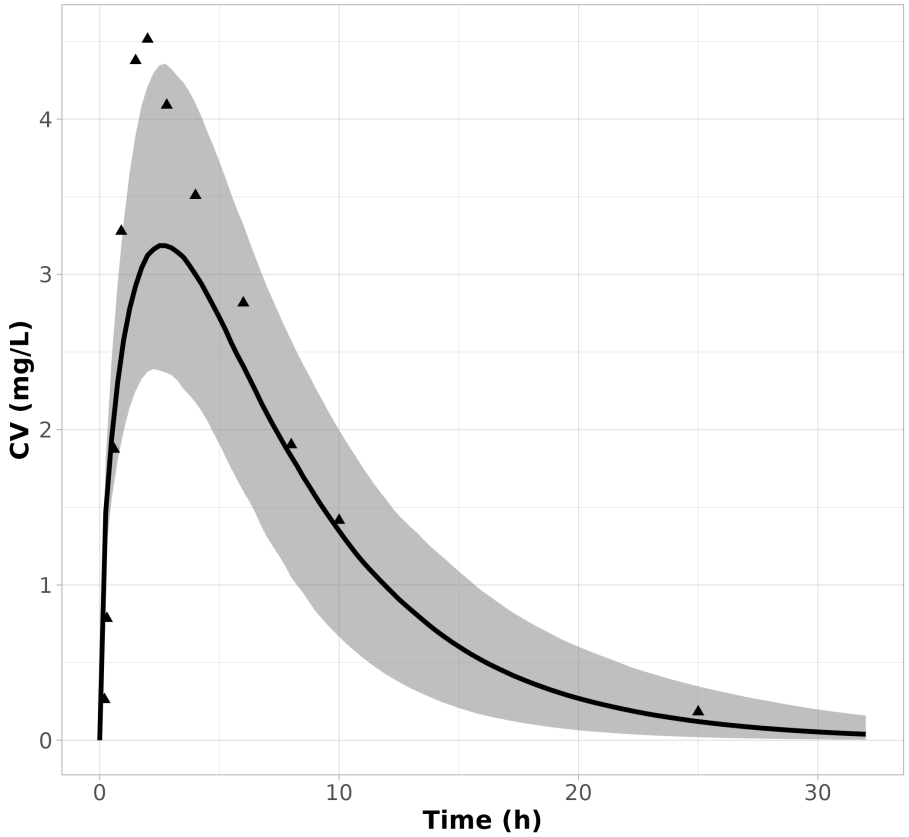


Lelo et al., (1986) doi.org/10.1111/j.1365-2125.1986.tb05246.x

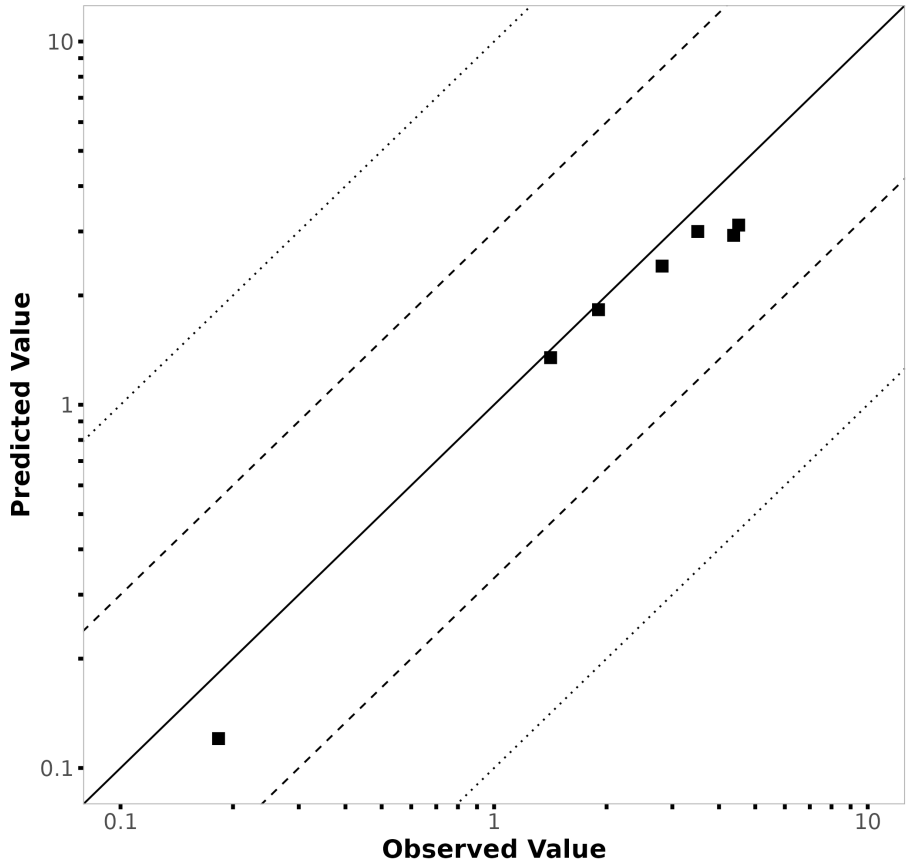
CAFFEINE– FORWARD DOSIMETRY

MC simulated trajectory

Median, lower-2.5% and upper 97.5% quantiles, pointwise in time

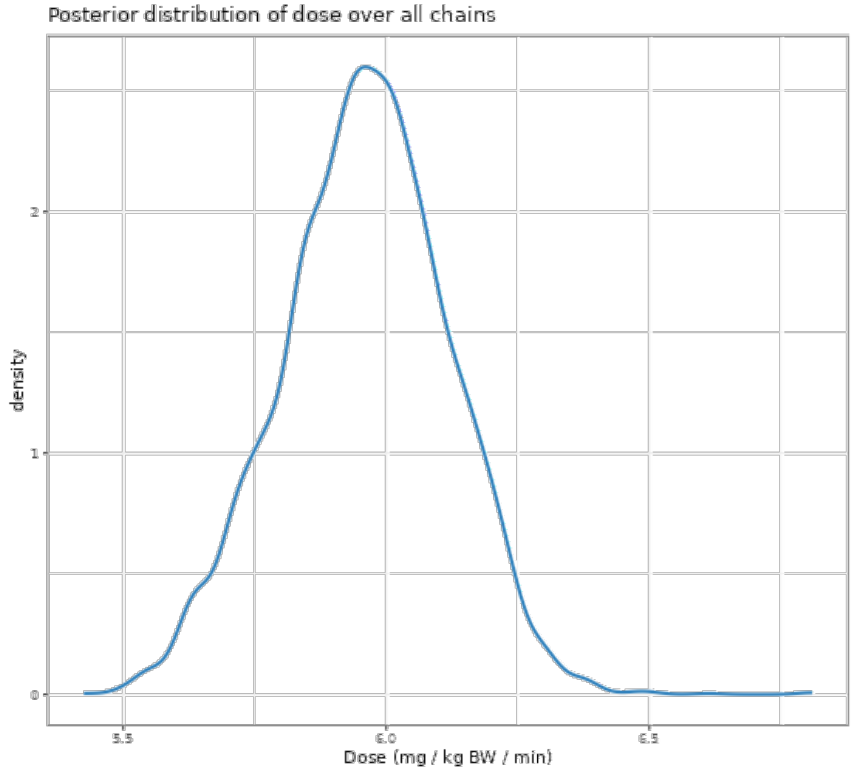


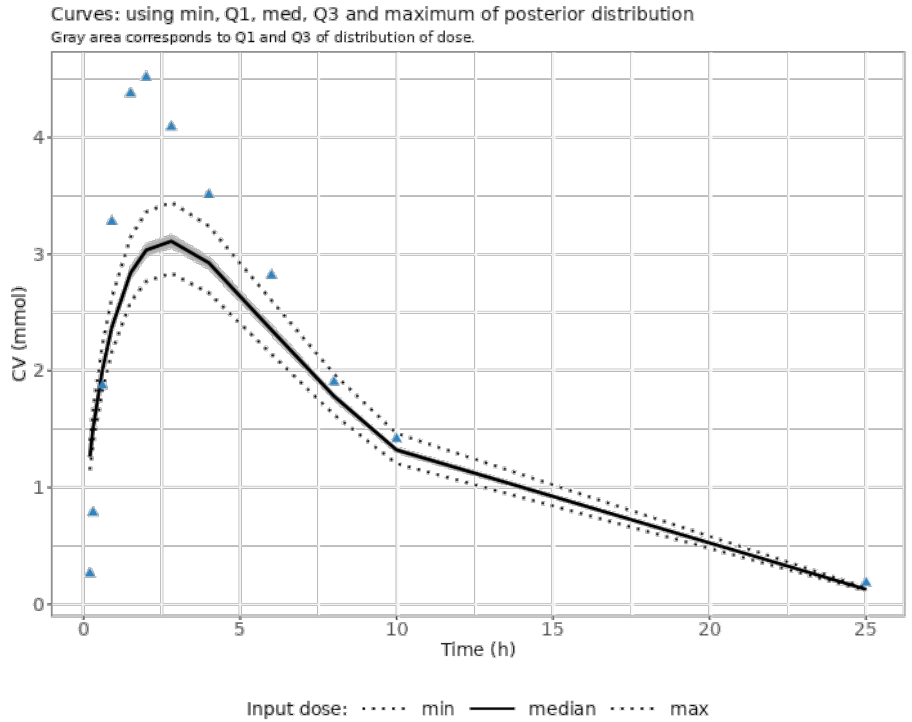
Predicted vs observed concentrations.



CAFFEINE – REVERSE DOSIMETRY

Using Caffeine time concentration profiles (Lelo et al., 1986) to recalculate exposure: reverse dosimetry
Satisfactory redictions: Exposure 270 mg oral-Reverse dosimetry prediction median : 250 mg





	Min	Q1	Median	Q3	max
Dose (mg)	228	246	250	255	286

NEW MODELS FOR THE PLATE

New Human and animal models

- Pregnancy/Gestational models
- Ontogenesis of enzymes
- Generic models for metabolites (detoxification/bioactivation)
- Reverse dosimetry models for metabolites/HBM/urine etc
- Bioaccumulation models (EFSA/ECHA)

Animal models

- Physiologically-based for cats, minipig, goat, turkey etc
- PBK/DEB models for salmon
- Web TKTD Tool to assess effect of pesticides on bird reproduction

ERA models

- Generalise DEB and TKTD models across species

CONCLUSION AND FUTURE PERSPECTIVES

- **TKPlate and Reverse dosimetry Training**
  - Reverse dosimetry models providing outputs for blood
  - Need to include urine, parent compound and metabolites, other organs

TKPlate Training

- Pilot planned for EFSA Staff and experts on 21-22 Nov 24 and Jan 25
- Moving towards recorded online training available open access ?

- **Moving towards application of TKPlate in EFSA panels**
  - Differences in NAM across EFSA panels: regulations, history
  - Change management may be needed: from in vivo to NAMs

- **EC/International collaborations**
  - PARC/ASPIS EU : follow up on models and data developed, uptake TKPlate
  - Future APRCA case study on use of TKPlate for QIVIVE ?

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