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REVERSE DOSIMETRY IN TKPLATE TO RECONSTRUCT EXPOSURE DISTRIBUTIONS USING BIOMONITORING DATA



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OUTLINE

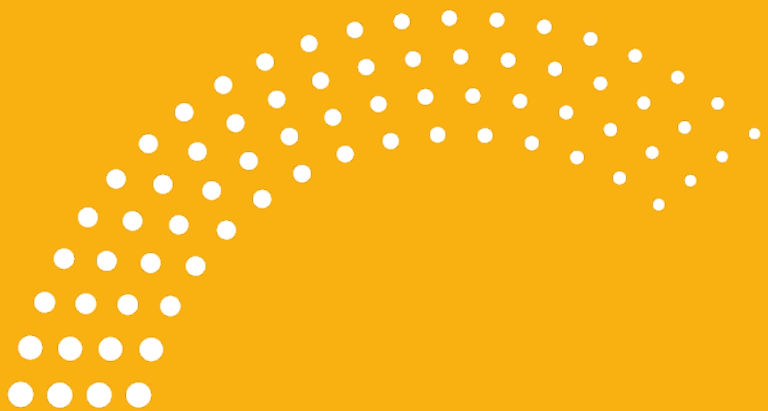
TKPlate 1.0 : Introduction and
General Workflow

TKPlate : Reverse Dosimetry

Caffeine Case Study

Current and Future perspectives

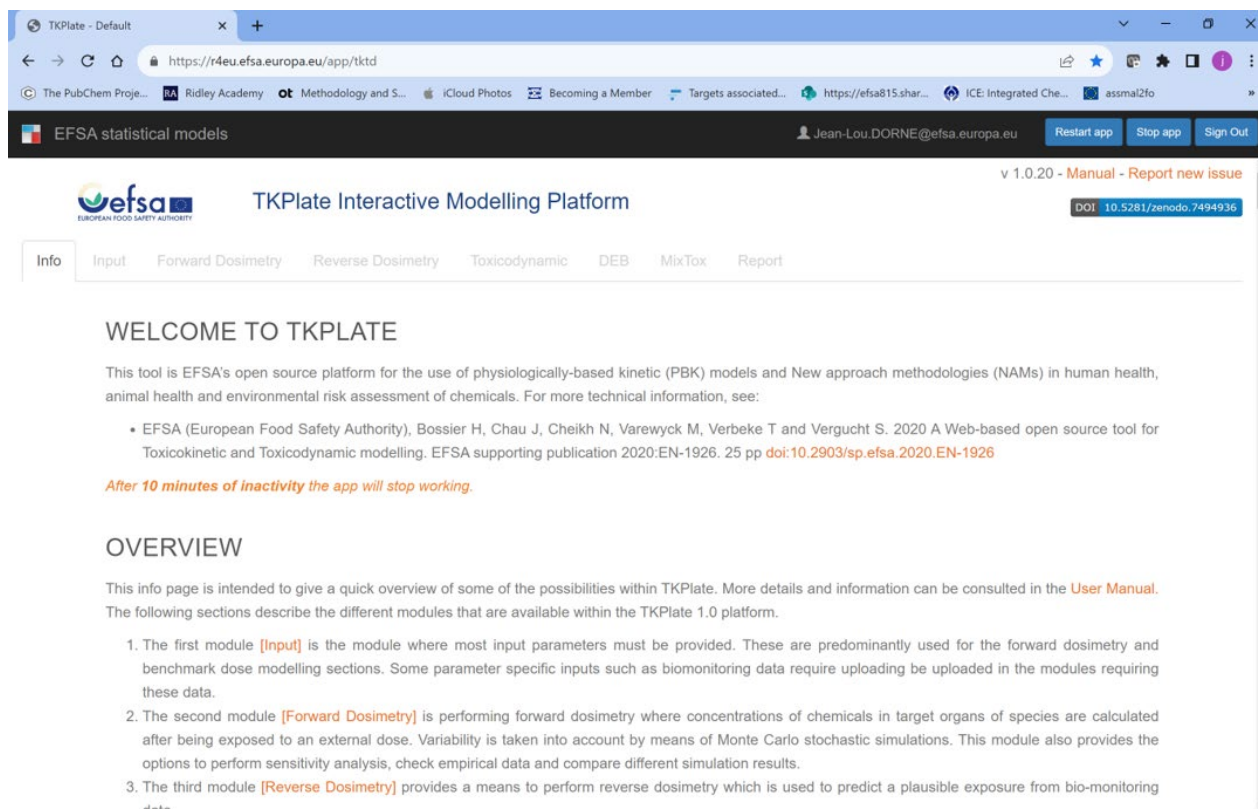




TKPlate General Workflow and Reverse Dosimetry



TKPLATE 1.0: INFO PAGE AND GENERAL WORKFLOW



The screenshot shows the TKPlate Interactive Modelling Platform interface. The browser address bar displays <https://r4eu.efsa.europa.eu/app/tktd>. The page header includes the EFSA logo and the title "TKPlate Interactive Modelling Platform" with version "v 1.0.20 - Manual - Report new issue" and a DOI: [10.5281/zenodo.7494936](https://doi.org/10.5281/zenodo.7494936). A navigation menu contains: Info, Input, Forward Dosimetry, Reverse Dosimetry, Toxicodynamic, DEB, MixTox, Report. The main content area features a "WELCOME TO TKPLATE" section with a brief description of the tool and a list of references. Below this is an "OVERVIEW" section with an introductory paragraph and a numbered list of three modules: 1. Input module, 2. Forward Dosimetry module, and 3. Reverse Dosimetry module.

WELCOME TO TKPLATE

This tool is EFSA's open source platform for the use of physiologically-based kinetic (PBK) models and New approach methodologies (NAMs) in human health, animal health and environmental risk assessment of chemicals. For more technical information, see:

- EFSA (European Food Safety Authority), Bossier H, Chau J, Cheikh N, Varewyck M, Verbeke T and Vergucht S. 2020 A Web-based open source tool for Toxicokinetic and Toxicodynamic modelling. EFSA supporting publication 2020:EN-1926. 25 pp [doi:10.2903/sp.efsa.2020.EN-1926](https://doi.org/10.2903/sp.efsa.2020.EN-1926)

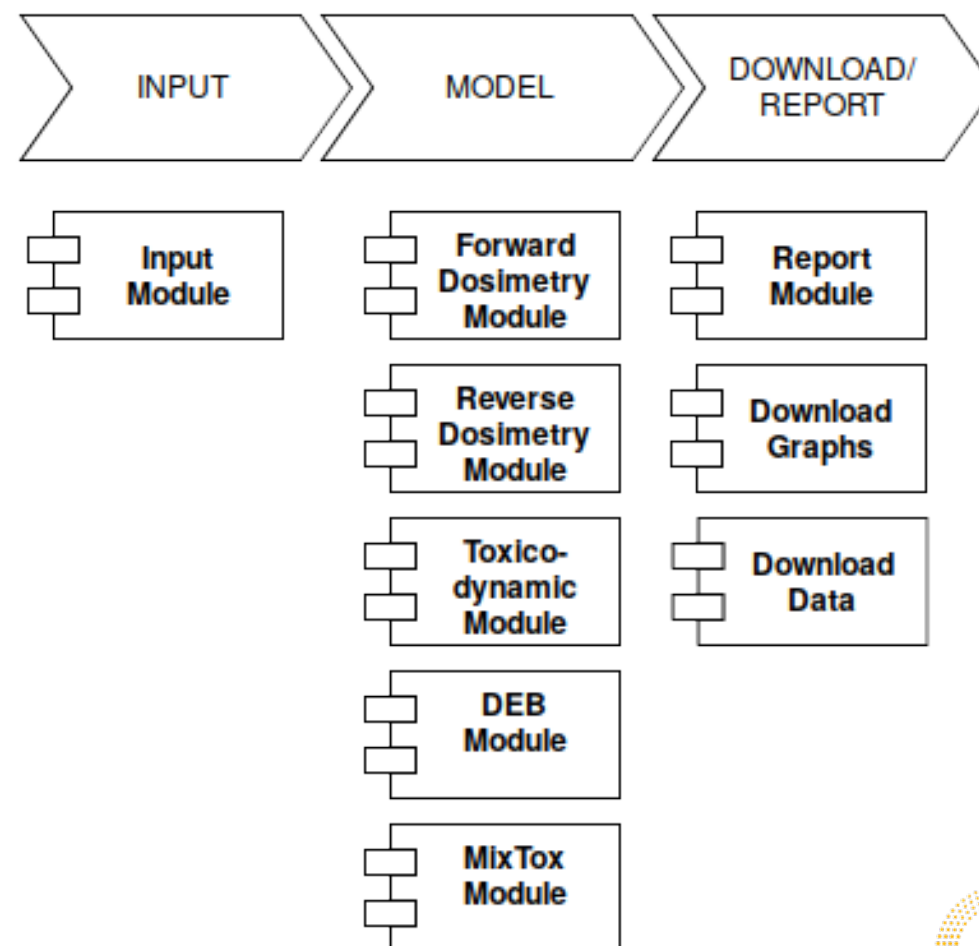
After 10 minutes of inactivity the app will stop working.

OVERVIEW

This info page is intended to give a quick overview of some of the possibilities within TKPlate. More details and information can be consulted in the [User Manual](#). The following sections describe the different modules that are available within the TKPlate 1.0 platform.

1. The first module [**Input**] is the module where most input parameters must be provided. These are predominantly used for the forward dosimetry and benchmark dose modelling sections. Some parameter specific inputs such as biomonitoring data require uploading be uploaded in the modules requiring these data.
2. The second module [**Forward Dosimetry**] is performing forward dosimetry where concentrations of chemicals in target organs of species are calculated after being exposed to an external dose. Variability is taken into account by means of Monte Carlo stochastic simulations. This module also provides the options to perform sensitivity analysis, check empirical data and compare different simulation results.
3. The third module [**Reverse Dosimetry**] provides a means to perform reverse dosimetry which is used to predict a plausible exposure from bio-monitoring data.

TKPlate 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's OpenFoodTox, 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



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



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

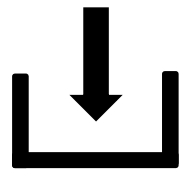




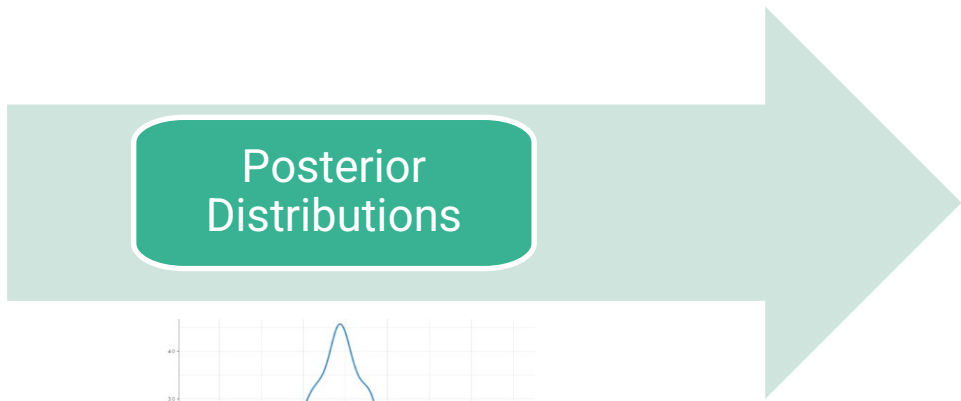
TKPlate: Reverse Dosimetry



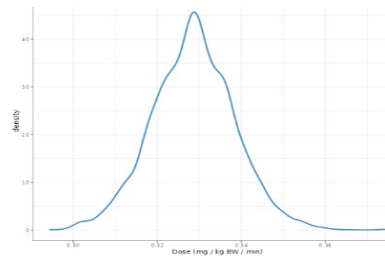
REVERSE DOSIMETRY MODULE : WHAT THE BODY DOES TO THE CHEMICAL : FROM THE INSIDE TO THE OUTSIDE



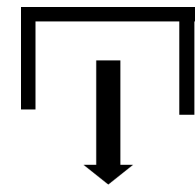
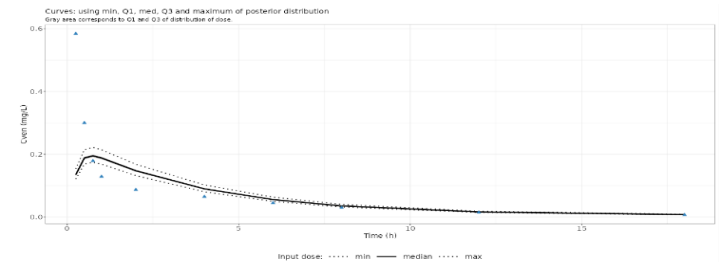
Prior Distributions



Posterior Distributions



Exposure Distribution



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



INTRODUCTION TO REVERSE DOSIMETRY

- **Definition:** Reconstruct 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

The screenshot displays the TKPlate Interactive Modelling Platform interface. The top navigation bar includes 'Info', 'Input', 'Forward Dosimetry', 'Reverse Dosimetry' (selected), 'Toxicodynamic', 'DEB', 'MixTox', and 'Report'. The version is v 1.0.23 - Manual - Report new issue, and the DOI is 10.5281/zenodo.10068769.

The 'Reverse Dosimetry' section is active, showing the following settings:

- Biomonitoring data:**
 - Selected model (Input tab): pbtk1cpt
 - Select model compartment: Compartment
 - Time unit of measured data: hour min sec
 - Exposure time (same unit as above): 0.5
- Markov Chain Monte-Carlo settings:**
 - Choose prior distribution for exposed dose (mg/ kg BW / min): Truncated Normal
 - Mean: 5, SD: 1000, min: 0, max: 50
 - Number of independent chains: 4 (indicated by a slider)
 - For each chain, set number of:
 - sampling iterations: 2000
 - burn-in (i.e. discarded) iterations: 1000
 - Use custom starting seeds.
 - (Re-)run MCMC

The right sidebar contains the 'Upload Data' section with 'General Information' and 'Upload Data (CSV)' options. The 'General Information' section lists five points: 1. File needs to be in a .csv format. 2. One column needs to be called "time" and contains the time points of the data. 3. Another column needs to be called "value" and contains the observed data of the compartment selected at the left hand side in milligram. 4. For the 1 compartment and farm animal model, fictional data is available. In these cases, click on "Load fictional data". 5. **Warning** : data and plots are automatically reset whenever a new model is chosen in the input tab! The 'Upload Data (CSV)' section includes a 'Browse...' button (No file selected), a 'Clear data' button, and a 'Load fictional data' button.



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

Info **Input** Forward Dosimetry Reverse Dosimetry Toxicoc

Input

Model Type
Changing the model resets all filled-in parameter values.
1-compartment

Species
Changing the species resets all filled-in parameter values.
Human

Chemical
Available options for chemical selection
Melatonin
User Defined Chemical
 Show EPA CompTox Search URL

Exposure Settings

Dose unit
 g mg microg

Time unit
 d h min sec

Exposure Metric
 absolute (mg) dose (mg/kg BW) rate (mg/kg BW / h)

Magnitude of each input (mg / kg BW / h)
0

Timepoint of first input (h)
0

Exposure time (h) (Cannot be zero)
0.5

Single or multiple doses?
 Single
 Multiple

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

Selected model (Input tab):
pbtk1cpt

Select model compartment

Compartment

2.3. MCMC setting

Markov Chain Monte-Carlo settings

Choose prior distribution for exposed dose (mg/ kg BW / min)

Truncated Normal

Mean: 5, SD: 1000, min: 0, max: 50

Number of independent chains: 4

For each chain, set number of:

sampling iterations: 2000, burn-in (i.e. discarded) iterations: 1000

Use custom starting seeds.

(Re-)run MCMC!

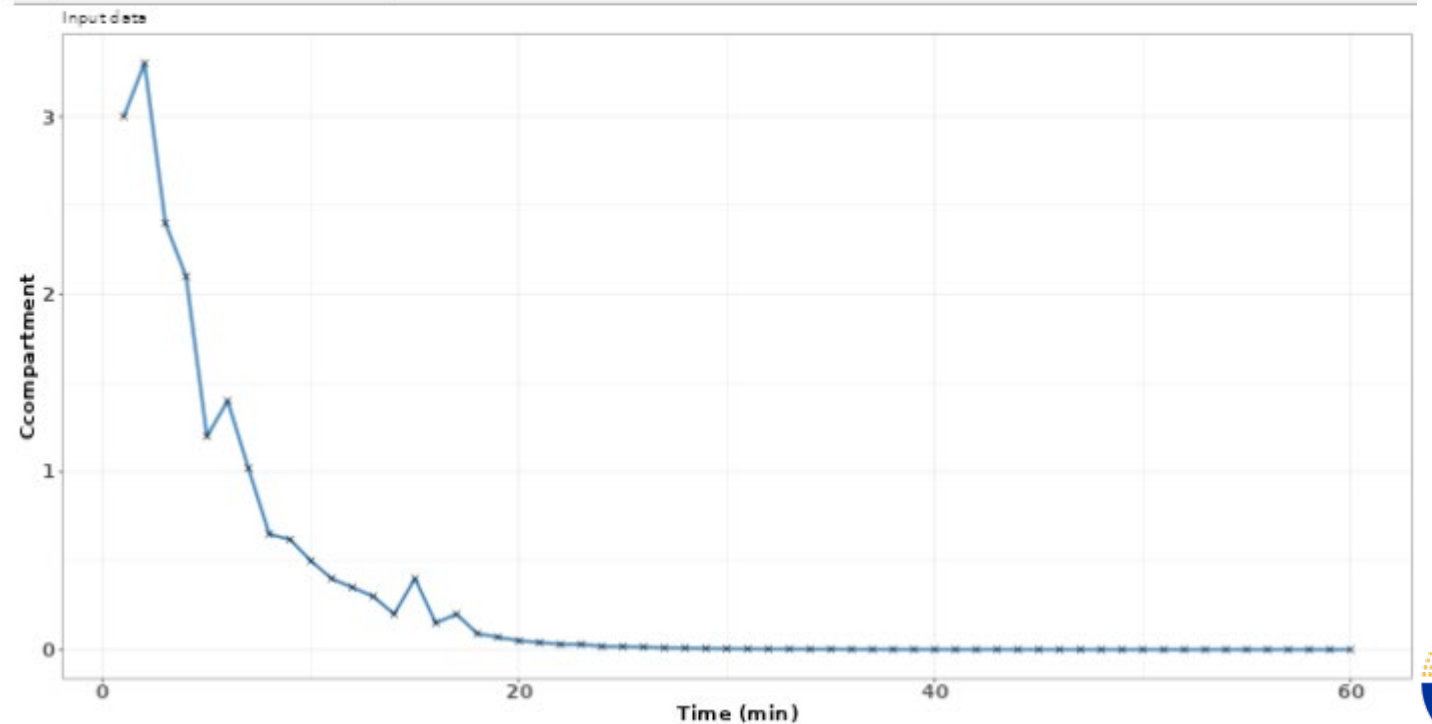
2.2. Upload Biomonitoring data

Upload Data (CSV)

Browse... ReverseDosimetryMela Clear data Load fictional data

Upload complete

	compartment	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_10	T_11	T_12	T_13	T_14	T_15
1	Compartment	3	3.3	2.4	2.1	1.2	1.4	1.02	0.65	0.62	0.5	0.4	0.35	0.3	0.2	



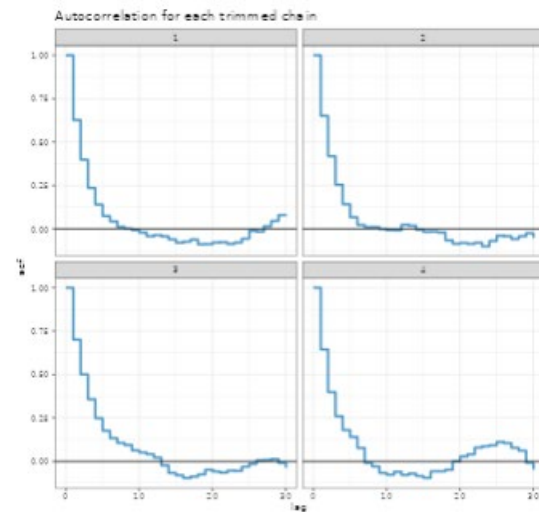
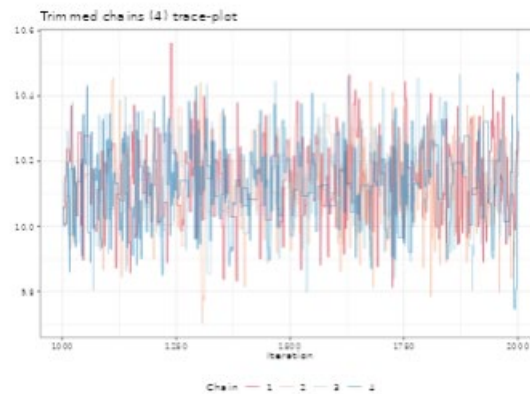
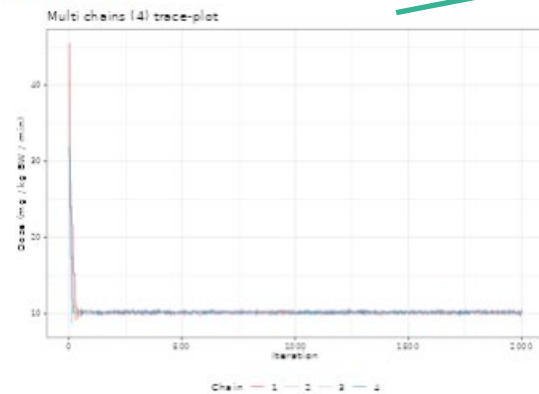
Once everything is uploaded and select, run the MCMC procedure



STEPS IN REVERSE DOSIMETRY: OUTPUT

3.1. Model diagnostic

Diagnostics



How to interpret the diagnostic plots?

Trace-plot:
Shows you the sampled value for dose for each iteration.
You would like to see trace-plots where the chains seem to
1) converge to a range (i.e. they stabilize)
2) visit the entire range of the resulting posterior distrib

Trimmed trace-plot:
Using the left trace-plot, one can determine if enough iterations
discarded (i.e. the burn in) or too many of them are discarded.
See it yourself: adjust the burn in on the left and see what

Autocorrelation:
Due to the nature of the sampling algorithms, there should be
a high correlation between iterations within a chain.
However as we compare more distant iterations (i.e. increase
we should see the correlation going to 0.

If there seems to be a problem with any of these, try to:
* increase the number of chains
* increase the number of iterations per chain

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

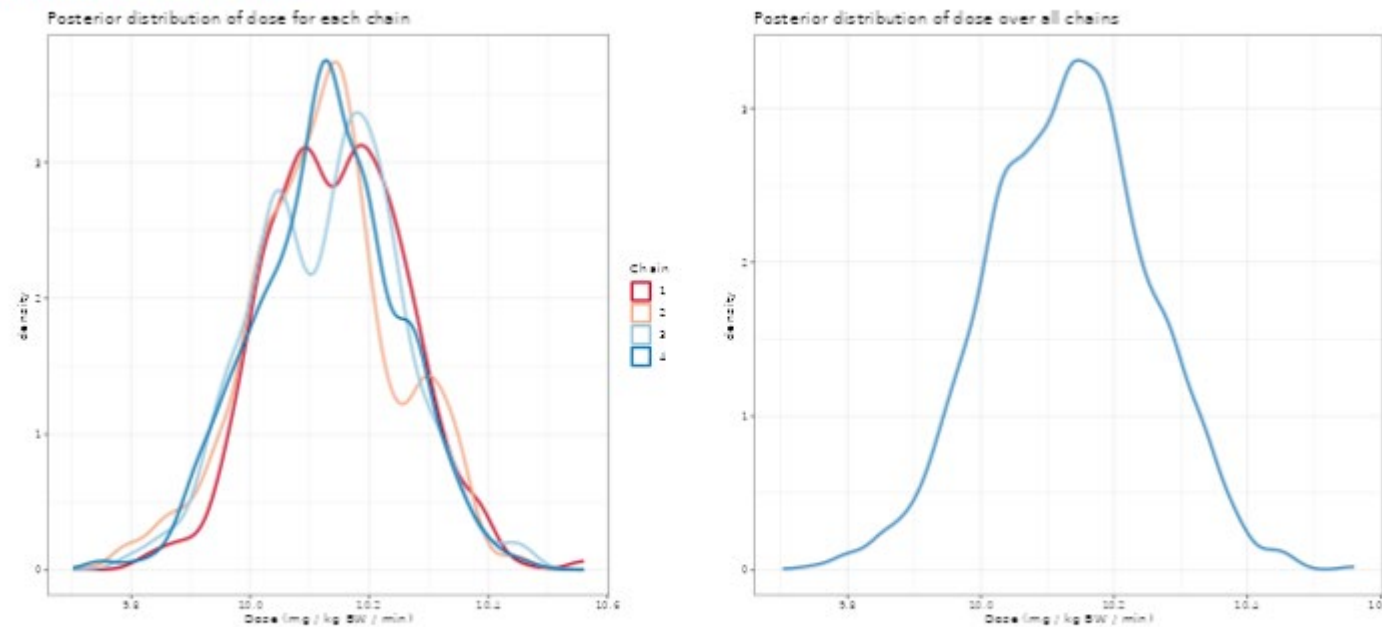
Autocorrelation plot showing how well the chains are mixing, with low autocorrelation indicating good mixing and convergence is achieved



STEPS IN REVERSE DOSIMETRY: OUTPUT

3.2. Posterior distribution of external dose

Density (trimmed chains)



Summary of posterior of dose (over all chains):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
9.783	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

Exposure Settings

Dose unit

g mg microg

Time unit

d h min sec

Exposure Metric

absolute (mg) dose (mg/kg BW) rate (mg/kg BW / h)

Magnitude of each input (mg)

270

Timepoint of first input (h)

0

Exposure time (h) (Cannot be zero)

0.01

Single or multiple doses?

Single

Multiple

Time Scale

Upload custom time points

time steps /h

4

Simulation duration (h)

32

In vitro/QIVIVE US-EPA Comptox data

CL_{int} = 0.2855 μL/min/million hepatocytes

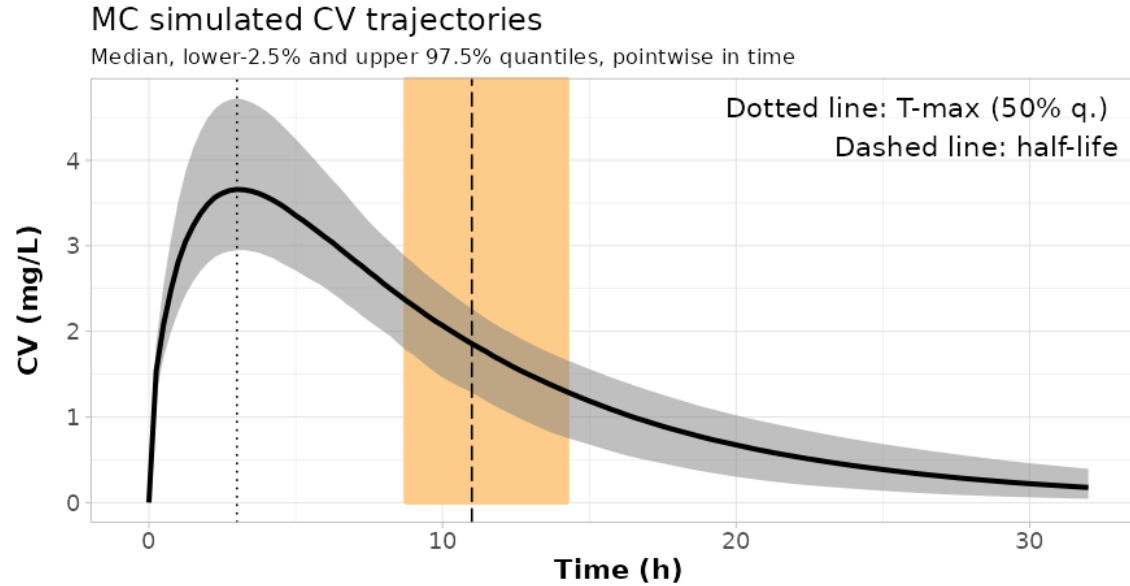
- CL_{in vivo} = 0.2855 x 140 (million hepatocytes/g liver) x 2000 (g liver) = 0,08 L/min metabolism via CYP1A2
- Exposure **270 mg oral**
- Simulation with variability in CYP1A2 35% (Dorne et al., 2001)

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



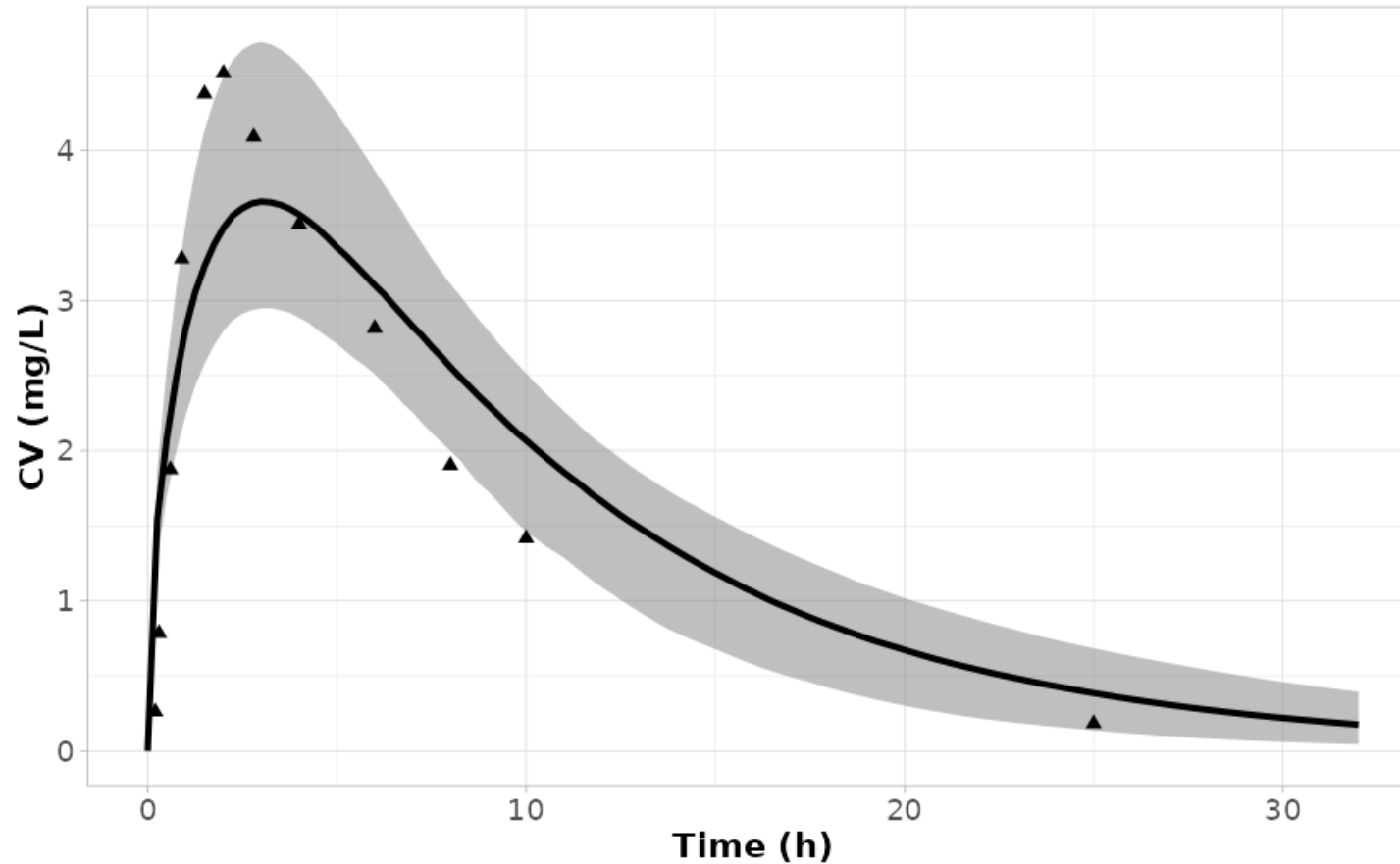
	0%-quantile	2.5%- quantile	50%-quantile	97.5%- quantile	100%-quantile
T-max (h)	2.50E+00	2.74E+00	3.00E+00	3.50E+00	3.75E+00
C-max (mg/L)	2.67E+00	2.95E+00	3.66E+00	4.73E+00	5.19E+00
Half-life (h)	5.00E+00	6.00E+00	8.00E+00	1.08E+01	1.20E+01
AUC (h * mg/L)	2.90E+01	3.49E+01	4.44E+01	5.36E+01	5.78E+01



Caffeine : Model Evaluation Predictions vs Experimental Data

MC simulated trajectory

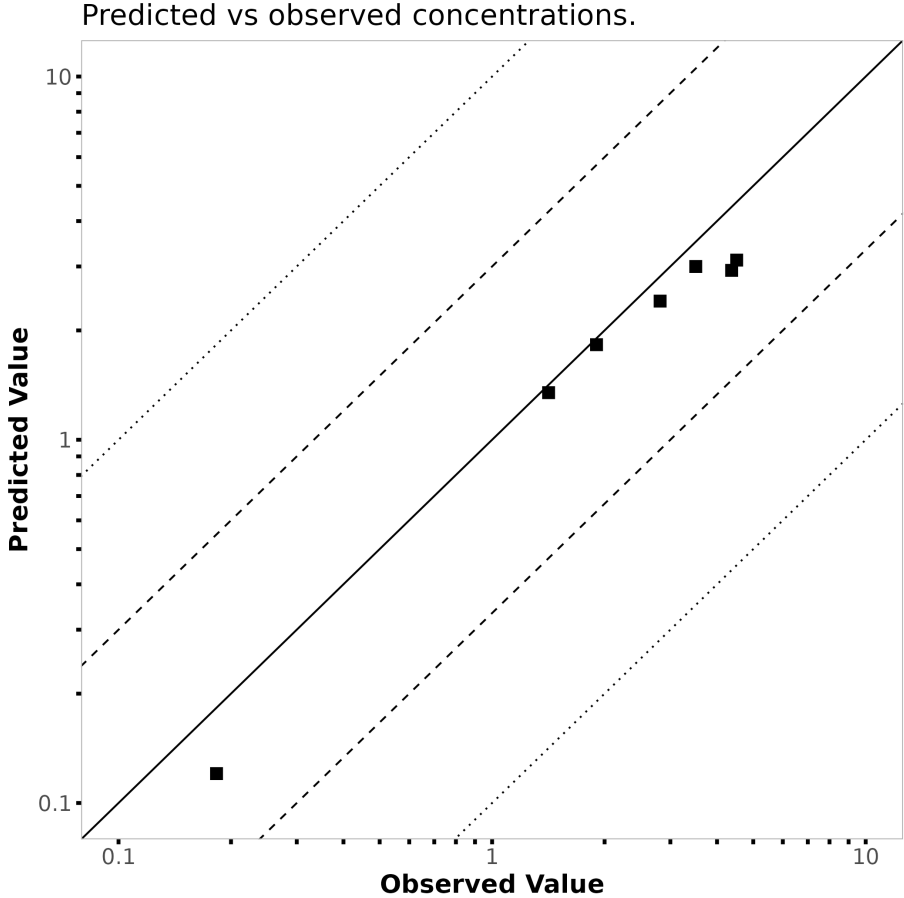
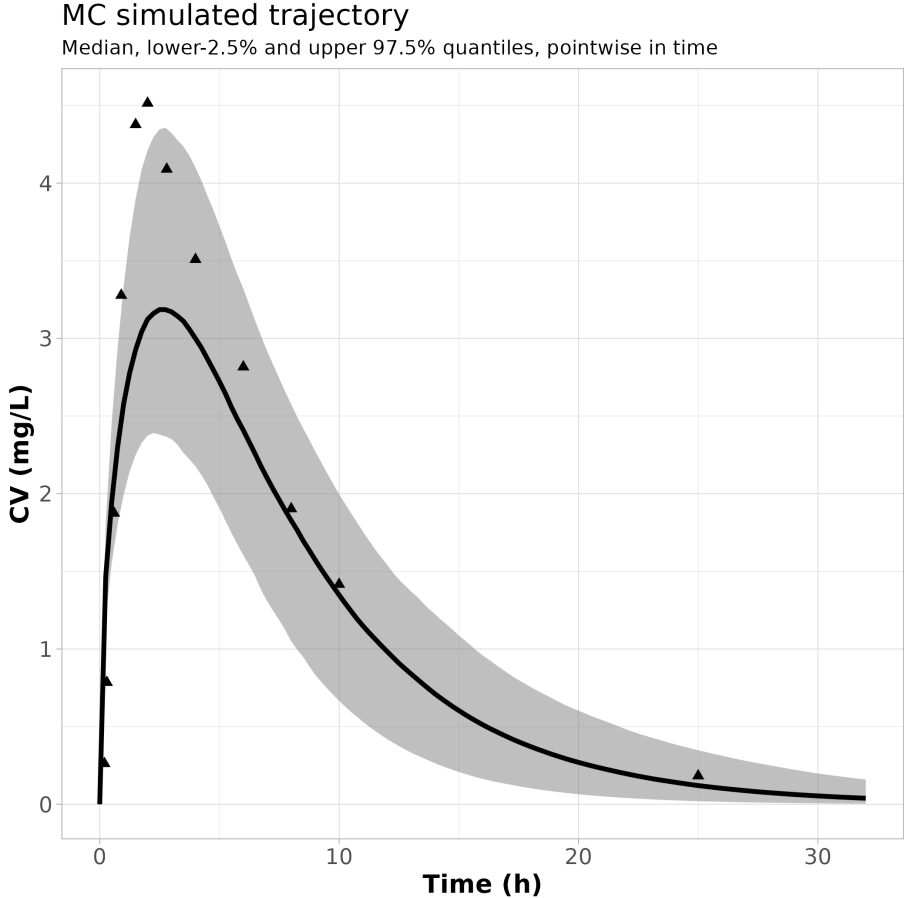
Median, lower-2.5% and upper 97.5% quantiles, pointwise in time



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

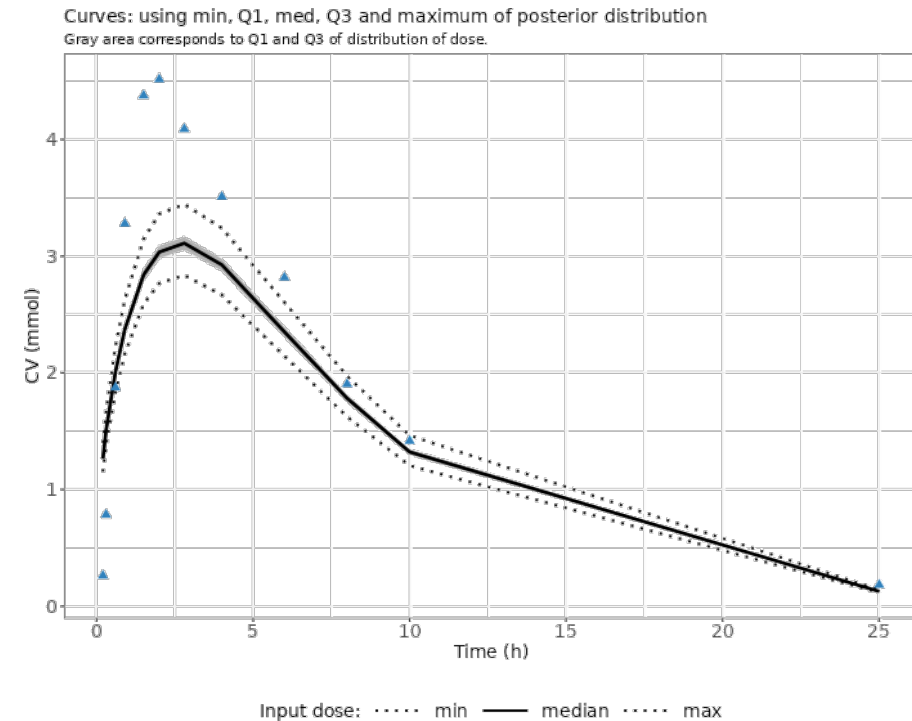
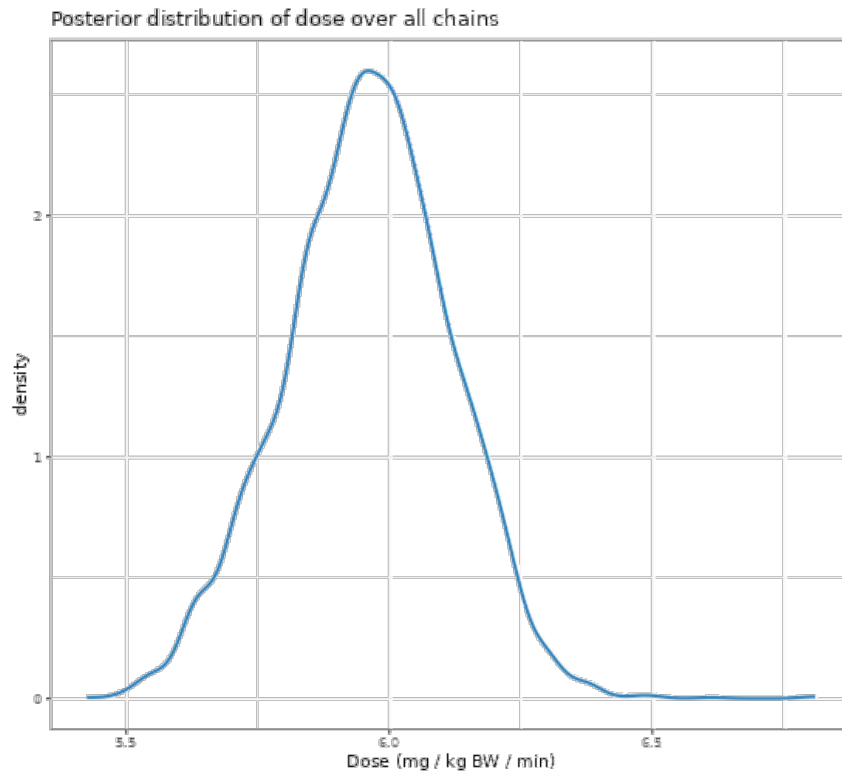


CAFFEINE- FORWARD DOSIMETRY



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



Triangles are original data points.

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



NEW MODELS FORKPLATE

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

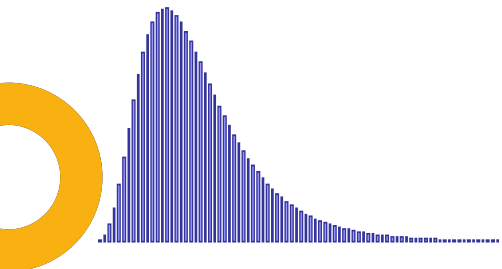
- Pilot planned for EFSA Staff and experts on 21-22 Nov 24 and Jan 25
- Moving towards recorded online training available open access ?

▪ 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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- Mario Negri, Milan, Italy
- RIVM, Bilthoven, The Netherlands
- Health and Safety Laboratory, UK
- US-EPA/NIEHS, USA





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