7th October 2024

# QIVIVE AND VARIABILITY DISTRIBUTIONS IN ELIMINATION USING TKPLATE

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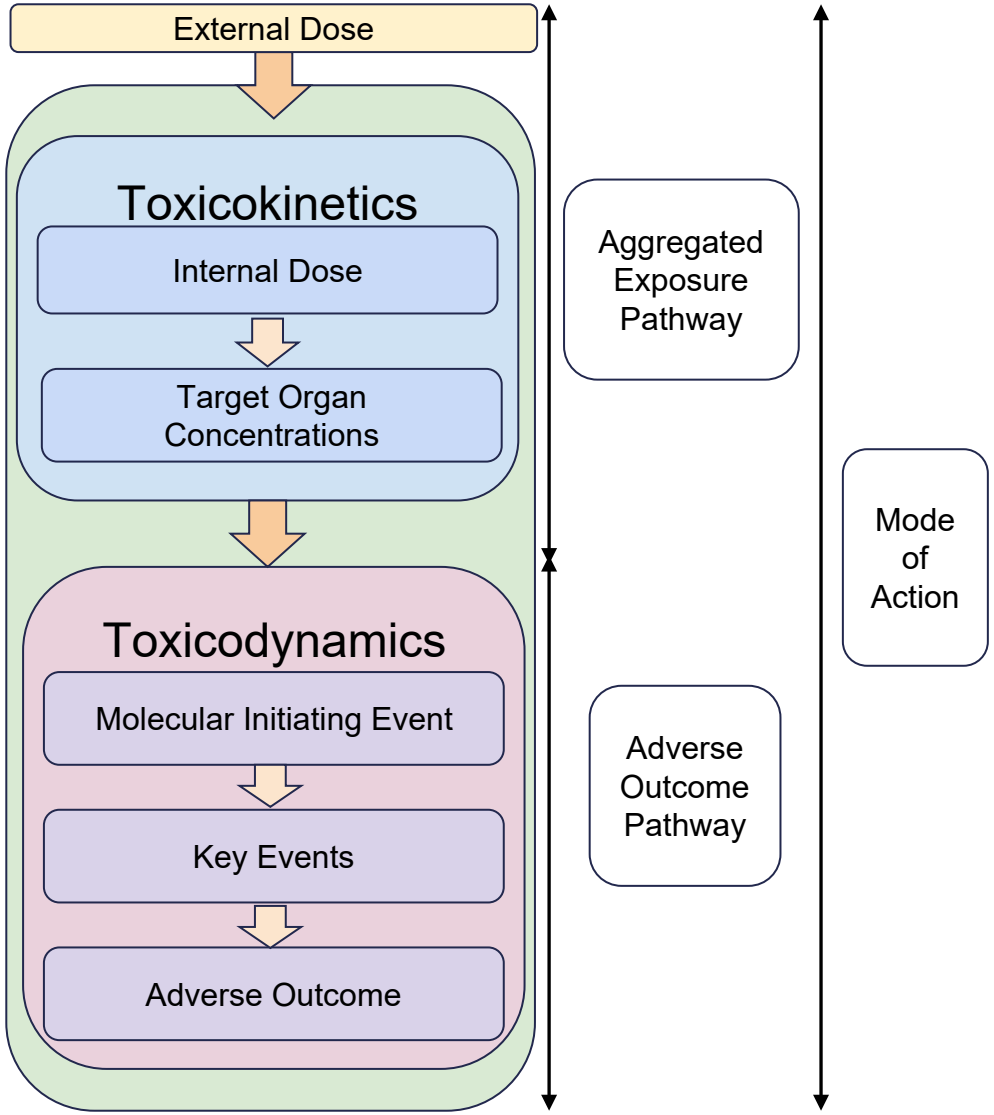
EUROPEAN FOOD SAFETY AUTHORITY

# OUTLINE

- New Approach Methodologies and EFSA case studies
- Human variability in metabolism and pathway-related uncertainty factors
- TKPlate and QIVIVE
- Moving Forward

# New Approach Methodologies and EFSA Case studies

# UNDERSTANDING TOXICOKINETIC AND TOXICODYNAMIC PROCESSES IN CHEMICAL RISK ASSESSMENT

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European Food Safety Authority
EFSA Journal 2014;12(4):3638

**SCIENTIFIC REPORT OF EFSA**

## Modern methodologies and tools for human hazard assessment of chemicals[1]

**European Food Safety Authority**[2,3]

European Food Safety Authority (EFSA), Parma, Italy

*This scientific output, published on 11 July 2014, replaces the earlier version published on 24 April 2014**

**ABSTRACT**

This scientific report provides a review of modern methodologies and tools to depict toxicokinetic and toxicodynamic processes and their application for the human hazard assessment of chemicals. The application of these methods is illustrated with examples drawn from the literature and international efforts in the field. First, the concepts of mode of action/adverse outcome pathway are discussed together with their associated terminology and recent international developments dealing with human hazard assessment of chemicals. Then modern methodologies and tools are presented including *in vitro* systems, physiologically-based models, *in silico* tools and OMICs technologies at the level of DNA/RNA (transcriptomics), proteins (proteomics) and the whole metabolome (metabolomics). Future perspectives for the potential applications of these modern methodologies and tools in the context of prioritisation of chemicals, integrated test strategies and the future of risk assessment are discussed. The report concludes with recommendations for future work and research formulated from consultations of EFSA staff, expert Panels and other international organisations.



**KEY WORDS**

mode of action, adverse outcome pathway, integrated testing strategy, physiologically-based models, *in silico*, OMICs

GUIDANCE

EFSA Journal

ADOPTED: 17 November 2021

doi: 10.2903/j.efsa.2021.7033

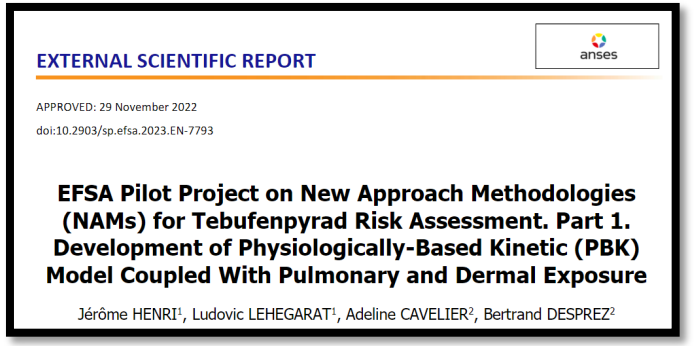
## Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals

EFSA Scientific Committee,
Simon John More, Vasileios Bampidis, Diane Benford, Claude Bragard, Antonio Hernandez-Jerez, Susanne Hougaard Bennekou, Thorhallur Ingi Halldorsson, Konstantinos Panagiotis Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Naegeli, Søren Saxmose Nielsen, Josef Rudolf Schlatter, Dieter Schrenk, Vittorio Silano, Dominique Turck, Maged Younes, Emilio Benfenati, Amélie Crépet, Jan Dirk Te Biesebeek, Emanuela Testai, Bruno Dujardin, Jean Lou CM Dorne and Christer Hogstrand

# EFSA NAMS CASE STUDY ON TEBUFENPYRAD

Aim: explore the use of NAMs to investigate the neurotoxicity potential of the pesticide Tebufenpyrad

- Part 1: 'Development of physiologically-based kinetic (PBK) model coupled with pulmonary and dermal exposure'
- Part 2: 'Hazard characterisation and identification of the Reference Point'


EXTERNAL SCIENTIFIC REPORT

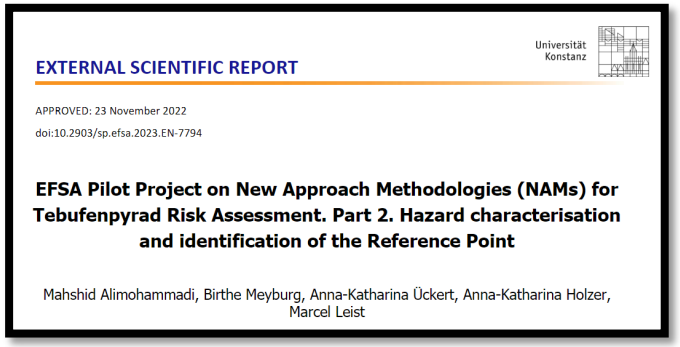
anses

APPROVED: 29 November 2022

doi:10.2903/sp.efsa.2023.EN-7793

**EFSA Pilot Project on New Approach Methodologies (NAMs) for Tebufenpyrad Risk Assessment. Part 1. Development of Physiologically-Based Kinetic (PBK) Model Coupled With Pulmonary and Dermal Exposure**

Jérôme HENRI[1], Ludovic LEHEGARAT[1], Adeline CAVELIER[2], Bertrand DESPREZ[2]


EXTERNAL SCIENTIFIC REPORT

Universität Konstanz

APPROVED: 23 November 2022

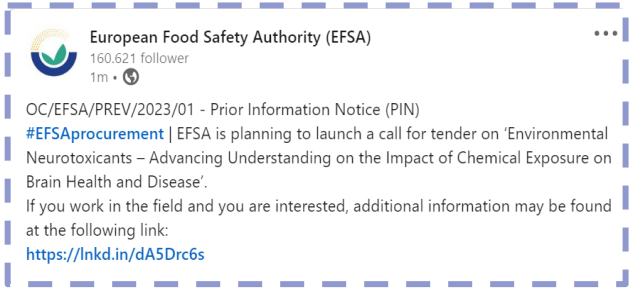
doi:10.2903/sp.efsa.2023.EN-7794

**EFSA Pilot Project on New Approach Methodologies (NAMs) for Tebufenpyrad Risk Assessment. Part 2. Hazard characterisation and identification of the Reference Point**

Mahshid Alimohammadi, Birthe Meyburg, Anna-Katharina Ückert, Anna-Katharina Holzer, Marcel Leist

**Q3 2020 – Q3 2022**

A Workshop on the results of the project and follow up activities was organised in September 2022


European Food Safety Authority (EFSA)
160.621 follower
1m •

OC/EFSA/PREV/2023/01 - Prior Information Notice (PIN)
#EFSAprocurement | EFSA is planning to launch a call for tender on 'Environmental Neurotoxicants – Advancing Understanding on the Impact of Chemical Exposure on Brain Health and Disease'.
If you work in the field and you are interested, additional information may be found at the following link:
https://lnkd.in/dA5Drc6s

# EFSA NAMS CASE STUDY ON PFAS

External Scientific Report

APPROVED: 2 July 2024
doi: 10.2903/sp.efsa.2024.EN-8926

## EFSA Project on the use of NAMs to explore the immunotoxicity of PFAS

Emanuela Corsini[1], Martina Iulini[1], Valentina Galbiati[1], Ambra Maddalon[1], Francesco Pappalardo[2], Giulia Russo[2], Ron L.A.P. Hoogenboom[3], Karsten Beekmann[3], Aafke W.F. Janssen[3], Jochem Louisse[3], Styliani Fragki[4], Alicia Paini[4]

[1]Università degli Studi di Milano, Italy; [2]Università degli Studi di Catania, Italy
[3]Wageningen Food Safety Research, The Netherlands; [4]ESQlabs GmbH, Germany

To develop and implement a NAM-based IATA for exploring the mode of action (MoA) for the observed immunosuppression effects and for addressing immunotoxicity of PFAS other than PFOS and PFOA, including the assessment of a common MoA and potency differences.

APCRA Case Study

# EFSA NAMS CASE STUDY ON ESSENTIAL OILS

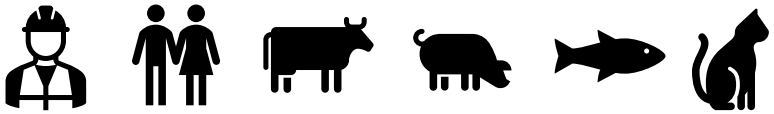
External Scientific Report

APPROVED: 15 May 2024
doi: 10.2903/sp.efsa.2024.EN-8820

EFSA Project on the use of NAMs to explore interspecies metabolic differences on essential oils as feed additives

Annelies Noorlander, Leonie Lautz, Wendy Jansen Holleboom, Patrick P.J. Mulder, Geert Stoopen, Ans Punt

Wageningen Food Safety Research, the Netherlands



Design and conduct a series of NAM-based experimental studies for assessing qualitative and quantitative differences and similarities in metabolic competences across different target species for essential oils components and to conduct a quantitative in vivo in vitro extrapolation (QIVIVE) and comparison among species.

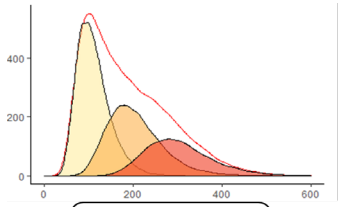
Table 5: Kinetic parameters for phase I metabolism of methyleugenol for the tested S9 fractions from different species

| Species | Overall CLint (µL/min/mg S9)[a] | 1'-Hydroxylation (µL/min/mg S9)[b] | Detoxification (µL/min/mg S9) | % Bioactivation |
|---|---|---|---|---|
| Cat | 17 | 5 | 12 | 29% |
| Chicken | 26 | 2 | 24 | 8% |
| Cow | 102 | 40 | 62 | 39% |
| Human | 33 | 5 | 28 | 15% |
| Pig | 69 | 27 | 42 | 39% |
| Rat | 16 | 5 | 11 | 31% |

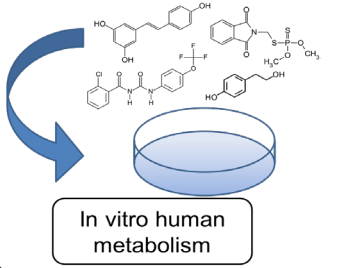
# Human Variability in Metabolism and Pathway-related Uncertainty factors

# TK MODELLING AND APPLICATIONS IN HUMAN RISK ASSESSMENT

## Kinetic Variability




Human pathway-related variability

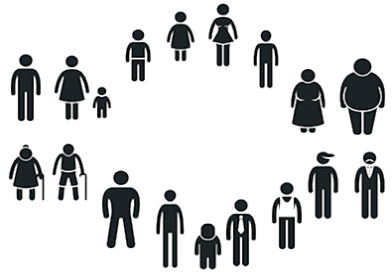


Human kinetic parameter (QIVIVE)

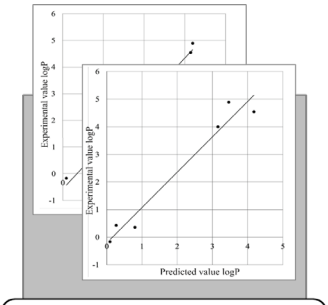


In vitro human metabolism

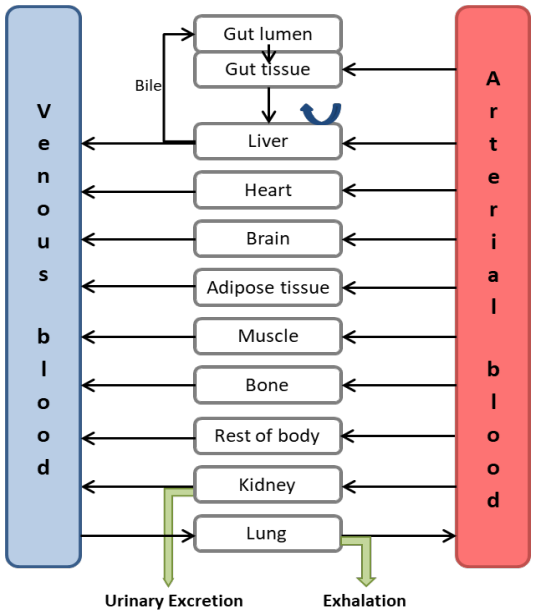
## Population



## Chemical




Chemical parameter estimation by QSAR

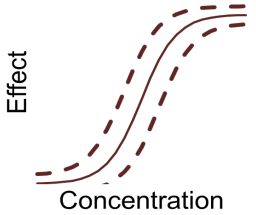



## Risk Assessment

- Population specific simulations
- Integration of kinetic parameters
- Internal Dose estimation for target organs


Exposure assessment

- In vitro in vivo extrapolations for effects
- In vivo Dose-response modelling based on target organ concentrations




Risk characterisation

# QUANTITATIVE IN VITRO IN VIVO EXTRAPOLATION FOR HUMANS

- New data requirements for pesticides (283/284 2013) :

  - Scientific Opinion on use of comparative in vitro metabolism-Test Species vs Humans
  - Use human in vitro metabolism data and QIVIVE in RA
  - Case studies-prediction of human kinetics for food and feed chemicals (e.g. pesticides, contaminants)
  - Use of OHT 58 (TK) and OHT 201 (intermediate effects) to structure datasets

  - Variability in metabolism within PBK models for QIVIVE

EFSA Journal

SCIENTIFIC OPINION

ADOPTED: 10 November 2021

doi: 10.2903/j.efsa.2021.6970

**Scientific Opinion of the Scientific Panel on Plant Protection Products and their Residues (PPR Panel) on testing and interpretation of comparative *in vitro* metabolism studies**

EFSA Panel on Plant Protection Products and their Residues (EFSA PPR Panel), Antonio F Hernandez-Jerez, Paulien Adriaanse, Annette Aldrich, Philippe Berny, Tamara Coja, Sabine Duquesne, Andreas Focks, Marina Marinovich, Maurice Millet, Olavi Pelkonen, Silvia Pieper, Aaldrik Tiktak, Christopher J Topping, Anneli Widenfalk, Martin Wilks, Gerrit Wolterink, Ursula Gundert-Remy, Jochem Louisse, Serge Rudaz, Emanuela Testai, Alfonso Lostia, Jean-Lou Dorne and Juan Manuel Parra Morte

EXTERNAL SCIENTIFIC REPORT

APPROVED: 22 February 2021

doi:10.2903/sp.efsa.2021.EN-6504

**Modelling human variability in toxicokinetic and toxicodynamic processes using Bayesian meta-analysis, physiologically-based modelling and *in vitro* systems**

Emanuela Testai, Camille Bechaux, Franca M. Buratti, Keyvin Darney, Emma Di Consiglio, Emma E.J. Kasteel, Nynke I. Kramer, Leonie S. Lautz, Nicoletta Santori, Zoi-Vasiliki Skaperda, Dimitrios Kouretas, Laura Turco, Susanna Vichi

# OECD GUIDANCE ON THE USE OF PBK MODELS IN RA (2021)

Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes

Series on Testing and Assessment
No. 331

**Chapter 2. PBK modelling workflow**



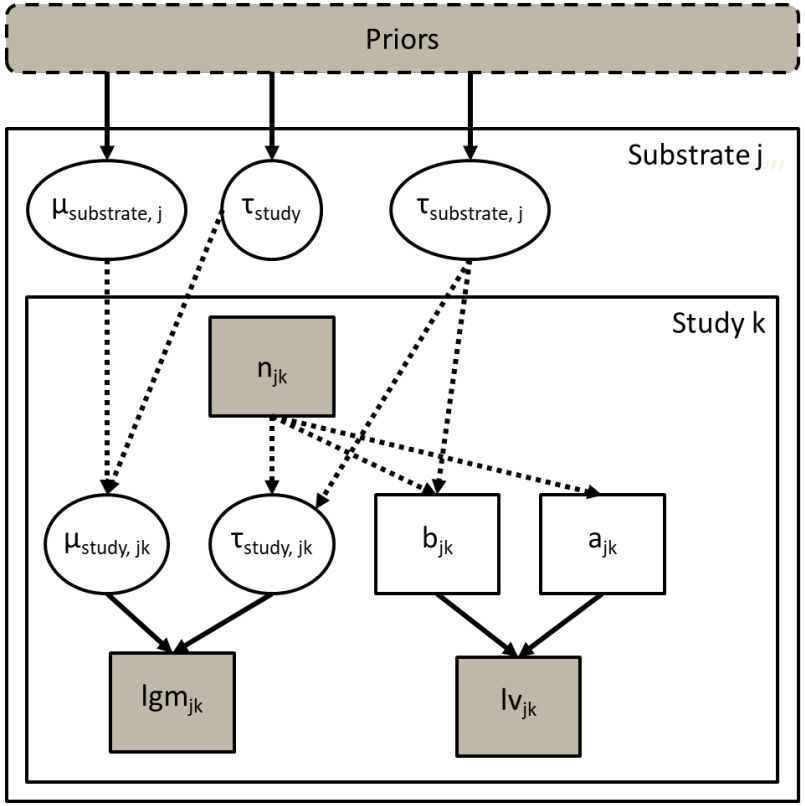
**Chapter 3. Regulatory assessment of PBK models**



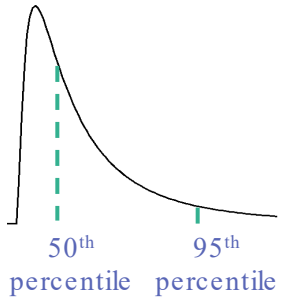
## EFSA Case Studies on PBK Models in Annex

- Humans
- Fish
- Farm animals

# Probabilistic Uncertainty Factors

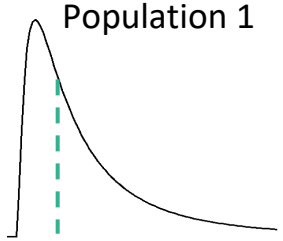



Population 1

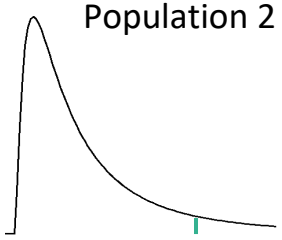



$$UF_{pop1} = \frac{P_{95}}{P_{50}}$$

Population 1

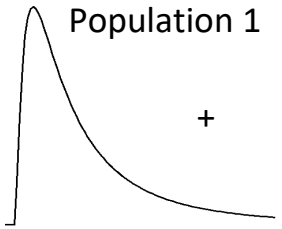



Population 2

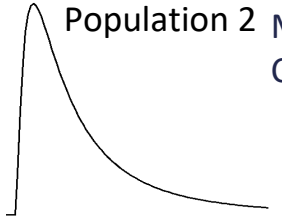



$$UF_{pop2} = \frac{P_{95,pop2}}{P_{50,pop1}}$$

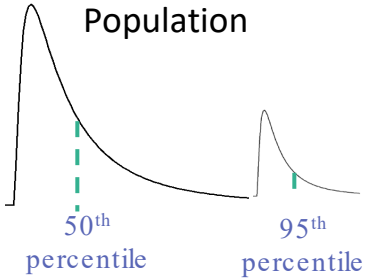
(1-α) pop1 x




+ α pop2 x




Monte-Carlo →




$$UF_{pop} = \frac{P_{95,pop}}{P_{50,pop}}$$

α : fraction of population 2 within general population

# CYP3A4

Variability and inter-individual differences in CYP3A4 metabolism:

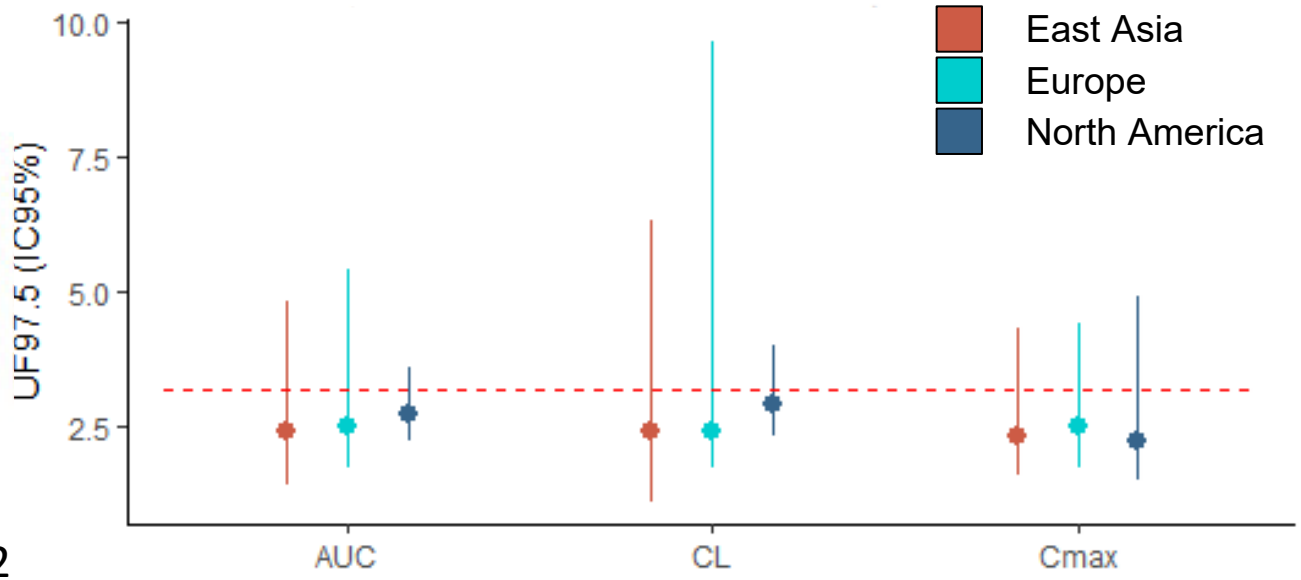
ELS of TK data for 15 CYP3A4 probe substrates to collect parameters reflecting acute (Cmax) and chronic exposure (clearance and AUC).

Variability after oarl vs IV injection ➔ 50%/ 30%(AUC)

Healthy European, East Asian and North American adults showed generally similar CYP3A4-related UFs ➔ limited interethnic differences.

| | N substrate | N studies | n |
|---|---|---|---|
| **Oral administration** | | | |
| AUC (ng.h/ml/dose) | 11 | 199 | 2921 |
| Cl (ml/min/kg bw) | 10 | 134 | 1603 |
| Cmax (ng/ml/dose) | 12 | 221 | 3211 |
| **Intravenous administration** | | | |
| AUC (ng.h/ml/dose) | 4 | 40 | 577 |
| Cl (ml/min/kg bw) | 6 | 50 | 734 |

Darney et al. (2019) doi:10.1016/j.comtox.2019.100092



# CYP3A4

These distributions allow to:

1. estimate UFs in the risk assessment process using variability distributions on metabolism,

2. Apply CYP3A4-related UFs in the risk assessment process for compounds for which *in vitro* CYP3A4 metabolism evidence are available,

3. Integrate CYP3A4-related variability distributions with *in vitro* metabolism data into physiologically based kinetic (PBK) models for quantitative *in vitro in vivo* extrapolation (QIVIVE).

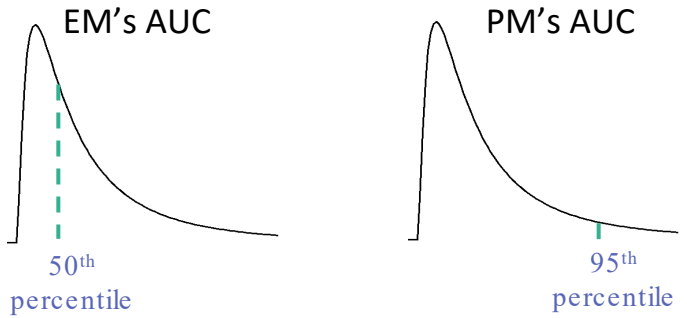
# CYP2D6 POLYMORPHISM

How to derive UF that are protective for Poor Metabolisers ?

Caucasian mainly are Extensive Metabolisers and Poor Metabolisers (8%)

Variability in EM (AUC and clearance) of 50-100%

EM/PM AUC ratio range from 4 to 54



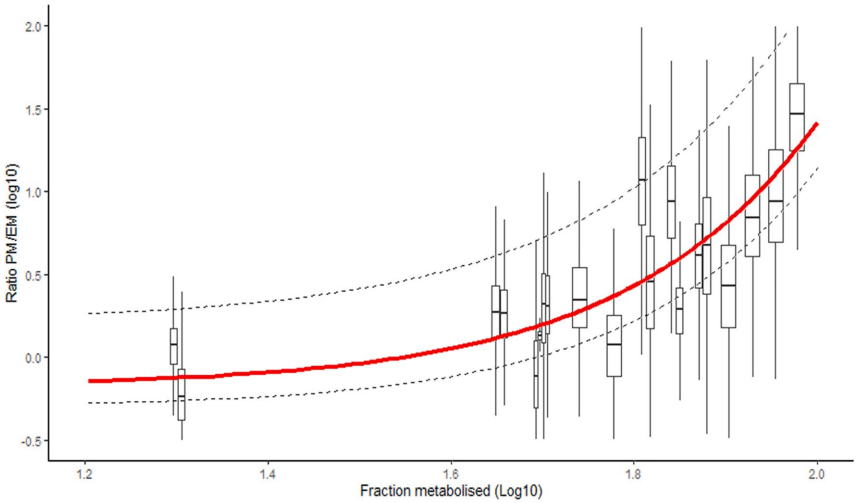

$$UF_{pop2} = \frac{P_{95,PM}}{P_{50,EM}}$$

PM UFs ranged for the AUC and clearance from 1.6-63.5 and 1.4-116 (P95)

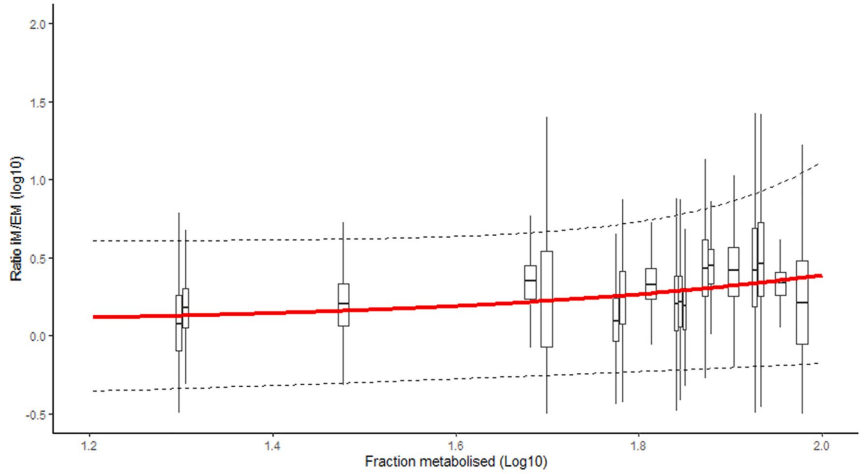
Darney et al. (2021) doi:10.1016/j.envint.2021.106760

# CYP2D6 polymorphism : Inter-phenotypic differences in Caucasian and Asian populations

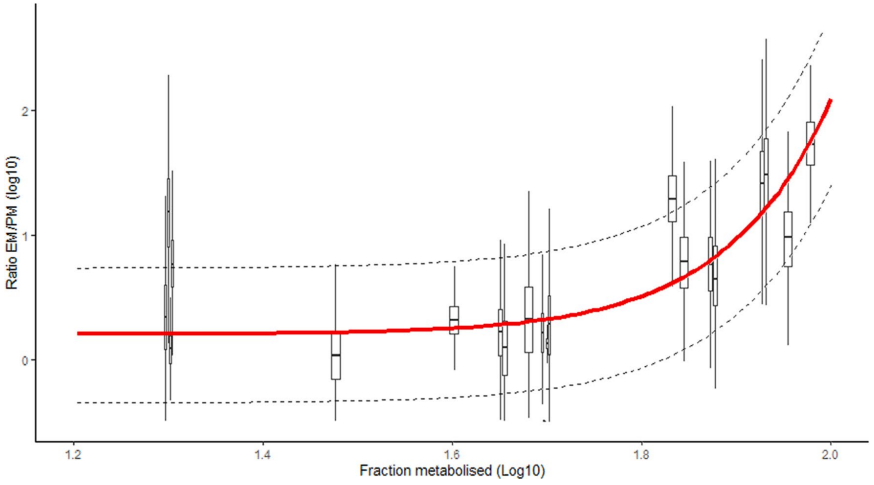
AUC Caucasian



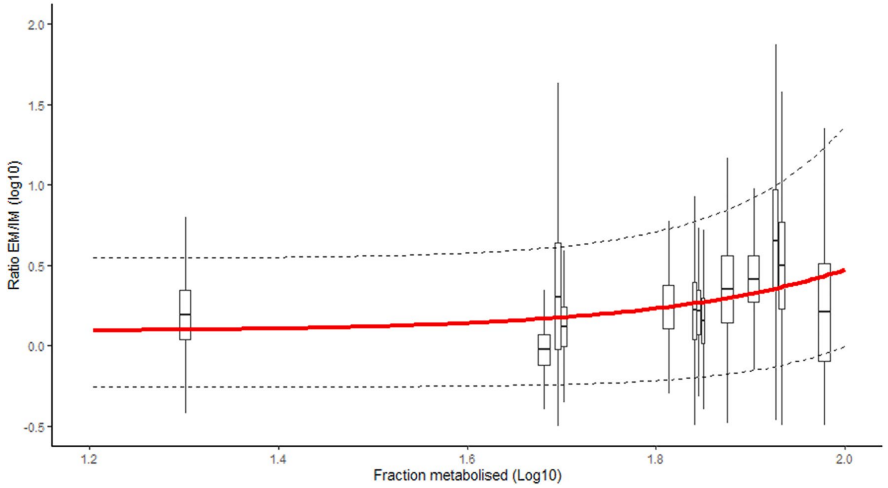

AUC Asian




Clearance Caucasian

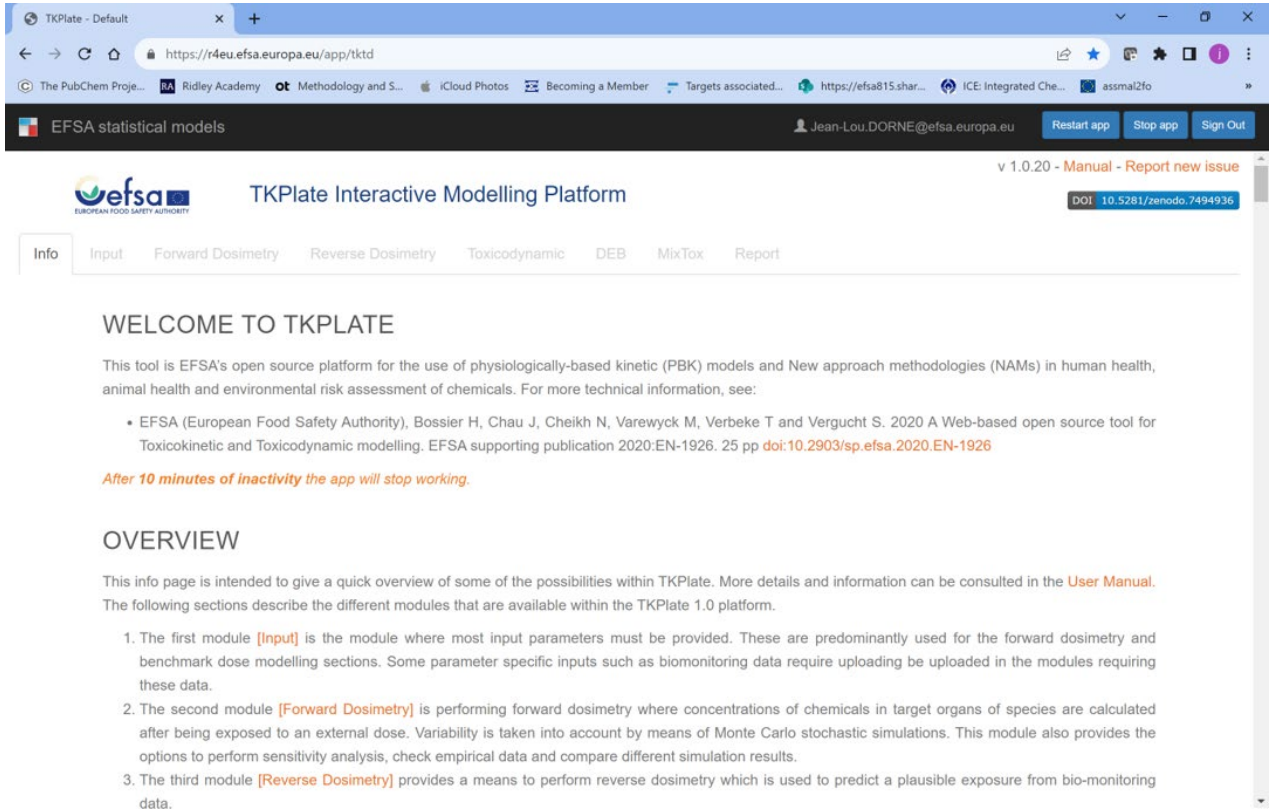


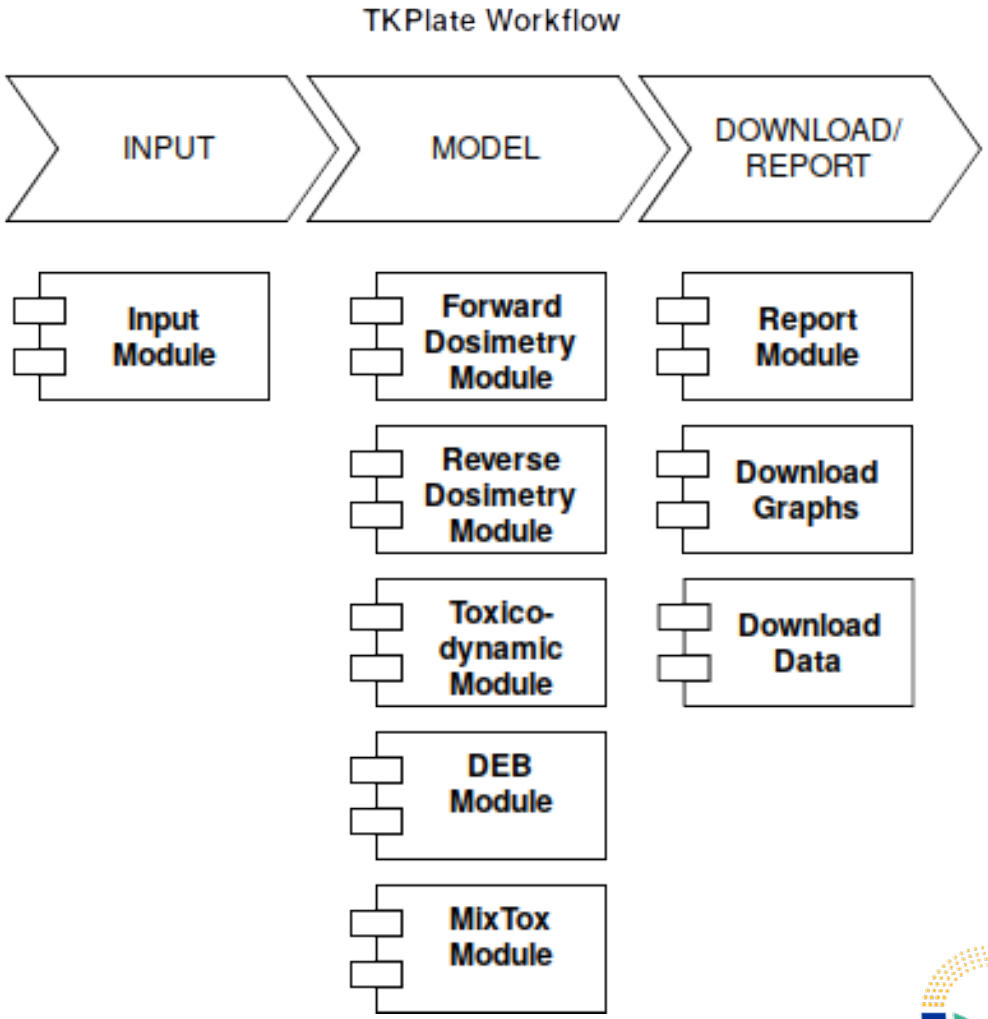

Clearance Asian



# TKPlate 1.0 and QIVIVE

# TKPLATE 1.0: INFO PAGE AND GENERAL WORKFLOW



# TKPLATE 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

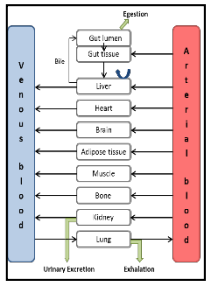
European Food Safety Authority (EFSA),
Han Bossier, Fotis Spyropoulos, Keyvin Darney, Leonie S Lautz, Pierre André Billat, Rémy Beaudouin, Florence Zeman, Cléo Bodin, José Cortiñas-Abrahantes, Jean Lou CM Dorne

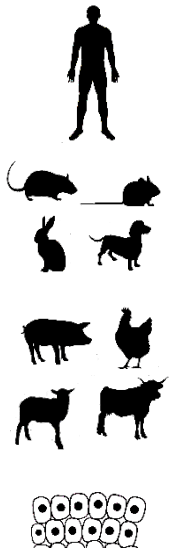
# INPUT MODULE

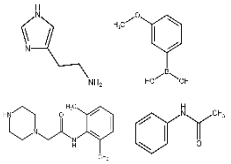
Generic Models

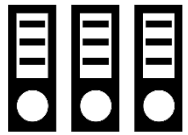
Chemical

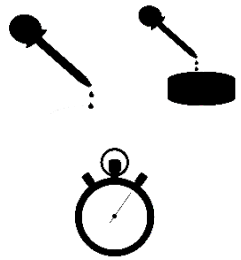
Exposure Time scale









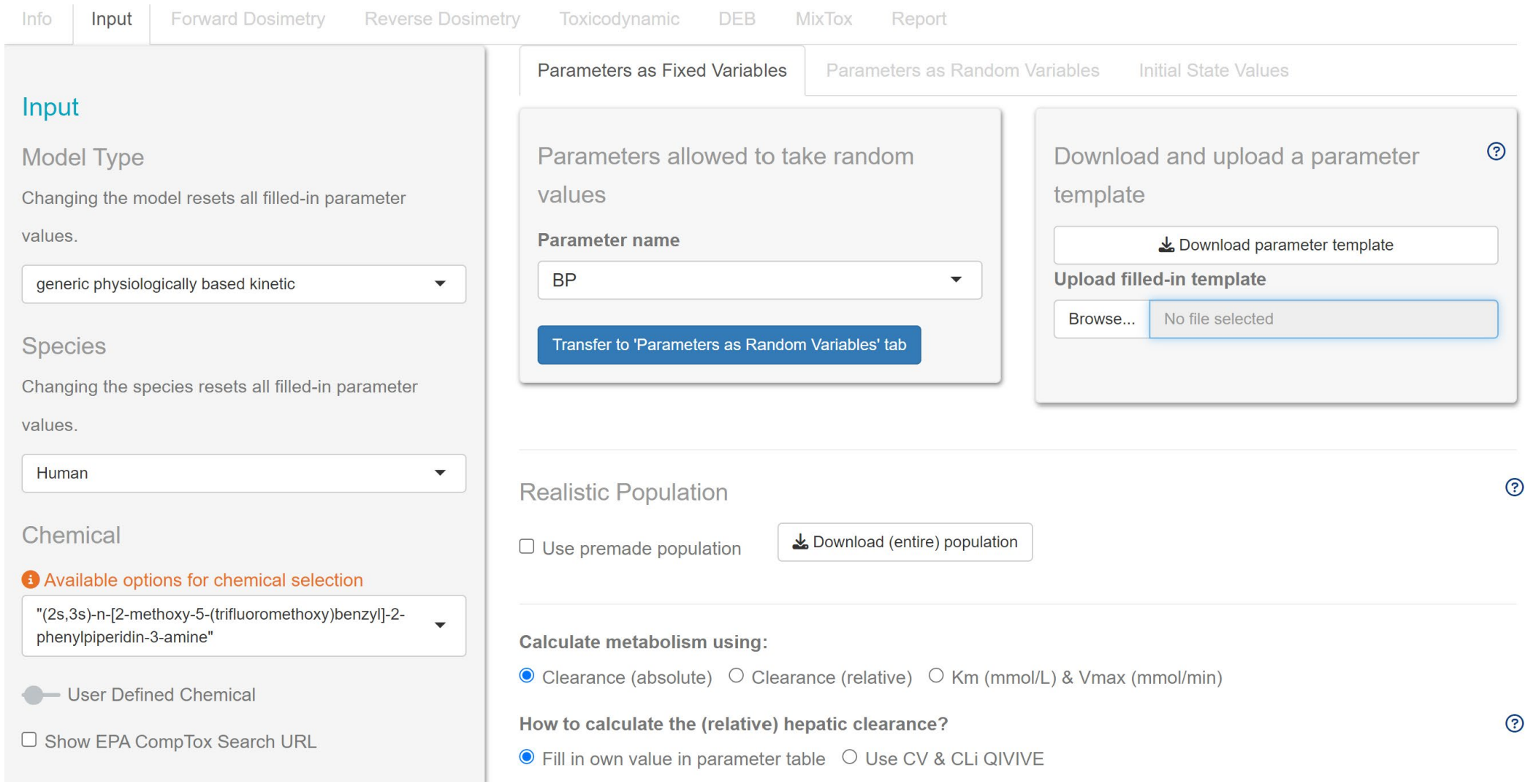
Input Parameters

Forward Dosimetry

Reverse Dosimetry

Toxicodynamics

# INPUT MODULE : SELECTING MODEL, SPECIES AND CHEMICAL



# INPUT MODULE : EXPOSURE SETTINGS, CHEMICAL PARAMETERS AND PHYSIOLOGICAL 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 / kg BW / h)**

0

**Timepoint of first input (h)**

0

**Exposure time (h) (Cannot be zero)**

0

**Single or multiple doses?**

◉ Single

○ Multiple

## Time Scale

Upload custom time points

**time steps /h**

4

**Simulation duration (h)**

24

### Chemical Specific Parameters

| | Parameter | Value | Unit | Description |
|---|---|---|---|---|
| 1 | BP | 1 | | Blood plasma ratio |
| 2 | cl_hepatic | | L/min | Hepatic clearance |
| 3 | frac_abs_gut | | | 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 | 380.4 | g/mol | Molecular Weight |
| 8 | P_adipose | 1.29773 | | Blood tissue partition coefficient in the adipose |
| 9 | P_gut | 1.321772 | | Blood tissue partition coefficient in the gut |
| 10 | P_kidney | 2.109585 | | Blood tissue partition coefficient in the kidney |
| 11 | P_liver | 2.579712 | | Blood tissue partition coefficient in the liver |
| 12 | P_rapid | 2.664955 | | Blood tissue partition coefficient in the rapid compartment |
| 13 | P_slow | 0.812618 | | Blood tissue partition coefficient in the slow compartment |

### Physiological Parameters

| | Parameter | Value | Unit | Description |
|---|---|---|---|---|
| 1 | Q_adipose | 0.42 | L/min | Blood flow in adipose |
| 2 | Q_gut | 1 | L/min | Blood flow in gut |
| 3 | Q_kidney | 1.23 | L/min | Blood flow in kidney |
| 4 | Q_liver | 0.41 | L/min | Blood flow in liver |
| 5 | Q_rapid | 1.28 | L/min | Blood flow in rapid compartment |
| 6 | Q_slow | 1.51 | L/min | Blood flow in slow compartment |
| 7 | V_adipose | 20.28 | L | Volume of the adipose |
| 8 | V_gut | 1.22 | L | Volume of the gut |
| 9 | V_kidney | 0.39 | L | Volume of the kidney |
| 10 | V_liver | 1.99 | L | Volume of the liver |
| 11 | V_rapid | 2.12 | L | Volume in the rapid compartment |
| 12 | V_slow | 36.74 | L | Volume of the slow compartment |

# FORWARD DOSIMETRY : WHAT THE BODY DOES TO THE CHEMICAL (FROM OUTSIDE TO INSIDE)

Input Parameters

Simulate Model

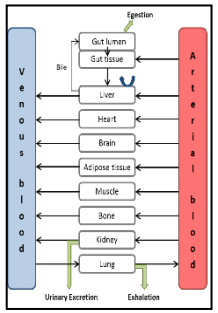
Sensitivity Analysis

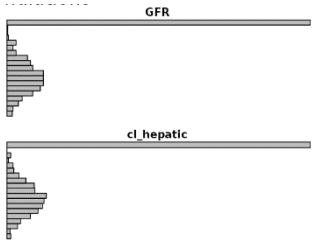
Model Evaluation

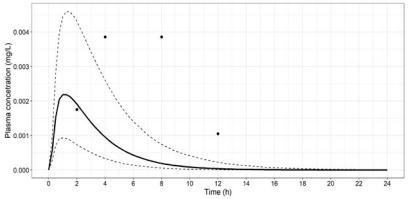
Compare Simulations

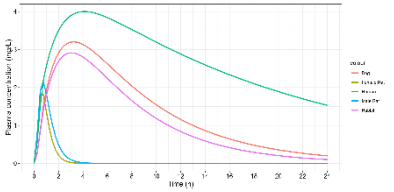
Kinetic Parameters

Concentrations in body fluids or Organs



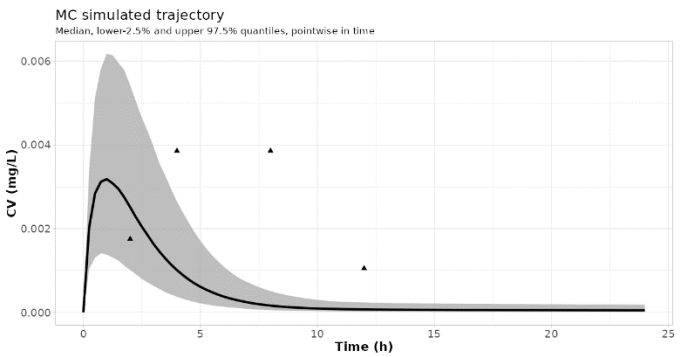
Predicting what the body does to the chemical (Toxicokinetics):

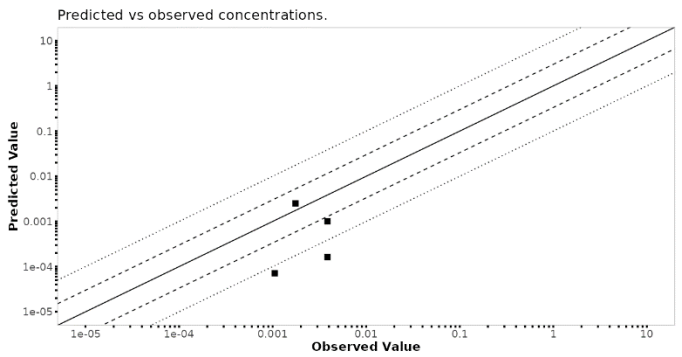
- Absorption, metabolism, elimination : Kinetic parameters
- Residues in blood, urine and organs of interest (e.g. liver, kidney etc..)

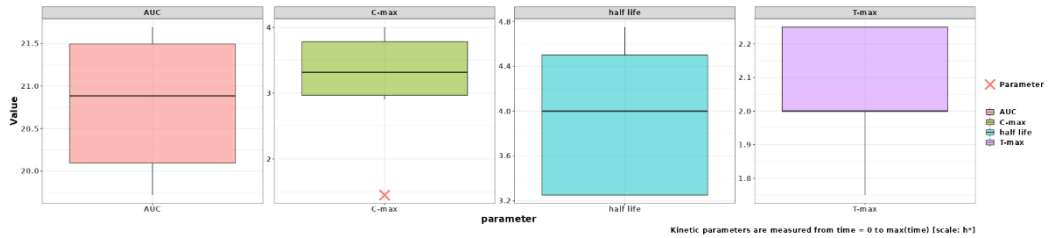
# FORWARD DOSIMETRY: OUTPUTS AND MODEL EVALUATION

## Outputs: Time Concentration Profiles/Kinetic Parameters

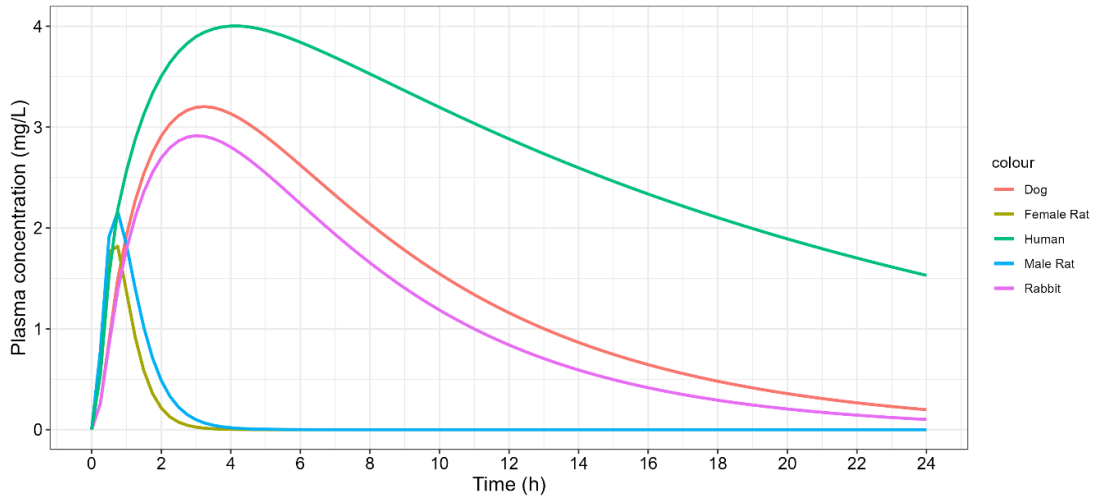
### Simulations for single Species




### Compare Simulations for multiple species



# TK PLATE QIVIVE MODULE

- CLint unit nmol product/(mg prot · min·µM)

➔ ml/ (mg prot · min)

In vitro results

Km & Vmax ➔ Cli (pmol product/nmolP450 · min · µM)

Relative Abundance (pmolP450/mg prot)

MPPGL = 40 mg prot/g liver

$Cl_{in\ vivo}$ = Cli * RA * MPPGL / 1000

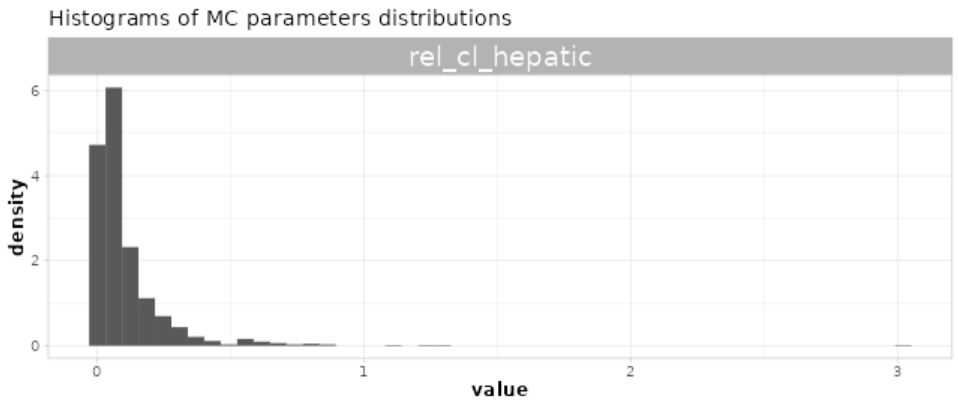
| enzyme | CV | CLint | unit |
|---|---|---|---|
| 2C8 | 0.3 | | nmol product/(mg prot · min·µM) |
| 2B6 | 0.3 | | nmol product/(mg prot · min·µM) |
| 3A4 | 0.5 | | nmol product/(mg prot · min·µM) |
| 2C9 | 0.5 | | nmol product/(mg prot · min·µM) |
| 2A6 | 0.3 | | nmol product/(mg prot · min·µM) |
| 2D6 | 0.5 | | nmol product/(mg prot · min·µM) |
| 1A1 | 0.3 | | nmol product/(mg prot · min·µM) |
| 1A2 | 0.35 | | nmol product/(mg prot · min·µM) |
| 2C19 | 0.5 | | nmol product/(mg prot · min·µM) |
| 2C18 | 0.3 | | nmol product/(mg prot · min·µM) |
| 3A5 | 0.3 | | nmol product/(mg prot · min·µM) |
| esterases | 0.4 | | nmol product/(mg prot · min·µM) |

# HANDLING POLYMORPHISM : A CASE STUDY

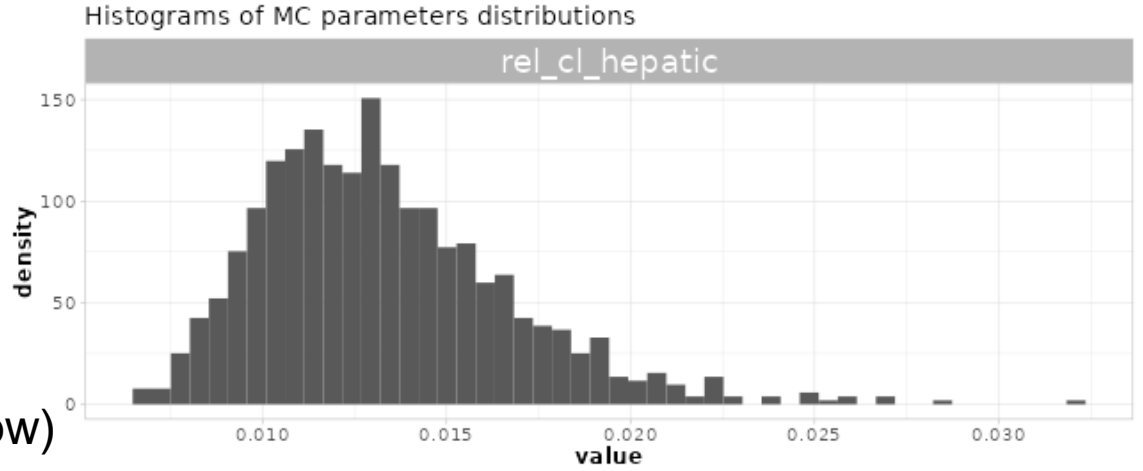
- Considering a compound metabolised by CYP3A4 and 2D6 in humans
  - $Cli_{CYP3A4} = 0.001$ nmol product/(mg prot · min·µM)

- CYP2D6 Extensive metabolisers and poor metabolisers Ratio of 5 for Clint
  - $CLint_{CYP2D6} = 0.008$ nmol product/(mg prot · min·µM)
  - $CLint_{CYP2D6} = 0.04$ nmol product/(mg prot · min·µM)

**PM**



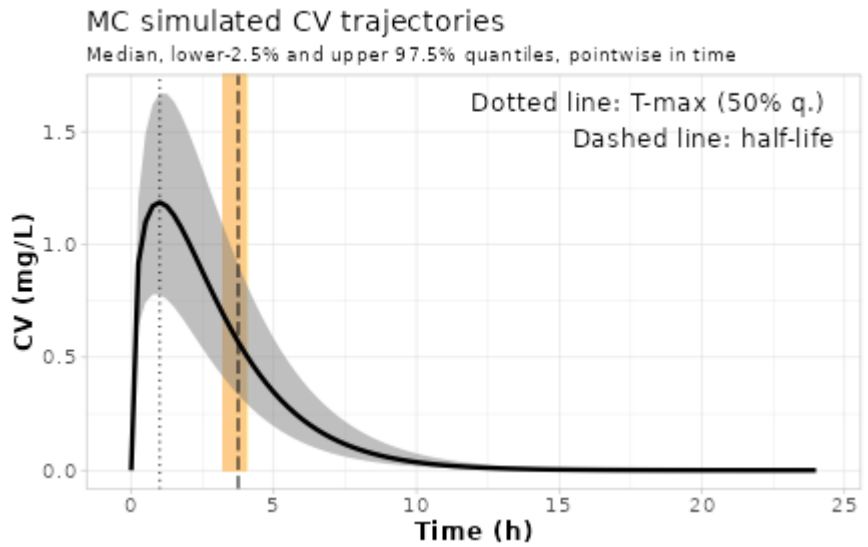

**EM**




Estimated CL (L/min/kg bw)

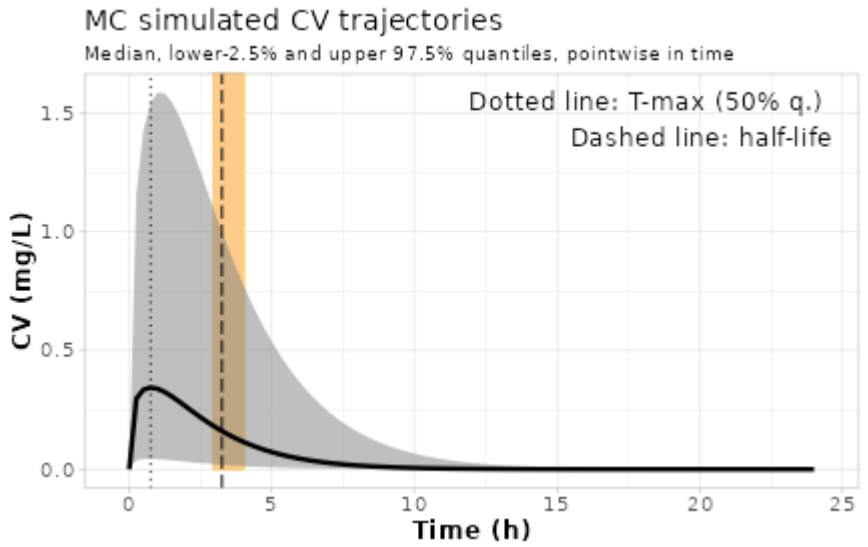
# SIMULATING THE KINETIC PROFILES IN CYP2D6 EXTENSIVE AND POOR METABOLISERS

**PM**




| | 0%-quantile | 2.5%-quantile | 50%-quantile | 97.5%-quantile | 100%-quantile |
|---|---|---|---|---|---|
| T-max (h) | 7.50E-01 | 7.50E-01 | 1.00E+00 | 1.00E+00 | 1.25E+00 |
| C-max (mg/L) | 5.41E-01 | 7.78E-01 | 1.19E+00 | 1.67E+00 | 1.96E+00 |
| Half-life (h) | 2.50E+00 | 2.50E+00 | 2.75E+00 | 3.00E+00 | 3.25E+00 |
| AUC (h * mg/L) | 2.00E+00 | 3.01E+00 | 4.90E+00 | 7.54E+00 | 9.30E+00 |

**EM**




| | 0%-quantile | 2.5%-quantile | 50%-quantile | 97.5%-quantile | 100%-quantile |
|---|---|---|---|---|---|
| T-max (h) | 7.50E-01 | 7.50E-01 | 7.50E-01 | 1.00E+00 | 1.25E+00 |
| C-max (mg/L) | 9.76E-03 | 4.36E-02 | 3.44E-01 | 1.59E+00 | 2.40E+00 |
| Half-life (h) | 2.25E+00 | 2.25E+00 | 2.50E+00 | 3.00E+00 | 3.50E+00 |
| AUC (h * mg/L) | 3.31E-02 | 1.48E-01 | 1.23E+00 | 7.05E+00 | 1.25E+01 |

# NEW MODELS FOR TKPLATE

New Human models

- Refine QIVIVE models
- Generic models for a range of metabolic pathways
- Introducing a microbiome compartment
- Pregnancy/Gestational models
- Ontogenesis of enzymes
- Generic models for metabolites (detoxification/bioactivation)
- Reverse dosimetry models for metabolites/HBM/urine etc
- Bringing a module for chemical-specific PBK models
- Bioaccumulation models (EFSA/ECHA)

# MOVING FORWARD

- TKPlate Training
  - Pilot planned for EFSA Staff and experts on 21-22 November 2024
  - Pending Feedback second training with ECHA planned for Jan 2025
  - Moving towards recorded online training available open access ?

- Moving towards application of QIVIVE and TKPlate in EFSA panels
  - Communicating outputs to panels through practical case studies
  - Difference in NAM acceptance across panels : regulations, history
  - Contaminants, pesticide, feed additive and novel food applications
  - Change management may be needed: from in vivo to NAMs

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

# ACKNOWLEDGEMENTS


- EFSA Staff: Jose Cortinas-Abrahantes, Fotios Spyropoulos, Djien Liem, Tobin Robinson, Georges Kass, Antony Smith, Jochem Louisse, Didier Verloo, Claudia Roncancio-Peña, Daniela Maurici, EFSA Senior Management
- Hans Bossier and Tobias , Open Analytics, Antwerp, Belgium
- Keyvin Darney, ANSES, Paris
- Leonie Lautz, Wageningen Agricultural Research Center, The Netherlands
- INERIS, Paris, France
- University of Utrecht, The Netherlands;
- ISS, Rome, Italy
- CERTARA Paris, London;
- Radboud University, Nijmegen, The Netherlands;
- Mario Negri, Milan, Italy
- RIVM, Bilthoven, The Netherlands
- Health and Safety Laboratory, UK
- US-EPA/NIEHS, USA

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