



The Future Of OpenFoodTox @EFSA

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**Stakeholders Forum Brussels
20th November 20, 2018**

Content

- **Background**
- **OpenFoodTox 2.0: a descriptive and predictive database**
- **The role of OECD templates and predictive models**
- **TKplate: A Toxicokinetic modelling platform**
- **Open call for data**
- **Future engagement of stakeholders**
- **Summary**

BACKGROUND



EFSA Strategy 2020 Trusted science for safe food

Protecting consumers' health with independent
scientific advice on the food chain



Trusted science for safe food

THE NIGHTMARE OF THE RISK ANALYST





FROM QUESTION TO ANSWER



Question?



Risk Assessment



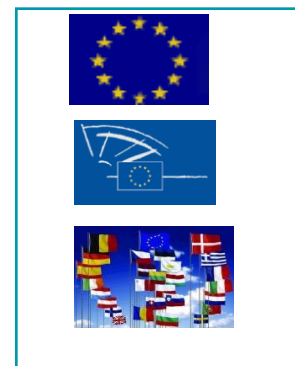
Problem Formulation

Terms of reference

Background



Opinion



Risk Management

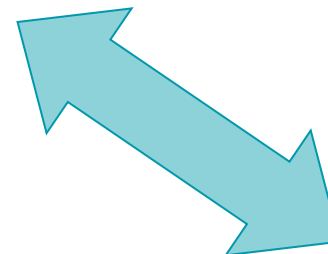
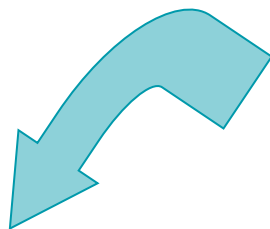
Consumers

Media

Industry

Professionals

Risk Communication



Four pillars of Chemical Risk Assessment

Risk assessment

- Fit for purpose
- Uses tiered approaches depending on data available, time and resources

Step 1

Hazard Identification

Identify toxic effects

Quantify toxic effects:

- Dose response
- Reference Point
- Reference value

Step 2
Hazard Characterisation

Step 3

Exposure Assessment

**Occurrence
x Consumption**

Step 4

Risk Characterisation

**Hazard vs
Exposure: Risk**

Deriving Safe Levels Of Chemicals In Humans : Tradition

➤ Chronic Exposure Daily

- **ADI: Acceptable Daily Intake** for regulated compounds
e.g. pesticides, food and feed additives, food contact materials
- **TDI: Tolerable Daily Intake** for Contaminants

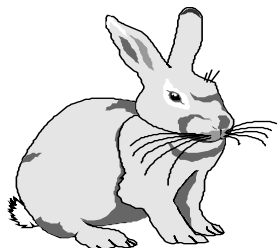
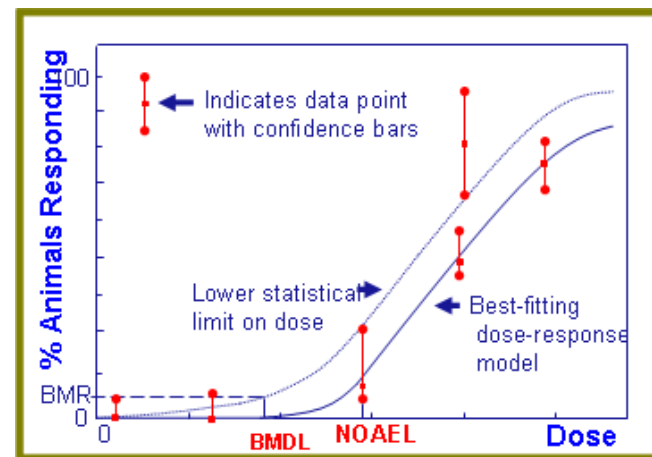
ADI or TDI = Reference Point/ 100

Basis for 100

10: Interspecies differences

10: Human variability

Reference Point



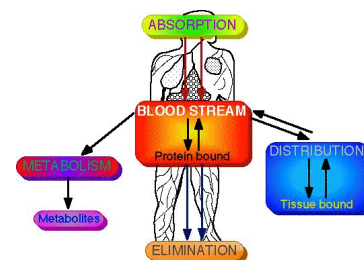
"All things are toxic and there is nothing without poisonous qualities: it is only the dose which makes something a poison"



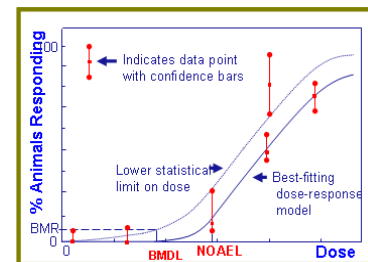
PARACELSUS
(1493-1541)

Toxicology: What the body does to a chemical and what a chemical does to the body

Toxicokinetics (TK): What the body does to a chemical



Toxicodynamics (TD) : What a chemical does to the body



Modern approaches in Chemical Risk Assessment

- Moving from testing in animals to mechanistic alternatives (e.g. *in vitro*) and modelling of biological systems (*in silico*)
- Quantitative metrics for risk

SCIENTIFIC REPORT OF EFSA

Modern methodologies and tools for human hazard assessment of chemicals¹

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*

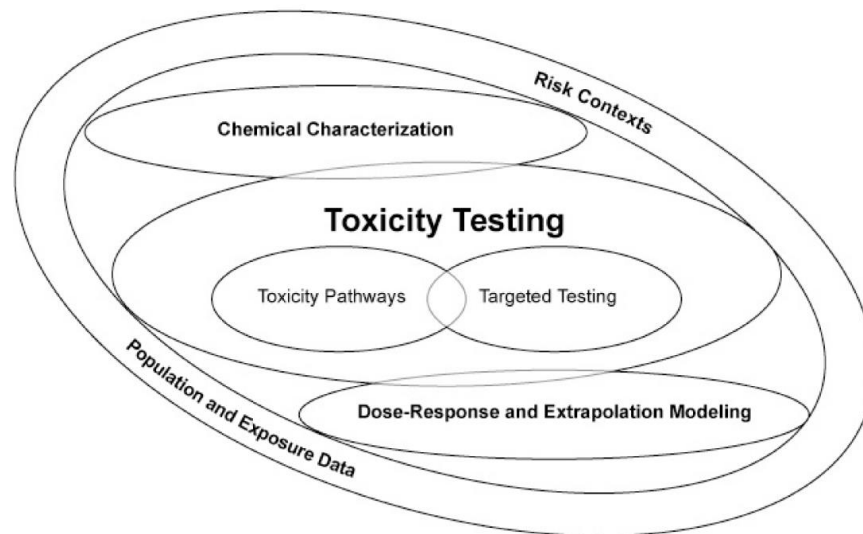
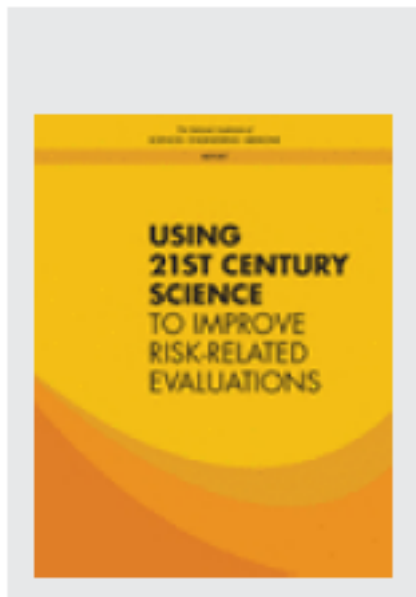
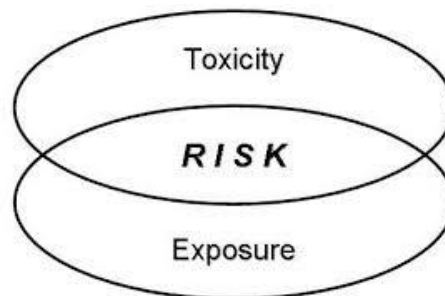
ABSTRACT

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.

© European Food Safety Authority, 2014

KEY WORDS

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

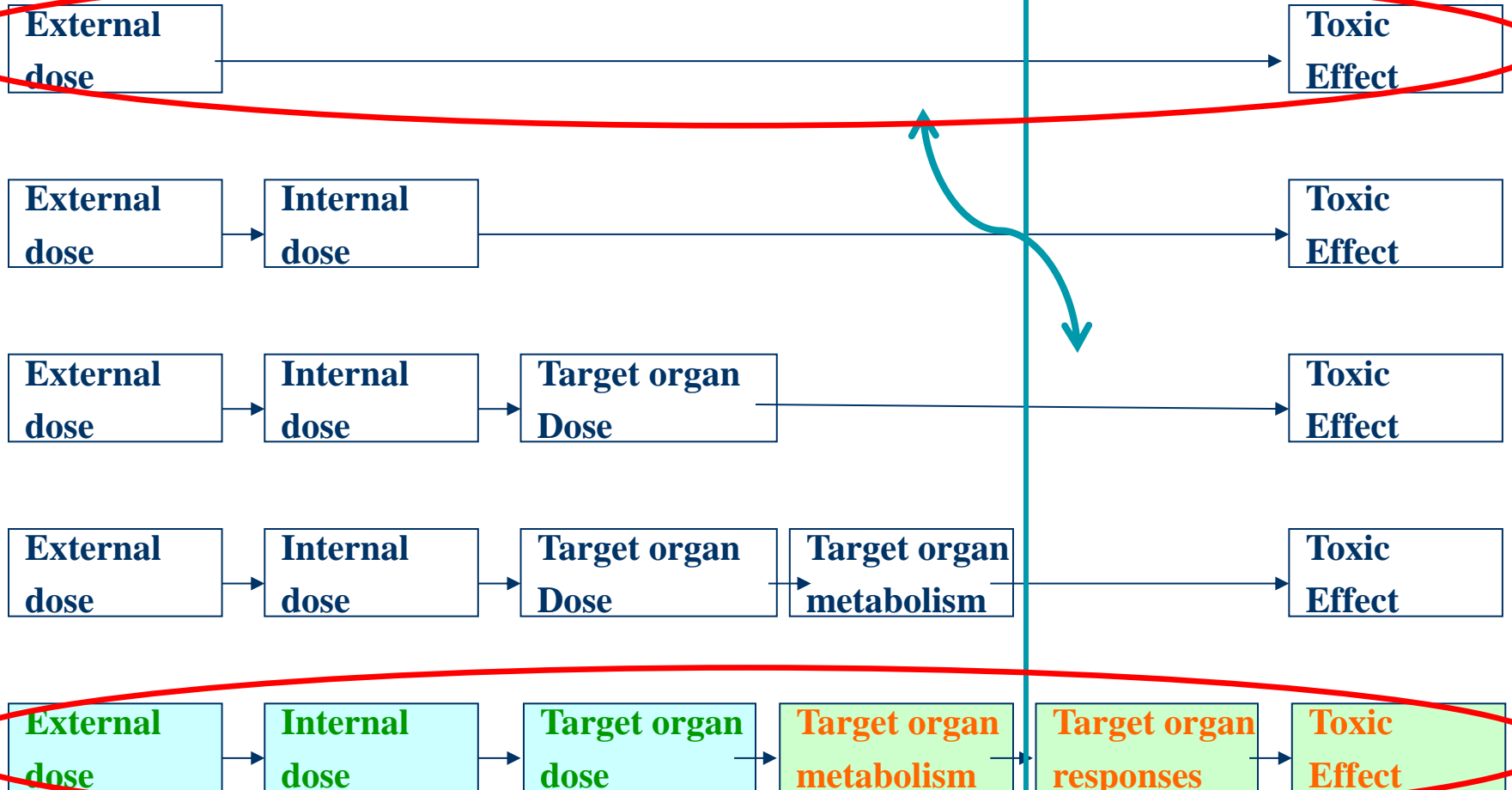


What the body does to the chemical

What the chemical does to the body

Toxicokinetics

Toxicodynamics



OpenFoodTox 2.0: A Descriptive and Predictive Database



The Future of OpenFoodTox 2.0 2018-2022

Collect new properties

- physico-chemical properties, TK data, bioaccumulation etc
- Summary exposure estimates
- Intermediate effects (mechanistic data)

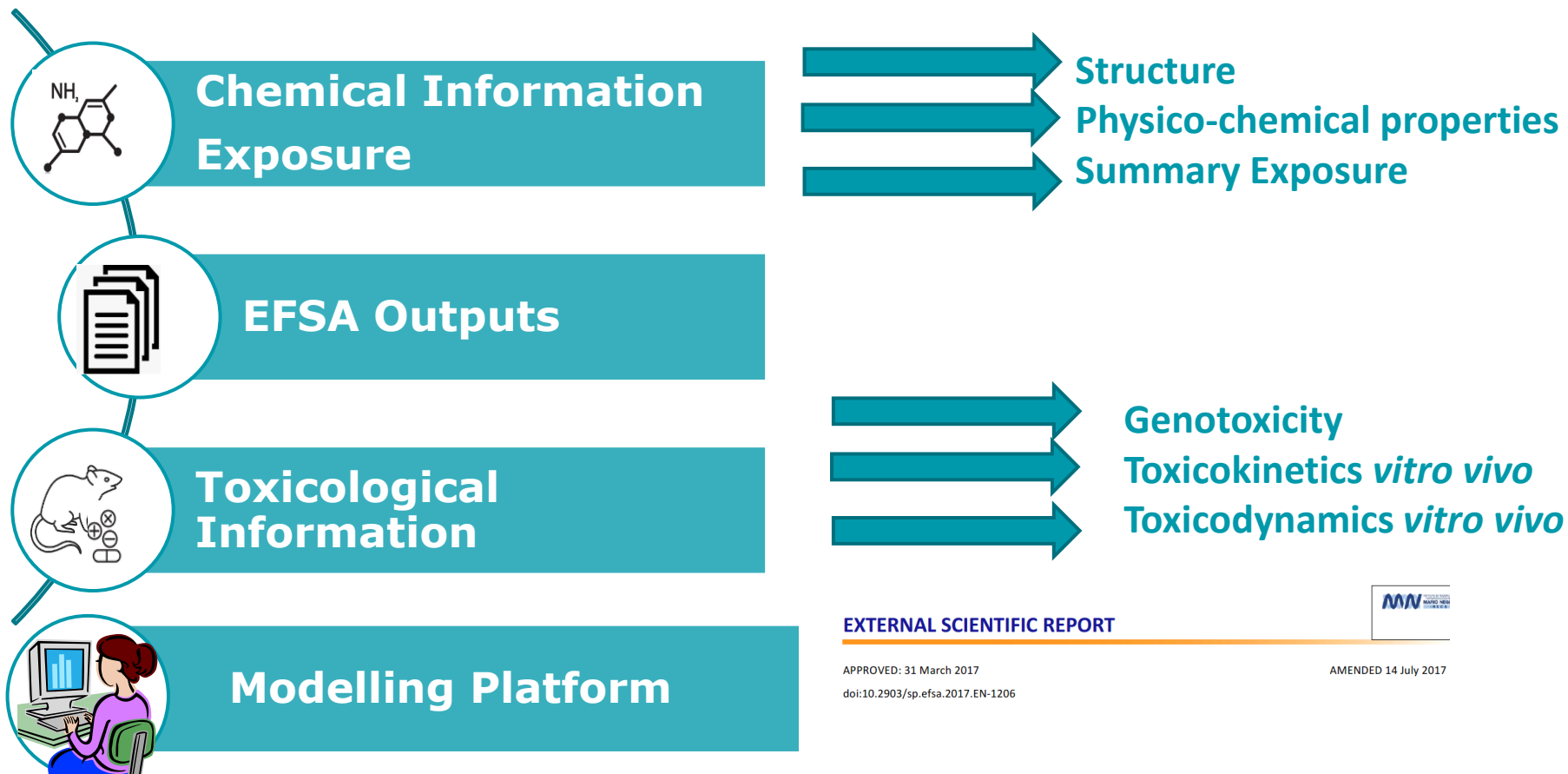
New and updated OECD harmonised Templates

- Design template for Weight of evidence, biological relevance and uncertainty
- Update mechanistic (OHT 201) and toxicokinetic template

Link OpenFoodTox with modelling platforms

- QSAR models e.g VEGA
- Published EFSA values and Predicted values

OpenFoodTox 2.0



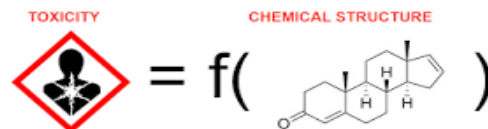
EXTERNAL SCIENTIFIC REPORT

APPROVED: 31 March 2017
 doi:10.2903/sp.efsa.2017.EN-1206

AMENDED 14 July 2017



Developing innovative *in silico* models with EFSA's
 OpenFoodTox database



OpenFoodTox and *in silico* tools

QSAR models from OpenFoodTox

- Pesticide Toxicity in bees
- Pesticide toxicity in rainbow trout
- NOAEL in rats
- NOAEL for liver toxicity in rats

EXTERNAL SCIENTIFIC REPORT



APPROVED: 31 March 2017

AMENDED 14 July 2017

doi:10.2903/sp.efsa.2017.EN-1206

Developing innovative *in silico* models with EFSA's OpenFoodTox database

Emilio Benfenati, Francesca Como, Marco Marzo, Domenico Gadaleta,
Andrey Toropov and Alla Toropova

Istituto di Ricerche Farmacologiche Mario Negri



Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com



The application of new HARD-descriptor available from the CORAL software to building up NOAEL models

Alla P. Toropova^{a,*}, A. Emilio Benfenati^a

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Monte Carlo method

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QSAR models for predicting acute toxicity of pesticides in rainbow trout using the CORAL software and EFSA's OpenFoodTox database

Andrey A. Toropov^a, Alla P. Toropova^{a,*}, Marco Marzo^a, Jean Lou Dorne^b, Nikolaos Georgiadis^b, Emilio Benfenati^a

^a Department of Environmental Health Science, Laboratory of Environmental Chemistry and Toxicology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milano, Italy

^b Scientific Committee and Emerging Risks Unit, European Food Safety Authority, Via Carlo Magno 1A, 43126 Parma, Italy



ARTICLE INFO

Keywords:

QSAR

NOAEL

ABSTRACT

Optimal (flexible) descriptors were used to establish quantitative structure – activity relationships (QSAR) for toxicity of pesticides (n = 116) towards rainbow trout. A heterogeneous set of hundreds of pesticides has been

The Role of OECD Harmonised Templates and Predictive Models



Robustness, Transparency and Openness

EDITORIAL



APPROVED: 26 March 2015

PUBLISHED: 27 March 2015

doi:10.2903/j.efsa.2015.e13031

Increasing robustness, transparency and openness of scientific assessments

**Hardy A, Dorne JLCM, Aiassa E, Alexander J, Bottex B,
Chaudhry Q, Germini A, Nørrung B, Schlatter J, Verloo D,
Robinson T**

Organisations should not aim at '*increase trust*' rather aim to demonstrate *Trustworthiness*

Information should be

- Accessible
- Intelligible
- Useable
- Assessable

*Professor David Spiegelhalter
EFSA 3rd scientific Conference
September 2018*

WEIGHT OF EVIDENCE AND BIOLOGICAL RELEVANCE

SCIENTIFIC OPINION



ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4971

Guidance on the use of the weight of evidence approach in scientific assessments

EFSA Scientific Committee,

Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig, Geoff Frampton, Matthias Greiner, Andrew Hart, Christer Hogstrand, Claude Lambre, Robert Luttik, David Makowski, Alfonso Siani, Helene Wahlstroem, Jaime Aguilera, Jean-Lou Dorne, Antonio Fernandez Dumont, Michaela Hempen, Silvia Valtueña Martínez, Laura Martino, Camilla Smeraldi, Andrea Terron, Nikolaos Georgiadis and Maged Younes

Abstract

The toolbox to combine evidence:

- Assemble
- Weigh
- Integrate

SCIENTIFIC OPINION



ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4970

Guidance on the assessment of the biological relevance of data in scientific assessments

EFSA Scientific Committee,

Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Maged Younes, Jean-Louis Bresson, John Griffin, Susanne Hougaard Benekou, Henk van Loveren, Robert Luttik, Antoine Messean, André Penninks, Giuseppe Ru, Jan Arend Stegeman, Wopke van der Werf, Johannes Westendorf, Rudolf Antonius Woutersen, Fulvio Barizzzone, Bernard Bottex, Anna Lanzoni, Nikolaos Georgiadis and Jan Alexander

Assessment of biological relevance

- The agent
- The subject
- The effects
- The conditions

e.g. Is the toxicity in the rat relevant to humans ?

WEIGHT OF EVIDENCE

Reporting weight of evidence assessment

Question		<i>Insert text of question here</i>
Assemble evidence	Select evidence	<i>Briefly summarise the methods used to search, select and extract the evidence (see Note 1).</i>
	Lines of evidence	<i>List the line(s) of evidence into which the evidence were assembled for assessment (see Note 2).</i>
Weigh the evidence	Methods	<i>Briefly summarise the method(s) used to weigh the lines of evidence (see Note 3).</i>
	Results	<i>Give a reference to the section of the assessment where the results of weighing the lines of evidence are presented (see Note 4).</i>
Integrate the evidence	Methods	<i>Briefly summarise the methods used to integrate the lines of evidence (see Note 5).</i>
	Results	<i>State the conclusions of integrating the evidence for this question (see Note 6).</i>

UNCERTAINTY GUIDELINES

GUIDANCE DOCUMENT



ADOPTED: 15 November 2017

doi: 10.2903/j.efsa.2018.5123

Guidance on Uncertainty Analysis in Scientific Assessments

EFSA Scientific Committee,

Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Maged Younes, Peter Craig, Andrew Hart, Natalie Von Goetz, Kostas Koutsoumanis, Alicja Mortensen, Bernadette Ossendorp, Laura Martino, Caroline Merten, Olaf Mosbach-Schulz and Anthony Hardy

Abstract

Uncertainty analysis is the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions. It is therefore relevant in all EFSA's scientific assessments and also necessary, to ensure that the assessment conclusions provide reliable information for decision-making. The form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each assessment and the degree of uncertainty that is present. This document provides concise guidance on how to identify which options for uncertainty analysis are appropriate in each assessment, and how to apply them. It is accompanied by a separate, supporting opinion that explains the key concepts and principles behind this Guidance, and describes the methods in more detail.

SCIENTIFIC OPINION



ADOPTED: 15 November 2017

doi: 10.2903/j.efsa.2018.5122

The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment

EFSA Scientific Committee,

Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Maged Younes, Peter Craig, Andrew Hart, Natalie Von Goetz, Kostas Koutsoumanis, Alicja Mortensen, Bernadette Ossendorp, Andrea Germini, Laura Martino, Caroline Merten, Olaf Mosbach-Schulz, Anthony Smith and Anthony Hardy

Abstract

To meet the general requirement for transparency in EFSA's work, all its scientific assessments must consider uncertainty. Assessments must say clearly and unambiguously what sources of uncertainty have been identified and what is their impact on the assessment conclusion. This applies to all EFSA's areas, all types of scientific assessment and all types of uncertainty affecting assessment. This current Opinion describes the principles and methods supporting a concise Guidance Document on Uncertainty in EFSA's Scientific Assessment, published separately. These documents do not prescribe specific methods for uncertainty analysis but rather provide a flexible framework within which different

Variability: if available , it is inherent to the biological process (inter-individual differences) we are looking at.

Uncertainty: can be reduced using appropriate tool
From descriptive to probabilistic methods

Designing and updating OECD Templates

■ **WoE, biological relevance and uncertainty**

- New template for WoE, biological relevance, uncertainty to structure methods through picklists
- Examples of methods include qualitative description, probabilistic, bayesian methods for:
 - WoE assessment
 - The assessment of biological relevance (test species vs humans)
 - Variability and uncertainty

■ **Updating OHT on TK and intermediate/mechanistic data**

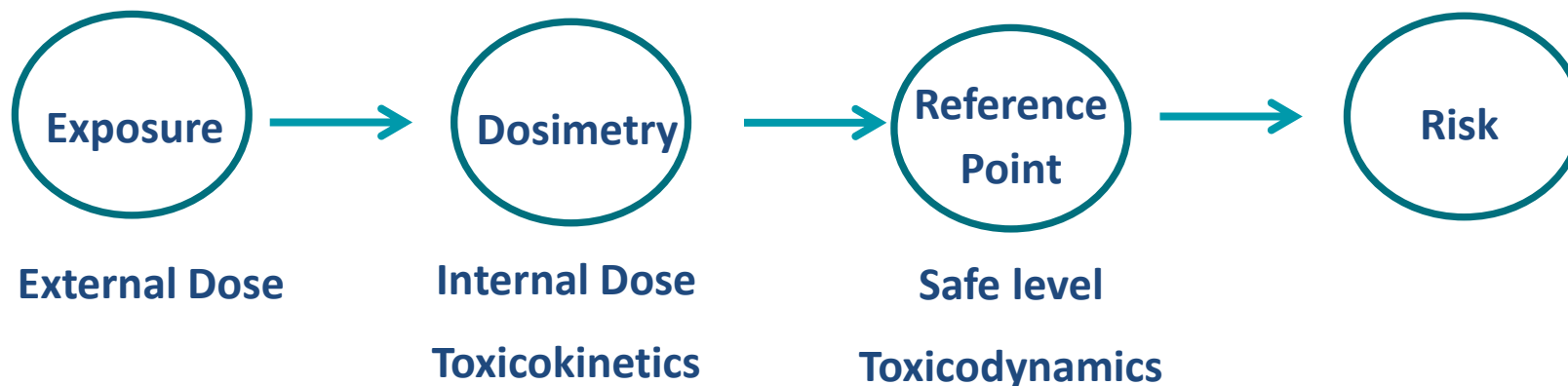
- Allow to include endpoints from new *in vitro* studies
- Allow to structure data for developing in silico tools

These OHTs further support sharing of data and cooperation between EFSA, sister agencies (ECHA), JRC, and international bodies (e.g. WHO, US-EPA, FDA).

Structuring Risk Assessment ?

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurrence	Consumption	TK	TD	TK	TD	
0	Semi-Q	Default values	No data	No data	<i>in silico</i> Read across	Default values TTC <i>In silico</i>	e.g. Default values Qualitative
1	Point estimates	Point estimates in food categories	<i>In silico</i> Limited data Semi-Q	<i>In silico</i> data Read across	<i>in silico</i> Basic TK Read across	<i>in silico</i> NOAEL Default UF	e.g. Semi-quantitative
2	Measured data	Measured in some food categories	Dossier data	Dossier Data	<i>in silico</i> ADME data	Quantitative	e.g. Quantitative Deterministic/ Probabilistic
3	Large measured dataset	Full patterns - food categories	Dossier and/or literature	Dossier and/or literature	Quantitative : Probabilistic etc		e.g. Quantitative Full probabilistic

The Role Of Predictive Models



Abstracts / Toxicology Letters 295S (2018) S12–S55

S29

S09-03

Reconnecting exposure, toxicokinetics and toxicity in food safety: OpenFoodTox and TKplate for human health, animal health and ecological risk assessment

J.-L.C.M. Dorne^{1,*}, B. Amzal², N. Quignot², W. Wiecek³, A. Grech⁴, C. Brochot⁴, R. Beaudouin⁴, F. Bois⁴, A. Ragas⁵, L. Lautz⁵, R. Oldenkamp⁵, C. Bechaux⁶, K. Darney⁶, N. Kramer⁷, E. Kasteel⁷, E. Testai¹³, L. Turco¹³, S. Vichi¹³, F. Buratti¹³, E. Di Consiglio¹³, J. Baas⁸, S. Augustine¹⁰, G. Marques⁹, G.E. Kass¹, L. Reilly¹, J. Richardson¹, M. Gilsenan¹, B. Dujardin¹, H. Verhagen¹, G. De Seze¹, D. Spyropoulos¹, A. Nougadere¹, J. Cortinas-Abrahantes¹, A. Livaniou¹, P. Manini¹, D. Verloo¹, A. Bassan¹², L. Ceriani¹², M. Pavan¹², C. Tebbi⁴, E. Benfenati¹¹, A. Paini¹⁴, D. Liem¹, T. Robinson¹

¹ EFSA, Parma, Italy

² Analytica laser, Paris, France

³ Analytica laser, London, UK

⁴ INERIS, Paris, France

In conclusion, the importance of international cooperation is emphasised, in particular between national, international scientific advisory bodies and academic institutions as the corner stone for the translation of 21st century toxicology into harmonised methodologies and tools and for the training of the next generation of risk assessors.

<https://doi.org/10.1016/j.toxlet.2018.06.1128>

S09-04

Free access platforms for integrating environmental chemical exposure and hazard information

C. Tan^{1,*}, J. Leonard², J. Wambaugh³, K. Isaacs¹, D. Villeneuve⁴, C. LaLone⁴, S. Edwards^{5,6}, A. Williams³, C. Grulke³

¹ US Environmental Protection Agency, National Exposure Research Laboratory, Research Triangle Park, North Carolina, US

² Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee, US

The role of structured data and predictive models

- **Create a workflow across exposure, internal dose, toxicity to Risk**
 - ✓ Support decision makers: fit for purpose RA and increase efficiency: high throughput
 - ✓ Data poor: QSAR, read-across, TK data ,Data rich: Refined model

- **Further support transparency, cooperation and training**
 - ✓ Support all stakeholders with fit for purpose tools
 - ✓ Data exchange with EFSA , sister agencies, MS, international
 - ✓ Case studies for fit for purpose training

- **Further support high throughput mixture risk assessment**
 - ✓ Using structured data and refine RA using internal dose

TK Plate : A Toxicokinetic Modelling Platform



Why would we use TK tools in RA?

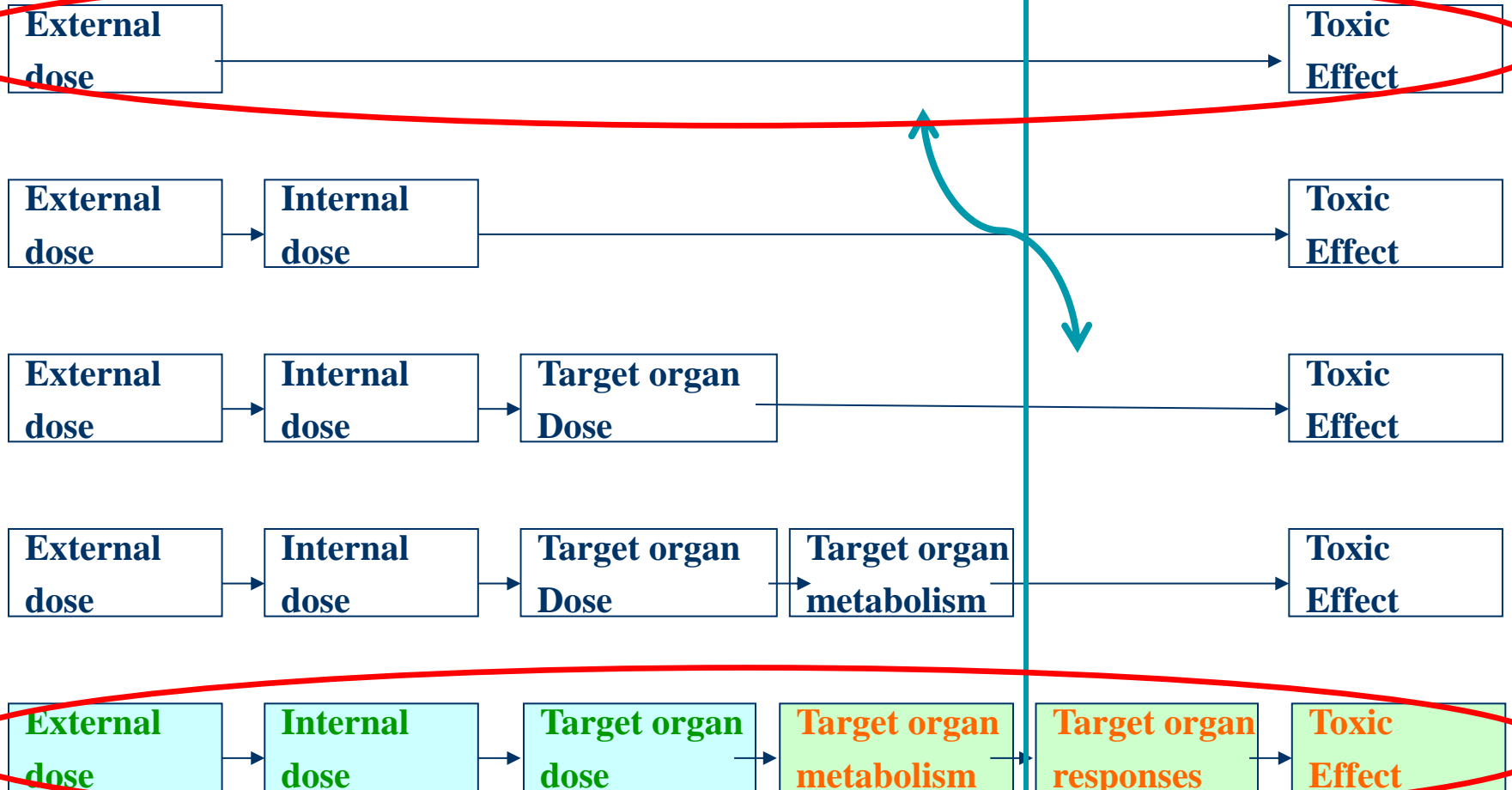
- **Priority@EFSA panels/International (2014): Generic Models**
- **Predict kinetic parameters** in relevant species: **Forward Dosimetry**
- **Integrate body burden in the derivation of safe levels** for chemicals including persistent compounds (e.g dioxins etc...)
- **Using Human biomonitoring data:** recalculate exposure from internal dose: Reverse Dosimetry
- **Quantitative *in vitro* to *in vivo* extrapolation (QIVIVE)**
- Quantify
 1. **Carry over/residues of regulated products /contaminants** in animal products (meat, eggs, milk)
 2. **Interspecies differences in kinetics** (farm animals, fish etc..)
 3. **Human variability in kinetics** (children, elderly, inter-ethnic)

What the body does to the chemical

What the chemical does to the body

Toxicokinetics

Toxicodynamics



Step Wise approach to develop and apply TK models

1.Data Collection

- Physiological and biochemical parameters for each species
- Chemical specific parameters including phys-chem, TK etc.

2.Integrate the data into an algorithm

- Physiologically-based model
- Harmonise sensitivity, variability and uncertainty analysis

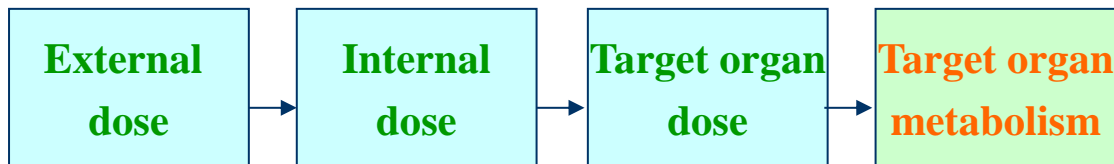
3. Develop case studies and guidance

- Compare published and predicted values
- Guidance document to use TK data/models in RA (OECD under preparation and EFSA starts 2020+)

4. Develop an Open source platform for users

- All Models integrated into a user friendly platform
- Data and models used to calculate or predict TK and TD properties
- Can accelerate the RA process

Visualisation: Physiologically-based Kinetic models

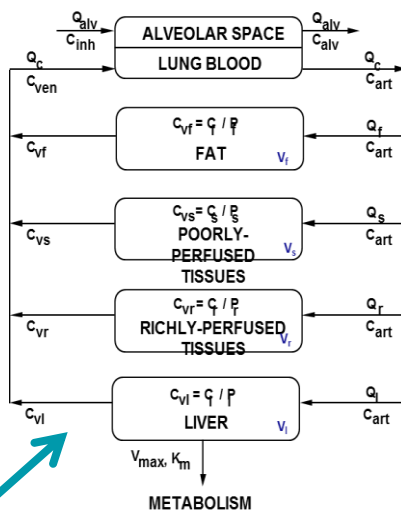


Physiological Data



Chemical Specific –Data

Exposure
 Physico-chemical
 Metabolism



Internal Dose
 TK parameters
 Tissue residues
 Reverse dosimetry

Species-specific TK
 Interspecies
 Differences
 Human Variability
 TKTD modelling

Sensitivity
Uncertainty

The R4Eu Project and EFSA Statistical models



bmd

benchmark dose modeling



MDR

multi-drug resistance analysis



MonteCarlo

risk assessment using Monte Carlo



mss-to-excel

transform MSS files into Excel files



ribess

risk based surveillance systems



sampelator

sample size calculator



spatial

exploratory analysis for spatio-temporal
epidemiology



Abstract Screening



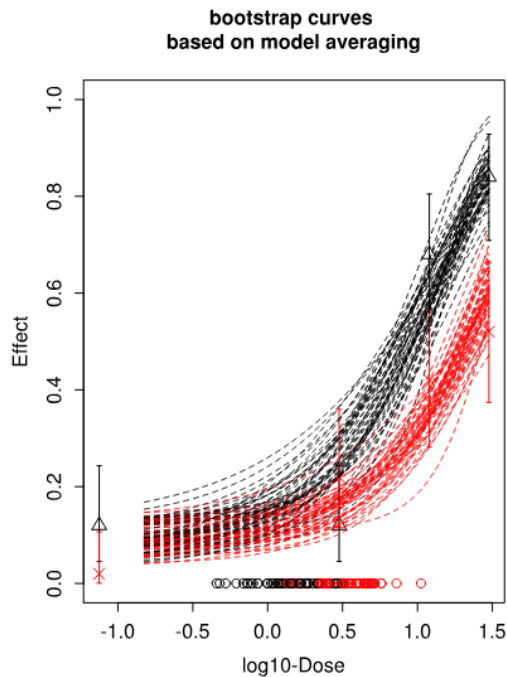
Benchmark dose Modelling

What is it for?

- Modelling dose response data dose corresponding to the benchmark response of interest. The software can apply model averaging.

Outputs?

- BMD report
- R code available: <https://zenodo.org/record/889583>
- [Manual](#) (under update)
- In 2017, EFSA organised a workshop on BMD (not specific on the tool). Information available on <https://www.efsa.europa.eu/en/events/event/170301-0>

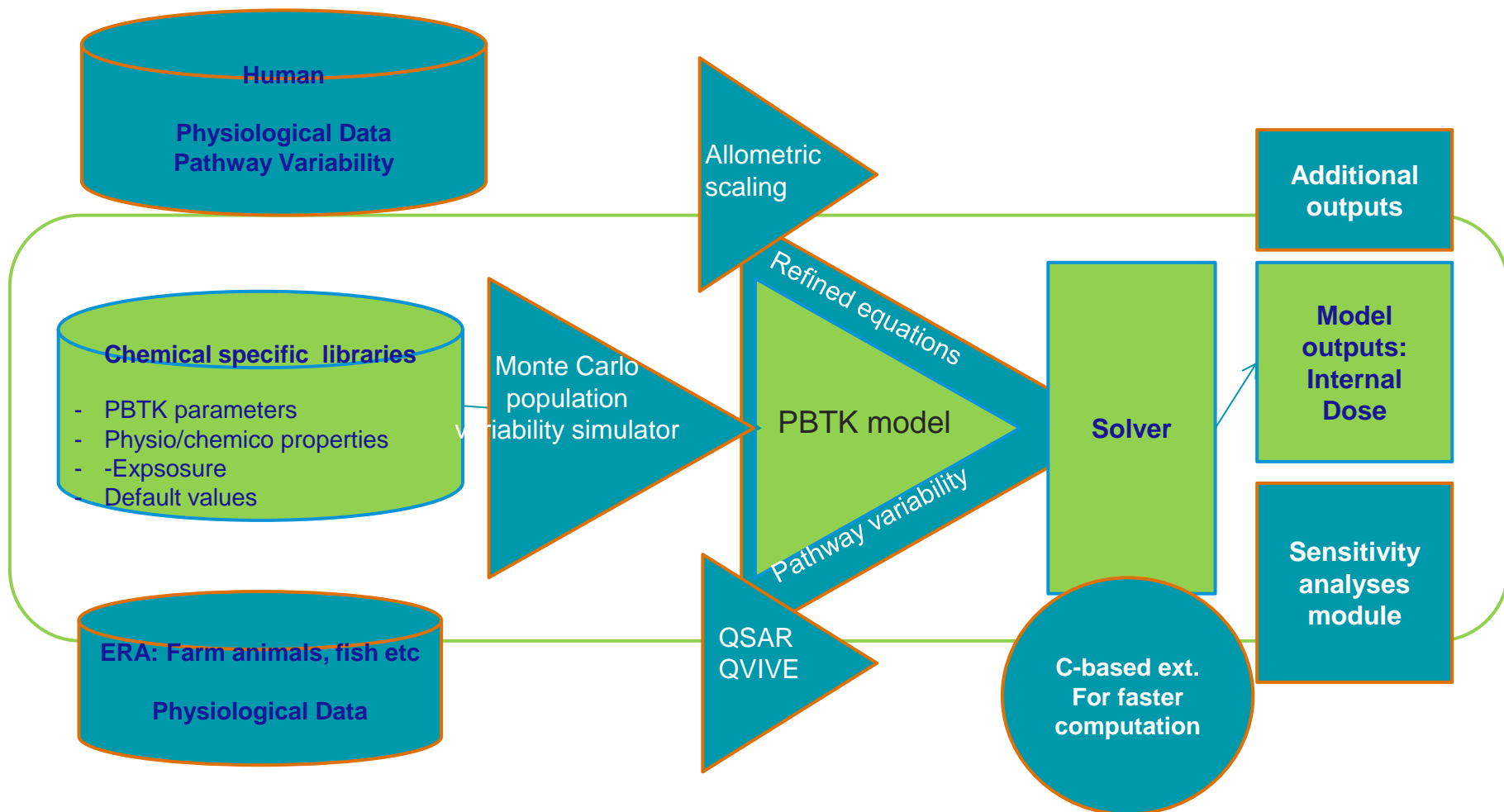


TKPlate : Prototype Platform in R

INPUT

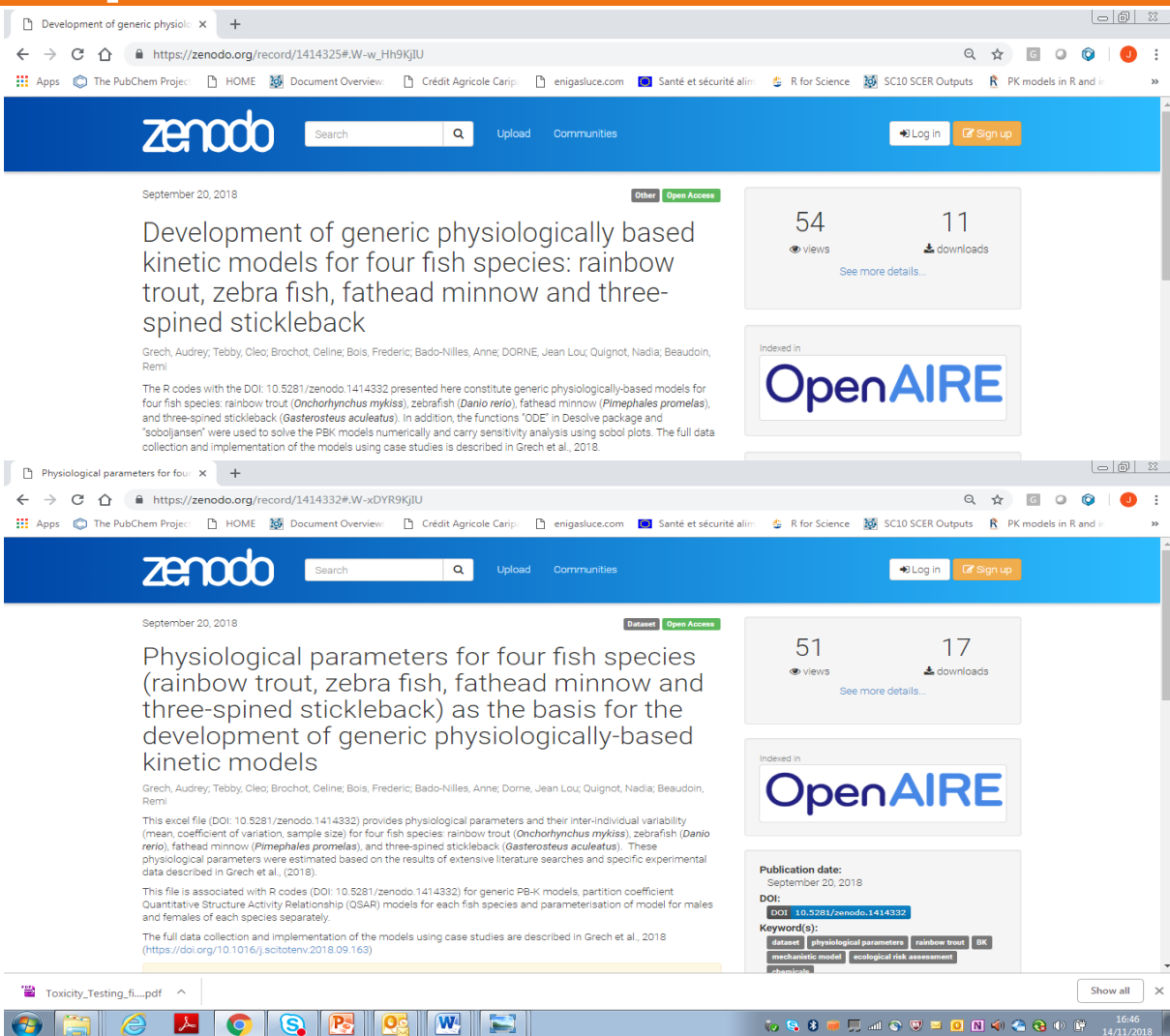
MODELLING WORKFLOW

OUTPUT



Open source PBK models in 4 Fish species@EFSA

- ✓ Open source model codes in R
- ✓ Open source Physiological data
- ✓ Model development, description, and case studies in



Development of generic physiologically based kinetic models for four fish species: rainbow trout, zebra fish, fathead minnow and three-spined stickleback

Grech, Audrey; Tebby, Cleo; Brochet, Celine; Bois, Frederic; Bado-Nilles, Anne; DORNE, Jean Lou; Quignot, Nadia; Beaudoin, Remi

The R codes with the DOI: 10.5281/zenodo.1414332 presented here constitute generic physiologically-based models for four fish species: rainbow trout (*Onchorhynchus mykiss*), zebrafish (*Danio rerio*), fathead minnow (*Pimephales promelas*), and three-spined stickleback (*Gasterosteus aculeatus*). In addition, the functions "ODE" in the Desolve package and "soboljansen" were used to solve the PBK models numerically and carry sensitivity analysis using sobol plots. The full data collection and implementation of the models using case studies is described in Grech et al., 2018.

54 views, 11 downloads

Indexed in OpenAIRE

Physiological parameters for four fish species (rainbow trout, zebra fish, fathead minnow and three-spined stickleback) as the basis for the development of generic physiologically-based kinetic models

Grech, Audrey; Tebby, Cleo; Brochet, Celine; Bois, Frederic; Bado-Nilles, Anne; Dorne, Jean Lou; Quignot, Nadia; Beaudoin, Remi

This excel file (DOI: 10.5281/zenodo.1414332) provides physiological parameters and their inter-individual variability (mean, coefficient of variation, sample size) for four fish species: rainbow trout (*Onchorhynchus mykiss*), zebrafish (*Danio rerio*), fathead minnow (*Pimephales promelas*), and three-spined stickleback (*Gasterosteus aculeatus*). These physiological parameters were estimated based on the results of extensive literature searches and specific experimental data described in Grech et al., (2018).

This file is associated with R codes (DOI: 10.5281/zenodo.1414332) for generic PB-K models, partition coefficient Quantitative Structure Activity Relationship (QSAR) models for each fish species and parameterisation of model for males and females of each species separately.

The full data collection and implementation of the models using case studies are described in Grech et al., 2018 (<https://doi.org/10.1016/j.scitotenv.2018.09.163>)

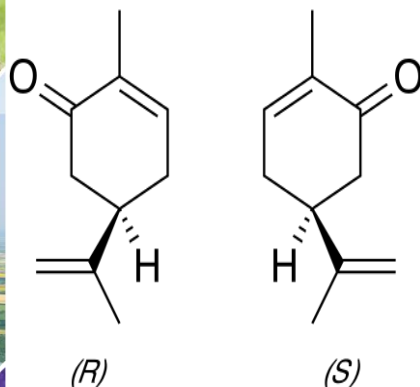
51 views, 17 downloads

Indexed in OpenAIRE

Publication date: September 20, 2018
DOI: DOI: 10.5281/zenodo.1414332
Keyword(s): dataset, physiological parameters, rainbow trout, zebrafish, mechanistic model, ecological risk assessment, zebrafish

Grech et al (2019). Generic physiologically-based toxicokinetic modelling for fish: Integration of environmental factors and species variability. STOTEN_651(Pt (1):516-531

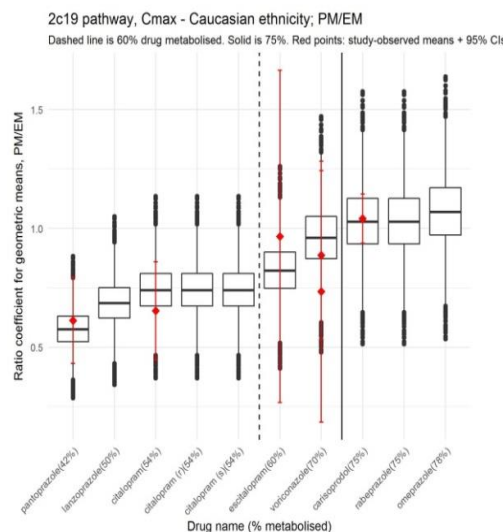
PREDICTING KINETICS IN HUMANS :CARVONE



Main metabolic route(s)	CYP2C9 CYP2C19
Case/pathway-specific input data used	In vitro human data extrapolated to in vivo via QIVIVE Variability in CYP2C9 and CYP2C19 pathway
Model structure	One-compartment model
Exposure scenario	Single oral dose based set to BMDL10
Model predictions	Plasma time-course concentrations TK parameters
External validation data	Published TK parameters in humans

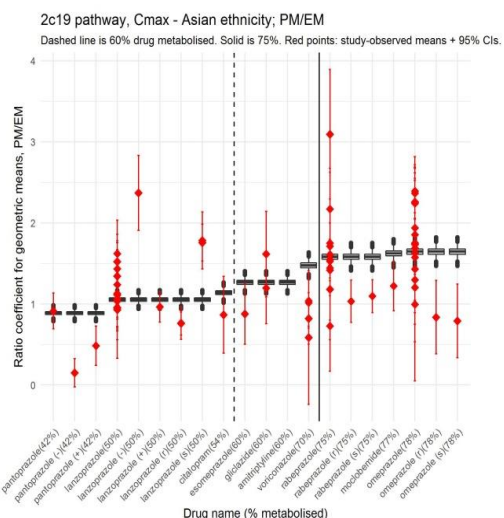
Parameters (mean (CI 95))	C_{max} (µg/L)	$t_{1/2}$ (h)	AUC_{0-24} (µg/L)
One compartment model for selected population	16.56 (9.88 – 34.57)	2 (1.25 – 3.75)	49 (15 – 200)
Published TK parameters (mean ± SD)	14.80 ± 10.40	2.40 ± 1.20	28.90 ± 20.00

INCORPORATING VARIABILITY IN METABOLISM



**Meta-regression for PK parameters-
Inter-ethnic and inter-phenotypic
differences for polymorphic CYP2C9
and CYP2C19**

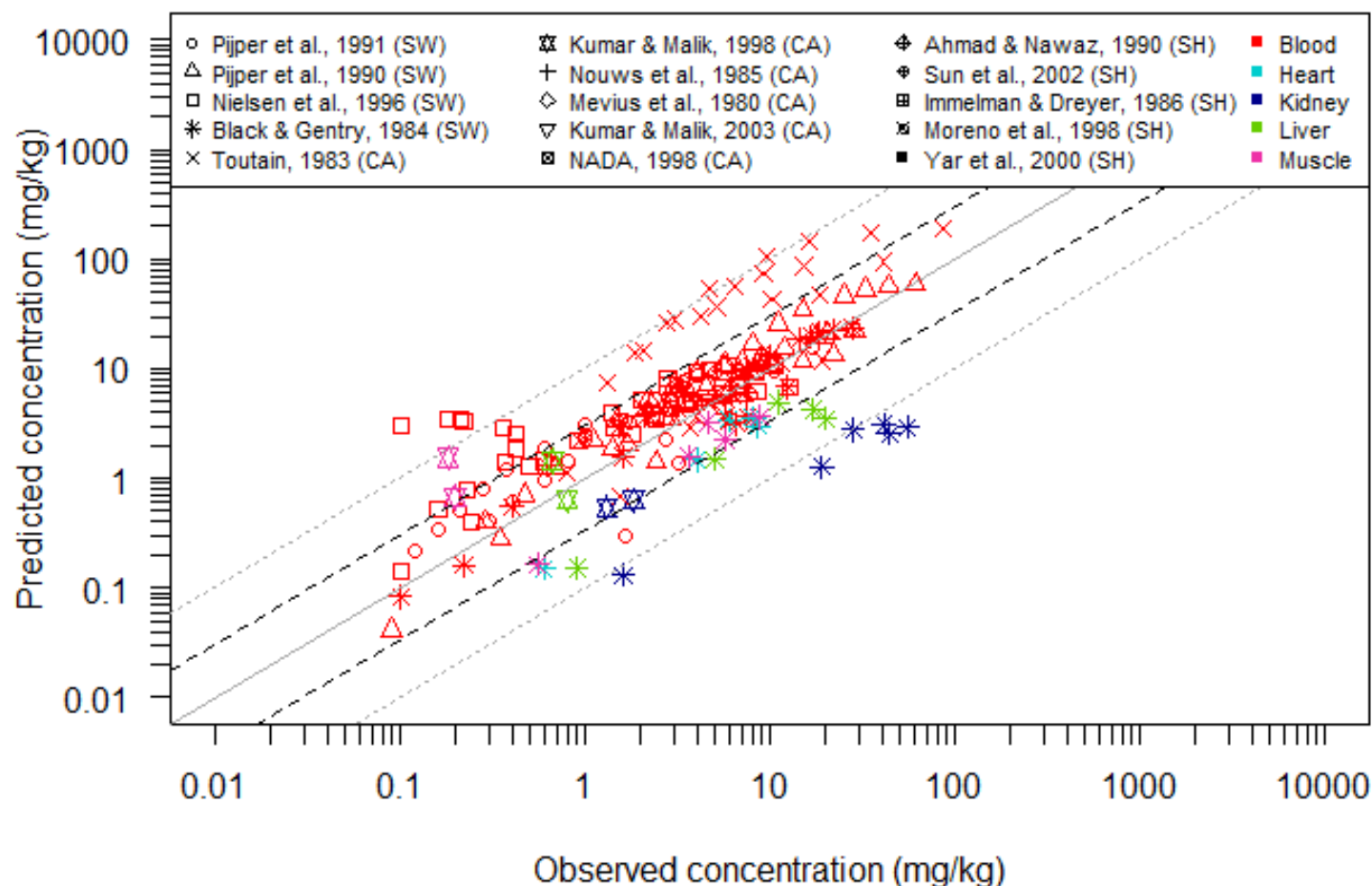
**Prediction (red)
Published (black)**



**Integration of enzyme isoform
specific variability in generic PK and
PB-K models**

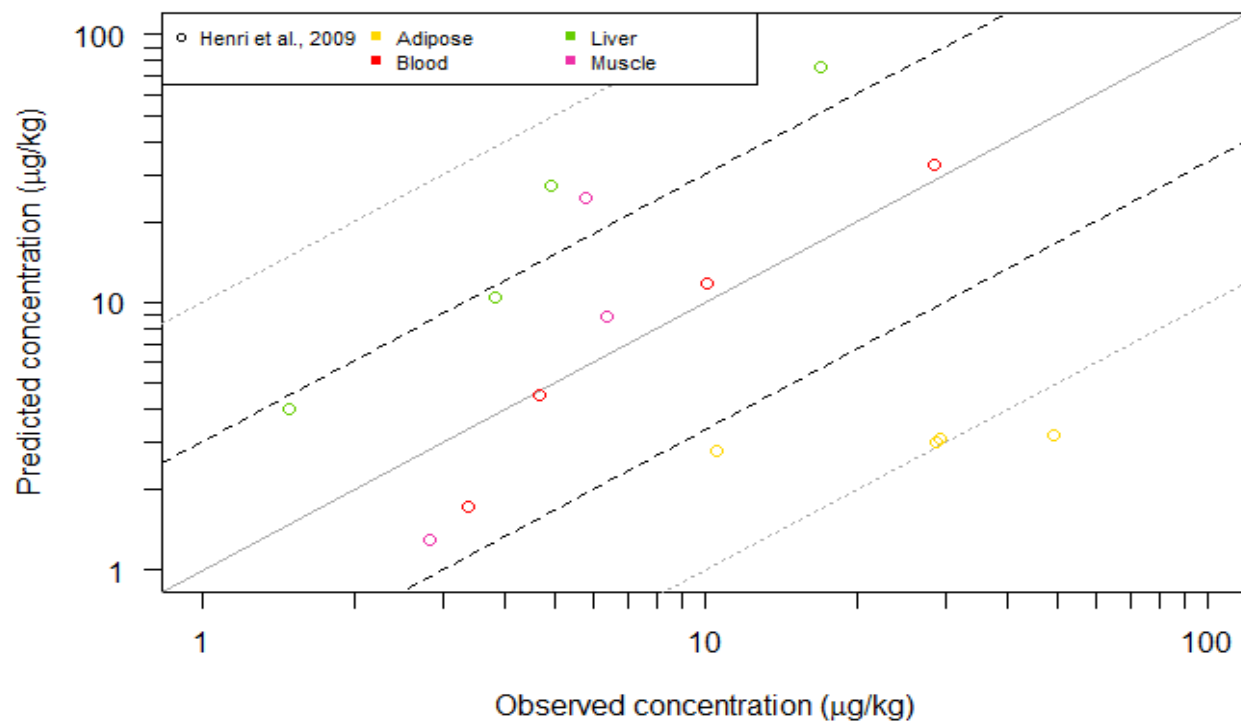
Predicting Tissue Concentrations in Farm Animals

Comparison between observed and PBK predictions of [C] in blood and tissues of cattle (CA), sheep (SH), and swine (SW) for oxytetracycline

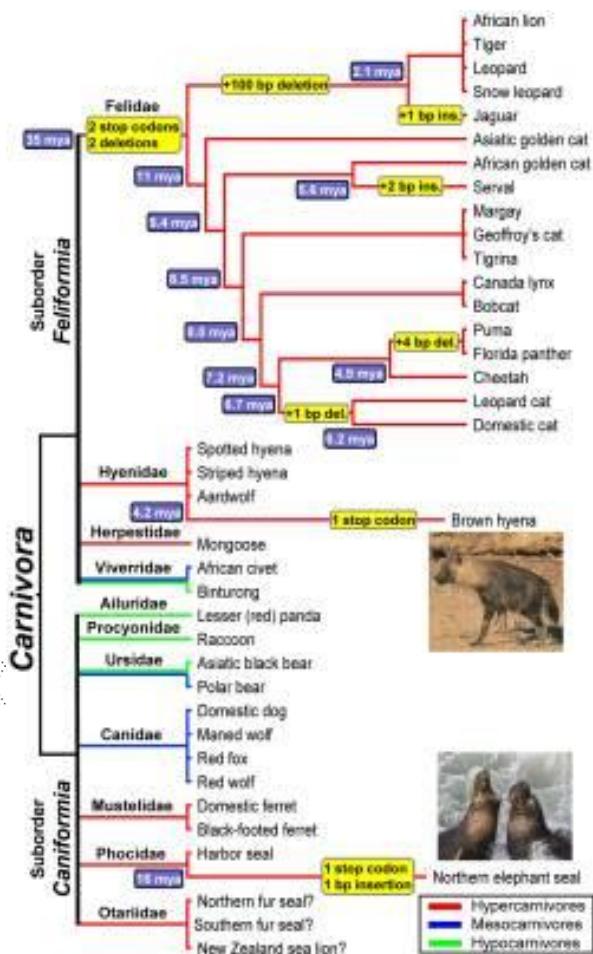


Predicting Tissue Concentrations in chicken

1. For monensin (coccidiostat), *in vitro* data for metabolism to estimate clearance
2. Scale clearance to the whole liver using a quantitative *in vitro in vivo* extrapolation model
3. Predict tissue concentrations and compare with measured data



CATS AND RISK ASSESSMENT OF FEED ADDITIVES



Cats have low activity of conjugation enzymes as hyper-carnivores: No induction by plants

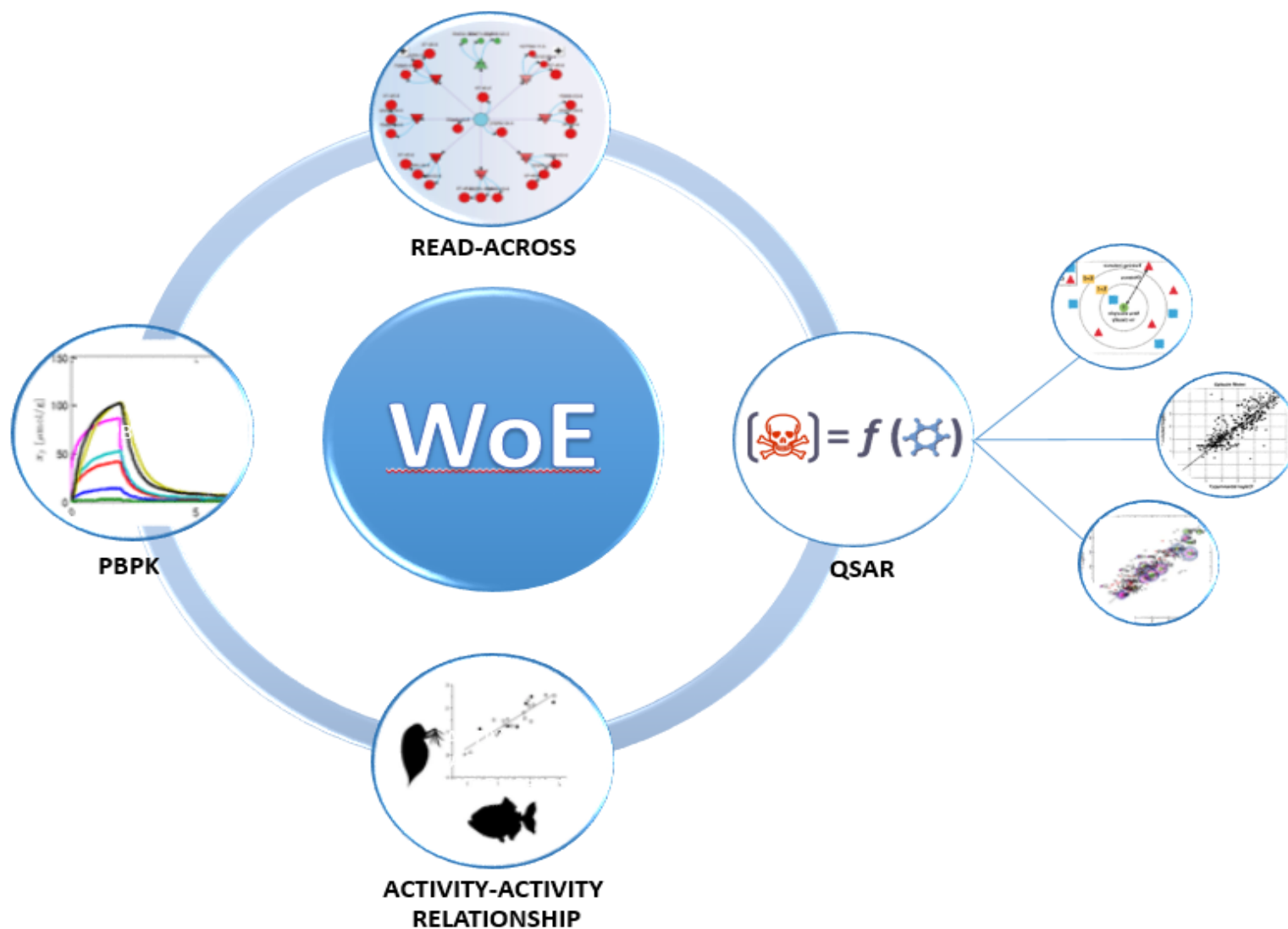
An uncertainty factor of 500 is used to go from the rat to the cat (extra UF of 5 from 100)

Generic PBK model supports quantification:

-Differences in internal dose vs other species for same external dose due to Taxa-TK specific traits.

-Rationale for specific UFs for cats depending on enzymes using available PK/TK data in cats

OpenFoodTox 2.0



OPEN CALL FOR DATA

■ **Publication of an EFSA open call for data in 2019 ?**

- Support open data for structured tox information in OpenFoodTOx 2.0 from stakeholders (e.g. MS, academia, industry etc..)
- Can support the development of case studies within TKPlate

■ **Toxicokinetic and toxicological data for chemicals in food and feed**

- Data in humans, animals and species for ecological risk assessment
- *In vivo* data (e.g. kinetic studies)
- *In vitro* data (e.g. *in vitro* metabolism etc..)

■ **Mechanistic (effect) data**

- *In vivo* data, *In vitro* data
- Include OMICs datasets ?

■ **Discussion: views and way forward**

FUTURE INVOLVEMENT OF STAKEHOLDERS

- **Regular update on data collection and available tools**
 - EFSA and Stakeholders can provide update on new databases and models available for the food and feed safety area
 - Data Sharing ?
- **Development of case studies**
 - Illustration of the application of tools for risk assessment using case studies
 - Provides training material for a range of stakeholders
- **New Computational toxicology section within EUROTOX**
 - Platform for exchange of good practice, data, models and training
 - Stakeholders
- **Discussion : views and ways forward**

Summary

■ **OpenfoodToX 2.0**

- New properties included, linked to models: Descriptive and Predictive
- New template for WoE, biological relevance, uncertainty

■ **OECD harmonised templates**

- Structured data critical for harmonisation, sharing and cooperation

■ **Predictive models and TK plate**

- Models and web based interface for human, animal and ecological RA
- Support RA for many applications including rapid RA
- Guidance document needed for food and feed safety

■ **Future perspectives : critical issues**

- Open call for data and engagement of EFSA and stakeholders
- Open source tools and cooperation with MS and international bodies
- Training the current and next generation of RA to use tools

Cooperation is Key: Acknowledgments

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 - 3.Molecular networks, Germany; 4. JRC, Ispra
- **TK Platform**
 - 1.Laser Analytica, Paris, France; 2. INERIS, Paris, France; 3.Radboud University, Nijmegen, The Netherlands 4. Open Analytics, Antwerp, Belgium
- **TK/TD**
 - 1.ANSES, Paris, France; 2. ISS, Rome, Italy; 3.University of Utrecht, Utrecht, The Netherlands; 4.University of Bretagne, Brest, France
- **DEB Models**
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THANK YOU!



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