

14 November 2019



Open Source Models and Tools For Chemical Risk Assessment in Humans, Animals and the environment

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Trusted science for safe food

EDITORIAL



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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, Nørnung B, Schlatter J, Verloo D, Robinson T



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

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

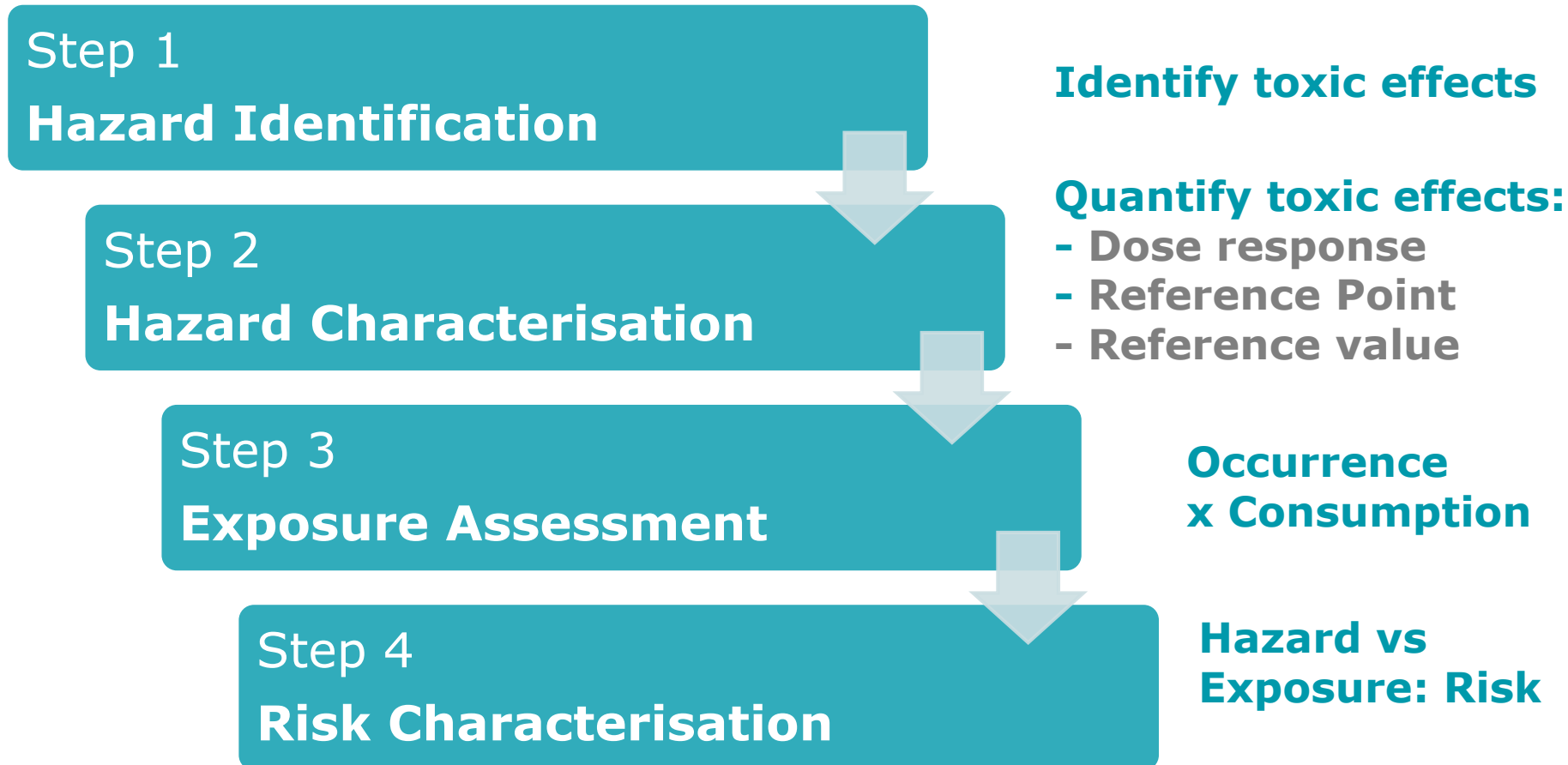
Information should be

- Accessible
- Intelligible
- Useable
- Assessable

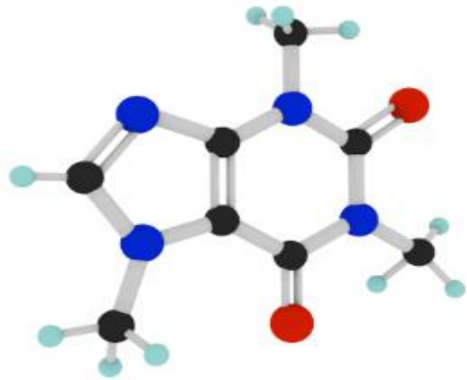
*Professor David Spiegelhalter
EFSA 3rd scientific Conference
September 2018*

Risk assessment

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



What does OpenFoodTox Contain?



4,750
Substances

**Inventory of EFSA's chemical
RA since its creation in 2002**

Easy Reference and Crisis

- Crisis: Free, Quick, Easy access to EFSA's Chemical Hazards Data
- Tool for stakeholders

Avoid duplication of efforts

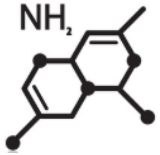
**International Harmonisation
and Data Sharing**

- OECD Harmonised Templates
- Data sharing



1,800 Scientific
outputs

What does OpenFoodTox Contain? (2)



Chemical Information



EFSA Outputs



Toxicological Information

Substance Identity : CAS, IUPAC, SMILES etc.

- Single Substances (e.g. flavourings)
- Group of Substances (e.g. mixture/formulation)

- **Opinions**
- **Conclusions on Pesticides**
- **Statements**

Title, Publication date, link etc.

Genotoxicity Reference Points

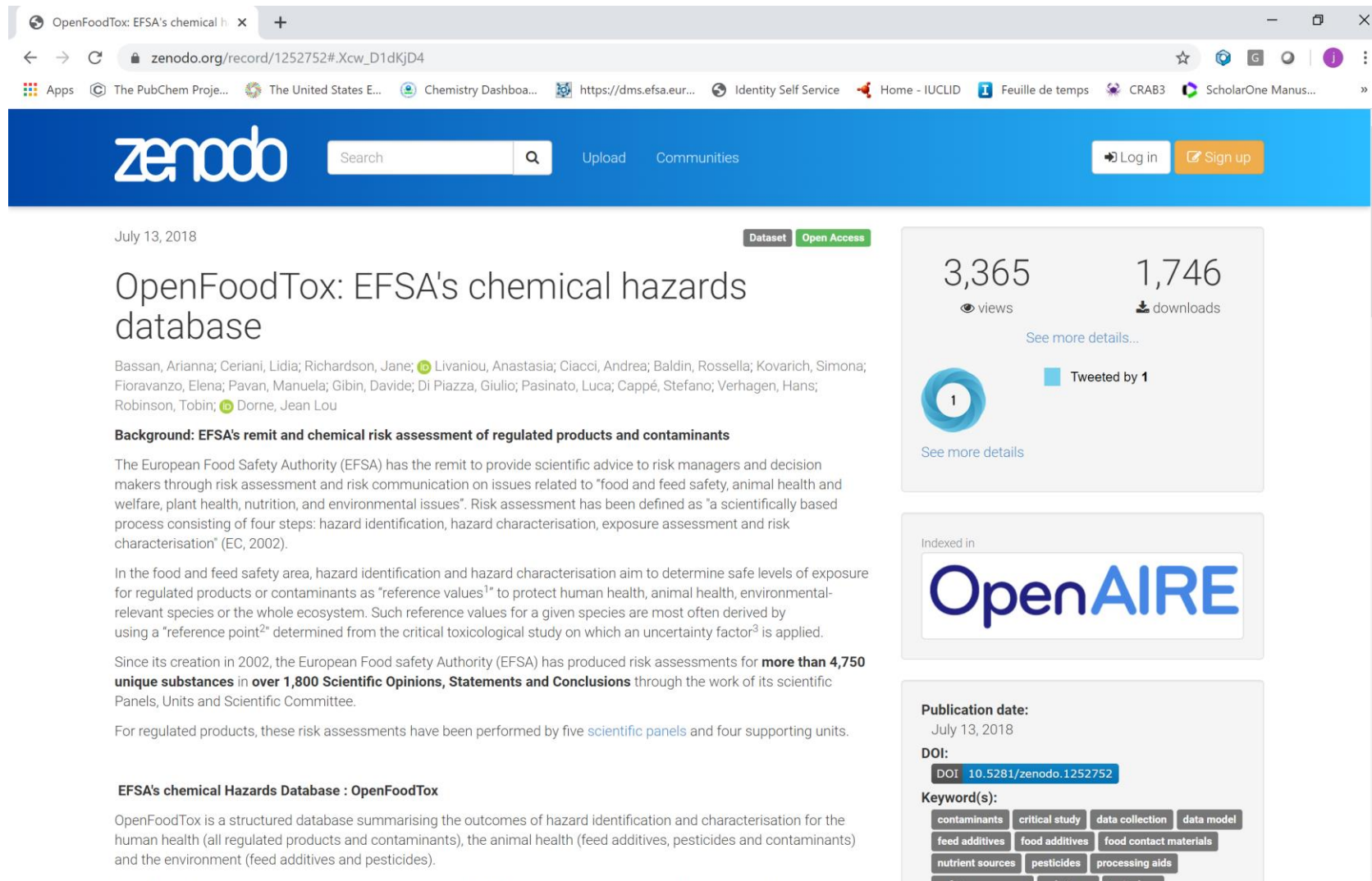
- Human and Animal health and Ecological RA

Reference Values

- Regulated products: e.g. ADI for pesticides
- Nutrients: e.g. DRV for vitamins and minerals
- Contaminants: TDI for acrylamide

Downloading All Data From OpenFoodTox

<https://doi.org/10.5281/zenodo.780543>



The screenshot shows a web browser window displaying a Zenodo record. The browser's address bar shows the URL <https://doi.org/10.5281/zenodo.780543>. The Zenodo header is blue with the logo, a search bar, and links for 'Upload' and 'Communities'. The record itself is dated 'July 13, 2018' and is labeled as a 'Dataset' and 'Open Access'. The title is 'OpenFoodTox: EFSA's chemical hazards database'. The authors listed are Bassan, Arianna; Ceriani, Lidia; Richardson, Jane; Livaniou, Anastasia; Ciacci, Andrea; Baldin, Rossella; Kovarich, Simona; Fioravanzo, Elena; Pavan, Manuela; Gibin, Davide; Di Piazza, Giulio; Pasinato, Luca; Cappé, Stefano; Verhagen, Hans; Robinson, Tobin; and Dorne, Jean Lou. The background section explains that EFSA's remit is to provide scientific advice on food and feed safety, animal health, and environmental issues, and that the database contains data from more than 4,750 unique substances. The publication date is July 13, 2018, and the DOI is 10.5281/zenodo.1252752. The keywords include contaminants, critical study, data collection, data model, feed additives, food additives, food contact materials, nutrient sources, pesticides, and processing aids. On the right side, there are statistics showing 3,365 views and 1,746 downloads, a tweet count of 1, and an 'Indexed in OpenAIRE' badge.

July 13, 2018

OpenFoodTox: EFSA's chemical hazards database

Bassan, Arianna; Ceriani, Lidia; Richardson, Jane; Livaniou, Anastasia; Ciacci, Andrea; Baldin, Rossella; Kovarich, Simona; Fioravanzo, Elena; Pavan, Manuela; Gibin, Davide; Di Piazza, Giulio; Pasinato, Luca; Cappé, Stefano; Verhagen, Hans; Robinson, Tobin; Dorne, Jean Lou

Background: EFSA's remit and chemical risk assessment of regulated products and contaminants

The European Food Safety Authority (EFSA) has the remit to provide scientific advice to risk managers and decision makers through risk assessment and risk communication on issues related to "food and feed safety, animal health and welfare, plant health, nutrition, and environmental issues". Risk assessment has been defined as "a scientifically based process consisting of four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation" (EC, 2002).

In the food and feed safety area, hazard identification and hazard characterisation aim to determine safe levels of exposure for regulated products or contaminants as "reference values"¹ to protect human health, animal health, environmental-relevant species or the whole ecosystem. Such reference values for a given species are most often derived by using a "reference point"² determined from the critical toxicological study on which an uncertainty factor³ is applied.

Since its creation in 2002, the European Food safety Authority (EFSA) has produced risk assessments for **more than 4,750 unique substances** in **over 1,800 Scientific Opinions, Statements and Conclusions** through the work of its scientific Panels, Units and Scientific Committee.

For regulated products, these risk assessments have been performed by five [scientific panels](#) and four supporting units.

EFSA's chemical Hazards Database : OpenFoodTox

OpenFoodTox is a structured database summarising the outcomes of hazard identification and characterisation for the human health (all regulated products and contaminants), the animal health (feed additives, pesticides and contaminants) and the environment (feed additives and pesticides).

3,365 views
1,746 downloads
[See more details...](#)

1
[See more details](#)
Tweeted by 1

Indexed in
OpenAIRE

Publication date:
July 13, 2018

DOI:
DOI [10.5281/zenodo.1252752](https://doi.org/10.5281/zenodo.1252752)

Keyword(s):
contaminants critical study data collection data model
feed additives food additives food contact materials
nutrient sources pesticides processing aids
safety assessment substances toxicology

Microstrategy Tool (1)

<https://www.efsa.europa.eu/en/microstrategy/openfoodtox>

Chemical hazards | Europ x

Secure | <https://www.efsa.europa.eu/en/microstrategy/openfoodtox>

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FILE

FILTER

Substance Browser

Apply

Substance name (1 S...)

Boron co... x

Compound CAS number

Search Compound CAS number

Please, use one search field at a time and click on "Apply". If more than one filter is used, the tool will intersect all searched data. If you wish to see the alternative names (synonyms) of a substance please, select the substance name in the Substance characterisation table.

Substance Characterisation

Substance	has	Component	CAS number	EC Ref No	Molecular formula	Smiles	Synonym
Boron compounds	not part of group assessment	Borate			(BO3)3-	B([O-])([O-])[O-]	Boron compounds
Boron compounds	not part of group assessment	Boric acid	11113-50-1		BH3O3	B(O)(O)O	E 284

EFSA outputs

Substance	Author	Published	Output Id	Title	Output Type	Legal Basis	Url
Boron compounds	EFSA CONTAM	07/13/2005	43	Opinion of the Scientific Panel on Contaminants in the Food Chain on a request of the Commission related to concentration limits for boron and fluoride in natural mineral waters	EFSA opinion	Regulation (EC) No 178/2002	http://dx.doi.org/10.2903/j.efsa.2005.237

Hazard Characterisation: Reference points

Substance	Author	Year	Output Id	Study	Test Type	Species	Route	Duration (days)	Endpoint	Qualifier	Value	Unit	Effect	Toxicity
Boron compounds	EFSA NDA	2004	2	Human health	reproduction toxicity	Rat	oral; feed	21	NOAEL	=	9.6	mg/kg bw/day	body weight	teratogenic
Boron compounds	EFSA CONTAM	2005	43	Human health	reproduction toxicity	Rat	oral; feed	21	NOAEL	=	9.6	mg/kg bw/day	body weight	teratogenic

Hazard Characterisation: Reference values

Substance	Author	Year	Output Id	Assessment	Qualifier	Value	Unit	Population
Boron compounds	EFSA NDA	2004	2	UL	=	0.16	mg/kg bw/day	Consumers - Adult women, lactating
Boron compounds	EFSA NDA	2004	2	UL	=	0.16	mg/kg bw/day	Consumers - Adult women, pregnant

Genotoxicity

Substance	Author	Year	Output Id	Genotoxicity
Boron compounds	EFSA NDA	2004	2	Negative
Boron compounds	EFSA CONTAM	2005	43	No data
Boron compounds	EFSA AFC	2006	377	No data
Boron compounds	EFSA CEF	2012	472	No data
Boron compounds	EFSA CEF	2013	2392	No data

Substance Browser Reference Values Reference Point Background Documents

15:23 19/07/2018

Microstrategy Tool (2)

Chemical hazards | Europ x

Secure | <https://www.efsa.europa.eu/en/microstrategy/openfoodtox>

Apps | The PubChem Project | HOME | Document Overview | Crédit Agricole Carip | enigasluce.com | Santé et sécurité alim | R for Science | SC10 SCER Outputs | PK models in R and i

FILE

Overview of studies, species and reference points available in OpenFoodTOx - click on the box to view reference points records

Filter

Reference Point

Apply

Study (5)

- ☒ (All)
- ☒ Animal (non-target species) ...
- ☒ Animal (target species) health
- ☒ Ecotox (soil compartment)
- ☒ Ecotox (water compartment)
- ☒ Human health

Reference points

Species	Endpoint	Substance	Study	Test type	Route	Duration (days)	Qualifier	Value	Unit	Effect	Toxicity
American mink	BMDL10	Nivalenol and Nivalenol-3-glucoside	Human health	acute toxicity	oral: gavage	0	=	0.14	mg/kg bw/day	clinical signs	system
American mink	BMDL10	T-2 toxin, HT-2 toxin, Neosolaniol and its phase II metabolites	Human health	acute toxicity	intraperitoneal	0	=	2.97	µg/kg bw	clinical signs	system
American mink	RPF	Nivalenol	Human health	acute toxicity	oral: gavage	0	=	1	dimensionless	clinical signs	system
American mink	RPF	Nivalenol-3-glucoside	Human health	acute toxicity	oral: gavage	0	=	1	dimensionless	clinical signs	system
Cynomolgus monkey	NOAEL	Campechlor	Human health	chronic	Not reported	231	=	100	µg/kg bw/day	immunology	immunity

Substance Browser | Reference Values | Reference Point | Background Documents

15:29 19/07/2018

Collect new properties

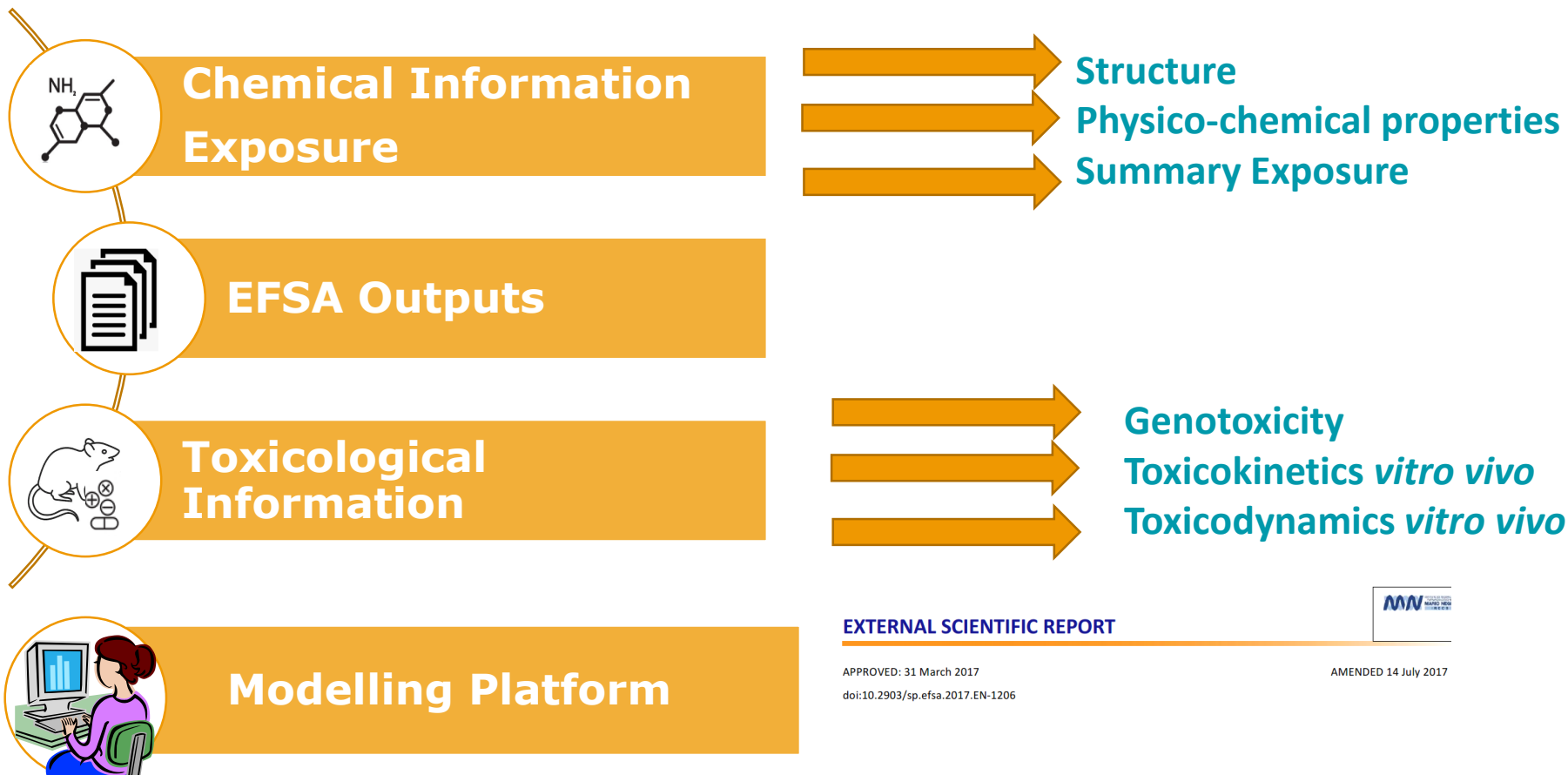
- Physico-chemical properties, TK data, bioaccumulation etc
- Summary exposure estimates
- Intermediate effects (mechanistic data)

New and updated OECD harmonised Templates

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

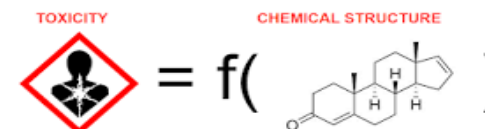
Link OpenFoodTox with modelling platforms

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



New Approach Methodologies (NAMs)

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

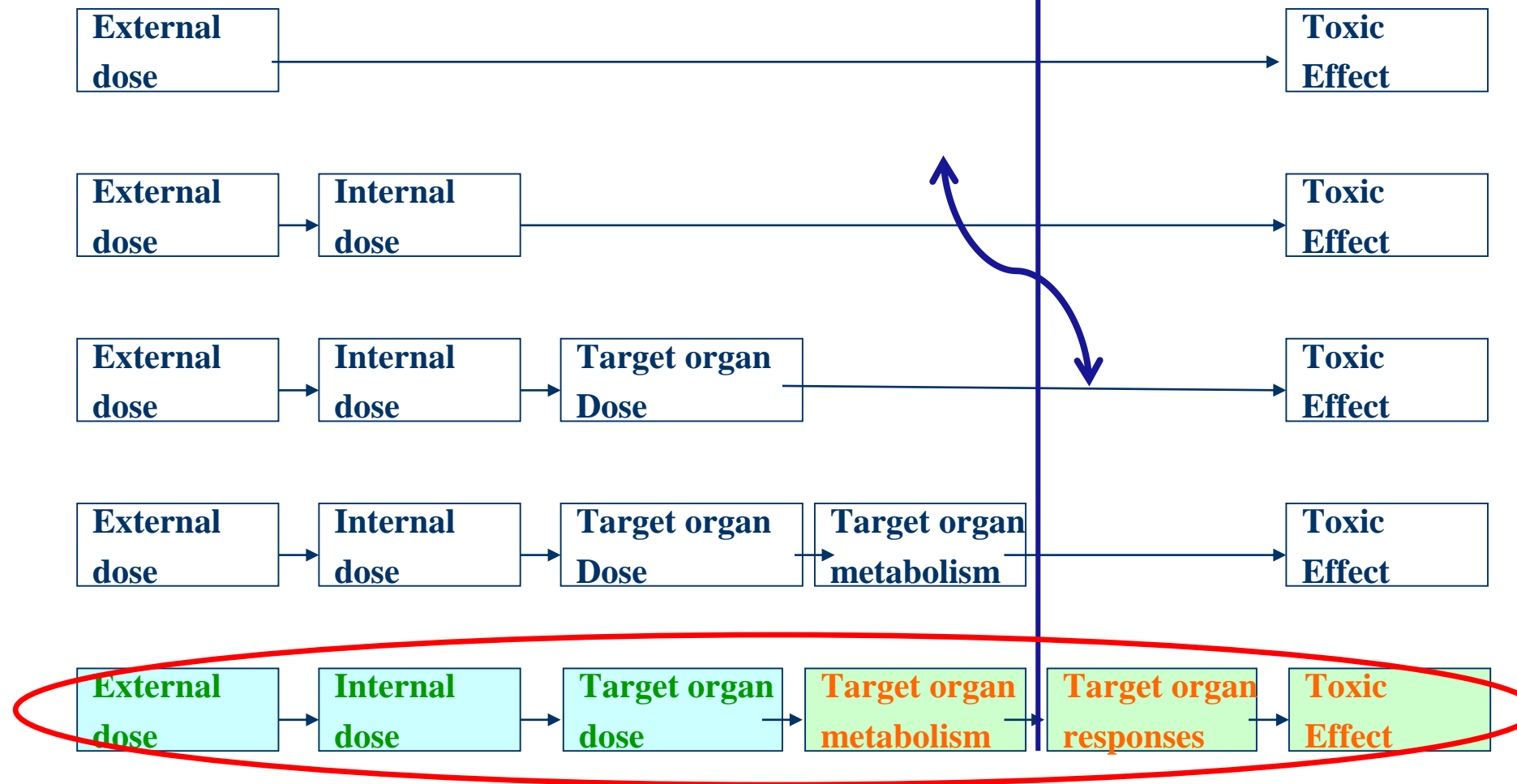


What the body does to the chemical

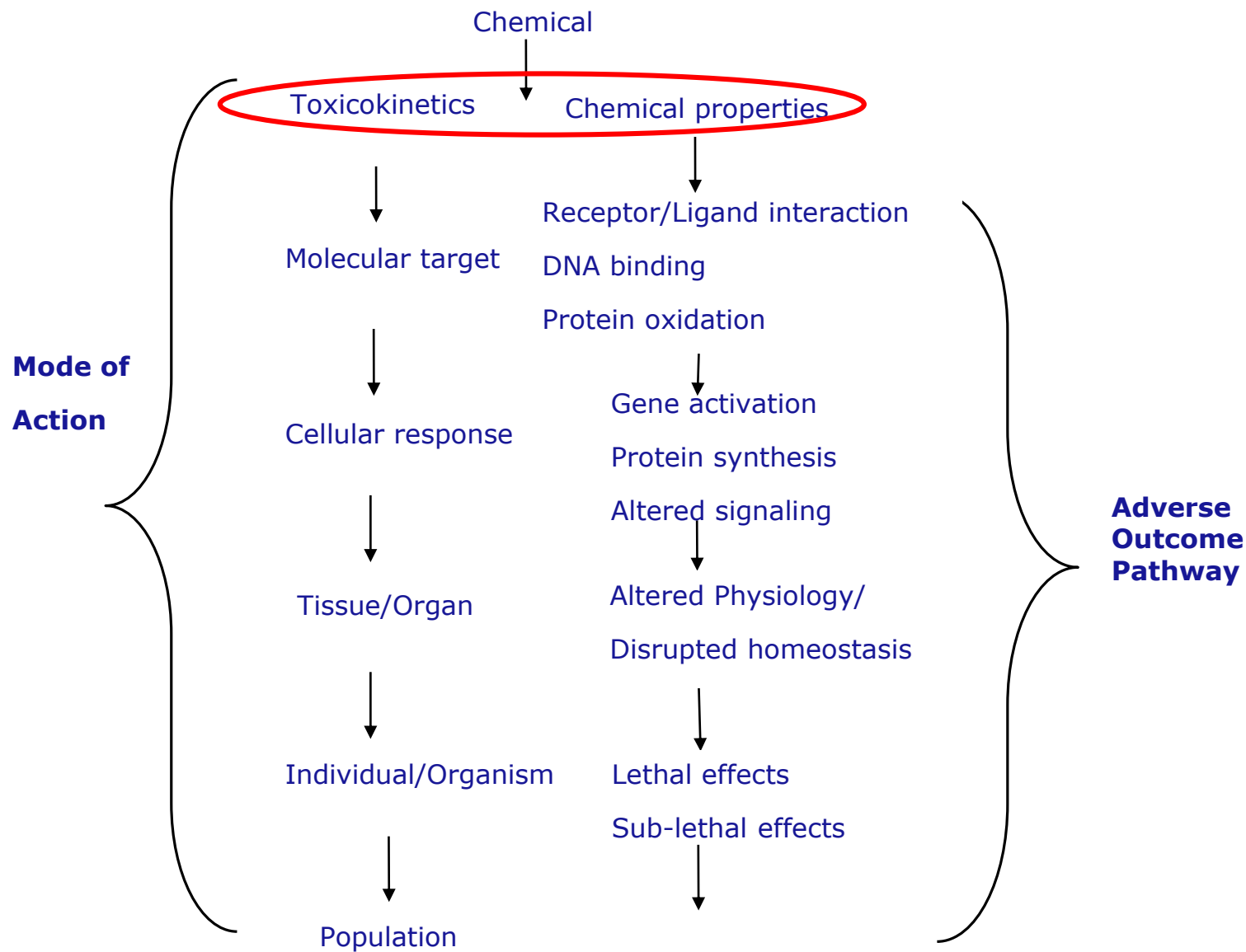
What the chemical does to the body

Toxicokinetics

Toxicodynamics



Mode of Action and Adverse Outcome Pathways



- **Alternatives to animal testing are key for EFSA:**

- Development of new tools for chemical risk assessment (RA): Fit for purpose for regulatory contexts (data poor, data rich)
- 178 REFIT exercise of the EU Food Law requires publications of all available data used in EFSA : Open data and *in silico* models
- EFSA's upcoming Chemical Risk Assessment strategy

- **EFSA active in this area:**

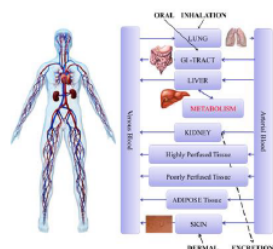
- Open source toxicological databases (OpenFoodTox)
- Development of physiologically-based kinetic (PB-K) models for humans (incl. TK and IVIVE), farm animals and fish
- International cooperation: OECD PBK guidance for RA applications
- Platform for generic TK and IVIVE modelling

- International Cooperation (2016-2020)
- State of the art Workshop at JRC with national and international bodies (US-EPA, FDA, EFSA, RIVM, HSE, etc)
- OECD Guidance document: Use of TK/PB-K models in RA (2020)

JRC CONFERENCE AND WORKSHOP REPORTS

EURL ECVAM WORKSHOP ON NEW GENERATION OF PHYSIOLOGICALLY-BASED KINETIC MODELS IN RISK ASSESSMENT

Paini A, Joossens E, Bessems J, Desalegn A, Dorne JL, Gosling JP, Heringa MB, Klaric M, Kramer N, Loizou G, Louisse J, Lumen A, Madden JC, Patterson EA, Proença S, Punt A, Setzer RW, Suci N, Troutman J, Yoon M, Worth A, Tan YM.



2017



Next generation physiologically based kinetic (NG-PBK) models in support of regulatory decision making

A. Paini^{a,*}, J.A. Leonard^b, E. Joossens^a, J.G.M. Bessems^{a,c}, A. Desalegn^a, J.L. Dorne^c, J.P. Gosling^d, M.B. Heringa^e, M. Klaric^f, T. Kliment^g, N.I. Kramer^h, G. Loizou^h, J. Louisse^{i,m}, A. Lumen^j, J.C. Madden^k, E.A. Patterson^l, S. Proença^{n,g}, A. Punt^m, R.W. Setzerⁿ, N. Suci^o, J. Troutman^p, M. Yoon^{q,s}, A. Worth^a, Y.M. Tan^l

^aEuropean Commission Joint Research Centre, Ispra, Italy

^bOak Ridge Institute for Science and Education, 100 ORAU Way, Oak Ridge, TN 37830, USA

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^dSchool of Mathematics, University of Leeds, Leeds, UK

^eRIVM - The National Institute for Public Health and the Environment, Bilthoven, The Netherlands

^fCosmetics Europe, Brussels, Belgium

^gInstitute for Risk Assessment Sciences, Utrecht University, P.O. Box 80177, 3508TD Utrecht, The Netherlands

^hHealth and Safety Executive, Buxton, UK

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^jDivision of Biochemical Toxicology, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AR 72079, USA

^kSchool of Pharmacy and Biomedical Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

^lSchool of Engineering, University of Liverpool, Liverpool L69 3GH, UK

^mRIKILT Wageningen University and Research, Alkenmaalse 2, 6708 WB Wageningen, The Netherlands

ⁿU.S. Environmental Protection Agency, National Exposure Research Laboratory, 109 TW Alexander Drive, Research Triangle Park, NC 27709, USA

^oDEITAS, Università Cattolica del Sacro Cuore, Piacenza, Italy

^pCentral Product Safety, The Procter & Gamble Company, Cincinnati, OH, USA

^qSclavoVation, 6 Davis Drive, PO Box 110566, Research Triangle Park, NC 27709, USA

^rFlemish Institute for Technological Research (MTO), Mol, Belgium

^sTacStrategies, Research Triangle Park Office, 1249 Kildaire Farm Road 134, Cary, NC 27511, USA

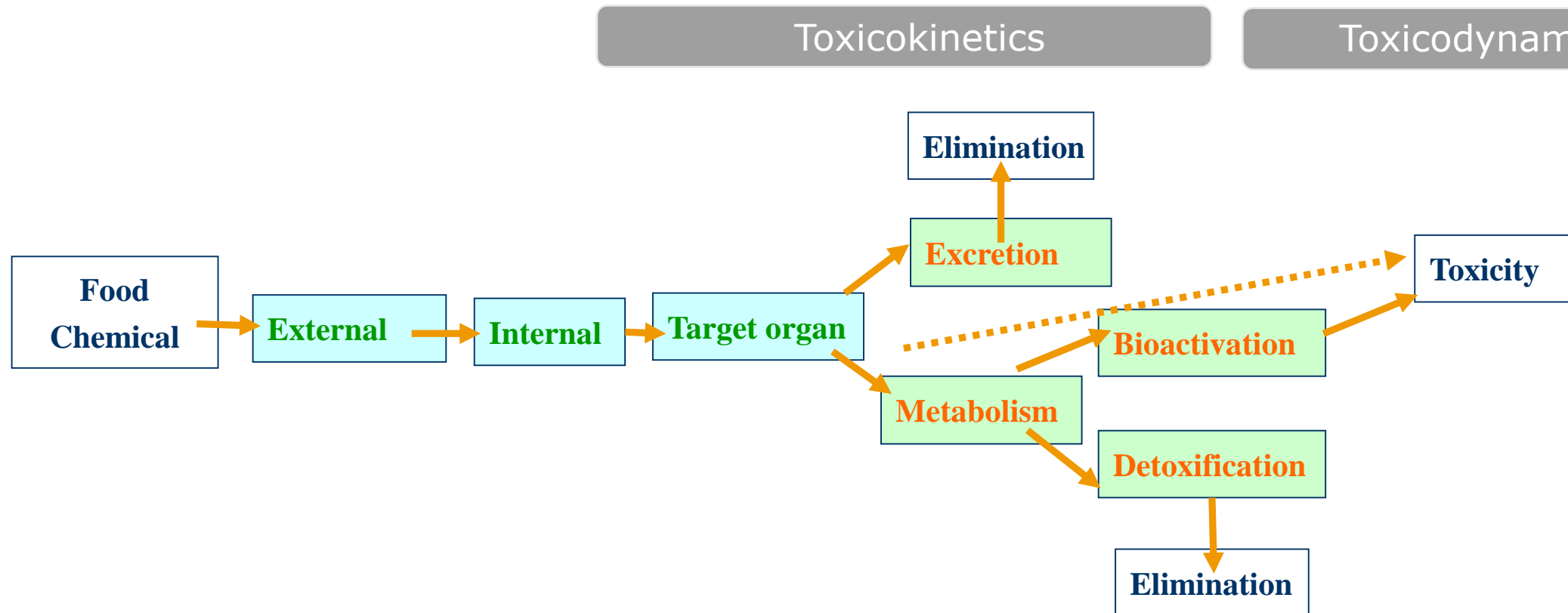
Toxicokinetics and Toxicity

- ✓ **Main evolutionary goal of biotransformation: DETOX (TOXIFY ?)**

Metabolism (liver + other tissues):

From Lipophilic (+ absorption) to hydrophilic (+ excretion in urine or bile).

- ✓ **Can we predict Kinetics quantitatively for humans, animals and other species ?**



Toxicology in Vitro 60 (2019) 61–70



Review

Physiologically based kinetic models for farm animals: Critical review of published models and future perspectives for their use in chemical risk assessment

L.S. Lautz^{a,*}, R. Oldenkamp^a, J.L. Dorne^b, A.M.J. Ragas^{a,c}

^a Department of Environmental Science, Institute for Water and Wetland Research, Radboud University Nijmegen, Houtlaan 4, 6525 XP Nijmegen, The Netherlands

^b European Food Safety Authority, Via Carlo Magno, 1A, 43126 Parma, Italy

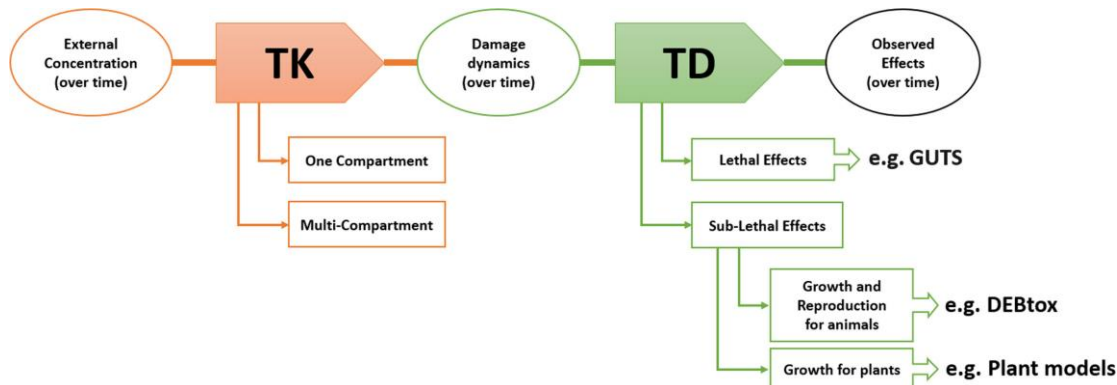
^c Department of Science, Faculty of Management, Science & Technology, Open University, 6419 AT Heerlen, The Netherlands



Review

Dynamic energy budget models in ecological risk assessment: From principles to applications

Jan Baas^{a,*}, Starrlight Augustine^b, Gonçalo M. Marques^c, Jean-Lou Dorne^d



Science of the Total Environment 651 (2019) 516–531



Generic physiologically-based toxicokinetic modelling for fish: Integration of environmental factors and species variability

Audrey Grech^{a,b,c}, Cleo Tebby^a, Céline Brochet^a, Frédéric Y. Bois^a, Anne Bado-Nilles^c, Jean-Lou Dorne^d, Nadia Quignot^b, Rémy Beaudouin^{a,c,*}

^a Institut National de l'Environnement Industriel et des Risques (INERIS), Models for Ecotoxicology and Toxicology Unit, Parc ALATA, BP2, 60550 Verneuil-en-Halatte, France

^b Analytica Laser, 3 rue de l'arrivée, 75015 Paris, France

^c Institut National de l'Environnement Industriel et des Risques (INERIS), UMR-I 02 SEBIO, Parc ALATA, BP2, 60550 Verneuil-en-Halatte, France

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



SCIENTIFIC OPINION



ADOPTED: 27 June 2018

doi: 10.2903/j.efsa.2018.5377

Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms

EFSA Panel on Plant Protection Products and their Residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Antonio F Hernandez-Jerez, Susanne Hougaard Bennekou, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Robert H Smith, Michael Stemmer, Ingvar Sundh, Aaldrik Tiktak, Christopher J. Topping, Gerrit Wolterink, Nina Cedergreen, Sandrine Charles, Andreas Focks, Melissa Reed, Maria Arena, Alessio Ippolito, Harry Byers and Ivana Teodorovic

Stepwise approach to develop physiologically-based Kinetic 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 document

- Compare published and predicted values
- Guidance : TK data/models in RA (OECD in prep, EFSA 2020+)

4. Develop an Open source platform for users

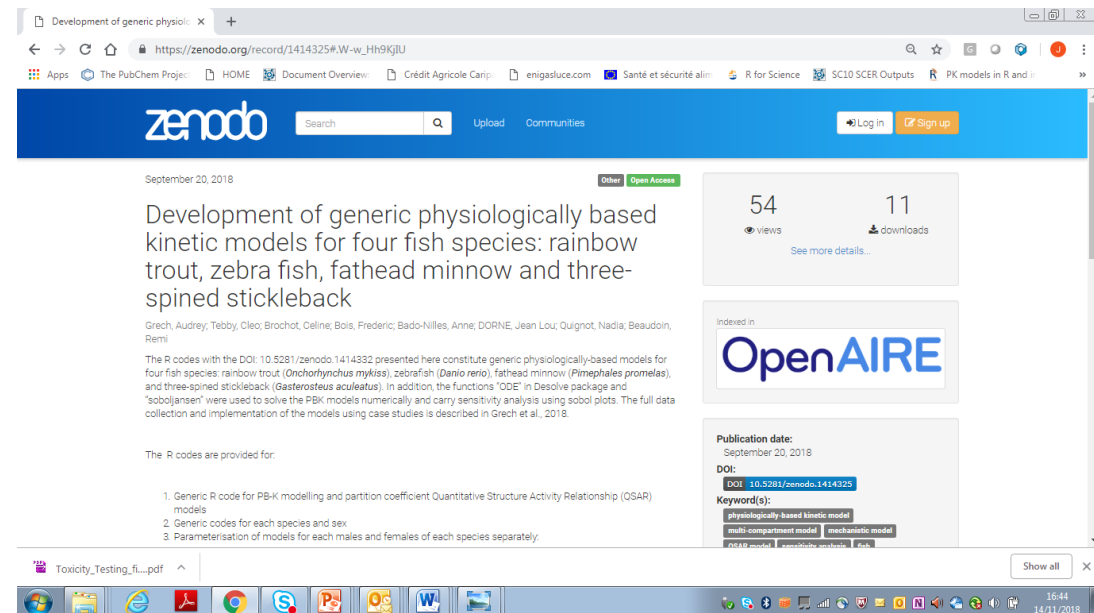
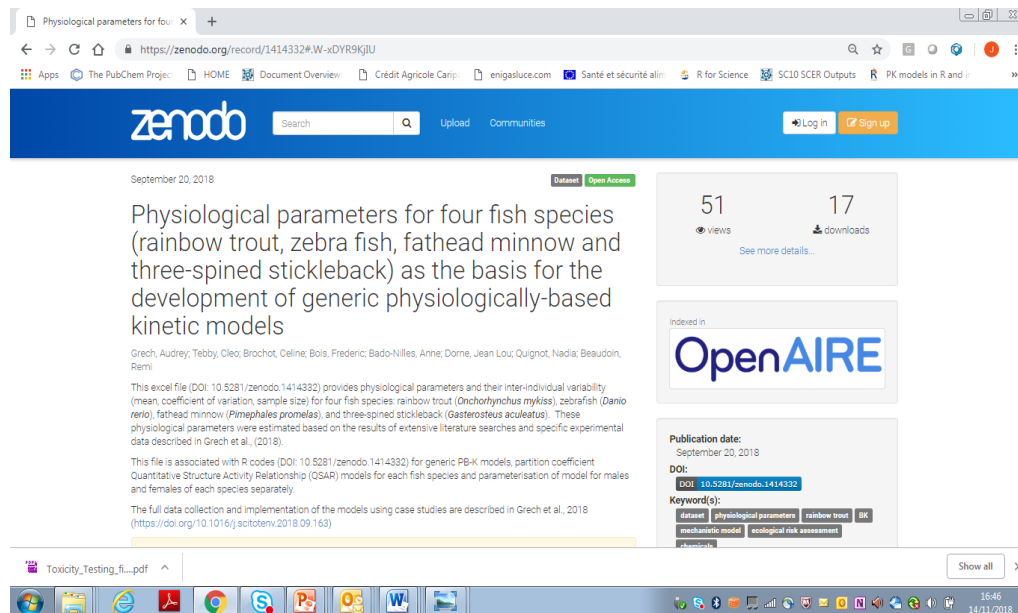
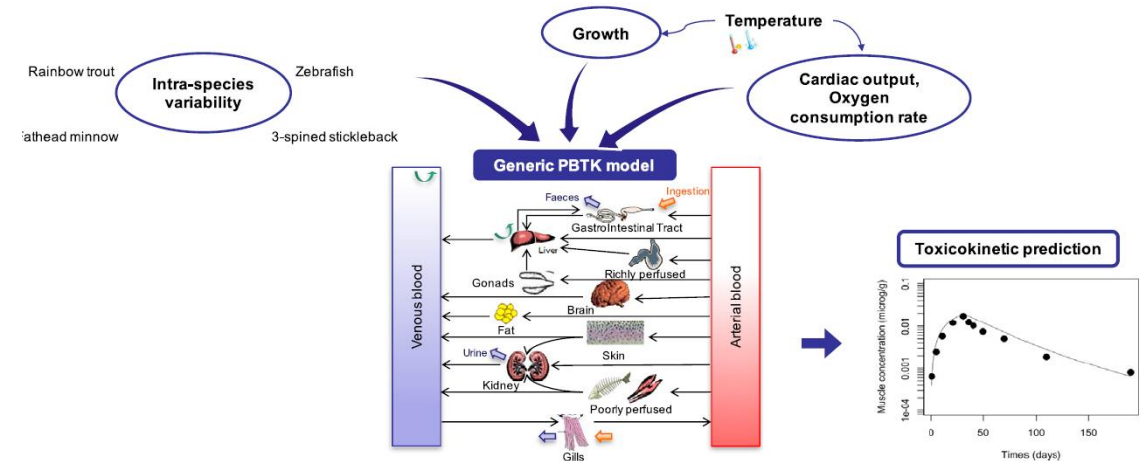
- All Data and models integrated into a user-friendly platform
- Predict TK and TD properties and accelerate the RA process

Open source PBK models in 4 Fish species@EFSA



Generic physiologically-based toxicokinetic modelling for fish: Integration of environmental factors and species variability

Audrey Grech^{a,b,c}, Cleo Tebbi^a, Céline Brochot^a, Frédéric Y. Bois^a, Anne Bado-Nilles^c, Jean-Lou Dorne^d,
Nadia Quignot^b, Rémy Beaudouin^{a,c,*}

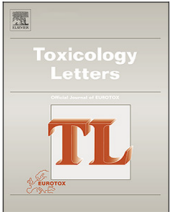




Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet



Generic physiologically based kinetic modelling for farm animals: Part II. Predicting tissue concentrations of chemicals in swine, cattle, and sheep

L.S. Lautz^{a,*}, S. Hoeks^a, R. Oldenkamp^a, A.J. Hendriks^a, J.L.C.M. Dorne^b, A.M.J. Ragas^{a,c}

^a Department of Environmental Science, Radboud University Nijmegen, Houtlaan 4, 6525 XZ, Nijmegen, the Netherlands

^b European Food Safety Authority, Via Carlo Magno 1A, 43126, Parma, Italy

^c Department of Science, Faculty of Management, Science & Technology, Open University, 6419 AT, Heerlen, the Netherlands

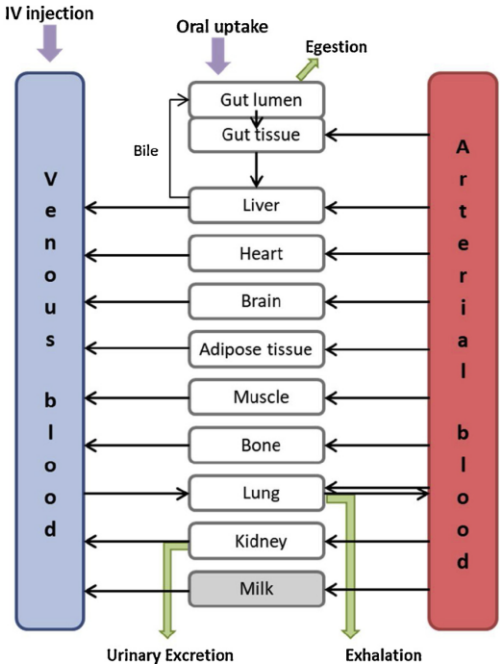


Fig. 1. Schematic description of the PBK model developed for cattle, sheep, and swine. Uptake and excretion sites are presented in the purple and green, respectively.

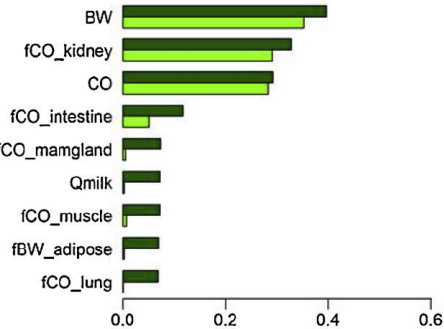
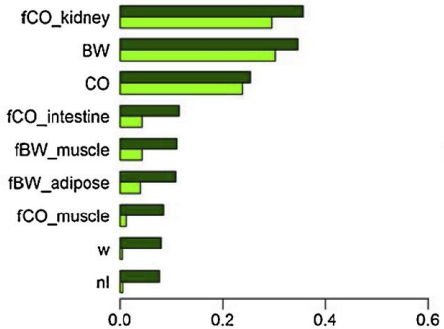
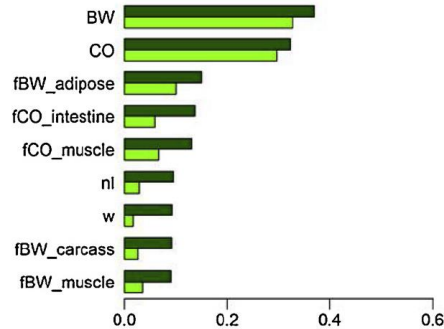
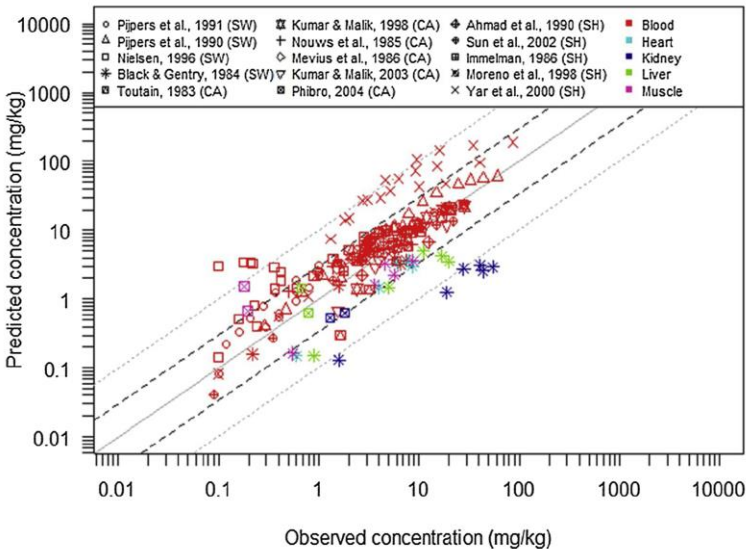


Fig. 5. Sensitivity analysis of the cattle (upper panels), sheep (middle panels) and swine (lower panels) PBK model applied to oxytetracycline.

- New data requirements for pesticides (283/284 2013) : Compare in vitro metabolism rat/human

➤ Collaborative case studies with national/international (2016-2020):

1. Use of human *in vitro* metabolism data and QIVIVE models in RA
2. Prediction of human kinetics for compounds relevant to EFSA panels (e.g. pesticides, contaminants, food additives, botanicals)



Metabolism of triflururon in the human liver: Contribution of cytochrome P450 isoforms and esterases

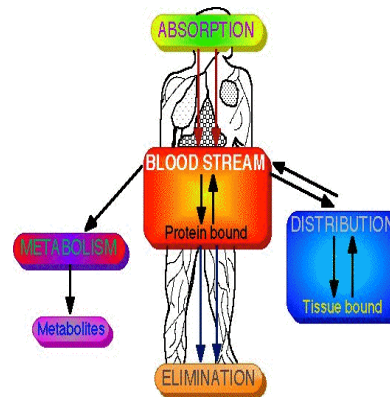
Rim Timoumi^{a,b}, Franca M. Buratti^{c,*}, Salwa Abid-Essefi^a, Jean-Lou C.M. Dorne^d, Emanuela Testai^c

^a Laboratory for Research on Biologically Compatible Compounds, Faculty of Dental Medicine, University of Monastir, Rue Avicenne, 5019, Monastir, Tunisia

^b Higher Institute of Biotechnology of Monastir, Avenue Taher Hadad 5000, Monastir, Tunisia

^c Istituto Superiore di Sanità, Environment & Health Dept., Viale Regina Elena, 299, Roma, Italy

^d EFSA (European Food Safety Authority), Via Carlo Magno, 1A, Parma, Italy



Inter-ethnic differences in CYP3A4 metabolism: A Bayesian meta-analysis for the refinement of uncertainty factors in chemical risk assessment

Keyvin Darney^{a,*}, Emanuela Testai^b, Franca M. Buratti^b, Emma Di Consiglio^b, Emma E.J. Kasteel^c, Nynke Kramer^c, Laura Turco^b, Susanna Vichi^b, Alain-Claude Roudot^d, Jean-Lou Dorne^e, Camille Béchaux^a

^a Risk Assessment Department, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 14 rue Pierre et Marie Curie, Maisons-Alfort F-94701, France

^b Department of Environment and Health, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome RM, Italy

^c Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80177, 3508TD Utrecht, The Netherlands

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- Guidance on use of human *in vitro* metabolism studies to be developed by Pesticide panel (Nov 2019-2021)
- Take into account difference in metabolism for human risk assessment

- **TK plate** : Generic PBK and QIVIVE models for single compounds and mixtures in humans, farm animals and fish (**Prototype in 2020**)
- **OpenFoodTox 2.0**: Integrating Tox data and QSAR models (**2019-2022**)
- **Case studies** for interactions (humans, fish, bees etc)

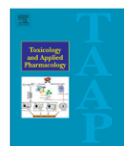
Toxicology and Applied Pharmacology 370 (2019) 184–195



Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap



Investigating the interaction between melamine and cyanuric acid using a Physiologically-Based Toxicokinetic model in rainbow trout

Cleo Tebby^a, Céline Brochot^a, Jean-Lou Dorne^b, Rémy Beaudouin^{a,c,*}

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

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Archives of Toxicology

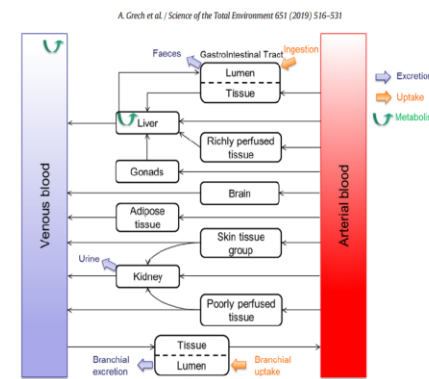
<https://doi.org/10.1007/s00204-018-2325-6>

TOXICOGENOMICS

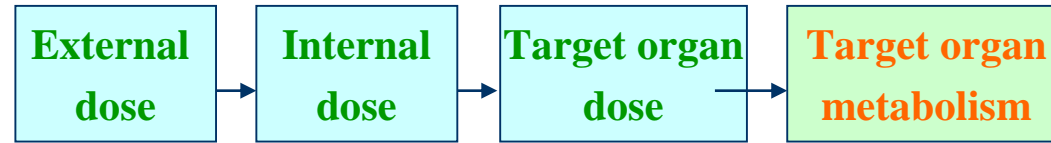


The Yin–Yang of CYP3A4: a Bayesian meta-analysis to quantify inhibition and induction of CYP3A4 metabolism in humans and refine uncertainty factors for mixture risk assessment

Nadia Quignot¹  · Witold Wiecek² · Billy Amzal¹ · Jean-Lou Dorne³



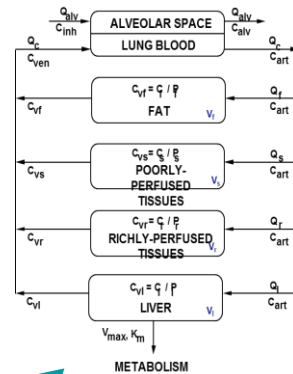
Building a TK platform for species of relevance



Physiological Data



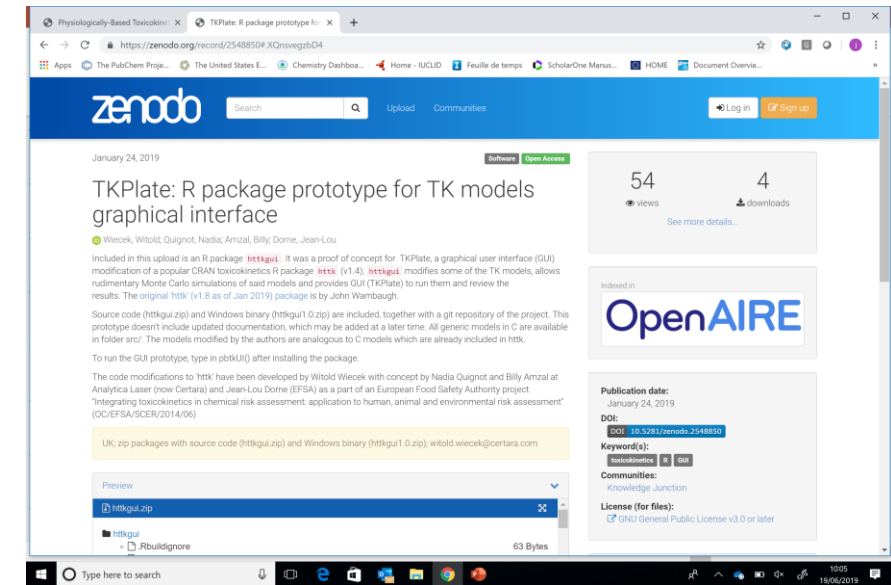
Chemical Specific –Data Exposure Physico-chemical Metabolism



Internal Dose TK parameters Tissue residues Reverse dosimetry

Species-specific TK Interspecies Differences Human Variability TKTD modelling

Sensitivity Uncertainty



In vitro metabolism

Toxicology Letters 312 (2019) 173–180

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet



Metabolism of triflururon in the human liver: Contribution of cytochrome P450 isoforms and esterases

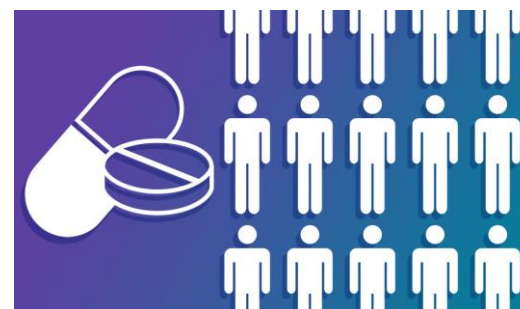
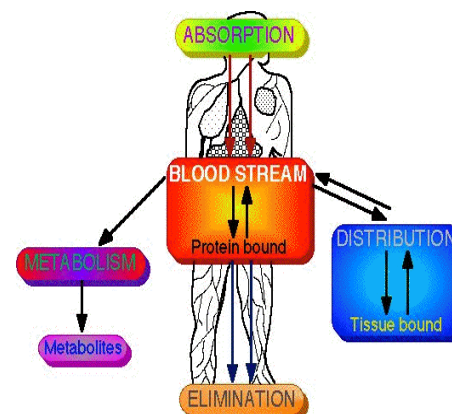
Rim Timoumi^{a,b}, Franca M. Buratti^{c,*}, Salwa Abid-Essefi^a, Jean-Lou C.M. Dorne^d, Emanuela Testai^c

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In vivo variability/ uncertainty

Computational Toxicology 12 (2019) 100092

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox



Inter-ethnic differences in CYP3A4 metabolism: A Bayesian meta-analysis for the refinement of uncertainty factors in chemical risk assessment

Keyvin Darney^{a,*}, Emanuela Testai^b, Franca M. Buratti^b, Emma Di Consiglio^b, Emma E.J. Kasteel^c, Nynke Kramer^c, Laura Turco^b, Susanna Vichi^b, Alain-Claude Roudot^d, Jean-Lou Dorne^e, Camille Béchaux^a

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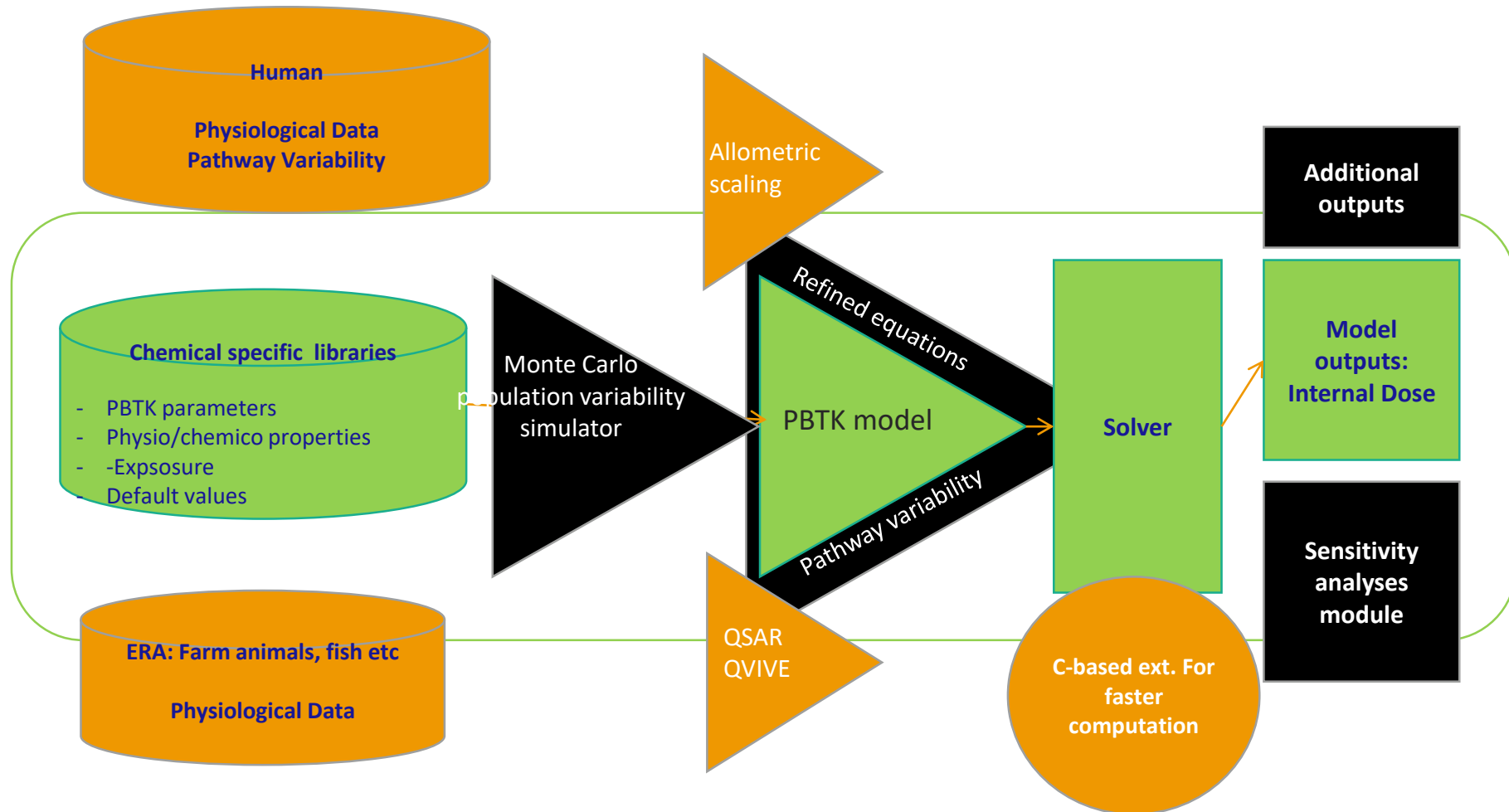
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MODELLING WORKFLOW



- APCRA “Accelerating the Pace of Chemical Risk Assessment”
- Created under the lead of US-EPA together with EFSA, ECHA, Health Canada, NTP and other agencies (Japan, Singapore etc.).
- Aims to provide 1. Common understanding of NAMs (regulatory contexts and examples), 2. Master list of common chemicals of interest for ongoing and future NAM applications, 3. Potential sources of NAM information for sharing and use. 4. Develop and share case studies of mutual interest.
- Desired outcomes 1. Address data gaps in existing evaluations, 2. Evaluate data poor chemicals, 3. screening and prioritisation 4. Acceleration of the pace of assessments and risk-based evaluations.
- Yearly meetings in the US, Europe, Canada with the next meeting planned for October 2019 in Research Triangle Park US-EPA

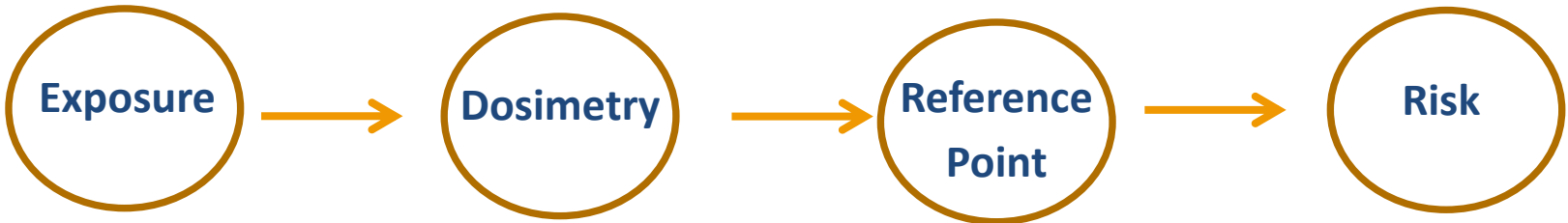
- Successful collaborations within ACPRA
 - US-EPA led Case study (2017): How conservative are *in vitro* predictions compared with *in vivo* point of departures (PODs) ?
 - Cooperation with Health Canada, ECHA, ECHA and others.
 - EFSA's support
 1. Regular conference calls,
 2. Curated *in vivo* Tox data for relevant compounds from OpenFoodTox,
 3. Description OpenFoodTox

Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman*, Matthew Gagne[†], Lit-Hsin Loo[‡], Panagiotis Karamertzanis[§], Tatiana Netzeva[§], Tomasz Sobanski[§], Jill Franzosa[¶], Ann Richard*, Ryan Lougee*, Andrea Gissi[§], Jia-Ying Joey Lee[‡], Michelle Angrish^{||}, Jean-Lou Dorne^{|||}, Stiven Foster^{||||}, Kathleen Raffaele^{||||}, Tina Bahadori^{||}, Maureen Gwinn*, Jason Lambert*, Maurice Whelan^{IV}, Mike Rasenberg[§], Tara Barton-Maclaren[†], Russell S. Thomas*

- Sharing opensource databases + relevant models
- Joint case studies and training. Illustrate NAM applications (human, animals, ecology) incl. *in vitro* data, metabolism and TK modelling, OMICs, biomonitoring and risk-based evaluations.
- Identify common mid-term and long-term priority areas for collaboration for new tools and case studies
 1. TK models for all test species in regulatory area,
 2. Tools integrating state of the art information (in vitro, AOP, OMICs etc.) ?,
 3. Common guidance documents
- PhD Programmes ?
- Feedback proposal from focal point ?

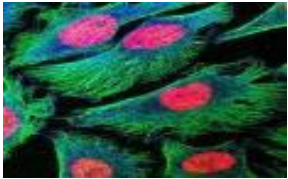
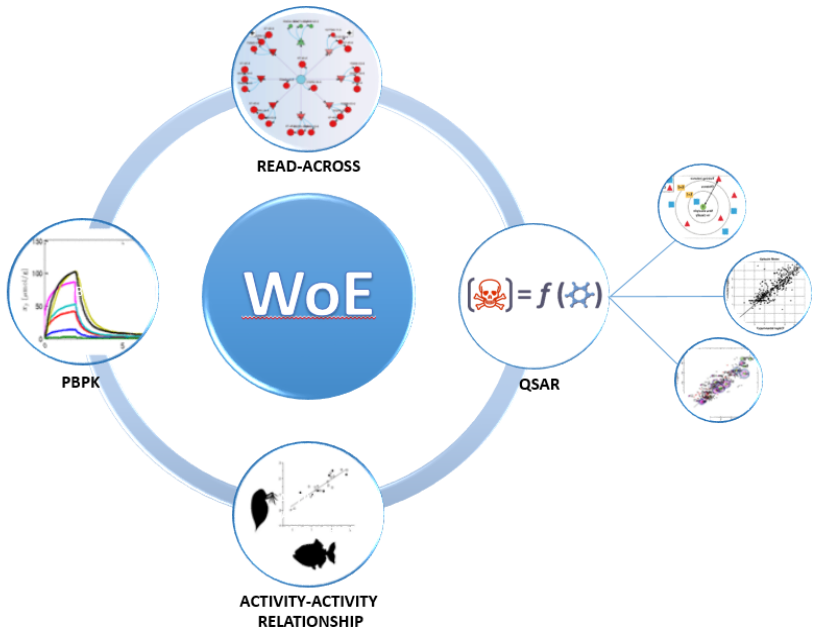
Integrating State Of The Art Methods And Data Streams



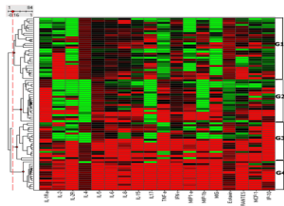
*OpenFoodTox and
MATRIX*



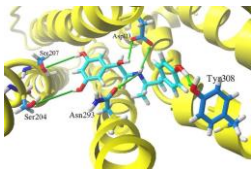
*Epidemiological
Data*



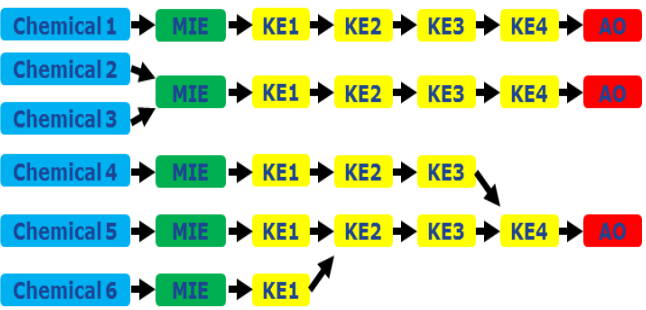
In vitro



OMICS



In Silico



AOP/MoA

- **Open source Tools support risk assessment**

- Reduce animal testing
- Train current and next generation of Risk Assessors

- **TKPlate**

- Support Open source models for RA community
- Open source models on EFSA knowledge junction (Zenodo)
- Further development: Range of test species + case studies
- Training staff and RA community

- **Future Collaboration with Member States**

Sharing data, models, developing common case studies ?

- **New speciality section in EUROTOX: IN²TOX (*In vitro in silico*)**

Kick off 9 Sep 2019 Helsinki



➤ **Data collection, Modelling, TK platform**

- CERTARA Paris, London;
- INERIS, Paris, France;
- Radboud University, Nijmegen, The Netherlands;
- ISS, Rome, Italy;
- University of Utrecht, The Netherlands,
- ANSES, Paris;
- Open Analytics, Antwerp, Belgium
- EFSA: Jose Cortinas-Abrahantes



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