OpenFoodTox and other Open Source *In silico* Tools @ EFSA

Jean Lou Dorne
Senior Scientific Officer
Scientific Committee and Emerging Risks Unit
EFSA

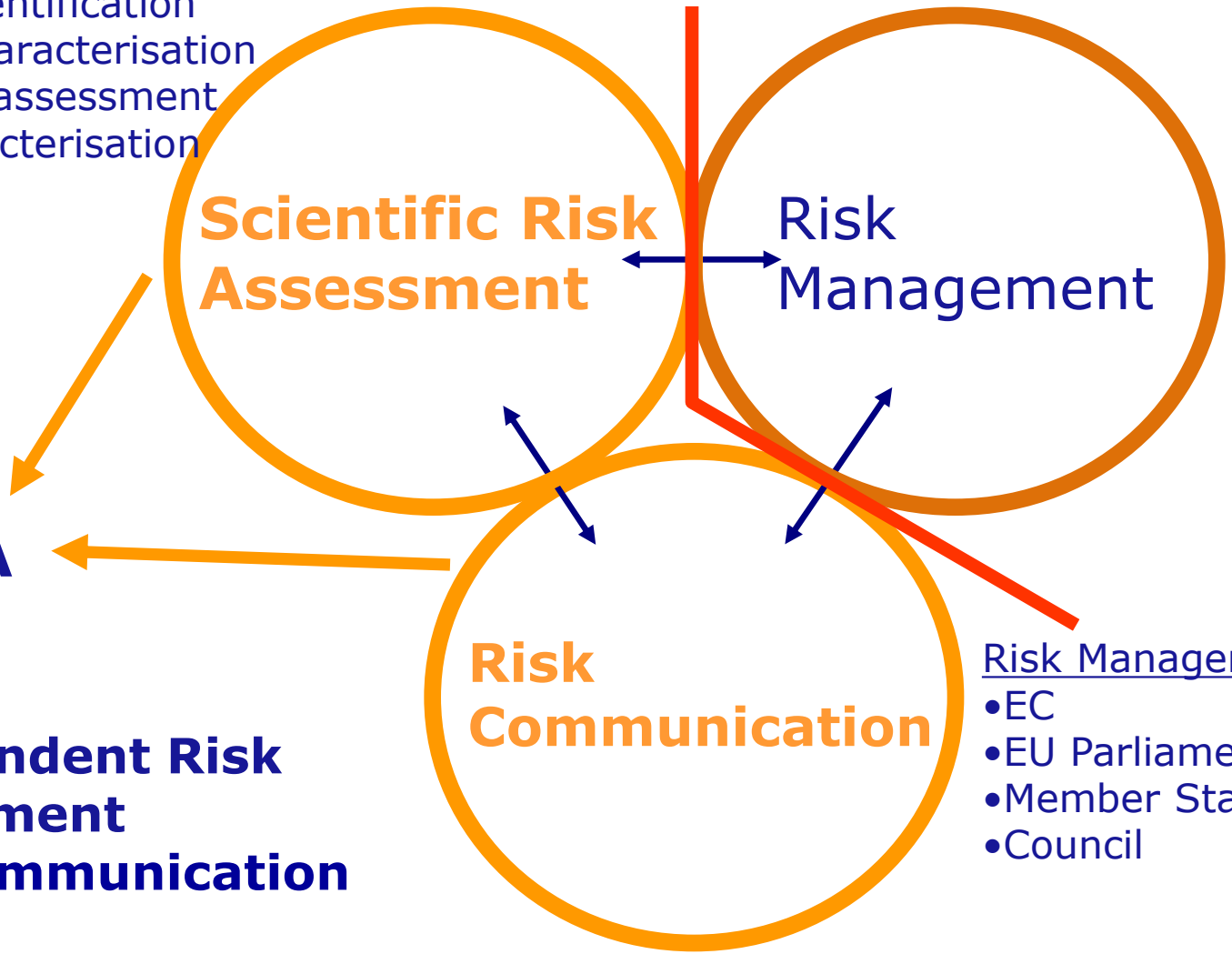
Summer School
"In silico methods in food safety"
14th June 2017

efsa
European Food Safety Authority

EFSA's Role in Risk Analysis

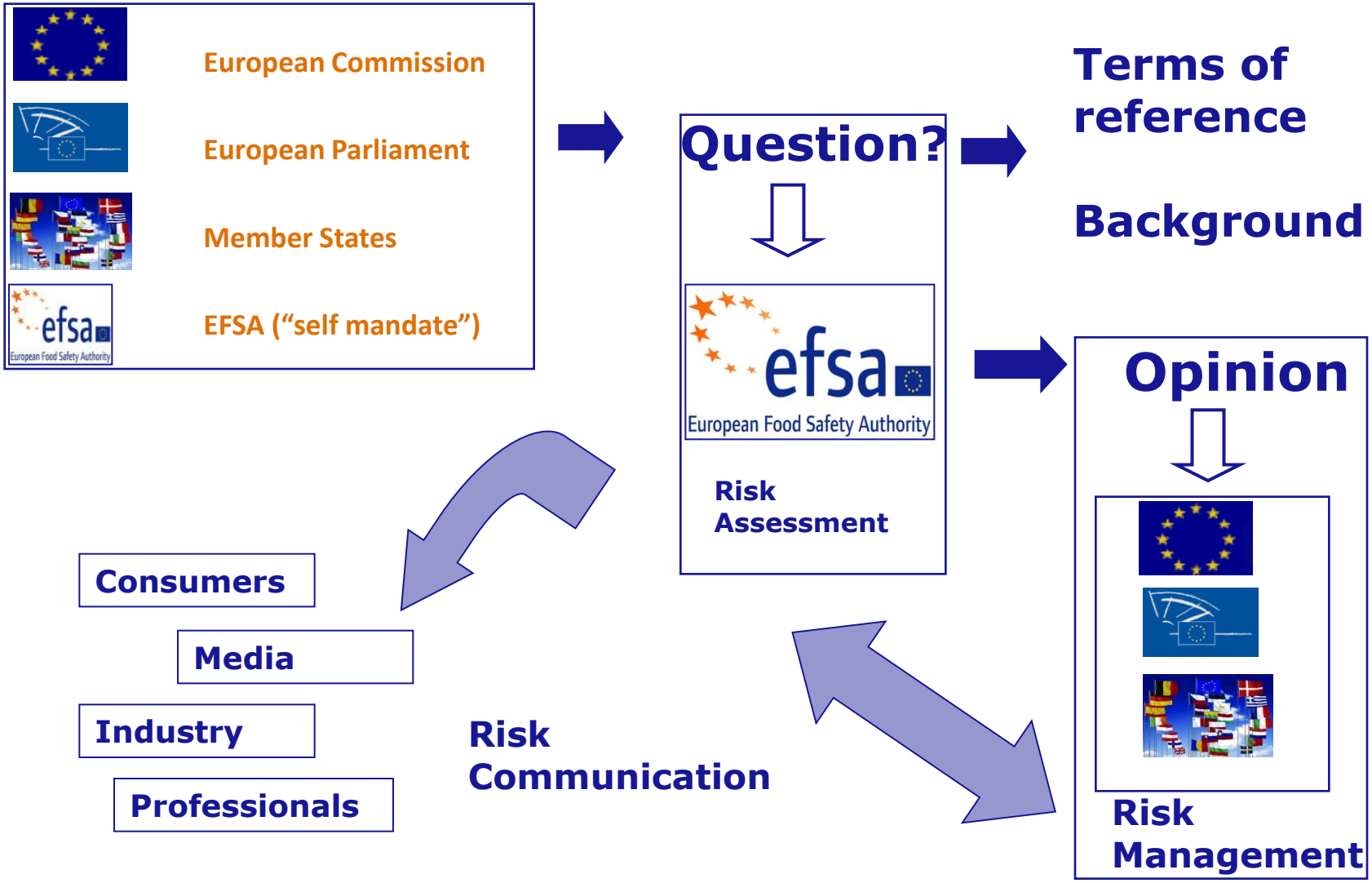
Methodology Codex Alimentarius:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation

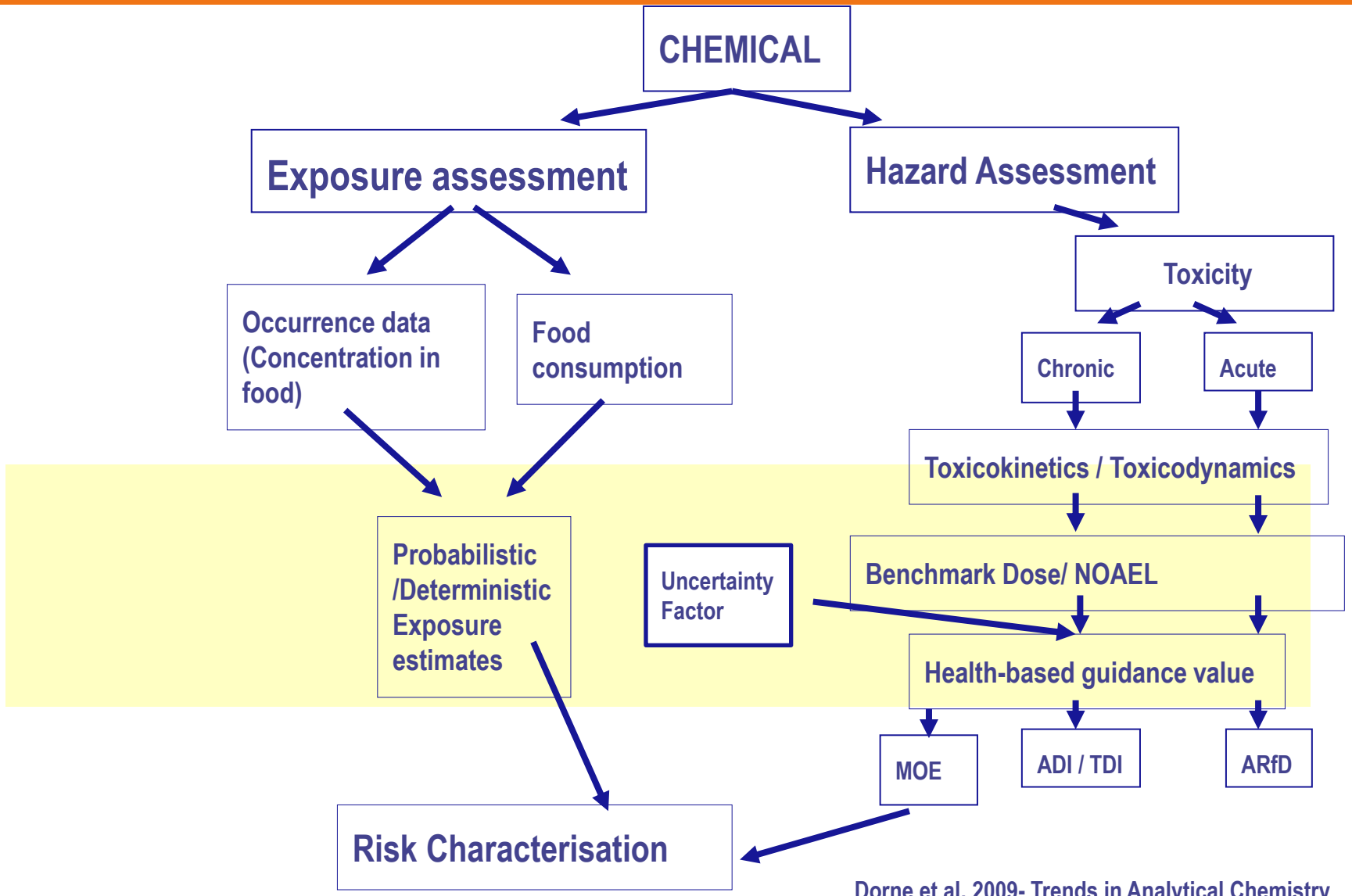


- **Independent Risk Assessment**
- **Risk communication**

FROM QUESTION TO ANSWER



IN A NUTSHELL…



Dorne et al, 2009- Trends in Analytical Chemistry

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

PARACELSUS (1493-1541)

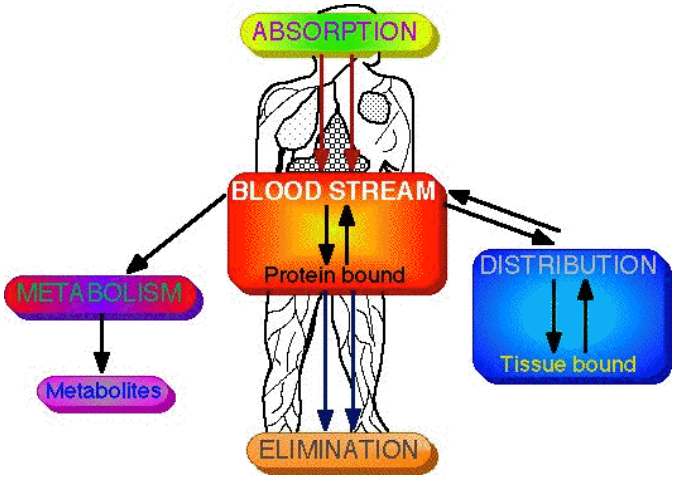
Toxicology

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

Toxicokinetics

What the body does to a chemical

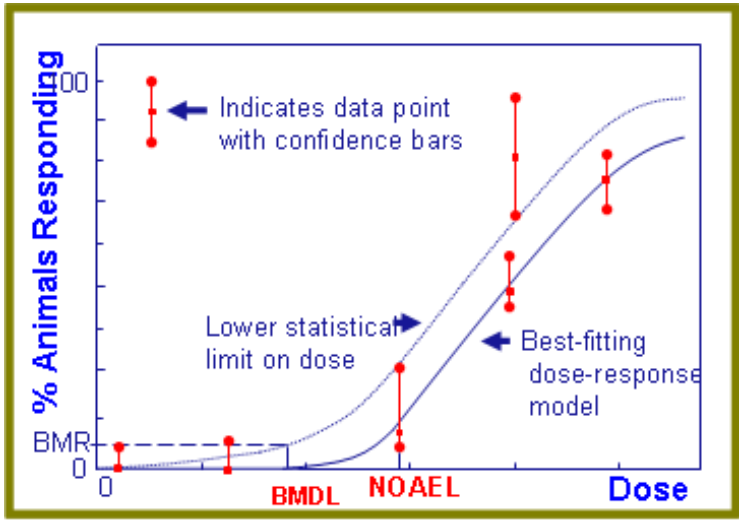
How the chemical is eliminated from the body or activated into a toxic species (ADME)



Toxicodynamics

What a chemical does to the body

How the chemical exerts its toxicity target receptor/cell/organ



EDITORIAL

EFSA Journal

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

Scientific assessments are evidenced-based and demand rigorous methodologies to collect, evaluate and integrate scientific evidence, together with transparent and open communication of the processes and results of the assessment. A structured and clearly documented approach is essential if the outcome of the scientific assessment is to be communicated unambiguously to decision makers, the wider scientific community and stakeholders. This will help to clearly focus on key issues and allow reproducibility of the assessments between expert groups and organisations.

Scientific advisory bodies recognise a need to improve the transparency and openness of scientific assessments in line with today's normative and societal expectations. Open scientific assessment can be defined as a decision support process where there is not only full transparency (showing what has

DATA/EVIDENCE AVAILABLE IN CHEMICAL RA

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurence	**Consumption**	**TK**	**TD**	**TK**	**TD**	
0	Semi-Q	Default values	No data	No data	*in silico* Read across	Default values TTC Read across *In silico* Default UF	e.g. Default values Qualitative
1	Point estimates	Point estimates in food categories	*In silico* Limited data Semi-Q	*In silico* Limited data Read across	*in silico* Basic TK Read across	*in silico* Read across NOAEL Default UF	e.g. Semi-quantitative
2	Measured data	Measured in some food categories	Dossier data Qttve	Dossier Data	*in silico* ADME data	NOAEL/ BMDL Default *in silico* UF	e.g. Quantitative Deterministic/ Probabilistic
3	Large measured dataset	Full patterns - food categories	Dossier and/or lit. (*in vitro*, *in vivo*)	Data in dossier and/or lit. (*in vitro*, OMICs, epi)	MoA/AOP, Epi data, PB-PK model, BBDR, BMDL Chemical specific adjustment factor (CSAF)		e.g. Quantitative Full probabilistic

DATA FROM DOSSIER: REGULATED PRODUCT

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurence	Consumption	TK	TD	TK	TD	
2	Measured data	Measured in some food categories	Dossier data Qttve	Dossier Data: genotox, tox	*in silico* ADME data	NOAEL/ BMDL Default UF	e.g. Quantitative Deterministic/ Probabilistic

DATA-RICH CHEMICAL: CADMIUM

Tier	Exposure Assessment		Hazard identification		Hazard charact		Risk Characterisation
	Occurence	Consumption	TK	TD	TK	TD	
3	Large measured dataset	Full patterns - food categories	Human Data Biomarker excretion/ blood	Human data Biomarker renal toxicity	PB-PK-BMDL (Human data) Chemical specific adjustment factor (CSAF)		e.g. Quantitative Full probabilistic

DATA-POOR: EMERGING MYCOTOXIN

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurence	Consumption	TK	TD	TK	TD	
0	Semi-Q	Default values	No data	No data	*in silico* Read across	Default values TTC Read across *In silico* Default UF	e.g. Default values Qualitative

OpenFoodTox: EFSA's Open Source Hazards Database

OPENFOODTOX: EFSA' S CHEMICAL HAZARDS DATABASE

- **Catalogue of EFSA's chemical toxicity data since creation**

  -Contaminants (Human and Animal health)

  -Vitamins and minerals (Human health) (NDA),

  -Food additives and Nutrient Sources, Food contact materials, Flavourings and processing aids (Human Health)

  -Feed Additives (Human and Animal Health, Ecotoxicology)

  -Pesticides (Human and Animal health, Ecotoxicology)

- **Easy Reference and Crisis**

  -One reference DB Chemical Hazards: Search easily and efficiently

  -Crisis: Quick and Easy access to all EFSA's Hazard Data

- **International Harmonisation**

  - Use OECD Harmonised Templates (OHT) for data model (ECHA/OECD) compatible with IUCLID/ ECHA-OECD QSAR toolbox

  -Search compounds by name, CAS number on e-chem portal

  -Generate data sheet as summary of hazard id and charact (June 2016)

WHAT DOES OPENFOODTOX CONTAIN ?

- **Chemical Information**

Information on chemical nomenclature (EU nomenclature, IUPAC, CAS...), trade name, chemical group/panel (i.e. pesticide), chemical use (i.e fungicide), chemical structure (i.e triazoles, organophosphates….).

- **Document descriptors**

Information on EFSA's opinion for the specific chemical or group of chemicals. Info from EFSA 's RAW system (question number, mandate, number), link to the document

- **Toxicity Endpoint/ Hazard identification**

Information on critical toxicity study using OECD picklists when possible (species, dose, target organ…)

- **Critical study to demonstrate genotoxicity status**

Providing essential information of critical genotoxicity study when assessed

- **Hazard /Risk characterisation**

Information for health based guidance values (ADI/TDI) uncertainty factors…

TOWARDS AN OPENSOURCE HAZARD DATABASE

Tier	Exposure Assessment		Hazard identification		Hazard characterisation		Risk Characterisation
	Occurence	**Consumption**	**TK**	**TD**	**TK**	**TD**	
0	Semi-Q	Default values	No data	**No data**	*in silico* Read across	**Default values TTC *In silico***	e.g. Default values Qualitative
1	Point estimates	Point estimates in food categories	*In silico* Limited data Semi-Q	***In silico* data Read across**	*in silico* Basic TK Read across	***in silico* NOAEL Default UF**	e.g. Semi-quantitative
2	Measured data	Measured in some food categories	Dossier data Qttve	**Dossier Data**	*in silico* ADME data	**NOAEL/ BMDL Default *in silico* UF**	e.g. Quantitative Deterministic/ Probabilistic
3	Large measured dataset	Full patterns - food categories	Dossier and/or lit. (*in vitro*, *in vivo*)	**Dossier and/or lit. (*in vitro*, OMICs, Epi)**	**MoA/AOP, Epi data, PB-PK model, BBDR, BMDL, CSAF**		e.g. Quantitative Full probabilistic

CONTENT

Microstrategy Tool: https://dwh.efsa.europa.eu/bi/asp/Main.aspx?rwtrep=400

Full Download Knowledge junction: https://zenodo.org/record/344883#.WUDqK_mGPIU

1,650 Scientific outputs (metadata + DOI)

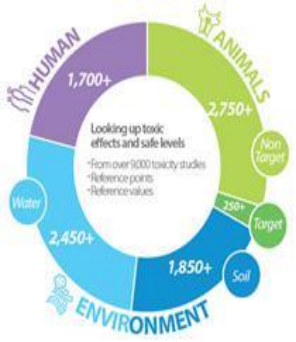
4,400 Substances (chemical identifiers including SMILES)

10,000 Toxicological endpoint studies

140 Positive genotoxicity studies

12,000 risk assessment summaries

Use OpenFoodTox for



FILTER

Substance Browser

Sub Name (4352)

- (All)
- (-)-3,7-Dimethyl-6-octen-1-ol
- (-)-Alpha-cedrene
- (-)-Alpha-elemol
- (-)-alpha-Santalene
- (-)-Bornyl acetate
- (-)-Hyoscyamine and (-)-Sc...
- (-)-Rhodinol
- (-)-Scopolamine
- ((E)-2-(2-hydroxymethylphe...
- ({2-[(2-Ethyl-6-methylpheny...
- ({2-[(Ethoxymethyl)(2-ethyl-...
- (+)-Alpha-cedrene
- (1R,2R,5S) 5-Isopropenyl-2...
- (1R,2R,5S)-Isodihydrocarveol
- (1R,2S,5R)-5-methyl-2-(1-m...
- (1R,2S,5R)-Menthyl hexan...
- (1R,2S,5R)-Menthyl salicyl...
- (1R,2S,5R)-N-(2-(Pyridine-2...
- (1R,2S,5R)-N-(4-Methoxyp...
- (1R,2S,5R)-N-[(Ethoxycarb...
- (1R,2S,5R)-N-Cyclopropyl-...
- (1R,2S,5R)N,N-Dimethyl m...
- (1R,2S,5S)-3-Menthoxy-2-...
- (1R,2S,5S)-neo-Dihydrocar...

Substance Characterisation

Substance	has	Component	CAS Number	EC Ref No	Molec formu
(-)-3,7-Dimethyl-6-octen-1-ol	as such	(-)-3,7-Dimethyl-6-octen-1-ol	7540-51-4	231-415-7	C10H2
(-)-Alpha-cedrene	as such	(-)-Alpha-cedrene	469-61-4	207-418-4	C15H2

EFSA outputs

Substance	Output Id	Legal Basis	Panel	Published	Title
(-)-3,7-Dimethyl-6-octen-1-ol	2180	Commission Regulation (EC)	EFSA CEF	02/20/2013	Scientific Opinion on Flavouring Group Revision 4 (FGE.06Rev4): Straight- ar

Hazard Characterisation: Reference points

Substance	Author	Year	Output ID	Study	Test Type	Species	Route	Duratio (days)
(-)-Hyoscyamine and (-)-Scopolamine group	EFSA CONTAM	2013	2396	Human health	study with volunteers	Human	Not reported	
(1R,2S,5R)-N-(2-(Pyridine-2-yl)ethyl)-3-p-menthanecarboxamide	EFSA CEF	2014	2524	Human health	subchronic	Rat	oral: feed	90

Hazard Characterisation: Reference values

Substance	Author	Year	Output Id	Assessment	qualifier	value	unit
(-)-3,7-Dimethyl-6-octen-1-ol	EFSA CEF	2013	2180	TTC Cramer Class I	=	30	µg/kg bw/day
(-)-Alpha-elemol	EFSA AFC	2006	2232	TTC Cramer Class I	=	30	µg/kg bw/day

Genotoxicity

Substance	Author	Year	Output Id	Genoto
9,10-Dihydroxy stearic acid oligomers	EFSA AFC	2003	344	Not det
Acrylic acid, methyl ester, telomer with 1-dodecanethiol, C16-C18 alkyl esters	EFSA AFC	2003	344	Negativ

Open Source in silico Tools to Quantify Toxicological Processes

OPENFOODTOX AND *IN SILICO* TOOLS

- Case studies to develop *in silico* tools
  - QSAR model on pesticide Toxicity in bees (OpenFoodTox, US-EPA, DEMETRA DB) : Classifier
  - QSAR model to predict LC_{50} in rainbow trout (OpenFoodTox) : Continuous model

-Physico-chem properties, structure, toxicity : R^2 >0.75

  - QSAR model to predict NOAEL in rats (OpenFoodTox, Fraunhofer) : Continuous model

-Physico-chem properties, structure, toxicity : R^2 >0.75

- Scientific report Summer 2017
  - QSAR model to predict NOAEL for liver toxicity in rats (OpenFoodTox, Fraunhofer) : Continuous model

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

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

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
OECD
Monte Carlo method
Rainbow trout
Toxicity
CORAL software

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 used, taken from the EFSA's chemical Hazards Database: OpenFoodTox. Optimal descriptors are preparing from simplified molecular input-line entry system (SMILES). So-called, correlation weights of different fragments of SMILES are calculating by the Monte Carlo optimization procedure where correlation coefficient between endpoint and optimal descriptor plays role of the target function. Having maximum of the correlation coefficient for the training set, one can suggest that the optimal descriptor calculated with these correlation weights can correlate with endpoint for external validation set. This approach was checked up with three different distributions into the training (≈85%) set and external validation (≈15%) set. The statistical characteristics of these models are (i) for training set correlation coefficient (r^2) ranges 0.72–0.81, and root mean squared error (RMSE) ranges 0.54–1.25; (ii) for external (validation) set r^2 ranges 0.74–0.84; and RMSE ranges 0.64–0.75. Computational experiments have shown that presence of chlorine, fluorine, sulfur, and aromatic fragments is promoter of increase for the toxicity.

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, *], Andrey A. Toropov[a], Marco Marzo[a], Sylvia E. Escher[b], Jean Lou Dorne[c], Nikolaos Georgiadis[c], 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] Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hannover, Germany
[c] Scientific Committee and Emerging Risks Unit, European Food Safety Authority, Via Carlo Magno 1A, 43126 Parma, Italy

ARTICLE INFO

Article history:
Received 11 November 2016
Received in revised form 16 March 2017
Accepted 28 March 2017
Available online xxx

Keywords:
QSAR
NOAEL
OECD principles
Monte Carlo method
CORAL software

ABSTRACT

Continuous QSAR models have been developed and validated for the prediction of no-observed-adverse-effect (NOAEL) in rats, using training and test sets from the Fraunhofer RepDose® database and EFSA's Chemical Hazards Database: OpenFoodTox. This paper demonstrates that the HARD index, as an integrated attribute of SMILES, improves the prediction power of NOAEL values using the continuous QSAR models and Monte Carlo simulations. The HARD-index is a line of eleven symbols, which represents the presence, or absence of eight chemical elements (nitrogen, oxygen, sulfur, phosphorus, fluorine, chlorine, bromine, and iodine) and different kinds of chemical bonds (double bond, triple bond, and stereo chemical bond). Optimal molecular descriptors calculated with the Monte Carlo technique (maximization of correlation coefficient between the descriptor and endpoint) give satisfactory predictive models for NOAEL. Optimal molecular descriptors calculated in this way with the Monte Carlo technique (maximization of correlation coefficient between the descriptor and endpoint) give amongst the best results available in the literature. The models are built up in accordance with OECD principles.

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmac

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

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

Andrey A. Toropov[a], Alla P. Toropova[a,*], Marco Marzo[a], Jean Lou Dorne[b], Niko Emilio Benfenati[a]

[a] *Department of Environmental Health Science, Laboratory of Environmental Chemistry and Toxicology, IRCCS-Istituto di Ricerche Farma 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

ABSTRACT

Optimal (flexible) descriptors were used to establish quantitativ toxicity of pesticides (n = 116) towards rainbow trout. A hetero

Contents lists available at ScienceDirect

Chemosphere

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

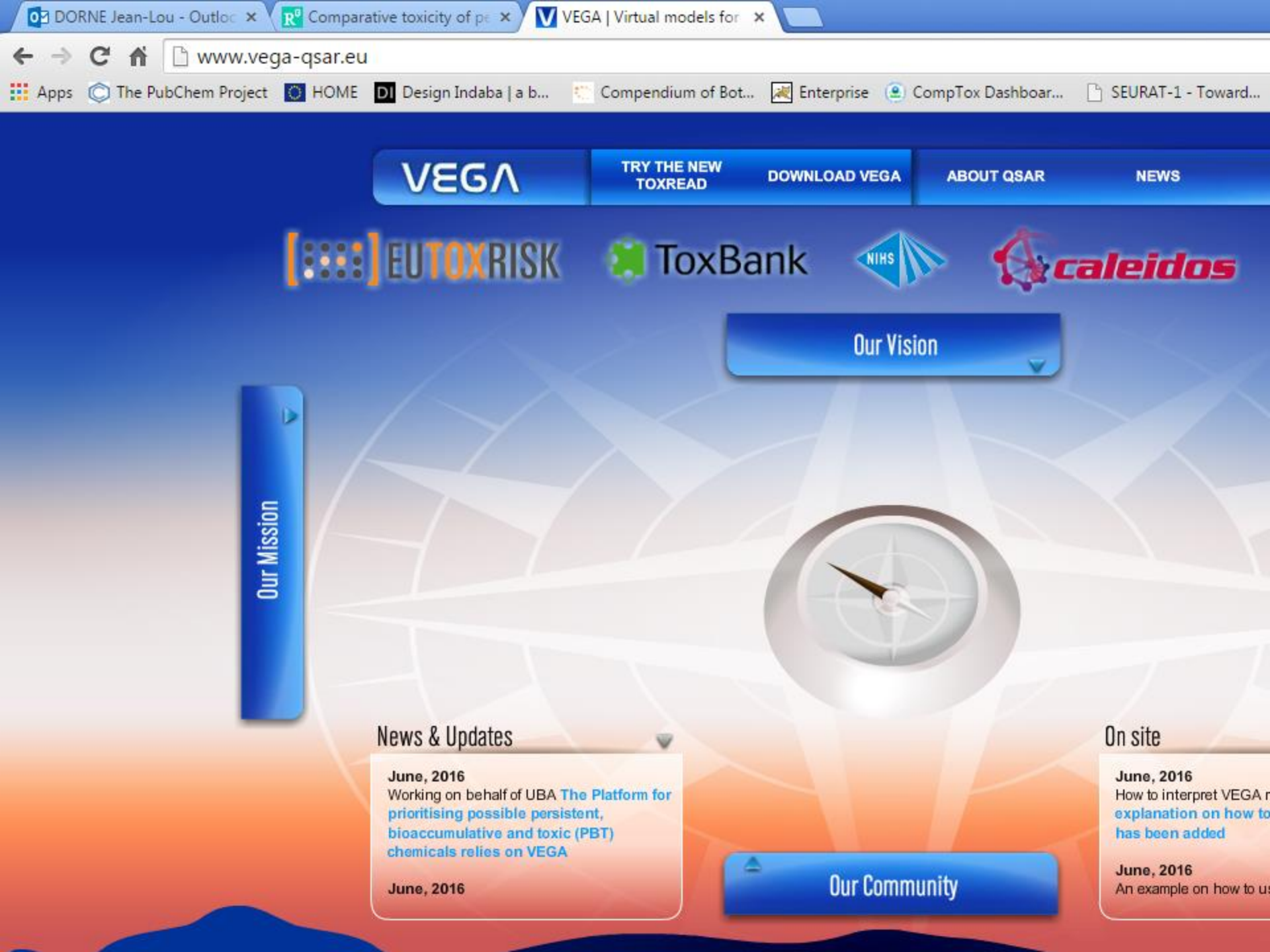
Predicting acute contact toxicity of pesticides in honeybees (*Apis mellifera*) through a k-nearest neighbor model

F. Como [a, *], E. Carnesecchi [b], S. Volani [b], J.L. Dorne [b], J. Richardson [b], A. Bassan [c], M. Pavan [c], E. Benfenati [a]

[a] *IRCSS Istituto di Ricerche Farmacologiche Mario Negri, via La Masa 19, 20146 Milano, Italy*
[b] *European Food Safety Authority, Via Carlo Magno 1A, 43126 Parma, Italy*
[c] *S-IN Soluzioni Informatiche S.r.l., via G. Ferrari 14, 36100 Vicenza, Italy*

HIGHLIGHTS

- A model to predict acute contact toxicity for bees was built for screening pesticides.
- The model developed will address future risk assessments of pesticides of concern.
- The accuracy of k-NN model is good and equal to 65% for the highly toxic compounds.


DORNE Jean-Lou - Outloc
Comparative toxicity of pe
VEGA | Virtual models for
www.vega-qsar.eu
Apps
The PubChem Project
HOME
Design Indaba | a b...
Compendium of Bot...
Enterprise
CompTox Dashboar...
SEURAT-1 - Toward...
VEGA
TRY THE NEW TOXREAD
DOWNLOAD VEGA
ABOUT QSAR
NEWS
EUTOXRISK
ToxBank
NIHS
caleidos
Our Vision
Our Mission
News & Updates
June, 2016
Working on behalf of UBA The Platform for prioritising possible persistent, bioaccumulative and toxic (PBT) chemicals relies on VEGA
June, 2016
Our Community
On site
June, 2016
How to interpret VEGA
explanation on how to
has been added
June, 2016
An example on how to u

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**

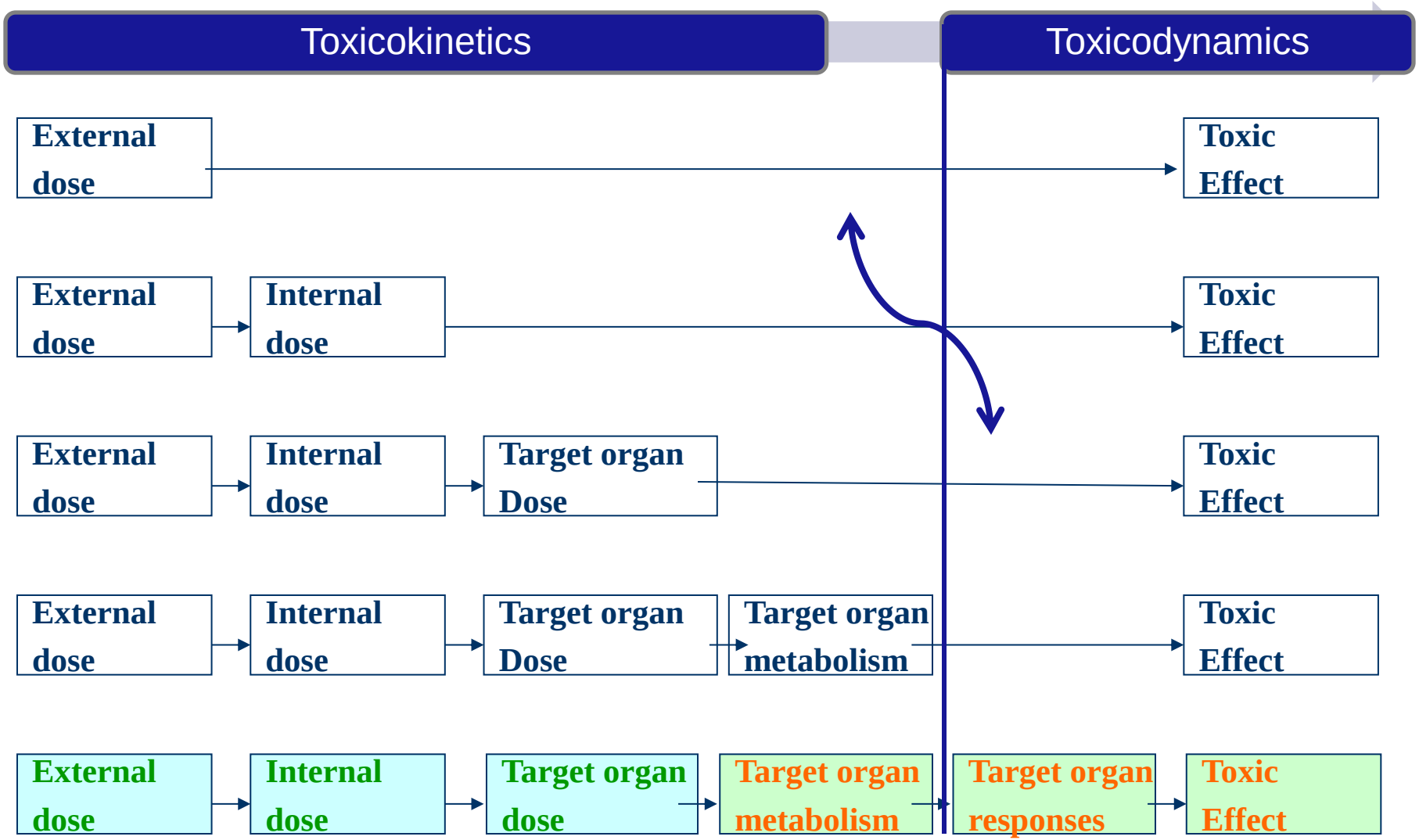
ABSTRACT

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

-Levels of Knowledge, Toxicokinetic and Toxicodynamic processes



New Data requirements for pesticides Regulation 283- 284/2013 : TK Data

In vivo TK studies in animals

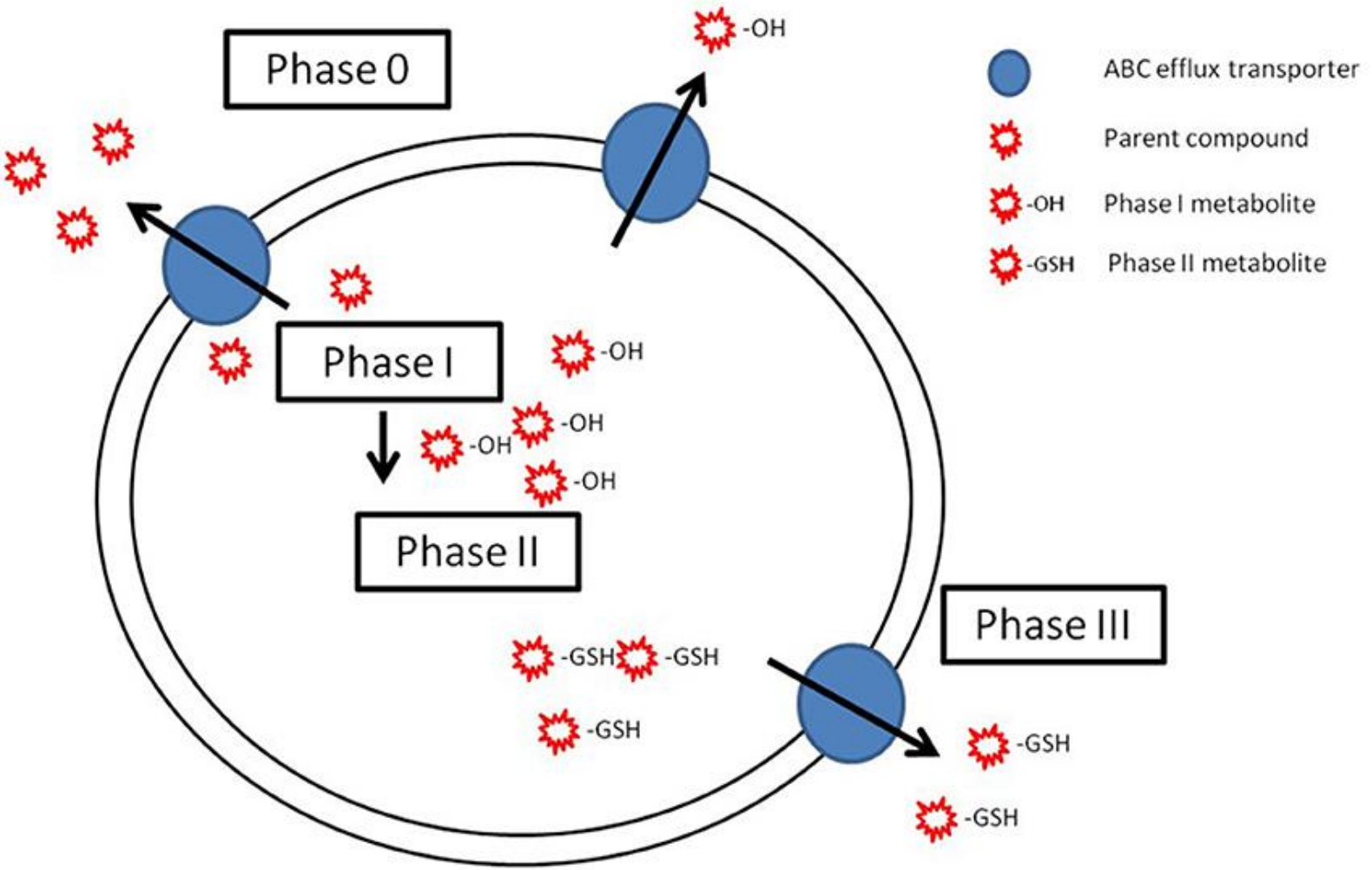
- ✓ Blood/ tissues [C] for active substance/relevant metabolites ($C_{max;}$ AUC) in relevant species understanding toxicity studies
- ✓ Investigating entero-hepatic circulation

Comparative Animal versus human microsomes or intact cell systems

Relevance animal tox -guide interpretation, further define testing strategy e.g. human *in vitro* metabolite not in test species

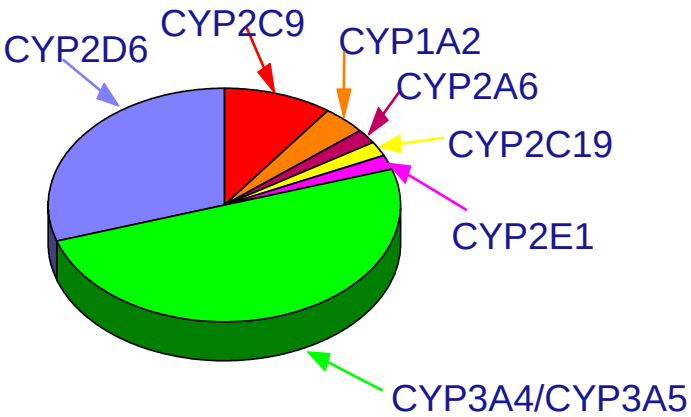
- ✓ Protocols available publicly incl. ECVAM work on developing TK standards
- ✓ *In vitro* models hepatic/ non-hepatic microsomes (e.g. intestinal)
- ✓ Major human metabolites (>10% of AD) not at sufficient levels in animal studies further investigated for their toxicity profile.

MAJOR METABOLIC/EXCRETION ROUTES IN HUMANS



MAJOR METABOLIC/EXCRETION ROUTES IN HUMANS

Phase I enzymes
Cytochrome P-450,
ADH, Esterases…



Phase II enzymes
Conjugation reactions

UDP-Glucuronyltransferases,
Sulphotransferases
Glutathione-s-transferases
Methyl-transferases
N-acetyltransferases
Amino acid conjugation

Transporters
Phase 0- Uptake transporters:
e.g OATPs, OCTs.

Phase III-Efflux pumps:
e.g ABCs (P-glycoproteins and MRPs)

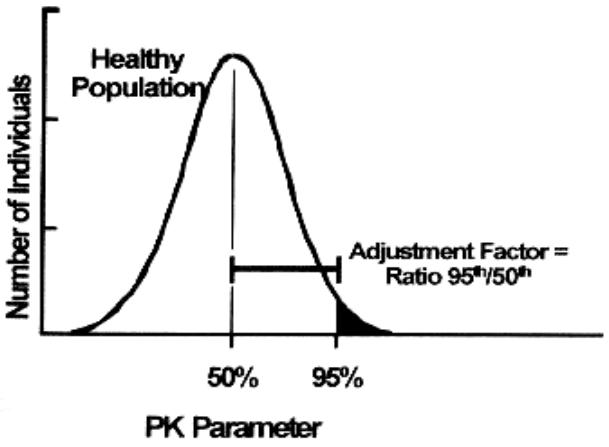
Renal excretion

-HUMAN VARIABILITY IN TOXICOKINETICS-

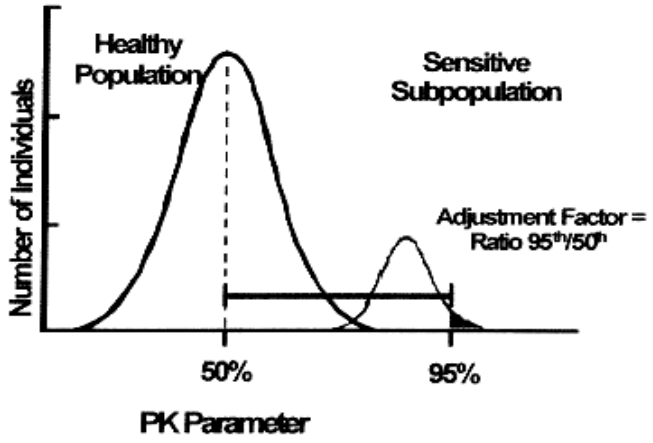
From pharmaceutical database and compounds relevant to food safety,

- ✓ *Identify Phase O, 1, 2, 3 isoforms in vitro , excretion data etc.*
- ✓ *PK parameters of acute and chronic exposure: Meta-analysis*
- ✓ *Human variability distributions -isoform specific for different subgroups of the population.*

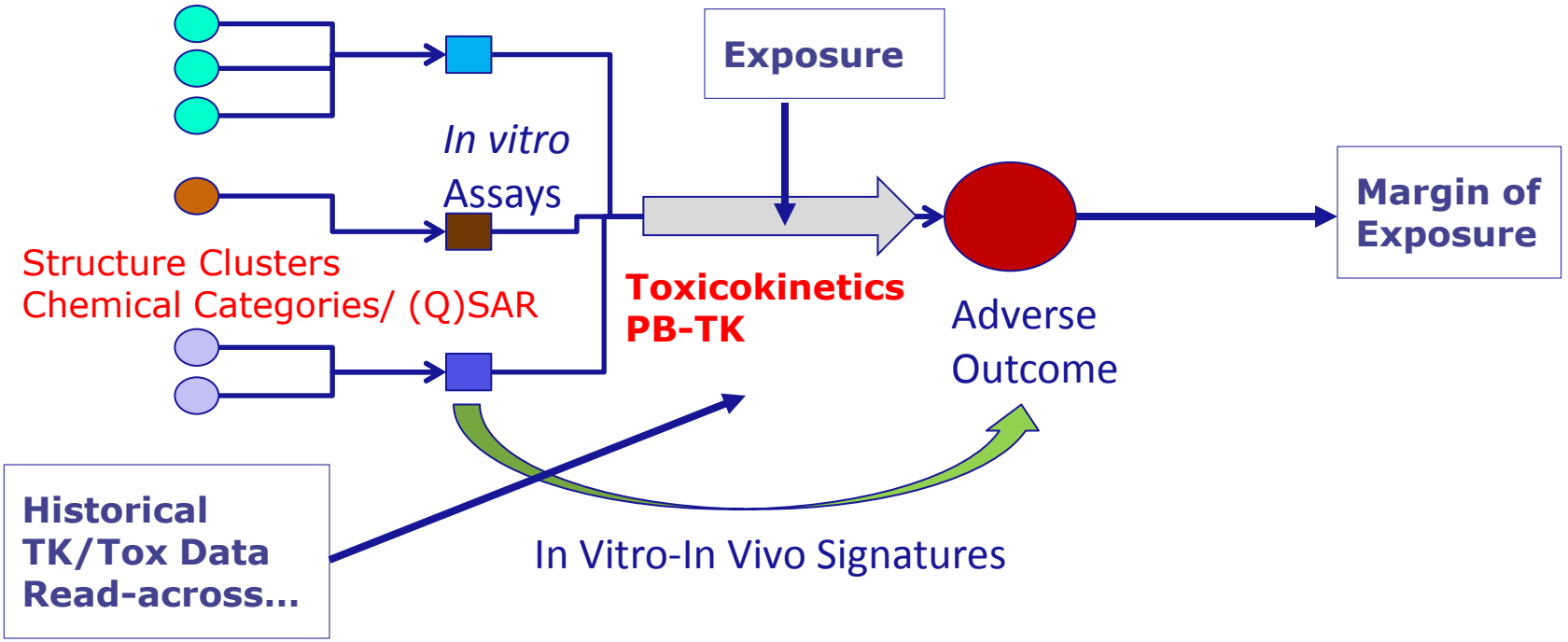
✓ **Unimodal Population**



Bimodal Population



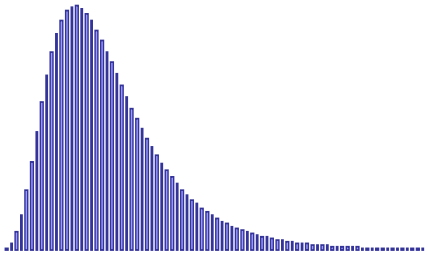
TK AND INTEGRATED TESTING STRATEGIES



Toxicokinetics

In vitro id isoforms phase I, II, transporters.
Consequences of metabolism id of toxic moiety(ies)
TK parameters (Vm,Km, Clint, Fu).
Use human Variability in TK from historical databases and software
IVIVE

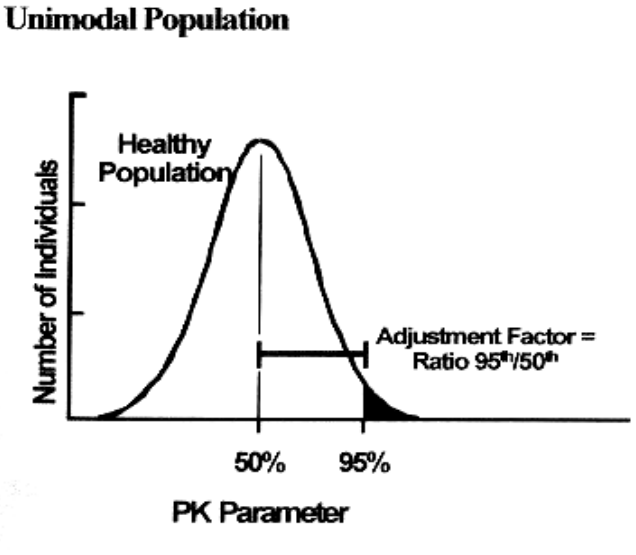
-HUMAN VARIABILITY IN TOXICOKINETICS AND UF-

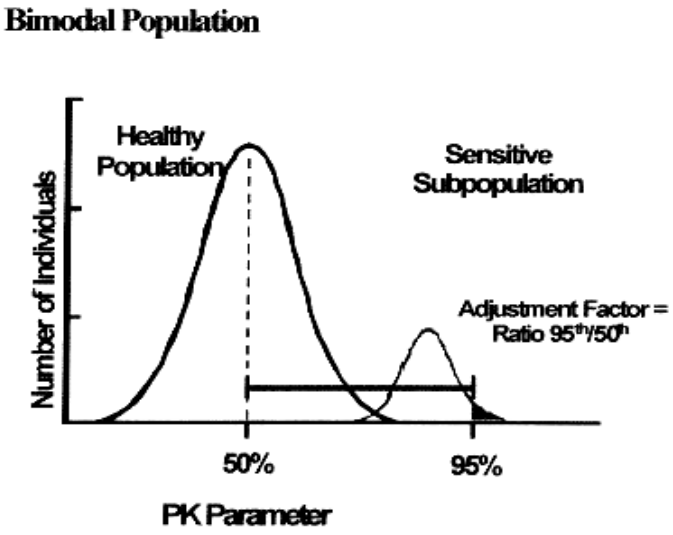


From pharmaceutical database human variability in TK available for many drugs /enzyme isoforms in different subgroups of the population.

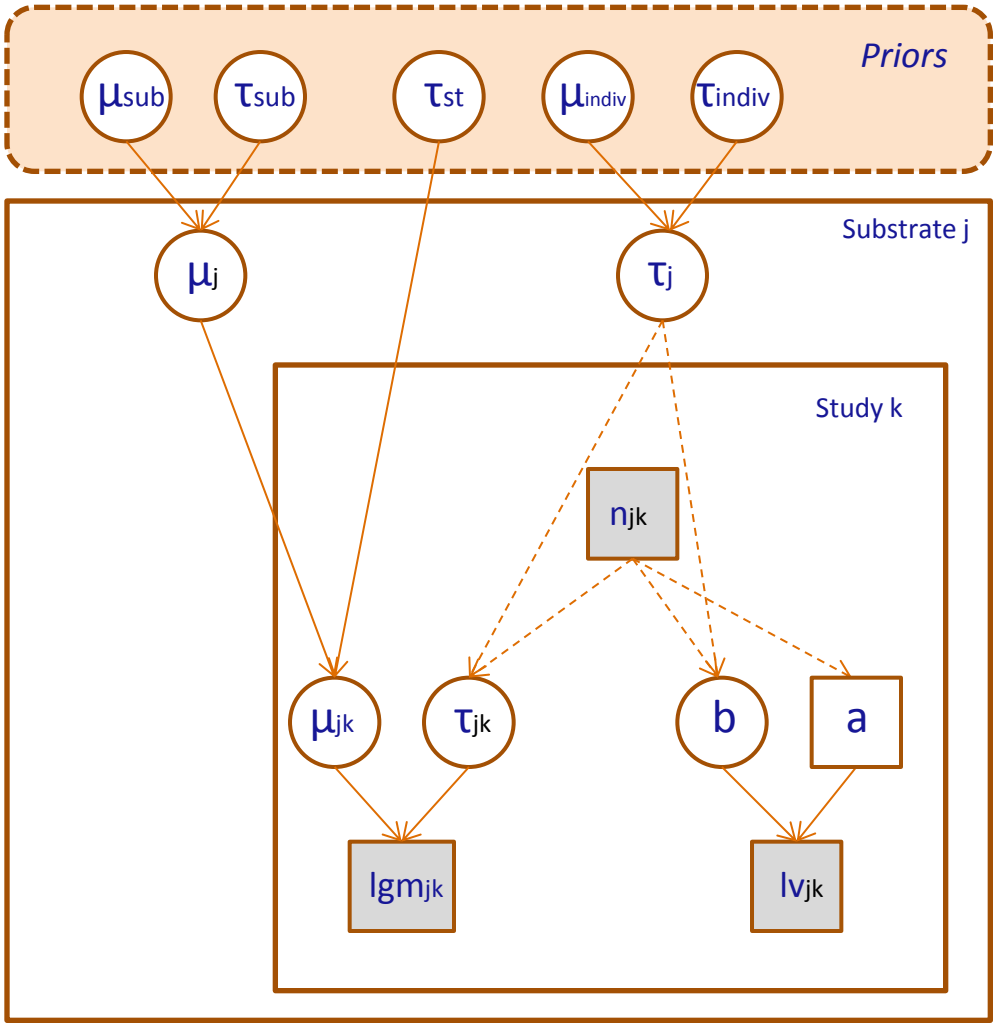
Rationale for meta-analysis of TK data to derive pathway-related uncertainty factors- default distributions.

Can be refined in the future





Bayesian Meta-analysis of TK data



3 levels :inter-study, inter-substrate et inter-individual Variability

$$\tau_j \sim Normal(\mu_{ind}, \frac{1}{\tau_{ind}})$$

$$\mu_j \sim Normal(\mu_{sub}, \frac{1}{\tau_{sub}})$$

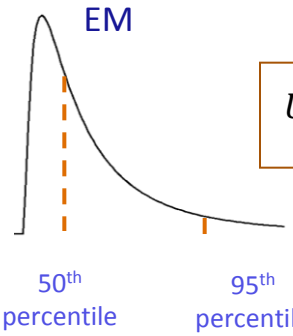
$$\mu_{jk} \sim Normal(\mu_j, \frac{1}{\tau_{st}})$$

$$\lg m_{jk} \sim Normal(\mu_{jk}, \frac{1}{n_{jk}\tau_j})$$

$$lv_{jk} \sim \frac{1}{n_{jk}\tau_j} Chi^2(n_{jk} - 1)$$

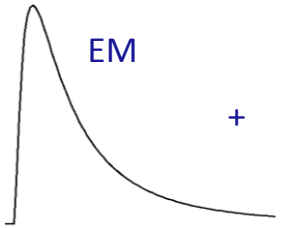
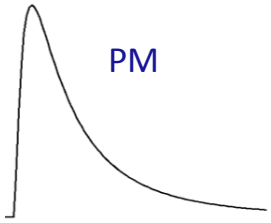
Amzal et Dorne, 2008

Polymorphic CYP2D6 Example

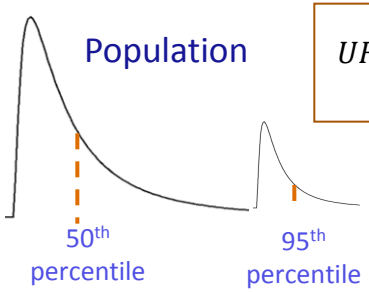


$$UF_{EM} = \frac{p95_{EM}}{p50_{EM}}$$

$$UF_{PM} = \frac{p95_{PM}}{p50_{EM}}$$

(1-α) EM x  + α PM x 

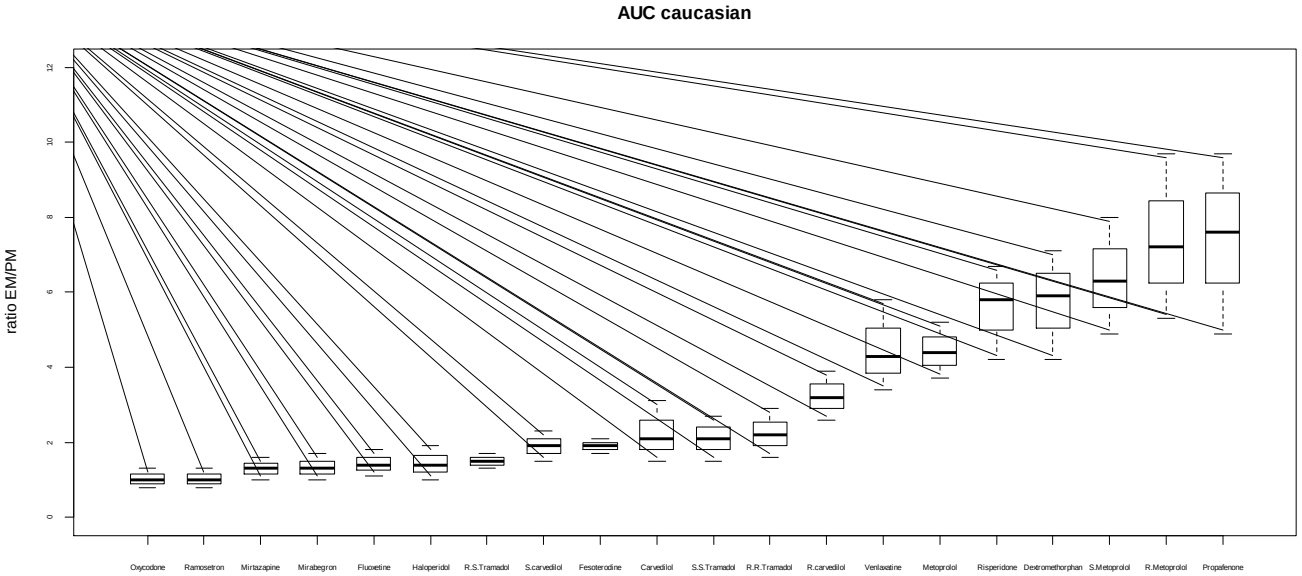
Monte-Carlo →

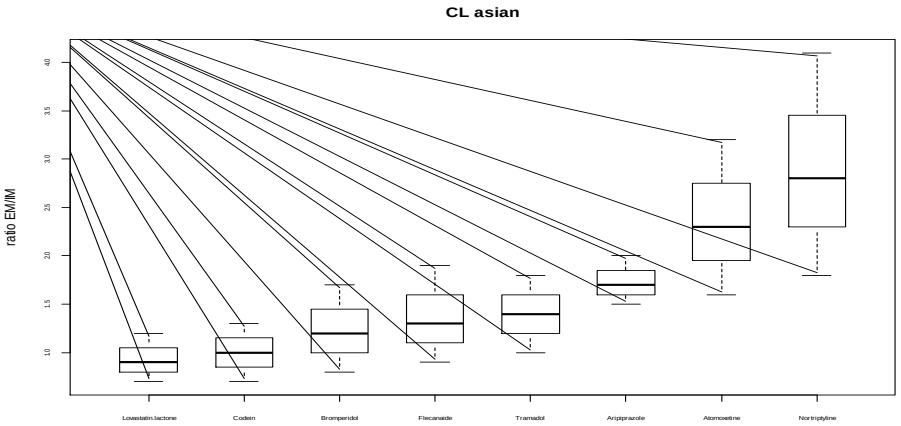


$$UF_{pop} = \frac{p95_{pop}}{p50_{pop}}$$

Bechaux et al (in preparation)

Polymorphic CYP2D6 Example





% Dose metabolised by CYP2D6 and differences between Extensive and poor metabolisers in Caucasian and Asian populations

OPEN SOURCE TK MODELS: DATA AND MODELS

- ✓ Collection data physio/ biological param- calibrate TK tools
- Body weight, variability enzymes expression Gut/liver etc…
- Human Variability metabolism (CYP isoforms) and excretion using Pharmaceutical DB

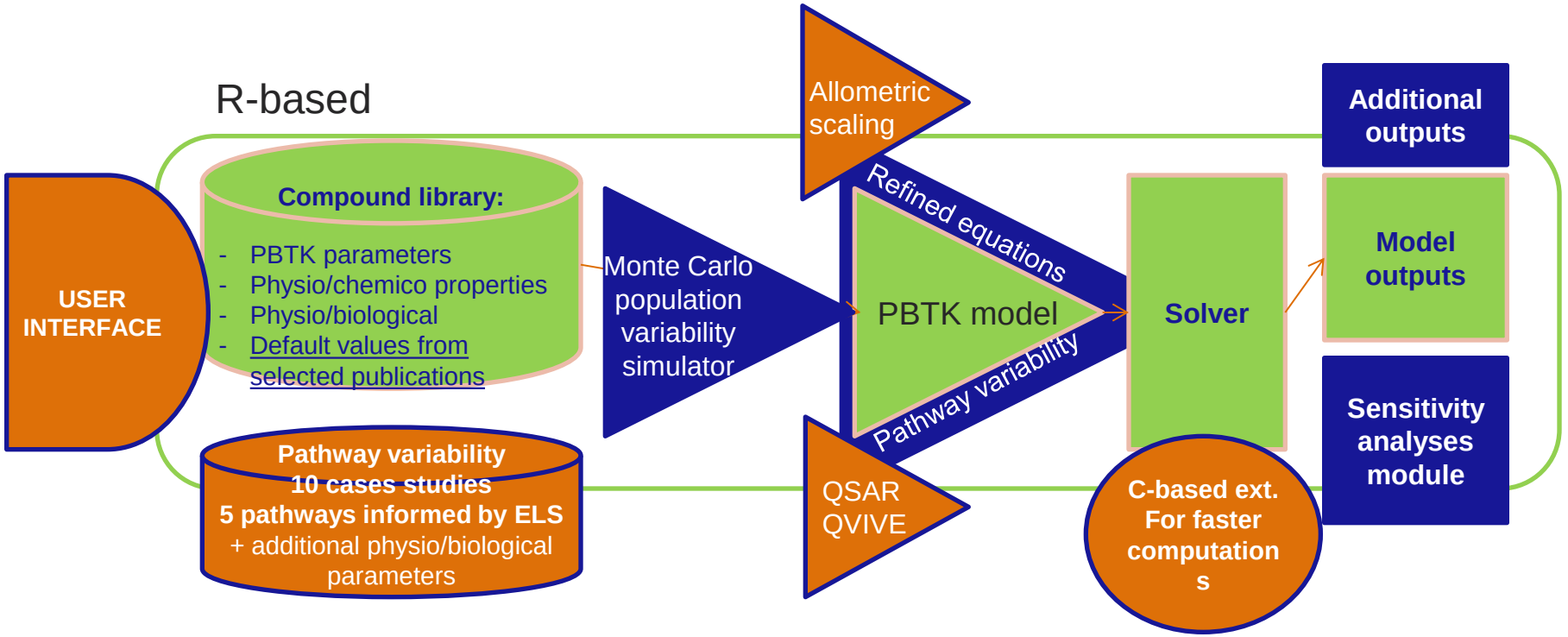
- TK tools from one compartment to multi compartment/PB-PK e.g. blood/liver/gut/kidney

- Case studies 10 compounds relevant to food and feed safety combining TK and TD: regulated, contaminants

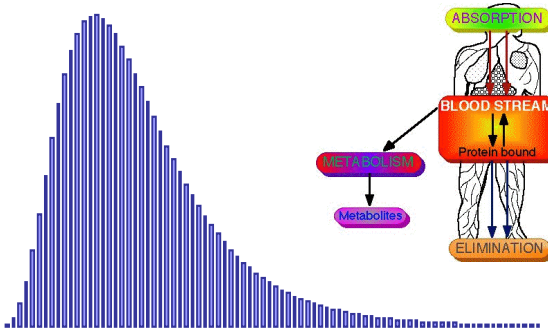
- ✓ In Future Open TK tools in R (spring 2018)

- ✓ In Parrallel, TK tools for 5 veterinary species (cow, pig, cat, chicken etc..) and ERA (zebra, trout, earth worm)

Prototype TK Modelling Platform

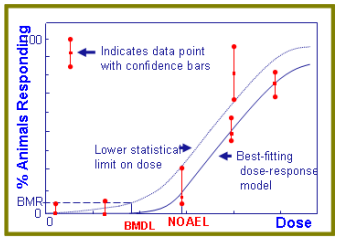


COMBINING VARIABILITY IN TK AND IN VITRO DATA : OPENSOURCE PLATEFORM



TK

TD



Isoform-specific Variability Distribution : Open Source Tool

Meta-analysis TK studies (acute, chronic) and TD studies (vivo, vitro, epidemio)

Phase I and Phase II enzymes and Transporters

In Vitro Human cell system

Isoform-specific Metabolism

Combine Human TK data and Tox data

Combine Human TK data and human epi data

Combine TK data and in vitro TD data

Modelled CASF

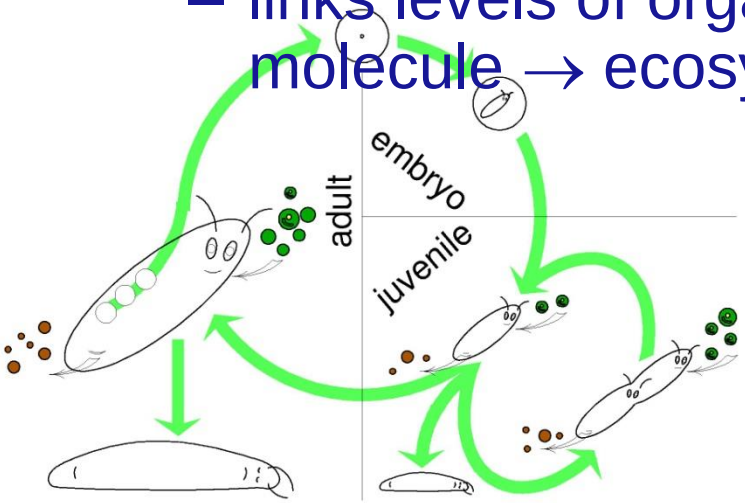
DEB MODELS

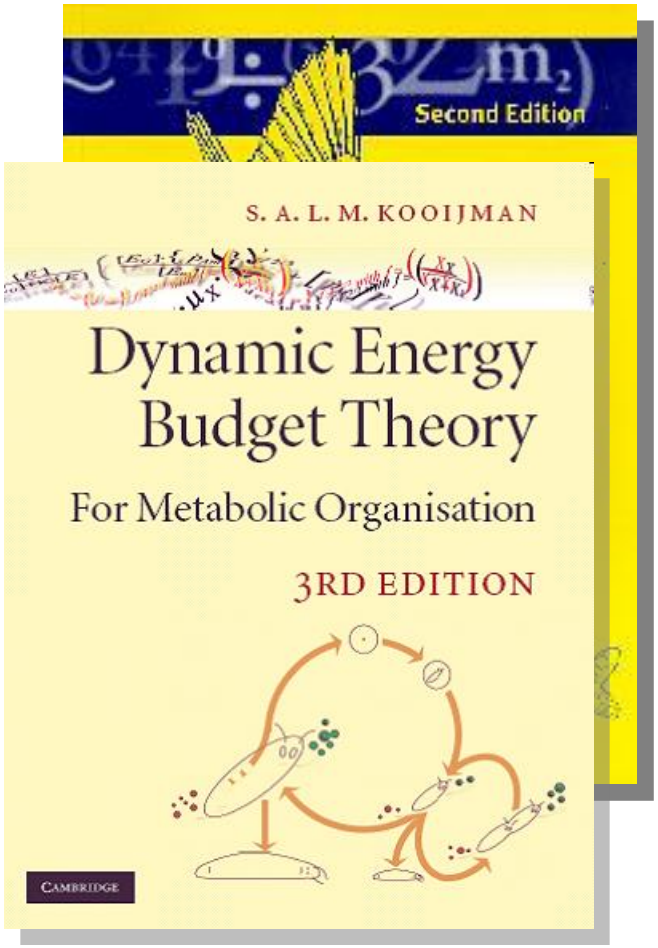
Quantitative theory for metabolic organisation from 'first principles'

- time, energy and mass balance

Life-cycle of the individual

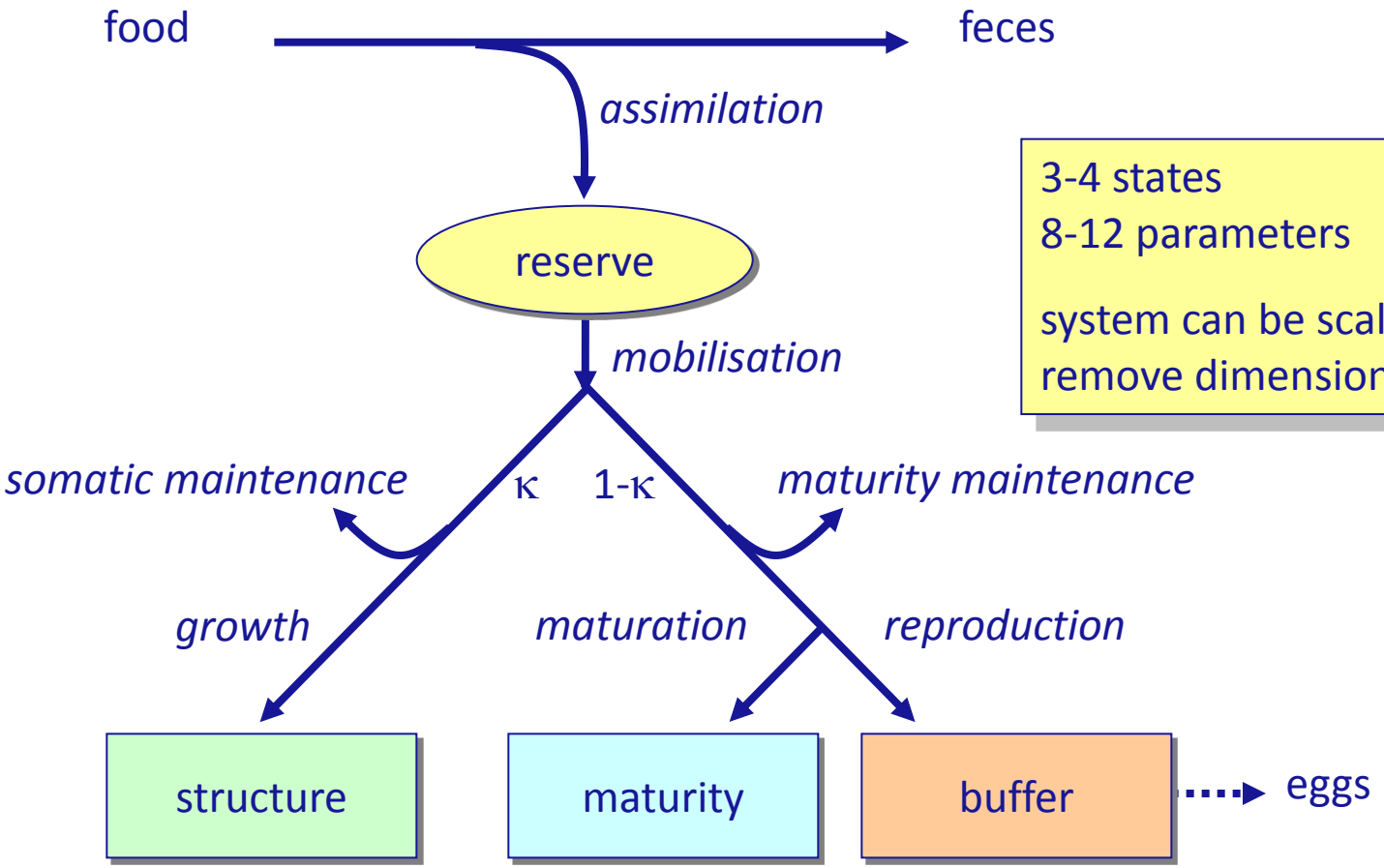
- links levels of organisation: molecule → ecosystems





Kooijman (2010)

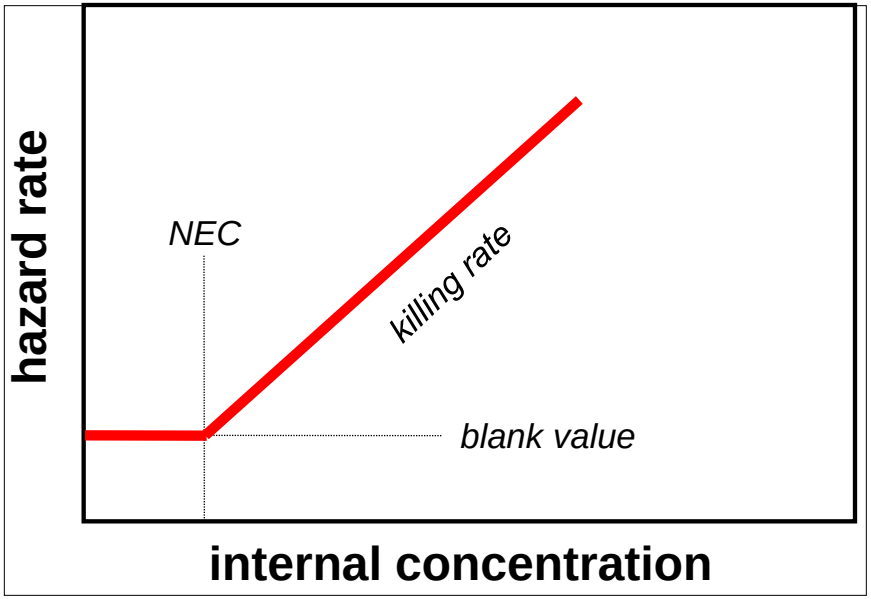
What are DEB MODELS ?

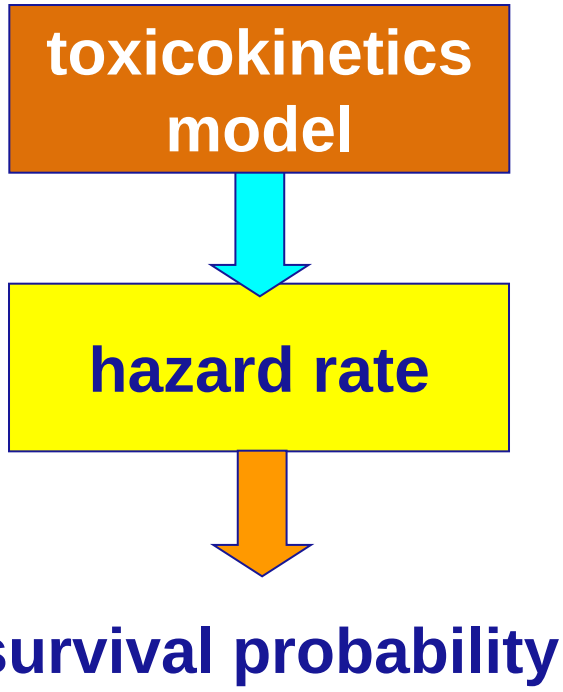


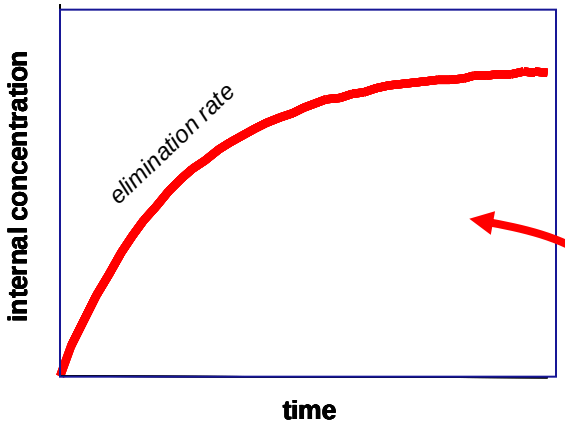
3-4 states
8-12 parameters

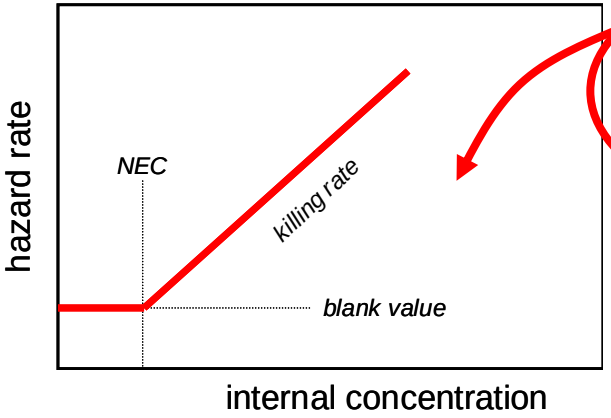
system can be scaled to remove dimension ‘energy’

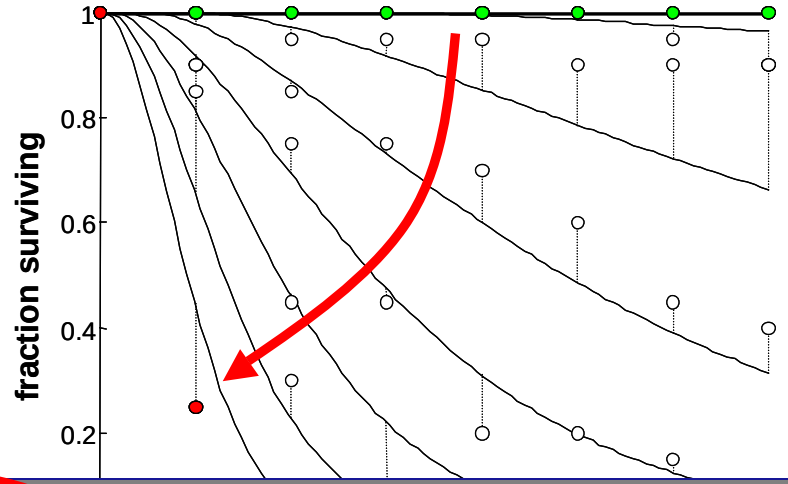
- Chemical affects the ***probability*** to die
  - hazard modelling



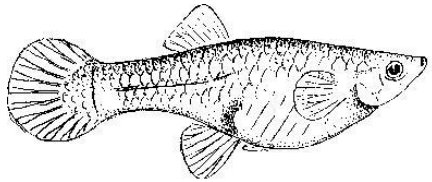




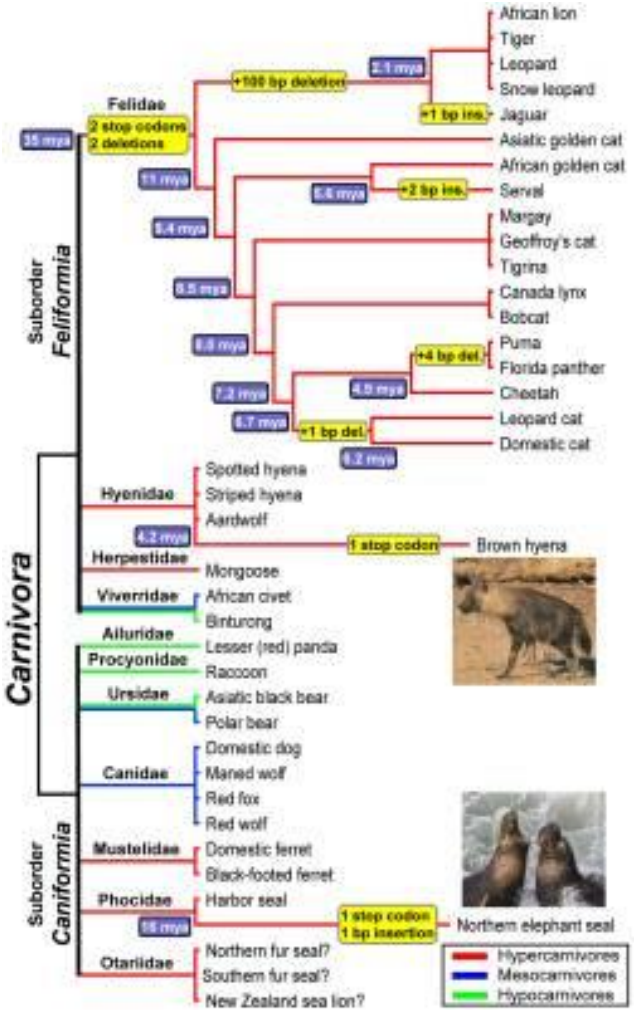




Elimination rate	0.73	d^{-1}
Blank hazard rate	0.0064	d^{-1}
NEC	2.8 (2.1-3.1)	µg/L
Killing rate	0.031	L/(µg d)



CAT EVOLUTION , HYPERCANIVORY AND DIET



Cat in UGT enzymes (hypercanivory) no induction by plant compounds

Lacking

-Glycine conjugation

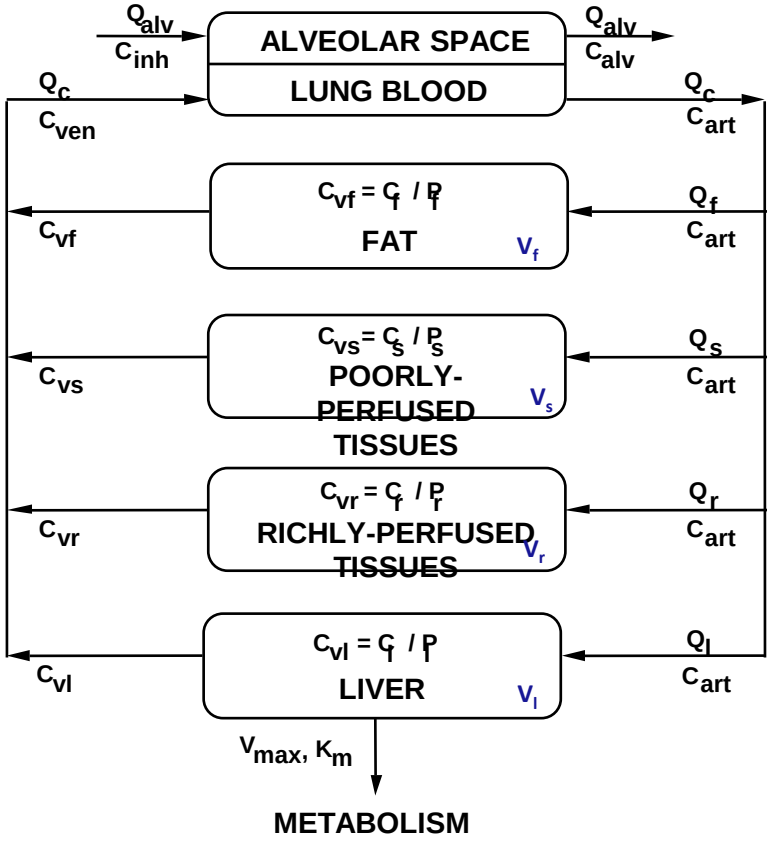
-N-acetyltarnsferases

-Thiopurine s-methyltransferases

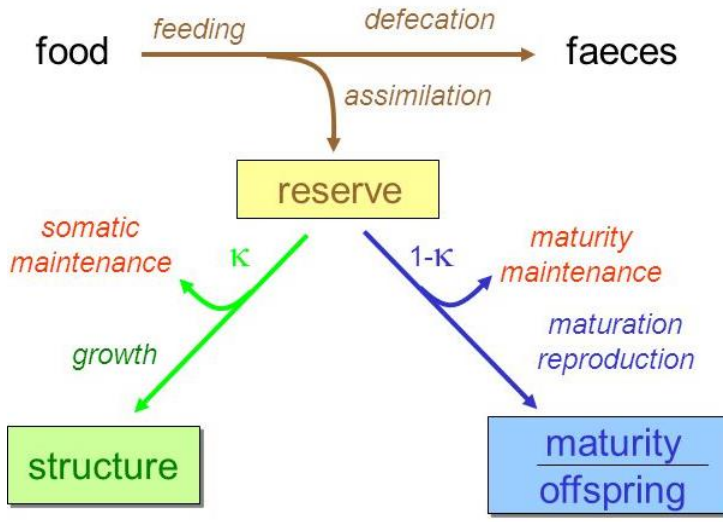
In context of Ecological RA and endangered species can we predict toxicity using physico-chemcial properties, structure ?

-Building Open source TK and DEB tools-

External dose → Internal dose → Target organ dose → Target organ metabolism → Target organ responses → Toxic Response



PB-TK models



DEB Models

14 November 2016

Methodology

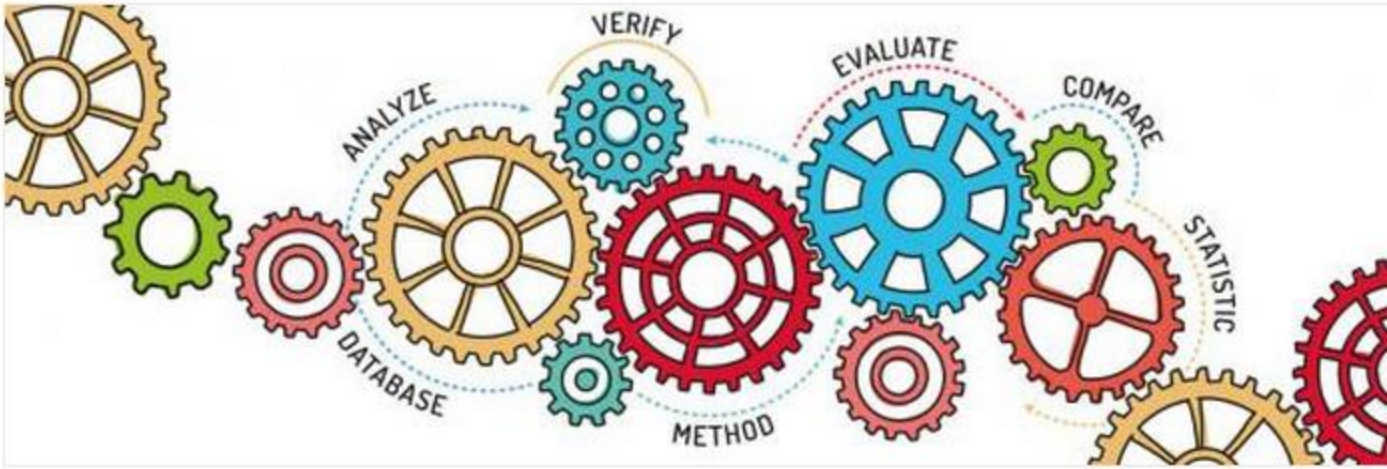
print

Tweet

Share

Share

Knowledge Junction – open access to scientific mode



Scientific models used by EFSA over the last 15 years have been brought togeth in a new EFSA community: the Knowledge Junction. The models can be shared and cited and you can submit your own. A selection of these tools are also available as web applications on the new EFSA Statistical Models Platform; just

CONCLUSION AND RECOMMENDATIONS

- ✓ **OpenFoodTox** provide **historical data** from EFSA RA Human, animal helath and Eccological RA
- ✓ **QSAR models** developed from OpenFoodTox **support 3Rs**
- ✓ **Open Source TK models** to integrate exposure (external) to TK (internal) and Toxicity **by 2018**
- ✓ **Open Source DEB models:** Taxa-specific data to link internal dose to toxicity **by 2018**
- ✓ **TK/TD platform:** Integration of population variability in TK and TD processes for RA **(by 2020-2021)**

THANKS TO PARTNERS

- ✓ **OpenFoodTox:** S-IN : Vicenza, Italy
- ✓ **QSAR models :** Istituto Mario Negri, Milan, italy
- ✓ **TK platform:**

1.Laser Analytica, Paris, France
2. INERIS, Paris, France
3.Radboud University, Niemigen, The Netherlands

- ✓ **TK/TD platform:**

1.ANSES, Paris, France
2. ISS, Rome, Italy
3.University of Utrecht, UtrechtThe Netherlands
4.University of Bretagne, Brest, France

- ✓ **DEB Models**

1.Center for Ecology and Hydrology , UK
2. Technico Lisboa, Lisbon, Portugal
3.Akvaplan Niva, Tromso, Norway

Many Thanks

Questions ?