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

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Senior Scientific Officer  
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EFSA

Summer School  
“In silico methods in food safety”  
14th June 2017
EFSA’s Role in Risk Analysis

Methodology Codex Alimentarius:

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

Scientific Risk Assessment

Risk Management

Risk Communication

EFSA

- Independent Risk Assessment
- Risk communication

Risk Manager

- EC
- EU Parliament
- Member States
- Council
FROM QUESTION TO ANSWER

European Commission
European Parliament
Member States
EFSA ("self mandate")

Question?

Terms of reference
Background

Opinion

Risk Assessment

Risk Communication

Consumers
Media
Industry
Professionals
IN A NUTSHELL...

Exposure assessment
- Occurrence data (Concentration in food)
- Food consumption

Hazard Assessment
- Toxicity
  - Chronic
  - Acute

Toxicokinetics / Toxicodynamics
- Benchmark Dose/ NOAEL
  - Health-based guidance value
    - MOE
    - ADI / TDI
    - ARfD

Risk Characterisation

Probabilistic / Deterministic Exposure estimates
- Uncertainty Factor

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

APPROVED: 26 March 2015

doi:10.2903/j.efsa.2015.e13031

PUBLISHED: 27 March 2015

Increasing robustness, transparency and openness of scientific assessments


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

<table>
<thead>
<tr>
<th>Tier</th>
<th>Exposure Assessment</th>
<th>Hazard Identification</th>
<th>Hazard Characterisation</th>
<th>Risk Characterisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occurrence</td>
<td>Consumption</td>
<td>TK</td>
<td>TD</td>
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<td>Semi-Q</td>
<td>Default values</td>
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<td>Point estimates</td>
<td>Point estimates in food categories</td>
<td>In silico Limited data Semi-Q</td>
<td>In silico Basic TK Read across</td>
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<td>Measured data</td>
<td>Measured in some food categories</td>
<td>Dossier data Qtyve</td>
<td>Dossier Data</td>
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<tr>
<td>3</td>
<td>Large measured dataset</td>
<td>Full patterns - food categories</td>
<td>Dossier and/or lit. (in vitro, in vivo)</td>
<td>Data in dossier and/or lit. (in vitro, OMICs, epi)</td>
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</tbody>
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# DATA FROM DOSSIER: REGULATED PRODUCT

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<td>2</td>
<td>Measured data</td>
<td>Measured in some food categories</td>
<td>Dossier data Qttve</td>
<td>Dossier Data: genotox, tox</td>
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</table>
# DATA-RICH CHEMICAL: CADMIUM

<table>
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<th>Hazard charact</th>
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<td>Large measured dataset</td>
<td>Full patterns - food categories</td>
<td>Human Data Biomarker excretion/blood</td>
<td>Human data Biomarker renal toxicity</td>
</tr>
</tbody>
</table>

- **Occurence**: TK
- **Consumption**: TD
- **Risk Characterisation**: TK
- **Risk Characterisation**: TD

### Data

- 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

### Exposure Data

- Human data
- Biomarker excretion/blood
- Biomarker renal toxicity

### Chemical Specific Adjustment Factor (CSAF)

- e.g. Quantitative
- Full probabilistic

---

**Source:** European Food Safety Authority
### DATA-POOR: EMERGING MYCOTOXIN

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<td>in silico Read across</td>
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<td>Read across</td>
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<td>Default UF</td>
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<td>e.g. Default values</td>
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<td>Qualitative</td>
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</table>
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...
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<td>Dossier Data</td>
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<td>Qttve</td>
<td>ADME data</td>
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<tr>
<td>3</td>
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<td>Full patterns -</td>
<td>Dossier and/or lit.</td>
<td>MoA/AOP, Epi data,</td>
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<tr>
<td></td>
<td>dataset</td>
<td>food categories</td>
<td>(in vitro, in vivo)</td>
<td>PB–PK model, BBDR,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMDL, CSAF</td>
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</tr>
</tbody>
</table>

*TK*: Toxicological characterization; *TD*: Toxicological data; *In silico*: In silico data; *ADME*: Absorption, Distribution, Metabolism, Excretion; *MoA/AOP*: Mode of Action/Ambient Operating Parameter; *BBDR*: Brain–Blood Distribution Ratio; *CSAF*: Critical Stressor Assessment Factor; *default UF*: Default uncertainty factor; *Qttve*: Quantitative toxicity evaluation; *Dossier Data*: Dossier data; *Dossier*: Dossier; *(in vitro, in vivo)*: In vitro, in vivo data.
CONTENT


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
### Substance Characterisation

<table>
<thead>
<tr>
<th>Substance</th>
<th>has</th>
<th>Component</th>
<th>CAS Number</th>
<th>EC Ref No</th>
<th>Molecule Form</th>
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<tr>
<td>(-)-3,7-Dimethyl-6-octan-1-ol</td>
<td>as such</td>
<td>(-)-3,7-Dimethyl-6-octan-1-ol</td>
<td>7560-51-4</td>
<td>223-415-7</td>
<td>C10H22O</td>
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<tr>
<td>(-)-Alpha-cedrene</td>
<td>as such</td>
<td>(-)-Alpha-cedrene</td>
<td>486-61-4</td>
<td>207-416-4</td>
<td>C15H26</td>
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### EFSA outputs

<table>
<thead>
<tr>
<th>Substance</th>
<th>Output Id</th>
<th>Legal Basis</th>
<th>Panel</th>
<th>Published</th>
<th>Title</th>
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<tbody>
<tr>
<td>(-)-3,7-Dimethyl-6-octan-1-ol</td>
<td>2180</td>
<td>Commission Regulation (EC)</td>
<td>EFSA CEF</td>
<td>02/20/2013</td>
<td>Scientific Opinion on Flavouring Group 2</td>
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### Hazard Characterisation: Reference points

<table>
<thead>
<tr>
<th>Substance</th>
<th>Author</th>
<th>Year</th>
<th>Output Id</th>
<th>Study</th>
<th>Test Type</th>
<th>Species</th>
<th>Route</th>
<th>Duration (days)</th>
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</thead>
<tbody>
<tr>
<td>(-)-Hyoscyamine and (-)-Scopolamine group</td>
<td>EFSA CONTAM</td>
<td>2013</td>
<td>2386</td>
<td>Human health</td>
<td>study with volunteers</td>
<td>Human</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>(1R,2S,5R)-N-(2-Pyridine-2'-yl)ethyl-3'-p-menthene-carboxamide</td>
<td>EFSA CEF</td>
<td>2014</td>
<td>2524</td>
<td>Human health</td>
<td>subchronic</td>
<td>Rat</td>
<td>oral feed</td>
<td>90</td>
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</tbody>
</table>

### Hazard Characterisation: Reference values

<table>
<thead>
<tr>
<th>Substance</th>
<th>Author</th>
<th>Year</th>
<th>Output Id</th>
<th>Assessment</th>
<th>qualifer</th>
<th>value</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-3,7-Dimethyl-6-octan-1-ol</td>
<td>EFSA CEF</td>
<td>2013</td>
<td>2180</td>
<td>TTC Cramer Class I</td>
<td>=</td>
<td>30</td>
<td>µg/kg bw/day</td>
</tr>
<tr>
<td>(-)-Alpha-cedrene</td>
<td>EFSA AFC</td>
<td>2006</td>
<td>2232</td>
<td>TTC Cramer Class I</td>
<td>=</td>
<td>30</td>
<td>µg/kg bw/day</td>
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</tbody>
</table>

### Genotoxicity

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<thead>
<tr>
<th>Substance</th>
<th>Author</th>
<th>Year</th>
<th>Output Id</th>
<th>Genotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,10-Dihydroxy stearic acid oligomers</td>
<td>EFSA AFC</td>
<td>2003</td>
<td>344</td>
<td>Not detected</td>
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<tr>
<td>Acrylic acid, methyl ester, tolemer with 1-dodecanethiol, C16-C18 alkyl esters</td>
<td>EFSA AFC</td>
<td>2003</td>
<td>344</td>
<td>Negative</td>
</tr>
</tbody>
</table>
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
QSAR models for predicting acute toxicity of pesticides in rainbow trout using the CORAL software and EFSA’s OpenFoodTox database

Andrey A. Toropova, Alla P. Toropova, Marco Marzo, Jean Lou Dorne, Nikolaos Georgiadis, Emilio Benfenati

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

A R T I C L E   I N F O

Keywords:
QSAR
OECD
Monte Carlo method
Rainbow trout
Toxicity
CORAL software

A B S T R A C T

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

Alla P. Toropova\textsuperscript{a, *}, Andrey A. Toropov\textsuperscript{a}, Marco Marzo\textsuperscript{a}, Sylvia E. Escher\textsuperscript{b}, Jean Lou Dorne\textsuperscript{c}, Nikolaos Georgiadis\textsuperscript{c}, Emilio Benfenati\textsuperscript{a}

\textsuperscript{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
\textsuperscript{b} Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hanover, Germany
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\textbf{ARTICLE INFO}

\textbf{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.
QSAR models for predicting acute toxicity of pesticides in rainbow trout using the CORAL software and EFSA’s OpenFoodTox database.

Andrey A. Toropov\textsuperscript{a}, Alla P. Toropova\textsuperscript{a,}\textsuperscript{*}, Marco Marzo\textsuperscript{a}, Jean Lou Dorne\textsuperscript{b}, Nikos Archontoulis\textsuperscript{a}, Emilio Benfenati\textsuperscript{a}

\textsuperscript{a} Department of Environmental Health Science, Laboratory of Environmental Chemistry and Toxicology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Masa 19, 20156 Milano, Italy
\textsuperscript{b} Scientific Committee and Emerging Risks Unit, European Food Safety Authority, Via Carlo Magno 1A, 43126 Parma, Italy

\textbf{A R T I C L E I N F O}

\textbf{Keywords:}
QSAR

\textbf{A B S T R A C T}

Optimal (flexible) descriptors were used to establish quantitative structure-activity relationship (QSAR) models to predict the acute toxicity of pesticides \((n = 116)\) towards rainbow trout. A heteroaromatic core (HC) with a high number of surface atoms was identified as a promising descriptor to predict acute toxicity in rainbow trout. A new descriptor, \(r_{pol}\), which characterizes the polarizability of the molecule, was introduced to predict acute toxicity. Both the descriptors were found to be effective in predicting acute toxicity in rainbow trout, and the developed models have the potential to be used in the environmental risk assessment of pesticides.
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 IRCCS 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 85% for the highly toxic compounds.
SCIENTIFIC REPORT OF EFSA

Modern methodologies and tools for human hazard assessment of chemicals

European Food Safety Authority

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
Levels of Knowledge, Toxicokinetic and Toxicodynamic processes

Toxicokinetics

External dose

Internal dose

Target organ dose

Target organ metabolism

Toxic Effect

Toxicodynamic processes

Target organ responses

Toxic Effect
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 0, 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.

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**Unimodal Population**

- Healthy Population
- Number of individuals (50% to 95%)

**Bimodal Population**

- Healthy Population
- Sensitive Subpopulation
- Number of individuals (50% to 95%)

*Adjustment Factor = Ratio 95th/50th*
**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.
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

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

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

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

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

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

Amzal et Dorne, 2008
Polymorphic
CYP2D6 Example

Monte Carlo
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 Parallel, TK tools for 5 veterinary species (cow, pig, cat, chicken etc..) and ERA (zebra, trout, earth worm)
Prototype TK Modelling Platform

**Compound library:**
- PBTK parameters
- Physio/chemico properties
- Physio/biological
- Default values from selected publications

**Pathway variability**
10 cases studies
5 pathways informed by ELS
+ additional physio/biological parameters

**PBTK model**
Monte Carlo population variability simulator
Refined equations
Allometric scaling
Solver

**Additional outputs**

**Model outputs**

**Sensitivity analyses module**

**User interface**
COMBINING VARIABILITY IN TK AND IN VITRO DATA: OPENSOURCE PLATEFORM

Isoform-specific Variability Distribution: Open Source Tool

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

Phase I and Phase II enzymes and Transporters

In Vitro Human cell system

Isoform-specific Metabolism

TK

TD

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
Quantitative theory for metabolic organisation from ‘first principles’
– time, energy and mass balance

Life-cycle of the individual
– links levels of organisation: molecule → ecosystems
What are DEB MODELS?

- food \rightarrow \text{assimilation} \rightarrow \text{feces}
- \text{somatic maintenance} \rightarrow \kappa \rightarrow \text{mobilisation} \rightarrow \text{reserve}
- \text{reserve} \rightarrow 1-\kappa \rightarrow \text{maturity maintenance}
- \text{reserve} \rightarrow \kappa \rightarrow \text{growth}
- \text{reserve} \rightarrow 1-\kappa \rightarrow \text{maturity maintenance} \rightarrow \text{maturation}
- \text{maturation} \rightarrow \text{reproduction}
- \text{reproduction} \rightarrow \text{buffer} \rightarrow \text{eggs}

- 3-4 states
- 8-12 parameters
- system can be scaled to remove dimension ‘energy’
Chemical affects the **probability** to die

- hazard modelling

**Diagram:**
- Hazard rate vs. internal concentration
  - NEC (No Effect Concentration)
  - Blank value
  - Killing rate

- Toxicokinetics model
- Hazard rate
- Survival probability
Elimination rate $0.73 \text{ d}^{-1}$
Blank hazard rate $0.0064 \text{ d}^{-1}$
NEC $2.8 (2.1-3.1) \mu g/L$
Killing rate $0.031 \text{ L/(µg d)}$
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-chemical 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
Knowledge Junction – open access to scientific models

Scientific models used by EFSA over the last 15 years have been brought together 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 Ecological 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)**
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Questions ?