



EFSA'S OPENFOODTOX 3.0: INNOVATIVE IN SILICO TOOLS AND INTEROPERABILITY WITH THE EU COMMON DATA PLATFORM ON CHEMICALS



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Data Officer - iDATA Unit

OUTLINE

EFSA' OpenFoodTox 2.0 project

EFSA' OpenFoodTox 3.0 project

In silico tools

Conclusions



EFSA's OpenFoodTox (2.0) database



#OpenEFSA



STEPS IN CHEMICAL RISK ASSESSMENT

Risk assessment: question to answer is the **problem formulation** step, then:

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

Step 1

Hazard Identification

Identify toxic effects

Step 2

Hazard Characterisation

Quantify toxic effects:

- Dose response
- Reference Point/Point of Departure
- Reference value

Step 3

Exposure Assessment

Occurrence x Consumption

Step 4

Risk Characterisation

Hazard vs Exposure: Risk



OPENFOODTOX: EFSA'S CHEMICAL HAZARDS DATABASE

Open-source database of toxicological information since EFSA's creation (2002)

- "One-click" tool for risk assessors, risk managers and stakeholders

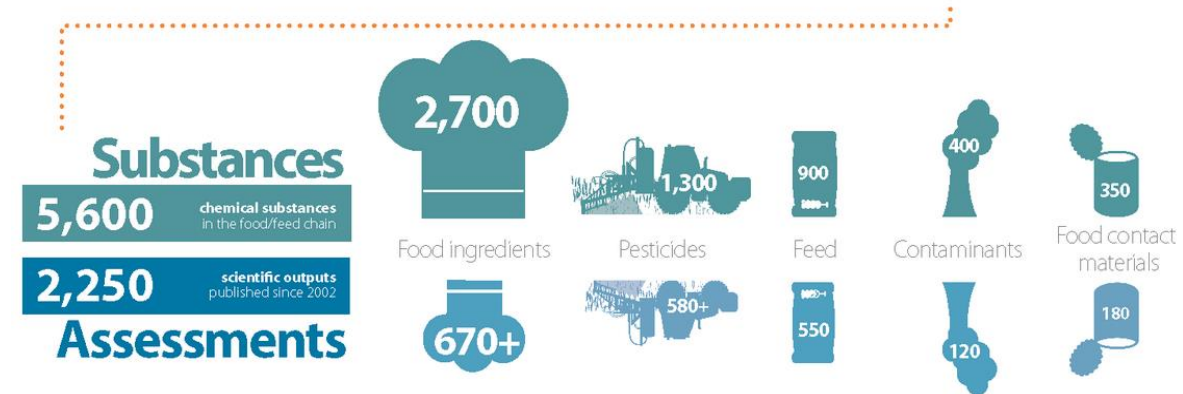
International data harmonisation and sharing

- OECD Harmonised Templates

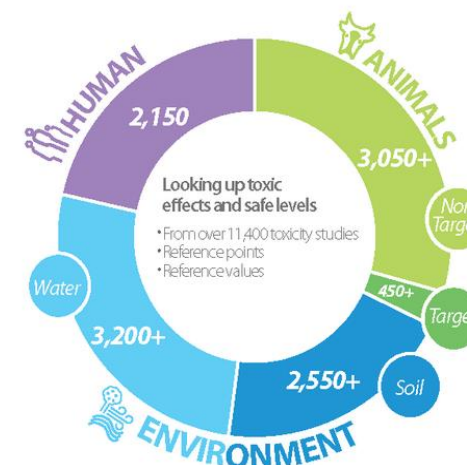
Developing future methods and tools as alternatives to animal testing

- Basis for developing *in silico* models

OpenFoodTox provides **chemical hazards data**:



Use OpenFoodTox for

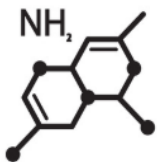


information on chemical characterisation, regulations, EFSA outputs, toxicity, reference points (NOAEL, BMD, LD50, etc.) and reference values (ADI, TDI, PNEC, etc.)*, uncertainty factors, EFSA scientific outputs.



developing future **methods and tools** as alternatives to animal testing.

WHAT DOES OPENFOODTOX CONTAIN?



Chemical Information



EFSA Outputs



(Eco)toxicological Information

Substance identifiers (CAS n., IUPAC, SMILES):

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

Metadata

- Literature reference (title, publication date)
- link (doi) to the literature

Reference points

- No Observed Adverse Effect Level (NOAEL)
- Lethal Dose 50 (LD₅₀)

Reference Values

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



OPENFOODTOX: MICROSTRATEGY TOOL AVAILABLE ONLINE

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 | | | | | | | Synonym | |
|-------------------------------|---------|-------------------------------|------------|-----------|-------------------|--------|---|--|
| Substance | has | Component | CAS number | EC Ref No | Molecular formula | Smiles | | |
| (-)-3,7-Dimethyl-6-octen-1-ol | as such | (-)-3,7-Dimethyl-6-octen-1-ol | 7540-51-4 | 231-415- | C10H20O | | 2,2-Bis(4-hydroxyphenyl)propane Bisphenol A BPA | |

| EFSA outputs | | | | | | | |
|---|----------|------------|-----------|--|--------------|---|--|
| Substance | Author | Published | Output Id | Title | Output Type | Legal Basis | Url |
| 1-(4-Methoxyphenyl)-4-methylpent-1-en-3-one | EFSA FAF | 11/11/2019 | 3348 | Scientific Opinion on Flavouring Group Evaluation 215 Revision 1 (FGE.215Rev1): seven a,b-unsaturated cinnamyl ketones from subgroup 3.2 of FGE.19 | EFSA opinion | Commission Regulation (EC) No 1565/2000 (Repealed by Com. Implementing Reg. (EU) No 872/2012) | http://dx.doi.org/10.2903/j.efsa.2019.5875 |
| 1-(4-Methoxyphenyl)pent-1-en-3-one | EFSA FAF | 11/11/2019 | 3348 | Scientific Opinion on Flavouring Group Evaluation 215 Revision 1 (FGE.215Rev1): seven a,b-unsaturated cinnamyl ketones from subgroup 3.2 of FGE.19 | EFSA opinion | Commission Regulation (EC) No 1565/2000 (Repealed by Com. Implementing Reg. (EU) No 872/2012) | http://dx.doi.org/10.2903/j.efsa.2019.5875 |

| Hazard Characterisation: Reference points | | | | | | | | | | | | | | |
|---|-------------|------|-----------|--------------------------------|-----------------------|---------|--------------|-----------------|----------|-----------|-------|--------------|----------------|--------------|
| Substance | Author | Year | Output Id | Study | Test Type | Species | Route | Duration (days) | Endpoint | Qualifier | Value | Unit | Effect | Toxicity |
| (-)-Hyoscyamine and (-)-Scopolamine group | EFSA CONTAM | 2013 | 2396 | Animal (target species) health | not reported | Pig | Not reported | 0 | NOAEL | = | 1500 | µg/kg | not reported | not reported |
| (-)-Hyoscyamine and (-)-Scopolamine group | EFSA CONTAM | 2013 | 2396 | Human health | study with volunteers | Human | Not reported | 0 | NOAEL | = | 0.16 | µg/kg bw | clinical signs | systemic |
| (1R,2S,5R)-N-(2-(6-oxoheptan-2-ylideneamino)ethyl)acetamide | EFSA CEF | 2014 | 2524 | Human health | subchronic | Rat | oral; feed | 90 | NOAEL | = | 5 | mg/kg bw/day | histopathology | endocrine |

| Hazard Characterisation: Reference values | | | | | | | | | |
|---|----------|------|-----------|--------------------|-----------|-------|--------------|------------|---|
| Substance | Author | Year | Output Id | Assessment | Qualifier | Value | Unit | Population | Remarks |
| (-)-3,7-Dimethyl-6-octen-1-ol | EFSA CEF | 2013 | 2180 | TTC Cramer Class I | = | 30 | µg/kg bw/day | Consumers | METABOLISM: The candidate substance is expected to be metabolised in this group the data available do not give rise to safety concerns. |

| Genotoxicity | | | | |
|-------------------------------|-------------|------|-----------|----------------|
| Substance | Author | Year | Output Id | Genotoxicity |
| (-)-3,7-Dimethyl-6-octen-1-ol | EFSA CEF | 2013 | 2180 | Negative |
| (-)-3,7-Dimethyl-6-octen-1-ol | EFSA FEEDAP | 2016 | 2864 | Not determined |
| (-)-Alpha-cedrene | EFSA AFC | 2008 | 2299 | Not determined |
| (-)-Alpha-cedrene | EFSA CEF | 2010 | 2039 | Not determined |
| (-)-Alpha-cedrene | EFSA CEF | 2011 | 2102 | Not determined |
| (-)-Alpha-elemol | EFSA AFC | 2006 | 2232 | Negative |
| (-)-Alpha-elemol | EFSA AFC | 2009 | 2314 | Negative |

| Substance Browser | | | |
|--------------------------|--------------------------|--------------------------|--|
| Reference Values | Reference Point | Background Documents | |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

FILTER

Substance Browser

Apply

▼ Substance

Q Search Substance

▼ Synonym

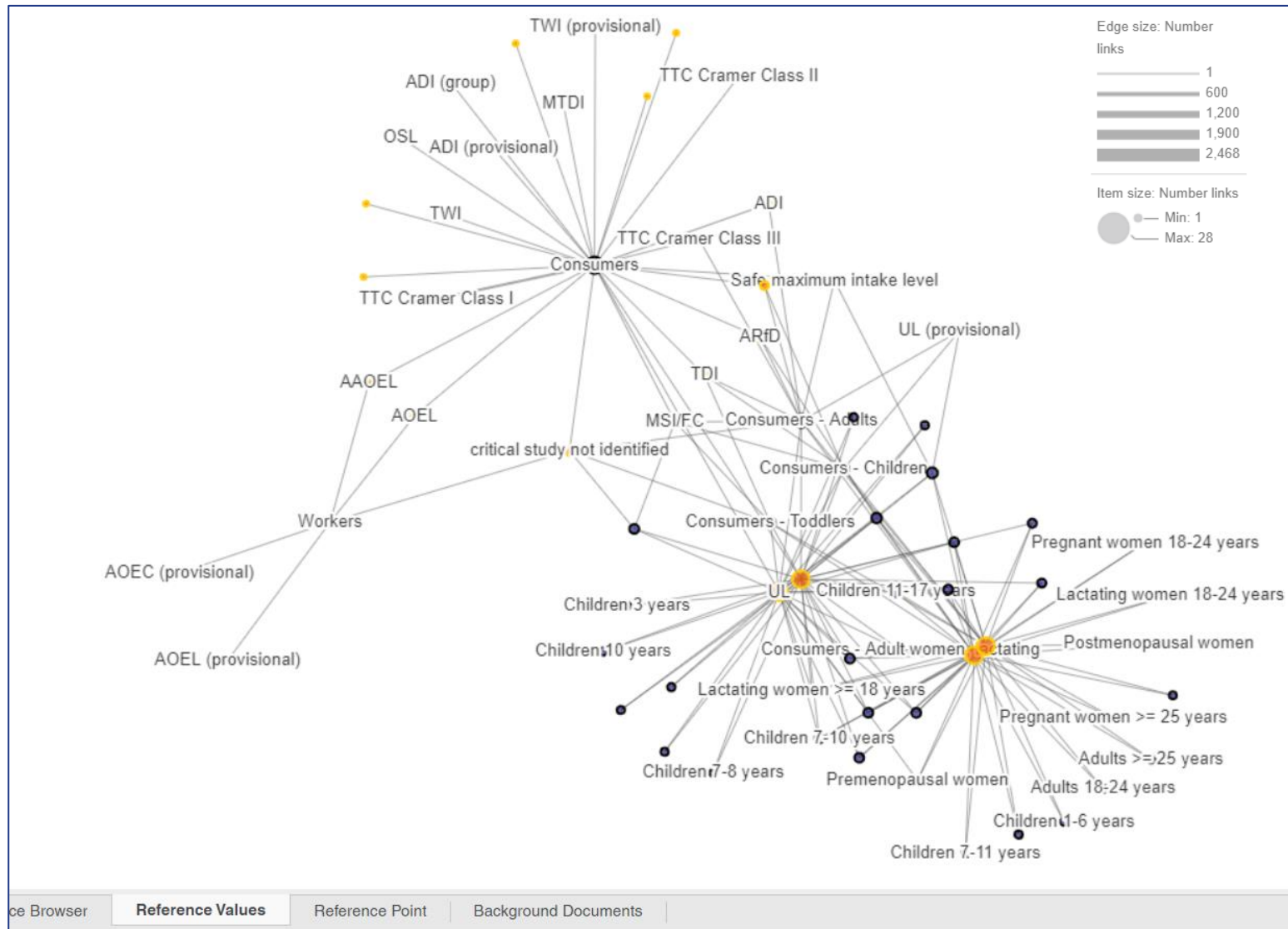
Q Search Synonym

▼ CAS number

Q Search CAS number



MICROSTRATEGY TOOL: REFERENCE VALUES

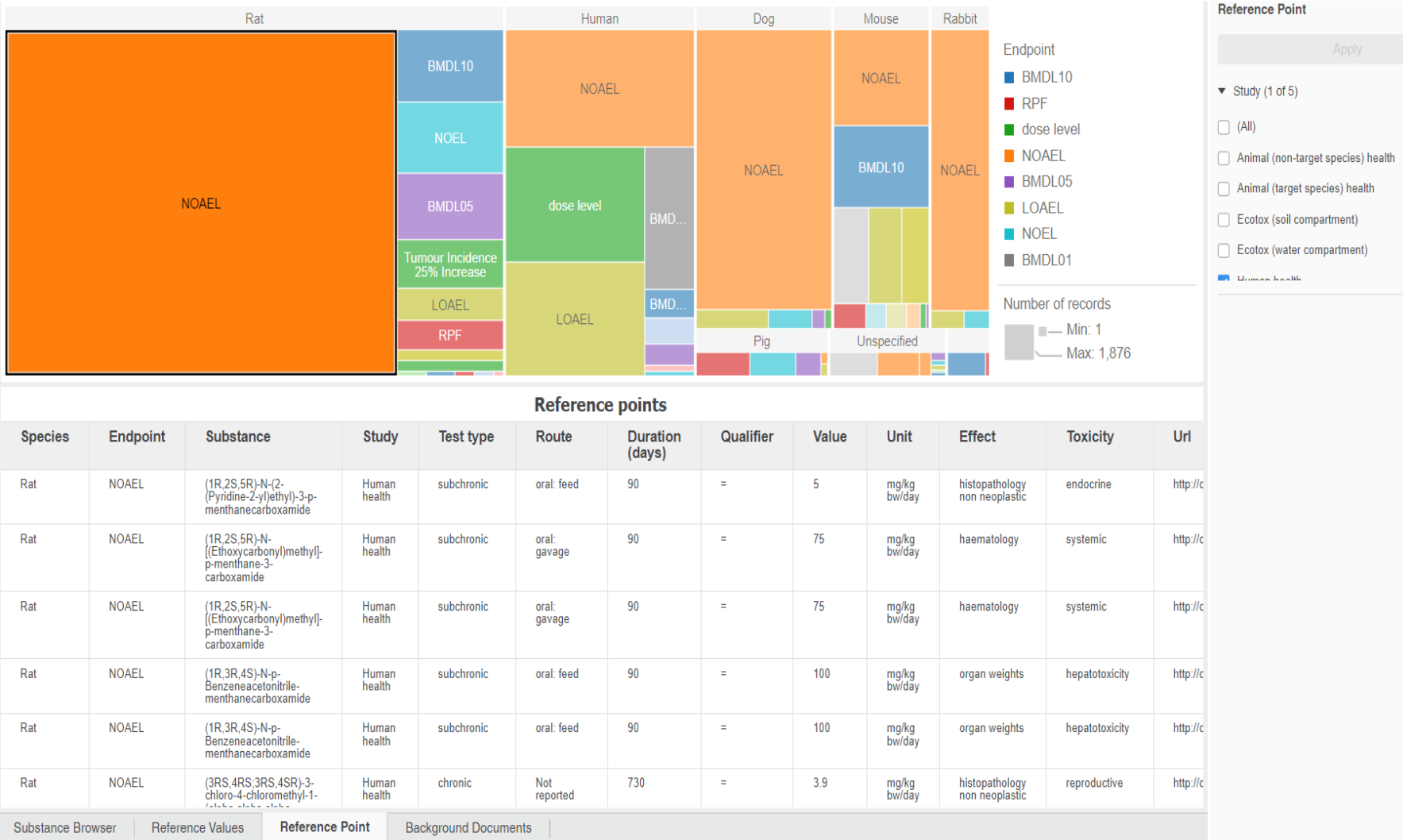


11,400 toxicity studies

- Reference Values
- Populations



MICROSTRATEGY TOOL: REFERENCE POINTS



2,250 Assessments

- Reference Points
- Studies
- Species



EFSA's OpenFoodTox (3.0) database



#OpenEFSA



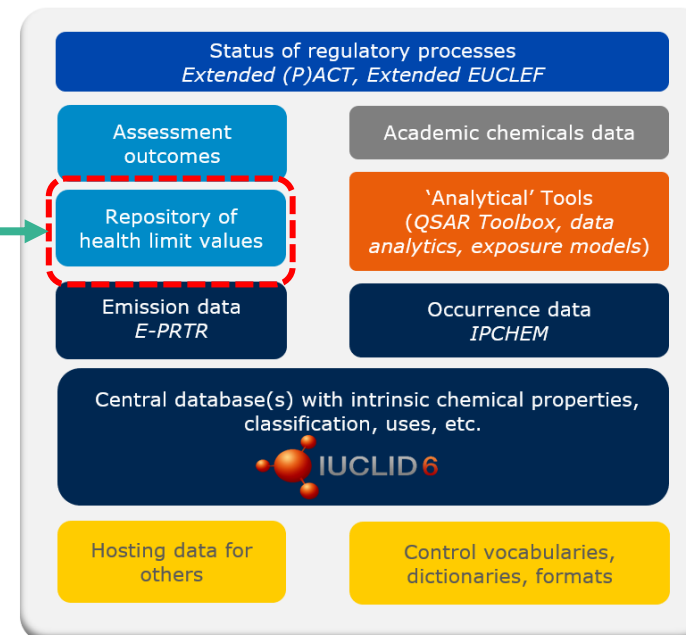
OPENFOODTOX 3.0 - PROJECT OVERVIEW



- Improving the **interoperability** of EFSA's OFT 3.0 database with **IUCLID 6** and the **EU Common Data Platform on Chemicals (1S1A)**;
- Developing **NAMs** such as *in silico* tools to enhance OFT usability as a supporting tool for **risk assessment activities**.



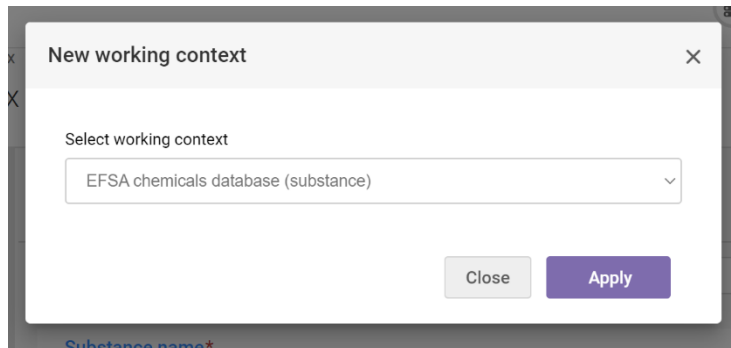
[OC/EFSA/IDATA/2022/02](https://oc.efsa.europa.eu/oc/EFSA/IDATA/2022/02)
Tender specs



EFSA OPENFOODTOX WORKING CONTEXT IN IUCLID



1. **New Working Context “EFSA Chemicals Database”** available in IUCLID 7 (May 2022 release)



2. **Substance and Mixture datasets** available in *EFSA Chemicals database Working Context*
3. **Key information** (*Flexible/Endpoint Summaries*) and **Detailed results** (*EndpointStudyRecords*)
4. Potential application/extension to other chemicals db (food additives/flavourings, botanicals).

| EFSA chemicals database (substance) | |
|--|---|
| TESTOpenFoodTox_Fluxaproxad | |
| 1 Key information | 7 |
| > 1.1 Substance identification | 1 |
| > 1.2 Substance composition | 1 |
| > 1.3 Metabolites | 1 |
| > 1.4 Reference values | 1 |
| > 1.5 Function, mode of action and possible resistance | |
| > 1.6 Human health | 3 |
| 2 Detailed results | 8 |
| > 2.1 Human health | 6 |
| > 2.2 Animal health | |
| > 2.3 Ecotoxicology (Soil-Terrestrial) | |
| > 2.4 Ecotoxicology (Aquatic) | 1 |
| > 2.5 Fate and behaviour in the environment | 1 |
| > 2.6 Physical and chemical properties of the active substance | |
| Inherited templates | |

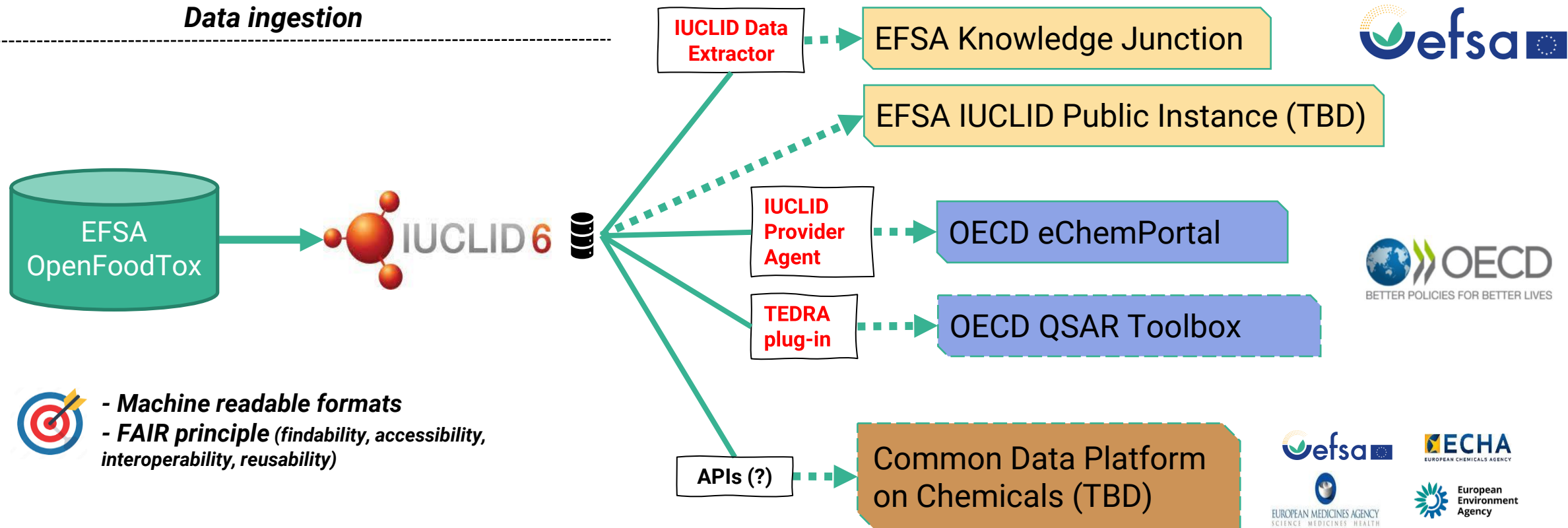
OPENFOODTOX 3.0 – OBJECTIVE 1

1. Update of OFT 2.0:

- Migrating OFT 2.0 database (xlsx) to **IUCLID 6**
- Data quality check of OFT 2.0

Data dissemination

Data ingestion



OPENFOODTOX 3.0 – OBJECTIVE 2

2. Further development of OFT 3.0 - collection/integration of new properties into IUCLID:

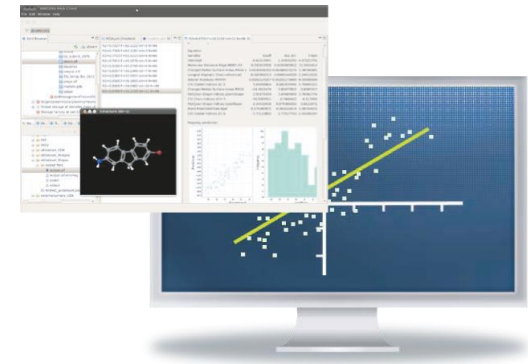
- **Physico-chemical properties** (OHTs 1-23);
- **Environmental Fate and Behaviour** (OHTs 24 to 40 & 401) (pesticides, feed additives, contaminants)
- **Use and exposure** (summary data) (OHTs 301 to 306);
- **Intermediate effects/mechanistic data** (OHT 201).
- ***In vitro* and *in vivo* toxicokinetic** data (HHRA; AHRA; ERA) (OHTs 58; 201)
- ***In vivo* critical and non-critical** toxicological data (i.e., CAGs, non-critical target organs for all chemicals)



OPENFOODTOX 3.0 – OBJECTIVE 3

3. Development of *in silico* models and implementation within EFSA tools:

- New *in silico* models using new properties (collected in Objective 2):
 - Predicting environmental fate, TK and *in vitro* toxicity in species of relevance to EFSA's for human, animal and environmental RA.
- Integration of **read-across** and **grouping tools** according to **mode of action/mechanistic understanding** of substances in mammals:
 - Considering RA of combined exposure to multiple chemicals (EFSA GD 2021).
 - VERA, ToxRead, QSAR for MoA or AOP (e.g., SA based)
 - Publishing EFSA Knowledge Junction (Zenodo), peer reviewed literature



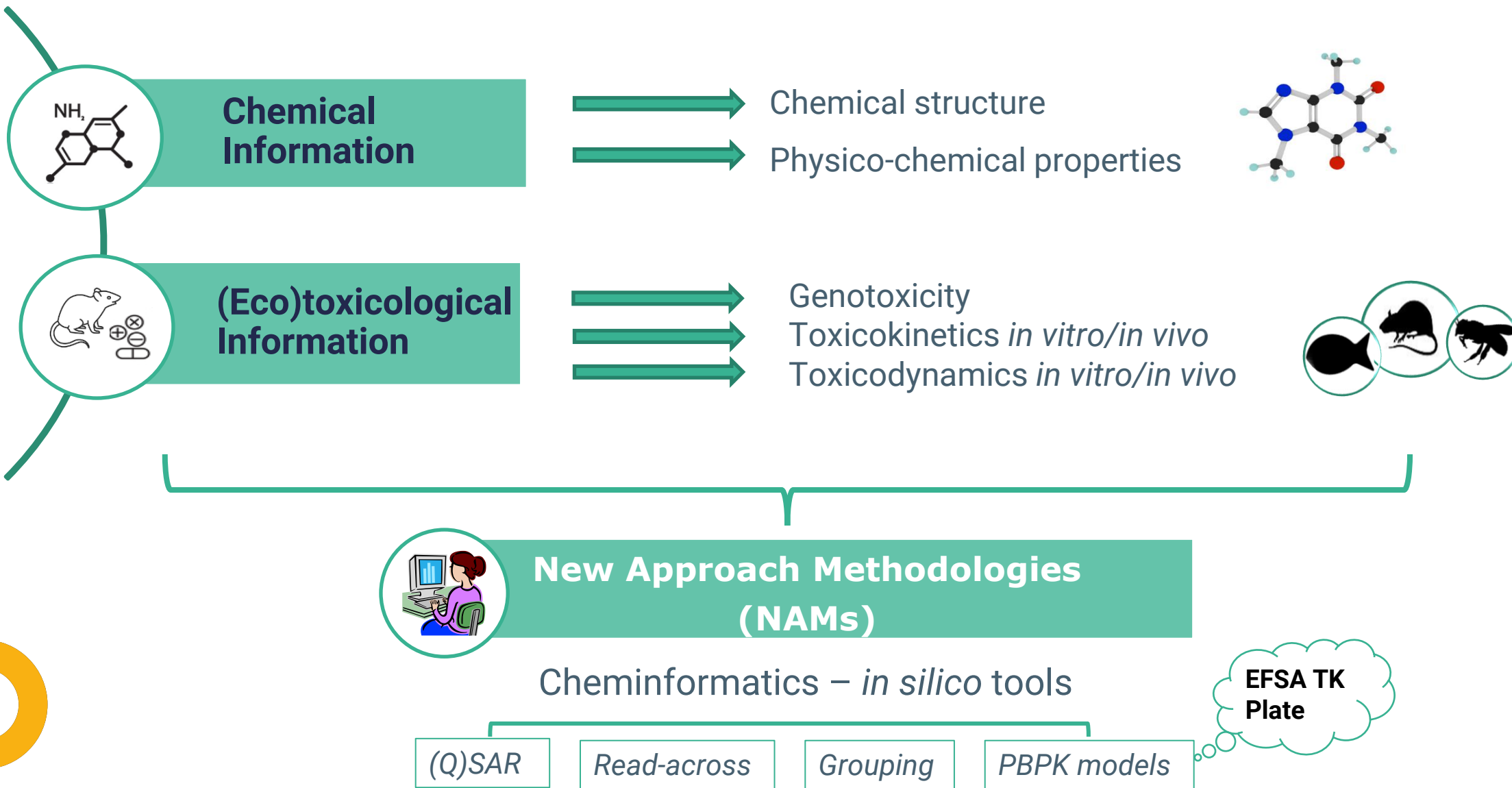


NAMs - in silico tools

#OpenEFSA



OPENFOODTOX AS BASIS FOR DEVELOPING NAMs



OPENFOODTOX AS BASIS FOR DEVELOPING QSAR MODELS



Research Paper
 QSAR models for soil ecotoxicity: Development and validation of models to predict reproductive toxicity of organic chemicals in the collembola *Folsomia candida*

Giovanna J. Lavado^{a,1}, Diego Baderna^{b,c,1}, Edoardo Carnesecci^b, Alla P. Toropova^a, Andrey A. Toropov^a, Jean Lou C.M. Dorne^c, Emilio Benfenati^a



In silico models

- More than **15 QSAR models** developed (different species of **human** health and **ecological** relevance such as mice, fish, earthworms, bees)

“From animal testing to computer testing”



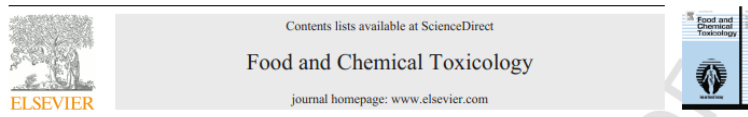
A regression-based QSAR-model to predict acute toxicity of aromatic chemicals in tadpoles of the Japanese brown frog (*Rana japonica*): Calibration, validation, and future developments to support risk assessment of chemicals in amphibians

Andrey A. Toropov^{a,1}, Matteo R. Di Nicola^{b,c,d,1}, Alla P. Toropova^a, Alessandra Roncaglioni^a, Edoardo Carnesecci^{b,c}, Nynke I. Kramer^{c,d}, Antony J. Williams^e, Manuel E. Ortiz-Santaliestra^a, Emilio Benfenati^a, Jean-Lou C.M. Dorne^b



Exploring QSAR modeling of toxicity of chemicals on earthworm

Sulekha Ghosh^a, Probir Kumar Ojha^a, Edoardo Carnesecci^{b,c}, Anna Lombardo^a, Kunal Roy^{a,b}, Emilio Benfenati^{c,d}



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



First report on a classification-based QSAR model earthworm

Joyita Roy¹, Probir Kumar Ojha¹, Edoardo Carnesecci^{2,3}, Ann: Emilio Benfenati^{3,4}

¹ Drug Theoretics and Cheminformatics Laboratory, Department of Pharmaceutical Technology, Jadavpur Univ.

² Institute for Risk Assessment Sciences, Utrecht University, PO Box 80177, 3508 TD Utrecht, the Netherlands

³ Laboratory of Environmental Chemistry and Toxicology, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri, 2, 20156, Milano, Italy



Integrating QSAR models predicting acute contact toxicity and mode of action profiling in honey bees (*A. mellifera*): Data curation using open source databases, performance testing and validation

Edoardo Carnesecci^{a,b,c,1}, Cosimo Toma^{a,b,1}, Alessandra Roncaglioni^b, Nynke Kramer^a, Emilio Benfenati^b, Jean Lou C.M. Dorne^c



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,b}, Marco Marzo^a, Jean Lou Dorne^b, Nikolaos Georgiadis^c, Emilio Benfenati^b

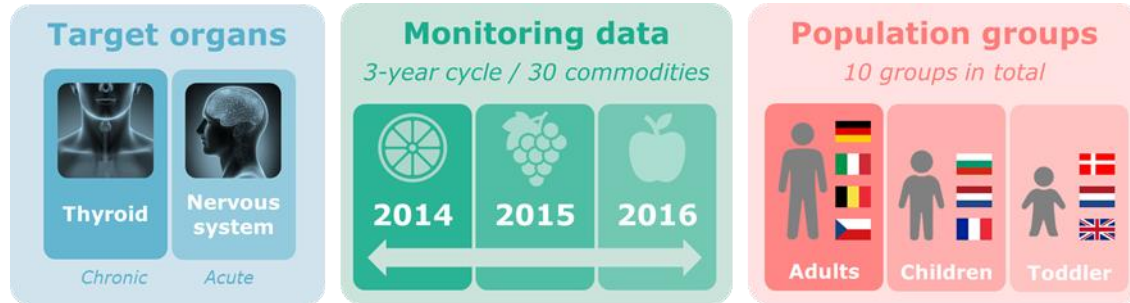
^a Department of Environmental Health Science, Laboratory of Environmental Chemistry and Toxicology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milano, Italy

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

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

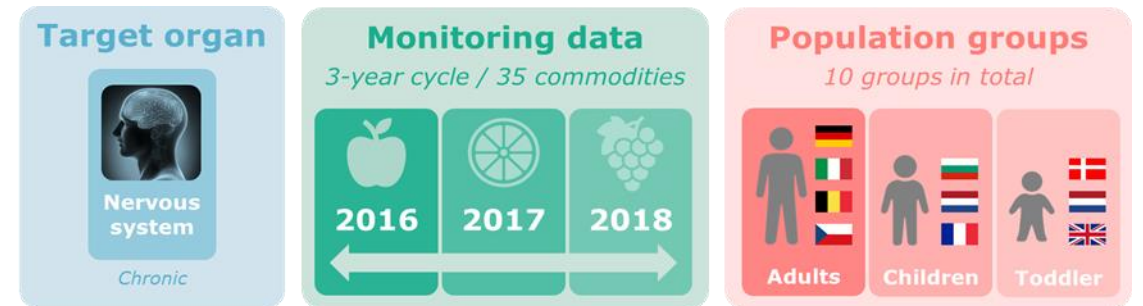
OPENFOODTOX 3.0 FOR CRA PESTICIDES

Pilot assessment



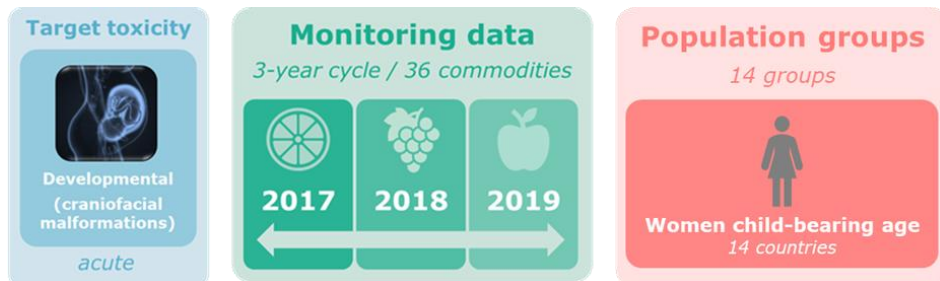
2019

Chronic AChE inhibition



2020

Cranio-facial malformations



2021

2022

- **In vivo critical** and **non-critical** toxicological data (i.e., CAGs, non-critical target organs for all chemicals)



OPENFOODTOX 3.0 - BENCH MARK DOSE CALCULATIONS

- Trial of new table in Repeated dose toxicity in IUCLID/OpenFoodTox to support Bench Mark Dose calculations within EFSA's R4EU

Detailed toxicology results

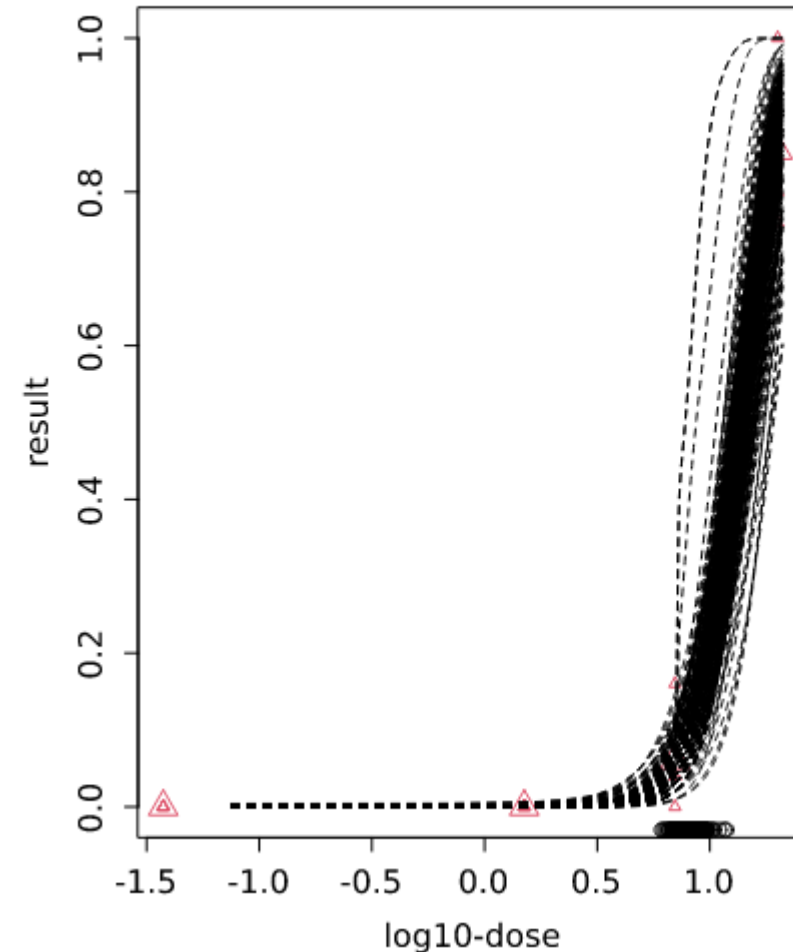
[Detailed toxicology results](#)

[+ New item](#)

[📄 Import file](#) ▼

| # | Sex | Additional cov... | Dose / conc. | No. of animals... | Examination | Experimental |
|-----|------|-------------------|--------------|-------------------|-------------|--------------|
| ⋮ 1 | male | other: F0 | 0 | 25 | granuloma | 0 |
| ⋮ 2 | male | other: F0 | 1.5 | 25 | granuloma | 0 |
| ⋮ 3 | male | other: F0 | 7 | 25 | granuloma | 1 |
| ⋮ 4 | male | other: F0 | 20 | 25 | granuloma | 20 |

bootstrap curves
based on model averaging



version: 70.0
model averaging results
dtype 6
selected all
dose scaling: 1
conf level: 0.9
number of runs: 200
extra risk 0.1
BMD CI
6.8 9.59

OPENFOODTOX 3.0 TO REPORT MECHANISTIC DATA (OHT 201)



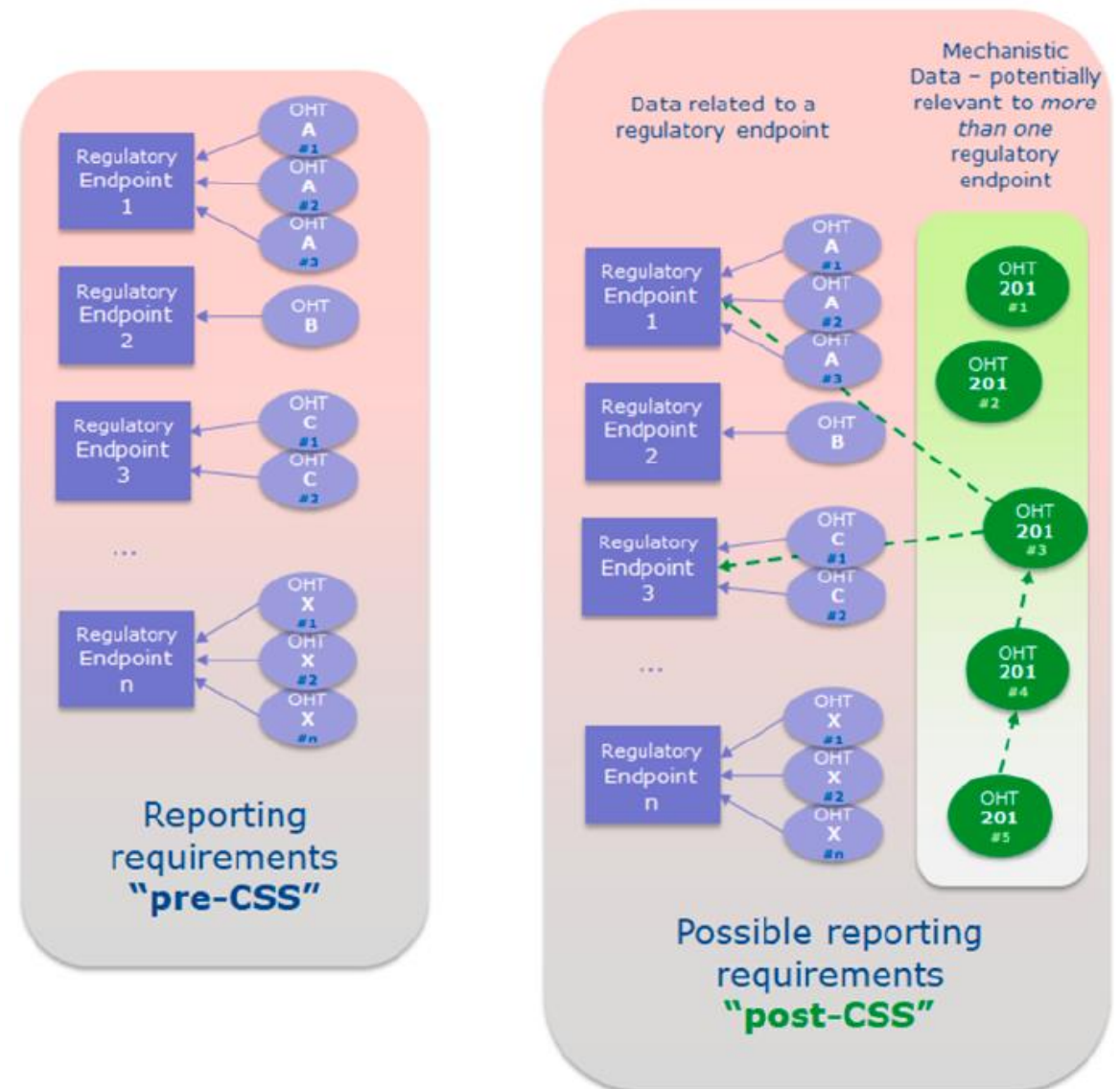
Regulatory Toxicology and Pharmacology

Volume 142, August 2023, 105426



OECD harmonised template 201:
Structuring and reporting mechanistic
information to foster the integration of
new approach methodologies for hazard
and risk assessment of chemicals

[Edoardo Carneseccchi](#)^{a 1} , [Ingrid Langezaal](#)^b, [Patience Browne](#)^a,
[Sofia Batista-Leite](#)^b, [Ivana Campia](#)^b, [Sandra Coecke](#)^b, [Bertrand Dagallier](#)^a,
[Pierre Deceuninck](#)^b, [Jean Lou CM. Dorne](#)^c, [Jose V. Tarazona](#)^{c 2}, [Francois Le Goff](#)^d,
[Eeva Leinala](#)^a, [Siegfried Morath](#)^b, [Sharon Munn](#)^b, [Jane Richardson](#)^c, [Alicia Paini](#)^{b 3},
[Clemens Wittwehr](#)^b



EFSA-ECHA PROJECT ON REPORTING QSAR DATA IN IUCLID/OHTS AND OPENFOODTOX 3.0

- IUCLID 6 fully implements the OECD Harmonised Templates (OHTs) for reporting chemical test summaries;
- **QSAR data** can be reported in IUCLID 6 using the **QPRF**; however, the QPRF is provided by IUCLID users as pdf attachment thus limiting data extraction/analysis.
- **QSAR** specific fields are NOT available in IUCLID (e.g., reliability, analogues)



Revising current OHTs structure to further **harmonise the reporting of QSAR-based data** in structured format in **IUCLID/OHTs** by:

- mapping **QPRF** fields to **OHTs structure**
- implementing the new fields in the **OHT format/IUCLID**.

| QSAR Prediction Reporting Format (QPRF) template | | |
|--|--|-----------------|
| | A | B |
| 1 | QPRF mapping | New QPRF number |
| 2 | Administrative information | 1 |
| 3 | Date of QPRF | 1.1 |
| 4 | QPRF author and contact details | 1.2 |
| 5 | | |
| 6 | Substance* | 2 |
| 7 | CAS number | 2.1 |
| 8 | EC number | 2.2 |
| 9 | Other numerical identifiers | 2.3 |
| 10 | Chemical name | 2.4 |
| 11 | Structural formula | 2.5 |
| 12 | Structural and composition information | 2.6 |
| 13 | SMILES | 2.6.a |
| 14 | InChi | 2.6.b |
| 15 | Other structural representation | 2.6.c |
| 16 | Stereochemical features | 2.6.d 2.6.e |
| 17 | Composition information | |
| 18 | Comments on substance information | - |
| 19 | | |
| 20 | Model and software | |
| 21 | Model name | 3.1.a |
| 22 | Version | 3.1.b |
| 23 | Reference to QMRF | 3.1.c |
| 24 | Comments on model | - |
| 25 | Software implementation | 3.2.a |
| 26 | Software name | 3.2.b 3.2.c |
| 27 | Software version | |
| 28 | Software reference | 3.2.d |



CONCLUSIONS AND FUTURE PERSPECTIVES

OpenFoodTox (OFT) 2.0

- Updated version of DB available [open source](#) (Zenodo, Micro-strategy tool) including **new** properties (**1,240 substances** from 667 Opinions):
 - **ADME/PK/TK**
 - **Phys-chem**
- New QSAR models and VERA tool developed using OFT data for a range of species and endpoints;
- Predicted values using **23 VEGA models** for a range of pp;
- Final External Report (by contractors) by June 2023.



EXTERNAL SCIENTIFIC REPORT



APPROVED: dd/mm/yyyy

PUBLISHED: dd/mm/yyyy

Maintenance, update and further development of EFSA's Chemical Hazards: OpenFoodTox 2.0

Emilio Benfenati, Alessandra Roncaglioni, Nadia Iovine, Marco Marzo, Andrey Toropov, Alla Toropova, Andrea Ciacci, Marta Lettieri, Luca Sartori, Chihae Yang, Tomasz Magdziarz, Bryan Hobocienski, Aleksandra Mostrag

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CONCLUSIONS AND FUTURE PERSPECTIVES

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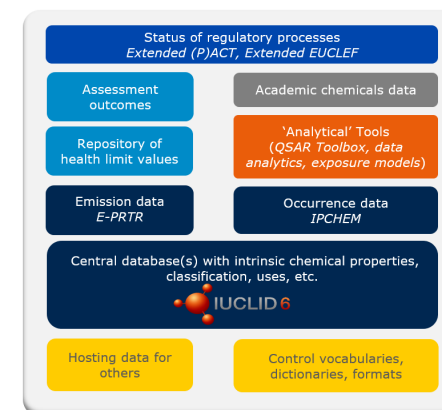
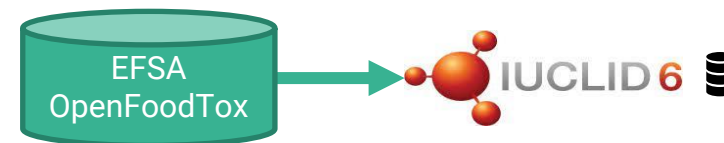
Emilio Benfenati, Alessandra Roncaglioni, Nadia Iovine, Marco Marzo, Andrey Toropov, Alla Toropova, Andrea Ciacci, Marta Lettieri, Luca Sartori, Chihae Yang, Tomasz Magdziarz, Bryan Hobocienski, Aleksandra Mostrag

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CONCLUSIONS AND FUTURE PERSPECTIVES

OpenFoodTox (OFT) 3.0

- **First** available version of **OFT** db in **IUCLID 6** by Dec 2023;
- **Additional** EFSA's hazard **datasets** (e.g., food flavourings, botanicals, food enzymes) integrated into OFT;
- **Interoperability** of OFT with **EU Common Data Platform on Chemicals** (EU CDPC) and **OECD IT environment** (e-ChemPortal, OECD QSAR Toolbox);
- New ***in silico*** tools (e.g., QSARs, read-across, grouping based on AOPs) available in 2025.



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