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Review article

EFSA's OpenFoodTox: An open source toxicological database on chemicals in food and feed and its future developments

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ABSTRACT

Since its creation in 2002, the European Food Safety Authority (EFSA) has produced risk assessments for over 5000 substances in >2000 Scientific Opinions, Statements and Conclusions through the work of its Scientific Panels, Units and Scientific Committee. OpenFoodTox is an open source toxicological database, available both for download and data visualisation which provides data for all substances evaluated by EFSA including substance characterisation, links to EFSA's outputs, applicable legislations regulations, and a summary of hazard identification and hazard characterisation data for human health, animal health and ecological assessments. The database has been structured using OECD harmonised templates for reporting chemical test summaries (OHTs) to facilitate data sharing with stakeholders with an interest in chemical risk assessment, such as sister agencies, international scientific advisory bodies, and others. This manuscript provides a description of OpenFoodTox including data model, content and tools to download and search the database. Examples of applications of OpenFoodTox in chemical risk assessment are discussed including new quantitative structure–activity relationship (QSAR) models, integration into tools (OECD QSAR Toolbox and AMBIT-2.0), assessment of environmental footprints and testing of threshold of toxicological concern (TTC) values for food related compounds. Finally, future developments for OpenFoodTox 2.0 include the integration of new properties, such as physico-chemical properties, exposure data, toxicokinetic information; and the future integration within *in silico* modelling platforms such as QSAR models and physiologically-based kinetic models. Such structured *in vivo*, *in vitro* and *in silico* hazard data provide different lines of evidence which can be assembled, weighed and integrated using harmonised Weight of Evidence approaches to support the use of New Approach Methodologies (NAMs) in chemical risk assessment and the reduction of animal testing.

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Table 1
Chemical risk assessment and EFSA scientific panels.

Chemicals	EFSA Scientific Panel
Food additives and flavourings	Food additives and Flavourings (FAF)
Food contact materials, enzymes, processing aids	Food Contact Materials, Enzymes and Processing Aids (CEP)
Vitamins, minerals, novel foods	Dietetic Products, Nutrition and Allergies (NDA)
Feed additives, flavourings, coccidiostats, histomonostats	Feed additives (FEEDAP)
Plant Protection Products e.g. insecticides, herbicides, fungicides	Plant Protection Products and their Residues (PPR) EFSA Pesticide Peer Review Unit (PREV)
Contaminants-Anthropogenic e.g. brominated flame retardants, dioxins), environment (e.g. heavy metals), food/feed processing (e.g. acrylamide), -Toxins of natural origin e.g. alkaloids, mycotoxins, marine biotoxins	Contaminants in the food chain (CONTAM)

1. Introduction

The European Food Safety Authority (EFSA) is the keystone of European Union (EU) risk assessment (RA) food and feed safety. In close collaboration with national authorities and stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks. EFSA provides scientific advice to risk managers and decision makers through RA and risk communication on all issues related to "food and feed safety, animal health and welfare, plant health, nutrition, and environmental issues" (EC, 2002). RA has been defined as 'a scientifically based process consisting of four steps: hazard identification, hazard characterisation, exposure assessment and risk characterisation' (EC, 2002; WHO, 2009).

A key feature of RA in the food and feed safety areas is the determination of safe levels of exposure for chemicals to protect human health, animal health or the environment though hazard identification and characterisation. This is performed most commonly using toxicology studies in test species (rats, mice, dogs, rabbits, fish, daphnia etc) that provide the basis for a Reference Point (RP) or point of departure (PoD). These are then divided by uncertainty factors (UF) to derive Reference Values (RV). Examples of RPs for human health and animal health effects include Lowest or No-Observed–Adverse-Effect-Level (LOAEL/NOAEL), the upper limit of the Benchmark Dose (BMDL, e.g. BMDL10) or No Observed Effect Concentration (NOECs) for ecotoxicological effects (daphnia, fish, bees, etc.). Examples of RVs in the human health area include health-based guidance values for chronic exposure in humans such as acceptable daily intake (ADI) for food and feed additives, pesticides and food contact materials, Tolerable Upper Intake Levels (UL) for vitamins and minerals and tolerable daily intake (TDI) for contaminants (EFSA NDA, 2006). Since 2002, EFSA has assessed over 5000 regulated substances and contaminants in >2000 scientific opinions on single substances and groups of substances (e.g. flavourings). For regulated compounds and contaminants, such RAs have been mostly performed in EFSA by five scientific panels and five supporting units highlighted in Table 1.For compounds falling under the remit of more than one panel, the RA have been performed by the Scientific Committee of EFSA, supported by the Scientific Committee and Emerging Risks Unit (SCER); a relevant example is the risk assessment of carvone used as a plant protection product and a flavouring (EFSA Scientific Committee, 2014a).

From all these risk assessments performed at EFSA, it has been recognised that a structured database summarising the toxicological endpoints and reference values on a substance-specific basis would be instrumental in disseminating these results to a wider community, and would be of great support for the work of EFSA experts and staff in providing scientific advice. This was further highlighted in EFSA's

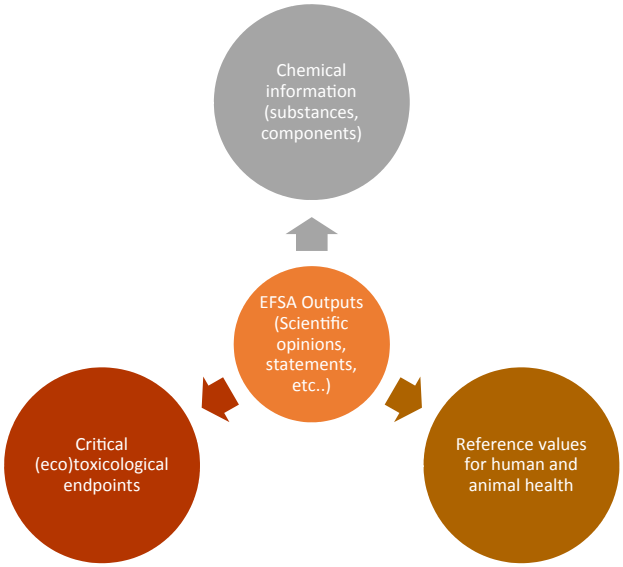

Fig. 1. Qualitative overview of data organisation in OpenFoodTox.

Strategy 2020 to "Widen EFSA's evidence base and optimise access to its data" and this underpinned EFSA's plan to "migrate towards structured scientific data" as a move towards efficiency, innovation (EFSA, 2016). In addition, the EFSA Strategy also promoted the structuring of data from monitoring schemes, regulated product applications and EFSA outputs, in agreed formats and, where possible, on existing international standards to allow re-use and modelling of such data to develop tools including for the development of *in silico* tools and the likes for predicting toxicity properties of chemicals when hazard data are lacking.

Consequently, EFSA developed a structured database as a repository for all hazards data used by EFSA in its risk assessment since the creation of the agency. The data collection started in 2011 with the creation of a data model using OECD (Organisation for Economic Co-operation and Development) Harmonised Templates[4] for Reporting Chemical Test Summaries (OHTs). OHTs are international standard data formats for reporting information on chemicals to determine their properties or effects on human health and the environment (e.g. toxicokinetics, skin irritation, repeated dose toxicity, biodegradation in soil, metabolism of residues in crops, etc.) and also to describe their use and related exposure to workers, consumers and the environment. In addition, access through the OECD's Global Portal to Information on Chemical Substances (e-ChemPortal), enables sharing of hazard data with sister agencies (i.e. European Chemical Agency (ECHA), European Medicines Agency (EMA), national and international scientific advisory bodies (FDA, US-EPA, WHO, FAO) (S-IN, 2013, 2014, 2015).

This manuscript describes EFSA's OpenFoodTox database including its structure, data model and content as well as tools to respectively download and access the database. In addition, available applications of OpenFoodTox in chemical risk assessment are described and include the development of new quantitative structure–activity relationship (QSAR) models, its integration into *in silico* platform (OECD QSAR Toolbox and AMBIT-2.0), assessment of environmental footprints and testing of threshold of toxicological concern (TTC) values for food related compounds (Benfenati et al., 2017; Reilly et al., 2019; Saouter et al., 2018). Finally, the future development of OpenFoodTox are highlighted particularly in relation to the implementation of New Approach Methodologies (NAMs) in the food and feed safety (EFSA, 2014b; Benfenati et al., 2017; Benfenati et al., 2020).

[4] https://www.oecd.org/ehs/templates/

2. Structure and data model

2.1. Basic structure

OpenFoodTox summarises chemical information, (eco)toxicological reference points and reference values of the substances evaluated by all EFSA panels in their Scientific opinions, Statements, or Conclusions since its creation in 2002 (Benfenati et al., 2020). Fig. 1 provides a qualitative overview of OpenFoodTox as a relational database for which the data are structured and integrated according to:

- Chemical identification of the chemical entities assessed in the EFSA documents, including information on nomenclature, chemical formula, and structure (e.g., name, formula, CAS and EC numbers, IUPAC, InChI and SMILES).
- Description of EFSA outputs, with the background regulation of interest underlying the panel's evaluation.
- Conclusions on the mutagenicity, genotoxicity and carcinogenicity of the substance as discussed in the corresponding EFSA output.
- Hazard identification and characterisation reporting:

1. The critical toxicological studies and reference points (NOAEL, BMDL, LOAEL, LC_{50}. LD_{50}) identified and selected for human health, animal health or ecological endpoints with additional data on non-target and target species (animal health) and ecotoxicological data for soil and water compartments.
2. Reference values such as Health-Based Guidance Values (HBGV) for humans (e.g., ADI, TDI, UL) and environmental standards (i.e. PNEC), as derived from the reference points while applying uncertainty factors (most often the 100-fold default factor has been applied).

2.2. Data model

The data model was first designed using a critical review of OHTs (i.e. generic elements for all OHTs, health effect series, effects on biotic systems) to ensure that the data groups and the implemented fields would cover most of the key data related to chemical identification and toxicity. In a second step, the data model was modified to systematically include data reporting chemical identification, EFSA outputs, hazard identification and hazard characterisation (OECD, 2020).

2.2.1. Substance identification: Substances and components

Substance identification within OpenFoodTox includes each individual chemical entity (compounds or products) assessed in a relevant EFSA output and is associated with a critical (eco)toxicological study as a reference point and a reference value and when assessed the related genotoxicity, and/or carcinogenicity. Notably, when only exposure information is described in EFSA scientific outputs, neither the corresponding EFSA Scientific Opinion, nor the substance are included in the database. In summary, registered substances are entities that have been assessed for their hazards in each EFSA output.

It should be noted that substances are either chemical entities (compounds or mixtures or formulations) or food products (e.g. chia seeds) (EFSA, 2009, 2005a). A substance may also be a group of compounds undergoing a group assessment (e.g., fumonisins) (EFSA, 2005b). In general, organisms or biotechnology products (e.g. microorganisms, fungi, nematodes, and enzymes) are excluded from OpenFoodTox, although some complex products (e.g., natural products) are included in the database. Whenever possible, a substance is described in terms of individual chemical components.

Qualifiers for chemical identification for substances and components include substance/component name, component type, EC ref number, CAS number, IUPAC name, molecular formula, structure shown of component, InChI and SMILES notation, synonyms and have been retrieved from EFSA outputs and from publicly available resources, such as ChemSpider, PubChem, and ChemIDPlus. Each substance is tagged according to a classification analogous to the one defined by EFSA (2012) which describes the type of substance (e.g., single chemical entity, mixture, complex product). This classification is illustrated in Table 2.

Table 2
Substance identification in OpenFoodTox.

Substance Tags	Description
Single chemical entity	A chemical that cannot be further described in terms of other defined chemical entities.
Mixture or formulation	Substances that can be decomposed in terms of different chemical entities which are possibly described in the related component table. The components of a mixture or formulation are the chemical compounds forming the mixture or formulation.
Complex product (from botanical sources)	Products or complex mixtures derived from botanical sources (e.g., steviol glycosides from Stevia, or rosemary extracts).
Complex product (from microorganisms)	Complex product: microorganisms or derived from microorganisms.
Complex mixtures	Complex mixtures not derived from botanical sources (e.g., mineral hydrocarbons, beeswax, shellac).
Polymer	Polymers.
Group	A group of substances undergoing a group assessment (e.g., mycotoxins). A substance that is defined as a group may also fulfil the definition of complex mixture. The classification of group or complex mixture strongly depends on the assessment described in the opinion. The group may be of two types: group closed, i.e. the components of the group are well defined, and the assessment refers only to the well-defined components of the closed group; group open, i.e. the components of the group are not well defined, and the assessment refers to the generic definition of this group.

Table 3
Bibliographic details of the EFSA documents included in OpenFoodTox.

Bibliographic details	Description
Title	Title of the document
Reference type	Type of document: EFSA opinion or statement or conclusion on Pesticides Peer Review
Adoption date	The adoption date of the opinion/statement/conclusion
Publication date	The publication date of the opinion/statement/conclusion
Regulation	The main regulation triggering the assessment discussed in the corresponding document
Question number	Question number(s) associated with the document

2.2.2. EFSA outputs

Individual EFSA scientific outputs produced by EFSA panels and units are stored in the database as EFSA opinions, statements or conclusions on pesticides peer review and the most relevant descriptors of the documents are reported in Table 3.

2.2.3. Hazard identification for genotoxicity

The main classification classes for genotoxicity that are available OpenFoodTox include as qualifiers: positive, negative, ambiguous, no data or not determined. Other qualifiers in the database report the conclusion of the mutagenicity (M), genotoxicity (G), and carcinogenicity (C) for the substances assessed by EFSA as they are reported in the relative EFSA outputs.

Whilst the three terms "Positive/Negative/Ambiguous" are characterised by a straightforward meaning. It is noticed that the difference between the terms "no data" and "not determined" may lead to ambiguous interpretation of the assigned classification as inserted into the OpenFoodTox.

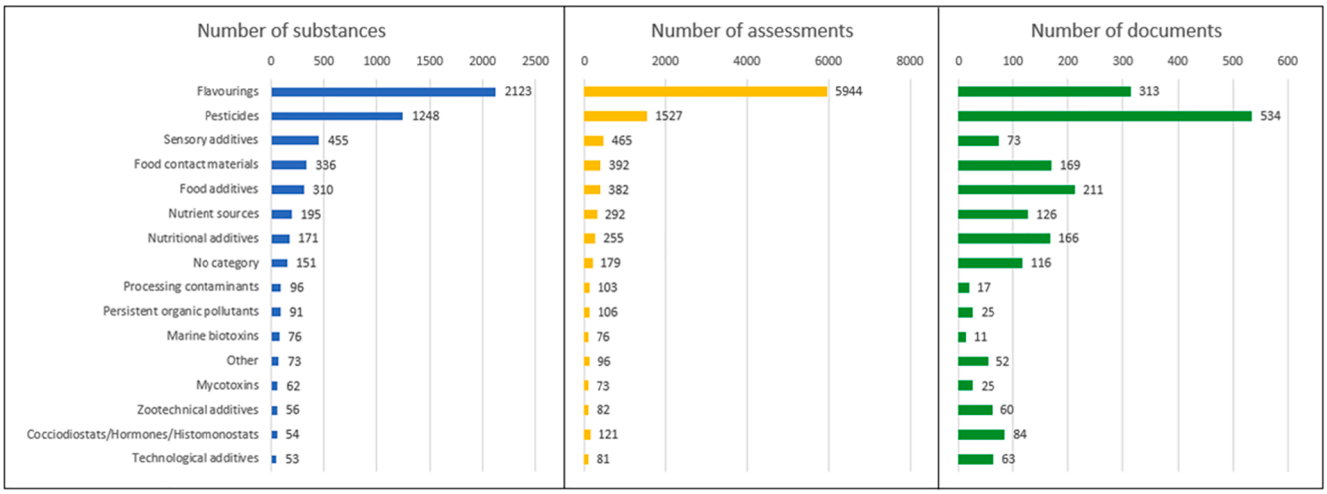

Fig. 2. Chemical hazards data available in OpenFoodTox with regards to number of substances, assessments and EFSA outputs (documents) for different EFSA regulatory areas. EFSA outputs include opinions, statements and conclusions. Number of assessments include assessment of a substance in a given opinion. Substances may be assessed in more than one document. A document of a given regulatory area may also deal with more than one substance. The category named "Other" includes the following classes: Melamine, Processing aids, Heavy metal ions and metalloids, Feed intended for particular nutritional purposes, Natural plant product contaminants, substances as part of meat inspection.

The term "No data" is selected whenever one specific endpoint (i.e., M, G, C) is not mentioned or discussed in the EFSA output for that specific substance. As a typical example, when no carcinogenicity assessment has been performed for a specific plant protection product, and the endpoint is not cited in the EFSA document, the qualifier "no data" is assigned. "No data" is also assigned for specific flavouring substances for which no carcinogenicity studies are available, although, the procedure is reported to be applicable to the single substance (or to its flavouring group) when no safety concern has been concluded.

The term "Not determined" has been selected when the investigated endpoint (i.e., M, G, C) is did not allow a conclusion to be clearly formulated, reached or reported due to insufficient data from the EFSA output.

The above-described use of "No data" and "Not determined" aims at reporting only what is clearly stated in the EFSA output to avoid misinterpretation of the available data or the data gaps that have been identified.

Finally, the term "Other" is generally used for special cases namely a) when a substance is reported to induce co-carcinogenic effects; b) when either carcinogenic or genotoxicity effects are deemed not to be relevant to humans; c) when a substance is reported to be a likely threshold carcinogen; d) when a substance is negative in the *in vivo* genotoxicity tests, but positive in the *in vitro* genotoxicity tests, e) when no additional conclusions are provided and f) when the endpoint of interest (M, G, C) is waived. Conclusions of genotoxicity based on substances' predictions are addressed in the same way as those based on experimental data. The current 2020 version of OpenFoodTox includes further details of the genotoxicity studies only for substances classified as "Positive" for M and/or G.

2.2.4. Hazard identification and characterisation: Reference points and reference values

The database contains all available hazard data as critical or apical toxicological endpoints that have been used by EFSA for hazard identification and hazard characterisation with regards to human health, animal health and ecological risk assessment. For human health, these reference points form the basis for the derivation of reference values in the hazard characterisation most of which as health-based guidance values (i.e. ADIs for regulated substances and TDIs for contaminants) or margin of exposure (MOE) or margin of safety (MOS) values in the risk characterisation. Reference points and reference values are described in the database by a number of properties and values, including:

- Hazard identification category: Human health, Animal health (non-target species), Animal health (target species), Ecotoxicology (soil compartment), Ecotoxicology (water compartment)
- Any guideline followed in the toxicity tests
- Species
- Route of administration
- acute, sub-chronic and chronic exposure
- Type of reference point (e.g., NOAEC, NOAEL, LOAEL, LOEL, EC50, LC50, LD50)
- Toxicity target (e.g., Systemic, Hepatotoxicity, Nephrotoxicity, Neurotoxicity etc)
- Observed effects

These properties are thoroughly described elsewhere and summarised in the supplementary material Table S1. Picklists for each field had been defined through a terminology catalogue (S-IN Soluzioni Informatiche, 2018).

Overall, hazard data were available for 12 broad taxa including aquatic invertebrates, aquatic fish, aquatic algae, aquatic plants, mammals, birds, earthworms, honeybees, arthropods other than bees, terrestrial plants, collembolan and soil mites, sediment organisms. Data for all reported endpoints are described in the hazard identification and characterisation section below (S-IN Soluzioni Informatiche, 2018; Benfenati et al., 2020).

3. Hazard identification and characterisation

3.1. General content

OpenFoodTox logically maps the structure of 2040 EFSA outputs (scientific opinions, statement and conclusions) a total 10,174 assessments published between 2003 and May 2019 and includes summary data for hazard identification and characterisation for 49,580 substances. Overall, 92% of the substances are organic compounds with very few inorganic compounds (8%). The majority of the chemicals is associated with a molecular structure expressed as SMILES and InChI which is tagged as "representative" when the chemical cannot be uniquely defined by a single molecular representation (e.g. 2-Pentyl-5 or 6-keto-1,4-dioxane).

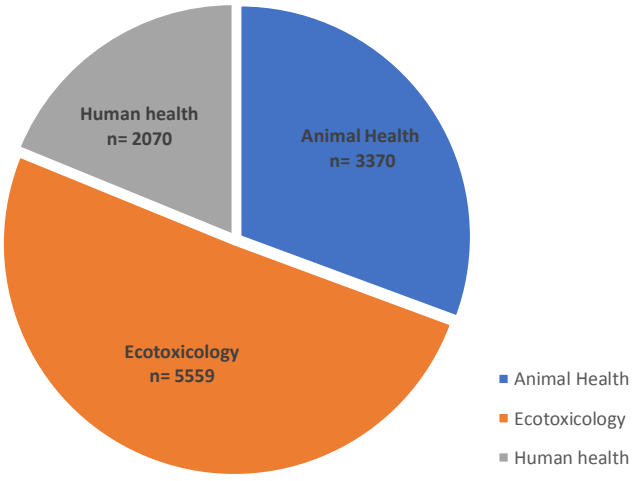

Fig. 3. Classification of toxicity studies collected in OpenFoodTox.

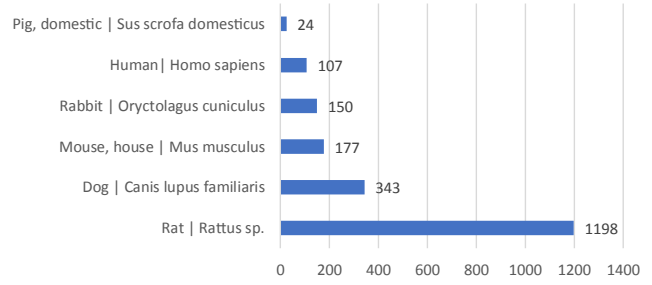

Fig. 4. Classification of toxicity and epidemiological studies in OpenFoodTox for the human health area. Data entries in the database are shown for sub-chronic and chronic studies for reported species with sample size > 15.

Fig. 2 illustrates the general content of the database:

- -Flavourings (2124 substances, 5944 assessments and 313 opinions and statements);
- -Pesticides (1248 substances, 1527 assessments and 534 conclusions);
- -Feed additives as sensory additives and zootechnical additives (455 and 56 substances, 465 and 82 assessments, 73 and 60 scientific opinions respectively); coccidiostats, hormones and histomonostats (54 substances, 121 assessments and 84 scientific opinions).
- -Food contact materials (455 substances, 465 assessments and 73 scientific opinions)
- -Food and technological additives (310 and 53 substances, 382 and 81 assessments and 211 and 63 scientific opinions respectively).
- -Nutritional sources (195 substances, 292 assessments and 126 scientific opinions)
- -Contaminants: processing contaminants and persistent organic pollutants (96 and 91 substances, 103 and 106 assessments and 17 and 25 scientific opinions respectively); marine biotoxins and mycotoxins (76 and 62 substances, 76 and 73 assessments and 11 and 25 scientific opinions respectively). Other substances include compounds with no category and other substances (151 and 73 substances, 179 and 96 assessments, 116 and 52 scientific opinions respectively). In this classification, other substances include melamine, processing aids, heavy metal ions and metalloids, feed intended for nutritional purposes, natural plant product contaminants and substances as part of meat inspection.

Fig. 3 illustrates the general classification of available toxicity studies in the human health (n = 2070), animal health (n = 3370) and ecotoxicology (n = 5559) areas.

For the human health hazard assessment, Fig. 4 illustrates available hazard data which are mostly available for test species (rat > Dog > mouse > rabbit > pig) with limited epidemiological data in humans.

For the animal health area, Fig. 5 highlights the largest number of sub-chronic and chronic toxicological studies:

- Mammalian species include the rat > mouse > rabbit > pig > cattle > dog > sheep > horse.
- Bird species include Bobwhite quail > mallard duck > Japanese quail > Chicken > Pheasant > turkey > common quail.

For the ecotoxicological area, OpenFoodTox reports large datasets for terrestrial and aquatic plant and animal species and analysis are provided in the following Section 3.3.

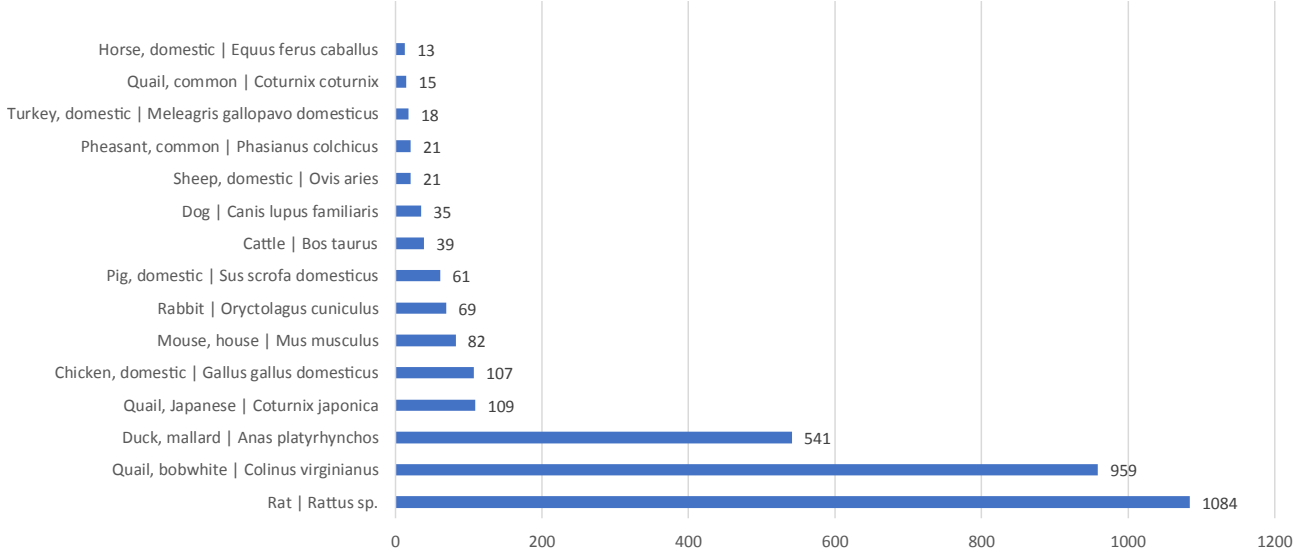

Fig. 5. Classification of toxicity studies in OpenFoodTox for the animal health area. Data entries in the database are shown for sub-chronic and chronic studies for reported species with sample size > 10.

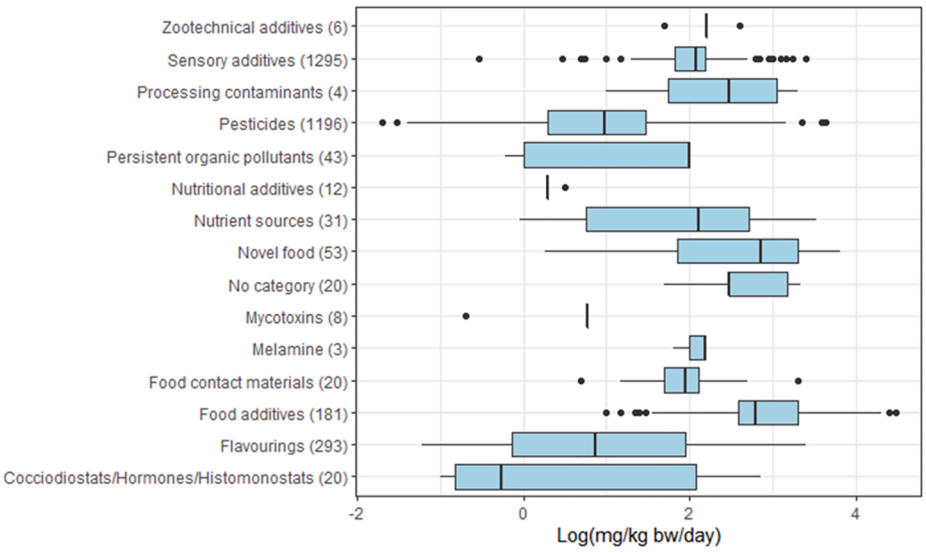

Fig. 6. Box and whisker plots of reference points in OpenFoodTox for human health risk assessment of non-cancer effects. Reference points are expressed on the log-scale as No-observed-effect-levels (NOEL) and No-observed-adverse-effect level (NOAEL) (mg/kg bw per day) from sub-chronic to chronic studies in rats for all chemicals. The box plot represents the median with the extremes as the 1st and 3rd quartiles. The whiskers represent 1.5-fold inter-quartile distance on either side of the median. The dots represent outliers from the box and whisker plots.

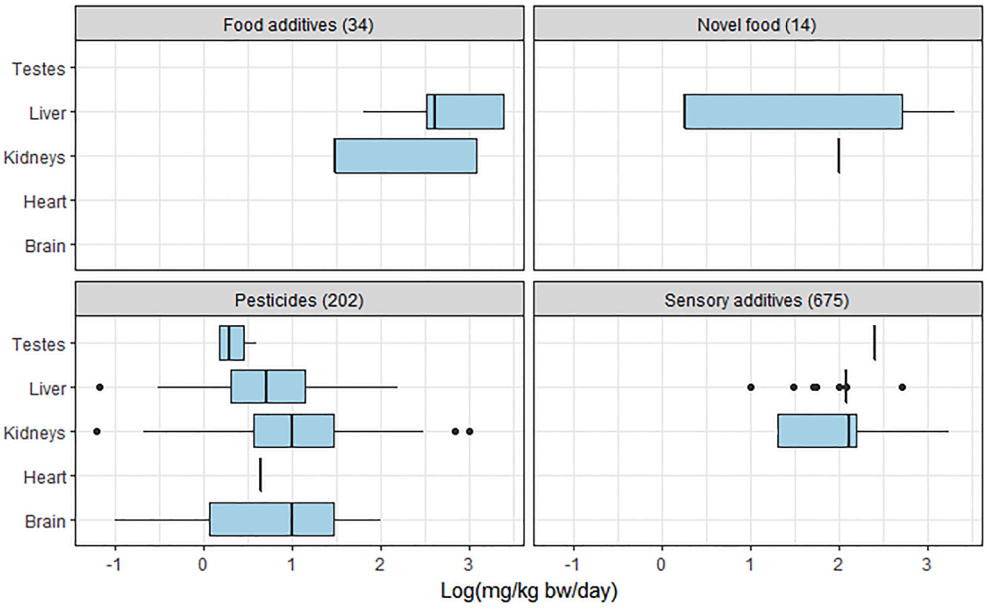

Fig. 7. Box and whisker plots of reference points in OpenFoodTox for human health risk assessment of non-cancer effects classified by target organ toxicity. Reference points are No-observed-effect-levels (NOEL) and No-observed-adverse-effect level (NOAEL) values from sub-chronic to chronic studies in rats. For food additives, novel foods, pesticides and sensory additives The box plot represents the median with the extremes as the 1st and 3rd quartiles. The whiskers represent 1.5-fold inter-quartile distance on either side of the median. The dots represent outliers from the box and whisker plots.

3.2. Hazard data for human health risk assessment

A thorough analysis of the available hazard data in OpenFoodTox has been performed in the freeware R to visualise all available reference points by regulatory areas. Data were expressed on the log scale in mg/kg body weight per day to visualise toxic potencies in box and whisker plots highlighting median, extremes as the 1st and 3rd quartiles, as well as outliers Fig. 6 highlight the results of the analysis for reference points derived from sub-chronic to chronic rat studies reporting non-cancer effects (NOAELs and NOELs).

Fig. 7 illustrates the available NOAELs and NOELs in rats for regulated chemicals that have been sub-classified by target organs. This analysis is illustrated here for food additives, novel food, pesticides and sensory additives for which key target organs (tests, liver, kidney and brain) are known for a significant number of compounds (n > 10). For pesticides (n = 220), analysis of liver toxicity provided a median of 5 [range 0.065–157] while potency was 2.5-fold higher in the testes [median: 2, range 1.5–3.9] and two fold lower [median:10] in the kidney [range 0.065–157] and brain [range 0.1–100] respectively. For sensory additive assessments (n = 675), liver and kidney toxicity were much lower than that for pesticides with medians and ranges of 120–128 and range [10–500] and [20–1730] respectively. For food additives (n = 34), potency for kidney toxicity was higher [median: 30, range 30–1206] than that for liver toxicity [median: 400, range 63–2400]. Data for novel food were the most limited in the database (n = 14) and values for liver toxicity indicated a median of 1.8 mg/kg bw/day with a wide range between 1.8 and 2000.

For cancer effects, data are limited to contaminants and are illustrated in Fig. 8 with BMDL values from carcinogenesis studies in rats (n = 12), mouse (n = 58) and human epidemiological studies (n = 18). Aflatoxin B1 is shown as the most potent compound for liver carcinogenesis [median: 0.00017, range 0.000078–0.00087] and is orders of magnitude more potent compared with the least potent compound in the database: nitrofurantoin [median: 29.5, ranging: 29.5–61].

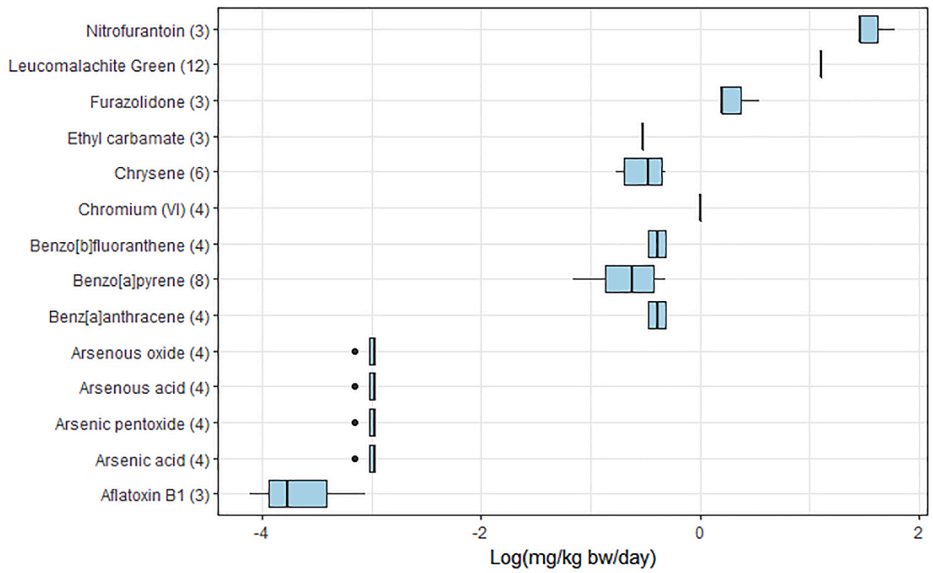

Fig. 8. Box and whisker plots of reference points in OpenFoodTox for human health risk assessment of cancer effects. Reference points are expressed as benchmark dose limit (BMDL) from carcinogenesis studies in rats, mice and epidemiological studies in humans. The whiskers represent 1.5-fold inter-quartile distance on either side of the median. The dots represent outliers from the box and whisker plots.

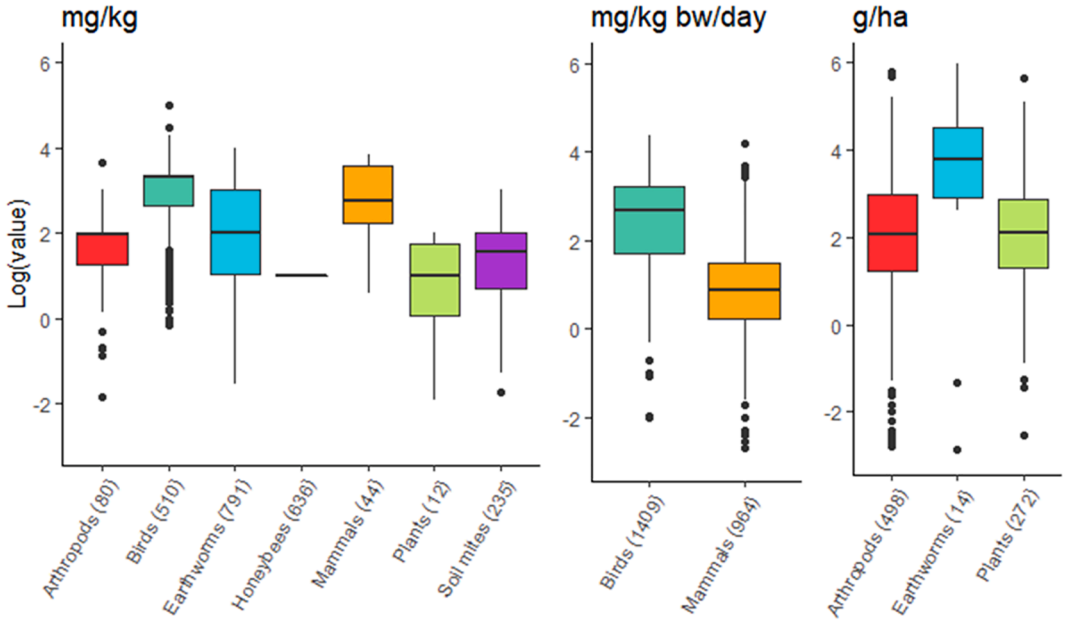

Fig. 9. Box and whisker plots of reference points in OpenFoodTox for the toxicity of plant protection products in terrestrial organisms. Reference points expressed in 1. mg/kg are Lethal Dose 50% (LD_{50}) available for arthropods, birds, earthworms; honeybees, mammals, plants and soil mites; 2.mg/kg body weight per day are No-observed adverse Effect level (NOAEL) for birds and mammals. 3. g/ha are application rates per hectare and are available for arthropods, earthworms and plants. The whiskers represent 1.5-fold inter-quartile distance on either side of the median. The dots represent outliers from the box and whisker plots.

3.3. Hazard data for animal health and ecological risk assessment

3.3.1. Hazard data for terrestrial organisms

Hazard data for terrestrial organisms are available in OpenFoodTox for plant protection products and are highlighted in Fig. 9 for non-target arthropods, earth worms, honey bees, soil mites, plants, mammals and birds. These reference points are reported on the log scale for LD_{50} expressed in mg/kg (arthropods, birds, earthworms; honeybees, mammals, plants and soil mites); NOAEL in mg/kg body weight per day (birds and mammals) and as application rates in g/ha (arthropods, earthworms and plants).

3.3.2. Hazard data for aquatic organisms

Hazard data for aquatic organisms are also available in OpenFoodTox for plant protection products and are highlighted in Fig. 10 for algae, fish, invertebrates and plants. The available reference points values are three-fold namely median effective concentration (EC_{50}), median lethal concentration (LC_{50}) and no observed effect concentration (NOEC) for different aquatic species expressed on the log scale.

4. Open access tools

Open access tools to download OpenFoodTox include EFSA knowledge junction which provides the full database for download as well as a

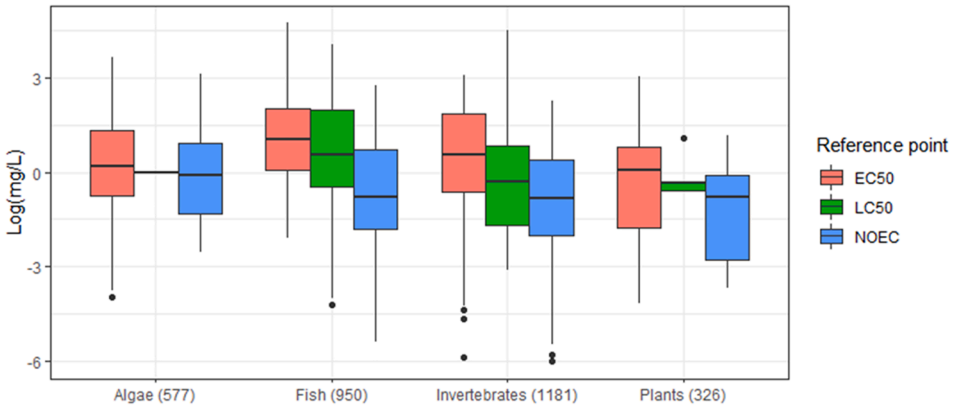

Fig. 10. Box and Whisker plots of reference point values for aquatic organisms (EC_{50}, LC_{50} and NOEC) (mg/L) in OpenFoodTox EC_{50}: Effective concentration 50%, LC_{50}: Lethal dose 50%, NOEC: No-Effect-Concentration. The whiskers represent 1.5-fold inter-quartile distance on either side of the median. The dots represent outliers from the box and whisker plots.

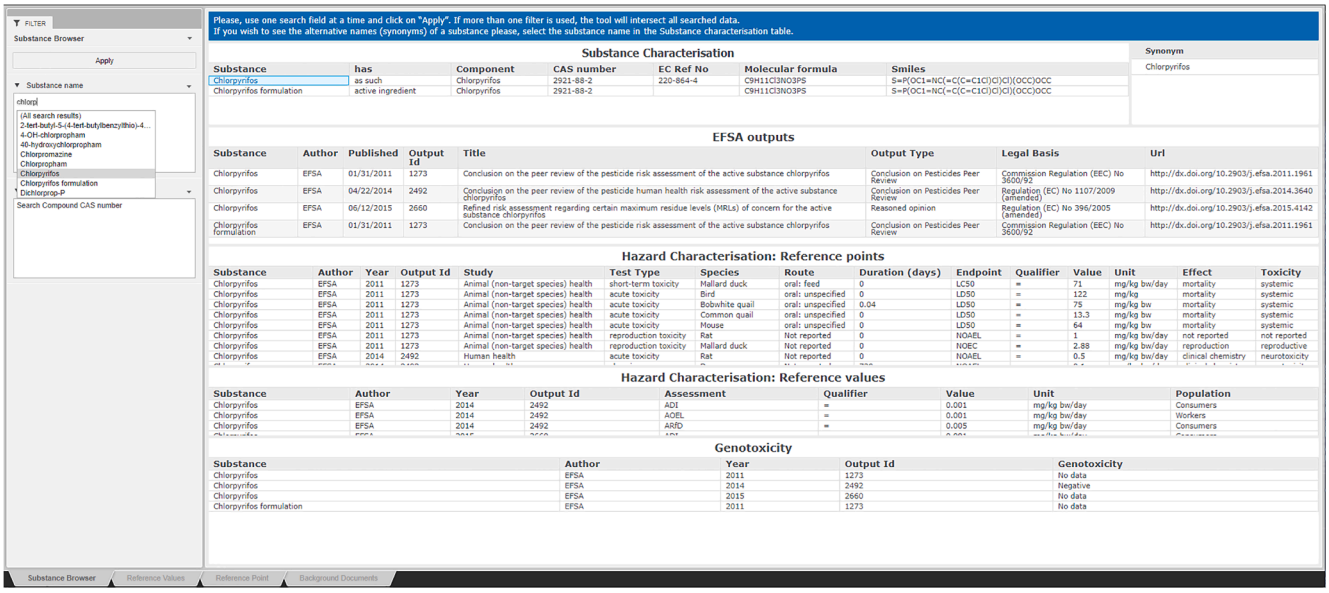

Fig. 11. OpenFoodTox substance browser and summary tables.

micro-strategy tool which allows to search the database and download selected datasets. These are described below.

4.1. Zenodo: EFSA's knowledge junction community

OpenFoodTox data (27 March 2020) and its related meta-data are published on the EFSA's Knowledge Junction community on Zenodo (Benfenati et al., 2020) under:

- The persistent Digital Object Identifier: https://doi.org/10.5281/zenodo.780543always
- Link to latest version: https://zenodo.org/record/3693783#.XrKufagzZeU

This dataset provides access to six downloadable XLSX spreadsheets including one spreadsheet containing the full, and five individual spreadsheets providing all data on: 1. Substance characterisation 2. EFSA outputs, 3. Reference points, 4. The Reference values, and 5. Genotoxicity results.

4.2. Micro-strategy tool

OpenFoodTox can also be searched for using a simple viewer through Micro-strategy, a business intelligence and data analytics tool providing an interface to the data available in EFSA's Scientific Data Warehouse. This is done in an intuitive and interactive way providing a user-friendly means to navigate through reports and/or dashboards, offering responsive design, visual filters and diversity in visualisations[5]. The OpenFoodTox MicroStrategy Dashboard offers a click-of-a-mouse tool to visualise the summaries of EFSA's Hazard Assessments and allows downloading of data sheets for each individual substance. It can be accessed on personal computers, smartphones and tablets through this link: https://www.efsa.europa.eu/en/microstrategy/openfoodtox.

The "substance browser" allows filtering the database by Substance name (or synonym) or by CAS number. On the left-hand window of the screen, the substance name/CAS number is inserted, and all available toxicological data appear in the right-hand side window (Fig. 11).

The "reference points" tab offers a browser for the critical endpoints that can be filtered by type of study (i.e. assessing human health, animal

[5] https://www.microstrategy.com/us

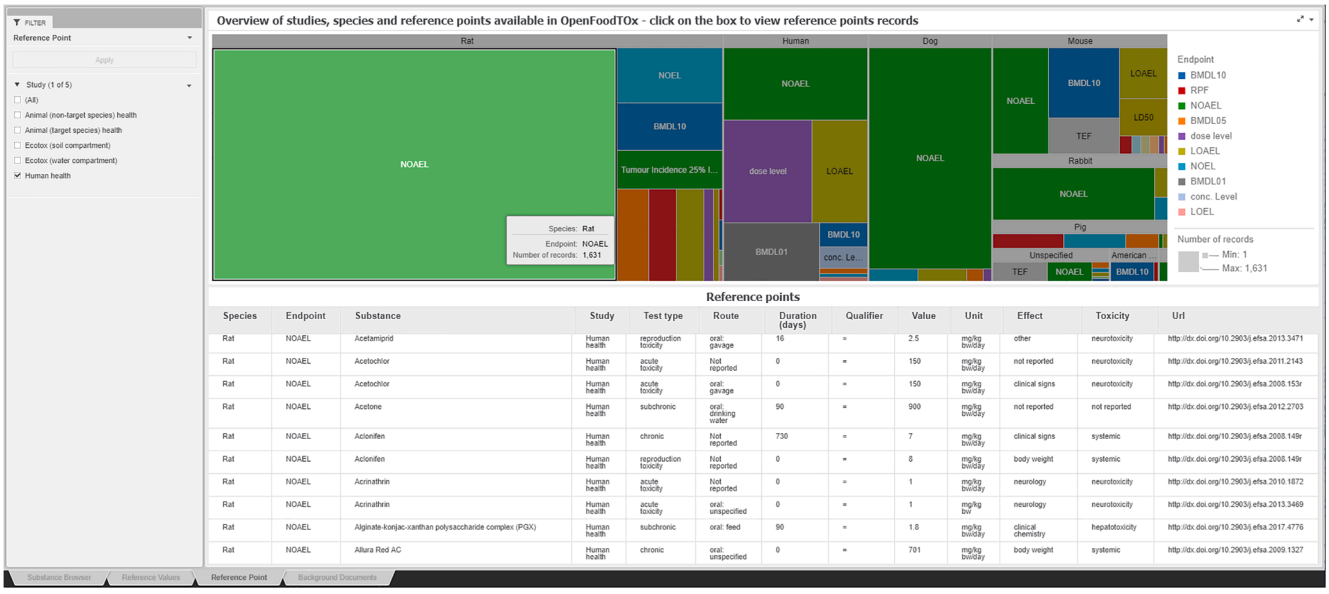

Fig. 12. OpenFoodTox reference point browser per study type, species and endpoints.

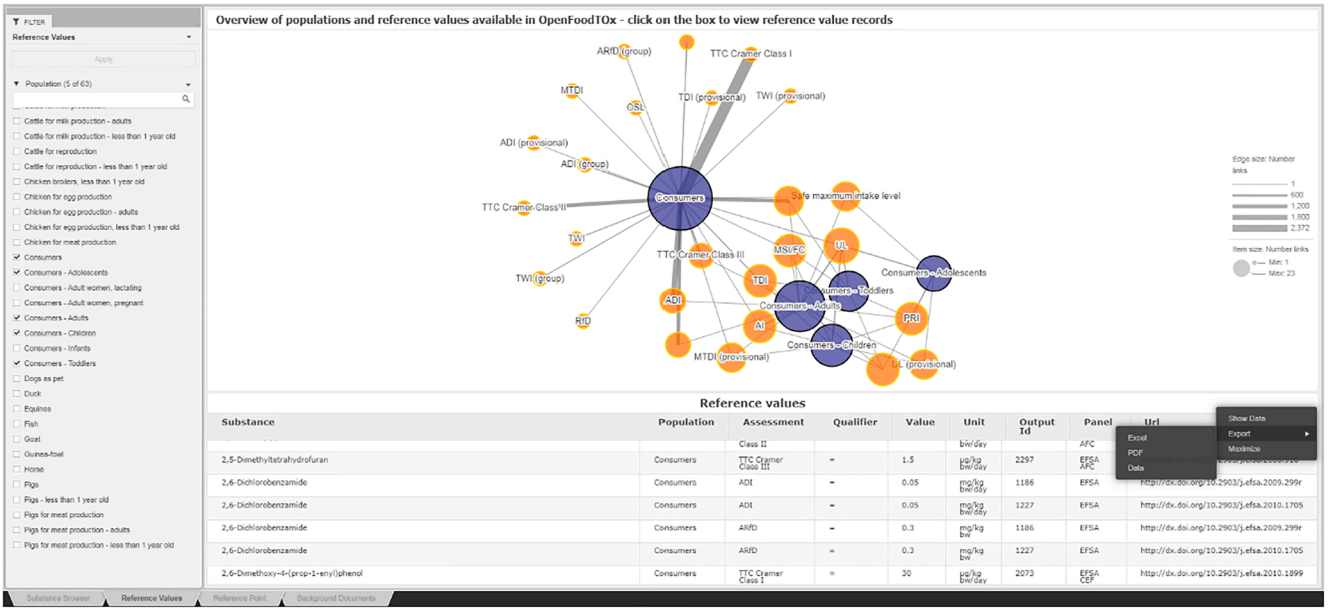

Fig. 13. OpenFoodTox reference reference value browser per population group and assessment for data export.

health, ecotox studies), species and different endpoints (Fig. 12).

The "reference values" tab provides an overview of all Reference values available downloadbale in PDF, XLS or CSV format per population group, as defined by EFSA's expert Panels (Fig. 13).

5. Applications

5.1. Development of in silico models

A number of new open source QSAR models as *in silico* models have recently been developed using OpenFoodTox datasets and other databases in some instances (US-EPA and Fraunhofer databases) for a range of test species and endpoints of relevance to human health, animal health and ecological risk assessment. Relevant references for the calibration and validation of these QSAR models for bees, fish, rats, earth worms and quails are provided in Table 4. All these models and others are available within the open source VEGA platform (Benfenati et al., 2017; Como et al., 2017; Toropov et al., 2017; Toropova et al., 2018). Overall, these QSAR models provide good prediction results ($R^2 > 0.70$) and support to risk assessors for the evaluation of human and (eco)-toxicological properties offering the possibility to extend the information present in OpenFoodTox for chemicals with no toxicity data available.

Furthermore, innovative perspectives include options to relate hazard data with a series of related features using data on multiple endpoints and increasing the number of properties within the database. This perspective has been further discussed in the EFSA guidance document on the use of the weight-of-evidence (WoE) approach in scientific assessments including non-testing methods, such as *in silico* models and read-across methods (EFSA SC, 2017; Benfenati et al., 2019; Carnesecchi et al., 2020a).

Table 4
Available open source QSAR models in the VEGA platform developed using OpenFoodTox and other datasets.

Species	Predicted hazard property	Type of model	Chemical domain
Honeybee[1] *Apis mellifera*	Acute Contact Toxicity (LD_{50})	Classification-based	PPP
Rainbow Trout[2] *Oncorhynchus mykiss*	Acute Contact Toxicity (LC_{50})	Regression-based (CORAL)	PPP
Rat3 *Rattus norvegicus*	Sub-chronic toxicity (NOAEL)	Regression-based (CORAL)	All classes
Earth worm4 *Eisenia fetida*	Acute contact toxicity (LC_{50})	Regression-based	PPP
Honeybee[5] *Apis mellifera*	Acute contact toxicity (LD_{50})	Classification and Regression-based	PPP
Honeybee[6] *Apis mellifera*	Acute Contact Toxicity (LD_{50}) and MoA	Regression based MoA profiler	PPP
Honeybee[7] *Apis mellifera*	Acute contact toxicity (LD_{50}) Binary mixture Synergism / Non-synergism LD_{50} mixture as Toxic Units	Classification and Regression-based (CORAL)	PPP and veterinary drugs
Earth worm[8] *Eisenia fetida*	Acute Oral Toxicity (LC_{50})	Classification-based	PPP
Rat[9] *Rattus norvegicus*	Sub-chronic toxicity (NOAEL and LOAEL)	Regression-based (CORAL)	All classes
Earth worm[10] *Eisenia fetida*	Acute Oral Toxicity (LC_{50})	Classification-based (CORAL)	PPP
Bobwhite quail[11] *Colinus virginianus*	Acute Oral toxicity (LD_{50})	Classification and regression-based (CORAL)	PPP

References: [1]Como et al., 2017; [2]Toropov et al., 2017; [3]Toropov et al., 2018; [4]Ghosh et al., 2020; [5]Carnesecchi et al., 2020 (a); [6]Carnesecchi et al., 2020 (a); [7]Carnesecchi et al., 2020 (b); [8]Roy et al., 2020; Ghosh et al., 2020; [9]Gadaleta et al., 2020 in press; [10]Carnesecchi et al., in preparation(a); [11]Carnesecchi et al., in preparation(b). Abbreviations: PPP: plant protection products, LD50: Lethal dose 50%, LC50: Lethal concentration 50%; NOAEL: No-observed-adverse-effect-level; LOAEL: Lowest-observed-adverse-effect-level.

5.2. Contribution of OpenFoodTox to the OECD QSAR toolbox and AMBIT 2.0

The OECD QSAR Toolbox is an open source software (https://www.oecd.org/chemicalsafety/oecd-qsar-toolbox.htm). It has been designed to support chemical hazard assessment while increasing the use of mechanistic data and other type of chemical information to ultimately support the use of alternatives to animal testing and reduce testing without compromising chemical safety for human health and the environment. The OECD QSAR toolbox allows the use of QSAR models and read across methods using a category approach to predict chemical toxicity, supports testing through intelligent testing strategies when data gaps are identified as well as sustainable development and green chemistry through toxicity predictions before the chemicals are produced. Stakeholders using the toolbox include governments, chemical industry and other stakeholders. Over the last couple of years, hazard data from OpenFoodTox have been integrated in the OECD QSAR toolbox 4.4 together with other databases from a wide range of governmental organisations and scientific advisory bodies (Dimitrov et al., 2016; Kuseva et al., 2019).

Recently, the AMBIT 2.0 tool was created through a research project funded by the European Chemical Industry Council (CEFIC)'s Long Range Research Initiative (LRI). The tool has integrated both ECHA's REACH and EFSA's OpenFoodTox databases to predict hazard properties of data poor chemicals and is compatible with the IUCLID software format. The tool allows substance identification and composition, search similar structures and substructures, assign structures to constituents and impurities as well as retrieval and management of IUCLID6 substance data. Overall, AMBIT-2 allows read-across/category formation within a workflow that facilitates searches for target and source structures while generating data matrices, data gap filling and the generation of assessment reports with predefined formats automatically. Prediction tools that have been integrated within AMBIT 2.0 include the VEGA platform, Toxtree, Cramer rules, protein binding and it can downloaded from the Cefic LRI website: http://ambitlri.ideaconsult.net/ through registration with a username and password.

5.3. Assessment of environmental footprint of chemicals

The Joint Research Center (JRC) of the European Commission has recently performed computational analyses to assess the Environmental footprint of chemicals and products while integrating OpenFoodTox and the ECHA's REACH database using hazard data for aquatic organisms and relevant toxicity for human risk assessment based on test species (rat, mouse, rabbit, dog). Data have been harmonised across both databases including unit conversions, exclusion of values (> or < than, mixtures of formulae) and correction of species names to allow possible grouping with the REACH database. From a total of 2695 included test results, final extraction resulted in 1956 individuals hazard datasets (1058 and 898 chronic and acute respectively). Ecotoxicity datasets were used as inputs to derive hazard values reflecting 20% of the affected fraction from chronic EC_{10} Species Sensitivity distribution while ED_{50} were derived from human hazard data (oral and inhalation route for pesticides). Full details of the procedures, datasets and conclusions are available elsewhere (Saouter et al., 2018).

5.4. Testing the threshold of toxicological concern for food relevant substances

Values for the Threshold of Toxicological Concern (TTC) were originally derived from a non-cancer dataset of 613 compounds with a relatively small domain of applicability. In order to test the relevance of TTC values for food and feed-relevant compounds, OpenFoodTox data were analysed and provided a dataset for 329 substances categorised under the Cramer decision tree, into low (Class I), and high (III) toxicity profile. Overall, the applicability of the TTC values to food relevant compounds was confirmed for Cramer Classes I and III with threshold values of 1000 μg/person per day (90% confidence interval: 187–2190) and 87 μg/person per day (90% confidence interval: 60–153) respectively, compared to of the original TTC values of 1800 and 90 μg/person per day. Chemicals from the Cramer Class II were excluded from the analysis because of the very limited number of compounds. (Reilly et al., 2019).

6. Conclusion and future developments

OpenFoodTox provides EFSA's structured hazard data for over 5000 chemicals in food and feed which have been peer-reviewed by scientific experts (>30) from the agency's working groups and Panels (Dorne et al., 2017). It is available open source as a downloadable database, open access via a searchable micro-strategy tool and supports the use of predictive *in silico* models and NAMs in chemical risk assessment (Dorne et al., 2017; Benfenati et al., 2019; Carnesecchi et al., 2020a,b). In an international context, Openfoodtox is part of a broader range of open source databases and tools developed by national, European and international scientific advisory bodies including the ECHA's REACH database, the OECD EChem Portal and QSAR toolbox, the JRC tools, the US-EPA Computational chemistry dashboard to cite but a few (Thomas et al., 2019). In addition, large European research consortiums have also contributed to such open source databases particularly the COSMOS DB (https://ng.cosmosdb.eu) through the SEURAT-1 research initiative cluster (http://www.seurat-1.eu/) aiming to achieve "Safety Evaluation Ultimately Replacing Animal Testing". The COSMOS Datashare Point

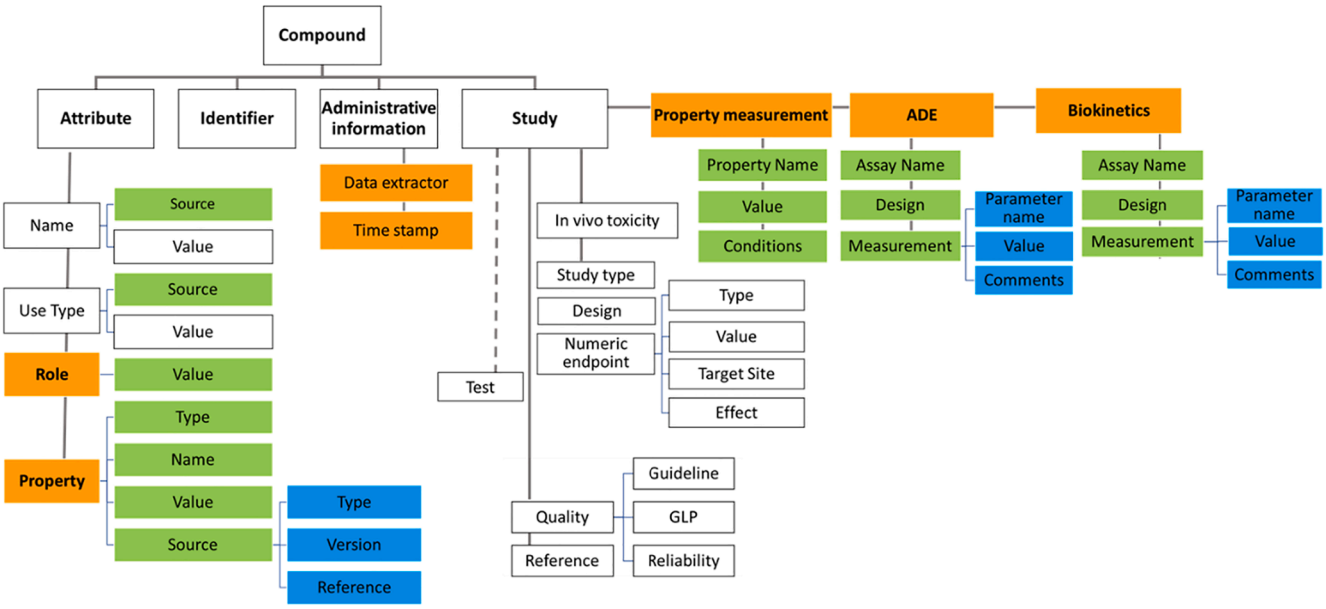

Fig. 14. OptiTOX Data Model extended from the current OpenFoodTox Data model. Extensions are highlighted in colour.

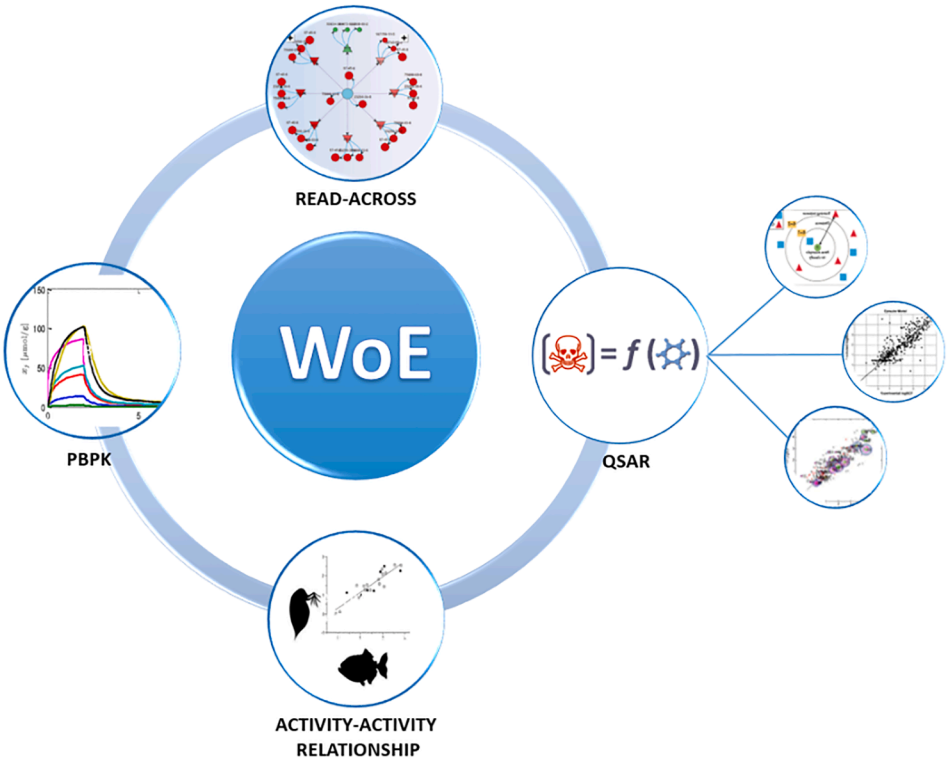

Fig. 15. Innovative workflow of OptiTOX. Weight of evidence approaches provide a basis to integrate results from multiple QSAR models, activity-activity relationships, read-across approaches and physiologically based pharmacokinetic (PBPK) models.

(https://www.mn-am.com/projects/cosmosdatasharepoint) provides data for a range of cosmetic ingredients (and other compounds), legacy data from the US FDA PAFA (Priority-based Assessment of Food Additives) DB, the COSMOS TTC dataset (https://ng.cosmosdb.eu) *in silico* models for the prediction of human repeated dose toxicity, DNA and protein binding and AOP/MoA network-based structural alerts for liver toxicity (Sala et al., 2017; Yang et al., 2017; Cronin et al., 2019).

Future developments within the new version OpenFoodTox 2.0 will be implemented under the OptiTOX project (OpenfoodTox Integrated with non-testing methods for TOXicity evaluation) which encompasses three key activities:

1. Update and maintenance of the database with the most updated EFSA hazard data from recent risk assessments and open source publication on a yearly basis for the scientific and risk assessment community.
2. Update of the data model and data collection to include new chemical properties i.e. physico-chemical properties (OHT 1 to 23–5),

degradation and bioaccumulation (OHT 32 and 33), toxicokinetic data (OHT 58), intermediate effects and NAMs (OHT 201) as well as exposure information (OHT 301 to 306). This update of the data model may require a synchronised update of these OHTs as well as harmonisation between controlled vocabularies from EFSA catalogues and OHTs to ensure data inter-operability and support straightforward exchange of information across agencies and platforms. Finally, the new OpenFoodTox data model is also being expended to handle a range of datasets beyond EFSA documents including experimental and *in silico* data from ongoing European and International projects (e.g., toDIVINE, LIFE VERMEER library, LIFE CONCERT, LIFE COMBASE, JANUS). A prototype of such an extended data model for OptiTOX is displayed in Fig. 14.

The established quality of the database is maintained and ensured through the implementation of automatic quality control checks at the data entry stage followed by manual revision of identified inconsistent records. Integration of OpenFoodTox 2.0 within *in silico* modelling platforms to support the integration of NAMs in chemical risk assessment. This development is piloted using the VEGA platform with a prospect to extend to other key platforms as depicted in Fig. 15 i.e. OECD QSAR toolbox, the REACH database from ECHA and the CompTox chemistry dashboard of the US-EPA. A critical aspect for the integration and use of NAMs in chemical risk assessment is to allow assembling, weighing and integrating different lines of evidence in an iterative manner (i.e. *in vivo, in vitro* data, predictions from *in silico* models) and reporting of the overall uncertainty using harmonised WoE approaches (EFSA SC, 2017; Benfenati et al., 2019). In this context, new properties collected within OptiTOX including physico-chemical properties, exposure and toxicokinetic information will provide a range of lines of evidence of experimental and predicted nature and create a basis to apply such WoE approaches for NAMs and is illustrated in Fig. 15 for a. Multiple QSARs, b. Read-across models from several open source models taking into account similarities between target and analogue compound (s) (e.g., structure-based, physico-chemical properties-based) c. Activity-activity relationships d. physiologically-based kinetic (PB-K) models for humans, farm animals (swine, cattle, sheep, chicken) and a range of test species (e.g. rat, mice, fish) recently developed and validated (Grech et al., 2019; Lautz et al., 2020a,b,c; EFSA SC, 2017; Gadaleta et al., 2020).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The view expressed in this manuscript are the authors only and do not represent the views of the European Food Safety Authority and the European Chemicals Agency.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106293.

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