

ECOTOXicology Knowledgebase:

Modernizing the Literature Review and Data Curation Processes, and Mapping Ecological Toxicity of Per- and Polyfluoroalkyl Substances (PFAS)

Jennifer Olker, Postdoctoral Researcher
Colleen Elonen, ECOTOX coordinator

US EPA ECOTOX Project Team:

Colleen Elonen
Jennifer Olker
Dale Hoff
Carlie LaLone

Rong-Lin Wang
GDIT contract staff
SEE staff



- Background and History for ECOTOX Knowledgebase
- Modernizing the ECOTOX Pipeline (C. Elonen, SOT 2020)
- Mapping ecological toxicity of PFAS with ECOTOX Protocols (J. Olker, SOT 2020)



What is the ECOTOX Knowledgebase?

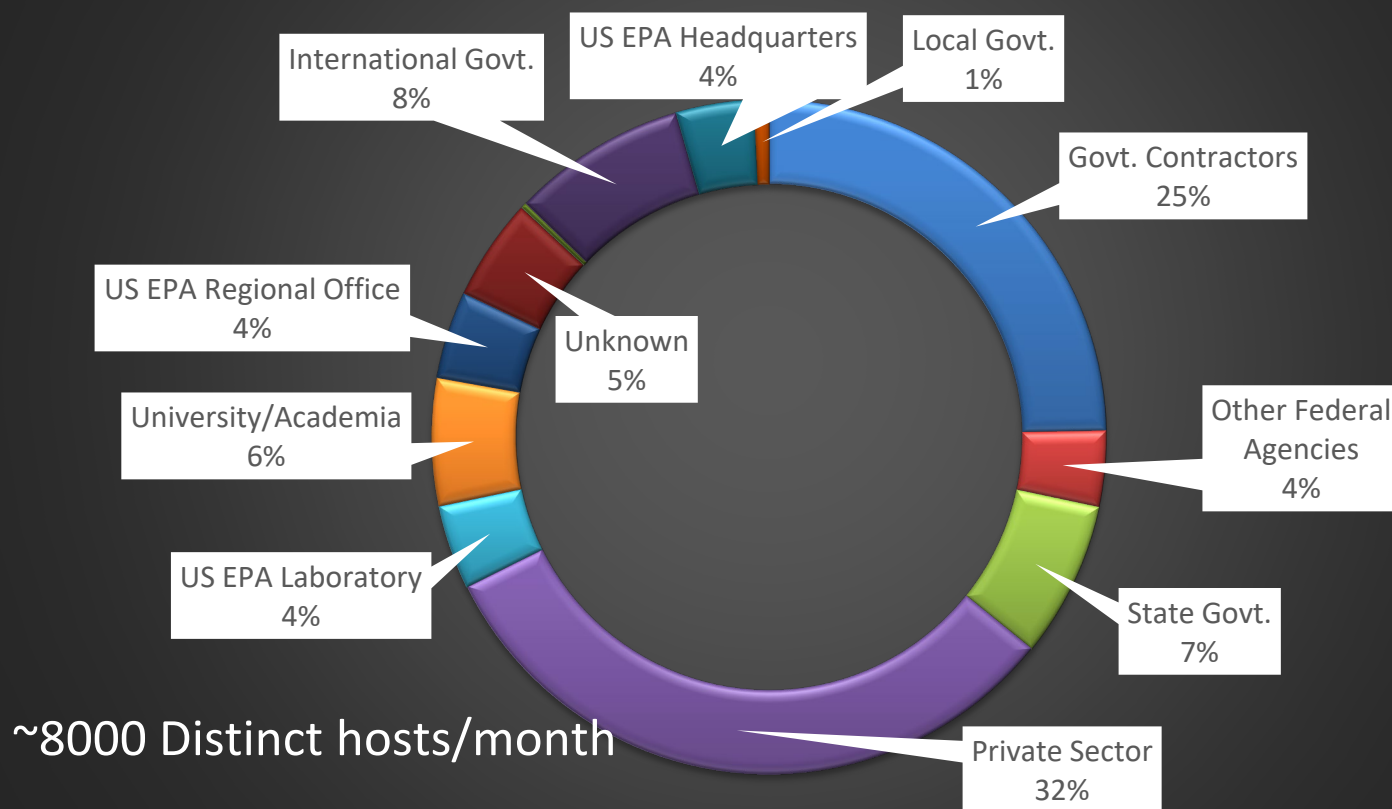
Publicly available, curated database providing toxicity data from single-chemical exposure studies to aquatic life, terrestrial plants, and wildlife

- From comprehensive search and review of open and grey literature
 - Data extracted from acceptable studies, with up to 250 fields
 - Updated quarterly

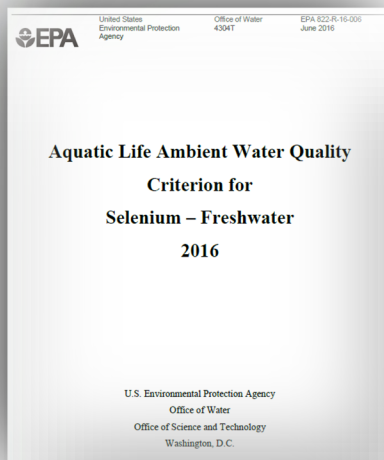
The screenshot shows the ECOTOX Knowledgebase homepage. At the top, there's a navigation bar with links for Home, Search, Explore, Help, and Contact Us. Below this, a dark blue section displays key statistics: 'Data last updated Mar 12, 2020', 'Recent chemicals with full searches and coding completed' (listing 1,1-Dichloroethane, 1,2-Dichloroethane, 1,1,2-Trichloroethane, Aminopyralid, Butyl benzyl phthalate, Dibutyl phthalate, Fenazaquin, Flutriafol, and Per- and Polyfluoroalkyl Substances ... Pyrasulfotole), and 'Total in database' (12,089 Chemicals, 13,138 Species, 50,092 References, 988,806 Results). A green banner below this says 'WELCOME TO ECOTOX VERSION 51' and 'Please click here to provide feedback so that we can continue to improve your experience.' The main content area is divided into three columns: 'About ECOTOX' (describing the database and including a 'Learn More' button), 'Getting Started' (with links to Search, Explore, and various guides), and 'Other Links' (with links to Limitations, Frequent Questions, Other Tools/Databases, and Recent Additions, plus a 'Get Updates via Email' button). At the bottom, there's a 'Download' section with a 'Download ASCII Data' button and the URL 'www.epa.gov/ecotox/'.

- 30+ year history:
Originated in the early 1980s,
US Environmental Protection Agency Office of Research and Development

Clients Contacting ECOTOX Support line 2005 - 2016 (n = 2813)

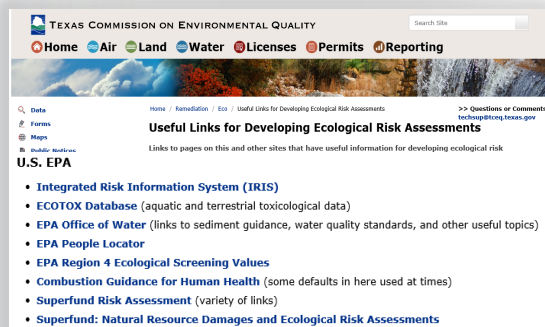
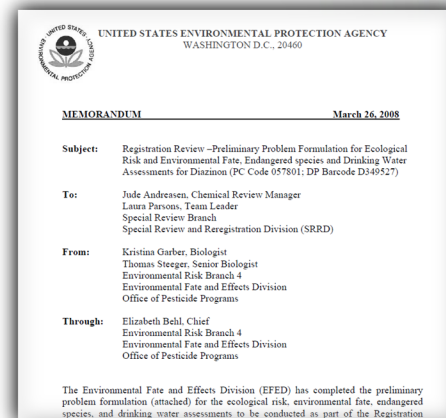


Program Offices & Regions Applications: use in environmental decision making



Used for every Ambient Water Quality Criteria for Aquatic Life since 1985.

Used for every Ecological Risk Assessment for Office of Pesticides for chemical registration and re-registration (FY19 – 30 chemicals).



Used by OLEM (Superfund and RCRA), HQ, Regions and States for site assessments and in emergency response

Providing ecological hazard data for the prioritization and assessment of chemicals for TSCA/Lautenberg Act

Overview of TSCA Work Plan Methodology

Maria Doa

U.S. EPA, Office of Pollution Prevention and Toxics

December 11, 2017

PFOA & PFOS
U.S. manufacturers voluntarily phased out PFOA and PFOS, two specific PFAS chemicals.



GenX Chemicals
GenX chemicals are a replacement for PFOA.



Providing ecological toxicity data for PFAS to researchers, EPA ERA Forum, DoD Tri-Services ERA Work Group, and others

Ecological Hazard

Ecological hazard data are extracted from the EPA ToxValDB database where it had been compiled from the EPA ECOTOX database. Although data are available for a variety of species, only data for aquatic species are used in the current illustration. The data can come from any of the following study types: mortality:acute, mortality:chronic, reproductive:acute, reproductive:chronic, growth:acute, growth:chronic (all from ECOTOX). The types of effect levels are LDxx/LCxx/ECxx/EDxx where xx can range from 1% to 100%, and LOEL/NOEL/LOEC/NOEC. Values must be in units of mg/L. For each chemical, the lowest toxicity value was separately determined for acute and chronic studies, regardless of species. The

ECOTOX Knowledgebase

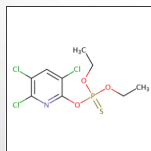
*Chemical
environmental
toxicity data for
aquatic life,
terrestrial plants
and wildlife*



Interoperability with databases/tools

DTXSID/CASRN

Chemicals
Dashboard



Species ID; Protein ID

SeqAPASS



Integrated ontology

Adverse
Outcome
Pathway
WIKI

Reference ID

HERO
(Health &
Environmental
Research
Online)

EPA Program Offices and Regions, States, Tribes, Other Federal Agencies and International Entities

Ecological Risk Assessments
Ambient Water Quality Criteria
Ecological Screening Values
Chemical Prioritization
Emergency Response

Tools and Applications

Species Sensitivity Distributions (e.g., US EPA's WebICE, NOAA's CAFÉ)
PNECs and threshold values (e.g., EcoTTC)
QSAR (e.g., ECOSAR, TEST, OECD QSAR Toolbox)
BCF modeling and validation
Adverse Outcome Pathway (AOP) development

ECOTOX Pipeline: Systematic Review/Data Curation

Identification

Chemical verification
and development of
search terms

Chemical-based Search Terms:

- Chemical name and CASRN
- Synonyms, tradenames
- Other relevant forms (metabolites, degradants, parent compound, related chemicals)

Sources include:

- STN
- Pesticide Action Network (PAN)
- EPA's Pesticide Fate Database (PFATE)
- EPA's Chemistry Dashboard.

Screening

Identify and acquire
potentially applicable
studies

Literature search: Use chemical-specific search terms to query multiple literature search engines

| | | | | | | | |
|-----------------|------------------|-------------------|--------|---------------------------|----------|---------------------------|----------------------|
| Citations from: | ProQuest/ CSA | Science Direct | ToxNet | Dissertation Abstracts | Agricola | Current Contents (WoS) | Already in Unify* |
| n = | 5,631 | 11,178 | 317 | 234 | 4,861 | 15,347 | 333 |

*Internal USEPA ECOTOX database

Eligibility

Review literature for
applicability to
ECOTOX

~37,000 citations downloaded

Initial removal of duplicates

Included

Extract data into
ECOTOX
Knowledgebase

Title and Abstract Screening

n = 8,653 references

Not applicable (excluded):
n = 8,265 references

| | |
|---------------------|------------------|
| Chem Methods: 3,462 | No Toxicant: 221 |
| Human Health: 1,797 | Duplicate: 153 |
| False Hit: 1,333 | Review: 50 |
| Fate: 510 | Mixture: 12 |
| Survey: 287 | Other: 121 |
| Bacteria: 233 | |

For Review (Full Text Screening)

n = 388 references

No PFAS in reference: n = 85 references

Did not meet acceptability criteria (excluded):
n = 142 references

Data Extracted from Acceptable Papers

n = 245 references with
7,496 total records

Awaiting Review and Data Extraction
n = 1 references

ECOTOX Pipeline: Systematic Review/Data Curation

Identification

Chemical verification
and development of
search terms

Conduct literature
searches

Screening

Identify and acquire
potentially applicable
studies

Eligibility

Review literature for
applicability to
ECOTOX

Included

Data extraction

Study quality
evaluation

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n = 1 references

Data Extracted from Acceptable Papers
n = 245 references with 7,496 total records

Data from High Quality Studies
n = ____ references

Identify, Test, and QA Search Terms

Search various sources for chemical terms,
Synonyms, verify CAS, eliminate poor search terms

Tak(Acilid OR Albrass OR Bexton OR "CP 31393" OR "Kartex
A" OR Muharicid OR Niticid OR Propachlor OR Propachlore
OR Ramrod OR Satecid OR "US EPA PC Code 019101")

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and development of
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searches

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Review literature for
applicability to
ECOTOX

Included

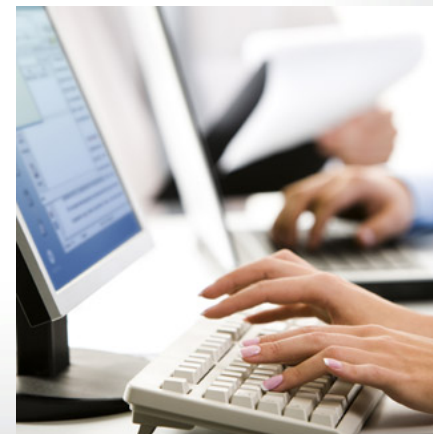
Data extraction

Study quality
evaluation



Couple hour process

Enter chemical terms
into template for
abstracting databases



Identify, Test, and QA Search Terms

Web-based tool to identify and document relevant search terms

Identification

Chemical verification
and development of
search terms

Conduct literature
searches

Screening

Identify and acquire
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studies

Eligibility

Review literature for
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evaluation

Search Engine version v14
Results for search: fluoxastrobin

Searching Bing: 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Done.

Reading files: 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Done.

Click to remove above info

Search Engine version v14
Results for search: fluoxastrobin

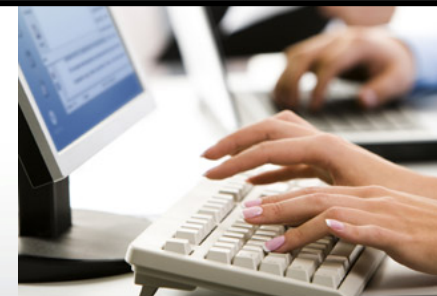
| 1 Site | 2 Site | 3 Meta | 4 File | 5 CAS | 6 Flags | 7 Bing# | 8 Google# | 9 Search Terms | 10 Comments |
|--------|--------------------------|--------|--|-------|---------|---------|-----------|----------------|-------------|
| ✓ | pubchem.ncbi.nlm.nih.gov | html | Fluoxastrobin | 0 | 0 | 1 | - | 0 terms | |
| ✓ | www3.epa.gov | pdf | fu_PC-028869_01-Nov-05.pdf | 1 | 5 | 2 | - | 0 terms | |
| ✓ | www.federalregister.gov | html | fluoxastrobin-pesticide-tolerances | 0 | 3 | 3 | - | 0 terms | |
| ✓ | www.fluoridealert.org | html | fluoxastrobin.page.html | 2 | 3 | 4 | - | 0 terms | |
| ✓ | www.agprofessional.com | html | arysta-lifescience-license-fluoxastrobin-bayer | 0 | 0 | 5 | - | 0 terms | |
| ✓ | ag.tennessee.edu | pdf | MS labeled fung for p | | | | | | |
| ✓ | www.federalregister.gov | html | fluoxastrobin-pesticide | | | | | | |
| ✓ | www.domyown.com | html | disarm-fungicide-p-13 | | | | | | |
| ✓ | media.clemson.edu | pdf | 2014_disease_cont_ta | | | | | | |
| ✓ | www.alanwood.net | html | fluoxastrobin.html | | | | | | |
| ✓ | www3.epa.gov | pdf | 066330-00064-20111 | | | | | | |
| ✓ | www.fluoridealert.org | pdf | fluoxastrobin 2004 art | | | | | | |
| ✓ | www.fmcprosolutions.com | html | FameSCFungicide.asp | | | | | | |
| ✓ | en.wikipedia.org | html | Strobilurin | | | | | | |

PAN Results for search: fluoxastrobin

| Name | Subtitle | Synonyms | Link for Details |
|---|--|---|---|
| 2,6-(2-Chlorophenyl)-5-fluoro-4-pyrimidinyl | HEC 5725 Hydroxyphenyl (metabolite of fluoxastrobin) | | http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PR114687 |
| Benzenacetamide, 2,6-(2-chlorophenyl)-5-fluoro-4-pyrimidinyl | HEC 5725 AMIDE (Metabolite of Fluoxastrobin) | | http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PR114682 |
| Benzenecarboxylic acid, 2,6-(2-chlorophenyl)-5-fluoro-4-pyrimidinyl | HEC-5725-carboxylic acid (metabolite of fluoxastrobin) | | http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PR114697 |
| Fluoxastrobin | Fluoxastrobin | (1E)-2-[[6-(2-Chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl (5,6-dihydro-1,4,2-dioxazin-3-yl)-methanone, O-methylloxime, 028869 [US EPA PC Code, Text] ; 05913 (CA DPR Chem Code Text) ; 193740-76-0 (CAS number) ; 193740760 (CAS number without hyphens) ; 28869 [US EPA PC Code, Numeric] ; 361377-29-9 (CAS number) ; 361377299 (CAS number without hyphens) ; 5915 (CA DPR Chem Code) ; AGJ (PDP Code) ; Fluoxastrobin ; Fluoxastrobin, HEC 5725 ; Methanone, 2-[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxyphenyl (5,6-dihydro-1,4,2-dioxazin-3-yl)-methanone, [2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazin-3-yl)-O-methylloxime (CAS NA | http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PR13321 |

| CAS | Relation | Reason | Chemical Name | Chem Use Type |
|--|----------|--------|--|-------------------|
| 193740-76-0, 361377-29-9 | Parent | P | Fluoxastrobin | Fungicide |
| 207515-50-2 | Related | 5a | 2,6-(2-Chlorohydroxyphenoxy)-5-fluoro-4-pyrimidinyl | Breakdown product |
| 340168-32-3 | Related | 5a | Benzenacetamide, 2,6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl | Breakdown product |
| | Related | 5a | Benzenecarboxylic acid, 2,6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl | Breakdown product |
| | Related | 5a | HEC 5725-deschlorophenyl (metabolite of fluoxastrobin) | Breakdown product |
| | Related | 5a | HEC 5725-oxazepine (metabolite of fluoxastrobin) | Breakdown product |
| 519002-09-6 | Related | 5a | HEC 5725-phenoxy-hydroxypyrimidine (metabolite of fluoxastrobin) | Breakdown product |
| HEC 5725-deschlorophenyl (metabolite of fluoxastrobin) | | | | |

Chemical terms
automatically formatted
for abstracting databases



ECOTOX Literature Searches

Identification

Chemical verification
and development of
search terms

Conduct literature
searches

Screening

Identify and acquire
potentially applicable
studies

Eligibility

Review literature for
applicability to
ECOTOX

Included

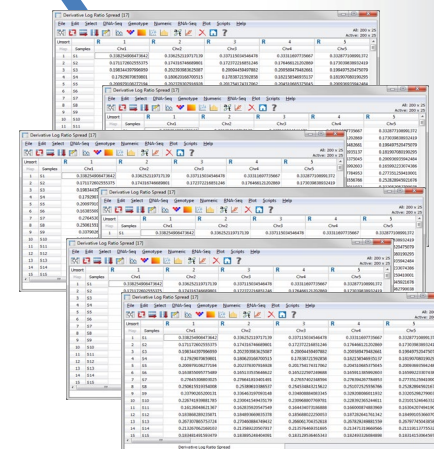
Data extraction

Study quality
evaluation

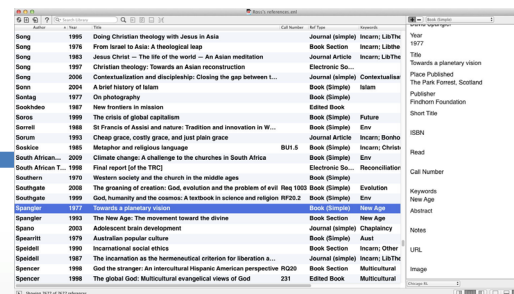
Chemical specific searches
(using terms from chemical verification step)
OR
Monthly electronic searches
of 11 highly relevant journals

Search Engines

1. Science Direct
2. AGRICOLA
3. TOXNET
4. ProQuest ESPM
5. ProQuest Dissertation Abstracts
6. Web of Science/ Current Contents



In 2019: 159,727
references were
manually skimmed
for applicability



Collate data and remove duplicates

ECOTOX Literature Searches

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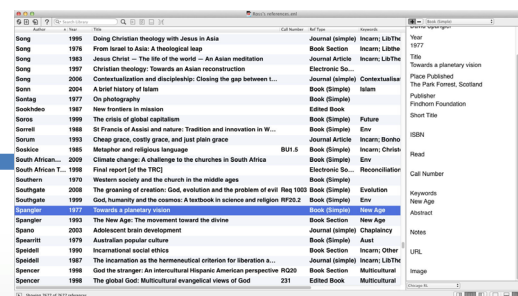
Study quality
evaluation

Excel-based tool
(Abstract-Sifter Plus) to
search multiple sources

The image shows the Abstract-Sifter Plus Excel spreadsheet and the ScienceDirect search interface. The spreadsheet has columns for Doc ID, PMID, flux, toxic, fish, and Pub Yr. The ScienceDirect interface shows a search for 'fluoaxstrobin' with options to select a source and enter a query.

| Doc ID | PMID | flux | toxic | fish | Pub Yr | Title |
|--------|------------|------|-------|------|--------|--|
| 13 | 1514875067 | 2 | 2 | 0 | 2014 | Fluoaxstrobin; Pesticide Tolerances |
| 14 | 2056759587 | 3 | 7 | 0 | 2018 | Evaluating subchronic toxicity of Fluoaxstrobin using earthworms (Eisenia fetida). |
| 15 | 755782521 | 2 | 0 | 0 | 2010 | Fluoaxstrobin; Pesticide Tolerances |
| 16 | 216541481 | 2 | 0 | 0 | 2006 | CLIPPINGS |
| 17 | 1566653210 | 2 | 2 | 0 | 2014 | Fluoaxstrobin; Pesticide Tolerances |
| 18 | 1786130189 | 3 | 0 | 0 | 2016 | Risk assessment posed by diseases in context of integrated management of wheat |
| 19 | 883915249 | 2 | 1 | 0 | 2011 | Fluoaxstrobin; Pesticide Tolerances |
| 20 | 1945223789 | 1 | 0 | 0 | 2017 | Fluoaxstrobin; Pesticide Tolerances |
| 21 | 1114878227 | 1 | 0 | 0 | 2012 | Fluoaxstrobin; Pesticide Tolerances |
| 22 | 2268770603 | 1 | 0 | 0 | 2019 | Fluoaxstrobin; Pesticide Tolerances |
| 23 | 1735916450 | 2 | 0 | 0 | 2015 | Fungicide sensitivity of five commonly encountered Phytophthora species in Maryland nurseries |
| 24 | 1494368943 | 1 | 0 | 0 | 2013 | Zhaoqing Zheng Biotechnology Co Ltd Files Chinese Patent Application for Fluoaxstrobin-Containing Fungicide Combination |
| 25 | 2064213595 | 1 | 0 | 0 | 2018 | Li Xiangying Submits Chinese Patent Application for Pesticide Composition Containing Fluoaxstrobin and Dimethomorph |
| 26 | 2109281311 | 1 | 0 | 0 | 2018 | Tian Wenhua Seeks Patent for Sterilized Composition Containing Fluoaxstrobin and Cnidium Lactone |
| 27 | 2064181572 | 1 | 0 | 0 | 2018 | Li Xiangying Applies for Patent on Pesticide Composition Containing Fluoaxstrobin and Metrafenone |
| 28 | 2117769694 | 1 | 0 | 0 | 2018 | Hailir Pesticides & Chemical Group Submits Patent Application for Fungicidal Composition Containing Tetramycin |
| 29 | 1010984345 | 1 | 0 | 0 | 2012 | Fluoaxstrobin; Pesticide Tolerances |
| 30 | 19623731 | 2 | 0 | 0 | 2007 | Control of ergot by seed treatment |
| 31 | 1856879923 | 1 | 0 | 0 | 2017 | Guangdong Zhongxin Agricultural Technology Files Chinese Patent Application for Fosthiazate and Fluoaxstrobin-Containing |

References can be
'sifted', reviewed,
or exported as .ris



Collate data and remove duplicates

Skimming for Applicability: Title and Abstract

Identification

Chemical verification
and development of
search terms

Conduct literature
searches

Screening

Identify and acquire
potentially applicable
studies

Eligibility

Review literature for
applicability to
ECOTOX

Included

Data extraction

Study quality
evaluation



Skim titles and
abstracts, use exclusion
criteria to eliminate
non-applicable

4. J Econ Entomol. 2016 Jul 18. pii: tow146. [Epub ahead of print]
Sulfur Dust Bag: A Novel Technique for Ectoparasite Control in Poultry Systems.
Murillo AC(1), Mullens BA(2).

Author information:
(1)Department of Entomology, University of California, Riverside, CA 92521
(alock001@ucr.edu; bradley.mullens@ucr.edu) alock001@ucr.edu, (2)Department of
Entomology, University of California, Riverside, CA 92521 (alock001@ucr.edu;
bradley.mullens@ucr.edu).

Animal welfare-driven legislation and consumer demand are changing how laying chickens are housed, thus creating challenges for ectoparasite control. Hens housed in suspended wire cages (battery cages) are usually treated with high-pressure pesticides. This application type is difficult in enriched-cage or cage-free production. Alternatives to pesticide sprays are needed in enriched-cage or cage-free systems. In this study, we tested the efficacy of sulfur dust deployed in "dust bags" for control against the northern fowl mite (*Ornithonyssus sylviarum*), which causes host stress, decreased egg production, and reduced feed conversion efficiency. Dust bags were hung from the tops of cages or were clipped to the inside front of cages. We also tested permethrin-impregnated plastic strips, marketed for ectoparasite control in caged or cage-free commercial and backyard flocks. Previous work has shown sulfur to be very active against poultry ectoparasites; however, we found that the placement of bags was important for mite control. Sulfur in hanging bags reduced mites on treatment birds by 95 or 97% (depending on trial) within one week of being deployed, and mite counts on these birds were zero after 2 wk. Clipped sulfur bags acted more slowly and did not significantly reduce mites in one trial, but reduced mite counts to zero after 4 wk in trial 2. Permethrin strips had no effect on mite populations. This may have been due to mite resistance, even though this mite population had not been exposed to pyrethroids for several years. Sulfur bags should be effective in caged or cage-free systems.

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doi: 10.1093/jee/tow146

Send applicable reference
list for acquisition

Skimming for Applicability: Title and Abstract

Partnering with NTP/SCIOME to develop language learning tool for skimming/prioritizing abstracts



Skimming for Applicability: Full text

Identification

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Study quality
evaluation



Ecotoxicology 2, 93–120 (1993)

The impact of the Cyanamid Canada Co. discharges to benthic invertebrates in the Welland River in Niagara Falls, Canada

MIKE DICKMAN and GRAZYNA RYGIEL

Biological Sciences Department, Brock University, St. Catharines, Ontario, Canada L2S 3A1

Received 15 July 1992; accepted 6 December 1992

In 1986, the International Joint Commission (IJC) recommended that the Niagara River watershed should be declared an Area of Concern (AOC). This IJC recommendation was ratified by the 4 signatories of the Great Lakes Water Quality Agreement. In order to delist an AOC, it is necessary to locate any areas of impairment within the watershed and carry out remediation projects that permit uses that were previously impaired. To this end we attempted to determine whether or not the sediments at 7 study sites near the Cyanamid Canada (Chemical) Co. were contaminated at levels that would result in the impairment of the natural biota which inhabit the watershed.

The Cyanamid Canada (Chemical) Co. discharges ammonia wastes, cyanide, arsenic and a variety of heavy metals into treatment systems which ultimately discharge to the Welland River, the major Canadian tributary to the Niagara River. This portion of the Welland River near the factory was designated a Provincially significant (Class one) wetlands by the Ontario Ministry of Natural Resources. In 1986, the mean discharge to a creek from Cyanamid Canada Co. was 27,342 m³ per day (MOE, 1987). Similar discharge volumes occurred in 1989. In 1991, the total discharge was 25,000 m³ per day (MOE, 1991).

The majority of the benthic invertebrates collected from the study area were pollution tolerant taxa (e.g., sludge worms constituted 68% of all the organisms collected). The lowest chironomid densities were observed at stations 1, 2, and 4, which were the only stations situated close to Cyanamid's discharge pipes. The absence, of clams and mayflies which burrow to greater depths than do chironomids and sludge worms, probably reflects the inability of the deeper dwelling burrowers to tolerate the contaminants which we recorded at these 3 stations. The absence of all crustaceans from these same 3 stations (stations 1, 2 and 4) when coupled with their low biotic diversity and the elevated heavy metal concentrations in the sediments were cause for concern. In addition, stations 2 and 4 displayed the highest frequency of chironomid mentum deformities.

Stations 1 and 2 were located near a pipe which was one of Cyanamid Canada Company's major discharge point sources to the Welland River until a court order in 1980 stopped the company from discharging toxic material to the Welland River via that pipe. Elevated levels of cobalt (10 times above background), molybdenum (6 times above background), nickel (8 times above background), tungsten (284 times above background) and zinc (20 times above background) near the abandoned discharge pipe were correlated with the presence of pollution tolerant chironomid taxa such as *Polypedilum* and *Procladius*. The highest sludge worm densities were also observed at the abandoned pipe site which was the only site where oily wastes were found in the sediments.

Among the 1,275 chironomids taken from the seven Cyanamid Canada stations, the great majority were pollution tolerant taxa. The low biotic diversity and the presence of considerable numbers of pollution tolerant benthic macroinvertebrates in combination with the chemical

0965-9292 © 1993 Chapman & Hall



Moves on to be curated
into ECOTOX.

Dec. 2018 – Dec. 2019
1,468 References were
added to the public website

Skimming for Applicability: Full text

Exploring options for data mining
and extraction of information
from a variety of sources



Journal of Experimental & Clinical Cancer Research

Nestin and CD133: valuable stem cell-specific markers for determining clinical outcome of glioma patients

Mingyu Zhang, Tao Song, Liang Yang, Ruoshan Chen, Lei Wu, Zhuanyi Yang and Bingheng Fang

Journal of Clinical Epidemiology

Volume 62, Issue 5, May 2009, Pages 506-510

ELSEVIER

Abstract

Aim: Gliomas represent the most frequent neoplasm of the nervous system. Unfortunately, surgical cure of it is practically impossible and their clinical course is primarily determined by biological behaviors of the tumor cells. The aim of this study was to investigate the correlation of the stem cell markers Nestin expression with the grading of gliomas, and to evaluate the prognostic value. Methods: The tissue samples consisted of WHO grade II, III, IV (WHO grade III, IV) grade glioma normal brain tissues. The expression levels of Nestin and C proteins were detected using IHC immunohistochemical method. Then, the correlation of the two markers' expression with the grading of patients and their prognostic value were determined. Results: Immunohistochemical analysis with anti-Nestin and anti-CD133 antibodies revealed dense and spotty staining cells and their expression levels became significantly high.

4. Drag and drop text from document:

The user can select text from the document and can start dragging the text out of the document to the outcome database.

During the dragging action, the user can view the text being dragged. This feature facilitates accurate data extraction.

treatment

Patients were stratified according to their KPS (<80 versus ≥ 80) and randomized 1:1:1 to 1 of the 3 parallel treatment arms: PFE + CIL1W, PFE + CIL2W, and PFE (Figure 1). See supplementary Data, available at

Background: recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) over-expresses $\alpha\beta$ integrin. Cixutum selectively inhibits $\alpha\beta$ and $\alpha\beta$ integrins and is investigated as a treatment strategy.

5. Extract and parse information from tables:

The user can select tabular data from the document and can then click on the table icon on the toolbar.

The user must enter the number of rows selected.

The user will specify the rows to be copied and will indicate whether the rows and columns must be transposed. All the rows or only selected rows can be copied.

The selected rows are copied to the clipboard. Then, they can be pasted into the outcomes database.

| Number of patients at risk | | | | | | | | | | | |
|----------------------------|----|----|----|----|----|----|---|---|---|---|---|
| | 62 | 47 | 36 | 24 | 20 | 13 | 8 | 3 | 2 | 2 | 1 |
| PFE | 62 | 47 | 36 | 24 | 20 | 13 | 8 | 3 | 2 | 2 | 1 |
| PFE + CIL1W | 62 | 51 | 42 | 25 | 16 | 9 | 6 | 2 | 0 | 0 | 0 |
| PFE + CIL2W | 60 | 42 | 32 | 13 | 7 | 4 | 2 | 0 | 0 | 0 | 0 |



Moves on to be curated
into ECOTOX.

Dec. 2018 – Dec. 2019
1,468 References were
added to the public website

- Paper must meet these criteria

- Single chemical exposure
- Ecologically-relevant species
- Must be able to verify CAS registry numbers
- Must be able to verify taxonomic information for test species
- Exposure to live organism, viable tissue or cells
- Report concurrent exposure concentration, dose or application rate
- Report duration of exposure
- Must have a control treatment
- Primary source of the data
- Study must be a full article in English

Review literature for
applicability to
ECOTOX



- The following studies are excluded

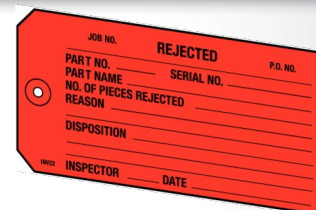
- Air pollution studies related to CO2 and ozone
- Studies on humans, monkeys, bacteria, viruses and yeast
- Review and summary articles
- Terrestrial studies with an inhalation route of exposure
- Non-English publications and abstracts





ECOTOX Applicability Criteria

All Excluded and Non-Applicable studies are Tagged with the reason for rejection



- Abstract – Published as an abstract
- Bacteria – only test organism is a Bacteria
- CAS # Unavailable – could not verify/locate chemical CAS Registry number
- Chemical method – description of chemical analysis procedures
- Fate – only report chemical distribution in media
- Human Health – data on human subjects of surrogate animal subjects for human health risk assessment
- Incident – reports death of animal by poison, but does not provide concentration/duration of exposure
- Method – paper only reports methods for conducting a toxicity test or other aspect of an experiment
- Mixture – paper reports results from mixture of chemicals; no single chemical exposure results
- Modeling – results of the development of a model; no primary data available
- No Conc – the authors report a response in an organism but do not provide conc/dose/app rate
- No Duration – duration of exposure is not presented
- No Effect – paper does not report observed responses adverse of otherwise
- No Toxicant (ozone, CO₂)
- Non-English
- Nutrient – in situ chemical tested as nutrient
- PUBL AS – duplicate data published elsewhere
- Retracted – paper retracted by Journal
- Review – primary data published elsewhere
- Sediment – only sediment concentration presented
- Survey – chemical measured in organism, but lack quantification of exposure (dose/duration)
- Virus – virus is only test organism
- Yeast – yeast is only test organism

ECOTOX Data Extraction

Identification

Chemical verification
and development of
search terms

Conduct literature
searches

Screening

Identify and acquire
potentially applicable
studies

Eligibility

Review literature for
applicability to
ECOTOX

Included

Data extraction

Study quality
evaluation

Unique Identifiers

- Chemical ID
- Taxonomic ID
 - NCBI taxid
 - ITIS TSN

Test Species

- Species Groups
 - Animals
 - Plants
 - Special Interests
- Lifestage
- Gender
- Organism source

Chemical

- Chemical Analysis
- Concentration type
- Chemical Formulation
- Chemical Grade
- Chemical ions
- Chemical Radiolabel
- Chemical Groups
 - Organic groups
 - EDCs *Example*
 - PCBs *groups*
 - Metal / organometal
 - Antimony *Example*
 - Arsenic *groups*

Test Condition

- Test Method
- Test Location
 - Lab
 - Field
 - Sub-habitat
 - Geographic text
 - Depth units
- Duration Units
- Exposure Type
 - Diet
 - Injection
 - Multiple application
 - Aquatic only
 - Aquatic lab
 - Aquatic Field
 - Topical Application
 - Environmental Exp.
 - Application Type
 - Exposure Type
 - In vitro
- Application Frequency
- Application Type
- Exposure media
 - Media Type
 - Aquatic Media
 - Terrestrial Media
 - Soil Type
 - Organic Matter
 - Exp. Media Character.
- Control Type
- Sample Unit
- Exposure Dose Units

Results

- Response Site
- Endpoint
 - Terrestrial
 - Aquatic
 - Both
- Trend
- Effect
 - Effect Groups
 - Effect Measurement
 - Accumulation
 - Behavior
 - Avoidance
 - General Behavior
 - Feeding Behavior
 - Biochemistry
 - Biochemical
 - Enzyme
 - Hormone
 - Reproduction
 - Cellular
 - Cellular
 - Genetic
 - Histological
 - Growth
 - Growth
 - Development
 - Morphology
 - Mortality
 - Physiology
 - General Phys
 - Injury
 - Immunity
 - Intoxication
 - Reproduction
 - General Repro
 - Egg
 - Population

| | |
|----------------|---|
| Identification | Chemical verification and development of search terms |
| | Conduct literature searches |
| Screening | Identify and acquire potentially applicable studies |
| Eligibility | Review literature for applicability to ECOTOX |
| Included | Data extraction |
| | Study quality evaluation |

The diagram illustrates the relationship between different identifiers. At the top, a blue arrow points to a yellow box labeled 'Chemical ID'. Below it, a red arrow points to a red box labeled 'Taxonomic ID'. To the right of 'Taxonomic ID', a blue arrow points to a yellow box labeled 'NCBI taxid'. Below 'NCBI taxid', a blue arrow points to a yellow box labeled 'ITIS TSN'.

- ▶ Test Method
- ▼ Test Location
 - ▶ Lab
 - ▼ Field
 - ▶ Sub-habitat
 - ▶ Geographic text
 - ▶ Depth units

- ▶ Response Site
- ▼ Endpoint
 - ▶ Terrestrial
 - ▶ Aquatic
 - ▶ Both
- ▶ Trend
- ▼ Effect
 - ▶ Effect Groups

- Automated data extraction

[illegible]

lms **QFT-26** endogen
 angiotensinase c215fab-sea spc matur
SOCs-1 corral dai peptid result restor
 breast diseases c-4118-lysate exspos fungal period gm-csf-c-mifc
 cancer progress combin donor **CD69** decin lozin ascorbyl interrupt abi
 mdm polymorph **anti-CD40** local sequenc liposm hivcd4 vdwnd armetastat viral **XCCL8**
 hypersensit x-irradiation **CD72** rate **interferon** develop gain **IL-10** monkei sarcoma **caspace-1**
 rnyvac-c efflux **IL-18 cDNA** non-responders epitop dna mmw assesses spcv hiv-1-specific b7-1 cytotox
 dose adminstr transactiv **IL-23** product liver nkt hiv-1 t-cell medline alert ifi vitamin fusion method
 macaqu anti-tumor candida test **IL-12** **infect** **respons** mice effect heapt ad migrat fibroblast n-2a
 combinatori secret viru tuberculosis **IL-18**
 transform dermatolog vector **cd8** pituitari
IL-2 **CSF-1** gamma-gal salmonella treatment
 radiat dnt gammedata journal signal cdt express tumor actv macrophag coinfect t-cells infant chanc
 cuttur fgr2b gloma mdma gyhd scienc individui **cd4** hiv therapy lung **cd-IL-18** **interleukin-18** protect
 skin intestin sly osteosarcoma synergist resist assai control latent mac pregnanc advanc posaconazole
 plaqui ifn-alpha beta 18 dunn melanoma us pleural hov pmf **neopterin** councit function
CD40L hiv-infected subject host escap colon transfect integ **IRF-1** **CXCL10**
 (IFigamma hlc tumor hiv-2-beta-sitosterol **SeV** mortal adut tuberculosis-specific
 FITTG popu radioemist d-fraction cdt 11c recog latent
 therapuut acut draquigant gene asc

<https://www.knime.com>

- ▶ Chemical Analysis
- ▶ Concentration type
- ▶ Chemical Formulation
- ▶ Chemical Grade
- ▶ Chemical ions
- ▶ Chemical Radiolabel
- ▼ Chemical Groups

- ▶ EDCs *Example*
- ▶ PCBs *groups*

Metal / organometal

- ▶ Antimony *Example*
- ▶ Arsenic *groups*

▶ In vitro

- ▶ Application Type
- ▼ Exposure media
 - ▼ Media Type

- ▶ Aquatic Media
- ▼ Terrestrial Media
 - ▶ Soil Type
 - ▶ Organic Matter
- ▶ Exp. Media Character.

Exp. Media Character.

- ▶ Sample Unit
- ▶ Exposure Dose

Exposure Dose Units

Cellular

Genetic

Histological

Growth

Growth

Development

Development
Morphology

▶ **Mod**

Mortality

Physiology

General Phys

Injury

Immunity

Intoxication

Reproduction

General Repro

Egg

Population


```
graph LR
    subgraph Identification
        A[Chemical verification and development of search terms]
        B[Conduct literature searches]
    end
    subgraph Screening
        C[Identify and acquire potentially applicable studies]
    end
    subgraph Eligibility
        D[Review literature for applicability to ECOTOX]
    end
    subgraph Included
        E[Data extraction]
        F[Study quality evaluation]
    end
    A --> B
    B --> C
    C --> D
    D --> E
    E --> F
```

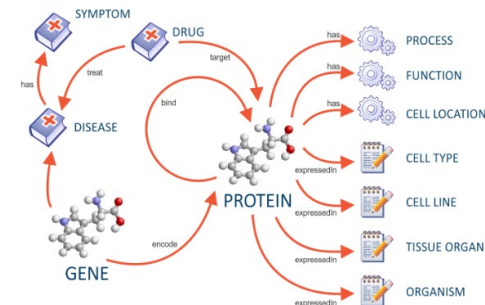
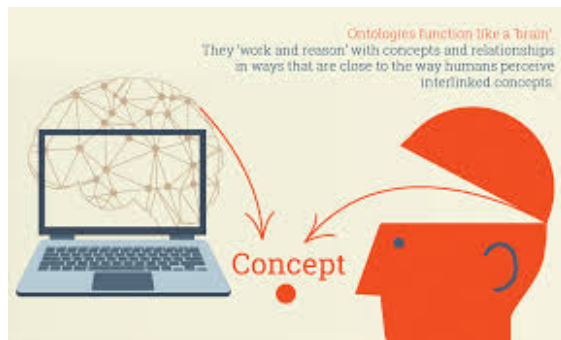
| Identification | Screening | Eligibility | Included |
|---|---|---|--------------------------|
| Chemical verification and development of search terms | | | |
| Conduct literature searches | | | |
| | Identify and acquire potentially applicable studies | | |
| | | Review literature for applicability to ECOTOX | |
| | | | Data extraction |
| | | | Study quality evaluation |

- ## Documents
- Document title
- A common haplotype of interleukin-6 gene is associated with severe respiratory viral disease in Korean children
- Analysis of the microsatellite polymorphisms of IL-6 and IL-4 in viral-induced childhood pneumonia
- Common cytokine pathway associates risk of meningitis after viral infection
- Genetic polymorphisms of interleukin-10 and interleukin-18 in children with viral-induced pneumonia
- A strategy for detection of Epstein-Barr virus (positive) through IL-6 gene is targeting interleukin-12 to the linear insertion site
- Genetic polymorphisms of interleukin-10 and interleukin-18 in children with viral-induced pneumonia
- Activation of cytokines in Hodgkin's disease
- Interleukin-induced dendritic maturation (ADC) associated with cytokine receptors to assess impact of ADC in etiology of diseases
- Effect of interleukin-6 on interleukin-12 production in human monocytes and regulatory principal cells
- Alteration of interleukin and tumor necrosis factor micro RNA profile and processed nucleic particle in head and neck cancer
- Effect of interleukin-6 on interleukin-12 production in human monocytes and regulatory principal cells
- Association of viral and human cytokine levels with urinary excretion in the first year and later
- Beneficial effects of interleukin-6 on interleukin-12 production in human monocytes and regulatory principal cells
- Characterization and growth factor expression of cytokines and lymphocytes
- Interleukin-12 dependency of the in vitro culture of human natural killer cells
- Clinical impact of cytokine levels of interleukin-6, interleukin-10, tumor necrosis factor- α , and interferon- γ in patients with colorectal cancer
- Effect of interleukin-6 on interleukin-12 production in human monocytes and regulatory principal cells
- Correlation of serum interleukin-6 levels in breast tissue stroma after systemic or mucosal irradiation with cytokine antigen levels
- Effect of interleukin-6 on interleukin-12 production in human monocytes and regulatory principal cells
- Genetic polymorphisms of interleukin-10 and interleukin-18 in children with viral-induced pneumonia



IL-17
 ImS QFT-25 endogen
 angiospines c215fab-secsu mator
 SOCS-1 correl da pepid result restor
 breast disease d-118 lysate exocur fungal period gm-crm-cmu-specific
 cancer response combin dour CD69 declin toun astrocyt interrupt alh
 mdrn polymorph anti-CD40 local sequenc liposom hivhcv CD4 wound antimetastat viral CXCL8
 hypersensit-xirradiation CD72 rate interferon develop gain IL-10 monkei sarcosa caspase-1
 rnyvac-c efflux IL-18 cDNA non-response epitop gain dnmw assesses speet hiv-1-specific b7-1 cytotox
 dose administ transactiv IL-23 product liver nkt hiv-1 t-cell mediet alert Irf vitamin fusion method
 macaqui anti-tumor candida test IL-12 infect respons mice effect healt ad migrat fibroblast n-2a
 combinatori secret viru tuberculosi IL-18
 transform dermatolog vectur cd8 pituitari
 cell vaccin IFN-gamma BLf fortschritt leue
 immunpatient der antitumor substanti diagnosi
 IL-2 CSF-1 gene-gam salmonella treatment
 radiat dnt gammeda journal signal cl express tumor acty macrophag coinfect-cells infant chan
 cuttur gfr/2b glioma mtda gyvhd scienc individui cd4 hiv therapy lung dc IL-18IR interleukin-18 protect
 skin intestin vsy osteosarcosa synergist resist assai control latent mac pregnanc advanc posasonazi
 plaqui irf-alphabeta nr18 dunn melanoma us pleural hiv pmg1 neopterin concnq function
 CD40L Irf-infectd subiect hscap concnq transfect injct Irf-1 CXCL10
 IFNgamma hsc tumor hiv-2 beta2-sitocster SEV mortal aduq tuberculosi-specific
 PTTG popul radiosenst d-fraction c11c1 recog listeria
 thepateut acq praquidant genic asc
<http://www.kjpmi>

- Standardized unique identifiers
 - Chemicals: CASRN, DTXSID
 - Species: USGS IT IS taxonomic serial number, NCBI Taxid
 - Genes: NCBI Gene ID
 - Proteins: UniProt ID, NCBI protein accession(s)
- Development of ontologies for ecotoxicology



<https://www.ontotext.com>

- Linking effects to biological pathways

Study Quality Evaluation

- Many fields in ECOTOX can inform study evaluation

| Category | Select study evaluation questions with relevant ECOTOX field(s) |
|------------------------|--|
| Chemical | <ul style="list-style-type: none"> Is test substance identified? Required for inclusion in ECOTOX inclusion Is the purity of test substance reported? <u>Chemical Purity</u> Were chemical concentrations verified? <u>Chemical Analysis</u> (e.g., nominal versus measured concentrations) |
| Species | <ul style="list-style-type: none"> Is the species given? Verifiable species (Scientific Name, etc.) required for inclusion in ECOTOX Are the organisms well described? <u>Organism Source</u>, <u>Lifestage</u>, <u>Age</u>, <u>Gender</u>, <u>Initial</u> and <u>Final Weight</u> |
| Test Conditions | <ul style="list-style-type: none"> Are appropriate controls performed? A control is required for inclusion in ECOTOX, type described in <u>Control</u> Is a guideline method (e.g., OECD) used? <u>Test Method</u> Are the experimental conditions appropriate and acceptable for the test substance and organism? <u>Test Method</u>, <u>Media Type</u>, <u>Test Location</u>, <u>Experimental Design</u>, Physical and Chemical Soil and Water Parameters (e.g., <u>pH</u>, <u>Temperature</u>, <u>Dissolved Oxygen</u>) |
| Test Results | <ul style="list-style-type: none"> Are the reported effects and endpoints appropriate for the purpose, test substance and organism? <u>Effect Measurement</u>, <u>Endpoint</u> Is the response/effect statistically significant? <u>Statistical Significance</u>, <u>Significance Level</u> |

Identification

Chemical verification and development of search terms

Conduct literature searches

Screening

Identify and acquire potentially applicable studies

Eligibility

Review literature for applicability to ECOTOX

Included

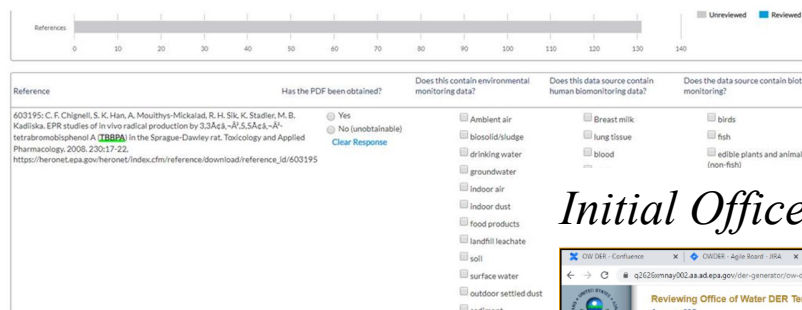
Data extraction

Study quality evaluation

Study Quality Evaluation

- Working towards a unified study quality evaluation method

Pilot with 1st 10 Priority TSCA Chemicals



Initial Office of Water DER Templates

Critical Domains

- Test Substance
- Test Design
- Exposure Characteristics
- Test Organism
- Outcome Assessment
- Confounding/variable Control
- Data Presentation and Analysis

- Test Substance
- Exposure Pathway
- Protocols Followed
- Study Design and Methods
- Test Organism
- Study Parameters
- Test Conditions
- Dose/response data
- Statistical Verification

Identification

Chemical verification and development of search terms

Conduct literature searches

Screening

Identify and acquire potentially applicable studies

Eligibility

Review literature for applicability to ECOTOX

Included

Data extraction

Study quality evaluation

- Background and History for ECOTOX Knowledgebase
- Modernizing the ECOTOX Pipeline (C. Elonen, SOT 2020)
- Mapping ecological toxicity of PFAS with ECOTOX Protocols (J. Olker, SOT 2020)



Background & Objectives

- Persistence and wide distribution of some PFAS in the environment
 - Detection of PFAS across the world in water and other media
 - Detection in tissue samples of invertebrates, fish, amphibians, birds, marine mammals, terrestrial mammals
- Potential to bioaccumulate
- Effects on ecological species
- Ecological toxicity information needed to inform risk assessment and management
 - Sensitive and susceptible species
 - Bioaccumulation
 - Benchmarks and thresholds for ecological toxicity

} Across
range of
PFAS



Background & Objectives

- Persistence and wide distribution of some PFAS in the environment
- Potential to bioaccumulate
- Effects on ecological species
- Ecological toxicity information needed to inform risk assessment and management

Objectives

- Identify and describe available empirical evidence for ecological effects of PFAS
- Identify potential ecological toxicity pathways

Data last updated

Mar 12,
2020

See update totals

Recent chemicals with full searches and coding completed

1,1-Dichloroethane

1,2-Dichloroethane

1,1,2-Trichloroethane

Aminopyralid

Butyl benzyl phthalate

Dibutyl phthalate

Fenazaquin

Flutriafol

[Per- and Polyfluoroalkyl Su...](#)

Pyrasulf [Click to Explore Per- and Polyfluoroalkyl Substances \(PFAS\)](#)

Total in database

12,089

Chemicals

13,138

Species

50,092

References

988,806

Results

WELCOME TO ECOTOX VERSION 5!

Please click [here](#) to provide feedback so that we can continue to improve your experience.

About ECOTOX

The ECOTOXicology knowledgebase (ECOTOX) is a comprehensive, publicly available knowledgebase providing single chemical environmental toxicity data on aquatic life, terrestrial plants and wildlife.



[Learn More](#)

Disclaimer: You should consult the original scientific paper to ensure an understanding of the context of the data retrieved from ECOTOX.

Getting Started

- Use [Search](#) if you know exact parameters or search terms (chemical, species, etc.)
- Use [Explore](#) to see what data may be available in ECOTOX (including data plots)
- [ECOTOX Quick User Guide](#) (2 pp, 141 K)
- [ECOTOX User Guide](#) (84 pp, 1120 K)
- [ECOTOX Terms Appendix \(PDF\)](#) (825 pp, 7145 K, [About PDF](#))

Other Links

- [Limitations](#)
- [Frequent Questions](#)
- [Other Tools/Databases](#)
- [Recent Additions](#)

[Get Updates via Email](#)

Download

Download the entire database as an ASCII file via the button below.

[Download ASCII Data](#)



☒ Aquatic

☒ Terrestrial

Group Summary

Records

Plot View

Send Query Filters to Search

Query Filters

Select one or more of each filter to reduce the records.

Chemicals (112)

All

▼

Species Group (14)

All

▼

Class (37)

All

▼

Order (111)

All

▼

Family (200)

All

▼

Genus (322)

All

▼

11,974 Plottable Records — 18,140 Total Records

(showing first 3,000)

Records are **plotted** if they can be converted to **Standardized Concentration Units** . Ordered by **Concentration (low-high)**.

Effect × Chem

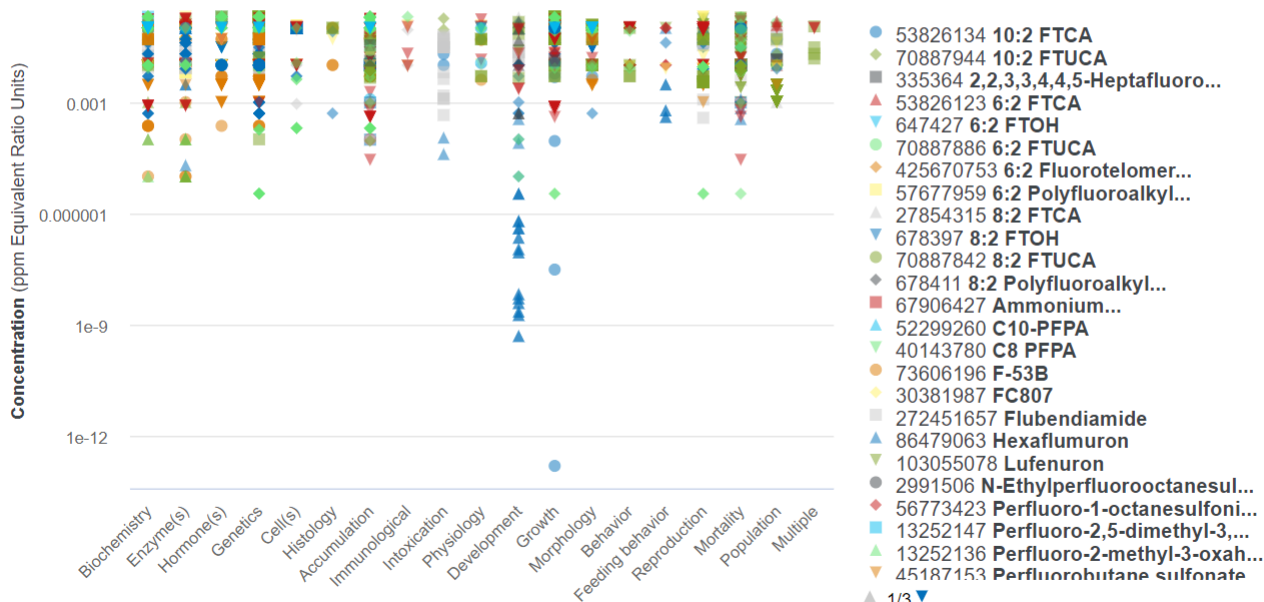
Dur × Chem

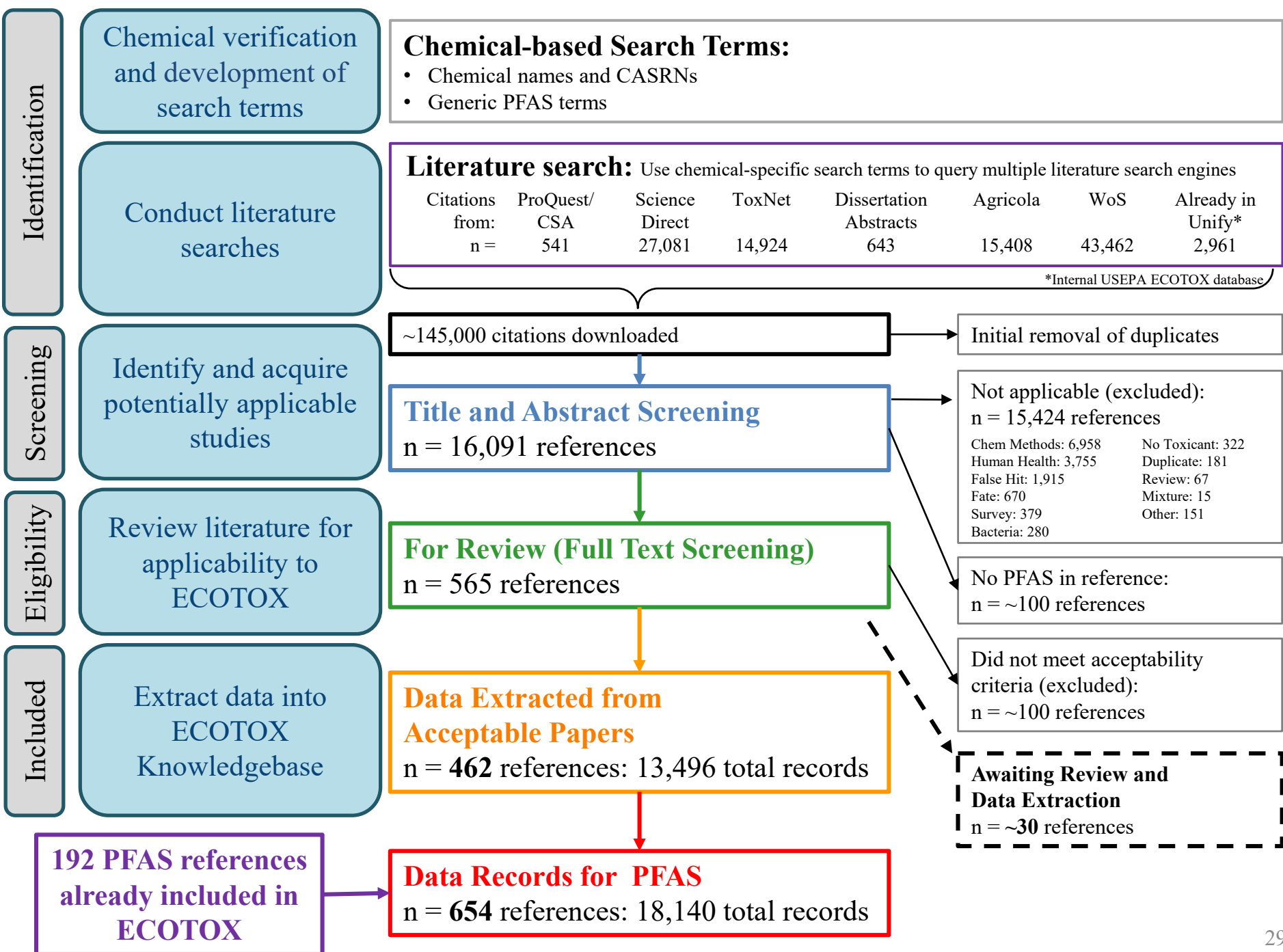
Dur × Endpt

Export

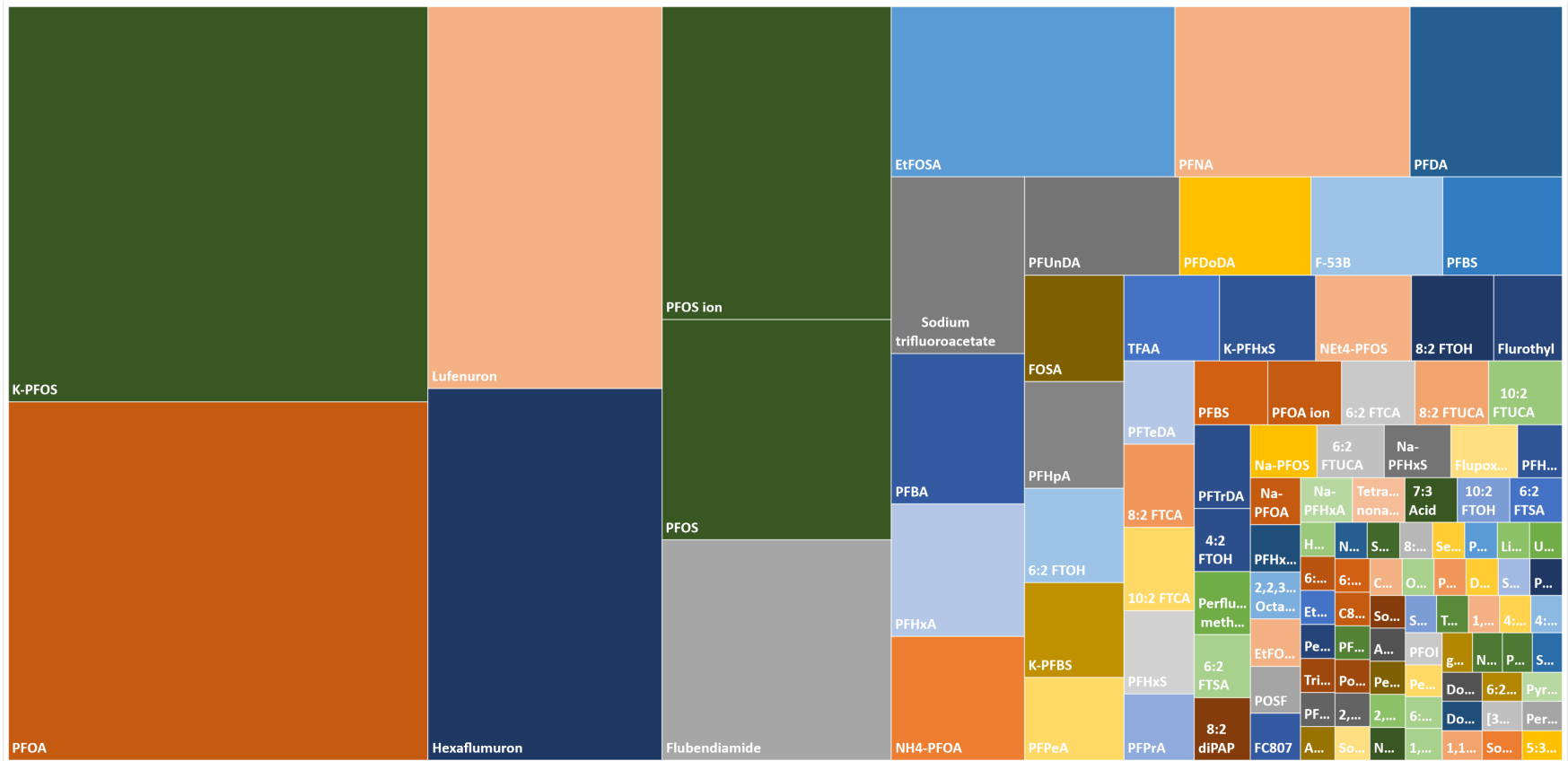
Y-axis scale: ☐ Linear ☒ Logarithmic

Click and drag to zoom in. Hold down shift key to pan.



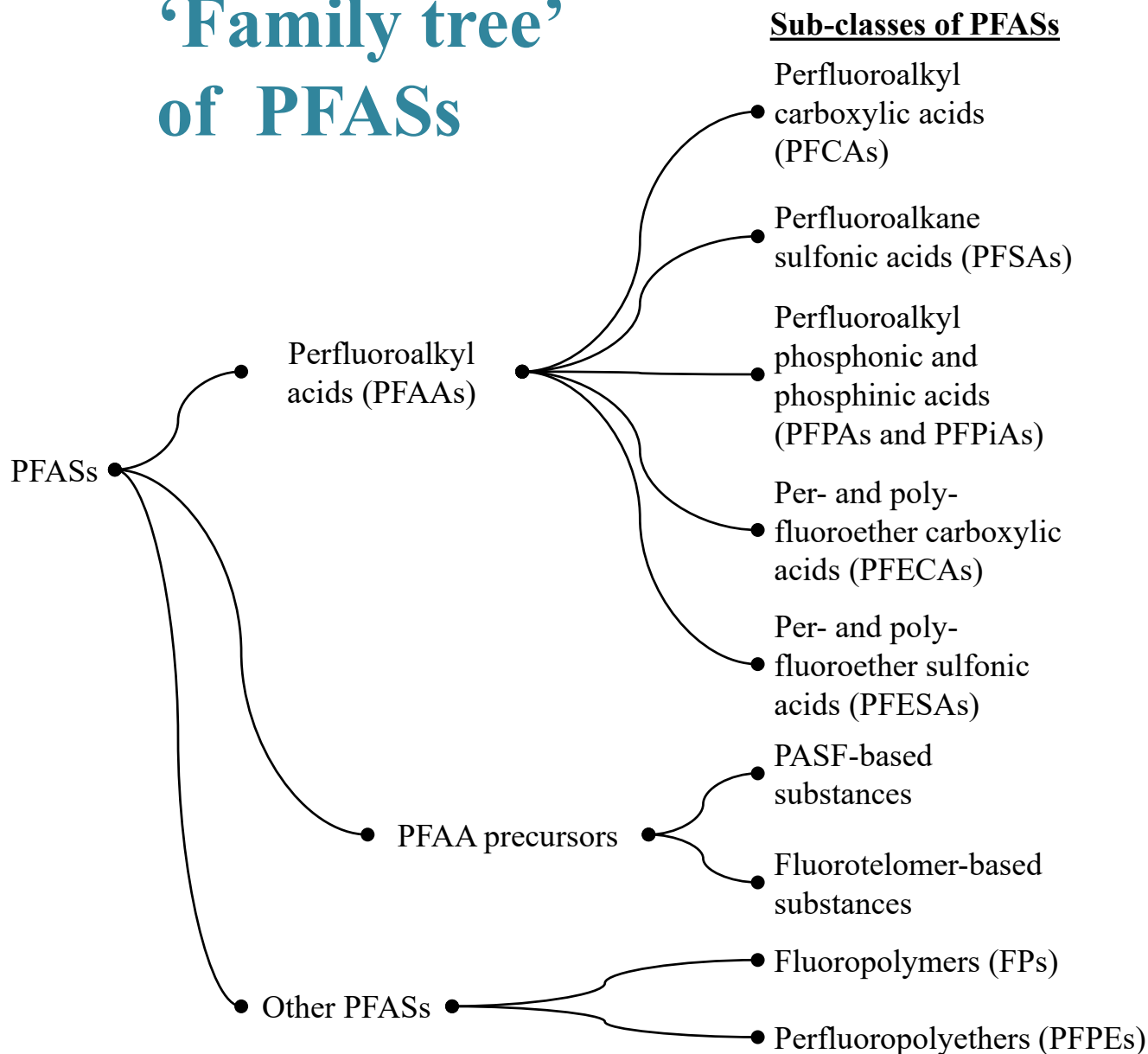


654 Publications, 112 PFAS with Ecological Toxicity Data



Box size represents # references that include relevant and acceptable ecological toxicity data

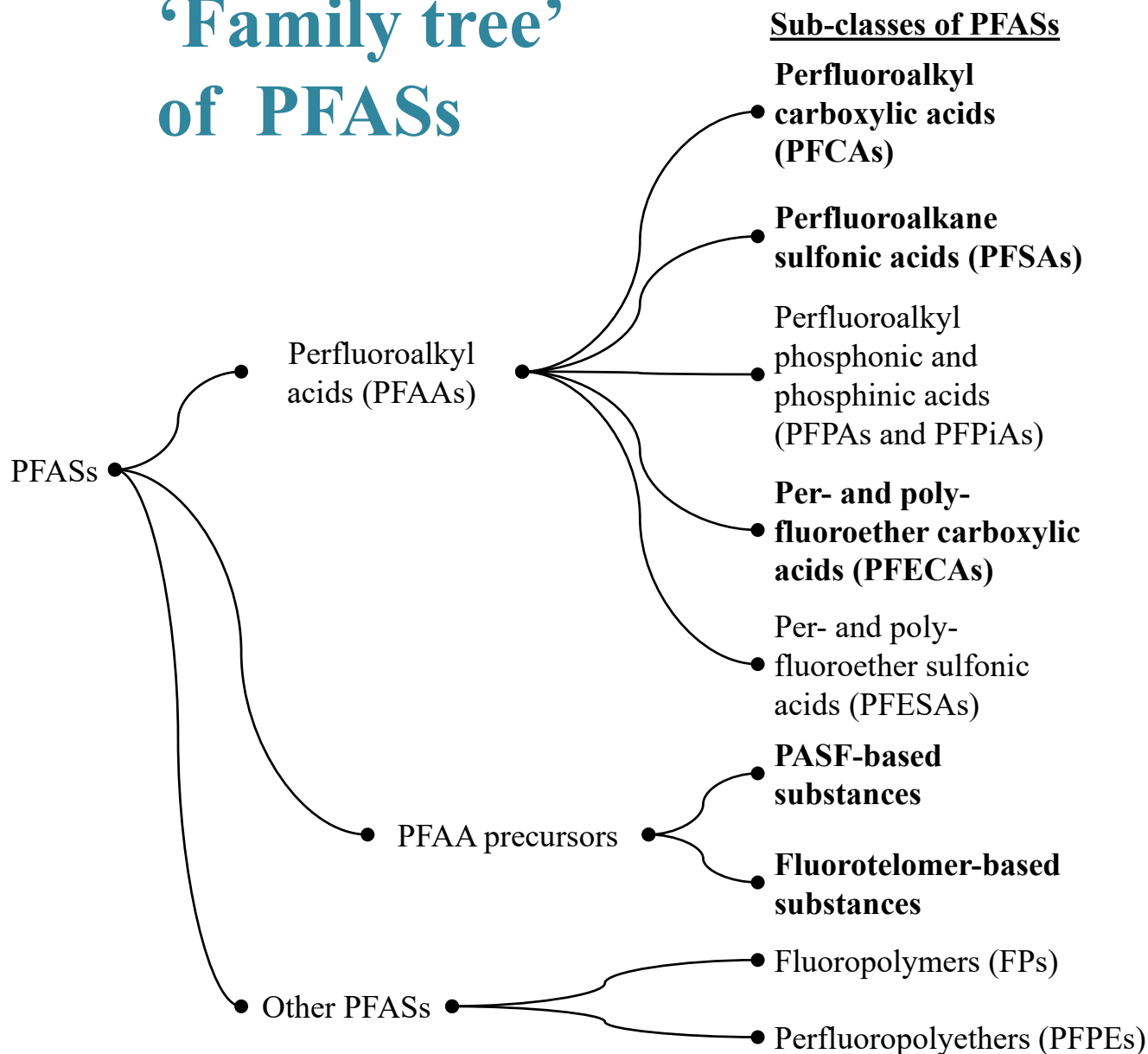
‘Family tree’ of PFASs



Literature Search Terms

- 322 chemical names with associated CASRNs
- General PFAS search terms (e.g., Dodecafluoro, Fluorotelomer, Nonafluoro, Pentafluoropropanoic, Perfluorobutanesulfon, Perfluoroheptanoate, Perfluorohexanoate, Perfluoropentyl)

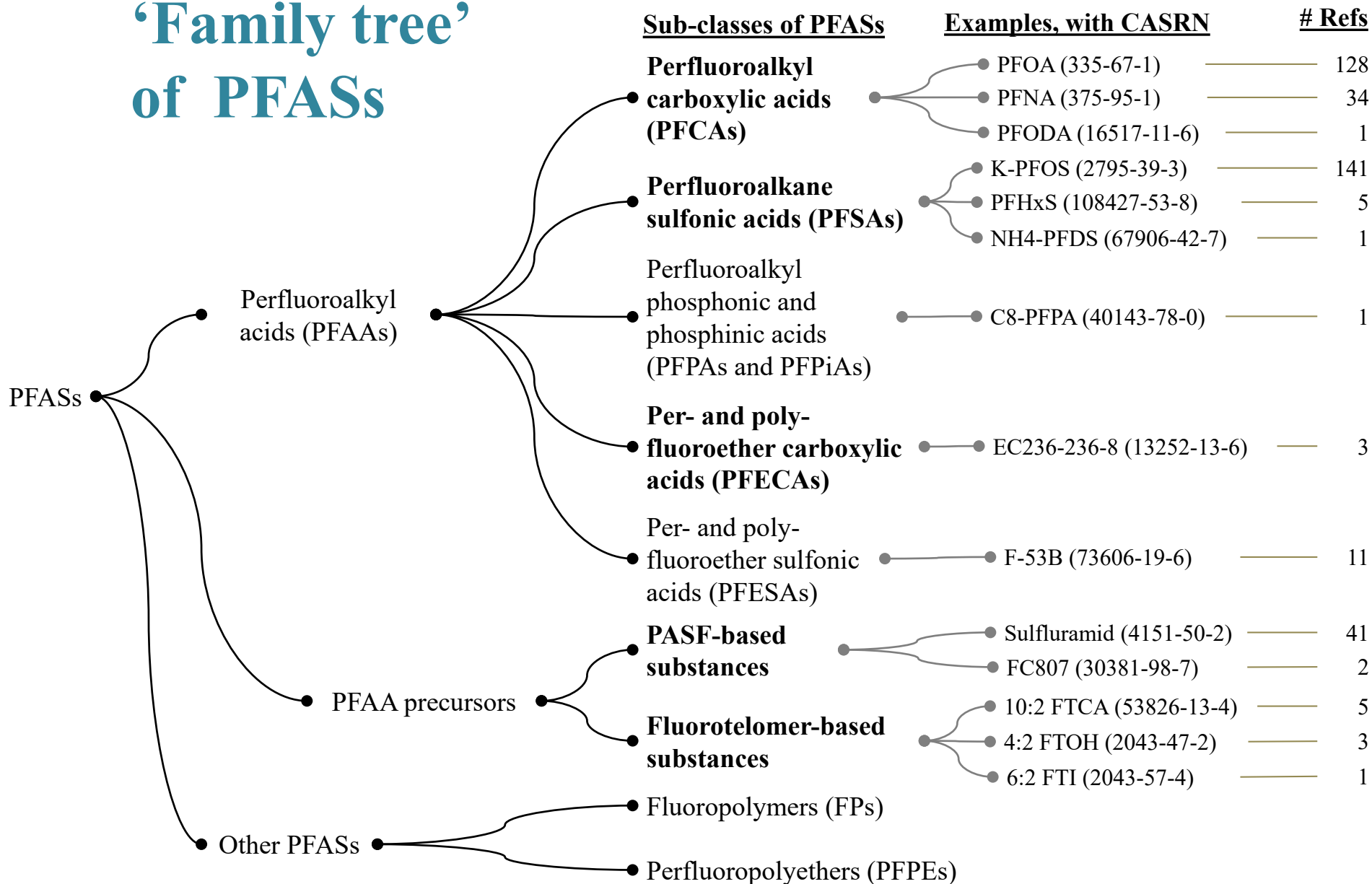
‘Family tree’ of PFASs



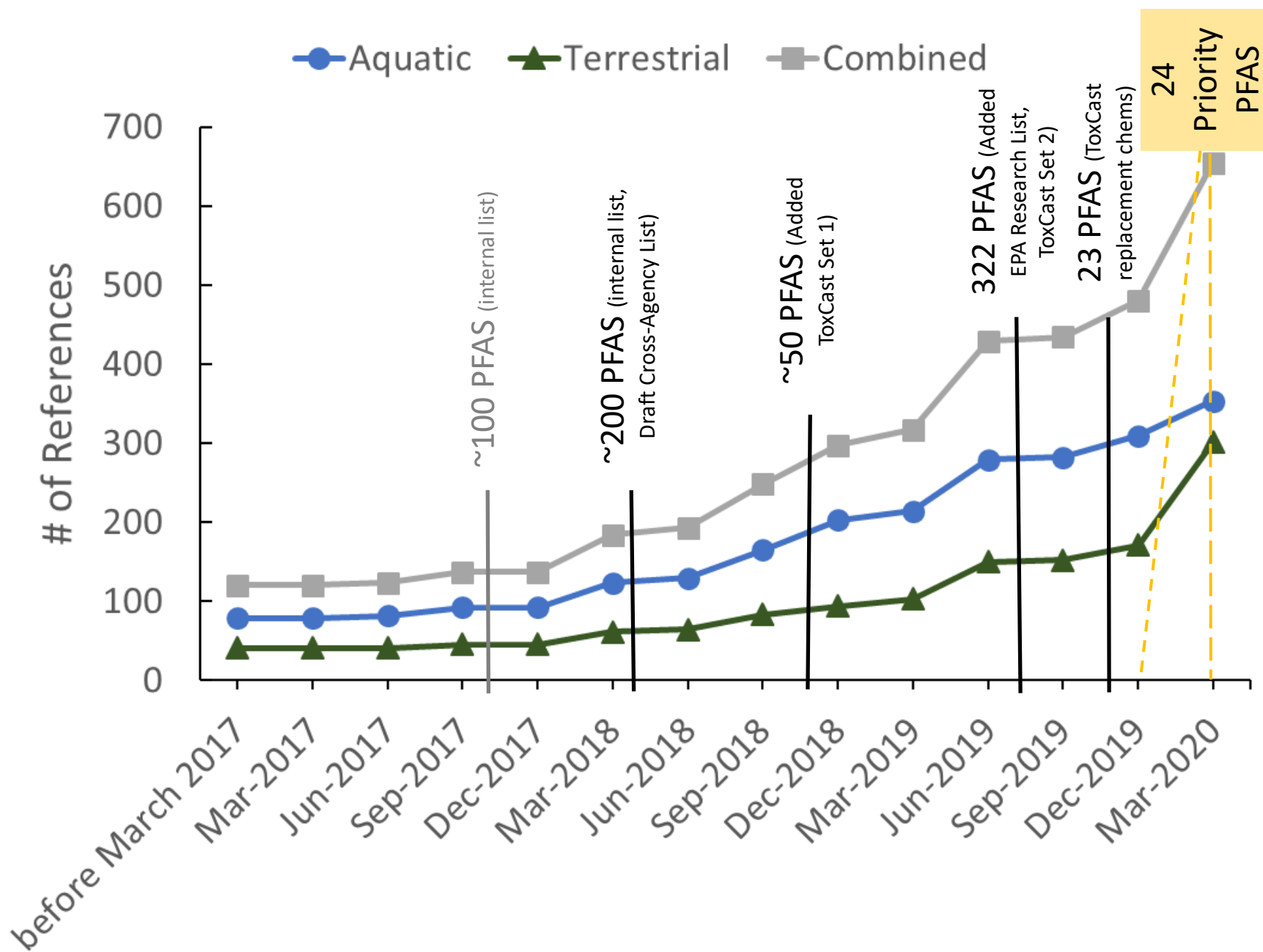
Literature Search Terms

- 322 chemical names with associated CASRNs
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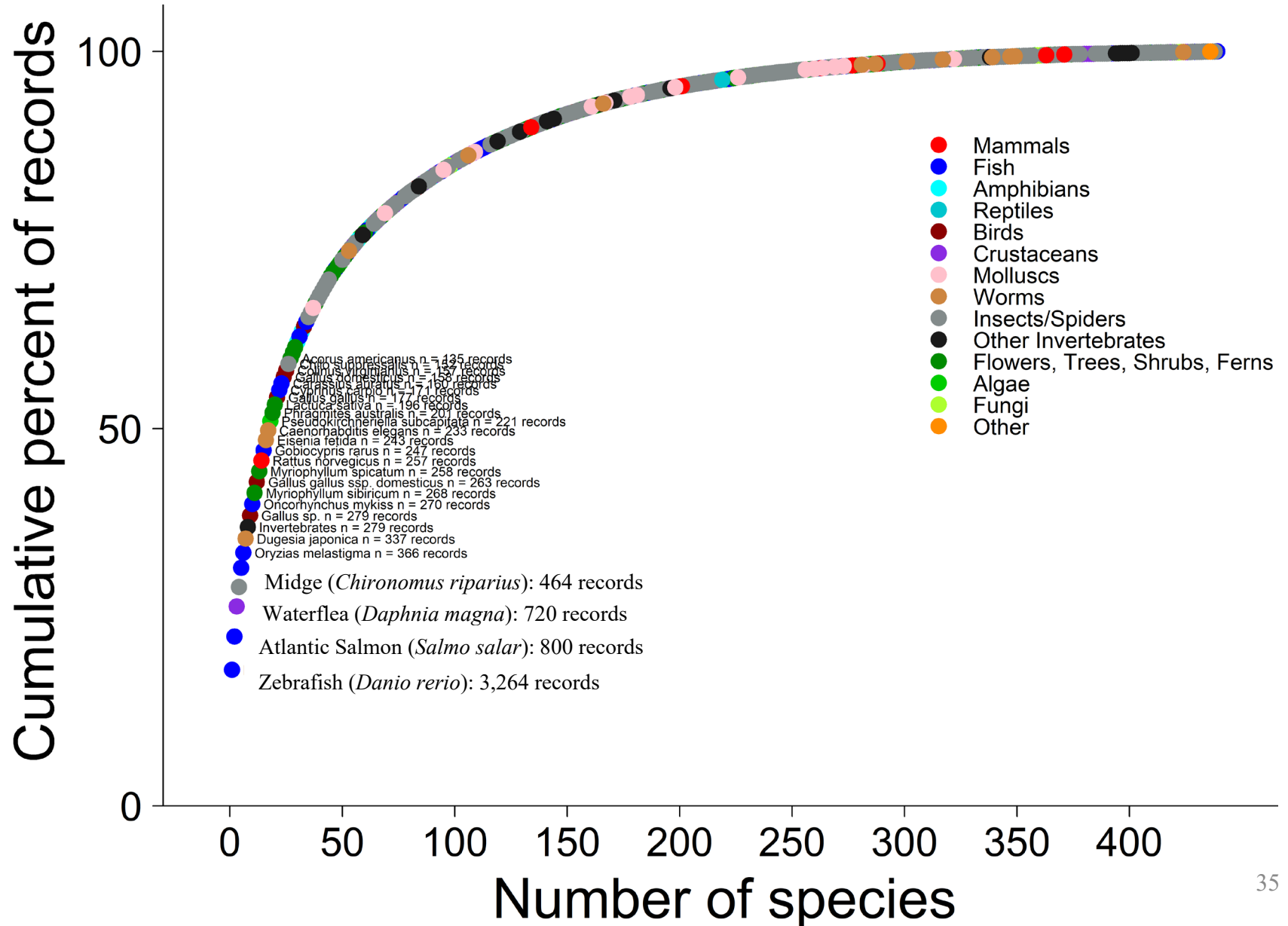
‘Family tree’ of PFASs



PFAS References in ECOTOX Knowledgebase



PFAS Data for 440 Biological Species



Diversity in Types of Effects



PFAS records for Fish

| | Effect | # Records |
|----------------------|------------------|--------------|
| Cellular Responses | Genetics | 2,660 |
| | Biochemistry | 802 |
| | Enzyme(s) | 305 |
| | Hormone(s) | 268 |
| | Cell(s) | 70 |
| Organ Responses | Histology | 58 |
| | Accumulation | 294 |
| | Immunological | 3 |
| | Physiology | 154 |
| | Injury | 26 |
| Organism Responses | Intoxication | 4 |
| | Development | 98 |
| | Growth | 364 |
| | Morphology | 402 |
| | Behavior | 266 |
| | Avoidance | 19 |
| | Feeding behavior | 4 |
| | Reproduction | 120 |
| | Mortality | 545 |
| | | |
| Population Responses | Population | 7 |
| Other | Multiple | 70 |
| | Total | 6,539 |

Reproduction

Fecundity
 Fertility
 Fertilization
 Gamete production
 Hatch
 Mean spawns per female
 Motility
 Number spawning
 Pregnant, Paris or Gravid
 Progeny counts/numbers
 Spawning frequency
 Sperm cell counts
 Time to spawn
 Velocity
 Viability

Ongoing Literature Search, Review, Data Extraction

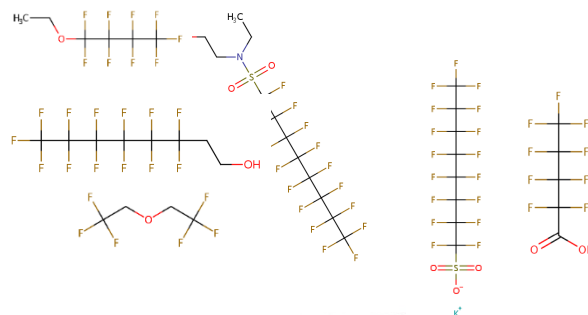
Updated list of >300 unique
CASRNs and associated
chemical names

Conduct literature searches

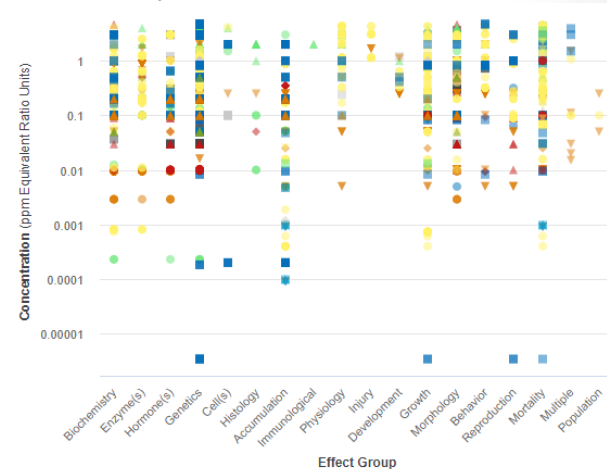
Identify and acquire
potentially applicable studies

Review literature for
applicability to ECOTOX

Extract data and encode into
ECOTOX Knowledgebase



Quarterly data releases to ECOTOX

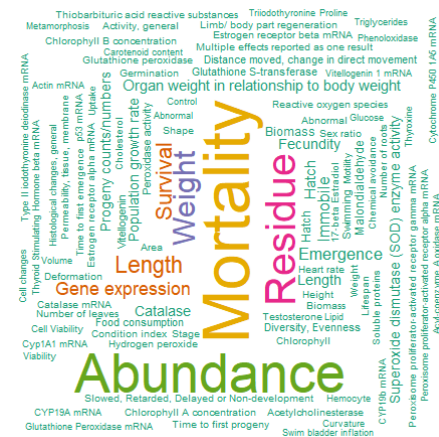
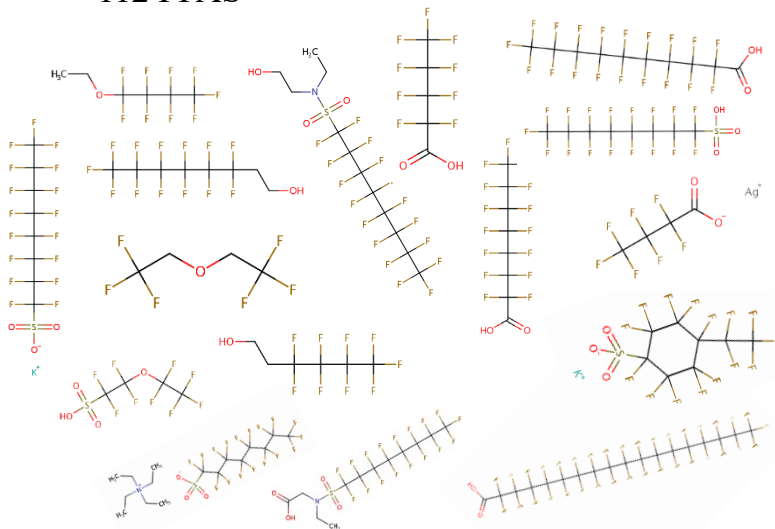


Data Inventory \rightarrow Summary/Synthesis

440 Biological Species

112 PFAS

Measurements of 1,126 Effects

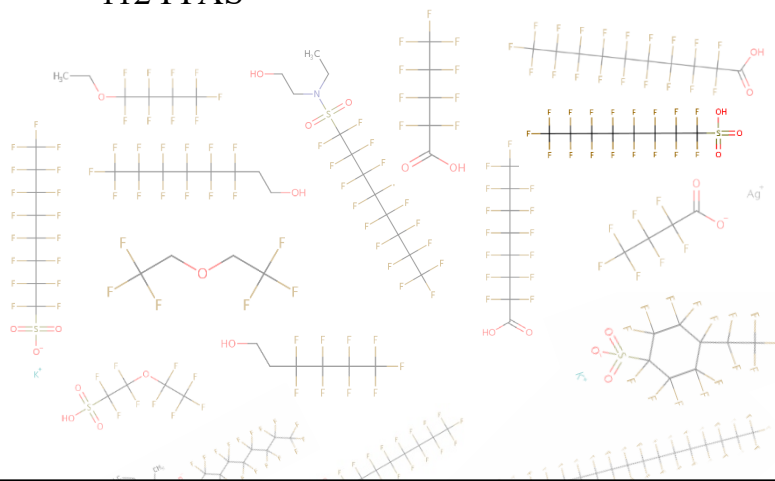
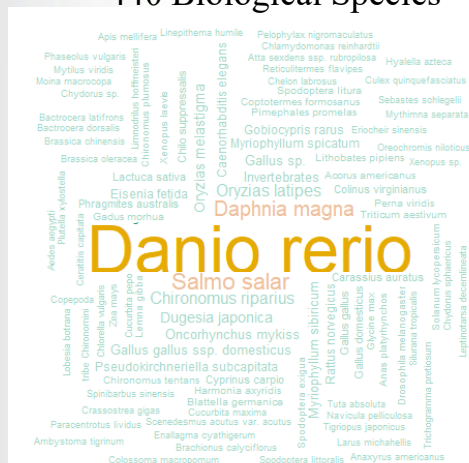


Data Inventory → Summary/Synthesis

440 Biological Species

112 PFAS

Measurements of 1,126 Effects



Toxicant

Cellular Responses

Tissue/Organ Responses

Organism Responses

PFOS
(1763-23-1)

K-PFOS
(2795-39-3)

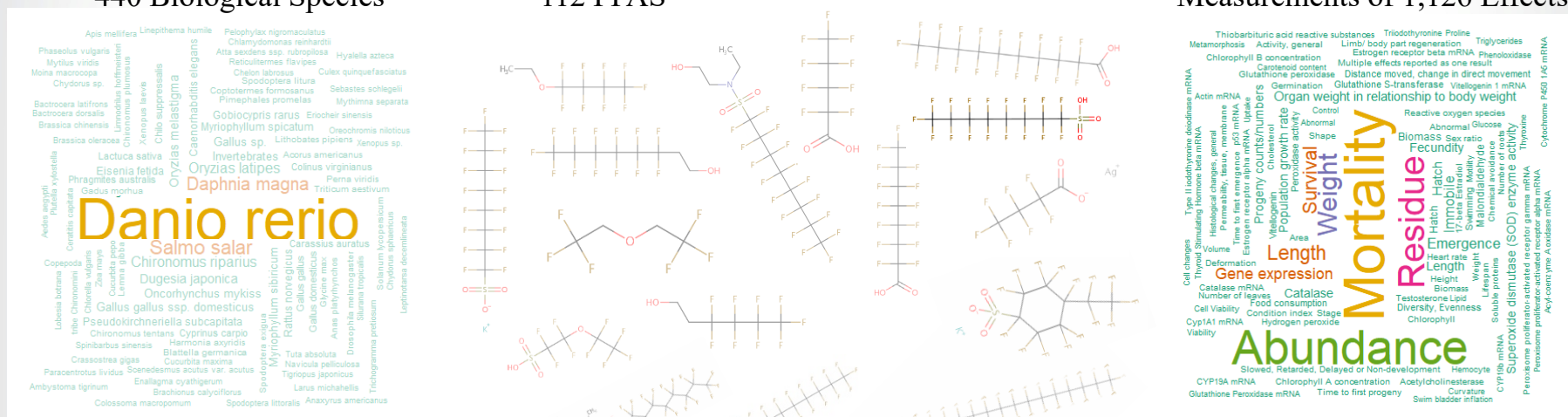
Mortality ↑
Length & Weight ↓ or ↑ or Δ
Behavior (swimming, distance moved) Δ
Abnormal development ↑
Sperm cell counts ↓

Data Inventory → Summary/Synthesis

440 Biological Species

112 PFAS

Measurements of 1,126 Effects

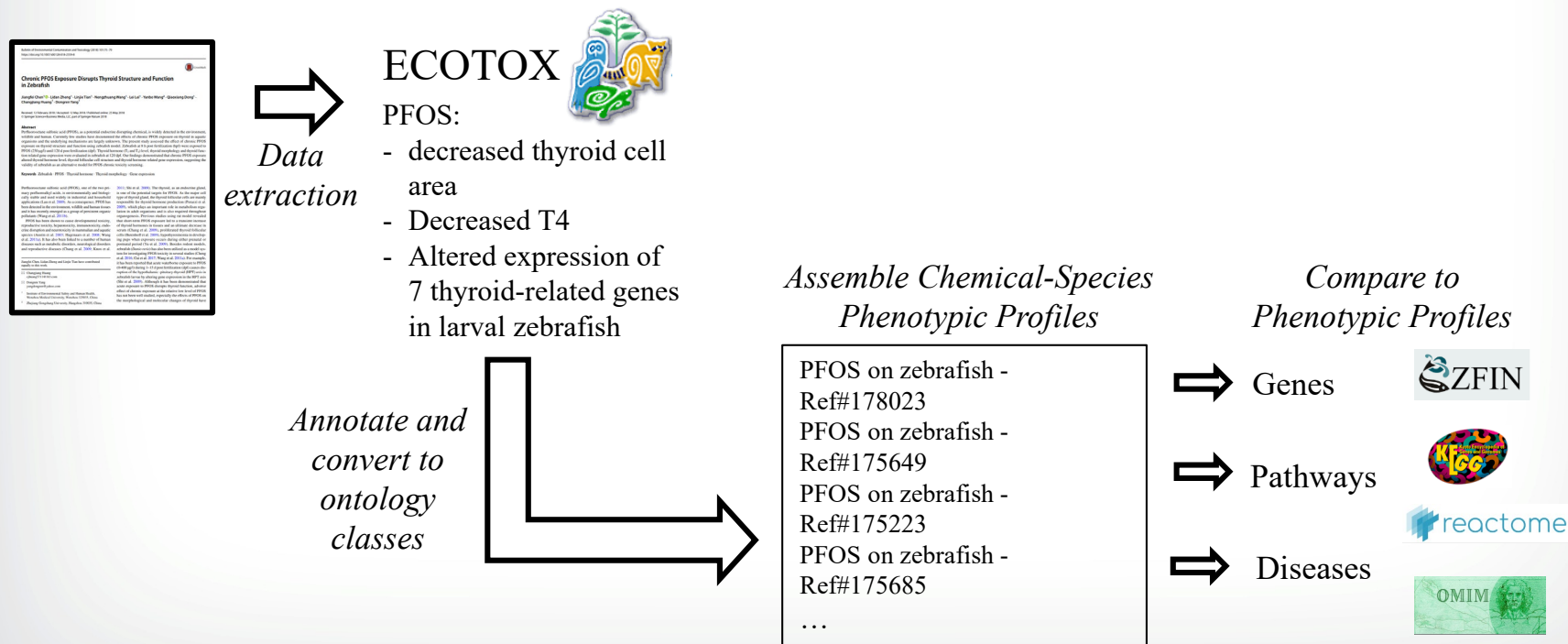


| Toxicant | Cellular Responses | Tissue/Organ Responses | Organism Responses |
|-----------------------|--|---|--|
| PFOS (1763-23-1) | T4 & T3 ↓ Estrogen and 17-β Estradiol Δ | Heart rate Δ Swim bladder inflation Δ | Mortality ↑ Length & Weight ↓ or ↑ or Δ |
| K-PFOS (2795-39-3) | Vitellogenin Δ Acetylcholinesterase Δ Cholesterol & Lipids Δ <u>Δ in expression of:</u> PPAR-mediated genes (multiple) Thyroid-relevant genes (multiple) ... | Organ:Body weight Δ Vacuolization (Liver) Δ Accumulation: Residue, Uptake ↑ | Behavior (swimming, distance moved) Δ Abnormal development ↑ Sperm cell counts ↓ |

Identify Potential Toxicity Pathways

Ontology-based semantic analysis

- Bridge the gap between the molecular/non-molecular phenotypes
- Lead to a better understanding of the underlying MOAs
- Allow comparisons across chemicals, both within and across species

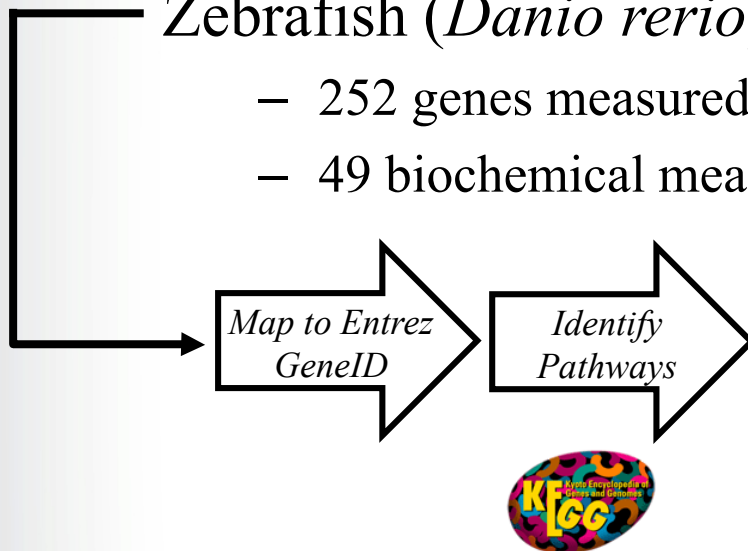


Identify Potential Toxicity Pathways

- 40% of the effect measurements are biochemical or genetic effects

Zebrafish (*Danio rerio*) PFAS references include:

- 252 genes measured for changes in expression
- 49 biochemical measurements (e.g., proteins, enzymes, hormones)



73 Zebrafish Pathways Investigated

Carbohydrate metabolism (3): Glycolysis/Gluconeogenesis; Starch and sucrose metabolism

Lipid metabolism (5): Fatty acid elongation and degradation; Steroid hormone biosynthesis

Energy metabolism (1): Oxidative phosphorylation

Immune system (7): Toll-like receptor signaling pathway; NOD-like receptor signaling pathway

Endocrine system (6): PPAR signaling pathway; Insulin signaling pathway; Progesterone-mediated oocyte maturation

Circulatory system (2): Adrenergic signaling in cardiomyocytes; Vascular smooth muscle contraction

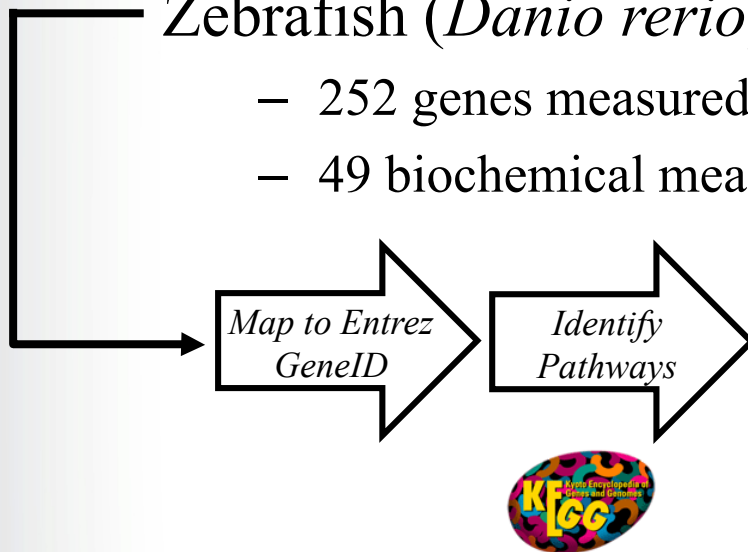
Endocrine and metabolic disease (1): AGE-RAGE signaling pathway in diabetic complications

Identify Potential Toxicity Pathways

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Genes with
sig. change in
transcription

73 Zebrafish Pathways Investigated

Carbohydrate metabolism (3): Glycolysis/Gluconeogenesis; Starch and sucrose metabolism

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Circulatory system (2): Adrenergic signaling in cardiomyocytes; Vascular smooth muscle contraction

Endocrine and metabolic disease (1): AGE-RAGE signaling pathway in diabetic complications

- Extent and distribution of literature of ecological toxicity of PFAS
 - Curated toxicity data for multiple applications
 - Identification of data gaps
- Literature identified for other areas of PFAS research
- Ontology-based semantic analysis could advance synthesis and interpretation
- Limitations:
 - Mixtures currently not included
 - Observational and (most) field data not represented here
 - Limited gene and pathway information for many ecological species

Thank you!

Questions?

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ecotox.support@epa.gov

EXTRA SLIDES

Terms for Literature Search

| List | # of Chemicals |
|---|----------------|
| PFAS list internal to ECOTOX | 69 |
| EPA Cross-Agency List – <i>Chem Dashboard</i> | 199 |
| ToxCast Set 1 List of 75 Test Samples – <i>Chem Dashboard</i> | 74 |

April – Nov 2018

- 254 chemical names with associated CASRNs (if applicable)
- General PFAS search terms (e.g., Dodecafluoro, Fluorotelomer, Nonafluoro, Pentafluoropropanoic, Perfluorobutanesulfon, Perfluoroheptanoate, Perfluorohexanoate, Perfluoropentyl)

Terms for Literature Search

| List | # of Chemicals |
|--|----------------|
| PFAS list internal to ECOTOX | 69 |
| EPA Cross-Agency List – <i>Chem Dashboard</i> | 199 |
| ToxCast Set 1 List of 75 Test Samples – <i>Chem Dashboard</i> | 74 |
| Additional chemicals found in literature from 1 st search | 7 |
| EPA Research List – <i>Chem Dashboard</i> | 165 |
| ToxCast Set 2 List of 75 Test Samples – <i>Chem Dashboard</i> | 75 |

April – Nov 2018

- 254 chemical names with associated CASRNs (if applicable)
- General PFAS search terms (e.g., Dodecafluoro, Fluorotelomer, Nonafluoro, Pentafluoropropanoic, Perfluorobutanesulfon, Perfluoroheptanoate, Perfluorohexanoate, Perfluoropentyl)

July – August 2019

- 322 chemical names with associated CASRNs (if applicable)
- General PFAS search terms

Terms for Literature Search

| List | # of Chemicals |
|--|------------------|
| PFAS list internal to ECOTOX | 69 |
| EPA Cross-Agency List – <i>Chem Dashboard</i> | 199 |
| ToxCast Set 1 List of 75 Test Samples – <i>Chem Dashboard</i> | 74 |
| Additional chemicals found in literature from 1 st search | 7 |
| EPA Research List – <i>Chem Dashboard</i> | 165 |
| ToxCast Set 2 List of 75 Test Samples – <i>Chem Dashboard</i> | 75 |
| ToxCast Replacement Test Samples – <i>Chem Dashboard</i> | 36 26 |

April – Nov 2018

- 254 chemical names with associated CASRNs (if applicable)
- General PFAS search terms

July – August 2019

- 322 chemical names with associated CASRNs (if applicable)
- General PFAS search terms

October 2019

- 23 chemical names with associated CASRNs (if applicable)

On-going Literature Searches for PFAS

Already in ECOTOX

185 PFAS refs
✓ March 2018
and before

2018-2019 Efforts

Lit search for
>250 PFAS
✓ April-Nov
2018

✓ June 2019

Lit search for
>300 PFAS
✓ July/Aug
2019

Lit search for 23
'replacement'
PFAS
✓ Oct 2019

247 PFAS refs
added to ECOTOX

Future

Dec 2019

March 2020

Lit search for
>300 PFAS
June 2020

Sept 2020

Literature searches:
comprehensive or selective
? ?

Update from
July/Aug 2019
search

Update from
Oct 2019
search

Update from
June 2020 search

Criteria for inclusion in ECOTOX

| Recently developed PECO statement for ECOTOX | | Requirements/Inclusionary Criteria from ECOTOX SOP |
|--|---|---|
| P (Population) | <p>Animal: Aquatic and terrestrial species (live, whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Include wild mammals (e.g. <i>Peromyscus</i> sp.), insects, spiders, amphibians, birds, crustaceans, fish, molluscs, reptiles, worms and invertebrates. Bacteria and viruses are not included.</p> <p>Plants: Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species</p> | <ul style="list-style-type: none"> • Ecologically-relevant species • Live, whole organisms • Organism taxonomic information verifiable against standard taxonomic sources • Priority species are wild (test results for terrestrial domestic and laboratory species are used to fill data gaps when needed) • In vitro studies (with viable cells or tissue) flagged for possible inclusion as requested by Programs • NOT: humans, monkeys, bacteria, viruses, yeast |
| E (Exposure) | <p>Relevant forms: Chemical of Concern, name and CASRN (plus synonyms, tradenames); when requested: Metabolites, degradants, parent compound and related chemicals</p> <p>Animal: Any exposure to relevant forms of the chemical of concern including via water, injection, diet, and dermal, with reported concentration and duration. Inhalation studies are excluded unless this is the primary route of environmental exposure (e.g., for volatile compounds).</p> <p>Plants: Exposure to relevant forms of the chemical of concern via water or soil, with reported concentration and duration.</p> <p>* Studies involving exposures to mixtures will be included only if they include exposure to a relevant form for the chemical alone.</p> <p>* Chemical exposures for aquatic organisms where only sediment concentrations are reported from field studies are excluded (unless porewater concentration measured); laboratory-based sediment studies are retained</p> | <ul style="list-style-type: none"> • Verifiable Chemical Abstract Services (CAS) number • Single chemical exposure • Relevant to environmental exposure • Report exposure concentration, dose or application rate • Report duration of exposure • Sediment studies must have a water concentration reported to be included • NOT: Air pollution studies related to CO2 and ozone |
| C (Comparison/ Control) | A concurrent control group exposed to vehicle-only treatment and/or untreated control (control could be a baseline measurement). | <ul style="list-style-type: none"> • Must have a control treatment |
| O (Outcome) | All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations). | <ul style="list-style-type: none"> • Biological effect measured • Effect concurrent with associated chemical exposure • Adverse effects are priority (beneficial, nutritional effects are lower priority) |
| Publication/ Data Format | | <ul style="list-style-type: none"> • Primary source of the data • Study must be a full article in English • NOT: Reviews or abstract only |

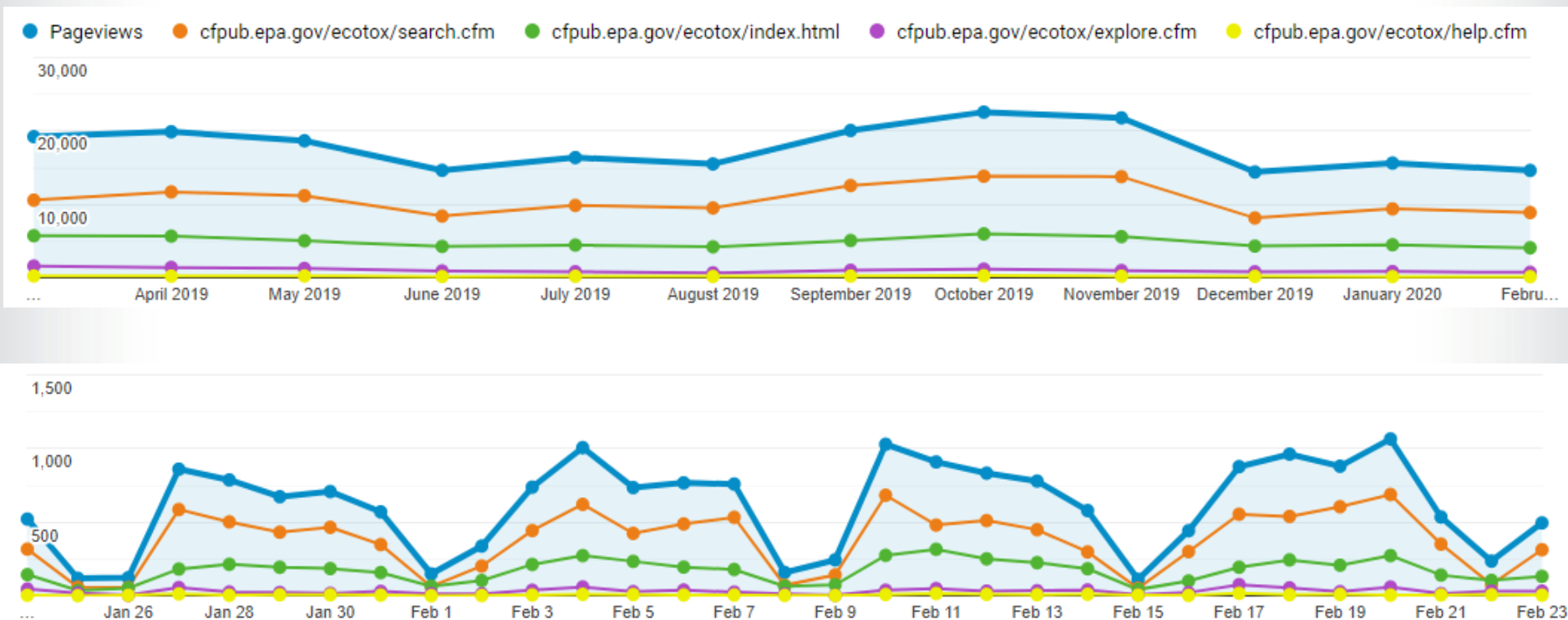


ECOTOX by the numbers

March 2019 – February 2020 (Google Analytics):

17,800 page views per month

8,400 unique page views per month



Curated ecological data from ~50,000 papers, with >11,000 chemicals and >13,000 species