EPA United States Environmental Protection Agency

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
Rong-Lin Wang

GDIT contract staff
SEE staff

www.epa.gov/ecotox

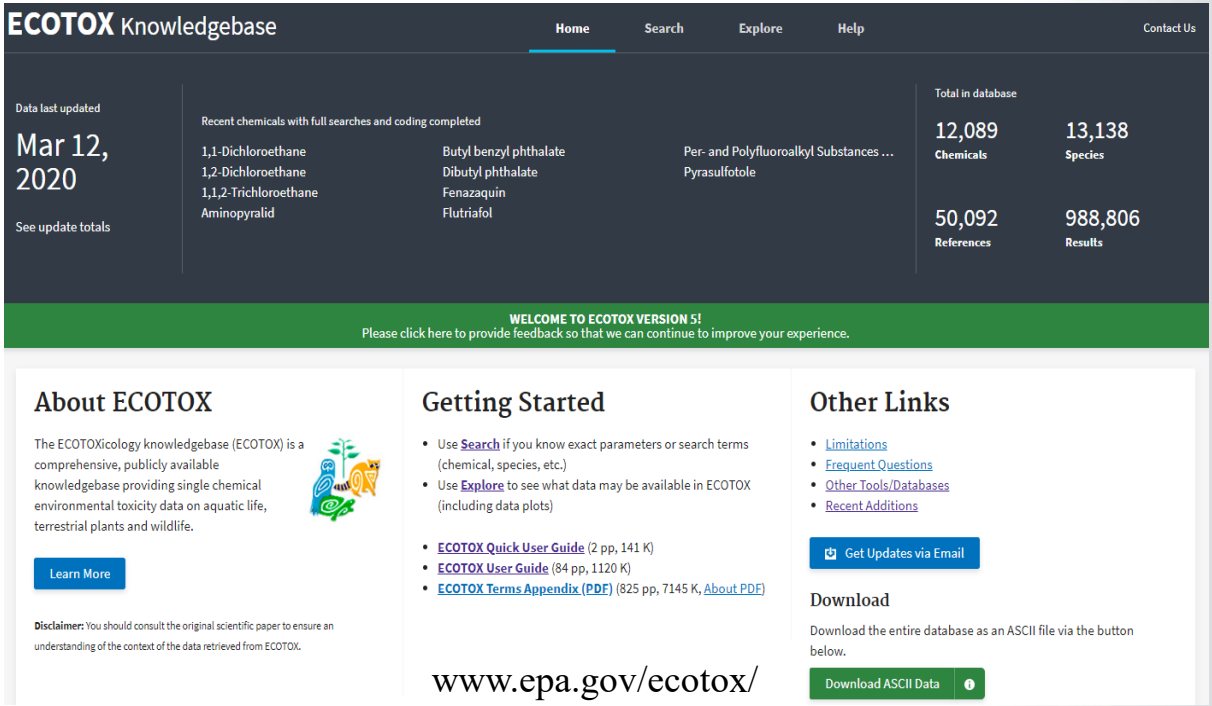
Overview

- 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?

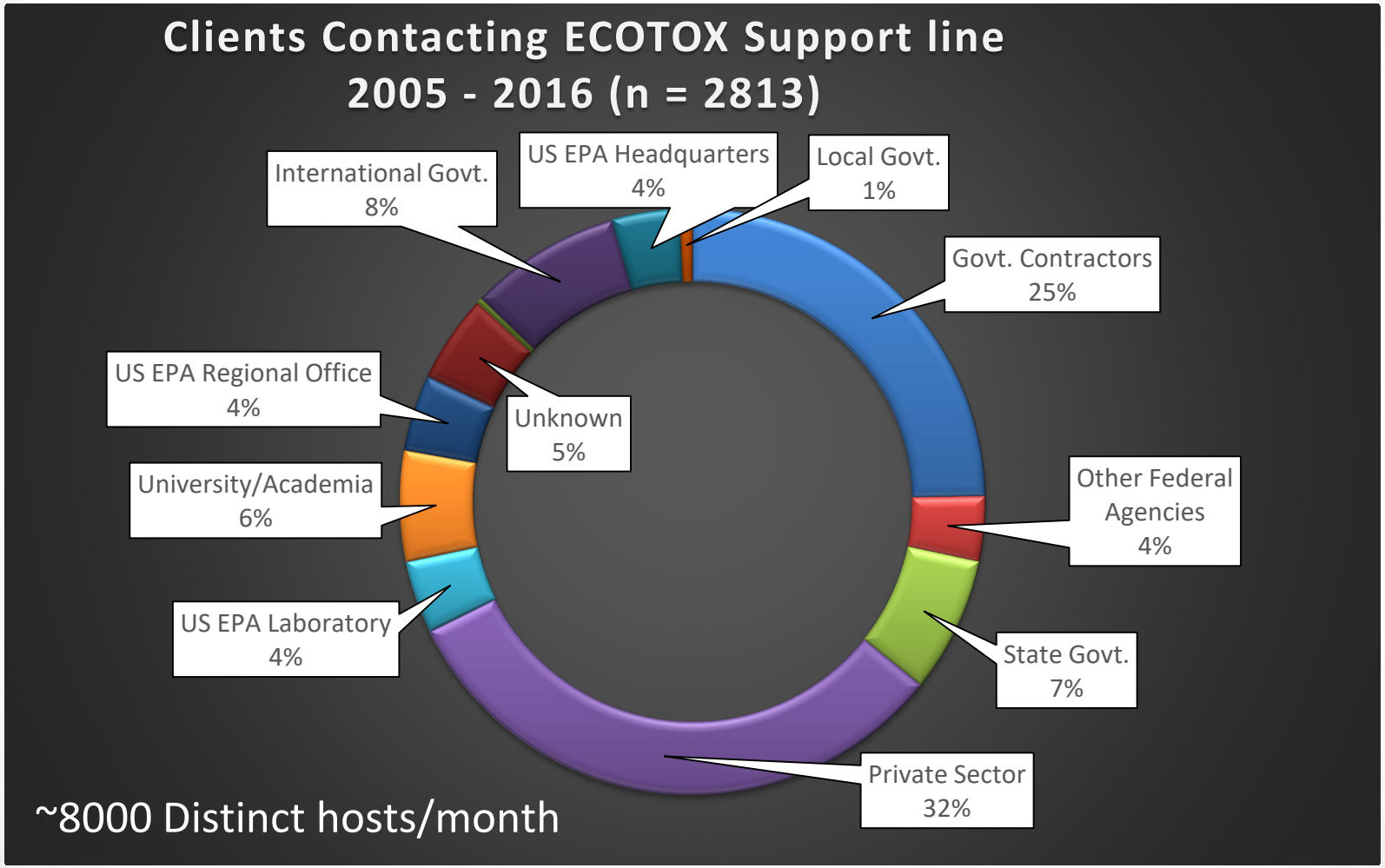
Publicly available, curated database providing toxicity data from single-chemical exposure studies to aquatic life, terrestrial plants, and wildlife

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

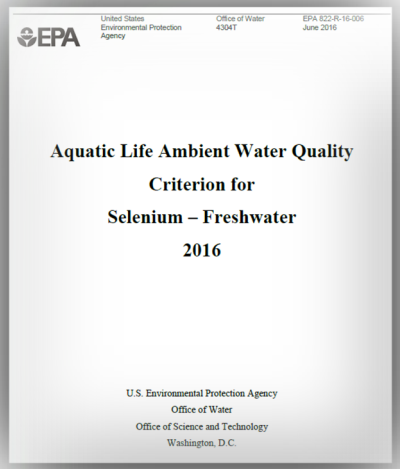


- 30+ year history:
  Originated in the early 1980s,
  US Environmental Protection Agency Office of Research and Development

Who uses the ECOTOX Knowledgebase?



Program Offices & Regions Applications: use in environmental decision making


United States Environmental Protection Agency | Office of Water 4304T | EPA 822-R-16-006 June 2016

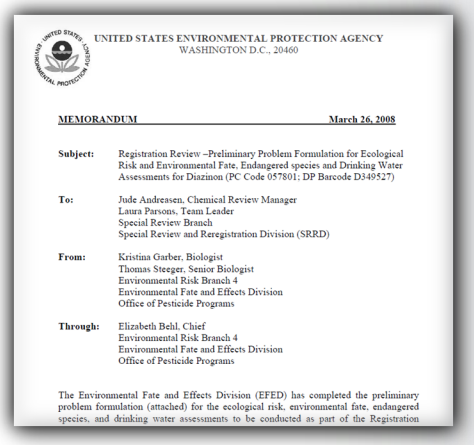
EPA

Aquatic Life Ambient Water Quality Criterion for Selenium – Freshwater 2016

U.S. Environmental Protection Agency
Office of Water
Office of Science and Technology
Washington, D.C.

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).


UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

MEMORANDUM March 26, 2008

Subject: Registration Review –Preliminary Problem Formulation for Ecological Risk and Environmental Fate, Endangered species and Drinking Water Assessments for Diazinon (PC Code 057801; DP Barcode D349527)

To: Jude Andreasen, Chemical Review Manager
Laura Parsons, Team Leader
Special Review Branch
Special Review and Reregistration Division (SRRD)

From: Kristina Garber, Biologist
Thomas Steeger, Senior Biologist
Environmental Risk Branch 4
Environmental Fate and Effects Division
Office of Pesticide Programs

Through: Elizabeth Behl, Chief
Environmental Risk Branch 4
Environmental Fate and Effects Division
Office of Pesticide Programs

The Environmental Fate and Effects Division (EFED) has completed the preliminary problem formulation (attached) for the ecological risk, environmental fate, endangered species, and drinking water assessments to be conducted as part of the Registration


TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Home | Air | Land | Water | Licenses | Permits | Reporting

Useful Links for Developing Ecological Risk Assessments

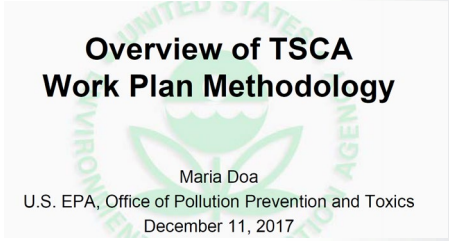
Links to pages on this and other sites that have useful information for developing ecological risk

U.S. EPA

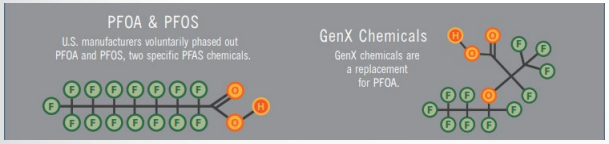
- Integrated Risk Information System (IRIS)
- ECOTOX Database (aquatic and terrestrial toxicological data)
- EPA Office of Water (links to sediment guidance, water quality standards, and other useful topics)
- EPA People Locator
- EPA Region 4 Ecological Screening Values
- Combustion Guidance for Human Health (some defaults in here used at times)
- Superfund Risk Assessment (variety of links)
- Superfund: Natural Resource Damages and Ecological Risk Assessments

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

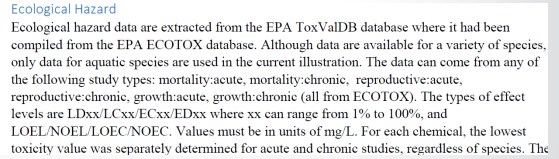

PFOA & PFOS

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

Applications of ECOTOX

ECOTOX Knowledgebase

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

Interoperability with databases/tools

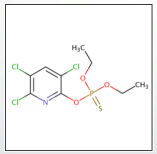
DTXSID/CASRN

Species ID; Protein ID

Integrated ontology

Reference ID

Chemicals Dashboard



SeqAPASS

Adverse Outcome Pathway WIKI

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.

Conduct literature searches

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

Screening

Identify and acquire potentially applicable studies

~37,000 citations downloaded → Initial removal of duplicates

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	

Eligibility

Review literature for applicability to ECOTOX

For Review (Full Text Screening)
n = 388 references

No PFAS in reference: n = 85 references

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

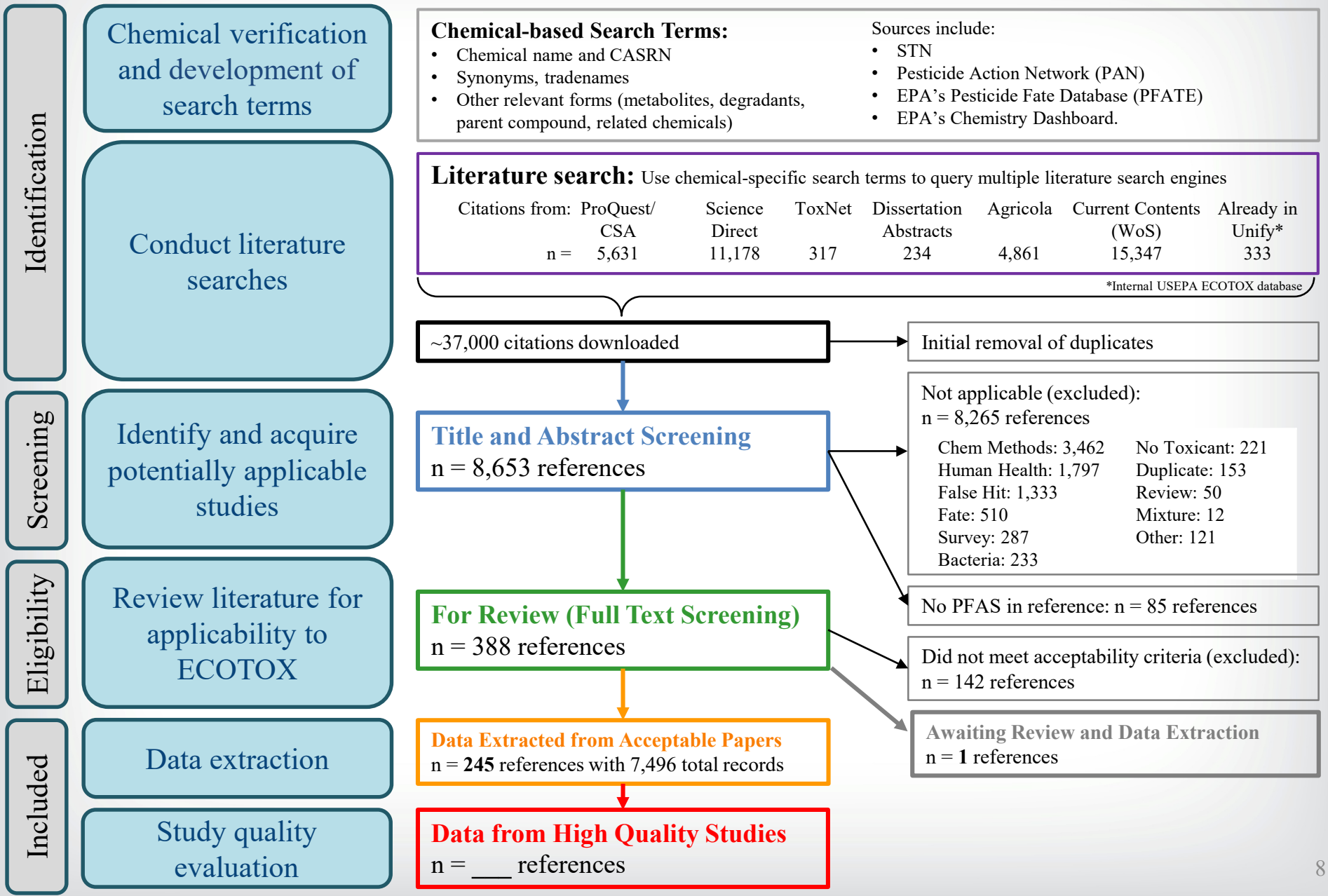
Awaiting Review and Data Extraction
n = **1** references

Included

Extract data into ECOTOX Knowledgebase

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

ECOTOX Pipeline: Systematic Review/Data Curation

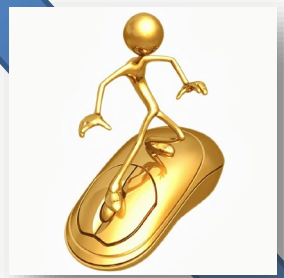


Identify, Test, and QA Search Terms

- 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

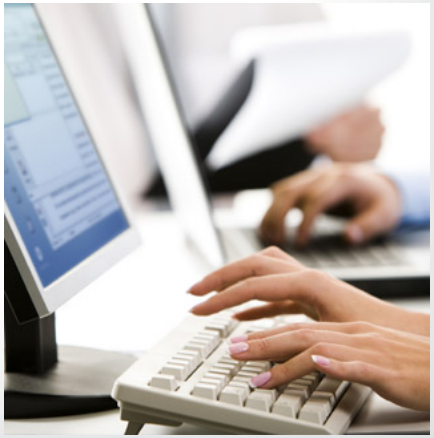
Search various sources for chemical terms,
Synonyms, verify CAS, eliminate poor search terms

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")



Couple hour process

Enter chemical terms into template for abstracting databases



Identify, Test, and QA Search Terms

Identification

Chemical verification and development of search terms

Conduct literature searches

Screening

Identify and acquire potentially applicable studies

Eligibility

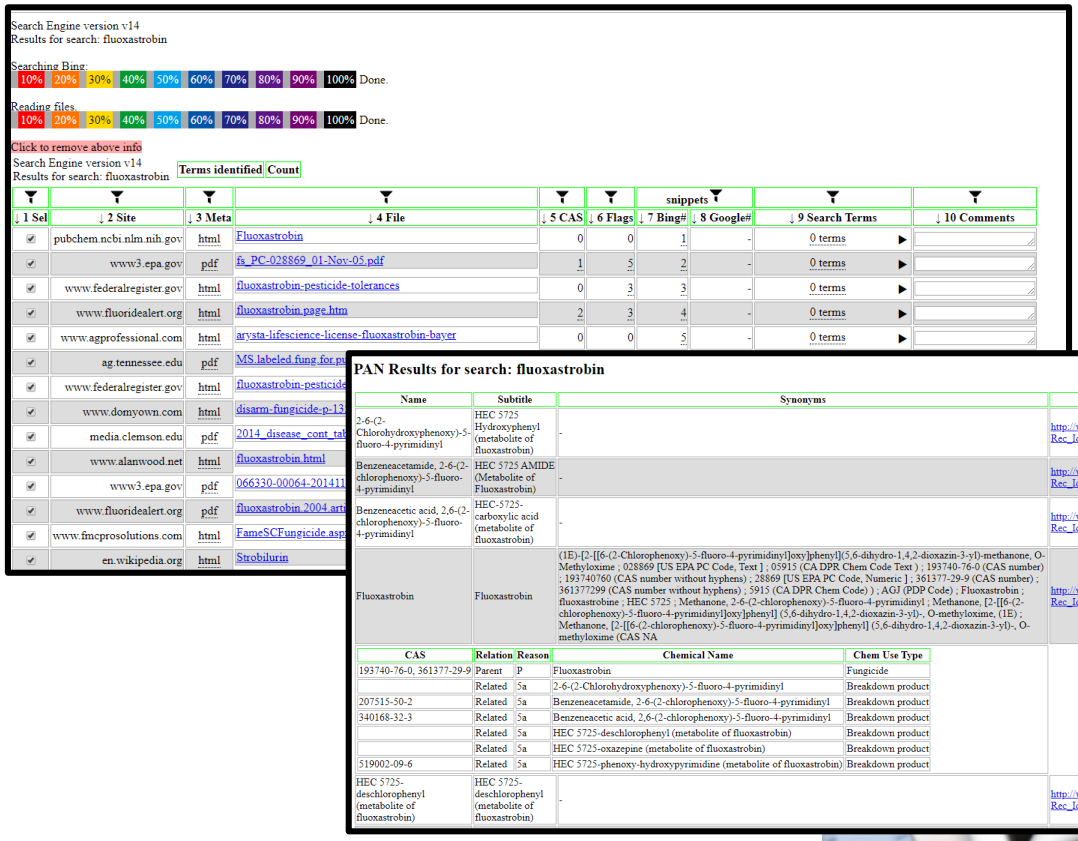
Review literature for applicability to ECOTOX

Included

Data extraction

Study quality evaluation

Web-based tool to identify and document relevant search terms


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 Terms identified Count

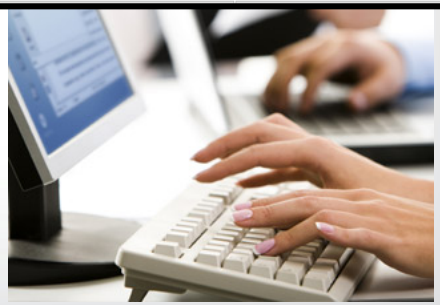
1 Sel	2 Site	3 Meta	4 File	5 CAS	6 Flags	snippets 7 Bing#	8 Google#	9 Search Terms	10 Comments
☑	pubchem.ncbi.nlm.nih.gov	html	Fluoxastrobin	0	0	1	-	0 terms	
☑	www3.epa.gov	pdf	fs_PC-028869_01-Nov-05.pdf	1	5	2	-	0 terms	
☑	www.federalregister.gov	html	fluoxastrobin-pesticide-tolerances	0	3	3	-	0 terms	
☑	www.fluoridealert.org	html	fluoxastrobin.page.htm	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.pu						
☑	www.federalregister.gov	html	fluoxastrobin-pesticide						
☑	www.domyown.com	html	disarm-fungicide-p-13						
☑	media.clemson.edu	pdf	2014_disease_cont_tab						
☑	www.alanwood.net	html	fluoxastrobin.html						
☑	www3.epa.gov	pdf	066330-00064-201411						
☑	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-Chlorohydroxyphenoxy)-5-fluoro-4-pyrimidinyl	HEC 5725 Hydroxyphenyl (metabolite of fluoxastrobin)	-	http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PRI14687
Benzeneacetamide, 2-6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl	HEC 5725 AMIDE (Metabolite of Fluoxastrobin)	-	http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PRI14682
Benzeneacetic acid, 2,6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl	HEC-5725-carboxylic acid (metabolite of fluoxastrobin)	-	http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PRI14697
Fluoxastrobin	Fluoxastrobin	(1E)-[2-[[6-(2-Chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)-methanone, O-Methyloxime ; 028869 [US EPA PC Code, Text] ; 05915 (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)) ; AGI (PDP Code) ; Fluoxastrobin ; fluoxastrobune ; HEC 5725 ; Methanone, 2-6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl ; Methanone, [2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazin-3-yl)-, O-methyloxime (1E) ; Methanone, [2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl] (5,6-dihydro-1,4,2-dioxazin-3-yl)-, O-methyloxime (CAS NA	http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PRI3321

CAS	Relation	Reason	Chemical Name	Chem Use Type
193740-76-0, 361377-29-9	Parent	P	Fluoxastrobin	Fungicide
	Related	5a	2-6-(2-Chlorohydroxyphenoxy)-5-fluoro-4-pyrimidinyl	Breakdown product
207515-50-2	Related	5a	Benzeneacetamide, 2-6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl	Breakdown product
340168-32-3	Related	5a	Benzeneacetic 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)	HEC 5725-deschlorophenyl (metabolite of fluoxastrobin)	-	http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PRI14726

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

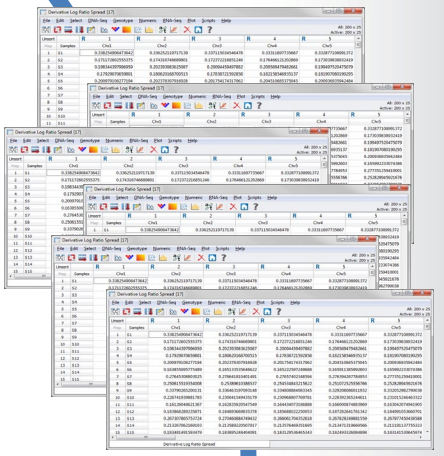
Data extraction

Study quality evaluation

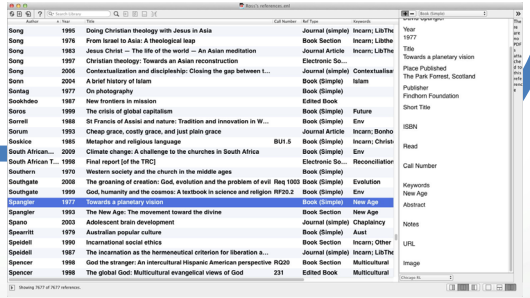
Chemical specific searches
(using terms from chemical verification step)
OR
Monthly electronic searches
of 11 highly relevant journals

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

Identification

Chemical verification and development of search terms

Conduct literature searches

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Identify and acquire potentially applicable studies

Eligibility

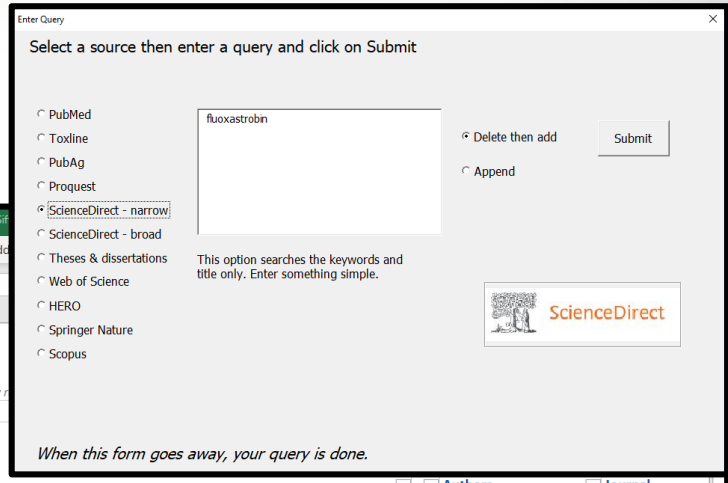
Review literature for applicability to ECOTOX

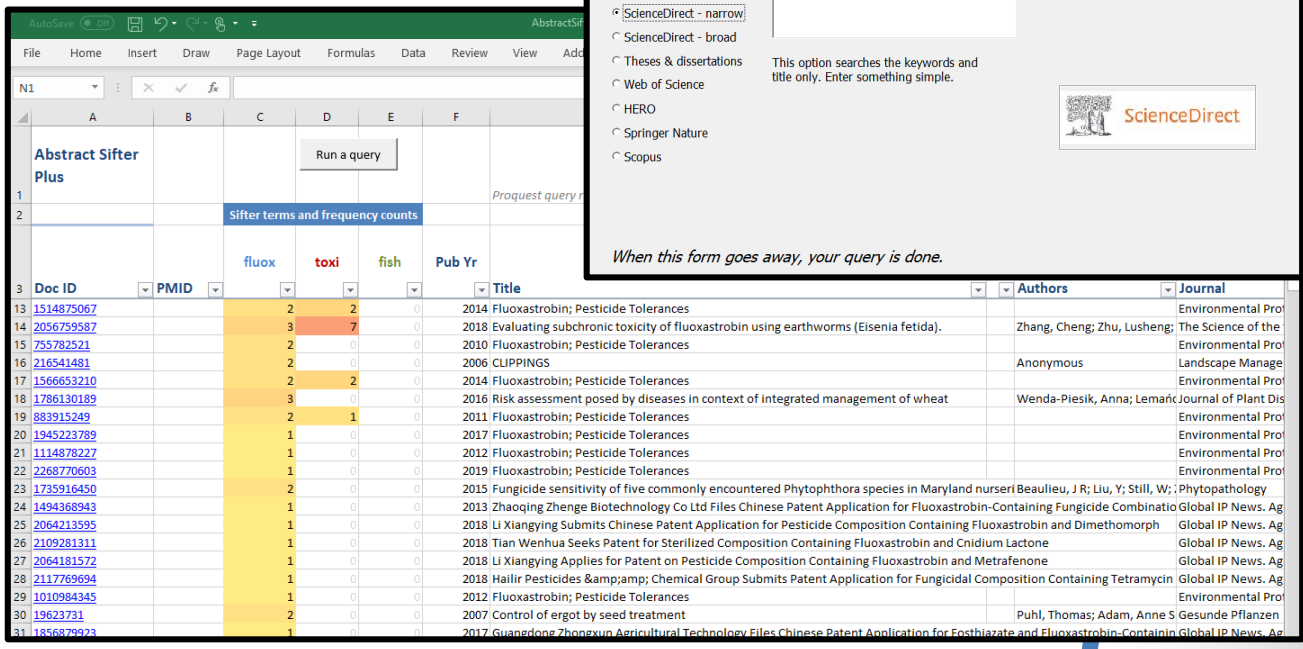
Included

Data extraction

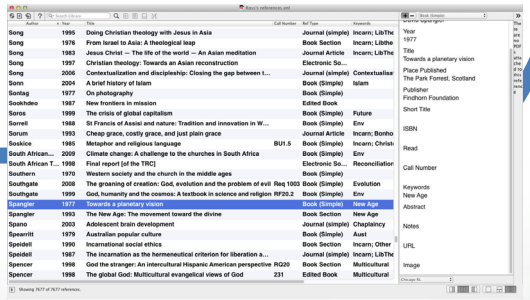
Study quality evaluation

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





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]

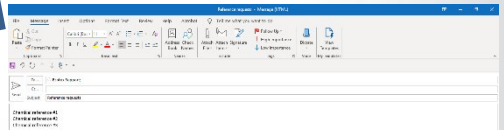
Sulfur Dust Bag: A Novel Technique for Ectoparasite Control in Poultry Systems.

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.

DOI: 10.1093/jee/tow146



Send applicable reference list for acquisition

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

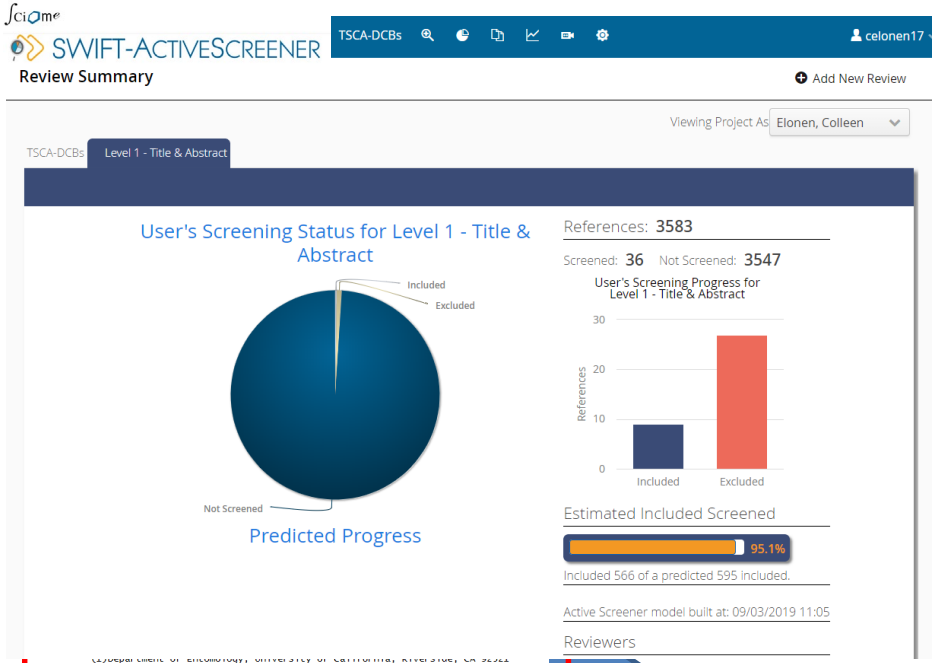
Review literature for applicability to ECOTOX

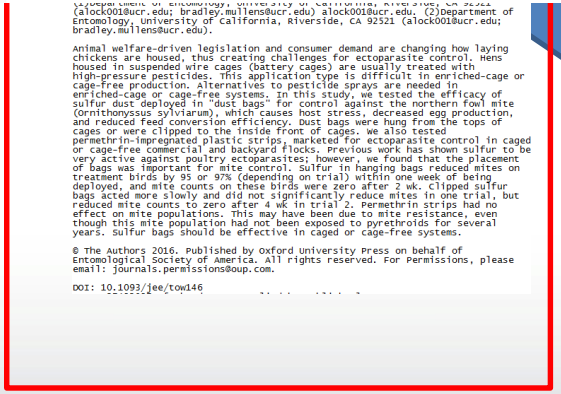
Included

Data extraction

Study quality evaluation

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





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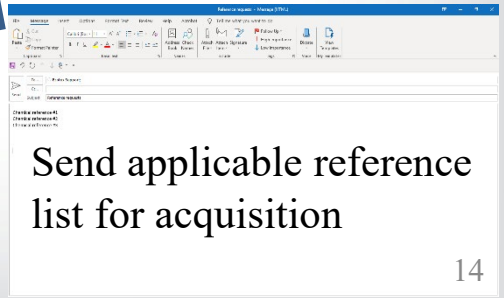
DOI: 10.1093/jee/tow146



Send applicable reference list for acquisition

Skimming for Applicability: Full text

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

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

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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 m^3 per day (MOE, 1987). Similar discharge volumes occurred in 1989. In 1991, the total discharge was 25,000 m^3 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

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

Identification

Chemical verification and development of search terms

Conduct literature searches

Screening

Identify and acquire potentially applicable studies

Eligibility

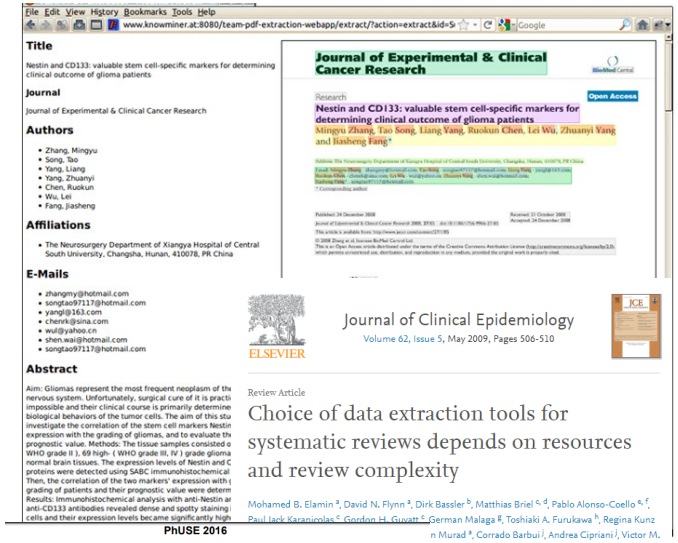
Review literature for applicability to ECOTOX

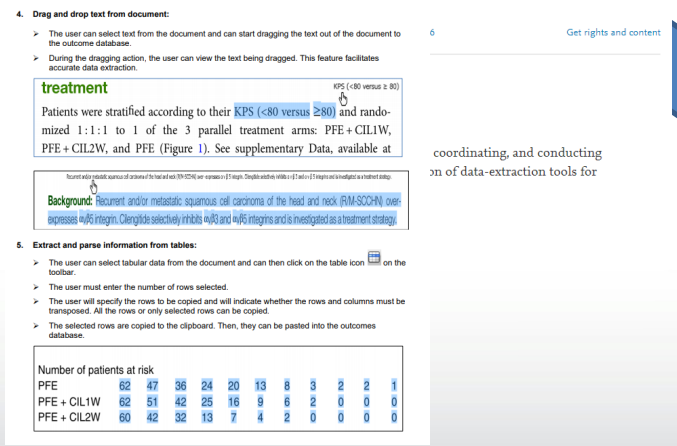
Included

Data extraction

Study quality evaluation

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





Moves on to be curated into ECOTOX.

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

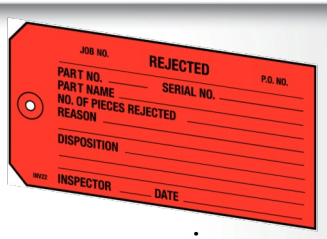
ECOTOX Applicability Criteria

- 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
- 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

Review literature for applicability to ECOTOX

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

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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
    - PCBs

  Example groups
  - Metal / organometal
    - Antimony
    - Arsenic

  Example 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

ECOTOX Data Extraction

Identification

- Chemical verification and development of search terms
- Conduct literature searches

Screening

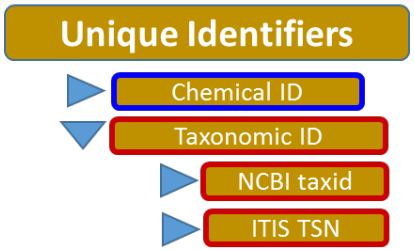
- Identify and acquire potentially applicable studies

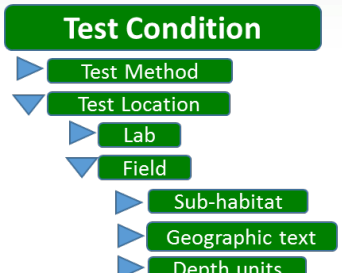
Eligibility

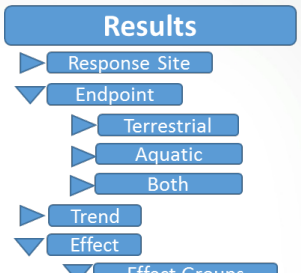
- Review literature for applicability to ECOTOX

Included

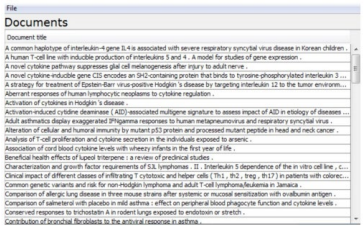
- Data extraction
- Study quality evaluation

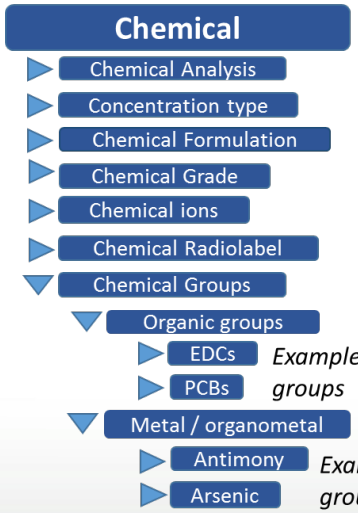


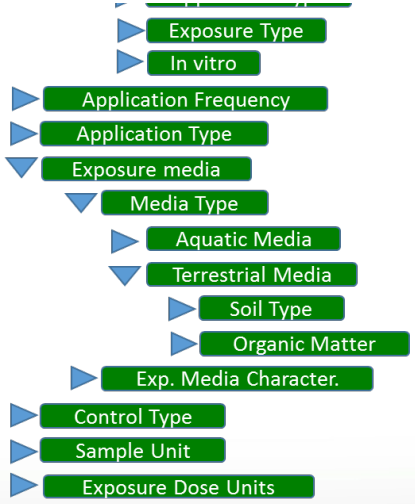




- Automated data extraction



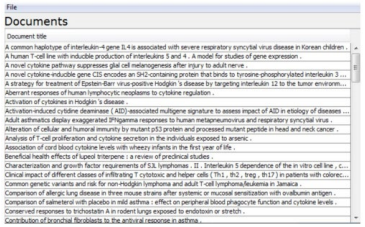




ECOTOX Data Extraction

- 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

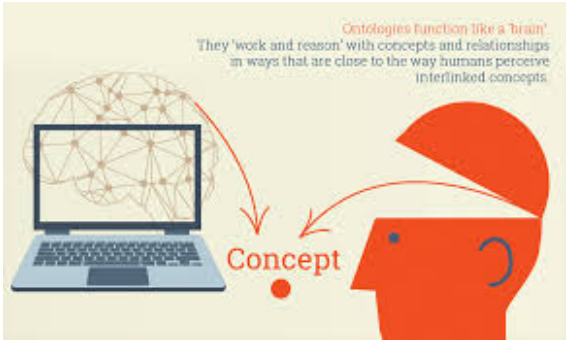
- Automated data extraction

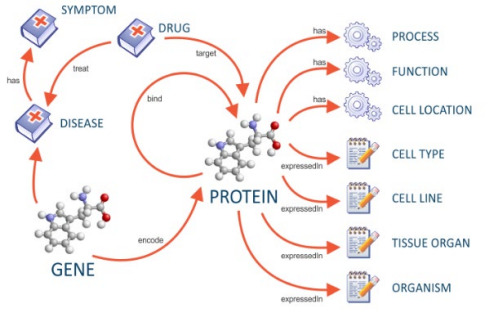


https://www.knime.com

- 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

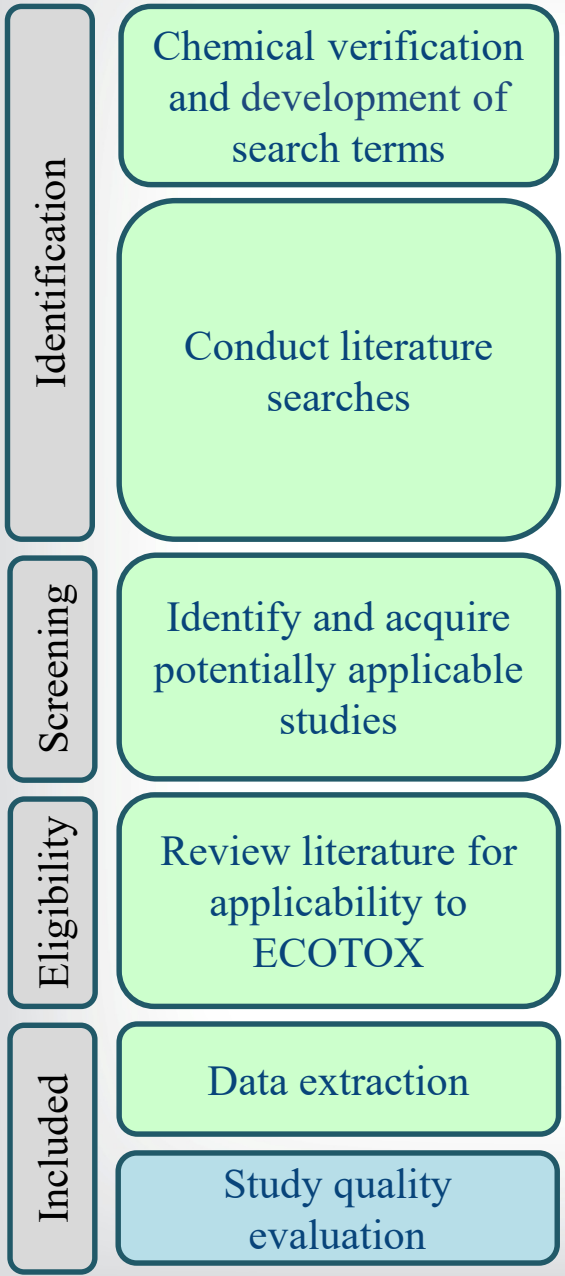




https://www.ontotext.com

- Linking effects to biological pathways

Study Quality Evaluation



- Many fields in ECOTOX can inform study evaluation

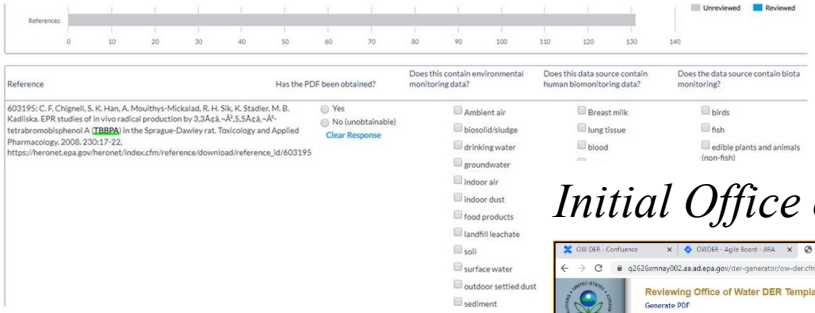
Category	Select study evaluation questions with relevant ECOTOX field(s)
Chemical	• Is test substance identified? **Required for inclusion in ECOTOX inclusion** • Is the purity of test substance reported? **Chemical Purity** • Were chemical concentrations verified? **Chemical Analysis** (e.g., nominal versus measured concentrations)
Species	• Is the species given? **Verifiable species (Scientific Name, etc.) required for inclusion in ECOTOX** • Are the organisms well described? **Organism Source**, **Lifestage**, **Age**, **Gender**, **Initial** and **Final Weight**
Test Conditions	• Are appropriate controls performed? **A control is required for inclusion in ECOTOX**, type described in **Control** • Is a guideline method (e.g., OECD) used? **Test Method** • Are the experimental conditions appropriate and acceptable for the test substance and organism? **Test Method**, **Media Type**, **Test Location**, **Experimental Design**, Physical and Chemical Soil and Water Parameters (e.g., **pH**, **Temperature**, **Dissolved Oxygen**)
Test Results	• Are the reported effects and endpoints appropriate for the purpose, test substance and organism? **Effect Measurement**, **Endpoint** • Is the response/effect statistically significant? **Statistical Significance**, **Significance Level**

Study Quality Evaluation

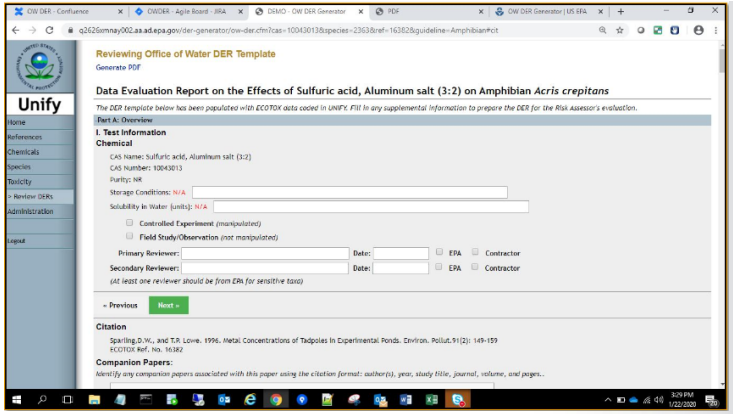
- Identification
  - Chemical verification and development of search terms
  - Conduct literature searches
- Screening
  - Identify and acquire potentially applicable studies
- Eligibility
  - Review literature for applicability to ECOTOX
- Included
  - Data extraction
  - Study quality evaluation

- 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

Overview

- 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

Houde *et al*. 2006 *Environ. Sci. Technol.* 40:3463-3473
McCarthy *et al*. 2017 *Curr. Pollution Rep.* 3:289-301

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

ECOTOX Knowledgebase

Home | Search | Explore | Help | Contact Us

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

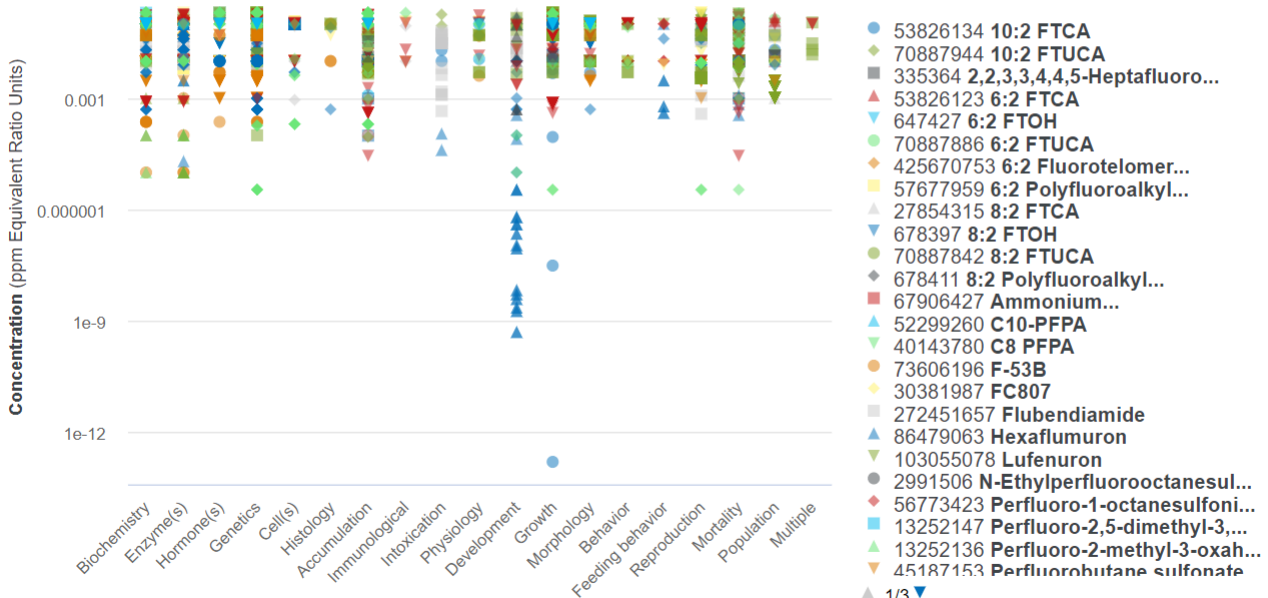
(showing first 3,000)

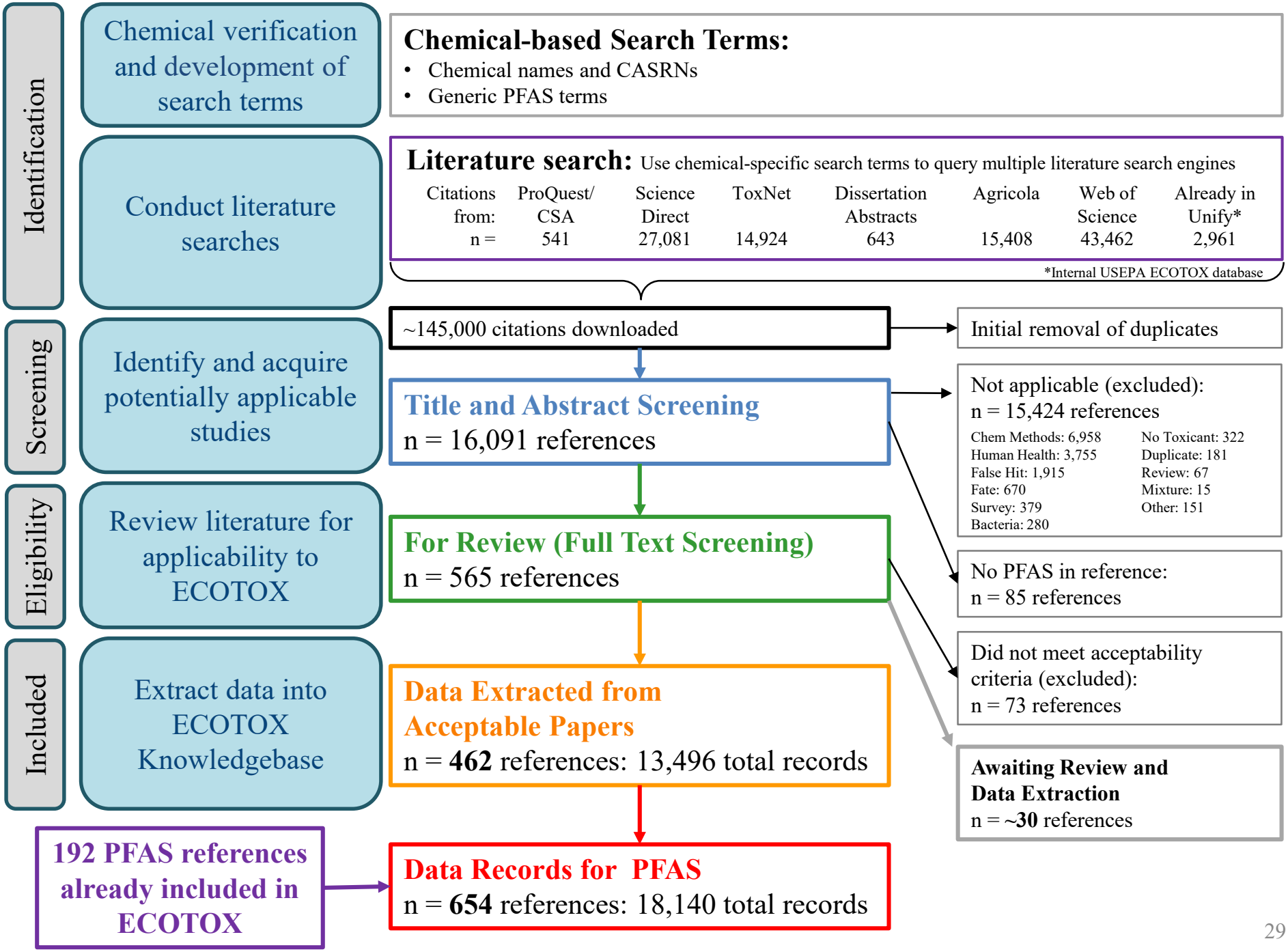
Records are **plotted** if they can be converted to **Standardized Concentration Units**. Ordered by **Concentration (low-high)**.

Effect × Chem | Dur × Chem | Dur × Endpt | Export

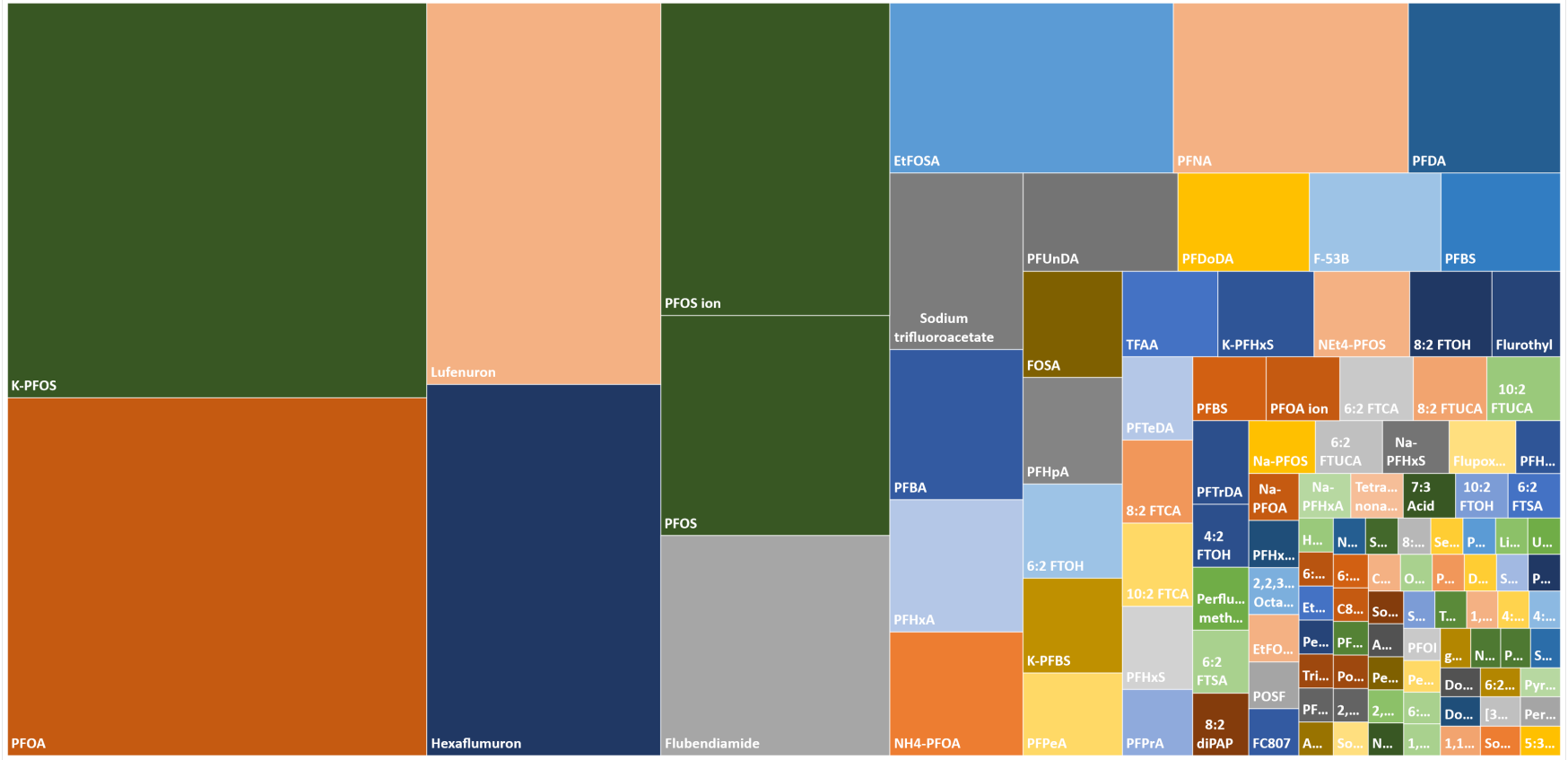
Y-axis scale: Linear Logarithmic

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



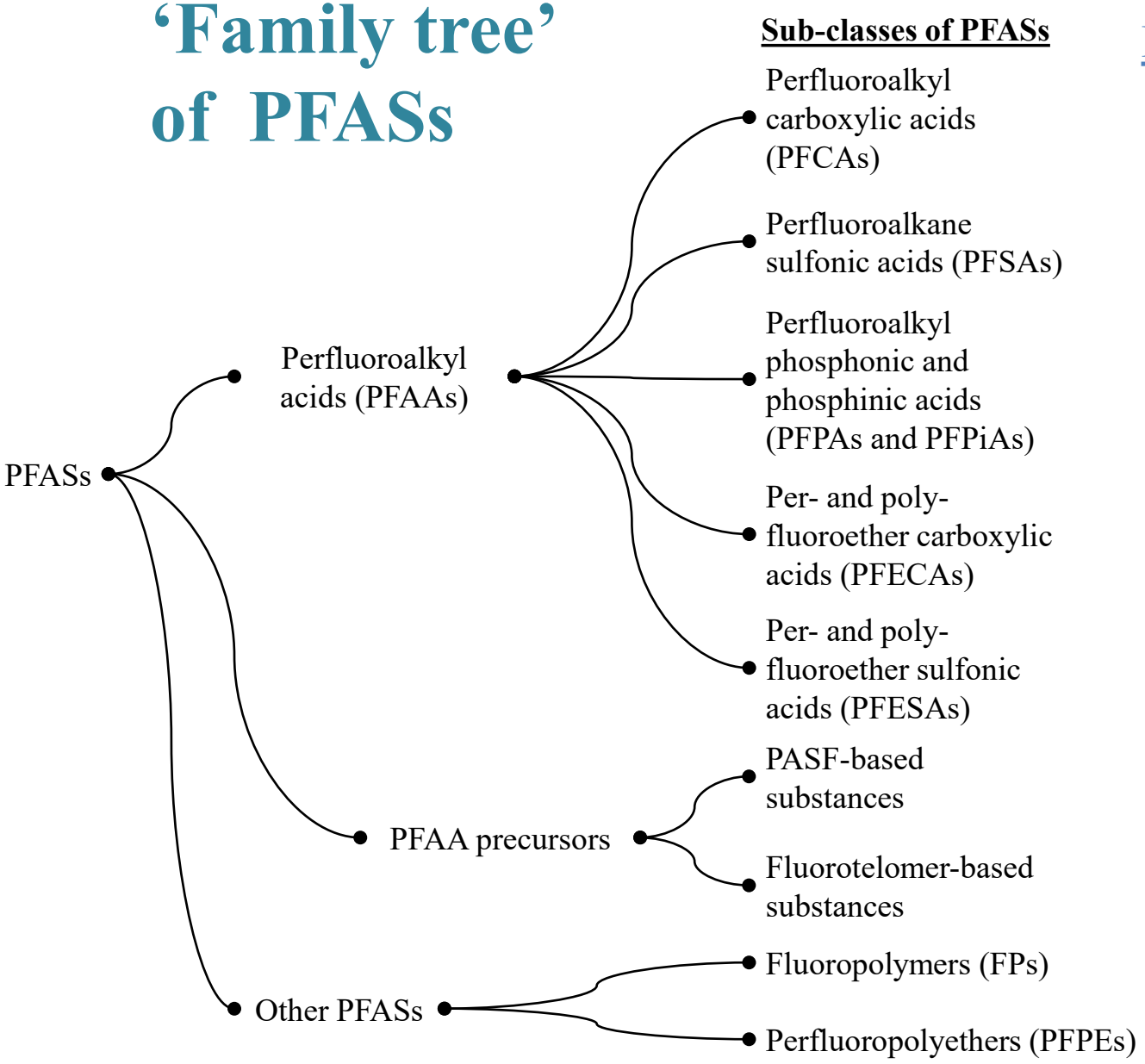

Identification
Screening
Eligibility
Included
Chemical verification and development of search terms
Conduct literature searches
Identify and acquire potentially applicable studies
Review literature for applicability to ECOTOX
Extract data into ECOTOX Knowledgebase
Chemical-based Search Terms:
• Chemical names and CASRNs
• Generic PFAS terms
Literature search: Use chemical-specific search terms to query multiple literature search engines
Citations from: ProQuest/ CSA n = 541
Science Direct 27,081
ToxNet 14,924
Dissertation Abstracts 643
Agricola 15,408
Web of Science 43,462
Already in Unify* 2,961
*Internal USEPA ECOTOX database
~145,000 citations downloaded
Initial removal of duplicates
Title and Abstract Screening
n = 16,091 references
Not applicable (excluded):
n = 15,424 references
Chem Methods: 6,958
Human Health: 3,755
False Hit: 1,915
Fate: 670
Survey: 379
Bacteria: 280
No Toxicant: 322
Duplicate: 181
Review: 67
Mixture: 15
Other: 151
For Review (Full Text Screening)
n = 565 references
No PFAS in reference:
n = 85 references
Did not meet acceptability criteria (excluded):
n = 73 references
Data Extracted from Acceptable Papers
n = 462 references: 13,496 total records
Awaiting Review and Data Extraction
n = ~30 references
192 PFAS references already included in ECOTOX
Data Records for PFAS
n = 654 references: 18,140 total records

654 Publications, 112 PFAS with Ecological Toxicity Data



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

‘Family tree’ of PFASs

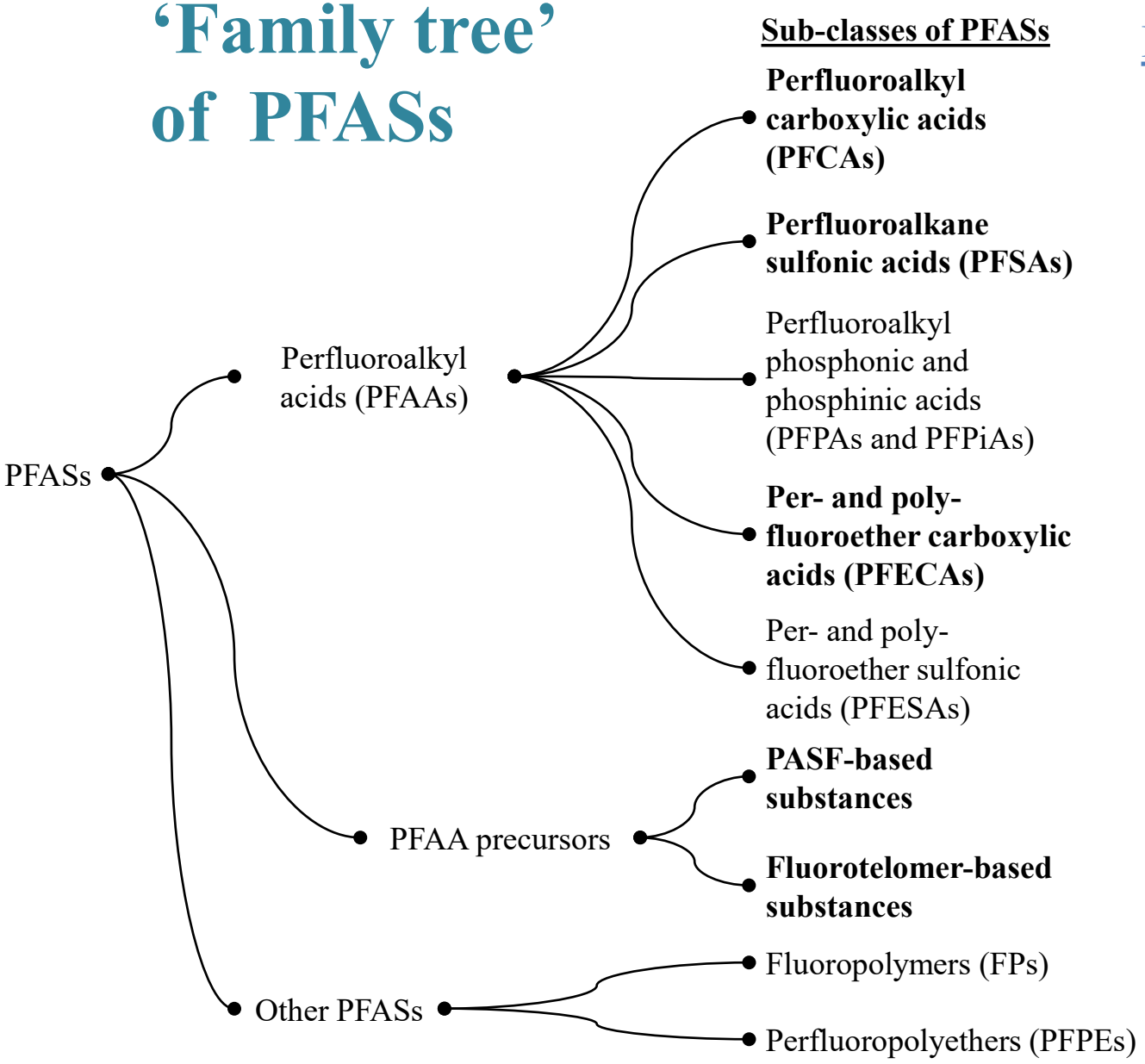


Literature Search Terms

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

OECD 2018 ENV/JM/MONO(2018)7
Wang et al. 2017 *Environ. Sci. Technol.* 51:2508-2518

‘Family tree’ of PFASs



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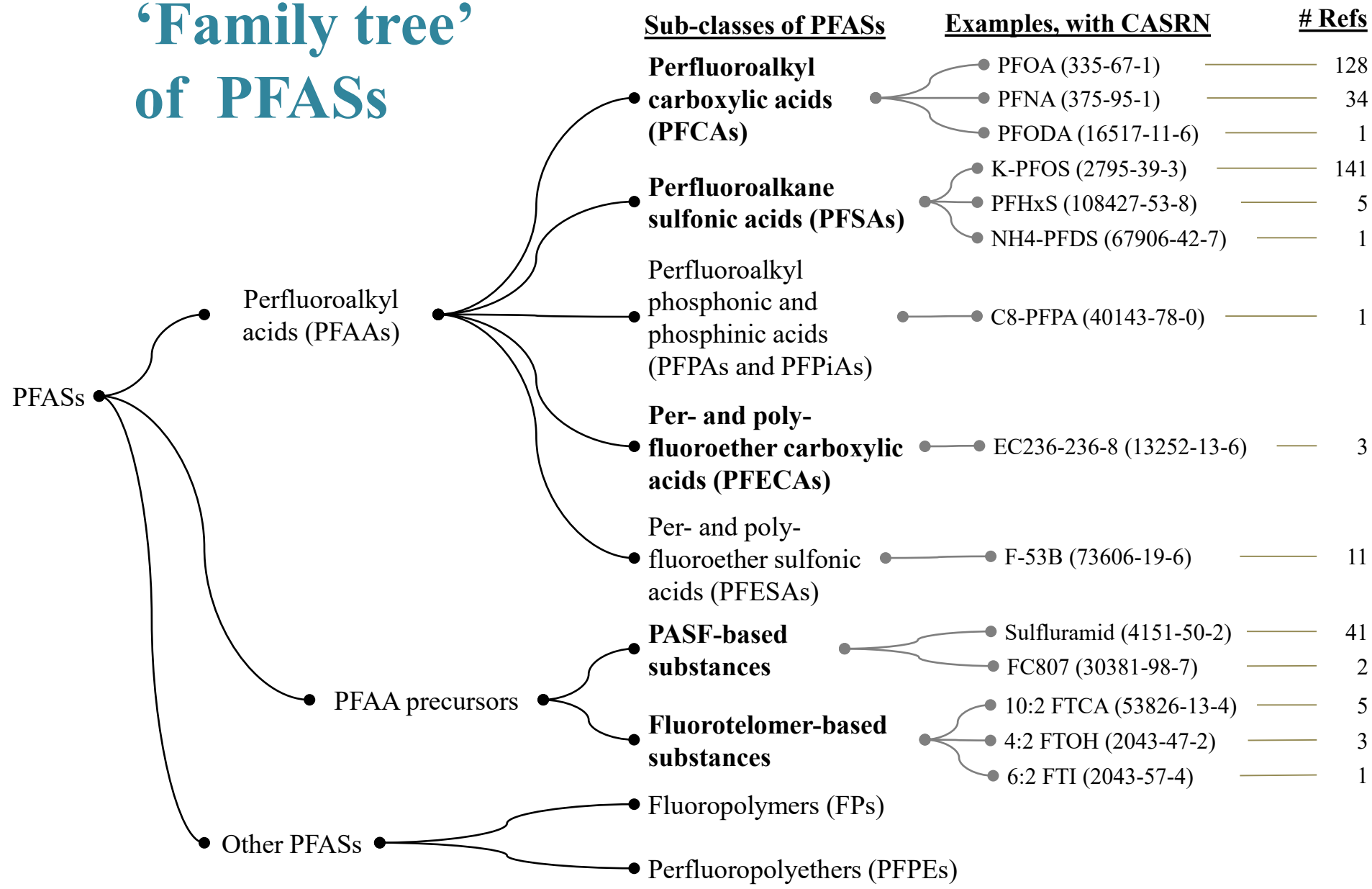

OECD 2018 ENV/JM/MONO(2018)7
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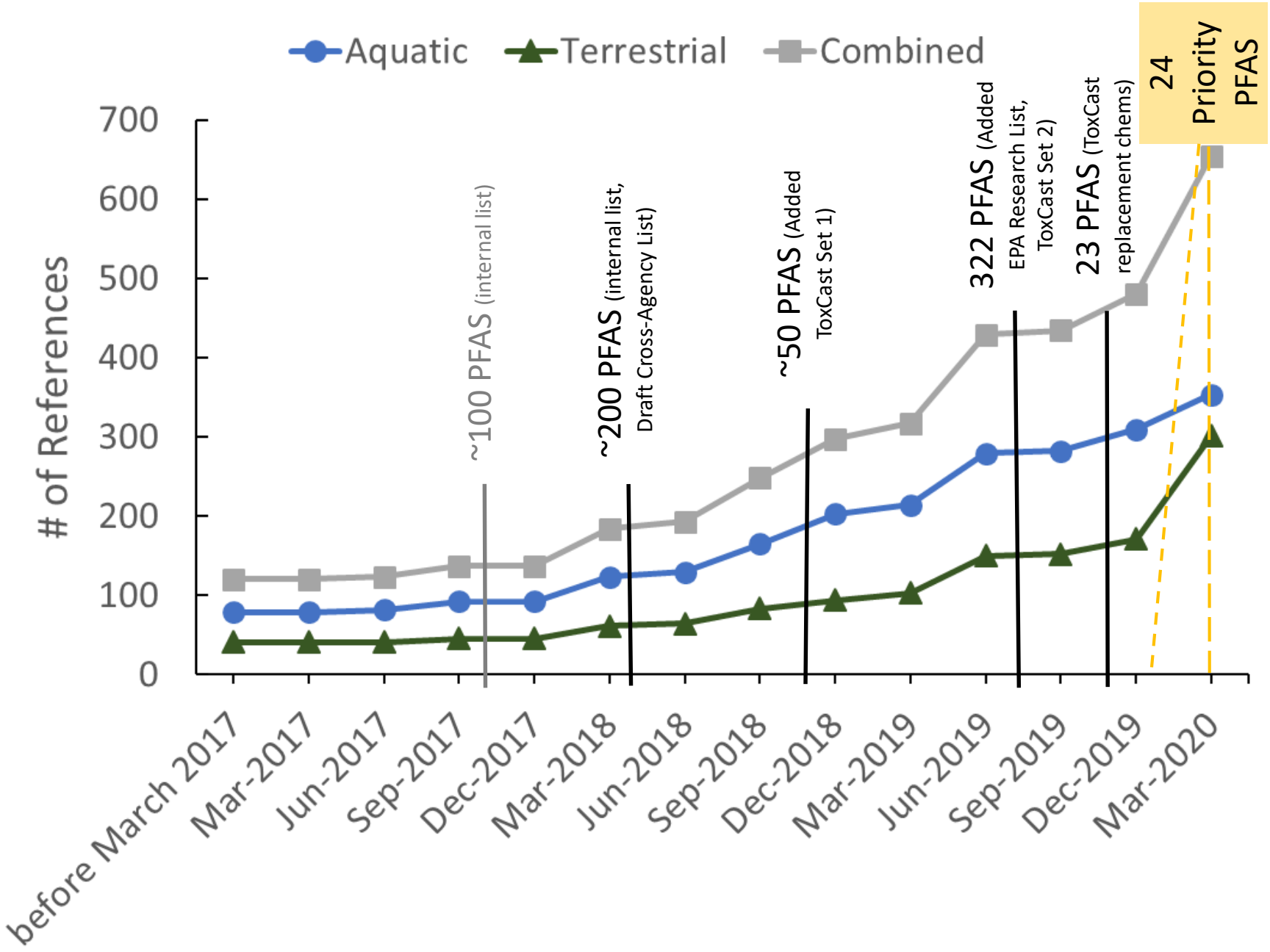
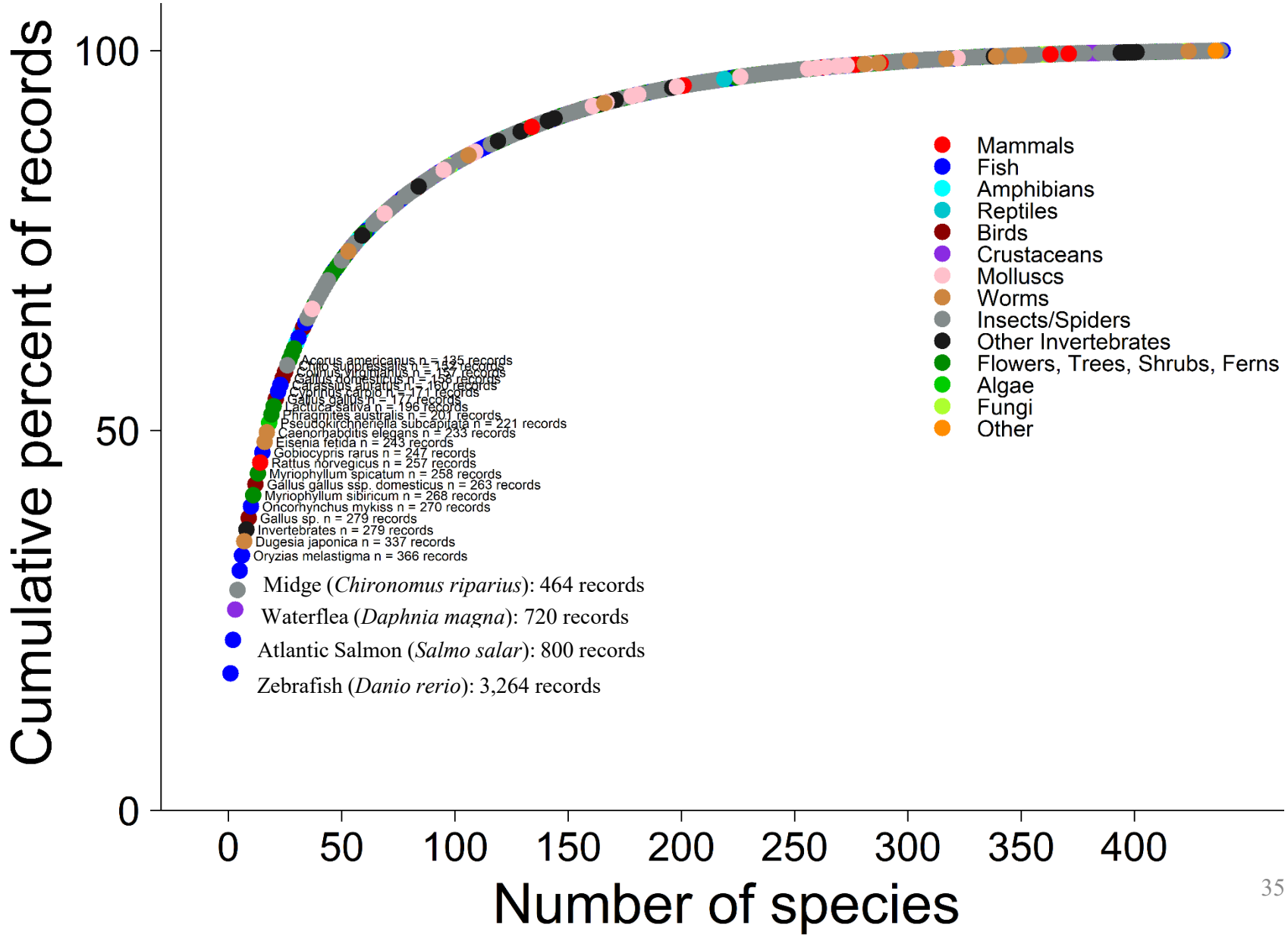
PFAS References in ECOTOX Knowledgebase



PFAS Data for 440 Biological Species



35

Diversity in Types of Effects

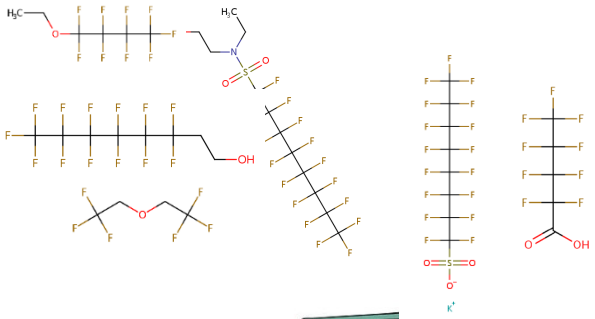
PFAS records for Fish

	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
Organism Responses	Injury	26
	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**

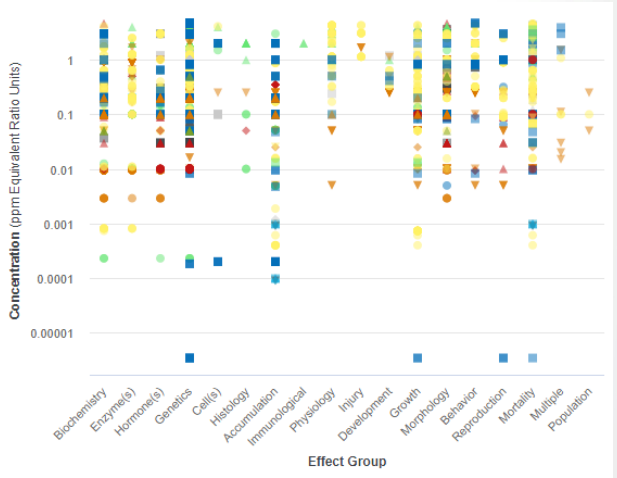
Reproduction
Fecundity
Fertility
Fertilization
Gamete production
Hatch
Mean spawns per female
Motility
Number spawning
Pregnant, Paris or Gravid
Progeny counts/numbers
Spawning frequency
Sperm cell counts
Time to spawn
Velocity
Viability

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



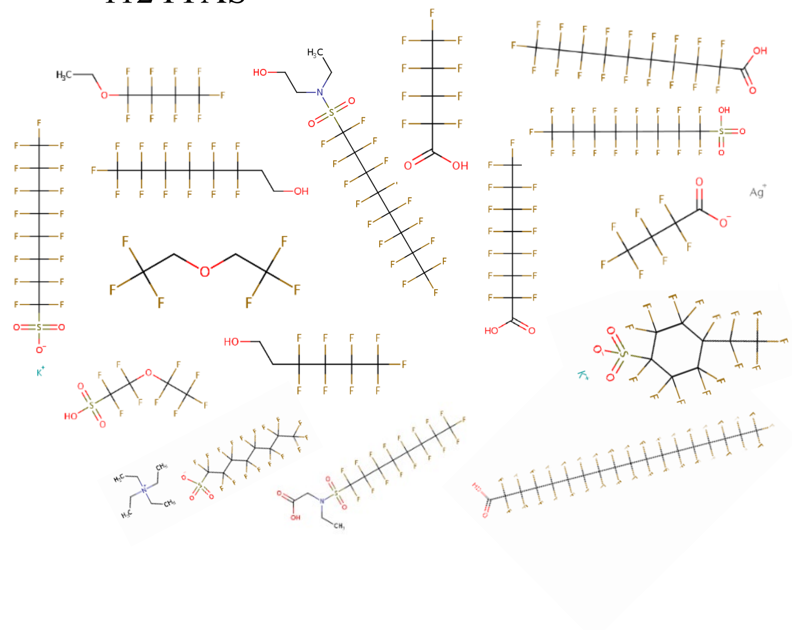
Quarterly data releases to ECOTOX



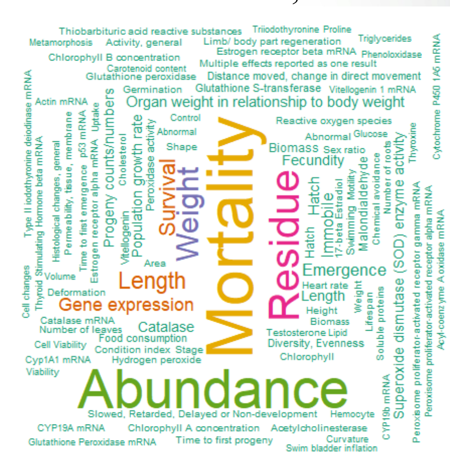
Data Inventory → Summary/Synthesis

440 Biological Species

112 PFAS



Measurements of 1,126 Effects



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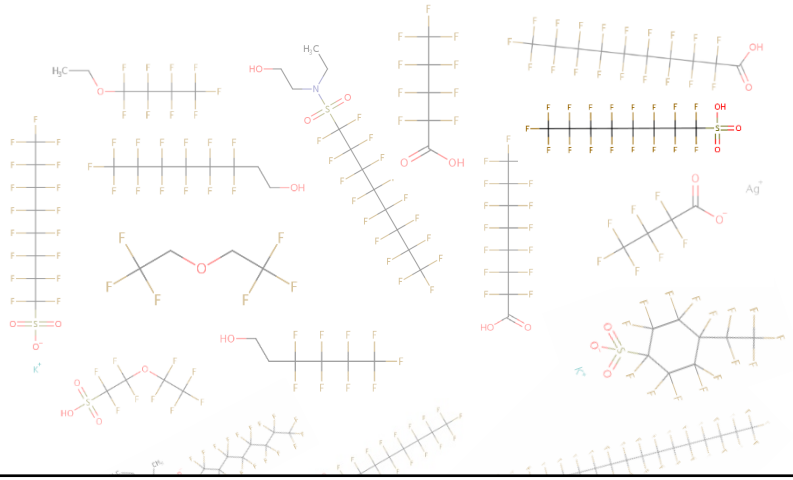

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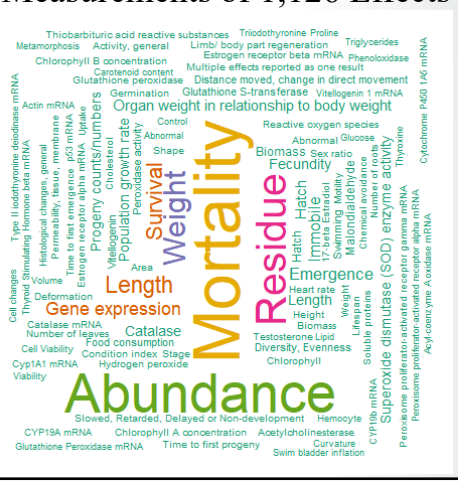

Toxicant	Cellular Responses	Tissue/Organ Responses	Organism Responses
PFOS (1763-23-1) K-PFOS (2795-39-3)			Mortality ↑ Length & Weight ↓ or ↑ or Δ Behavior (swimming, distance moved) Δ Abnormal development ↑ Sperm cell counts ↓

Data Inventory → Summary/Synthesis

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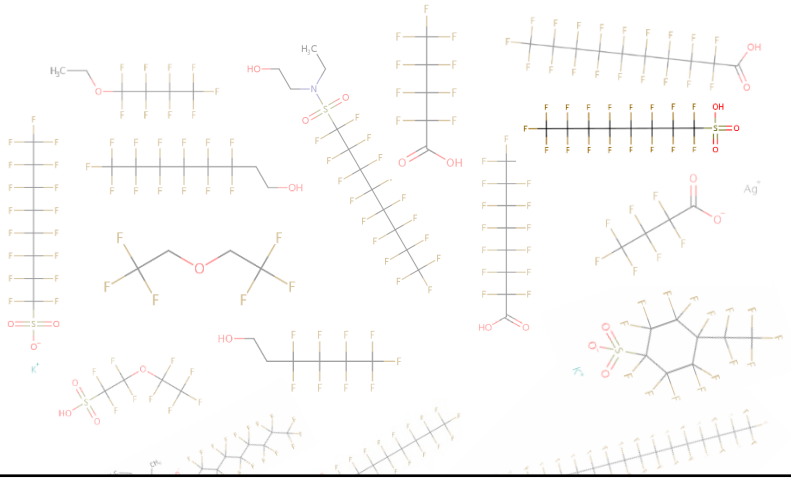

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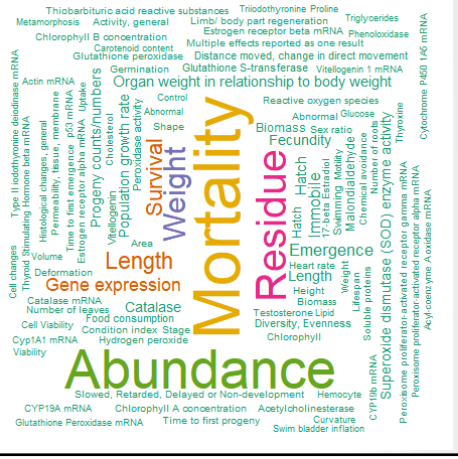


Toxicant	Cellular Responses	Tissue/Organ Responses	Organism Responses
PFOS (1763-23-1) K-PFOS (2795-39-3)	T4 & T3 ↓ Estrogen and 17-β Estradiol Δ Vitellogenin Δ Acetylcholinesterase Δ Cholesterol & Lipids Δ <u>Δ in expression of</u>: PPAR-mediated genes (multiple) Thyroid-relevant genes (multiple) …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


Chronic PFOS Exposure Disrupts Thyroid Structure and Function in Zebrafish

Data extraction

ECOTOX

PFOS:
- decreased thyroid cell area
- Decreased T4
- Altered expression of 7 thyroid-related genes in larval zebrafish

Annotate and convert to ontology classes

Assemble Chemical-Species Phenotypic Profiles

PFOS on zebrafish - Ref#178023
PFOS on zebrafish - Ref#175649
PFOS on zebrafish - Ref#175223
PFOS on zebrafish - Ref#175685
…

Compare to Phenotypic Profiles

Genes — ZFIN

Pathways — KEGG, reactome

Diseases — OMIM

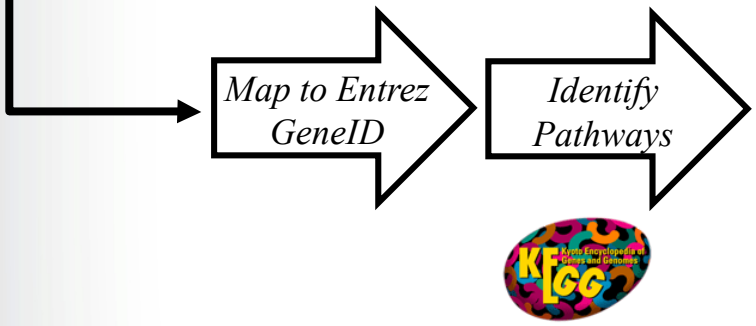
Wang et al. 2019 *Toxicology* 412:89-100

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/Gluconeogensis; 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

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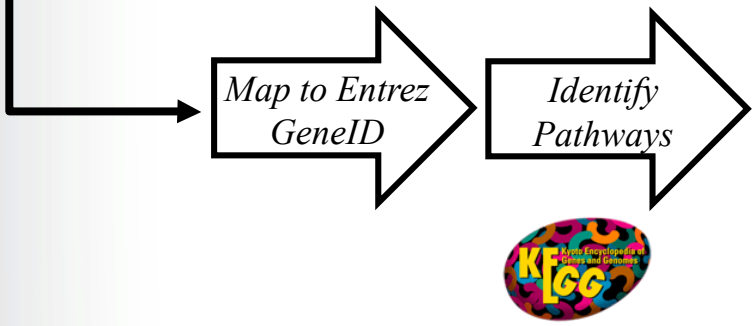

Genes with sig. change in transcription

73 Zebrafish Pathways Investigated

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Summary

- 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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Great Lakes Toxicology and Ecology Division
Duluth, MN

http://cfpub.epa.gov/ecotox

ECOTOX Support: 218-529-5225 ecotox.support@epa.gov

EXTRA SLIDES

Terms for Literature Search

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

April – Nov 2018

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

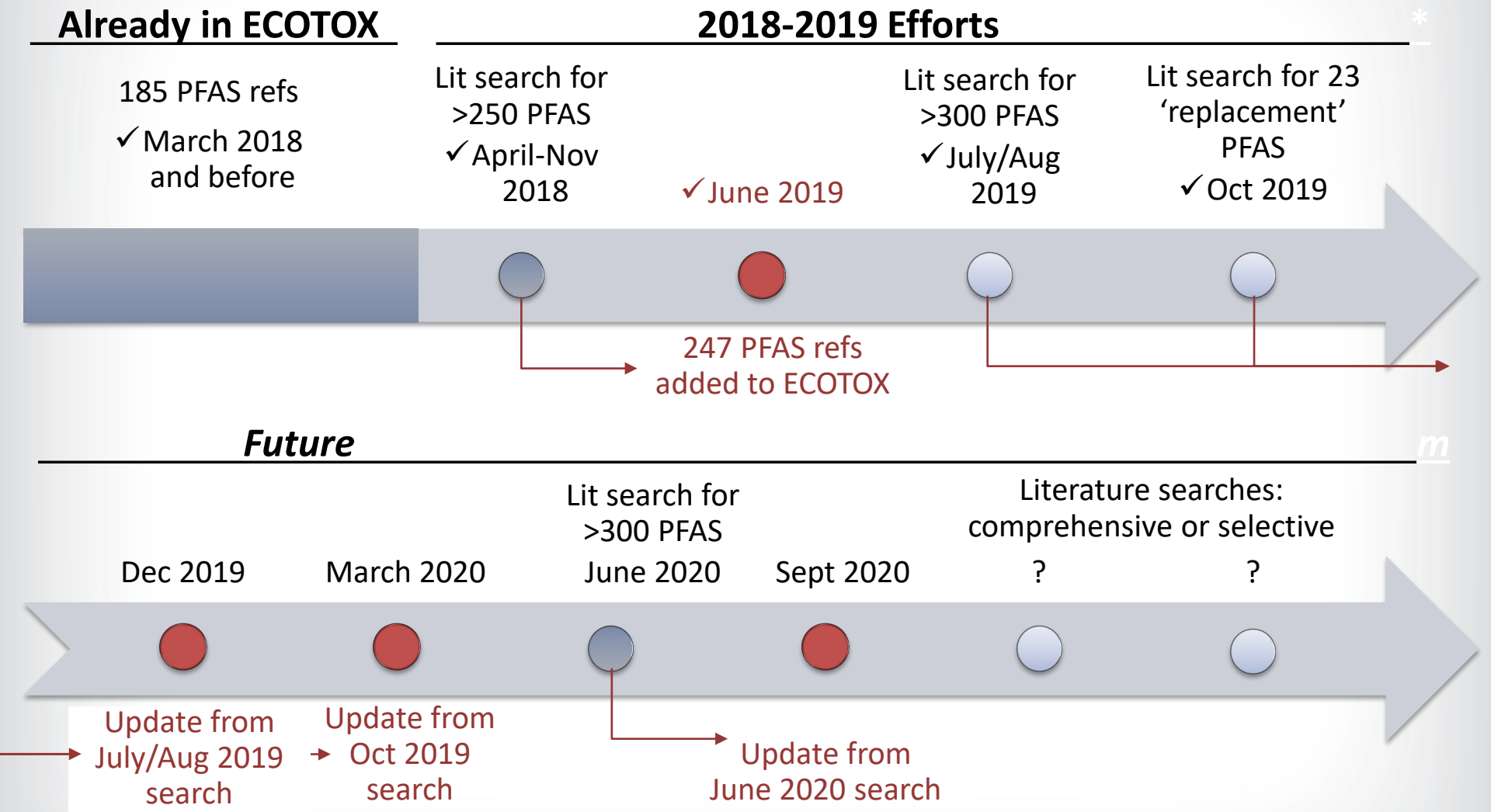
July – August 2019

- 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



Criteria for inclusion in ECOTOX

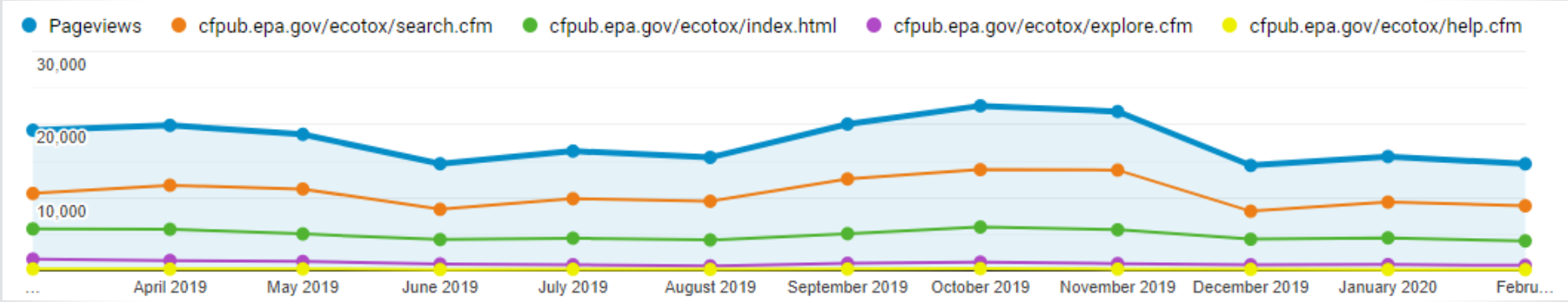
Recently developed PECO statement for ECOTOX		Requirements/Inclusionary Criteria from ECOTOX SOP
P (Population)	Animal: Aquatic and terrestrial species (live, whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Include wild mammals (e.g. Peromyscus sp.), insects, spiders, amphibians, birds, crustaceans, fish, molluscs, reptiles, worms and invertebrates. Bacteria and viruses are not included. Plants: Aquatic and terrestrial species (live), all plants including algal, moss, lichen and fungi species	• 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)	Relevant forms: Chemical of Concern, name and CASRN (plus synonyms, tradenames); when requested: Metabolites, degradants, parent compound and related chemicals 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). Plants: Exposure to relevant forms of the chemical of concern via water or soil, with reported concentration and duration. * Studies involving exposures to mixtures will be included only if they include exposure to a relevant form for the chemical alone. * 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	• 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).	• Must have a control treatment
O (Outcome)	All biological effects (including bioaccumulation from laboratory studies with concurrently measured water and tissue concentrations).	• Biological effect measured • Effect concurrent with associated chemical exposure • Adverse effects are priority (beneficial, nutritional effects are lower priority)
Publication/ Data Format		• Primary source of the data • Study must be a full article in English • NOT: Reviews or abstract only

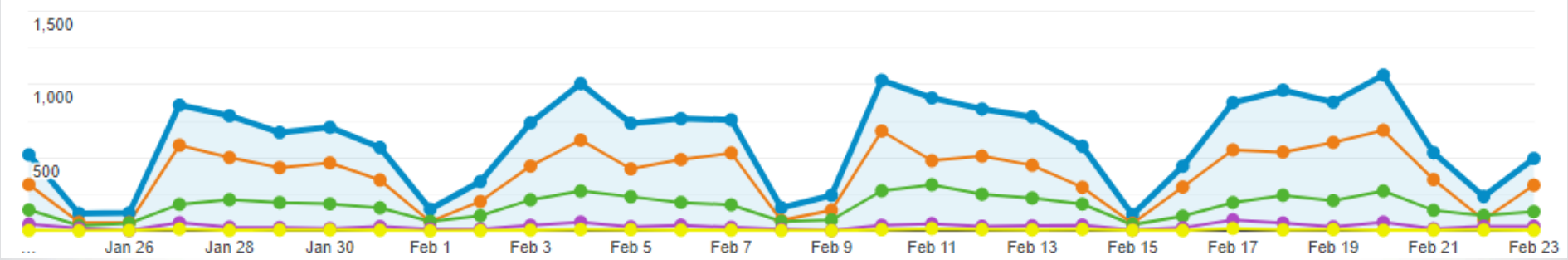
ECOTOX by the numbers

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