Computational Toxicology and Exposure Communities of Practice

Sharing research and promoting collaboration

Thursday, May 23, 11 AM-12 PM ET

Agenda:

- **Introduction: Sammy Hanf**
  Communications Specialist, ORD Center for Computational Toxicology and Exposure
- **Presentation: Jennifer Olker**
  Biologist, ORD Center for Computational Toxicology and Exposure
- **Q&A**
- **Closing remarks: Sammy Hanf**

For more information on the CompTox CoP, visit:
epa.gov/chemical-research/computational-toxicology-communities-practice

ECOTOXicology Knowledgebase: Update with Ecologically Relevant Data for Emerging Contaminants

Jennifer Olker
Physical Scientist, ORD Center for Computational Toxicology and Exposure

ECOTOXicology Knowledgebase:
Update with Ecologically Relevant Data for Emerging Contaminants

Jennifer H. Olker
USEPA Office of Research and Development
Center for Computational Toxicology and Exposure

USEPA CompTox Communities of Practice
May 23, 2024

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the US EPA.

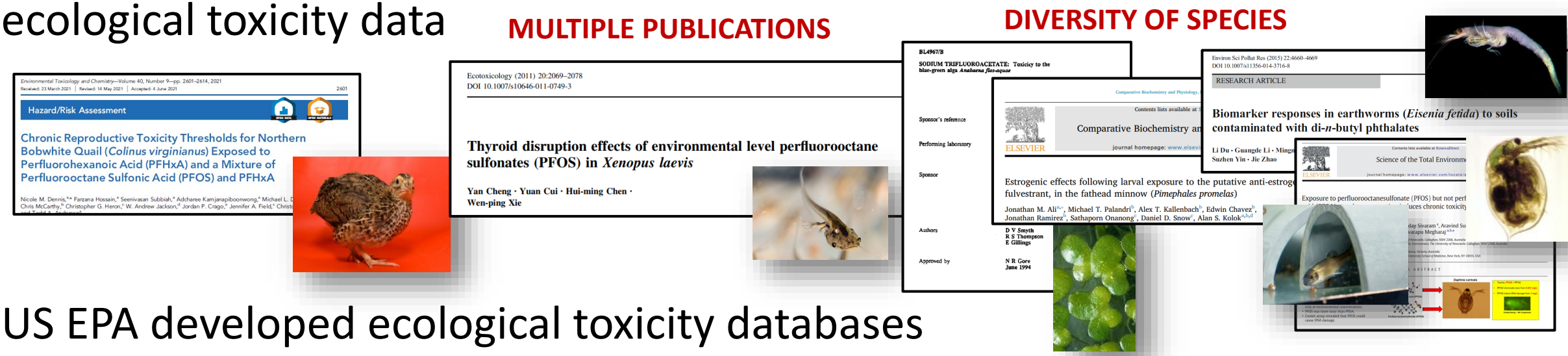
Outline

- What is the ECOTOXicology Knowledgebase?
- Overview of literature search and data curation pipeline
- Examples of updates for several contaminants of emerging and immediate concern
  - Per- and Polyfluoroalkyl substances (PFAS)
  - 6PPD-quinone
  - Cyanotoxins

Background of ECOTOX

Background and History

- Ecological risk assessors need cost-effective methods to locate high-quality ecological toxicity data



- US EPA developed ecological toxicity databases
  - AQUatic toxicity Information Retrieval (AQUIRE) database (Duluth, MN lab)
  - PHYTOTOX (Corvallis, OR lab)
  - TERRETOX (Corvallis, OR lab)

Early 1980s
- AQUIRE, PHYTOTOX, TERRETOX developed

Early 1990s
- Major updates to AQUIRE

Late 1990s
- Combined system was created (ECOTOX)

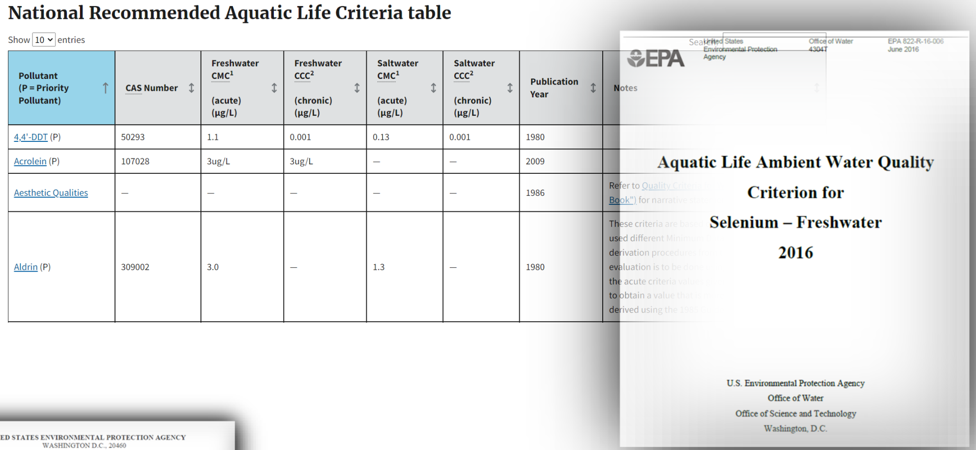
2017
- Interactive version of ECOTOX developed

5

Background and History

- Ecological risk assessors need cost-effect methods to locate high-quality ecological toxicity data

<u>Ambient Water Quality Criteria for Aquatic Life</u> (USEPA Office of Water)

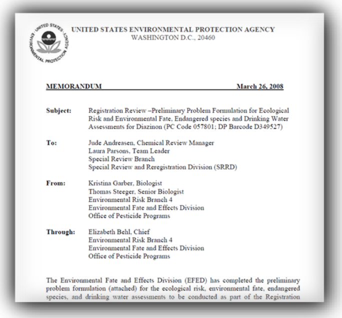

National Recommended Aquatic Life Criteria table

Show 10 entries

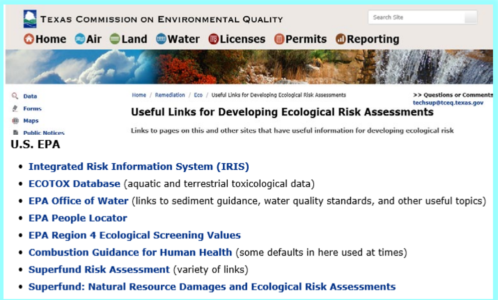
Pollutant (P = Priority Pollutant)	CAS Number	Freshwater CMC[1] (acute) (µg/L)	Freshwater CCC[2] (chronic) (µg/L)	Saltwater CMC[1] (acute) (µg/L)	Saltwater CCC[2] (chronic) (µg/L)	Publication Year	Notes
4,4'-DDT (P)	50293	1.1	0.001	0.13	0.001	1980	
Acrolein (P)	107028	3ug/L	3ug/L	—	—	2009	
Aesthetic Qualities	—	—	—	—	—	1986	Refer to Quality Criteria ... Book") for narrative ...
Aldrin (P)	309002	3.0	—	1.3	—	1980	These criteria ... used different ... derivation proced... evaluation is to be ... the acute criteria ... to obtain a value ... derived using the ...

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

Ecological hazard data for the <u>Prioritization and Assessment of Chemicals for Toxic Substances</u> Control Act/Lautenberg Act (USEPA Office of Pollution Prevention and Toxics)


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

<u>Ecological Risk Assessment</u> for chemical registration and re-registration (USEPA Office of Pesticide Programs)

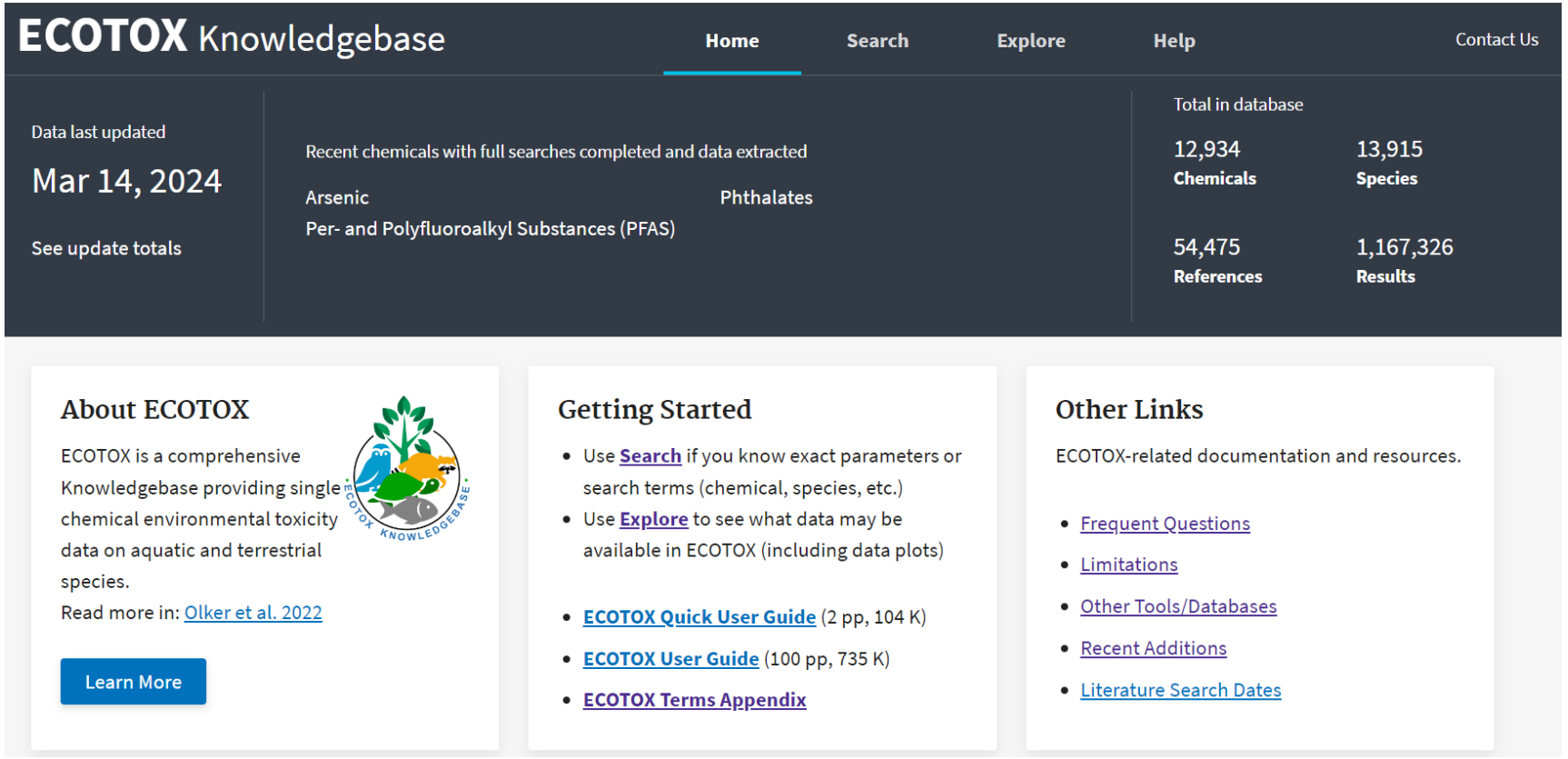

Texas Commission on Environmental Quality
Home Air Land Water Licenses Permits Reporting
Useful Links for Developing Ecological Risk Assessments
Links to pages on this and other sites that have useful information for developing ecological risk
U.S. EPA
Integrated Risk Information System (IRIS)
ECOTOX 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

<u>Ecological Site Assessments</u> and in <u>Emergency Response</u>

(USEPA Office of Land and Emergency Management - Superfund and Resource Conservation and Recovery Act; Regions and States).

What is the ECOTOX Knowledgebase?

- From comprehensive search and review of open and grey literature
- Chemical-based literature searches
- Accessible, structured empirical data from *in vivo* toxicity tests
- Updated quarterly to public website
- 30+ year history



www.epa.gov/ecotox

ECOTOX Overview: Olker et al. 2022 https://doi.org/10.1002/etc.5324

Applications of ECOTOX

Chemical environmental toxicity data for aquatic and terrestrial organisms

Provides data to

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

Data used for

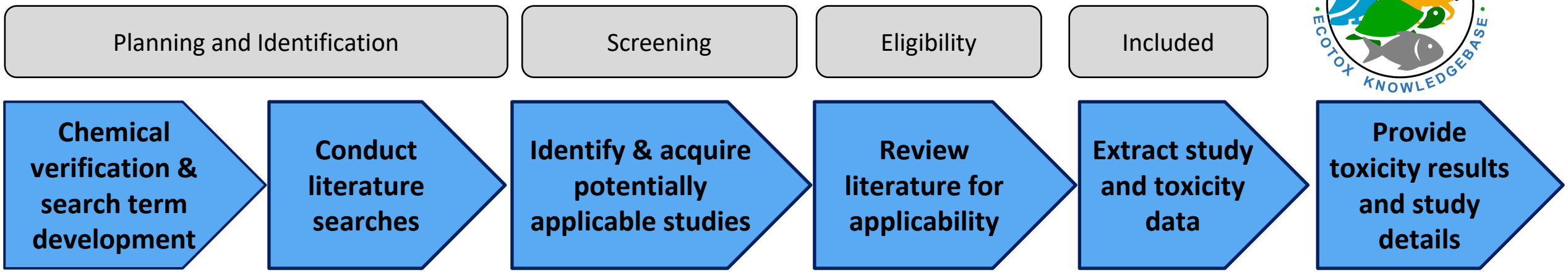
Tools and Applications

Species Sensitivity Distributions
Predicted No-Effect Concentrations and Eco-Thresholds for Toxicological Concern
Quantitative Structure–Activity Relationships
Bioaccumulation Factor Modeling and Validation
Adverse Outcome Pathway Development

Data linked to

Databases/Resources

ECOTOX Pipeline



Chemical-based Search Terms*

- Chemical name and CASRN
- Synonyms, tradenames
- Other relevant forms

Literature Search

Use chemical-specific search terms to query multiple literature search engines.

Title/Abstract Screening

Full Text Review

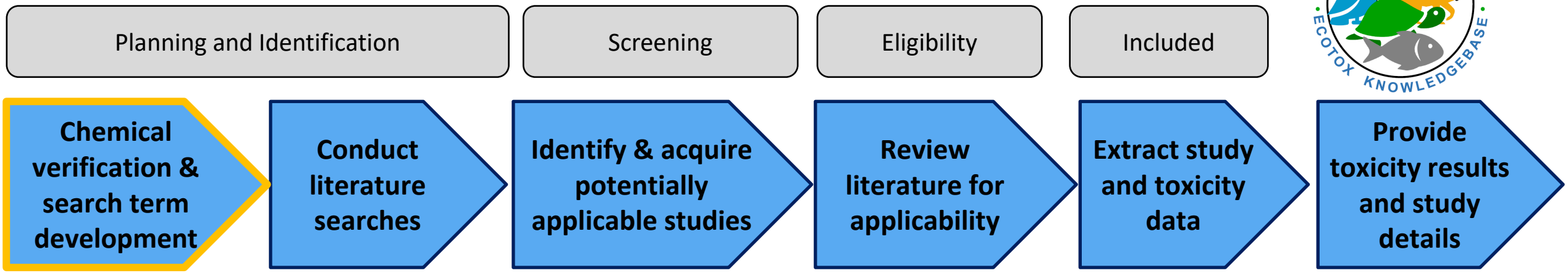
- Established applicability (inclusion) criteria
- Documentation of exclusion reason

Data Extraction

- ECOTOX-specific Controlled Vocabularies
  - Test chemical
  - Test organism
  - Study methods and test conditions
  - Toxicity results
- Updated to public website, with downloadable outputs

* 40-90 searches conducted per year, not possible to update data for all chemicals each year

ECOTOX Pipeline

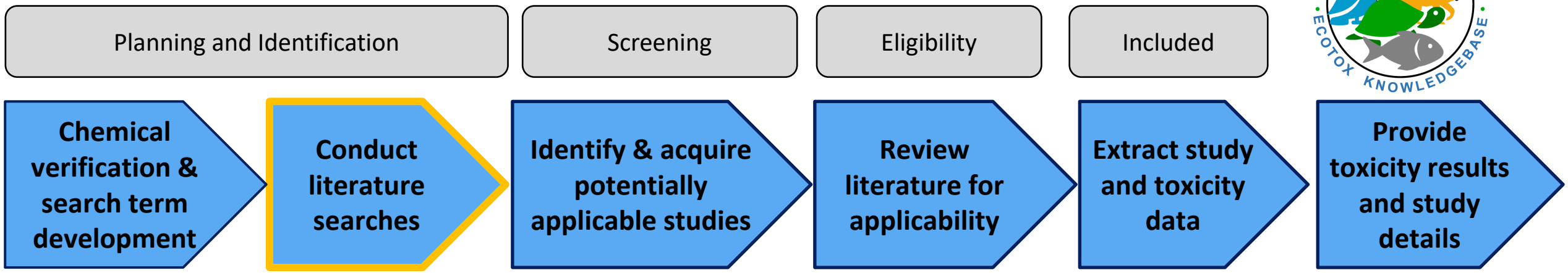


Chemical-based Search Terms

- Verify CASRN
- Search various sources for chemical terms
  - STN
  - Pesticide Action Network
  - EPA's Pesticide Fate Database
  - EPA's Chemicals Dashboard
- Synonyms
- Eliminate poor search terms
- Develop search string

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")

ECOTOX Pipeline

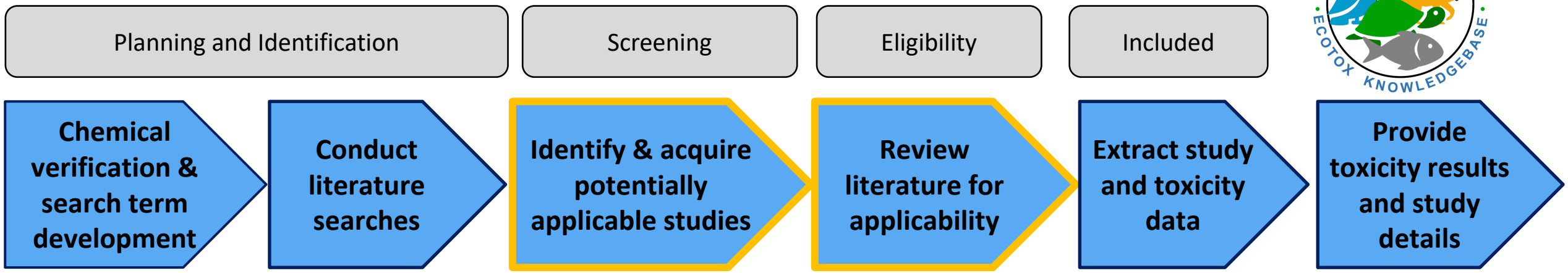


Chemical-based Literature Searches

Search Engines

1. Scopus/Science Direct
2. ProQuest
3. Web of Science
4. PubAg or AGRICOLA
5. PubMed, Toxline/TOXNET (opt.)
6. Dissertation Abstracts

ECOTOX Pipeline



Title/Abstract Screening

Full Text Review

- Established applicability (inclusion) criteria which can be expressed as PECO statement
- Documentation of exclusion reason

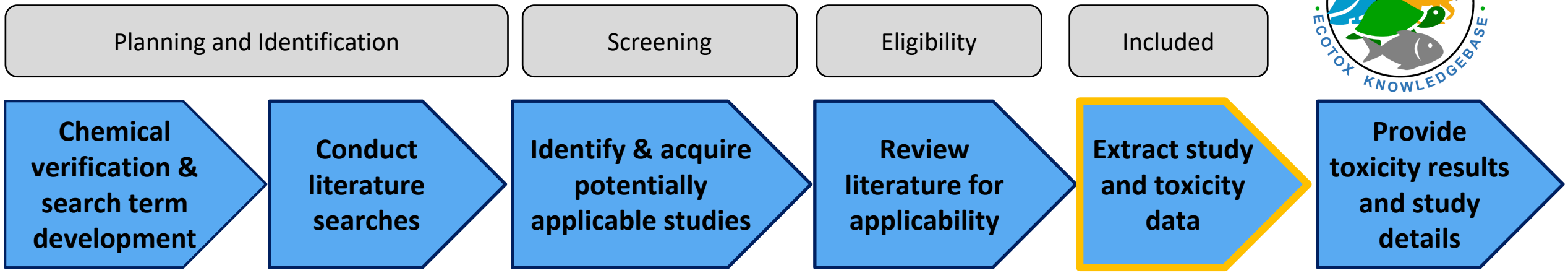
Inclusion Criteria

Identify and acquire potentially applicable studies → **Review literature for applicability**

	Key Area	Data Requirement
P (Population)	Species	• Taxonomically verifiable, ecologically-relevant organisms (including cells, organs, gametes, embryos, plant cuttings) [NOT bacteria, humans, monkeys, viruses, or yeast]
E (Exposure)	Chemical	• Single, verifiable chemical toxicants, administered through an acceptable route
	Exposure Amount (Concentration)	• Exposure amount is quantified, either as a concentration in the environment when administered via soil or water, or as a dosage when introduced directly into or on the organism, via injection, orally, or topically
	Exposure Duration	• Known duration from the time of initial exposure to the time of measurement
C (Comparator/ Control)	Control	• Must have a control treatment
O (Outcome)	Effect	• Biological effect measured • Effect concurrent with associated chemical exposure
	Publication Type	• Primary source of the data [NOT a Review] • Study must be a full article in English

Adapted from Olker et al. 2022

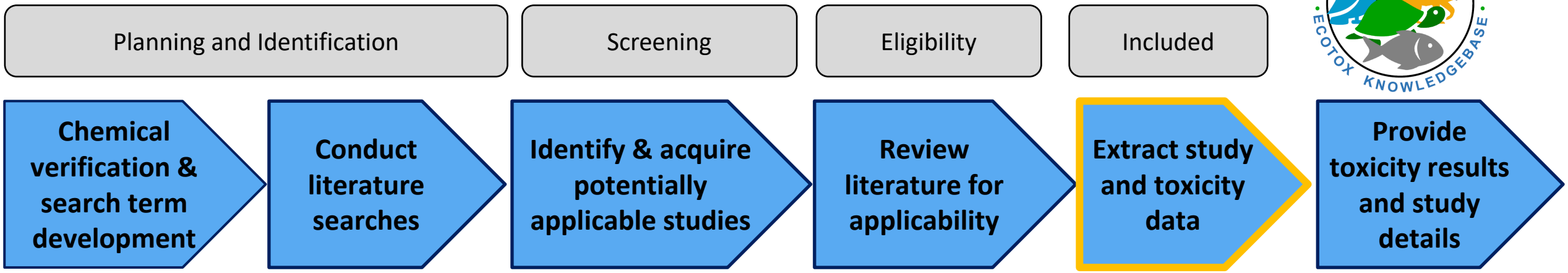
ECOTOX Pipeline



Data Extraction

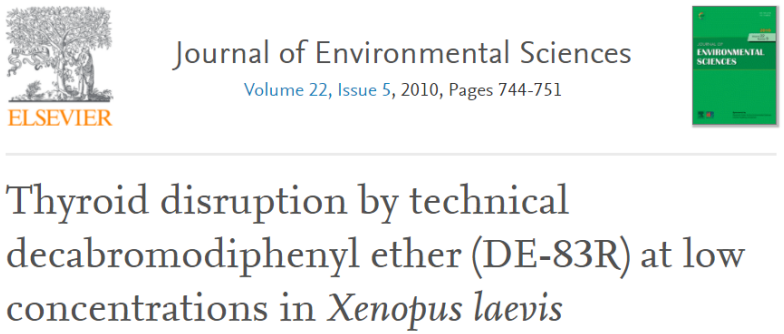
- **ECOTOX Data Fields** consist of ~90 entities
- **ECOTOX-specific Controlled Vocabularies**
- Developed from 30+ years reviewing the ecotoxicological literature
- **Custom GUI designed for ECOTOX data extraction**
  - Computationally-assisted forms constrained to controlled vocabularies

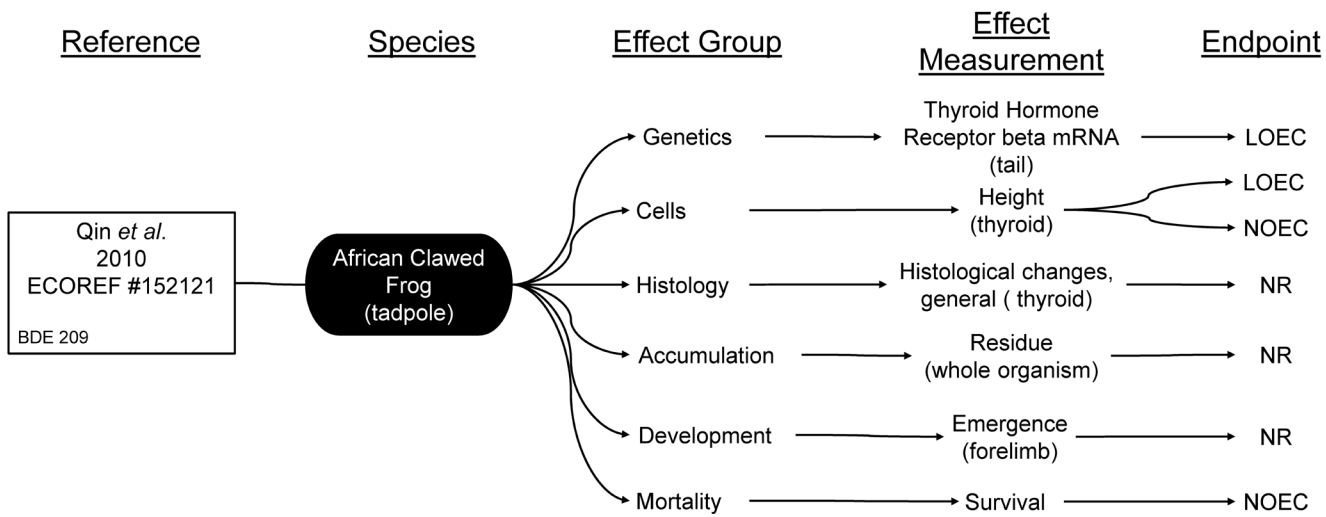
ECOTOX Pipeline



Data Extraction

Example of multiple ECOTOX records from a single study:





NOEC = No Observed Effect Level LOEC = Lowest Observed Effect Level NR = Not Reported

ECOTOX Data Fields

Extract study and toxicity data

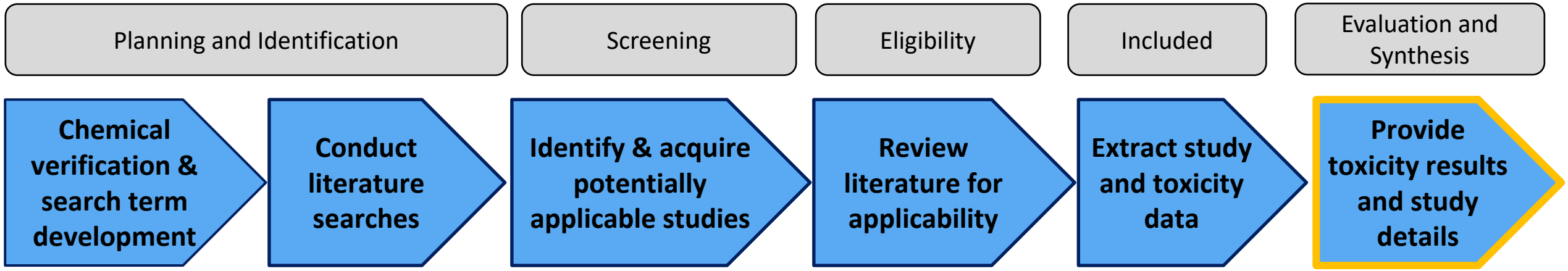
Category	ECOTOX data fields (examples)
Chemical	• Chemical identifier (CASRN, DTXSID) • Chemical Analysis • Chemical Formulation & Grade • Concentration(s)/Dose(s) tested
Species	• Species identifiers (ITIS TSN, NCBI TaxID, Taxonomy) • Life stage, Age, Sex • Organism Source
Study Methods & Test Conditions	• Experimental design • Control(s) • Test location and method • Exposure type, route, and media • Study and exposure duration • Physical and Chemical Soil and Water Parameters (e.g., pH, Temperature, Dissolved Oxygen)
Test Results	• Specific Effect Measured (with higher-level groups) • Calculated Endpoint • Concentration associated with effect and endpoint • Response site (e.g., whole organism, specific organ or body part) • Statistical significance and level of response

*** ECOTOX Data Fields**
https://cfpub.epa.gov/ecotox/help.cfm?sub=wi-definitions

*** ECOTOX Vocabularies:**
https://cfpub.epa.gov/ecotox/help.cfm?sub=term-appendix

Adapted from Olker et al. 2022

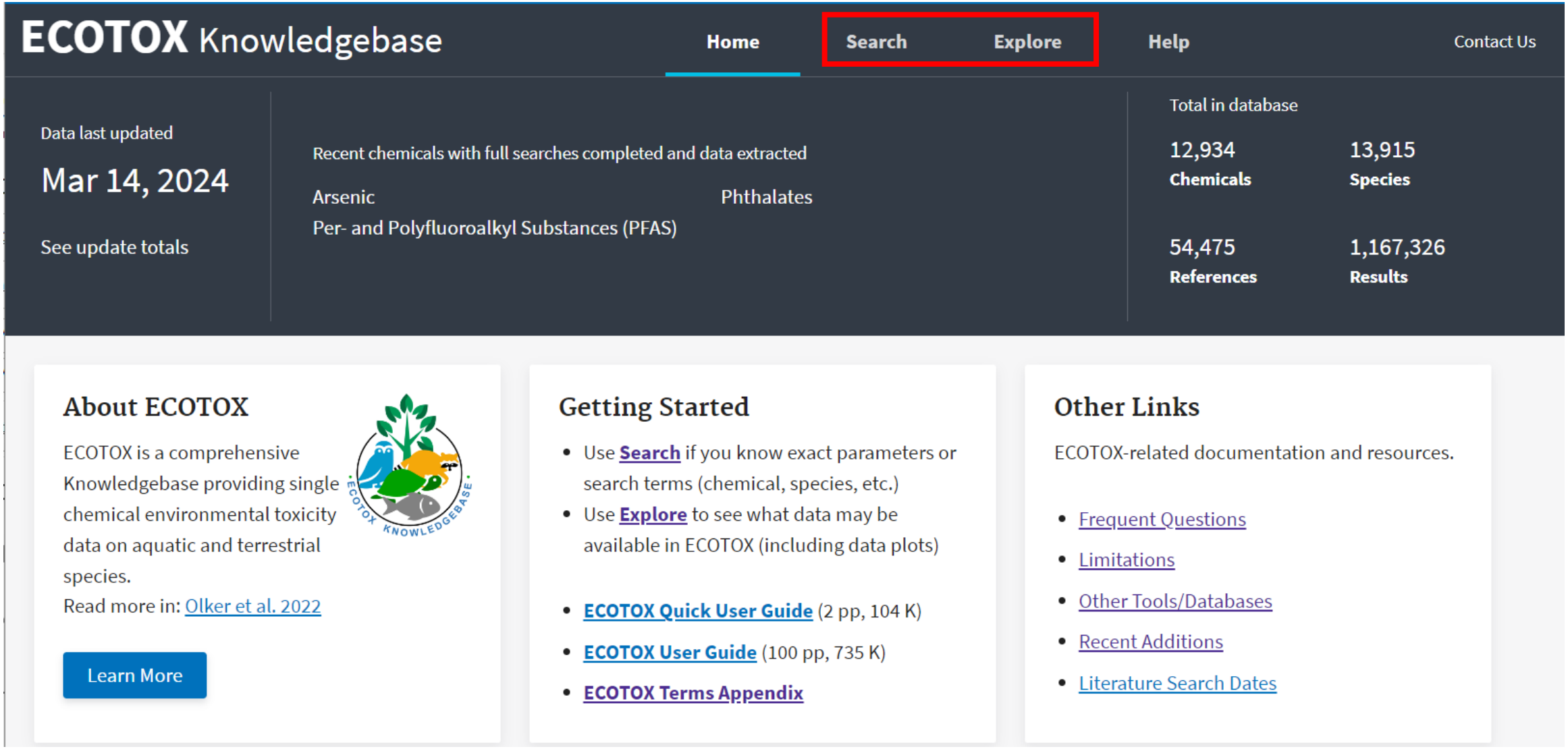
ECOTOX Pipeline



Supporting Study Evaluation and Data Synthesis

- **ECOTOX inclusion criteria** overlaps with standard study evaluation questions
- **ECOTOX data fields for study design, test conditions, and results** inform detailed study evaluation
- **Multiple output options** for further analysis and synthesis

ECOTOX: www.epa.gov/ecotox



Recent Updates

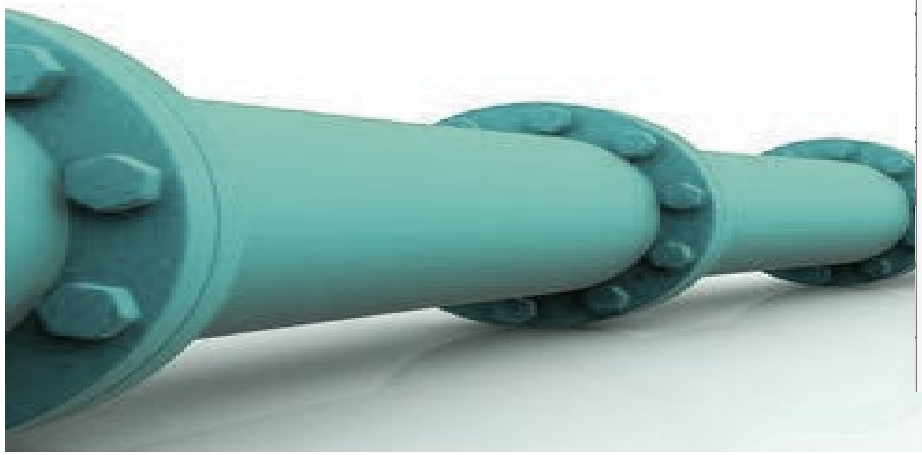
Applying ECOTOX Data Curation Pipeline to PFAS

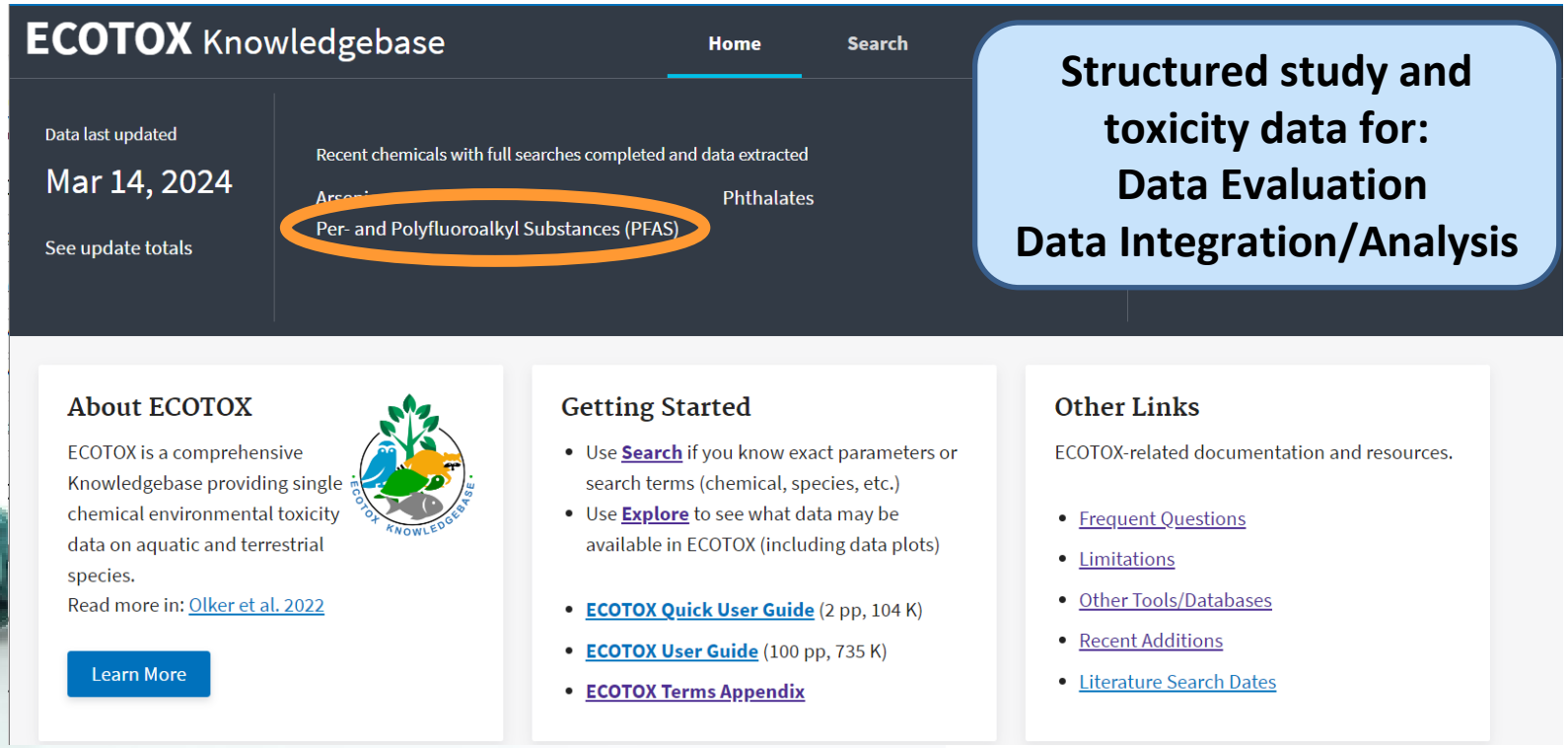
Chemical verification & development of search terms → **Conduct literature searches** → **Identify and acquire potentially applicable studies** → **Review literature for applicability** → **Extract study and toxicity data**

PFAS literature searches 2018 – 2023

2022 search for 14,735 PFAS + synonyms (PFASSTRUCT_v5)

2023 refresh search for PFASSTRUCT_v5 (published Jan 2021 – July 2023)

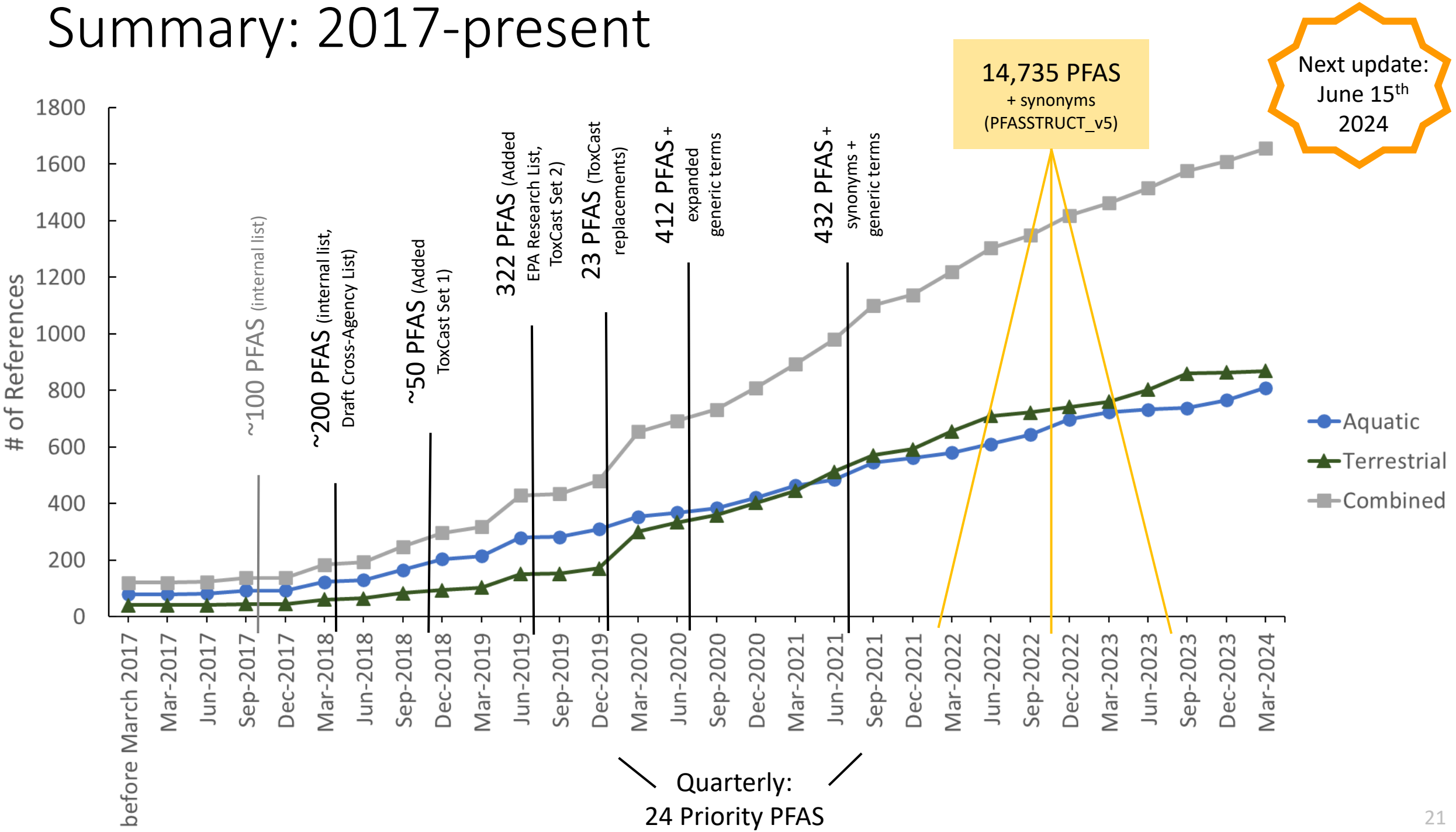




Structured study and toxicity data for:
Data Evaluation
Data Integration/Analysis

https://cfpub.epa.gov/ecotox/explore.cfm?cgid=36

Summary: 2017-present



Literature searches

Search Month-Year	Chemical List	# of PFAS	# of citations			
			Down-loaded	Screened at Title/ Abstract	Full-text Review	
					Identified	New additions to queue
April 2018	EPA Cross-Agency from CompTox Chemicals Dashboard (CCD)	207	29,775	8,181	373	332
Nov 2018	ToxCast Set 1 List of 75 Test Samples (50 not on above)	75	8,474	472	15	14
July 2019	Annual Search : All above + EPA Research List (CCD) + ToxCast Set 2 List of 75	322	88,688	6,425	97	73
Oct 2019	ToxCast Replacement Test Samples (23 not in above)	36	1,109	137	3	3
Jan 2020	PFAS Quarterly Update [a]	24	15,695	615	18	16
April 2020	PFAS Quarterly Update [a]	24	18,831	3,443	451	53
July 2020	Annual Search [b] : All previous lists + any PFAS found in literature screening	412	451,862	136,771	3,573	392
Oct 2020	PFAS Quarterly Update [a]	24	32,688	2,958	110	38
Jan 2021	PFAS Quarterly Update [a]	24	30,011	3,296	94	25
April 2021	PFAS Quarterly Update [a]	24	29,376	2,952	633	29
July 2021	Annual Search [b] : All previous lists + any PFAS found in literature screening	432	601,140	38,658	1,822	1133
Feb 2022	Annual Search [c] : PFAS Structure list PFASSTRUCTv4 + PFAS chemicals without explicit structures (PFASDEV1) from CCD	12,039	1,180,470	88,628	1,917	530
Nov 2022	Supplemental search for PFAS on new PFAS Structure list (PFASSTRUCTv5) that were not in Feb 2022 search	4,149	575,987	35,112	823	118
July 2023	Annual Search [c] (Refresh): PFAS Structure list (PFASSTRUCTv5) [published Jan 2021 -present]	14,735	455,113	7,498	582	446

[a] Quarterly update searches were conducted Jan 2020 – April 2021 for 24 priority PFAS. [b] Annual searches in 2020 and 2021 also included expanded set of general PFAS terms. [c] Annual searches in 2022 and 2023 included chemical names and synonyms.

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Priority PFAS (n=24)

Analyte Name	Acronym	CASRN linear	Application
Perfluorotetradecanoic acid	PFTreA	376-06-7	
Perfluorotridecanoic acid	PFTriA	72629-94-8	
Perfluorododecanoic acid	PFDoA	307-55-1	
Perfluoroundecanoic acid	PFUnA	2058-94-8	
Perfluorodecanoic acid	PFDA	335-76-2	DoD ESV [a]
Perfluorononanoic acid	PFNA	375-95-1	DoD ESV
Perfluorooctanoic acid	PFOA	335-67-1	DoD ESV; OW [b]
Perfluoroheptanoic acid	PFHpA	375-85-9	
Perfluorohexanoic acid	PFHxA	307-24-4	DoD ESV
Perfluoropentanoic acid	PFPeA	2706-90-3	
Perfluorobutyric acid	PFBA	375-22-4	DoD ESV
Perfluorodecanesulfonic acid	PFDS	335-77-3	
Perfluorononanesulfonic acid	PFNS	68259-12-1	
Perfluorooctanesulfonic acid	PFOS	1763-23-1	DoD ESV; OW [b]
Perfluoroheptanesulfonic acid	PFHpS	375-92-8	
Perfluorohexanesulfonic acid	PFHxS	355-46-4	DoD ESV
Perfluoropentanesulfonic acid	PFPeS	2706-91-4	
Perfluorobutanesulfonic acid	PFBS	375-73-5	DoD ESV
Perfluorooctanesulfonamide	PFOSA	754-91-6	
Fluorotelomer sulphonic acid 8:2	FtS 8:2	39108-34-4	
Fluorotelomer sulphonic acid 6:2	FtS 6:2	27619-97-2	
Fluorotelomer sulphonic acid 4:2	FtS 4:2	757124-72-4	
N-ethyl-N-((heptadecafluorooctyl)sulfonyl) glycine	NEtFOSAA	2991-50-6	
N-(Heptadecafluorooctylsulfonyl)-N-methylglycine	NMeFOSAA	2355-31-9	

[a] Department of Defense (DoD) Ecological Screening Values (ESVs)

[b] USEPA Office of Water (OW) draft criteria, included related forms for PFOA and PFOS (i.e., K-PFOS)

PFAS Results

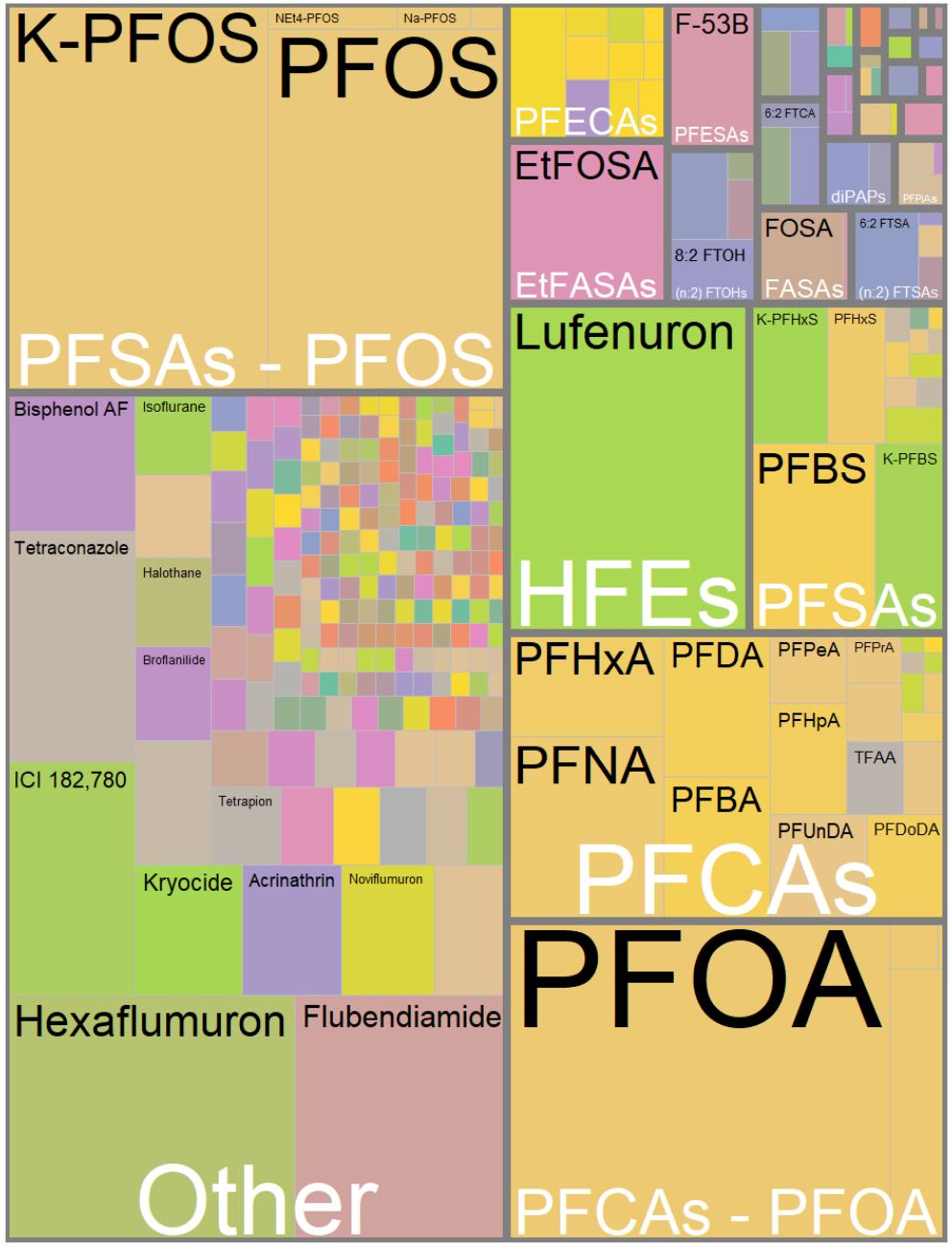
Curation available as of 3/14/2023

>1,600 Publications

- **809 Aquatic**
- **869 Terrestrial**

- 360 PFAS with ecotoxicity data (PFOS, PFOA dominate)

- 813 species (aquatic and terrestrial vertebrates, invertebrates, plants)

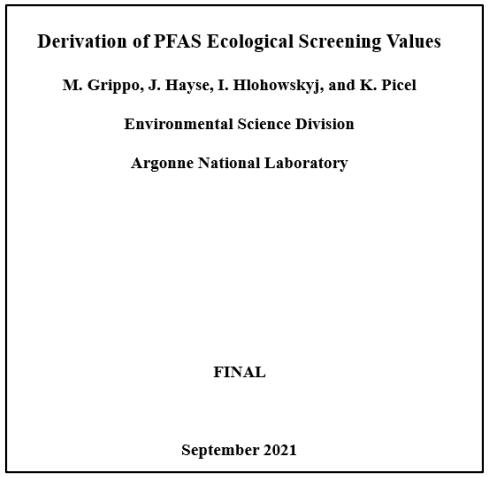


Box size represents # of references for each chemical

Benchmark Derivation Applications

DoD Tri-Services ERA Work Group

- Ecological Screening Values (ESVs) for screening-level ecological risk assessments at DOD federal facilities (*Final Report Sept 2021*)
- Coordination with USEPA OLEM, OW, ORD, and Regions


Derivation of PFAS Ecological Screening Values

M. Grippo, J. Hayse, I. Hlohowskyj, and K. Picel

Environmental Science Division

Argonne National Laboratory

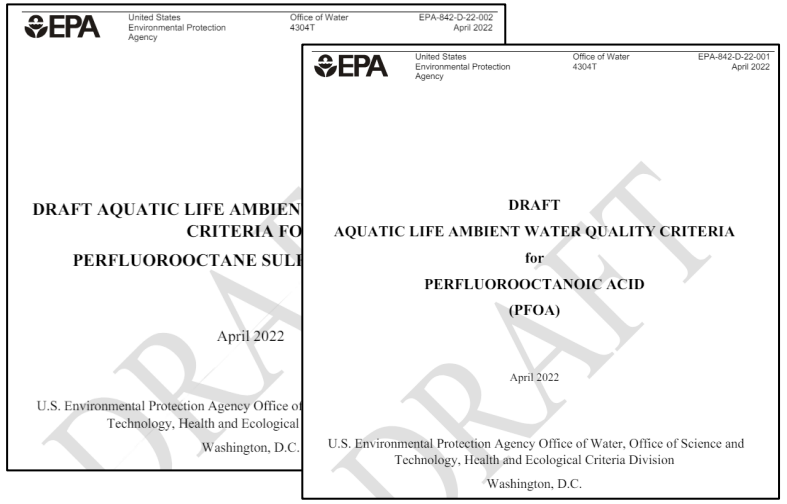
FINAL

September 2021

https://www.denix.osd.mil/dodepa/

US EPA Office of Water

- Data for PFOS and PFOA aquatic life criteria development
  - 2022 draft criteria
  - New studies since draft
- Routine searches for additional possible ALC PFAS


EPA United States Environmental Protection Agency Office of Water 4304T EPA-842-D-22-002 April 2022

DRAFT AQUATIC LIFE AMBIEN
CRITERIA FO
PERFLUOROOCTANE SULI

April 2022

U.S. Environmental Protection Agency Office of
Technology, Health and Ecological
Washington, D.C.

EPA United States Environmental Protection Agency Office of Water 4304T EPA-842-D-22-001 April 2022

DRAFT
AQUATIC LIFE AMBIENT WATER QUALITY CRITERIA
for
PERFLUOROOCTANOIC ACID
(PFOA)

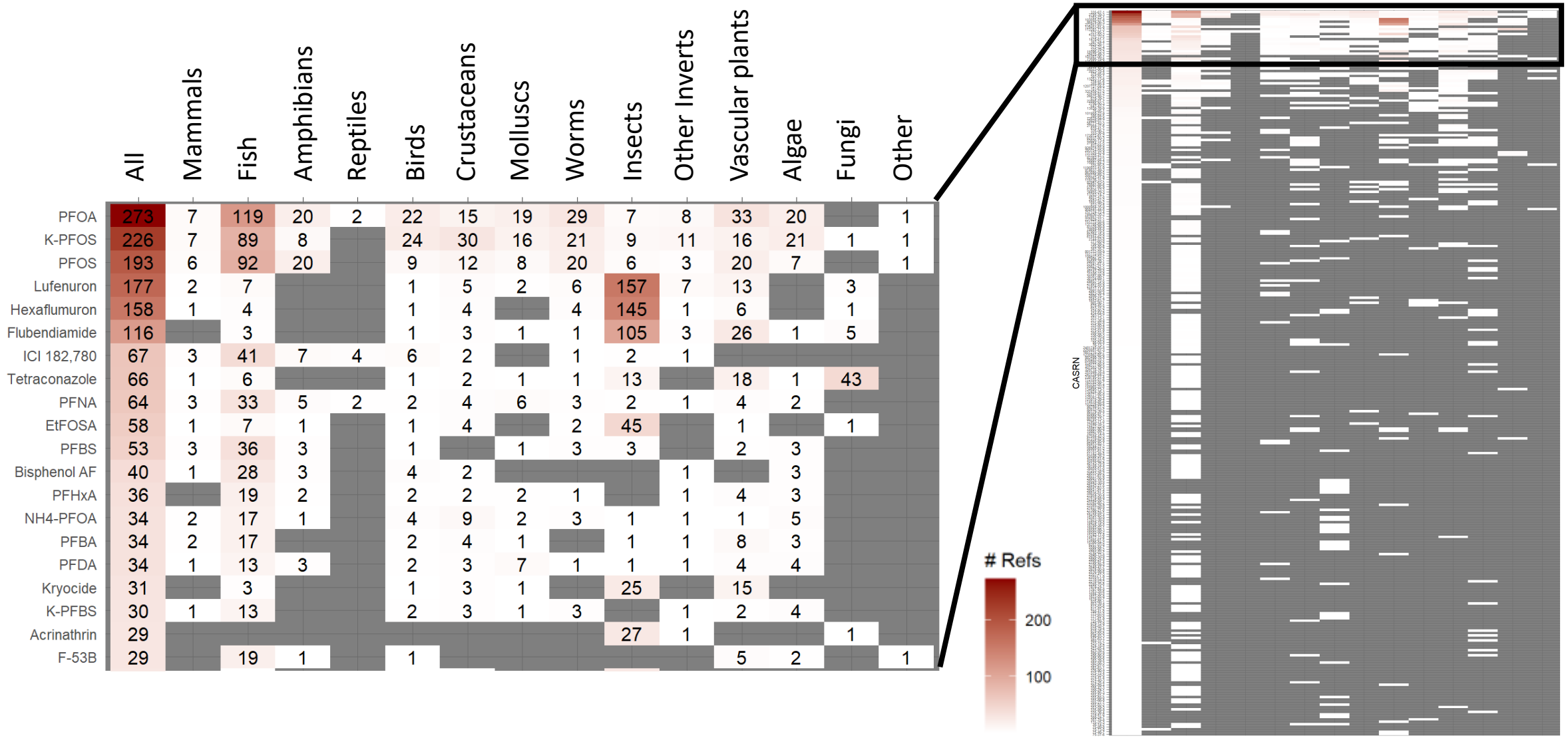
April 2022

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

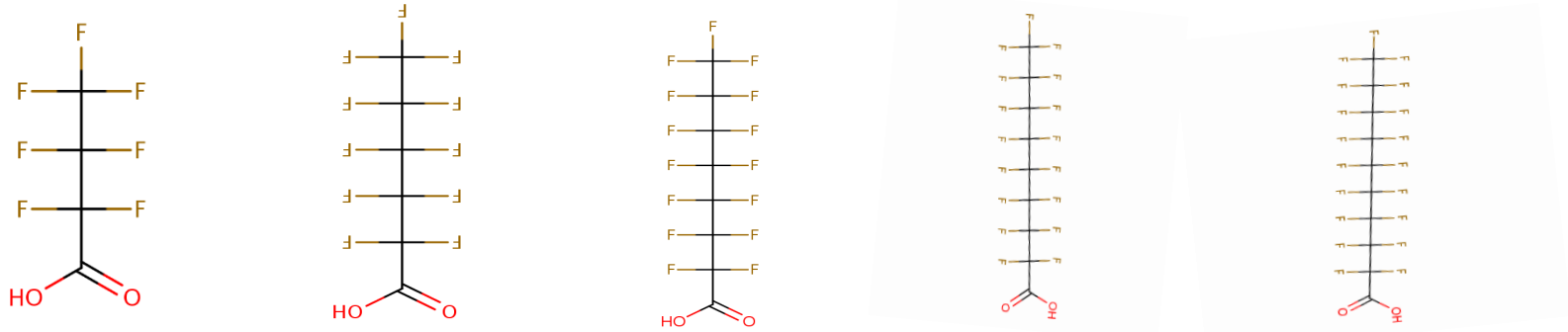
DRAFT DRAFT

https://www.epa.gov/wqc/aquatic-life-criteria-perfluorooctanoic-acid-pfoa
https://www.epa.gov/wqc/aquatic-life-criteria-perfluorooctane-sulfonate-pfos

Highlighting Chemical and Taxonomic Data Needs



Data Gaps: Perfluorinated Carboxylic Acids



	PFBA		PFHA		PFOA		PFNA		PFDA	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Molluscs					X	X		X		X
Crustaceans	X			X	X	X	X	X	X	
Fish	X	X		X	X	X	X	X	X	X
Worms					X	X				
Amphibians					X	X	X		X	
Other Invertebrates	X		X		X	X				
Insects/Spiders		X			X	X		X		
Plants						X		X		X

<u>Aquatic only</u>
Acute: <= 96 hour exposure; Mortality; LC50, EC50
Chronic: = > 7 Days; Behavior, Development, Growth, Mortality, Population, Reproduction; all “Endpoints”

On-going Process

- Prioritization of data extraction

of pending studies by type of PFAS

Category		Papers not yet received	In Full-text Screening	Acceptable for ECOTOX, but data extraction PENDING
Standard PFAS		0	4	22
Endocrine active compounds		0	1	17
Pesticides	Aquatic or Bee studies	0	0	21
	Terrestrial – data limited	0	0	26
	Terrestrial – 5 well-studied compounds*	8	129	512
Anesthetics		0	0	69
	Total		**134**	**667**

Current priorities

*Flubendiamide, Hexaflumuron, Lufenuron, Cryolite, Tetraconazole

- Development of systematic evidence map & manuscript

6PPD-quinone

Common tire chemical implicated in mysterious deaths of at-risk salmon

Coho salmon in urban streams have been dying in the U.S. Pacific Northwest

3 DEC 2020 • BY ERIK STOKSTAD

https://www.science.org/content/article/common-tire-chemical-implicated-mysterious-deaths-risk-salmon

RESEARCH

ECOTOXICOLOGY

A ubiquitous tire rubber–derived chemical induces acute mortality in coho salmon

Zhenyu Tian[1,2], Haoqi Zhao[3], Katherine T. Peter[1,2], Melissa Gonzalez[1,2], Jill Wetzel[4], Christopher Wu[1,2], Ximin Hu[3], Jasmine Prat[4], Emma Mudrock[4], Rachel Hettinger[1,2], Allan E. Cortina[1,2], Rajshree Ghosh Biswas[5], Flávio Vinicius Crizóstomo Kock[5], Ronald Soong[5], Amy Jenne[5], Bowen Du[6], Fan Hou[3], Huan He[3], Rachel Lundeen[1,2], Alicia Gilbreath[7], Rebecca Sutton[7], Nathaniel L. Scholz[8], Jay W. Davis[9], Michael C. Dodd[3], Andre Simpson[5], Jenifer K. McIntyre[4], Edward P. Kolodziej[1,2,3]*

In U.S. Pacific Northwest coho salmon (*Oncorhynchus kisutch*), stormwater exposure annually causes unexplained acute mortality when adult salmon migrate to urban creeks to reproduce. By investigating this phenomenon, we identified a highly toxic quinone transformation product of *N*-(1,3-dimethylbutyl)-*N*′-phenyl-p-phenylenediamine (6PPD), a globally ubiquitous tire rubber antioxidant. Retrospective analysis of representative roadway runoff and stormwater-affected creeks of the U.S. West Coast indicated widespread occurrence of 6PPD-quinone (<0.3 to 19 micrograms per liter) at toxic concentrations (median lethal concentration of 0.8 ± 0.16 micrograms per liter). These results reveal unanticipated risks of 6PPD antioxidants to an aquatic species and imply toxicological relevance for dissipated tire rubber residues.

https://www.science.org/doi/epdf/10.1126/science.abd6951

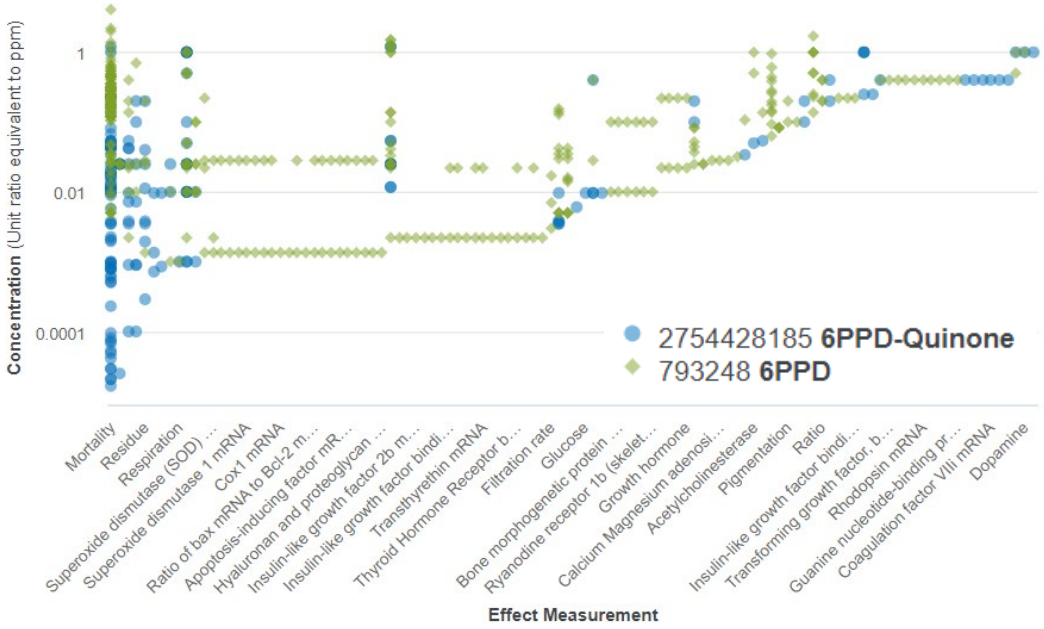
6PPD & 6PPD-quinone: Identification and curation of ecotoxicity results

- Identify and curate relevant ecotoxicity studies on tire rubber antioxidant 6PPD and its transformation product 6PPD-quinone.

Lit Search	# Refs reviewed	Identified by Title and Abstract	# Refs in ECOTOX
April 2021	6,129	4	2
Sept 2022 'Refresh'	1,264	13	21
Sept 2023 'Refresh'	2,364	22 (18 new)	36

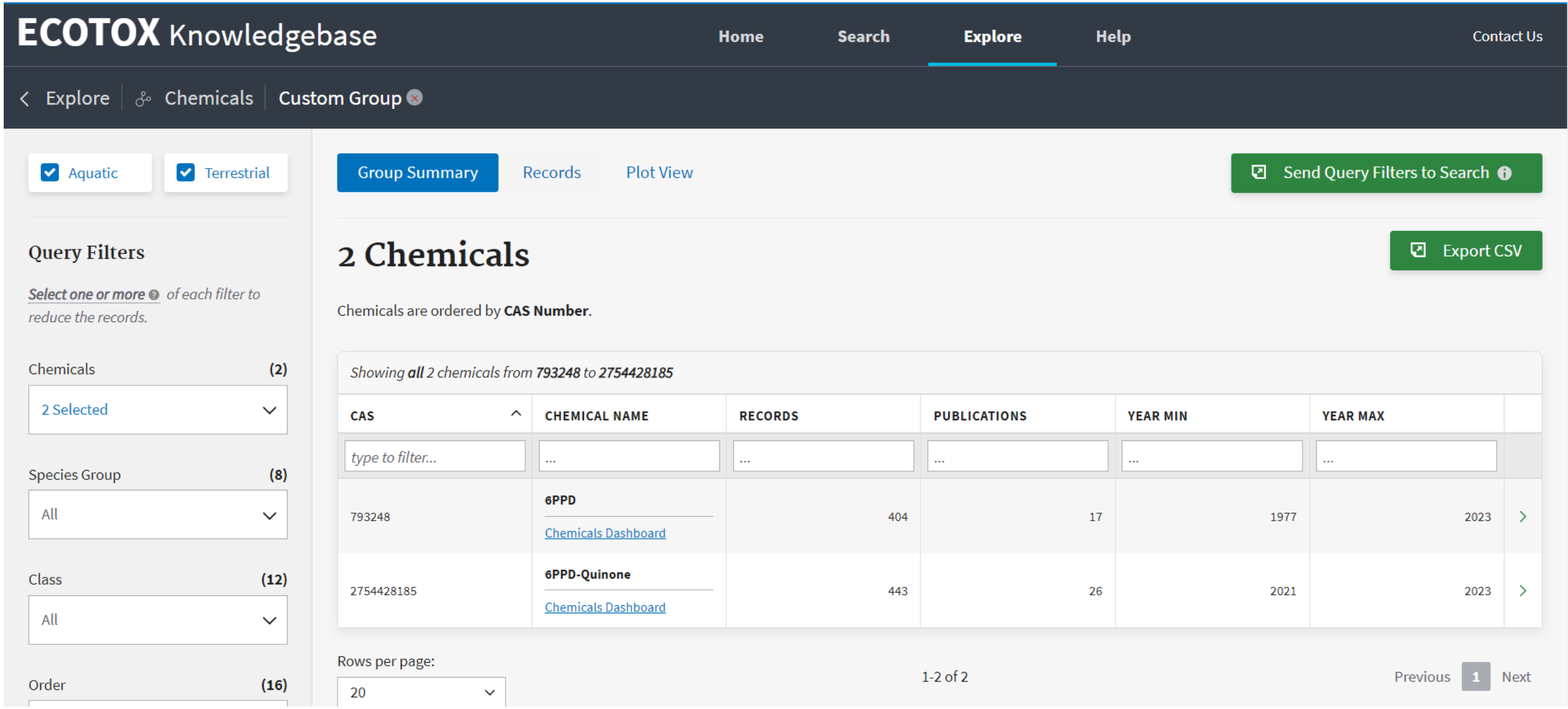
- Rapid identification of recent publications:
  - Monthly reviews
  - Consultation OW & Regions

6PPD and 6PPD-quinone:
36 references, 847 records



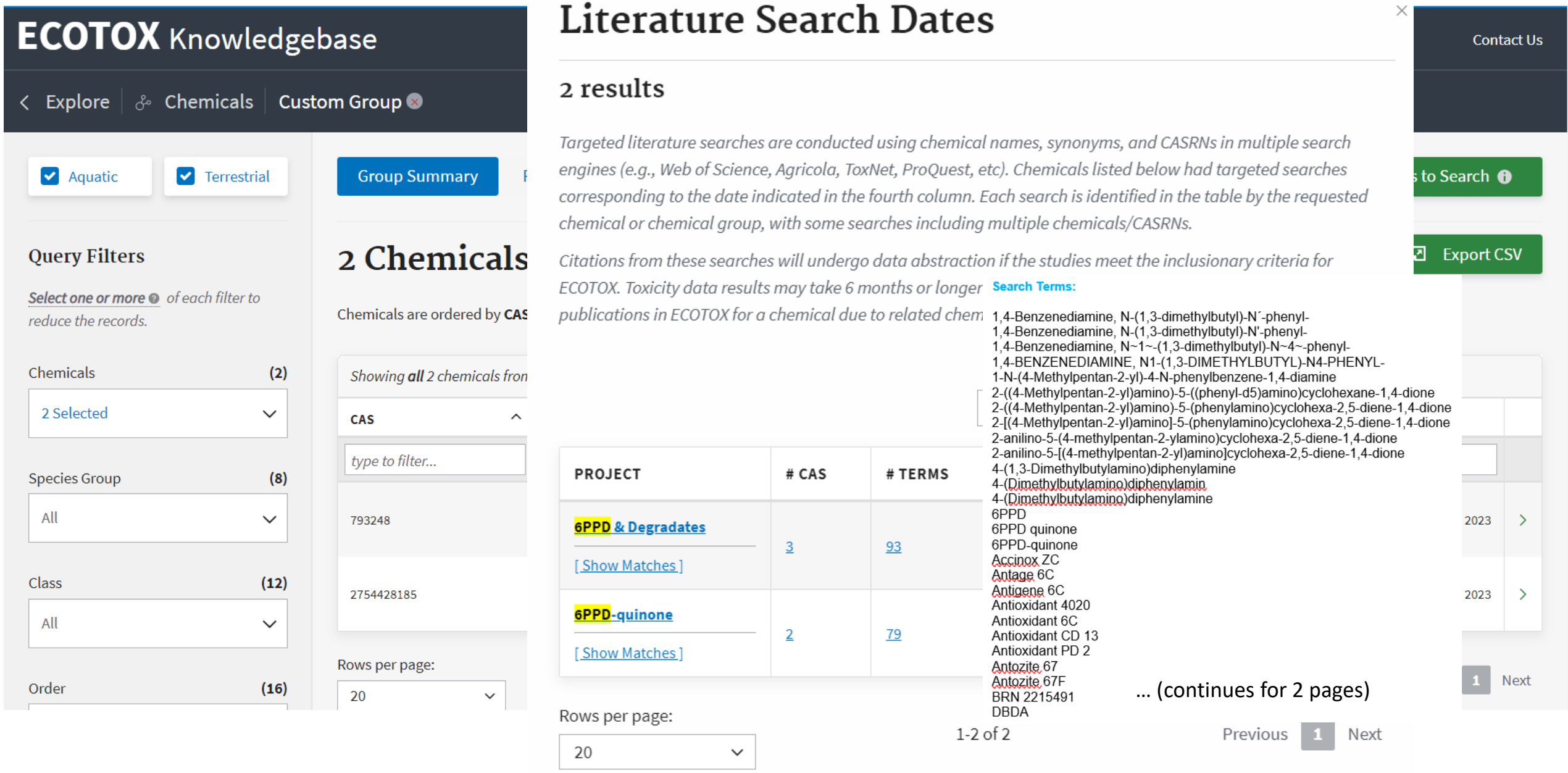
https://cfpub.epa.gov/ecotox/explore.cfm?cas=2754428185,793248

6PPD & 6PPD-quinone



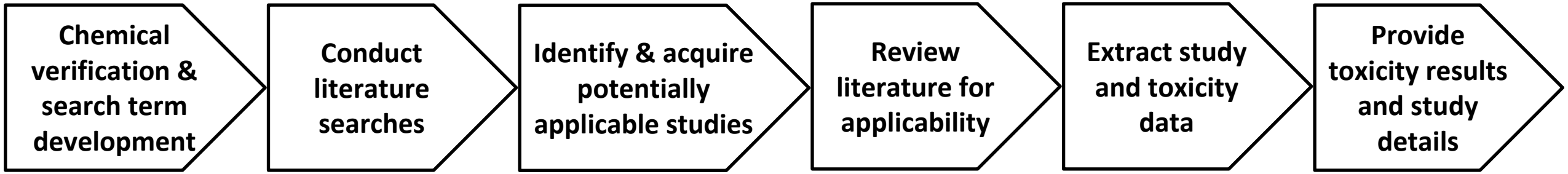
https://cfpub.epa.gov/ecotox/explore.cfm?cas=2754428185,793248

6PPD & 6PPD-quinone



6PPD & 6PPD-quinone – 2023 Search

Problem Statement: Toxicity data of 6PPD-quinone on aquatic organisms needed for evaluation of toxicity effects, species sensitivity, and determination of mode of action.



6PPD and 6PPD-quinone Search – Sept 2023 (Refresh)

<u>One (N=1) requested chemical</u>
6PPD-quinone (2754428-18-5)

<u>Parent chemical</u>
6PPD (793-24-8)

<u>Related</u>
6PPD di-cation (64535-00-8)

N = 9,127 refs

Title and Abstract Screening

N = 22 refs

Full Text Screening

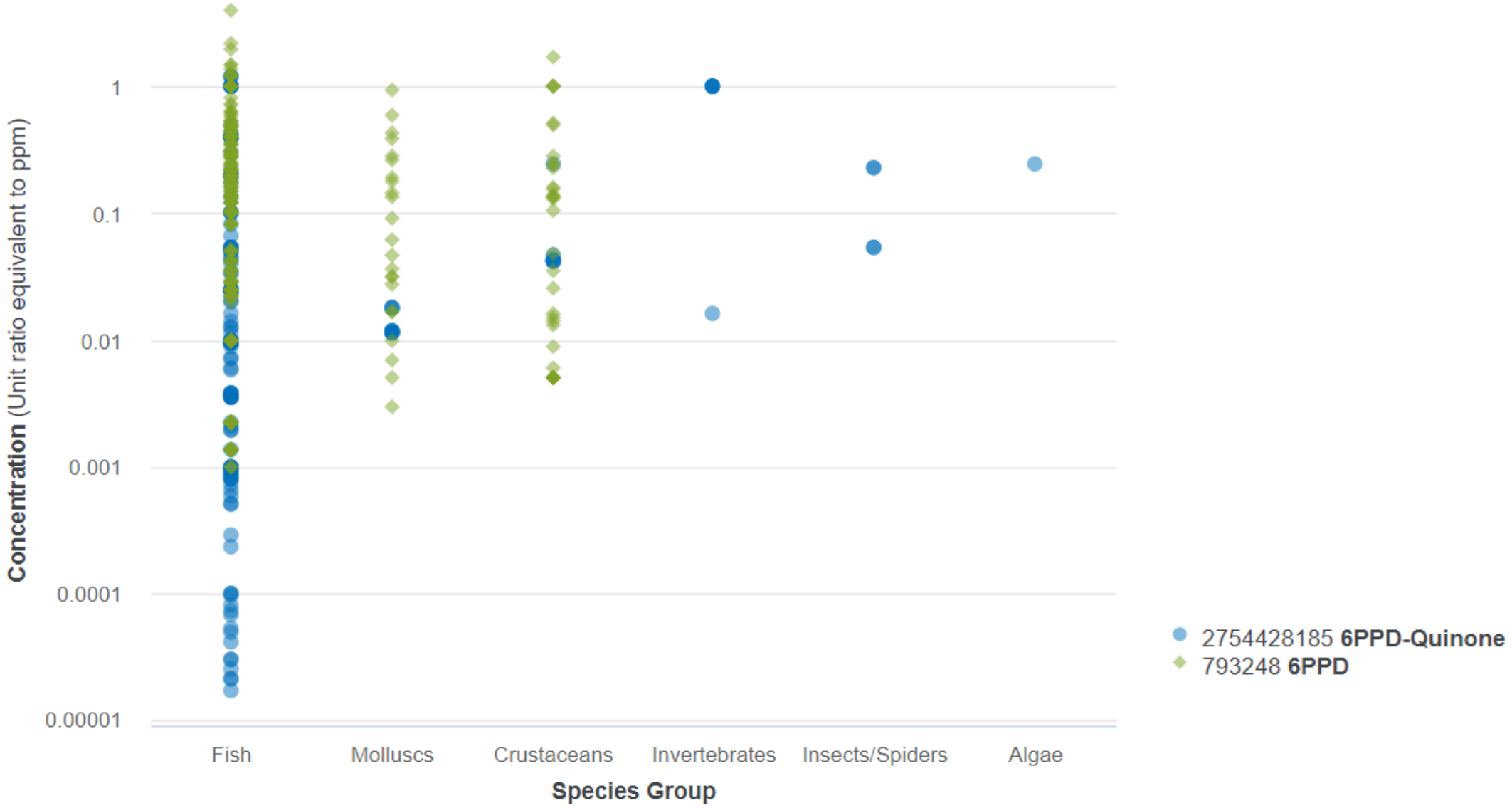
- 4 previously identified

N = 18 refs

Data Extraction and Delivery

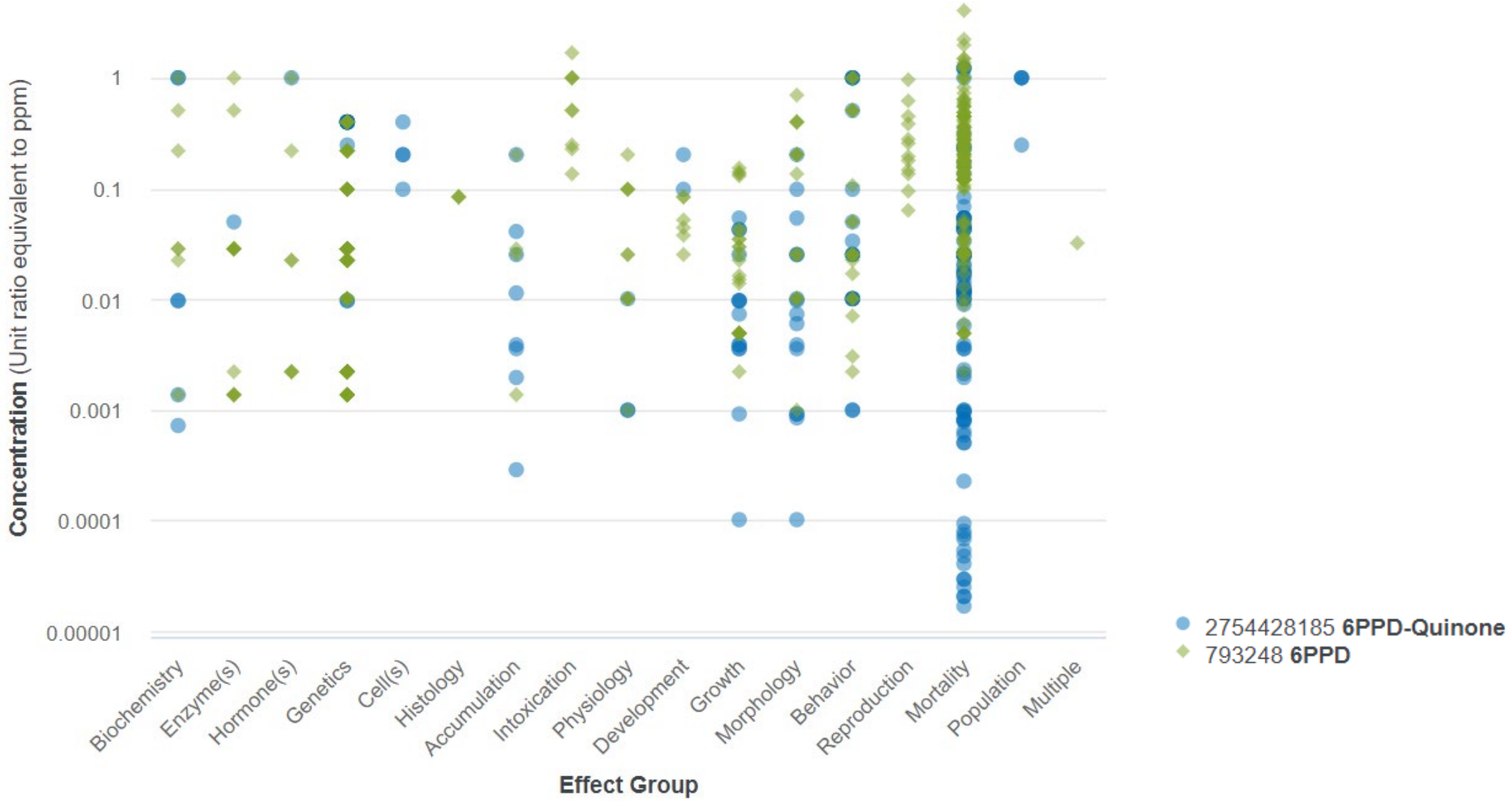
Added to previously identified references
N=36 total

6PPD-quinone & 6PPD: 36 refs, 847 records



Curated data available on ECOTOX: https://cfpub.epa.gov/ecotox/explore.cfm?cas=2754428185,793248

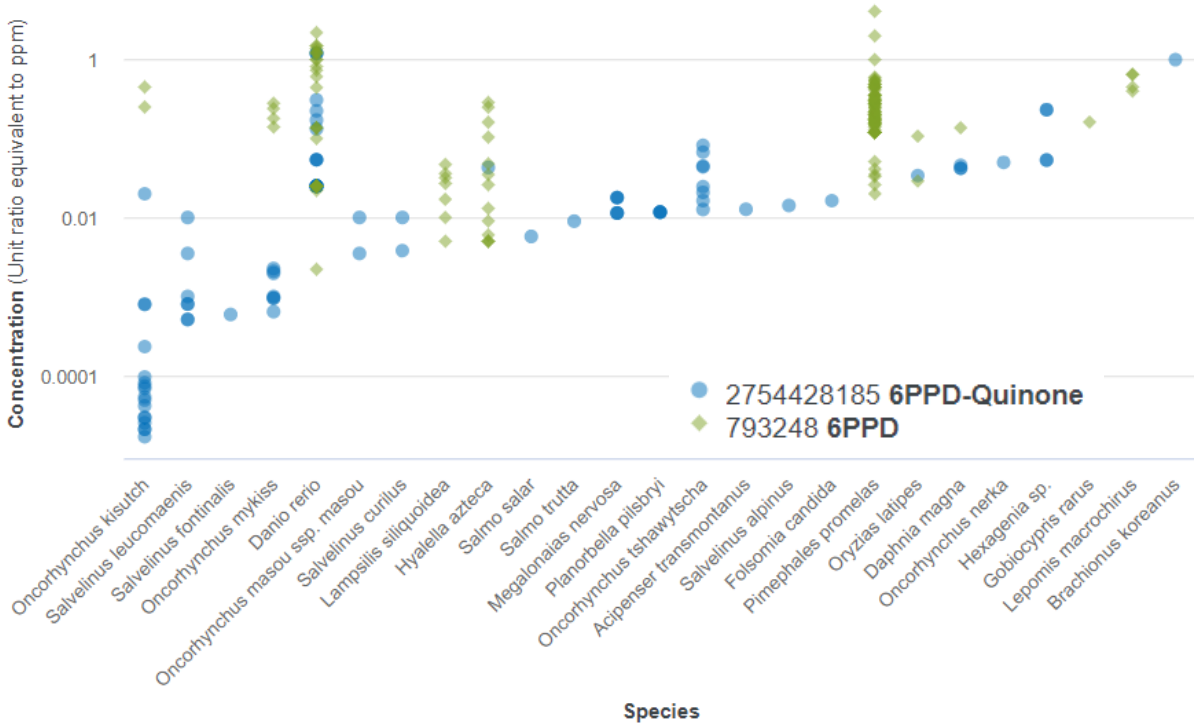
6PPD-quinone & 6PPD: 36 refs, 847 records



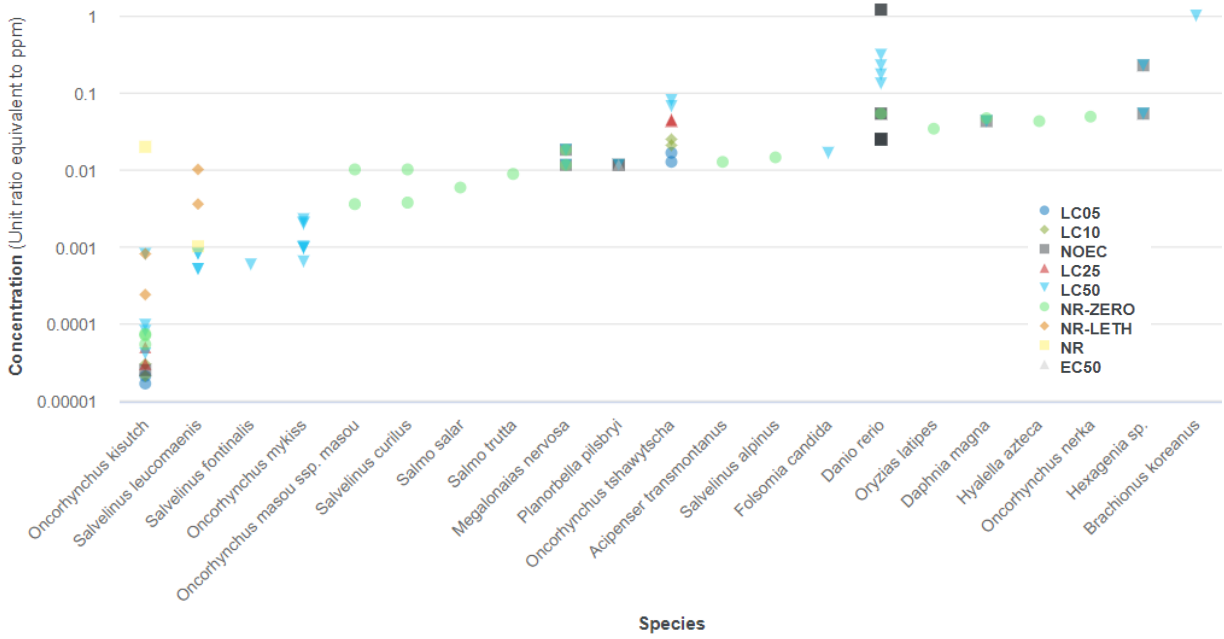
Curated data available on ECOTOX: https://cfpub.epa.gov/ecotox/explore.cfm?cas=2754428185,793248

6PPD-quinone & 6PPD: Mortality data

Mortality by chemical



Mortality 6PPD-quinone, by endpoint



Data available in March 2024 update

6PPD-quinone & 6PPD: Mortality data

Example export of records – Mortality data for Fish

CAS Number	Chemical Name	Chemical Grade	Chemical Analysis	Chemical Purity	Species Scientific Name	Species Common Name	Organism Lifestage	Organism Age	Age Units	Exposure Type	Media Type	Test Location	Number of Doses
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	NR	Salvelinus alpinus	Arctic Char	Juvenile	~3	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>98.0	Danio rerio	Zebra Danio	Embryo	<16	Cell stage	Renewal	Culture	Lab	10
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>98.0	Danio rerio	Zebra Danio	Embryo	<16	Cell stage	Renewal	Culture	Lab	10
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>98.0	Danio rerio	Zebra Danio	Embryo	<16	Cell stage	Renewal	Culture	Lab	10
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>98.0	Danio rerio	Zebra Danio	Embryo	<16	Cell stage	Renewal	Culture	Lab	10

6PPD-quinone & 6PPD

Next Steps:

- Update literature search every 6 months
  - Next search planned for June 2024

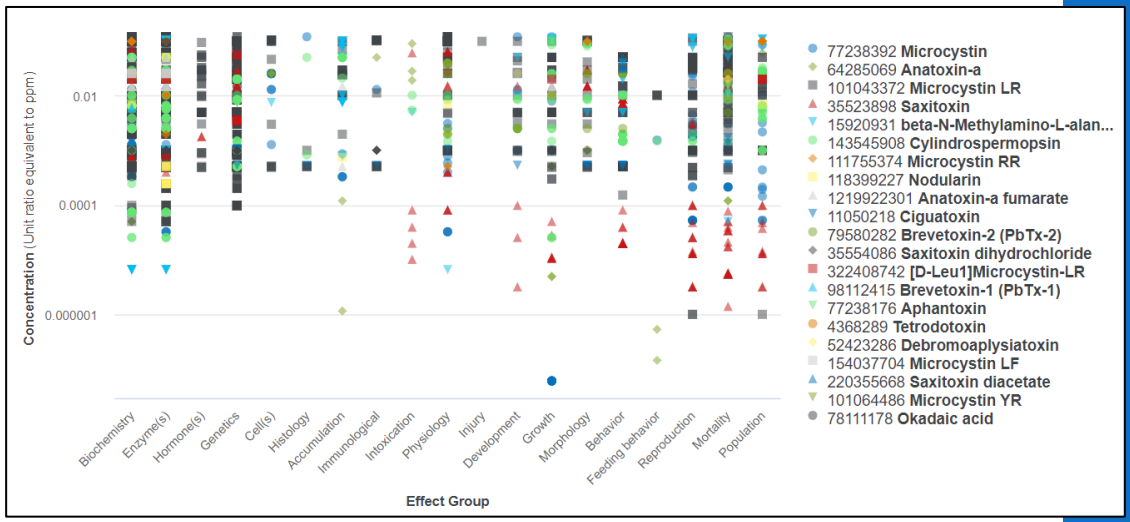
- Add new publications as identified (between lit searches)
  - Continued consultation with EPA programs and regions

- Expand literature search to include related PPDs and alternatives

Applying ECOTOX Data Curation Pipeline to Cyanotoxins

- Identify and curate relevant ecotoxicity studies for cyanotoxins associated with harmful algal blooms (HABs)
- Literature searches for 15 priority cyanotoxins + 98 additional cyanotoxins
- Rapid identification of additional recent publications:
  - Monthly reviews
  - Consultation HABs researchers
- Provide structured effects data for priority cyanotoxins, including study details and toxicity results

Cyanotoxins data: 514 references, 14,954 records



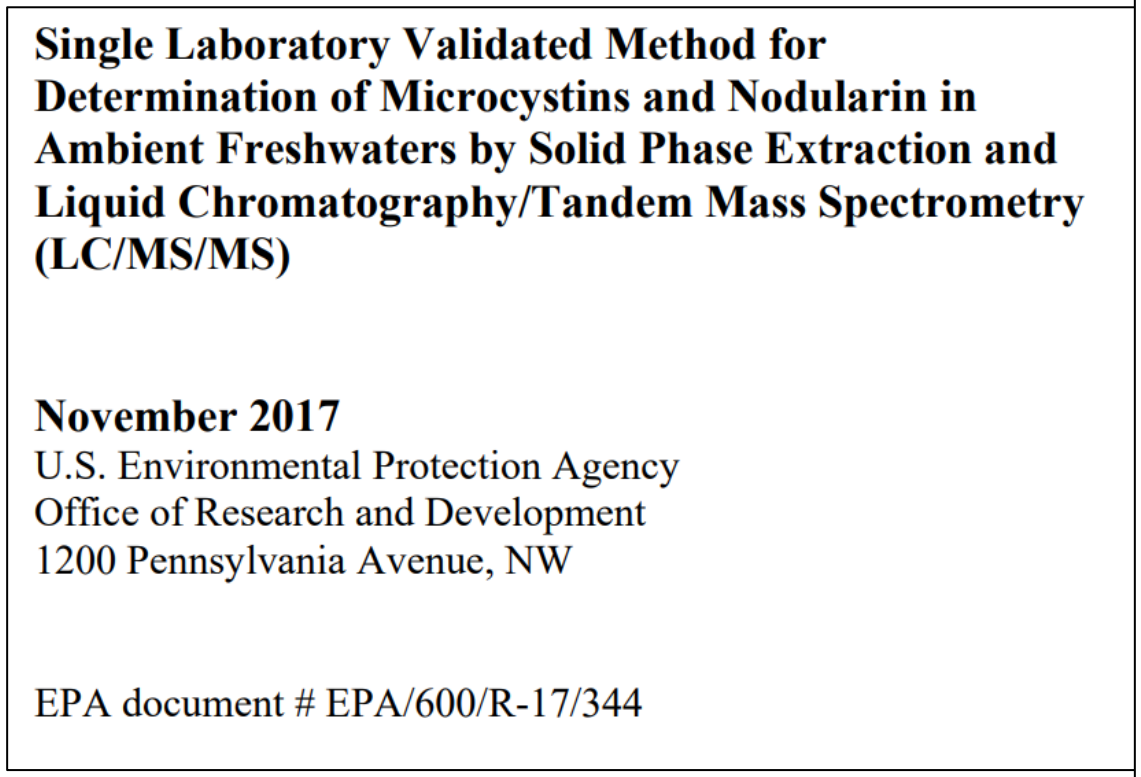
https://cfpub.epa.gov/ecotox/explore.cfm?cgid=40

Priority cyanotoxins

	Priority cyanotoxins	CASRN	Activity
1	Microcystin-LR [a]	101043-37-2	Hepatotoxic
2	Microcystin-RR [a]	111755-37-4	Hepatotoxic
3	Anatoxin-a [a]	64285-06-9	Neurotoxic
4	Guanitoxin [Anatoxin-a(S)] [b]	103170-78-1	Neurotoxic
5	Saxitoxin [a]	35523-89-8	Neurotoxic
6	Prymnesin 1 [a]	168180-17-4	Hemolytic
7	Prymnesin 2 [a]	168010-52-4	Hemolytic
8	Beta-methylamino-L-alanine (BMAA) [a]	15920-93-1	Neurotoxic
9	Cylindrospermopsin [a]	143545-90-8	Hepatotoxic
10	Lyngbyatoxin-a [a]	70497-14-2	Dermatoxic, cytotoxic
11	Oscillatoxin [b]	66671-95-2	Dermatoxic, cytotoxic
12	Aplysiatoxin [b]	52659-57-1	Dermatoxic, cytotoxic
13	Debromoaplysiatoxin [b]	52423-28-6	Dermatoxic, cytotoxic
14	Neo-debromoaplysiatoxin [b]	2334247-91-3	Dermatoxic, cytotoxic
15	19-bromoaplysiatoxin [b]	66648-18-8	Dermatoxic, cytotoxic

[a] March 2021 literature search
[b] November 2022 supplemental literature search.

Sources for list of additional cyanotoxins

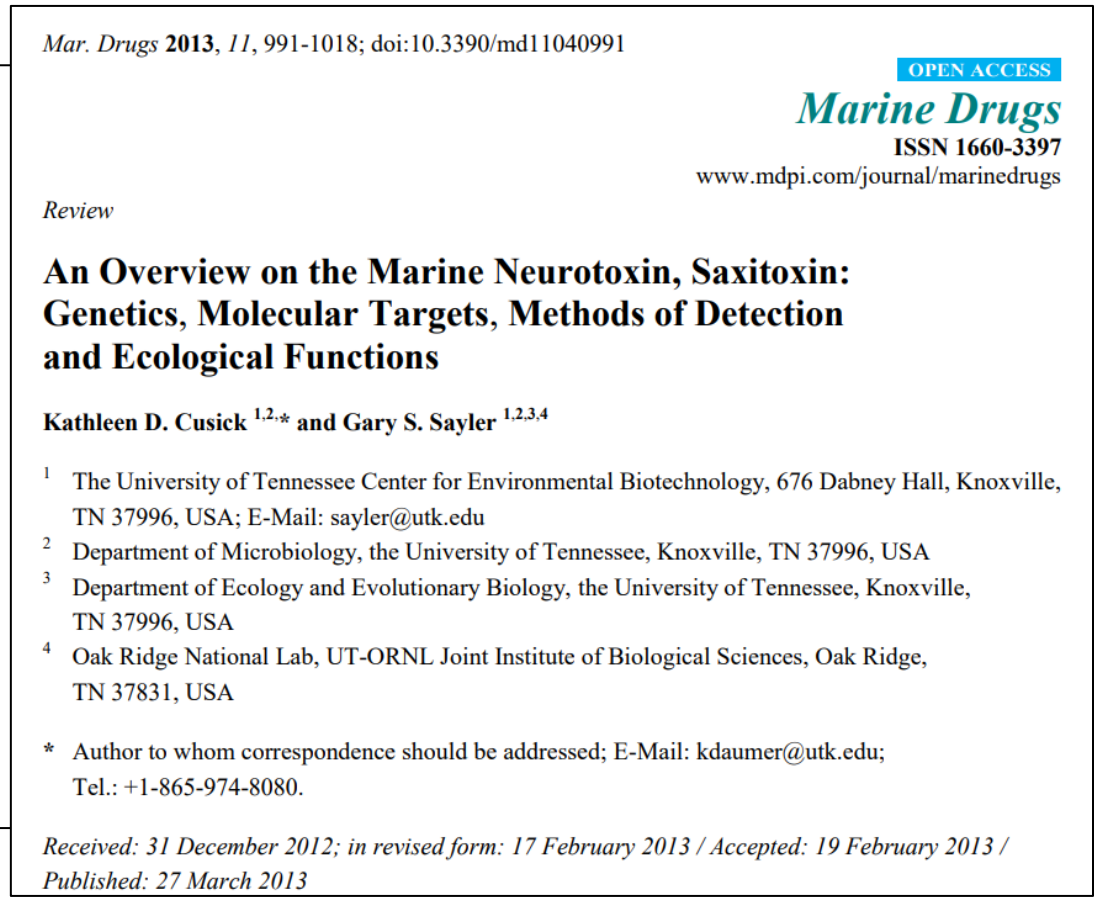


Single Laboratory Validated Method for Determination of Microcystins and Nodularin in Ambient Freshwaters by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)

November 2017
U.S. Environmental Protection Agency
Office of Research and Development
1200 Pennsylvania Avenue, NW

EPA document # EPA/600/R-17/344

EPA Report # EPA/600/R-17/344



Mar. Drugs **2013**, *11*, 991-1018; doi:10.3390/md11040991

OPEN ACCESS
Marine Drugs
ISSN 1660-3397
www.mdpi.com/journal/marinedrugs

Review

An Overview on the Marine Neurotoxin, Saxitoxin: Genetics, Molecular Targets, Methods of Detection and Ecological Functions

Kathleen D. Cusick [1,2,*] and Gary S. Sayler [1,2,3,4]

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2 Department of Microbiology, the University of Tennessee, Knoxville, TN 37996, USA
3 Department of Ecology and Evolutionary Biology, the University of Tennessee, Knoxville, TN 37996, USA
4 Oak Ridge National Lab, UT-ORNL Joint Institute of Biological Sciences, Oak Ridge, TN 37831, USA

* Author to whom correspondence should be addressed; E-Mail: kdaumer@utk.edu; Tel.: +1-865-974-8080.

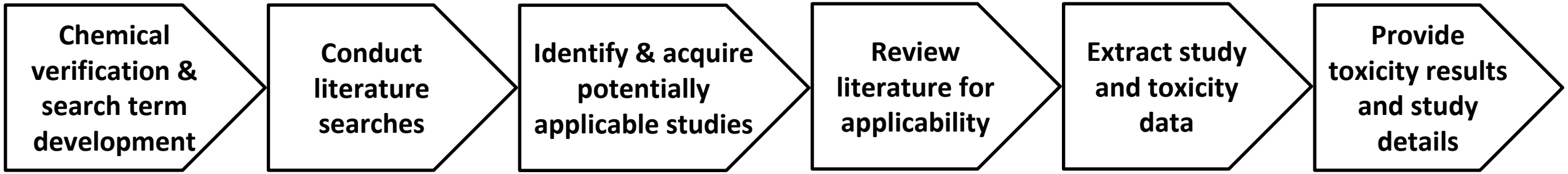
Received: 31 December 2012; in revised form: 17 February 2013 / Accepted: 19 February 2013 / Published: 27 March 2013

Cusick and Sayler 2013 doi: 10.3390/md11040991

98 additional cyanotoxins included in the March 2021 literature search

Cyanotoxins

Problem Statement: Toxicity data of cyanotoxins on aquatic organisms needed for evaluation of toxicity effects, species sensitivity, and determination of mode of action.



Cyanotoxins Search → **Title and Abstract Screening** → **Full Text Screening** → **Data Extraction and Delivery**

Primary Literature Search
9 priority + 98 additional cyanotoxins

N = 7,501 refs → **N = 1,330 refs**

Supplemental Search
6 additional priority cyanotoxins

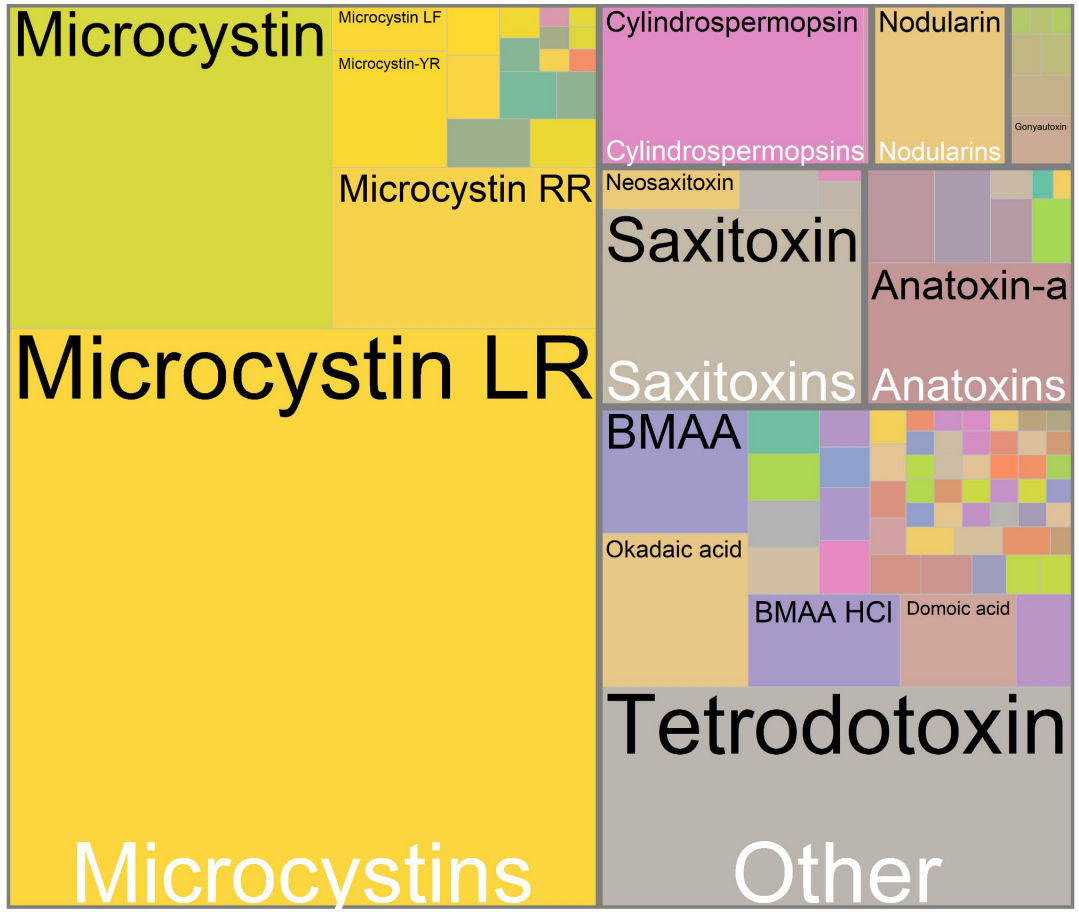
N = 398 refs → **N = 45 refs**

N = 1,108 refs

On-going N=514 to-date

Cyanotoxins: Literature Inventory

1,108 References tagged with 99 cyanotoxins



Box size represents # of references for each chemical

As of May 1, 2024:

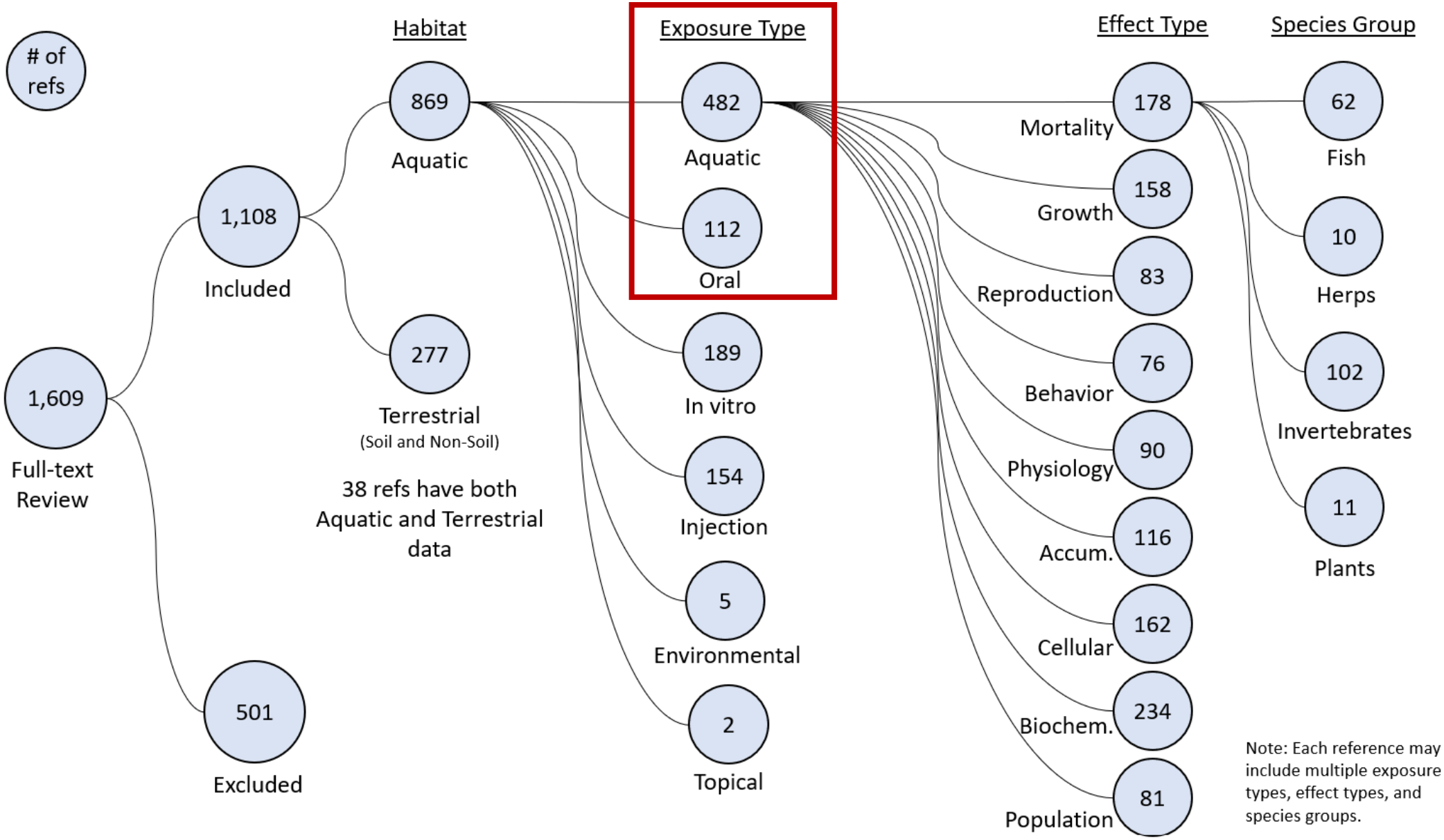
1,108 publications identified
869 Aquatic
277 Terrestrial

Full Data Extraction:

On-going process

514 publications
470 Aquatic
56 Terrestrial

Cyanotoxins: Literature Inventory



Cyanotoxins: Full Data Extraction

Current Priorities:
Exposure route: Aqueous, Oral, Dietary
Aquatic test organisms
Wild birds and mammals
15 priority cyanotoxins

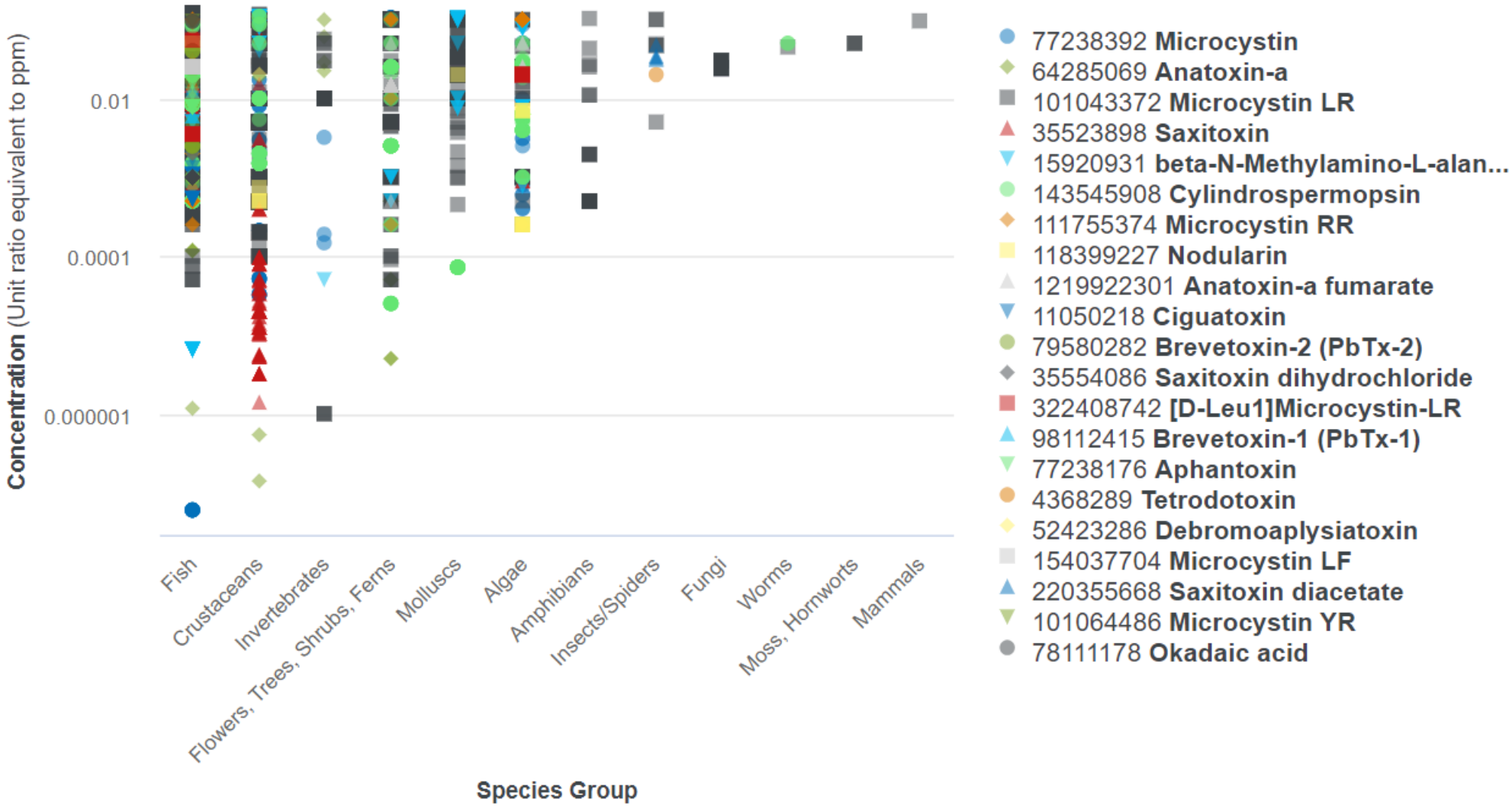
Full Data Extraction:

On-going process

514 publications
470 Aquatic
56 Terrestrial

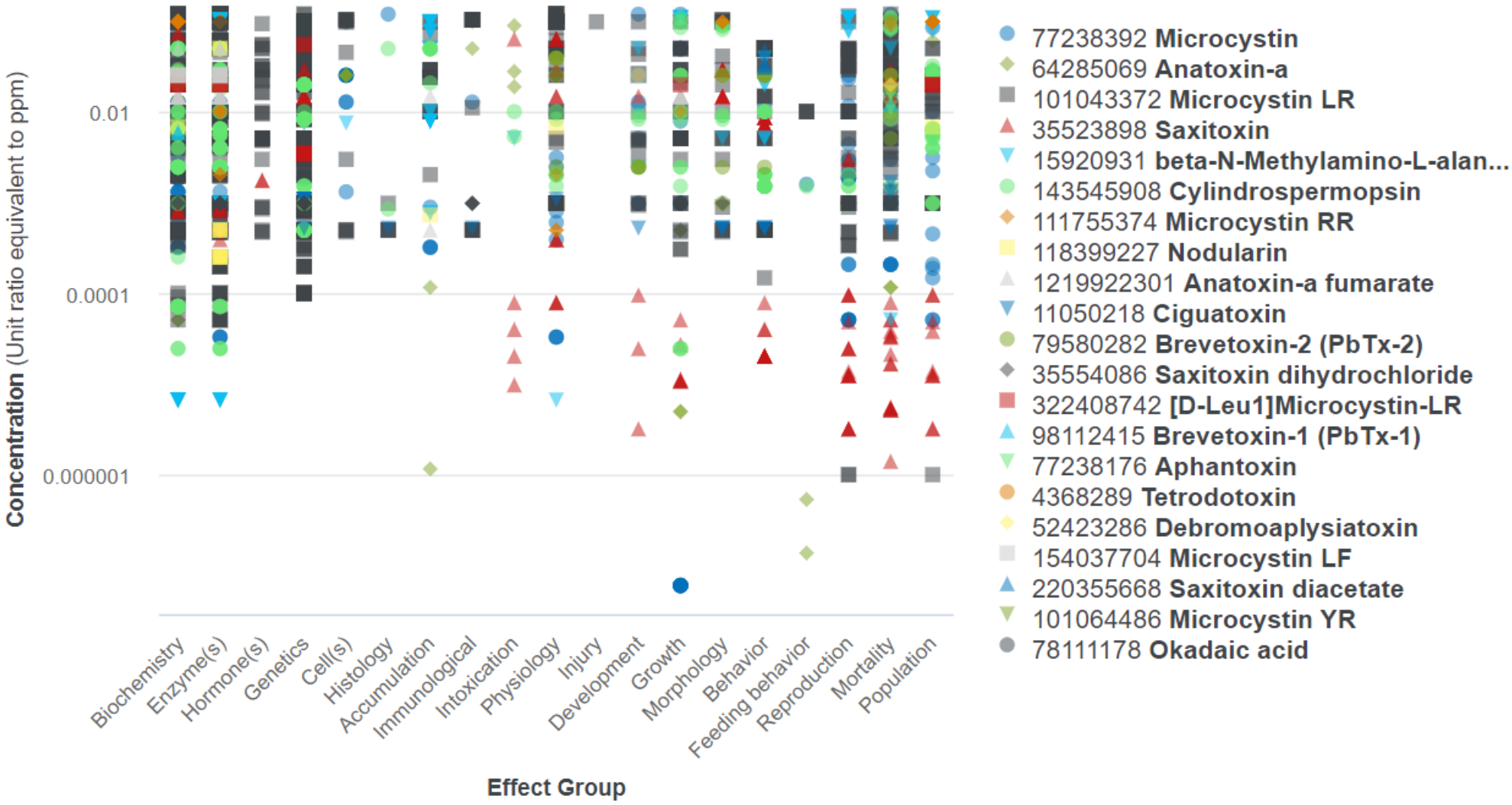
Deprioritized
Exposure: Injection, *In vitro*
Terrestrial plants & invertebrates, rodents & domestic birds (i.e., quail, chicken)
Studies lacking calculated toxicity value / endpoint (i.e., LC50)
Additional MLR studies with zebrafish (n=25) Aquatic invert studies with non-priority cyanotoxins (n=24)

Cyanotoxins: Data on ECOTOX



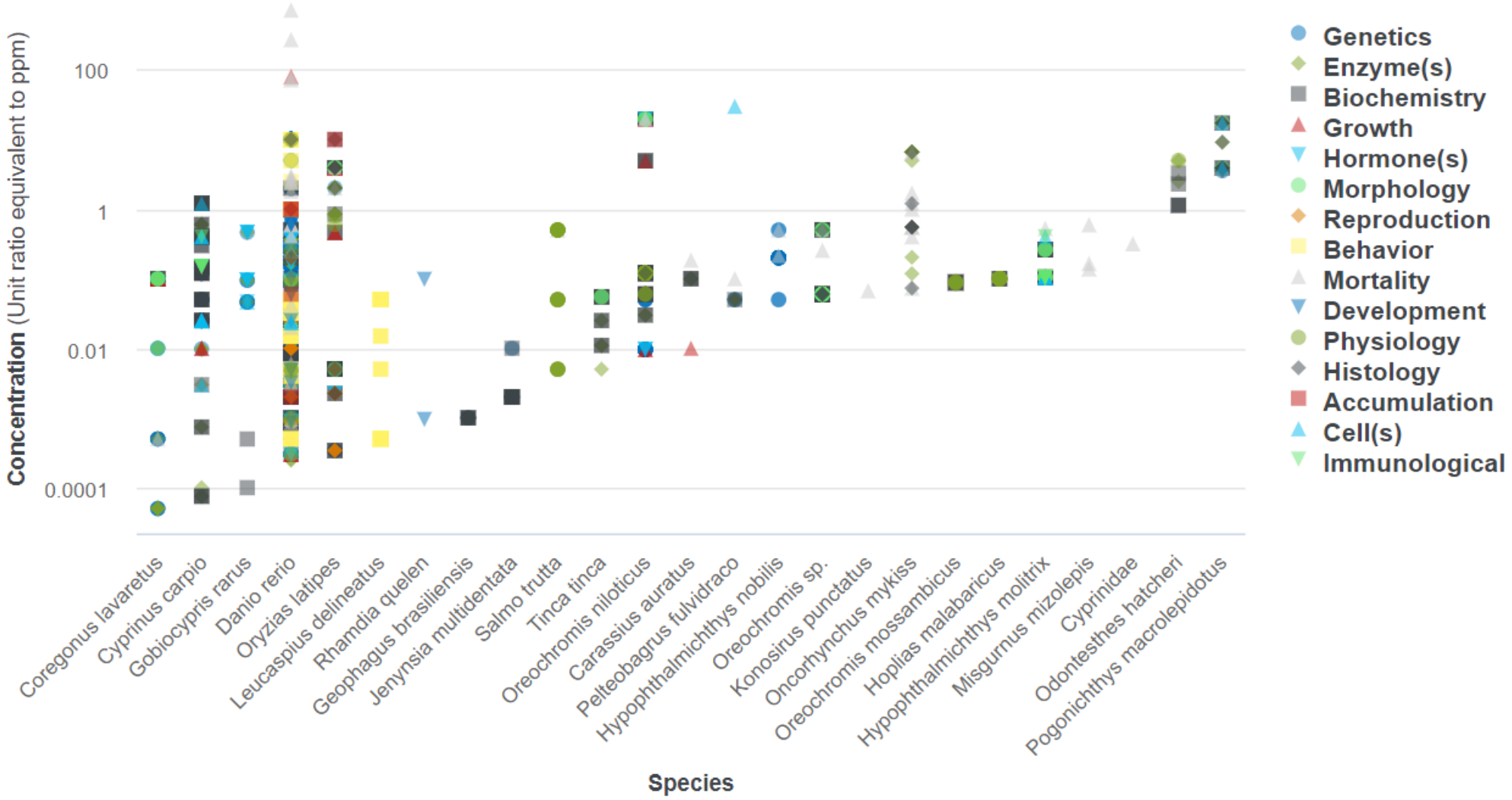
Curated data available on ECOTOX: https://cfpub.epa.gov/ecotox/explore.cfm?cgid=40

Cyanotoxins: Data on ECOTOX



Curated data available on ECOTOX: https://cfpub.epa.gov/ecotox/explore.cfm?cgid=40

Cyanotoxins: Data on ECOTOX – Fish Microcystin LR



Priority cyanotoxins

	Priority cyanotoxins	CASRN	# of refs with data extracted
1	Microcystin-LR	101043-37-2	253[a]
2	Microcystin-RR	111755-37-4	29[a]
3	Anatoxin-a	64285-06-9	26[b]
4	Guanitoxin [Anatoxin-a(S)]	103170-78-1	1
5	Saxitoxin	35523-89-8	20[b]
6	Prymnesin 1	168180-17-4	0
7	Prymnesin 2	168010-52-4	0
8	Beta-methylamino-L-alanine (BMAA)	15920-93-1	15[b]
9	Cylindrospermopsin	143545-90-8	41
10	Lyngbyatoxin-a	70497-14-2	2
11	Oscillatoxin	66671-95-2	0
12	Aplysiatoxin	52659-57-1	0
13	Debromoaplysiatoxin	52423-28-6	2
14	Neo-debromoaplysiatoxin	2334247-91-3	0
15	19-bromoaplysiatoxin	66648-18-8	0

[a] 70 additional publications have toxin identified only as “microcystin” (CASRN 77238-39-2)

[b] Publications for related chemicals extracted but not included in counts

Pending data extraction (as of 5/1/24)

Aquatic

3 PLANT studies (1 MLR, 1 CYL, 1 CYAT)
26 INVERT studies (3 MLR / MRR, 24 CYAT)
28 FISH studies
(25 MLR [zebrafish],
1 MLR & MRR [zebrafish],
2 CYAT [rainbow trout])

Terrestrial

59 PLANT studies
16 INVERT studies
2 RODENT studies (1 MLR, 1 CYAT)
4 Dom. Bird studies (fowl, chicken, quail)

On-going Process

- Prioritization of data extraction
  - Aquatic and Aquatic-dependent wildlife
  - Priority Cyanotoxins

- Providing aquatic results to EPA Programs & HAB researchers

- Development of systematic evidence map & manuscript

Thank you! Questions?

ECOTOX Team

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Great Lakes Toxicology and Ecology Division
US EPA ORD Center for Computational Toxicology and Exposure
Olker.Jennifer@epa.gov

Dale Hoff, GLTED Division Director

Contract staff:

- General Dynamics Information Technology (GDIT)
- SpecPro Professional Services (SPS)

Senior Environmental Employment (SEE) staff

www.epa.gov/ecotox

ECOTOX Support:

218-529-5225

ecotox.support@epa.gov

To cite ECOTOX or read more details: Olker et al. 2022, https://doi.org/10.1002/etc.5324

EPA hosts webinar series dedicated to delivering the latest information and training on our cutting-edge research addressing environmental and public health issues.

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Webinar dates and topics are subject to change.

Tools and Resources Training

June 6: *EnviroAtlas*

Registration and Additional Information Coming Soon!

Healthy and Resilient Communities Research

June 11: *Cumulative Impacts: How Potential Flood Exposures, Resource Access, and Social Vulnerability Affect Resilience Outcomes*

Registration and Additional Information

Computational Toxicology and Exposure Communities of Practice

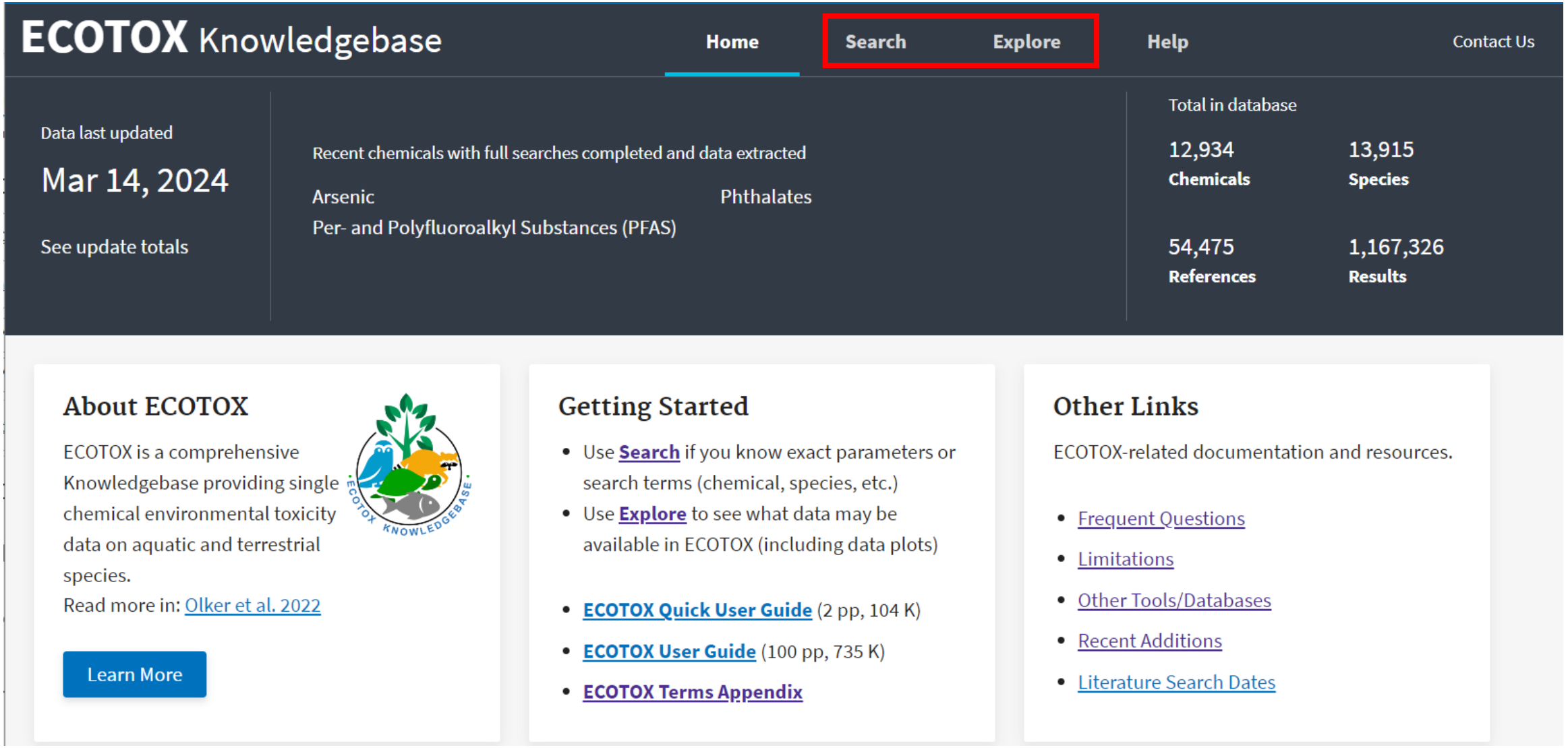
June 27: *Chemical Transformation Simulator*

Registration and Additional Information

Extra slides:

- Basic ECOTOX demo
- Taxonomic distribution of PFAS toxicity data
- 6PPD-quinone example data extraction
- Cyanotoxins literature flow diagram

Demo of ECOTOX: www.epa.gov/ecotox



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ECOTOX Overview: Olker et al. 2022 https://doi.org/10.1002/etc.5324

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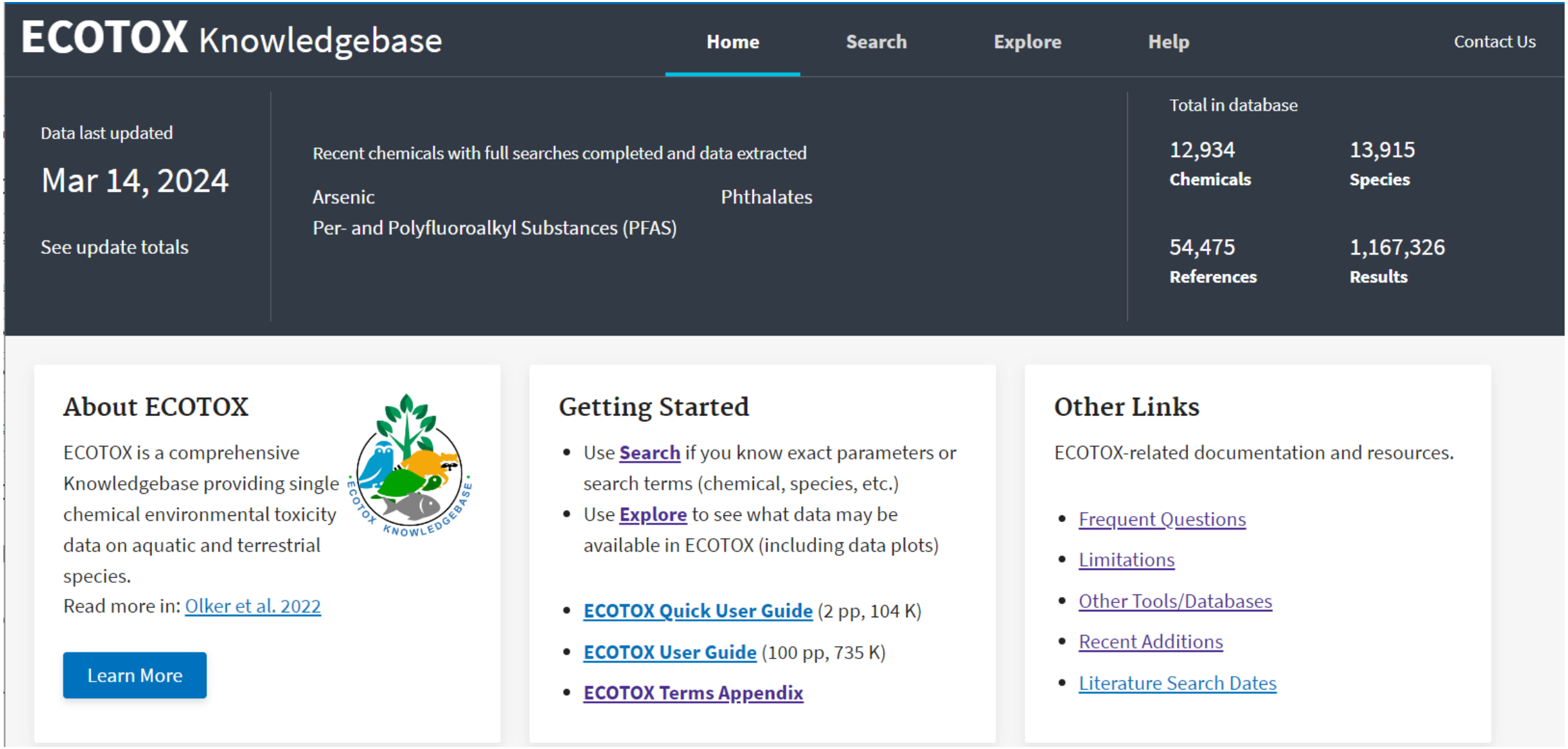
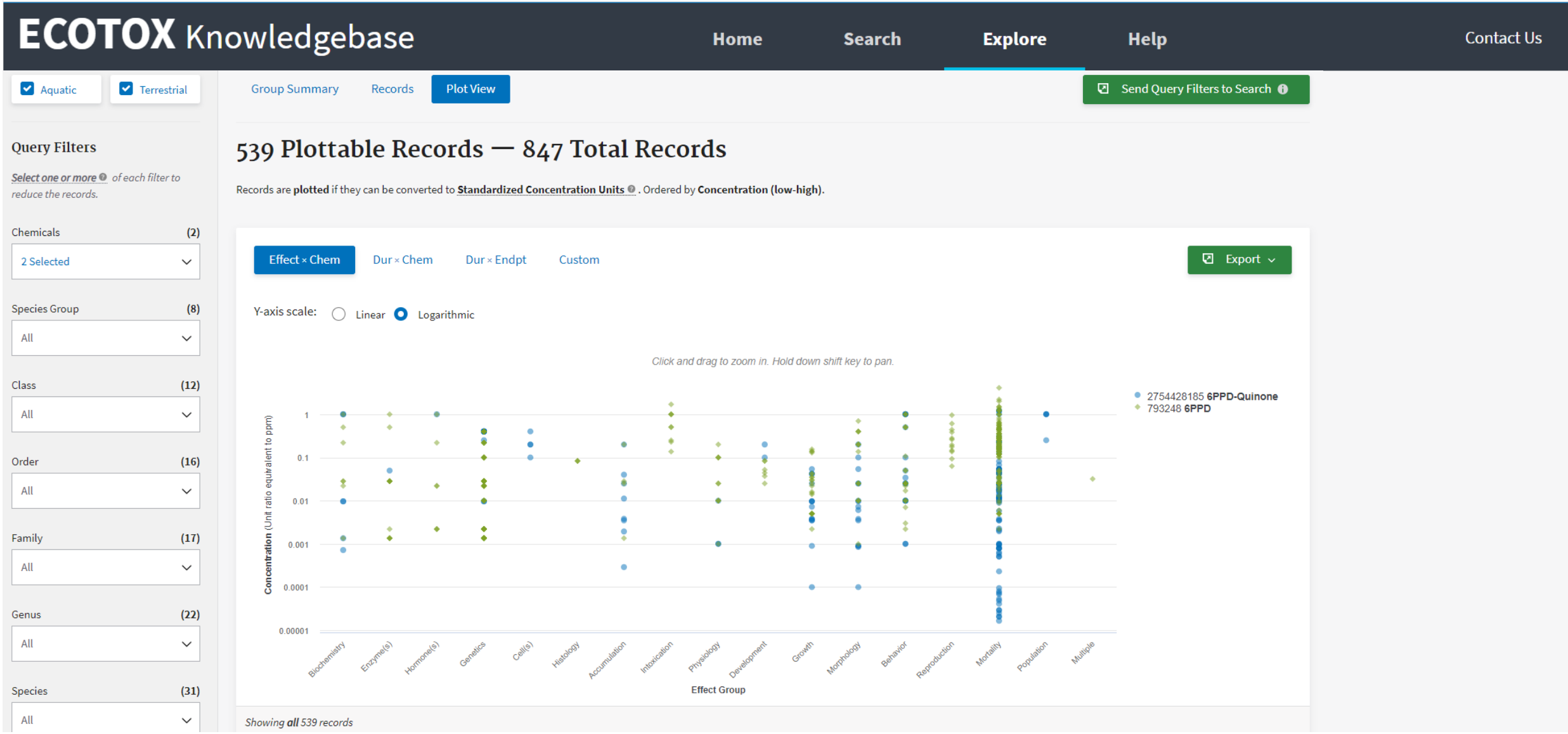


ECOTOXicology Knowledgebase: Explore



ECOTOXicology Knowledgebase: Search

ECOTOX Knowledgebase

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Parameters

Aquatic | Terrestrial

- All Chemicals +
- All Effects +
- All Endpoints +
- All Species +
- All Test Conditions +
- All Publication Options +

Customize Output Fields

CAS Number	Chemical Name	Chemical Grade	Chemical Analysis	Chemical Purity	Species Scientific Name	Species Common Name	Organism Lifestage	Organism Age	Age Units	Exposure Type	Media Type	Test Location	Number of Doses
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
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2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus curilus	Southern Dolly Varden	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	NR	Salvelinus alpinus	Arctic Char	Juvenile	~3	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	2
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Oncorhynchus masou ssp.	Cherry Salmon	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Measured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Renewal	Fresh water	Lab	6
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>95	Salvelinus leucomaenis	Whitespotted Char	Juvenile	<1	Year(s)	Static	Fresh water	Lab	3
2754428185	2-[(1,3-Dimethylbutyl)amino]-5-(phenylamino)2,5-cy		Unmeasured	>98.0	Danio rerio	Zebra Danio	Embryo	<16	Cell stage	Renewal	Culture	Lab	10
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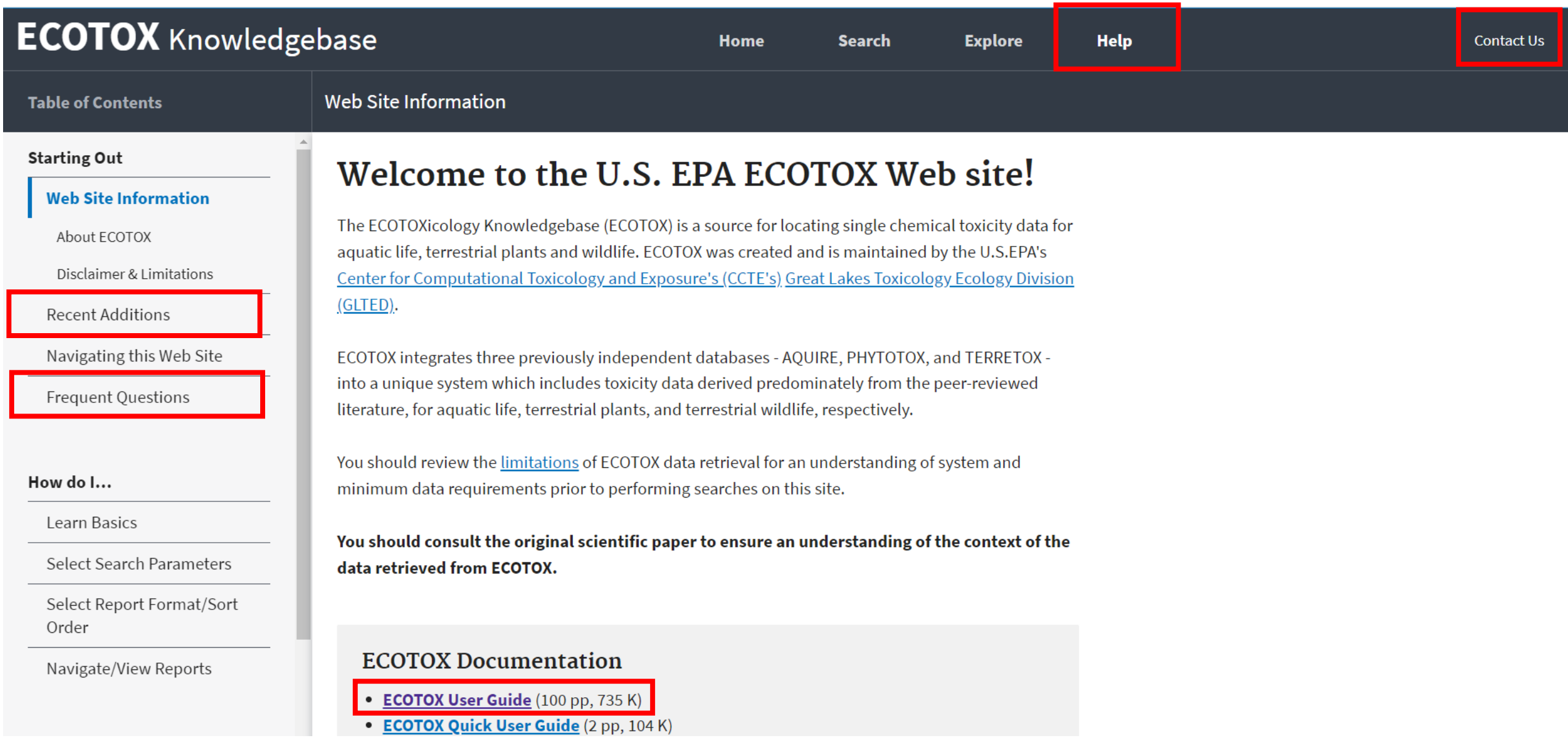
ECOTOXicology Knowledgebase: Help



ECOTOXicology Knowledgebase: Search Planner

ECOTOX Knowledgebase

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- Select Search Parameters
- Select Report Format/Sort Order
- Navigate/View Reports

Search Planner (PDF) (5 pp, 133 K, About PDF)

Taxonomic Searching

Within ECOTOX you may conduct a search by entering the Species Name or number(s), Genus/Species Name(s), or Common Name or Other Taxonomic Name(s). The Contains and Exact Match radio buttons allow for partial or exact name matches. You can also search by Species Group. All data records within ECOTOX include a Scientific name for the test species. All names and predefined groups have been verified in reliable taxonomic sources.

The ECOTOX species file includes historical synonyms for the species. If a search is conducted using a species name that is noted as a taxonomic synonym in our system, ECOTOX will present the results using the currently acceptable genus and species name.

Taxonomic Entry

Species Number: All species in ECOTOX have been assigned a unique number. You can include numbers and text information (either Scientific or common names) in one search. Species numbers are always searched as an exact match.

Example Taxonomic Search

The example below is the correct method of entering query text. You can enter a mix of numbers and species terms. Number will always be treated as exact matches by the ECOTOX query.

Example Genus/Species Name Query

ECOTOX SEARCH PLANNING FORM

Use this form to help plan your searches or to document searches for yourself or others to perform.

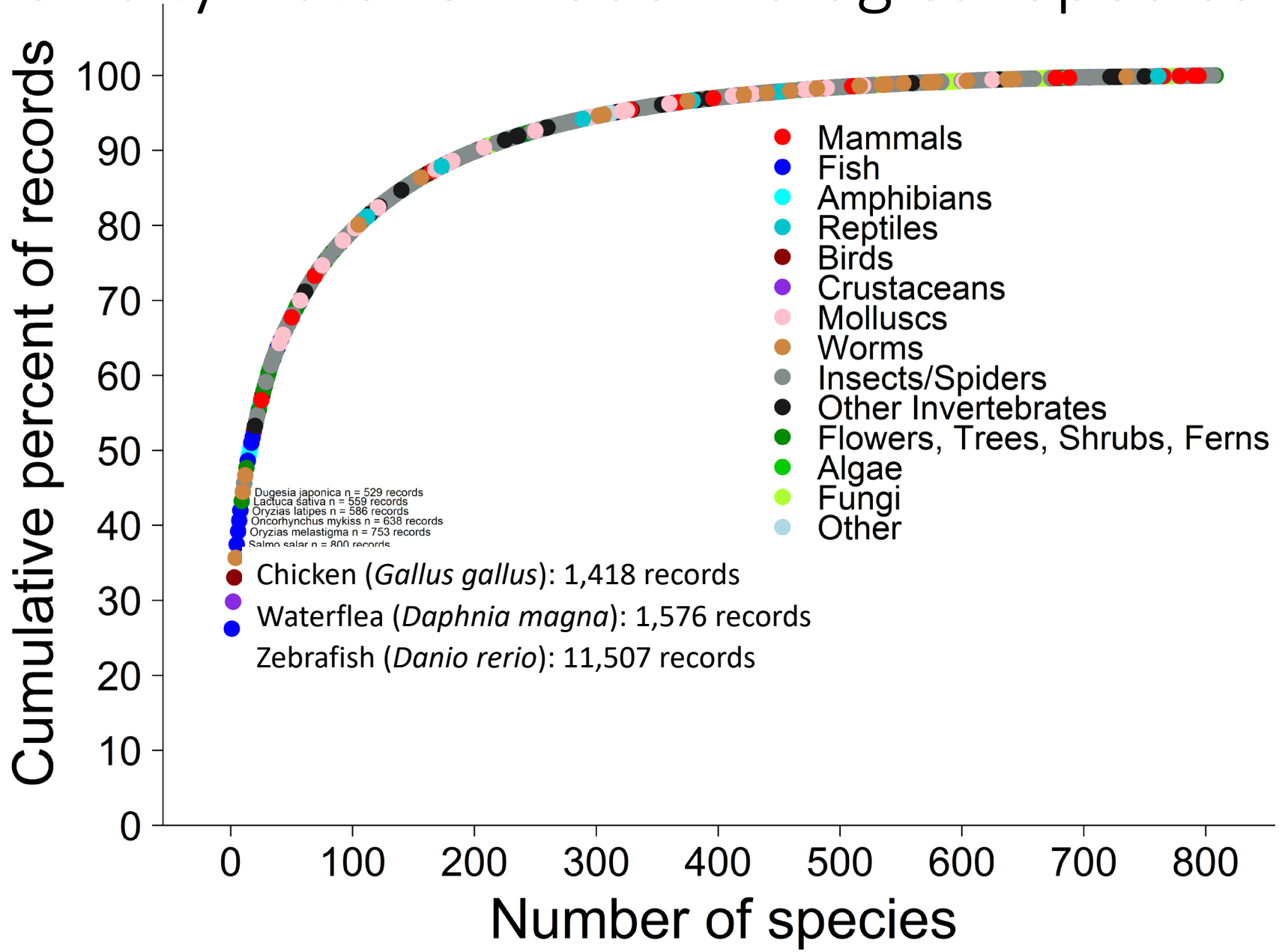
Chemicals

Chemical Names	CAS Numbers	Predefined Groups	
		Metal Compounds	**Organic Compounds**
		Aluminum	Conazoles
		Antimony	Cyanotoxins
		Arsenic	DDT and metabolites
		Barium	Dibenzofurans
		Beryllium	Explosives
		Cadmium	Glycol Ethers
		Chromium	Major Ions
		Cobalt	Neonicotinoids
		Copper	Nitrosamines
		Iron	Perchlorates
		Lead	Phthalate Esters
		Manganese	Polyaromatic Hydrocarbons (PAH)
		Mercury	Polychlorinated Biphenyls (PCB)
		Nickel	Polybrominated Diphenyl Ethers (PBDE)
		Organotin	Pharmaceutical Personal Care (PPCP)
		Selenium	Strobins
		Silver	
		Vanadium	Per- and Polyfluoroalkyl Substances (PFAS)
		Zinc	

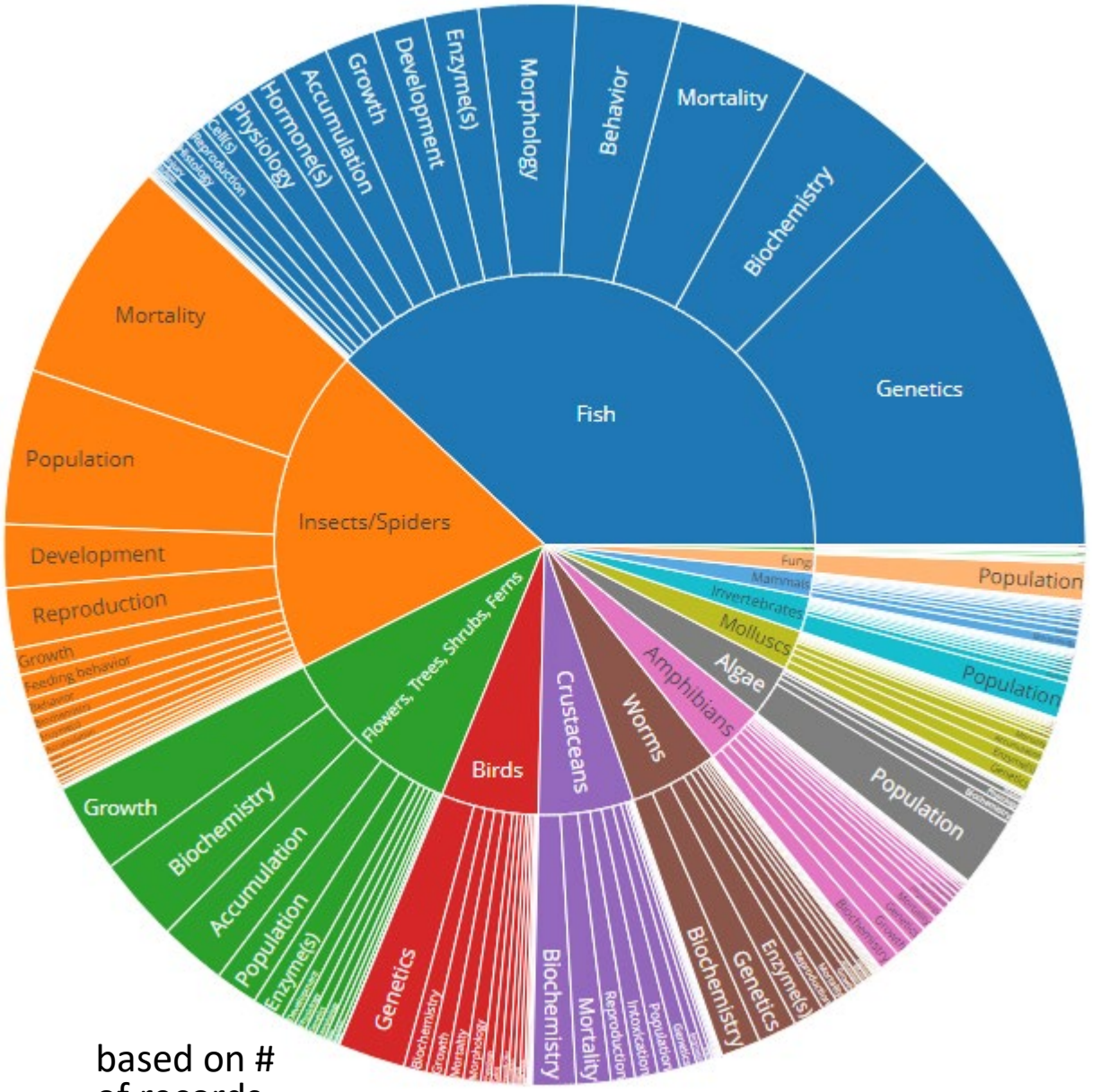
Species

Scientific Names/ Taxonomic Levels	Common Names	Species ECOTOX Numbers or NCBI TaxIDs	Predefined Taxonomic Groups
			All Animals
			Amphibians
			Insects/Spiders
			Molluscs
			Birds
			Other Invertebrates
			Reptiles
			Crustaceans
			Mammals
			Worms
			Fish
			All Plants
			Algae
			Moss/Hornworts, Fungi,
			Flowers, Trees, Shrubs, Ferns
			Special Interest
			Standard Test Species
			US Threatened/Endangered Species
			US Exotic/Nuisance

PFAS Toxicity Data for >800 Biological Species



Taxonomic Distribution of PFAS Toxicity Data



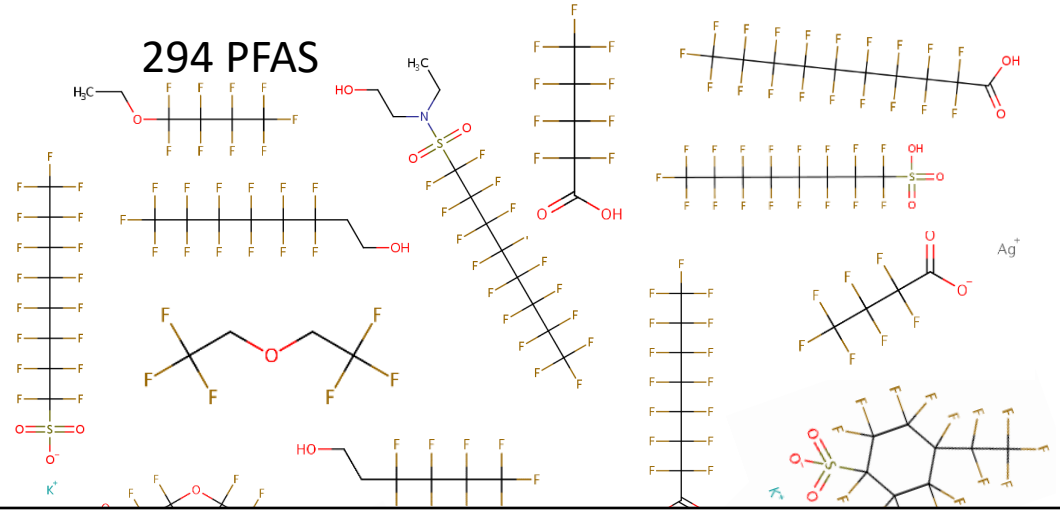
based on # of records

Group	PFAS data in ECOTOX		
	# of Compounds	# of References	# of Records
All Species	294	1,609	43,873
Fish	210	464	16,669
Insects/Spiders	50	584	8,514
Flowers, Trees, Shrubs, Ferns	61	199	4,971
Birds	45	77	2,559
Worms	33	79	2,347
Crustaceans	57	101	2,500
Algae	56	74	1,368
Amphibians	27	53	1,596
Molluscs	58	45	1,038
Other Invertebrates	34	39	918
Mammals	27	33	637
Fungi	11	57	560
Reptiles	3	8	137
Miscellaneous	8	4	29

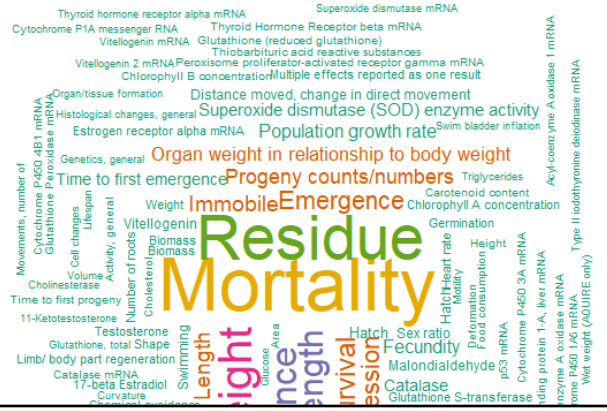
Data Inventory → Summary/Synthesis

808 Biological Species

294 PFAS

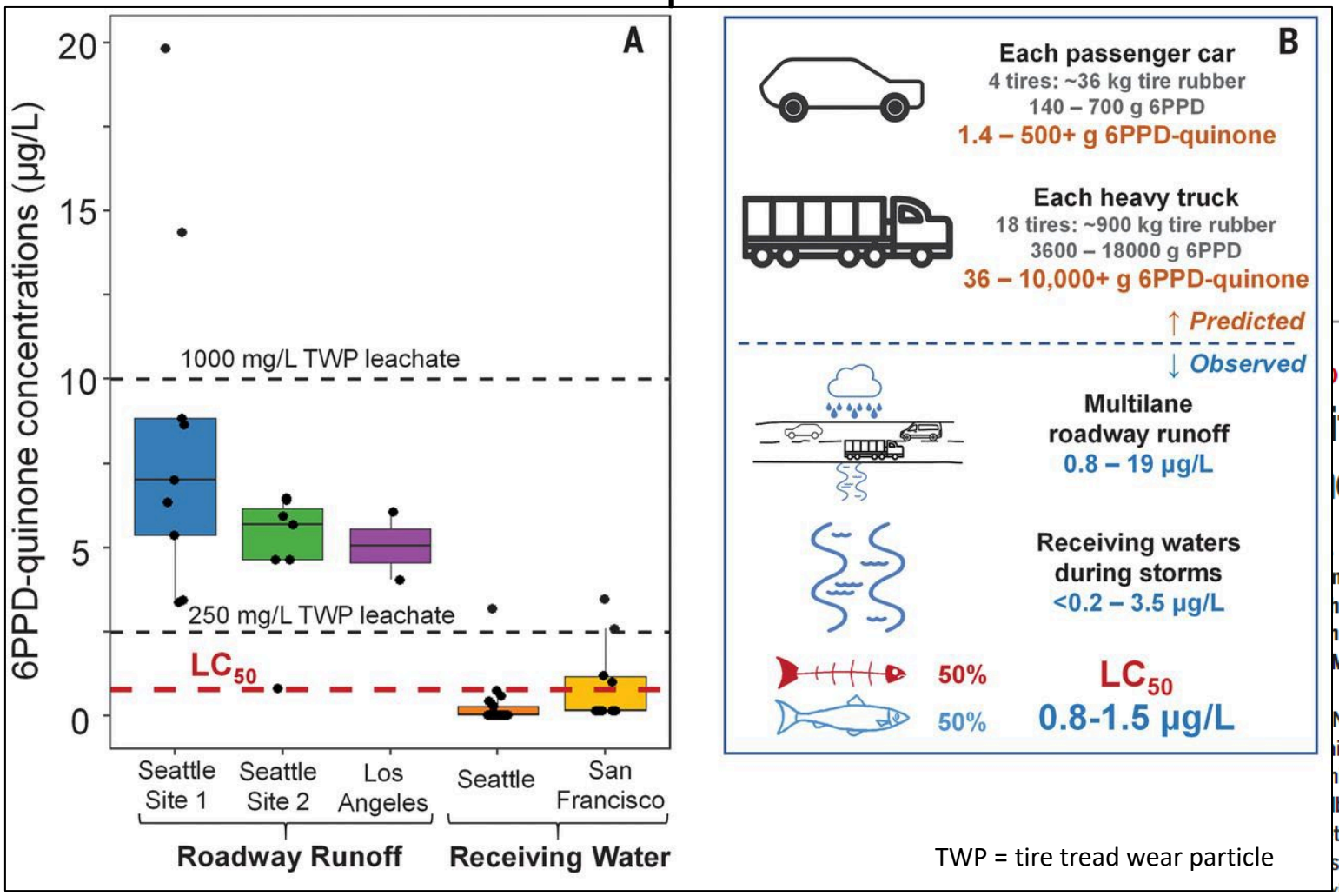


Measurements of 2,486 Effects



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 ↓

6PPD & 6PPD-quinone



TWP = tire tread wear particle

Fig. 4. Environmental relevance of 6PPD-quinone. (**A**) Using retrospective UPLC-HRMS analysis of archived sample extracts, 6PPD-quinone was quantified in roadway runoff and runoff-affected receiving waters. Each symbol corresponds to duplicate or triplicate samples, and boxes indicate first and third quartiles. For comparison, the 0.8 µg/liter LC_{50} value for juvenile coho salmon and detected 6PPD-quinone levels in 250 and 1000 mg/liter TWP leachate are included. (**B**) Predicted ranges of potential 6PPD-quinone mass formation in passenger cars (for example, four tires, ~36 kg tire rubber mass) and heavy trucks (for example, 18 tires, ~900 kg of tire rubber) (represented in orange) and measured 6PPD-quinone concentrations in affected environmental compartments (represented in blue, with experimental data italicized). Predicted ranges reflect calculations applying 0.4 to 2% 6PPD per total vehicle tire rubber mass followed by various yield scenarios (1 to 75% ultimate yields) for 6PPD reaction with ground-level ozone to form 6PPD-quinone.

LOGY

itous tire rubber–derived chemical induces ortality in coho salmon

Haoqi Zhao[3], Katherine T. Peter[1,2], Melissa Gonzalez[1,2], Jill Wetzel[4], Christopher Wu[1,2], mine Prat[4], Emma Mudrock[4], Rachel Hettinger[1,2], Allan E. Cortina[1,2], n Biswas[5], Flávio Vinicius Crizóstomo Kock[5], Ronald Soong[5], Amy Jenne[5], Bowen Du[6], n He[3], Rachel Lundeen[1,2], Alicia Gilbreath[7], Rebecca Sutton[7], Nathaniel L. Scholz[8], Michael C. Dodd[3], Andre Simpson[5], Jenifer K. McIntyre[4], Edward P. Kolodziej[1,2,3]*

Northwest coho salmon (*Oncorhynchus kisutch*), stormwater exposure annually ined acute mortality when adult salmon migrate to urban creeks to reproduce. By is phenomenon, we identified a highly toxic quinone transformation product of lbutyl)-*N*′-phenyl-p-phenylenediamine (6PPD), a globally ubiquitous tire rubber trospective analysis of representative roadway runoff and stormwater-affected creeks st Coast indicated widespread occurrence of 6PPD-quinone (<0.3 to 19 micrograms ic concentrations (median lethal concentration of 0.8 ± 0.16 micrograms per liter). anticipated risks of 6PPD antioxidants to an aquatic species and imply for dissipated tire rubber residues.

ence.org/doi/epdf/10.1126/science.abd6951

6PPD & 6PPD-quinone

Tian,Z., H. Zhao, K.T. Peter, M. Gonzalez, J. Wetzel, C. Wu, X. Hu, J. Prat, E. Mudrock, R. Hettinger, A.E. Cortina, R.. A Ubiquitous Tire Rubber-Derived Chemical Induces Acute Mortality in Coho Salmon. Science 371(6525): 185-189, 2021. ECOREF #189223

RESEARCH

ECOTOXICOLOGY

A ubiquitous tire rubber–derived chemical induces acute mortality in coho salmon

Zhenyu Tian[1,2], Haoqi Zhao[3], Katherine T. Peter[1,2], Melissa Gonzalez[1,2], Jill Wetzel[4], Christopher Wu[1,2], Ximin Hu[3], Jasmine Prat[4], Emma Mudrock[4], Rachel Hettinger[1,2], Allan E. Cortina[1,2], Rajshree Ghosh Biswas[5], Flávio Vinicius Crizóstomo Kock[5], Ronald Soong[5], Amy Jenne[5], Bowen Du[6], Fan Hou[3], Huan He[3], Rachel Lundeen[1,2], Alicia Gilbreath[7], Rebecca Sutton[7], Nathaniel L. Scholz[8], Jay W. Davis[9], Michael C. Dodd[3], Andre Simpson[5], Jenifer K. McIntyre[4], Edward P. Kolodziej[1,2,3]*

In U.S. Pacific Northwest coho salmon (*Oncorhynchus kisutch*), stormwater exposure annually causes unexplained acute mortality when adult salmon migrate to urban creeks to reproduce. By investigating this phenomenon, we identified a highly toxic quinone transformation product of

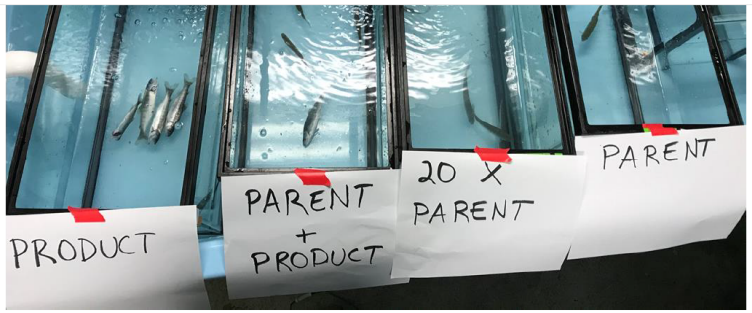
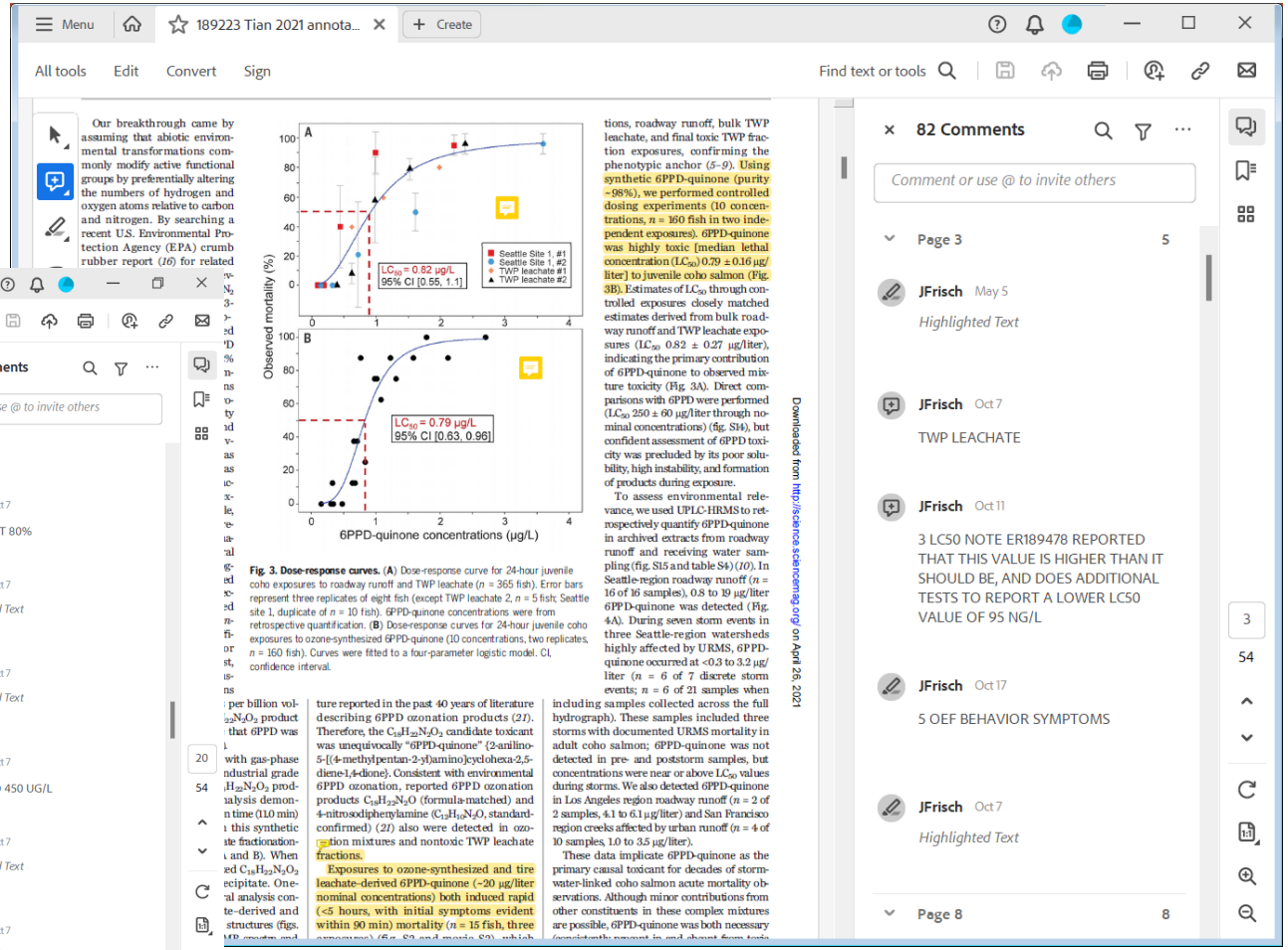


Fig. S2.

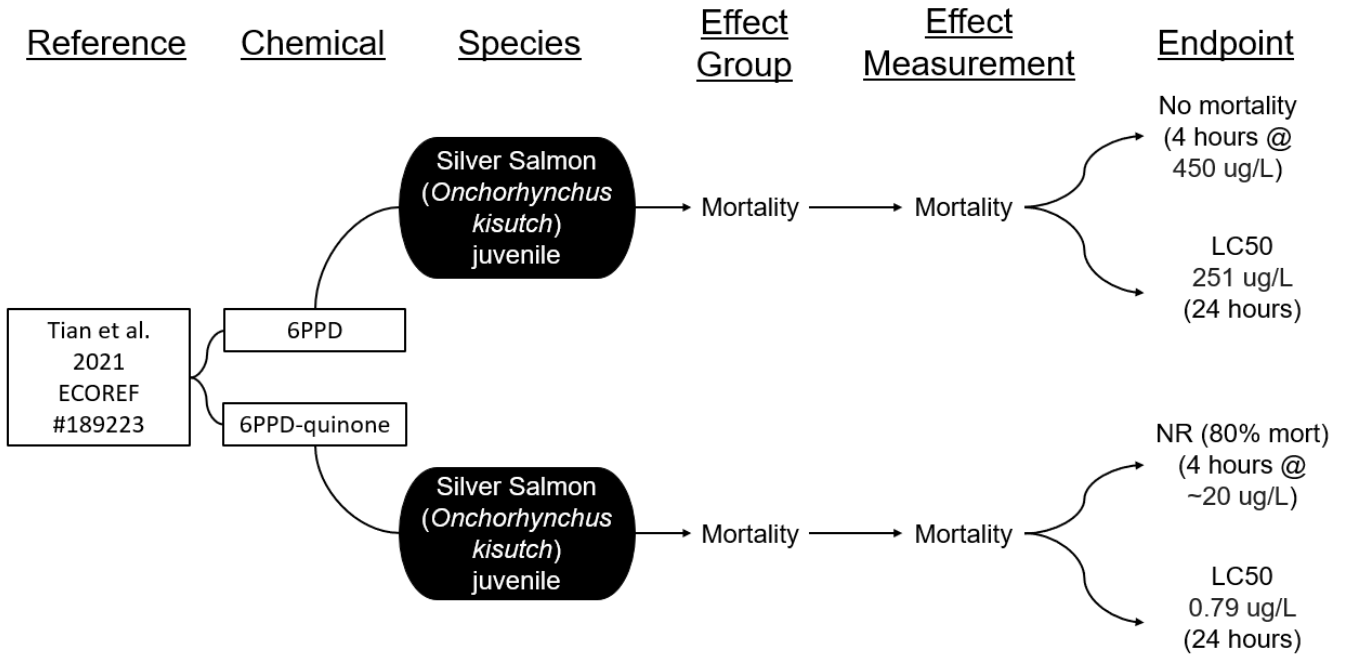
URMS-affected coho photos in the field and the lab. (**A**) Field-observed adult female coho that died from URMS in Miller Creek, Burien, WA, USA on Oct 23, 2019. The intact egg sack at right confirmed its status as a pre-spawn female. See **Movie S1** for details. (**B**) Observed juvenile coho salmon mortality (experiment in progress) upon exposure to 250 mg/L TWP leachate. TWP leachate was acutely (~2-6 h) lethal to juvenile coho (250 mg/L positive controls, 98.5% mortality in 24 h exposure, N=135 fish from 27 exposures over 2+ years). (**C**) Juvenile coho salmon (experiment in progress) that were exposed to purified ozone-synthesized 6PPD-quinone (nominal concentrations ~20 µg/L "product"), unpurified 6PPD ozonation mixture (~20 µg/L "parent + product"), and 6PPD at 450 µg/L ("20X parent") and 6PPD at 30 µg/L ("parent"). At the time photo was taken (~4 h exposure), purified 6PPD-quinone had killed 4/5 coho, with a remaining symptomatic fish (See **Movie S2** for details.), the unpurified mixture killed 2/5 coho (with another one symptomatic), and both 6PPD concentrations had not induced any observed symptoms or mortality in juvenile coho.



6PPD & 6PPD-quinone

Problem Statement: Toxicity data of 6PPD-quinone on aquatic organisms needed for evaluation of toxicity effects, species sensitivity, and determination of mode of action.

Chemical verification & search term development → **Conduct literature searches** → **Identify & acquire potentially applicable studies** → **Review literature for applicability** → **Extract study and toxicity data** → **Provide toxicity results and study details**



RESEARCH

ECOTOXICOLOGY

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Data Extraction and Delivery

Cyanotoxins: Literature search and study selection flow diagram