

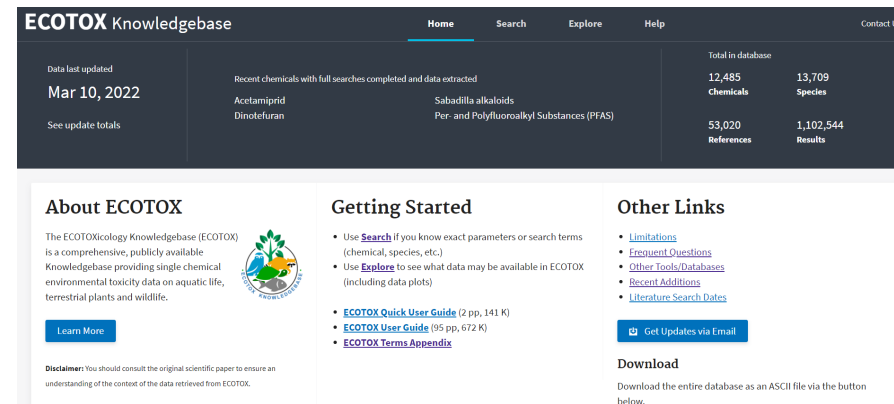
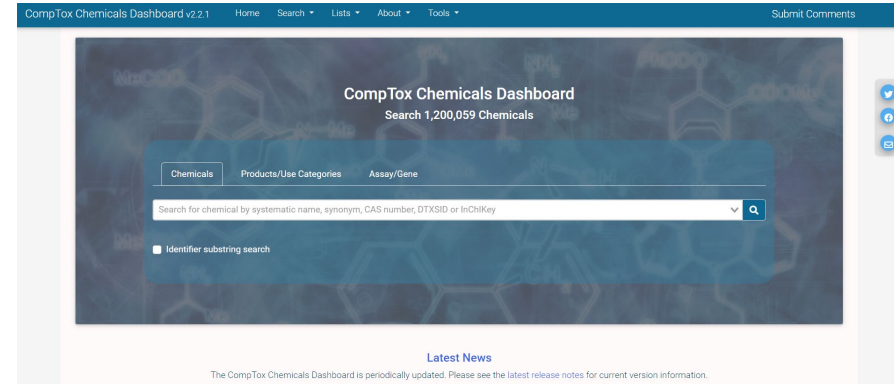
EPA Tools & Resources Training Webinar: Computational Toxicology and Exposure Online Tools

Nisha Sipes, Jennifer Olker and Carlie LaLone
US EPA Office of Research and Development

October 12, 2023

Agenda

- Welcome
- Intro to Computational Toxicology
- CompTox Chemicals Dashboard
- EcoTox
- SeqAPASS



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](#) (95 pp, 672 K)
- [ECOTOX Terms Appendix](#)

Other Links

- [Limitations](#)
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[Get Updates via Email](#)

Download

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

Computational Toxicology

Developing, gathering, integrating, and evaluating data and information using mathematical and computer-based approaches to better understand chemical hazards and risks to human health and the environment

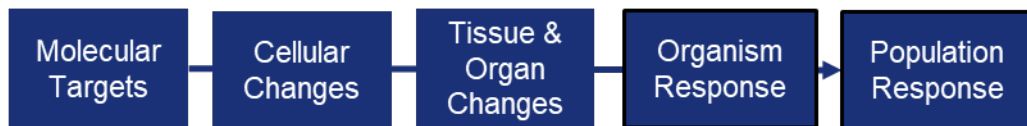
- Hazard + exposure
- New Approach Methodologies (NAMs)



New Approach Methodologies (NAMs)

- **Adverse outcome pathways (AOPs)**

Pathway identification and knowledge integration



Molecular initiating event (MIE)

Key Events (KE)

- ***In vitro* assays**

- Broad / screening (transcriptomics, cell painting)
- Targeted (receptors, enzymes)
- *In vitro* PODs, modes/mechanisms of action

- ***In vitro* toxicokinetics**

Allow conversion of an *in vitro* Point of Departure (POD) to *in vivo* (IVIVE)



Image: <https://ncats.nih.gov/news/releases/2018/tox21-strategic-plan>



- **Databases of existing toxicology data**

Enables training and evaluation of NAM models



Image: <https://comptox.epa.gov/dashboard>

- ***In silico* (e.g., QSAR and read-across)**

Estimate effects and doses

- **Computer models**

Integrate multiple *in silico* and *in vitro* data streams

CompTox Chemicals Dashboard (CCD)

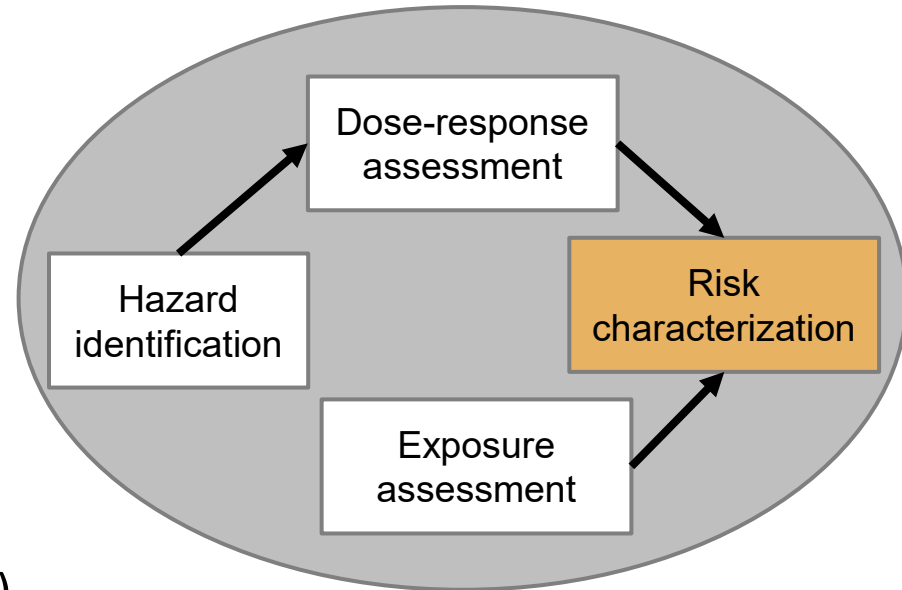
CompTox Chemicals Dashboard

- **Centralized location** for publicly available chemical toxicity data
 - Chemistry, exposure, hazard, bioactivity and dosimetry
 - Combination of existing data and predictive models
 - Periodically updated and curated
- Publicly accessible
- Support EPA and partner decision making
- Easy access to data improves efficiency and ultimately accelerates chemical risk assessment

<https://comptox.epa.gov/dashboard/>

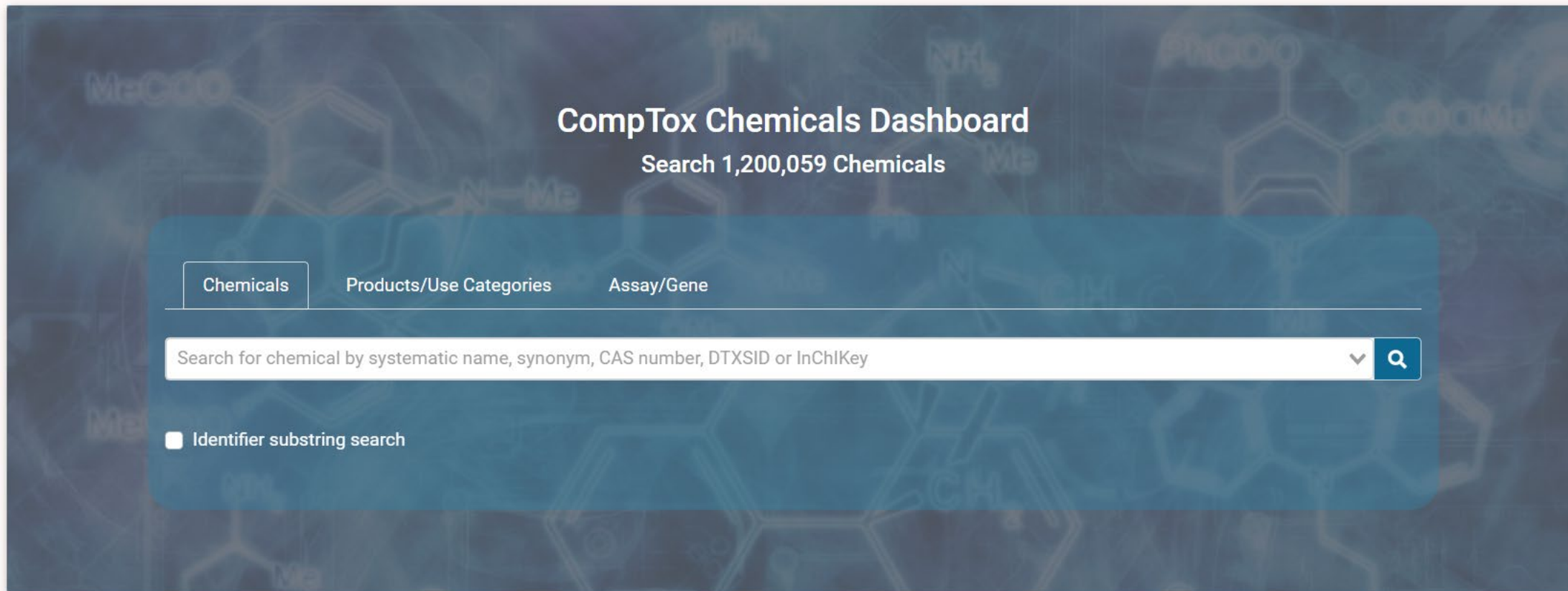
Dashboard Data Contents

- Chemical characterization
- Hazard/Bioactivity: safety classifications, human health & ecological data, *in vivo* animal data, biological targets (effect), dose-response characterization (dose)
- Toxicokinetics
- Exposure: exposure levels



+ online web applications:

- webTEST (hazard and physchem QSAR predictions)
- GenRA (read-across)
- Abstract Sifter (literature search)



The image shows the main search interface of the CompTox Chemicals Dashboard. It features a dark blue background with faint chemical structures. At the top center, the text reads "CompTox Chemicals Dashboard" and "Search 1,200,059 Chemicals". Below this is a search bar with a dropdown menu and a search icon. The search bar contains the text "Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey". To the left of the search bar are three tabs: "Chemicals", "Products/Use Categories", and "Assay/Gene". Below the search bar is a checkbox labeled "Identifier substring search". On the right side of the dashboard, there are three social media icons: Twitter, Facebook, and Email.

Latest News

The CompTox Chemicals Dashboard is periodically updated. Please see the [latest release notes](#) for current version information.

CCD Help Page

<https://www.epa.gov/comptox-tools/comptox-chemicals-dashboard-help>

CompTox Chemicals Dashboard v2.2.1

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Chemicals

Products/Use Categories

Assay/Gene

Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey



Identifier substring search

Latest News

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Submit Comments

CompTox Chemicals Dashboard v2.2.1

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Chemicals

Products/Use Categories

Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey

Identifier substring search

Latest News

The CompTox Chemicals Dashboard is periodically updated. Please see the [latest release notes](#) for current version information.

Please report issues, comments and questions using “Submit Comments”

Live CompTox Chemicals Dashboard Demonstration

ECOTOX

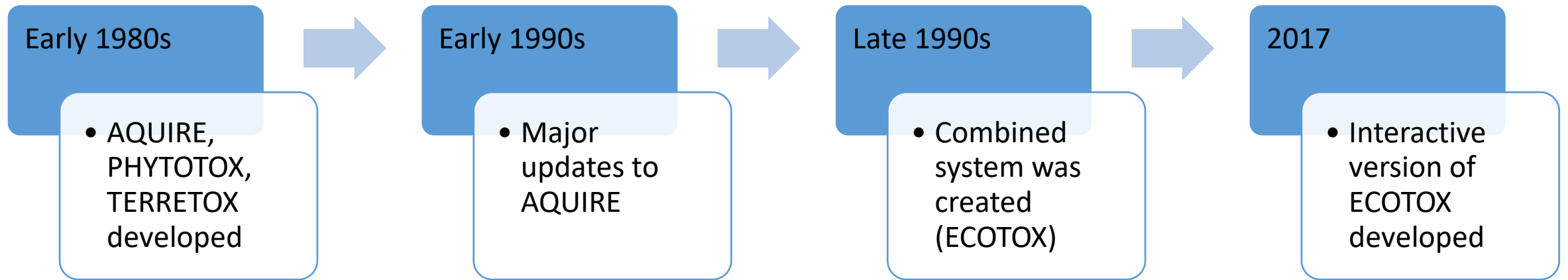
History of ECOTOX

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

- *Ambient Water Quality Criteria for Aquatic Life (USEPA Office of Water)*
- *Ecological Risk Assessment for chemical registration and re-registration (USEPA Office of Pesticide Programs)*
- *Ecological hazard data for the Prioritization and Assessment of Chemicals for Toxic Substances Control Act/Lautenberg Act (USEPA Office of Pollution Prevention and Toxics)*
- *Ecological Site Assessments and in Emergency Response (USEPA Office of Land and Emergency Management - Superfund and Resource Conservation and Recovery Act; Regions and States)*

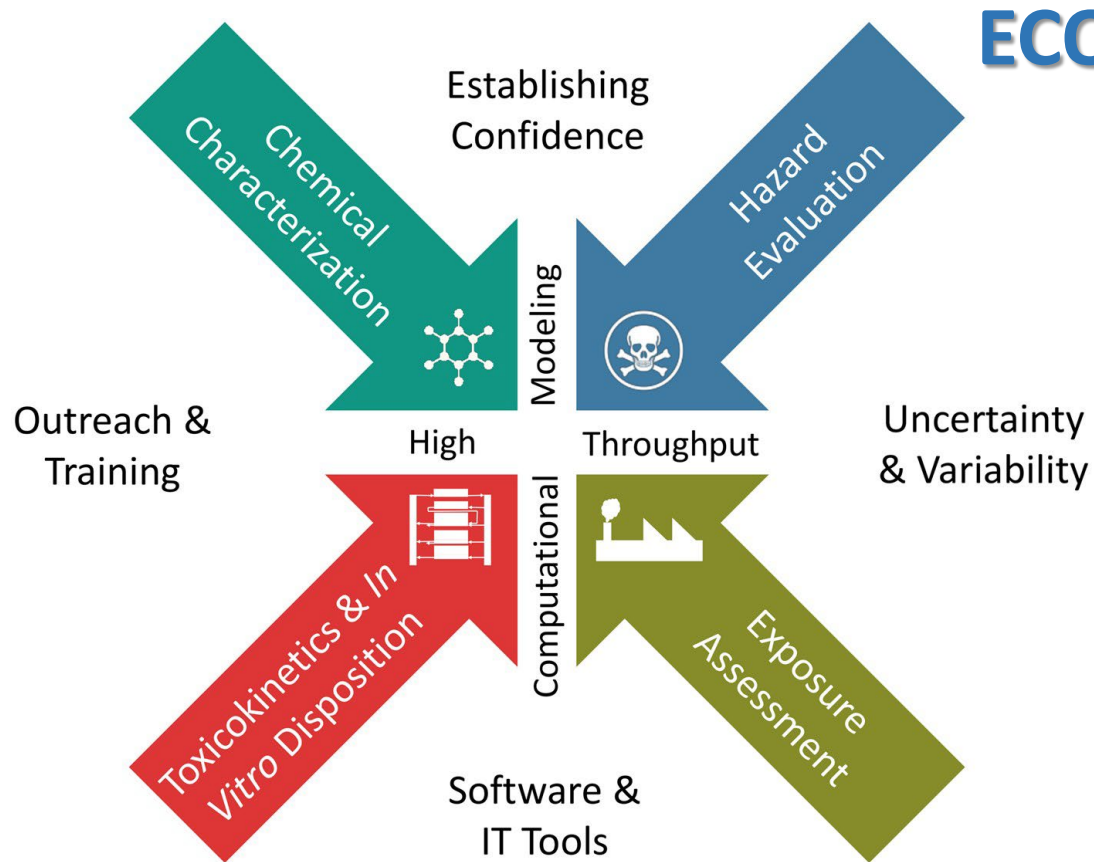
History of ECOTOX

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



- Authoritative source of toxicological data
- Document literature searches of data
- Development and validation

ECOTOX and the next generation of chemical safety evaluation



- ECOTOX** Accessible, structured empirical data from *in vivo* toxicity tests
- Chemical risk assessments
 - Identify data gaps and guide targeted testing
 - Development of computational models
 - Support development, evaluation, and adoption of new approach methodologies



What is the ECOTOX Knowledgebase?

- From comprehensive search and review of open and grey literature
- Updated quarterly to public website
- 30+ year history
- 8,000 distinct hosts search the Knowledgebase each month

ECOTOX Knowledgebase [Home](#) [Search](#) [Explore](#) [Help](#) [Contact Us](#)

Data last updated Sep 14, 2023 See update totals	Recent chemicals with full searches completed and data extracted Chlorinated Solvents Cyanide Cyanotoxins	Ethylene Dibromide HHCB Per- and Polyfluoroalkyl Substances (PFAS)	Total in database 12,837 Chemicals	13,895 Species
			54,228 References	1,154,843 Results

About ECOTOX

ECOTOX is a comprehensive Knowledgebase providing single chemical environmental toxicity data on aquatic and terrestrial species.

Read more in: [Olker et al. 2022](#)

[Learn More](#)

Getting Started

- Use [Search](#) if you know exact parameters or search terms (chemical, species, etc.)
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- [ECOTOX Quick User Guide](#) (2 pp, 104 K)
- [ECOTOX User Guide](#) (100 pp, 735 K)
- [ECOTOX Terms Appendix](#)

Other Links

ECOTOX-related documentation and resources.

- [Frequent Questions](#)
- [Limitations](#)
- [Other Tools/Databases](#)
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- [Literature Search Dates](#)

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

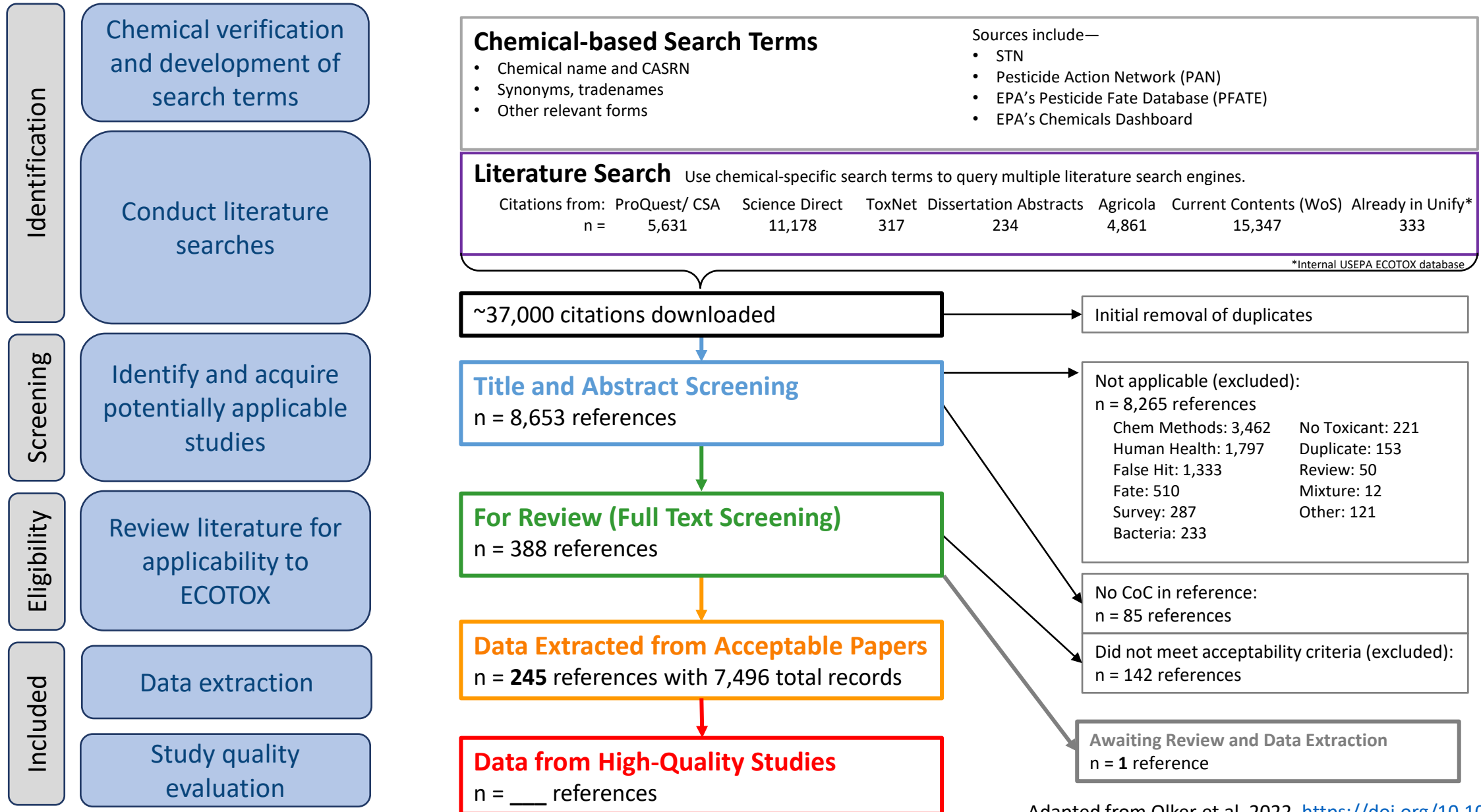
Tools and Applications

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



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[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

Help and Contact Us

ECOTOX Knowledgebase

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Web Site Information

Welcome to the U.S. EPA ECOTOX Web site!

The ECOTOXicology knowledgebase (ECOTOX) is a source for locating single chemical toxicity data for aquatic life, terrestrial plants and wildlife. ECOTOX was created and is maintained by the U.S.EPA's [Center for Computational Toxicology and Exposure's \(CCTE's\) Great Lakes Toxicology Ecology Division \(GLTED\)](#).

ECOTOX integrates three previously independent databases - AQUIRE, PHYTOTOX, and TERRETOX - into a unique system which includes toxicity data derived predominately from the peer-reviewed literature, for aquatic life, terrestrial plants, and terrestrial wildlife, respectively.

You should review the [limitations](#) of ECOTOX data retrieval and system requirements prior to performing searches on this site.

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

ECOTOX Documentation

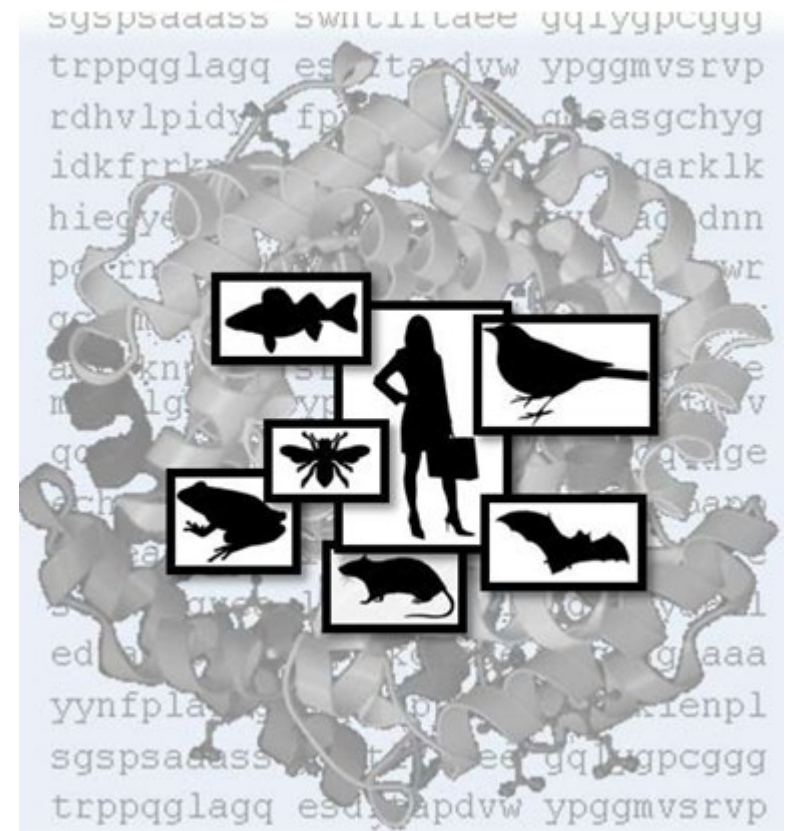
- [ECOTOX User Guide](#) (89 pp, 663 K)

Live EcoTox Demonstration

SeqAPASS: Sequence Alignment to Predict Across Species Susceptibility

SeqAPASS

- Fast, online screening tool to extrapolate toxicity information across species
- For some species, such as humans, mice, rats and zebrafish, large amount of data
- Toxicity data for numerous other plants and animals is limited



- Decreasing testing resources, international interest in reducing animal use, and increasing demand to evaluate chemicals in a more timely manner means increased demand for good predictive approaches to maximize use of existing data
- Uses existing data along with publicly available protein sequence and structure information to better understand the effects of chemicals on non-target species
- If a chemical is known to interact with a protein in one organism, can efficiently:
 - 1) Identify whether that protein sequence/structure is present in other species of interest, and
 - 2) Use this information as an *initial, screening level, line of evidence to predict chemical susceptibility* to hundreds of other species where limited or no toxicity information exists

Robust: Pulls information from the [National Center for Biotechnology Information \(NCBI\) protein database](#), information on over 289,000,000 proteins representing more than 141,000 organisms

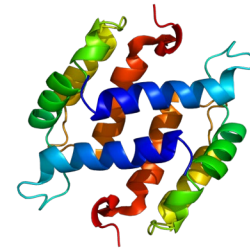
Flexible: Flexibility in the analysis, moving from primary amino acid sequence evaluations to structural consideration, allows users to capitalize on any existing information pertaining to chemical-protein interactions in known sensitive species

Innovative: Allows users to extrapolate from any species to all other species for which protein sequence data exist

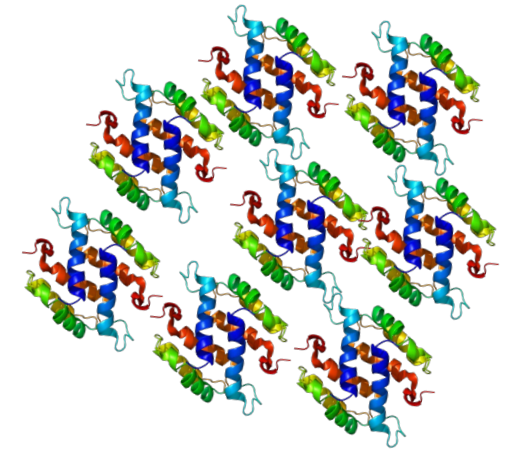
Interoperable with EPA's [CompTox Chemicals Dashboard](#)

Addressing the Challenge of Species Extrapolation

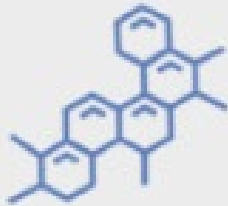
- Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)
 - Assume:
 - That presence of molecular target in non-target species is one critical route via which a chemical could cause adverse effects
 - greater similarity = greater likelihood
 - interact with molecular target in non-target species
- Query Species
vs.
- All species with available protein sequence information



|||



SeqAPASS



IDs chemical interaction with protein targets of species known to be sensitive to the chemical



Predicts likely or unlikely chemical interaction for untested species



Evaluates protein target similarities in other species

Case Studies

Multiple case studies demonstrate applicability and use to predict cross species susceptibility to chemicals

- **Endocrine system in humans and wildlife**
- **Molting processes in insects and invertebrates**
- **Survival of honey bee colonies**

Live SeqAPASS Demonstration

Learn More: EPA NAMs Pilot Training Program

- New Approach Methodologies (NAMs) Training program is a deliverable in the Agency's NAM Workplan *first released in 2019 and updated in 2021
- **Goal: Develop, implement and maintain an engaging training program**
 - Interactive case studies to encourage active learning
 - Train the trainer
 - Obtain feedback
- Additional trainings (virtual and in-person) are being planned
- EPA's NAMs Training website includes existing training resources, including recordings and guidance documents



EPA NAMs Training: www.epa.gov/chemical-research/new-approach-methods-nams-training

EPA NAMs Work Plan: <https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical>

Contact

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