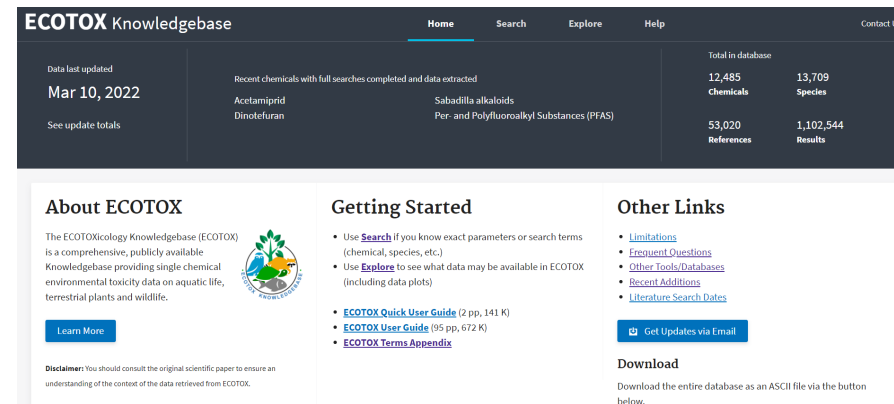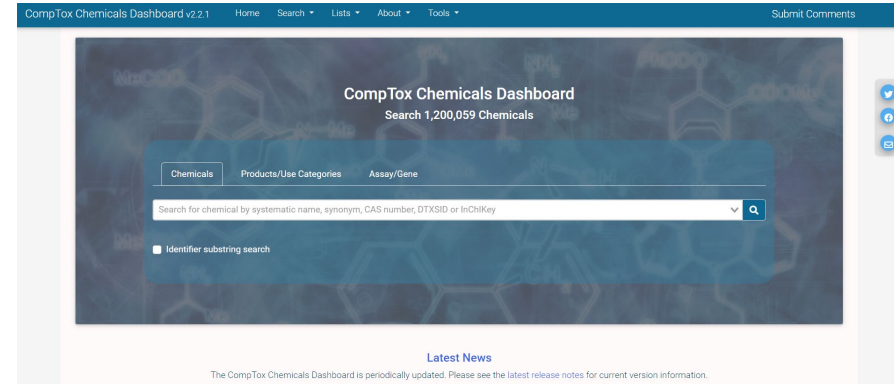# EPA Tools & Resources Training Webinar:

Computational Toxicology and Exposure Online Tools

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US EPA Office of Research and Development

October 12, 2023

Agenda

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

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
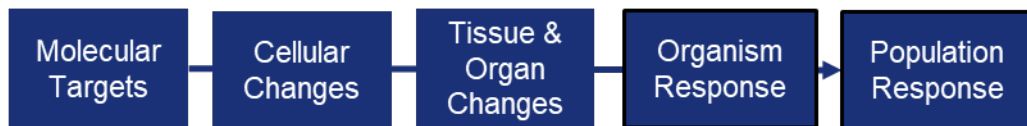
- Hazard + exposure

- New Approach Methodologies (NAMs)

models

predictions

pathways

New Approach Methodologies (NAMs)

- **Adverse outcome pathways (AOPs)**
  Pathway identification and knowledge integration

  Molecular Targets → Cellular Changes → Tissue & Organ Changes → Organism Response → Population Response

  Molecular initiating event (MIE)   Key Events (KE)

- **Databases of existing toxicology data**
  Enables training and evaluation of NAM models

- ***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

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

Predictions

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

- **Computer models**
  Integrate multiple *in silico* and *in vitro* data streams
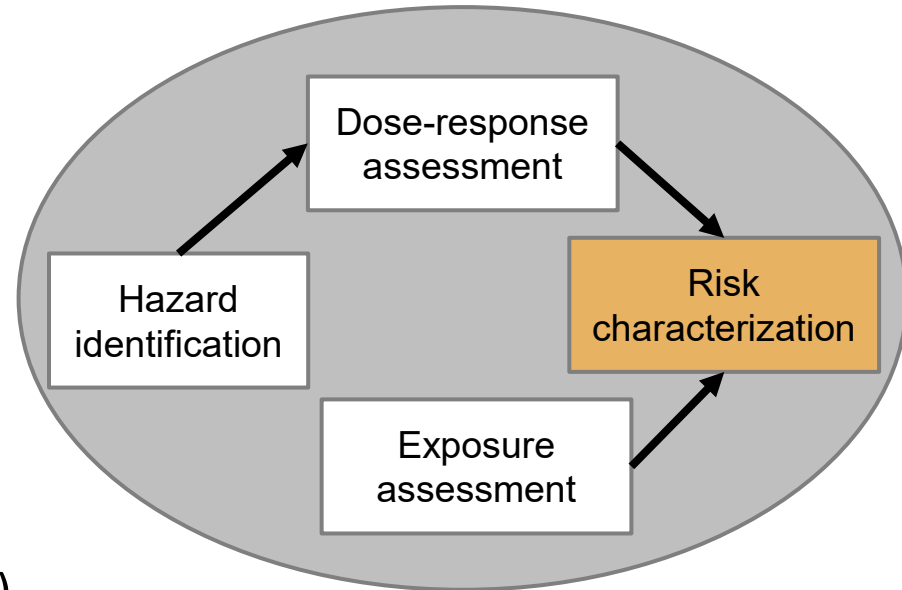
CompTox Chemicals Dashboard (CCD)

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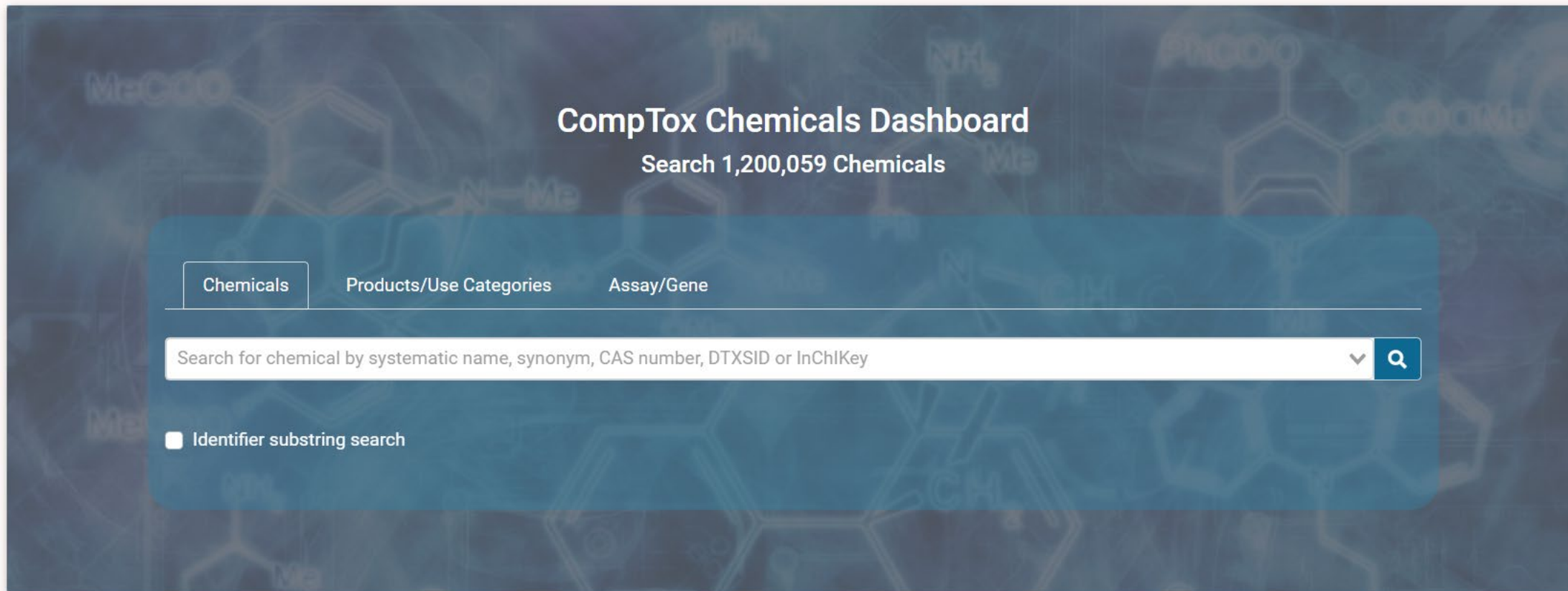
https://comptox.epa.gov/dashboard/

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)

CCD Main Page

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

CCD Help Page

Submit Comments

Please report issues, comments and questions using "Submit Comments"

Live CompTox Chemicals Dashboard Demonstration

ECOTOX

History of ECOTOX

Ecological risk assessors need cost-effect 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)

Early 1980s	Early 1990s	Late 1990s	2017
• AQUIRE, PHYTOTOX, TERRETOX developed	• Major updates to AQUIRE	• Combined system was created (ECOTOX)	• Interactive version of ECOTOX developed
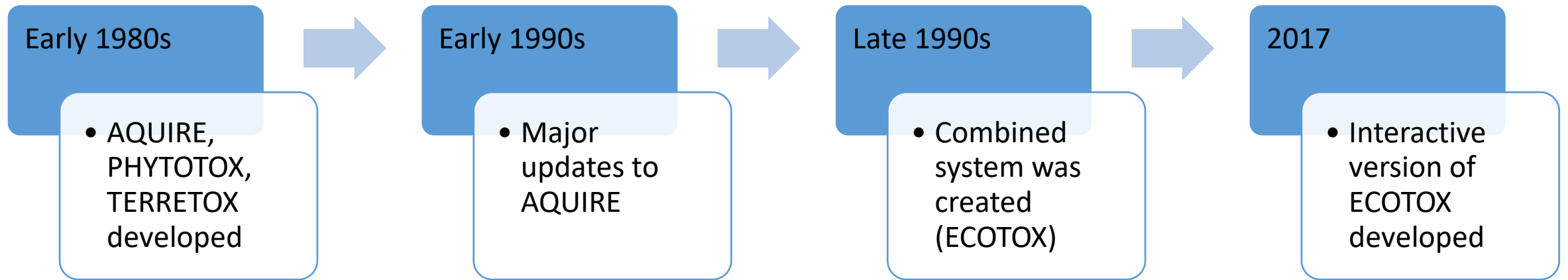
- Authoritative source of toxicological data
- Document literature searches of data
- Development and validation

ECOTOX and the next generation of chemical safety evaluation
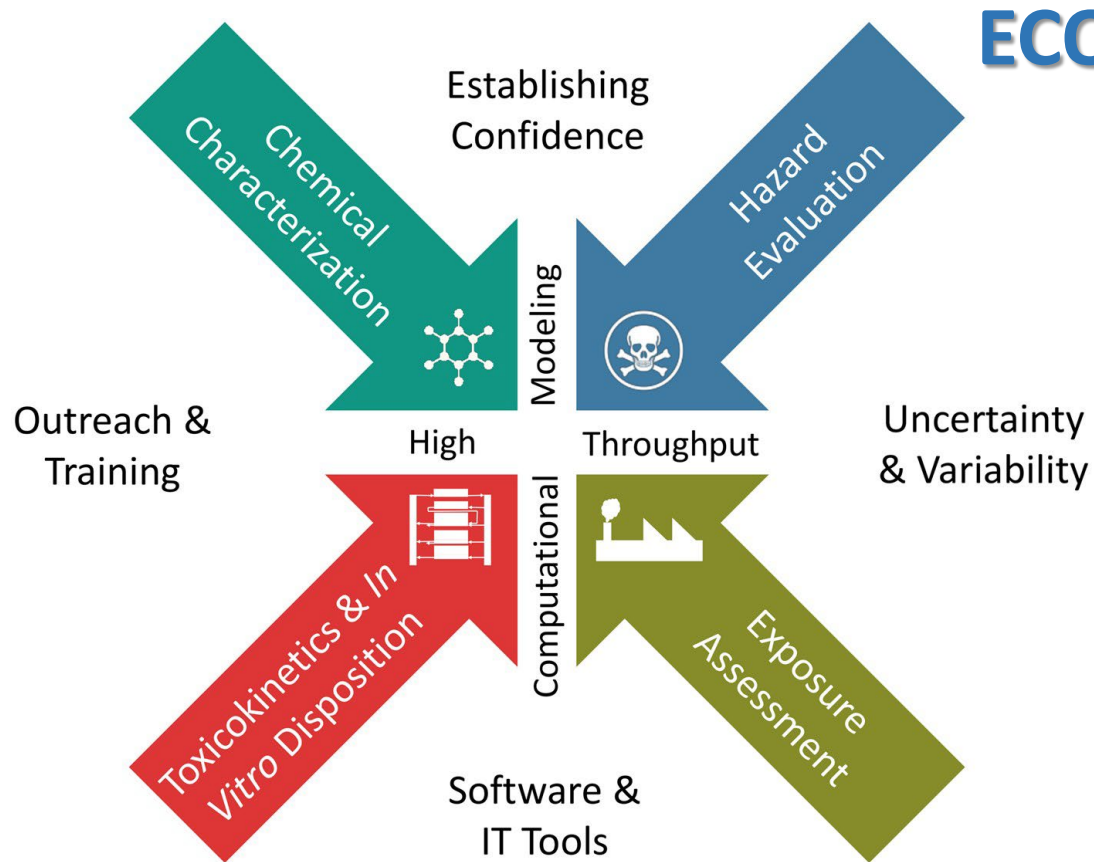
ECOTOX

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

Thomas et al. 2019 10.1093/toxsci/kfz058

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

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
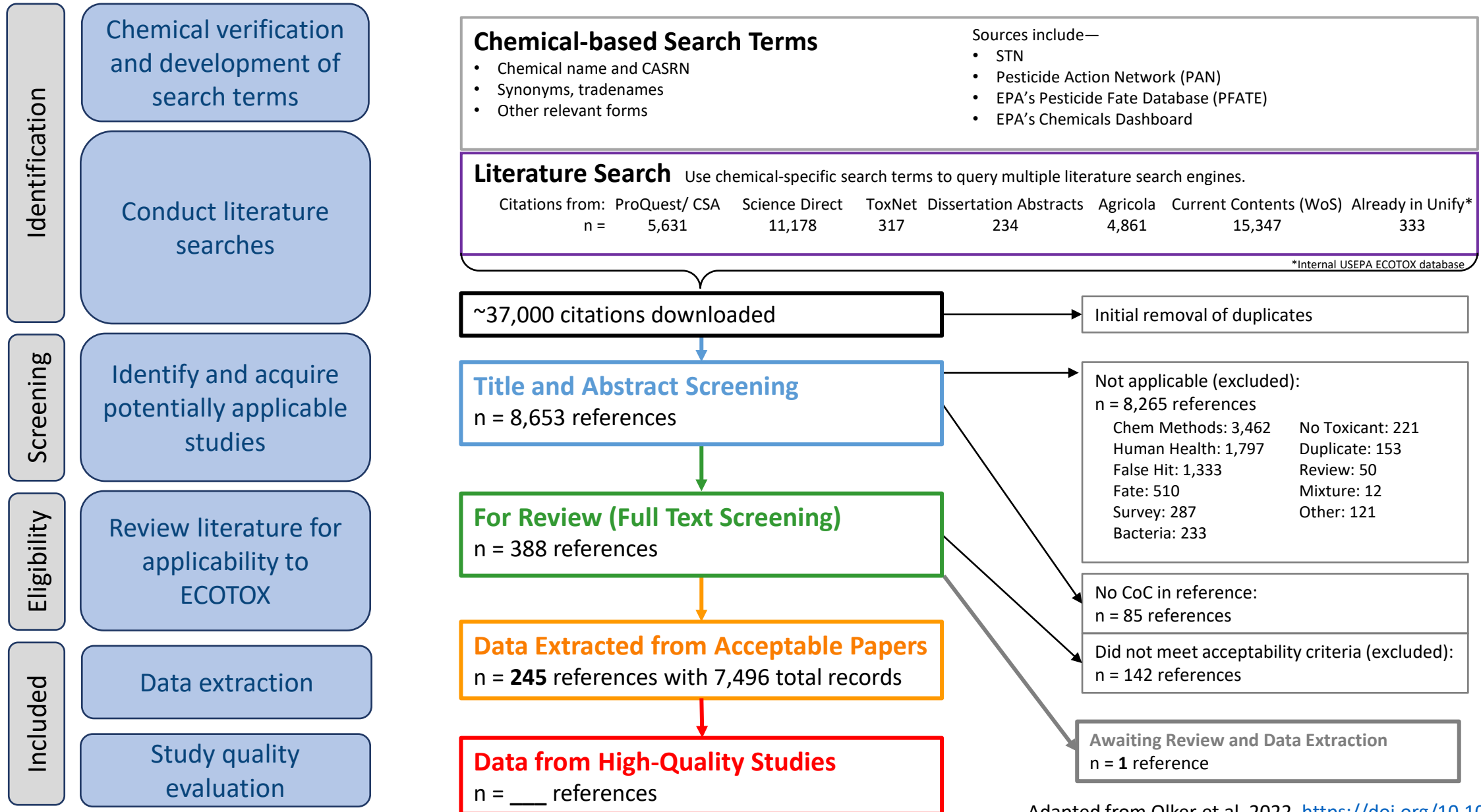Chemical Prioritization
Emergency Response

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

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-based Search Terms
- Chemical name and CASRN
- Synonyms, tradenames
- Other relevant forms

Sources include—
- STN
- Pesticide Action Network (PAN)
- EPA's Pesticide Fate Database (PFATE)
- EPA's Chemicals Dashboard

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

~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	

For Review (Full Text Screening)
n = 388 references

→ No CoC in reference:
n = 85 references

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

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

Data from High-Quality Studies
n = ___ references

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

Adapted from Olker et al. 2022 https://doi.org/10.1002/etc.5324

Search Planner

Help and Contact Us

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

SeqAPASS
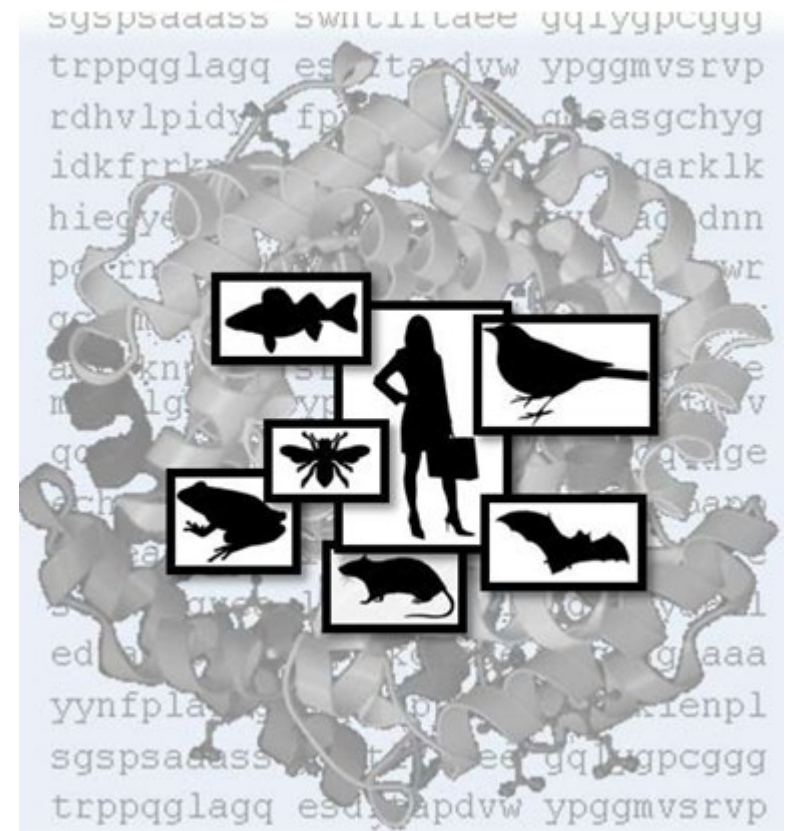
- Decreasing testing resources, international interest in reducing animal use, and increasing demand to evaluate chemicals in a more timely manner means increased demand for good predictive approaches to maximize use of existing data

- 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

SeqAPASS

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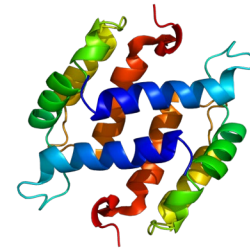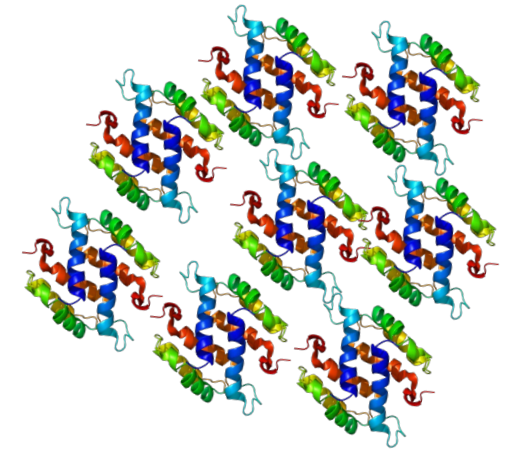
SeqAPASS
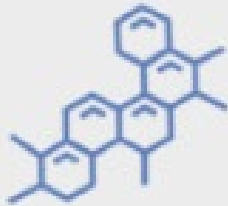
IDs chemical interaction with protein targets of species known to be sensitive to the chemical

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

Evaluate regulatory flexibility for accommodating NAMs

Develop baselines and metrics for assessing progress

Establish scientific confidence and demonstrate application

Develop NAMs that fill critical information gaps

Engage and communicate with stakeholders

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.