Application of Systematic Review (SR) Principles to Ecotoxicity Studies: ECOTOXicology Knowledgebase

Jennifer H. Olker
US Environmental Protection Agency
Center for Computational Toxicology and Exposure
Duluth, MN
Phone: 218.529.5119
Email: Olker.Jennifer@epa.gov

Conflict of Interest Statement

The author declares no actual or potential conflicts of interest.

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

Mention of software packages is not an endorsement by the authors or the US Environmental Protection Agency.

Abbreviations

- **AQUIRE**: Aquatic toxicity Information Retrieval Database
- **CASRN**: Chemical Abstracts Service Registry Number
- **DTXSID**: US EPA's Distributed Structure-Searchable Toxicity database (DSSTox) substance identifier
- **ECOTOX**: ECOTOXicology Knowledgebase (www.epa.gov/ecotox)
- **GUI**: Graphical User Interface
- **ITIS**: Integrated Taxonomic Information System
- **LC50**: Lethal concentration to 50% of test organisms
- **LOEC**: Lowest Observed Effect Concentration
- **LOEL**: Lowest Observed Effect Level
- **NCBI**: National Center for Biotechnology Information
- **NOEC**: No Observed Effect Concentration
- **NOEL**: No Observed Effect Level
- **NR**: Not Reported
- **OECD**: Organisation for Economic Co-operation and Development
- **PECO**: Population, Exposure, Comparator/Control, Outcome
- **SR**: Systematic Review
- **STN:** Scientific and Technical information Network
- **TSN**: Taxonomic Serial Number
- **US EPA**: United State Environmental Protection Agency

Objective and Outline

- Systematic and transparent methods used for identification and review of ecotoxicity data

- Background and History
- Current Status and Applications
- ECOTOX Pipeline

- Ecotoxicology-specific considerations
- Examples with recently completed chemicals

Background and History

- Ecological risk assessors needed cost-effective methods to locate high quality ecological toxicity data for use in:
  - Prioritizing chemical cleanup at hazardous waste sites
  - Assessment of potential hazards of pollutants through the Clean Air Act, the Clean Water Act, the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act.
- US EPA developed ecological toxicity databases:
  1) Authoritative source of toxicological data
  2) Efficient documentation of literature searches and data acquisition
  3) Data available for development and validation of in vitro and modeling methods
  4) Avoid duplicative efforts for data gathering across programs and agencies

Background and History

Early 1980s:

- AQUatic toxicity Information Retrieval (AQUIRE) database for acute laboratory toxicity tests on aquatic life
  - Expanded to field and chronic exposures in early 1990s
- PHYTOTOX database for toxicity tests with terrestrial plants
- TERRETOX database for toxicity studies with terrestrial wildlife

Late 1990s:

- ECOTOXicology Knowledgebase (ECOTOX): AQUIRE, PHYTOTOX, TERRETOX combined into unified database and available on web

What is the ECOTOX Knowledgebase?

- Systematic and transparent protocols developed over 30 years:
  - Conduct comprehensive literature searches for toxicity data in the peer-reviewed and grey literature
  - Review applicability of studies following established criteria
  - Extract relevant study and toxicity results into a structured database

- Accessible, structured empirical data from *in vivo* toxicity tests

- Toxicity data provided to US EPA Programs, Regions, and researchers
- Updated quarterly to public website (www.epa.gov/ecotox)

What is the ECOTOX Knowledgebase?

ECOTOX Knowledgebase

Home | **Search** | **Explore** | **Help** | Contact Us

Data last updated

Dec 15, 2022

See update totals

Recent chemicals with full searches completed and data extracted

6PPD
Cyanotoxins
Per- and Polyfluoroalkyl Substances (PFAS)
Thallium

Total in database

12,714 **Chemicals**
13,803 **Species**
53,763 **References**
1,134,537 **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.)
- 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

ECOTOX-related documentation and resources.

- Frequent Questions
- Limitations
- Other Tools/Databases
- Recent Additions
- 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

ECOTOX KNOWLEDGEBASE

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

General SR Process Overview

1. Planning
2. Framing the question
3. Developing and publishing of the protocol
4. Searching for evidence
5. Selecting the evidence
6. Extracting data
7. Assessing the evidence (evaluation)
8. Analyzing data
9. Interpreting the results
10. Report

Adapted from Hoffmann et al. 2017

General SR Process Overview

ECOTOX Systematic Protocols

Parallel general SR Steps

Inform study evaluation

1. **Planning**
2. **Framing the question**
3. **Developing and publishing of the protocol**
4. **Searching for evidence**
5. **Selecting the evidence**
6. **Extracting data**
7. **Assessing the evidence (evaluation)**
8. *Analyzing data*
9. *Interpreting the results*
10. *Report*

Adapted from Hoffmann et al. 2017

General SR Process Overview

ECOTOX Systematic Protocols

Parallel general SR Steps

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1. **Planning**
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4. **Searching for evidence**
5. **Selecting the evidence**
6. **Extracting data**
7. **Assessing the evidence (evaluation)**

Application Specific

8. *Analyzing data*
9. *Interpreting the results*
10. *Report*

Adapted from Hoffmann et al. 2017

ECOTOX Pipeline: Literature Search, Review, and Data Curation

Planning and Identification		Screening	Eligibility	Included	Evaluation and Synthesis
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**

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

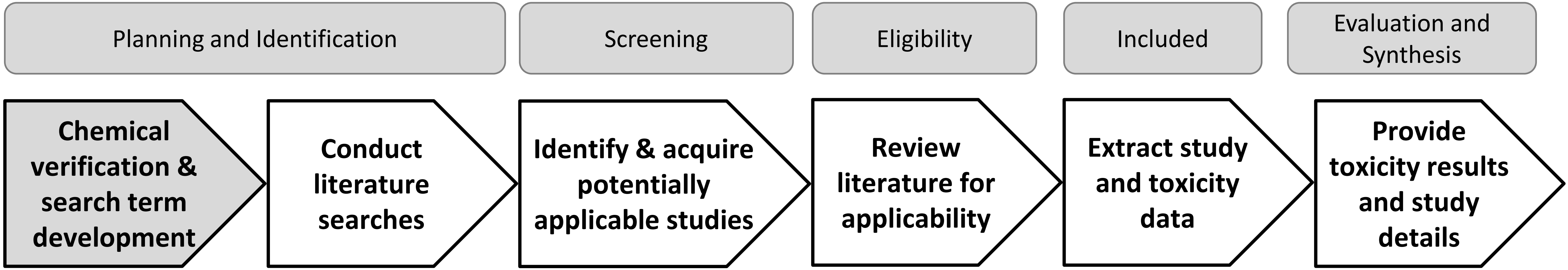
- ECOTOX-specific Controlled Vocabularies
  - Test chemical
  - Test organism
  - Study methods and test conditions
  - Toxicity results
- Updated to public website, with downloadable outputs

Considerations for Ecotoxicology

- Sources used in literature searches
- Population of interest includes many species
- Diversity in types of effects measured
- Diversity of study design

- Data to support multiple applications

ECOTOX Pipeline: Literature Search, Review, and Data Curation



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")

***No ecotoxicology-specific considerations**

ECOTOX Pipeline: Literature Search, Review, and Data Curation

Planning and Identification | Screening | Eligibility | Included | Evaluation and Synthesis

1. Chemical verification & search term development
2. Conduct literature searches
3. Identify & acquire potentially applicable studies
4. Review literature for applicability
5. Extract study and toxicity data
6. Provide toxicity results and study details

Chemical-based Literature Searches

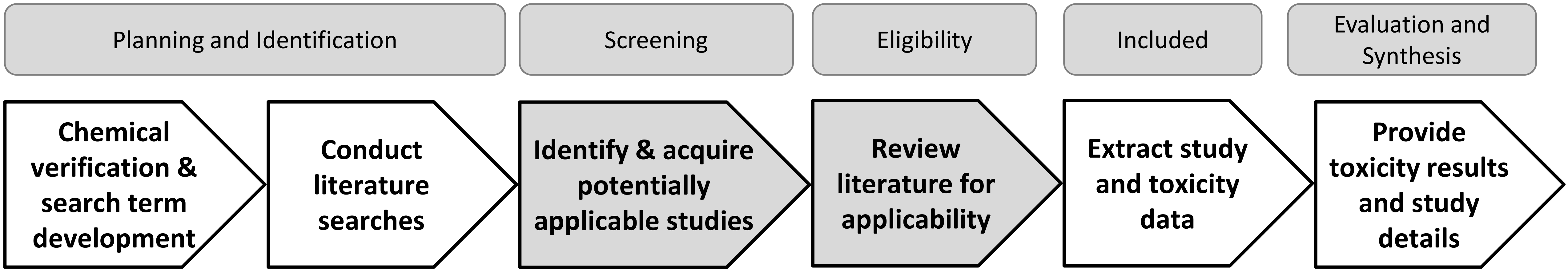
Search Engines

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

***Considerations for ecotoxicology**

- Variety of sources needed to find published studies on aquatic and terrestrial organisms
- Journals with highest applicability rate are often not found through PubMed

ECOTOX Pipeline: Literature Search, Review, and Data Curation



Title/Abstract Screening **Full Text Review**

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

***Considerations for ecotoxicology**

- Population of interest includes many species
- Diversity in types of effects

Inclusion Criteria (PECO)

Identify & 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

Examples of Species and Effects in Ecological Toxicity Studies

Species Group	**Habitat(s)**	**Num. Species in ECOTOX**	**Standard Test Species**
Fish	Aquatic	1,006	42 species *Examples: Rainbow Trout, Zebrafish, Fathead Minnow, Common Carp*
Amphibians	Aquatic, Terrestrial	229	7 species *Examples: African clawed frog (Xenopus laevis), Northern leopard frog, Bullfrog, Wood frog*
Reptiles	Aquatic, Terrestrial	75	none
Birds	Terrestrial	283	11 species *Examples: Mallard duck, Japanese quail, Zebra finch*
Mammals	Terrestrial, Aquatic*	205	9 species *Examples: Norway rat, House mouse, European rabbit*

*currently only *in vitro* studies for aquatic mammals

Examples of Species and Effects in Ecological Toxicity Studies

Species Group	Habitat(s)	Num. Species in ECOTOX	Standard Test Species	Effects and Endpoints (examples)
Fish	Aquatic	1,006	42 species *Examples: Rainbow Trout, Zebrafish, Fathead Minnow, Common Carp*	Mortality (i.e., LC50) Time to death Hatch Fecundity Progeny counts Spawning frequency Weight, Length Condition index Limb/body part regeneration Sexual development Vitellogenin 17-beta Estradiol
Amphibians	Aquatic, Terrestrial	229	7 species *Examples: African clawed frog (Xenopus laevis), Northern leopard frog, Bullfrog, Wood frog*	Mortality Time to death Hatch Viability Ovulation rate Weight, Length Condition index Snout-vent length Metamorphosis Limb/body part regeneration Acetylcholinesterase Testosterone Thyroxine
Reptiles	Aquatic, Terrestrial	75	none	Mortality Time to death Hatch Courtship behavior Weight, Length Snout-vent length Testosterone 17-beta Estradiol

Examples of Species and Effects in Ecological Toxicity Studies

Species Group	Habitat(s)	Num. Species in ECOTOX	Standard Test Species	Effects and Endpoints (examples)
Birds	Terrestrial	283	11 species *Examples: Mallard duck, Japanese quail, Zebra finch*	Mortality Time to death Hatch Viability Progeny counts Eggs per nest Pipped Weight, Length Condition index Growth rate Fledged/female Food conversion efficiency Cholinesterase Cholesterol
Mammals	Terrestrial, Aquatic	205	9 species *Examples: Norway rat, House mouse, European rabbit*	Mortality Time to death Viability Progeny counts Resorbed embryos Gestation time Weight, Length Weight gain Acetylcholinesterase Hemoglobin Testosterone

Examples of Species and Effects in Ecological Toxicity Studies

Species Group	Habitat(s)	Num. Species in ECOTOX	Standard Test Species
Worms	Aquatic, Terrestrial	75	14 species *Examples: Earthworm (Eisenia fetida), Nematode (Caenorhabditis elegans), Oligochaete (Lumbriculus variegatus)*
Crustaceans	Aquatic, Terrestrial	936	46 species *Examples: Daphnia magna, Daphnia pulex, Ceriodaphnia dubia, Hyalella azteca, Opossum shrimp*
Molluscs	Aquatic, Terrestrial	678	12 species *Examples: Common bay mussel, Virginia oyster, Great pond snail*
Insects/ Spiders	Aquatic, Terrestrial	3,590	18 species *Examples: Honeybee, Yellow fever mosquito, Midge (Chironomus riparius, Chironomus tentans, Chironomus dilutus)*
Other Invertebrates	Aquatic, Terrestrial	648	15 species *Examples: Purple-spined sea Urchin, Brown shrimp, Rotifer (Brachionus calyciflorus), Springtail (Folsomia candida)*

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Examples of Species and Effects in Ecological Toxicity Studies

Species Group	**Habitat(s)**	**Num. Species in ECOTOX**	**Standard Test Species (examples)**
Algae	Aquatic, Terrestrial	1,265	23 species *Examples: Green algae (Chlorella vulgaris, Chlamydomonas reinhardtii), Diatoms (Skeletonema costatus, Phaeodactylum tricornutum), Blue-green algae (Microcystis aeruginosa, Anabaena flosaquae)*
Vascular Plants	Aquatic, Terrestrial	3,232	30 species *Examples: Corn, Soybean, Duckweed, Common onion, Mouse-ear cress*
Fungi	Aquatic, Terrestrial	862	none
Moss, Hornworts	Aquatic, Terrestrial	65	none

Examples of Species and Effects in Ecological Toxicity Studies

Species Group	Habitat(s)	Num. Species in ECOTOX	Standard Test Species (examples)	Effects and Endpoints (examples)	
Algae	Aquatic, Terrestrial	1,265	23 species *Examples: Green algae (Chlorella vulgaris, Chlamydomonas reinhardtii), Diatoms (Skeletonema costatus, Phaeodactylum tricornutum), Blue-green algae (Microcystis aeruginosa)*	Mortality Population abundance and growth rate Biomass Growth rate Photosynthesis	Respiration Germination Chlorophyll Catalase Fluorescence
Vascular Plants	Aquatic, Terrestrial	3,232	30 species *Examples: Corn, Soybean, Duckweed, Common onion, Mouse-ear cress*	Mortality Germination Seed number Fruit, fruiting Viability Fertility Weight, Height	Length Biomass # of leaves, # of roots Chlorophyll Photosynthesis Respiration Nitrogen content
Fungi	Aquatic, Terrestrial	862	none	Mortality Germination Seed or spore production Viability Weight, Length	Biomass Time to harvest Respiration Aflatoxin B1 Hydrogen peroxide
Moss, Hornworts	Aquatic, Terrestrial	65	none	Mortality Germination Length, Diameter	Chlorophyll Photosynthesis

Inclusion Criteria (PECO)

Identify & 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.
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	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

Documentation of Exclusion Reasons

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, CO_2)
- 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

***Allows for re-use of literature search and screening results**

ECOTOX Pipeline: Literature Search, Review, and Data Curation

Planning and Identification		Screening	Eligibility	Included	Evaluation and Synthesis
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**

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

*__Considerations for ecotoxicology__

- Diversity of study methods and types
- Pertinent study details and test conditions vary greatly, requiring many data fields

Fields Included in ECOTOX Data Extraction

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

Extract study and toxicity data

*** 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

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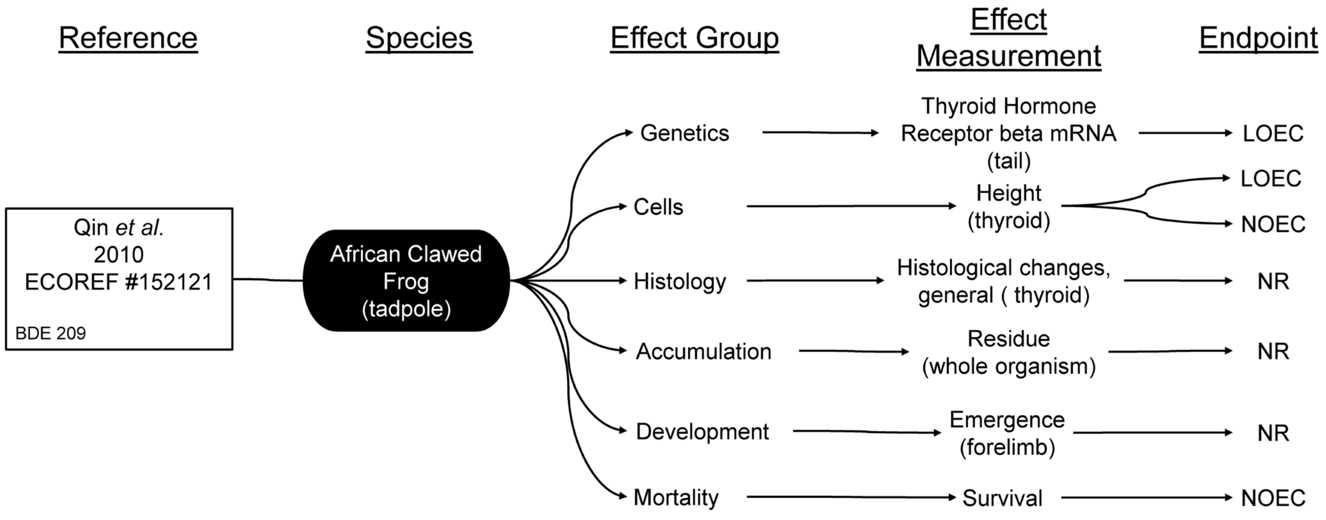
<u>Data Extraction</u>

Example of multiple ECOTOX records from a single study:



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

ECOTOX Pipeline: Literature Search, Review, and Data Curation

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*__Considerations for ecotoxicology__

- Toxicity data from ECOTOX are used for multiple applications with potentially differing criteria for relevance and reliability
- Methodology varies across diversity of taxa

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

Informing Study Evaluation

Provide toxicity results and study details

Category	Select study evaluation questions* with relevant ECOTOX field(s)
Chemical	• Is the test substance identified? **Required for inclusion in ECOTOX** • Is the purity of the 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**
Study Methods & Test Conditions	• Are appropriate controls performed? **Control 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**

Adapted from Olker et al. 2022

*based on published evaluation guidelines (Kaltenhauser et al. 2017; Moermond et al. 2016; Schneider et al. 2009)

Example: Thallium

Problem Statement: Updated toxicity data are needed to develop an ecological screening value for Thallium, a naturally occurring elemental metal which also has industrial sources.

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

Thallium Search – Nov 2021

One (N=1) requested chemical.
Thallium - 7440-28-0 – Parent (PAN)

Thirty-one (N=31) additional related chemicals

Thallium Search String

Search Terms:

(eta5-2,4-Cyclopentadien-1-yl)thallium
(eta5-Cyclopentadienyl)thallium
21H,23H-Porphine, 2,3,7,8,12,13,17,18-octaethyl-, thallium complex
Acetic acid, thallium(1) salt
Acetic acid, thallium(1+) salt
Acetic acid, thallium(1+) salt (1:1)
Acetic acid, thallium(3+) salt
Acetic acid, thallium(3+) salt (3:1)
Acetic acid, thallium(I) salt
AceticacidThallium1+salt
Aluminum thallium sulfate
Carbonic acid, dithallium(1+) salt
Carbonic acid, thallium(1+) salt (1:2)
Caswell No. 849
Chromic acid (H2CrO4), dithallium(1+) salt
Chromium thallium oxide (CrTl2O4)
Cyclopentadienylthallium
Dithallium carbonate
Dithallium chromate
Dithallium malonate
Dithallium monosulfide
Dithallium oxide
Dithallium sulfate
Dithallium sulfide
Dithallium trioxide
Dithallium(1+) carbonate
Dithallium(1+) propanedioate
Dithallium(1+) selenite
Dithallium(1+) sulfate
Dithallium(1+) sulfide
Dithallium(1+) tetraoxidochromate(2-)
Dithallium(I) sulfate
Dithalliumtrioxid
Dithalloxane-1,3-dione

Thallic acetate
Thallic chloride
Thallic fluoride
Thallic nitrate
Thallic oxide
Thallic triacetate
Thallium
Thallium (I) sulfate
Thallium (III) acetate
Thallium (III) chloride
Thallium acetate
Thallium acetate (Tl(OAc)3)
Thallium acetate (TlOAc)
Thallium bromide
Thallium bromide (Tl2Br2)
Thallium bromide (TlBr)
Thallium bromide (TlBr), dimer
Thallium carbonate
Thallium carbonate (6CI, 7CI)
Thallium carbonate (Tl2CO3)
Thallium chloride
Thallium chloride (TlCl)
Thallium chloride (TlCl3)
Thallium chromate (Tl2CrO4)
Thallium chromate(VI) (Tl2CrO4)
Thallium cyclopentadienide
Thallium element
Thallium ethoxide
Thallium fluoride
Thallium fluoride (Tl4F4)
Thallium fluoride (TlF)
Thallium fluoride (TlF3)
Thallium formate
Thallium hydroxide (Tl(OH)), monohydrate

… (continues for 5 pages)

Thallium Search Results

Data Base	References Downloaded
ProQuest	7,029
PubAg	2,338
PubMed/Toxline	51
Scopus	5,182
Theses	5
Web of Science	24,259
UNIFY	295
Total Downloaded	**39,159**

Example: Thallium

Problem Statement: Updated toxicity data are needed to develop an ecological screening value for Thallium, a naturally occurring elemental metal which also has industrial sources.

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**

Literature Search Results		Initial DeDuplication		Species Filter		Title and Abstract Screening
		Title, Author		Swift Review*		SwiftActive Screener*
Thallium	**N = 39,159 refs**		**N = 26,659 refs**		**N = 3,538 refs**	

*Sciome SR Tools (Howard et al. 2016, 2020)

Example: Thallium

Problem Statement: Updated toxicity data are needed to develop an ecological screening value for Thallium, a naturally occurring elemental metal which also has industrial sources.

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Thallium Search – Nov 2021

One (N=1) requested chemical
Thallium - 7440-28-0

Thirty-one (N=31) additional related chemicals

Title and Abstract Screening

Full Text Screening

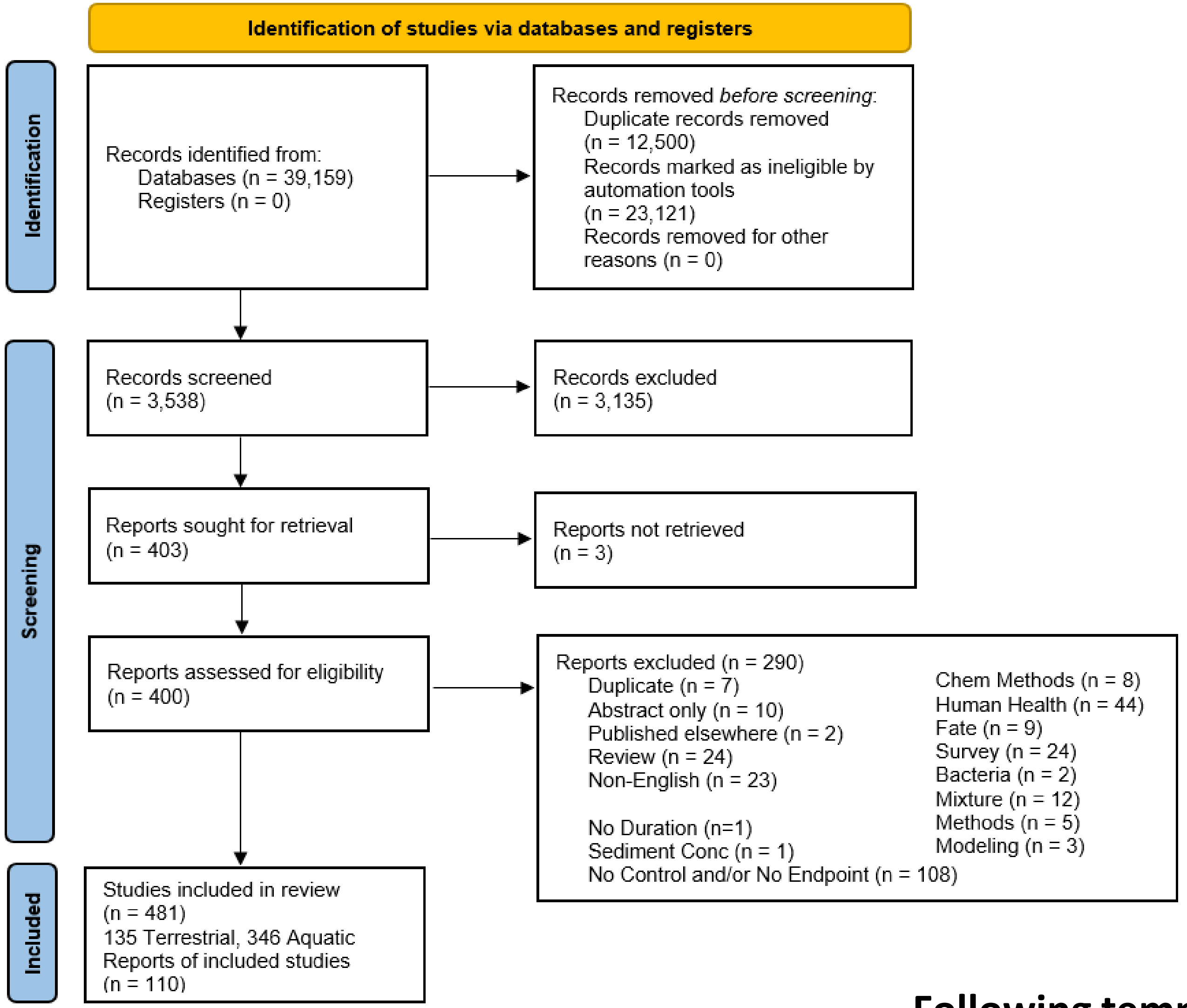
Data Extraction and Delivery

9 of 32 searched chemicals have ecological toxicity data extracted

Thallium → **N = 39,159 refs** → **N = 403 refs** → **N = 110 refs**

Example: Thallium

Study Flow Diagram



Following template from Page et al. 2021

Example: Thallium

ECOTOX Knowledgebase

Home | Search | **Explore** | Help | Contact Us

< Explore | Chemicals | Thallium

☑ 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 (9)
All

Species Group (12)
All

Class (25)
All

Order (57)
All

9 Chemicals

Export CSV

Chemicals are ordered by **CAS Number**.

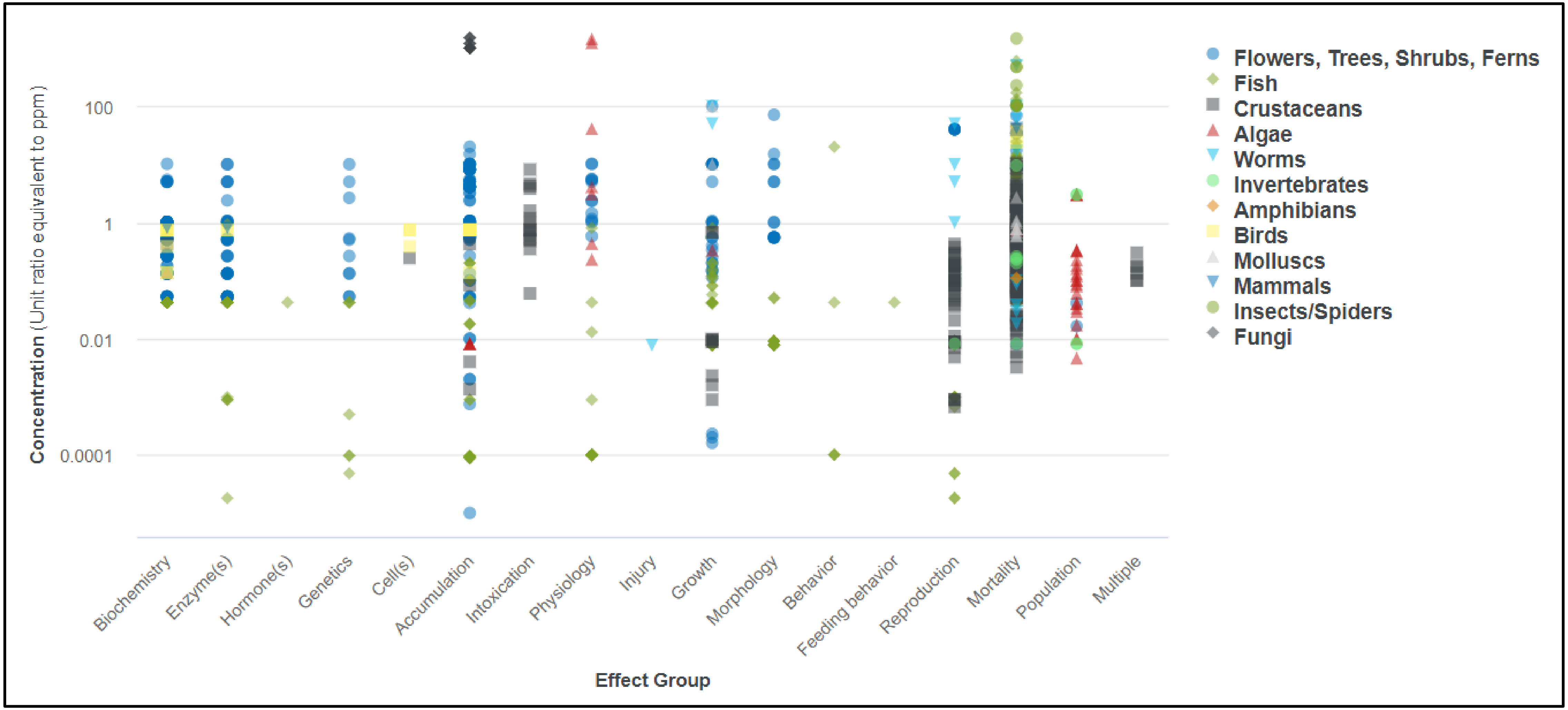
*Showing **all** 9 chemicals from **563688** to **13746980***

CAS	CHEMICAL NAME	RECORDS	PUBLICATIONS	YEAR MIN	YEAR MAX
type to filter...	...	...	...	...	...
563688	**Thallium (I) acetate** Chemicals Dashboard	198	12	1975	2021
2570630	**Thallium (III) acetate** Chemicals Dashboard	2	1	2005	2005
6533739	**Thallium carbonate (Tl2CO3)** Chemicals Dashboard	15	1	2002	2002

https://cfpub.epa.gov/ecotox/explore.cfm?cgid=41

Example: Thallium

ECOTOX Explore Plot view



https://cfpub.epa.gov/ecotox/explore.cfm?cgid=41

Example: Thallium

Export of records –

Mortality data for Terrestrial Invertebrates

CAS Number	Chemical Name	Chemical Grade	Chemical Purity	Species Scientific Name	Species Common Name	Organism Lifestage	Media Type	Test Locatio	Exposure Type	Chemical Analysis Method	Number of Doses
7440280	Thallium		NR	Caenorhabditis elegans	Nematode	Adult	Culture	Lab	Culture medium	Unmeasured	
7440280	Thallium		NR	Caenorhabditis elegans	Nematode	Adult	Culture	Lab	Culture medium	Unmeasured	
7440280	Thallium		NR	Caenorhabditis elegans	Nematode	Adult	Culture	Lab	Culture medium	Unmeasured	
7440280	Thallium		NR	Caenorhabditis elegans	Nematode	Adult	Culture	Lab	Culture medium	Unmeasured	
6533739	Carbonic acid, Thallium(1+) salt (1:2)		NR	Arianta arbustorum	Copse Snail	Egg	Artificial s	Lab	Culture medium	Unmeasured	6
6533739	Carbonic acid, Thallium(1+) salt (1:2)		NR	Eisenia fetida	Earthworm	Mature	Artificial s	Lab	Culture medium	Unmeasured	7
6533739	Carbonic acid, Thallium(1+) salt (1:2)		NR	Eisenia fetida	Earthworm	Mature	Artificial s	Lab	Culture medium	Unmeasured	7
563688	Acetic acid, Thallium(1+) salt (1:1)		>99.995	Caenorhabditis elegans	Nematode	Larva	Aqueous	Lab	Aqueous	Unmeasured	8
563688	Acetic acid, Thallium(1+) salt (1:1)		>99.995	Caenorhabditis elegans	Nematode	Larva	Aqueous	Lab	Aqueous	Unmeasured	8
563688	Acetic acid, Thallium(1+) salt (1:1)		>99.995	Caenorhabditis elegans	Nematode	Larva	Aqueous	Lab	Aqueous	Unmeasured	8
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode		Culture	Lab	Culture medium	Unmeasured	2
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	8
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	8
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3
563688	Acetic acid, Thallium(1+) salt (1:1)		NR	Caenorhabditis elegans	Nematode	Larva	Culture	Lab	Culture medium	Unmeasured	3

Example: Thallium

Reference	Chemical	Species	Effect and Endpoint
Williams and Dusenbery 1990	**Thallium** (CASRN 7440-28-0)	Nematode (*Caenorhabditis elegans*)	1-day LC50 >200,000 ug/L 2-day LC50 = 194,000 ug/L 3-day LC50 = 172,000 ug/L 4-day LC50 = 123000 ug/L
Heim et al. 2002	**Thallium carbonate (Tl2CO3)** (CASRN 6533-73-9)	Copse Snail (*Arianta arbustorum*)	Hatch LOEL = 1 mg/kg soil
Heim et al. 2002	**Thallium carbonate (Tl2CO3)** (CASRN 6533-73-9)	Earthworm (*Eisenia fetida*)	28-day Mortality NOEL = 500 mg/kg soil LOEL = 500 mg/kg soil
Varao et al. 2021	**Thallium (I) acetate** (CASRN 563-68-8)	Nematode (*Caenorhabditis elegans*)	25-hr Mortality LC50 = 59.5 mg/L NOEL = 50 µM LOEL = 100 µM
Hurtado-Diaz et al. 2020	**Thallium (I) acetate** (CASRN 563-68-8)	Nematode (*Caenorhabditis elegans*)	Mortality 1-hr LOEL = 15 µM 24-hr LOEL = 2.5 µM 16-day 100% lethality = 5 µM

Example: Thallium

Reference	Chemical	Species	Effect and Endpoint	Control
Williams and Dusenbery 1990	**Thallium** (CASRN 7440-28-0) Nominal concentrations	Nematode (*Caenorhabditis elegans*)	1-day LC50 >200,000 ug/L 2-day LC50 = 194,000 ug/L 3-day LC50 = 172,000 ug/L 4-day LC50 = 123000 ug/L	✓
Heim et al. 2002	**Thallium carbonate (Tl2CO3)** (CASRN 6533-73-9) Nominal concentrations	Copse Snail (*Arianta arbustorum*)	Hatch LOEL = 1 mg/kg soil	✓ Concurrent
Heim et al. 2002	**Thallium carbonate (Tl2CO3)** (CASRN 6533-73-9) Nominal concentrations	Earthworm (*Eisenia fetida*)	28-day Mortality NOEL = 500 mg/kg soil LOEL = 500 mg/kg soil	✓ Concurrent
Varao et al. 2021	**Thallium (I) acetate** (CASRN 563-68-8) >99.995% Purity Nominal concentrations	Nematode (*Caenorhabditis elegans*)	25-hr Mortality LC50 = 59.5 mg/L NOEL = 50 µM LOEL = 100 µM	✓ Concurrent
Hurtado-Diaz et al. 2020	**Thallium (I) acetate** (CASRN 563-68-8) Nominal concentrations	Nematode (*Caenorhabditis elegans*)	Mortality 1-hr LOEL = 15 µM 24-hr LOEL = 2.5 µM 16-day 100% lethality = 5 µM	✓ Concurrent

Challenges and Limitations

- Immensity of ecotoxicological literature
- Missing information due to insufficient reporting in publications
- Mixture data not included
- Evolving toxicology testing requires evolution of ECOTOX while continuing to support traditional risk assessment

- Collaboration and alignment with human health hazard assessment methodologies

Summary and Conclusion

- ECOTOXicology Knowledgebase was developed for and continues to support chemical risk assessment and research
- Protocols and vocabulary evolved over 30+ year history

- Methods consistent with much of current systematic review guidelines
- Must consider ecotoxicological-specific aspects for species, effects, and sources of information

ECOTOX Protocols Parallel SR

1. Planning **2. Framing the question** **3. Developing and publishing of the protocol**	**ECOTOX Standard Operating Procedures** - Updated and reviewed annually **Established ECOTOX Inclusion Criteria**
4. Searching for evidence **5. Selecting the evidence**	**Chemical-based literature searches** **Study identification and screening** **-** Documented and reproducible
6. Extracting data **7. Assessing the evidence (evaluation)**	**ECOTOX-specific data extraction application** -Structured data to support data evaluation and synthesis
8. Analyzing data *9. Interpreting the results* *10. Report*	*Application Specific*

Adapted from Hoffmann et al. 2017

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