Evidence Map for Ecological Toxicity of Cyanotoxins using ECOTOXicology Knowledgebase Systematic Protocols

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Safe and Healthy Communities

Background

Harmful Algal Blooms (HABs) are a growing concern due to the potential to impact water quality, restrict recreation, and cause health risks due to associated toxins. HABs produced by cyanobacteria can result in release of cyanotoxins that are deadly to humans, pets, livestock, fish, and wildlife. Cyanotoxins can have acute and chronic effects that are not well characterized across the multiple cyanotoxins (e.g., most studies are in microcystins) or potentially exposed organisms (e.g., limited information on effects in microbes, plants, and wildlife).

Mehinto et al. 2021 doi: 10.1016/j.scitotenv.2021.148864; Christensen and Khan 2020 doi: 10.1016/j.scitotenv.2020.139515; https://www.epa.gov/cyanohabs

Objectives

- Comprehensively and systematically assemble ecological effects of cyanotoxins using the well-established protocols of the ECOTOXicology Knowledgebase (ECOTOX, www.epa.gov/ecotox)
- Create a literature inventory of the extent, distribution, and types of toxicity effects of cyanotoxins on aquatic and terrestrial organisms
  - Provide foundation for evaluation of ecological risk from HABs and occurrence of cyanotoxins in the environment
  - Inform future research through identification of data gaps (species, toxins, and endpoints)
- Provide structured effects data for priority cyanotoxins, including study details and toxicity results
  - Identify most potent cyanotoxins and sensitive species
  - Characterize variability in responses across species and cyanotoxin classes

Priority Cyanotoxins

Table 1 Priority cyanotoxins for literature search and data extraction, selected based on production by the most common HAB-forming cyanobacteria in the U.S. freshwater and marine ecosystems.

	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] Included in March 2021 literature search, along with an additional ~100 cyanotoxins documented in publications and government reports (i.e., EPA Report # EPA/600/R-17/344; Cusick and Sayler 2013 doi: 10.3390/md11040991). March 2021 literature search included total of 165 chemical names and associated CASRNs; [b] Included in November 2022 supplemental literature search.

Literature Inventory

1,125 References tagged with 101 Cyanotoxins

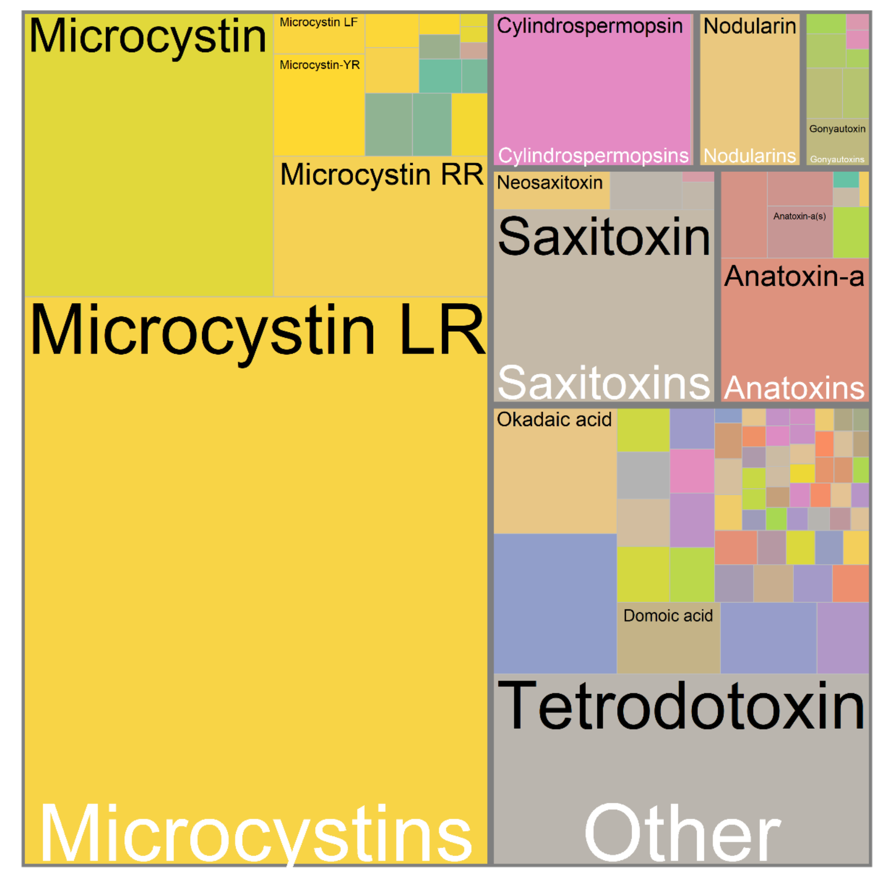


Figure 2. Number of publications by cyanotoxin, shown by box size, for those identified in full-text screening as relevant for ECOTOX. Black labels = cyanotoxin name, white labels = cyanotoxin group.

Habitat, exposure route, effect, and species tags assigned during full-text screening

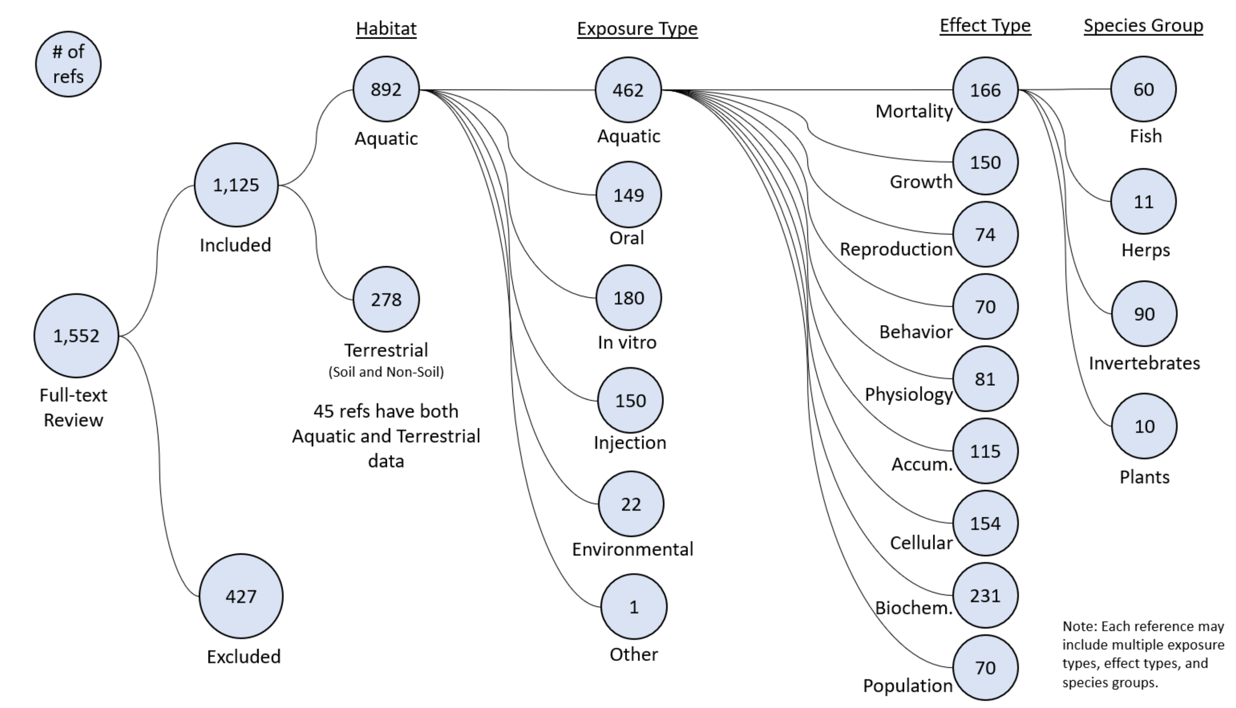


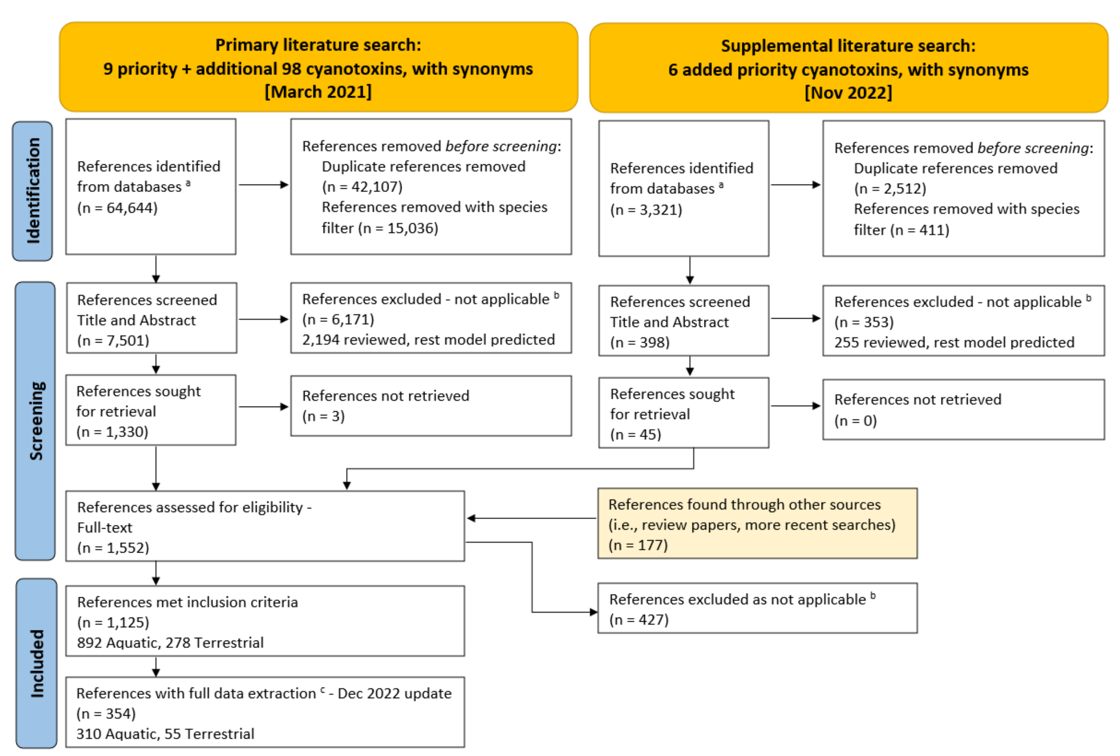
Figure 3. Literature tag tree for the 1,125 included cyanotoxin references, showing expansion of the aquatic habitat and exposure type to show the diversity of effect types and species with cyanotoxin studies reported (based on full-text screening). Number in circle indicates # of references in each category.

Methods

The literature search, review, and data extraction for cyanotoxin studies followed the well-established ECOTOX protocols described in Olker et al. 2022 doi: 10.1002/etc.5324.

Literature search and study selection flow diagram

Figure 1. Literature search and study selection flow diagram, following guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and MetaAnalyses, https://prisma-statement.org/). Criteria for inclusion in ECOTOX are listed in Table 2.



[a] Chemical-based literature searches in multiple databases: ProQuest, Scopus, ToxLine, Theses, PubAg, Web of Science, Unify (internal USEPA database)
[b] References tagged with reason for exclusion at both title and abstract screening and full-text review.
[c] Data extraction includes pertinent study details (species, chemicals, test methods, and toxicity results) following the ECOTOX controlled vocabulary.
Toxicity results are updated to the ECOTOX public website on a quarterly basis.

Criteria for inclusion in ECOTOX

Table 2. Criteria and requirements for inclusion in ECOTOX following well-established Standard Operating Procedures.

Species	• Ecologically relevant species • Live, whole organisms • Organism taxonomic information verifiable against standard taxonomic sources • Priority species are wild (test results for terrestrial domestic and laboratory species are used to fill data gaps when needed) • In vitro studies (with viable cells or tissue) flagged for possible inclusion as requested by Programs • NOT: humans, monkeys, bacteria, viruses, yeast
Chemical Exposure	• Verifiable Chemical Abstract Services (CAS) number • Single chemical exposure • Relevant to environmental exposure • Report exposure concentration, dose or application rate • Report duration of exposure • Sediment studies must have a water concentration reported to be included • NOT: Air pollution studies related to CO2 and ozone
Effect/ Response	• Biological effect measured • Effect concurrent with associated chemical exposure • Adverse effects are priority (beneficial, nutritional effects are lower priority)
Publication/ Data Format	• Primary source of the data • Study must be a full article in English • NOT: Reviews or abstract only

Toxicity Data Curation

Full data extraction completed for 354 Publications

- 9,891 Total data records
  - 8,689 Aquatic
  - 1,202 Terrestrial
- Curated data available on ECOTOX: www.epa.gov/ecotox

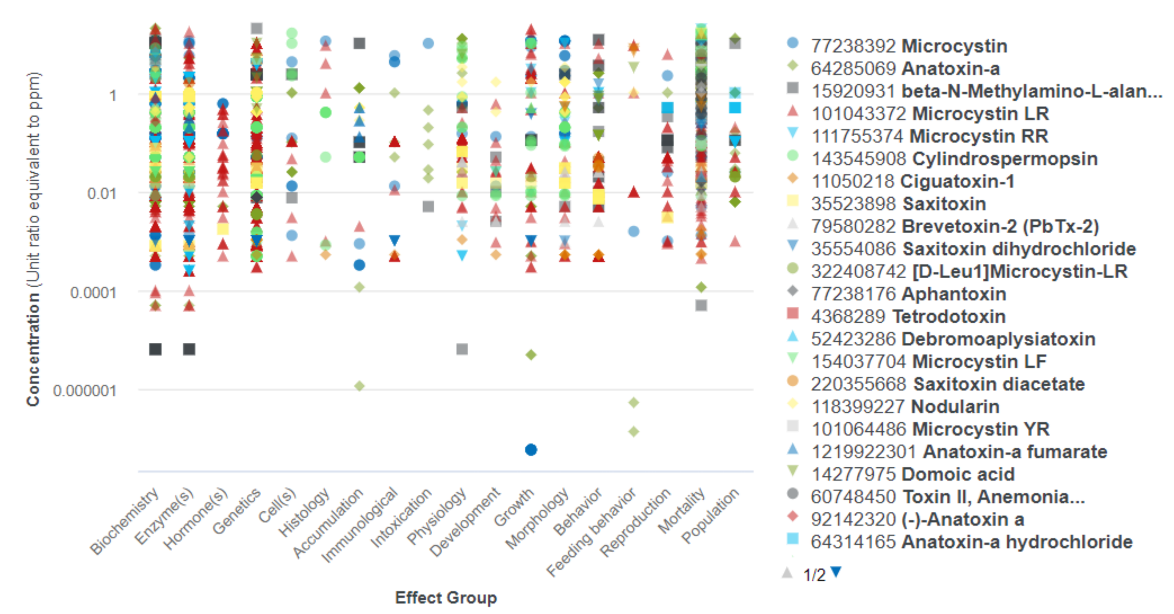


Figure 4. Data for effects of cyanotoxins shown by exposure concentration and species group. [Endpoints include BAF, LCXX, LDXX, LTXX, ECXX, ICXX, LOEC/LOER, and lethality; NOEC/NOEL/NOER and no lethality data (n=2,259 records) and records with no endpoint reported (n=483) excluded.] https://cfpub.epa.gov/ecotox/explore.cfm?cgid=40

Number of references by cyanotoxin

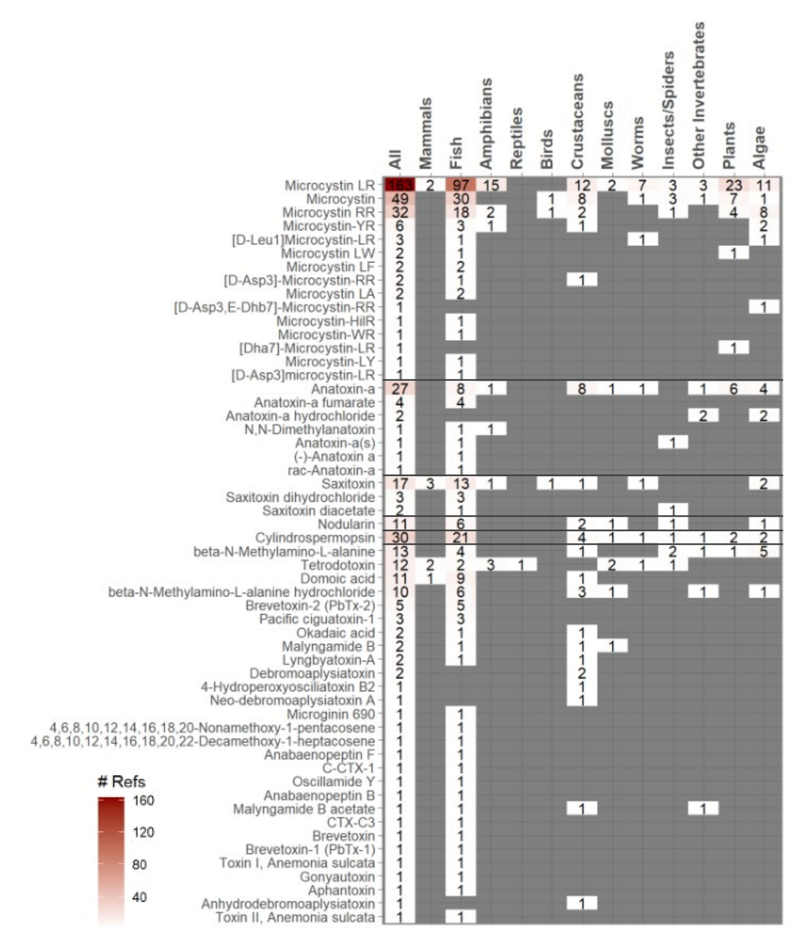


Table 3. Number of references with data in ECOTOX by cyanotoxin for each species group, sorted by cyanotoxin group. Grey indicates no references with data extracted as of December 2022.

Data array for select toxicity studies

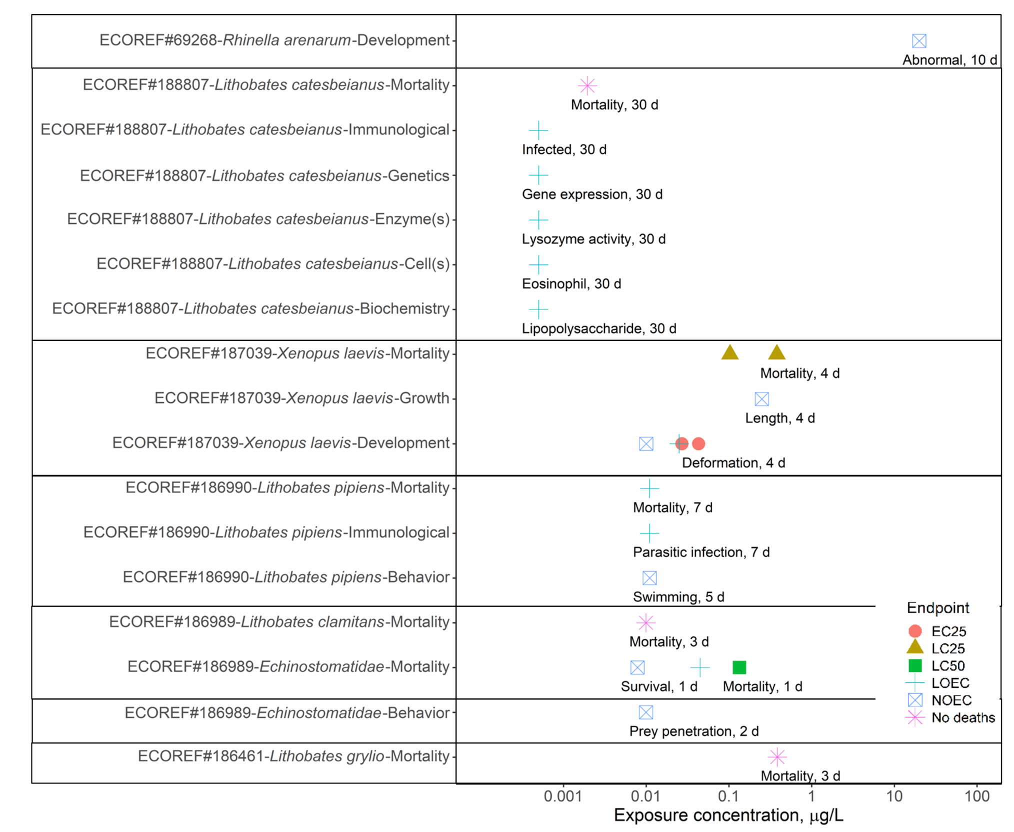


Figure 5. Array of data records for select amphibian studies on toxicity of microcystin-LR (CASRN 101043-37-2).

ECOREF #69268. Chernoff et al. Toxicol.22(1): 13-17, 2002; ECOREF #188807. Shu et al. Ecotoxicol. Environ. Saf.238:10 p., 2022; ECOREF #187039. Dvorakova et al. Environ. Toxicol.17(6): 547-555, 2002; ECOREF #186990. Milotic et al. Parasitol. Res.117(2): 513-520, 2018; ECOREF #186989. Buss et al. Chemosphere220:731-737, 2019; ECOREF #186461. Zhang, et al. Phycol. Res.60(1): 20-26, 2012.

SOT Annual Meeting, 19-23 March, 2023, Nashville, TN

ECOTOX originated in the early 1980s and is maintained by U.S. EPA ORD at: www.epa.gov/ecotox
Read more about the ECOTOX Knowledgebase in Olker et al. 2022
doi: 10.1002/etc.5324