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A comprehensive approach for evaluation of acute toxic responses after microcystin ingestion

JIYOUNG LEE, PhD
Associate Professor
Division of Environmental Health Sciences

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Outline

- Current HAB-related research effort at OSU
- Plan for the acute toxicity study

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Focus Areas and Priorities

- Focus Areas:
  - Blooms: Sources and Movement
  - Produce Safe Drinking Water
  - Protect Public Health
  - Educate and Engage
- Priority categories:
  - Treatment Optimization
  - Cyanotoxin Toxicity
  - Reservoir Management
  - Bloom Dynamics
  - Analytical Methods
  - Nutrient Load Reduction Methods

(Slide credit: Dr. Chris Winslow)

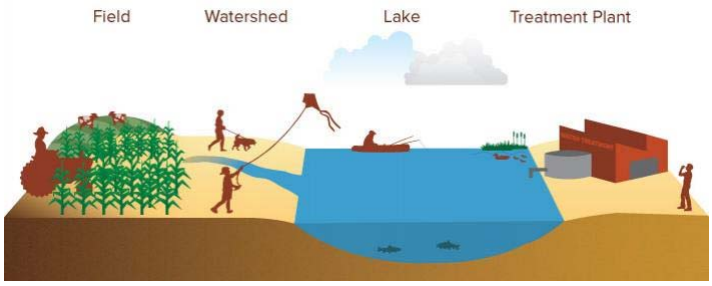
HAB Research at Ohio State University

Field to Faucet program

"Field to Faucet is an integrated suite of research, education and outreach activities designed to deliver end-to-end solutions to harmful algal blooms and other water quality issues."

(Slide credit: Field to Faucet program & Global Water Institute)

Global Water Institute



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HAB & health impact

- Harmful cyanobacteria are known to produce various types of cyanotoxins: hepatotoxins, neurotoxins, cytotoxins, irritants and/or gastrointestinal toxins
- Some of the most common genera found in freshwater, such as *Microcystis, Planktothrix,* and *Anabaena,* produce a liver toxin, known as microcystin (MC).
- In North American water bodies, MCs are also the most commonly found cyanotoxins, while anatoxins, saxitoxins, and cylindrospermopsins have also been reported occasionally.
- Among the MC variants, MC-LR is the most potent and has the potential to impact human and animal health on a large scale.

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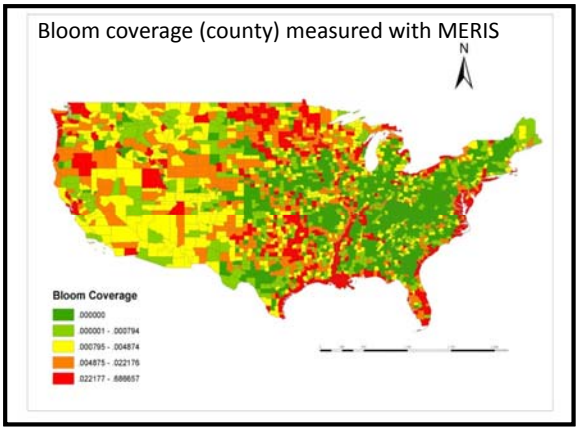
MC & health impact

- A recent US study (Zhang et al., 2015) showed that there are significant clusters of deaths attributable to non-alcoholic liver disease impacted by cyanobacterial blooms in freshwater bodies.
- While the liver is the primary target of MC toxicity, there have been some reports of effects in other systems, including hematological, kidney, cardiac, reproductive, and gastrointestinal effects.



Zhang, Lee et al. (2015) Environmental Health.

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Research needs

- Our review of the relevant literature has identified an urgent need for reproducible acute toxicity data for MC exposure via ingestion using both genders of mice at various oral doses.
- The most recent US EPA's Health Effects Support Document for the Cyanobacterial Toxin Microcystins (2015) has also pinpointed research needs beyond liver toxicity, such as MC toxicity to reproductive systems in both male and female (→ Objective 1).
- While histopathological examination provides clear sign of acute toxicity, biomarkers allow for the early detection of disease in advance of other available measureable clinical indicators (→ Objective 2).

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Acute Toxicity Study

Objective 1: Conduct an acute toxicity study of MC via oral exposure. Eight-week-old male and female mice (CD-1) will be exposed four doses of MC-LR administered via gavage for a period of seven days.

- Histopathological endpoints: liver, kidneys, epididymis, testes, prostate, seminal vesicles, ovaries, and uterus.
- Blood will also be collected for clinical chemistry outcomes.
- Before the main study, a preliminary study will be conducted to determine effective dose range.

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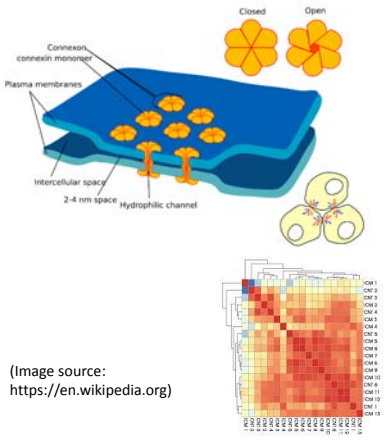
Acute Toxicity Study

Objective 2: Determine the cellular and molecular basis of toxicological responses occurring in mouse hepatocytes exposed to microcystin acutely.

- Whole livers exposed to various doses of MC *in vivo* will be evaluated for alterations in;
  - gap junctional-mediated intercellular communication
  - the expression of 84 key genes in 13 different biological pathways activated in response to MC.



(Image source: https://en.wikipedia.org)

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Research team

Interdisciplinary team has been formed.

- Jiyoung Lee, PhD (PI)
- Chris Weghorst, PhD
- Randy Ruch, PhD
- Mark Morse, PhD

Project partners:

- US EPA
- CDC
- Ohio EPA
- Toledo-Lucas Health Department

Funding source: Ohio Dept. of Higher Education

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On-going related work

- Evaluation of Cyanobacteria and Their Toxins in a Two-Staged Model of Hepatocarcinogenesis (PI: C. Weghorst, Collaborating Partner: J. Lee).
  - We are using environmentally relevant levels of both pure compound (MC-LR, 10µg/L) and whole cell biomass (normalized to 10µg/L MC-LR equivalents) to define the contribution of these natural liver toxins to cancer promotion, progression, and endstage disease.
- Microcystin in Lake Erie source water and finished drinking water (PI: J. Lee)
- Relationship between cyanobacteria blooms and human cancer cases (PI: J. Lee).
- MC exposure through food (PI: S. Ludsin, co-PI: J. Lee, J. Martin, S. Schwartz, K. Riedl).

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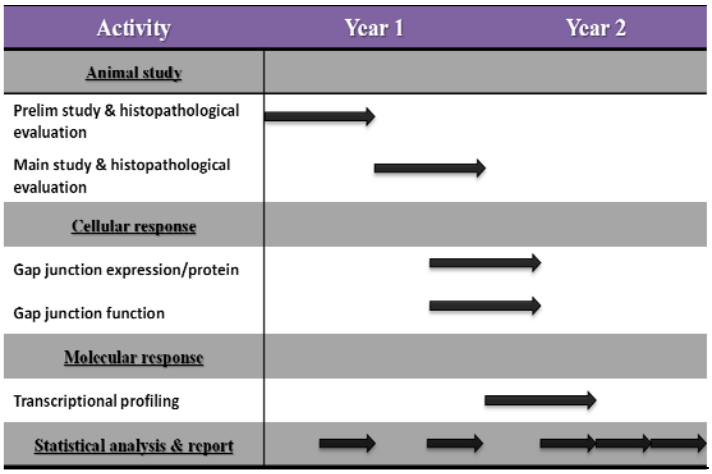
Project schedule (2016 – 2018)



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Thank you.

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