Cyanobacterial toxins and the intestines – What are we missing?

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Objectives

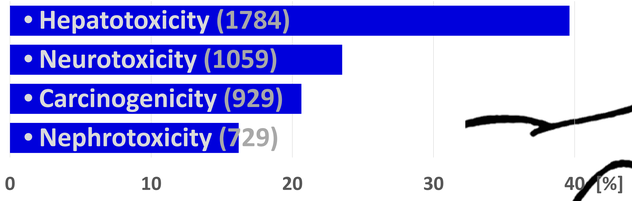
Addressing the **data gap**: Review of freshwater bloom effects on the gastrointestinal tract, including:

- Environmental **mixtures**
- **Novel** cyanobacterial toxins & metabolites
- Implications for **drinking water safety**

Background

- Anthropogenic eutrophication of freshwater bodies and climate change increase the occurrence of toxic cyanobacterial **blooms**[1]
- Prolonged dry heat periods in summer pose a hazard to **drinking water safety**
- Upon (human) exposure to cyanotoxins, **gastrointestinal symptoms** (e.g. nausea, vomiting, diarrhea) are frequently reported[2,3]
- Most likely exposure route to water-borne cyanobacteria: accidental consumption of contaminated drinking water[4]
- Epithelia of the gastrointestinal tract (GIT) are the first barrier to be overcome for causing specific organ toxicities

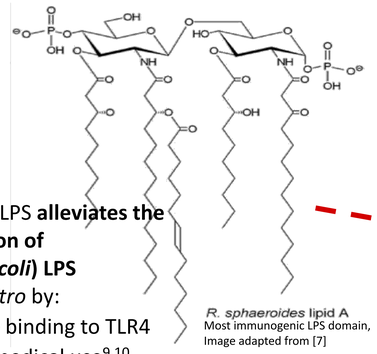
- Most studied toxic effects (of **isolated toxins**)[5]:



- Cyanobacterial metabolites diversity is not sufficiently reflected by toxicological studies, mixture effects are very likely to significantly contribute to the symptoms and illness severity[6]

Cyanobacterial LPS

- LPS = lipopolysaccharide
- Structural feature of the Gram-negative bacterial cell wall
- Recognized by the innate immune systems
  pattern recognition receptor TLR4, expressed particularly on epithelial, endothelial and immune cells (phagocytes)[8]
- Suggested to contribute to GIT inflammation
- Facilitate epithelial penetration of other cyanotoxins

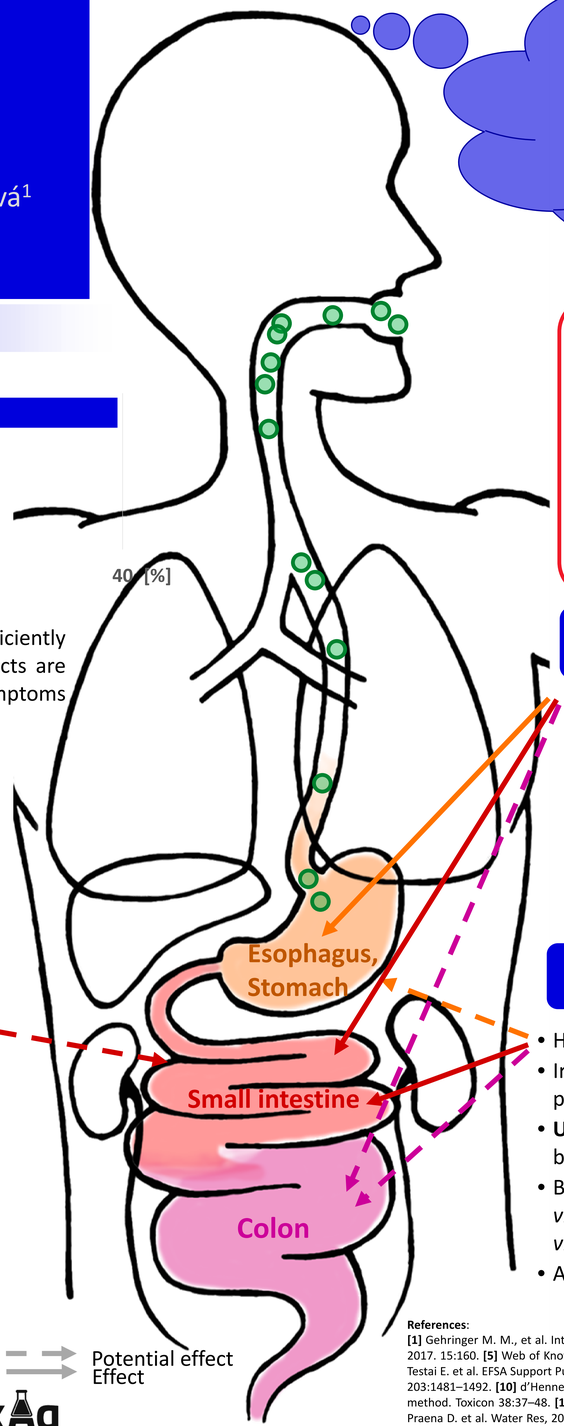


R. sphaeroides lipid A
Most immunogenic LPS domain,
Image adapted from [7]

BUT:

Cyanobacterial LPS **alleviates the immune reaction of eubacterial (*E. coli*) LPS** *in vivo* and *in vitro* by:

- Competitively binding to TLR4
- Potential for medical use[9,10]
- Contribution to gastrointestinal irritation upon cyanobacterial intoxication is possible but yet **inconclusive** due to the lack of toxicological data
- Cyanobacteria and their LPS structure are **phylogenetically distant** from eubacteria[7]



Conclusions & Data gaps

- Toxicity assessment of **novel toxins & metabolites** needed
- **Little information** on distinct gastro-intestinal effects
- Safe drinking Water: **Low toxin concentrations** need to be toxicologically covered
- **Mechanistic data** (e.g. from advanced *in vitro* assays) needed for accurate hazard characterization
- **Reassessment** of CYN and MC-LR for enterotoxicity recommended
- **Characterization** of the (non-)toxic **bloom metabolome**

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Effects of cyanobacterial toxins on the human gastrointestinal tract and the mucosal innate immune system
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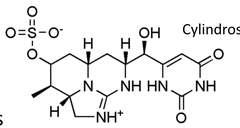
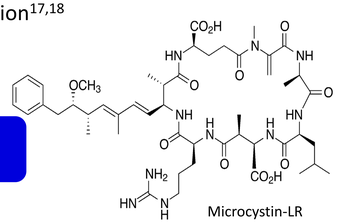
Cylindrospermopsin


Cylindrospermopsin

- Hepatotoxin, cytotoxin
- Irreversible inhibition of protein biosynthesis
- Oral exposure causes ulceration of the **stomach** and lesions in the **(small) intestine** *in vivo* (mouse) and acts on **colon epithelia** *in vitro* (human, CaCo-2 cells)[14,15,16]
- **Pro-inflammatory** action[17,18]

Microcystins


Microcystin-LR

- Hepatotoxins
- Irreversible inhibitors of the ubiquitous intracellular protein phosphatase 1 and 2A
- **Uptake** via organic anion transport polypeptides and the bile acid system in the **small intestine**
- Besides liver, impact also the **(small) intestine** upon *in vivo* oral exposure (rodent models) and **colon epithelia** *in vitro* (human, CaCo-2 cells)[11,12,13]
- Activate macrophages *in vitro*[14]

What about other compounds?

Mixtures

- Blooms: biomass + exudate
- **Most probable** form of exposure to cyanobacteria
- **Highly variable** in biological and chemical composition (associated bacteria, cyanobacterial taxa, metabolites…), **poorly characterized**[6]
- Symptoms upon exposure: **gastroenteric disease, nausea, diarrhoea, abdominal pain**[3,19]
- → **co-action** of many factors

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