Priority setting for hazard assessment in recreational waters affected by freshwater cyanobacteria: Death or Itching?

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Consequential premise: That near-term future efforts should be directed towards understanding the clinical epidemiology of *severe* morbidity arising from acute exposure to cyanotoxins in recreational waters

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Challenges for field epidemiology of recreational exposure to cyanobacteria:

Diverse range of adverse health outcomes: "*Omnibus epidemiology*"

Ephemeral nature of blooms

Biomarkers: exposure, outcome, susceptibility

Recruitment and follow-up

Mechanistic toxicity of the cyanotoxins: neurotoxins, hepatotoxins

Parking-lot science?

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Cutaneous reactions to *freshwater* cyanobacteria / cyanotoxins:

Epidemiology: poorly understood, from a very low base

"Humans are affected with a range of symptoms including skin irritation, stomach cramps, vomiting, nausea, diarrhoea, fever, sore throat, headache, muscle and joint pain, blisters of the mouth and liver damage." **Agrawal A & Gopal K (2013) Chapter: Toxic cyanobacteria in water and their public health consequences, in: *Biomonitoring of water and waste water* Springer India**

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"Recreational exposure by skin contact or inhalation to microcystins is now recognized to cause a wide range of acute illnesses which can be life-threatening."

de la Cruz AA *et al* (2013) *Anticancer Agents Med Chem* 11(1):19-37

The above statement can be challenged: exposure to MCs in recreational waters resulting in life-threatening illness is likely to have occurred by the *ORAL* EXPOSURE ROUTE

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Cutaneous reactions to *freshwater* cyanobacteria / cyanotoxins:

Excluding consideration of the *Lyngbya majuscula*-related toxins:

The important freshwater cyanotoxins are *water soluble*: microcystins, saxitoxins, cylindrospermopsin, anatoxin-a, nodularin

Therefore systemic intoxication via the dermal exposure route during natural exposure conditions in individuals with intact skin barrier function is *unlikely*

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Experimental evidence for systemic intoxication via the dermal exposure route:

Lethal intoxication of guinea pigs by MC-LR and saxitoxin (separately) via dermal exposure

Wannemacher RW Jr *et al* (1987) In *Progress in venom and toxin research: proceedings of the 1st Asia-Pacific Congress on Animal, Plant and Microbial Toxins; Singapore Edited by: Gopalakrishnakone P, Tan CK.* Faculty of Medicine, National University of Singapore, in collaboration with the International Society of Toxinology, Asia-Pacific Section pp.718-724.

BUT these were highly artificial exposures, using the polar aprotic solvent DMSO as a vehicle

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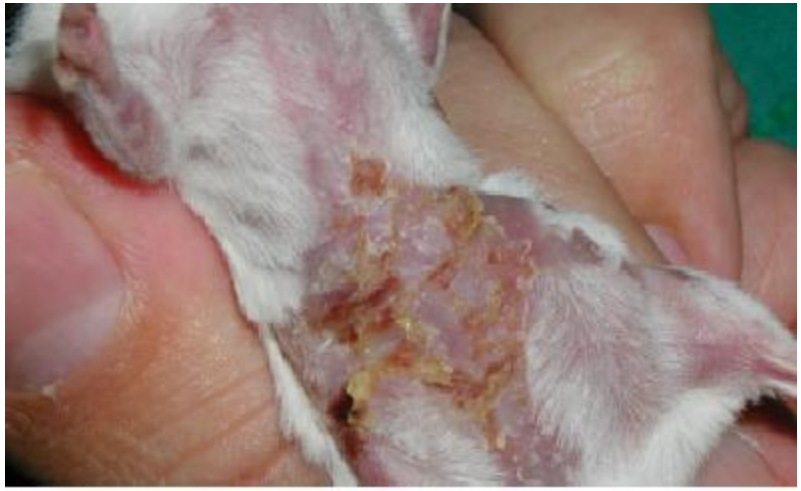
Experimental evidence for cutaneous reactivity via the dermal exposure route:



CYN 100ppm in 70% EtOH

Control: 70% EtOH

Stewart I *et al* (2006) *BMC Dermatol* 6:5

No evidence of systemic intoxication by CYN

DISPOSAL SAFE
FOR SHARPS &
CLINICAL WASTE
BIOHAZARD

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Cutaneous reactions to *freshwater* cyanobacteria / cyanotoxins:

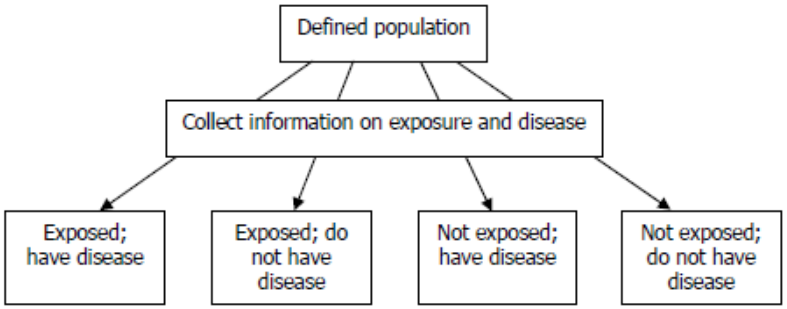
Understanding of cutaneous reactivity to *freshwater* cyanobacteria in humans is largely based on anecdotal reports

Prevalence / incidence essentially unknown, but probably low

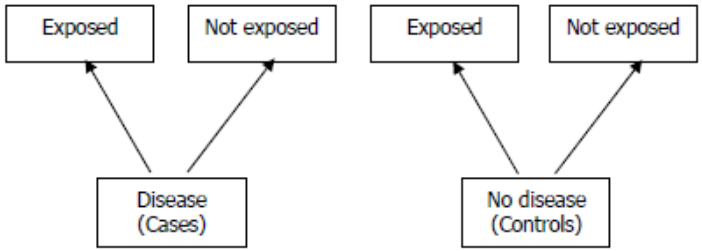
Weak evidence for irritant reactions from *freshwater* planktonic cyanobacteria; majority likely to be allergic reactions

Willingness to tolerate minor cutaneous reactions from recreational water exposure to cyanos has not been investigated

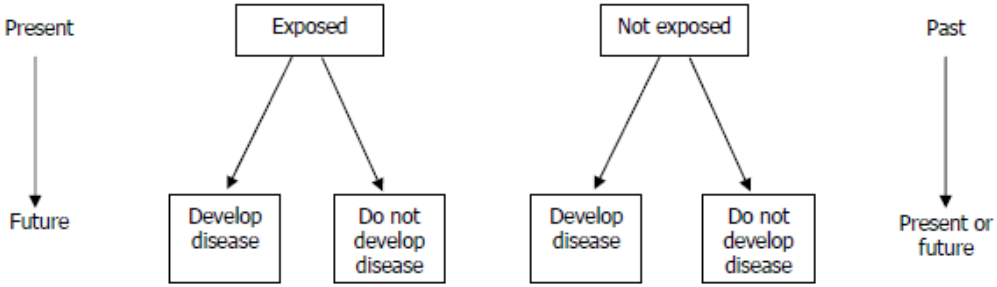
Common epidemiological study designs



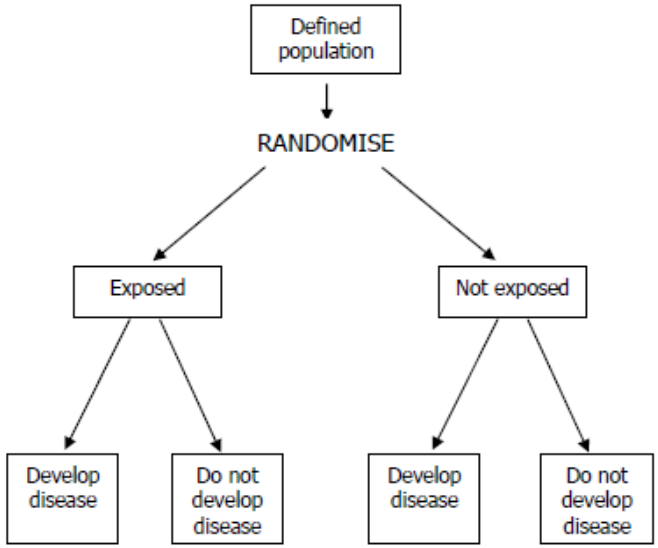
Cross-sectional design



Case-control design



Cohort design



Randomised controlled design

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Epidemiology of recreational exposure to *freshwater* cyanobacteria / cyanotoxins:

Reviews of formal studies & anecdotal and case reports:

Stewart I, Webb PM, Schluter PJ, Shaw GR (2006) *Environ Health* 5:6

Stewart I, Carmichael WW, Backer LC, Fleming LE, Shaw GR (2011) in: *Encyclopedia of Environmental Health* pp. 776-88

See also: Stewart I *et al* (2009) *Environ Health* 8:52

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Pilotto *et al* (1997) *Aust N Z J Public Health* 21:562-6

Of 22 logistic regression models run:

One model is uninterpretable (OR=1.87, CI 0.68 to 1.54)

Only one model is significant (OR 3.44, CI 1.09 to 10.82): exposed group *n* = 93, unexposed group *n* = 43

Increased symptom reporting at 7 days but not at 2 days

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Epidemiology of recreational exposure to *freshwater* cyanobacteria / cyanotoxins:

Biomarkers of exposure: toxins (?)

Biomarkers of outcome: ???

Prospective epidemiology needs to be more focused and targeted: cutaneous reactivity, inhalational exposure. Problem of omnibus epidemiology

Mechanisms of toxicity vary widely across cyanotoxin groups: channelopathies, protein phosphatase inhibition, ACh agonists, anticholinesterases

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Epidemiology of recreational exposure to *freshwater* cyanobacteria / cyanotoxins:

Clinical epidemiology of cyanotoxin-related acute illness:

Diagnostic investigations, therapeutic interventions, natural history, follow-up

***n*-of-1 studies ??**

Thorough and comprehensive case reports and case series

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Epidemiology of recreational exposure to *freshwater* cyanobacteria / cyanotoxins:

Case report: 19yo jet-skier, Argentina

Acute respiratory and G-I S&S; febrile, hepatic insufficiency, bil. lower lobe pneumonia, hypoxaemia, hypercapnia

Required IPPV, supportive treatment

Discharged after 20 days, 8 days in ICU

Giannuzzi L *et al* (2011) *Mar Drugs* 9(11):2164-75

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Case report: 39yo windsurfer, UK

Investigated 6 weeks after exposure; LFTs, liver biopsy

MC isolated from reservoir, sheep & dog deaths

Probert CS *et al* (1995) *Arq Gastroenterol* 32(4):199

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Epidemiology of recreational exposure to *freshwater* cyanobacteria / cyanotoxins:

Cyanobacterial neurotoxins?

Measure nerve conduction deficit?

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Image attribution: Vloka JD *et al* (1999) *Internet J Anesthesiol* Vol3N4

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CONCLUSIONS

Prospective field epidemiology is unlikely to address information gaps for *severe* acute intoxications following recreational exposure to cyanobacteria

Detailed clinical investigations can inform about predisposing risk factors, exposure route/s, natural history of disease, diagnostic support, pharmacotherapy and follow-up of *severe* acute illnesses

Outreach programs targeting high-risk conditions, risky behaviours