

## Author's response to reviews

**Title:** Recreational and occupational field exposure to freshwater cyanobacteria - a review of anecdotal and case reports, epidemiological studies and the challenges for epidemiologic assessment

### Authors:

Ian Stewart ([i.stewart@uq.edu.au](mailto:i.stewart@uq.edu.au))  
Penelope M Webb ([Penny.Webb@qimr.edu.au](mailto:Penny.Webb@qimr.edu.au))  
Philip J Schluter ([philip.schluter@aut.ac.nz](mailto:philip.schluter@aut.ac.nz))  
Glen R Shaw ([g.shaw@uq.edu.au](mailto:g.shaw@uq.edu.au))

**Version: 5 Date:** 23 June 2005

### Author's response to reviews:

Responses to reviewers' comments:

JOHN COLFORD COMMENTS: The principal criticism of A/Prof. Colford pertains to our search strategy. Our response follows, with responses to A/Prof Colford's other comments following that. This initial discussion addresses both A/Prof Colford's concerns about the systematic nature of our review, and editors' comments flowing from those concerns. While A/Prof Colford noted that our inclusion of references from the "grey literature" was appropriate and laudable, the editor comments suggested that we should delete references that met the entry criteria for inclusion in Table 2 but were not found by the use of electronic databases.

We reviewed the following authoritative sources in order to answer two questions:

1. What is the appropriate methodology to maximise the number of relevant citations in a systematic review, with particular reference to "grey literature" (i.e. references in book chapters, conference proceedings, government reports etc)
2. What is an appropriate search strategy with regard to the number of titles to search?

Sources:

1. Khan KS, Kunz R et al (2003) Systematic reviews to support evidence-based medicine: how to review and apply findings of healthcare research. Royal Society of Medicine Press, London.
2. Glasziou P, Irwig L et al (2001) Systematic reviews in health care: a practical guide. Cambridge University Press, Cambridge.
3. Mulrow C, Cook D (Eds) (1998) Systematic Reviews: synthesis of best evidence for health care decisions. American College of Physicians, Philadelphia.

4. Oxman AD, Cook DJ et al (1994) Users' guides to the medical literature. VI. How to use an overview. JAMA; 272:1367-71.
5. Sackett DL, Straus SE et al (2000) Evidence-based medicine: how to practice and teach EBM (2nd Edn). Churchill Livingstone, Edinburgh.
6. Greenhalgh T (2001) How to read a paper: the basics of evidence based medicine (2nd Edn). BMJ Books, London.
7. Friedland DJ, Go AS et al (1998) Evidence-based medicine: a framework for clinical practice. Appleton & Lange, Stamford CT.
8. Hunink MGM, Glasziou PP et al (2001) Decision making in health and medicine: integrating evidence and values. Cambridge University Press, Cambridge.

With regard to the first question, all of the above sources suggest that it is not only appropriate but essential to search beyond electronic databases: e.g.

"Inaccurate or incomplete indexing of articles and journals in electronic bibliographic databases requires the examination of other sources of citations. Reference lists from identified studies and related reviews provide a rich source of potentially relevant citations" (Khan et al, p27).

"If they did carry out a search, we seek reassurance that it went beyond standard bibliographic databases, as these have been shown to fail to correctly label up to half of the published trials in their own files. A more rigorous [systematic review] would include hand-searching journals (the starting point for any Cochrane review), conference proceedings, theses..." (Sackett et al, p134).

and

"it is important that authors conduct a thorough search...this should include the use of bibliographic databases...checking the reference lists of the articles they retrieved..." (Oxman et al).

We would therefore be reluctant to delete citations that met our inclusion criteria because they were found by methods other than the use of electronic databases.

Regarding the second question (appropriate number of titles to scan):

Sackett et al (p55) suggest that 243 references is "a daunting number" to search

Friedland et al (p111): 2,126 citations: "we don't want to look through all of them..."

Friedland et al (p127) suggest that an appropriate electronic search strategy involves "narrow[ing] your search to fewer than 100 or so... [and]...scroll through the titles."

We conducted searches in reverse, by broadening our search terms per A/Prof Colford's suggestion ("Cyanobacter\*" in PubMed = 9,127 hits). This search would only identify seven of the 20 citations we currently have from peer-reviewed journals; the other 13 citations are from journals not monitored in PubMed. The broadest search strategy we could devise, which would require searching more than 28,000 titles in both PubMed and Web of Science, would still only find 13 of the 20 citations.

We therefore submit that our revised search strategy is a reasonable and efficient approach to this matter. Our review is the first to specifically examine recreational exposure to cyanobacteria, and our collation of references far outweighs (numerically) any other review conducted to date; other reviews discussing anecdotal reports of acute illness following exposure to cyanobacteria usually discuss selected papers incorporating multiple exposure routes, e.g. recreational, drinking water outbreaks, and haemodialysis. We submit that this review is by far the most comprehensive paper to specifically look at recreational exposure to cyanobacteria.

It was not our intention to cast unfavourable light on the methodology of evidence-based medicine by drawing attention to the fact that most of the

citations that met our inclusion criteria were beyond the reach of electronic databases. Quite the contrary, we are all firm supporters of EBM. However, after refreshing our memories by returning to EBM guideline literature, it is probably not surprising to find that electronic databases, which are most useful for searching formal epidemiological studies, particularly randomised trials, were not as helpful in identifying anecdotal reports of acute illness following recreational exposure to cyanobacteria. This topic is very much in its infancy with respect to indexing, and the sources of information are at

present very diffuse. The overwhelming proportion of publications about cyanobacteria appear to relate to the ecology and molecular biology of these organisms, with a much smaller proportion devoted to human health aspects. While there may well be other suitable references buried in the huge body of multi-disciplinary literature on cyanobacteria, we submit that our revised search strategy and our review represent an important first step, and will be a valuable tool for researchers who progress this field of environmental epidemiology.

Our revised search strategy also addresses the reviewer comments about English vs. non-English publications, by examining the proportion of English and non-English papers. There wouldn't appear to be a "hidden" body of literature in non-English articles.

Re A/Prof. Colford's other comments:

Review and discussion of the advantages and disadvantages of various study designs deleted (& associated figures deleted). A/Prof. Colford notes that this section would be "not helpful...to the audience of epidemiologists who would be reading this paper..." We agree that is the case, though I would like to register my personal disappointment at this, as the original intention was to have this work able to be interpreted and understood by cyanobacteriologists, who by and large do not have a background in epidemiology or human health care. Harmful Algal Bloom researchers come from a broad range of disciplines to study cyanotoxins, e.g. biochemists, ecologists, structural chemists, GIS specialists, water treatment and supply engineers. Many of these workers know that epidemiology is important - they keep hearing that more, and especially better epidemiology is needed - but several have expressed to me their lack of understanding of the topic. I had rather hoped to combine discussion of the work already done on recreational exposure to cyanobacteria with a primer on common epidemiological approaches, tailored to the field of aquatic exposures. However, we submit this revised manuscript in response to reviewers' critiques.

PAUL LAM COMMENTS:

Review of potential application of other epidemiological study designs to this topic removed per discussion above.

Table 3 added to summarise published epidemiological studies. I presume that Prof. Lam was referring to the epidemiological studies in regard to his request that we should tabulate summary statistics; the descriptive discussion of the anecdotal reports I submit should remain descriptive, as it is important not to

over-interpret anecdotal reports because they lack controls. I feel that our tabulation of the primary features from anecdotal and case reports, which allows for comparison of key features in table columns, is as far as we should take this aspect of the work. The table also shows important information that is missing from many anecdotal reports, which hopefully will be a pointer to those collecting similar reports in future at cyanobacteria-affected waters.

#### JAMES SPENCER METCALF COMMENTS;

Dr Metcalf notes that papers submitted for publication should not be cited in a review paper. I agree; I may have taken on too much in attempting to publish a number of related works in different journals simultaneously. There are two possible approaches here:

1. I can delete all "Submitted for publication" citations and refer instead to my PhD thesis
2. If the editors will agree to withhold publication until we have acceptance notifications for "Submitted for publication" references, which can then be published as "In Press".

I would prefer the latter approach, as the works submitted for publication are more up-to-date, concise and (presumably) authoritative. In any event, I suggest that the accompanying review submitted to Environmental Health: A Global Access Science Source (on cyanobacterial lipopolysaccharides) would, if accepted, be most suited for publication in the same issue of the journal.

Sentence added re LPS common to all Gram-negative bacteria.

#### EDITOR COMMENTS:

Sentence and citation added per suggested inclusion of paper by Cox et al on BMAA (Proc Nat Acad Sci USA). Your suggestions were made in your reply to our submitted review on cyanobacterial LPS, but this review would appear to be the most suitable paper for this reference.

#### SUMMARY OF CHANGES:

1. Revised discussion of search strategy and systematic review
2. Removal of discussion of potential epidemiological study designs and their application to this topic
3. Table 3 added (uploaded as a separate file)
4. Table 2 (landscape format) removed from the main manuscript and uploaded as a separate file.
5. References reformatted as requested.
6. List of abbreviations and author contributions sections added.
7. References for papers published since submitting the original manuscript added, with relevant discussion (citations # 10, 53, 134). Also refs 45-47 added per revised discussion of systematic reviews.