

Reviewer's report

Title: Cyanobacterial lipopolysaccharides and human health - a review

Version: 3 **Date:** 31 May 2005

Reviewer: Claudia Wiegand

Reviewer's report:

General

The manuscript needs major compulsory revisions before it can be considered for publication. The recommendation for this manuscript is to thoroughly check the paragraphs concerning LPS from pathogenic bacteria for further possibilities to either compare to the limited knowledge from the cyanobacterial LPS, or point out the required research steps.

Furthermore, the current knowledge about the cyanobacterial LPS urgently needs to be described in more detail. This review should intend to bring the reader up to date with the main findings of the field, and their impact, as well as the lack of knowledge.

Essential is the change of the tone. Even although I am aware of the fact, that the terminology is sometimes used wrong, I strongly disagree with this way of presenting it !!!

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract:

Even if cyanobacterial LPS will be characterized eventually to be as diverse as that of other Gram-negative bacteria, if effects can be traced down to purified LPS, there is no difficulties to name them.

Tab 1 can be summarized in a few sentences.

There is no need to reason, why several refs are not mentioned. Negative examples are to be avoided.

P5: first paragraph is non agreeable: specify, avoid negative sentences, name the results obtained using cyanobacterial LPS and compare to other LPS.

P5 Second paragraph is inconclusive, the statements why cyanoLPS is accused for many effects, namely the extrapolation from other Gram-negative bacteria should start this whole sequence cyanoLPS and symptoms in humans. All the descriptive or assumptive effects can be shortened and summarized.

P5: Last paragraph repeats the introduction, and should be included there or deleted.

P6: An explanation of the molecular details in the cell wall of cyanobacteria, classifying them as Gram-negative or positive is highly welcome. The reasons for classification should be mentioned i.e. why Gram-staining worked or not instead of detailing possible wrong classifications by the one or other author. For the current review it is enough to state, weather or not all of the cyanos contain LPS.

P7: It doesn't speak for a scientist to detail names and mistakes (refs 35-43). For any reader of this review, it should be of greatest help to just name the fact, that misuse of the term endotoxins occurs in literature, and then go on explaining how it should be used (as you did).
The term exotoxin is misleading too, as we don't know for sure yet about the ecological function of most of these toxins.

Page 8,9: Several sentences are just a list of other reviews, without commenting or comparing. Please either name the main results or shorten.
Page 10: why judge the refs?

I don't agree with the statement, that LPS should be non-toxic, as removing the molecular target of a toxicant doesn't mean that the substance became non-toxic.

Page 17: again, it is important to point out the lack of analytical data of cyanobacterial LPS and consequent research, but not how the cyanobacterial research community should handle the data. If the lipid A varies with the species is likely, but still speculative by the authors.

Page 20: it is correct to view cyanobacterial illness as intoxication rather than infection, so why give detailed explanations about infection? Emphasis should be on the difference between pathogen and toxic.

If the classical cyanotoxins (microcystins, anatoxins, etc) would be able to stimulate vomiting, it would have been observed during the numerous animal testings (mouse toxicity).

What are the consequences intoxication with SE in comparison to the intoxication with cyanobacteria???

Page 24: skip the definition of humans as bags for housing and transport of bacteria
It would be of interest, by which mechanism the gut cells are adapted to LPS of E. coli, and if /why this adaptation works for the variety of existing LPSs as introduced before.
Maybe the explanation using the citation 123 from page 26 can be moved to here.

The anecdotal description can be shortened. The list of intoxications and deaths due to the ingestion of toxic cyanobacteria and action of the toxins (microcystins, anatoxins) would fill pages. It should be clearly stated, that the oral route is the only one referred to in this paragraph.

Page 25: the sentences: Evidence for harmful effects of orally and that the authors have been able to find some literature is not at all of interest for the reader. Rather name the fact, e.g. as: Two reports describe in vivo LPS activity by the oral route

Page 26: please relate these paragraphs to the possible actions of ingested cyanobacteria.

Page 27: again, delete the first few lines, as the reader might rather be interested in the outcome than in the process of the literature study.

Page 28: same as for page 27. Why describing the use of literature databases????
Please comment, compare or evaluate the different methods, or name at least the main results of the comparison carried out by Papageorgiou. Otherwise there is no connection of this sentence to the rest of the paragraph.

Table 2 would be of greater value, if lethality data from other Gram-negative bacteria (E. coli, Salmonella etc.) could be included for comparison (even if they are not new).

Page 29: please comment on the findings of the researchers investigating the Schwartzmann reaction.

Best et al., is mentioned twice. You might connect these two sentences and furthermore name the consequences of their findings.

Please let us know about the outcome of the thermoregulation study. The readers might not all have attended the conference lecture about it and lack the time for additional reading of the PhD-thesis.

Connect all literature for purification and describing of cyanobacterial LPS at one place. Comment/compare them or shorten.

I would recommend changing the sequence of this part: 1. purification, 2. determination (LAL including all its pros and cons), 3. LD and then 4. the other findings in much more detail. It is only few literature available about effects of cyanobacterial LKPS, hence it needs to be presented in detail.

Page 31: first paragraph: unsecured date should not be cited/commented

Page 32: please give more details about the results of Ians investigations in comparison to Tornabene et al., and Falconer et al.

Page 35/35: it is unnecessary to explain in this context the mechanisms by which allergies might be prevented in early childhood, and give some additional lit for further reading (188-191).

Page 36: the style of citing refs is numbers.

Page 37: last 4-5 lines: sentence unclear, please correct.

Page 38: the first paragraph needs to be changed in the direction of the several steps of required research.

Page 39: almost completely relies on data, currently being under review themselves. Hopefully these articles will be in the accepted stage, before this review is ready for printing. Otherwise, the results need to be detailed here, or the PhD-thesis needs to be cited again.

Page 40/41: please replace the facetious and educational paragraphs by a more seriously outline of the future research in the field of the cyanobacterial LPS.

Literature:

At many sites, literature is cited to be complete, without describing the findings, main results, or giving comments or comparing them, e.g. page 8,

Page 9: there are many reviews in the literature on cytokines and LPS, a few examples are 44-46, 48, 52,53,59,60. Question: what would the main findings of these be?

Same for pages 28, 29,

The authors need to check, if all the citations are required to support the statements.

Several citations are at the submitted stage. If this stage does not change during the review process of this manuscript, they should be replaced before final printing.

Please check for the following missing citations, they are not mentioned in the text:

69, 70, 72, 73, 189, 190, 191.

Obviously there was another paragraph in planning, which is not included in the current state of the

manuscript. Please either include in the text or delete the citations from 208-235.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Hierarchy of the headlines is not clear throughout the manuscript.

Page 21/22 is the difference between ref 115 and 116 just the animal (piglet versus cat) or are there other findings?

Page 25: Delete do serve to (second last line)

Discretionary Revisions (which the author can choose to ignore)

additional comments:

Page 11-17 summarizes nicely molecular mechanisms of LPS toxicity in relation to its structure. Moreover, some ecological functions of LPS are attributed to the different niches, inhabited by Gram-negative bacteria.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'