Reviewer's report

Title: Personal Endotoxin Exposure in School Children with Asthma

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Reviewer: Gert Doekes

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Main objectives of this study were to assess:

1. relations between personal measurements of airborne endotoxin and simultaneously measured endotoxin in the air at fixed sites in or outside the home, or at a central regional site at max 5-10 km distance;
2. relations between endotoxin and air pollutants like EC, OC, PM2.5 and NO2 measured in the same samples, or simultaneously at the same sites;
3. relations between personal endotoxin exposure levels and a number of home characteristics and other possible determinants.

Endotoxin was measured in personal and ambient samples from a study in a panel of 45 asthmatic 9-18 year old children, published previously in eg. EHP 2006 and 2008 (refs. 16, 17). All samples were 24 hr airborne dust samples, and as the authors correctly emphasize, the conclusions thus specifically or exclusively apply to short-term exposures which was the relevant parameter in the previous exposure-effect (= FeNO, lung function) panel studies.

The main answers to the present research questions appear to be that:

1. personal endotoxin exposure is hardly correlated with ambient levels, and the latter can thus not be reliably used as proxy for personal exposure; the authors claim to have confirmed previous findings of Rabinovitch et al (JACI 2005) but now in a larger population.
2. there are no clear correlation patterns between airborne endotoxin and other air pollutants – with some exceptions, like high correlations between indoor PM2.5 or EC and endotoxin. Personal exposure data however showed no clear and consistent correlations;
3. only a few determinants like pet ownership and flooding damage to the home could be identified as significant determinants of personal endotoxin exposure levels.

The study and its results might be of some interest since there are indeed very few studies with personal endotoxin exposure data from the home, outdoor, and/or school environment. The originality, relevance and robustness of the findings however may be a matter of debate, for reasons discussed below. Furthermore, the description of the study and its results lacks transparency; particularly the variable numbers of data available for analysis – without clear explanation for these variations – is a reason for concern. Finally, there is a lack
of essential technical details regarding the endotoxin measurements.

General and major comments

1. Why would (1) be a relevant question? Practically all airborne endotoxin exposures in the occupational but also in the indoor home environment have been linked to locally restricted, usually indoor sources and activities. In contrast to traffic-related air pollutants, there is little a priori reason to expect a main impact of regional outdoor background levels on indoor home or school airborne endotoxin levels and on personal exposures. The only exception might be the effect of local sources like concentrated animal feeding operations or other intensive agricultural activities, but those should be only incidentally and locally of relevance, particularly in an urban or sub-urban area.

2. Linked to this: there is extensive experience from decades of organic dust and endotoxin exposure research in occupational environments, that exposure assessment by personal monitoring gives practically always higher and much more reliable levels than ambient sampling. Apart from reasons mentioned in the MS (generation of ‘personal clouds’ due to someone’s own activities) the main reason is that ambient air sampling does not account for time activity patterns while endotoxin levels show very large spatial variation. The authors’ conclusion that ‘Fixed site measurements ……. do not adequately represent….’ (End abstract and begin Discussion and Conclusions) thus is not a remarkable new message. It seems highly unlikely that anyone with some experience in endotoxin research would seriously consider outdoor measurements at a central monitoring site at 5 km distance from a home or school as a useful proxy for either short- or long-term indoor exposure.

3. Results of Rabinovitch et al. were indeed confirmed, but not in a larger population, since a comparison with indoor and outdoor measurements around the home of the children could only be made for 14 children. In the larger group of 45 only data from the central regional measurement site were used – and as indicated above, it is unlikely that anyone would seriously consider to use these for short-term endotoxin exposure assessment.

4. Were any time activity data available? Apart from personal activities affecting the personal exposure the time spent at home, at school, in traffic etc should be major determinants of the daily exposure. It is difficult to imagine that such information was not collected in a panel study like this.

5. Where in the indoor home environment was the sampling conducted: the living room, the bedroom, etc? Was there any data how much time the study participant spent in that location during the sampling period?

6. Why would a relation be expected between other air pollutants and endotoxin (question 2)? Particularly typical traffic exhaust-related pollutants should not be associated since endotoxin is not a traffic exhaust pollutant. PM2.5 (or more likely, the unfortunately not measured PM10) might show a relation, especially in agricultural areas, where endotoxin may be associated with the non-traffic related fractions in airborne particulate matter.

7. A clear answer to question (3) also requires knowledge of time activity patterns
relations with home characteristics would only be expected if children spent much of their time at home – or more precisely, if most of the personal endotoxin exposure occurred at home.

8. The variable numbers of available samples and data are quite confusing and should be better explained. The description of the study design even tends to mask the fact that some analyses could only be done in much smaller subpopulations. This is mentioned in the discussion, but it would be much better to mention the n values also in the tables.

9. Many of the descriptive data of Table 1 have already been published in ref. 16 (EHP 2006; 116, table 3 on page 1738) – with slight modifications probably being due to some missing filters in the endotoxin analyses (?). It may indeed be useful to show these values again in the present MS but it should be clearly indicated when they are essentially the same data as published in ref. 16.

10. Endotoxin extraction and analyses were performed with methods specifically developed/adapted for this study, and suggested to be validated (page 7, : ‘a rapid an thorough method ….’). Has this procedure been published? I miss important details like the composition of the extraction fluid, which has been show to be a major factor determining endotoxin yields from filters and also affecting results in subsequent LAL assays (see eg. studies by Douwes, Thorne, Milton, Reynolds and Spaan et al.). Also the extraction volume, dilution factor of extracts in the LAL assay should be reported.

Minor and specific


12. P 3, line 8-10: It is not clear what this sentence exactly means: that Ryan et al showed (plural) that early life house dust endotoxin and traffic-related air pollutants showed a (positive?) interaction in their relations with the risk of persistent wheeze at age 3?

13. P 3, line 12-13: “Between-home” variation is exactly what the ‘many other studies’ wished to assess, and should thus not be included in this sentence starting with ‘However’ and mentioning objections against settled dust analyses.

14. P 4, line 10-11: the actual present panel with complete data was not larger but smaller than that of Rabinovitch et al (see point 3).

15. M&M, page 6, line 6: These data were not used. (see point 8: the authors should in general more clearly explain the variable numbers in their data analyses)

16. P 8, line 5: Correlations were different for Riverside and Whittier; these differed also in time of study. Were correlations also studied separately for the various study periods?

17. P 8, line 8: “data” (not the ‘distribution’) were log-normally distributed. Was a 10-log or a In-transfomation performed (this would be of relevance for interpretation of the axes of Figs 1 and 2).
18. P 9: what is meant by ‘most nonsignificant’ predictors?

19. Results ; page 9, line 2: Is 0.58 indeed the median for the combined two populations? How could then the GM of Riverside be 0.58 and that in Whittier 0.28 (Table 1)?

20. It would be better to present either GM’s and GSD’s (which would fit for log-normally distributed data and analyses of ln-transformed data with parametric methods as done in the GLM analyses), or median and IQRs – suitable for non-parametric analyses like Spearman correlation.

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

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.