Author’s response to reviews

Title: Respiratory health effects of exposure to low levels of airborne endotoxin - a systematic review

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Author’s response to reviews:

Prof. F. Forastiere
Associate Editor
Environmental Health

Utrecht, January 26th 2018

Dear Prof. Forastiere,

Hereby we submit a revised version of our manuscript entitled: “Respiratory health effects of exposure to low levels of airborne endotoxin – a systematic review”, which we amended in accordance with the Reviewers’ comments.

We thank the Reviewers for their enthusiasm about the manuscript, and for the supportive and helpful comments. Our detailed response to the Reviewers’ comments can be found attached to this letter.

We hope the revised manuscript is now acceptable for publication in Environmental Health.

Yours sincerely,

Azadèh Farokhi, Dick Heederik and Lidwien Smit

Reviewer #1: Thank you for a generally well-written review.
I can appreciate that this is a review on the potentially negative effects of low endotoxin exposure. However, I think that the potentially beneficial health effects of this exposure deserves mentioning. This dual effect of endotoxin exposure may cloud the message of this review; on the other hand, it should not be forgotten.

* Thank you for this important comment. Indeed, our focus on lung function and symptoms led to inclusion of studies showing adverse effects of endotoxin exposure, but the protective effect of endotoxin on atopy/allergic rhinitis needs to be discussed.

To the Introduction we added: “In addition to adverse health effects, occupational endotoxin exposure in agricultural workers has also been implicated in protective effects on allergic sensitisation and hay fever (16,17)”.

Furthermore, we added to the Discussion: “Living near a farm was also associated with a lower prevalence of allergic rhinitis (1,63). Several studies in occupationally exposed farming populations have shown a dual effect of endotoxin with both negative and protective effects, but these populations were exposed to average endotoxin levels above 100 EU/m3(16,17). Our focus on lung function and symptoms led to inclusion of studies showing adverse effects of endotoxin exposure. Furthermore, most studies that showed protective effects of endotoxin in homes analyzed endotoxin concentrations in house dust samples, whereas our systematic review only includes airborne endotoxin levels (64,65).”

It is important to elaborate on why you decided to use endotoxin exposure levels below <100 EU/m3 as cut-off point for low exposure. Perhaps refer to previous studies that suggested LOELs/NOELs below 100 EU/m3, and other relevant legislational exposure limits.

* We expanded the Introduction as follows: “Currently, the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council recommends a health-based occupational exposure limit of 90 EU/m³ (21). DECOS regards an exposure level of 90 EU/m3 as a NOEL (no observed effect level), based on the effects on FEV1 of six-hour exposure to endotoxins in the study by Castellan et al. (13). Based on the occupational exposure limit, a tentative limit of 30 EU/m³ was recommended for the general population living in the surroundings of livestock farms (21,22).

Furthermore, we added two references to: “Levels up to 100 EU/m³ are included since these levels can be compared to peak ambient levels of airborne endotoxin in livestock-dense areas (23,24).”

It is stated in abstract that a "significant exposure-response relationship between endotoxin and symptoms and FEV1 has been shown in several strong studies”. However, another systematic review and meta-analysis was published April 2017 (The effect of organic dust exposure on long-term change in lung function: a systematic review and meta-analysis, BMJ, Bolund et al. 2017) which found inconsistent results. Perhaps it is too early to make such a bold statement in the abstract.

* We have rephrased this sentence in order to state it less bold.
Minor comments

Line 50

You start out the background section by stating "Most people assume that air pollution is posing a threat to human health mainly in urban areas". I would agree that the general population perceives extreme urban pollution as "unhealthy", however probably only a few of them actually consider themselves to be exposed to seriously hazardous pollutants. In addition, most people probably do not understand or ponder the actual health effects of such exposures. We, the researchers, would obviously like everyone to care, and beginning the paragraph in this manner probably reflects more our wish than reality. Therefore, I think it should be tones down.

* We agree, and have amended the sentence as follows: “Health effects of air pollution have mainly been studied in urban areas, where pollutant concentrations can be high due to emissions from industries and traffic.”

Line 168 - 170

This should be rephrased so that it is clear that 1 study from each of the last mentioned countries were included, instead of writing "and the others in...".

* We replaced “the others in” by “one each in”.

Line 178 - 181

I suggest that Table 3 is moved to the supplementary material, and only referred to here.

* We moved table 3 to the supplementary material.

Line 232 - 233

You refer to Smit et al (ref 36) and mention "a significant association between length of employment and increase in lower respiratory symptoms". First of all this sentence needs to be made clearer since "an increase in lower respiratory symptoms" intuitively seems like a contradiction. However, more importantly I miss a discussion of this type of finding. Is it healthy worker selection, or maybe something else

* We have rephrased the sentence as follows: “… a significant positive association between length of employment and lower respiratory tract (LRT) symptoms”, to clarify that this finding is in line with the main results of the current review.
The results from the selected articles are described as having wide confidence intervals and often not significant. This leaves me wishing for an explanation of the few studies that do show significance, how do they differ from the others?

* Indeed, several studies appeared to be underpowered to address all of the studied associations. In general, those showing significant results belong to the studies with larger study populations. However, further explanation of heterogeneity in results (e.g. by meta-regression) is hampered by the differences in study design. We added to the Discussion that ‘…a meta-analysis, or meta-regression, could not be performed’.

FYI Figure 3 seems to lack a heading.

* we have added a heading to figure 3 ‘Odds Ratio (OR) for symptoms per increase in exposure of 1 log endotoxin*’.

Line 312

The term "across shift" is used several times in this paragraph. Do you mean for example "showed larger decline across work shifts", assuming that shift refers to work shift.

* We have rephrased shift to ‘work shift’ in order to make clear we are referring to work shifts.

Line 338 - 339

It is not clear if you refer to an aggravating effect here.

* We have rephrased the sentence.

Line 340 - 342

Would it maybe be appropriate to discuss the Janus faced effect of endotoxin here? Though here there is only mention of the effect on cough right?!

* The dual effect of endotoxin is now further discussed in the Introduction and the Discussion (see our reply to the first comment).

Line 426 - 428

Atopy and atopic disposition are loosely mentioned throughout the review, since it obviously has been mentioned in the included articles. However, somehow it has not been dwelled upon at all. Again it connects with the dual effect of endotoxin exposure.
* See our reply to the first comment. In the studies retrieved by our search, atopy was mainly used as a confounder or effect modifier and not as an outcome of interest.

Reviewer #2: This review manuscript is a well-written and conducted study that applied a systematic review process to ultimately review 31 articles to compile a comprehensive review on the respiratory effects of exposure to low levels of airborne endotoxin. Due to the heterogeneity of the studies, a meta-analysis could not be conducted and instead a best evidence synthesis was performed. The presentation of data is comprehensive and easy to follow. The authors conclude that respiratory health effects from low levels of airborne endotoxin are plausible, and the discussion appropriately gives the strengths and weakness of this report. It would serve as an appropriate guide for researchers in this field. In all studies, it appears that the LAL assay for measuring endotoxin was used, and perhaps the authors could briefly comment upon the strengths/weakness of this measurement and sampling methods utilized across the studies in the discussion.

* To the Results section we added: “Endotoxin was measured using the Limulus Amebocyte Lysate (LAL) assay, which is the most accepted assay for endotoxin exposure measurements.” To the Discussion we added: “All studies used the functional LAL assay to measure endotoxin exposure. Although within-laboratory precision of the assay is good, variation between laboratories may be substantial, in particular if different extraction and analysis procedures are used (21). Underestimation of endotoxin levels, especially when using older protocols, may have resulted in the inclusion of studies with true mean endotoxin levels above 100 EU/m3, although most studies had mean exposure levels far below this threshold.”