Author's response to reviews

Title: Personal Endotoxin Exposure in School Children with Asthma

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Author's response to reviews: see over
RE: manuscript MS 7240178905456155 entitled: "Personal Endotoxin Exposure in a Panel Study of School Children with Asthma."

Dear Editor,

Please find enclosed the above revised manuscript for submission to *Environmental Health* as an original research article. We have submitted a tracked changes version and clean version of the revised manuscript. The Editor’s requested edits have been made.

The following is a detailed point-by-point response to the few remaining reviewer concerns regarding the first revised manuscript.

Sincerely,

Ralph J. Delfino, MD, PhD

**Reviewer:** Gert Doekes

**Reviewer's report:**
The authors have adequately responded to most of mine and other reviewers’ comments. Just a few items remain, as pointed out below.

**Comment A.** The size of the various parts of the study, as given by the numbers of samples in the analyses, are now more correctly given, but not on all relevant sites. Given the importance of the abstract, I particularly find the adjusted third line of the abstract M&M confusing. The text suggests that the number of ambient air endotoxin measurements was 339 but it was only $34 + 63 = 97$, of which each was used 3-4 times, namely as a potential predictor of the (339)
personal exposure results for 3-4 participants measured on the same day. This might be simply solved by substituting (N=339 person-days etc....) by (N=97 or “N = 34 and 63”).

Response:
We agree with this interpretation and have substituted N=339 person-days by (N=97).

Comment B. Similarly, the total numbers of indoor and outdoor home air measurements were 109 and 111, not 116 and 113 (Abstract M&M), but this small difference is much less misleading.

Response:
Thanks, we made the same change for indoor and outdoor endotoxin Ns.

Comment C. Table 1 has been accordingly adjusted and improved. Nevertheless I would recommend to add here also in extra columns the numbers of study participants for which each type of data was obtained (particularly in the first 4 lines dealing with endotoxin measurements). The present N’s only refer to the much larger numbers of samples. If I understand the text correctly, there were only 13 subjects in Riverside with personal, and 4 (?) with outdoor and indoor measurements; corresponding figures for Whittier would be 32 (personal) and 8 (indoor and outdoor) study participants.

Response:
You do not understand this correctly. The Ns refer the precise number of exposure measurements. As clearly stated in the methods, this is a repeated measures study so the N refers correctly to the number of exposure measurements, not subjects (the N of subjects is discussed in the text and new Table 1). We now place a footnote at the bottom of Table 2 to re-emphasize this point. We also have added a new Table 1 as described under reviewer Joanne Sordillo to clarify the Ns further.

Comment D. My comment on time-activity patterns (Comment 7) seems to be only partly understood, or misinterpreted. Detailed data appear to be available for many study participants, but only averages are given in the Discussion for for time spent in various locations/activities (page 15 lower half), with results that may be expected for a schoolchildren population. Unfortunately, no attempt was undertaken to relate these specific time-activity data per individual and for the days on which personal exposure was measured, to the personally measured endotoxin exposure on the same day. I realize that this would imply a considerable amount of additional stat analyses, but since the data are in principle available it is unsatisfactory to see only a discussion and speculations on this issue, and no results of relevant additional analyses.

Response:
The temporal resolution of the endotoxin data (daily) does not match the time-activity data (hourly). More importantly, locations other than the 12 homes (14 subjects) and central sites were not monitored. What you are asking for is beyond the scope of the present analysis and incongruous with the predictive capability of the data at hand. Simply put, the statistical power is completely inadequate to construct a personal endotoxin exposure model. The only available predictor for the complete 45-subject panel that would have adequate power is ambient endotoxin (Table 3). However, to predict indoor and outdoor personal exposures weighted by relative time in home microenvironments we only have indoor-outdoor home endotoxin for 12 homes and no valid way to extrapolate that to other non-monitored homes.
Comment E. Comment 16: Unfortunately I cannot agree with the authors’ apparent interpretation of (all?) differences between (endotoxin) values for the Riverside and Whittier substudies – and between correlations and other relations within the substudy datasets – as being only due to ‘regional’ determinants. Without any additional data one might just as well argue that the major explanatory factor would be ‘year’ (2003 versus 2004). The authors argue correctly that an effect of seasonal factors is not likely – but annual variation in weather or other conditions – seems to be overlooked. In this regard it may be of relevance that the median outdoor temperature was several degrees higher, and the RH considerably lower in Riverside 2003 than in Whittier 2004. Or can these differences also be ascribed to spatial, more than annual variation? (This can probably be checked via meteo databases?)

Response:
These differences are due to the spatial locations of the two sites in southern California. We now describe this in the Methods section, first paragraph:

“Riverside experiences higher temperatures and lower relative humidity than Whittier as a result of being further from the Pacific Ocean and closer to the inland desert.”

Reviewer: Joanne Sordillo

Comments:
The authors have addressed all of my comments/concerns from the last review in a way that is acceptable to me.

Discretionary Revision:
Upon re-reading the revised manuscript, I found that the study design (and number of samples/subjects for each section) was still a bit confusing. (Although, the authors added the numbers of available samples to the tables- which helps things considerably). I think the manuscript would benefit from a figure or diagram in the beginning that shows the flow of the study design, with corresponding N's for the samples.

Response:

We have included a new Table 1 that reiterates all of the various sample sizes. The “flow” of the study design is explained in the text and in a footnote of the new table.