Reviewer's report

Title: Fraction of exhaled nitric oxide after experimental exposure to diesel exhaust or ozone

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Reviewer: William Linn

Reviewer's report:

1. General comments: I consider this an interesting study of an important environmental-health issue, well designed given ethical and practical limitations on controlled exposures of volunteers. It is unfortunate, though not surprising given the technical complexity of these investigations, that data for some diesel subjects were lost or unusable. The negative results for ozone seem quite robust, given the relatively large subject population. The positive results for slow-flow FENO increases after diesel exposure also seem convincing, and tend to corroborate other evidence of airway inflammation previously found by these authors and others. In contrast to the authors' interpretation, I consider that the reported fast-flow FENO data 6 hr post diesel exposure do not rule out a meaningful increase, i.e. do not rule out distal (along with proximal) airway inflammatory responses. The nonsignificant increases at faster flows might be due to unavoidably imprecise NO measurements at very low concentrations, rather than lack of response. To help resolve the issue, further research into the proper interpretation of FENO flow dependence, as well as further studies of response to diesel exhaust exposure, will be needed. Following are specific issues noted for discretionary revision:

2. Abstract, p. 2: "FeNO did not differ at higher flow rates" - statement is not well supported by data. Based on proportionate differences in tabulated point estimates (means) 6 hr post minus pre exposure, the excess change after diesel at 270 ml/sec is roughly similar to that at 10 ml/sec. The lack of significance at 270 might be due more to the NO analyzer's less favorable signal/noise ratio at lower concentrations, than to lack of excess NO in the peripheral lung. Thus, the question whether diesel exhaust exposure induces a localized inflammation in proximal airways, or a more generalized inflammatory response, is still open.

3. Study Design, p. 6: More description is needed. How long was the washout period between diesel (or ozone) and filtered-air exposures for a given subject? Was the order of exposures randomized?

4. Exposures, p. 7: Were the persons performing the FeNO measurements (investigators or technical staff) blinded to the exposure conditions? If not, it is possible (at least in principle) that unconscious bias might influence the data, if they had discretion to exclude particular test maneuvers that did not meet expectations.
5. Statistical Analyses, p. 8: Based on the description of ANOVA, the reader would expect significance tests for the exposure main effect, the time main effect, and the interaction between them, with the dependent variable being the difference in FENO post- minus pre-exposure. However, results are reported in terms of difference in post-exposure means, diesel versus filtered air, as if from a t-test. Clarification is needed. In larger populations, FENO data are commonly distributed more lognormally than normally. That may be true here, since the means usually appear to exceed the medians, judging from data shown in the figure. It may be useful to compare statistical conclusions between untransformed and log-transformed FENO data, particularly in relation to the question whether diesel effects are truly significant at low but not at high flow rates.

6. Results, p. 9 paragraph 2: See comment on statistical analyses.

7. Discussion, p. 10 paragraph 1: More correct to say that FENO has not been studied previously in diesel exposures, and not at multiple flows in ozone exposures.

8. Discussion, p. 11: Reference #s 21-23 in the text appear to refer to #s 20-22 in the reference list. Other references were not checked, so there may be similar problems elsewhere.


Level of interest: An article of importance in its field

Quality of written English: Acceptable

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.