Reviewer’s report

**Title:** Longitudinal Follow-up of Health Effects among Workers Handling Engineered Nanomaterials: A Panel Study

**Version:** 0 **Date:** 06 Aug 2019

**Reviewer:** Paul Schulte

**Reviewer's report:**

This is a thoughtful follow-up of a pioneering effort to study a cohort of workers exposed to engineered nanomaterials.

In the abstract and throughout it is important to clearly distinguish between hazards, risks, and effects. A hazard is a source of potential harm. A risk is the probability of harm given exposure. I suggest that instead of hazard you use "potential adverse health effects." These effects have not been validated as health endpoints.

The authors should describe how this paper relates to all the other papers on this cohort that they have studied.

1. There have, in fact, been studies of makers of health effects among carbon nanotube exposed workers. These should be discussed in the introduction. Specifically, the following papers deserve mention:


2. "Since smoking is a strong confounder, it was forced to be adjusted for every effect marker." Smoking may affect some markers, but may not affect all markers. Authors need to describe how smoking is associated with exposure to nanomaterials, since a confounder is associated with both the exposure and outcome. I highly recommend providing the results without adjustment for potential confounders or using a stepwise selection process since many covariates may not be confounders.

3. This study includes a wide variety of nanomaterial facilities, and a wide variety of different nanomaterials.

   Nano silver, silicon dioxide, titanium dioxide, carbon nanotubes, and others likely affect markers of health effects in different ways. By combining many different materials into one exposure, this study introduces a large amount of exposure misclassification which results in bias towards
the null. The researchers mention exposure misclassification in the context of not having individual exposure estimates, but the mixing of different types of nanomaterial exposures is the larger contributor to exposure misclassification. The null results should be interpreted with this in mind, and examination of results by facility or materials handled would be informative.

4. Tables 3 - 6 should include which covariates are included in the models.

5. No rationale is provided for using control bands rather than estimating exposure using a job exposure matrix. Control bands incorporate information on toxicity which could increase exposure misclassification compared to a traditional exposure assessment. Especially since nanomaterial toxicity is not well understood in humans, it seems more informative to just use exposure or exposure potential.

6. This study was designed as a repeated measures panel study. With this design, people are measured at multiple points in time, so changes within the same person over time can be modeled, as well as differences between people. So for models of changes within the same person over time, time-invariant confounders do not need to be adjusted. It seems that in this paper the results were mostly focused on comparisons of groups of control bands, but I think that the more important interpretation if the intra-variability among individuals over time.

7. Healthy worker survivor bias was not discussed and may be an important limitation, if workers with higher exposures were less likely to participate in additional follow-up exams.

Editorial Comments:

Page 7, Line 6: "consuming" should be changed to "consumer"

Page 7, Line 32: "Most the documents" should be changed to "Most of the documents"

Page 9, Line 3: "Control banding…" should be the start of a new paragraph

Page 10, Line 57: "Among them, 39 plants have been site-visited and invited" should be "Among them, 39 plants were visited and invited"

Page 11, Line 7: "We have performed five repeat examinations during the four-year." should be "We performed five repeat examinations during the four years."

Page 16, Line 6: "participated" should be "participating"

Page 25, Line 22: "fail" should be "failure"

Page 26, Line 9: "dramatic" should be "dramatically"
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