Reviewer's report

Title: Long-term Follow-up of Beryllium Sensitized Workers From a Single Employer

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Reviewer: Laura Welch

Reviewer's report:

Long-term follow-up of beryllium sensitized workers from a single employer by Duggal et al.

This is a valuable paper, presenting new and useful information on a beryllium exposed population. The paper reports that that 1/3rd of beryllium exposed workers with a biopsy diagnosis of CBD progressed to clinical CBD in an average of 8 years of follow-up, that few of those without a baseline diagnosis of CBD developed clinical CBD over the same period, and that workers without a diagnosis of CBD had a drop in lung function more than expected from aging.

I am unable to decide on a recommendation for acceptance until the authors have responded to the major compulsory revisions.

Here are my responses to the specific questions requested, with details below.

1. Is the question posed by the authors well defined?
   Yes

2. Are the methods appropriate and well described?
   See comments, I cannot tell without additional information

3. Are the data sound?
   Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   See comments below. I think the discussion could be clearer and that the conclusions extend beyond the analysis reported

6. Are limitations of the work clearly stated?
   Yes

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   For the most part. There is one paper which presented an analysis of the same
data set but which is not acknowledged, and I think it needs to be added to the paper. See comments below.

8. Do the title and abstract accurately convey what has been found?
   Yes

9. Is the writing acceptable?
I have made some suggested changes to clarify the paper

Major Compulsory Revisions

(1) Description of the cohort included in the analysis.

The Dugall paper describes that the cohort comprised both former and current workers at plants in Elmore Ohio, Reading Pennsylvania and Tucson Arizona who were positive on the BeLPT surveillance test between 1992 and 2002 during employment (on page 7 the time period is described as 1992 and 2001), and had at least one confirmatory test. The paper states that “the parent company provided contact information for 185 employees initially identified”. The same population of workers was described in a paper published in the International Archives Of Occupational And Environmental Health in 2007 by Donovan et al entitled “Performance Of The Brilliant Blood Lymphocyte Proliferation Test Based On A Long-Term Occupational Surveillance Program”. (The paper by Donovan does include information from one additional facility, the Delta plant.). The paper by Donovan is not referenced in the Dugall paper under review.

Table 2 in the Donovan paper describes the prevalence of confirmed BeLPT positives in workforce surveys at the three plants included in the Dugall paper. There were 157 confirmed positive cases in screenings between 1992 and 2000 presented in the Donovan paper. The paper also states that there were 415 screened at Elmore between 2002 and 2004, 77 screened at Tucson between 2001 and 2004, and 123 screened at Reading between 2001 and 2004, results for whom are not included in the Donovan paper. Dugall is presenting information on an additional 28 individuals, and presumably those additional 28 come out of the proportion of this additional group of 615 individuals screened after 2000 but before 2002. Because the Dugall paper does not present details on the distribution of the 185 employees between plants or years I cannot assure myself that the 185 are a complete cohort of the individuals with confirmed positive tests at these three facilities. If the authors are confident that this is a complete ascertainment of all workers with confirmed positive BeLPTs they should state that. I suggest that Dugall et al add a table to their paper describing the entire population screened, which could be similar to the table in Donovan.

(2) The Donovan paper states that “In a previously published analysis of these data nine confirmed positive BeBLPT results in the 2000 Reading survey were attributed to technical problems at one of the testing laboratories and were excluded from the reported rate of confirmed BeBLPT positive results (in Schuyler 2005). Those nine individuals were included in the present analysis for consistency purposes and therefore result in a substantial difference in the
reported rate of confirmed BeBLPT positive results at the Reading facility.” Were those nine cases included in the 185 cases presented in this paper? If they were they should be excluded and the analysis repeated. If they were not included the authors can decide whether or not to clarify this in the text or leave it out.

(3) The paper refers to baseline and follow-up testing, but the description of the process, and of which results come from which time period is somewhat unclear. It appears that the company had a policy that workers were referred for diagnostic testing after the initial BeLPT screening, and the workers who agreed to participate in this study were referred for testing a second time as part of this study. This is not clearly stated in the paper. A chest radiologist read all chest radiographs - did that include the x-rays taken under the company program? Were all prior radiographs available? The authors state that clinics followed the ATS guidelines. Is this in reference to the baseline, the follow-up, or both sets of testing? I would also suggest deleting the heading on p 6 “criteria for diagnosis of clinically overt CBD” – this apparently is part of the classification of baseline status, and presenting it as a separate heading made me think it was not. (Although see below, I had a question about whether there were any clinically overt cases at baseline.)

(4) The baseline pulmonary function for the workers participating in the study is normal. The authors describe that workers with CBD were less likely to participate in the follow-up. In the comparison of participants and non-participants, can the authors also compare baseline PFT data? The authors conclude that there was no difference in lung function decline between workers participating in the study with CBD and those participating with BeS at baseline. However, if the workers with more serious CBD at baseline did not participate one should be cautious in interpreting these data. We know that individuals with obstructive lung disease lose lung function faster than those without disease (the horse-racing effect). It may be the case that workers with clinically overt CBD also lose lung function faster, but if those workers did not participate the study could not detect this effect. At some point the authors should describe how many of the participants had clinically overt CBD at baseline – I can’t tell this from the paper.

(5) The discussion on p 13 about predictors of overt CBD seems to imply that none of the workers had overt CBD at baseline, but it would be helpful to provide that information. If 31.8% of those with CBD at baseline have overt CBD at follow-up, we need to know if any of them had overt CBD at baseline. If none of the participants had it at baseline, was this due to a participation bias?

(6) In the conclusion, the authors imply that this group of workers has had higher exposure than other exposed individuals. However, they do not discuss the basis for this statement. This employer has been very active in reducing exposures to its workers, and without information on measures of exposure in this industry versus other industries this statement is too broad and should be re-written.

(7) Other statements in the conclusion do not follow from the data presented. The authors state in the conclusion that workers who remain in exposed work do not
have obviously greater risk than those who chose to leave exposed work. Table 3 shows that only 2 of the 8 patients with overt CBD had remained in exposed work; this sample size is too small to support a conclusion that there is no difference in outcome for workers with CBD. It would be preferable if the conclusions focused on the findings of the study – that 1/3rd of the workers with a biopsy diagnosis of CBD progressed to clinical CBD in an average of 8 years of follow-up, that few of those without a baseline diagnosis of CBD developed clinical CBD, and that workers without a baseline or clinical diagnosis of CBD had a drop in lung function more than expected from aging. There appears to be a slow loss of lung function in all the workers (on average), with a greater loss in those with biopsy proven CBD. The study is not able to identify factors that predict progression.

If workers with more serious CBD at baseline did not participate, the findings of this study cannot be used to generalize to all screened workers. Results of the study support medical surveillance of exposed workers in conjunction with long term clinical follow-up. Although I would agree that the added benefit of transbronchial biopsy and BAL beyond periodic clinical evaluation is unproven, this study has not addressed the question.

Minor Essential Revisions

(8) Be sure the dates of testing are the same throughout the text (2001 mentioned on one page, 2002 on another for last screening date included).

Discretionary Revisions

(9) Tables 1 and 2 present two analyses, one including the 2 workers with COPD and one excluding them. The tables are difficult to read, and the column titles with “CBD COPD in”, etc., are not intuitive. I would recommend the authors present the analysis they find to be more valuable, and describe the secondary comparison in the text but not include it in the tables. Table 2 suggests that the 2 patients with both COPD and CBD have a different clinical picture, so I would recommend they be excluded from the group comparisons, but the authors can decide otherwise as long as they describe their rationale.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests