Author's response to reviews

Title: Incidence of chronic bronchitis among pulp mill workers with repeated peak exposures to sulphur dioxide and other irritant gases

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Author's response to reviews: see over
Dear Prof. Philippe Grandjean and Prof. David Ozonoff, Editors in Chief of Environmental Health

Thank you very much for considering our manuscript. To include the study design we have changed the title of our manuscript: “Incidence of chronic bronchitis in a cohort of pulp mill workers with repeated gasings to sulphur dioxide and other irritant gases.” Further changes have been made following reviewers suggestions and are marked in yellow in the text. Suggested formatting changes have been made. Since an unanimous request by both reviewers was to have more information and analyses about occupational exposures and smoking habits we have added these information in the text and as additional tables/figure. We are really thanking the reviewers for making the paper better and hopefully easier to understand.

Specific answers to reviewer 1

Comment 1. This is an interesting paper reporting results on irritant exposures and chronic bronchitis in paper and pulp mill workers in Sweden. The topic is important and there is actually little evidence on the effects of these type of exposures that are quite prevalent in many workplaces. I have only a few minor comments.

Minor comments

Comment 2. It would be useful to present more completely data on departments. Perhaps add a table with major departments and also those with highest probability for frequent irritant exposures. The information provided in the results is quite limited.

We are happy to add a table about main departments and the frequency of exposure there. See table 2.

Comment 3. The authors have grouped ever smokers including current and ex-smokers. Ex-smokers actually seem to be different than current smokers and they report higher prevalence of peak exposures and frequent peak exposures than current smokers (see table 3). Although differences are not very big this could be related to selection out. Given the comments on the lack of an additive effect with smoking and exposure to irritants, perhaps it would be interesting to evaluate separately the ex-smokers from the current smokers.

We presented ever-smokers as there are quite few cases but we have done these analyzes and they show about the same HR except for frequent gasings where the risk is a bit higher for ex-smokers. We have now added that in the text. We have also added a table 6 with stratified analyses for smoking and gasings where current smokers are shown. New analyses restricted to ever-smokers are also presented but only in text.

Comment 4. Page 9, comment on asthma. It would be of interest to indicate how many of the subjects reporting doctor diagnosed asthma had also chronic bronchitis.

18%, now added in the text.

Comment 5. An obvious comment refers to the findings on asthma and irritant exposures (see table 2). These are not commented. If the authors are preparing another paper on asthma, this is fine. If not just add also in this paper the results on asthma.
We are preparing one more paper with analyses on asthma, wheeze and rhinitis but we will only analyse the time period 1981 to 2000 then.

Comment 6. The authors do not comment on changes in exposure. During the period of the study there have been significant changes in production and exposures with a reduction in the use of specific chemicals including (as far as I know) chlorine and an increase in the use of other chemicals such as ozone. How much may this have affected results? If time periods of exposures and symptoms are available it might be useful to do also an analysis prior to 1990 when chlorine use (I think) was highest.

Exposure to chlorine have decreased as is shown on the added Figure 1, but gassings to sulphure dioxide remained high throughout the period. Ozone was not used that much in these mills, exposure to ozone and some other irritants is added in the text under Exposure. It doesn’t seem that incidence has decreased during the years but it is difficult to evaluate, the workers get older and it could be hard to remember all the information (first episode, year at the first onset and so on). See also answer on comment 2 beneath.

Comment 7. The authors have published several papers on pulp and paper workers and respiratory symptoms. It is not always easy to understand which studies include the same population. It would be helpful to indicate this in the introduction, in case one of the earlier studies included subjects reported in this paper.

In the Methods section is already stated that “Part of the cohort had previously been analysed regarding incidence of asthma and work-related disability [8,11]. We have added that the other studies about irritants are from other mills.

Comment 8. Related to the previous comment: in an earlier paper (Murgia, BMC PH 2011) the authors use the term “gassings”. They do not use this in the current paper. Perhaps make a reference so that the readers know how much coincidence there is in exposure assessment between studies/papers.

We have changed back to gassings, we defined that in the same way in this study as the above mentioned. We did not understand that it will confuse readers. We just thought it have become a bit old fashioned, most used in North America and is closely related to pulp mills, so that peak exposure would be more easy to understand. But the reviewer is right it can confuse especially as we define it as peak exposure with respiratory symptoms. Thank you!

Comment 9. Page 5, paragraph titled “Exposure”. Probably delete the word “Objective” in the sentence “Objective information about the departments in which the subjects had worked, ....”, there is no need for that.

We have deleted “objective”.

Comment 10. Reference 17, there is a minor typo “andchronic”

Thank you, done.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
No competing interests

Specific answers to reviewer 2

Reviewer's report:
Andersson et al reported in this study the incidence of chronic bronchitis in pulp mill workers. The data were obtained by questionnaire. The response rate was 44%. They found incidence rate for chronic bronchitis among workers with repeated peak exposures was about two times that of unexposed workers. The risk was even higher in a subgroup with frequent peak exposures. The authors recommended that preventive actions be considered for this work environment. A major strength of the study was the inclusion of a very large cohort of workers. The study was well executed given the constraints of this kind of study. The results support the association between occupational exposure to irritants and chronic bronchitis.

Major comments:
Comment 1. Material and Methods:
a. Cohort, 2nd para: What was the rationale for limiting the study period to 1970-2000, especially since the data were available since 1940?

We had information on employees and work periods from 1940 in the cohort but, as we need questionnaire information for this study, we did not think it was possible to reach people and get relevant answers for more than 30 years back in time.

b. Exposure. Page 5. It would help the readers that the authors describe the exposure condition in the work environment in more detail, including the tasks workers in different departments did, estimated (or measured) levels of irritant gases (SO2 etc) at work and in different departments, cumulative exposure over the time of employment, use of protective devices, etc. A table that describes the number of workers in each department stratified by the level of exposure will be helpful.

We have included Table 2. Numbers of workers in different departments differ with time so it is given in ever worked and for a few departments only worked in these departments. We don’t have all the information, such as use of protective devices, but the gassings are defined as an exposure giving rise to respiratory symptoms (regardless if protective devices are used or not). We don’t think cumulative exposure is very important for this study as it seems that the peak exposures are the real problem. More about exposures in pulp mills are described in another paper (now reference 19), were some measurements are presented. Some of them are from these mills but Table 2 together with Figure 1 will give a lot information. We don’t think it is possible to go into more detail in this paper but we are thankful adding these.

c. Exposure, 2nd para: Please define “few periods of acute exposure” and “frequent periods of exposure”.

The wordings of the questions and answer alternatives are now added.

d. Statistics. Page 6, last sentence. How did you know it had no influence before you ran the model? Gender needs to be included in the Cox model for ever smokers.
We did not know that before. We tried to avoid too many factors to adjust for as the cases are not so many especially in women, but of course we can include that. Changes are done in Table and Methods section.

Comment 2) Results. Was the incidence rate or prevalence of chronic bronchitis constant during the study period, or was there a time trend?

The incidence rate was similar, from 1981-2000 it was 1.6/1,000 person-years for unexposed and 3.4/1,000 person-years for exposed workers as well as from 1991-2000. This means that it was slightly lower during the 70ies but we think that is due to poorer recall for years long ago. Now it is added in the Results section: “There was no decrease in incidence during the years (data not shown). Calculating for every 5 or 10 years period should be complicated as data is now.

Comment 3) Table 4 showed that hazard ratio for smokers was lower than that for nonsmokers. The authors tried to explain it by hypothesizing “healthy subjects, irrespective of exposure to irritants and peak exposure episodes, could start or continue smoking” (Discussion, 3rd para). However, the explanation could not explain the greater pack-year in exposed workers. Since smoking may also cause symptoms of chronic bronchitis, were there differences between smokers and nonsmokers in response rate to questionnaire, employment time, etc?

Thanks to reviewers we have got into more detailed information and performed stratified analyses (table 6), showing that, compared to unexposed nonsmokers, both smokers and nonsmokers have the same risk when exposed to gassings while the exposed smokers do not have an additive risk for smoking. Anyway, smoking only clearly showed an increased risk for chronic bronchitis. As added now in the discussion, there was no significant difference between responders and nonresponders regarding smoking or exposure. We have done several changes to and shortened the discussion related to this topic.

Comment 4) How do you account for recall bias that may lead to misclassification of smokers and nonsmoker since your definition of smoking is quite liberal, daily smoking 1 year? If you use stricter criteria for smoking (such as pack-year), would the results be the same? Any correlation between smoking and exposure?

We are using both pack-years and current smoking (1/0) in the Cox regressions. Former smokers had higher exposure to gassings which is added in the results.

Comment 5) Discussion, 5th para. Whether or not non-response bias will affect the results also depend on the nature of the study (i.e. what questions and endpoints one uses for the study in what population). Its specific effects thus should be assessed by statistics and potential impact be discussed. Dismissing this bias based on studies in different population on different endpoints is not advisable, especially since the response rate was only 44%.

True. The study was presented to the workers as a study of work environment and health; exposure to irritants and different respiratory symptoms took a big share of the questionnaire but there were questions about shift work and some other exposures such as hand-arm vibrations and how physically demanding their work was as well as other
health outcomes. We have added shortly about that and taken away other parts given the fair advice from the reviewer.

Comment 6) Please provide statistics for exposed vs. unexposed in Tables 2 and smokers vs. nonsmokers in Table 3.

Done, now in table 3 and 4.

Minor comments:
Comment 1) The term “combinative effect” is used in the discussion to describe the interaction between smoking and exposure. It should be antagonistic or negative effect.

This is now changed to lack of additive effect and stratified analyses are presented in table 6.

Comment 2) Methods, Exposure, 1st para. Please define “acutely exposed” more clearly. The definition of “peak exposure” is vague. “Peak exposure” usually refers to exposure to peak concentration of irritants. It appears that in this manuscript, the authors used “peak exposure” to refer to the exposure episodes associated with symptoms. Perhaps a different terminology should be used to better reflect this definition to avoid confusion (such as symptomatic exposure). In 3rd paragraph, if the subjects did not report exposures, there should be no “peak exposure”.

We have changed to “gassings” see reviewer 1, and added more detailed definition with asked questions. As to the 3rd paragraph, “other” now there is added text to clarify that it is referred to peroxide, ozone and other irritants.

Please clarify the definitions for all the terms related to exposure.

Done, hopefully now clarified see also some of the answers above.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
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