Author’s response to reviews

Title: Lung cancer mortality in towns near paper, pulp and board industries in Spain

Authors:

   Susana Monge-Corella (smonge@isciii.es)
   Javier Garcia-Perez (jgarcia@isciii.es)
   Nuria Aragones (naragones@isciii.es)
   Marina Pollan (mpollan@isciii.es)
   Beatriz Perez-Gomez (bperez@isciii.es)
   Gonzalo Lopez-Abente (glabente@isciii.es)

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Author’s response to reviews: see over
Dear Editor,

First of all, we would like to thank the comments contributed by the two Reviewers. We have sincerely appreciated their content and have found them extremely useful. Attached to this letter we have sent a revised version of the manuscript that corresponds to the third draft. In this version we tried to incorporate the suggestions made by both reviewers. Also, in the following paragraphs we will address the comments made by the Referees one by one.

Sincerely,
Gonzalo López-Abente

Reviewer 1: Mark Clemens

No major compulsory revisions

Minor essential revisions with answers

1. I have two concerns with the epidemiology and biostatistics of the paper. First, the authors obliquely note (first paragraph, page 9) that there are concerns with “the latency of lung cancer”; this is a critical point, where the authors have made the strong assumption that exposure today will tell us something about exposure over the last 20-30 years. It would be useful for the authors to expand on this point. In particular, is there any evidence as to whether air pollution works as an initiator or as a promoter for lung cancer?

The lack of historical and good quality emission data does not permit the consideration of emission levels for the analysis, though of course could be related to a possible association between some industrial sites and cancer. In the revised manuscript we have added some additional comments on the lack of quality of the data of emissions, as declaration of emissions to the EPER was not mandatory until 2007. However, even if the quantity of emissions cannot be included, the case for the majority of the plants in this study is that they have been active for more than 40-50 years, so it is correct to assume that adjacent population has been exposed for decades to their emissions, that could be more important and higher in the past, due to the present more restrictive regulations. We have also added details on the new text (see seventh paragraph of the “Discussion” section).

In relation with the second part of the question, chemically air pollution are complex mixtures of carcinogens with substances that could act as promoters (viz: PAHs and PM) or initiators (viz: benzene).

2. Second, the authors do not discuss the issue of multiple comparisons, particularly when interpreting associations for each industry site (e.g. Table 3). In the light of multiple comparisons, the authors should interpret the association for Industry 3730 very carefully; the association for Industry 2761 would probably be robust, even given a conservative Bonferroni correction.

We agree that the result of the industrial site 3730 has to be interpreted with caution. We have added a comment on this at the end of the first paragraph of the “Discussion” section.


Done

4. Background, third paragraph: could the authors summarise the grade of evidence for the associations in the paper, pulp and board industries, please?
As stated in the third paragraph of the background section, eight studies showed significant association between working in a paper and pulp mill and lung cancer. We have tried to clarify this in the reviewed text.

5. Background, second to last paragraph, last sentence: what will be the effect of voluntary reporting on representativeness?

We have added comments on voluntary reporting in the seventh paragraph of the “Discussion” section. In any case, one of the results of the study is that joint analysis of the paper and pulp sector may not be very informative, due to the heterogeneity found between the different plants (see first paragraph of the “Discussion”). Considering this, it would be interesting to study additional industrial plants that failed to report to the EPER, but their absence may not have affected the global result for the sector.

6. Methods, paragraph 2: Under ICD-9, code 162 is “Malignant neoplasm of trachea, bronchus, and lung”; under ICD-10, C34 is “Malignant neoplasm of bronchus and lung” and C33 is “Malignant neoplasm of trachea”. This suggests that both C33 and C34 should be included for comparability with code 162.

Done

7. Methods, paragraph 2: would there be any differences between populations from the “1996 municipal roll and 2001 census”?

Those are the official middle period populations and are considered of equal validity.

8. Methods, second paragraph on page 5: what happened to the “intermediate group”? Were they excluded from further analysis? It is questionable whether their risk will be “intermediate”, as other sources of air pollution may be more or less harmful.

In the reviewed version of the paper, we tried to better explain the purpose of the categorization of the exposure in three levels: towns near a paper and pulp mill; towns near other industrial sites; and towns near no industrial site. The objective of this work is to study the possible association between paper and pulp industry and lung cancer, so studying the influence of other kind of industries was beyond the objective and scope that we established. In any case, the middle category is a miscellanea of industries; some of them may be related to lung cancer and others may not. Our study tries to go one step further and test the association between a specific type of industry and lung cancer. This middle category was therefore used to avoid the confounding effect of industries other than paper and pulp mills in towns exposed to them, and to establish a ‘clean’ reference group of towns not exposed to any industry. This is the reason why we didn’t further explore the association between the middle (present in the models) and the reference categories.

9. Methods, third paragraph on page 5, fourth sentence: can you re-phrase the expression “proportion of illiterates”?

In our opinion this expression is OK

10. Methods, third paragraph on page 5: how were the variables for adjustment chosen? How would this relate to potential confounding with smoking status?

This covariates has been chosen for their availability at municipal level and include an income indicator. In Spain (and in other countries) the privation indexes have some relationship with data of smoking prevalence. In general the validity of the relative risk estimators is improved with the adjustment.
11. Methods, fourth paragraph on page 5, second sentence: how many industries had neighbouring towns (ie how many industries were included in the analysis)?

This information was missing in previous text. We have now specified the number of industries with neighboring towns in the first paragraph of the results section.

12. Methods, last paragraph: how were cases and person-time calculated for the concentric bands?

The cases observed and expected in each town were calculated as was explained in the methods section (second paragraph) and for that does not matter the distance to the focus nor the geographic position of the town.

13. Results, first and second paragraphs: could the authors provide some commentary on Tables 1 and 2, please?

Done

14. Results, fifth paragraph: I suggest care in the interpretation of site 3730, given multiple comparisons.

We have added a comment about that at the end of the first paragraph of the “Discussion” section.

15. Discussion, second paragraph: are the authors suggesting that occupational case-control and cohort studies can only be used to “formulate hypotheses and guide research”? I agree that other study designs would provide further evidence on such associations, however I suggest that the occupational case-control and cohort studies will remain the gold (or silver?) standard for assessing such associations.

We agree with your comment. We have rewritten the sentence in the second paragraph of the “Discussion” to clarify this concept.

16. Figure 3: How were the curves estimated?

The curves were fitted using a lowess() function provided by the R package with a smoothing parameter of span=0.3. A little note was added in the figure legend.

Discretionary revisions

17. There are a large number of references (n=68) for such a concise report. It would be useful if the authors could be more selective in their referencing.

OK. The list of references was carefully reviewed

18-22 OK. Done.

23 The corrections using the GIS are described with detail in reference [51].
Reviewer 2: Denis Zmirou-Navier

Surprisingly, the Material and Methods section states (page 5, paragraph 2) that exposure was indexed as a 3 levels variable: (a) towns whose centroid is less than 2km from the plants ("exposed group"); (b) "intermediate group": towns at distance less than 2 km from any air polluting industry other than paper, pulp and board; (c) towns having no EPER-registered industry within a 2 km radius of the municipal centroid. Firstly, based on this categorization, this so called......

In the reviewed version of the paper, we tried to better explain the purpose of the categorization of the exposure in three levels: towns near a paper and pulp mill; towns near other industrial sites; and towns near no industrial site. The objective of this work is to study the possible association between paper and pulp industry and lung cancer, so studying the influence of other kind of industries was beyond the objective and scope that we established. In any case, the middle category is a miscellanea of industries; some of them may be related to lung cancer and others may not. Our study tries to go one step further and test the association between a specific type of industry and lung cancer. This middle category was therefore used to avoid the confounding effect of industries other than paper and pulp mills in towns exposed to them, and to establish a 'clean' reference group of towns not exposed to any industry. This is the reason why we didn’t further explore the association between the middle (present in the models) and the reference categories.

Also, as previously mentioned, in this version we have also included some additional comments on the lack of quality of the data of emissions. This variable will be considered for future studies when the new registry E-PRTR be available.

Despite the fact that the overall analysis did not show associations between cancer risks and short distance (<2 km; table 2) to the plants, the authors focus on two particular plants (n° 3730 and 2761) and proceed to analyse the risk trend with increasing distances (<5km, 5-10, 10-15, 15-20, 20-50 km; table 3). Why plant 3730 when table 2 does not show an increased risk? The distance split is not justified and the authors should explain on what basis they hypothesize that carcinogens emitted by the plants may disperse over such long distances, 15, 20............

Regarding the second point of the comment, as stated in the last paragraph of page 5 ("Material and Methods"), all 11 industries with exposed towns were subject to the relative risk trend analysis, not only numbers 3730 and 2761. As said at the beginning of the fourth paragraph of the “Results” section, those two were the only ones that rendered any positive results. The table 2 is only about specific towns less than 2 km from paper industries.

A paragraph explaining the rationale for the cutoffs for the risk trend analysis has also been added to the “Material and Methods” section in the third draft, as well as a comment in the “Results” section on the limitations derived from the multiple comparisons.

Finally, regarding the last comment, please note that differences between results in men and women are discussed in the fourth paragraph of the “Discussion” section.

In general, important limitations are specified in the “Discussion” section of the study, where derived implications for the interpretation of the results are clearly pointed out. In any case, as said in the “Conclusions”, the methodology of this work tends towards a more conservative approach, rather than to overestimate any associations.

Minor Essential Revisions
In relation to the first comment on the “Minor Essential Revisions” section, we consider that there is enough evidence to make a hypothesis on the carcinogenic effects of SO2, not only tested in animal models (which may not be very recent, but are nevertheless not outdated), but also in occupational studies and in population based studies, as stated both in the “Background” and “Discussion” sections. This hypothesis is not tested in this work, but certainly contributes to justify the study.

Because industrial plants tend to aggregate in some locations, had the authors shown associations of cancer risks with distance, this would not have allowed them to conclude that paper, pulp and board industries would be the causal factors. So that their claim that “introduction of province as a random effect term partly solves this problem” (of confounding) is inaccurate (p8, 3rd paragraph).

Eight of eighteen paper industries shown in Table 1 have another industrial plant at a distance of 2 kilometres, with 2 installations near to the industry 2761 and none for the 3730. This is a problem with a difficult analytical treatment and we don’t have yet a solution. A paragraph about that has been included in the discussion section. We agree with the reviewer comment about the last sentence of the paragraph that was deleted and the paragraph rewritten.