

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Enduring health effects of asbestos use in Belgian industries: a record-linked cohort study of cause-specific mortality (2001-2009)
AUTHORS	Van den Borre, Laura; Deboosere, Patrick

VERSION 1 - REVIEW

REVIEWER	Eduardo Algranti FUNDACENTRO São Paulo, Brazil
REVIEW RETURNED	22-Jan-2015

GENERAL COMMENTS	<p>The manuscript describes mortality due to occupational asbestos exposure in the period 2001-2009 in the male active (employed) Belgian population, aged 18-65 years, identified by the 1991 census. Until now, Belgium, in contrast with other Western European countries, has produced limited epidemiological data on the consequences of its extensive use of asbestos. Occupational exposure was ascertained according to an industrial sector presenting at least 3 mesothelioma deaths plus documental reviews of asbestos consumption.</p> <p>The objective is clearly stated and the study design is appropriate to answer the research questions.</p> <p>The manuscript has a very rich content. The significant excess of oral cancer deaths is an important contribution to the literature. In parts of the text it is difficult to follow results and discussion without going back to Methods. As a general comment I would suggest to revise results and discussion in order to facilitate the reading and understanding. If there is no restriction to include a couple of charts summarizing the significant findings shown in Table 4, it could facilitate the reading.</p> <p>I would ask the authors to clarify the following points:</p> <ol style="list-style-type: none">1. Introduction<ul style="list-style-type: none">- On pg 6, 1st paragraph, lines 3-12: what does it mean "first major ban in 1998"? Please, provide an explanation.2. Methods<ul style="list-style-type: none">- On pg 8, lines 34-39: the distinction on industrial sectors with at least 3 mesothelioma deaths refers to Industry or Industrial activity (see Table 1)? This criterion was also used for the typical asbestos industry? It should be better explained.- On pg 11, Table 2: as presented it is difficult to understand because it lacks captions - Manual, Non-manual and Total.
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	<p>3. Results</p> <ul style="list-style-type: none"> - On pg 12 line 20: "active population (n=1.428.621)". This number differs from the studied population quoted at pg 7 (Study Design) <p>4. Discussion</p> <ul style="list-style-type: none"> - On pgs 20-21: lines 56-57 and line 3: Please rephrase it. As it stands it is of difficult understanding - On pg 21: lines 25 to 32: This comment has already been made and can be deleted - On pg 21: line 35: There's a good and recent reference on the relationship between asbestos exposure and smoking that should be quoted along with Gustavsson: Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. Am J Respir Crit Care Med. 2013 Jul 1;188(1):90-6. doi: 10.1164/rccm.201302-0257OC.
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REVIEWER	Paul Demers Occupational Cancer Research Centre Toronto, Canada
REVIEW RETURNED	08-Feb-2015

GENERAL COMMENTS	<p>This was an interesting paper because of the high rates of mesothelioma in Belgium. It is a relatively simply census record linkage study, as is commonly done in the Nordic countries. Calling this a retrospective cohort study, although technically correct, may imply a different set of methods, at least in occupational epidemiology. I have a number of other comments and questions.</p> <p>What does "i.a." means in the 4th paragraph of the introduction? This is not a standard abbreviation.</p> <p>I presume that the "detailed occupational information" (Methods, 1st paragraph) is actually occupation and industry coded using a standardized system. I presume that NACE was used for industry, but the occupational coding system should be stated, as well as more detail on how manual workers were defined.</p> <p>What percentage of deaths occurred outside the Flanders and Brussels Capital Region? It seems as though this is a limitation that does not get much discussion, but without knowing the percentage it is difficult to judge.</p> <p>I presume that the SMR's were calculated using standard 5-year age and calendar periods, but this should be stated.</p> <p>It is unclear to me which industries were chosen based on 3 mesothelioma cases and which were chosen based on the literature review. Together these industries make up a sizable percentage of the working population and I would guess the majority of blue collar/manufacturing workers.</p> <p>Part of the heading for Table 2 is missing in my copy of the manuscript.</p> <p>To keep the focus on asbestos, I would recommend greatly reducing the size of Table 4 to only include "all causes," "all neoplasms," and</p>
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	<p>causes of death potentially related to asbestos. The observed number of cases should be included in Table 4. If the numbers of men were included in the headings Table 2 could be deleted.</p> <p>It would be good to know whether the excess of oral cancer is driven by a particular site. Pharyngeal cancer is long suspected of being associated with asbestos, but the evidence is limited because of small numbers.</p> <p>The industry categories were quite broad and the prevalence of exposure in most could be low, at least in 1991. Given the nature of the cohort, with information only available for a single year, I would be cautious in labelling these broad industries as high risk. For example in the automotive industry the attention has focused primarily on manufacture and operations involving brake pads, which historically contained asbestos, but that would only be a small percentage of the industry. It is not surprising that many of the selected industries would have an excess of mesothelioma, given they were chosen because of having a high number of cases.</p> <p>I was surprised by the relative lack asbestosis cases in the groups predicted to have high asbestos exposure, even in the asbestos industry itself. This does not get much discussion (it is not even in the Discussion section). Is it not occurring or is it being misdiagnosed in Belgium?</p> <p>In the limitations paragraph, it should be added that confounding can also occur in the current job.</p>
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REVIEWER	Andrew Darnton Health and Safety Executive, UK
REVIEW RETURNED	09-Feb-2015

GENERAL COMMENTS	<p>This is an interesting and informative analysis following up the mortality experience of a large number of Belgian workers with varying potential for exposure to asbestos.</p> <p>I've set out my detailed comments below, most of which are relatively minor.</p> <ol style="list-style-type: none"> 1. Page 5, line 35. It would be very helpful to have more background information about the use of different kinds of asbestos products and how use of crocidolite varied according to the industry sectors considered later. These factors may help explain some of the variation in the sizes of the excess risks seen across industry sectors. If there is any documentary evidence about this it would be well worth including. 2. Page 6, line 2: "i.a." seems to be a typographical error. 3. Page 7, line 33-53: The significance of the comment about death certificates being available only for the Flanders and Brussels Capital region is not immediately obvious, but presumably relates to the availability of cause specific information. I think it would be helpful to clarify the precise definition of the cohort – for example, something like: "the 1,397,699 individuals with a valid occupation code at the 1991 census in the Flanders and Brussels Capital region, or who had died during 1 October 2001 and 1 January 2010 in that region". 4. 1 January 2010 seems a strange date for the end of the
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observation period unless it means individuals dying before this date – i.e. up until the end of 31 December 2009 inclusive. It would be helpful to clarify this.

5. Page 8, line 34. It is not entirely clear how the information about the number of mesotheliomas in industry groups and information from the literature about asbestos use was combined to produce the categories. Presumably at least 3 deaths AND document evidence of exposure was needed?

6. Page 9, line 16: It would be useful to explain that the “active population” means those in work in any other industry at the time of the census.

7. Page 11, Table 2: there are no column headings for manual, non-manual, and total categories.

8. Page 12, line 13: it would be clearer to say “194 deaths from a total of 173,137 workers rather than use “n=...”

9. Page 12, line 33, and analyses in Table 3: Some form of age-standardised rates would be useful here to help show the differences in levels of mortality among the different groups in the active and non-active population. For example, the relatively high mortality in non-active men aged <65 is said to be indicative of a healthy worker effect. However, it is not clear to me that a relatively high rate in this category is not partly to do with age differences: for example, although they have the same overall age range as the active population, there could still be a bias towards people being older and therefore having a higher mesothelioma rate due to past exposure. It is difficult to interpret this without age-standardisation.

10. Table 4: I realise it takes more space, but the observed number of deaths in each cell needs to be included along with the SMRs and confidence intervals. I realise with a bit of work you can estimate observed and expected using the confidence intervals but it would be much more helpful to have the numbers shown.

11. Also in term of the industrial breakdown, given the relatively large size of the construction industry, it would be interesting to know whether this could be broken down any further. In the UK, for example, we found very big differences in risk for different kinds of construction workers, carpenters, plumbers and electricians being particularly high risk.

12. Page 13, line 49. The lack of asbestosis deaths seems surprising given the very high mesothelioma and lung cancer risks, though the expected number must have been small. It would be useful to state the expected number.

13. Page 14, line 3. Although laryngeal cancer was much higher than expected in non-manual asbestos industry workers, lung cancer was not, which may tend to detract from this finding, particularly in the light of potential confounding by smoking and alcohol consumption, and also the important issue that a higher proportion of non-manual workers may previously have been manual workers than vice-versa. The effects seen among non-manual workers may to some extent still be a reflection of earlier manual work. I think this latter issue need to be pointed out more clearly (and also in the discussion of the limitations).

14. Page 14, line 21-33: The mesothelioma excess in shipbuilding and railroad work do not seem to be mentioned.

15. Page 18, line 31: I think it would be worth mentioning that a suggestive excess of circulatory disease in the asbestos industry (even though not statistically significant). More generally, I think it is important to look for consistency in effects across different industries and not focus entirely on statistical significance (though it is important, of course). In particular, how consistent are the suggested excesses of other outcomes among those groups where there is

	<p>clearly a mesothelioma and lung cancer excess?</p> <p>16. Page 19, line 11. The point about alcoholic liver disease is interesting and relevant to the interpretation of findings about oral and laryngeal cancer in construction workers: the excesses seen may be partly attributable to this, and also tobacco smoking.</p> <p>17. More generally, one of the limitations of the analysis is the lack of control such confounding factors. It would strengthen the paper if there was an assessment of how much of the excesses might reasonably be attributed to such confounding factors – for example, how much different with respect to these factors would the construction (and other exposed groups) have to be compared with the reference population to account the observed effects? This also relates to the comment in the discussion on page 21, line 2.</p> <p>18. Page 21, line 47. I think it would be clearer to say: "...higher mortality due to COPD, which is known to be caused predominantly by smoking." And it would be worth adding that occupational exposures to various gases, dusts and fumes are known to contribute to COPD.</p> <p>19. Finally, much of the document is written in the present rather than the past tense, which is the more usual style.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Eduardo Algranti

Institution and Country FUNDACENTRO

São Paulo, Brazil

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The manuscript describes mortality due to occupational asbestos exposure in the period 2001-2009 in the male active (employed) Belgian population, aged 18-65 years, identified by the 1991 census. Until now, Belgium, in contrast with other Western European countries, has produced limited epidemiological data on the consequences of its extensive use of asbestos. Occupational exposure was ascertained according to an industrial sector presenting at least 3 mesothelioma deaths plus documental reviews of asbestos consumption.

The objective is clearly stated and the study design is appropriate to answer the research questions. The manuscript has a very rich content. The significant excess of oral cancer deaths is an important contribution to the literature. In parts of the text it is difficult to follow results and discussion without going back to Methods. As a general comment I would suggest to revise results and discussion in order to facilitate the reading and understanding. If there is no restriction to include a couple of charts summarizing the significant findings shown in Table 4, it could facilitate the reading.

I would ask the authors to clarify the following points:

1. Introduction

a) On pg 6, 1st paragraph, lines 3-12: what does it mean "first major ban in 1998"? Please, provide an explanation.

Reply by the authors: We have rephrased this paragraph: "Industrial asbestos use was reduced dramatically with a major ban on all asbestos types in 1998. Some exceptions for chrysotile products remained until 2001, when the use and transaction of all types of asbestos were finally banned."
(Revised manuscript, p.6)

2. Methods

a) On pg 8, lines 34-39: the distinction on industrial sectors with at least 3 mesothelioma deaths refers

to Industry or Industrial activity (see Table 1)? This criterion was also used for the typical asbestos industry? It should be better explained.

Reply by the authors: The benchmark set at a minimum of three mesothelioma deaths refers to the broad industries (under the heading Industry in Table 1). We agree with the reviewer and have adapted our text: "We have combined the distribution of mesothelioma deaths in Belgian industries with an extensive literature review to determine the industries most at risk of asbestos-related health effects." (Revised manuscript, p 8)

A new phrase states: "We have cross-referenced these findings with the published literature." (Revised manuscript, p 9)

We rephrase: "Finally, industries with at least three mesothelioma deaths in the period 2001-2009 and with conclusive evidence of asbestos use were considered as high-risk industries." (Revised manuscript, p 9)

This criterion is used for all selected industries, including the asbestos industries. Table 2 shows that the number of mesothelioma deaths among all workers in the selected industries is at least three cases.

b) On pg 11, Table 2: as presented it is difficult to understand because it lacks captions - Manual, Non-manual and Total.

Reply by the authors: The necessary modifications have been made. (Revised manuscript, p 12)

3. Results

a) On pg 12 line 20: "active population (n=1.428.621)". This number differs from the studied population quoted at pg 7 (Study Design)

Reply by the authors: We thank the reviewer for this comment. We have corrected this number to n= 1 397 699. (Revised manuscript, p 13)

4. Discussion

a) On pgs 20-21: lines 56-57 and line 3: Please rephrase it. As it stands it is of difficult understanding

Reply by the authors: We have modified this section: "Tobacco and alcohol consumption are considered to be major risk factors.(22) However, occupational asbestos exposure has also been reported as a possible causal factor for oral cancer types,(23-25) and for pharyngeal cancer.(26)" (Revised manuscript, p 23)

b) On pg 21: lines 25 to 32: This comment has already been made and can be deleted

Reply by the authors: We agree with the reviewer.

c) On pg 21: line 35: There's a good and recent reference on the relationship between asbestos exposure and smoking that should be quoted along with Gustavsson: Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. *Am J Respir Crit Care Med.* 2013 Jul 1;188(1):90-6. doi: 10.1164/rccm.201302-0257OC.

Reply by the authors: We thank the reviewer for this suggestion. (Revised manuscript, p 24)

Reviewer Name: Paul Demers
Institution and Country Occupational Cancer Research Centre

Toronto, Canada

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This was an interesting paper because of the high rates of mesothelioma in Belgium. It is a relatively simply census record linkage study, as is commonly done in the Nordic countries. Calling this a retrospective cohort study, although technically correct, may imply a different set of methods, at least in occupational epidemiology. I have a number of other comments and questions.

Reply by the authors: In order to avoid misunderstandings, we removed the two references to a 'retrospective' cohort study.

1. What does "i.a." means in the 4th paragraph of the introduction? This is not a standard abbreviation.

Reply by the authors: The abbreviation 'i.a.' refers to 'inter alia'. We acknowledge grounds for confusion and have changed the sentence: "Despite declining asbestos exposure levels, occupational exposure in e.g. asbestos products manufacturing, shipbuilding, and construction remained relatively common until the end of the 1990s." (Revised manuscript: p 6)

We also rephrase: "Considering the use of various carcinogens such as nickel, cadmium or PAHs in the selected industries, concomitant occupational exposure is highly likely." (Revised manuscript: p 24)

2. I presume that the "detailed occupational information" (Methods, 1st paragraph) is actually occupation and industry coded using a standardized system. I presume that NACE was used for industry, but the occupational coding system should be stated, as well as more detail on how manual workers were defined.

Reply by the authors: We agree that the description of the methodology can be improved. Industry of employment was in fact coded using the NACE, as mentioned in the manuscript (p. 8-9).

We have added the following phrase to the Method section: "The 1991 census includes information on the type of performed labour: self-employed, blue-collar, white-collar, management, etc." (Revised manuscript: p 9-10)

Only occupational type, as described above, and industry of employment were used in our analyses. A more detailed classification of occupations was not used in this study, but will be considered for further investigation.

3. What percentage of deaths occurred outside the Flanders and Brussels Capital Region? It seems as though this is a limitation that does not get much discussion, but without knowing the percentage it is difficult to judge.

Reply by the authors: Additional information is added to the text: "According to data from the Scientific Institute for Public Health, all-cause mortality in Flanders and Brussels accounts for 65% of all Belgian male deaths in 2003-2010. Approximately 80% of all male mesothelioma mortality occurs among Flemish and Brussels men.(12)" (Revised manuscript: p 7)

4. I presume that the SMR's were calculated using standard 5-year age and calendar periods, but this should be stated.

Reply by the authors: The phrase has been adapted to "Standardised mortality rates (SMRs) are calculated by 5-year age group with reference to workers in all other industries (Category C)." We further explain: "Data for the study period 2001-2009 are combined because of the small number of cases per year for some of the industries under investigation." (Revised manuscript: p 12)

5. It is unclear to me which industries were chosen based on 3 mesothelioma cases and which were chosen based on the literature review. Together these industries make up a sizable percentage of the working population and I would guess the majority of blue collar/manufacturing workers.

Reply by the authors: We agree and refer to comment 2a by Eduardo Algranti. In addition, the following phrases are added to the manuscript: "Out of 704 458 manual workers in 1991, 40% were active in high-risk industries. All other occupational types in these industries account for approximately 15% of all 693 241 non-manual workers." (Revised manuscript: p 10)

6. Part of the heading for Table 2 is missing in my copy of the manuscript.

Reply by the authors: The necessary modifications have been made. (Revised manuscript: p 12)

7. To keep the focus on asbestos, I would recommend greatly reducing the size of Table 4 to only include "all causes," "all neoplasms," and causes of death potentially related to asbestos. The observed number of cases should be included in Table 4. If the numbers of men were included in the headings Table 2 could be deleted.

Reply by the authors: We agree that the readability of table 4 should be improved. The causes of death in table 4 are limited according to the suggestions of the reviewer. However, the numbers of workers per industry in 1991 are still presented in table 2. The automotive industry, the electro-technical products manufacturing industry, and the textile industry are not presented in table 4 because of the low relevance. In order to give readers the opportunity to compare the relative importance of industries in the Belgian work force, table 2 provides an overview of all industries under investigation and the reference population.

8. It would be good to know whether the excess of oral cancer is driven by a particular site. Pharyngeal cancer is long suspected of being associated with asbestos, but the evidence is limited because of small numbers.

Reply by the authors: More detailed data on oral cancer deaths is provided in table 5. We have also rewritten the results section on oral cancer mortality: "Results indicate significantly more oral cancer deaths among manual workers in the asbestos industry, the railroad industry, the shipping industry, and the construction industry. When examining more closely, high oral cancer mortality is driven by excess deaths due to cancers of the mouth (ICD-10 C01-C06) in all four industries. Mouth cancer mortality is nine times higher among asbestos workers (SMR 938; CI 305-2189). Railroad workers experience about four times more mouth cancer deaths (SMR 390; CI 213-655). Shipping workers have an elevated SMR of 211 (CI 96-400). Construction workers experience 40% more mouth cancer deaths than expected (CI 101-189). For construction workers, we also find significant excess in pharyngeal cancer mortality (SMR 151; CI 104-212)." (Revised manuscript: p 18)

9. The industry categories were quite broad and the prevalence of exposure in most could be low, at least in 1991. Given the nature of the cohort, with information only available for a single year, I would be cautious in labelling these broad industries as high risk. For example in the automotive industry the attention has focused primarily on manufacture and operations involving brake pads, which historically contained asbestos, but that would only be a small percentage of the industry. It is not surprising that many of the selected industries would have an excess of mesothelioma, given they were chosen because of having a high number of cases.

Reply by the authors: We recognize the reviewer's concerns about the use of the term 'high-risk industry'. However, we found any alternative wording would be at the expense of the readability of the

text. Readers are notified about the limitations of the study design, including the use of broad industries, in the discussion section.

10. I was surprised by the relative lack asbestosis cases in the groups predicted to have high asbestos exposure, even in the asbestos industry itself. This does not get much discussion (it is not even in the Discussion section). Is it not occurring or is it being misdiagnosed in Belgium?

Reply by the authors: The reviewer is right to suggest further explanation. We believe this is due to the fact that not all asbestosis cases are coded as an underlying cause of death.

Because asbestosis can lead to a number of fatal complications, this disease may have been coded as a contributing cause of death. We are aware of the possible underestimation of asbestosis cases. However, we feel the underlying deaths provide the best assessment of potential excesses in cause-specific mortality for the selected industries. Considering the complex associations between underlying and contributing causes of death, we have planned an in-depth assessment of the mortality pattern with all cause-of-death categories in the near future. Additional data has already been requested for this purpose.

The following phrase has been added to the discussion section: "An underestimation of asbestosis mortality is possible because asbestosis is frequently coded as a contributing cause of death and this study is based on underlying causes of death." (Revised manuscript, p 23)

11. In the limitations paragraph, it should be added that confounding can also occur in the current job.

Reply by the authors: We thank the reviewer for this comment and have added: "Occupational information after the 1991 census is not available. Hence, potential confounders related to the last job have not been taken into account. Due to the long period between asbestos exposure and onset of related diseases, we believe this does not alter the interpretation of our results." (Revised manuscript, p. 26)

This information has been included in the box: "Potential confounders after the census date are not taken into account." (Revised manuscript, p. 4)

Reviewer Name: Mr Andrew Darnton

Institution and Country Health and Safety Executive, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is an interesting and informative analysis following up the mortality experience of a large number of Belgian workers with varying potential for exposure to asbestos.

I've set out my detailed comments below, most of which are relatively minor.

1. Page 5, line 35. It would be very helpful to have more background information about the use of different kinds of asbestos products and how use of crocidolite varied according to the industry sectors considered later. These factors may help explain some of the variation in the sizes of the excess risks seen across industry sectors. If there is any documentary evidence about this it would be well worth including.

Reply by the authors: We agree with this comment. Unfortunately, information about asbestos exposure is very limited for Belgium. One of our research goals is to make an inventory of the available exposure data. We are currently looking for more specific information on the manufacturing of asbestos products in Belgium.

2. Page 6, line 2: "i.a." seems to be a typographical error.

Reply by the authors: We refer to remark 1 from Paul Demers.

3. Page 7, line 33-53: The significance of the comment about death certificates being available only for the Flanders and Brussels Capital region is not immediately obvious, but presumably relates to the availability of cause specific information. I think it would be helpful to clarify the precise definition of the cohort – for example, something like: “the 1,397,699 individuals with a valid occupation code at the 1991 census in the Flanders and Brussels Capital region, or who had died during 1 October 2001 and 1 January 2010 in that region”.

Reply by the authors: We have clarified the statement on the availability of death certificate data: “Death certificates are not available for all three Belgian regions. The cause-specific mortality data only covers Flanders and the Brussels Capital Region, where the majority of Belgian asbestos firms were located.(1)”

In order to improve the understanding of cohort characteristics, we have deleted the phrase “The study includes all occupationally active men (18-65 years) in 1991 that did not die or emigrate before October 1st 2001”.

This information is incorporated in the following phrases: “Based on the 1991 census, we have identified 1 537 805 occupationally active men (18-65 years) in Flanders and the Brussels Capital Region. Prior to October 1st 2001, 3.5% of these workers emigrated and 3.6% died. Due to missing occupational information, 30 922 workers could not be classified.”

We conclude with “The study investigates 72 074 deaths between 1 October 2001 and 31 December 2009 among a cohort of 1 397 699 Flemish and Brussels men with valid occupational information at the time of the 1991 census.” (Revised manuscript, p.7-8)

4. 1 January 2010 seems a strange date for the end of the observation period unless it means individuals dying before this date – i.e. up until the end of 31 December 2009 inclusive. It would be helpful to clarify this.

Reply by the authors: The study takes into account deaths before 1 January 2010. 31 December 2009 is the last day of the observation period. We rephrased: “An anonymous record linkage has been performed between detailed occupational information from the 1991 Belgian census and cause-specific mortality data from 1 October 2001 to 31 December 2009.” (Revised manuscript: p 7)
This change was applied throughout the manuscript consistently.

5. Page 8, line 34. It is not entirely clear how the information about the number of mesotheliomas in industry groups and information from the literature about asbestos use was combined to produce the categories. Presumably at least 3 deaths AND document evidence of exposure was needed?

Reply by the authors: We agree and refer to comment 2a by Eduardo Algranti.

6. Page 9, line 16: It would be useful to explain that the “active population” means those in work in any other industry at the time of the census.

Reply by the authors: This phrase has been modified: “Category C consists of workers in all industries excluded from categories A or B.” (Revised manuscript: p 9)

7. Page 11, Table 2: there are no column headings for manual, non-manual, and total categories.

Reply by the authors: The necessary modifications have been made. (Revised manuscript: p 12)

8. Page 12, line 13: it would be clearer to say “194 deaths from a total of 173,137 workers rather than use “n=....”

Reply by the authors: We have rephrased accordingly: "194 deaths occurred among 173 137 men past the retirement age of 65 in 1991 and 351 deaths occurred among 510 681 non-active men aged 18 to 65." (Revised manuscript: p 13)

9. Page 12, line 33, and analyses in Table 3: Some form of age-standardised rates would be useful here to help show the differences in levels of mortality among the different groups in the active and non-active population. For example, the relatively high mortality in non-active men aged <65 is said to be indicative of a healthy worker effect. However, it is not clear to me that a relatively high rate in this category is not partly to do with age differences: for example, although they have the same overall age range as the active population, there could still be a bias towards people being older and therefore having a higher mesothelioma rate due to past exposure. It is difficult to interpret this without age-standardisation.

Reply by the authors: In order to facilitate the interpretation of table 3, standardized mortality ratios have been added with reference to all Flemish and Brussels men between the ages of 18 and 65. (Revised manuscript: p 14)

10. Table 4: I realise it takes more space, but the observed number of deaths in each cell needs to be included along with the SMRs and confidence intervals. I realise with a bit of work you can estimate observed and expected using the confidence intervals but it would be much more helpful to have the numbers shown.

Reply by the authors: We have modified the tables by adding the observed number of deaths. (Revised manuscript: p 17; 20-21)

11. Also in term of the industrial breakdown, given the relatively large size of the construction industry, it would be interesting to know whether this could be broken down any further. In the UK, for example, we found very big differences in risk for different kinds of construction workers, carpenters, plumbers and electricians being particularly high risk.

Reply by the authors: A decomposition of occupation in the construction is possible though not in the limited time period for this revision. The 1991 census provides very detailed information on occupations. Because of the extensive amount of information, disentangling specific occupations at risk within the construction industry is a lengthy process. We feel this topic deserves our full attention and is best covered in a separate article.

12. Page 13, line 49. The lack of asbestosis deaths seems surprising given the very high mesothelioma and lung cancer risks, though the expected number must have been small. It would be useful to state the expected number.

Reply by the authors: We refer to comment 10 by Paul Demers. We believe the addition to the discussion section provides sufficient grounds for interpreting the small numbers of asbestosis deaths.

13. Page 14, line 3. Although laryngeal cancer was much higher than expected in non-manual asbestos industry workers, lung cancer was not, which may tend to detract from this finding, particularly in the light of potential confounding by smoking and alcohol consumption, and also the important issue that a higher proportion of non-manual workers may previously have been manual workers than vice-versa. The effects seen among non-manual workers may to some extent still be a reflection of earlier manual work. I think this latter issue need to be pointed out more clearly (and also in the discussion of the limitations).

Reply by the authors: We have pointed out in the results section: “Contrary to their colleagues in manual labour jobs, non-manual workers do not seem to experience higher lung cancer mortality (SMR 29; CI 1-161)” (Revised manuscript, p 15)

Although exposure to previous manual work is possible, we believe this is only the case for a small number of workers. The difference between blue-collar and white-collar occupational types is established in a rigid labour market organisation in Belgium. Not many workers made the shift from blue-collar work to other occupational types (or vice versa).

14. Page 14, line 21-33: The mesothelioma excess in shipbuilding and railroad work do not seem to be mentioned.

Reply by the authors: We have made the necessary changes. (Revised manuscript: p 15)

15. Page 18, line 31: I think it would be worth mentioning that a suggestive excess of circulatory disease in the asbestos industry (even though not statistically significant). More generally, I think it is important to look for consistency in effects across different industries and not focus entirely on statistical significance (though it is important, of course). In particular, how consistent are the suggested excesses of other outcomes among those groups where there is clearly a mesothelioma and lung cancer excess?

Reply by the authors: We have rewritten this section in accordance with the suggestion from the reviewer. (Revised manuscript: p 18-19)

16. Page 19, line 11. The point about alcoholic liver disease is interesting and relevant to the interpretation of findings about oral and laryngeal cancer in construction workers: the excesses seen may be partly attributable to this, and also tobacco smoking.

Reply by the authors: We agree and mention in the discussion section: “Construction workers also experience significant excess in mortality due to alcoholic liver disease, oesophageal cancer, mouth cancer, and pharyngeal cancer suggesting high alcohol use.” (Revised manuscript: p 24)

17. More generally, one of the limitations of the analysis is the lack of control such confounding factors. It would strengthen the paper if there was an assessment of how much of the excesses might reasonably be attributed to such confounding factors – for example, how much different with respect to these factors would the construction (and other exposed groups) have to be compared with the reference population to account the observed effects? This also relates to the comment in the discussion on page 21, line 2.

Reply by the authors: Unfortunately, no such assessment is available for Belgium. We have some indications of higher prevalence of smoking among construction workers compared to the general workforce. Deboosere and Gadeyne already reported excess lung cancer mortality among Belgian construction workers in the period 1991-1995. [1] With this exception for construction workers, we have no other information to assume significant differences between the broad industrial categories with regards to smoking or alcohol use.

18. Page 21, line 47. I think it would be clearer to say: “...higher mortality due to COPD, which is known to be caused predominantly by smoking.” And it would be worth adding that occupational exposures to various gases, dusts and fumes are known to contribute to COPD.

Reply by the authors: We have changed the sentence accordingly and added: “Occupational exposure to dusts, fumes, and gases have been associated with increased incidence of COPD.(32)” (Revised manuscript: p 24)

19. Finally, much of the document is written in the present rather than the past tense, which is the more usual style.

Reply by the authors: We have made some revisions of the tense used. If the editor and reviewers consider the use of the past tense throughout the manuscript more suitable, we are willing to make the necessary adjustments.

Reference:

1 Deboosere P, Gadeyne S. Sterfterisico's naar beroep in België. In: Eeckhaut MCW, Van de Putte B, Van Rossem R, et al., eds. Het sociaal-demografisch perspectief. Gent: Academia Press 2010. 41–71.