Author's response to reviews

Title: Non-occupational exposure to paint fumes during pregnancy and risk of congenital anomalies: a cohort study

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Version: 2 Date: 26 June 2012

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Response to the reviewers

Response to reviewer #1: Ann Aschengrau

The reviewer suggests compulsory and minor revisions. We agree with the reviewer and have addressed all comments below.

1. Add an appendix that gives information on the specific defects that were observed in the study population. This information should be organized by exposure status.

   Answer:
   We have expanded the manuscript with Appendix 1: ‘Distribution of congenital anomalies using the International Classification of Diseases 10th Revision (ICD10) among the 1086 cases in the study, according to exposure status.’

2. Provide further discussion of other sources of solvent exposure that appear to be missing, such as hobbies, drinking water contaminants.

   Answer:
   We agree with the reviewer that this issue should be discussed. The paragraph in the discussion has therefore been expanded with the following: ‘On the other hand, information on potentially important confounders such as sources of solvent exposure in the home environment including use of cleaning agents or hobbies was not available for the study.’

3. Give more information on the diagnoses captured by the ICD codes that were excluded.

   Answer:
   We agree with the reviewer that the description concerning this is insufficient and have revised the manuscript as follows. The section in the Method description on assessment of congenital anomalies has been expanded with the following: ‘Moreover, the following ICD-codes were excluded from our study: Q40.0 (pyloric stenosis), Q67.3 (plagiocephaly – head asymmetry), Q68.0 (torticollis) and Q75.3 (macrocephalus) were all excluded because they mainly occur at birth or after birth, and thus, unlikely to be associated with paint fumes exposure during the first trimester of pregnancy; Q38.1 (tongue tie – short frenum) and Q27.0 (hypoplasia of umbilical artery) were excluded because these are often not considered as congenital anomalies; Q40.1 (hiatus hernia) was excluded since it most often does not cause any symptoms and/or often disappears within the first years of life; Q32.0 (tracheomalacia) and Q31.4-Q31.5 (laryngomalacia) representing weakness and floppiness of the walls of the trachea were excluded since these conditions most often disappear within 18 month of age.’

4. Please clarify that the excluded stillbirths did not have any birth defects.

   Answer:
   We agree with the reviewer that this point is unclear. The paragraph in the Methods section: Assessment of congenital anomalies has been expanded with the following: ’All pregnancy outcomes are reported to and recorded in this register, including congenital anomalies in live born children, whereas congenital anomalies in stillbirths, abortions and terminated pregnancies are not registered in the National Hospital Register.’
   The paragraph in the discussion has been expanded with the following: ‘However, it is a limitation to the study that we were only able to include live born children with congenital
anomalies. Assuming that exposure to paint fumes affects the risk of severe congenital anomalies that may result in abortion or stillbirth, the risk estimates of such anomalies would be underestimated in our study.’

5. The discussion should also mention studies of environmental solvent exposure.
   Answer:
   We agree with the reviewer and have expanded the paragraph in the discussion with the following: ‘Also, some environmental studies have indicated positive associations between solvents in drinking water and neural tube defects, which support our findings regarding congenital anomalies in the nervous system [17, 18].’

6. The discussion should focus more on the small number of exposed cases and resulting statistical instability of the findings.
   Answer:
   We agree with the reviewer. The discussion has been expanded with several comments: ‘However, due to small number of cases in these two congenital anomaly groups in the present study (28 and 58, respectively) the results should be treated with caution.’
   And furthermore: ‘Our study suggests that exposure to paint fumes might increase the risk for congenital anomalies in the ear, face and neck. Occupational studies have failed to find positive associations between exposure to organic solvents and congenital anomalies in the ear, face and neck [7] and as our analyses are based on a small number of cases (36) and as our results are statistically insignificant, this suggests that the observed tendency is a chance finding.’
   And furthermore: ‘This can be due to different groupings of the particular congenital anomaly, but may also be explained by low power in our study to detect associations (only 39 cases) or by exposures to different organic solvents.’
   And finally: ‘The fact that our study is based on small number of exposed cases may have resulted in statistical instability of our findings.’

Minor Essential Revision

1. The authors should consider omitting the reference to the multiple testing "problem." The paper by Rothman (Epidemiology 1990; 1:43-46) will clarify the rationale behind this suggestion.
   Answer:
   We are uncertain which reference in our paper the reviewer refers to? We agree with the reviewer that the paper by Rothman addresses an important point regarding the multiple comparison issue and have edited our description on the multiple testing in the second last paragraph of the discussion: ‘The consistency between our results and previous findings indicates the associations we find might be true, although it is possible that our findings may be due to chance.’
Response to reviewer #2: Martine Vrijheid

The reviewer suggests that the discussion need some clarification. We agree with the reviewer and have addressed all suggestions below.

1. One main potential limitation is not discussed: the study appears to include only anomalies that occurred in live births. This means that a large potential case group is not included, i.e. congenital anomalies occurring in stillbirths, abortions, and those detected by prenatal diagnosis and subsequently terminated. It would be good to see some discussion of this. What effect may the exclusion of this case group have on the risk estimates?
   Answer:
   We agree with the reviewer that this issue needs to be discussed in more details:
   The paragraph in the Methods section: Assessment of congenital anomalies has been expanded with the following: 'All pregnancy outcomes are reported to and recorded in this register, including congenital anomalies in live born children, whereas congenital anomalies in stillbirths, abortions and terminated pregnancies are not registered in the National Hospital Register.
   The paragraph in the discussion has been expanded with the following: 'However, it is a limitation to the study that we were only able to include live born children with congenital anomalies. Assuming that exposure to paint fumes affects the risk of severe congenital anomalies that may result in abortion or stillbirth, the risk estimates of such anomalies would be underestimated in our study.'

2. The anomaly subgroups used are very broad; obviously the numbers are too small to examine more specific groups. However, it is clear that this may lead to dilution of effects by mixing very diverse outcomes. This issue should be discussed.
   Answer:
   We agree with the reviewer that this issue should be discussed. The paragraph in the discussion has therefore been expanded with the following: 'Overall the subgroups used are rather large with some etiological heterogeneity. The rationale behind this grouping was that the numbers of congenital anomalies were too small to examine more specific subgroups. However, this might have diluted the effect of more specific groups of anomalies.'

3. On page 11 misclassification of the diagnosis is discussed. Please clarify what type of misclassification is meant here – anomalies wrongly classified as other anomalies, or anomalies not classified at all?
   Answer:
   We agree with the reviewer that this is unclear. The paragraph in the discussion has been expanded with the following: ‘The diagnosis may however be subjects to some misclassification, as some anomalies may wrongly be classified as other anomalies. This non-differential misclassification is most likely not associated with the exposure to paint fumes in the residence and would as such, either not affect the risk estimates or bias it towards the neutral value.’

4. It is unclear why the authors did not include some general measures of socio-economic status as in their a-priori confounders, e.g. maternal education, although I admit that the confounding effects are likely to be small.
   Answer:
The analyses have been conducted with further adjustment for the mother’s occupational status: high-grade professional, low-grade professional, skilled worker, unskilled worker, student, economical inactive and unclassifiable. Including this variable resulted in only minor changes in the estimates, but reduced the power of the analyses. Together with the overall literature showing discrepant results regarding the association between SES and congenital anomalies (some find an association and others do not) we therefore decided not to include occupational status as a confounder in our primary analyses. However, we agree that mentioning this will improve the paper and therefore write the following in the result section: ‘Further adjustment of the analyses by the mother’s occupational status did only result in minor changes in the estimates’.

5. Recall bias – the authors state that misclassification due to recall problems would have been non-differential. Again, what about prenatally diagnosed cases – mothers may already know at week 30 that their child will be born with an anomaly?

Answer:
We agree with the reviewer and thank her for pointing this out. The paragraph in the discussion has been expanded with the following: ‘Although the overall ultrasonic examination for structural anomalies and developmental defects as a general offer to all pregnant women were first introduced in Denmark in 2004 (that is after the DNBC enrolment period), it cannot be ruled out that some pregnant mothers may have been ultrasonic examined on indication resulting in that they, already in the 30th pregnancy week, knew that their child would be born with an congenital anomaly. This can have introduced some recall bias with regard to the questions regarding painting.'