Author's response to reviews

Title: Exposure to Benzene at Work and the Risk of Leukemia: A Systematic Review and Meta-analysis

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Version: 2 Date: 6 February 2010

Author's response to reviews: see over
A POINT-BY-POINT RESPONSE TO REVIEWERS’ COMMENTS:
Reviewer: Pier Alberto Bertazzi

This is a relevant paper, clearly written and presented, which quantifies the risk entailed by exposure to benzene concentrations that used to be present in most industrialized countries and that may still be present today especially in countries undergoing rapid and sometimes tumultuous development.

Minor Essential Revisions:

1) I found no specific reference in the text to Figure 1.

Figure 1 is cited on p. 10, para 1, line 5.

2) There are a couple of typos.

Typos corrected.

Discretionary Revisions:

1) It might be useful to add some further argument for the exclusion of sources of heterogeneity other than the different levels of exposure.

These results are presented in the revised version of the manuscript (abstract: conclusions; text p. 11 paras 2 and 5; p. 14, para 1; p. 16, para 2).

2) I do not think the data support a dose-response pattern, although only suggestive, for CLL (p.16 in the manuscript).

We conducted meta-regression analyses to further elaborate the dose-response pattern. The results indicated a statistically significant dose-response pattern for any leukemia, but failed to show any significant dose-response pattern for AML. These results are presented in the abstract, results and discussion.
3) In “Conclusions” a reference, at least indicative, to the current occupational and environmental levels of exposure to benzene may help the reader appreciate the relevance of the risk estimates.

Current occupational limits added (p. 17, para 3)

Level of interest: An article of importance in this field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: ‘I declare no competing interests’
Reviewer: Bengt Järvholm

Major:

1) The authors say that there is a dose-response both for leukemia in general and AML. However, that is true for the point estimates, while confidence intervals are overlapping and the difference in risk between dose intervals are rather small. I am not convinced that the data for e.g. AML significantly show a dose-response as presented here (the point estimates show it, but just a random finding).

There was a clear dose response relationship between cumulative exposure to benzene and the risk of any leukemia. We fitted a meta-regression model for ln(effect estimate) by cumulative exposure and found a moderate, statistically significant association with the R-squared value of 26% and p value of 0.015.

In the meta-regression model, the relation between cumulative exposure to benzene and the risk of AML showed no association (R-squared value of 3% and p=0.401).

These results are presented in the revised version of the manuscript (abstract: conclusions; text p. 11 paras 1: p. 12, para 2; p. 14, para 1; p. 17, para 2).

2) The diagnoses/classification of leukemias have changed over years. I miss a discussion if that could have any influence of the findings.

We appreciate the diagnoses/ classification of leukemia changing over years. We elaborated the role of the year of the study which did not influence the effect estimate.

3) The classification of exposure is very different in the studies and there may be differential and non-differential mis-classification. That is not at all discussed. Furthermore, there is also no discussion about possible other cancerous substances occurring in the studies industries. I am not
convinced about the quantitative estimates and they are not contrasted to previous estimations.

We have discussed about exposure assessment in the revised version (p. 15, para 1). We were able to retrieve some type of quantitative estimate for cumulative exposure to benzene from 10 studies. Table 1 displays estimates of cumulative exposure for different exposure categories. Although exposure assessment varied between studies, each study applied similar approaches to different levels of exposure.

4) **Schnatter’s review included 22 studies, this fewer. What are the differences and how may that change the interpretation.**

The reasons why we excluded some of the studies included by Schnatter 2005 is provided in table A below.

5) **The overall point estimate does not exclude an increased risk for AML (or ANLL) but you conclude from the dose-response that there is no risk. Such an analysis is strongly dependent on power and the exposure classification is correct. I doubt that the exposure classification is of such standard, and I miss discussion about it.**

We have conducted meta-regressions for any leukemia and AML which provide more information on dose-response pattern. The exposure classification may be compromised by random error whereas systematic error is less likely.

6) **I cannot follow the discussion about “healthy worker selection”. I am not aware of which preemployment morbidity that increase the risk of leukemia and would influence employability!**

We agree with the reviewer that the reasoning was not clear enough and have excluded the sentence about “health worker effect” (p. 15, para 1).

**Minor**
1) **The reference Sorahan is missing in the reference list.**

We have added this reference.

2) **I would like to have the quality index in Table 1. The authors say they have used it but the results are not present anywhere.**

We think that the role of quality index in the analyses is so small that it is unnecessary to display the study-specific indices.

**Discretionary**

1) **It would be nice to show the difference in this review and the Schnatter review (which studies are included/not included).**

We present below a table which gives reasons for exclusion for each study. A detailed comparison between Schnatter review and our systematic review and meta-analysis is beyond scope of the paper.

2) **I would like a reference to the statement that “the pattern differs from a typical publication bias, in which… positive values.”**


3) **I would like to have the number of cases in the different exposure groups (table 2). E.g. how many cases is the point estimate for AML (high exposure) based on (I assume that it is quite a few)**

Unfortunately, these figures are not available for all the studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Reason not used in study</th>
<th>Study group</th>
<th>Geographic location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigliani (1964)</td>
<td>Individual Case reports</td>
<td>Patients exposed to benzene</td>
<td>Italy</td>
</tr>
<tr>
<td>Aksoy (1974)</td>
<td>No risk measure</td>
<td>Shoe workers exposed to benzene</td>
<td>Italy</td>
</tr>
<tr>
<td>Linos (1980)</td>
<td>Very limited benzene data</td>
<td>Residents in Olmsted County</td>
<td>USA</td>
</tr>
<tr>
<td>DeCoufle (1983)</td>
<td>Estimated risk rather than calculated</td>
<td>Chemical workers exposed to benzene and other agents</td>
<td>USA</td>
</tr>
<tr>
<td>Tsai (1983)</td>
<td>No leukemia cases</td>
<td>Refinery workers</td>
<td>Texas</td>
</tr>
<tr>
<td>Flodin (1986)</td>
<td>No Benzene exposure</td>
<td>Radiation, electrical workers</td>
<td>Sweden</td>
</tr>
<tr>
<td>Linet (1987)</td>
<td>Limited occupational history attained from census data</td>
<td>CLL diagnosed patients</td>
<td>Baltimore</td>
</tr>
<tr>
<td>Malone (1989)</td>
<td>Heavily reliant on questionnaire</td>
<td>Population based case control study</td>
<td>USA</td>
</tr>
<tr>
<td>Crane (1992)</td>
<td>Environmental exposures alongside occupational</td>
<td>Patients newly diagnosed with AML</td>
<td>Texas</td>
</tr>
<tr>
<td>Richardson (1992)</td>
<td>Haematological records for over 30 year olds not all diagnosed</td>
<td>Many patients hospitalized in clinical department</td>
<td>France</td>
</tr>
<tr>
<td>Ciccone (1993)</td>
<td>Concentrating on chromosome aberrations</td>
<td>Patients from Torino Hospital</td>
<td>Italy</td>
</tr>
<tr>
<td>Crump (1994)</td>
<td>Overlap with Rinsky 2002</td>
<td>Pilofilm cohort</td>
<td>Ohio</td>
</tr>
<tr>
<td>Mele (1995)</td>
<td>Environmental exposures alongside occupational</td>
<td>Multicentre case control study</td>
<td>Italy</td>
</tr>
<tr>
<td>Li (1997)</td>
<td>Does not satisfy inclusion criteria of only English papers</td>
<td>Workers in 12 cities</td>
<td>China</td>
</tr>
<tr>
<td>Lynge (1997)</td>
<td>Occupational exposure to exhaust fumes were not included as many people were exposed to gasoline</td>
<td>Service station workers</td>
<td>Norway, Denmark, Sweden and Finland</td>
</tr>
<tr>
<td>Albin (2000)</td>
<td>Concentrating on chromosome</td>
<td>Patients from Lund Hospital</td>
<td>Sweden</td>
</tr>
<tr>
<td>aberrations</td>
<td>Guenel (2002)</td>
<td>Workers exposed to benzene in gas and electric occupations</td>
<td>France</td>
</tr>
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<td>-------------</td>
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<td>----------------------------------------------------------</td>
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<tr>
<td>No exposure data available, therefore mostly based on assumptions</td>
<td>Adegoke (2003)</td>
<td>Residents in Shanghai</td>
<td>China</td>
</tr>
<tr>
<td>Heavily reliant on interview</td>
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</tbody>
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