Acute myeloid and monocytic leukaemia and benzene exposure in petroleum distribution workers in the United Kingdom

Editor,—We read the paper by Rushton and Romaniuk with much interest, and were particularly pleased to see that leukaemia data were analysed by cell type, as we have recommended on several occasions. However, we wish to comment on the quality of the data in the study, particularly the employment histories, and to discuss several methodological issues. We have previously reviewed earlier versions of the same report submitted to the Institute of Petroleum in the United Kingdom.1,4 We thought that the quality of the data in the study needed a close scrutiny, and suggested to Rushton that sensitivity analyses be done. Although some sensitivity analyses have subsequently been conducted, we think that several areas still need clarification and that some limitations of the data need to be made more explicit.

Included in the final analysis were 90 leukaemia cases (table 3 in the published paper). Sensitivity analysis for all leukaemia cases was not presented in the published paper, but in the final University of Nottingham report.1 The employment histories of only 48 cases were based on personnel records (table 1 in appendix 3). That is, only about 53% of the cases’ complete employment histories (job titles, departments, and dates) were based on personnel records. The employment histories of the remaining 47% of the cases were reconstructed or “synthesised” from sources such as recall interviews, entries in medical records, etc. Similarly, the work histories of only 55% (193/354) of controls were based on complete personnel records. Furthermore, although these percentages for the cases and controls in the entire study seemed comparable, this was not true for some important subcohort analyses.

An example was the analysis for acute myeloid and monocytic leukaemia (AMML) Table 1 presents the number of cases of AMML and their controls, and odds ratios (ORs) by cumulative exposure category in the analyses based on all subjects (regardless of quality of employment histories) and on subjects whose employment histories were based on personnel records only, which served as a sensitivity analysis. Based on the analysis of all subjects (regardless of quality of employment histories), the authors found an increased OR of 2.82 (non-significant at the 0.05 level) for cumulative exposure of 4.5–44.9 ppm-years, and put much emphasis on this finding. However, of the nine cases assumed to have 4.5–44.9 ppm-years, the employment histories of only two (22%) were based on personnel records. Furthermore, there was a strong possibility of differential bias between the cases and controls in this exposure category, as the employment histories of 65% (15/23) controls were based on personnel records.

If the analysis was restricted to workers with complete employment histories from personnel records, the OR for the >4.5 ppm-year group was 0.33 (table 1). Clearly the excess based on all subjects came from those workers with employment histories of poorer quality. Based on tables 5 and 7 in the published paper,1 we have constructed a 2×2 table for those whose employment histories were synthesised from sources other than personnel records (table 2), and conducted an unmatched analysis. The OR (95% CI) based on the Mantel-Haenszel procedure was 11.7 (1.2–111.0). Thus, the group with synthesised employment histories based on poorly documented sources (such as personnel records only was greatly reduced, implying that the sensitivity analysis on personnel records only was greatly weakened by the lack of internal consistency, even if we were to ignore the source or quality of employment history data. For example, the model treating cumulative exposure as a continuous variable did not find any increased risk (OR 1.00, 95% CI 0.96–1.04).1 In general, a model based on continuous variables is more informative and less vulnerable to multiple comparison issues created by categorisation. Analyses based on grouped data can be influenced heavily by the grouping itself (how the categories were chosen).

Furthermore, in many of the 50 models on AMML presented in the earlier report dated April, 1995,1 no increased risk was found for cumulative exposure of >4.5 ppm-years. Unfortunately these models were not presented, nor were their results discussed in the published paper by Rushton and Romaniuk.

Unfortunately, as in any historical exposure assessment, the accompanying exposure estimates introduced potential uncertainties. Unfortunately, all the uncertainties in employment histories and exposure assessment seemed to have been lost in the statistical manipulation of the data. For example, the authors mentioned several analyses to discriminate potential differences in risk resulting from exposure to 0.2, 0.3, or 0.4 ppm. We doubt very much that the quality of the employment and exposure data in this study warranted such a fine distinction. In fact, we question whether measurements in the early part of the study period, even if such data were available, were that precise. To infer a difference of 0.1 ppm even for a single person would require multiple samples. The level of analysis was inappropriate given the uncertainties of the original data. No mathematical manipulation could reduce the uncertainties of the original data.

Another problem in the paper4 is the multiple comparison issue. An extremely large number of risk estimates were calculated, and not every estimate was presented in the published paper. For example, according to the earlier report dated April, 1995,5 50 models were used in analysing the AMML data, which consisted of 32 cases. In these 50 models for AMML, about 110 ORs were calculated. In the entire report, close to 300 ORs, not counting those for sensitivity analyses, were presented. With this many ORs calculated, several would be significant due to chance alone. Indeed, the authors themselves recognised the multiple comparison problem, and labelled the entire investigation as “hypothesis generating” in the earlier report.1 Unfortunately, for no stated reason, the label hypothesis generating was dropped in the published version of the report.1

In summary, the interpretation of Rushton and Romaniuk that exposure to low concentrations of benzene in the range of 4.5–45 ppm-years could increase the risk of developing AMML was not justified for reasons already discussed. Peto at the Institute of Cancer Research (London) commented on an earlier version of the Rushton and Romaniuk report, summarised his comments on the report as follows. “Many employment histories are seriously incomplete, and it is possible that the construction of exposure measures was biased in some way.” This unexplained result (of a marked increase of chronic lymphatic leukaemia for the status of “still being in employment”) cannot be due to benzene, and it casts doubt on the reliability of the findings related to benzene.

“There is no clear evidence of any effect of benzene.” (Peto J. Comments on the Institute of Petroleum benzene study. 24 July 1995. Unpublished report.) We could not have

<table>
<thead>
<tr>
<th>Cumulative exposure (ppm-y)</th>
<th>All subjects</th>
<th>Subjects with personnel records</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>&lt;0.45 ppm-y</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>0.45–4.49 ppm-y</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>4.5–44.9 ppm-y</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>≥45 ppm-y</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>120</td>
</tr>
</tbody>
</table>

Table 1: Risk of acute myeloid and monocytic leukaemia by source of employment history

Table 2: Two by two table for workers with synthesised employment histories

<table>
<thead>
<tr>
<th>Cumulative exposure</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.5 ppm-y</td>
<td>9</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>&lt;0.45 ppm-y</td>
<td>15</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>32</td>
<td>40</td>
</tr>
</tbody>
</table>
agreed more with Peto’s summary of the Rushon and Romanuk paper.

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2 Rushon L, Romanuk H. Results of a case-control study to investigate the risk of leukaemia with exposure to benzene. Nottingham: University of Nottingham, March, 1995.

3 Rushon L, Romanuk H. Results of a case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Nottingham: University of Nottingham, April, 1995.

4 Rushon L, Romanuk H. Results of a case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Nottingham: University of Nottingham, June, 1995.

5 Rushon L, Romanuk H. Results of a case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Nottingham: University of Nottingham, August, 1995.

Authors’ reply—Occupational studies are often hampered by less than perfect data. Wong and Raabe continue to place emphasis on the work history information in our recent case control study of leukaemia in oil distribution workers and exposure to benzene. However, as we have discussed at length in our paper, as well as deficiencies in these data, there are many other limitations, including the quality of the information on distribution terminals and inconsistencies in some of the analyses.

We think it important to point out that the final report submitted to the Institute of Petroleum took account of comments (sometimes conflicting) from very many people, including independent reviewers from outside the United Kingdom. The paper gave the main findings from the report, but space precluded presentation of all available tables.

Wong and Raabe focus on only one of the four sensitivity analyses carried out on the quality of the work histories, that including only cases and controls for whom a personnel record was still in existence. Their unmatched analysis in table 2 is inappropriate as the study cases and controls were matched. They focus on the one of the three sensitivity analyses for which results tend to be similar to those for the total sample. They seem to be confusing the quality of information compared with the source of information. The data point out in our discussion the use of work histories from only existing personnel records excluded much good quality and reliable information from other sources.

Although not wishing to encourage selective quoting from unpublished material, Peto, in the covering letter of his review, also commented “the study seems to have been very well conducted and analysed”. We are tempted to ask why Wong and Raabe continue to devote so much effort to trying to extract...
size is small (say <50), presenting all the information economically. Box and whisker plots present in ascending order the minimum value, the first quartile, the median, the third quartile and the maximum value. These values are enough to convey the main points about the distribution of the data, also showing the possible outliers.

It is important to construct graphical representations of a publication avoiding too simplistic figures—such as dynamite plunger plots.’ This plot does not convey adequately the distribution of the data, and may lead to confusion in the interpretation of the results.

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NOTICES

3rd International Scientific Conference on Prevention of Work Related Musculoskeletal Disorders
13th International Symposium on Epidemiology in Occupational Health

General:
- Work related disorders in various professional groups
- Exposure assessment

- Health assessment
- Methodological aspects
- Intervention studies
- Health surveillance
- Hazard surveillance

Prevention of work related musculoskeletal disorders:
- Classification of musculoskeletal disorders
- Low back disorders
- Neck shoulder disorders
- Upper and lower extremity disorders
- Pathomechanisms of musculoskeletal disorders
- Biomechanical aspects of musculoskeletal disorders

Epidemiology in occupational health:
- Occupational cancer
- Cardiovascular diseases
- Respiratory diseases
- Reproductive effects
- Neuro behavioural diseases
- Cytotoxins and solvents
- Noise
- Communicable diseases
- Accidents at work

Contact:
Ms Mirja Kallio, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a, FIN-00250 Helsinki, Finland. Tel: 00358 9 4747 4771; Fax: 00359 9 4747 548; email: mkal@occuphealth.fi; Internet: http://www.occuphealth.fi/eng/project/premus


The 1998 SOEH meeting is organised by the Society for Occupational and Environmental Health in association with The John E Fogarty International Center for Advanced Study in the Health Sciences and World Health Organization Office of Global Environmental Health.

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- To identify opportunities for collaborative research, education and training, and public policy
- To learn about collaborative projects and meet potential collaborators from many countries
- To speak with representatives of major funding agencies and foundations.

For Information contact: SOEH, ATTN: Marge Degnon, 6728 Old McLean Village Road, McLean, VA 22101, USA. Tel: 001 703 556 9222, Fax: 001 703 556 8729.

XVth World Congress on Occupational Safety and Health: a Global Challenge. 12–16 April 1999. São Paulo, Brazil.

This congress is organised by the Ministry of Labour of Brazil through FUNDACENTRO and the Secretariat of Occupational Safety and Health, the International Labour Office (ILO) in Geneva, and the International Social Security Association (ISSA) in Geneva. The Congress will provide in a worldwide forum unique opportunities for experts from regional bodies, such as MERCOSUL, NAFTA, the European Union, and others representing regional concerns, to meet and discuss individual approaches, experiences, and solutions found for protecting mankind and the environment and to deliberate their interrelation.

Besides the thorough and in depth coverage of the overall theme of the Congress “Safety, health and environment: a global challenge”, the innovative concept for this Congress aims at:
- Providing participants with dynamic perspectives on how to anticipate and adapt to changes in the world
- Providing maximum interaction among all those involved or interested in prevention through their exchanges of views and experiences in personal contacts and through oral and poster corner presentations.

4th International film and video festival
The 4th International film and video festival on occupational safety and health, will be held within the framework of the Congress, organised by the ISSA International Section “Electricity”.

As in previous Congresses, a worldwide review of the current film and video productions will be provided. Films and videos will be described in a multilingual register. An international jury will award the best films and videos.

Further information from: Secretaria de XV Congresso Mundial Sobre Segurança e Saúde no Trabalho Fundacentro, Rua Capote Valente 710, 05409-002 São Paulo, SP, Brazil.
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doi: 10.1136/oem.55.5.361a

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