CORRESPONDENCE

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

EDITOR.—We read the paper by Rushton and Romaniuk¹ 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.²⁻⁵ 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 paper¹). Sensitivity analysis for all leukaemia was not presented in the published paper, but in the final University of Nottingham report.⁵ The employment histories of only 48 cases were based on personnel records (table 1 in appendix 3).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.¹

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 2x2 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 personal recall, interviews, entries in medical records, etc) showed an extremely high risk, which was completely inconsistent with that derived from the analysis restricted to employment histories documented in personnel records. Therefore, this analysis, even if it does not completely invalidate the analysis in table 5 in the published paper,¹ should at least provide some perspectives to the importance of the sensitivity analysis. This analysis also indicates that the statement in the abstract that "Analyses exploring the sensitivity of the results to the source and quality of the work histories showed similar patterns in general"¹ is not valid at all in the case of the result for AMML.

Rushton and Romaniuk seemed to downplay the sensitivity analysis for AMML by arguing that the number in the analysis based on personnel records only was greatly reduced, implying that the sensitivity analysis was not reliable. That is precisely the point of a sensitivity analysis: there were few reliable data on employment histories in the group with cumulative exposure of >4.5 ppm-years (only two cases with complete employment histories from personnel records).

The finding for AMML of an increased OR of 2.82 for the 4.5-44.9 ppm-year cumulative exposure group was further 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 artifacts 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

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

Cumulative exposure	Cases	Controls	Total
>4.5 ppm-y	7	9	16
<0.45 ppm-y	1	15	16
Total	8	24	32

April, 1995,³ 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.¹

Furthermore, as in any historical exposure estimates, the accompanying exposure assessment introduced additional 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 attempted several analyses to discriminate potential difference 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 the 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 paper¹ 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, 1995,³ 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 reports.³ 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), a reviewer of an earlier version of the Rushton and Romaniuk report,⁵ 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 1 Risk of acute myeloid and monocytic leukaemia by source of employment history

Cumulative exposure (ppm-y)	All subjects			Subjects with personnel records					
	Cases	Controls	OR	Cases		Controls		OR	
<0.45	7	46	(1)	6	86%	31	67%	(1)	
0.45-4.49	15	51	2.17	12	80%	26	51%	1.42	
4.5-44.9	9	23	2.82	2	22%	15	65%	0.33	
≥45	0	1	0	0	—	0	—		
Total	31	120	—	20	64%	72	60%	—	

agreed more with Peto's summary of the Rushton and Romaniuk paper.

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- 1 Rushton L, Romaniuk H. A case-control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med* 1997;54:152-66.
- 2 Rushton L, Romaniuk H. Results of a case-control study to investigate the risk of leukemia with exposure to benzene. Nottingham: University of Nottingham, March, 1995.
- 3 Rushton L, Romaniuk H. Results of a case-control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Nottingham: University of Nottingham, April, 1995.
- 4 Rushton L, Romaniuk H. Results of a case-control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Nottingham: University of Nottingham, June, 1995.
- 5 Rushton L, Romaniuk H. Results of a case-control study to investigate the risk of leukemia 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 nested 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 were other limitations, including the quality of the information on distribution terminals and inconsistencies in some of the analyses.

We think it is 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 oil industry. 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 do not comment on the other 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. As we point out in our discussion, 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 seeking to estab-

lish that benzene exposure is associated with no risk, by criticising a paper, the conclusions of the summary of which state "There is no evidence in this study of an association between exposure to benzene and lymphoid leukaemia, either acute or chronic.... However, in view of the limitations of the study, doubt remains as to whether the risk of acute myeloid and monocytic leukaemia is increased by cumulative exposures of <45 ppm-years. Further work is recommended to review the work histories and redefine their quality, to explore the discrepancies between results for categorical and continuous variables, and to develop ranges around the exposure estimates to enable further sensitivity analyses to be carried out."

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- 1 Rushton L, Romaniuk H. Results of an Case-control study to investigate the risks of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. London: Institute of Petroleum, 1995.

Occupational asthma due to amylase

EDITOR—In their report on occupational asthma due to porcine pancreatic amylase,¹ Aiken *et al* state that occupational asthma specifically due to amylase has only been described previously in bakers, and quoted a 1986 paper by Baur *et al*.²

In 1979, I reported five patients with asthma due to powdered α -amylase (derived from *Aspergillus oryzae*).³ All gave positive skin prick tests (and subsequently positive RAST tests). Three were process workers, engaged in diluting enzyme concentrate with a carrier powder for the bakery trade; one worked in a laboratory doing quality control assay; and one worked in an office immediately above the enzyme mixing plant.

Hitherto, reported cases of enzyme sensitisation and asthma had been due to proteases, such as subtilopeptidase⁴ and papain,⁵ but this finding with α -amylase confirmed the likelihood that enzymes were sensitisers by virtue of their being high molecular weight proteins irrespective of their specificity.⁶ The recommendation that all enzymes must be assumed to be allergenic has recently been strikingly endorsed in a study by Johnsen *et al* of workers exposed to proteases, lipases, cellulases, and carboxyhydrolases.⁷

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- 1 Aiken TC, Ward R, Peel ET, *et al*. Occupational asthma due to porcine pancreatic amylase. *Occup Environ Med* 1997;54:762-4.
- 2 Baur K, Fruhmman G, Haug B, *et al*. Role of *Aspergillus* amylase in Baker's asthma. *Lancet* 1986;i:43.
- 3 Flindt MLH. Allergy to α -amylase and papain. *Lancet* 1979;i:1407-8.
- 4 Flindt MLH. Pulmonary disease due to the inhalation of derivatives of *Bacillus subtilis* containing proteolytic enzyme. *Lancet* 1969;ii:1177-81.
- 5 Flindt MLH. Respiratory hazards from papain. *Lancet* 1978;ii:430-2.
- 6 Flindt MLH. Health and safety aspects of working with enzymes. *Process Biochemistry* 1978;13(8):3-7.
- 7 Johnsen CR, Sorensen TB, Larsen AI, *et al*. Allergy risk in an enzyme producing plant. *Occup Environ Med* 1997;54:671-5.

Author's reply—Flindt admonishes us for failing to accord precedence to him for recognising amylase induced occupational asthma outside the baking industry. We apologise for our inadequate literature search, and we are very happy to acknowledge Flindt's earlier contribution of 1979 to the relevant literature. In fact, his invaluable work with enzymes was well known to us, although we had failed to review his particular letter to the *Lancet* of 1979.¹

In this he reported, for the first time, evidence of immunological sensitivity to α -amylase. He also augmented existing evidence of occupational sensitisation to the proteolytic enzyme papain. He argued that clinical symptoms in workers exposed to proteolytic enzymes were not primarily a consequence of proteolytic activity, but of allergenicity of enzymes in general because of their large molecular weights. The findings of skin reactions and symptoms in workers exposed to the non-proteolytic enzyme, α -amylase, therefore supported this hypothesis. He reported investigations on eight people who had "rhinitis and/or asthma", of whom seven gave positive skin prick test reactions to papain and five to α -amylase. Only one reacted to α -amylase alone, but the table in his letter in the *Lancet* indicated that this person did have chest symptoms. No inhalation provocation tests were reported, and so it is questionable whether such an association provides adequate evidence of causality.

In his letter in response to our article, Flindt indicates that the five people with apparent sensitisation to α -amylase were in fact working to produce the enzyme for the bakery trade, although they were not actually bakers. Our inadequately researched statement that "occupational asthma specifically due to amylase has only been described previously in bakers" may not therefore have been too misleading or unduly inaccurate.

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- 1 Flindt MLH. Allergy to α -amylase and papain. *Lancet* 1979; i:1407-8.

Dynamite plunger plots should not be used

EDITOR—The function of graphical displays is to offer information globally through one only sight. In some occasions, however, they can produce misleading impressions leading to erroneous interpretations.¹ It has been suggested that, within reason, the ratio of the amount of information should be maximised to the amount of ink.²

Bar charts showing the mean value with its error bar, usually referred to as a "dynamite plunger plot" have appeared in several papers of your *Journal* during the past year.³⁻⁷ Error bars, however, are not universally defined. They are usually based on the standard error (SEM), which sometimes may be chosen because it is smaller than alternatives such as the standard deviation (SD), leading to confusion of the reader. This type of presentation is to be avoided as it violates Tuft's principle² in that only two numbers are conveyed with a large amount of ink, and any sense of the distribution of the data is lost.

For quantitative data alternative graphical displays—such as dot plots or box and whisker plots, have been suggested instead of dynamite plunger plots.⁸ Dot plots show the distribution of continuous data, if the sample

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.⁹ 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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- 1 Huff D. *How to lie with statistics*. London: Penguin, 1973.
- 2 Tufte ER. *The visual display of quantitative information*. Cheshire, Connecticut: Graphics Press, 1983.
- 3 Egan CE, Espie BH, McGrann S, et al. Acute effects of vibration on peripheral blood flow in healthy subjects. *Occup Environ Med* 1996;53:663–9.
- 4 Rosa RR, Hörmö M, Pulli K, et al. Rescheduling a three shift system at a steel rolling mill: effects of a one hour delay of shift starting times on sleep and alertness in younger and older workers. *Occup Environ Med* 1996;53:667–85.
- 5 Gilmour PS, Brown DM, Lindsay TG, et al. Adverse effects of PM₁₀ particles: involvement of iron in generation of hydroxyl radical. *Occup Environ Med* 1996;53:817–22.
- 6 Clottens FL, Verbeken EK, Demedts M, et al. Pulmonary toxicity of components of textile paint linked to the Ardystil syndrome: intratracheal administration in hamsters. *Occup Environ Med* 1997;54:376–87.
- 7 Nortier J, Bernard A, Roels H, et al. Urinary neutral endopeptidase in workers exposed to cadmium: interaction with cigarette smoking. *Occup Environ Med* 1997;54:432–6.
- 8 Campbell MJ, Machin D. *Medical statistics: a common sense approach*. Chichester: Wiley, 1993.
- 9 Campbell MJ. Presenting numerical results. In: Reece D, ed. *How to do it*. Vol 2. *Examinations, academia, research, and communication*. London: BMJ Publishing Group, 1995:77–83.

- 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
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- Noise
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- Accidents at work

Contact:

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International collaboration in research, education and training, and public policy in environmental and occupational health. 19–23 October, 1998. Natcher Center, National Institutes of Health, Bethesda, Maryland.

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.

Environmental and occupational health professionals in the United States and other developed countries increasingly recognise the need to collaborate with colleagues in developing countries to advance shared goals in research, education and training, and public policy.

This meeting will bring together environmental and occupational health researchers, educators, and practitioners from industrialised countries, their counterparts from developing countries, and representatives of many agencies and institutions.

- 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.

NOTICES

3rd International Scientific Conference on Prevention of Work Related Musculoskeletal Disorders

13th International Symposium on Epidemiology in Occupational Health
PREMUS-ISEOH'98. 21–25 September 1998. Marina Congress Center, Helsinki, Finland.

General:

- Work related disorders in various professional groups
- Exposure assessment