

Published in final edited form as:

Occup Environ Med. 2015 March ; 72(3): 165–170. doi:10.1136/oemed-2014-102382.

## RISK OF CANCER IN WORKERS EXPOSED TO STYRENE AT EIGHT BRITISH COMPANIES MAKING GLASS-REINFORCED PLASTICS

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### Abstract

**Objectives**—To provide further information on the risks of lympho-haematopoietic (LH) and other cancers associated with styrene

**Methods**—We extended follow-up to December 2012 for 7,970 workers at eight companies in England which used styrene in the manufacture of glass-reinforced plastics. Mortality was compared with that for England and Wales by the person-years method, and summarised by standardised mortality ratios (SMRs) with 95% confidence intervals (CIs). A supplementary nested case-control analysis compared styrene exposures, lagged by five years, in 122 incident or fatal cases of LH cancer and 1,138 matched controls.

**Results**—A total of 3,121 cohort members had died (2,022 since the last follow-up). No elevation of mortality was observed for LH cancer, either in the full cohort (62 deaths, SMR 0.90, 95% CI 0.69-1.15), or in those with more than background exposure to styrene (38 deaths, SMR 0.82, 95% CI 0.58-1.14). Nor did the case-control analysis suggest any association with LH cancer. In comparison with background exposure, the odds ratio for non-Hodgkin lymphoma/chronic lymphocytic leukaemia in workers with high exposure (estimated eight-hour time-weighted average of 40-100 ppm) for 1 year was 0.54 (95% CI 0.23-1.27). Mortality from lung cancer was significantly elevated, and risk increased progressively across exposure categories, with an SMR of 1.44 (95% CI 1.10-1.86) in workers highly exposed for 1 year.

**Conclusions**—We found no evidence that styrene causes LH cancer. An association with lung cancer is not consistently supported by other studies. It may have been confounded by smoking, but would be worth checking further.

### Keywords

Styrene; glass-reinforced plastics; mortality; lung cancer; non-Hodgkin lymphoma; leukaemia

### Introduction

Styrene is a high-volume industrial chemical, used principally in the manufacture of plastics, resins and synthetic rubbers [1,2]. Exposures are highest in the workplace, but may also

occur at lower levels from products used in the home (e.g. packaging materials, wood-fillers) and from tobacco smoke. Occupational exposure to styrene causes formation of DNA adducts [1], and several epidemiological studies have suggested an association with lymphatic and haematopoietic cancers [1,3]. However, elevations in risk have been small and inconsistent, and may have been a consequence of chance, bias or confounding. Tests for carcinogenicity in animals have generally been negative, with the notable exception of an inhalation study, which produced an increased incidence of pulmonary tumours in female mice [1]. This may have occurred because mouse lung has a high capacity (much greater than rat or human lung) to metabolise styrene to styrene 7,8 oxide, which is both mutagenic and an established animal carcinogen. When last reviewed by the International Agency for Research on Cancer (IARC), styrene was classed as possibly carcinogenic to humans (Group 2B) [1].

During the 1980s we assembled a cohort of workers exposed to styrene in the British glass-reinforced plastics (GRP) industry [2], which subsequently was incorporated into an international collaborative study, coordinated by IARC [4]. To provide further information on the risks of lymphatic, haematopoietic and other cancers in relation to styrene, we have now extended follow-up of our cohort to the end of 2012.

## Methods

As described in the original report of the study [2], the cohort comprised all workers who were employed during specified periods at eight companies in England which made various GRP products, using styrene (Table 1). Men and women who were eligible for inclusion in the study were identified from personnel and wages records, and information was abstracted on their name; address; sex; date of birth; National Insurance number; and history of employment at the company (up to the time of data abstraction), including the dates of starting and finishing each job.

With assistance from managers and staff at the factories, jobs were classified to four categories, according to their potential for exposure to styrene. These categories were labelled “high” (hand laminators), “moderate” (people who regularly entered areas of GRP production or worked close to laminating operations), “low” (people who occasionally entered areas of GRP production or experienced a constant but low-level exposure at a situation remote from the laminating operation) and “background” (all other jobs). Jobs held before or after the time when styrene was used at a factory were all classed as having background exposure, as were a few periods of employment for which job title was missing (333 jobs in 325 subjects). No hygiene data were available for the early years of styrene use, but from measurements at five of the factories after 1975, it was estimated that the high exposure category corresponded to an eight-hour time-weighted average exposure of 40-100 ppm. Other substances to which workers may have been exposed included glass fibre, acetone, methyl ethyl ketone, organic peroxides, and (at companies C and F only) asbestos.

The cohort was traced through the National Health Service Central Register (now the Health and Social Care Information Centre (HSCIC)), and in some cases through national insurance records, and followed to 31 December 2012. For those who had died, we obtained the

underlying cause of death, coded to the International Classification of Diseases (ICD) Version 9 (deaths up to the end of 2000) or 10 (deaths after 2000). For those with registered cancers, we obtained the type of cancer and date of registration.

Statistical analysis was carried out with Stata v 13 software (StataCorp. College Station, TX). The mortality of cohort members was compared with that of the national population of England and Wales by the person-years method, with expected numbers of deaths calculated for combinations of sex, five-year age band and five-year calendar period (except for deaths during 2010-2012, for which rates during 2005-12 were applied). Each person was considered to be at risk from the latest of: a) his/her date of first employment; b) the date from which employees at the relevant company were eligible for inclusion in the cohort; and c) the date when he/she first entered the category of exposure under consideration. He/she then remained at risk until the earliest of: a) death; b) loss from follow-up for other reasons (e.g. emigration); c) 31 December 2012; and d) (only in analyses by level of exposure) moving to a higher exposure category. Results were summarised by standardised mortality ratios (SMRs) with associated 95% confidence intervals (CIs).

To explore risks of lympho-haematopoietic (LH) cancer further, we also carried out a nested case-control analysis, in which cases were identified not only from certified underlying causes of death, but also from cancer registrations and contributing causes of death. A prescribed algorithm was used to match each case with up to 10 controls of the same sex, who worked at the same factory, were under follow-up at the date of diagnosis of the case (i.e. the first date at which the case was known to have LH cancer), and were born within two years of the case. Associations with level of exposure to styrene, lagged by five years, were assessed by conditional logistic regression, and summarised by odds ratios (ORs).

Ethical approval for the study was originally provided by the British Medical Association Ethics Committee, and later reaffirmed by the National Research Ethics Service Committee South Central - Portsmouth.

## Results

From the original cohort of 8,354 subjects, 383 were excluded because of missing information on sex, date of birth or date of first employment, and one who began work before styrene was used, had an unknown date of leaving, and may never have been employed at a time when the chemical was present in the workplace. This left 7,970 (6,650 men and 1,320 women) who were suitable for analysis (Table 1). They included six men who had each worked at two of the participating companies, and whose exposure histories at the two factories were combined. Almost half (3,488) had worked at some time in high exposure jobs, including 1,402 who did so for a year or longer. Eight hundred and thirteen (10.2%) were still employed at a participating company at the time when the cohort was assembled, and therefore had incomplete employment histories..

By the end of 2012, 3,121 cohort members had died (an additional 2,022 deaths since the last follow-up for the IARC study in 1990), 3,935 were still alive, and 914 had been lost to

follow-up. The last included 206 subjects who could not be traced through HSCIC or social security records, and were followed only to their last known date of employment.

Table 2 summarises the cause-specific mortality of the cohort. Results are presented for all cohort members, and for the subset of workers who had higher than background exposure. In both groups, the total number of deaths was close to what would be expected from rates in the national population (SMRs 0.97 and 0.99), as was overall mortality from cancer (SMRs 1.01 and 1.05) and from other major cause of death categories.

As regards specific types of cancer (Table 3 and Supplementary Table S1), mortality from lung cancer was significantly elevated, both in the cohort as a whole (329 deaths, SMR 1.20, 95% CI 1.08-1.34) and in workers with exposures above background (229 deaths, SMR 1.27, 95% CI 1.11-1.45). In addition, the latter group experienced a significant excess of deaths from cancer of the brain and nervous system (26 deaths, SMR 1.55, 95% CI 1.02-2.28). No elevation of mortality was observed for LH cancer, either in the full cohort (62 deaths, SMR 0.89, 95% CI 0.68-1.14), or in those with more than background exposure (38 deaths, SMR 0.82, 95% CI 0.58-1.14). Nor was there any excess of non-Hodgkin lymphoma (NHL) or leukaemia specifically.

Table 4 breaks down mortality from the more common cancers, and those of a priori interest, according to highest level of exposure to styrene. Because of limited numbers, the categories of low and moderate exposure were combined. Risk of lung cancer increased progressively across the exposure categories, with an SMR of 1.44 (95% CI 1.10-1.86) in workers with high exposure for 1 year. Monotonic exposure-response relationships were also observed for cancers of the oesophagus and large intestine, but even in the highest exposure category the excesses of deaths were only small (10 observed v 7.1 expected and 11 v 9.8).

Analyses of mortality from lung cancer by factory indicated excesses of deaths at each of factories A to F, but not at factories G and H (data not shown). This applied both to workers with more than background exposure, and also to those with high exposure for a year or longer.

When the analyses for Tables 2-4 were repeated with all exposures lagged by 10 and 20 years, the pattern of results was similar, but exposure-response relationships for cancers of the lung, oesophagus and large intestine were less clear (Supplementary Tables S2-S5).

In addition to the 62 deaths from lymphatic and haematopoietic cancers, a further 61 cases of these diseases were ascertained from cancer registrations and contributing causes of death on death certificates (Supplementary Table S6). No suitable controls were available for one case, which therefore had to be excluded. The remainder were matched with a total of 1138 controls. When exposures were lagged by five years, there was no indication of any association with LH cancers overall, or with NHL/Chronic lymphocytic leukaemia (CLL) specifically (Table 5). In comparison with background exposure, the odds ratio for NHL/CLL in workers with high exposure for 1 year was 0.54 (95% CI 0.23-1.27).

To assist possible meta-analyses in the future, Supplementary Tables S7-S8 show the results of analyses similar to those for Tables 2-3, but restricted to deaths occurring after 1990 (i.e. after the last published follow-up of the cohort [4]).

## Discussion

Prolonged follow-up of this cohort, which included 3,488 laminators with high exposures to styrene (an estimated 40-100 ppm), in many cases for a year or longer, provided no indication of a hazard of LH cancer, or of NHL or leukaemia specifically. There was however, significantly increased mortality from lung cancer, especially in workers with high exposure for 1 year.

Strengths of the study include the large number of subjects with relatively high exposures (much higher than occur in most modern workplaces), and the long duration of follow-up. On the other hand, there were limitations in the characterisation of exposures. Data on exposure were missing for a small proportion of subjects (~ 4%) because occupational records were incomplete. Also, we did not attempt to update employment histories after cohort members were first identified, which meant that information about exposure was censored for those who were still employed when the cohort was first established. However, the loss of data from occupational records occurred before the cohort was assembled, and thus before most of the deaths accrued. Furthermore, only a small proportion of the total cohort (10.2%) was still employed when the study began, and of these, almost one third were already in the highest exposure category (data not shown). For these reasons, it seems unlikely that the shortcomings in classification of exposures will have resulted in any major bias.

The absence of associations with LH cancer is consistent with findings from a recent systematic review [3], and from a recently updated cohort study of GRP workers in the United States [5]. Moreover, the upper 95% confidence limit for the SMR in subjects with more than background exposure (1.14) suggests that an important elevation of risk is unlikely to have been missed by chance. The nested case-control analysis, which included an additional 61 cases identified from cancer registrations and contributing causes of death, gives further weight to this conclusion. In comparison with workers who had only background exposure, those who had worked as laminators for >1 year had an OR of 0.76 (95% CI 0.40-1.44) for LH cancer overall, and 0.54 (95% CI 0.23-1.27) for NHL/CLL specifically. We did not carry out a person-years analysis of cancer incidence because historically cancer registration was incomplete in some regions of England and Wales, and therefore there was no reliable population rate with which to compare.

Styrene has also been linked previously with cancer of the oesophagus [6,7], but again we found little evidence to support such a relationship. We did, however, find significant associations of high exposure with lung cancer. There was a possibility of exposure to asbestos at two of the participating factories (C and F), but the increased risk of lung tumours was not limited to these plants, and there were more deaths than expected from lung tumours at six of the eight factories. An excess of lung cancer has also been reported in the most recent follow-up of a large US cohort of GRP workers, although with an inverse trend

in relation to cumulative exposure [5]; and in a US study of boat builders, mortality from lung cancer was non-significantly elevated among workers with high exposure to styrene (SMR = 1.29, 95% CI 0.76-2.04) [7]. Other epidemiological studies, however, have not suggested a hazard of lung cancer [4,8,9], and although it was found to cause an increased frequency of lung tumours in an inhalation study in female mice [1], that may have been a species-specific effect related to differences in metabolism [10]. The finding should therefore be regarded only as a prompt to further investigation in other cohorts, especially as we cannot rule out a confounding effect of smoking, about which information was not available.

Mortality from cancer of the brain and nervous system was significantly elevated in exposed workers (SMR 1.55, 95% CI 1.02-2.28), and especially in those who had worked as laminators for 1 year (9 deaths v 4.1 expected – see Table 4). However, the finding is not supported by other studies [4,5,8], and may have occurred simply by chance.

Overall, our study provides no evidence that styrene carries a hazard of LH cancer or of NHL/CLL. An increased risk of brain cancer may have occurred by chance. An association with lung cancer may have arisen through confounding by smoking, but would be worth checking in further follow-up of styrene-exposed workers. Our results provide no basis for tighter regulatory control of styrene at this stage.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We thank the staff of the Health and Social Care Information Centre for their assistance with tracing of subjects, and Vanessa Cox who prepared the data file for analysis.

The study was supported by a grant from the Colt Foundation (CF/03/10).

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### What this paper adds

- Several epidemiological studies have suggested that styrene is associated with lymphatic and haematopoietic cancers, but elevations in risk have been small and inconsistent.
- In an extension to an earlier cohort study of 7,970 workers at eight companies in England which used styrene in the manufacture of glass-reinforced plastics, we found no evidence that styrene causes lymphatic or haematopoietic cancers.
- An association was found with lung cancer, but is not consistently supported by other studies.
- Our results provide no basis for tighter regulatory control of styrene at this stage.



Table 1

## Description of cohort

| Company | Location        | Product                                    | Period in which styrene was used | Subjects eligible for inclusion in study                                   | Number of subjects analysed <sup>a</sup> |
|---------|-----------------|--|----------------------------------|--|--|
| A       | Staffordshire   | Car bodies                                 | 1953-                            | All employees, 1.1.67-31.12.81   | 949                                      |
| B       | Lancashire      | Panels for vehicles                        | 1956-81                          | All employees in the glass-reinforced plastics department, 1.1.56-31.12.81 | 523                                      |
| C       | Avon            | Car bodies, fuel tanks and other mouldings | 1960-                            | All employees, 1.1.63-29.2.84  | 3133                                     |
| D       | Dorset          | Boats                                      | 1947-                            | All employees, 1.1.46-1.7.82   | 751                                      |
| E       | Avon            | Panels for vehicles                        | 1968-                            | All employees, 1.1.68-1.4.82   | 515                                      |
| F       | West Yorkshire  | Pipes and vessels                          | 1954-                            | All employees, 1.1.58-1.9.82   | 448                                      |
| G       | Nottinghamshire | Fabrications and decorative panels         | 1961-                            | All employees, 1.7.77-30.10.82   | 178                                      |
| H       | Bedfordshire    | Fabrications and mouldings                 | 1953-60                          | All employees, 1.1.53-31.12.60   | 1473                                     |

<sup>a</sup> Six workers were each employed by two of the participating companies, and in this table were arbitrarily assigned to the first factory at which they worked. In subsequent analyses by level of exposure, their exposure histories at the two factories were combined.

**Table 2**  
**Mortality of cohort from major categories of disease, 1946-2012**

| Cause of death       | ICD Codes        |                         | All workers     |                 |      | Workers with more than background exposure to styrene |                 |      |           |
|----------------------|------------------|-------------------------|-----------------|-----------------|------|---|-----------------|------|-----------|
|                      | ICD 9            | ICD 10                  | Deaths observed | Deaths expected | SMR  | 95% CI  | Deaths expected | SMR  | 95% CI    |
| All cancers          | 140-208          | C00-C97                 | 973             | 962.5           | 1.01 | 0.95-1.08   | 622.1           | 1.05 | 0.97-1.13 |
| Circulatory disease  | 390-459          | I00-I99                 | 1283            | 1345.5          | 0.95 | 0.90-1.01   | 841.3           | 0.99 | 0.92-1.06 |
| Respiratory disease  | 460-519          | J00-J99                 | 360             | 388.2           | 0.93 | 0.83-1.03   | 236.5           | 0.97 | 0.85-1.11 |
| Digestive diseases   | 008-009, 520-579 | K00-K93                 | 109             | 120.3           | 0.91 | 0.74-1.09   | 77.5            | 0.93 | 0.73-1.17 |
| Injury and poisoning | 800-999          | U509, V01-Y89           | 117             | 125.2           | 0.93 | 0.77-1.12   | 84.3            | 0.95 | 0.75-1.18 |
| All Causes           | 001-999          | A00-R99, U5009, V01-Y89 | 3121            | 3225.9          | 0.97 | 0.93-1.00   | 2036.1          | 0.99 | 0.95-1.04 |

**Table 3**  
**Mortality of cohort from specific cancers, 1946-2012**

| Cancer <sup>a</sup>               | ICD Codes              |           |                 | All workers     |      |           | Workers with more than background exposure to styrene |                 |      |           |
|-----------------------------------|------------------------|-----------|-----------------|-----------------|------|-----------|---|-----------------|------|-----------|
|                                   | ICD 9                  | ICD 10    | Deaths observed | Deaths expected | SMR  | 95%CI     | Deaths observed                                       | Deaths expected | SMR  | 95%CI     |
| Pharynx <sup>b</sup>              | 146-149.1              | C09-C14.2 | 9               | 6.7             | 1.34 | 0.61-2.54 | 7   | 4.6             | 1.51 | 0.61-3.11 |
| Oesophagus                        | 150                    | C15       | 47              | 44.2            | 1.06 | 0.78-1.41 | 35  | 30.3            | 1.16 | 0.80-1.61 |
| Stomach                           | 151                    | C16       | 43              | 57.0            | 0.75 | 0.55-1.02 | 31  | 36.1            | 0.86 | 0.58-1.22 |
| Large intestine                   | 153                    | C18       | 49              | 63.8            | 0.77 | 0.57-1.02 | 36  | 40.6            | 0.89 | 0.62-1.23 |
| Rectum                            | 154                    | C19-C21   | 33              | 39.4            | 0.84 | 0.58-1.18 | 21  | 25.7            | 0.82 | 0.51-1.25 |
| Liver <sup>c</sup>                | 155.0-155.1            | C22       | 16              | 13.6            | 1.18 | 0.67-1.91 | 10  | 9.4             | 1.07 | 0.51-1.96 |
| Pancreas                          | 157                    | C25       | 48              | 42.5            | 1.13 | 0.83-1.50 | 27  | 27.6            | 0.98 | 0.64-1.42 |
| Larynx                            | 161                    | C32       | 13              | 7.6             | 1.70 | 0.91-2.91 | 6   | 5.2             | 1.15 | 0.42-2.50 |
| Lung                              | 162                    | C33-C34   | 329             | 273.6           | 1.20 | 1.08-1.34 | 229   | 180.2           | 1.27 | 1.11-1.45 |
| Melanoma <sup>b</sup>             | 172                    | C43       | 9               | 10.0            | 0.90 | 0.41-1.71 | 4   | 6.8             | 0.59 | 0.16-1.51 |
| Breast                            | 174, 175               | C50       | 24              | 31.2            | 0.77 | 0.49-1.15 | 11  | 11.6            | 0.95 | 0.47-1.70 |
| Prostate                          | 185                    | C61       | 63              | 73.0            | 0.86 | 0.66-1.10 | 44  | 50.7            | 0.87 | 0.63-1.17 |
| Bladder <sup>b</sup>              | 188                    | C65-C68   | 38              | 32.8            | 1.16 | 0.82-1.59 | 28  | 21.6            | 1.29 | 0.86-1.87 |
| Kidney <sup>b</sup>               | 189                    | C64       | 28              | 21.1            | 1.33 | 0.88-1.92 | 18  | 14.4            | 1.25 | 0.74-1.98 |
| Brain and nervous system          | 191,192                | C71-C72   | 32              | 24.5            | 1.31 | 0.89-1.84 | 26  | 16.7            | 1.55 | 1.02-2.28 |
| Hodgkin's disease                 | 201                    | C81       | 2               | 4.1             | 0.49 | 0.06-1.77 | 2   | 2.6             | 0.75 | 0.09-2.73 |
| Non-Hodgkin lymphoma <sup>b</sup> | 200,202.0, 202.1,202.8 | C82-C85   | 24              | 25.2            | 0.95 | 0.61-1.42 | 14  | 16.9            | 0.83 | 0.45-1.39 |
| Multiple myeloma <sup>b</sup>     | 203.0                  | C90       | 13              | 13.9            | 0.94 | 0.50-1.60 | 9   | 9.1             | 0.99 | 0.45-1.88 |
| Leukaemia                         | 204-208                | C91-C95   | 23              | 25.3            | 0.91 | 0.58-1.36 | 13  | 16.7            | 0.78 | 0.42-1.33 |
| Lympho-haematopoietic cancer      | 200-208                | C81-C96   | 62              | 69.8            | 0.89 | 0.68-1.14 | 38  | 46.1            | 0.82 | 0.58-1.14 |

<sup>a</sup>Data are limited to cancers with at least four deaths observed or expected in the analysis for all workers. Results for other cancers can be found in Supplementary Table S1.

<sup>b</sup>Because of changes in disease classification, the earliest follow-up for these cancers was from 1950.

<sup>c</sup>Because of changes in disease classification, the earliest follow-up for this cancer was from 1958.

Table 4

## Mortality from selected cancers by highest level of exposure to styrene, 1946-2012

| Cancer                            | Highest level of exposure <sup>a</sup> |          |      |              |          |      |                  |           |          |                 |        |           |          |      |        |           |
|-----------------------------------|--|----------|------|--------------|----------|------|------------------|-----------|----------|-----------------|--------|-----------|----------|------|--------|-----------|
|                                   | Background                             |          |      | Low/Moderate |          |      | High for <1 year |           |          | High for 1 year |        |           |          |      |        |           |
|                                   | Observed                               | Expected | SMR  | Observed     | Expected | SMR  | 95% CI           | Observed  | Expected | SMR             | 95% CI | Observed  | Expected | SMR  | 95% CI |           |
| Oesophagus                        | 12                                     | 13.9     | 0.86 | 0.45-1.51    | 13       | 12.7 | 1.02             | 0.54-1.74 | 12       | 10.2            | 1.18   | 0.61-2.06 | 10       | 7.1  | 1.41   | 0.68-2.60 |
| Stomach                           | 12                                     | 20.9     | 0.57 | 0.30-1.00    | 19       | 16.9 | 1.12             | 0.68-1.76 | 7        | 10.7            | 0.65   | 0.26-1.34 | 5        | 8.2  | 0.61   | 0.20-1.43 |
| Large intestine                   | 13                                     | 23.2     | 0.56 | 0.30-0.96    | 12       | 17.5 | 0.69             | 0.35-1.20 | 13       | 12.9            | 1.01   | 0.54-1.72 | 11       | 9.8  | 1.13   | 0.56-2.02 |
| Rectum                            | 12                                     | 13.7     | 0.88 | 0.45-1.53    | 11       | 11.2 | 0.98             | 0.49-1.75 | 8        | 8.2             | 0.97   | 0.42-1.92 | 2        | 6.0  | 0.33   | 0.04-1.20 |
| Pancreas                          | 21                                     | 14.9     | 1.41 | 0.87-2.15    | 11       | 11.6 | 0.95             | 0.47-1.70 | 10       | 9.0             | 1.11   | 0.53-2.03 | 6        | 6.7  | 0.89   | 0.33-1.95 |
| Lung                              | 100                                    | 93.4     | 1.07 | 0.87-1.30    | 98       | 81.4 | 1.20             | 0.98-1.47 | 68       | 55.6            | 1.22   | 0.95-1.55 | 60       | 41.6 | 1.44   | 1.10-1.86 |
| Prostate                          | 19                                     | 22.4     | 0.85 | 0.51-1.33    | 20       | 25.2 | 0.79             | 0.48-1.22 | 15       | 14.6            | 1.03   | 0.58-1.70 | 9        | 10.5 | 0.86   | 0.39-1.63 |
| Bladder <sup>b</sup>              | 10                                     | 11.2     | 0.90 | 0.43-1.65    | 16       | 10.1 | 1.58             | 0.90-2.57 | 8        | 6.5             | 1.23   | 0.53-2.43 | 3        | 4.8  | 0.62   | 0.13-1.81 |
| Kidney <sup>b</sup>               | 10                                     | 6.7      | 1.49 | 0.72-2.75    | 7        | 5.9  | 1.18             | 0.47-2.43 | 7        | 4.9             | 1.43   | 0.58-2.95 | 4        | 3.4  | 1.17   | 0.32-3.00 |
| Brain and nervous system          | 6                                      | 7.8      | 0.77 | 0.28-1.68    | 12       | 6.4  | 1.88             | 0.97-3.29 | 5        | 6.1             | 0.82   | 0.27-1.92 | 9        | 4.1  | 2.20   | 1.01-4.19 |
| Non-Hodgkin lymphoma <sup>b</sup> | 10                                     | 8.3      | 1.20 | 0.58-2.21    | 3        | 6.8  | 0.44             | 0.09-1.28 | 6        | 5.8             | 1.04   | 0.38-2.26 | 5        | 4.1  | 1.22   | 0.40-2.85 |
| Leukaemia                         | 10                                     | 8.7      | 1.15 | 0.55-2.12    | 6        | 7.0  | 0.86             | 0.31-1.87 | 4        | 5.6             | 0.72   | 0.20-1.84 | 3        | 4.0  | 0.76   | 0.16-2.22 |

<sup>a</sup>At each time-point during follow-up, subjects were classed according to the highest grade of exposure experienced up to that date

<sup>b</sup>Because of changes in disease classification, the earliest follow-up for these cancers was from 1950

**Table 5**  
**Associations of lymphatic and haematopoietic cancers with exposure to styrene in nested case-control analyses**

| Cancer   | Background |          |    | Highest exposure to styrene |          |            |              |       |          |             |       |       |          |            |
|--|------------|----------|----|-----------------------------|----------|------------|--------------|-------|----------|-------------|-------|-------|----------|------------|
|  | Cases      | Controls | OR | Low/moderate                |          |            | High <1 year |       |          | High 1 year |       |       |          |            |
|  |            |          |    | Cases                       | Controls | OR         | 95%CI        | Cases | Controls | OR          | 95%CI | Cases | Controls | OR         |
| Hodgkin's disease  | 3          | 27       | 2  | 11                          | 1.50     | 0.17-13.56 | 1            | 21    | 0.39     | 0.03-5.09   | 1     | 11    | 0.74     | 0.06-9.94  |
| Non-Hodgkin lymphoma (including chronic lymphocytic leukaemia) | 26         | 175      | 14 | 166                         | 0.53     | 0.24-1.15  | 18           | 187   | 0.61     | 0.30-1.25   | 11    | 118   | 0.54     | 0.23-1.27  |
| Multiple myeloma   | 6          | 76       | 7  | 63                          | 2.15     | 0.51-9.12  | 6            | 41    | 2.66     | 0.67-10.64  | 5     | 35    | 2.66     | 0.62-11.35 |
| Other leukaemia  | 8          | 59       | 5  | 57                          | 0.60     | 0.13-2.79  | 6            | 56    | 0.84     | 0.23-3.02   | 3     | 35    | 0.62     | 0.13-3.03  |
| All lymphatic and haematopoietic cancer                        | 43         | 337      | 28 | 297                         | 0.73     | 0.40-1.33  | 31           | 305   | 0.81     | 0.47-1.41   | 20    | 199   | 0.76     | 0.40-1.44  |

All risk estimates are relative to background exposure, and relate to exposure status five years before the case (for controls, the matched case) was first known to have been diagnosed.