Renal disease and occupational exposure to organic solvents: a case referent approach

J M HARRINGTON,¹ HELEN WHITBY,¹ C N GRAY,¹ FIONA J REID,¹ T C AW,¹
J A WATERHOUSE²

From the Institute of Occupational Health¹ and Regional Cancer Registry,² University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

ABSTRACT Several recent studies have suggested that a relation may exist between exposure to occupational organic solvents and diseases of the kidney—particularly malignancy and glomerulonephritis. Two case referent studies were undertaken in the West Midlands to investigate these possibilities. In the case of renal cancer 54 live cases of biopsy proved adenocarcinoma of the kidney were compared with an equal number of community based healthy referents matched for age, sex, place of residence, and socioeconomic and ethnic grouping. For glomerulonephritis, 50 biopsy proved cases were matched in the same manner with 50 referents. Fourteen other patients were also reviewed who, on biopsy, proved not to have glomerulonephritis. For both sets of cases and their referents each individual was interviewed and a detailed account obtained of medical history and environmental exposures. Exposure to solvents was assessed independently and “blind” in a semiquantitative way by an experienced occupational hygienist. Past exposure was estimated for 10 different solvent types and 17 material types. No relation was found between exposure to solvents and renal cancer or glomerulonephritis. In the case of renal cancer the numbers studied only precluded a fourfold excess risk. For glomerulonephritis, the study, although methodologically superior to most other published studies and of similar size, was of similar power to the renal cancer investigation.

During the past ten years considerable attention has been paid to the health effects of occupational exposure to organic solvents. One aspect of these reports that has generated much interest is the possible link between these solvents and renal disease. The results of such studies have been conflicting, however. Research in this area has tended to concentrate on two types of kidney disease: renal cancer and glomerulonephritis.

In this report we have looked at both diseases using the case referent approach. Renal cancer has tended to be reported by means of cohort studies. By contrast, glomerulonephritis—being an eminently manageable disease these days—has tended to be studied by means of case referent studies. In many cases the cohort studies were hypothesis generating exercises which, by the very nature of the multiple associations reviewed, may well uncover statistically significant excesses. The case referent studies of glomerulonephritis have, almost without exception, had serious methodological flaws. The cooperation of nephrologists and the Regional Cancer Registry has enabled us to study both

these diseases in a way which avoids many of the earlier criticisms, though the statistical power of our investigations was inadequate to exclude other than large risk estimates. The impracticalities and costs of much larger studies, however, rendered them not feasible at present.

Uniquely, we have undertaken a detailed “blind” exposure assessment which we hope will prove a valuable tool in further studies of this nature.

Methods

The study populations were drawn from the West Midlands and it was decided to use community based referents. For the renal cancer study the study population was drawn from the names of all living patients with histologically proved renal adenocarcinoma (clear cell) diagnosed from May 1984 to April 1985 and recorded in the West Midlands Regional Cancer Registry. By limiting the diagnosis of renal cancer to adenocarcinoma (which forms 80–90% of all renal cancer), it was hoped that the study would be more specific than extant reports. Limiting the cases to the immediate past 12 months also ensured that most

cases would be alive. After permission was granted by the hospital doctor concerned, each patient was contacted by post. After agreement to participate by the subject, one of the investigators used a standardised questionnaire to conduct a structured interview at the patient's home.

For the glomerulonephritis study, the cases were identified from those patients attending for renal biopsy at the Queen Elizabeth Hospital, Birmingham, under the care of two consultant nephrologists. The patients were thus collected prospectively and interviewed on the ward before biopsy. To some extent such an interview was blind as some of the patients proved not to have acute glomerulonephritis (g/n cases): this group formed a second, smaller, referent population (non-g/n cases) as they had experienced the same diagnostic procedures as the cases.

Referent subjects were selected from the community. After each case interview, the general practitioner of the case was contacted and asked to select randomly from within the practice using an agreed procedure, a referent subject of similar age (within five years), sex, and ethnic group as the case. Matching was also made for geographical location and socioeconomic group. Selected controls were then contacted by post and asked to take part in the study. Those who refused to take part were replaced by another person drawn from the same practice and matched in the same way. For ten cases of renal cancer, matching was not possible without resort to using controls from the glomerulonephritis study. For a few glomerulonephritis subjects, the reverse procedure applied. The matching criteria were, however, identical except that geographical location was more approximate—that is, rural, market town, county town, suburb, inner city. In general, the referents were interviewed at home.

The reasons for refusal to participate on the part of referents suggested that convenience motivated the decision. Community based referents, while often more appropriate, are notoriously difficult to recruit compared with hospital referents.

The questionnaire used consisted of three sections. The first part contained questions on personal details and social habits. A full list of past addresses was obtained as well as detailed inquiries about past and present consumption of alcohol, coffee, and cigarettes. The second part reviewed the medical history of the interviewee, including a drug history with specific questions about known nephrotoxins such as gold, penicillamine, and analgesics. The third part of the questionnaire dealt with a life time occupational history and was designed so that the interviewee was allowed to give general information about employment and materials handled, together with details on a number of key groups of materials or processes in which organic solvents were considered important.

Here an attempt was made to reduce the subjectivity of exposure estimation by detailing exposures to specific jobs, materials, and solvents in terms of periods and duration of exposure, as well as how and where the material was handled. This part of the questionnaire was detached from the other two and assessed "blind" by an experienced chemist/occupational hygienist and exposure indices (EI) (appendix) were computed for each relevant solvent type up to the time of diagnosis or retirement, whichever was the earlier.

In summary, exposures were categorised as zero, low, medium, or high and given scores of 0, 1, 10, or 100 respectively. EIs were then calculated by multiplying the score by the total duration of exposure, adjusted so that one year full time heavy exposure corresponded to an exposure index of 100. An EI of 100 could also be attained, therefore, by ten years full time moderate exposure etc. An overall EI for "total solvent" exposures was obtained simply by summing the EIs for individual solvents.

Data from the questionnaire were coded and transferred to the university mainframe computer in a format compatible with statistical analysis using the SPSS-X package. Paired analyses¹ with odds ratios were calculated for two and three exposure categories according to the Schlesselman² and Pike *et al*³ respectively.

Results

For the renal cancer study, there were 309 cases registered in the West Midlands in 1984–5, of whom 101 were living at the time of the study. Medical consent was obtained to contact 85 of these and 56 patients agreed to be interviewed. For five of these it was not possible to find matched controls. The study population thus consisted of 54 pairs of individuals (33 men, 22 women). All were white and 95% described themselves as Protestant. The mean age ($\pm$ standard deviation) was 60.8 ± 11.5 years (range 33–85 years) for cases and 59.6 ± 11.8 years (range 32–83 years) for referents. Most cases and controls were classified as socioeconomic group three (73.7% and 66.0% respectively). Most interviewees were retired—reflecting the late age of onset of the tumour.

For the glomerulonephritis study, 67 patients were interviewed in 1985–6, 52 of them had biopsy proved glomerulonephritis, seven had no abnormality, and eight had a different renal pathology. Forty matched referents were also interviewed and 10 suitable referents from the renal cancer study were found for 10 other cases for whom the original matching procedure had failed. Fourteen subjects whose biopsy diagnosis proved not to be glomerulonephritis were included as a second referent group (non-g/n case). The 50 case-referent pairs consisted of 37 men and 13 women. Of

these, 47 were white and three were from the Indian subcontinent, with a mean age of 47.5 ± 14.8 years (range 20–79 years) for case and 47.8 ± 14.8 (range 22–79 years) for referents. Eighty per cent of the subjects claimed to be Protestant, the remainder being either Roman Catholic, Jewish, Hindu, or Muslim. No case or referent lived near any potentially hazardous individual process or source of environmental pollutant.

Most cases in both studies had previously worked in offices, shops, or in various trades such as metal working, reflecting the industrial bias of the West Midlands.

Forty one (76%) patients with cancer and 35 (65%) referents smoked cigarettes at some time. Categorisation as light, medium, and heavy smokers was made by the "pack-years" method used by McLaughlin *et al.*⁴ For women, the percentages did not vary between cases and referents by more than 5%, but for the men the case/referent ratios for light, medium, and heavy were: 40.6/68.0, 43.3/20.0, and 16.6/12.0 respectively. These differences were not, however, statistically significant. For the glomerulonephritis study, a history of cigarette smoking was common in all subjects, 32 (64%) of the g/n cases and 37 (74%) of the controls having smoked at some time. Categorisation by light, moderate, and heavy smoking showed no significant differences between cases and referents.

Alcohol consumption, assessed using the criteria of the Health Education Council⁵ and coffee consumption showed no statistically significant differences between cases and referents in either study.

Eight (14.8%) of the cases of renal cancer compared with one (2%) referent has a history of other cancer. The cancers concerned were, however, separate primaries and apparently unconnected with present

malignancy (three colon, one rectum, one prostate, one breast, one neurological, one basal cell).

The renal tumours were roughly equally distributed between the left and right kidneys and 29 (53.7%) were stage I, with 46 (85.2%) patients node free and 48 (88.9%) metastasis free.

Eighteen (36%) of the g/n cases and seven (14%) of the referents had a history of hypertension, this being the major difference in medical history between the groups. As this condition is a risk factor for renal disease, it seemed prudent to investigate it further. Ten g/n cases had suffered from hypertension for several years before developing renal symptoms. All were well controlled at the time of the biopsy. The remaining eight hypertensive g/n cases developed raised blood pressure concurrently or after renal symptoms became apparent.

Two g/n cases had received gold treatment in the past and three had taken hydrallazine. The patients receiving gold treatment had taken medication 5–15 years previously at normal doses and renal function during treatment was unaffected by the medication. The three patients taking hydrallazine for hypertension had been taking the drug for longer than 12 months at normal therapeutic doses before the onset of renal symptoms. A history of analgesic medication—in particular the non-steroidal anti-inflammatory drugs (NSAIDs)—was found in eight (16%) g/n cases and 11 (22%) referents (a higher frequency than for the renal cancer study, four (7.4%) and five (9.3%) respectively). None of the cases and referents had been taking NSAIDs medication for renal symptoms.

Among the g/n cases, 21 (42%) were histologically diagnosed to have focal proliferative glomerulonephritis or IgA nephropathy, eight (16%) had mem-

Table 1 Proportion (%) of subjects claiming exposure to various workplace material types by case and referent groups for glomerulonephritis and renal cancer

Material type	Glomerulonephritis (n = 50)	Referent (n = 50)	Cancer (n = 54)	Referent (n = 54)
Paints, varnishes	30.0	22.0	25.9	22.2
Glues	16.0	28.0	14.8	27.8
Inks	4.0	4.0	7.4	5.6
Dyes	2.0	10.0	7.4	1.9
Drycleaning fluids	0	4.0	0	0
Degreasing agents	22.0	24.0	16.7	22.2
Cleaning materials	14.0	6.0	1.9	7.4
Pesticides/herbicides	2.0	6.0	1.9	3.7
MacAdam/Asphalt	6.0	0	0	0
Fuels, oils, paraffins	38.0	32.0	37.0	29.6
Asbestos	6.0	2.0	11.1	1.9
Fibreglass/resins/body fillers	8.0	2.0	7.4	3.7
Lead, cadmium, mercury, and other heavy metals	10.0	8.0	13.0	11.0
Dusty materials	10.0	0	11.1	1.9
Rubber products	4.0	0	7.4	1.9
Plastics	2.0	2.0	5.6	3.7
Miscellaneous solvents, fumes	24.0	26.0	24.1	18.5

branous nephropathy, and the remainder had either minimal change, acute vasculitic mesangial proliferative, or focal glomerulosclerotic disease. Most patients had had these symptoms for less than four months.

Table 1 shows the proportion of cases and referents reporting exposures to various substance types. The most frequently encountered solvent type materials were fuels and oils, degreasing agents, paints, varnishes, and glues.

A large proportion (two thirds to four fifths) of cases and controls in both study groups claimed to have had some contact with solvent containing materials, though some of these exposures were judged to be insignificant by the occupational hygienist and were assigned exposure indices of zero (table 2).

For the purpose of analysis, two classifications of exposure were used. A classification of "exposed" ($EI \geq 100$) and "non-exposed" ($EI < 100$) was established for both the cases with cancer, those with

Table 2 Proportion (%) of subjects exposed to different solvent types in case and referent groups at various exposure indices for cancer (54 pairs) and glomerulonephritis (50 pairs)

Solvent type	Cancer cases (n = 54)			Referents			Glomerulonephritis cases (n = 50)			Referents		
	>0	≥1	≥100	>0	≥1	≥100	>0	≥1	≥100	>0	≥1	≥100
Unidentified solvents	66.7	31.5	1.8	57.4	35.2	3.7	56	26	2	56	28	6
Aliphatic hydrocarbons	55.6	42.6	7.4	48.2	35.2	1.8	58	46	4	48	42	10
Aromatic hydrocarbons	31.5	25.9	3.7	29.6	18.5	0	38	20	0	36	30	2
Alcohols	3.7	1.8	0	1.9	0	0	4	4	0	0	0	0
Ketones	3.7	1.8	0	9.3	5.6	0	12	4	2	10	6	2
Esters	3.7	0	0	5.6	1.8	0	6	4	2	4	2	0
Ethers	0	0	0	1.9	1.8	0	0	0	0	0	0	0
Glycol ethers	1.9	1.8	0	5.6	0	0	8	4	0	14	6	0
Halogenated aliphatics	20.4	4.5	0	29.6	20.4	0	24	10	0	30	14	4
Halogenated aromatics	0	0	0	0	0	0	2	0	0	0	0	0
Non-solvent chemicals	81.5	24.1	0	66.7	14.8	0	72	22	8	72	16	2
Total solvents	81.5	59.3	14.8	66.7	50.0	14.8	70	50	18	72	60	18

Table 3 Contingency tables and odds ratios for two exposure categories for malignant renal disease or glomerulonephritis and total solvent exposure

	Renal cancer				Glomerulonephritis		
	Exposed	Non-exposed	Total		Exposed	Non-exposed	Total
Referents:							
Exposed	3	5	8		5	4	9
Non-exposed	5	41	46		4	37	41
Total	8	46	54		9	41	50
Odds ratio		1.0				1.0	
95% confidence interval		0.2-4.9				0.16-6.3	

Table 4 Contingency tables and odds ratios for three exposure categories for malignant renal disease or glomerulonephritis and total solvent exposure

	Renal cancer					Glomerulonephritis			
	Exposed	Intermediate	Not exposed	Total		Exposed	Intermediate	Not exposed	Total
Referents:									
Exposed	3	3	2	8		5	2	2	9
Intermediate	3	8	8	19		3	9	9	21
Non-exposed	2	13	12	27		1	5	14	20
Total	8	24	22	54		9	16	25	50
Odds ratio (95% confidence interval):									
Exposed/non-exposed			1.30 (0.31-8.50)				0.67 (0.03-3.36)		
Intermediate/non-exposed			1.54 (0.69-4.10)				0.50 (0.12-1.36)		

glomerulonephritis, and their respective referents. The resulting contingency tables are shown in table 3. A three category grouping of "non-exposed" ($EI < 1$), intermediate ($1 \leq EI < 100$), and exposed ($EI \geq 100$) is outlined in table 4. The odds ratio for solvent exposed versus non-exposed in table 3 was 1.0 for both renal cancer and glomerulonephritis. The odds ratio for exposed versus non-exposed and intermediate exposure versus non-exposure in table 4 was 1.3 and 1.54 respectively for renal cancer. For glomerulonephritis it was 0.67 and 0.5 respectively. The 95% confidence intervals for all the odds ratios calculated straddled 1.0, indicating no statistically significant increased odds of solvent exposure in cases of renal cancer and glomerulonephritis compared with their referents. Neither set of contingency tables show a statistically significantly raised odds ratio, neither is there any evidence of any trend with increasing exposure trends.

Discussion

The renal cancer study failed to show any statistical significant differences between cases and referents for any of the variables dealing with social habits, drug medication, or medical history. Although there was a significant difference between cancer cases and their referents with regard to past history of malignant disease, there was no histologically plausible explanation for a link when the tumour sites were reviewed. The lack of any association with cigarette smoking contrasts with the findings of McLaughlin *et al.*⁶ They showed a "causal" relation with an estimated attribution of renal cancer to smoking of 30% for men and 24% for women. The differing results here could be due to the lower power of the present study to detect such a relation. If there is indeed a causal relation between renal cancer and cigarette consumption the absence of evidence here weakens any other conclusions that may be drawn from a study of only 54 pairs.

The higher number of transport workers in the group with cancer was the only result of note from an assessment of occupation. The numbers, though small, might support the findings of Rushton and Alderson (unpublished data). The drivers in Rushton and Alderson's study are, however, not entirely comparable with the group described in the present study. Furthermore, unpublished correspondence between Alderson and the Institute of Petroleum after the non-refinery worker drivers report suggests that there is some doubt about the validity of the originally reported excess (P Jones, personal communication).

For the glomerulonephritis study, there was also no statistically significant difference noted between cases and referents for any of the variables dealing with

social habits, drug medication, or medical history of hypertension. In addition, the use of nephrotoxins such as gold or hydrallazine was only evident in the glomerulonephritis group, though there was little reason to believe that these small numbers produced a serious confounding effect in this study.

The classification of diagnoses indicated that 40% of the cases had a diagnosis of proliferative glomerulonephritis. This figure, together with those of the other diagnostic categories noted from the renal biopsy results compares well with the percentages cited by Van de Laan⁷ and Ravnskov *et al.*⁸ In the study by Bell *et al.* all the patients had proliferative glomerulonephritis.⁹

There were no major differences in frequencies of job types between the groups, though for the solvent type used, exposure to dyes was more prevalent in the referent group than in the g/n cases. Those with cancer showed a tenfold excess of asbestos and dust exposure whereas glues show a twofold deficit. Exposure assessments for asbestos, however, were judged to be insignificant. More importantly, an independent assessment of lifetime solvent exposures showed no significant excess for either cases with cancer or with glomerulonephritis whether consideration was given to "total" solvent exposure or specific solvent type. Latency could be important here for renal cancer but as most of the cases and referents were retired, this was not deemed a major source of bias. The glomerulonephritic cases and referents were younger but latency is less likely to be as relevant here.

Nevertheless, a wide range of chemicals, including some aromatic hydrocarbons, N-nitroso compounds, and metal salts have been shown to induce renal cancer in experimental animals. A dose dependent association between unleaded petrol vapour and renal cancer has been shown for male rats¹⁰ though it has been suggested that the male rat kidney is uniquely prone to renal disease. In well defined epidemiological studies, however, such associations in man have not been confirmed. Most studies investigating renal cancer and petroleum based chemicals have been of the cohort design and most have been generated from cohorts of petroleum industry employees. In 1984 a review of cancer risks in oil refinery workers critically examined eight industry based and six general population surveys.¹¹ The reviewers concluded that methodological shortcomings may be responsible for some of the contradiction in the published results, and thought that, overall, refinery populations did not seem to experience any "substantial rises" in cancer risks. What remained unrevealed was whether smaller sections of the workforce experienced an excess of certain cancers—particularly melanoma, brain, stomach, kidney, and pancreas.

In the same year Enterline and Viren specifically

addressed the epidemiological evidence for an association between petrol and kidney cancer.¹² They concluded that there was little support for an aetiological link in the 12 cohort, three case referent, and three ecological studies included in their review. Similar conclusions had been reached in a workshop on the subject a year earlier.^{13,14} A more recent review of 15 cohort studies confirmed the lack of a clear relation between organic solvents and renal cancer. Risk ratios ranged from 0.44 to 1.55, but none was statistically significant.¹⁵ None of these cohort studies showed any dose response effect nor any difference in renal cancer rates by duration of employment. Two studies with "non-positive" findings had considerable statistical power and thus lend credence to the argument against a causal association.^{7,16}

A methodological shortcoming of all of the above studies was the lack of quantitative estimations of hydrocarbon or petroleum product exposure. Furthermore, diagnostic specificity was absent and cigarette smoking habits unknown. Some of the shortcomings of earlier work were largely overcome in the recent case referent study of risk factors and renal carcinoma undertaken by McLaughlin and his co-workers.⁶ Their study of 495 cases and matched controls reviewed occupational factors as well as lifestyle and medical history. Patients with renal cancer had a significantly increased exposure to petroleum, tar, and pitch products (relative risk 1.6). An update of this study, however, showed a relative risk of 1.0 for exposure to petroleum.⁴ No quantitative assessment of exposure was made.

The present cancer study, though much smaller than the McLaughlin series, attempted to collect detailed occupational exposure histories from cases and referents and to assess exposure to specific organic solvents using a structured, computerised methodology developed for this study. We are not aware of any similar case referent study.

Whereas reports of occupational links between renal cancer and organic solvents have come mainly from cohort studies of petroleum populations, the putative association of solvents with glomerulonephritis has come from animal studies, case reports, and a few case referent studies. Reviews of these studies have been recently made by Churchill *et al.*,¹⁷ Phillips,¹⁸ and Harrington.¹⁵ Case reports have dealt with a variety of non-malignant kidney conditions such as Goodpasture's syndrome,¹⁹ membranous nephropathy,²⁰ and subacute proliferative glomerulonephritis.²¹ Descriptions of potential causative agents include hydrocarbon solvents, paints, and jet fuel. Although rather vague, the product types implicated are more specific than in the study on renal cancer. It is generally agreed, however, that case reports do little more than point the way to the need for more

analytical epidemiological studies.

Out of six case referent studies undertaken to investigate glomerulonephritis and exposure to hydrocarbon solvents, five gave a positive, but weak correlation.²²⁻²⁵ The sixth study by Van de Laan⁷ aimed to replicate that of a previous weakly positive study of Ravnskov *et al.*⁸ but the results were "non-positive." The designs of all but two of these studies, however, have been criticised on methodological grounds. Unfortunately, these studies of Van de Laan and Ravnskov *et al.* exhibit conflicting results which do nothing to resolve the aetiological question. In brief, the methodological shortcomings of most of the studies were defined in two reviews as: non-specificity of cases, the use of inappropriate referents, the use of unblinded interviewers, the problem of recall bias, and the failure to quantify the hydrocarbon solvent exposure.^{7,18} In a recent study which attempted to overcome some of these criticisms 50 patients with biopsy proved glomerulonephritis were questioned "blind" for solvent exposure using the method described by Ravnskov.⁹ The referents were hospital-based. The results indicated an occupational exposure to solvents significantly greater for case subjects than for controls.

The present study investigated a similar sized group but used community based referents and a structured, computerised assessment of past exposure to solvents. Comparing the present results with the three best extant studies shows a concordance with one⁷ and disagreement with the other two.^{8,9} It is, however, impossible to compare the assessment of solvent exposure between the studies as methods vary considerably. None of the previously published studies attempted any systematic quantitative assessment of solvent exposure. We believe that the methods used in this study improve on the previous assessment of solvent exposure in terms of reliability and reproducibility as well as specificity and, in addition, reduce somewhat the subjective element in the retrospective respondent based histories of exposure. The question of latency in the renal cancer study was not addressed and could be a source of bias. Most of the interviewees were retired however, thus this factor may not be a major one. Furthermore, the choice of referent group in the present study is considered to be a superior option to hospital based referents,²⁶ despite the fact that such community based referents are far more difficult to recruit. The need to obtain a detailed work history necessitated the use of live cases. There is, however, no reason to believe that the dead "cases" differ in any significant way from the referents so far as exposures are concerned.

Nevertheless, a major difficulty of interpretation emanates from the relatively weak statistical power of both the renal cancer study and the glomerulonephritis

phritis study, even though the size of the glomerulonephritis section is as large as any published. A case referent study based on 50 pairs has a 90% power to detect a relative risk of four or greater if the prevalence of exposure to solvents in the general population is 50%.² Whatever their size, case referent studies are prone to bias.^{26,27} In this study refusal to participate was largely the result of the poor state of health of some of the patients. We have acquired no evidence to suggest that these refusals could be construed as relevant to the broad health outcomes nor to the exposure assessments. Recall bias could have been relevant but evidence from drug histories—which could be confirmed to a large extent from hospital records—suggests that this was not so.

The exposure questionnaire has been modified in the light of this study but nevertheless represents a considerable advance over previous attempts to quantify past exposures to solvents. In general, it parallels the assessment procedure of Gerin *et al.*²⁸ but includes a more detailed analysis of the exposures elicited.

In short, the study design was methodologically relevant, provided a detailed and moderately objective assessment of exposure, and yet failed to show any relation between exposure to organic solvents and renal cancer or glomerulonephritis. The power of the study, however, precludes a definitive judgment on causation as much larger studies would be required to be reasonably certain of detecting a twofold excess risk.

Appendix

EXPOSURE ASSESSMENT AND CALCULATION OF EXPOSURE INDICES

Retrospective exposure assessment involved the use of a detailed interviewer administered questionnaire on occupational history and non-occupational activities which could involve relevant exposures. The complexity and branching nature of the questionnaire made it unsuitable for self administration. Completed questionnaires were identified by numbers which hid the medical status of the subject and were given to the occupational hygienist for assessment. All objective data on the questionnaire—for instance, dates, frequency and duration of exposures, material codes, etc—were coded and recorded on a database without further interpretation. Exposures were categorised from the job and material descriptions by reference to an independent checklist of exposures to solvents. The results of exposure categorisation were recorded on the database. Final calculation of exposure indices (EIs) was performed by a computer program that used a system of scoring for exposure categories in which low exposures earned one point, medium 10, and heavy 100 points. EIs were obtained by multiplying the

exposure score by the total duration of exposure measured in standard work years. Thus one year's light exposure, as might be experienced by a forecourt attendant in a self service petrol station, would earn an EI of one, whereas one year's heavy exposure—for example, during certain types of shoe assembly work—would earn an EI of 100.

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