ORIGINAL ARTICLE

New insight into solvent-related end-stage renal disease: occupations, products and types of solvents at risk

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Objectives: It has been shown that all-solvent exposure is associated with the progression of primary glomerulonephritis to end-stage renal disease (ESRD), but little is known about the type of solvents that are high risk. The aim of this study was to investigate the role of solvents by occupation, product and type.

Methods: Using a retrospective cohort design, the authors studied 269 patients with non-end-stage and biopsy-proven primary glomerulonephritis diagnosed between 1994 and 2001 in Paris and its suburbs. Two industrial hygienists evaluated patients' exposures from lifetime occupational histories collected by interview from 2002–4, and using a list of the 30 most common solvents. The studied outcome was ESRD, defined as glomerular filtration rate <15 ml/mn/1.73 m² or dialysis. It was recorded during a mean follow-up of five years. Cox models were used to estimate adjusted hazard ratios (HR) of ESRD related to exposures.

Results: Eighteen per cent of the patients had ever been exposed to solvents. Those with the highest risk of progression to ESRD were exposed machinery fitters and machine assemblers (HR 4.7, 95% CI 1.2 to 17.4) and plumbers/welders (HR 4.2, 95% CI 1.3 to 13.6), as compared to never exposed patients, as well as those who ever handled printing inks and petroleum products (HR 12.6 (95% CI 1.7 to 94.9) and 3.2 (95% CI 1.4 to 7.2), respectively). Among solvents, the highest risks were found for: toluene/xylene (HR 5.1, 95% CI 1.8 to 14.8), gasoline, fuel and gas-oil (HR 8.6, 95% CI 2.7 to 27.4), and ketones (HR 13.3, 95% CI 1.4 to 123.5).

Conclusion: This study highlights the potential nephrotoxicity of several solvents. Intervention to promote screening for proteinuria in exposed workers may prevent the progression of glomerulonephritis to ESRD.

End-stage renal disease (ESRD) has a considerable human and social cost. In France, 52 000 patients are treated, with an annual cost of €1.7 billion. Glomerulonephritis are the third leading cause of ESRD, affecting 13% of the cases, after hypertension (21%) and diabetes (20%).¹ There are few well-established risk factors of ESRD, but both human and experimental studies suggest that many chemicals can affect the kidney.² Of these chemicals, the role of organic solvents in chronic kidney diseases, particularly chronic glomerulonephritis, has long been debated.³ Our first findings, based on a case-control study, did not favour an effect of solvent exposure in glomerulonephritis incidence, but rather suggested a role in the progression to ESRD.⁴ Using an appropriate cohort study design, we recently showed that this exposure was indeed associated with faster progression to ESRD in patients with IgA and membranous glomerulonephritis.⁵ Solvents, however, include hundreds of chemicals used in a wide variety of products or processes. About 15% of French workers are exposed.⁶ The identification of specific solvents and exposed job categories at risk would improve intervention to prevent or delay chronic glomerulonephritis progression to ESRD in the occupational setting.

Very few case-control studies investigated the links between specific solvents or solvent-containing products and the risk for chronic or end-stage kidney disease. Oxygenated and aromatic solvents were associated with chronic renal failure in two studies,^{4,7} and cleaning/degreasing agents with ESRD in two others.^{8,9} A number of cross-sectional studies of early markers of renal injury were carried out in workers exposed to aromatic or halogenated solvents without yielding conclusive evidence of their nephrotoxicity.^{10–14} Only one occupational cohort study examined the association between hydrocarbon exposure and ESRD incidence, showing significant increased risk with chlorinated solvents and JP4 gasoline in aircraft workers.¹⁵

Using data from the GN-PROGRESS cohort study, including a large number of new patients with primary glomerulonephritis,

we therefore systematically investigated the risk of progression to ESRD, by solvent-exposed job category, type of solvent-containing products, and by solvent or solvent family.

MATERIALS AND METHODS

Study population

The design of the GN-PROGRESS retrospective cohort study has been described in detail elsewhere.⁵ Briefly, all new Caucasian adult patients with biopsy proven IgA nephropathy (IgAN), membranous nephropathy and focal and segmental glomerulosclerosis, diagnosed between January 1994 and June 2001 in 11 nephrology departments in the Paris area (see Appendix) were invited to participate in the study between January 2002 and March 2004. The diagnosis and primary nature of all glomerulonephritis were confirmed by expert nephrologists and pathologists. Of 538 eligible non-ESRD cases, 18 had died before the study started, 91 could not be traced despite intensive search, 7 refused to participate, 82 were unable to come to a nephrology outpatient clinic to complete the study interview and blood testing mainly because they had moved far from the Paris region, and 2 had poor exposure data, leaving 338 patients including 194 patients with IgAN, 75 with membranous nephropathy and 69 with focal and segmental glomerulosclerosis. In this analysis, we focused on the 269 patients with either IgAN or membranous nephropathy, in whom we previously described an excess risk of ESRD with overall solvent exposure.⁵

Exposure

On the day of enrolment in the study, patients were asked about their lifetime occupational activities by trained interviewers using

Abbreviations: ESRD, end-stage renal disease; GFR, glomerular filtration rate; IgAN, IgA nephropathy; ISCO, International Standard Classification of Occupations

a detailed questionnaire to detect solvent exposure as previously described.^{4,5} For each job period—defined as any period of continuous employment of more than six months in a given job category—we recorded job title, economic activity, period and duration. Participants were asked about any contact with products or processes involving solvents using a detailed list of commonly named items—that is, paints, varnishes, adhesives, printing inks, degreasing and cleaning agents, paint stripping, aerosols and pesticides, chemical and pharmaceutical processes, oil extraction, and petroleum products including fuel, kerosene, gasoline, gas oil or crude oil. Working conditions and frequency of use (every day, at least once a week occasionally) were also recorded. Occupations were coded according to the International Standard Classification of Occupations (ISCO).¹⁶ Job periods were reviewed—blind with respect to patient renal function stage—by two industrial hygienists⁵ who first determined whether reported products were actually solvents on the basis of the context of use including industrial activity, employment period, tasks and working conditions. This step permitted the exclusion of several solvent-free products such as the so-called “glue” reported by construction workers which was actually cement, or some cleaning agents which were actually detergents. Secondly, they identified the types of solvent using a list of the 30 most common ones grouped in five large chemical families: halogenated, aliphatic, aromatic or mixture of both aliphatic and aromatic, oxygenated solvents. For each substance, the experts evaluated the exposure intensity (low, moderate or high) and frequency (occasional (less than once a week) or regular (once a week) subdivided as <2, 2–20, and >20 h/week). These were further combined to define exposure in both a sensitive and more specific way as follows: any exposure level for subjects who had experienced exposure to solvents at any intensity and at any frequency; high exposure level for subjects who had been moderately or highly exposed for more than two hours per week.

Information about smoking habits and alcohol consumption was also obtained by interview. Information on known risk factors for glomerulonephritis progression such as hypertension, proteinuria and serum creatinine level was collected from medical records. Hypertension was defined as a blood pressure >140/90 mm/Hg or antihypertensive treatment. To evaluate renal function at baseline, we estimated glomerular filtration rate (GFR in ml/min/1.73 m²), using the abbreviated Modification of Diet in Renal Disease Study equation based on serum creatinine, age and gender.¹⁷ This information was available for all eligible patients with IgAN or membranous nephropathy whether they were participants or non-participants in the study. The occupation at the time of diagnosis or the last occupation in those who were retired was available from medical records for 48% of the latter. Using these

data and similar data from the questionnaire for participants, we defined social class as a dummy variable as follows: blue collars, including service, agricultural and production workers—that is, ISCO two digit codes ≥53—versus white collars including all other job categories—that is, ISCO two digit codes <53.

Outcome

The studied outcome was ESRD, defined according to the classification from the National Kidney Foundation as chronic kidney disease stage 5—that is, either an estimated GFR <15 ml/min/1.73 m² or the start of renal replacement therapy (dialysis or preemptive graft).¹⁸ GFR was estimated from serum creatinine measured in all patients at the time of interview, except those who were on dialysis or leaving with a functioning graft. Events were registered over a mean follow-up of five years (median 4.6 years; interquartile range 2.6–7.1 years).

Statistical analyses

IgAN and membranous nephropathy participants' baseline characteristics were described and compared with those of non-participant eligible patients. To study the progression of glomerulonephritis to ESRD, the time to the event is important, not simply whether or not the event occurs. Therefore, to analyse the relations between solvent exposure and ESRD risk, we used the Cox proportional hazards models adjusted for well-established risk factors of disease progression: age, gender, histological type, proteinuria and hypertension. As solvent exposure is strongly related to social class, we also adjusted for this variable. First, we studied the hazard ratios and 95% confidence intervals (95% CI) of ESRD associated with solvent-exposed job categories. Second, we estimated the hazard ratio associated with exposure to solvent-containing products. Finally, we analysed ESRD risk associated with each of the five solvent families as well as with specific solvents. These analyses were carried out for all job categories, or products, or chemicals with at least five exposed patients. The reference group was that of never exposed patients, which was thus the same in all the above analyses. Bonferroni correction for multiple comparisons was applied by adjusting p values.¹⁹ The corrected p values were the p values estimated by models multiplied by the number of tests within each subgroup of job-titles, products, chemical families or substances.

The study protocol was approved by the relevant institutional review board in compliance with French law (Paris Saint Louis Hospital, CCPPRB, decision P001104, 2001). All patients gave written informed consent before enrolment in the study.

Table 1 Baseline patients' characteristics

	Participants IgAN and MN, n = 269	Non-participants IgAN and MN, n = 150	p Value
Mean (SD) age (years)	41 (16)	45 (19)	NS
Men	76%	75%	NS
Blue-collar*	35%	46%	NS
Histological type			NS
IgAN	72%	63%	
MN	28%	37%	
Hypertension	54%	57%	NS
Nephrotic range proteinuria (≥3 g/24 h)	35%	39%	NS
GFR (ml/min/1.73 m ²)			NS
≥90	28%	38%	
60–90	37%	33%	
15–60	36%	29%	

IgAN, IgA nephropathy; MN, membranous nephropathy; GFR, glomerular filtration rate; NS, not significant (p>0.05).

*Blue-collar includes service, agricultural, production and transport workers.

Table 2 Main solvent-exposed job categories

Patients with at least one job as:	ISCO code*	n	% Exposed at any level
Professional and technical workers	0-1	93	27%
Physician scientists and related technicians	01	3	33%
Architects, engineers and related technicians	02,03	34	44%
Life scientists	05	2	50%
Sculptors, painters, creative artists	16	11	40%
Administrative and managerial workers	2	16	12%
Clerical workers	3	63	1%
Sales workers	4	41	0%
Service workers	5	68	4%
Agricultural workers	6	16	0%
Production and transport workers	7-8-9	104	47%
Production supervisor and general foremen	70	10	30%
Blacksmiths, toolmakers and machine tool operators	83	10	40%
Machinery fitters, machine assemblers	84	15	47%
Electrical and electronics workers	85	14	36%
Plumbers, welders	87	17	53%
Printers	92	2	100%
Painters	93	6	100%
Construction workers	95	21	52%
Transport workers	98	17	12%
Manual workers	99	10	20%

*First digits (bold) or first two digits of the 1968 International Standard Classification of Occupations.¹⁶

RESULTS

Cohort description

Among participants, three patients out of four were men and 35% were blue-collar (table 1). More than a half were hypertensive, about a third had nephrotic range proteinuria, and more than a third had chronic renal failure (GFR <60 ml/min/1.73 m²) at the time of renal biopsy. The participants did not significantly differ from their 150 non-participant counterparts with respect to baseline characteristics as listed in table 1.

Hazard ratios of progression to end-stage renal disease by solvent-exposed job category

Patients reported a mean of three job periods, 18% of which were classified as exposed to solvents by the experts. The distribution of jobs held at least once by the patients are presented in table 2.

The number of these jobs is higher than that of the patients because most patients had more than one job, but it is lower than that of job periods because a patient may have had more than one job period in a given subcategory. Nearly half of the patients in production and transport job categories were classified as exposed to solvents, and one fourth of those in professional and technical job categories. In all other job categories, solvent exposure was scarce. Seventy two per cent of the patients (194) reported no exposed jobs, 30% of whom had been production workers. No significant excess risk of progression to ESRD was observed in glomerulonephritis patients with at least one exposed professional and technical job as compared to those never exposed (table 3). In contrast, this risk was nearly three times higher in patients with at least one exposed production and transport job, independent of age, gender, social class, and kidney risk factors for progression. In that category, significant hazard ratios before Bonferroni correction were observed in those who were machinery fitters, machine assemblers and plumbers or welders, but none of them reached statistical significance after correction (10 exposed job-categories tested).

Hazard ratios of progression to end-stage renal disease by type of solvent-containing product

Paints, degreasing and cleaning agents, and petroleum products were the most common types of reported solvent-containing products (table 4).

Printing inks and petroleum products were significantly associated with an excess risk of progression to ESRD, after controlling for potential confounders and the multiple tests. The elevated adjusted hazard ratio observed for degreasing and cleaning agents was no longer significant after Bonferroni correction, as well as those of other reported products.

Hazard ratios of progression to end-stage renal disease by solvent or solvent family

Aliphatic, oxygenated and halogenated solvents were the most frequent types of chemicals coded by the experts. Solvent families associated with the highest risk of progression to ESRD were aromatic and mixtures of aromatic and aliphatic solvents (table 5). Among these two families, the chemicals most strongly associated with ESRD risk were toluene, xylene and gasoline/fuel/gas-oil. We also observed an excess risk for any exposure level to methylene chloride as well as for high

Table 3 Adjusted hazard ratios of ESRD associated with exposure by solvent-exposed job category*

Job titles	n	ESRD	Hazard ratio† (95% CI)
Never exposed	194	29	Ref
Ever exposed as:			
Professional and technical workers	25	4	1.7 (0.5 to 6.2)
Physician scientists and related technicians	1	0	—
Architects, engineers	14	3	2.4 (0.5 to 11.4)
Life scientists and related	1	0	—
Sculptors, painters, creative artists	4	1	2.8 (0.4 to 22.7)
Production and transport workers	49	22	2.8 (1.4 to 5.5)
Production supervisor and general foremen	3	2	3.6 (0.7 to 18.1)
Blacksmiths, toolmakers and machine tool operators	4	2	3.0 (0.7 to 13.2)
Machinery fitters, machine assemblers	7	5	4.7 (1.2 to 17.4)
Electrical and electronics workers	4	2	3.1 (0.6 to 16.4)
Plumbers, welders	9	4	4.2 (1.3 to 13.6)
Printers	2	1	5.5 (0.5 to 60.6)
Painters	6	1	0.6 (0.1 to 4.4)
Construction workers	11	4	2.5 (0.8 to 7.8)
Transport workers	2	1	1.7 (0.2 to 14.3)
Manual workers	2	1	4.9 (0.4 to 55.7)

*Solvent exposure at any level.

†Adjusted for age, gender, histological type, baseline proteinuria, hypertension and social class.

Table 4 Adjusted hazard ratios of ESRD associated with exposure by type of solvent-containing product*

	Any level		Hazard ratio† (95% CI)
	n	ESRD	
Never exposed	194	29	Ref
Ever exposed to:			
Any product	75	25	2.2 (1.2 to 3.9)
Paints, lacquers, varnishes	34	9	1.6 (0.7 to 3.6)
Glues, adhesives	13	5	2.7 (1.0 to 7.4)
Printing inks	5	2	12.6 (1.7 to 94.9)‡
Degreasing/cleaning agents	48	14	2.2 (1.0 to 4.6)
Paint stripping	12	5	2.7 (0.9 to 7.7)
Disinfectants	8	2	2.1 (0.5 to 9.3)
Petroleum products§	19	10	3.2 (1.4 to 7.2)‡

*Only products reported by at least five patients.

†Adjusted for age, gender, histological type, baseline proteinuria, hypertension and social class; §including fuel, kerosene, gasoline, gas oil or crude oil.

‡Bonferroni corrected $p < 0.05$ (7 products tested).

exposure to ketones. In contrast, no significant association was observed for other halogenated or oxygenated solvents, and for aliphatic solvents. With a few exceptions, hazard ratios tended to be stronger when the analysis was restricted to high solvent exposure levels.

DISCUSSION

The prospective study of solvent-related renal risk faces two major obstacles: the low incidence of ESRD, about 130 per million population in France,¹ and the wide variety of potential solvents to be tested. Moreover, because, as we have previously shown,³ these substances tend to hasten renal function decline rather than to induce chronic kidney disease, the classic occupational cohort study may not be the best design. Using an appropriate study design based on a large cohort of patients with biopsy-proven glomerulonephritis, we obtained new insights into the types of solvents most strongly associated with progression to ESRD. We found that aromatic hydrocarbons (toluene and xylene), mixtures of aromatic and aliphatic hydrocarbons, ketones and possibly methylene chloride were associated with the highest risks. Among solvent-containing

products, the highest risks were consistently related to inks, cleaning or degreasing agents and petroleum products; among solvent-exposed job categories, risks were found for machinery fitters, machine assemblers, plumbers and welders. These findings have straightforward implications for the prevention of solvent-related nephrotoxicity in the workplace.

Assessment of solvent exposure is a critical issue in occupational epidemiology. Studying renal risk by chemical or chemical family is the most relevant approach with respect to aetiology and underlying biological mechanisms. These, however, are most often unknown to exposed workers, and can therefore hardly be later reported whatever the quality of questionnaires and interviewers. To overcome these difficulties, we developed a specific questionnaire in which patients are asked about solvent exposure as they are commonly known to workers. Using this information, together with that on working conditions, experts can assign exposure from three angles: solvent-exposed job categories, solvent-containing products, and types of solvents or solvent families at risk. We analysed solvent-exposed occupations instead of occupations per se—in contrast with most classic epidemiology, because we focused on solvent-related renal injury.

Comparison of our results with others is limited by the scarcity of available data and differences in study design. Only two case-control studies analysed the role of solvent families in association with primary glomerulonephritis or chronic renal failure.^{4,7} In the first one, aromatic solvents were significantly associated with an increased odds ratio of IgAN, and in the other one, they were associated with a non-significant doubling of all-cause chronic renal failure risk, but that study may have lacked power. The potential nephrotoxicity of aromatic solvents was also studied in several cross-sectional surveys, based on early biomarkers of glomerular and/or tubular injuries.¹³ Some showed an increase in the urinary excretion of tubular markers in toluene and/or xylene exposed workers,^{10,12,20} but no increase in albuminuria.¹⁰ In our study, exposure to toluene and xylene was strongly associated with the risk of progression to ESRD. Regarding styrene, both positive^{20,21} and negative results^{11,20,22} were found. Only one patient in our cohort reported a job in the rubber and plastic industry with heavy styrene exposure. He rapidly progressed to ESRD within five years after diagnosis, but we cannot draw any conclusion from this single observation. With respect to oxygenated solvents, our finding of an

Table 5 Adjusted hazard ratios of ESRD associated with exposure by type of solvents and solvent family*

	Any exposure level			High exposure level		
	n	ESRD	Hazard ratio† (95% CI)	n	ESRD	Hazard ratio† (95% CI)
Never exposed	194	29	Ref	194	29	Ref
Ever exposed to:						
Any solvent	75	25	2.2 (1.2 to 3.9)	40	16	2.5 (1.3 to 5.0)
Halogenated solvents	33	10	2.2 (1.0 to 5.1)	20	7	2.4 (1.0 to 5.9)
Trichlorethylene	20	6	2.5 (0.9 to 6.5)	10	3	2.7 (0.7 to 10.1)
Methylene chloride	5	3	6.4 (1.7 to 24.8)§	1	1	—
Aromatic hydrocarbons	21	8	4.4 (1.9 to 10.1)‡	15	7	5.9 (2.3 to 14.7)‡
Toluene and xylene	18	7	4.1 (1.7 to 9.8)§	11	5	5.1 (1.8 to 14.8)§
Aliphatic hydrocarbons	33	10	2.2 (1.0 to 4.8)	18	7	2.3 (0.9 to 5.7)
Disaromatised white spirit	21	7	2.4 (1.0 to 6.3)	7	4	2.8 (0.8 to 9.7)
Special boiling point solvents	8	2	1.3 (0.3 to 5.9)	7	2	1.3 (0.3 to 5.9)
Mixture of aromatic and aliphatic hydrocarbons	28	15	3.3 (1.6 to 6.7)‡	18	11	3.3 (1.6 to 7.1)‡
Gasoline, fuel, gas-oil	9	7	7.5 (2.9 to 19.4)§	5	4	8.6 (2.7 to 27.4)§
White spirit	14	6	2.1 (0.8 to 5.6)	9	3	1.2 (0.4 to 4.2)
Oxygenated solvents	40	9	1.2 (0.6 to 2.8)	23	6	1.2 (0.4 to 3.0)
Ketones	8	5	3.1 (1.0 to 10.1)	4	3	13.3 (1.4 to 123.5)§
Alcohols	9	1	0.8 (0.1 to 6.1)	4	1	1.5 (0.2 to 11.8)
Esters	19	3	0.9 (0.3 to 3.0)	10	2	0.9 (0.2 to 3.8)

*Only solvents or solvent families assigned by experts to at least five patients.

†Adjusted for age, gender, histological type, baseline proteinuria, hypertension and social class.

‡Bonferroni corrected $p < 0.05$ (5 chemical families tested).

§Bonferroni corrected $p < 0.05$ (10 substances tested).

excess risk with ketones is consistent with that from Nuyts's case-control study.^{4,7} In a recent occupational cohort study in US aircraft workers, the authors pointed to the risk of all-cause ESRD associated with trichloroethylene, 1,1,1-trichloroethane, methylene chloride, and JP4 gasoline.¹⁵ The latter two were also at risk in our study. Finally, the higher albuminuria rate observed in refinery workers exposed to mixtures of aliphatic and aromatic solvents as compared to controls²³ is consistent with the risk related here to gasoline, fuel or gas-oil.

In two case-control studies, cleaning/degreasing agents and petroleum products were found to be associated with all-cause ESRD^{8,9} and primary glomerulonephritis,⁹ as we also did for the progression to ESRD. As these solvents were very frequently reported in machinery fitters and assemblers as well as in plumbers/welders, it was not surprising to find excess risks for these job categories. In contrast, although painters were once identified as a group at high risk,²⁴ we did not observe excess risks either for painters or for the use of paints, lacquers and varnishes, which was also the case in the study by Steenland *et al.*⁸

Experimental evidence of solvent-induced accelerated renal function decline is limited for several reasons. First, most toxicity studies focused on acute effects of solvents on renal tubules and were not designed to assess chronic nephrotoxicity. Second, experimental models are often unable to mimic exposure conditions in the workplace, making the extrapolation of animal data to human even more difficult. Third, there are very few animal species and strains that are suitable to test the hypothesis that solvents would aggravate rather than cause chronic kidney disease. This was performed, however, in one study designed specifically to assess the role of styrene in the progression of Adriamycin nephrosis in female Sprague-Dawley rats, a well-established model of glomerulopathy.²⁵ It showed that co-exposure to styrene and adriamycin increased the urinary excretion of both albumin and low molecular weight proteins, and was also associated with higher interstitial fibrosis score and greater cellular infiltrates as compared with adriamycin treatment alone. Although limited to a single solvent, this experiment provides some evidence of the role of solvents in kidney disease progression through several potential pathogenic mechanisms including enhanced proteinuria and tubulointerstitial damage. Further experimental studies are, nevertheless, needed to assess other types of solvent.

This study has three limitations. Despite considering all incident patients over a six-year period from all major nephrology centres in the Paris area, we identified only 419 eligible IgAN and membranous nephropathy cases, of whom two thirds were interviewed. Participants did not significantly differ from non-participants with respect to major baseline determinants of glomerulonephritis progression—that is, hypertension, proteinuria and GFR. Neither did they differ with respect to social class, a characteristic strongly related to solvent exposure, but this information recorded from medical records in non-participants was poor. Selection bias as a result of non-participation, therefore, cannot be completely ruled out. Another drawback was the study's lack of power, which prevented us from analysing several subgroups of solvents or job categories because of our small sample size. That, together with the need for Bonferroni correction (a very conservative method), may have reduced our chance of finding more significant associations, particularly regarding job categories and specific solvents. Retrospective exposure assessment is a critical issue in this type of study. Using a highly detailed and structured questionnaire and blind evaluation of exposures by experts, however, has proved to be reliable.²⁶ We used it in a previous case-control study,⁴ and it is worth noting that we obtained similar results, providing indirect evidence of reproducibility of the

Main messages

- This study showed the potential role of toluene and xylene, some petroleum products, ketones and possibly methylene chloride in the progression of glomerulonephritis to end-stage renal disease (ESRD).
- The highest risks for progression to ESRD were found for solvent-exposed machinery fitters/machine assemblers and plumber/welders.

Policy implications

- Further epidemiological studies should be conducted to confirm these associations and investigate other solvents.
- Intervention to promote screening for proteinuria in solvent exposed workers may prevent the progression of glomerulonephritis to ESRD.

assessment method. A possible weakness of this method, however, is that it strongly relies on individual recall of past exposures. Although most interviews were carried out blind with respect to the patient's glomerulonephritis stage, this was not possible to achieve for some patients who were seen at the dialysis centre. Recall bias therefore may have contributed to our findings, if patients without ESRD tended to under-report exposures in comparison with those with ESRD or vice versa (if the latter tended to over-report exposures). The specificity of ESRD risk, with respect to solvent types, however, argues against differential bias. Such bias would have indeed increased all hazard ratios independent of the type of solvents, which we did not observe. Nevertheless, the expert assessment was sometimes based on poor information from patient questionnaires but blind with respect to the patient's glomerulonephritis stage, resulting in possible non-differential misclassification of exposure. Finally, social class may have been a potential confounder for the observed associations, because of its links with both chronic renal failure and solvent exposure,²⁷ but they were not altered after adjustment.

In conclusion, this study highlighted the potential role of toluene and xylene, some petroleum products (gasoline, fuel or gas-oil), ketones and possibly methylene chloride in the progression of chronic kidney disease to ESRD. Further epidemiological studies, however, are needed to confirm these associations and investigate other solvents, such as styrene. It would also be worth studying the effect of these solvents in adequate animal models of renal disease progression in order to better understand the underlying pathogenic mechanisms. Because glomerulonephritis is a major cause of ESRD, interventions to promote screening for proteinuria in solvent exposed workers and discontinuation of exposure in those who are identified with glomerulonephritis at an early stage may prevent or slow the progression to ESRD. Strong interaction between nephrologists and occupational physicians is also important to improve the early detection of renal injury in exposed workers and to manage the care of those diagnosed with glomerulonephritis.

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REFERENCES

- 1 **Couchoud C**, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant* 2006;**21**:411–18.
- 2 **Pfaller W**, Gstraunthaler G. Nephrotoxicity testing in vitro—what we know and what we need to know. *Environ Health Perspect* 1998;**106**(Suppl 2):559–69.
- 3 **Brautbar N**. Industrial solvents and kidney disease. *Int J Occup Environ Health* 2004;**10**:79–83.
- 4 **Stengel B**, Cenée S, Limasset JC, et al. Organic solvent exposure may increase the risk of glomerular nephropathies with chronic renal failure. *Int J Epidemiol* 1995;**24**:427–34.
- 5 **Jacob S**, Héry M, Protois JC, et al. Effect of organic solvent exposure on chronic kidney disease progression: The GN-PROGRESS Cohort Study. *J Am Soc Nephrol* 2007;**18**:274–81.
- 6 **Triolet J**. Panorama de l'utilisation des solvants en France fin 2004. In: *Hygiène et Sécurité du Travail*, INRS, 2005.
- 7 **Nuyts GD**, Van Vlem E, Thys J, et al. New occupational risk factors for chronic renal failure. *Lancet* 1995;**346**:7–11.
- 8 **Steenland NK**, Thun MJ, Ferguson CW, et al. Occupational and other exposures associated with male end-stage renal disease: a case/control study. *Am J Public Health* 1990;**80**:153–7.
- 9 **Yaqoob M**, Bell GM, Percy DF, et al. Primary glomerulonephritis and hydrocarbon exposure: a case-control study and literature review. *Q J Med* 1992;**83**:409–18.
- 10 **Askergrén A**, Allgen LG, Karlsson C, et al. Studies on kidney function in subjects exposed to organic solvents. I. Excretion of albumin and beta-2-microglobulin in the urine. *Acta Med Scand* 1981;**209**:479–83.
- 11 **Vyskocil A**, Emminger S, Malir F, et al. Lack of nephrotoxicity of styrene at current TLV level (50 ppm). *Int Arch Occup Environ Health* 1989;**61**:409–11.
- 12 **Ng TP**, Ong SG, Lam WK, et al. Urinary levels of proteins and metabolites in workers exposed to toluene. A cross-sectional study. *Int Arch Occup Environ Health* 1990;**62**:43–6.
- 13 **Hotz P**. Occupational hydrocarbon exposure and chronic nephropathy. *Toxicology* 1994;**90**:163–283.
- 14 **Verplanke AJ**, Leumens MH, Herber RF. Occupational exposure to tetrachloroethene and its effects on the kidneys. *J Occup Environ Med* 1999;**41**:11–16.
- 15 **Radican L**, Wartenberg D, Rhoads GG, et al. A retrospective occupational cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons. *J Occup Environ Med* 2006;**48**:1–12.

- 16 International standard classification of occupations. In: Office IL, ed. *International Labour Office, revised edition*. Geneva: ILO, 1968.
- 17 **Stevens LA**, Coresh J, Greene T, et al. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006;**354**:2473–83.
- 18 **K/DOQI**. clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(Suppl 1):S1–266.
- 19 **Miller RGJ**. *Simultaneous statistical inference*. New York, 1991.
- 20 **Franchini I**, Cavatorta A, Falzoi M, et al. Early indicators of renal damage in workers exposed to organic solvents. *Int Arch Occup Environ Health* 1983;**52**:1–9.
- 21 **Viau C**, Bernard A, De Russis R, et al. Evaluation of the nephrotoxic potential of styrene in man and in rat. *J Appl Toxicol* 1987;**7**:313–16.
- 22 **Verplanke AJ**, Herber RF. Effects on the kidney of occupational exposure to styrene. *Int Arch Occup Environ Health* 1998;**71**:47–52.
- 23 **Viau C**, Bernard A, Lauwerys R, et al. A cross-sectional survey of kidney function in refinery employees. *Am J Ind Med* 1987;**11**:177–87.
- 24 **Ravnskov U**, Lundstrom S, Norden A. Hydrocarbon exposure and glomerulonephritis: evidence from patients' occupations. *Lancet* 1983;**2**:1214–16.
- 25 **Muti A**, Coccini T, Alinovi R, et al. Exposure to hydrocarbons and renal disease: an experimental animal model. *Ren Fail* 1999;**21**:369–85.
- 26 **Siemiatycki J**, Fritschi L, Nadon L, et al. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *Am J Ind Med* 1997;**31**:280–6.
- 27 **Fored CM**, Ejerblad E, Fryzek JP, et al. Socio-economic status and chronic renal failure: a population-based case-control study in Sweden. *Nephrol Dial Transplant* 2003;**18**:82–8.

APPENDIX: GN-PROGRESS STUDY GROUP

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