

Exhibit 232

Case–Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part II: Epidemiological Aspects

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To test the effect of the exposure to trichloroethylene (TCE) on renal cell cancer (RCC) risk, a case–control study was performed in the Arve Valley (France), a geographic area with a high frequency and a high degree of such exposure. Cases and controls were selected from various sources: local general practitioners and urologists practicing in the area and physicians (urologists and oncologists) from other hospitals of the region who might treat patients from this area. Blinded telephone interviews with cases and controls were administered by a single trained interviewer using occupational and medical questionnaires. The analysis concerned 86 cases and 316 controls matched for age and gender. Three approaches were developed to assess the link between TCE exposure and RCC: exposure to TCE for at least one job period (minimum 1 year), cumulative dose (number of p.p.m. of TCE per job period multiplied by the number of years in the job period) and the effect of exposure to peaks. Multivariate analysis was performed taking into account potential confounding factors. Allowing for tobacco smoking and Body Mass Index, a significantly 2-fold increased risk was identified for high cumulative doses: odds ratio (OR) = 2.16 (1.02–4.60). A dose–response relationship was identified, as was a peak effect; the adjusted OR for highest class of exposure-plus-peak being 2.73 (1.06–7.07). After adjusting for exposure to cutting fluids the ORs, although still high, were not significant because of lack of power. This study suggests an association between exposures to high levels of TCE and increased risk of RCC. Further epidemiological studies are necessary to analyze the effect of lower levels of exposure.

Keywords: cancer; exposure; kidney; occupation; trichloroethylene

Trichloroethylene (TCE) is a solvent used in numerous industries as a degreaser in metal manufacturing and as a solvent for oils, resins, etc. Several studies have investigated the association between TCE exposure and renal cell cancer (RCC), but findings have been inconsistent. An incidence study carried out among Finnish workers exposed to halogenated hydrocarbons including TCE found no link with kidney cancer (Anttila *et al.*, 1995); the standardized incidence ratio (SIR) for kidney cancer was 1.2 (95% CI 0.4–2.5). In a cohort study performed by Blair *et al.* (1998) on aircraft maintenance workers

exposed to TCE and other chemicals, kidney cancer incidence was not significantly greater than that in the general population of Utah, standardized mortality ratio (SMR) 122 (95% CI 85–174). The rate ratio for a TCE-exposed worker compared with cohort members without chemical exposure was 1.6 (0.5–5.4). A mortality cohort study conducted in California among aircraft manufacturing workers found no increased risk of kidney cancer for workers exposed to TCE or perchloroethylene (Boice *et al.*, 1999). Another cohort study of workers exposed to low-level TCE found no significantly increased RCC rate (Axelson *et al.*, 1994). In contrast, a slightly elevated rate ratio was found in a study on the mortality of aerospace workers exposed to TCE (Morgan *et al.*, 1998). In those with peak exposures at medium

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and high levels, the rate ratio was 1.89 (0.85–4.23). A link between RCC and chlorinated solvents in general was also observed in a number of case–control studies (McCredie and Stewart 1993; Mellemsgaard *et al.*, 1994a; Mandel *et al.*, 1995).

A cluster investigation performed in a cardboard factory in Germany showed increased RCC incidence (Henschler *et al.*, 1995). The SIR for renal cancer in workers exposed to TCE compared with that of the cancer register of Denmark was 8.0 (2.6–8.6), and the SMR was 3.3 (95% CI 0.4–11.8). In a case–control study performed in the same area (Vamvakas *et al.*, 1998), the odds ratio (OR) for exposure, after adjusting for age, gender, smoking, BMI and blood pressure, was significantly increased, at 10.8 (95% CI 3.4–34.8). As these results did not corroborate those of other studies, a scientific polemic arose (Bloemen and Tomenson, 1995; Swaen 1995), and certain recruitment biases were suggested (Green and Lash, 1999). According to Vamvakas *et al.* (2001a, b) the negative outcomes reported in other epidemiological studies could be accounted for by low exposure levels, contrasting with the high level found in their own study population, suggesting a threshold effect. Comparisons between the exposure rates measured in the studies by Blair *et al.* and by Vamvakas *et al.* and Henschler *et al.* (Cherrie *et al.*, 2001), however, concluded that any differences in TCE exposure intensity between these various studies could not account for the differences in risk observed.

For these reasons a new case–control study was performed in a geographic area with a high prevalence and a high degree of exposure, testing the effect of exposure to high levels of TCE over a long period. The Arve valley in France was of special interest for such a study, as a wide-scale screw-cutting industry, using TCE as a degreasing agent, has been developed there since before the Second World War.

MATERIAL AND METHODS

Study design

Cases were selected retrospectively from 1993, and prospectively for 1 year up to the end of June 2003, from various medical practitioners: all the local urologists practicing in the Arve valley, and urologists and oncologists from other hospitals of the region who might treat patients from this area. To ensure the power of the study, deceased subjects were includable. In these cases, next of kin (of the cases and controls) were interviewed.

The Mainz classification is the most widely used for RCC (Diaz *et al.*, 1999). Renal clear cell cancer (RCCC) represents 70% of all RCCs. In most studies (Henschler *et al.*, 1995; Mandel *et al.*, 1995; Blair *et al.*, 1998), the International Classification of Diseases is used and, in particular, the diseases coded

189-0 (WHO, 1977). Some studies use the term RCC (Mellemsgaard, 1994a; Vamvakas *et al.*, 1998), with no mention of subtypes. In light of the above, it was decided to include all RCC subtypes in the study.

For the cases from local urologists, controls were recruited among the patients of the same urologist (but without RCC). For patients treated in teaching hospitals, controls were recruited among the patients of the case's general practitioner. Controls were selected based on being resident in the geographic study area at the time of diagnosis of the case's disease and were matched on gender and year of birth (± 2 years). Controls were excluded if they had been treated for chronic kidney disease or cancer of bladder, renal pelvis or ureter. Lists of patients who corresponded to the matching criteria were obtained from computerized medical files or directly from non-computerized records. Controls were subsequently randomly selected. We aimed to recruit four controls for each case, although the number of patients contacted to find four controls per case was limited to 12.

Cases and controls were first approached by telephone. Then a letter was sent to obtain their written consent or that of their family for deceased patients (deceased controls were included if the corresponding case was deceased).

Telephone interviews with cases and controls were administered by a single trained interviewer. As far as possible, the interviewer was blinded to the subject's medical status, as the medical questionnaire was administered after the occupational questionnaires and all telephone contacts, letters and appointments were managed by a research unit physician. One exception to this rule was interviews of the next-of-kin of living controls.

For subjects who refused to participate in the study or who were lost to follow-up, a short questionnaire was used to assess the quality of selection and to control for selection bias.

The medical questionnaire included familial kidney disease and medical history, such as kidney stones, infection, chronic dialysis, hypertension and use of drugs (anti-hypertensive drugs, diuretics and analgesics). Body mass index (BMI), present and maximum at any previous time, was calculated as weight per height². Information about lifestyle considered smoking habits (pack-years) and coffee consumption.

An expert performed the exposure assessment by using information from the occupational questionnaires (a questionnaire devoted to the screw-cutting industry and a general one for any other jobs) and a task exposure matrix for screw-cutting tasks. For each job described, the employer's activity and the job title were encoded (ISCO 1968; NACE Rev 1. 1999). The exposures assessed were: solvents (TCE, other chlorinated solvents, oxygenated solvents, petroleum derivatives, including gasoline, white-spirit and other

petroleum solvents), oils (cutting fluids and other oils), welding fumes, lead, cadmium, asbestos and ionizing radiations. Solvents, oils, welding fumes, lead, cadmium and asbestos were assessed because they had been identified as possible occupational risk factors for RCC (Partanen *et al.*, 1991; Edelman 1992; Fowler 1992; Steenland *et al.*, 1992; McCredie and Stewart 1993; Poole *et al.*, 1993; Schnatter *et al.*, 1993; Mellemegaard *et al.*, 1994a; Fu and Boffetta 1995; Mandel *et al.*, 1995; Sali and Boffetta 2000). Ionizing radiation was added as there was one large company in the area where this exposure was prevalent. The assessment was semi-quantitative for exposure to TCE and qualitative: (low/medium/high level) for the other occupational exposures. A confidence score was given: 3-certain/2-probable/1-possible to each of the exposures assessed.

Statistical analysis

The statistical analysis was performed using the SAS system 9.1.3®. All analyses were performed on matched pairs (conditional logistic regression). In the first stage, cases and controls were described. Qualitative data were expressed as frequency and percentage; differences between cases and controls were tested by chi-square. Means and standard deviations were calculated for quantitative data (age, etc.) and differences tested by *t*-test. For non-TCE occupational exposures, subjects were considered to have been exposed when such exposure was noted for at least one job period (i.e. for at least 1 year). Levels were taken into account when a difference had been observed between cases and controls at the 10% threshold ($P = 0.10$). Potential confounding factors identified were further taken into account at the 10% threshold ($P = 0.10$). A multivariate analysis was performed when an association between TCE exposure and RCC was found at the 10% threshold, taking into account the potential confounding factors identified in the descriptive part. For a prevalence of exposure to TCE of 20%, the power of the study was 80% to detect a 2-fold increase in RCC risk ($\alpha = 0.05$).

Three exposure metrics were used to investigate the association between TCE exposure and RCC:

- (i) Ever versus never exposed, irrespective of exposure duration and level.
- (ii) Cumulative dose, calculated as the sum of total exposure doses (d_i) for each job period: cumulative dose = $\sum_i(E_i \times y_i)$ (where E_i = TCE (in p.p.m.) for job period $_i$ and y_i = duration (in years) in job period $_i$). Three levels of cumulative dose were established according to the control exposure tertiles.
- (iii) The effect of exposure to peaks was assessed, dividing exposed subjects into four exposure groups (exposed to low or medium cumulative

dose without peaks, low or medium cumulative dose with peaks, high cumulative dose without peaks and high cumulative dose with peaks).

The main analysis was replicated including only good quality information on exposure to TCE. Indeed, some misclassification bias may have occurred due to: (i) inclusion of deceased patients (proxy interviews for these cases and their controls), (ii) elderly patients (over 80 years of age), (iii) low confidence of exposure assessment and (iv) difference in the quality and validation of the TCE exposure when using the specific screw-cutting questionnaire or the general occupational questionnaire. To assess the impact of these points, a specific analysis was performed including only alive patients <80 years of age and only job periods described with the screw-cutting questionnaire and having a high level of confidence with respect to TCE exposure.

RESULTS

The urologists reported 117 cases of RCC of which 87 participated in the study, giving a participation rate of 74%. Reasons for non-participation were: lost to follow-up ($n = 8$) and refusal ($n = 22$). One case was excluded from analysis, because it was impossible to find controls for him. Most of the cases were included via local urologists (75.6%). Patients' year of birth ranged from 1911 to 1964, with two-thirds of the cases being male. Of the 86 cases studied, 19 were deceased. About 80% of histological types were RCCC.

A total number of 404 matching controls were identified, of which 78 refused to participate and 10 controls were lost to follow-up, resulting in a participation rate of 78%. The age and sex of non-participants were similar to that of participants. The little information available on their possible occupational exposure did not allow any further comparison with the study subjects. A total of 316 controls were included; 95 women (30.1%) and 221 men (69.9%).

The mean age of cases and controls was ~61–62 years at the time of diagnosis of the cases (Table 1). Univariate analyses suggested an increased risk of RCC with increasing BMI (Table 2). Cases were more often current or former smokers than controls and the OR for tobacco smoking was 1.84 (1.04–3.25). The maximum risk was observed for patients who had smoked >40 pack-years (Table 2). The frequency of hypertension was the same for cases and controls, although the frequency of treatment for hypertension tended to be greater among cases, but not significantly. History of kidney and urinary infection tended to be more frequent in controls than cases, but the differences were not significant. On the basis of information given by patients or family, β -blocker

Table 1. General characteristics

	Cases (86)	Controls (316)
Age ^a (years)		
Mean (Standard deviation)	61.8 (10.7)	61.1 (10.4)
Sex		
Women	27 (31.4%)	95 (30.1%)
Men	59 (68.6%)	221 (69.9%)
Vital status		
Dead	19 (22.1%)	7 (2.2%)
Alive	67 (77.9%)	309 (97.8%)
Tobacco smoking ^b (Pack-years)		
Non-smoker	32 (38.1%)	152 (49.2%)
[1–20]	23 (27.4%)	77 (24.9%)
[20–40]	13 (15.5%)	51 (16.5%)
40 and more	16 (19.0%)	29 (9.4%)
BMI ^c (Last known)		
<25.00 ‘Normal’	29 (33.7%)	145 (46.8%)
25.00–29.99 ‘Pre-obesity’	39 (45.3%)	123 (39.7%)
≥30.00 ‘Obesity’	18 (21.0%)	42 (13.5%)
Coffee consumption		
Coffee with caffeine	73 (84.9%)	270 (85.4%)
Coffee without caffeine ^d	7 (8.3%)	25 (8.0%)
Medical history		
Hypertension	34/85 (40.0%)	126/314 (40.1%)
Kidney infection	3 (3.5%)	24/313 (7.7%)
Urinary infection	12 (14.0%)	55/312 (17.6%)
Kidney stones	12 (14.0%)	63/314 (20.1%)
Dialysis	0	2/314 (0.6%)
Medical treatments ^e		
Treatment for hypertension	25/84 (29.8%)	62/310 (20.0%)
β-blockers identified with the drug’s name	5/73 (6.8%)	18/285 (6.3%)
Diuretics	5/82 (6.1%)	28/306 (9.2%)
Analgesic drugs	16/85 (18.8%)	63/312 (20.2%)
Phenacetin	0/75	0/280
Paracetamol	11/82 (13.4%)	42/300 (14.0%)

^aAge at diagnosis (date of the diagnosis of the case being taken as reference for the controls of the same group).

^bFor one case, tobacco smoking status was totally unknown; for two cases and six controls with a history of tobacco smoking, the number of pack-years was unknown.

^cLast BMI unknown for six controls.

^dDecaffeinated coffee consumption unknown for two cases and two controls.

^eMedical treatments, for cases and for controls, were recorded only when the beginning of treatment had started prior the year of the case’s diagnosis of RCC.

treatment appeared to be more frequent among cases. As it can be difficult for patients to know if they have really taken β-blockers, a specific assessment was made assuming that subjects had been treated with β-blockers when treated for hypertension, even if they had answered they had never taken any β-blockers. In this assessment, no significant difference was observed.

Table 2. Crude ORs for general characteristics (conditional regression, matching on sex and age)

	Crude OR (95% CI)	P
Tobacco smoking (Pack-years)		
Non-smokers	1	
[1 to 20]	1.62 (0.83–3.17)	0.16
[20 to 40]	1.44 (0.66–3.15)	0.36
40 and more	3.27 (1.48–7.19)	<0.01
BMI (Last known)		
<25.00 ‘Normal’	1	
25.00–29.99 ‘Pre-obesity’	1.61 (0.93–2.78)	0.09
≥30.00 ‘Obesity’	1.98 (1.01–3.86)	0.05
Treatment of hypertension	1.57 (0.90–2.72)	0.11

Tests for trend: tobacco smoking ($P = 0.008$), BMI ($P = 0.03$).

The proportion of subjects who have been working in any metalwork industry, involving possible cleaning, was almost the same in both groups (Table 3), and the same proportion of metal workers as such was observed in cases and controls (Table 4). However, cases tended to be more often employed in the manufacture of metal products than controls, notably in screw-cutting workshops. OR = 1.39 (0.75–2.58) but these differences were not significant. A few subjects worked in textile washing and dry-cleaning; the difference between cases and controls was not significant, and the same pattern was found when analyzed by job titles.

The percentage of cases employed in the chemical industry was twice that of controls. The OR for ever employment in the chemical industry was 2.69 (1.02–7.09). Of these patients, nine were employed as electricians or mechanical maintenance operators, some being exposed to TCE in these maintenance activities.

In non-industrial sectors, cases were more often employed in health and social work. This result was confirmed by the analysis of job titles. A significant increased risk was also identified for participants employed in food product and beverage manufacturing. Three of eight such cases and two of eleven controls were exposed to TCE during their employment in the food industry (maintenance workers) or during another job period.

Cases tended more often to be subject to a range of occupational exposures than controls, except for exposure to petroleum derivatives (including gasoline and white-spirit), to other solvents and to brazing (Table 5), but the differences did not reach statistical significance. Exposures to cutting fluids and other petroleum oils were significantly different at the 10% level ($P = 0.10$) between cases and controls and were, therefore, included as potential confounders in the multivariate analysis.

In terms of exposure *per se*, regardless of level or duration, cases were more often exposed to TCE during at least one job period than controls, and the

Table 3. Risk of RCC by Industry (NACE codes): percentages and conditional logistic regression, matched for gender and age

Branches (NACE Code)	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Any metal work involving possible cleaning (28.0–35.0 except 32.0)	28 (32.6%)	106 (33.5%)	1.02 (0.61–1.69)	1.02 (0.59–1.76)
Manufacture of metal products other than machinery (28.0)	23 (26.7%)	73 (23.1%)	1.32 (0.75–2.30)	1.28 (0.70–2.34)
Screw-cutting workshops (28.52)	22 (25.6%)	64 (20.3%)	1.48 (0.83–2.63)	1.39 (0.75–2.58)
Washing and dry-cleaning of textiles (93.01)	2 (2.3%)	4 (1.3%)	1.90 (0.35–10.41)	1.51 (0.27–8.59)
Printing (22.0)	2 (2.3%)	7 (2.2%)	0.94 (0.19–4.69)	0.99 (0.20–4.93)
Chemical industry (24.0)	9 (10.5%)	17 (5.4%)	2.43 (0.96–6.16)	2.69 (1.02–7.09)
Manufacture of machinery, electrical equipment and transport equipment (29.0–35.0 except 32.0)	15 (17.4%)	51 (16.1%)	1.15 (0.61–2.17)	1.19 (0.61–2.33)
Motor vehicle repair (50.0)	4 (4.7%)	20 (6.3%)	0.73 (0.24–2.17)	0.73 (0.24–2.21)
Agriculture, hunting and forestry (01.0 and 02.0)	18 (20.9%)	59 (18.7%)	1.18 (0.63–2.22)	1.28 (0.64–2.57)
Woodwork (6.3, 7.31, 7.32, 8.1 and 9.54)	9 (10.5%)	27 (8.5%)	1.34 (0.57–3.17)	1.40 (0.57–3.45)
Construction (45.2–45.4)	12 (14.0%)	53 (16.8%)	0.81 (0.40–1.62)	0.84 (0.40–1.76)
Textile workers (17.0 and 18.0)	7 (8.1%)	13 (4.1%)	2.48 (0.81–7.59)	2.47 (0.76–8.02)
Manufacture of food products, beverages and tobacco (15.0)	8 (9.3%)	11 (3.5%)	2.68 (1.07–6.68)	2.71 (1.04–7.06)
Health and social work (85.1–85.3)	11 (12.8%)	23 (7.3%)	1.94 (0.77–4.91)	2.52 (0.96–6.62)
Health work (85.1 and 85.2)	8 (9.3%)	16 (5.1%)	1.99 (0.86–4.63)	2.33 (0.97–5.62)

Statistically significant results are in bold.

*Adjusted for tobacco smoking divided into four classes, and for BMI divided into three classes.

Table 4. Risk of RCC by job title (ILO 68 code): percentages and conditional logistic regression, matched for gender and age

Jobs title (ILO 68 Code)	Cases	Controls	Crude OR (95% CI)	Adjusted OR* (95% CI)
Metal workers: Machine-tool operators, machinery fitters (8.3 & 8.4)	25 (29.1%)	92 (29.1%)	1.04 (0.61–1.79)	1.00 (0.56–1.77)
Welders—plumbers, sheet metal workers (8.7)	3 (3.5%)	21 (6.7%)	0.53 (0.15–1.87)	0.59 (0.16–2.16)
Electrical and electronics laborers (8.5)	4 (4.7%)	20 (6.3%)	0.74 (0.24–2.27)	0.86 (0.26–2.88)
Electrical and electronics workers, any level (0.23, 0.34 & 8.5)	4 (4.7%)	23 (7.3%)	0.64 (0.21–1.93)	0.74 (0.23–2.41)
Launderers, dry-cleaners and pressers (5.6)	3 (3.5%)	3 (0.9%)	3.81 (0.77–18.94)	2.75 (0.54–13.99)
Printers (9.2)	2 (2.3%)	4 (1.3%)	2.00 (0.37–10.92)	2.16 (0.37–12.58)
Painters—construction and industry (9.3)	1 (1.2%)	7 (2.2%)	0.57 (0.07–4.64)	0.43 (0.05–3.74)
Scientific workers: researchers, engineers and technicians in physics, chemistry and biology (0.1, 0.2, 0.3 & 0.5)	6 (7.0%)	23 (7.3%)	0.97 (0.36–2.57)	1.00 (0.37–2.71)
Construction workers [9.5 (except 9.54)]	8 (9.3%)	17 (5.4%)	1.93 (0.80–4.66)	2.03 (0.82–5.04)
Woodworkers—any stage of wood processing (6.3, 7.31, 7.32, 8.1 & 9.54)	6 (7.0%)	22 (7.0%)	1.00 (0.37–2.70)	1.01 (0.34–2.97)
Farming (6)	19 (22.1%)	59 (18.7%)	1.25 (0.66–2.68)	1.33 (0.66–2.69)
Sales workers (40–45)	11 (12.8%)	65 (20.6%)	0.59 (0.30–1.17)	0.58 (0.29–1.17)
Food and beverage processors (77)	7 (8.1%)	14 (4.4%)	1.72 (0.69–4.32)	1.70 (0.64–4.51)
Building caretakers and cleaners (55)	6 (7.0%)	16 (5.1%)	1.40 (0.49–4.02)	1.52 (0.50–4.60)
Drivers (9.8)	4 (4.7%)	19 (6.0%)	0.84 (0.28–2.51)	0.86 (0.26–2.85)
Medical and related workers (0.6 & 0.7)	4 (4.7%)	7 (2.2%)	2.18 (0.60–7.85)	3.99 (1.06–15.03)
Administrative workers of any level (3.0)	22 (25.6%)	87 (27.5%)	0.85 (0.47–1.52)	0.77 (0.40–1.47)

Statistically significant results are in bold.

*Adjusted for tobacco smoking divided into four classes and for BMI divided into three classes.

difference was of borderline significance (crude OR = 1.60 (0.95–2.69); adjusted OR = 1.64 (0.95–2.84)) (Table 6).

The cumulative dose tertiles defined on controls' exposure were 1–150 p.p.m. × years,

155–335 p.p.m. × years and more than 335 p.p.m. × years, respectively, classified as low, medium and high cumulative doses. Among controls the median of exposure was 60, 252 and 630 p.p.m., respectively. Among cases the figures were 30, 300 and 885 p.p.m.,

Table 5. Other occupational exposures: descriptive data and conditional logistic regression (matching on sex and age)

Exposure	Cases	Controls	OR (95% CI)	P
Solvents				
Chlorinated (other than TCE)	9 (10.5%)	25 (7.9%)	1.48 (0.65–3.36)	0.35
Petroleum derivatives	27 (31.4%)	112 (35.4%)	0.87 (0.51–1.50)	0.51
Oxygenated	14 (16.3%)	37 (11.7%)	1.52 (0.75–3.09)	0.24
Other	1 (1.2%)	7 (2.2%)	0.55 (0.07–4.47)	0.58
Oils				
Cutting fluids				
Any level	25 (29.1%)	70 (22.2%)	1.60 (0.93–2.77)	0.09
Low	11 (12.8%)	26 (8.2%)	1.80 (0.85–3.79)	0.12
Medium	4 (4.7%)	11 (3.5%)	1.79 (0.47–6.81)	0.39
High	10 (11.6%)	33 (10.4%)	1.37 (0.62–3.03)	0.44
Other petroleum oils				
Any level	16 (18.6%)	40 (12.7%)	1.74 (0.90–3.37)	0.10
Low	14 (16.3%)	27 (8.5%)	2.24 (1.10–4.56)	0.03
Medium	2 (2.3%)	10 (3.2%)	0.89 (0.18–4.34)	0.89
High	0	3 (1.0%)	-	
Welding				
Brazing	6 (7.0%)	23 (7.3%)	1.00 (0.40–2.50)	1.00
Other	15 (17.4%)	49 (15.5%)	1.21 (0.62–2.36)	0.56
Lead	12 (14.0%)	40 (12.7%)	1.19 (0.59–2.39)	0.63
Cadmium	8 (9.3%)	16 (5.1%)	2.00 (0.79–5.12)	0.15
Asbestos	20 (23.3%)	67 (21.2%)	1.22 (0.67–2.25)	0.51
Ionizing radiation (source)	5 (5.8%)	7 (2.2%)	2.53 (0.75–8.56)	0.14

Statistically significant results are in bold.

Table 6. Relation between exposure to TCE and RCC as a function of the three indicators [Conditional logistic regression (matching on sex and age)]

	Cases	Controls	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
Exposed to TCE during at least one job period				
Non-exposed	49 (57.0%)	206 (65.2%)	1	1
Exposed	37 (43.0%)	110 (34.8%)	1.60 (0.95–2.69)	1.64 (0.95–2.84)
Cumulative dose^b				
Non-exposed	49 (57.0%)	206 (65.2%)	1	1
Low	12 (14.0%)	37 (11.7%)	1.51 (0.71–3.17)	1.62 (0.75–3.47)
Medium	9 (10.5%)	36 (11.4%)	1.16 (0.51–2.65)	1.15 (0.47–2.77)
High	16 (18.6%)	37 (11.7%)	2.23 (1.09–4.57)	2.16 (1.02–4.60)
Cumulative dose plus peaks				
Non-exposed	49 (57.0%)	206 (65.2%)	1	1
Low/medium No peaks	18 (20.9%)	65 (20.6%)	1.27 (0.68–2.39)	1.35 (0.69–2.63)
Low/medium + peaks	3 (3.5%)	8 (2.5%)	1.88 (0.44–8.08)	1.61 (0.36–7.30)
High No peaks	8 (9.3%)	23 (7.3%)	1.84 (0.73–4.69)	1.76 (0.65–4.73)
High + peaks	8 (9.3%)	14 (4.4%)	2.70 (1.09–6.67)	2.73 (1.06–7.07)

Statistically significant results are in bold.

^aAdjusted for tobacco smoking divided into four classes, and for BMI divided into three classes.

^bTest for trend: cumulative dose ($P = 0.04$).

respectively. A significantly increased risk of RCC was identified for the highest cumulative dose: the adjusted OR was 2.16 (1.02–4.60). A significant trend was also identified between cumulative dose and RCC risk ($P = 0.04$).

When considering the combined effect of cumulative and peak exposure, the OR for any given cumulative exposure class was higher when peak exposures were also experienced. However, only for high cumulative dose plus peaks was a

significant increase in adjusted OR observed [OR = 2.73 (1.06–7.07), compared with the non-exposed group] (Table 6). Moreover the OR for exposed with peaks was not significantly elevated compared with exposed without peaks (corresponding contrast not significant).

Exposure to TCE was strongly associated with exposure to cutting fluids and petroleum oils. About 90.3% of subjects exposed to cutting oils were also exposed to TCE, and 57.9% of those exposed to TCE were exposed to cutting oils. For other petroleum oils, 83.6% of subjects exposed to other oils were also exposed to TCE, and, conversely, 31.7% of those exposed to TCE were also exposed to other oils. When exposure to cutting fluids and to other petroleum oils were added to the conditional logistic regression model, the OR for RCC in the highest class of cumulative TCE exposure was reduced to 1.96 (0.71–5.37). When considering the combined effect of cumulative and peak, the OR for the high-exposure group with peaks was 2.63 (0.79–8.83), after adjusting for smoking, BMI and exposure to cutting fluids and other petroleum oils. This result was similar to the RCC risk observed for this class in the model presented in Table 6.

To assess the impact of including deceased patients (proxy interviews) and elderly patients (>80 years of age), a specific analysis was performed including only alive patients <80 years of age. Moreover, only job periods with a high level of confidence with respect to TCE exposure were considered here as exposure periods. The analysis concerned 60 cases and 225 controls. Results are presented in Table 7. A total of 16 (26.7%) cases were exposed to TCE, as against only 37 (16.4%) controls. The difference in

TCE exposure history was substantial for the highest cumulative exposure doses; 18.3% of cases were in the high cumulative TCE dose range, as against only 7.1% of controls, adjusted OR = 3.34 (1.27–8.74). The same is true for the highest cumulative dose plus peaks: 11.7% of cases were in this group as against only 3.6% of controls, adjusted OR = 3.80 (1.27–11.40).

DISCUSSION

This case-control study, carried out in a geographic area where occupational exposure to TCE was known to be frequent, provides new information on the possible association between TCE exposure and RCC.

As there is no cancer register in the local area, recruitment was done with the help of the urologists of the area who usually treat this disease and also of urologists and oncologists from the nearest teaching hospitals (Lyon, Grenoble and Geneva). However, a few cases living in the geographic area may have been treated by other practitioners, in private clinics in Lyon or Grenoble, or in the teaching hospitals in Paris, and, to rule out any consequent selection bias, controls were selected from the list of the case-patient's urologist or general practitioner. Moreover, after obtaining lists of patients matching criteria of age, sex and place of residence, a selection was randomly performed using a table of random numbers. On the contrary, a bias due to overmatching may have occurred, as cases and controls often came from exactly the same towns and might, therefore,

Table 7. Conditional logistic regression considering only job periods with a good level of confidence for TCE exposure assessment: confidence score 2 or 3 and periods described with the screw-cutting questionnaire

	Cases (n = 60)	Controls (n = 225)	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Ever Exposed to TRI				
Non-exposed	44 (73.3%)	188 (83.6%)	1	1
Exposed	16 (26.7%)	37 (16.4%)	2.09 (1.03–4.26)	1.88 (0.89–3.98)
Cumulative dose				
Non-exposed	44 (73.3%)	188 (83.6%)	1	1
Low	1 (1.7%)	8 (3.6%)	0.69 (0.08–5.82)	0.85 (0.10–7.41)
Medium	4 (6.7%)	13 (5.8%)	1.36 (0.42–4.41)	1.03 (0.29–3.70)
High	11 (18.3%)	16 (7.1%)	3.57 (1.42–8.99)	3.34 (1.27–8.74)
Cumulative dose plus peaks				
Non-exposed	44 (73.3%)	188 (83.6%)	1	1
Low/medium No peaks	4 (6.7%)	18 (8.0%)	1.03 (0.33–3.23)	0.90 (0.27–3.01)
Low/medium + peaks	1 (1.7%)	3 (1.3%)	1.84 (0.18–18.44)	1.34 (0.13–14.02)
High No peaks	4 (6.7%)	8 (3.6%)	2.97 (0.77–11.37)	2.74 (0.66–11.42)
High + peaks	7 (11.7%)	8 (3.6%)	4.16 (1.45–12.00)	3.80 (1.27–11.40)

Statistically significant results are in bold.

Only living patients <80 years of age were considered.

^aOR matched for sex and age.

^bOR matched for sex and age, adjusted for tobacco smoking divided into four classes, and for BMI divided into three classes.

tend to run a very similar risk of exposure to TCE or other such occupational exposures. Cases and controls were all patients (they all had been treated for a disease by the physician who included them), and the study was presented to them as an epidemiological study analyzing the link between occupation and disease in general; they were not aware of their 'case' or 'control' status, and measurement bias is not likely. However, a measurement bias may have happened for deceased cases as the rate of deceased controls was lower than that of cases and the quality of information collected from the proxy of an alive or of a deceased subject is probably different. To assess any impact of interviewer bias a specific analysis was performed, excluding deceased cases and matched controls.

Another well-known form of bias in case-control studies is interviewer bias. In the present study, prior telephone contact and appointments were all coordinated by a research unit physician, and the medical questionnaire was not administered until the end of the interview, so that the interviewer was blind to the patient's medical status up to that time. One exception to this rule was interviews of the next-of-kin of living controls when the corresponding case was deceased.

The participation rate was good for such a mainly retrospective study, at 74.4% for cases and 78.2% for controls.

The majority of cases were male (69%), which is similar to sex ratios for RCC observed by others (Yu *et al.*, 1986; Motzer *et al.*, 1996; Marshall *et al.*, 1997). Estimates from both cohort and case-control studies place cigarette smokers at about twice the risk level of non-smokers for developing RCC (La Vecchia *et al.*, 1990; McCredie and Stewart, 1992a; Kreiger *et al.*, 1993). The present study found a higher frequency of tobacco smoking history among cases, the OR for tobacco smoking amounting to 1.84 (1.04–3.25). Some studies have reported a dose-response relationship to the quantity of cigarettes smoked (La Vecchia *et al.*, 1990; Mellemegaard *et al.*, 1994b). In a study conducted by Mellemegaard *et al.* (1994b), total consumption of >40 pack-years was associated with an increased risk compared with non-smokers: the OR was 2.3 (1.1–5.1). In the present study, a dose-effect relation was found between RCC and smoking ($P < 0.001$). For the highest class (>40 pack-years), the OR was 3.27 (1.48–7.19).

McCredie and Stewart (1992b) found risk to increase with BMI, with the highest risk in the upper tertile (BMI >23.3 for men and >30.8 for women). This increasing risk was also found by other authors (Wynder *et al.*, 1974; Asal *et al.*, 1988). In the present study, increased risk of RCC was identified for a BMI of ≥ 30 , indicating a link between obesity and RCC.

Other non-occupational factors for RCC have been identified. Associations have been reported with kidney stones and kidney infection (McLaughlin *et al.*, 1984), and with chronic dialysis (Motzer *et al.*, 1996). In the present study, no significant differences emerged between cases and controls for these factors owing to selection of non-RCC patients from urologists.

Diagnosed hypertension also seems to raise the risk of RCC (Vogelzang and Stadler, 1998), as do anti-hypertensive drugs. McCredie *et al.* (1992b) found a risk ratio of 1.8 (1.3–6.6) for β -blockers and of 1.6 (1.1–2.4) for α -blockers. In the present study, irrespective of the variable considered (diagnosed hypertension, or treatment for hypertension), there was no significant difference between cases and controls. Diuretics, analgesics, phenacetin or paracetamol have also been suspected of increasing the risk of RCC (Lindblad *et al.*, 1993; McCredie *et al.*, 1993). The present study, however, did not identify any significant difference between the two groups for these factors. In the aforementioned studies, controls were recruited from the general population, whereas in the present study controls were physicians' patients, with a greater probability of being ill and taking medication.

Mattioli *et al.* (2002) found an increased RCC OR of 2.21 (0.99–5.37) for metalworkers. In the consecutive case-control study carried out in Germany by Brüning *et al.* (2003), any exposure in metal degreasing was an RCC risk factor: the OR was 5.57 (2.33–13.32). In the present study, no significant difference was observed between cases and controls regarding employment in industries associated with potential TCE exposure, such as manufacture of metal products and metalwork involving possible cleaning. Cases tended more often to have been working in the screw-cutting industry and metal-product manufacturing than controls, but these differences were not significant. Significant results only appeared for TCE exposure as such.

The chemical industry appeared to be associated with an increased risk of RCC: 10.5% of cases worked in such branches, compared with 5.4% of controls: the OR was 2.66 (1.02–6.91).

A few differences between cases and controls were found on analysis of coded job titles (ISCO, 1968). An increased risk of RCC was identified for laundriers, dry-cleaners and pressers; but because of the low number of patients concerned, the difference failed to attain significance: the OR was 2.75 (0.54–13.99). Nevertheless, these results are in agreement with the increased risk of RCC for people exposed to chlorinated solvents previously described in several studies (McCredie and Stewart 1993; Mellemegaard *et al.*, 1994a; Mandel *et al.* 1995).

The main occupational exposures described in the literature as increasing the risk of RCC were assessed

in the present study: solvents, oils, welding fumes, metals and asbestos. No association between RCC and these exposures was found to be significant at the 5% threshold, although maybe in some cases simply because of a lack of statistical power. Two associations with renal cancer, for cutting fluids and other petroleum oils, did reach the 10% threshold, and these exposures were taken into account in the conditional logistic regression, as were tobacco smoking habits and BMI.

In the present study the OR between RCC and TCE exposure was 1.6 and did not reach statistical significance. A statistically significantly increased RCC risk was only observed in the high TCE dose category. Allowing for tobacco smoking and BMI, a significantly 2-fold increased risk was shown for high cumulative doses: the OR was 2.16 (1.02–4.60). A dose-response relationship was also identified, as was an effect of peak exposure. The adjusted OR for the highest class of cumulative exposure plus exposure to peaks was even higher, at 2.73 (1.06–7.07).

After adjustment for exposure to cutting fluids and other petroleum oils, the increased risk of RCC linked with the highest cumulative dose was still high but no longer statistically significant. Indeed, many patients had been exposed to TCE in screw-cutting workshops, where cutting fluids are widely used, making it difficult to distinguish between cutting oil and TCE effects. However, modeling all factors significant at the 10% threshold showed the OR for cutting oils to be almost equal to 1, whereas the OR for the highest level of exposure to TCE was close to two. Moreover, when exposure to cutting oils was divided into three levels, a decrease in OR with level of exposure was found. A link between RCC and exposure to cutting oils has already been identified in a case-control study (Brüning *et al.*, 2003), with an OR of 4.92 (1.70–14.27). However, the analyses of this study did not take into account exposure to TCE.

For deceased cases and their controls, the interviews were performed with a next of kin and this may have led to a misclassification for exposure to TCE due to the lower levels in the quality of information collected. The same was true for job periods assessed with the general occupational questionnaire. To address this issue a specific analysis has been performed including subjects and job periods for which data were confident enough. The ORs obtained were even higher. Whereas it is not always true (Jurek *et al.*, 2005), in this case the misclassification bias may have led to an underestimation of the risk.

The results of the present study do not corroborate those obtained by most of the cohort studies carried out to investigate the association between TCE exposure and RCC that have shown no statistically significant increase in risk (Axelson *et al.*, 1994; Anttila *et al.*, 1995; Blair *et al.*, 1998; Morgan *et al.*, 1998; Boice

et al., 1999), probably because of the lower levels of TCE exposure in these cohort studies. The comparison between the exposure levels identified in the present study and other epidemiological populations indicates that our study population was in an intermediate situation in terms of TCE exposure (see exposure assessment part). Nevertheless, some cohort populations, and especially that in the German cardboard factory, have shown higher exposure. These differences in levels of exposure could partly explain the differences observed between the present study and those carried out in Germany by Brüning and Vamvakas.

CONCLUSIONS

The present study provides new information on an association between occupational TCE exposure and increased risk of renal cell carcinoma, although the overall degree of association did not reach statistical significance. The association seemed to be less strong than previously reported by certain epidemiological studies conducted in Germany and concerned only the highest exposure levels. After adjustment for the confounding effect of tobacco smoking and BMI, a significantly 2-fold increased risk was found for high cumulative doses OR = 2.16 (1.02–4.60), and a dose-response relationship was identified. A history of exposure to TCE peaks also increased the risk of RCC, OR = 2.73 (1.06–7.07) for high cumulative doses plus peaks. When focusing on information of high confidence level, the risks identified were even higher, for high cumulative doses OR = 3.34 (1.27–8.74) and when including peaks OR = 3.80 (1.27–11.40). The results of the present study do not agree with the negative results obtained by a number of large cohort studies. Higher levels of exposure were found in the screw-cutting industry of our study population than in most of the cohort studies, although higher exposure levels were probably experienced in several of the workplaces included in the epidemiological studies conducted in Germany. Although this study shows a possible link between high levels of exposure to TCE and increased risk of RCC, further epidemiological studies are necessary to assess the effect of lower levels of exposure.

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