Case-control study on renal cell cancer and occupational trichloroethylene exposure, in the Arve valley (France). Final report

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FINAL REPORT

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Abstract

Objectives: A case-control study was performed in a geographic area with a high frequency and degree of exposure to trichloroethylene (TRI), to test the effect of such exposure on Renal Cell Cancer (RCC) risk. A method for a semi quantitative retrospective assessment of exposure to trichloroethylene (TRI) was implemented using the large quantity of well-documented measurements collected by teams of occupational physicians from the Arve Valley.

Material and methods: The main occupational exposures described in the literature as increasing the risk of RCC were studied, as were the general and medical factors. A Task-Exposure Matrix was developed to link the main working circumstances in a screw-cutting workshop to corresponding TRI-exposure levels: a 'basic level' was assigned to each task, standing for usual working procedures; exposure circumstances, such as duration or distance from the TRI-source, were introduced as corrective factors.

In parallel, all 402 study subjects (86 cases and 316 controls matched for age and gender) described their successive jobs and working circumstances in a detailed questionnaire, setting subjects' descriptions against levels assessed in the matrix. An average level of exposure to TRI was attributed to each job-period in turn, which was then categorized into 6 classes: 0; 5-35; 35-50; 50-75; 75-100; and >100 ppm. Thus 19% of the 1,486 job periods described were assessed as being exposed to TRI; of these, 13.2% were up to 50 ppm.

Three main approaches were developed to assess the link between TRI exposure and RCC: exposure to at least 5 ppm for at least one job period (minimum one year), cumulative dose (number of ppm of TRI 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.

Results: An increased risk of RCC emerged with increasing Body Mass Index (Odds Ratio = 1.98 [1.01; 3.86] when BMI $\geq$ 30.0) and with increasing consumption of tobacco (OR = 3.27 [1.48; 7.19] for total consumption of more than 40 pack-years). Allowing for tobacco smoking and Body Mass Index, a significantly (twofold) increased risk was shown for high cumulative doses: 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]. When adjusted for exposure to cutting fluids, these ORs, although still high, were not significant.

Conclusion: This study suggests that there is a weak association between exposures to TRI and increased risk of RCC. Compared with levels encountered in other studies, the more severely exposed part of our study population seems more exposed than most other populations previously studied, due to vapor degreasing practices. This could explain the significant increase in risk observed in our epidemiological study in contrast to other studies in the general population.

Contents

1 Introduction

Trichloroethylene (TRI) is a solvent used in numerous industries, as a degreaser in metal manufacturing, as a solvent for oils and resins, and in the production of rubber. It was used in dry-cleaning and as an anaesthetic drug during the 1960s. Several cohort studies have been carried out to investigate the health impact of TRI [1,7,11]. Findings regarding linkage between TRI exposure and renal cell cancer (RCC) were discordant. Some case-control studies found an increased odds ratio (OR) for exposure to dry-cleaning solvents [61, 53,48]. A cluster investigation conducted in a cardboard factory and a case-control study conducted in the same area in Germany found RCC increased significantly with occupational TRI exposure [34,80]. As these results did not corroborate results from other studies, a scientific polemic arose. Indeed, the first cohort study by Henschler et al. was initiated after diagnosis of a cluster of renal cell cancers. A case-control study was carried out in the same area, but excluding the cases from the cohort study. In the latter study, controls came from a slightly different geographic area and were younger and therefore tended to show a different pattern of exposure to high levels of TRI [29]. According to Vamvakas et al., 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 [81,82]. Cherrie et al. [16] made comparisons between the exposure rates measured in the studies by Blair et al. and by Vamvakas et al. and Henschler et al. They concluded that any differences in the TRI exposure intensity in these various studies could not account for the differences in risk observed. A working group convened by IARC in 1995 assessed the study by Henschler et al. but did not judge it relevant to the evaluation of TRI carcinogenicity in humans [IARC vol. 63 1995 p 134], mainly because of its cluster design.

For these reasons a new case-control study was performed in a geographic area with a high prevalence and degree of exposure, testing the effect of exposure to high levels of TRI over a long period. The Arve valley in France was of special interest for such a study as a screw-cutting industry was stronglydeveloped there before the Second World War, using TRI as a degreasing (“washing”) agent. For example, in 1982, 13,000 workers were employed in the screw-cutting industry, using 1,300 tonnes of TRI per year. In 1993, 2,000 tonnes were used for 14,600 workers. Another aspect which suited the choice of the population of this valley for such a study were the high exposure levels occurring over many years. Occupational physicians had published reports on workers in which the subjective symptoms described by Henschler et al. and Vamvakas et al. [10]. Independent data on exposure were readily available for this study, including both biomonitoring and atmospheric data.

Study design: a population-based case-control study in the area of the Arve valley (France).

Objectives: to test the hypothesis of a link between extended exposure to high levels of trichloroethylene and risk of RCC.

2 Bibliography

2.1 Non-occupational factors for renal cell cancer

Renal cell cancer accounts for an estimated 95,000 deaths per year world-wide [87]. Men show two or three times as high a risk as women [50]. The median age at diagnosis is 65 years. No single risk factor seems dominant and several environmental or genetic factors could be synergistically carcinogenic. The risk of RCC is higher for people in the lowest socio-economic band [62]. Cigarette smoking is a risk factor found in several epidemiological studies on RCC [51 44,41]. An odds ratio (OR) of 2.3 [1.1; 5.1] was found in Denmark for male cigarette smokers with a total consumption of over 40 pack-years compared with non-smokers [62]. La Vecchia et al. [44] observed a significant dose-risk relationship among current smokers, with risk ratios (RR) of 1.1, 1.9, and 2.3 for moderate, intermediate, and heavy smokers respectively. The risk was directly related to duration of smoking and inversely to age at starting. On the basis of the calculation of attributable risks, it was estimated that 30% of RCCs in men and 24% in women were due to smoking habits. A case-control study conducted by Kreiger et al. [41] showed a non-significant increase in RCC frequency in people exposed to passive smoking. The OR was 1.6 [0.5; 4.7] in men and 1.7 [0.8; 3.45] in women. The risks involved in the use of alcoholic beverages, coffee or tea have been investigated in a number of studies. A few studies found an increased risk of RCC with coffee consumption [93]. The OR for decaffeinated coffee consumption in men and women combined was 1.9 [1.0; 3.8] in a case-control study including 267 cases conducted between 1977 and 1983 in 18 hospital centres in the USA [28].

Various urological conditions have been implicated in the etiology of renal parenchyma cancer. Associations have been reported with kidney stones and infection [56], chronic dialysis [65], and diagnosed hypertension [55, 87]. A link exists between RCC and high blood pressure, but it is unclear whether this condition contributes, directly or indirectly, to the causation of RCC, rather than itself resulting from RCC. Anti-hypertensive drugs were also found to be a risk factor for RCC. McCredie et al. found an RR of 1.8 [1.3; 6.6] for β-blockers and 1.6 [1.1; 2.4] for α- blockers (RR adjusted for age, sex, obesity and smoking). Diuretic use also seems to increase the risk of RCC [46]. Several authors studied the link between RCC and analgesic drugs [55,46]. McCredie et al. [55] found similar degrees of increased risk of RCC with phenacetin/aspirin compound analgesics and with paracetamol taken in any form. They postulated that phenacetin/aspirin compounds were weakly carcinogenic for renal parenchyma through the metabolic conversion of phenacetin to paracetamol.

The population attributable risk for hypertension is second only to that for smoking as an etiologic factor in RCC. Obesity, another common problem of modern society, is associated to the same degree. In McCredie's study [54] the risk associated with obesity was assessed by body mass index (BMI) calculated as weight/(height^2) for men and weight/(height$^{1.5}$) for women. There was a rising risk with increasing BMI, with the highest risk seen in the upper tertiles of BMI (>23.3 for men and 30.8 for women). This increasing risk was also found in a number of other studies [87,92,2].

Familial RCC increases the risk fourfold, but only a small fraction of patients have an affected family member [65]. Von-Hippel-Lindau disease is a familial syndrome which predisposes to various cancers including RCC. Renal cysts are frequently bilateral and contain malignant tumours. Nearly 40% of VHL patients develop RCC, which is a major cause of death among these patients.

2.2 Occupational factors for renal cell cancer

2.2.1 Trichloroethylene

Several cohort studies have been carried out to investigate the association between TRI exposure and RCC.

Axelson et al. [4] found no significantly increased RCC rate in a cohort study of 1,670 workers exposed to low-level TRI.

Anttila et al. studied incidence among Finnish workers (2,050 males and 1,924 females) exposed to halogenated hydrocarbons, including TRI, and found no association between TRI and kidney cancer [1]. The standardised incidence ratio (SIR) observed for kidney cancer was 1.2 [0.4; 2.5].

In a cohort of 14,457 aircraft maintenance workers exposed to TRI and other chemicals, kidney cancer incidence was not significantly greater than in the general population of Utah [7]. The ratio for kidney cancer was 1.6 [0.5; 5.4].

A mortality cohort study conducted in California among 77,965 aircraft manufacturing workers found no increased risk of kidney cancer for workers exposed to TRI or perchloroethylene [11].

A slightly elevated rate ratio was found in a study on mortality of aerospace workers exposed to TRI [64]. Among those with peak exposures at medium and high levels, the rate ratio was 1.89 [0.85; 4.23].

A cluster investigation study carried out in a cardboard factory in Germany showed increased RCC incidence [34]. This study included 169 males exposed to TRI for at least one year and 190 unexposed workers from the same factory. The SIR for renal cancer among workers exposed to TRI compared to the cancer register of Denmark was 8.0 [2.6; 8.6] whereas the standardised mortality ratio (SMR) was 3.3 [0.4; 11.8].

A case-control study was performed in the same area but excluding all RCC cases from the previous cluster investigation study [80]: 58 RCC cases and 84 controls from the casualty wards of three general hospitals were included. The OR for exposure, after adjusting for age, gender, smoking, BMI and blood pressure, was significantly increased, at 10.8 [3.4; 34.8]. A significant increase in OR with exposure level was also identified. The controls were patients from the casualty wards of 3 hospitals other than the study hospital, but within a radius of about 20 km of it, and were recruited in 1993 (whereas the cases dated back to 1987-92); this chronological difference may have involved some difference in exposure to high levels of TRI [29]. RCC risk for TRI exposure was then re-evaluated in the same region of Germany, in a consecutive case-control study with cases and controls recruited from the same geographic area [14]. The TRI-related RCC risk was confirmed after adjustment for age, gender and smoking. Working from the CAREX database, a significant excess risk of RCC was found for jobs involving any TRI exposure (OR 1.80 [1.01; 3.20] for the longest-held jobs involving exposure). A significant excess risk was also associated with self-assessed exposure to TRI (OR 2.47 [1.36; 4.49]).

An association between RCC and chlorinated solvents in general was observed in several other case-control studies [48, 53, 61].

2.2.2 Other occupational exposures

Other occupational exposures have been suspected of being associated with RCC. A case-control study in Denmark [61] investigated occupational exposure and RCC in three steps: types of employment (sector), jobs, and job-related occupational exposure (self-reported exposure). Trends towards increased risk were found for employment in oil refineries, gasoline stations and the iron and steel industry. Significantly increased risks were observed for exposure to gasoline or cutting oil, and trends for solvents, asbestos and insecticides or herbicides. Two specific jobs also involved increased risk: truck drivers and plumbers, with respective ORs of 3.1 [1.3; 7.7] and 8.5 [1.1; 66.0].

In a case-control study conducted in New South Wales [53], a significantly raised OR was found in the dry-cleaning business (2.7 [1.1; 6.7]). A trend towards increased risk was found for people working in or with the iron and steel industry, oil refineries, blast furnaces or coke ovens, and for the specific jobs of machinist and machine tool operator. RCC risk ratios associated with occupational exposure were significant for asbestos 1.58 [1.02; 2.44], solvents 1.54 [1.11; 2.14], cutting oils 1.99 [1.23; 2.99] and other petroleum products 1.96 [1.28; 2.99]. After adjustment for sex, age, method of interview, smoking and BMI, significant odds ratios were observed for exposure to asbestos and dry-cleaning activities.

The Danish and Australian results were also included in an international multi-centre population-based case-control study [48]. A total of 1,732 RCC cases were interviewed in Australia, Denmark, Germany, Sweden and the United States. Significant associations were found with employment in blast-furnaces or coke-ovens, with an OR of 1.7 [1.1; 2.2], in the iron and steel industry (OR=1.6 [1.2; 2.2]), and in work involving exposure to cadmium (OR=2.0 [1.0; 3.9]), asbestos (OR=1.4 [1.1; 1.8]), dry-cleaning solvents (OR=1.4 [1.1; 1.7]), or gasoline and other petroleum products (OR=1.6 [1.3; 2.1]).

An increased RCC risk with exposure to petroleum products was observed in cohort studies [74,67]. However, there is no strong evidence from case-control studies [26]. For example, a case-control study conducted in 1985 by McLaughlin et al. [59] found no overall association between RCC risk and exposure to petroleum products. In contrast, gasoline exposure was significantly associated with RCC risk in a case-control study among Finnish residents [66] as observed in other case-control studies [48]; these results, however, are not replicated consistently across studies. A slightly increased risk was mentioned in a review about occupational and environmental exposure to polycyclic aromatic hydrocarbons [9], but results were not significant in most of the studies reviewed [66].

A few North American studies showed a significantly increased SMR for kidney cancer in people exposed to asbestos [22]. A meta-analysis on asbestos exposure and kidney cancer was carried out [70] on a number of cohort studies. A total of 169 kidney cancer deaths and 69 incident cases were included. The overall pooled kidney cancer OR was 1.1 [0.9; 1.6] and was higher for workers with undefined asbestos exposure (1.2 [0.9; 1.6]) than for workers with either predominantly chrysotile (0.9 [0.7; 1.3] or amphibole exposure (0.96 [0.6; 1.5]). Studies with high asbestos exposure and elevated lung cancer SMR tended to show an increased kidney cancer risk as well.

Most toxic metals (arsenic, cadmium, lead and mercury) are known to produce cell injury in the kidney [22] and could induce kidney cancer. Indeed, cadmium and inorganic lead compounds have been presumed to be determinants of kidney cancer. An increased risk was observed for cadmium in a few studies [48], but was not always significant. For example, in a case-control study among Finnish residents [66] the odds-ratio for cadmium exposure was 4.37 [0.4; 43.0]. In the same study, a trend towards increased risk was observed for lead and inorganic lead compounds 2.9 [0.9; 9.7].

In a cohort mortality study among lead-smelter workers, an excess kidney cancer rate was shown in the high lead-exposure group, with an SMR of 2.62 [1.13; 5.16] [73]. A review on this topic identified a trend [25] but estimated that it was impossible either to confirm or rule out an association between kidney cancer and exposure to lead. On the other hand, animal experimental studies provided evidence for the induction of renal adenoma and carcinoma after oral doses of inorganic lead, and an increased RCC risk was found among plumbers.

2.3 Exposure assessment in trichloroethylene studies

Only in a few of the studies on the relationship between RCC and TRI exposure, have exposure levels been determined quantitatively by means of actual measurements [90]. In the incidence study by Antilla et al., [1] exposure was assessed by biological monitoring. Urine concentrations of trichloroacetic acid (U-TCA) were recorded from 1965 to 1982. In addition, workers reported by their employers as TRI-handlers and others reported as TRI poisoning cases were included. The overall median U-TCA was 63µmol/l for women and 48µmol/l for men. Before 1970 the U-TCA was higher in men (80 to 90µmol/l). There were on average 2.5 measurements of U-TCA per individual. No atmospheric data were available on the study population but in the health-and-safety measurements performed by the Finnish Institute of Occupational Health between 1982 and 1985 the concentration of TRI in degreasing was usually less than the health threshold of 50 parts per million (ppm) (8-hour time-weighted average).

In the Swedish cohort, Axelson et al. [4] used mean urinary TCA for all available samples. Exposure time was taken into account as the interval from the year of the first urine sample recorded until the end of employment. In this study, an overwhelming majority of male subjects had quite low TRI exposure, with a mean urinary-TCA level below 50mg/L for 81% of them. According to the authors, this level corresponds to 20 ppm or 110mg/m^3 in the air.

In the cohort mortality study of workers at an aircraft maintenance facility [72], long term employees were interviewed and available industrial hygiene data were collected. As atmospheric levels could not be straightforwardly linked to the relevant work area, exposure to TRI was estimated in terms of tasks. For TRI and mixed solvents, an equation was developed taking into account frequency of use, duration of use, and an index of level to reflect changes in exposure over time based on past reports, all related to an eight-hour workday. To determine cumulative exposure, the index was multiplied by the number of years spent in each job.

Henschler et al. [34] did not have information on atmospheric trichloroethylene or on trichloroethylene metabolites, but interviewed long-term employees to assess exposure levels and conditions. There were three locations, with various types of job associated with TRI exposure: the cardboard machine, the locksmith's area and the electrical workshop. In the cardboard-machine area TRI was widely used to clean the felts and remove grease from machines (surface temperatures sometimes reaching 80° to 120°C), with poor ventilation of the work area. On these tasks, workers often left the work area for a short time to get fresh air. In the locksmith's area and the electrical workshop, TRI was used for degreasing metal parts, manually dipped in cold open baths without protective gloves. TRI was also used to clean the floor, work clothes and workers' hands.

Vamvakas et al. used two types of information to assess exposure level: description of exposure conditions (duration, frequency, intensity) and frequency and type of acute symptoms following exposure, graded from 0 (none) to 3 (severe symptoms such as daze vertigo, severe headache, or nausea such as to prevent the subject remaining exposed). Vamvakas et al. [82] point out that none of the studies on TRI explored the type, frequency and duration of subnarcotic symptoms, as they did in their case-control study.

3 Material and methods

3.1 Study design

3.1.1 Case recruitment

Cases were selected ***retrospectively*** from 1993 to the start of study date, and ***prospectively for*** one year ***up to the end of June 2003*** from ***various*** physicians:

- Local urologists: physicians practising in the High Savoy area (Sallanches, Cluses, Annemasse, Evian, Saint-Julien en Genevois, and Annecy).
- Urologists from other hospitals of the region who might treat patients from the Arve valley: the Lyon Teaching Hospital, the Léon Berard Centre (the Lyon oncology centre), the Grenoble Teaching Hospital and the Geneva Teaching Hospital.

Information on cases was obtained from the urologists: date of birth, date of diagnosis, anatomo-pathological results, date of last consultation, place of residence and name of the family G.P. (Appendix 3).

In order obtain information on the vital status of the patient and not to make the mistake of writing to patients who were deceased, the first contact with the patient was by telephone. Patients were informed about the study and their oral consent was asked for. Then a letter was sent to confirm participation and to obtain written consent (or the consent of their family when the patient was deceased). No mention of cancer or of occupational exposure to TRI was made (to avoid information bias).

Inclusion criteria were:

- Medical diagnosis of primary RCC (with anatomopathologic confirmation), between 1st January 1993 and 30th June.2003;
- Residence in the geographic study area at the date of diagnosis;
- More than 20 years old on diagnosis.

In order to include as many cases as possible, deceased subjects were includable, to ensure the power of the study. In these cases, next-of-kin (of the cases and controls) were interviewed.

Histological aspects

The Ninth International Classification of Disease classifies as number 189 all "malignant neoplasm of kidney and other and unspecified urinary organs" [91]. Number 189-0 is the subgroup dedicated to "Kidney except pelvis". Renal cell cancer is one of the subgroup of kidney cancers, but it is itself made up of subtypes. These subtypes have been described step by step over three decades.

RCC can be classified according to cell type or according to tumour architecture. The Mainz classification seems to be one of the most widely used (Table 1) [21].

In recent years new classifications have appeared considering cytogenetic aspects.

Renal clear cell cancer is often differentiated by authors from the other RCC subtypes because of typical histological aspects (Table 2). As it represents 70% of all RCCs, authors have a tendency to confuse "renal cell cancer" (RCC) and "renal clear cell cancer" (RCCC).

In most studies the International Classification of Diseases is used, taking into account the diseases coded 189-0. This is true for several occupational studies [7,26,34,48]. Some studies use the term renal cell carcinoma: for example, Vamvakas et al. [62,81]; however, no mention of the subtypes of RCC was made by these authors.

In light of the above, it was decided to include all RCC subtypes in the study.

Table 1: The Mainz Classification of Renal Cell Tumours [21]

Tumour type	Relative frequency
Renal Cell Carcinoma	
- Clear cell	70%
- Chromophil (eosinophil, basophil)	15%
- Chromophobe (typical, eosinophil)	5%
Collecting Duct Carcinoma	2%
Renal oncocytoma	5%

Table 2: Histological and cytogenetic features of Renal Cell Carcinomas [21]

Tumour type	Histopathology	Cytogenetics
Clear Cell RCC	- Compact alveolar, tubular, and cystic architecture. - Clear cytoplasm, low N:C ratio - Vascular stroma	3p loss 3:8 reciprocal translocation 5q gains
Chromophil RCC*	- Papillary architecture with aggregates of foamy histiocytes - Basophil cytoplasm and low N:C ratio or eosinophil cytoplasm and high N/C ratio	Trisomy and tetrasomy 7 & 17 Loss of Y chromosome
Chromophobe RCC	- Compact solid architecture - Clear or eosinophil cytoplasm - Prominent cell membranes - Great variability in cell size - Positive colloidal iron stain - 150-300 nm cytoplasmic microvesicles	Loss of chromosomes 1, 2, 6, 10, 13, 17, & 21
Collecting duct carcinoma	- Medullary location - Tubular and glandular architecture - Hobnail cells - Desmoplasmic stroma	Loss of chromosomes 1, 6, 14, 15, & 22

*** Also called tubulopapillary RCC**

3.1.2 Controls

In a first version of the protocol we had proposed including controls from the general population. The scientific committee, however, asked us to include patients treated by the same urologist who had treated the case. For patients treated in teaching hospitals or in Annecy Hospital, it was not possible to find such controls, so the controls were recruited among the patients of the case's general practitioner.

Inclusion criteria were:

- to have been living in the geographic study area at the time of diagnosis of the case's disease:
- to have been born the same year (±2 years) as the case;
- to match the corresponding case for gender.

Exclusion criteria were:

- failure to fulfil any inclusion criterion, including living outside of the geographic study area when the disease of the case was diagnosed;
- having been treated for kidney or bladder cancer.

Lists of patients were obtained from computerized files or using medical files (for GPs). From the list of patients who corresponded to the matching criteria, selection was made using a random number table.

Like the cases, controls were first contacted by telephone. Patients were informed about the study and their consent was requested. Then a letter was sent to confirm participation and to obtain written consent (or that of their family when the patient was deceased).

Four controls were selected for each case. A maximum of 12 people were contacted to try to recruit the 4 controls.

3.1.3 Geographic area

The upper Arve valley is mainly devoted to tourism, with very few people in a position to work in the local screw-cutting industry; therefore it was necessary to define a geographical area adapted to this epidemiological study, with the prevalence of exposure as main criterion (Appendix 1). On this basis, a precise list of villages and towns located in the geographic area and concerned by the epidemiological study was drawn up (Appendix 2).

According to the most recent population census, 160,000 women and men over 20 years old were living in this area when the study started. According to occupational physicians in the valley, 15,000 were working in the screw-cutting industry. Therefore, the current prevalence of exposure was at least 9.4%. Though it remains difficult to give more precise numbers without data about ages and turnover in the industry, estimations about still active workers who had left screw-cutting, plus retired from the industry, showed **a current prevalence of around 15% to 20% of people who were or had at some time been involved in screw-cutting in the region**.

3.2 Exposure assessment

3.2.1 General strategy for the exposure assessment

➢ The occupational questionnaire (appendix 5)

An occupational questionnaire was designed to help all study subjects (cases and controls) to describe their successive jobs accurately:

The first part of the occupational questionnaire was devoted to the respondent's Job History, listing any job (either in screw-cutting or in any other field) s/he had held after leaving school until the date of the interview, or retirement.

After the Job History, subjects were asked to describe each job in turn, either with the support of a Screw-Cutting Questionnaire (SCQ, Appendix 5) if the job was related to that business, or of a General Occupational Questionnaire (GOQ, Appendix 4), if not.

The GOQ and SCQ followed the same structure:

- some questions devoted to the company (name, address, activity and size);
- list of main tasks and working conditions (duration, etc.);
- description of the workshop and other workers;
- some questions devoted to possible exposure to other occupational risk factors for RCC (asbestos, cutting oils, etc.);

- as many activities or jobs might involve exposure to TRI (textile cleaning, or metal cleaning in workshops other than screw-cutting), the GOQ, like the Screw-Cutting Questionnaire, asked about possible exposure to solvents in general, and to TRI in particular, and for a description of working conditions.

General plan of the occupational part of subject's interview:

Step1: fill in the Job History form:
Job 1 / starting-year 1 to ending-year 1
Job 2 / starting-year 2 to ending-year 2
...
Job x / last Job / last starting-year to last ending-year (= year of interview or retirement)

Steps 2 to x: for each job in turn, fill in:
General Occupational Questionnaire 1 or Screw-Cutting Questionnaire 1
+ General Occupational Questionnaire 2 or Screw-Cutting Questionnaire 2
...
+ Last General Occupational Questionnaire or Last Screw-Cutting Questionnaire x

To optimise collection of occupational information, the interviewer received some occupational assessment training: an in-depth look at the Occupational Questionnaires (explanations on technical words, synonyms, etc.) and some visits to screw-cutting workshops, to visualise the main tasks.

➢ Occupational information given to the assessor:

Subject identification:
All subjects were identified by a number composed of:
the identification number attributed to the physician who provided the case and controls;
+ an identification number related to each such group of 5 subjects (1 case, 4 controls);
+ a final number, from 1 to 5, randomly attributed to each subject in the group of 5
E.g.: *02 0101 / 02 0102 / 02 0103 / 02 0104 / 02 0105*
= five subjects provided by local urologist number 2, one being a case.

Personal information given to the assessor:
birth: date and place;
year of leaving school and highest qualification;
military service (compulsory for men in France): dates and jobs done in the army.

Occupational information given to the assessor:
The occupational history, starting from the first job or technical studies;
+ for each job: either a GOQ, or an SCQ.

➢ Strategy of the occupational assessment (see the general plan, Appendix 8)

STEP I:

Knowing that control recruitment in the general population is always longer and less easy than case recruitment, we decided not to assess new subjects consecutively: over one year of recruitment, such a strategy would tend to reduce consistency between the first assessments comprising more cases and the latest assessments of more controls; therefore subjects were sorted into groups, each including one case and the corresponding four (or sometimes less, but at least one) controls, and the first round of the assessment was only made the whole group of 5 subjects was constituted. In this way, the final percentage of cases and controls was respected, as well as the comparability in the assessment of a case and the corresponding controls. Moreover, in the first step of the occupational assessment, the career of each subject in the group was first examined job period by job period, so as to get a detailed overview of the whole job history.

For each job in turn, the employer's activity and the job title were encoded (NACE Rev 2, and ISCO 1968 respectively) and a qualitative assessment (no/possible/probable/definite exposure to a low/medium/high level) was made of all exposures except to TRI.

The occupational exposures in question (see Appendix 9) were those forecast in the protocol as plausible causes of RCC [48, 61, 88, 25], and as their prevalence looked high enough in our study population: an industrial population mainly involved in metal working is likely to be exposed to other solvents (chlorinated as well as petroleum solvents), to metals and especially cadmium (some workshops in the valley were involved in nickel, chromium and cadmium plating), and obviously to mineral oils (cutting fluids are a wide source of exposure, used as coolants in screw-cutting), and to asbestos. In addition, some other exposures were added:

- solvent and oil exposure was examined in detail;
- the presence of a source of ionising radiation was added when we saw that one employer in the area (CERN, in Geneva) might tend to increase the prevalence of this form of exposure in the study population;
- and finally we added exposure to welding fumes, which appeared in the literature as a new etiological hypothesis after the beginning of our study. For welding tasks, a new question was introduced into the occupational questionnaire, but answers were not communicated to the assessor, so as to be able to validate the first blind assessments of that particular exposure.

Unlike in the case of TRI, all these other exposures were merely assessed as exposed/non-exposed, from the job descriptions, and from relevant questions introduced into the occupational questionnaires.

For TRI assessment, on the other hand, Step I was only seen as a filter to dispatch jobs (already assessed for the other exposures) into 3 categories:

(1) Firstly, in order to ensure consistency in the screw-cutting assessment, all job periods in screw-cutting workshops were collected for Step II.

This category comprised jobs described in the Screw-Cutting Questionnaire (SCQ) - even those describing no exposure to TRI - plus certain which had been investigated using the General Occupational Questionnaire (GOQ), but which were in fact in factories involved in screw-cutting (about 10 cases, where the subject was deceased and the actual respondent was a relative had not realised that the job concerned screw-cutting).

(2) Any job period involving at least possible TRI exposure was collected for Step III. The choice was very broad, so as not to leave anybody out.

(3) Job periods definitely not exposed even to a minimal level of TRI were collected in a third category. Some of them (mainly white-collar jobs) were not examined deeply, but assessed in only one round. But all those involving tasks or activities presenting any possible presence of TRI in the usual occupational population were reviewed a second time with all similar jobs or activities to ensure consistency in these areas (Step IV).

STEP II:

All jobs involved in the screw-cutting industry were reviewed consecutively, first by task, then by company, then by period, in order to improve the consistency of the assessment. A score (ppm of TRI) was attributed to each screw-cutting job period, using both a task/TRI-exposure matrix (see below) and the SCQ description, which details:

- tasks with their duration and machines: lathe, automatic-transfer machine, washing machine (open or not), other;
- use of hot or cold TRI, duration, equipment protection;
- physical description of the workshop: size, number of workers and machines;
- presence and distance of a hot or cold degreasing machine.

This score was built as an average based on a usual working day as described in the questionnaire: Score for job period x = Σ_i(level of task i in the matrix x duration of task i) / 8-hour working day. In case of combined cutaneous and respiratory exposure, levels were added together.

This score was matched with a confidence score: 3 levels related to the certainty of exposure, rather than to the assessment of level:

Score 3 = this subject was certainly exposed to TRI

Score 2 = this subject was probably exposed to TRI

Score 1 = this subject could possibly have been exposed to TRI.

In addition to this average level of exposure, over-exposure (TRI peak: see below) was also assessed, at 3 levels.

Validation of the assessment of screw-cutting shops:

At the end of Step II, validation was attempted with information gathered from occupational physicians in the valley during systematic surveys of TRI exposure. As the policy was to use degreasers as ‘sentinels’ for the workshops, most of the degreasers were checked in a biological (urinary trichloroacetic acid (U-TCA) or trichloroethanol (U-TCE)) survey, resulting in the following classification:

Low exposure	= U-TCA+TCE < 40 mg/g creatinine	< 50 mg/l
Medium exposure	= U-TCA+TCE = 40-100 mg/g	= 50–130 mg/l
High exposure	= U-TCA+TCE = 100-170 mg/g	= 130 - 220
	and/or U-TCA > 70 mg/g	>100 mg/l
Intoxication	= U-TCA+TCE = 170-300 mg/g	> 220 mg/l

Any medium exposure led to a follow-up examination some months later, while high exposure or intoxication led to an intervention in the workshop: measurements at the degreasing machine and at various points of the shop, and proposals to modify the technology and work practices. This gave us a lot of individual measurements for degreasers, but only general atmospheric levels (mainly in polluted shops) to validate other tasks.

In addition, examination of personal files was not allowed without permission of the subject and the physician. Our strategy for validation was therefore to send a file to the 8 occupational physicians in Cluses who had agreed to collaborate, including: Subject ID n°, period of job, job title and tasks, name and location of factory, and technical description as given in the questionnaire (number of workers, size and distribution of the various workshops, to validate the identification of the company); thus validation was not carried out at an individual level but by job in a given workshop at a given time.

In parallel, the first assessment of exposure to other chlorinated solvents was reviewed, mainly with the help of occupational physicians, as the answers regarding these solvents were very poor in the questionnaires. Likewise, other exposures were reviewed (especially exposure to cutting fluids, omnipresent in these workshops).

STEP III:

All non-screwcutting jobs attributing at least possible TRI exposure in Step I were reviewed consecutively to assess actual TRI exposure, as in Step II: though no occupational descriptions as precise as the screw-cutting questionnaire were available, the qualitative description of the tasks, plus some precise questions on use of solvents / TRI / hot or cold / with a rag, or a bath, etc., allowed these tasks and processes to be calibrated on those in the screw-cutting industry with respect to TRI exposure.

As in Step II, the first assessment of other chlorinated solvents and other exposures was reviewed.

STEP IV:

While TRI exposure in screw-cutting was assessed with maximum possible consistency, other jobs exposed to TRI were reviewed randomly, which might lead to some lack in the assessment of identical jobs or activities. To remedy this, the main jobs or sectors involving TRI exposure were brought together and consecutively reconsidered. Moreover, to make quite sure that jobs or sectors eliminated at Step I were indeed exposure-free, they were re-included in this review.

The main jobs and sectors thus reviewed were:
tasks (per ISCO code):

machine tool operators,
machinery fitters, industrial mechanics,
garage mechanics,
watch and clock-makers and jewellers,
electrical workers,
woodworkers (carpenters, furniture makers),
leatherworkers;

sectors or employers (per NACE code):

watch and clock-making, jewellery (Nickles, Rollex, Piaget, etc.),
physics research (CERN, Geneva),
bicycle manufacturing (Chatelain),
manufacture of paints and coatings (SICPA),
inorganic basic chemicals (Pechiney, Chesdes).

As for Steps II and III, the first assessments of other chlorinated solvents and other exposures (mainly those relevant to one or other of the above jobs or sectors) were reviewed.

3.2.2 TRI exposure assessment

➢ TRI exposure circumstances in the screw-cutting population: design of a Task-Exposure Matrix

Since mere job titles in the screw-cutting industry (as indeed also in other sectors) are not informative enough to enable direct assessment either of the reality of TRI exposure (a ‘screw-cutter’ may or not dip metal parts in cold TRI to clean and check their size), or of degree of exposure (a ‘degreaser’ in a little workshop may operate the degreasing tank only for a few hours a week, performing non-exposed tasks the rest of the time), a **Task-Exposure Matrix** was used to link the main tasks or working circumstances in a screw-cutting workshop to corresponding TRI-exposure levels: a score (atmospheric level of TRI) was assigned to each task in the matrix, standing for the average TRI level for usual working procedures, and task-duration and divers exposure circumstances such as distance from the TRI-source or use of protective equipment were introduced as corrective (increasing or reducing) factors for these scores.

The main tasks involving active TRI-exposure were:

- cleaning metal parts - in hot or cold TRI;
- emptying-cleaning-filling the TRI tank;
- distillation-regeneration of dirty TRI;
- cleaning floors, overalls, etc. with TRI.

The main working circumstances entailing passive TRI-exposure, or having an effect on doses, were:

- task duration;
- working close to or at a distance from a (hot or cold) TRI source;
- technical specifications of the degreasing machine: from fully open to fully enclosed process; from fully manual to fully automated process;
- quality of the maintenance for the degreasing machine: leaks in the TRI piping, etc.;
- drying technology: using a drying channel, blow-drying parts with compressed air, open-air drying in the workshop, etc.;
- use and efficiency of personal and collective protective equipment.

TRI-exposure levels, to be linked to each task or working circumstance, were assessed from various data collected over 25 years by occupational physicians in the Valley:

- Annual reports gave an overview of TRI levels and changes in TRI levels over years, as well as changes in the machines in use in the Valley.
- Each worker in the screw-cutting industry undergoes at least one annual TCA assessment (workers identified as degreasers are monitored twice a year); when excessive levels are detected, workshop measurements are undertaken and repeated biological measurements performed until fair conditions are restored.
- In addition to these systematic tasks for occupational physicians, some undertook various studies on degreasing exposure in workshops of the Valley (see below).

➢ <u>Historical exposure to TRI in the study area</u>

Some of the various studies carried out in the Valley by the occupational physicians focussed especially on degreasing machines, with atmospheric levels, and their possible technical improvements, or on biological monitoring of degreasers or of other screw-cutting workers [10]. In all these studies, atmospheric results were obtained by means of various types of apparatus (Draeger, Miran), and biological monitoring was mainly done on the urine of workers (measurement of urinary levels of trichloroacetic acid (U-TCA), or of trichloroethanol (U-TCE), at the end of a working day or week); the measurement circumstances, as well as the workshops, degreasing machines, tasks, and other technical points, were, however, described. Most studies devoted to workers also recorded subjective symptoms such as headache or dizziness. The main studies providing data are listed below.

At the beginning of the 1960s, a study of the hepatic toxicity of TRI was undertaken in a very large degreasing workshop employing 3 half-open machines. Atmospheric samples at various points showed levels between 180 to 600 ppm, and TCA levels in washers' urine were from 220 to 505 mg/l [78].

A health and safety survey conducted in 1975 for washing/drying exposure in 6 workshops (with a total of 886 workers) reported atmospheric levels from 70 to 800 ppm of TRI in the washing workshops, and from 2 to 50 ppm in adjacent areas [10]. The French regulatory limits at that time were 75 ppm as "*VME*" (threshold limit values (TLV) for an 8-hour working day), and 200 ppm as "*VLE*" (short-term <15min exposure limit) [35,36]. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends TLVs of 50 ppm (269mg/m^3) for an 8-hour time-weighted average (TWA) and 100 ppm (537mg/m^3) for a short-term (15-min) exposure [37].

A French PhD thesis on pathology in the screw-cutting industry reported 'atmospheric levels of 300- 400 ppm close to open washing machines, and U-TCA up to 600 mg/l in the Cluses area' [27].

In the late '70s, 188 workers (representing all usual tasks) from 89 workshops of various sizes were examined and questioned about their tasks and possible signs of TRI-intolerance. These men (92%) and women (8%) had been exposed to TRI for an average 7.5 years (range: 1 to 35 years). Washing tasks involved 51% of the workers; of these, 94% were exposed to more than 50 ppm, and 50% to up to 150 ppm. In the latter (≤150 ppm) category, 40% of subjects showed signs of inebriety. Only 42% of the workers never directly involved in washing or drying metal parts (screw-cutters, storekeepers, etc.) did not work in the same area as the degreasing machines; and 50% of screw-cutters had an open tin of cold TRI at their disposal [69].

In 1984, a survey was undertaken in a medium sized company, concerning 18 workers in one workshop (including 10 screw-cutters, 6 other machine operators, and 1 washer), to measure the exposure of non-washing workers due to the presence of the new half-open degreasing machine. Atmospheric TRI levels varied from 15-20 ppm in the general surroundings, to 200 ppm at 6 metres from the machine each time it was opened and baskets left to cool on the floor close to the machine (about twice an hour, for 5 min each time) [19].

In 1988, a health and safety survey was run on TRI washing machines currently in use. Thirty machines still in use, from six categories representing the main specifications of interest (open, half open or closed, and manual or with a conveyor), were monitored. Results showed that open manual machines presented emissions above the TLV (with some up to 300 ppm) even in the static phase (no washing), while only 1 of the 4 best types (totally closed and automatic) presented excessive values, and even then only in the dynamic phase at the exit hole [83].

In 1997, 104 workers from 78 different workshops underwent biological monitoring at their annual medical examination. Seven of them (screw-cutters and storekeepers) were not exposed, and 13 (12.5%) presented biomonitoring results above the French Biological Limit (IBE: TCA+TCE>300, or TCA >100 mg/g creatinine) [36].

Though few other published studies in other industrial populations provide enough information (accurate description of tasks and measurements), an attempt was made to validate these Arve Valley data against external data (assessment of pre-narcotic symptoms and/or atmospheric/biological measurements) in other French metal degreasing shops [12,6] Swedish welding shops, various metal degreasing shops [33, 72,43,64], an Italian electronics facility, and a German cardboard factory [34]. Other studies, based on general population data, have only a limited value with respect to exposure assessment as they consist of very different populations and tasks, without any accurate occupational description of work processes.

➢ The Task-Exposure Matrix

Each main category of tasks involving any use of TRI was considered; for each one a 'basic level' was defined, taking into account measurements (and their circumstances) described in the literature, and especially those from the Arve Valley such as in the study by Venjean et al. [83]. Local measurements are not systematically provided in this report, as they are too numerous and mainly unpublished, but whenever possible an attempt was made to compare the task-levels proposed to those observed or used in the international occupational or epidemiological literature.

For degreasing machines, the 'basic level' represented the potential emission of TRI vapours in the workshop, to which corrective factors were then applied depending on whether workers were actively operating the machine, or were simply located in the same workshop, and at what distance from it.

- **Corrective factors for distance from the machine**

It is quite impossible to come up with a general rule, as specific workshop geometry, ventilation and activity are critical; nevertheless, generally speaking, levels seemed to decrease only slightly in the immediate vicinity of the machine (within 5 metres of the machine there is usually no physical activity going on that could have the effect of stirring the air and thus reducing the TRI level), then drop off proportionally to distance between 10 and 30 m and according to the number and kinds of activities going on there (screw-cutting machines operating at high speed and emitting oily vapours, etc.), and finally fall to minimal atmospheric levels.

The corrective factors chosen for this study were:
10% lower at 5m
25% lower at 10m
40% lower at 15m
55% lower at 20m
75% lower at 30m

- **Corrective factors for operating a degreaser**

Being involved in degreasing tasks does not necessarily mean being continuously right above the tank, as this task also involves taking baskets to and from the truck. It is therefore assumed here that the washing task comprises only half of the time actually above the tank, the other half being spent in the immediate vicinity, exposed to the basic level.

- **Peaks of exposure to TRI**

Exposure peaks obviously contribute to higher average levels, and thus have already partially been taken into account of by the assessment of these high levels. Nevertheless, they are not totally integrated in the average TRI concentration continuously released at the top of a degreaser, as they represent additional exposures (such as moving the boiling TRI when removing the baskets).

As a result, the occurrence of exposure peaks was also assessed, as a separate factor: subjects exposed to a peak were considered to be exposed to the average assessed level, plus an additional exposure, a certain number of times per day, week or month.
Definition of peaks in this study:

- Peak = any exposure reaching 200 ppm for 1 min or more:
- Peak Level 1 = workers seldom exposed to peaks, some times a year,
- Peak Level 2 = workers exposed to peaks some times a month,
- Peak Level 3 = workers frequently exposed to peaks, some times a week.

The minimum of 200 ppm chosen to define a peak means that only people exposed to hot TRI, either in a direct task, or by close contact with the hot degreaser, were involved in this category of assessment.

- **Use or presence in the workshop of an open cold tank**:

Basic Level, open cold degreaser = 15-18 ppm
Working above the tank to dip in a basket = 50 ppm [20].

E.g.: During the 1970s (with an average working day = 9 hours), a 20 metre-long workshop, an open cold tank at one end, and each worker dipping in his/her own production in turn, 6 x 10 min a day on average:
Exposure level for a screw- cutter at the other end of the workshop = (18 x 0.5 + 50 x 0.5 + 10 x 8) / 8 = 14 ppm

- **Use or presence in the workshop of an open / hot tank:**

These tanks were rarely in their dynamic stage (washing cycle) for the full week: they tended to be heated for only some days towards the end of the week, functioning as cold open tanks for the other days, or else to be hot but in a static stage (waiting for a washing cycle) for some hours each day. The levels around these machines are quite different during the static and dynamic stages (ranging from 50 to 200 ppm), and a **basic level of 120 ppm was defined for an open hot machine, while working above the tank leads to levels of about 300 ppm, with peaks up to 400 ppm. [16, 72, 89]**

E.g.: During the 1970s (with an average working day = 9 hours), a 20 metre-long workshop, an open hot tank at one end only operated on Thursday and Friday by a washing operative performing no other task involving TRI during the other days (spent helping the screw-cutters):

average exposure of washing operative:
3 days (9 hrs) x atmospheric level at 10 m from a cold degreaser

+ 2 x ½ day above the hot tank
+ 2 x ½ day close to the hot tank
= (27 x10 + 9 x 300 + 9 x 120) / 40 = 100 ppm+ Peaks.
Level for a screw-cutter at the other end of the workshop: (27 x 10 +18 x 95) / 40 = 50 ppm.

- **Use or presence in the workshop of a half-open hot tank:**

Basic level of 35 ppm for a half-open hot machine,
working above the tank: 75 ppm,
with peaks up to 200 ppm. [12]

E.g.: During the 1970s (with an average working day = 9 hours), a 20 metre-long workshop, a half-open hot tank at one end, 1 washing operative for Thursday and Friday, performing no other task involving TRI during the other days (spent helping the screw-cutters)
average exposure of washing operative:
3 days (9 h) x 5 ppm background exposure
+ 2 x ½ day active degreasing, at 75 ppm
+ 2 x ½ day close to the hot tank, at 35 ppm
= (27 x5 + 9 x 75 + 9 x 35) / 40 = 30 ppm+ Peaks
Level for a screw-cutter at the other end of the workshop: (27 x 5 + 18 x 28) / 40 = 15 ppm

- **Use or presence in the workshop of a totally closed hot degreaser:**

The first machines of this category arrived in the early '80s and could lead to a **basic level of 5 ppm, and a maximum of 35 ppm for operatives working close to the end of the channel. All closed machines in use after 1990 may be taken to expose the worker at the exit to no more than 10 ppm.**

- **Emptying-cleaning and refilling the degreaser**

Old degreasing machines (open, and most of the half-open tanks) are cleaned manually or semi-manually. The frequency of this cleaning is highly dependent on the frequency of use of the machine, but the duration of the most exposing part of the task is always at least 2 hours (on Saturday morning, the degreaser having been stopped and cooled the night before). The main tasks are: to empty the tank; to remove the sludge (mixture of oil and solvent) from the bottom of the tank (mainly accomplished by physically entering the tank, usually without proper protection); to clean it with jets of TRI; and then to fill it with new TRI.
The average level of exposure for these 2 hours is 300 ppm, with presence of very high exposure peaks (up to 600 ppm).

- **Hand-dipping in cold TRI**

For many years ('50s to '90s), many workers had at their disposal little tins of cold TRI, to dip and check their production samples, and to clean their hands before stopping work. Although the area of skin in contact was quite small (mainly the tips of 2 or 3 fingers), the question arises of the actual dermal uptake from this situation, as the gesture was generally repeated a number of times a day. Although 'skin notations' for TRI vary from one country to another [39], biological measurements taken on Arve Valley workers who were exposed only

cutaneously clearly showed that some uptake occurred from such dermal TRI penetration. The main question is to assess the penetration level and combine it with inhalation levels, and there are very few tools available to the industrial hygienist [17].
At the end of the '90s, a systematic survey was made of screw-cutting shop workers who were working with the degreaser (Dr V. Cuisse, and Dr P. Muller-Beauté, personal files); some of them were only dermally exposed to TRI, as described above (no degreaser in the control, assembly or machine-tool shop), and results for these workers were used to assess a basic level (expressed as an 'equivalent inhalation rate') of 30 ppm for a worker dipping metal parts in an individual open tin every 10min.

➢ Assessment based on this Matrix

This Task-Exposure Matrix enabled average TRI doses to be calculated for each job, insofar as the job's tasks, duration and relevant working circumstances were described in the occupational questionnaire.

These doses were then used to categorize job periods into 5 classes, with the French and international legal values as cut-off levels:

Very low exposure	= 5-35 ppm	(35 ppm = ½ French limit)
Low exposure	= 35-50 ppm	(50 ppm = ACGIH limit)
Medium exposure	= 50-75 ppm	(75 ppm = French limit)
High exposure	= 75-100 ppm	
Very high exposure	> 100 ppm	

As these categories are the result of exposure levels averaged over a working day, they may represent any pattern of exposure, ranging from a single constant source of exposure throughout the working day, to a variety of unstable exposures resulting in discontinuous levels.

Nevertheless, each category of exposure may be linked to a certain way of using TRI:

Very low exposure	= rare to infrequent use of small quantities of cold TRI; = hot washing machine in another part of the workshop; = fingers dipped into cold TRI a certain number of times a day; = exposure only due to some peak levels.
Low exposure	= idem, but more frequent contact or closer distance to the machine; = very low exposure + some peaks.
Medium exposure	= habitual contact with hot or cold TRI; = close contact with a half-open hot machine; = low exposure + some peaks.
High exposure	= habitual hot washing tasks; = possibility of exposure to frequent peaks.
Very high exposure	= habitual high exposure; + maintenance of the washing machine; or + work close to an open hot machine; peaks might be frequent.

- <u>Assessment of TRI from narcotic symptoms</u>

Acute symptoms following TRI exposure were investigated by a specific questionnaire, to assess their severity, frequency and duration. This questionnaire was used for all cases and controls. Thus, TRI exposure was assessed as by Vamvakas et al., and the findings compared to the assessment derived from the Task-Exposure Matrix. The subjective aspects of such a TRI-exposure assessment approach was analysed by comparing the frequency of narcotic symptoms in the exposed and non-exposed groups.

3.3 Data collected

After obtaining the subject's agreement to participate, blinded telephone interviews were administered by a trained interviewer. All of the interviews were conducted by the same interviewer. The interviewer could be considered blind to the subject's medical status, as the medical questionnaire was the last to be administered. Telephone contacts, letters and appointments were managed by a research unit physician.

For subjects who refused to participate to the study or who were lost to follow-up, a short questionnaire was used (when possible) to collect information on their age, place of residence, occupation and potential TRI exposure, in order to assess the possibility of selection bias.

3.3.1 The occupational questionnaire (Appendix 5)

The interviews started with the occupational questionnaire. The first part of this was devoted to job history; the second part mainly queried tasks and working circumstances.

3.3.2 Narcotic symptoms questionnaire (Appendix 6)

A specific questionnaire was designed to assess the presence of narcotic signs at work, as in Vamvakas et al. Several signs were investigated: headache, stomach pains, nausea, vertigo or inebriation. Patients were also asked if these symptoms were more frequent when they had drunk alcohol, and if they felt flushing in their cheeks. More serious signs were also assessed (dizzy spells, need to leave the workshop to get fresh air outside), as well as the link between workdays and these signs: they were asked if their symptoms stopped during weekends and holidays. At the end of the questionnaire, the duration of the narcotic signs was assessed. Patients were then asked to specify the period of their life and the job being done when they experienced/had experienced these signs.

3.3.3 General medical questionnaire (Appendix 7)

Review of the literature found various RCC risk factors and these were taken into account in drawing up the general questionnaire.

- **Date and place of birth**.
- **Socio-economic status** (assessed by job).
- **Family medical history** (familial kidney cancer).
- **Individual medical history:** kidney stones and infection, chronic dialysis, diagnosis of hypertension (year of diagnosis).
- **Drugs:** Anti-hypertensive drugs, diuretic use, frequency, dose and time period of use of analgesic drugs (phenacetin/aspirin or paracetamol).
- **Body mass index (BMI),** present and maximum at any previous time, calculated as weight/(height^2).
- **Lifestyle:** Smoking: pack-years were calculated as number of cigarettes smoked per day divided by 20 and multiplied by the number of years in question; coffee (decaffeinated or not) consumption, quantitatively assessed as number of cups per day, and period in question.

3.4 Statistical analysis

The statistical analysis was performed using the SAS system 9.1.3.

<u>General characteristics of cases, description:</u>

Age, sex, year of diagnosis, location of treatment (local urologist / hospital), vital status, histologic RCC type.

<u>Comparison between cases and controls:</u>

- Age and sex.
- Respective frequencies of all general and occupational factors relevant to the TRI exposure analysis.

Qualitative data were expressed in frequency and percentage; differences between cases and controls were tested by chi-square testing. Means and standard deviations were calculated for quantitative data (age, etc.) and differences tested by t-test.

It was impossible to take into account of non-TRI occupational exposure levels because of the small number of subjects exposed. (A subject was considered to have been exposed when such exposure was noted for at least one job period: i.e., for at least one year.)

Potential confounding factors identified were taken into account at the threshold limit of 10 % ($p = 0.10$).

3.4.1 Analytical step

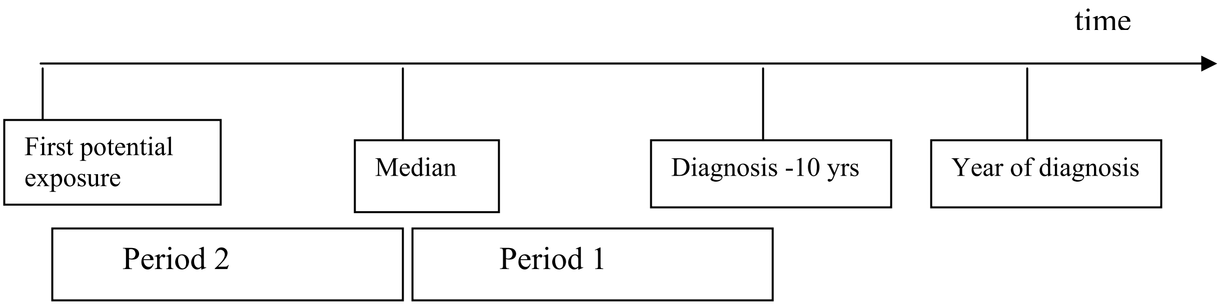
Four approaches were developed to assess the link between TRI exposure and RCC.
All the following analyses were performed on matched pairs (conditional logistic regression).

➢ Exposed /non-exposed:

Regardless of exposure duration, any subject exposed to at least 5 ppm for at least one job period, was considered exposed.

This analysis concerned:

- Any job period until the year of diagnosis, for the case in a given group (of one case plus four matched controls).
- Any job period up to 10 years before diagnosis.
- In order to look for a possible latency effect, 2 periods of follow up were studied: the median control exposure duration (with a lag of 10 years before diagnosis) was used as the cut-off point between these 2 periods.



➢ Analysis based on cumulative dose:

A cumulative dose was calculated as the sum of total exposure doses (d_i) for each job period: cumulative dose = $\Sigma_i (d_i * y_i)$ – i.e., number of ppm of TRI per job period multiplied by the number of years (y_i) in the job period.

This analysis concerned:

- The cumulative dose from the beginning of job history to the year of diagnosis (of the case in each group)
- The cumulative dose up to 10 years before diagnosis.

Three levels of cumulative dose were established according to the control exposure tertiles. Analysis sought a link between cumulative dose and RCC risk, testing the dose-effect relation.

- <u>Assessment of peak effect:</u>

As the number of subjects exposed to peaks was low, only one factor was studied: “having been exposed to TRI peaks in at least one job period, whatever the magnitude of the peaks”.

Two time periods were considered:
- Whole life until the year of diagnosis
- The period up to 10 years before diagnosis.

An odds ratio was calculated to assess the association between TRI peak exposure and RCC.

- <u>Search for an exposure threshold linked with a level of exposure during a job period:</u>

To search for a threshold effect, three exposure levels were chosen according to occupational exposure limits:

- 75 ppm (the French VME)
- 50 ppm (the ACGIH’s TWA)
- 35 ppm (half of the VME).

For each threshold, subjects exposed at or above threshold and subjects exposed below threshold were differentially compared to the non-exposed subjects, and odds ratios were calculated.
This analysis was performed for:
- The whole life
- The period up to 10 years before diagnosis.

For an exposure prevalence of 20%, the power of the study was 80% to detect a 2-fold increase in RCC risk (one-sided test, α=0.05).

- <u>Multivariate analysis</u>

A multivariate analysis was performed when an association between TRI exposure and RCC had been found at the 10% threshold. In this analysis, potential confounding factors identified in the descriptive part were taken into account.

3.4.2 Narcotic symptoms

A first glance at the Narcotic Questionnaire (NQ) showed that some signs described were not attributable to work (e.g., headache described by the subject as resulting from cranial trauma).

For this reason, a scale was created to assess narcotic symptoms and their link with work.

Two experts (M. Hours and B. Charbotel) independently gave scores on the scale from their reading of the NQ. The experts discussed any differences between their assessments, and if their opinions were still divergent, a third expert (A. Bergeret) was asked to give the final answer.

The following assessment scale was used for scoring:

0: No narcotic sign, or signs that can be linked to a non-occupational pathology.
1: Only one sign that can be linked to work.
2: Association of several signs that can be linked to work.
3: Patent narcotic syndrome, with work rhythm underlying the rhythm of the signs (several signs or vertigo alone).
4: Severe narcotic syndrome with dizzy spells, the worker needing to leave the workstation to go outside.

These 5 narcosis scores were attributed to culprit job periods identified by the subject in the NQ. When no culprit job period was identified as such, the score was attributed to all job periods of the subject's job history.

The analysis assessed the reality of a link between TRI exposure and narcotic symptoms.

Association between RCC and narcotic signs during the career was assessed by comparing groups in each narcosis score category to the group without signs. Some groups had to be combined when the number of subjects per group was too small.

3.4.3 Comment

A specific analysis was performed to rule out memory bias in old patients (more than 80 years old at time of interview) or when a proxy had been interviewed.
Groups of relevant patients were extracted from the analysis and the impact of this extraction on the odds ratios was assessed.

3.5 Legal approval

Approval by the French Ministry of Research (*Comité consultatif pour le traitement de l'information en matière de recherché dans le domaine de la santé*) and the French data protection authority (*Commission Nationale de l'Informatique et des Libertés*) was obtained before starting the study.

3.6 Scientific committee

A scientific committee was created by ECSA in order to improve the quality of the study and to ensure scientific independence. The Committee initially consisted of Paolo Boffetta, head of the department of environmental cancer, IARC, and Gerard Swaen, assistant professor at the University of Limburg, the Netherlands (both epidemiologists), and John Cherrie, industrial hygienist at the Department of Environmental and Occupational Medicine of the University of Aberdeen and the Institute of Occupational Medicine, Edinburgh, UK.

In February 2005, Gerard Swaen decided to give up his seat on the Advisory Committee, since he had started to work for the Dow Chemical company and "there [could have been] some form of conflict of interest with his current job and being on the Advisory Committee".

4 Results

4.1 Exposure aspects

4.1.1 Occupations and exposure other than TRI:

A total of 86 groups, involving the 86 cases and 316 controls, were assessed. Sixteen of them comprised less than 5 subjects, and a possible information bias in these groups – where the probability of a given subject being a case was intrinsically higher, despite blinding – have occurred.

- **Jobs and activities**

Out of a total of 2,059 periods, **1,486 job-periods,** for **402 subjects,** were assessed; this average of 3.7 job periods/subject is quite usual for this category of the French population.

Distribution of activity codes **(NACE codes, see Table Appendix 11)** shows that farming (4%), wood-working (3%), chemical production (3%), metal products/machines (20%), construction (8%), and garages (2.5%) were the main 'blue collar' activities in the study. As expected, the proportion of metalwork and, to a lesser extent, woodwork jobs was higher than in the general French working population.

For metal workers, **175 jobs were described in a Screw-Cutting Questionnaire** (12% of job periods, but 20% of subjects), and were seen at STEP II.

About **120 job-periods** in various other activities were deemed possibly/probably/surely exposed to some TRI, and therefore set aside for STEP III.

- ***Non-TRI exposure:***

As foreseeable in a metalworking population, petroleum oils (cutting and lubricating), metals (specially cadmium), petroleum solvents, welding (but not brazing) and asbestos seemed to be over-represented with respect to average values in France (see table 3).

Table 3: Frequency and levels of other exposures for job-periods

Level / Exposure		Low (1) Number (% of 1,486 job periods)	Medium (2) Number (% of 1,486 job periods)	High (3) Number (% of 1,486 job periods)	Total Number (% of 1,486 job periods)
Solvents	Chlorinated (Other than TRI)	36 (2.4%)	10 (0.7%)	4 (0.3%)	50 (3.4%)
	Petroleum derivates	220 (14.8%)	63 (4.2%)	7 (0.5%)	290 (19.5%)
	Oxygenated	56 (3.8%)	16 (1.1%)	2 (0.1%)	74 (5.0%)
	Other	8 (0.5%)	3 (0.2%)	0 (0.0%)	11 (0.7%)
Oils	Cutting fluids	99 (6.7%)	44 (3.0%)	80 (5.3%)	223 (15.0%)
	Other petroleum oils	82 (5.5%)	17 (1.1%)	4 (0.3%)	103 (6.9%)
Welding	Brazing	24 (1.6%)	12 (0.8%)	3 (0.2%)	39 (2.6%)
	Other	82 (5.5%)	33 (2.2%)	17 (1.1%)	132 (8.9%)
Lead		62 (4.2%)	8 (0.5%)	2 (0.1%)	72 (4.8%)
Cadmium		29 (2.0%)	7 (0.5%)	2 (0.1%)	38 (2.6%)
Asbestos		143 (9.6%)	20 (1.3%)	1 (0.1%)	164 (11.0%)
Ionising radiation (source)					17 (1.1%)

- ***Welding fumes:***

As the ECSA and the scientific committee asked us during the course of the study also to assess welding activities [14], we introduced questions about welding in the occupational set for the last 217 subjects interviewed. However, the answers to these questions were not communicated to the assessor, who was asked to carry out the welding exposure assessment in the same way for all subjects; this assessment and the answers to the welding questions were compared later for the 217 subjects concerned, in order to validate the general welding exposure assessment. For 7 of the 217 subjects, information on welding exposure was unknown. The agreement between the assessor's welding assessment and answers given by the patients or their next-of-kin in the questionnaire was incomplete (kappa = 0.62, p = 0.07). While only 3.7% of patients (n=6) who declared they had not been exposed to welding fumes were considered by the assessor as having been exposed, 40.8% (n=20) of those who declared they had been exposed to such fumes were classified as non-exposed by the assessor.

This disagreement was mainly due to very low-level incidental or indirect exposure (to fumes from welding being carried out by colleague). However, at least 8 of these 20 patients could be considered as being exposed to low levels of welding fumes.

Table 4: Comparison of welding exposure assessment by the assessor to information given by questionnaires

		Welding exposure declared by patients (or proxies) Specific questionnaire for welding activities			
		No	**Yes**	**Unknown**	**Total**
Assessment of welding exposure based on the general occupational questionnaire	**No welding exposure**	155	20	6	181
	Welding exposure (brazing, other)	6	29	1	36
	Total	161	49	7	217

Table 5: Quality of Information about TRI exposure given by subjects in occupational questionnaires

Which machines and materials were in the main workshop or room you were working in, (and in the other ones if applicable)?		
	Number and percentage of valid answers	**Number and percentage of "YES" responses in valid answers**
Screw-cutting machines	133 (96.4%)	92 (69.2%)
Digitally driven machines	130 (94.2%)	78 (60.0%)
Washing machines in cold phase	126 (91.3%)	26 (20.6%)
Washing machines in hot phase (or vapour)		
- open washing machine	121 (87.7%)	18 (14.9%)
- half open washing machine	121 (87.7%)	16 (13.2%)
- closed	121 (87.7%)	18 (14.9%)
- with a drying channel	119 (86.2%)	10 (8.4%)
Did you do one or more of the following jobs?		
	Number and percentage of valid answers	**Number and percentage of "YES" responses in valid answers**
Screw-cutter, or screw-cutting assistant	136 (98.6%)	63 (46.3%)
Digitally driven machine operator	135 (97.8%)	38 (28.1%)
If yes, were metal parts still wet with TRI when you received them?	37 (94.4%)	7 (18.9%)
Metal parts checking	135 (97.8%)	12 (8.9%)
If yes, were metal parts still wet with TRI when you received them?	10 (83.3%)	4 (40.0%)
Washing with cold trichloroethylene	130 (94.2%)	22 (16.9%)
Washing with hot trichloroethylene	130 (94.2%)	18 (13.8%)
Cleaning the washing machine, scraping mud, etc.	131 (94.9%)	10 (8.3%)
Were you exposed, in your own jobs or via those of a neighbouring worker, to any chemical used as solvent, thinner, degreasing agent or cleaning agent (except detergents or soaps)? How did you use it, or how was it used by your neighbour?		
	Number and percentage of valid answers	**Number and percentage of "YES" responses in valid answers**
Trichloroethylene	1,181 (95.0%)	165 (14.0%)
Cold use	153 (92.7%)	143 (93.5%)
Hot use, or as vapour	154 (93.3%)	19 (12.3%)
In a large open batch	153 (92.7%)	144 (94.1%)
In a large closed batch	153 (92.7%)	8 (5.2%)

4.1.2 Exposure to TRI

- **Information about TRI exposure as given by subjects:**

As seen in Table 5, subjects were able to give accurate answers concerning possible exposure to TRI, in both the general and in the screw-cutting questionnaire.
- Comparing a certain number of single subjects' answers confirmed good knowledge of the use of TRI: in the GOQ, nobody answered 'yes' to both petroleum solvent and 'hot use'; reasons given for the use of TRI were coherent with the task and/or the materials (cleaning of neoprene glue, etc.)
- From the general occupational questionnaire it appears that about 13% of the job periods was associated with occupational exposure to TRI – which is not surprising, as 86% of these respondents (wood-workers, industrial mechanics, machine fitters, etc.) used it cold and in small quantities.
- In contrast, 63% of the 21% exposed to TRI in the screw cutting industry used it hot and for an average 1 hour per day.
- The only difficulty arose with the screw-cutting questionnaire item about 'presence of a cold washing machine in the workshop': while about 87% of respondents were able to testify to a hot washing machine even when it was far away, only those actually working in close proximity to cold machines seemed able to answer accurately, with only 31% of valid answers to this question, which may represent an under-assessment of TRI in such workshops.

- **Validation of the screw-cutting workshop assessment:**

Eight occupational physicians in the Valley agreed to help validate our assessment; by the end of the assessment process, they received a file including all job periods in workshops in their catchment area (i.e., all job periods in screw-cutting shops around Cluses, those in the Bonneville and Annemasse areas coming under a different team).

These job periods were described by subject ID n°, job period, job title and tasks, name and location of factory, and technical description as given in the questionnaire (number of workers, and size and distribution of the various workshops, to validate company identification). Out of these job periods, the 8 physicians identified 31 in workshops which were in their catchment area at one time or another since they had joined the group (mainly in the 1980s), and made their own assessment for these 31 jobs, based on their knowledge of and on atmospheric measurements in the workshop, and on biological data in their possession for some workers whom they were able to identify. This was done blind to any other assessment information.

As explained in § 3.2.1, the categories used by the occupational physicians to classify workers were as follows:

Low exposure	= U-TCA+TCE < 50 mg/l
Medium exposure	= U-TCA+TCE = 50–130 mg/l and U-TCA < 100 mg/l
High exposure	= U-TCA+TCE = 130 - 220 and/or U-TCA >100 mg/l
Intoxication	= U-TCA+TCE > 220 mg/l

While not exactly identical in terms of level, mainly because of the shift from biological to atmospheric values [86,47,60, 79], the two types of assessment may be related as follows:

Low biological exposure means atmospheric levels < 30 ppm
Medium biological exposure means atmospheric levels 30-60 ppm
High biological exposure means atmospheric levels 60-80 ppm
Intoxication corresponds to atmospheric levels above 80 ppm, and /or peaks

For 22 (71.0%) of these periods, there was good agreement between occupational physicians and our assessment (Table 6). 5 hot degreasers were identified (anonymously) by their physicians and were attributed high exposure levels, as in our own assessment.

Of the other jobs,

3 job periods not initially assessed as being exposed were attributed low exposure levels by the physicians (general workshop conditions).

In the contrary, for 1 job period, the low level exposure initially assessed proved to be inappropriate, as TRI was not yet in use at that date according to the physicians.

1 job period initially assessed in the low category (< 50 ppm) was split into 2 different jobs, the first with medium exposure (probably < 60ppm) as assessed by the physicians, and the second with low exposure.

1 subject was assessed as low exposed in the second part of his job, according to the change in tasks he described, whereas the physicians had attributed high exposure for the whole period.

3 job periods were considered as involving medium exposure by the physicians in contrast to the very low exposure assessed from the questionnaire.

Table 6: Validation of the screw-cutting workshop assessment

By physicians **By questionnaire**	**No exposure**	**< 30 ppm**	**30-60 ppm**	**60-80 ppm**	**> 80 ppm**
No exposure	4	**3**			
5-35 ppm = Very low	**1**	7	**3**	**1**	
35-50 ppm = Low		**1**	3		
50-75 ppm = Medium			2	1	
75-100 ppm = High				1	
> 100 ppm = Very high					5

In addition to this validation, the physicians provided some additional information that improved the job description, and therefore assessment, of some workshops: date of changing the degreasing machine, location of the degreaser in the workshop, etc.).

- **Trichloroethylene assessment information**

295 out of 1,486 job periods (19 %) involved TRI exposure; 175 were in the screw-cutting industry and 120 in other activities, though mainly in other metal workshops.

Of these 295 job periods, 72.2% involved levels under 35 ppm, 14.6 % from 35 to 50 ppm, 7.8% from 50 to 75 ppm (French TWA), 2.9 % from 75 to 100 ppm, and 10 (3.4 %) could be considered as very highly exposed, exceeding 100 ppm. For 88.8% of these job periods, the TRI exposure assessment confidence score was 2 or more (Table 7).

Forty one job periods included exposure with peaks; all but one of the highest exposure levels and peaks occurred before 1980, which is consistent with technological evolution. In 14.0% of job periods involving TRI exposure, peaks were also identified.

Table 9 shows TRI consumption to have grown between the ’50s and ’70s. The number of job periods involving TRI exposure reached a maximum (146) during the ’70s, as did the percentage of highly exposed subjects. Then, during the ’80s, a decline in TRI use is observed: the number of job periods involving TRI exposure was lower, although exposure levels were still high (9% above 75 ppm); this decade corresponds to a period of economic crisis when some workshops were closed and others made no long-term investments such as in expensive closed washing machines.

Table 7: Frequency of periods with an exposure to TRI, by class of exposure levels

	Confidence Score			
Levels	**1** N (% of score)	**2** N (% of score)	**3** N (% of score)	**Total**
<35	30 (90.9%)	45 (86.6%)	138 (65.7%)	213 (72.2%)
[35-50[	3 (9.1%)	5 (9.6%)	35 (16.6%)	43 (14.6%)
[50-75[	0	2 (3.8%)	21 (10.0%)	23 (7.8%)
[75-100[			6 (2.9%)	6 (2.0%)
100 & more			10 (4.8%)	10 (3.4%)
Total	**33 (100.0%)**	**52 (100.0%)**	**210(100.0%)**	**295 (100.0%)**

Table 8: exposure to peaks according to level of TRI exposure by period

Class of exposure (ppm)	PEAKS				Total N (%)
	0 N (%)	1 N (%)	2 N (%)	3 N (%)	
<35	201 (79.1%)	11 (31.6%)	1 (10.0%)	-	213 (55.6%)
[35-50[	36 (14.2%)	4 (47.4%)	2 (20.0%)	1 (8.3%)	43 (14.6%)
[50-75[	14 (5.5%)	2 (10.5%)	4 (40.0%)	3 (25.0%)	23 (7.8%)
[75-100[	1 (0.4%)	2 (10.5%)	2 (20.0%)	1 (8.3%)	6 (2.0%)
100 & more	2 (0.8%)	-	1 (10.0%)	7 (58.4%)	10 (3.4%)
Total	**254 (100.0%)**	**19 (100.0%)**	**10 (100.0%)**	**12 (100.0%)**	**295 (100.0%)**

Table 9: Levels of TRI exposure by decade and job period

Class of exposure (ppm)	Number of job periods involving TRI exposure							
	1930-1939	**1940-1949**	**1950-1959**	**1960-1969**	**1970-1979**	**1980-1989**	**1990-1999**	**2000-2003**
<35	3 (100.0%)	17 (73.9%)	54 (71.1%)	103 (74.1%)	99 (67.8%)	72 (72.7%)	33 (80.5%)	6 (75.0%)
[35-50[	0	3 (13.0%)	13 (17.1%)	22 (15.8%)	22 (15.1%)	12 (12.1%)	3 (7.3%)	1 (12.5%)
[50-75[	0	2 (8.7%)	6 (7.9%)	10 (7.2%)	13 (8.9%)	6 (6.1%)	3 (7.3%)	1 (12.5%)
≥ 75	0	1 (4.4%)	3 (3.9%)	4 (2.9%)	12 (8.2%)	9 (9.1%)	2 (4.9%)	0
Total	**3 (100.0%)**	**23 (100.0%)**	**76 (100.0%)**	**139 (100.0%)**	**146 (100.0%)**	**99 (100.0%)**	**41 (100.0%)**	**8 (100.0%)**

4.2 Epidemiological aspects

4.2.1 Recruitment

➢ Cases

As specified in the protocol, only cases with a diagnosis of RCC were selected for the study. All in all, 117 cases of RCC were reported by urologists.

Patients were included from local urologists (7 physicians), from Annecy hospital, from the Lyon teaching hospital, the Lyon Léon Berard cancer centre and the Grenoble teaching hospital; one case was recruited thanks to the Geneva district Cancer Register.

Thirty of these 117 cases were not interviewed:

- 8 could not be contacted by the physician in charge of the cases and were definitively lost to follow up; their vital status was unknown.
- 22 subjects refused to participate: including 8 deceased subjects whose families refused to be interviewed; for the other cases, the reason for refusal was often their age and feeling of asthenia.
- In 7 of these 30 cases, cancer was not confirmed on histology by the anatomo-pathologist.

Finally, a total of 87 cases with confirmed diagnosis of RCC were interviewed. One of these cases was finally excluded from analysis because it was not possible to find a control subject for him.

Nineteen of the 86 cases studied were deceased at the moment of the study, and medical and occupational information were obtained from next-of-kin.

The distribution of histological types among the cases was similar to that usually described in the literature, with 80% of renal clear cell cancer (see Table 1). Most of the cases were included via local urologists (75.6%). The distribution of diagnosis dates is shown in Table 11.

Table 10: Histological types

	Frequency	Percentage
Clear cell*	73	84.9%
Chromophobe (typical, eosinophil)	4	4.7%
Tubulopapillary (or chromophil)	9	10.4%
Total	86	100.0%

* 2 RCCC associated with another histological type

Table 11: Year and place of diagnosis of the cases

Year / Origin	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	Total
Local Urologist	6	3	5	7	6	4	8	4	5	11	6	**65**
Annecy					2		1					**3**
Lyon TH	1	1	1	5	2	2	2		1			**14**
Grenoble TH			2					1				**3**
Geneva Cancer Register						1						**1**
Total Cases	7	4	8	12	10	7	11	5	6	11	5	**86**
Deceased	3	3	5	1	2	3	2					**19**

Patients' year of birth ranged from 1911 to 1964; 55.8% were in the 1920 to 1939 bracket (see Table 12).

Table 12: Year of birth, sex and vital status of the cases

Year of birth	**Number of cases Total (women/men)**	**Number of deceased cases Total (women/men)**
1910-1919	4 (2/ 2)	1 (1/0)
1920-1929	22 (7/15)	10 (2/8)
1930-1939	26 (7/19)	6 (2/3)
1940-1949	19 (7/12)	2 (0/3)
1950-1959	14 (3/11)	
1960-1969	1 (1/ 0)	
Total	86 (27/59)	19 (5/14)

➢ <u>Controls</u>

For cases from the Lyon teaching hospital, Grenoble teaching hospital and Annecy hospital, controls were recruited from the list of the general practitioner (GP).

For the cases from local urologists, controls were recruited from the urologist's list. When it was not possible to find enough controls via the GP or local urologist, controls were selected from the list of another practitioner in the same geographic area.

It was sometimes difficult to recruit the full number of controls (4 per case). 78 controls refused to be included; 10 controls were lost to follow-up. The reasons for refusal given by the controls were the same as those given by the cases.

Nine of the non-included controls were dead, 64 were alive, and vital status was unknown for 15.

A total of 316 controls were included: 95 women (30.1%) and 221 men (69.9%).

The mean age of cases and controls at the time of diagnosis of the cases did not differ: respectively 61.8 (SD +/- 10.7) and 61.1 (SD +/- 10.4). The distribution of birth years is shown in Table 13. Two-thirds of the cases were male.

Cases tended to have been born more often in France, particularly in the High Savoy district, than controls (respectively, 90.7% and 85.4%) but the difference was not significant (p=0.26).

Body mass index (BMI) at 20 years of age was more often normal among cases than among controls (p = 0.09). The date at which the maximum BMI was observed was often after the date of diagnosis of the case in the group of patients: this was true for 50% of the cases and for 70% of the controls. However, the ECSA asked for the analysis to be based on the last BMI known, considering that "kidney cancer patients generally resume their BMI as before the disease but do not increase in bodyweight more than healthy individuals". The last BMI known was also the maximum BMI for 78% of the cases and 76% of the controls. An increased risk of RCC emerged with increasing BMI: OR = 1.61 [0.93; 2.78] for pre-obesity, and 1.98 [1.01; 3.86] for obesity.

Cases were more often current or former smokers than controls: 62.9% and 51.6% respectively. The odds ratio for tobacco smoking was 1.84 [1.04; 3.25]. The maximum risk was observed for patients who had smoked more than 40 pack-years, with an odds ratio of 3.27 [1.48; 7.19].

The proportion of patients consuming coffee, with or without caffeine, was the same in both groups.

The frequency of hypertension was the same for cases and controls, at 40%. 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 treatment appeared to be more frequent among cases. As it can be difficult for patients to know if they have really taken β-blockers (confusions are possible, and some treatments for hypertension contain β-blockers), a specific assessment was made. This assessment considered patients had been treated with β-blockers when their treatment for hypertension was in fact a β-blocker, even if they had answered they had never taken any β-blockers. Only information of great reliability was taken into account. In this assessment, no significant difference was observed.

The proportion of patients who had been treated with the other drugs considered in the questionnaire (diuretics, analgesic drugs, phenacetin and paracetamol) was slightly but not significantly greater among controls than among cases. The frequency of treatment for hypertension tended to be greater among cases, but this difference was not significant (p = 0.11).

Table 13: Distribution according to year of birth

	Cases	**Controls**	Total
1910-1919	4 (4.7%)	9 (2.8%)	13 (3.2%)
1920-1929	22 (25.6%)	77 (24.4%)	99 (24.6%)
1930-1939	26 (30.1%)	95 (30.2%)	121 (30.2%)
1940-1949	19 (22.1%)	82 (25.9%)	101 (25.1%)
1950-1959	14 (16.3%)	50 (15.8%)	64 (15.9%)
1960-1969	1 (1.2%)	3 (0.9%)	4 (1.0%)
Total	86 (100.0%)	316 (100.0%)	402 (100.0%)

Global Chi-Square = 1.16, p = 0.95

Table 14: General characteristics

		Cases (86)	**Controls (316)**
Age (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%)
Tobacco smoking (Pack-years)	Non-smoker	32/84 (38.1%)	152/309 (49.2%)
	[1 to 20[	23/84 (27.4%)	77/309 (24.9%)
	[20 to 40[	13/84 (15.5%)	51/309 (16.5%)
	40 and more	16/84 (19.0%)	29/309 (9.4%)
Body Mass Index 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 (20.9%)	42 (13.5%)
Coffee consumption	Coffee with caffeine	73/86 (84.9%)	270/316 (85.4%)
	Coffee without caffeine	7/84 (8.3%)	25/314 (8.0%)
Medical history	Hypertension	34/85 (40.0%)	126/314 (40.1%)
	Kidney infection	3/86 (3.5%)	24/313 (7.7%)
	Urinary infection	12/86 (14.0%)	55/312 (17.6%)
	Kidney stones	12/86 (14.0%)	63/314 (20.1%)
	Dialysis	0/86	2/314 (0.6%)
Medical treatments	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%)

- Age at diagnosis (date of the diagnosis of the case being taken as reference for the controls of the same group)
- For 1 case, tobacco smoking status was totally unknown; for 2 cases and 6 controls with a history of tobacco smoking, the number of pack-years was unknown.
- Last BMI unknown for 6 controls.
- Decaffeinated coffee consumption unknown for 2 cases and 2 controls.
- Medical 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.

Table 15: Crude Odds Ratios for general characteristics

		Crude OR[a] [95.0% 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**
Body Mass Index 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

*Confidence interval
[a] **Matched for sex and age**
Linear regression for tobacco smoking divided into 4 classes (non-smoker; from 1 to less than 20 pack-years; 20 to less than 40 pack-years; 40 pack-years or more): chi-square test = 7.02, **p = 0.008**.

4.2.2 Occupations

The proportion of cases working in screw-cutting workshops was higher than that of controls: respectively, 25.6% and 20.3%, OR = 1.48 [0.83; 2.63]. More generally, cases tended to be more often employed in the manufacture of metal products than controls: 26.7% versus 23.1% respectively. The proportion of patients working in any metalwork industry involving possible cleaning was almost the same in both groups: 32.6% of cases, and 33.5% of controls (Table 16), and the proportion of metal workers as such was exactly the same in both groups: 29.1% (Table 17).

Cases also tended to be more often employed in manufacturing machinery, electrical equipment or transport equipment than controls, but the difference was not significant.

A few patients worked in textile washing and dry-cleaning: 2 (2.3%) cases and 4 (1.3%) controls; the difference between these groups was not significant, OR = 1.90 [0.35; 10.41]. The analysis of job titles found the same tendency: 3 cases (3.5%) and 3 controls (0.9%) were employed as launderers, dry cleaners or pressers; but again the difference was not significant, OR=3.81 [0.77; 18.94]. One of the cases was highly exposed to perchloroethylene and trichloroethylene during his job period as a dry-cleaner.

A total of 26 patients, 9 cases and 17 controls, were employed in the chemical industry; i.e., the percentage of cases was the double of that of controls: crude OR = 2.43 [0.96; 6.16], adjusted OR = 2.69 [1.02; 7.09]. Of these patients, only 6 were directly involved with chemicals (2 as labourers, 3 as technicians and 1 as an engineer), and two were exposed to TRI in their job (1 case and one control). Nine other patients in the chemical industry were employed as electricians or mechanical maintenance operators, some being exposed to TRI in these maintenance activities. The main sectors concerned were mineral chemistry, the ink industry and the pharmaceutical industry. Three other patients worked in petroleum oil or paint processing, packaging and selling. Most of the other patients in the chemical industry had administrative jobs.

In non-industrial sectors, cases were more often employed in health and social work: crude OR = 1.99 [0.86; 4.63]. This result was confirmed by analysis of job titles: 4 (4.7%) cases and 7 (2.2%) controls were health workers (crude OR = 2.18 [0.60; 7.85]); the adjusted OR shows a significant increase in risk of RCC: OR = 3.99 [1.06; 15.03].

An increased risk was also identified for patients employed in food product and beverage manufacturing: OR = 2.68 [1.07; 6.68]. Of a total of 19 patients (8 cases and 11 controls) employed in these activities, 8 worked in dairy products, 3 in the meat industry, 4 in beverage production, and 4 in other food industry branches (mainly confectionary). Three of the cases and 2 of the controls were exposed to TRI during their employment in the food industry (maintenance workers) or during another job period.

A quarter of the patients were employed in wholesale and retail trade; no significant difference found between cases and controls here, or in the construction sector.

More than one fifth of the cases worked in agriculture, hunting and forestry activities – a rate slightly but not significantly higher than that observed for the controls.

Table 16: Major branches in which cases and controls were employed during their occupational history, according to NACE codes

percentages and conditional logistic regression,

	NACE Code	Cases	Controls	Crude OR [a] [95% CI*]	Adjusted OR [b] [95% CI*]
Screw-cutting workshops	28.52	22 (25.6%)	64 (20.3%)	1.48 [0.83; 2.63]	1.39 [0.75; 2.58]
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]
Any metal work involving possible cleaning	28.0 to 35.0 (except 32.0)	28 (32.6%)	106 (33.5%)	1.02 [0.61; 1.69]	1.02 [0.59; 1.76]
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 to 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 & 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 & 9.54	9 (10.5%)	27 (8.5%)	1.34 [0.57; 3.17]	1.40 [0.57; 3.45]
Construction	45.2 to 45.4	12 (14.0%)	53 (16.8%)	0.81 [0.40; 1.62]	0.84 [0.40; 1.76]
Textile workers	17.0 & 18.0	7 (8.1%)	13 (4.1%)	2.48 [0.81; 7.59]	2.47 [0.76; 8.02]
Wholesale and retail trade	51.0 & 52.0	22 (25.6%)	77 (24.4%)	[c]	[c]
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 work	85.1 & 85.2	8 (9.3%)	16 (5.1%)	1.94 [0.77; 4.91]	2.52 [0.96; 6.62]
Health and social work	85.1 to 85.3	11 (12.8%)	23 (7.3%)	1.99 [0.86; 4.63]	2.33 [0.97; 5.62]

* confidence interval
[a] Matched for gender and age
[b]. Matched for gender and age, adjusted for tobacco smoking divided into four classes, and for BMI divided into three classes
[c] The validity of the model fit is questionable

Table 17: Main jobs titles found among cases and controls according to the ILO 68 code: percentages and conditional logistic regression

	ILO 68 Code	Cases	Controls	Crude [a] OR [95% CI*]	Adjusted OR [b] [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 labourers	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 to 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		22 (25.6%)	87 (27.5%)	0.85 [0.47; 1.52]	0.77 [0.40; 1.47]

* confidence interval
[a] Matched for gender and age
[b] Matched for gender and age, adjusted for tobacco smoking divided into four classes and for BMI divided into three classes.

4.2.3 General occupational exposure (TRI excluded)

Whether over their whole life or over their whole life excluding the ten last years, cases tended more often to be subject to a range of occupational exposures (excluding TRI) than controls, except for exposure to petroleum and other solvents and to brazing (For two types of exposure, to oils (cutting fluids and other petroleum oils), the differences were significant at the level of 10% (p = 0.10) and were considered as potential confounders in the multivariate analysis.

Table 18), but the differences did not reach statistical significance.

For two types of exposure, to oils (cutting fluids and other petroleum oils), the differences were significant at the level of 10% (p = 0.10) and were considered as potential confounders in the multivariate analysis.

Table 18: Other occupational exposures: descriptive data and conditional logistic regression

Exposure			Cases	Controls	OR [a] [95.0% CI*]	p
Solvents	**Chlorinated (other than TRI)**		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 category**	**25 (29.1%)**	**70 (22.2%)**	**1.60 [0.93; 2.77]**	**0.09**
		Level 1	11 (12.8%)	26 (8.2%)	1.80 [0.85; 3.79]	0.12
		Level 2	4 (4.7%)	11 (3.5%)	1.79 [0.47; 6.81]	0.39
		Level 3	10 (11.6%)	33 (10.4%)	1.37 [0.62; 3.03]	0.44
	Other petroleum oils	**Any category**	**16 (18.6%)**	**40 (12.7%)**	**1.74 [0.90; 3.37]**	**0.10**
		Level 1	**14 (16.3%)**	**27 (8.5%)**	**2.24 [1.10; 4.56]**	**0.03**
		Level 2	2 (2.3%)	10 (3.2%)	0.89 [0.18; 4.34]	0.89
		Level 3	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
Ionising radiation (source)			5 (5.8%)	7 (2.2%)	2.53 [0.75; 8.56]	0.14

***CI = confidence interval**
[a] OR matched for sex and age

4.2.4 TRI exposure

In terms of exposure *per se,* regardless of level or duration, 37 (43.0%) cases and 110 (34.8%) controls were exposed to at least 5 ppm of TRI during at least one job period, and the overall odds ratio for RCC was 1.60 [0.95; 2.69]. Taking into account tobacco smoking status and last known BMI, the gender- and age-matched OR was 1.64 [0.95; 2.84].

The cumulative dose tertiles defined on the cumulative exposure distribution of controls were 5 to 150 ppm.years, 155 to 335 ppm.years and more than 335 ppm.years, respectively classified as low, medium and high cumulative doses. A significantly increased risk of RCC was identified for the highest cumulative dose: adjusted OR = 2.16 [1.02; 4.60]. A significant linear relation was also identified between cumulative dose and RCC risk (p=0.04).

To assess the effect of exposure to peaks of TRI, odds ratios were calculated for exposure to low or medium cumulative doses with or without peaks and for high cumulative doses with or without peaks. All classes of peak were grouped together, because only 33 persons were in fact exposed to peaks and very few to high peaks.

This specific analysis showed a trend towards an effect of peak exposure, the OR for a cumulative exposure class tending to be higher when peak exposures were also experienced (although these subjects may have experienced higher levels of cumulative exposure). Only one class, however, (high cumulative dose plus peaks) showed a significant increase in adjusted OR: OR = 2.73 [1.06; 7.07].

Two occupational exposures – to cutting fluids and to other oils – were found to increase RCC risk at the 10% threshold. (p=0.09 and p=0.10, respectively), but without correlation between the level of exposure and the magnitude of the relative risk.

However, there was a strong correlation between exposure to TRI and exposure to cutting fluids and other petroleum oils. In the case of cutting oils, 90.3% of patients exposed to cutting oils were also exposed to TRI, and 57.9% of those exposed to TRI were exposed to cutting oils. Moreover, 56.0% of cases exposed to cutting oils were also exposed to a high cumulative dose of TRI, as against only 44.0% of controls (Table 20).

Concerning other petroleum oils – the second occupational exposure identified as a potential confounding factor – the findings were similar to those for cutting oils: 83.6% of patients exposed to other oils were also exposed to TRI, and conversely 31.7% of those exposed to TRI were also exposed to other oils.

Finally, when exposure to cutting fluids and to other petroleum oils was added to the conditional logistic regression model (model 1), the OR for RCC in the highest class of cumulative TRI exposure was 1.96 [0.71; 5.37]. In this model, the OR for cutting fluids was close to 1 (Table 21).

In another conditional logistic regression including general factors (tobacco and BMI), cumulative exposure to TRI with or without peaks, and exposure to cutting fluids and other petroleum oils, the OR for high cumulative TRI exposure plus peaks was 2.63 [0.79; 8.83], close to the RCC risk observed for this class in the model presented in table 19. In this model the OR for cutting fluids exposures was less than 1.

Table 19: Conditional logistic regression

		Cases	Controls	Crude OR [a] [95.0% CI*]	Adjusted OR [b] [95.0% CI*]
Exposed to TRI 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	**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]**

*** Confidence interval**
[a] OR matched for sex and age
[b] OR matched for sex and age, adjusted for tobacco smoking divided into 4 classes, and for BMI divided into 3 classes.

Table 20: Proportion of patients exposed to TRI and cutting oils

Cutting fluids / **TRI exposure**	**No** Cases / Controls / Total	**Yes** Cases / Controls / Total	**Total** Cases / Controls / Total
No	46(75.4%)/200(81.3%)/246(80.1%)	3(12.0%)/6(8.6%)/9(9.5%)	49(57.0%)/206(65.2%)/255(80.7%)
Low	8(11.1%)/23(9.3%)/30(9.8%)	4(16.0%)/15(21.4%)/19(20.0%)	12(14.0%)/37(11.7%)/49(15.5%)
Medium	5(8.2%)/18 (7.3%)/23(7.5%)	4(16.0%)/18(25.7%)/22(23.2%)	9(10.5%)/36(11.4%)/45(14.2%)
High	2(3.3%)/6(2.4%)/8(2.6%)	14(56.0%)/31(44.3%)/45(47.4%)	16(18.6%)/37(11.7%)/53(16.8%)
Total	61(100%)/246(100%)/307(100%)	25(100.0%)/70(100%)/95(100.0%)	86(100.0%)/316(100.%)/402(100.0%)

Table 21: Conditional logistic regression including all potential confounding factors

		OR [a] [95.0% CI*]	p
Model 1			
Cumulative exposure to TRI	Low	1.52 [0.66; 3.49]	0.32
	Medium	1.07 [0.39; 2.88]	0.90
	High	1.96 [0.71; 5.37]	0.19
Cutting fluids		1.04 [0.47; 2.32]	0.91
Other petroleum oils		1.19 [0.56; 2.56]	0.65
Tobacco smoking (Pack-years)	[1 to 20[	1.62 [0.81; 3.24]	0.17
	[20 to 40[	1.54 [0.69; 3.45]	0.30
	40 and more	**3.26 [1.44; 7.41]**	**<0.01**
Body Mass Index	25.00 – 29.99 “Pre-obesity”	**1.92 [1.08; 3.41]**	**0.02**
	≥ 30.00 “Obesity”	**2.18 [1.08; 4.39]**	**0.03**
Model 2			
Cumulative dose plus peaks	Low/medium No peaks	1.30 [0.60; 2.19]	0.51
	Low/medium + peaks	1.52 [0.32; 7.15]	0.59
	High No peaks	1.64 [0.51; 5.28]	0.40
	High + peaks	2.63 [0.79; 8.83]	0.12
Cutting fluids		0.97 [0.43; 2.19]	0.94
Other petroleum oils		1.22 [0.56; 2.63]	0.62
Tobacco smoking (Pack-years)	[1 to 20[	1.63 [0.81; 3.26]	0.17
	[20 to 40[	1.54 [0.69; 3.44]	0.29
	40 and more	**3.14 [1.39; 7.09]**	**<0.01**
Body Mass Index	25.00 – 29.99 “Pre-obesity”	**1.91 [1.07; 3.40]**	**0.03**
	≥ 30.00 “Obesity”	**2.19 [1.09; 4.43]**	**0.03**

*** confidence interval**
[a] OR matched for sex and age

To search for a possible threshold effect, three exposure levels were chosen according to occupational exposure limits: 75 ppm (the French *VME*), 50 ppm (the ACGIH’s TWA), and 35 ppm (half the French *VME*). A significant link was observed between RCC and an exposure level of 50 ppm or more during at least one job period, with an OR of 3.13 [1.32; 7.44]. This increase in RCC risk remained significant after the possible confounding effect of tobacco smoking and BMI were taken into account: OR = 2.80 [1.12; 7.03]. After adjustment for all confounding factors, exposure to cutting fluids and other oils included, the odds ratio, although high, was no longer statistically significant OR = 2.76 [0.87; 8.80].

The same applies to an exposure level of 75 ppm or more, the OR amounting to 3.48 [1.11; 10.90] and the OR adjusted for all confounding factors to 2.59 [0.63; 10.71].

4.2.5 Analysis with a lag of 10 years

Excluding the last 10 years of exposure before the date of the case's RCC diagnosis did not greatly modify the results. In fact the number of exposed cases was the same and only 2 controls considered exposed for the whole-life period were re-classified as non-exposed. The consequence of this modification of exposure status was a slightly higher and almost significant odds ratio for exposure status alone, regardless of cumulative dose (Table 22).

The cumulative dose category distribution of patients is slightly different. However, the odds ratios are almost the same as when all exposure periods are considered.

Finally the only major difference concerns the crude and adjusted odds ratio observed for the high class of exposure with peaks, which are about 10% higher in the lagged analysis.

To further test for a latency effect, the earliest exposures, occurring around the beginning of patients' careers (epoch 2: before the median control exposure duration) were examined. Percentage TRI exposure was very low for this epoch and very similar in both groups: 5.8% for cases and 5.7% for controls.

Table 22: Conditional logistic regression with a lag of 10 years for exposure to TRI

		Cases	Controls	Crude OR [a] [95.0% CI*]	Adjusted OR [b] [95.0% CI*]
Exposed to TRI during at least one job period	**Non-exposed**	49 (57.0%)	208 (65.8%)	1	1
	Exposed	37 (43.0%)	108 (34.2%)	1.66 [0.99; 2.79]	1.68 [0.97; 2.91]
Cumulative dose	**Non-exposed**	49 (57.0%)	208 (65.8%)	1	1
	Low	12 (14.0%)	37 (11.7%)	1.51 [0.72; 3.18]	1.61 [0.75; 3.45]
	Medium	10 (11.6%)	37 (11.7%)	1.29 [0.58; 2.89]	1.27 [0.53; 3.03]
	High	15 (17.4%)	34 (10.8%)	**2.25 [1.09; 4.65]**	**2.16 [1.01; 4.65]**
Cumulative dose plus peaks	**Non-exposed**	49 (57.0%)	206 (65.2%)	1	1
	Low/medium No peaks	19 (22.1%)	65 (20.6%)	1.37 [0.73; 2.56]	1.44 [0.74; 2.80]
	Low/medium + peaks	3 (3.5%)	9 (2.9%)	1.66 [0.40; 6.88]	1.38 [0.32; 6.02]
	High No peaks	7 (8.1%)	22 (7.0%)	1.64 [0.61; 4.37]	1.50 [0.53; 4.21]
	High + peaks	8 (9.3%)	12 (3.8%)	**3.08 [1.22; 7.76]**	**3.15 [1.19; 8.38]**

*** Confidence interval**
[a] OR matched for sex and age
[b] OR matched for sex and age, adjusted for tobacco smoking divided into 4 classes, and for BMI divided into 3 classes.

4.2.6 Analysis of high-confidence TRI exposure data for non-deceased subjects under 80 years of age

To assess the impact of including deceased patients (proxy interviews) and elderly patients (over 80 years of age), a specific analysis was performed including only alive patients under 80 years of age. Moreover, only job periods with a high level of confidence with respect to TRI exposure were here considered as exposure periods. In other words, when the confidence level for a job period was 1, the patient was considered as non-exposed for this period. Otherwise, the analysis was performed as previously described.

The analysis concerned 60 cases and 225 controls. Results are presented in Table 23.

A total of 25 (41.7%) cases were exposed to TRI, as against only 79 (35.1%) controls. The difference in TRI exposure history was substantial for the highest cumulative exposure doses. 21.7% of cases were in the high cumulative TRI dose range, as against only 12.4% of controls: crude OR = 2.18 [0.99; 4.83] and adjusted OR = 2.04 [0.90; 4.65].

The same is true for the highest cumulative dose plus peaks: 13.3% of cases were in this group as against only 5.3% of controls: crude OR = 2.88 [1.13; 7.36] and adjusted OR = 2.70 [1.02; 7.17].

Finally, the ORs are very similar to those observed in the first step of analysis, where all patients were included whatever their age, vital status and TRI exposure confidence level.

Table 23: Conditional logistic regression considering only job periods with a medium or high level of TRI exposure confidence. Only living patients under 80 years of age were considered.

		Cases (n=60)	**Controls (n=225)**	**Crude OR[a] [95.0% CI*]**	**Adjusted OR[b] [95.0% CI*]**
Exposed to TRI during to at least one job period	**Non-exposed**	35 (58.3%)	146 (64.9%)		
	Exposed	25 (41.7%)	79 (35.1%)	1.51 [0.80; 2.86]	1.43 [0.74; 2.74]
Cumulative dose	**Non-exposed**	35 (58.3%)	146 (64.9%)	1	1
	Low	4 (10.0%)	23 (10.2%)	0.82 [0.24; 2.74]	0.91 [0.28; 2.97]
	Medium	8 (13.3%)	28 (12.4%)	1.32 [0.52; 3.36]	1.19 [0.45; 3.15]
	High	13 (21.7%)	28 (12.4%)	**2.18 [0.99; 4.83]**	2.04 [0.90; 4.65]
Cumulative dose plus peaks	**Non-exposed**	35 (58.3%)	146 (64.9%)	1	1
	Low/medium No peaks	10 (16.7%)	44 (19.6%)	1.06 [0.46; 2.43]	1.03 [0.44; 2.41]
	Low/medium + peaks	2 (3.3%)	7 (3.1%)	1.32 [0.25; 6.99]	1.12 [0.21; 6.06]
	High No peaks	5 (8.3%)	16 (7.1%)	1.53 [0.50; 4.70]	1.39 [0.43; 4.46]
	High + peaks	8 (13.3%)	12 (5.3%)	**2.88 [1.13; 7.36]**	**2.70 [1.02; 7.17]**

*** Confidence interval**
[a] OR matched for sex and age
[b] OR matched for sex and age, adjusted for tobacco smoking divided into 4 classes, and for BMI divided into 3 classes.

4.2.7 Analysis of data for cases with a diagnosis of Renal Clear Cell Cancer (RCCC)

On the scientific committee's request, this specific analysis was added because some studies of occupational factors for RCC have considered only RCCC.

73 cases had a diagnosis of RCCC, and this specific analysis further concerned 273 controls. The rate of cases exposed to TRI tended to be higher than that of controls, at 42.5% versus 35.2%, but this difference was not significant, and the odds ratio was slightly lower than when all RCC cases are taken together (Table 24).

The same pattern was observed for cumulative TRI exposure, cases tending to be more often exposed to TRI than controls, mainly for the high category of TRI exposure, but with no significant difference and the odds ratio lower than for all RCC cases taken together OR = 1.83 [0.83; 4.01].

Only one association between RCCC and TRI exposure remained strong – for the highest exposure level plus peaks: OR = 2.60 [0.99; 6.83].

Table 24: Conditional logistic regression for RCCC only

		Cases (n=73)	Controls (n=273)	Crude OR [95.0% CI*]	Adjusted OR** [95.0% CI*]
Exposed to TRI during at least one job period	**Non-exposed**	42 (57.5%)	170 (64.8%)	1	1
	Exposed	31 (42.5%)	96 (35.2%)	1.50 [0.86; 2.63]	1.55 [0.86; 2.80]
Cumulative dose	**Non-exposed**	42 (57.5%)	170 (64.8%)	1	1
	Low	11 (15.1%)	34 (12.5%)	1.46 [0.67; 3.15]	1.58 [0.71; 3.50]
	Medium	8 (10.9%)	30 (11.0%)	1.23 [0.51; 2.98]	1.17 [0.45; 3.04]
	High	12 (16.4%)	32 (11.7%)	1.83 [0.83; 4.01]	1.85 [0.81; 3.21]
Cumulative dose plus peaks	**Non-exposed**	42 (57.5%)	170 (64.8%)	1	1
	Low/medium No peaks	17 (23.3%)	59 (21.6%)	1.30 [0.68; 2.51]	1.36 [0.67; 2.74]
	Low/medium + peaks	2 (2.7%)	5 (1.8%)	1.91 [0.31; 11.60]	1.60 [0.25; 10.47]
	High No peaks	5 (6.9%)	20 (7.3%)	1.25 [0.42; 3.72]	1.24 [0.39; 3.92]
	High + peaks	7 (9.6%)	12 (4.4%)	**2.60 [0.99; 6.83]**	**2.71 [0.98; 7.52]**

*** Confidence interval**
**** OR adjusted for tobacco smoking divided into 4 classes, and for BMI divided into 3 classes.**

4.2.8 Data analysis for patients lost to follow-up and for those who refused to participate

18 (60.0%) of the cases not included were patients of local urologists, 10 (33.3%) had been treated in one of the teaching hospitals, and 2 (6.7%) had been put forward by the Geneva cancer register. For the cases included in the study, the figures are respectively 67 (77.9%), 18 (20.9%), and 1 (1.2%). In other words, it was more difficult to include cases not treated by a local urologist (p=0.06).

78 (88.6%) of controls lost to follow-up or who refused to participate had been treated by local urologists and 10 (13.2%) were selected from GP lists, while 258 (81.6%) of controls included were recruited via local urologists and 58 (18.4%) via their GP. The difference between controls included and not included was not significant (p=0.12).

The birthdates distribution was similar between cases included and not included in the study (Table 25). In contrast, controls not included were older than those included, being more often born before 1940 (p=0.02).

The proportions of men and women were similar between cases not included and controls not included: 11 (36.7%) of cases were women and 19 (63.3%) men, and for controls the figures were 30 (34.1%) and 58 (65.9%) respectively. Likewise, 27 (31.4%) of cases included were women and 59 (68.6%) were men, while for controls the figures were respectively 95 (30.1%) and 221 (69.9%).

For 28 controls and 12 cases not included, no information on occupation and TRI exposure was available. Also, for 11 controls and 5 cases not included, exposure status was unknown, although information on occupation was available. Eight cases not included (or their family) declared they had never been exposed to TRI. The same was true for 37 non-included controls. Finally, 5 cases (16.6%) and 12 (13.6%) controls not included declared they had been exposed to TRI or had worked in screw-cutting workshops; however, it was difficult to determine to what extent these patients had been exposed: where information on their occupations was available, it concerned only their main or last job.

To assess the impact of controls lost to follow-up, an exposure value was randomly attributed to them in the light of the 34.8% exposure frequency found in included controls. The non-included control group was then added to the whole population and a new conditional logistic regression performed on 490 controls and 86 cases. The odds ratio obtained for RCC being linked to TRI exposure was 1.45 [0.89; 2.38], or slightly lower than that obtained with the population of patients actually included in the study (OR = 1.60 [0.95; 2.69]).

Table 25: Proportion of cases and controls according to their year of birth: comparison between patients included and not included in the study

	Cases included in the study	Cases lost to follow-up or who refused	Controls included in the study	Controls lost to follow-up or who refused
1910-1919	4 (4.7%)	2 (7.4%)	9 (2.8%)	5 (5.8%)
1920-1929	22 (25.6%)	6 (22.2%)	77 (24.4%)	27 (31.4%)
1930-1939	26 (30.1%)	9 (33.3%)	95 (30.2%)	29 (33.7%)
1940-1949	19 (22.1%)	8 (29.6%)	82 (25.9%)	13 (15.1%)
1950-1959	14 (16.3%)	2 (7.4%)	50 (15.8%)	10 (11.6%)
1960-1969	1 (1.2%)	0	3 (0.9%)	2 (2.3%)
Total	86 (100.0%)		316 (100.0%)	

4.2.9 Narcotic signs

➢ <u>Assessment of the level of narcotic signs</u>

Narcotic signs were assessed by two independent experts, on a previously designed scale. For each job period, a score was attributed according to the symptoms and how long the patient claimed to have experienced them. All in all, there was good inter-expert agreement (kappa = 0.71, p < 0.001; see

Table 26), although a few disagreements were observed, mainly in the choice between level 1 and absence of narcotic signs. In most cases, the experts finally managed to agree on re-examining the questionnaires in more detail. When a consensus was thus reached between the two experts, certain questionnaires were reassessed and the level of narcotic signs revised, so as to maximise inter-subject consistency. In the end, a third expert's assessment was requested for 14 patients.

Table 26: Assessment of the experts' agreement concerning presence and levels of narcotic signs.

		First expert					Total
		0	**1**	**2**	**3**	**4**	
Second expert	**0**	1,710	9	0	0	0	1,719
	1	84	136	6	3	11	240
	2	7	3	5	11	1	27
	3	5	2	2	23	1	33
	4	1	0	0	8	29	38
Total		1,807	150	13	45	42	2,057

narcotic signs were not assessed for two women who had never worked
Kappa = 0.71, p < 0.001

➢ Correlation between narcotic signs and TRI exposure level

From a more in depth analysis of the narcotic symptoms and their correlation with the TRI exposure level as assessed according to the task description, it can be seen that for 86.8% of non-exposed job episodes no narcotic signs were identified, and a further 9.9% job episodes were associated with only a few signs, scored at level 1 (Table 27). Likewise, 75.6% of exposed tasks resulted in no narcotic signs and a further 13.2% resulted in only a few signs. In other words, as a test for exposure in a given job period, the narcotic signs scale showed a sensitivity of 0.24 and a specificity of 0.87.

For 1730 (85.8%) of the 2,016 job periods considered associated with no peak, no narcotic signs were observed, and only 78 job periods (3.9%) were associated with narcotic signs at level 2 or above. For 23 (56.1%) of the job periods considered associated with exposure to peaks of TRI, the patients reported no narcotic signs. Narcotic signs at levels 2 and above were reported for only 12 (29.3%) of these job periods. As a test for exposure to peaks in a given job period, the narcotic signs scale showed a sensitivity of 0.43 and a specificity of 0.86

Table 27: Level of narcotic signs according to the class of exposure assessed by task description for each job period

class of exposure (ppm)	Level of narcotic signs estimated by the experts					
	0	**1**	**2**	**3**	**4**	**Total**
0	1,530	175	17	27	13	1,762
< 35 ppm	168	24	3	7	11	213
[35 to 50[ppm	32	7	1	1	2	43
[50 to 75[ppm	13	6	0	2	2	23
[75 to 100[ppm	4	1	0	0	1	6
100 and more	6	1	0	0	3	10
Total	**1,753**	**214**	**21**	**37**	**32**	**2,057**

➢ Link between narcotic signs and renal cell cancer

A total of 35 (40.7%) cases and 96 (30.4%) controls described narcotic signs of any level.

Over the whole occupational life level 1 was observed for 21 (24.4%) cases and 61 (19.4%) controls, level 2 for 4 (4.7%) cases and 10 (3.2%) controls, level 3 for 5 (5.8%) cases and 16 (5.1%) controls, and level 4 for 5 (5.8%) cases and 9 (2.9%) controls.

The increase in risk of RCC linked to the presence of narcotic signs during at least one job period was not significant for any level of narcotic sign: 1.63 [0.97; 2.74]. If only signs above level 2 are considered, the OR amounts to 1.69 [0.86; 3.34]. The link between narcotic signs and RCC was not significant even when comparing groups with a maximum level of narcotic signs with patients who had never experienced any symptoms. For level 4, the OR was 2.50 [0.82; 7.6].

5 Discussion

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

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). It was possible to complete the recruitment of patients with the help of these practitioners. 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 hospital in Paris, and, to rule out any consequent selection bias, controls were selected from the list of the case-patient's urologist or GP. 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 tend to run a very similar risk of exposure to TRI or other such occupational exposures. Cases and controls were all patients, and the study was presented to them as an epidemiological study analysing the link between occupation and disease in general; they were not aware of their "case" or "control" status, and measurement bias is not likely

Another well-known form of bias in case-control studies is interviewer bias. In the present study, prior telephone contact and appointments were all co-ordinated 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 status (case/control) up to that time. One exception to this rule were interviews of the next-of-kin of living controls when the corresponding case was deceased. To assess any impact of interviewer bias such cases, a specific analysis was performed, excluding deceased cases and matched controls.

To ensure the power of the study, very elderly patients were also included if they agreed. As some forms of memory bias can be greater with elderly patients, a further specific analysis was made, excluding them too.

The study was carried out in 2002 and 2003, retrospectively for cases that had undergone nephrectomy since 1993 and prospectively until the end of June 2003. The participation rate was quite good for such a mainly retrospective study, at 74.4% for cases and 78.2% for controls.

A specific analysis was performed for patients lost to follow-up or who refused to participate. It was shown that their age and sex characteristics closely resembled those of included patients. The little information available on their possible occupational exposure did not allow any further comparison with included patients.

Whatever the criterion considered – patient's age when the case's RCC was diagnosed or date of birth divided into 6 epochs – no significant age differences were observed between cases and controls. The fact that the requested number of controls per case was not always reached did not introduce any bias in the mean age of the groups. The sex ratio was also nearly similar in both groups: 68.6% of cases and 69.9% of controls were men. This sex ratio for RCC has already been observed [93]. In the United States, RCC occurs nearly twice as often in men as in women [65].

Estimates from both cohort and case-control studies place cigarette smokers at about twice the risk-level of non-smokers for developing renal cell carcinoma [51, 44, 41]. The present study found a higher frequency of tobacco smoking history among cases, with 62.9% of current or former smokers compared to 51.6% for controls. The odds ratio for tobacco smoking was consistent with the literature, amounting to 1.84 [1.04; 3.25].

Some studies have reported a dose-response with the amount of cigarettes smoked [62, 44]. In a study carried out by Mallengaard et al., total consumption of more than 40 pack-years was, in male subjects, associated with an increased risk compared to non-smokers (OR = 2.3 [1.1; 5.1]). For Kreiger et al., duration rather than intensity of smoking was associated with an increased risk of RCC [41]. In the present study, a dose-effect relationship was found between RCC and smoking, cumulative dose being calculated in pack-years and divided into four classes: non-smokers, 1 to 20 pack-years, 20 to 40 pack-years, and more than 40 pack-years ($p<0.001$). For the highest class, the odds ratio was 3.27 [1.48; 7.19].

As obesity has also been associated with an increased risk of RCC, BMI was calculated and classified into 3 categories (WHO definition: normal weight, pre-obesity and obesity). McCredie's study [54] 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 [92, 2]. In the present study, cases were found to have a lower BMI at the age of 20 than controls; nevertheless, a significantly increased risk of RCC was identified for BMI of 30 or more, indicating a link between obesity and RCC.

Other non-occupational factors for RCC have been identified in the literature. Various urological conditions have been suspected in the etiology of renal parenchyma cancer. Some studies found associations with kidney stones and infection [56]. Chronic dialysis is also an exacerbating factor [65]. In the present study, no significant differences emerged between cases and controls for these factors: indeed, a history of kidney stones tended to be more frequent among *controls*, a great number of whom were recruited from urologists.

Diagnosed hypertension also seems to raise the risk of RCC [87, 41], as do anti-hypertensive drugs. McCredie et al. found a risk ratio of 1.8 [1.3; 6.6] for β-blockers and 1.6 [1.1; 2.4] for α- blockers (RR adjusted for age, sex, obesity and smoking). In the present study, whatever the variable considered (diagnosed hypertension, or treatment for hypertension), there was no significant difference between cases and controls. Only one type of treatment – β-blockers – seemed at first to be more frequent among cases; but more detailed analysis of the treatments that patients declared they had taken showed the proportion actually treated with β-blockers to be the same in both groups.

Diuretics, analgesics, phenacetin or paracetamol have also been suspected of increasing risk of RCC [55, 46]. The present study 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 therefore a greater probability of being ill and taking medications.

As in other case-control studies, cases had more often than controls been employed in industries associated with potential TRI exposure, such as manufacture of metal products and metal-work involving possible cleaning. Mattioli et al. found an increased OR of 2.21 [0.99; 5.37] for metalworkers [51]. In the consecutive case-control study carried out in Germany by

Brüning et al., any exposure in metal degreasing was an RCC risk factor (OR = 5.57 [2.33; 13.32]) [14].

In the present study, 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 were only obtained for exposure toTRI.

Employment in the chemical industry appears to be associated with an increased risk of RCC: 10.5% of cases worked in such branches, compared to 5.4% of controls (OR, 2.66 [1.02; 6.91]).

Analysing job titles coded according to the ILO 68 code found few differences between cases and controls. Only one category appeared to be more often observed among cases: medical and related workers. An increased risk of RCC was also identified for launderers, dry cleaners and pressers; but the difference failed to attain significance (OR = 2.75 [0.54; 13.99]). Nevertheless, these results are in agreement with the increased risk of RCC for people exposed to chlorinated solvents, as previously described in several studies [48,53,61].

The main occupational exposures described in the literature as increasing the risk of RCC were assessed in the present study: solvents (chlorinated, petroleum derivatives, oxygenated, other solvents), oils (cutting fluids, other petroleum oils), welding fumes, metals (lead and cadmium), asbestos and ionising radiation. No association between RCC and these exposures was found to be significant at the 5% testing level, maybe in some instances 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.

In the present study the odds ratio between RCC and TRI exposure was 1.6 and did not reach statistical significance. A statistically significantly increased RCC risk was only observed in the high dose category of TRI. Allowing for tobacco smoking, a significant twofold risk could be shown for high cumulative doses (OR = 2.16 [1.02; 4.60]). A dose-response relationship was also identified, as was an effect of peak exposures. The adjusted OR for highest class of cumulative exposure plus exposure to peaks being even higher (OR = 2.73 [1.06; 7.07]).

After adjustment for exposure to cutting fluids, the increased risk of RCC linked with the highest cumulative dose was no longer statistically significant, probably because of lack of power. Indeed, many patients had been exposed to TRI in screw-cutting workshops, where cutting fluids are widely used, making it difficult to distinguish between effects from cutting oils and from TRI. However, modelling 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 TRI was close to 2. Moreover, when exposure to cutting oils is divided into 3 levels, a decrease in OR is observed with level of exposure, probably because workers exposed to high levels of cutting oil are exposed to low levels of TRI (e.g., screw-cutters are usually exposed to medium to high levels of cutting oil fumes and to low levels of TRI when checking their production) whereas workers exposed to high levels of TRI are exposed to low levels of cutting oil (e.g., washers are exposed to high levels of TRI with low exposure to cutting oils from the metal parts they receive for degreasing). A link between RCC and exposure to cutting oils has already been identified in a case-control study by Brüning et al. [14], with an OR for an exposure to cutting oils of 4.92 [1.70; 14.27]. However, interaction between exposure to cutting fluids and to TRI was not assessed in that study.

Brüning reported a smaller increase in RCC risk in subjects exposed to TRI than that described by Vamvakas et al. (OR 10.8 [3.4; 34.8]) in a case-control study carried out in a geographic area where occupational exposure to TRI had been identified as being very high. This study was criticised because of several sources of bias in control recruitment and of the exposure assessment methodology [8,16,29, 75]. In the same geographic area, a new case-control study was designed [14] and the TRI-related risk of RCC was confirmed after adjustment for age, gender and smoking. Using the CAREX database, a significant excess risk of RCC was found for industries with any TRI exposure (OR 1.80 [1.01; 3.20] for the longest-held job in such industries). A significant excess risk was associated with self-assessed TRI exposure (OR 2.47 [1.36; 4.49]).

Most of the cohort studies carried out to investigate the association between TRI exposure and RCC have shown no significant increase in risk.

Axelson et al. [4] found no significant increase in renal cell carcinoma in a cohort study including 1,670 workers exposed to low levels of TRI. Anttila et al. studied incidence in Finnish workers (2,050 males and 1,924 females) exposed to halogenated hydrocarbons including TRI, and did not identify any association with kidney cancer [1] (SIR, 1.2 [0.4; 2.5]).

In a cohort of 14,457 aircraft maintenance workers exposed to TRI and other chemicals, kidney cancer incidence was not significantly increased compared to the general population of Utah [7] (OR, 1.6 [0.5; 5.4]).

A cohort mortality study conducted in California on 77,965 aircraft manufacturing workers found no increased risk of kidney cancer for workers exposed to TRI or perchloroethylene [11].

A slightly elevated rate ratio was found in a study by Morgan et al. [64] of mortality in aerospace workers exposed to TRI. For those with peak exposure at medium and high levels, the rate ratio was 1.89 [0.85; 4.23].

More recently, cancer occurrence was assessed in 803 Danish workers exposed to TRI: no increase in RCC was found in this population (SIR for RCC = 0.9 [0.2; 2.6] [32]).

Few studies of RCC and TRI exposure have been based on a detailed TRI exposure assessment. Indeed, assessing historical exposure levels is always difficult and rather imprecise, especially in the general population, where working conditions and industrial health and safety measurements are very diverse. In the present study area, however, all the various screw-cutting plants may be assimilated to so many workshops in a single large factory: the occupational physicians of the area work together, dedicated to the same geographical and industrial network almost totally specialized in that kind of metal machining; moreover, they have collaborated in many health and safety surveys over a range of workshops (air monitoring) and workers (biological monitoring), so that the local hygiene data are more plentiful and coherent than one could expect in the general population.

The exposure assessment approach used in the present study is therefore close to that of some cohort studies [1, 45,64,72], but enhanced by the possibility of directly interviewing the subjects. The goal was to make ‘quantitative’ estimates that would be as precise as possible, combining existing data with detailed and accurate job descriptions. Consequently, a documented occupational questionnaire was developed, alongside exposure estimates for the main routine tasks in screw-cutting shops. These exposure estimates were based on both biological and air monitoring data, sometimes resulting in comparisons and connections between these two parallel ways of monitoring exposure. As far as possible, we tried to compare the levels obtained from our task-estimates with those in the scientific literature; while numerous measurements have been made for open and half-open hot degreasers, few data were available for cold use of TRI, either in tanks or in individual tins. Nevertheless, generally speaking, measurements found in the industrial hygiene literature testify to the same range of levels as those from the Arve Valley:

- An emission level of 15 ppm, or 30 to 100 ppm [20,42] above an open-top cold tank; cf. our own washing-estimates of 18 ppm as the basic emission level around the tank, and 50 ppm directly above the tank.
- Peaks from 400 to 600 ppm for work above an open-top vapour degreaser, with an average emission level from 100 to 150 ppm [5,72,89]; cf. our estimates of 120 ppm as basic emission level, and 300 ppm + peaks above 400 ppm directly above the tank.
- Peaks from 200 to 400 ppm for work above a half-open vapour degreaser, with an average emission level from 20 to 70 ppm [43,60]; cf. our estimates of 35 ppm as basic emission level, and 75 ppm + peaks above 200 ppm directly above the tank.

Regarding job descriptions, which are quite as important as the task exposure matrix for the quality of the assessment, it appears that most subjects were able to answer technical questions about TRI use satisfactorily, giving an accurate description of their jobs/tasks/activities, with the help of a trained interviewer. Not surprisingly, in the part of the study population not involved in screw-cutting, use of TRI, while not rare, was limited to little cold degreasing tasks. Workers involved in screw-cutting shops were not systematically exposed to TRI (use of petroleum solvents, degreasers in closed area, etc.), but 60% of them described hot TRI use in the shop – which was one of the features that lead us to undertake a study in that area in the first place.

The level of information about TRI asked for in screw-cutting shops was quite different from that asked for in other occupations; nevertheless the usual way of using TRI, as a cold degreaser on a rag or in a little tin, was easy to describe in the general questionnaire.
Other more incidental uses of TRI (in the chemical industry, for example) were less easy for subjects to describe, and for the interviewer to understand and transcribe, with resultant imprecision and possible under- or over-estimation.
The question in the screw-cutting questionnaire about the presence of a cold degreaser in the workshop was a lot less frequently affirmatively answered than most, and only appliances in close proximity to the respondent were described; the under-assessment this could entail was, however, minimal, as exposure levels due to emissions from a cold tank are very slight, even within a few meters from it. Nevertheless, some very low level TRI exposures may have been overlooked here.

Though comparison between our task-exposure matrix and exposure levels reported in the scientific literature shows more-or-less equivalent assessments for equivalent tasks, and information obtained from subjects' descriptions seemed coherent with what is known in general and what the Valley's occupational physicians were able to confirm, it is also important to compare the final levels assessed in our study population to those in other populations exposed to TRI in other epidemiological studies.

The Danish population in Raschou-Nielsen's study presented geometric means of about 60 ppm for people exposed between 1947 and 1959, then 48 ppm, 10 ppm and 0.5 ppm for the 3 subsequent decades. This population included Danish workers and jobs monitored by the Danish Labour Inspection, sometimes during routine surveys, but also in response to complaints, and therefore partly in worst-case situations. Results showed that "the proportion of exposed workers decreased with increasing size of the company in all industries", which is coherent with our findings in the Arve Valley of a high rate of workers exposed and a lot of small companies, even at the present day. The Danish results in the metal industry and especially in metal degreasing, as well as the literature presented in the report, are totally comparable with ours, with individual values for degreasers of above 75 ppm (and some arithmetic means reaching 140 ppm).

In the cohort described by Axelson et al, almost all Swedish workers exposed to TRI ("some 1,100 workers with exposure in 1970 and later, most of them with a fairly low exposure") were examined (biomonitoring performed by Swedish TRI producers for all customers). Exposure in this cohort was assumed to be about 20 ppm or less for over 80% of subjects, depending on how urine sampling and atmospheric levels were correlated [3].

In almost the same way, all Finnish workers "regularly exposed" to TRI were biomonitored between 1963 and 1992 and included in a cohort [1,77], with very low U-TCA levels: median exposure below 15 ppm before 1970 and below 10 ppm later. In addition to the results provided by the routine survey, 109 measurements secondary to TRI poisoning were included, which would tend to raise the average levels.

These averages are to be seen in relation to the recruitment of the Finnish and Swedish subjects, who were mostly comparable those of our subjects who answered the general occupational questionnaire and were assessed in the 5-35 ppm exposure bracket.

The populations in these 3 cohort studies came from the general working population of their respective countries, as did ours – but with 2 main differences: French occupational exposure limits are higher (occupational exposure limits in 1975: French = 75 ppm, Danish and Swedish = 30 ppm), and our study population, though a general one, was specifically chosen to present relatively great use of TRI.

In the cohort study presented in 1998 by Morgan et al. for aerospace workers either working with degreasing machines or located more or less in their vicinity, 'high exposed' subjects were assessed as being exposed to about 50 ppm.

In their study of aircraft workers, Stewart et al. provided a semi-quantitative exposure assessment with descriptions and estimated levels for the main exposing tasks in the facility. These descriptions were close to what was observed in the Arve Valley workshops (degreasers located in the general hangars, with poor maintenance and ventilation at the beginning of the study period, etc.) leading to peak levels consistent with those observed in our study. While not explicitly stated, average exposure may be estimated from certain information given (frequency, duration and level of tasks). Depending on how they are calculated, these levels may reach 50 ppm for vapour degreasers (TWA-8h at the earliest time), and 10 ppm for those involved in manual cold TRI use at the bench (Cherrie, 2001); or, applying our own Task-Exposure Matrix estimates to Stewart's task descriptions, [(300 ppm x 15 min x 5 times a day) + a background exposure of about 20 ppm in the shops housing the degreasers] = 65 ppm + peaks, as a maximum average exposure to TRI in our study. As far as it is possible to make comparisons, levels of 'high' exposure, even in the worst period were lower than ours, probably due to the lower frequency of degreasing tasks for the 'washers' described by Stewart, and to slower technological progress in degreasing machines in these small French workshops. In that mortality study, no trend in RCC risk was identified, based on 23 cases.

Other cohort studies do not allow comparison of exposure levels, except for a small cohort study in a cardboard factory (Henschler et al.), which includes some exposure descriptions to correlate with levels of TRI consumption in the factory. As in Stewart's study, an assessment of TRI levels may be attempted. Cherrie proposed a long-term average exposure of about 10 to 225 ppm for the most exposed people involved in hot felt degreasing, with peaks reaching 2,000 ppm. Using our own estimates, these tasks would be assessed at an extreme exposure of 2,000 ppm x 2.5 times a month x 5h each time = 135 ppm (from 60 to 270 ppm depending on how ‘extreme’ the level). Of the 5 cases observed in Henschler et al.’s study, only 2 were exposed in this way, while 3 were ‘continuously exposed to lower levels’ of cold TRI by hand dipping; these 3 cases might be exposed to 30 to 80 ppm at most, depending on the size of the container they used and concomitant practices (use of TRI to clean floors, overalls and hands was also described in the cardboard factory). Therefore, insofar as these assumptions approximate the actual exposure, levels in this cohort study could be much higher than ours, mainly in terms of high and peak exposure.

Most case control studies in general populations do not provide precise enough information about exposure to TRI for any comparison to be made. The information mainly provided is whether a degreasing agent was used or not.

This comparison with other epidemiological populations would seem to indicate that our study population was in an intermediate situation in terms of TRI exposure: while 50% of subjects received low exposure, under 15 ppm, 10% were exposed to levels above the health and safety limits of many countries in the main study period (e.g., ACGIH and MAK= 50 ppm), with 11% exposed to peaks above 200 ppm; nevertheless some cohort populations, and especially the one in the German cardboard factory, have shown higher exposure.

Narcotic symptoms were studied using a specific questionnaire. As some signs such as headaches were linked with specific diseases (such as migraine), signs were assessed by two experts and classified on a dedicated 5-point scale. While patients described symptoms classified as narcotic signs for a few job periods considered associated with zero exposure, only 24.4% of the job periods involving TRI exposure were described by patients as inducing narcotic symptoms. The sensitivity of narcotic signs for predicting exposure to TRI was higher for peaks: narcotic signs were identified for 43.9% of the 41 job periods considered to be associated with an exposure to TRI peaks. A few studies have focused on the link between narcotic signs and TRI exposure levels. Two studies carried out in France found no link with narcotic signs, some workers exposed to high TRI levels having no sign while workers exposed to lower levels described headaches or nausea [6]. Therefore, it seems impossible to use these signs to assess occupational exposure to TRI. Vamvakas et al. used this approach combined with a task-based assessment to quantify levels of exposure to chlorinated solvents. However, the narcotic symptoms assessed were those following exposure to trichloroethylene or to perchloroethylene. In the present study, narcotic signs were collected for all of the patients (cases and controls) and the link between signs and work was assessed by asking whether the rhythms of signs and work matched. Levels of exposure were assessed independently. It is quite surprising that all of Vamvakas’s cases exposed to TRI described narcotic signs, whereas in the present study several subjects exposed to high levels of TRI did not report any sign. Indeed, as for other solvents, habituation phenomena are observed for exposure to TRI.

6 Conclusion

In summary, the present study suggests that there is a weak association between occupational TRI exposure and increased risk of renal cell carcinoma although the overall measure of association did not reach statistical significance. The association seems to be less strong than previously reported by some epidemiologic studies conducted in Germany and concerns only the highest exposure levels. After adjustment for the confounding effect of tobacco smoking and body mass index, a significant twofold 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 TRI peaks also increased the risk of RCC. 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 epidemiologic studies conducted in Germany.

If epidemiological arguments for TRI's carcinogenicity are now available, the biological mechanisms remain to be explained. A specific pattern of Von Hippel-Lindau mutation has been reported in renal cell carcinoma in individuals with a history of prolonged high-level TRI exposure [13]. It will therefore be interesting to consider the results of a molecular study currently being performed on VHL mutations associated with trichloroethylene among cases included in the present case-control study.

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8 Appendices

Appendix 1: Geographic area

Appendix 2: List of towns

Zone1:

Canton de BONNEVILLE

- ▫ AYSE
- ▫ BONNEVILLE
- ▫BRIZON
- ▫CONTAMINE SUR ARVE
- ▫ENTREMONT
- ▫FAUCIGNY
- ▫MARCELLAZ
- ▫MARIGNIER
- ▫MONT SAXONNEX
- ▫PEILLONNEX
- ▫LE PETIT BORNAND LES GLIÈRES
- ▫THYEZ
- ▫VOUGY

Canton de CLUSES

- ▫ARÂCHES
- ▫CLUSES
- ▫MAGLAND
- ▫SAINT SIGISMOND

Canton de REIGNIER

- ▫ARBUSIGNY
- ▫FILLINGES
- ▫MONNETIER-MORNEX
- ▫LA MURAZ
- ▫NANGY
- ▫PERS-JUSSY
- ▫REIGNIER
- ▫SCIENTRIER

Canton de La ROCHE-SUR-FORON

- ▫AMANCY
- ▫ARANTHON
- ▫CHAPELLE-RAMBAUD
- ▫CORNIER
- ▫ÉTAUX
- ▫LA ROCHE-SUR-FORON
- ▫SAINT LAURENT
- ▫SAINT PIERRE EN FAUCIGNY
- ▫SAINT-SIXT

Canton de SALLANCHES

- ▫CORDON
- ▫COMBLOUX
- ▫DEMI-QUARTIER
- ▫DOMANCY
- ▫PRAZ SUR ARLY
- ▫SALLANCHES

Canton de SCIONZIER

- ▫MARNAZ
- ▫NANCY-SUR-CLUSES
- ▫LE REPOSOIR
- ▫SCIONZIER

Canton de SAINT JEOIRE

- ▫MÉGEVETTE
- ▫ONNION
- ▫ SAINT JEAN DE THOLOME
- ▫ SAINT JEOIRE
- ▫LA TOUR
- ▫VILLE-EN-SALLAZ
- ▫VIUZ-EN-SALLAZ

Canton de TANINGES

- ▫COTE D'ARBROZ
- ▫MIEUSSY
- ▫LA RIVIÈRE ENVERSE
- ▫TANINGES

Canton de BOËGE

- ▫BOËGE
- ▫BOGÈVE
- ▫BURDIGNIN
- ▫HABERE-LULLIN
- ▫HABERE-POCHE
- ▫SAINT-ANDRE-DE-BOEGE
- ▫SAXEL
- ▫VILLARD

Canton de SAINT GERVAIS

- ▫LES CONTAMINES MONTJOIE
- ▫PASSY
- ▫LE FAYET
- ▫SAINT GERVAIS LES BAINS

Zone 2:

Canton d'ANNEMASSE SUD

- ▫ARTHAZ-PONT-NOTRE-DAME
- ▫BONNE
- ▫ÉTREMBIERES
- ▫GAILLARD
- ▫VÉTRAZ-MONTHOUX

Canton d'ANNEMASSE NORD

- ▫AMBILLY
- ▫CRANVES SALES
- ▫JUVIGNY
- ▫LUCINGES
- ▫MACHILLY
- ▫SAINT-CERGUES
- ▫VILLE-LA-GRAND

Canton d'ANNEMASSE

- ▫ANNEMASSE

Appendix 3: Data from urologists

Urologist name:

Family Physician:

Patient family name: **Code Number**:

Given name:

Date of birth: **Place of birth**:

Sex:

Last known address:

Profession:

Date of diagnosis:

Anatomo-pathological diagnosis:

Date:
Diagnosis:

Anatomo-pathologist:

Name:
Address:

Other physician in charge of the treatment:

Date of the last medical examination:

Vital status of the patient:

Appendix 4: General occupational questionnaires

OCCUPATIONAL QUESTIONNAIRES:
THE JOB HISTORY (JH)

Could you please, list all jobs you have held after leaving school, until your current job or your retirement.

Include all major changes within a same company as separate jobs.

For each one, please detail
- ***starting and ending years***
- ***name and address (at least the city), of the company***
- ***your job title***

Subject's Identification Number: - - - - -

Job 1: from - - - - to - - - -
Company name:
Address of the company:
Job title:

Job 2: from - - - - to - - - -
Company name:
Address of the company:
Job title:

Job 3: from - - - - to - - - -
Company name:
Address of the company:
Job title:

Job 4: from - - - - to - - - -
Company name:
Address of the company:
Job title:

Job 5: from - - - - to - - - -
Company name:
Address of the company:
Job title:

Now, I would like to ask you some questions about each of your jobs in turn, starting by the oldest one. We are interested in the kind of tasks you have done, and the places you did these tasks, to get a picture as precise as possible of your various jobs and their environment.

OCCUPATIONAL QUESTIONNAIRES:

THE GENERAL OCCUPATIONAL QUESTIONNAIRE

Code Number:

JOB N° --- FROM - - - TO - - -

Q1: Can you describe in more detail the activities or products made by your company or employer?

Q 1b: How many people worked in your company?

Q2: Can you describe the place (room...) where you usually worked?

Indoor	|__|	in an office or a store	|__|
Outdoor	|__|	in a warehouse	|__|
underground	|__|	in production workshop / a plant	|__|
at home	|__|	in a laboratory	|__|

other place? If yes, which kind of place? ……………………

Q2a: How many people worked in this same place (or around you if you were outdoor)?

Q2b: What was approximately the size of the room?

Q3: Please, describe your specific tasks (what you did, and how you did it). If you performed different tasks, please start with the main one (the most time consuming).

Main task :

Other tasks:

Q 3a: How much time did you spend on your main task? (% of the day or of the week or of the month, or hours/day, hours/week, days/week: please specify)

Q 4: Which machine or equipment did you use?

Q 4a: If you used machines did you clean or maintain them?

YES --- NO ---

If YES, please describe how you did it:

Q 5: What kind of different jobs were done by others working nearby to you?

Note for interviewers: in case of clerical work without any possibility of exposure, please go straight to the next job description

Q 6: Were you exposed from your own tasks, or from a neighbour, to any chemical used as solvent, thinner, degreasing agent or cleaning agent (except detergents or soaps)?

YES - - - NO - - -

If yes, was it:

	Yes	No	DK	If yes, % time	If yes, for which use
Trichloroethylene					
Perchloroethylene					
Other chlorinated Solvent					
White spirit					
Kerosene					
Gasoline					
Other Petroleum solvents					
Other solvent, thinner, Degreasing agent Which one?					

Q 6a: If you were exposed to any chlorinated solvent, how did you used it, or how was it used by your neighbour?

	Yes	No	D K
In a cold way			
In a hot way, or as a vapour			
In a small box			
In a large open batch			
In a large closed batch			
Other: how was it used?			

Q 7: Were you exposed from your own tasks, or from a neighbour, to some petroleum oils?

YES - - -   NO - - -

If yes, was it:

	Yes	No	DK
Cutting fluids			
Lubricating oils			
Hydraulic fluids			
Other oils? Which ones?			

Q8: Were you exposed from your own tasks, or from a neighbour, to some metal dust?

YES - - -   NO - - -

If yes, was it:

	Yes	No	DK	If yes, for which use?
Lead				
Cadmium, or Cadmium plated parts				
Other metal?, which ones?				for which use? ....

Q 9: Did you install or remove any kind of insulation for thermal or phonic purpose?

YES - - -   NO - - -

If yes, was it:

	Yes	No	DK	If yes, for which use?
Glass or rock fiber				
asbestos				
Other insulating material? Which ones?				for which use? ....

Q10: What other materials or chemicals than those described before, did you use or were you exposed to?

For each one, can you specify their use (e.g. colouring agent,...) or function (e.g. raw material), or source of exposure (e.g. from a painter at my side)

Material or chemical	Use, or function, or source of exposure

Q 11: For one or more tasks, did you have any protective equipment?

YES - - - NO - - -

If yes, was it:

	Yes	No	DK	For which task?
Simple dust mask				
Air supplied mask				
Asbestos made equipment (gloves, screens)				
Exhaust ventilation				
Other (please specify)				

Appendix 5: Screw cutting questionnaire

Code Number:

JOB N° --- FROM - - - TO - - -

Q1: Can you describe in more detail the production of your company?

Q 1b: How many people worked in your company?

Q2: Can you describe the place (room, workshop ...) where you usually worked:

Which size? ....

How many people were working in this room? ....

Q 3: Did you have to move in other rooms / or workshops? YES - - NO - -

If Yes, for which reasons?
....
And for how many time?
....

Q 4: which were the machines and materials in the main workshop or room you were working in, (and in the other ones if necessary)

	In your main workshop		**In a secondary shop**		**How far were you from the closer one**
	NO	If Yes, How many	NO	If Yes, How many	
Screw cutting machines					
Digital driven machines					
washing machines in a cold phase					
Washing machines in a hot phase (or vapour) - open washing machine - half open washing machine - closed - with a drying channel					
Other machines? Which ones?					

Q 5: Did you do one or more of the following tasks?

	YES	NO	If Yes, % time
Screw cutter, or screw cutting helper			
Digital driven machine operator If yes, were metal parts still wet with TRI when you received it?	………..	………..	....
Metal parts checking If yes, were metal parts still wet with TRI when you received it?	………..	………..	………..
Metal plating If yes, was it nickel plating Chromium plating Cadmium plating	 ……….. ……….. ………..	 ……….. ……….. ………... .	 ……….. ……….. ………..
Washing with a cold solvent If yes, was it in a little box ('boite à Nétoline') In a large open batch With Trichloroethylene With another chlorinated solvent? Which one? With a petroleum solvent With another chemical? Which one?	 ……….. ……….. ……….. ……….. ……….. ………..	 ……….. ……….. ……….. ……….. ……….. ………..	 ……….. ……….. ……….. ……….. ……….. ………...
Washing with a hot solvent If yes, was it With Trichloroethylene With another chlorinated solvent? Which one? With a petroleum solvent With another chemical? Which one?	 ……….. ……….. ……….. ………..	 ……….. ……….. ……….. ………..	 ……….. ……….. ……….. …………
Emptying / filling in washing machines with solvent If yes, was it done in a manual way automatically	 ……….. ………..	 ……….. ………..	 ……….. ………..
Cleaning of the washing machine, scraping mud, ... If yes, was it done with a ventilated mask?	 ………..	 ………..	 ………..
Solvent distillation	………..	………..	………..

Other tasks involving a Trichloroethylene use (cleaning floors, ...) If yes, which ones?	………..	………..	………..
Machine maintenance, other than for TRI cleaning or recovering If yes, did you do maintenance of brakes or clutches?	………..	………..	………..
Installation or removal of any insulation material If yes, was it rock or glass wool Asbestos Other? Which ones?	……….. ……….. ………..	……….. ……….. ………..	……….. ……….. ………...
Other tasks than those described above? If yes, which ones and			how many time? ....

Appendix 6: Narcotic symptoms questionnaire

Code Number:

Did you have headache at work

☐yes ☐No
(1) (0) |______|

Was this headache frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Did you feel stomach pains at work, or were you overcome with nausea at work

☐yes ☐No
(1) (0) |______|

Was this symptom frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Did you get vertigo or kind of inebriation at work?

☐yes ☐No
(1) (0) |______|

Was this symptom frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Was this symptom more frequent when you had drunk alcohol?

☐yes ☐No
(1) (0) |______|

When you had drunk alcohol did you feel flushing cheeks?

☐yes ☐No
(1) (0) |______|

Was this symptom frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Did you sometimes feel dizzy spell?

☐yes ☐No
(1) (0) |______|

Was this symptom frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Did you need to leave the workshop to get fresh air outside?

☐yes ☐No
(1) (0) |______|

Was this symptom frequent?

☐ Every day (1)
☐ Several times a week(2)
☐ Several times a month (3)
☐ Several times a year (4)
☐ Rarely (5) |______|

Did these symptoms stopped during

The week-end?
☐yes ☐No
(1) (0) |______|

Holidays?
☐yes ☐No
(1) (0) |______|

Were these symptoms more frequent when coming back from holidays?

☐yes ☐No
(1) (0) |______|

How many years did you feel these symptoms? |______|

Could you explain in which job(s) you used to feel the symptoms

Jobs **Years**

____

____

____

Appendix 7: General Medical Questionnaire

Code Number:

1-General information:

Date of birth: |___|___|______|

Place of birth:____________ |______|

(1)-Haute Savoie
(2)-other France
(3)-other country

2-Life habits

Have you ever smoke (=1 cigarette or 1 pipe/day)

☐Yes ☐No
(1) (0) |______|

Age at the beginning: |______|

How many cigarettes per day on average: |______|

Or how many tobacco packets (40 g) per week: |______|

Did your consumption vary during your life?

Minimum |______| during |______| years

Maximum |______| during |______| years

If you have stopped tobacco, age at the end of tobacco smoking: |______|

Do you drink or have you ever regularly drunk coffee (=1cup/day)?

☐Coffee with caffeine ☐decaffeinated coffee |______|
(1) (2) (1)+(2)=(3)

How many cups per day? |______|

How many years of consumption? |______|

3-Medical information:

Nowadays Weight (kg): |______|

Nowadays Height (cm): |______|

Maximal weight during the life: |______|

Corresponding year: |______|

Weight at 20 years old |______|

Nowadays arterial tension?

Maximum (Systolic mm Hg) |______|

Minimum (Diastolic mm Hg) ______|

Did a physician tell you that you have an hypertension?

☐Yes (1) ☐No (0) ______|

Maximal arterial tension during the life?

Maximum (Systolic mm Hg) |______|

Minimum (Diastolic mm Hg) ______|

Do you have health problems?

In particular, do you have kidney diseases ?

Infections?

☐Yes (1) ☐No (0) ______|

Kidney stones?

☐Yes (1) ☐No (0) ______|

How many times |______|

Age at the beginning |______|

Age at the end |______|

Medical history of dialysis?

☐Yes (1) ☐No (0) ______|

Pathology associated with dialysis? _____________

Age at the beginning |______|

Age at the end |______|

Did you have an operation before?

☐Yes (1) ☐No (0) |______|

For which pathology?

Pathology: ______________________ year: |______|

Pathology: ______________________ year: |______|

Do you have family members affected by an important medical history?

In particular, do you have family members affected by kidney diseases?

☐Yes (1) ☐No (0) |______|

Which kidney disease?

____

Family connection?

Father, mother	1(yes) 0(no)	|______|
Sister/brother	1(yes) 0(no)	|______|
Children	1(yes) 0(no)	|______|
Grandparents	1(yes) 0(no)	|______|
Other _____________	1(yes) 0(no)	|______|

Do you undergo or have you ever undergone any treatment for hypertension?

☐Yes (1) ☐No (0) |______|

Which treatment? Period (years)

____

____

Do you take or have you ever taken β-blockers?

☐Yes (1) ☐No (0) |______|

Which β- blockers? Period (years)

____

____

____

Do you take or have you ever taken diuretics?

☐Yes (1) ☐No (0) |______|

Which diuretics? Period (years)

____

____

____

Do you undergo or have you ever undergone any analgesic treatment?

☐Yes (1) ☐No (0) |______|

Have you ever undergone any treatment with Phenacetin (ASPHOGAN, FLEXALGIT, NEVRAL, THERMALGINE VITA C)?

☐Yes (1) ☐No (0) |______|

Date of beginning |______|

Date of end |______|

Do you undergo or have you ever undergone any treatment for hypertension (EFFERALGAN, DOLIPRANE, DIANTALVIC)?

☐Yes (1) ☐No (0) |______|

Date of beginning |______|

Date of end |______

Other analgesics? Period (years)

____

____

Appendix 8: Occupational exposure assessment, general schema

OCCUPATIONAL EXPOSURE ASSESSMENT, GENERAL SCHEMA

STEP I = all jobs from all subjects, group by group; in each group, subject by subject; for each subject, job by job

GROUP X → **subject X1** job X11 → all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

job X1n→ all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

....

subject X5 job X51 → all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

....

job X5n → all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

....

GROUP Y → subject Y1 job Y1n → all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

....

subject Y5 job Y5n → all expos except TRI → SC Quest? Yes → STEP II
No →TRI? Yes → STEP III
No → STEP IV or END of the assessment

End of STEP I:
all jobs are assessed for any exposure except TRI

STEP II:
all jobs described in a Screw Cutting Questionnaire, those describing an exposure to TRI in this screw cutting shop, as well as others

sorting out by employer (name of the company)
period
tasks
type of degreasing machine

assessment of	Trichloroethylene:	qualitative
	Other chlorinated solvents:	review and adjustment of assessment done in STEP I
	Other exposures:	review of assessment done in STEP I

STEP III:
all jobs non-described in a Screw Cutting Questionnaire, and having at least a possible minimal exposure to TRI

no first sort before the assessment

assessment of	Trichloroethylene:	qualitative, related to levels assessed in STEP II
	Other chlorinated solvents:	review and adjustment of assessment done in STEP I
	Other exposures:	review of assessment done in STEP I

STEP IV:
all jobs from STEPs I and III (all jobs but screw cutting), sorted out by activities or tasks usually exposing to TRI
review of comparability in the assessment between same tasks or employers:

tasks (sorting by ISCO code) = machine tool operators
machinery fitters, industrial mechanics
garage
Watch, clock makers and jewellery
electrical work
woodwork (carpentry, furniture makers)
Leather work

Activities / employers (NACE code) = Watch, clock makers and jewellery (Nickles, Rollex, Piaget, ..)
physical research (CERN / Geneva)
manufacture of bicycles (CHATELAIN)
manufacture of paints and coatings (SICPA)
inorganic basic chemicals (PECHINEY/Chesdes)

Appendix 9: List of exposures

SOLVENTS: TRICHLOROETHYLENE
CHLORINATED other than TRI (Trichloroethane, perchloroethylene, methylene choride, ..)
OXYGENATED (alcohols, glycol ethers, ketones, ...)
PETROLEUM derivates (White Spirit, gasoline, ...)
OTHER (turpentine, Carbon bisulfide, ...)

OILS: **CUTTING FLUIDS** (straight oils, synthetic oils, ..)
OTHER PETROLEUM OILS (hydraulic fluids, motor oils, ...)

WELDING: **BRAZING** (soft brazing)
WELDING other (arc and gas welding, hard brazing, resistance welding)

LEAD (any inorganic form)

CADMIUM (any inorganic form)

ASBESTOS

IONISING RADIATION (source)

EXPOSURE INDICATORS (except for TRI and radiation):
low, medium high level of exposure
possible, probable, definite exposure

EXPOSURE INDICATORS for IONISING RADIATION:
possible, probable, definite presence of a source of ionising radiation

Appendix 10: Job period activities

Table 28: Other periods than job-periods

	Frequency	Percent
Military	179	31.2
Unemployment	23	4.0
Illness	32	5.6
At home	94	16.4
Studies	15	2.6
Retirement	193	33.7
War period	17	3.0
Sabbatical period	4	0.7
Unknown	16	2.8
Total		100.0

Appendix 11: NACE code for job-periods

NACE	Frequency	Percent
2852	176	11.8
121	42	2.8
4521	42	2.8
130	36	2.4
7511	31	2.1
5020	29	2.0
8022	29	2.0
4531	28	1.9
2030	27	1.8
5511	27	1.8
8511	25	1.7
9500	25	1.7
2410	23	1.5
5212	23	1.5
5224	22	1.5
5530	20	1.3
3614	19	1.3
4533	19	1.3
4544	18	1.2
6024	18	1.2
6411	18	1.2
7420	18	1.2
5211	17	1.1
3350	16	1.1
4522	16	1.1
2940	15	1.0
5222	15	1.0
6010	15	1.0
2222	14	0.9
8010	14	0.9
6512	12	0.8
1822	11	0.7
3320	11	0.7
8021	11	0.7
9302	10	0.7
2442	9	0.6
8531	9	0.6
9272	9	0.6
1551	8	0.5
2612	8	0.5
2921	8	0.5
2956	8	0.5
4511	8	0.5
5242	8	0.5
7310	8	0.5
7412	8	0.5
7522	8	0.5
8514	8	0.5
9301	8	0.5
120	7	0.5
201	7	0.5
2430	7	0.5
4543	7	0.5
6603	7	0.5
8512	7	0.5
9262	7	0.5
113	6	0.4
2875	6	0.4
2960	6	0.4
3542	6	0.4
3613	6	0.4
5030	6	0.4
5153	6	0.4
5248	6	0.4
8042	6	0.4
9131	6	0.4
112	5	0.3
3640	5	0.3
5010	5	0.3
5131	5	0.3
5134	5	0.3
7524	5	0.3
1823	4	0.3
2840	4	0.3
2851	4	0.3
2911	4	0.3
2971	4	0.3
3161	4	0.3
3210	4	0.3
3410	4	0.3
3511	4	0.3
5147	4	0.3
5152	4	0.3
5165	4	0.3
5244	4	0.3
5523	4	0.3
7411	4	0.3
7414	4	0.3
7512	4	0.3
1584	3	0.2
1754	3	0.2
2010	3	0.2
2466	3	0.2
2862	3	0.2
2922	3	0.2
2923	3	0.2
3220	3	0.2
3310	3	0.2
3530	3	0.2
3622	3	0.2
3663	3	0.2
4010	3	0.2
4523	3	0.2
4525	3	0.2
5040	3	0.2
5139	3	0.2
5225	3	0.2
5227	3	0.2
5245	3	0.2
5262	3	0.2
5540	3	0.2
6021	3	0.2
6210	3	0.2
6523	3	0.2
7440	3	0.2
8532	3	0.2
111	2	0.1
122	2	0.1
1511	2	0.1
1552	2	0.1
1596	2	0.1
1598	2	0.1
1716	2	0.1
1721	2	0.1
1824	2	0.1
2052	2	0.1
2112	2	0.1
2411	2	0.1
2522	2	0.1
2750	2	0.1
2812	2	0.1
2822	2	0.1
2873	2	0.1
2924	2	0.1
2952	2	0.1
3110	2	0.1
3120	2	0.1
4534	2	0.1
4541	2	0.1
4542	2	0.1

4545	2	0.1
5050	2	0.1
5112	2	0.1
5132	2	0.1
5144	2	0.1
5151	2	0.1
5162	2	0.1
5246	2	0.1
5512	2	0.1
5552	2	0.1
7031	2	0.1
7032	2	0.1
7415	2	0.1
7470	2	0.1
7514	2	0.1
7521	2	0.1
7525	2	0.1
7530	2	0.1
8030	2	0.1
8041	2	0.1
8520	2	0.1
9000	2	0.1
9261	2	0.1
9271	2	0.1
123	1	0.1
1110	1	0.1
1310	1	0.1
1320	1	0.1
1513	1	0.1
1582	1	0.1
1583	1	0.1
1585	1	0.1
1586	1	0.1
1591	1	0.1
1600	1	0.1
1713	1	0.1
1724	1	0.1
1730	1	0.1
1740	1	0.1
1930	1	0.1
2020	1	0.1
2040	1	0.1
2121	1	0.1
2212	1	0.1
2221	1	0.1
2223	1	0.1
2320	1	0.1
2400	1	0.1
2415	1	0.1
2420	1	0.1
2440	1	0.1
2524	1	0.1
2621	1	0.1
2622	1	0.1
2630	1	0.1
2661	1	0.1
2670	1	0.1
2710	1	0.1
2745	1	0.1
2751	1	0.1
2753	1	0.1
2754	1	0.1
2830	1	0.1
2861	1	0.1
2863	1	0.1
2872	1	0.1
2912	1	0.1
2914	1	0.1
2954	1	0.1
3001	1	0.1
3230	1	0.1
3280	1	0.1
3330	1	0.1
3420	1	0.1
3430	1	0.1
3520	1	0.1
3611	1	0.1
3612	1	0.1
3650	1	0.1
3661	1	0.1
3914	1	0.1
4020	1	0.1
4524	1	0.1
5111	1	0.1
5115	1	0.1
5117	1	0.1
5121	1	0.1
5122	1	0.1
5130	1	0.1
5141	1	0.1
5154	1	0.1
5155	1	0.1
5156	1	0.1
5157	1	0.1
5164	1	0.1
5170	1	0.1
5214	1	0.1
5226	1	0.1
5231	1	0.1
5250	1	0.1
5271	1	0.1
5521	1	0.1
5551	1	0.1
6022	1	0.1
6600	1	0.1
7011	1	0.1
7012	1	0.1
7250	1	0.1
7430	1	0.1
7450	1	0.1
7460	1	0.1
7484	1	0.1
7513	1	0.1
8010	1	0.1
8530	1	0.1
9112	1	0.1
9191	1	0.1
9220	1	0.1
9999	1	0.1