Exhibit 283

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Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany

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Background This case-control study was conducted to estimate the renal cell cancer (RCC) risk for exposure to occupation-related agents, besides other suspected risk factors.

Methods In a population-based multicentre study, 935 incident RCC cases and 4298 controls matched for region, sex, and age were interviewed between 1991 and 1995 for their occupational history and lifestyle habits. Agent-specific exposure was expert-rated with two job-exposure matrices and a job task-exposure matrix. Conditional logistic regression was used to calculate smoking adjusted odds ratios (OR).

Results Very long exposures in the chemical, rubber, and printing industries were associated with risk for RCC. Males considered as 'substantially exposed to organic solvents' showed a significant excess risk (OR = 1.6, 95% CI : 1.1–2.3). In females substantial exposure to solvents was also a significant risk factor (OR = 2.1, 95% CI : 1.0–4.4). Excess risks were shown for high exposure to cadmium (OR = 1.4, 95% CI : 1.1–1.8, in men, OR = 2.5, 95% CI : 1.2–5.3 in women), for substantial exposure to lead (OR = 1.5, 95% CI : 1.0–2.3, in men, OR = 2.6, 95% CI : 1.2–5.5, in women) and to solder fumes (OR = 1.5, 95% CI : 1.0–2.4, in men). In females, an excess risk for the task 'soldering, welding, milling' was found (OR = 3.0, 95% CI : 1.1–7.8). Exposure to paints, mineral oils, cutting fluids, benzene, polycyclic aromatic hydrocarbons, and asbestos showed an association with RCC development.

Conclusions Our results indicate that substantial exposure to metals and solvents may be nephrocarcinogenic. There is evidence for a gender-specific susceptibility of the kidneys.

Keywords Cadmium, cadmium compounds, case-control study, gender differences, job-exposure matrix, occupation, renal cell carcinoma, trichloroethylene

Malignant tumours of the kidney account for about 4% of all new cancer cases in German men and 3% of cancer in women.[1] The majority of kidney tumours are renal cell cancers (RCC) with a less clear aetiology than tumours of urothelial origin.[2] Unlike urothelial cancer, RCC is not considered an occupation-related tumour. However, higher incidence rates in East Germany, where industrial production used lower technological standards, and the striking increase in mortality among West German males in the 1970s and in both genders in East Germany in the 1980s[3] support a possible association also with occupational risk factors.

In historical cohort studies, insulators[4] and asbestos products workers[5] showed significantly elevated mortality rates for kidney cancer. Thus far, the International Agency for Research on Cancer (IARC) considered only iron and steel founding an occupational setting which may exert a cancer risk for the kidneys.[6] This was mainly based on a 1972 report of excess risk among coke-oven workers,[7] but this was no longer seen after 30 years of follow-up.[8]

Limited epidemiological evidence of risk has been found for solvents and petrochemicals.[9–14] Chlorinated solvents in particular have attracted attention as an occupational hazard.[15–17] Recently, IARC concluded that tetrachloroethylene (PCE) and trichloroethylene (TCE) are probably carcinogenic to humans.[18] There is evidence, based on animal experiments

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and limited epidemiological data, for both nephrotoxicity and nephrocarcinogenicity.

The historical finding of an impact of cadmium exposure on RCC development[19] was investigated in subsequent studies on heavy metal exposure with conflicting results.[12,20–22] Cadmium can be stored in the renal cortex at much higher levels than in other tissues.[23] Cadmium was evaluated as a human carcinogen, but the kidneys were not implicated as a target organ.[24]

For cadmium and TCE exposure, gender differences in susceptibility are known.[25] Higher risks in solvent-exposed women found in a recent study support earlier findings.[26] Our study included two East German regions with a high employment rate for women.

Our multicentre population-based case-control study was conducted from 1991 to 1995 and aimed to estimate the RCC risk for occupation-related agents besides other risk factors. A structured questionnaire was used by centrally trained interviewers to obtain detailed exposure information. Expert-rating approaches were adapted or developed to assess lifetime exposure to the agents under study. The present paper reports the possible impact of occupation-related agents on RCC development. The excretory portion of the kidney was analysed among urothelial carcinomas. Further results are reported elsewhere.[27,28]

Material and Methods

Details of the study design and methods for exposure assessment are reported elsewhere[28] and are described briefly here.

Cancer cases and controls

From 1991 to 1995, this population-based case-control study was conducted in five German regions (West Berlin, Bremen, Leverkusen, Halle, Jena). Eligible were German nationals without age limit for both cases and controls. Two case series were enrolled simultaneously, with a total of 1035 urothelial cancer cases and 935 RCC cases. For 95% of RCC cases, diagnosis was confirmed histologically in the 6 months before recruitment, and for 5% of RCC cases diagnosis was confirmed by sonography only. In all 88.5% of RCC cases were interviewed in the first 2 months after diagnosis. Participation of the large hospitals in the study areas assured a population-based enrolment of cases but this was ascertained by a preceding cancer incidence study.[27]

The controls were frequency-matched to cases by region, sex (Table 1), and age (5-year age groups). The matching procedure aimed for a 1 : 2 matching for urothelial cancer and a 1 : 4 matching for RCC cases to controls. During the recruitment, an increase in the incidence rates of RCC was observed. Therefore, the recruitment period of RCC cases was expanded to clarify possible causes. Finally a group of 4298 randomly selected population controls from local residency registries was enrolled. This control group was used in the statistical analysis of both cancer sites.

In all, 570 male and 365 female incident RCC cases and 2650 male and 1648 female population controls were interviewed face-to-face with a structured questionnaire. Basic characteristics of the cases and controls are given in Table 2. The differences of the age distributions between cases and controls result from the sharing of the control group with older urothelial cancer cases. The response rates were 88% for cases, and 71% for controls. For RCC cases, the response rates varied from 84% to 95% between the study regions. For controls the rates varied between 63% and 75% due to the lower percentage of households with telephones in East Germany.

Table 1 Distribution of cases and controls by study region and gender

	Males		Females	
Study region	Cases (n = 570)	Controls (n = 2650)	Cases (n = 365)	Controls (n = 1648)
West Germany				
West Berlin	283	1333	171	800
Bremen	73	350	53	235
Leverkusen	43	195	26	116
East Germany (former German Democratic Republic)				
Halle	130	580	83	356
Jena	41	192	32	141

Table 2 Selected characteristics of cases and controls

	Cases (n = 935)		Population controls (n = 4298)	
Variable	Males (n = 570)	Females (n = 365)	Males (n = 2650)	Females (n = 1648)
Place of interview	Hospital	Hospital	Home	Home
Median age (years)	61	66	63	67
⩾10 years of school (%)	34	29	40	33
Never a regular smoker (%)	20	64	24	67
⩾20 years consumption of analgesics (%)	7	11	6	9
Median body mass index	26	25	26	25

Exposure assessment

The assessment of exposure to occupational risk factors was based on the subject's occupational history (job titles) and supplemental information on job tasks with suspected exposure to the agents under study. Every job title held for at least one year was classified according to the International Standard Classification of Occupations (ISCO) of the International Labour Office.[29] The subject's lifetime exposure with respect to a specified job title was quantified by the total sum of years working in this job. For job tasks, the quantification of exposure was the corresponding weighted sum of years, where the weights were the fractions of working time spent on the task. We referred to those exposure variables as 'duration'. Furthermore, the longest held job was analysed at the three-digit level of ISCO.

For quantifying the exposure to specified agents, we adapted two job-exposure matrices (JEM) (the so-called British JEM[30] and the so-called German JEM[31]). Experts within our study group developed a corresponding job task-exposure matrix (JTEM). For every job title and job task, respectively, the exposure matrix provided an expert rating in terms of the probability and the intensity of exposure to a specified agent. To obtain an agent-specific measure of a subject's lifetime exposure, the

Table 3 Odds ratios (OR) of the conditional logistic regression for possible confounders

Risk factor	Males					Females				
	No. of cases	OR[a]	95% CI[a]	OR[b]	95% CI[b]	No. of cases	OR[a]	95% CI[b]	OR[b]	95% CI[b]
Socioeconomic status										
Very high	134	1.00		1.00		21	1.00		1.00	
High	86	0.91	0.67–1.23	0.89	0.65–1.20	78	2.12	1.26–3.58	2.12	1.26–3.57
Medium	301	1.22	0.97–1.53	1.17	0.93–1.48	127	1.83	1.11–3.00	1.83	1.12–3.01
Low	49	0.96	0.67–1.38	0.90	0.62–1.31	138	2.46	1.49–4.07	2.47	1.49–4.07
Cigarette smoking										
Never	116	1.00				232	1.00			
Other smokers only	23	1.36	0.82–2.24							
1–<10 pack-years	93	1.19	0.88–1.61			43	1.02	0.71–1.47		
10–<20 pack-years	78	1.02	0.74–1.39			39	1.13	0.77–1.66		
20–<40 pack-years	163	1.31	1.01–1.71			34	0.98	0.65–1.48		
40+ pack-years	97	1.30	0.96–1.76			17	1.77	0.98–3.17		
Smoking status										
Current smokers	215	1.34	1.04–1.72			71	1.06	0.78–1.45		
Stopped smoking:										
1–<10 years ago	74	1.42	1.03–1.97			16	0.76	0.44–1.31		
10–<20 years ago	69	1.10	0.79–1.52			18	1.10	0.64–1.89		
20+ years ago	96	1.01	0.75–1.36			28	1.61	1.02–2.53		

[a] OR and 95% CI adjusted for age and study centre.
[b] OR and 95% CI adjusted for age, study centre, and smoking.

products of duration, probability, and intensity were summarized over all jobs held or job tasks operated, respectively. We referred to these exposure variables as 'exposure indices'.

Statistical analysis

Conditional logistic regression models[32] were applied for risk estimation using the SAS procedure PHREG,[33] separately for males and females. The risk estimation was conditional on 45 strata resulting from nine age groups (<40, 40–49, 50–54,..., 75–79, 80+) and five study regions.

Considering possible highly non-linear associations between risk estimates and exposure measures, four exposure categories were defined for each exposure variable using the 30th, 60th and 90th percentiles of the distribution of the exposure variable among the exposed controls. Concerning exposure duration, we referred to these categories as 'short', 'medium', 'long' and 'very long duration' of exposure, and with respect to exposure indices, as 'low', 'medium', 'high' and 'substantial exposure'. The reference groups comprised the unexposed subjects and the subjects with 'short duration' or 'low exposure'.

Smoking was implemented as a confounder, because it is considered as a risk factor[34,35] and had a higher prevalence among German blue-collar workers.[36] It was measured as log (pack-years + 1). Additionally, the quitting of smoking and the exclusive smoking of other tobacco products were included. Socioeconomic status (SES) was not used since it can represent occupational risk to a high degree. Table 3 shows the risk estimates for tobacco smoking and SES. We ignored mutual confounding by other agents or occupations because of the low prevalence of people in high-risk jobs and the difficulty of disentangling the joint effect of mixtures, a ubiquitous circumstance in the workplace.

Results

Occupations and job tasks

Table 4 presents the regression results for the longest held job (three-digit ISCO) with a significant RCC risk. Workers in coke production and iron and steel founding, previously considered as high-risk occupations,[6] could not be analysed because of insufficient exposure prevalence. Both male and female assemblers of electrical and electronic equipment had a significant excess risk. Female cleaners and rubber workers had significant elevated risks. Among other blue-collar jobs, railway workers and female workers without a specific classification of the job title showed an excess risk. Among white-collar job jobs, male wholesale and retail trade managers were found to have an elevated odds ratio (OR).

The large number of job titles and the low exposure prevalence reduce the power and thus increase random results. Therefore, job titles with similar exposure circumstances were aggregated to form job groups. If painters were analysed in a group with tanners, dyers, and other related exposures, there was an excess risk for the longest held job among males.

Table 5 presents the logistic regression results for job groups and job tasks, selected for metal, solvent, or polycyclic aromatic hydrocarbon (PAH) exposure, based on duration of exposure. Male chemical workers, rubber workers, and printers with a 'very long' employment duration showed significantly elevated risks for RCC. Among the job tasks selected for risk estimation, there was a significant excess risk for females exposed in 'soldering, welding, milling' and a non-significantly elevated risk among males for galvanization. For metal degreasing, the OR were slightly, but insignificantly elevated for the majority of exposure categories in males and females.

Table 4 Odds ratios (OR) of the conditional logistic regression analyses for occupations at the three-digit level of ISCO[a] (ILO 1968) with a significant association in men or women (at the 5% level) for the development of renal cell cancer

ISCO	Occupation	Longest held job	
		No. of cases	OR[b] (95% CI[b])
400	**Managers (wholesale, retail trade)**		
	Males	6	3.3 (1.2–9.4)
	Females	1	1.1 (0.1–10.2)
552	**Cleaners and related workers**		
	Males	3	1.4 (0.4–5.2)
	Females	25	1.9 (1.2–3.1)
853	**Electrical and electronic equipment assembler**		
	Males	5	3.2 (1.0–10.3)
	Females	11	2.7 (1.3–5.8)
901	**Rubber and plastics product makers, except tyre makers and tyre vulcanizers**		
	Males	3	1.6 (0.4–5.9)
	Females	3	6.0 (1.0–36.0)
949	**Other production and related workers**		
	Males	3	0.6 (0.2–2.2)
	Females	12	2.8 (1.4–5.9)
984	**Railway brakemen, signalmen, and shunters**		
	Males	5	6.2 (1.6–23.4)
–[c]	**Painters, tanners, dyers, and related occupations**		
	Males	19	1.9 (1.1–3.3)
	Females	1	0.6 (0.1–5.2)

[a] International Standard Classification of Occupations.
[b] OR and 95% CI adjusted for age, study centre, and smoking.
[c] Aggregated ISCO job titles with exposure to paints.

Products and substances

Table 6 presents the regression results for expert-rated occupational exposure variables, adjusted for smoking. Occupation-related exposure to heavy metals, especially to cadmium, lead, and solder fumes, was associated with a RCC risk for males and females. Considering at least five substantially exposed cases, all OR of the exposure indices based on the JEM approach were at least slightly elevated.

The OR for exposure to solvents, especially to TCE, PCE and carbon tetrachloride, were slightly elevated in all exposure categories in males and females, if at least 10 exposed cases were considered. Significant effects were found in different exposure categories, but no dose-response trends.

Occupation-related exposure to aromatic amines based on both the JEM and JTEM approach was not associated with significant excess risk. Significant elevated OR were found with no clear pattern for the use of paints and pigments, of film developers and also cutting fluids. These products can produce exposure to aromatic amines, but also to other agents like solvents and metals.

Exposure variables for mineral oils and petrochemicals were occasionally associated with RCC development based on different expert ratings, but the lack of specificity of the exposure variables has to be taken into account. In the British JEM, mineral oil exposure was rated together with tar and pitch exposure. Among other agents with excess risks were PAH and asbestos.

Discussion

Exposure information

Poor exposure assessment and misclassification of exposure may have a strong impact on risk estimation. We have discussed the possible methodological shortcomings of population-based case-control studies in the investigation of occupational risk factors in detail elsewhere.[28]

The lower response rate of controls, 71%, compared to 88% of cases may be explained by the different mode of recruitment (cases were contacted in hospitals and controls at home) and cannot rule out a selection bias. However, the similar distribution of SES among male cases and controls does not indicate a strong selection bias. It further supports that SES-associated factors, especially tobacco smoking and occupation-related agents, did not contribute to RCC development, unlike urothelial cancer in men.[27,28] Smoking is not considered a strong risk factor for RCC.[34,35,37] Some studies have reported an even higher prevalence of selected white-collar occupations among cases,[11,38] but due to the large number of job titles variation by chance has to be taken into account.

The SES figures for females were different, with higher risks in lower social classes. A Danish study has also reported a more pronounced social class effect in females.[39] Smoking in women is not a strong risk factor which would explain this SES effect. A possible gender difference of susceptibility will be discussed.

Table 5 Odds ratios (OR) of the conditional logistic regression for selected occupations and job tasks by duration of occupational exposure

Occupation[a] or job task	Medium[b]		Long[b]		Very long[b] duration	
	No. of cases	OR[c] (95% CI[c])	No. of cases	OR[c] (95% CI[c])	No. of cases	OR[c] (95% CI[c])
Occupations						
Chemical workers						
Males	10	1.1 (0.5–2.2)	9	1.0 (0.5–2.1)	8	3.1 (1.2–7.9)
Females	7	1.4 (0.6–3.5)	6	1.4 (0.6–3.7)	0	
Rubber workers						
Males	2	1.5 (0.3–7.4)	0		4	4.3 (1.1–17.4)
Females	3	2.4 (0.6–10.1)	1	1.0 (0.1–9.0)	2	4.0 (0.6–28.3)
Printers						
Males	4	1.0 (0.3–2.9)	5	1.4 (0.5–3.7)	5	3.5 (1.1–11.2)
Females	2	0.7 (0.2–3.4)	0		2	2.1 (0.4–11.7)
Painters/dyers						
Males	12	1.6 (0.8–3.0)	10	1.4 (0.7–2.8)	5	2.3 (0.8–6.8)
Motor vehicle drivers						
Males	27	0.9 (0.6–1.4)	28	0.9 (0.6–1.4)	7	0.6 (0.3–1.4)
Females	0		1	0.9 (0.1–7.7)	1	1.9 (0.2–21.3)
Metal production						
Males	5	1.1 (0.4–2.8)	6	1.2 (0.5–3.0)	2	1.0 (0.2–4.9)
Females	0		2	1.8 (0.4–9.5)	1	4.5 (0.3–72.3)
Metal processing						
Males	74	1.3 (1.0–1.7)	61	1.0 (0.8–1.4)	21	1.1 (0.7–1.8)
Females	8	1.4 (0.6–3.0)	9	1.9 (0.8–4.1)	3	1.4 (0.4–5.3)
Job tasks						
Galvanization						
Males	2	2.7 (0.5–16.6)	3	2.3 (0.6–9.5)	1	3.3 (0.3–38.0)
Welding, soldering, milling						
Males	73	1.2 (0.9–1.6)	64	1.1 (0.8–1.4)	19	1.0 (0.6–1.6)
Females	6	0.9 (0.3–3.5)	8	1.1 (0.5–2.3)	7	3.0 (1.1–7.8)
Production and use of petroleum products[d]						
Males	9	0.5 (0.3–1.0)	10	1.1 (0.3–1.1)	8	1.3 (0.6–2.9)
Use of asbestos for heat protection						
Males	7	0.6 (0.3–1.4)	10	0.9 (0.5–1.8)	1	0.3 (0.04–2.4)
Metal cleaning/degreasing						
Males	47	1.3 (0.9–1.9)	38	1.1 (0.8–1.6)	15	1.3 (0.7–2.3)
Females	3	1.0 (0.3–3.5)	4	1.3 (0.4–3.9)	2	1.5 (0.3–7.7)

[a] Based on aggregation of job titles with similar exposure, ISCO codes in Greiser & Molzahn (1997).
[b] Exposure categories defined by 30th, 60th, and 90th percentiles of the distribution of duration of exposure (in years) among exposed controls.
[c] OR and 95% CI adjusted for age, study centre, and smoking.
[d] Including transport and use of mineral oil and fuel.

Self-assessed exposure to chemical agents has been considered of low reliability.[40] An expert-rating of exposure to selected agents can only be based on job titles or job tasks, resulting in crude categories for exposure probability and intensity.[41] The British JEM, developed for cancer studies in England and Wales, did not consider temporal changes in exposure after 1950. The German JEM was originally developed for Parkinson's disease, focusing on solvent exposure in East and West Germany. Exposures to solvents were more sensitively rated than in the British JEM. In all, 67% of the occupations classified unexposed to organic solvents using the British JEM were considered exposed with the German JEM. On the other hand, only 7% of the job titles considered unexposed using the German JEM were rated as exposed with the British JEM. The rating of experts was not significantly different with respect to unexposed occupations, but did differ in probability and intensity of exposure.

Exposure indices derived from an expert rating of job tasks can have a higher agent-specificity than indices derived from job titles. On the other hand, a loss of sensitivity has to be taken into account for job tasks where a knowledge of the technology or materials is necessary to gain exposure information. Limitations of exposure matrices also hold for the JTEM-based exposure indices.

Table 6 Odds ratios (OR) of the conditional logistic regression for occupational exposure to selected substances by expert-assessed exposure indices

	Exposure index								
	Medium[a]			High[a]			Substantial[a]		
Substances	No. of cases	OR[b]	(95% CI[b])	No. of cases	OR[b]	(95% CI[b])	No. of cases	OR[b]	(95% CI[b])
Metals and their compounds									
JEM[c] approach									
German JEM: metals									
Males	150	1.2	(1.0–1.5)	168	1.4	(1.1–1.7)	41	1.1	(0.7–1.5)
Females	34	1.4	(0.9–2.1)	37	1.4	(1.0–2.2)	11	1.3	(0.6–2.5)
British JEM: welding fumes									
Males	56	1.3	(1.0–1.8)	46	1.1	(0.8–1.6)	16	1.2	(0.7–2.1)
British JEM: solder fumes									
Males	66	1.1	(0.8–1.5)	61	1.1	(0.8–1.5)	27	1.5	(1.0–2.4)
Females	7	1.0	(0.4–2.2)	13	1.9	(1.0–3.8)	3	1.3	(0.3–4.7)
British JEM: cadmium and its compounds									
Males	58	1.4	(1.1–2.0)	47	1.3	(0.9–1.8)	14	1.2	(0.6–2.2)
Females	15	1.1	(0.6–2.0)	19	1.5	(0.9–2.6)	1	0.2	(0.03–1.7)
German JEM: cadmium and its compounds									
Males	48	0.8	(0.6–1.2)	99	1.4	(1.1–1.8)	34	1.4	(0.9–2.1)
Females	3	0.7	(0.2–2.5)	11	2.5	(1.2–5.3)	3	2.2	(0.6–9.0)
British JEM: lead and its compounds									
Males	84	1.2	(1.0–1.6)	71	1.2	(0.9–1.6)	29	1.5	(1.0–2.3)
Females	8	0.7	(0.4–1.6)	14	1.0	(0.6–1.9)	11	2.6	(1.2–5.5)
German JEM: lead and its compounds									
Males	69	0.9	(0.7–1.2)	81	1.2	(0.9–1.6)	30	1.3	(0.9–2.0)
JTEM[d] approach									
Metals									
Males	115	1.1	(0.8–1.3)	117	1.1	(0.8–1.3)	27	0.8	(0.5–1.2)
Females	19	1.0	(0.6–1.7)	17	0.9	(0.5–1.5)	11	1.7	(0.8–3.5)
Refined steel									
Males	41	1.0	(0.7–1.4)	42	1.0	(0.7–1.4)	10	0.7	(0.4–1.4)
Females	2	1.4	(0.3–6.8)	1	0.5	(0.1–4.0)	3	6.3	(1.0–37.6)
Chlorinated solvents									
JEM approach									
British JEM: organic solvents									
Males	87	1.1	(0.8–1.4)	71	1.0	(0.8–1.3)	38	1.6	(1.1–2.3)
Females	26	1.3	(0.8–2.0)	23	1.2	(0.7–1.9)	2	0.3	(0.1–1.3)
British JEM: carbon tetrachloride									
Males	76	1.1	(0.9–1.5)	85	1.2	(1.0–1.6)	23	1.1	(0.7–1.8)
Females	18	1.0	(0.6–1.7)	21	1.2	(0.7–2.1)	5	0.8	(0.3–2.0)
German JEM: trichloroethylene									
Males	135	1.1	(0.9–1.4)	138	1.1	(0.9–1.4)	55	1.3	(0.9–1.8)
Females	28	1.2	(0.8–1.8)	29	1.3	(0.8–2.0)	6	0.8	(0.3–1.9)
German JEM: tetrachloroethylene									
Males	154	1.4	(1.1–1.7)	119	1.1	(0.9–1.4)	50	1.4	(1.0–2.0)
Females	12	0.7	(0.4–1.3)	19	1.1	(0.7–1.9)	4	0.7	(0.3–2.2)
JTEM approach									
Solvents									
Males	86	1.3	(1.0–1.7)	74	1.1	(0.8–1.4)	33	1.5	(1.0–2.3)
Females	20	1.4	(0.8–2.4)	7	0.5	(0.2–1.1)	10	2.1	(1.0–4.4)
Chlorinated solvents									
Males	91	1.4	(1.1–1.9)	73	1.1	(0.9–1.5)	28	1.4	(0.9–2.1)
Females	16	1.2	(0.7–2.2)	14	1.1	(0.6–2.0)	6	1.3	(0.5–3.3)
Tetrachloroethylene									
Males	44	1.2	(0.9–1.7)	39	1.1	(0.7–1.5)	15	1.3	(0.7–2.3)
Females	8	2.2	(0.9–5.2)	6	1.5	(0.6–3.8)	3	2.0	(0.5–7.8)

Table 6 (continued)

Substances	Exposure index: Medium[a] No. of cases	OR[b]	(95% CI[b])	High[a] No. of cases	OR[b]	(95% CI[b])	Substantial[a] No. of cases	OR[b]	(95% CI[b])
Chlorinated solvents (cont'd)									
JTEM approach (cont'd)									
Trichloroethylene									
Males	68	1.3	(1.0–1.8)	59	1.1	(0.8–1.5)	22	1.3	(0.8–2.1)
Females	11	1.3	(0.7–2.6)	7	0.8	(0.4–1.9)	5	1.8	(0.6–5.0)
Aromatic amines									
JEM approach									
British JEM									
Males	54	1.1	(0.8–1.6)	37	0.9	(0.6–1.2)	20	1.4	(0.8–2.3)
Females	17	1.1	(0.6–1.9)	10	0.6	(0.3–1.1)	10	1.8	(0.9–3.8)
JTEM approach									
Males	37	0.7	(0.5–1.1)	44	0.9	(0.6–1.2)	16	1.0	(0.6–1.7)
Females	14	1.1	(0.6–2.1)	5	0.4	(0.2–1.0)	4	0.9	(0.3–2.9)
Paints, and related agents									
JEM approach									
British JEM: paints and pigments									
Males	75	0.9	(0.7–1.2)	66	1.1	(0.8–1.5)	32	1.6	(1.1–2.5)
Females	11	1.8	(0.9–3.8)	7	1.1	(0.5–2.5)	0		
German JEM: paints									
Males	135	1.1	(0.8–1.4)	151	1.3	(1.0–1.6)	41	1.1	(0.8–1.6)
Females	40	1.2	(0.8–1.8)	38	1.2	(0.8–1.7)	7	0.6	(0.3–1.4)
German JEM: developer (colour films)									
Males	7	1.1	(0.5–2.6)	4	0.7	(0.2–2.0)	6	2.9	(1.1–8.3)
German JEM: cutting fluids									
Males	68	1.3	(1.0–1.8)	55	1.1	(0.8–1.6)	20	1.2	(0.7–2.0)
Females	12	1.9	(1.0–3.6)	9	1.5	(0.7–3.5)	6	3.1	(1.1–8.2)
JTEM approach									
Use or production of paints									
Males	30	0.8	(0.5–1.2)	38	0.9	(0.6–1.3)	13	1.0	(0.6–1.9)
Females	9	1.1	(0.5–2.3)	44	0.9	(0.6–1.3)	14	1.0	(0.5–1.7)
Mineral oils and related products									
JEM approach									
British JEM: tar, pitch, mineral oil									
Males	86	1.1	(0.9–1.5)	96	1.2	(0.9–1.6)	34	1.4	(0.9–2.1)
Females	15	1.0	(0.6–1.7)	16	1.2	(0.7–2.0)	10	2.1	(1.0–4.5)
German JEM: benzene									
Males	159	1.2	(1.0–1.5)	156	1.2	(1.0–1.6)	52	1.4	(1.0–1.9)
Females	60	1.4	(1.0–1.9)	64	1.3	(1.0–1.8)	14	0.9	(0.5–1.7)
JTEM approach									
Mineral oil									
Males	62	1.3	(1.0–1.8)	45	0.9	(0.6–1.3)	13	0.8	(0.4–1.4)
Females	4	0.7	(0.2–2.0)	11	1.9	(0.9–4.0)	2	1.0	(0.2–4.4)
Polycyclic aromatic hydrocarbons									
JEM approach									
British JEM									
Males	71	0.9	(0.7–1.2)	96	1.3	(1.0–1.6)	32	1.2	(0.8–1.9)
Females	17	1.1	(0.6–1.8)	21	1.5	(0.9–2.4)	6	1.3	(0.5–3.3)
JTEM approach									
Males	80	0.9	(0.7–1.2)	67	0.8	(0.6–1.0)	26	0.9	(0.6–1.4)

Table 6 (continued)

Substances	Exposure index: Medium[a] No. of cases	OR[b]	(95% CI[b])	High[a] No. of cases	OR[b]	(95% CI[b])	Substantial[a] No. of cases	OR[b]	(95% CI[b])
Asbestos									
JEM approach									
British JEM									
Males	64	0.9	(0.7–1.2)	103	1.3	(1.0–1.7)	32	1.3	(0.9–2.0)
Females	5	0.5	(0.2–1.2)	15	1.5	(0.8–2.8)	3	1.0	(0.3–3.5)
JTEM approach									
Males	66	1.0	(0.7–1.3)	61	0.9	(0.6–1.2)	20	0.9	(0.6–1.5)
Females	3	0.7	(0.2–2.4)	10	1.7	(0.8–3.7)	1	0.7	(0.1–5.7)

[a] Exposure categories defined by 30th, 60th, and 90th percentiles of the distribution of the exposure index among exposed controls.

[b] OR and 95% CI adjusted for age, study centre, and smoking.

[c] Job exposure matrix.

[d] Job task-exposure matrix.

Dose-response relations

One of the postulates for epidemiological evidence is the demonstration of a dose-response relation. For many occupation-related risk factors, only a small fraction of the general population is substantially exposed which results in a limited power to detect dose-response relations in population-based case-control studies.[2]

Exposure misclassification tends to smooth dose-response relations towards the null value. For exposure variables based on duration of exposure only, which do not suffer from a strong recall bias or misclassification, excess risks were mainly found for the highest exposure category. For agent-specific exposure indices, which additionally implement the experts' ratings, excess risks were not predominantly found in the highest exposure category.

A possible misspecification of the exposure index has to be discussed as another methodological shortcoming which can smooth effects. For this study, cumulative exposure indices were developed according to the 1986 US EPA guidelines for carcinogenic risk assessment.[42] The underlying assumption of toxicological equivalence of exposure time and concentration may not be appropriate for solvents and metals. The 1996 revised guidelines of the US EPA refer to the growing evidence that defence mechanisms can detoxify low or even medium doses of xenobiotics,[43] e.g. cadmium via metallothionein binding and TCE via cytochrome P450-mediated oxidation.[44]

Occupations and job tasks

Historical cohort studies have shown excess risks for insulators,[4] asbestos product workers,[5] and coke-oven workers.[7] The IARC considered only coke production and iron and steel founding as occupational circumstances which may also be associated with kidney cancer.[6] The more recent International Renal Cell Cancer Study also found significant excess risks for these industries.[12] A high kidney cancer mortality was found in the East German centre of iron and steel founding (Eisenhüttenstadt) in both males and females.[3] In our study regions, coke production as well as iron and steel founding were not among the main industries. For metal production, females showed an excess risk, but based on three cases only. With the data of our study, occupations in the processing and assembling of metal products showed elevated OR for both males and females. Furthermore, men working in galvanization and women in welding, soldering, and milling were associated with elevated risks but based on few cases. An excess risk was also found in a Finnish study for metal manufacturing workers.[11]

The risk of RCC among oil refinery workers has been repeatedly investigated with conflicting results.[45–47] A high kidney cancer mortality in both genders was found in the East German centre of mineral oil refining (Grimmen).[3] From an updated mortality study, an excess risk was reported for US petroleum refining workers,[48] but the mortality of US refinery workers is still discussed with respect to methodological shortcomings.[49] Related exposures to petroleum products, especially gasoline, have been suggested as risk factors after the induction of RCC in male rats following gasoline exposure. Several case-control studies investigated the kidney cancer risk for exposure to petrochemicals.[10,12] Our agent-specific results indicate a possible risk of mineral oils and petrochemicals.

Among other occupations reported in the literature with elevated risks were painters,[50] printers,[11,51] chemical workers,[11] and textile workers.[38] We can support an RCC risk for chemical and rubber workers, as well as for printers and painters with a very long duration of exposure.

Heavy metal exposure and RCC risk

Damage to the kidneys is one of the primary actions of heavy metals at high doses. Cadmium, which can be stored in the renal cortex at much higher levels than in other tissues,[52] and inorganic lead, which was found to induce RCC in animal experiments,[6] have been investigated for nephrocarcinogeniticy in humans with conflicting results.[12,19–22] With the data of our study, cadmium exposure was shown to have a significant excess risk. Furthermore, we found significant effects for lead and solder fumes. In an updated cohort of lead smelter workers, an excess risk for kidney cancer was found.[21] Fu and Bofetta reviewed epidemiological studies of the carcinogenic effects of inorganic lead.[53] There is limited support for an elevated risk for kidney cancer but the epidemiological evidence is still inadequate.

Attributing effects to specific metals is difficult because of their common occurrence in ores or alloys, and in many occupational settings with solvents. Furthermore, different metals can compete for proteins like methyltransferases and

metallothionein.[54] Cadmium compounds can also increase synergistically the effects of other chemicals.[24]

The detoxification of metals by metallothionein-binding is a limiting factor in nephrotoxicity and supports the finding that it is mainly high levels of free metals which induce nephrotoxic effects.[55] A long-lasting exposure to low doses cannot be considered as toxic as very high concentrations with shorter duration of exposure.

Solvent exposure and RCC risk

Long-term carcinogenicity studies in animals suggest that some chlorinated hydrocarbons may be carcinogenic in humans.[18] Chlorinated solvents are widely used bulk chemicals. Tetrachloroethylene is a standard solvent for dry cleaning. There have been several studies of a RCC risk for dry cleaning solvents.[12,26,56,57] Trichloroethylene is an important vapour degreaser for the cold cleaning of metal parts and it is a general solvent for fats, rubber, paints, printing inks, and other products. Positive findings in German workers with TCE exposure have been reviewed,[58,59] and the epidemiological evidence is still considered limited.[60]

Our results could not demonstrate convincingly that chlorinated solvents are risk factors for RCC, but due to the many increased risks found among the multiple comparisons they merit further attention as potential renal carcinogens. The increase in relative risk was low, and a dose-response relation could not be shown, which we attribute to a possible misspecification of the exposure index. The health effects of TCE were reviewed by Kaneko *et al.*,[15] with evidence for the development of kidney disorders at high exposure levels. Trichloroethylene is detoxified in a cytochrome P450-mediated pathway. Under high TCE concentrations, a pathway with glutathione conjugation can be induced which is considered to produce the ultimate carcinogen.[44] Therefore, equitoxicity of low doses of TCE with long duration of exposures and high doses with shorter duration cannot be assumed.

Other occupation-related agents

Among the main hazards of coke-oven workers are PAH and aromatic amines. For high and substantial PAH exposure, assessed with the British JEM, we found a slightly increased risk among males. This effect corresponds to the risk estimates for asbestos. The role of asbestos in the aetiology of kidney cancer as causal agent was disputed by Smith *et al.*[61] McLaughlin *et al.* considered the association of asbestos and RCC development as the most consistently observed occupational link.[2] Confounding by heat in the workplace, for both asbestos and PAH exposure, has to be taken into account in the context of fluid balance and renal physiology.

Selected aromatic amines have been classified as carcinogens,[6] but the kidneys were not considered a target organ. Abuse of phenacetin, chemically related to aromatic amines, can induce nephropathies,[62] but the RCC risk is controversial.[2] The risks estimated for aromatic amine exposure based on agent-specific expert ratings were not significantly elevated, but excess risks were found for chemical and rubber workers, dyers, and printers, who can have contact to aromatic amines among other agents. Excess risks were also found for workers using cutting fluids and film developers which supports further investigations on aromatic amines.

Gender differences

Nephrotoxicity is one of the primary health effects of many suspected risk factors of RCC, among them phenacetin abuse[62] and cadmium exposure.[52] For TCE, tubular damage was demonstrated in highly exposed RCC patients.[63] Hypertension and diabetes can also induce nephropathic disorders. Benichou *et al.* attributed 12% of the RCC risk in men and 39% in women to hypertension.[35] In our study, hypertension and diabetes could be shown as risk factors especially in women.[27] Furthermore, gender effects may be important in heavy metal exposures. Females have been considered to be susceptible to cadmium toxicity.[64] Cadmium can accumulate in the renal cortex to high levels in females.[65]

For exposure to TCE, the gender effects to be expected are less clear. Domeseci *et al.* discussed higher risks for females exposed to solvents.[26] Due to the small numbers of occupationally exposed women, the results were of limited power. Gender differences in the biotransformation of TCE are likely, supported by higher levels of trichloroacetic acid in the urine of females.[66] More general factors, especially a higher elimination rate of xenobiotics in men or the higher body fat of women, which can store solvents, are relevant.[26]

Conclusions

Occupation-related heavy metal exposure and exposure to chlorinated solvents were associated with a significant excess risk for RCC among males and females. Exposure to petrochemicals, paints and other mixtures containing aromatic amines or solvents, PAH, and asbestos, also showed excess RCC risk. These agent-specific results have to be discussed with respect to methodological limitations. Very long exposures in the chemical, rubber, and printing industries were associated with an excess risk for RCC. In particular, soldering, but likely also other job tasks with heavy metal exposure, can be considered to exert an RCC risk. There is evidence for a high susceptibility of female kidneys to heavy metals.

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