Kidney Cancer

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Introduction

Malignant tumors of the kidney account for approximately 2 % of all new primary cancer cases diagnosed in the United States (US) and worldwide [1–3]. Renal cell carcinoma (RCC) of the renal parenchyma accounts for over 80 % of all kidney cancers, the majority of which are adenocarcinomas that arise from the renal parenchyma [3]. RCC is divided into distinct histological subtypes, clear cell being the most prevalent (80–85 %) followed by papillary RCC (10 %). Less common subtypes of kidney cancer include oncocytoma and chromophobe tumors [4, 5]. Another histological subtype of kidney cancer is transitional cell carcinoma (TCC) which is most often located in the renal pelvis [6]. Histologically, these tumors are considered more similar to TCC of the bladder [7]. In RCC, the major etiologic risk factors that are thought to explain approximately 50 % of cases include cigarette smoking, obesity (high body mass index or BMI), hypertension, and diabetes [6, 8, 9]. The increasing prevalence of these risk factors may explain temporal variations in renal cancer incidence rates by country/region and within particular subpopulations. While the etiologic factors associated with the remaining 50 % of renal cancer cases are for the most part unexplained, other risk factors that have been described in the literature include analgesic use [3], long-term hemodialysis [10], hormonal/reproductive factors [11], variations in diet [12, 13], family history of renal cancer [14], and genetic factors [15]. Although not generally considered an occupationally related cancer, several studies have pointed towards occupational and environmental exposures [16, 17]; many associations, however, remain inconclusive. The current review will focus upon renal cancer risk associated with exposure to various agents in the workplace that are suspected of being renal carcinogens. Initial studies we present will evaluate historical exposures using job and industry titles, in which exposures to carcinogens were "likely" to be encountered in the workplace. Subsequently, to reduce speculation and exposure misclassification, higher-quality studies that used more sophisticated exposure assessment techniques (i.e., expert-assessed or actual industrial hygiene measurements) will be presented.

Occupations and Industries

Studies of occupational history that classified individuals by job and industry titles provided the first clues to specific exposures as potential risk factors for renal cancer. Industries that have been significantly associated with elevated renal cancer risk include employment in the dry cleaning [18, 19], agricultural and food [20–22], petroleum and gasoline [23–25], iron and steel [23, 25, 26], paper and printing/publishing [6, 18, 25], and automotive [22, 27] industries. Specific job titles have been less consistently associated with kidney

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cancer risk; however, those that have shown significant associations with increased risk include employment as a manager [20, 22, 28], auto or airline mechanic [6, 18, 22, 28], painter [29, 30], firefighter [30, 31], architect [20, 32], engineer [20, 33], truck or bus driver [25, 34, 35], as well as metal [6, 25, 36], railroad [6, 29, 37], and sales [22, 28] workers. Specific agents are identified through studies that used detailed analyses of job and industry reports showing that exposure to solvents [29, 36], pesticides [25, 38], metals (i.e., lead, chromium, cadmium, arsenic, and nickel) [18, 23, 29], asbestos and other fibers/dusts [18, 23, 37], automotive fumes/diesel exhaust [18, 23, 36], polycyclic aromatic hydrocarbons (PAHs) [18, 29], and ultraviolet (UV) radiation [18, 33] could be responsible for the associations observed.

Solvents, Chlorinated Solvents, and Trichloroethylene

Results from occupational studies indicate that the increased kidney cancer rates observed among dry cleaners [39], architects [40], mechanics [41], and aerospace and aircraft maintenance workers [42] could be related to solvent exposures. In particular, chlorinated solvents, a subgroup of organic solvents, have been examined in relation to kidney cancer risk in a number of occupational studies [23, 35, 36, 43–46]; however, significant associations with risk have only been reported in a few case-control studies [23, 36, 45]. Schlehofer and colleagues observed a greater than twofold increase in RCC risk (relative risk (RR) = 2.5, 95 % confidence interval (CI) = 1.2–5.2) among men reporting exposure to chlorinated solvents (N = 27 cases, N = 12 controls) in Germany [36]. In a slightly larger study conducted in the USA, occupational exposure to chlorinated aliphatic hydrocarbons was associated with increased RCC risk (odds ratio (OR) = 2.1, 95 % CI = 1.1–3.9) among women (N = 29) [45]. In a large, internationally based study (the USA, Australia, Sweden, Denmark, and Germany), increased RCC risk was also observed among male (RR = 1.4, 95 % CI = 1.1–1.7) and female (RR = 1.6, 95 % CI = 1.0–2.7) participants who reported ever being occupationally exposed to dry cleaning solvents (N = 245 male cases, N = 223 male controls; number of exposed female subjects not reported); but no clear pattern of association was seen with increasing duration of employment, since the highest level of risk was observed among men in the midrange of exposure [23].

Included within the subgroup of chlorinated organic solvents is trichloroethylene (TCE). In 1997, the International Agency for Research on Cancer (IARC) classified TCE as a Group 2A, "probable" human carcinogen based on limited carcinogenic evidence in humans but sufficient evidence in animals [47]. Recently, the US Environmental Protection Agency (EPA) released its final health assessment for TCE and characterized the chemical as "carcinogenic to humans" based on additional carcinogenic evidence in human epidemiological studies [48]. Subsequently, the IARC working group also elevated TCE's classification to a Group 1 human carcinogen [49]. TCE was a prominent chlorinated solvent used in the 1970s, primarily for degreasing metal parts, but also as an anesthetic, surgical disinfectant, pet food additive, typewriter correction fluid, and extractant of spices in food [50]. Exposure to this solvent is also of concern as it remains a common water contaminant in the USA [51].

TCE has been the most extensively studied of all chlorinated solvents in relation to RCC risk (Table 25.1) [19, 29, 39, 43, 45, 52–67]. In animal studies, TCE exposure has been found to increase nephrotoxicity and nephrocarcinogenicity [68]. At relatively low exposure levels, rats have been shown to develop nonneoplastic kidney lesions, as well as increased incidence of renal adenoma and adenocarcinoma [47, 69]. Findings from animal studies have suggested that kidney tumors result as a consequence of continual cytotoxicity and regeneration [70, 71]. In humans, nephrotoxicity is thought to be a prerequisite for renal cancer development following TCE exposure [70].

Interest regarding TCE exposure as a potential human carcinogen first escalated after publication of two German epidemiological case-control studies that indicated very strong associations between occupational exposure and RCC risk [54, 63], although some have questioned the validity of these two studies due to study design issues such as control selection, potential interview bias, and matching [72, 73]. Since then, accumulating epidemiological evidence from a variety of study designs employing various exposure assessment methodologies has examined the association between occupational TCE exposure and kidney cancer risk, including four meta-analyses published over the past 13 years [72, 73]. The first meta-analysis published on occupational TCE exposure and kidney cancer risk by Wartenberg et al. in 2000 reported a significant summary RR of 1.17 (95 % CI = 1.1–2.7) for incidence cohort studies (N = 5) that assessed TCE exposure using urinary biomarkers, job exposure matrices (JEMs), or job histories. Elevated summary estimates were also reported for other types of study designs though not significantly [73]. In 2007, Kelsh and colleagues observed significant summary estimates for both cohort (N = 16, RR = 1.34, 95 % CI = 1.00–1.81, p-heterogeneity = 0.01) and case-control studies (N = 7, OR = 2.57, 95 % CI = 1.06–2.30, p-heterogeneity = 0.003) that assessed occupational TCE exposure in relation to kidney cancer risk, and estimates remained elevated after excluding outlier studies that introduced heterogeneity to the combined risk estimates [72]. Recently, a US EPA-conducted meta-analysis reported a significant RR with kidney cancer showing a 1.3 increase in risk overall and a 1.6 increase in risk for high exposure groups [74]. A subsequent updated meta-analysis conducted by the US National Cancer Institute (NCI)

Table 25.1 Kidney cancer risk and occupational studies that have examined exposure to trichloroethylene (TCE)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Coho9rt studies					
Axelson et al. (1994) [52]	Cohort study of men (N=1,670) from 115 Swedish workforce facilities	Cancer incidence follow-up from 1958 through 1987. Cancer mortality follow-up from 1958 through 1986. Various cancers evaluated including kidney (ICD-7 180; N=6). National incidence rates used to derive expected counts	TCE used in facilities from 1955 to 1975. Workers assessed for exposure to TCE using company urinary biomonitoring measurements (U-TCA). Of the 1,670 total subjects 1,727 were exposed to TCE	Never/ever exposed to TCE	Ever exposed to TCE SIR = 1.16 (0.42–2.52)
Anttila et al. (1995) [53]	Cohort study of 2,050 male and 1,924 female workers from Finland	Cancer incidence follow-up from 1967 through 1992. Various cancers evaluated including kidney (ICD-7 180; N=7). National incidence rates used to derive expected counts	Workers assessed for exposure to TCE using government urinary biomonitoring measurements (U-TCA, B-Per, B-TC). Of the 8,974 total subjects 3,089 were exposed to TCE	Never/ever exposed to TCE. Time in years since first measured for TCE exposure (<10 years, 10+ years)	Ever exposed to TCE SIR = 0.87 (0.32–1.89). Years since measured for exposure to TCE <10 years SIR = 0.53(0.01–2.95), 10+ years SIR = 1.39(0.45–3.24)
Henschler et al. (1995) [54]	Cohort study of 359 male cardboard manufacturing plant workers in Germany	Cancer incidence follow-up from 1956 through 1992. Various cancers evaluated including kidney (ICD-9 189; N=5). National incidence rates from two sources were used to derive expected counts	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, and company records. No actual measurements assessed. Of the 359 total subjects, 169 were assumed to be exposed to TCE	Never/ever exposed to TCE compared to Cancer Registry of the former German Democratic Republic	Ever exposed to TCE SIR = 9.66 (3.14–22.55)
Morgan et al. (1998) [55]	Cohort study of 20,508 aerospace manufacturing workers in Arizona, USA	Cancer mortality follow-up from 1950 through 1993. Various cancers evaluated including kidney (N=32 overall, N=8 in the TCE-exposed subcohort). US mortality rates used as a comparison. Internal comparison analyses also conducted	Exposure to TCE assessed using company work histories, where data for long-term employees was used to develop JEM. Of the 20,508 total subjects, 4,733 assumed to be exposed to TCE	Never/ever exposed to TCE. Never/ever exposed to low levels (<50 % of cumulative exposure score) of TCE. Never/ever exposed to high levels (≥50 % of cumulative exposure score) of TCE	Ever exposed to TCE SMR = 1.32(0.57–2.60). Ever exposed to low levels of TCE SMR = 0.47(0.01–2.62) or high levels of TCE SMR = 1.78(0.72–3.66). Internal comparison – ever exposed to low levels of TCE RR = 0.31(0.04–2.36) or high levels of TCE RR = 1.59(0.68–3.71)
Ritz (1999) [56]	Cohort study of 3,814 male uranium processing workers in Ohio, USA	Cancer mortality follow-up from 1951 through 1989. Various cancers evaluated, including that of the kidney (ICD-8 189; N=5). External US population mortality rates used as comparison as well as internal comparison analyses	Exposure to TCE and other chemicals assessed using company work histories where data for long-term employees used to develop JEM. Of the 3,814 total subjects, 2,971 assumed to be exposed to TCE	Never/ever exposed to TCE	Ever exposed to TCE SMR = 0.65(0.21–1.51)
Boice et al. (1999) [57]	Cohort of 77,965 aircraft manufacturing workers in California, USA	Cancer mortality follow-up from 1960 through 1996. Various cancers evaluated, including that of the kidney (ICD-9 189.0–189.2; N=125 overall, N=7 in TCE-exposed subcohort). General population of white Californian workers used to derive expected counts. Internal comparison analyses also conducted	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, industrial hygiene records which were used to develop JEM. Of the 77,965 total subjects, 2,267 assumed to be routinely exposed to TCE	Never/ever exposed to TCE. Internal comparison to assess years of exposure to TCE (none, <1 year, 1–4 years, 5+ years)	Ever exposed to TCE SMR = 0.99(0.40–2.04). Internal comparison for years of exposure to TCE <1 year RR = 0.97 (0.37–2.50), 1–4 years RR = 0.19(0.02–1.42), 5+ years RR = 0.69(0.22–2.12)

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Table 25.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Hansen et al. (2001) [39]	Cohort of 803 workers from 275 Danish companies	Cancer incidence follow-up from 1968 through 1996. Various cancers evaluated including kidney (ICD-7 180; $N=4$, for males $N=3$ for females $N=1$). National incidence rates used to derive expected counts	Exposure to TCE assessed using urinary biomonitoring (U-TCA) measurements or company air measurements	Never/ever exposed to TCE	Ever exposed to TCE among males SIR = 0.9(0.2–2.6), among females SIR = 2.4(0.03–14.0)
Raaschou-Nielsen et al. (2003) [58]	Cohort of 40,049 Danish blue-collar workers for 347 companies using TCE	Cancer incidence follow-up from 1968 through 1997. Various cancers evaluated, including RCC ($N=76$). National incidence rates used to derive expected counts	Exposure to TCE assessed using pension funding records, government industrial hygiene, and urinary biomonitoring (U-TCA) measurements where a "company exposure matrix" was developed. Of the 40,049 total subjects, 14,360 assumed to be exposed to TCE	Never/ever exposed to TCE. Never/ever exposed to TCE with a lag of 20 years. Duration of employment (none, <1 years, 1–4.9 years, 5+ years). Years since first employed and number of employees in each company also evaluated	Ever exposed to TCE among men SIR = 1.2(0.97–1.48), among women SIR = 1.2(0.55–2.11). A 20 year lag for ever exposure to TCE among males SIR = 1.3(0.8–1.9), among females SIR = 1.3(0.3–3.7). Duration of employment among males <1 year SIR = 0.8(0.5–1.4), 1–4.9 years SIR = 1.2(0.8–1.7), 5+ years SIR = 1.6(1.1–2.3); among females <1 year SIR = 1.1(0.1–3.8), 1–4.9 years SIR = 1.2(0.2–3.4), 5+ years SIR = 1.5(0.3–4.3)
Boice et al. (2006) [59]	Cohort of 41,351 aircraft workers in a rocket engine testing facility in the USA	Cancer mortality follow-up from 1948 through 1999. Various cancers evaluated including kidney (ICD-9 180.0–189.2; $N=17$). External comparison rates used	Exposure to TCE assessed using company work histories, walk-through surveys, and interviews to developed JEM. Of the 41,351 total subjects, 1,111 assumed to be exposed to TCE	Never/ever exposed to TCE. Intra-cohort assessment by years (no, <4 years, 4+ years) of potential TCE exposure among engine flush workers also reported	Ever exposed to TCE SMR = 2.22(0.89–4.57)
Radican et al. (2008) [60]	Cohort of 14,457 aircraft maintenance workers from Utah, USA	Cancer mortality follow-up from 1953 through 2000 and cancer incidence follow-up from 1953 through 1990. Various cancers evaluated including kidney (ICD-8 189; $N=15$). Utah population used as referent group for overall analysis	Exposure to TCE assessed using company work histories, walk-through surveys, interviews, industrial hygiene experts, and other company records to developed JEM. Of the 14,455 total subjects 7,204 assumed to be exposed to TCE	Never/ever exposed to TCE (estimates stratified by sex also reported). Sex-stratified risk estimates for cumulative exposure to TCE (presented in tertiles) also reported	Ever exposed to TCE among all subjects RR = 1.18(0.47–2.94), among males RR = 1.24(0.41–3.72), among females RR = 0.93(0.15–5.76)
Case-control studies					
Asal NR et al. (1988) [19]	US mixed-based (population- and hospital-based) case-control study	Participants included 315 RCC cases and 313 hospital- and 336 population-based controls	Self-reported lifetime occupation/industry collected assessed through questionnaires. Exposure to TCE ($N=29$) assumed in metal degreasing/cleaning industry workers	Never/ever employed in the metal degreasing/ cleaning industry (exposure to TCE assumed) adjusted for age, smoking, and weight	Ever employed in metal degreasing/ cleaning industry OR = 1.7 (0.7–3.8)

Harrington et al. (1989) [61]	Population-based case-control study conducted in the United Kingdom	Participants included 54 RCC cases and 54 population-based controls	Questionnaires and interviews used to collected data on self-reported lifetime occupational histories and exposure to solvents. Data assessed by occupational hygienist for solvent exposure. Exposure to TCE ($N=8$) assumed among metal degreasing/cleaning industry workers	Never/ever exposed to organic solvents (exposure to TCE assumed)	Ever exposed to degreasing solvents OR = 1.0 (0.2–4.9)
Sharpe et al. (1989) [62]	Hospital-based case-control study conducted in Canada from 1982 to 1987	Participants included 164 RCC (ICD-8 189.0) cases and 161 hospital-based controls	Questionnaires used to collected data on self-reported timing and proximity of occupational exposures to various agents. Exposure to TCE ($N=13$) assumed among workers handling degreasing solvents	Never/ever exposed to degreasing solvents (exposure to TCE assumed)	Ever exposed to degreasing solvents OR = 3.42 (0.92–12.66)
Siemiatycki (1991) [67]	Canadian mixed-based (population- and hospital-based) case-control study conducted from 1979 to 1985	Participants included 177 kidney cancer cases and 3,014 mixed-based controls	Self-reported lifetime occupational histories collected using occupation-specific questionnaires and interviews. Occupational data reviewed by an expert (subject-specific) for exposure to TCE ($N=4$ among those with kidney cancer)	Never/ever exposed to TCE	Ever exposed to TCE OR = 0.8(0.4–2.0)
Greenland et al. (1994) [63]	US population-based nested case-control study conducted from 1969 to 1984	Participants included various cancer cases including 12 with kidney cancer and 1,202 population-based controls	Insurance pension records containing work histories of TCE-using transformer assembly plant workers assessed by industrial hygienist. JEM developed for exposure to TCE	Never/ever exposed to TCE	Ever exposed to TCE OR = 0.99(0.30–3.32)
Vamvakas et al. (1998) [64]	German hospital-based case-control study conducted from 1987 to 1992	Participants included 58 RCC cases and 84 hospital-based controls	Questionnaire and interviews used to collected self-reported occupational histories that included hazardous chemicals, insurance, and worker compensation records (appears subject-specific) assessed by occupational hygienist for occupational exposure to TCE ($N=24$)	Never/ever exposed to TCE adjusted for age, sex, smoking, BMI, blood pressure, and use of diuretics	Ever exposed to TCE OR = 10.80(3.36–34.75)
Dosemeci et al. (1999) [45]	US population-based case-control study conducted from 1988 to 1990 in Minnesota, USA	Participants included 438 RCC cases and 687 population-based controls	Questionnaire and interviews used to collected self-reported most recent and usual job and industry with activities, and dates, and duration in 13 industries and 7 jobs. JEM for exposure to TCE exposure ($N=55$) created	Never/ever exposed to TCE adjusted for age, sex, smoking, body mass index, blood pressure, and use of diuretics or antihyper-tension medications	Ever exposed to TCE among all subjects OR = 1.3(0.9–1.9), among males OR = 1.04(0.6 = 1.7), among females OR = 1.96(1.0–4.0)
Pesch et al. (2000) [29]	German population-based case-control study conducted from 1991 to 1995	Participants included 935 RCC cases and 4,298 population-based controls	Questionnaire and interviews used to collected self-reported occupational histories with supplemental questions on tasks with exposures of interest, the exposure and frequency. A job and task exposure matrix applied to examine exposures to chlorinated solvents including TCE ($N=172$)	Exposure to TCE assessed in tertiles (30th, 60th, and 90th percentiles of the distribution of exposure)	Tertiles of exposure to TCE among males: 30th OR = 1.3(1.0–1.8), 60th OR = 1.1(0.8–1.5), 90th OR = 1.3(0.8–2.1) TCE exposure level; among females: 30th OR = 1.3(0.7–2.6), 60th OR = 0.8(0.4–1.9), 90th OR = 1.8(0.6–5.0) TCE exposure level

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Table 25.1 (continued)

Reference (year)	Study type, location, and size	Subjects	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)
Bruning et al. (2003) [76]	German hospital-based case-control study conducted from 1992 to 2000	Participants included 134 RCC cases and 401 hospital-based controls	Questionnaire and interviews used to collected self-reported lifetime occupational histories. A JEM for exposure to TCE ($N=63$) was applied	Never/ever exposed to TCE. Years of exposure to TCE assessed as none, <10 years, 10–<20 years, 20+ years	Ever exposed to TCE OR = 2.47(1.36–4.49). Years of exposure to TCE <10 years OR = 3.78(1.54–9.28), 10–<20 years OR = 1.80(0.67–4.79), 20+ years OR = 2.69(0.84–8.66)
Charbotel et al. (2006) [66]	A French, mixed-based (population- and hospital-based) case-control study conducted from 1993 to 2003	Participants included 86 RCC cases and 316 mixed-based controls	Questionnaire and interviews used to collected self-reported occupational histories. A task-specific JEM was applied. Exposure to TCE assumed among 147 subjects	Never/ever exposed to TCE adjusted for body mass index and smoking	Ever exposed to TCE OR = 1.64(0.95–2.84)
Moore et al. (2010) [43]	Central and Eastern European hospital-based case-control study conducted from 1999 to 2003	Participants included 1,097 RCC cases and 1,476 hospital-based controls	Interviews and occupation-specific questionnaires used to collected self-reported occupational histories which was assessed by occupational health experts (appears subject-specific) for exposure to TCE ($N=88$)	Never/ever exposed to TCE, adjusted for sex, age, and study center. Years (<13.5/13.5+ years), hours (<1,080/1,080+ hours), cumulative exposure (<1.58/1.58+), and average intensity (<0.076/0.076+) of exposure to TCE also examined	Ever exposed to TCE OR = 1.63(1.04–2.54). Years of exposure to TCE <13.5 years OR = 1.44(0.77–2.69), 13.5+ years OR = 1.82(0.99–3.34). Hour of exposure to TCE <1.58 h OR = 1.19(0.61–2.35), 1.58+ hours OR = 2.02(1.14–3.59). Average intensity of exposure to TCE <0.076 OR = 1.38(0.81–2.35), 0.076+ OR = 2.34(1.05–5.21)

RCC renal cell carcinoma, *N* number, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *ICD-O* international classification of disease for oncology, *US* United States, *JEM* job exposure matrix

observed significantly elevated RRs for cohort studies (RR = 1.26, 95 % CI = 1.02–1.56, *p*-heterogeneity = 0.56), case-control studies (OR = 1.35, 95 % CI = 1.17–1.57, *p*-heterogeneity = 0.41), and both types of studies combined (RR = 1.32, 95 % CI = 1.17–1.50, *p*-heterogeneity = 0.63) after removal of outlier studies, which, incidentally, were those reporting the highest associations between kidney cancer risk and TCE exposure [75]. Nonsignificant elevated summary estimates were observed for studies of workers exposed to the broader classification of chlorinated solvents, but not assessed specifically for TCE.

An important question raised by most critiques surrounds TCE exposure and its mode of action in the kidney. Findings from recent epidemiological studies suggest that the association between TCE exposure and kidney cancer risk may be modified by polymorphisms in genes important in the reductive metabolism of TCE [43, 76]. In particular, evidence from these studies has demonstrated that TCE-associated renal genotoxicity occurs predominantly through glutathione S-transferase (GST) conjugation and subsequent bioactivation by the enzyme renal cysteine beta-lyase (CCBL1) [43, 68, 76]. One early study of RCC and risk modification by *GST* genotypes among workers with long-term occupational exposure to high concentrations of TCE ($N = 45$ cases, $N = 48$ controls) observed positive associations among *GSTT1* active genotypes (OR = 4.2, 95 % CI = 1.16–14.91) [76]; however, findings from a reassessment of the same TCE-exposed kidney cancer cases and additional controls [originating from various sources] did not corroborate the findings [43, 77]. In a large case-control study of 1,097 RCC cases and 1,476 controls conducted in Central and Eastern Europe, job histories were assessed for the likelihood of exposure to organic solvents, chlorinated solvents, and specifically TCE [43]. RCC risk increased for subjects ever (compared to never) exposed to TCE ($N = 48$ cases, $N = 40$ controls), and an exposure–response trend was seen with higher estimated exposure levels. Elevated associations were not observed among individuals exposed to organic or chlorinated solvents. Subsequently, risk modification by *GSTT1* and *CCBL1* genotypes were also evaluated. A significant relationship (OR = 1.88, 95 % CI = 1.06–3.33) was found among likely TCE-exposed subjects with at least one intact *GSTT1* allele (active genotype $N = 32$ cases, $N = 23$ controls), but not among subjects with two deleted alleles (null genotype) [43]. These findings provided the strongest evidence to date that TCE exposure is associated with increased renal cancer risk that was limited to individuals with a particular genotype necessary for the reductive metabolism of TCE. In addition, increased risk was observed among those with an active *GST* genotype that would be able to conjugate and subsequently bioactivate TCE in vivo [43]. This finding adds biological plausibility of the association in humans and provides some understanding of its mechanism of carcinogenicity. Other pathways involved in the metabolism of TCE remain to be evaluated [43, 78].

High-quality exposure assessment and robustness of findings across studies that specifically focused upon TCE exposure raises the likelihood of an association. Weaknesses that exist across all studies conducted to date include potential confounding and exposure misclassification due to possible exposures to other solvents, although both factors would likely reduce risk estimates, rather than increase them. Additional studies, particularly more recently updated meta-analytic studies, are warranted to help support a human health risk assessment between TCE exposure and kidney cancer risk.

Agricultural Work and Exposure to Pesticides, Insecticides, and Herbicides

Increased renal cancer risk has been observed in several studies of agricultural workers and farmers [20, 22, 28, 79, 80]. Updated cancer mortality data among a cohort of US farmers who applied pesticides revealed a significant 62 % increase (95 % CI = 1.28–2.05) in renal cancer mortality [76]. Elevated mortality (standard mortality ratio (SMR) = 2.12) also was observed among a cohort of Italian farmers [80], but a significantly reduced renal cancer incidence was found among Swedish male (standardized incidence ratio (SIR) = 0.88) [28] and female (SIR = 0.81, 95 % CI = 0.68–0.97) [81] farmers. Mixed results have been shown in case-control studies reporting specific agricultural industries, occupations, and job titles [18–20, 22, 36, 82–84]. For example, findings from a recent renal cancer case-control study analyzing job and industry titles reported a significant 43 % (95 % CI = 1.03–2.00) increase in risk for subjects employed as agricultural and animal husbandry workers ($N = 107$ cases, $N = 108$ controls); an overall 35 % (95 % CI = 1.3–1.77) increase for participants in the agricultural, hunting, and related services industries ($N = 132$ cases, $N = 138$ controls); and a more than twofold increase in risk for female general farmers ($N = 16$ cases, $N = 7$ controls, OR = 2.73, 95 % CI = 1.05–7.13). Higher-risk estimates were also observed among those with a longer duration of employment (10+ years) for these jobs/industries [20]. On the other hand, no increase in cancer risk was observed among agricultural livestock workers ($N = 15$ cases, $N = 19$ controls, OR = 1.00) [20]. Additionally, an earlier review of cancer patterns among farmers in developed countries found a significant 8 % reduction in kidney cancer risk (combined RR = 0.92, 95 % CI = 0.86–0.98) (risks ranging from 0.6 to 1.5) based on results from 13 epidemiological studies of various designs [85].

The relationship between evaluation of likely occupational pesticide exposure and RCC risk has been examined in eight epidemiological studies (Table 25.2), and results have

Table 25.2 Renal cancer risk and occupational studies of pesticide, herbicide, and/or insecticide exposures

Reference (year)	Study type and location	Cases	Controls	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)	Adjustment
McCredie and Stewart (1993) [86]	Population-based case-control study of kidney cancer conducted in New South Wales, Australia, from 1989 to 1991	Incident renal parenchyma (ICD-9 189.0; *N* = 489) and renal pelvis (ICD-9 189.1; *N* = 147) cancer cases, 20–79 years old, identified from hospital cancer registries	Population-based controls (*N* = 523) identified from electoral roles	Face-to-face (256 RCC, 71 renal pelvis, 232 controls) and telephone (233 RCC, 76 renal pelvis, 291 controls) interviews conducted. Standardized questionnaires used to collect data on employment in certain industries and occupations and exposure to certain chemicals	Never/ever exposed to herbicides or insecticides/ pesticides	Ever exposed to insecticides/ pesticides RCC RR = 1.39(0.89–2.18). Ever exposed to herbicides RCC OR = 1.45 (0.87–2.40)	Adjusted for age, sex, method of interview, and education
Mellemgaard et al. (1994) [25]	Population-based case-control study of RCC conducted in Denmark from 1989 to 1992	Histologically verified RCC cases (*N* = 365), 20–79 years old, identified from the Danish Cancer Registry and repeat searches in files of all pathology departments in Denmark	Population-based control (*N* = 396) identified from the Central Population Registry and frequency matched to cases on sex and age	In-person interviews conducted to collect data on most recent and longest occupation held. Data pertaining to occupation, industry, and occupational exposures assessed	Never/ever exposed to insecticides or herbicides. Years of exposure to insecticides/herbicides (never, <20 years, 20+ years) among males	Ever exposed to insecticides among males OR = 2.2(0.8–6.3), among females OR = 5.7(0.6–58). Ever exposed to herbicides among males OR = 1.7(0.7–4.3), among females OR = 5.7(0.6–58). Years of exposure to insecticides/herbicides among males <20 years OR = 1.3(0.4–4.1), 20+ years OR = 3.9(1.0–15)	Adjusted for age, BMI, and smoking
Mandel et al. (1995) [23]	Multicenter, international (Australia, Denmark, Germany, Sweden, and USA) population-based case-control study of RCC	Incident RCC (ICD-9 189.0; *N* = 1,732) cases, verified by histology or cytology, 20–79 years old, were identified through active surveillance systems of clinical and pathology departments	Population-based controls (*N* = 2,309) were selected from the same registry areas as cases and identified through population, electoral, residential, and health care financing registries; all were frequency matched to cases on age and sex	Face-to-face interviews conducted to collect data on specific occupations, industries, and exposures of interest	Never/ever exposed to pesticides among males	Ever exposed to pesticides among males RR = 1.2 (0.9–1.5)	Adjusted for age, smoking status, BMI, education, and study center

Schlehofer et al. (1995) [36]	Population-based case-control study of RCC conducted in Germany from 1989 to 1991	Histologically confirmed incident RCC (ICD-9 189.0; *N* = 277) cases, 20–75 years old, identified from ten urology departments within the German Rhein-Neckar-Odenwald area	Population-based controls (*N* = 286) identified from the compulsory population registry of the study area and frequency matched to cases on age and sex	Personal interviews conducted using standardized questionnaires. Life occupational histories evaluated to assess employment in certain industries and occupations and exposure to certain chemicals	Never/ever exposed to pesticides with the referent category being subjects exposed for <5 years	Ever exposed to pesticides among men RR = 0.89 (0.42–1.89)	Adjusted for age and smoking
Hu et al. (2002) [24]	Population-based case-control study of RCC conducted in Canada between 1994 and 1997	Histologically confirmed incident RCC (ICD-O-2 64.9; *N* = 1,279) cases from eight Canadian provinces identified from cancer registries	Population-based controls (*N* = 5,380) included people without cancer selected from a random sample of individuals within a province and frequency matched to cases on age, sex, and province	Mailed questionnaires used to collected information on occupational histories and years of exposure to certain chemicals. Occupational exposures to chemicals evaluated for subjects exposed for at least 1 year	Never/ever exposed to pesticides or herbicides. Years of exposure to herbicides (never, 1–15 years, 16+ years) among men	Ever exposed to pesticide among males OR = 1.8 (1.4–2.3), among females OR = 1.3 (0.9–1.8). Ever exposed to herbicides among males OR = 1.6 (1.3–2.0), among females OR = 0.8 (0.5–1.3). Years of exposure to herbicides among males ≤15 years OR = 1.3 (0.9–1.8), 16+ years OR = 2.0 (1.4–2.7), *p*-trend = 0.001	Adjusted for age, province, education, BMI, pack-years of smoking, alcohol use, and total meat consumption
Buzio et al. (2002) [82]	Hospital-based case-control study of RCC conducted in Northern Italy from 1998 to 2000	Histologically verified RCC cases (*N* = 100) identified from the Parma University Hospital	Hospital-based controls (*N* = 200) identified from outpatient specialty centers at the same university hospital	In-person interviews conducted using a structured questionnaire to collect data on occupational histories and exposures	Duration of exposure to pesticides (never, short (<10 years), long (10+ years)). Never/ever exposed to pesticides with referent being no exposure to any of the major occupational determinants of risk	Duration of exposure to pesticides <10 years OR = 1.1 (0.2–5.9), 10+ years OR = 2.0 (0.8–4.7), *p*-trend = 0.33. Ever exposed to pesticides OR = 2.6 (0.7–9.8)	Adjusted for age
Mattioli et al. (2002) [37]	Hospital-based case-control study of RCC conducted in Northern Italy from 1986 to 1994	Histologically confirmed RCC cases (*N* = 324) were identified from patients registered at the University Hospital of Bologna	Hospital-based controls (*N* = 324) selected from patients from the same hospital as cases and frequency matched to cases on age, sex, and place of birth and residence	Mailed questionnaires (or telephone interviews for non-mail respondents) used to collect information on occupational histories. Job titles assessed by occupational physicians. Occupational exposures assessed by industrial hygienist	Never/ever exposed to pesticides	Ever exposed to pesticides among males OR = 1.24 (0.34–4.57), among females OR = 0.32 (0.01–9.20)	Adjusted for age, sex, birthplace, residence, BMI, smoking, coffee and alcohol consumption, phenacetin/diuretic use, and meat intake

(continued)

Table 25.2 (continued)

Reference (year)	Study type and location	Cases	Controls	Exposure assessment	Risk evaluated	Risk estimates (95 % CI)	Adjustment
Karami et al. (2008) [38]	Hospital-based case-control study of RCC conducted in Central and Eastern Europe from 1999 to 2003	Histologically confirmed incident RCC (ICD-O-2 64; *N* = 1,097) cases, 20–88 years old, identified from local participating hospital centers	Hospital-based controls (*N* = 1,476) selected from patients from the same hospital as cases with conditions unrelated to urological disorders and frequency matched to cases on age, sex, and place of residence	In-person interviews and standardized questionnaires used to collect lifetime occupational data on jobs held for at least 1 year. Job-specific questionnaires also used to collect data on specific occupational exposures. Exposure to pesticides evaluated by occupational health experts	High confidence exposure to pesticides evaluated as never/ever, years (never, ≤8 years, >8 years), hours (never, ≤1,230 h, >1,230 h), cumulative exposure (never, ≤0.86, >0.86), and average exposure (never, ≤0.03, >0.03)	Ever exposed to pesticides OR = 1.82 (1.1–3.00). Years exposed to pesticides ≤8 years OR = 1.0 (0.45–2.21), >8 years OR = 2.66 (1.38–5.12), *p*-trend = 0.01. Hours exposed to pesticides ≤1,230 h OR = 1.43 (0.70–2.93), >1,230 h OR = 2.24 (1.13–4.43), *p*-trend = 0.01. Cumulative exposure to pesticides ≤0.86 OR = 1.60 (0.77–3.32), >0.86 OR = 2.02 (1.04–3.94), *p*-trend = 0.02. Average exposure to pesticides ≤0.03 OR = 2.21 (1.15–4.25), >0.03 OR = 1.37 (0.63–2.96), *p*-trend = 0.06	Adjusted for age, sex, center, and smoking status

RCC renal cell carcinoma, *N* number, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *ICD-O* international classification of disease for oncology

been inconsistent [23–25, 36–38, 82, 86]. No associations were observed between RCC risk and occupational pesticide exposure in a large international multicenter population-based study of 1,723 cases and 2,309 controls [23] or in three smaller European case-control studies [36, 37, 86]. Nonsignificant increased risks were observed in two European case-control studies [25, 82]. When analyses were restricted to subjects occupationally exposed to pesticides for at least 20 years, one study reported a fourfold increase in risk in males ($N=10$ cases, $N=3$ controls, OR = 3.9, 95 % CI = 1.0–15.0) [25]. A large case-control study conducted in Central and Eastern Europe showed increased RCC risk among subjects whose job histories were assessed for likely pesticide exposure ($N=44$ cases, $N=34$ controls). Elevated risk was observed for ever exposure (OR = 1.60, 95 % CI = 1.00–2.55) and with years (p-trend = 0.01), hours (p-trend = 0.03), and cumulative (p-trend = 0.04) exposures, but no association was observed with average exposure indices (p-trend = 0.09) [38]. Resulting risk estimates from this study were strengthened when analyses were limited to jobs assessed by occupational health experts as having the highest confidence of exposures. Moreover, a significantly elevated RCC risk was reported among males exposed to herbicides ($N=131$ cases, $N=318$ controls, OR = 1.6, 95 % CI = 1.3–2.0) and pesticides ($N=157$ cases, $N=368$ controls, OR = 1.8, 95 % CI = 1.4–2.3) in a large Canadian case-control study of 1,279 cases and 5,370 controls, and risk also increased linearly with increasing years of exposure [24].

Some pesticides are comprised of halogenated compounds, which can be metabolized and subsequently bioactivated through mechanisms similar to chlorinated solvents like TCE [9, 87]. A few studies have examined RCC risk in relation to *GST* genotype [38, 88], with the hypothesis that an active *GST* genotype would result in renal bioactivation of halogenated pesticide compounds. Active genotypes are able to encode GST proteins; therefore, their presence would be required for conjugation and subsequent bioactivation of related metabolites in the kidney [38]. Since *GST* genes are expressed and enzymes are active in the kidney, GST activity associated with functional polymorphisms in the glutathione S-transferase mu (*GSTM1*) and theta (*GSTT1*) genes are hypothesized to modify cancer risk because of the differences in the ability to bioactivate halogenated compounds in the kidney [38, 88]. Although two small earlier studies of GSTs and pesticide exposure did not observe risk modification by *GST* genotype [87, 89], two recent studies have found that RCC risk was increased among likely pesticide-exposed participants with active *GSTM1* or *GSTT1* genotypes [38, 88]. Moreover, the results of both studies were further strengthened among subjects with both active genotypes.

The carcinogenic potential of specific pesticides has been evaluated by the IARC [90]. Most occupational epidemiological studies have not been able to examine cancer risk associated with exposure to specific pesticides given the small number of study participants, the lack of detailed information collected to identify individual classes of pesticides, and misclassification due to exposures to multiple pesticides. However, the carcinogenic risk posed to humans from occupational exposure during the spraying and application of insecticides has been evaluated by the IARC and classified as "probably" carcinogenic to humans (Group 2A) [90]. The need for additional studies is apparent given the limited number of studies that have evaluated occupational pesticide exposure in relation to kidney cancer and the important role of the kidneys in the metabolism of certain classes of pesticides.

Lead

Inorganic lead and lead compounds are classified as "probable" human carcinogens by the IARC [91] and listed as "reasonably anticipated to be human carcinogens" by the National Toxicology Program [92], based on limited evidence of carcinogenicity in humans and sufficient evidence in laboratory animals, particularly for cancers of the stomach and lung. Inconsistent evidence for an association between kidney cancer and exposure to lead or lead compounds has been shown [91–104]. Among lead-exposed workers, high exposure has been reported in lead smelting and lead battery plants, while moderate exposure has been shown for welders of metals containing lead or painted with lead (lead fumes), lead miners, lead glass workers, automobile radiator repair workers, leaded paint manufacture workers, as well as lead typesetting printing workers [93, 94].

Lead has been shown to induce renal cancers in rodents and chronic nephropathy among humans with high occupational exposures [91, 92]. The carcinogenic effect of lead on the kidneys is plausible since urinary elimination is the main route of excretion and the proximal tubules are particularly sensitive to lead given their high reabsorption activity [95]. Moreover, the tubular epithelium of the renal cortex is a major target for the carcinogenicity of inorganic lead salts in animals, although the type of lead used in animal experimentation was different than the type to which humans are occupationally exposed [91, 96].

Exposure to lead has been suspected for the elevated kidney cancer associations observed among welders [18, 28, 29, 86, 97], auto mechanics and technicians [20], painters [29, 30], and lead smelter [98–100] and production [101] workers. However, epidemiological studies examining the association between occupational lead exposure and kidney cancer have been inconsistent [18, 29, 98–100, 102, 103]. Three cohort studies of male lead smelter workers assessed for high lead exposure using air monitoring measurements [98, 99] and industrial hygiene surveys [98–100] observed a

1.4–2-fold increase in kidney cancer mortality risk when compared to national rates. In 1985, Selevan and coauthors reported a borderline significant increase in kidney cancer mortality (SMR = 301, 95 % CI = 98–703) among high-lead-exposed (airborne levels >200 μg/m^3) workers from Idaho (N = 5) [99]. Utilizing updated information from the same cohort, Steenland et al. also found non-statistically elevated risk for kidney cancer mortality among all workers 8 years later, but also a significant increase in risk (SMR = 2.39, 95 % CI = 1.03–4.71) for workers with high lead exposure (N = 8 observed deaths) [98]. Using an internal comparison of workers, Cocco and investigators observed an RR of 10.9 (95 % CI = 1.0–121.0, N = 2 observed cases) among lead smelter workers in Italy who had been employed for at least 21 years [100]. Studies of other lead-exposed occupational cohorts have not found a significant excess in kidney cancer risk [102, 103]. Similarly, a meta-analysis of published epidemiological studies on cancer risk and occupational exposure to lead using measurement of exposure levels or blood levels through the year 2000 (N = 7 studies, N = 40 deaths) did not find an association with kidney cancer (RR = 1.01, 95 % CI = 0.72–1.42) [93]. However, the use of JEMs or occupational experts to estimate likely lead exposures in case-control studies has usually shown an increase in kidney cancer risk [29, 65, 67, 96, 97, 104]. The most recent large-scale case-control study of approximately 1,100 cases and 1,500 controls reported a significant increase in RCC risk (OR = 1.55, 95 % CI = 1.09–2.21) among likely lead-exposed workers (N = 80 cases, N = 71 controls). Although no clear monotonic exposure–response was observed for either duration or cumulative exposure, RCC risk was 2.25 (95 % CI = 1.21–4.19) among subjects in the highest cumulative lead exposure category [96].

Lead is not considered to be directly genotoxic in vitro, and it has been shown to increase the mutagenicity of other carcinogens by acting as a cocarcinogen, possibly through inhibition of DNA repair [93]. One of the most important mechanisms of lead toxicity occurs through its ability to impede key enzymes within the heme biosynthetic pathway [105]. Therefore, previous studies of genetic susceptibility to lead exposure and cancer risk have analyzed risk modification by genetic variants in the δ (delta)-aminolevulinic acid dehydratase (*ALAD*) gene [105–107], the second enzyme in the heme biosynthetic pathway [105]. The gene that encodes *ALAD* exists in two polymorphic forms ($ALAD_1$, $ALAD_2$) [single nucleotide polymorphism (SNP) 1800436], the presence of which may influence an individual's susceptibility to lead poisoning [105, 108]. The substitution of an asparagine for lysine at residue 59 results in an increased affinity for lead by $ALAD_2$ compared to $ALAD_1$ [105, 109]. It is unclear whether other functional variants exist. One recent study found that rs8177796 CT/TT variants were associated with RCC risk overall (OR = 1.35, 95 % CI = 1.05–1.73), compared to the CC major allele. Joint effects of lead exposure and SNP rs2761016 suggested an increased RCC risk for the homozygous wild-type and heterozygous alleles (^{GG}OR = 2.68, 95 % CI = 1.17–6.12; ^{GA}OR = 1.79, 95 % CI = 1.06–3.04) with an interaction approaching significance (p-interaction = 0.06). In contrast, no modification of risk was observed for the functional SNP rs1800435 (K68N) [105], which had previously been associated with brain cancer and susceptibility to lead poisoning [106]. But, due to the limited analytic power (small number of participants) in that study to investigate interaction between *ALAD* and lead exposure in RCC, further investigations are needed to elucidate this relationship.

Results of studies of welders and renal cancer case-control studies of lead exposure may have been subject to confounding by other metal exposures. However, because of the important role of the kidney in metal excretion and reabsorption, and of genetic factors known to influence susceptibility to lead exposures, biological plausibility of the association exists, and additional studies designed to identify susceptible subpopulations are warranted.

Other Metals: Cadmium, Chromium, Nickel, and Arsenic

Cadmium, chromium, nickel, and arsenic are classified by the IARC as group 1, "known" human carcinogens, but this conclusion is based on associations with lung cancer [110]. Findings from studies of cadmium exposure and kidney cancer have for the most part yielded inconclusive results [23, 24, 29, 86, 96, 104, 111, 112]. Cadmium has a long residence time in the renal cortex and nephrotoxic effects associated with occupational and environmental exposures have been observed [113, 114]. Three major sources of cadmium exposure include diet, cigarette smoking, and occupation [115]. One of the earliest studies of cadmium exposure by Kolonel in 1976 reported a positive association between renal cancer risk and occupational cadmium exposure [116]. Three population-based RCC case-control studies, by Mandel et al. [23], Pesch et al. [29], and Hu et al. [24], have since reported significantly elevated cancer risk for self-reported exposure to cadmium and cadmium salts among male workers (N = 25 exposed cases, N = 15 exposed controls, RR = 2.0, 95 % CI = 1.0–3.9; N = 99 exposed cases (number of exposed controls not reported), OR = 1.4, 95 % CI = 1.1–1.8; and N = 19 exposed cases, N = 32 exposed controls, OR = 1.7, 95 % CI = 1.0–3.2, respectively). A significant increase in risk was also reported by Pesch et al. among female workers assessed for high cadmium exposure (OR = 2.5, 95 % CI = 1.2–5.3) [29]. However, further exposure–response analyses revealed no monotonic increase with cancer risk for years [23, 24] or level of exposure [29] in these studies. One of the highest

risk estimates observed with cadmium exposure was reported by Partanen et al., who found a greater than fourfold increase in RCC risk among subjects who were expert-assessed to have likely occupational cadmium exposure (OR = 4.4, 95 % CI = 0.4–43.0), although results were based on only three exposed cases [104]. Most recently, in a European case-control study that collected detailed occupational information and expert exposure assessment, an elevated RCC risk estimate was reported for cadmium exposure (OR = 1.46, 95 % CI = 0.82–2.85). Yet no exposure–response relationship for duration or cumulative exposure was observed, and the number of exposed cases was small (*N* = 25) [96]. Other epidemiological studies have not observed significant associations between occupational cadmium exposure and kidney cancer risk [86, 111].

Studies of occupational exposure to chromium and nickel with kidney cancer risk have been inconsistent [18, 24, 65, 96, 117–120]. To date, significant risk associated with occupational exposure to chromium has only been reported in one small case-control study from Germany that assessed exposure using a JEM in which a greater than twofold increase in risk was seen for both low (*N* = 16 cases, *N* = 28 controls, OR = 2.09, 95 % CI = 1.03–4.22) and high (*N* = 20 cases, *N* = 32 controls, OR = 2.21, 95 % CI = 1.15–4.25) levels of occupational exposure to chromium [65]. Evidence of association between occupational nickel exposure and kidney cancer risk has only been suggested in a large cohort study of nickel alloy plant workers from the USA. Though no increase in kidney cancer mortality risk was observed among all plant workers, a significant twofold increase in risk was reported for white male workers employed in smelting [118]. Arsenic exposure has been associated with kidney cancer mortality in ecologic studies of drinking water contamination [121], but, typically, associations between occupational arsenic exposure and renal cancer risk have not been observed [24, 96, 122].

Given the possibility of exposure misclassification due to the presence of mixed occupational exposures, and limited study power observed in many studies due to the low number of exposed cases, additional well-powered studies that examine the relationship between occupational exposure to each of these metals that are also "known" human carcinogens and kidney cancer are warranted.

Diesel and Automotive Fumes

Interest regarding exposure to diesel and automotive fumes as possible renal carcinogens grew following a study demonstrating RCC among rats chronically exposed to unleaded gasoline fumes [123]. In 1985, McLaughlin and coauthors identified an elevation in RCC risk with duration of employment among gas station attendants [124]. Similar findings in both cohort and case-control studies have since been reported in this group of workers [22, 23, 124–126]. Occupational cohort and case-control studies have also found elevated RCC risk among truck and urban bus drivers [25, 34], railroad workers [29, 37, 127], firefighters [30, 31], and automotive repairers/mechanics [22, 28]. Findings from these and other epidemiological studies further suggest that diesel and gasoline exhaust and fumes may be etiologic risk factors associated with renal cancer risk [18–20, 22, 25, 29, 34, 36, 65, 124, 127, 128].

Diesel exhaust, according to the IARC, is classified as a "probable" human carcinogen because of the limited evidence of carcinogenicity in humans coupled with sufficient evidence of in experimental animals exposed to whole engine exhaust [129]. Epidemiological studies on occupational diesel exhaust and kidney cancer in humans have produced mixed results [128–136]. A small but significant increase in kidney cancer risk (*N* = 2,243, SIR = 1.06, 95 % CI = 1.02–1.11) was shown among men with likely diesel exhaust exposure in a large Swedish occupational cohort study in which exposure was estimated using a JEM [128]. More recently, a similar association between kidney cancer risk and likely exposure to low levels (<2.0 mg/m^3-years) of diesel exhaust (*N* = 465 exposed cases) was observed among men in a cohort of Finnish workers (RR = 1.17, 95 % CI = 1.05–1.30); however, no increase in risk was seen for moderate or high levels of exposure or among female workers [130]. Several early studies of railroad workers reported small increased associations with kidney cancer risk and exposure to diesel [131, 132], but other occupational studies of diesel-exposed workers did not find an elevated risk [133–136].

Occupational gasoline exposure, classified as a Group 2B "possible" human carcinogen by the IARC [129], using both self-reported [23, 36] and JEM-based evaluations [104], has been associated with an elevated RCC risk. A population-based case-control study conducted in Germany found a significantly elevated kidney cancer risk among men reporting occupational exposure to gas exhaust (*N* = 37 cases, *N* = 23 controls, RR = 1.82, 95 % CI = 1.03–3.22) for at least 5 years [36]. A similar result was shown for men in an international study of workers who reported ever having been exposed to gasoline (*N* = 164 cases, 189 controls, OR = 1.6, 95 % CI = 1.2–2.0) [23]. Occupational gasoline exposure, assessed by industrial hygiene experts, was associated with a significant increase in RCC risk among ever versus never exposed workers (*N* = 39 cases, number of exposed controls not reported, OR = 1.72, 95 % CI = 1.03–2.87) and among men with the highest cumulative exposure levels (*N* = 9 cases, number of controls not reported, OR = 4.34, 95 % CI = 1.15–16.4) [104]. Other studies have found no elevation in risk among gasoline-exposed workers [62, 124] or among mechanics, automotive dealers, or service station employees [18, 137].

Limitations in assessing the intensity of exposure based on job title, the geographic differences in gasoline constituents, and the substantial improvements in work practices that have resulted in the decrease in daily exposures to gasoline attendants over time may explain the inconsistent findings between earlier and more recent studies. Moreover, several studies did not adjust for smoking, a known renal cancer risk factor, which may have confounded some of the results observed.

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are a group of chemical compounds found naturally in fossil fuels which are formed as by-products during the incomplete combustion of organic material such as coal, oil, wood, garbage, gas, tobacco, and charbroiled meat [138, 139]. Constituents of diesel and gasoline exhausts also contain PAHs [129]. PAHs comprise over 100 compounds that exist exclusively as complex mixtures [138–140]. PAHs have also been used in the production of plastics, dyes, medicines, aluminum, coke, and pesticides, and they are also present in tars and asphalts [138]. Specific PAHs, such as benzo[a]pyrene and benzo[a]anthracene, are considered known or suspected human carcinogens [138]. The IARC has identified several mixtures containing PAHs, including coal tar, diesel engine exhaust, and soot as carcinogenic or probably carcinogenic to humans [129].

In a few early occupational cohort studies, elevated RCC risk among coke oven and petroleum refinery workers (the latter associated with PAH by-products of the refining process) had generated interest in PAHs as occupational renal carcinogens [23, 141]. However, conflicting results have been reported in studies of employees assessed as highly exposed to PAHs, such as asphalt workers, printers, machinists, and mechanics [18, 25, 28, 86, 142]. Historically, county-level kidney cancer mortality rates in the USA have shown an ecologic correlation with the proportion of the population employed in the petroleum-refining and other petroleum-related industries [143]. Population- and hospital-based case-control studies have reported elevated risks for employment in the oil refinery industry [19, 23, 124]. Two studies have shown a suggestive exposure–response effect with the length of employment [83] and exposure intensity [62] among workers occupationally exposed to various PAHs.

Three European case-control studies that used JEMs to estimate likely PAH intensity did not report a positive association or an exposure–response effect [29, 104, 144]. Studies have also examined *GSTs* [145] and cytochrome p450 (*CYP450*) genotypes [144, 146], and modification of PAH associated risk was observed in one [146], but not both studies [144].

In addition to the duration and level of exposure, the carcinogenicity of PAHs depends on the specific chemical composition of the mixture that can influence toxicodynamics, toxicokinetics, and ultimately their biological effect [144]. Because certain PAHs are recognized as carcinogenic or possibly carcinogenic to humans, additional studies that are well powered for analyses of gene–environment interaction that can identify the unique chemical composition of PAHs are needed.

Asbestos

Exposure to all forms of asbestos, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite, has been classified by the IARC as carcinogenic to humans (Group 1), based on association with respiratory cancers [111]. Asbestos fibers have been shown to induce kidney cancer in animals, and asbestos bodies have been detected in the kidneys of individuals diagnosed with asbestosis [147–149]. Several industry- and occupationally based cohort and case-control studies have reported elevated kidney cancer risk among persons likely exposed to asbestos, including asbestos workers; shipyard, railway, and insulation workers; seafarers; and firefighters [18, 23, 25, 37, 86, 147, 150–153].

Studies that have assessed exposure to asbestos and kidney cancer risk have generally been null [154, 155]. Only two occupational cohort studies to date have reported a significant increase for kidney cancer risk and asbestos exposure [152, 156]. In 1987, Enterline et al. reported a nearly threefold increase in risk for kidney cancer mortality ($N=7$ observed deaths, SMR = 2.76, 95 % CI = 1.11–5.68) among asbestos production and maintenance workers when compared to US national death rates [152]. A few years later, Selikoff and Seidman observed a significant SMR of 1.70 (95 % CI = 1.16–2.39, $N=32$ observed deaths) for kidney cancer among a cohort of asbestos insulator workers from the USA and Canada [156]. Case-control studies utilizing JEMs or occupational health experts to assess likely exposure to asbestos have also shown significantly elevated kidney cancer risks ranging from 1.4 to 1.6 among exposed participants [23, 86]. However, positive trends with increasing intensity [29, 157] or duration [18, 23, 153, 157] of asbestos exposure from case-control studies have not been associated with kidney cancer risk. Moreover, other studies of similar design [24, 83, 104] and two meta-analyses [154, 155] of occupationally exposed cohorts have not corroborated the positive findings.

While animal studies have shown increased kidney cancer risk following exposure, the evidence linking occupational asbestos exposure to kidney cancer risk in humans has been weak. Given the significant findings observed in a few studies, which were mainly based on small case numbers, additional studies would be required to determine if asbestos should be considered a renal carcinogen. Furthermore, the

lack of supporting evidence from incidence cohort studies reduces the plausibility of an association between exposure and kidney cancer risk.

Other Fibers and Dusts

While a positive association between occupational fiber exposures has been observed for cancers of the respiratory system, associations with kidney cancer risk have been found in only a few occupational studies [157–162]. In a large Canadian cohort of 2,557 male fiberglass manufacturing workers, a significantly elevated kidney cancer risk ($N=14$ observed cases, SIR = 192, 95 % CI = 105–321) was observed in comparison to national cancer registry rates [158]. Yet a comparison of US mortality rates revealed no increase in kidney cancer mortality risk ($N=4$ observed cases, SMR = 0.77, 95 % CI = 0.21–1.97) in a cohort of 4,008 female fiberglass manufacturing plant workers [159]. No association with mortality was seen in a US cohort of man-made mineral fiber plant workers exposed to elevated airborne fiber concentrations of mineral wool and fiberglass [160]. However, likely occupational exposure to glass ($N=28$ cases, $N=19$ controls) and mineral wool ($N=22$ cases, $N=14$ controls) fibers (both of which share asbestos-like properties), assessed by industrial hygiene experts through the application of a JEM, was associated with an increase in kidney cancer risk (OR = 2.1, 95 % CI = 1.1–3.9; OR = 2.5, 95 % CI = 1.2–5.1, respectively) in a Central and Eastern European case-control study [157]. Significant trends were also observed with duration and cumulative exposure to glass and mineral wool fibers. However, increased associations between exposure to these fibers and kidney cancer risk have not been shown for all case-control studies [161, 162].

Results from studies on occupational dust exposure and kidney cancer have been mixed [25, 157, 163–169]. In a small group of European bricklayers with suspected brick dust exposure, a nonsignificant elevation in RCC risk was observed [25], and elevated kidney cancer mortality risk was reported in a surveillance study of US construction workers (concrete/terrazzo finishers) [163]. A JEM-based assessment of occupational brick dust exposure among participants in a large European case-control study also reported an increase in RCC risk ($N=72$ exposed cases, $N=80$ exposed controls, OR = 1.5, 95 % CI = 1.0–2.4). Duration and cumulative exposure to brick dust was also significantly associated with risk [157]. A study of female pottery workers, who were also exposed to silica, reported increased kidney cancer mortality [164]. A plausible cause for the relationship observed between brick dust and renal cancer may be related to the silica content of brick [157]. Silica is a Group 1 "known" human carcinogen, according to the IARC, based on sufficient epidemiological evidence from animal studies of lung cancer [165]. Scientific evidence has shown that chronic silica exposure can induce nephrotoxicity and fibrosis, glomerulonephritis, and degenerative changes in the renal tubular epithelium [165, 166, 170–172]. Silica exposure has been associated with cytogenetic damage in both animal and human studies of silica-exposed workers [165]. In 2005, Steenland and colleagues showed that silica exposure was associated with excess risk of end-stage renal disease [166]. A few years earlier, results from cohort studies (including one that assessed exposure using employment histories among silica-exposed taconite miners/millers and duration of employment in specific work areas [167] and a second Norwegian study of ferrosilicon/silicon metal plant workers that used dust measurements as estimates of silica exposure [168]) identified increased kidney cancer risk. Findings from the most recent US cohort study which assessed exposure using six environmental surveys and a JEM showed a significantly elevated threefold increase in kidney cancer mortality among silica-exposed granite workers with at least 15 years of employment [169].

In general, the lack of supporting evidence from cohort studies reduces plausibility of an association between RCC risk with dust and fiber exposures. Although these findings were for the most part negative, the fact that certain fibers are components of mixtures and may induce degenerative changes in renal tissue warrants future larger renal cancer studies with high-quality fiber exposure assessment. Additional studies that take into account silica content of brick dust exposures may help elucidate associations with specific dust subgroups as possible renal carcinogens.

Occupational Ultra Violet (UV) Exposure

Overall, ecologic studies examining the association between cancer risk and UV sunlight exposure have reported inverse associations for kidney cancer mortality and incidence [173–177]. However, results from occupational/industry studies have typically shown that employment as a farmer [20, 22, 28, 79, 80], railway worker [6, 29, 37, 127], gardener [18], or sailor [178], jobs assumed to have the highest UV exposures, is associated with higher kidney cancer risks. A large cohort of over 300,000 Swedish, male, outdoor construction workers observed a 30 % reduction in kidney cancer risk (RR = 0.7, 95 % CI = 0.4–1.0) among those with higher levels of occupational UV exposure ($N=23$ cases) when evaluated by an industrial hygienist from the construction industry [179]. More recently, in a larger European case-control study, JEM-based UV exposure estimates were associated with a significant 24–38 % reduction in RCC risk among males [180]. However, the strongest reduction in RCC risk in that study was observed among men residing at the highest latitudes; subjects suspected to have comparatively the weakest UV exposures may benefit from increased UV exposure overall.

The association between UV exposure and kidney cancer risk is biologically plausible since exposure to solar UV rays accounts for greater than 90 % of 1,25-dihydroxy vitamin D [181], the biologically active form of vitamin D. Moreover, the conversion of vitamin D to its biologically active form occurs within the kidney [181, 182]. Additionally, the kidney is the major organ for vitamin D metabolism, activity, and calcium homeostasis [183–185]. While emerging scientific data suggest that vitamin D has anticarcinogenic properties including inhibition of clonal tumor cell proliferation, induction of immune cell differentiation and apoptosis, and decreased angiogenesis [186, 187], epidemiological evidence in human studies for most cancer sites including kidney have been inconsistent [188–191]. In a recent large pooled cohort consortium study, no significant relationship between serum vitamin D levels and renal cancer risk was observed [188]. While there is general agreement that the serum vitamin D level is the best indicator of current vitamin D status, the short half-life of this biomarker may not reflect long-term exposure levels that are relevant to cancer latency and to lifetime occupational exposure studies [192].

Conclusion

Approximately 50 % of sporadic kidney cancer incidence remains unexplained by established risk factors; therefore, it remains important to investigate relationships with occupational exposures that may also contribute to risk. Although not normally considered an occupational cancer, associations between occupations and industries, as well as specific occupational exposures investigated, using a variety of epidemiological study designs over the past 30 years, have demonstrated some evidence of an occupational contribution to kidney cancer risk. The most consistent association has been observed with the solvent TCE. Elevated risk estimates and exposure–response relationships have been observed in both cohort and case-control studies that were designed to assess risk to TCE specifically, rather than to all chlorinated solvents or organic solvents as a combined group. The biological plausibility of the association appears to be supported by genetic work, but replication is needed. In addition to TCE, employment in farm/agricultural work and evaluation of occupational pesticide exposures have provided some evidence of association, although additional studies that evaluate specific types of pesticide exposures are needed. Similarly, studies of metal exposures, particularly lead and cadmium and other metals associated with nephrotoxicity, are warranted.

This review article covered risk factors for which the strongest associations with kidney cancer risk have been observed. Results from epidemiological studies are limited in their ability to establish causality due to inconsistencies in case definition, misclassification due to imprecise estimates of exposure (i.e., employment length, job title, or exposures to mixed agents), and a lack of control for confounding factors (i.e., smoking, comorbidities, etc.). Studies relying solely on job or industry titles to infer exposure are limited in that exposure may vary considerably among individuals with the same title. Results may also be inconsistent between studies of kidney cancer incidence or mortality, since renal cancer is not always accurately reported as a cause of death. Subsequently, risk estimates may be underestimated in studies of kidney cancer mortality compared to those evaluating incidence [6].

Other limitations of studies conducted to date include recall and selection bias. The application of new biological markers of exposure and internal dose, genotyping/phenotyping of subjects to identify variations in xenobiotic metabolism, as well as inclusion of intermediate biological endpoints that target RCC and related conditions associated with RCC risk could strengthen causal inference and lead to exposure reductions in subpopulations at greatest risk. Future occupational investigations designed to thoroughly address the weaknesses of previous epidemiological studies, identify specific factors influencing individual risk, and to explain the gender variations of kidney cancer risk merit future research.

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