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Occupational cancer in Britain

Urinary tract cancers: bladder and kidney

Terry Brown[3], Rebecca Slack[5] and Lesley Rushton[*,1] with the British Occupational Cancer Burden Study Group

[3]Institute of Environment and Health, Cranfield Health, Cranfield University, Cranfield MK43 0AL, UK; [5]School of Geography, University of Leeds, Leeds LS2 9JT, UK; [1]Department of Epidemiology and Biostatistics, School of Public Health and MRC-HPA Centre for Environment and Health, Imperial College London, St Mary's Campus, Norfolk Place, London W2 3PG, UK

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OVERVIEW OF CANCERS

Bladder cancer

Bladder cancer refers to any of several types of malignant growths of the urinary bladder, about 90–95% of which are transitional cell carcinomas (TCC); the remaining are squamous cell carcinomas and adenocarcinomas (Quinn *et al*, 2001). Every year in the United Kingdom almost 10 200 people are diagnosed with bladder cancer, with >4800 deaths, accounting for around 1 in 20 of all cancer registrations and 1 in 30 cancer deaths (Cooper and Cartwright, 2005). In GB, the age-standardised incidence rates increased throughout the 1970s and 1980s to reach a peak in the late 1980s, although the numbers of deaths have remained steady in recent years (Quinn *et al*, 2001). In most European countries, including England and Wales, bladder cancer is at least three times less frequent in women than in men, which has been seen as partly due to different smoking habits and also an indication for an occupational origin (Lilienfeld and Lilienfeld, 1980; Parkin and Muir, 1992). Patients with superficial non-penetrating tumours have an excellent prognosis with 5-year survival rates between 80 and 90%, whereas patients with muscle-invasive tumours have 5-year survival rates of <50%. Population-based bladder cancer survival rates have changed very little between the late 1980s and the late 1990s, with men having a persistent 6–10% survival advantage (Shah *et al*, 2008).

Many studies have suggested ~40 potentially high-risk occupations (Silverman *et al*, 2006). Despite this, the relationship between many of these occupations and bladder cancer risk is unclear, with evidence of a strong association for a few occupations: aromatic amine manufacturing workers, dyestuffs workers and dye users, painters, leather workers, aluminium workers and truck drivers (Silverman *et al*, 2006).

Tobacco smoking and occupational exposure to aromatic amines (AAs) are two established environmental risk factors for bladder cancer, and controlling exposure to these has been an important contributor to the reduction in mortality, particularly among men (Pelucchi *et al*, 2006). Up to 40% of all male and 10% of female cases might be ascribable to smoking (Cooper and Cartwright, 2005); the International Agency for Research on Cancer (IARC) has suggested that the proportion of cases attributable to prolonged smoking in most countries is of the order of 50% in men and 25% in women (IARC, 1986). The relative risks (RR) are around 2- to 4-fold (Ross *et al*, 1988; Vineis and Martone, 1996; Cooper and Cartwright, 2005).

Kidney cancer

This can refer to cancer of the renal cells only (renal cell carcinoma; RCC) or can include the less-common cancers of the renal pelvis, ureter and other non-bladder urinary organs such as the urethra (transitional cell carcinoma; TCC). Kidney TCCs are closely associated with bladder cancers (Quinn *et al*, 2001). Although the incidence of kidney cancers has increased in Caucasian populations, RCC has increased more rapidly than TCC. More men are affected than women, and most cases occur in the age range of 50–70 years (Quinn *et al*, 2001). The five-year RCC survival rate is currently about 50%, but if detected early enough may be >80%. Incidence, mortality and survival rates for kidney cancer in Great Britain are in the midpoint of the global range (Quinn *et al*, 2001). Cigarette smoking is the most well-established risk factor associated with RCC and particularly TCC, but other risk factors, which include body weight, diet, pre-existing kidney disease and genetic predisposition, have been identified (McLaughlin *et al*, 2006).

Although kidney cancer is not generally considered to be occupationally associated, occupational agents/exposure scenarios associated with RCC include asbestos, trichloroethylene (TCE), tetrachloroethylene, polycyclic aromatic hydrocarbons (PAH), diesel engine exhaust (DEE), heavy metals (e.g., cadmium, lead), polychlorinated biphenyls, coke production, oil refining and gasoline/diesel delivery (HSE, 2012b). Occupational associations for transitional cell carcinomas of the kidney resemble those for bladder cancer (McLaughlin *et al*, 2006) and include links to dyes or employment in leather and shoe manufacturing. Cancers of the renal pelvis and ureter have also been associated with exposure to coal/coke, natural gas and mineral oils, or employment in dry cleaning, iron and steel, chemical and petroleum refining industries (Jensen *et al*, 1988).

*Correspondence: Dr L Rushton; E-mail: l.rushton@imperial.ac.uk
See Appendix for the members of the British Occupational Cancer Burden Study Group.

METHODS

Occupational risk factors

Group 1 and 2A human carcinogens The agents that the IARC has classified as either definite (Group 1) or probable (Group 2A) human carcinogens for urinary cancers are summarised in Table 1. The IARC has not identified any agent that is common to both kidney and bladder cancers. Causes for kidney cancer include work in coke production (Group 1) and exposure to TCE (Group 2A). For bladder cancer, these include mineral oils (Group 1), magenta manufacture (Group 1), auramine manufacture (Group 1), aluminium production (Group 1), work as a painter (Group 1), work in the rubber industry (Group 1), boot and shoe manufacture/repair (Group 1), exposure to AAs (Group 1/2A), PAHs (Group 1/2A), DEE (Group 2A), work as hairdressers and barbers (Group 2A), intermediates in plastic and rubber manufacturing (Group 2A) and petroleum refining (Group 2A).

Choice of studies providing risk estimates for urinary tract cancers

Detailed reviews of occupational risk factor studies identified for urinary tract cancer are provided in the relevant Health and Safety Executive (HSE) technical reports (HSE, 2012a, b).

Occupational exposures considered for bladder cancer

Aluminium production The predominant exposure in aluminium manufacture is to PAHs, and thus those working in this industry will be considered among the estimates for PAHs. Although high risks of bladder cancer have been reported for those working in the aluminium industry, the causative agent(s) is unknown or unproven (IARC, 1987). Most of these workers were concurrently exposed to aluminium dust, or fumes containing other known carcinogens such as tobacco smoke or PAHs. The PAH exposures mostly originate from the evaporation of carbon electrode materials used in the electrolysis process (IARC, 1984a, b, c). For a more comprehensive summary of the studies undertaken, refer to the relevant HSE technical report (HSE, 2012a). Studies generally report that the incidence of bladder cancer is increased in this industry, but since 1980 there has been a downward trend in incidence. Only studies in Canada demonstrate an exposure–response relationship. In a UK case–control study of 80 urothelial cancer cases, there was an almost doubling of the risk among those involved in aluminium refining/smelting (Sorahan *et al*, 1998).

Aromatic amines Human exposure to AAs has been associated with an increased risk of bladder cancer, but their use has continued because of their industrial and commercial value. Well-established occupational causes of bladder cancer include the AAs 2-naphthylamine (β-naphthylamine), benzidine, 4-aminobiphenyl and chloraphazine (IARC, 1987; Vineis and Pirastu, 1997; Siemiatycki *et al*, 2004; Clapp *et al*, 2005). Aromatic amines have been used as antioxidants in the production of rubber and in cutting oils, as intermediates in azo dye manufacturing and as pesticides. They are also a common contaminant in several working environments, including the chemical and mechanical industries and aluminium transformation, and are widely used in the textile industry. Occupational exposures to AAs may explain up to 25% of bladder cancers in some Western countries (Vineis and Simonato, 1991; Vineis and Pirastu, 1997).

Risk estimates for occupational exposure to AAs and bladder cancer For the present study, a series of risk estimates were used for different groups of workers. These were selected from the study by Sorahan *et al* (1998) who investigated occupational exposure to AA and estimated the risk of developing urothelial cancer on the basis of a hospital-based case–control study in the West Midlands in the United Kingdom. Smoking-adjusted relative risks (RR) of >2.0 were obtained for seven occupations, including dyestuff manufacture (RR = 2.61, 95% CI = 0.98–7.00), leather work (RR = 2.51, 95% CI = 1.44–4.35), cable manufacturing (RR = 2.46, 95% CI = 1.20–5.04) and textile printing and dyeing (RR = 2.32, 95% CI = 0.98–5.45). Sorahan's RR estimates for the manufacture of rubber products (RR = 1.89, 95% CI = 1.34–2.66), plastics (RR = 1.73, 95% CI = 1.17–2.55) and organic chemicals (RR = 1.70, 95% CI = 1.05–2.76) are used for industrial exposure to 4,4′-methylenebis(2-chloroaniline) (MOCA). The authors also provided an estimate of RR for medical and nursing occupations (RR = 1.62, 95% CI = 1.03–2.55), as well as for laboratory technicians (RR = 1.05, 95% CI = 0.60–1.86), which have been used for lower-level exposure groups.

In a review of studies, Vineis and Pirastu (1997) reported considerable increased risks of bladder cancer in workers exposed to 2-naphthylamine, benzidine and 4-aminobiphenyl, but also stated that some of these studies were poorly designed and/or based on very small numbers (Vineis and Simonato, 1991; Vineis and Pirastu, 1997). A review of 11 European case–control studies also concluded that about 5–10% of bladder cancers in men could be attributed to occupational exposures, including, but not specifically, AAs (Kogevinas *et al*, 2003). Studies of *ortho*-toluidine and aniline have demonstrated elevated risks associated with bladder cancer. The use of 2-naphthylamine, benzidine and other carcinogenic arylamines has now been banned (OSHA, 1973; Swerdlow *et al*, 2001).

Auramine and magenta manufacture These exposures have been included in the general estimation of AAs and dyestuffs. Although IARC has classified the manufacture of auramine as Group 1, the responsible carcinogens are not known (IARC, 1987). The IARC summarises one epidemiological study that suggests auramine manufacture as an occupational bladder cancer risk (IARC, 1972). Case and Pearson (1954) also observed a significant risk among dyestuff workers in the United Kingdom coming into contact with auramine.

IARC (1987) also concluded that the manufacture of magenta entails exposures that are carcinogenic, but that overall there is inadequate evidence for human carcinogenicity of this dye. The manufacturing of magenta II involves the use of *ortho*-toluidine, formaldehyde, nitrotoluene, and for magenta the use of aniline, *ortho*- and *para*-toluidines and their hydrochlorides, nitrobenzene and *ortho*-nitrotoluene. In two studies of manufacturers from the United Kingdom and Italy, the risk of bladder cancer was highly significant (Case and Pearson, 1954; Rubino *et al*, 1982); in both cases there was evidence of *ortho*-toluidine and 4,4′-methylene-bis(2-methyl aniline) exposure, implicating these compounds in the increased rate of bladder cancer mortality observed.

Diesel engine exhaust An effect of DEE on the occurrence of bladder cancer is plausible because metabolites of PAH are present in DEE and are concentrated in the urine and may interact with the urothelium of the bladder (Silverman *et al*, 1986). Exposure to DEE occurs in many occupational settings, and levels of PAHs in this fume are highest in emissions from heavy-duty diesel engines and lower (and comparable) in emissions from light-duty diesel engines and from petrol engines without catalytic converters (Boffetta *et al*, 1997). Professional drivers, mechanics and people working in other related professions are exposed to elevated levels of emissions from combustion engines (Groves and Cains, 2000).

Risk estimates for occupational exposure to DEE and bladder cancer For this current study, a suitable RR was calculated by the research team as 1.24 (95% CI = 1.10–1. 41) for the 'high-exposed' group using estimates from studies reviewed by Boffetta and Silverman (2001). The RR was estimated using a random-effects

Table 1 Occupational agents, groups of agents, mixtures and exposure circumstances classified by the IARC monographs, Vols 1–88, into Groups 1 and 2A, which have the kidney and/or bladder as the target organ

Agents, mixture, circumstance	Main industry, use	Evidence of carcinogenicity in humans	Source of data for estimation of numbers ever exposed over REP	Comments
Group 1: Carcinogenic to humans				
Agents, groups of agents				
Aromatic amine dyes **4-aminobiphenyl** **Benzidine** **2-naphthylamine**	Production: dyestuffs and pigment manufacture	Bladder *strong*	CoE and LFS	
Coal tars and pitches	Production of refined chemicals and coal tar products (patent-fuel); coke production; coal gasification; aluminium production; foundries; road paving and construction (roofers and slaters)	Bladder *suggestive*	CAREX	Included with PAHs
Polyaromatic hydrocarbons **Benzo(a)pyrene**	Work involving combustion of organic matter; foundries; steel mills; fire-fighters; vehicle; mechanics	Bladder *suggestive*	CAREX	
Mineral oils, untreated and mildly treated	Production; used as lubricant by metal workers, machinists, engineers; printing industry (ink formulation); used in cosmetics, medicinal and pharmaceutical preparations	Bladder *suggestive*	LFS	
Exposure circumstances				
Coke production	Coal-tar fumes	Kidney *suggestive* Bladder *suggestive*	LFS	AF not calculated for kidney – RR < 1; included with PAHs for bladder
Aluminium production	Pitch volatiles; aromatic amines	Bladder *strong*	CAREX	Included with PAHs
Auramine manufacture	2-naphthylamine; auramine; other chemicals; pigments	Bladder *strong*	CAREX	Included with aromatic amines
Magenta manufacture	Magenta; ortho-toluidine; 4,4′-methylene bis(2-methylaniline); orthonitrotoluene	Bladder *strong*	CAREX	Included with aromatic amines
Rubber industry	Aromatic amines; solvents	Bladder *strong*	CoE and LFS	Risk confined to pre-1950 in GB
Boot and shoe manufacture and repair	Leather dust; benzene and other solvents	Bladder *suggestive*	CAREX	Exposure up to 1962 included with aromatic amines
Coal gasification	Coal tar; coal-tar fumes; PAHs	Bladder *strong*	CAREX	Included with PAHs
Painters		Bladder	LFS	
Group 2A: Probably carcinogenic to humans				
Agents, groups of agents				
Trichloroethylene	Production; dry cleaning; metal degreasing	Renal *suggestive*	CAREX LFS	Included with PAHs – benzo(a)pyrene above
Polyaromatic hydrocarbons **Dibenz(a,h)anthracene** **Cyclopenta(c,d)pyrene** **Dibenzo(a,l)pyrene**	Work involving combustion of organic matter; foundries; steel mills; fire-fighters; vehicle mechanics	Bladder *suggestive*	CAREX	
Diesel engine exhaust	Railroad, professional drivers; dock workers; mechanics	Bladder *suggestive*	CAREX	

Table 1 (*Continued*)

Agents, mixture, circumstance	Main industry, use	Evidence of carcinogenicity in humans	Source of data for estimation of numbers ever exposed over REP	Comments
Intermediates in plastics and rubber manufacturing	Production; curing agent for roofing and wood sealing	Bladder *suggestive*	CoE and LFS	
4,4′-methylene bis(2-chloroaniline)	Production; styrene glycol production; perfume preparation; reactive diluent in epoxy resin formulations; as chemical intermediate for cosmetics, surface coating, and agricultural and biological chemicals; used for treatment of fibres and textiles; in fabricated rubber products			
Styrene-7,8-oxide				
Aromatic amine dyes	Production; used in textile, paper, leather, rubber, plastics, printing, paint, and lacquer industries	Bladder *suggestive*	CAREX	Included in aromatic amine
Benzidine-based dyes	Dye and pigment manufacture; textile industry			
4-chloro-*ortho*-toluidine	Production; manufacture of dyestuffs, pigments, optical brightener, pharmaceuticals, and pesticides; rubber vulcanising; clinical laboratory reagent; cleaners and janitors			
***Ortho*-toluidine**				
Exposure circumstances				
Hairdressers and barbers	Dyes (aromatic amines, amino-phenols with hydrogen peroxide); solvents, propellants; aerosols	Bladder *suggestive*	LFS	
Petroleum refining	PAHs	Bladder *suggestive*	LFS	Included with PAHs

Abbreviations: CAREX = CARcinogen EXposure Database; CoE = Census of Employment; IARC = International Agency for Research on Cancer; LFS = Labour Force Survey; REP = relevant exposure period.

model based on an overall inverse-variance-weighted average of all RRs from the studies based on cancer incidence, but excluding overlapping exposure categories. Boffetta and Silverman (2001) reviewed 35 European and North American epidemiological studies published between 1977 and 1998 that examined the risk for bladder cancer and exposure to DEE among highly exposed workers (e.g., railroad workers, garage maintenance workers, truck drivers and drivers and operators of heavy machines in ground and road construction). They classified exposure to DEE using a job-exposure matrix (JEM) or an experts' assessment of individual occupational histories. Most of the cohort studies included did not control for smoking, whereas a majority of the case–control studies did. The studies based on routinely collected data were assumed to have been adjusted for smoking. An overall meta-analysis of the data was not carried out by Boffetta and Silverman (2001) because the results were heterogeneous owing to the fact that the studies used different definitions of exposure. Although the review did not offer an overall summary RR, because of this heterogeneity the value they calculated for all studies (RR = 1.18, 95% CI = 1.08–1.28) was in line with their observation of an overall RR in the range 1.1–1.3.

For low-exposure groups, an RR (based on a fixed effects model) of 1.03 (95% CI = 0.84–1.26) was estimated. This was based on a reassessment of 6 of 10 studies examined by Boffetta and Silverman (2001), for which they were able to classify exposure as 'low' on the basis of JEM. They noted that among these 10 studies although there were a few positive results (three above RR = 1.1) most were close to unity.

Hairdressers and barbers Elevated risk of bladder cancer in association with occupational exposure to hair dyes in hairdressers, barbers, beauticians and cosmetologists has been widely reported; for a wider review of these studies, refer to the relevant HSE report (HSE, 2012a). Hairdressers have used a wide range of chemical products, including hair colourants and bleaches, shampoos and conditioners (e.g., primarily AAs, aminophenols and hydrogen peroxide; nitro-substituted AAs, aminophenols, aminoanthraquinones and azo dyes; and metal salts). However, the individual chemicals used have varied over time, and only permanent and semi-permanent colourants are now used to a significant extent by hairdressers (IARC, 1993).

Risk estimates for employment as hairdressers and barbers and bladder cancer In the present study, a standardised incidence ratio (SIR) of 1.22 (95% CI = 0.98–1. 51) was used for men, and an SIR of 1.09 (95% CI = 0.81–1.43) for women. These figures were based on a study by Czene *et al* (2003) who followed up a large cohort of >45 000 male and female Swedish hairdressers recruited via the national census. These estimates were not adjusted for smoking. The study observed an increased risk among men and women irrespective of the census period over 39 years. The study reported the highest SIR of 2.56 for urinary bladder cancer in male hairdressers working in 1960 and followed up from 1960 to 1969. However, this risk decreased to 1.25 when these hairdressers were followed up for the whole period of 1960–1998. This reduction may have been because of the reduced use of brilliantine in male hair (Guberan and Raymond, 1985; Skov and Lynge, 1994). Other Scandinavian studies of hairdressers have shown a statistically significant increased risk for bladder cancer in Sweden, Norway, Finland and Denmark (Skov and Lynge, 1994).

Mineral oils Exposure to mineral oils, and in particular shale oil, is of historical interest, but metalworking fluids (MWF) appear to be the predominant route for exposure to mineral oils during the study period of interest. A comprehensive and systematic NIOSH review examined the association between MWF exposure and bladder cancer, and concluded that this association is well supported by studies from different geographical locations employing different study designs, all of which controlled for smoking (Calvert *et al*, 1998; National Institute for Occupational Safety and Health (NIOSH), 1998).

Risk estimates for occupational exposure to mineral oils and bladder cancer In the present study, the research team used papers from a review by Tolbert (1997) describing the relationship between mineral oil and cancer to calculate a risk estimate of 1.39 (95% CI = 1.20 – 1.61), assuming a random-effects model owing to significant heterogeneity across the different study results. This RR was used for those in situations of high exposure to MWF. The studies examined by Tolbert (1997) reported substantial dermal and inhalation exposure for occupations such as metal machining, print press operating, and cotton and jute spinning. The overall RR for bladder cancer related to exposure to mineral oils was taken as a weighted average across these case–control and population-based studies reviewed, and reflected incidence and mortality due to bladder and other urinary tract organs. Owing to the absence of sufficient exposure–response data for mineral oils, an RR of 1 was assigned to the lower and background exposure categories of workers in the Labour Force Survey (LFS) data set.

Occupation as a painter Many chemicals are used in paint products such as pigments, extenders, binders, solvents and additives. Painters are commonly exposed by inhalation to solvents and other volatile paint components; inhalation of less volatile and non-volatile compounds is common during spray painting.

Risk estimates for employment as a painter and bladder cancer For this study, an overall RR of 1.17 (95% CI = 1.11 – 1.27) was used to estimate the attributable fraction (AF) for work in this occupation. This overall estimate was obtained from a study by Bosetti *et al* (2005) who systematically reviewed all epidemiological studies on bladder cancer in painters published after the IARC (1989) monograph (this followed changes to paint technology and the nature of the exposures). This study examined cohort and case–control investigations from Europe and the United States, including one from the United Kingdom, up until 2004. Several RR estimates were obtained, including a pooled RR of 1.10 (95% CI = 1.03 – 1.18) for four cohort studies, a pooled RR of 1.23 (95% CI = 1.11 – 1.37) for mortality estimates and a pooled RR of 1.35 (95% CI = 1.19 – 1.53) from 14 case–control studies, which included a pooled analysis of another 11 case–control studies.

Other studies have lent weight to this evidence of an association between bladder cancer and painting as an occupation. Chen and Seaton (1998) undertook a meta-analysis of published papers (1966 – 1998) from Europe, North America, New Zealand and China, and derived a combined standardised mortality ratio (SMR) of 1.30 (95% CI = 1.14 – 1.50) for bladder cancer, based on 17 follow-up studies of painters. Occupational cohort studies also provided a combined SMR of 1.26 (95% CI = 0.98 – 1.62). In the United Kingdom, a hospital-based case–control study of urothelial cancers by Sorahan *et al* (1998) obtained a significant RR of 1.91 (95% CI = 1.41 – 2.91) in occupations specified as manufacturing paints or in the professional use of paints.

Polycyclic aromatic hydrocarbons Polycyclic aromatic hydrocarbons are formed by the incomplete combustion of carbon-containing fuels such as wood, coal, diesel, petrol, fat or tobacco. Polycyclic aromatic hydrocarbons are produced in a number of occupational settings including coal gasification, coke production, coal-tar distillation, chimney sweeping, coal tar and pitches, carbon black manufacture, carbon and graphite electrode manufacture, creosotes and others (IARC, 1984a, b, c, 1985). Higher risks have been reported for specific categories of painters, metal, textile and electrical workers, miners, transport operators, excavating-machine operators and also for non-industrial workers such as concierges and janitors (Kogevinas *et al*, 2003). Industries entailing a high risk included salt mining, manufacture of carpets, paints, plastics and industrial chemicals. A number of studies have documented an increased risk among workers exposed to petrochemicals and combustion products in different industries, suggesting an association with PAHs, and to their nitro-derivatives as well as DEE (Pirastu *et al*, 1996; Siemiatycki *et al*, 2004).

Risk estimates for occupational exposure to PAHs and bladder cancer For the present study, an overall RR of 1.4 (95% CI = 1.2 – 1.7) was based on 26 studies and was applied to those in 'high-exposed' groups in the manufacturing industry. This overall RR was obtained from Boffetta *et al* (1997) who reviewed the cancer risk from occupational and environmental exposure to PAHs, in aluminium production, coal gasification, coke production, iron and steel foundry work, DEE exposure, and workers exposed to coal tars and related products (i.e., tar distillation, shale oil extraction, creosote exposure, carbon black manufacture, carbon and graphite electrode manufacture, chimney sweeps and calcium carbide production). Results from all these sectors, with the exception of DEE exposure (for which AFs are calculated separately) and coke production (for which no evidence was found for a raised risk of bladder cancer), were used to calculate an inverse-variance-weighted combined estimate of RR.

The RR for the 'low-exposed' group was set to 1 on the basis of combined OR estimates from population-based case–control studies covered in the same review Boffetta *et al* (1997). These included lower relative risk estimates of 0.9 (95% CI = 0.8 – 1.1) for a large Montreal case–control study, and 1.2 (95% CI = 1.1 – 1.4) for a range of other smaller studies (both used a random-effects model). Exposures to DEE and driving, and to mineral oils (cutting fluids), were again excluded from this current analysis.

Rubber industry In 1982, IARC classified work in the rubber industry as Group 1(IARC, 1982), with numerous studies providing strong evidence that workers in the rubber industry had elevated risks for bladder cancer (Siemiatycki *et al*, 1994; Ward *et al*, 1997; Kogevinas *et al*, 1998; Clapp *et al*, 2005), and continued to be at risk even among former workers (Golka *et al*, 2004).

Risk estimates for employment in the rubber industry and bladder cancer More recent evidence suggests that the risk for bladder cancer ceased in the rubber industry in GB after 1950, and thus no AF has been calculated. For example, in a recently defined UK cohort of workers employed between 1982 and 1991, >8000 workers from 41 factories were followed up through 2004 (Dost *et al*, 2007). For both men and women, the incidence was nonsignificantly raised, and among men mortality was raised nonsignificantly. An analysis of 6500 male workers at a UK tyre factory who worked between 1946 and 1960 also found a nonsignificant excess in mortality (Veys, 2004b).

Mortality studies have been undertaken by the British Rubber Manufacturer's Association (Parkes, 1969; Parkes *et al*, 1982; Sorahan *et al*, 1989) and by HSE (Baxter and Werner, 1980). Detailed studies have also been undertaken because of inadvertent exposure of some workers to 2-naphthylamine (used as an antioxidant) (HSE, 2012a). In the most recent of these studies, men employed in the period 1945 – 1949 were compared with those first employed after January 1950 (when 2-naphthylamine was removed) and were followed up until 1995. Overall, bladder cancer incidence significantly increased (standardised risk ratio (SRR) = 1.23, 95% CI = 1.02 – 1.48), especially for those employed in the period 1945 – 1949 (SRR = 1.71, 95% CI = 1.30 – 1.48) compared with those first employed after 1950 (SRR = 1.02, 95% CI = 0.72 – 1.39).

Occupational exposures considered for kidney cancer

Coke production Coke production has been classified as an IARC Group 1 carcinogenic occupation (IARC, 1984c) related to the

exposure to PAHs. However, as there are few reports of a direct association between PAH exposure and kidney cancer (unlike for bladder cancer), it is not possible to derive a relative risk estimate for PAH as a causal factor of this cancer (Boffetta *et al*, 1997).

Risk estimates for coke production and kidney cancer The most appropriate study (considering cohort size and period of follow-up) for coke-oven workers in Britain was provided by Hurley *et al* (1991) who found risk estimates of 1.16. for coke-oven workers employed in 6 British steel industry plants (2790 men) and a deficit of risk of 0.16 for coke-oven workers at 13 National Smokeless Fuels plants in Britain (3883 men). If these two are combined, an overall SMR of 0.58 is obtained, showing no excess of kidney cancer. As this combined SMR was <1, no AF calculation was carried out for coke-oven workers. Another study by Davies (1977) reported an SMR of 2.52 for kidney cancer but in a much smaller cohort of 610 coke-oven workers.

Trichloroethylene Trichloroethylene is not widely used today, but has been used as a metal degreasant/solvent in a range of manufacturing industries including rubber, textile and paint manufacture, and as a dry cleaning solvent (IARC, 1995).

Risk estimates for occupational exposure to TCE and kidney cancer For the present study, the relative risk estimate for 'higher-exposure' situations was 1.2 (95% CI = 0.8 – 1.7), based on an average SMR calculated by Wartenberg *et al* (2000). Wartenberg *et al* (2000) provided a robust methodology to evaluate 20 cohort and 40 case – control studies of TCE exposure. They divided these cohort studies into three tiers based on the specificity of the exposure information and consideration of confounding influences from other exposures. For those situations considered as 'low exposures', the RR has been set to 1 based on a study by Morgan *et al* (1998) that provided a low-exposure SMR of 0.47 (95% CI = 0.01 – 2.62).

The majority of cohort studies of TCE exposure report small, usually nonsignificant, elevations or deficits in kidney cancer associated with TCE exposure (HSE, 2012a). As all the studies include exposure to a combination of organic solvents, of which TCE may be a component, it is difficult to determine whether TCE is the causal factor, suggesting that exposure is more likely to be to organic solvents rather than to TCE specifically. Renal cell carcinoma is usually associated with occupational exposures to TCE (IARC, 1995), but links have been made with exposure to TCC; thus, the risk estimate can be used for attributable risk estimation for all kidney cancers.

Estimation of numbers ever exposed

The data sources, major industry sectors and jobs for estimation of numbers ever exposed over the REP, defined as the period during which exposure occurred that was relevant to the development of the cancer in the target year 2005, are given in Table 1.

For bladder cancer, AFs were estimated for occupational groups as a whole for painters and hairdressers/barbers. Coal tar and pitches, aluminium production, coal gasification, coke production and petroleum refining have all been included within PAHs. Auramine and magenta manufacture have been included under AAs. Exposure to boot and shoe manufacture/repair was considered only up to 1962 and was included with AAs. For the rubber industry, the risk was confined to before 1950 in the United Kingdom.

The following occupations were designated as jobs with known exposure to soluble MWFs in large droplet form: press and machine tool setters, other centre lathe turners, machine tool operators, machine tool setter operators, press stamping and automatic machine operators, and toolmakers tool fitters markers out. In addition, there were a number of occupations assigned a background exposure, including foremen of metal polishers, shot blasters and fettlers dressers; metal polishers; fettlers, dressers and shot blasters.

Table 2 Urinary cancer burden estimation results for men and women

Agent	Number of men ever exposed	Number of women ever exposed	Proportion of men ever exposed	Proportion of women ever exposed	AF men (95% CI)	AF women (95% CI)	Attributable deaths (men) (95% CI)	Attributable deaths (women) (95% CI)	Attributable registrations (men) (95% CI)	Attributable registrations (women) (95% CI)
Bladder cancer										
Aromatic amines	101,654	94,170	0.0052	0.0045	0.0070 (0.0034 – 0.0151)	0.0060 (0.0024 – 0.0144)	21 (10 – 46)	10 (4 – 23)	49 (24 – 106)	17 (7 – 41)
Diesel engine exhaust	1,636,322	426,949	0.0843	0.0203	0.0145 (0.0026 – 0.0283)	0.0017 (0.0000 – 0.0054)	44 (8 – 86)	3 (0 – 9)	102 (18 – 198)	5 (0 – 15)
Hairdressers/ barbers	96,041	631,937	0.0050	0.0301	0.0011 (0.0000 – 0.0025)	0.0027 (0.0000 – 0.0134)	3 (0 – 8)	4 (0 – 21)	8 (0 – 18)	8 (0 – 38)
Mineral oils	4,426,581	466,252	0.2228	0.0222	0.0392 (0.0205 – 0.0598)	0.0073 (0.0038 – 0.0113)	119 (62 – 182)	12 (6 – 18)	275 (144 – 420)	21 (11 – 32)
PAHs	334,339	188,252	0.0172	0.0090	0.0008 (0.0004 – 0.0013)	0.0004 (0.0002 – 0.0007)	2 (1 – 4)	1 (0 – 1)	6 (3 – 9)	1 (1 – 2)
Painters	1,118,813	130,630	0.0577	0.0062	0.0097 (0.0064 – 0.0132)	0.0011 (0.0007 – 0.0014)	30 (19 – 40)	2 (1 – 2)	68 (45 – 92)	3 (2 – 4)
Totals[a]					**0.0706 (0.0457 – 0.0975)**	**0.0189 (0.0128 – 0.0386)**	**215 (139 – 296)**	**30 (21 – 62)**	**496 (321 – 684)**	**54 (37 – 110)**
Kidney cancer										
Trichloro-ethylene	43,861	42,288	0.0023	0.0020	0.0004 (0.0000 – 0.0016)	0.0004 (0.0000 – 0.0014)	1 (0 – 3)	1 (0 – 2)	2 (0 – 7)	1 (0 – 4)

Abbreviations: AF = attributable fraction; CI = confidence interval; PAHs = polycyclic aromatic hydrocarbons. [a]Totals are the product sums and are not therefore equal to the sums of the separate estimates of attributable fraction, deaths and registrations for each agent. The difference is especially notable where the constituent AFs are large.

For PAHs, workers involved in the manufacture of industrial chemicals, miscellaneous products of petroleum and coal, as well as other non-metallic mineral products, and workers in the iron and basic steel and non-ferrous metal basic industries were assigned a high-exposure level. For DEE, workers in the metal ore and other mining industries, construction, land transport and services allied to transport were assigned to the high-exposure level.

For TCE, high-exposure-category industries were taken as those manufacturing finished metal products where TCE was likely to have been used as a metal degreasant, as well as the textile industry for similar reasons. The CARcinogen EXposure Database (CAREX) records only 117 workers as being exposed to TCE in clothing manufacture, and thus it was assumed that 99% of these workers were men. For exposed service workers, it was assumed that 25% were men, based on numbers of drycleaners/launderers reported in the UK LFS 1979–2003 (19% male workers in 1979, 25% in 1991 and increasing to 38% in 2003).

Over the current burden period of 1956–1996, the number of workers employed in coke production industries decreased from $\sim$20,000 to $<$500.

RESULTS

Owing to assumptions made about cancer latency and working age range, only cancers in ages 25 years and above in 2005/2004 could be attributable to occupation. In the present study, a latency period of at least 10 years and up to 50 years has been assumed for urinary tract cancers. For bladder cancer, AFs have been calculated for exposure to mineral oil, AAs, PAHs (in coal tar and pitches, aluminium production, coal gasification, coke production and petroleum refining), DEE and for occupation as painters, and hairdressers and barbers. For the rubber industry, the risk for bladder cancer was confined to before 1950 in the United Kingdom; therefore, no AF was calculated. An AF has been calculated for kidney cancer for TCE exposure only. Table 2 provides a summary of the attributable deaths and registrations in Britain for 2005 and 2004 and shows the separate estimates for men and women, respectively.

For all exposure scenarios combined, the estimated overall AF for bladder cancer was 5.28% (95% CI = 3.43–7.72%). This resulted in a total of 245 attributable deaths (95% CI = 159–358) and 550 attributable registrations (95% CI = 357–795).

For all exposure scenarios combined, the estimated overall AF for kidney cancer was 0.04% (95% CI = 0.00–0.15%). This resulted in a total of one attributable death (95% CI = 0–5) and three (95% CI = 0–10) attributable registrations.

Exposures affecting bladder cancer

There were 101 654 men and 94 170 women 'ever exposed' to AAs over the REP. The overall AF for bladder cancer and exposure to AAs was estimated as 0.67% (95% CI = 0.30–1.49%), with 31 (95% CI = 14–69) deaths and 66 (95% CI = 30–147) registrations, respectively. Male workers in manufacture of wire and cable, as well as textile finishing, industries were most at risk, whereas women workers in the dry cleaning industry were most at risk.

There were an estimated 1 636 322 men and 426 949 women 'ever exposed' to DEE over the REP. The overall total AF for bladder cancer and exposure to DEE was estimated as 1.00% (95% CI = 0.17–2.03%), with 47 (95% CI = 8–94) deaths and 106 (95% CI = 18–214) registrations, respectively. Among men, workers in construction and land transport were at most risk.

There were in total 4,426,581 men and 466,252 women 'ever exposed' to mineral oils over the 40-year relevant period. The overall total AF for bladder cancer and exposure to mineral oils was estimated as 2.81% (95% CI = 1.47–4.31%), with 131 (95% CI = 68–200) attributable deaths and 296 (95% CI = 155–452) registrations. Metal workers were at most risk (231 male and 21 female registrations), especially machine tool operators (157 men and 15 women).

There were an estimated 334 339 men and 188 252 women 'ever exposed' to PAHs. Work with coal tar and pitches, aluminium production, coal gasification, coke production and petroleum refining were all included under PAHs. The overall total AF for bladder cancer and exposure to PAHs was estimated as 0.07% (95% CI = 0.03–0.11%), with three (95% CI = 1–5) deaths and seven (95% CI = 3–11) registrations, respectively. More than half of the total registrations occurred among workers in the iron and steel basic industries.

For work as a painter, 1 118 813 men and 130 630 women were estimated to have 'ever worked' in the occupation over the REP. The overall total AF for bladder cancer and work as a painter was estimated as 0.67% (95% CI = 0.44–0.91%), with 31 (95% CI = 20–42) deaths and 71 (95% CI = 47–97) registrations, respectively.

There were an estimated 96 041 male and 631 937 female hairdressers and barbers over the REP. The overall total AF for bladder cancer and work as a female hairdresser or barber was estimated as 0.16% (95% CI = 0.00–0.63%), with 8 (95% CI = 0–29) deaths and 15 (95% CI = 0–56) registrations, respectively.

Exposures affecting kidney cancer

Over the 40-year exposure period (1956–1996), a total of 43 861 male and 42 288 female workers were 'ever exposed' to TCE, with the majority ($\sim$85%) working in manufacturing industries. For women, there was a roughly equal split between manufacturing and services. Most exposures ($>$95% for men and women) were classified as 'high'. For kidney cancer, the estimated total AF was 0.04% (95% CI = 0.00–0.15), with one (95% CI = 0–5) attributable death and three (95% CI = 0–10) attributable registrations. Attributable deaths/registrations corresponded to exposure in the manufacturing industries for both sexes.

DISCUSSION

Our estimate of the AF figure of 7.06% for all bladder cancer in men is lower than that of the 10% estimated by Doll and Peto (1981) in their original critical review of literature, as well as the AF estimated by Nurminen and Karjalainen (2001) at 14.2% and the estimates for US white and non-white men of 21–27% (Silverman *et al*, 1989a, b). However, our overall estimate of male and female bladder cancer of 5.3% is higher than the 2% obtained by Dreyer *et al* (1997) for Nordic countries, and approximately the same as the 5.5% obtained for France by Boffetta *et al* (2010). It is also within the ranges observed in the qualitative reviews by Vineis and Simonato (1991), Imbernon (2003) and Steenland *et al* (2003), and a review of occupational studies in Italy (Vineis and Simonato, 1991; Vineis and Pirastu, 1997; Barone-Adesi *et al*, 2005).

Overall, the AF for kidney cancer obtained in this study was 0.04% (men and women), which is significantly lower than the figure quoted by Nurminen and Karjalainen (2001); that is, 4.7% for men and 0.8% for women.

It is possible that the overall AFs for kidney and bladder cancer reported here might be underestimated because certain agents and exposure circumstances were not considered. During 2009, IARC updated the critical review of Group 1 carcinogens as part of the 100th monograph. During this review process, the various committees reclassified arsenic as a Group 1 carcinogen for bladder cancer (Straif *et al*, 2009), and soots and coal tars

as Group 2A carcinogen (Baan *et al*, 2009). Arsenic was also classified as a Group 2A carcinogen for kidney cancer, as was cadmium.

The lack of consistency in occupational findings for both cancers may partly be explained by small sample size, recall bias, misclassification and low levels of exposures, inadequate adjustment for confounding factors and short duration of follow-up in some studies.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

British Occupational Cancer Burden Study Group

Lesley Rushton (PI)*,[1], Sanjeev Bagga[3], Ruth Bevan[3], Terry Brown[3], John W Cherrie[4], Gareth S Evans[2], Lea Fortunato[1], Phillip Holmes[3], Sally J Hutchings[1], Rebecca Slack[5], Martie Van Tongeren[4] and Charlotte Young[2].

[1]Department of Epidemiology and Biostatistics, School of Public Health and MRC-HPA Centre for Environment and Health, Imperial College London, St Mary's Campus, Norfolk Place, London W2 3PG, UK; [2]Health and Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN, UK; [3]Institute of Environment and Health, Cranfield Health, Cranfield University, Cranfield MK43 0AL, UK; [4]Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh EH14 4AP, UK; [5]School of Geography, University of Leeds, Leeds LS2 9JT, UK.