The burden of occupational cancer in Great Britain

Bladder cancer

Prepared by the **Health and Safety Laboratory**,
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The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer was the attributable fraction (AF) being the proportion of cases that would not have occurred in the absence of exposure; and the AF was used to estimate the number of attributable deaths and registrations. The study involved obtaining data on the risk of the cancer due to the exposure of interest, taking into account confounding factors and overlapping exposures, as well as the proportion of the target population exposed over the relevant exposure period. Only carcinogenic agents, or exposure circumstances, classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens were considered. Here, we present estimates for cancer of the bladder that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

The estimated total (male and female) AF, deaths, and registrations for bladder cancer related to overall occupational exposure is 5.28% (95% Confidence Interval (CI)= 3.43-7.72), which equates to 245 (95%CI=159-358) attributable deaths and 550 (95%CI=357-795) attributable registrations.

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EXECUTIVE SUMMARY

The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer used in this project was the attributable fraction i.e. the proportion of cases that would not have occurred in the absence of exposure; this was then used to estimate the attributable numbers. This involved obtaining data on the risk of the disease due to the exposure of interest, taking into account confounding factors and overlapping exposures, and the proportion of the target population exposed over the period in which relevant exposure occurred. Estimation was carried out for carcinogenic agents or exposure circumstances classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens. Here, we present estimates for cancer of the bladder that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

Aromatic amines, polycyclic aromatic hydrocarbons (PAH), mineral oils, work in the rubber industry and occupation as a painter have been classified by the IARC as a definite human carcinogens for bladder cancer and diesel engine exhaust (DEE) and occupation as a hairdresser or barber have been classified by IARC as probable human carcinogens. Occupational exposure to aromatic amines (arylamines) can occur in the production of rubber, in cutting oils, in pesticides, in the manufacture and use of dyes, in the textile industry and in the pulp and paper industry. PAHs are formed by the incomplete combustion of carbon-containing fuels in a number of occupational settings including coal gasification, coke production, coal-tar distillation, chimney sweeping (soots), and in use of coal tar and pitches, and creosotes. Mineral oils exposure, particularly oil mists, occur in metalworking, print press operating, and cotton and jute spinning. Exposure to DEE occurs in many occupations with professional drivers and motor mechanics being likely to be exposed to elevated levels

Due to assumptions made about cancer latency and working age range, only cancers in ages 25+ in 2005/2004 could be attributable to occupation. For Great Britain in 2005, there were 3039 total deaths in men aged 25+ and 1603 in women aged 25+ from bladder cancer; in 2004 there were 7020 total registrations for bladder cancer in men aged 25+ and 2858 in women aged 25+. As the risk from bladder cancer ceased in the UK rubber industry after 1950, no estimation has been carried out.

The estimated total (male and female) attributable fractions, deaths and registrations for bladder cancer related to occupational exposure is 5.28% (95% Confidence Interval (CI)=3.43-7.72), which equates to 245 (95%CI=159-358) attributable deaths and 550 (95%CI=357-795) attributable registrations. Results for individual carcinogenic agents for which the attributable fraction was determined are as follows:

- **Aromatic amines**: The estimated total (male and female) attributable fraction is 0.67% (95%CI=0.30-1.49), which equates to 31 (95%CI=14-69) deaths, and 66 (95%CI=30-147) registrations for bladder cancer related to exposure to aromatic amines.

- **Mineral oils**: The estimated total (male and female) attributable fraction is 2.81% (95%CI=1.47-4.31), which equates to 131 (95%CI=68-200) deaths, and 296 (95%CI=155-452) registrations for bladder cancer related to exposure to mineral oils.

- **PAHs:** The estimated total (male and female) attributable fraction is 0.07% (95%CI=0.03-0.11), which equates to 3 (95%CI 1-5) deaths, and 7 (95%CI 3-11) registrations for bladder cancer related to exposure to PAHs.

- **DEE:** The estimated total (male and female) attributable fractions is 1.00% (95%CI=0.17-2.03) which equates to 47 (95%CI=8-94) deaths, and 106 (95%CI=18-214) registrations for bladder cancer related to exposures to DEE.

- **Occupation as a hairdresser or barber**: The estimated total (male and female) attributable fractions is 0.16% (95%CI=0.00-0.63), which equates to 8 (95%CI=0-29) deaths, and 15 (95%CI 0-56) registrations for bladder cancer related to occupation as a hairdresser or barber.

- **Occupation as a painter:** The estimated total (male and female) attributable fractions is 0.67% (95%CI=0.44-0.91), which equates to 31 (95%CI=20-42) deaths, and 71 (95%CI=47-97) registrations for bladder cancer related to occupation as a painter.

Other exposures / occupations which were considered but for which AF were not determined included magenta manufacture, aluminium production, auramine manufacture, boot and shoe manufacture and repair, coal gasification, coke production, intermediates in plastics and rubber manufacturing, employment in the rubber industry and in petroleum refining.

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1   INCIDENCE AND TRENDS

Bladder cancer (ICD-10 C67; ICD-9 188) refers to any of several types of malignant growths of the urinary bladder. About 90-95% of bladder cancers are transitional cell carcinomas with the remainder being squamous cell carcinomas and adenocarcinomas (Quinn *et al*, 2001). Seventy-five per cent are superficial, limited to the mucosa, sub-mucosa or lamina propria (De Braud *et al*, 2002), the rest are invasive into the muscle. Every year in the UK, almost 10,200 people are diagnosed with bladder cancer, causing more than 4,800 deaths each year. In the UK and Ireland, bladder cancer accounted for around 1 in 20 of all cancer registrations and 1 in 30 cancer deaths in the 1990s (Cooper and Cartwright, 2005). Bladder cancer is the 5th most commonly diagnosed cancer for all population groups combined (21.0/100,000) (Clapp *et al*, 2005) and is the 4th commonest cancer affecting men and the 10th commonest cancer affecting women (excluding non melanoma skin cancer) (Cooper and Cartwright, 2005). In Great Britain, the age-standardised incidence rates rose throughout the 1970s and 1980s to reach a peak in the late 1980s of around 31 per 100,000 males and 9 per 100,000 females. Table 1 shows UK registration of newly diagnosed cases of bladder cancer from 1994 to 2004.

Table 1. Bladder cancer registration trends in England (Source: Office for National Statistics)

| Year | Males | | | Females | | |
	Total registrations	Bladder	Rate /100000	Total registrations	Bladder	Rate /100000
1994	112,145	8,516	33.7	112,175	3,286	12.5
1995	103,986	8,019	33.4	105,151	3,188	12.8
1996	104,103	7,629	31.6	105,461	2,985	12.0
1997	104,335	7,292	30.1	107,289	3,095	12.4
1998	106,745	7,529	30.9	109,957	2,999	11.9
1999	108,827	7,453	30.4	112,237	3,071	12.2
2000	111,543	6,587	27.6	112,066	2,634	10.5
2001	112,516	6,317	26.2	112,134	2,515	10.0
2002	112,579	5,725	23.6	112,210	2,297	9.1
2003	112,732	5,886	24.1	114,740	2,393	9.4
2004	117,805	5,800	23.6	110,840	2,337	9.2
Average	**109,756**	**6,978**	**28.7**	**110,387**	**2,800**	**11.1**

Source: ONS MB1 Series (ONS 2006)

Table 2 gives for 2004, cancer registrations for bladder cancer separately for England, Wales and Scotland.

Table 2. Number of registrations and incidence rates of bladder cancer, GB, 2004

	England	Wales	Scotland	GB
Number of Registration				
Males	5,800	663	549	7,012
Females	2,337	252	267	2,856
Persons	8,137	915	816	9,868
Crude rate per 100,000 population				
Males	23.6	46.2	22.4	
Females	9.2	16.6	18.2	
Persons	16.2	31.0	16.1	
Age-standardised rate (European) per 100,000 population				
Males		34.5	10.1	
Females		10.0	6.3	
Persons		20.6	12.3	

Source: ONS MB1 Series (ONS 2007a), Welsh Cancer Intelligence & Surveillance Unit (WCISU 2008), Information Services Division (ISD 2008)

Table 3 summarises the mortality trends in England and Wales for bladder cancer between 1999 and 2005. Overall numbers have remained steady in recent years. However, bladder cancer rates dropped between 2002 and 2003 from 100 to 87 for men and from 54 to 30 for women. Over the last 2 decades, mortality has shown downward trends in several western European countries (albeit 10-15 years later than similar trends in the US), but is still increasing in some eastern European countries (Pelucchi *et al*, 2006).

Table 3. Bladder cancer mortality trends in England and Wales

Year	Males Total Deaths	Bladder Deaths	Bladder Death Rate (per million)	Females Total Deaths	Bladder Deaths	Bladder Death Rate (per million)
1999	300,368	2,861	103	331,694	1,458	54
2000	290,186	2,881	103	318,180	1,532	56
2001	286,757	2,958	102	315,511	1,470	54
2002	287,835	2,919	100	318,381	1,501	54
2003	288,604	2,884	87	322,584	1,507	30
2004	244,130	2,840	84	268,411	1,461	28
2005	242,057	2,759	80	268,408	1,428	28
Average	**277,134**	**2,872**	**94**	**306,167**	**1,480**	**43**

Source: (ONS)

The annual number of deaths for males and females in GB and its constituent countries, together with the rates for the year 2004 are shown in Table 4. Incidence and mortality rates in women in England and Wales are high by international standards. England and Wales had the highest number of deaths, but Scotland had the highest rates (per 100,000 population). Within GB, geographical patterns in incidence are obscured by known differences among counties and regions of England and Wales in the classification and registration of bladder tumours. Mortality in both males and females was higher than average in Scotland and in a band across the north of England and noticeably lower in Northern

Ireland and Ireland (Quinn *et al*, 2005). Occupational exposure to chemicals, predominantly in male workers in the dye and rubber industries, may explain some of the observed geographical patterns (Quinn *et al*, 2005).

Table 4. Number of deaths and mortality rates of bladder cancer, GB, 2005 (Source: ONS, ISD)

	England & Wales	Scotland	GB
Number of Deaths			
Males	2,759	281	3,040
Females	1,428	176	1,604
Persons	4,187	457	4,644
Crude rate per 100,000 population			
Males	8.0	11.4	8.2
Females	2.8	6.7	3.9
Persons	4.9	9.0	5.1

In most European countries, including England and Wales, bladder cancer is at least three times less frequent in women than in men (worldwide ratio is about 3.5:1), which has been seen as an indication for an occupational origin in men (Lilienfeld and Lilienfeld, 1980, Parkin and Muir, 1992). In England and Wales female age-standardised rates have changed little from 3.2 in the 1971 to 2.8 in 2005 (ONS, 2006); the male rates have shown a consistent fall since 1971, from 12.4 to 8.0 per 100,000 in the year 2005, a fall of around 30%. The male:female ratio of age-standardised rates has consequently changed, from 3.9:1 in 1971 to 2.9:1 in 2005. The higher incidence among men can be attributed, in part, to the differences in smoking habits, with occupational exposures the second most important risk factor in men.

Few cases of bladder cancer occur under the age of 50, but thereafter the rates rise with age to reach a peak in the oldest age groups. Mortality trends by age show the largest fall in the younger (50-59) age group; the all-age rate for women masks substantial changes within different age-groups. Between 1979 and 2000 the mortality rates for men aged 50-59 fell by 53% from 10 to 4.7 per 100,000 and for women of the same age by 44% from 3.6 to 2 per 100,000. Eighty-eight percent of male deaths caused by bladder cancer and 91% of female deaths due to bladder cancer occur after the age of 65 years (ONS, 2006). Socio-economic differences in incidence and mortality rates are not large but show a tendency for slightly higher incidence and mortality in the more deprived populations.

In 2004, approximately 125,000 people in the European Economic Area were diagnosed with bladder cancer and it accounted for about 6% of all cancer cases (Boyle and Ferlay, 2005). In the same year, bladder cancer was the 10th most common cause of death from cancer accounting 3.1% (37,400 people) of all deaths**.**

Internationally, incidence rates of bladder cancer vary almost 10-fold (Parkin and Muir, 1992). In general, the highest incidence is found in developed countries including North America and Europe, with approximately 200,000 new cases worldwide annually (Parkin *et al*, 1994, Parkin, 1994). Relatively low rates are found in Eastern Europe and several areas of Asia. Bladder cancer is the fifth most commonly diagnosed cancer in the EU, preceded by bowel, female breast, lung and prostate cancer (Boyle and Ferlay, 2005). Some of the geographic variation may be the result of the practice of registering "benign" tumours or "papillomas" as malignant cancers.

Southern Europe is a high-risk area, with Italy exhibiting one of the highest incidences in the world (Ferlay *et al*, 2001). Applying IARC data to population projections, Bray and co-workers (2002) derived estimates of the burden of cancer, in terms of incidence and mortality for Europe in 2004. They reported the results for three areas: the 25 Member States of the European Union (EU); the European Economic Area (EEA) (the 25 European Union countries plus Iceland, Liechtenstein and

Norway) plus Switzerland; and Europe[1]. Their results for bladder cancer are summarised in Table 5. They were unable to estimate figures with adequate precision for Europe due to coding classification used in some countries. In the EU, bladder cancer was the fourth most common cancer, with 91,000 (8.2%) new cases. However, due to differences in coding practices between European countries, the rubric 'bladder cancer' includes non-invasive tumours.

Table 5. Estimated number of incident cases (2004) for bladder cancer and deaths (2005) (thousands) and cumulative risk (aged 0 – 74 years) (percent)

| | European Economic Area[1] | | European Union | |
	Incidence Cases	Risk	Incident Cases	Risk
Men	93.2	2.81	91.0	2.82
Women	25.8	0.52	25.1	0.52
	Deaths	Risk	Deaths	Risk
Men	27.5	0.60	26.9	0.61
Women	9.9	0.12	9.6	0.12

Cancer survival depends on prognostic factors, such as depth of tumour penetration and whether it is superficial or other factors such as multiple tumour foci, grade and tumour type. Patients with superficial tumours have an excellent prognosis with 5-year survival rates between 80-90%, Patients with muscle-invasive bladder cancer have 5-year survival rates of less than 50%. Population-based bladder cancer survival rates have risen from just over 40% in the early 1970s to between 58-67% in the late 1990s (Coleman *et al*, 2004). Although the survival rate is high, two-thirds of patients develop tumour recurrence within 5 years, sometimes with higher levels of malignancy and aggressiveness (Hung *et al*, 2004).

Bladder cancer is one of the few cancers in which men have a substantial survival advantage over women. Relative 5-year survival is 90% for men diagnosed when aged under 40, and just under 80% for women of the same age. Survival then falls with age and is below 50% for men aged 80 or over at diagnosis and less than 40% for elderly women (Quinn *et al*, 2001). Some bladder tumours (transitional cell papillomas) are recorded as malignant by some cancer registries and as non-malignant by others in the England. Survival rates for transitional cell papillomas are very high, so where cancer registries define these as malignant, this results in an apparently higher overall survival rate for bladder cancer (ONS, 2004). International comparisons of survival are especially difficult because of different registration practice with regard to papillomas.

Bladder cancer is generally described as a malignancy with a very long latency (Matanoski and Elliott, 1981), an observation that probably arises from the fact that bladder cancer is a disease of the elderly with the diagnosis being made in people in their sixties or seventies. In occupational studies, the latency period from first exposure to detection of the cancer is variable, mean or median values ranging from 15 to 40 years (Cohen *et al*, 2000). A recent review also showed a large range, up to 50 years (Matsumoto *et al*, 2005). This is important because the risk of bladder cancer due to smoking shows decreasing risks if the person has stopped smoking and declines with longer time since smoking cessation (Dresler *et al*, 2006). Interestingly, an increased bladder cancer risk due to aromatic amines is also seen when the occupational exposure ended decades ago (Golka *et al*, 2004).

It is hypothesized that the genetic polymorphisms involved in the metabolism of polycyclic aromatic hydrocarbons (PAHs) and aromatic amines can determine the individual susceptibility to bladder cancer in particular following relevant environmental exposures. Results from a hospital based case-control study among men in Northern Italy (Hung *et al*, 2004) suggested that individual susceptibility to bladder cancer may be modulated by glutathione s-transferase (GST) M1, T1 and NAT2 polymorphisms. They conclude that although the effect observed is moderate, these genetic variations could be responsible for a substantial proportion of bladder cancer cases due to their high prevalence.

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[1]   European Economic Area plus Bulgaria, Belarus, Moldova, Romania, Russian Federation, Ukraine, Albania, Bosnia and Herzegovina, Macedonia, Serbia, and Montenegro and Switzerland.

In addition, the results from Gago-Dominguez and co-workers study (2001) showed an over-representation of slow NAT2 acetylators among diseased female users. This genetic trait is a well-known additional risk factor for bladder cancer if exposure to aromatic amines has occurred (Golka *et al*, 2002; Vineis and Pirastu, 1997).

2   OVERVIEW OF AETIOLOGY

2.1   INTRODUCTION

Bladder cancer has often been reported to be associated with occupational exposures (Silverman *et al*, 2006). As early as the late 19th century, doctors reported unusual incidences in industries (Rehn, 1895). The study of occupational causes gained momentum in the 1950s with the identification of hazards in the British dyestuffs and rubber industries (Case and Hosker, 1954; Case and Pearson, 1954; Case *et al*, 1954). They were some of the first epidemiologists to apply a retrospective cohort design to investigate the effect of occupational exposure to a possible carcinogen. In their classic study, Case and Hosker (1954) reported an exceptionally high incidence in the British rubber industry. Since then many studies have suggested approximately 40 potentially high-risk occupations (Silverman *et al*, 2006). Despite this, the relationship of many of these occupations to bladder cancer risk are unclear, with strong evidence of an association reported for only a few occupational groups: aromatic amine manufacturing workers, dyestuffs workers and dye users, painters, leather workers, aluminium workers and truck drivers (Silverman *et al*, 2006). Findings related to other occupations have tended to be based on small numbers of exposed subjects and have been inconsistent.

Tobacco smoking and occupational exposure to aromatic amines are the two major established environmental risk factors for bladder cancer. Controlling exposure to these factors has been an important contributor to the reduction in mortality, particularly among men (Pelucchi *et al*, 2006). Substantial epidemiological evidence supports a relationship between bladder cancer and cigarette smoking. Aromatic amines are formed as combustion products and are present in both mainstream and side stream tobacco smoke, and so tobacco smoke is the most common and widespread source of exposure to aromatic amines (Talaska, 2003). It has been suggested that up to 40 per cent of all male and 10 per cent of female cases might be ascribable to this exposure (Cooper and Cartwright, 2005). In the US, cigarette smoking has been estimated to account for about 40% of bladder cancer deaths seen in the US each year (about 50% of male deaths and 28% of female deaths) (Fellows *et al*, 2002). IARC have stated that the proportion of bladder cancer cases attributable in most countries with a history of prolonged cigarette use is of the order of 50% in men and 25% in women (IARC, 1986). The relative risks are between 2 and 4 (Cooper and Cartwright, 2005; Ross *et al*, 1988; Vineis and Martone, 1996).

Environmental factors, in addition to tobacco smoke, that are suspected of playing an important role in the development of bladder cancer include the presence of arsenic and disinfection by-products in drinking water, fluid intake, dietary factors (coffee and alcohol intake, artificial sweeteners), drugs (analgesics, cyclophosphamide and chlornaphazine), hair dyes and a number of urologic conditions (Silverman *et al*, 2006).

The Occupational Health Decennial Supplement (OHDS) (Drever, 1995) examined mortality (1979-1980, 1982-1990) and cancer incidence (1981-1987) in men and women aged 20-74 years in England and Wales. It concluded that, for many diseases, differences in mortality between job groups appeared to be determined mainly by non-occupational influences. Occupations that had a high proportional mortality rate (PMR) for bladder cancer are not known to entail exposure to known bladder carcinogens (Table 6). Rubber manufacturers have the highest proportional registration rate (PRR) of all job groups in men (PRR=226, 58 registrations), and brewery workers for women (PRR=589, 3 registrations), followed by rubber manufacturers (PRR=350, 7 registrations) according to Drever (1995). The data further suggest that other occupations potentially exposed to chemical compounds, such as aromatic amines (used in the manufacture of dyes, pigments, rubber, etc) may also be at increased risk. The risk for men described as plastic goods makers, which is nearly twice that expected at 187 (19 registrations) is particularly noteworthy. Table 7 gives the mortality from the OHDS for 1991-2000 (Coggon *et al*, 2009). Considerably fewer occupations showed an excess of bladder cancer mortality compared to the previous supplement. Nevertheless, chemical workers and printers are known to be exposed to bladder carcinogens.

Table 6. Job codes with significantly high PRRs and PMRs for bladder cancer. Men and women aged 20-74 years, England, 1981-87

Job group			Incidence			Mortality	
SIC code	Description	N	PRR	95%CI	N	PMR	95%CI
Men							
006	Sales managers	168	117	100-137		122	106-140
018	Pharmacists	35	146	102-203			
023	Driving instructors	36	161	113-224			
054	Postal workers	222	114	100-131		131	116-146
063	Railway station workers	90	126	102-156			
085	Rubber manufacturers	58	226	172-293			
093	Plastic goods makers	19	187	113-293			
097	Printers	115	123	102-148			
124	Machine tool operators	735	112	105-121			
158	Coach painters	12	198	103-347			
166	Masons and stonecutters	23	164	104-247			
184	Other motor drivers	112	125	103-151			
Women							
017	Nurses	138	120	101-142			
072	Knitters	14	193	106-324			
077	Brewery workers	3	589	122-1723			
085	Rubber manufacturers	7	350	141-723			

* p≤0.05, based on at least three registrations. Adjusted for age, social class and region of registration. Adapted from Drever (1995)

Table 7. Job codes with significantly high PMRs for bladder cancer. Men and women aged 15-74 years, England, 1991-2000

Job group		N	PMR	95%CI
SIC code	Description			
Men				
075	Chemical workers	123	124	103-148
097	Printers	121	124	103-149
143	Electrical engineers	107	128	105-154
177	Railway guards	42	151	109-205
199	Vehicle body repairers, panel beaters	21	192	119-294

Source: Coggon *et al.* (2009)

IARC have assessed the carcinogenicity of a number of substances and occupational circumstances with those classified as Group 1 having sufficient evidence in humans and those classified as Group 2A having limited evidence in humans. Those classified as causing or possibly causing bladder cancer are given in Tables 8a and 8b. Siemiatycki *et al.* (2004) and Rousseau *et al.* (2005) summarise the evidence used in the classification of these agents and substances as strong and suggestive in human and this is also given in Tables 8a and 8b. In addition to these a number of other occupations have been suspected of entailing exposure to bladder carcinogens, including painters, chemists and electricity workers (non-ionising radiation) (Silverman *et al*, 2006)**.**

Table 8a. Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Volumes 1-98 (IARC, 1972-2008), into Group 1, which have the bladder as the target organ.

Agents, Mixture, Circumstance	Main industry, Use	Evidence of carcinogenicity in humans*	Strength of evidence$	Other target organs
Group 1: Carcinogenic to Humans				
Agents, groups of agents				
Aromatic amine dyes 4-aminobiphenyl Benzidine 2-naphthylamine	Production: dyestuffs and pigment manufacture	Sufficient	Strong	
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)	Sufficient	Suggestive	Skin, Lung
Polyaromatic hydrocarbons: Benzo(a)pyrene Benz(a)anthracene	Work involving combustion of organic matter; foundries; steel mills; fire-fighters; vehicle mechanics	Not available**	Suggestive	Lung, Skin
Mineral oils, untreated and mildly treated	Production; used as lubricants by metal workers, machinists, engineers: printing industry (ink formulation); used in cosmetics, medicinal and pharmaceutical preparations	Sufficient	Suggestive	Skin, Lung, Nasal sinuses
Exposure circumstances				
Aluminium production	Pitch volatiles; aromatic amines	Sufficient	Strong	Lung
Auramine manufacture	2-Naphthylamine; auramine; other chemicals & pigments	Sufficient	Strong	
Magenta manufacture	Magenta; ortho-toluidine; 4,4'-methylene bis(2-methylaniline); ortho-nitrotoluene	Sufficient	Strong	
Rubber industry	Aromatic amines; solvents	Sufficient	Strong	Stomach, Larynx, Leukaemia, Lung
Boot and shoe manufacture and repair	Leather dust; benzene and other solvents	Sufficient	Suggestive	Leukaemia, nose, paranasal sinuses
Coal gasification	Coal tar; coal-tar fumes; PAHs	Sufficient	Strong	Skin (including scrotum) Lung
Coke production	Coal-tar fumes	Sufficient	Suggestive	Skin (including scrotum), Lung, Kidney
Painters		Sufficient	Suggestive	Lung, Stomach

* Evidence according to the IARC monograph evaluation; $ taken from Siemiatycki *et al.* (2004), Rousseau *et al.* (2005); ** No epidemiologic evidence is available

Table 8b. Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Volumes 1-98 (IARC, 1972-2008), into Group 2A, which have the bladder as the target organ.

Agents, Mixture, Circumstance	Main industry, Use	Evidence of carcinogenicity in humans*	Strength of evidence$	Other target organs
Group 2A: Probably Carcinogenic to Humans				
Agents and groups of agents				
Polyaromatic hydrocarbons§: Dibenz(a,h)anthracene Cyclopenta(*cd*)pyrene, Dibenzo(*a*,*l*)pyrene	Work involving combustion of organic matter; foundries; steel mills; fire-fighters; vehicle mechanics	Not available	Suggestive	Lung, Skin
Diesel engine exhaust	Railroad, professional drivers; dock workers; mechanics	Limited	Suggestive	lung
Intermediates in plastics and rubber manufacturing§ 4,4'-methylene bis(2-chloroaniline)	Production; curing agent for roofing and wood sealing	Inadequate	Suggestive	
Styrene-7,8-oxide	Production; styrene glycol production; perfume preparation; reactive diluents 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	Inadequate	Suggestive	
Aromatic amine dyes Benzidine-based dyes§	Production; used in textile, paper, leather, rubber, plastics, printing, paint, and lacquer industries	Inadequate	Suggestive	
4-chloro-ortho-toluidine	Dye and pigment manufacture; textile industry	Limited	Suggestive	
ortho-Toluidine	Production; manufacture of dyestuffs, pigments, optical brightener, pharmaceuticals, and pesticides; rubber vulcanising; clinical laboratory reagent; cleaners and janitors	Limited	Suggestive	
Exposure circumstances				
Hairdressers and barbers	Dyes (aromatic amines, amino-phenols with hydrogen peroxide); solvents, propellants; aerosols	Limited	Suggestive	Lung, non-Hodgkin lymphoma, Ovary
Petroleum refining	PAHs	Limited	Suggestive	

* Evidence for bladder cancer according to the IARC monograph evaluation; $ taken from Siemiatycki *et al.* (2004), Rousseau *et al.* (2005); § Grading based on mechanistic evidence

2.2 EXPOSURES

2.2.1 Mineral Oils, untreated and mildly treated

Mineral oils are complex mixtures of aliphatic hydrocarbons, naphthenics, and aromatics, the relative distribution of which depends on the source of the oil and the method of refinement. End-use products contain a variety of additives, and contamination by other agents generally occurs during use (Tolbert, 1997). There are several occupational environments in which an oil mist is generated and in these situations the opportunities for exposure can be high. Such occupations include metalworking, print press operating, and cotton and jute spinning. A number of bladder cancer case-control studies have noted an association with work as a machinist, with studies of workers using metalworking fluids and mineral oils offering strong evidence for an association with bladder cancer (Calvert *et al*, 2008; Mirer, 2003; Siemiatycki *et al*, 1994; Tolbert, 1997).

Siemiatycki *et al*. (1994) carried out a population-based case-control study in Canada, identifying 484 persons with bladder cancer between 1979 and 1986, and matched them with 1879 controls with other cancer and 533 population controls. Job histories were evaluated for evidence of exposure to a list of 294 workplace chemicals. Occupations with the potential for exposure to mineral oils showed an excess risk including metal machinists (<10 years: OR=1.1; ≥10 years: OR=1.4). The metal fabricating/machining (<10 years: OR=1.4; ≥10 years: OR=1.2) and chemical production (<10 years: OR=1.1; ≥10 years: OR=1.0) also showed a small risk. Logistic regression analysis, after adjusting for numerous risk factors, indicated individuals with substantial exposure to cutting fluids, both mildly and highly refined, had an increased risk of bladder cancer. Time and dose-related ORs between bladder cancer and mildly refined cutting fluids showed non-significant excesses. For other mineral oils, individuals with definite exposure, medium/high exposure, high frequency of exposure, and duration of ≤10 and >10 years exposure also showed a small excess.

In 1989 Silverman *et al*. (1989a, 1989b) examined the relationship between occupation and bladder cancer risk in 2,100 white males (1989a) matched with 3,874 population controls, and 126 non-white men (1989b) matched with 383 controls. Among white males metal machinists (RR=1.3) and drill press operatives (DPO) (RR=1.4) who are exposed to cutting and lubricating oil mists used as coolants and lubricants showed an excess bladder cancer risk. For DPOs the risk increased significantly with duration of employment (<5 years – 1.0; 5-9 years – 1.8; 10+ years – 2.4). For non-white males excesses were seen among car mechanics (RR=1.4) and metal machining workers (RR=1.1), the risk increasing significantly with duration of employment (<5 years – 1.2; 5-9 years – 1.6; 10+ years – 4.7).

NIOSH carried out a comprehensive and systematic review of epidemiologic studies investigating the association between MWF exposure and cancer. The findings of this review can be found in the NIOSH Criteria for a Recommended Standard Occupational Exposure to MWFs (NIOSH, 1998). The main findings from this review were summarised by Calvert *et al*. (1998). The review identified two cohort studies, five PMR studies and ten population–based case-control studies. Only one PMR study (Vena *et al*, 1985) and all of the case-control studies reported an excess bladder cancer risk.

Tolbert (1997) reviewed studies of occupations involving substantial dermal and inhalational exposure and for which an epidemiologic literature exists: metal machining, print press operating, and cotton and jute spinning. He identified five cohort studies, four PMR studies and 13 case-control/population-studies (see Annex 1). The case-control studies suggest that bladder cancer cases tend to be more likely to have been metal machinists or engineers than controls, with ORs ranging from 1.5 to 5.0. However, these job groupings are broad and encompass exposure to a variety of agents. The cohort studies show a small excess, although a UK study of men with high exposure to printing inks showed a five-fold excess risk (Coggon *et al*, 1984). PMR studies also indicated a non-significant excess risk, with the exception of a study by Vena *et al*. (1985), which showed a seven-fold excess risk. The author stated this observation was perplexing in light of the fact that the case-control studies are likely to entail more heterogeneous exposures that the cohort studies.

Mirer (2003) selectively reviewed mortality studies of workers exposed to MWFs. However, although they noted that substantial evidence existed for increased risk of bladder cancer no evidence was presented.

Kazerouni *et al.* (2000) reported the mortality experience of a cohort of automotive workers followed from 1938 to 1967 who were exposed to cutting oil mist, presenting results for mortality through 1980. The cohort consisted of 23,698 men who had worked for at least one year in manufacturing jobs. There were 4,185 deaths among those ever exposed (SMR=0.96), and 2,695 among those with 'ever' heavy exposure (SMR=0.97). There were 26 bladder cancer deaths among those ever exposed to oil mist (SMR=1.05, 95%CI=0.68-1.56). There was no difference between those with low/moderate exposure (SMR=1.06, 95%CI=0.48-2.01) and high exposure (SMR=1.05, 95%CI=0.60-1.71).

Kvam *et al.* (2005) investigated cancer risk among Norwegian workers in the printing industry. Incidence was investigated from 1953 through 1998 in a cohort of 10,549 male trade union members. Skilled workers consisted of compositors, printers, reproduction photographers, etchers and bookbinders, and unskilled workers of printer's assistants, assistants and bookbinder's assistants. Among the total cohort, the risk for bladder cancer was significantly raised (SIR=1.27, 95%CI=1.08-1.50), the risk among skilled workers (SIR=1.47, 95%CI=1.19-1.79) being significantly greater than that among unskilled workers (SIR=0.97, 95%CI=0.70-1.31) (SIR ratio=1.52, 95%CI=1.05-2.23). Men born after 1930 (SI|R=1.59, 95%CI=1.01-2.38) and starting after 1945 had the greatest risk (1945-1954: SIR=1.89, 95%CI=1.30-2.65; 1955-: SIR=1.55, 95%CI=0.97-2.35). The risk was also greater in men aged less than 55 years, decreasing with increasing age.

Reulen *et al.* (2008) carried out a meta-analysis of studies that had provided bladder cancer risk for at least one occupation. Between 1963 and 2008 129 articles were eligible for inclusion in the analysis, almost all originating from Europe, Canada and the USA, New Zealand and Australia, with only four studies from Asia. Results were presented for 63 different occupations. Occupations with the potential for mineral oil exposure were shown to have significant excess risk of bladder cancer (Table 9).

Table 9. Meta-analysis results for selected occupations taken from Reulen *et al.* (2008)

Occupation (ISCO 1968)	Number of studies	Summary RR (95%CI)
Metal workers	31	1.10, 1.02-1.20
Machine tool setters	17	1.24, 1.09-1.42
Mechanics	30	1.21, 1.12-1.31
Motor mechanics	17	1.27, 1.10-1.46
Printers	27	1.13, 0.96-1.33
Machinist	14	1.18, 1.06-1.30
Metal processors	23	1.18, 1.06-1.32

In a recent case-control study in Barcelona, Spain, that examined the occupations and industries at high risk for bladder cancer in an area where the textile industry is predominant, and the incidence of bladder cancer is very high, 218 cases (1983-1993) were compared to 344 controls (Serra *et al*, 2000). A non-significant excess risk was observed (OR=1.13, 95%CI=0.79-1.63) overall, for ever having worked in the textile industry. An excess risk was observed for spinners and winders employed for more than 20 years (OR=3.28, 95%CI=1.08-9.97) and for machine setters employed between 1960 and 1974 (OR=4.26, 95%CI=1.09-16.7).

In 2002 Mastrangelo *et al.* (2002) reported a meta-analysis of cancer risk in textile industry workers, from studies published up until 1990. For individuals exposed to cotton (PRR=1.05, 95%CI=0.85-1.20), wool (PRR=1.15, 95%CI=0.87-1.43) or silk and synthetic fibres (PRR=1.50, 95%CI=0.93-2.07), the pooled RR was non-significantly increased. Similar non-significant excesses were also seen for carders and fibre processors (PRR=1.50, 95%CI=0.55-3.26) and spinners and weavers (PRR=1.19, 95%CI=0.80-1.57). However, the combined RR for weavers (PRR=2.40, 95%CI=1.62-3.18) and dyers

(PRR=1.39, 95%CI=1.07-1.71) was significantly raised. The risk among dyers was attributed to textile dye exposure. In an analysis of studies published up to 1990 and those since, the PRR was reduced to 1.33 (95%CI=1.09-1.57). Although not presented, there was a tendency for the risk estimate to move towards unity for all cancer risk estimates in studies published after 1990.

Eisen *et al.* (2001) described the extended follow-up of a cohort of 46,399 automobile manufacturing workers with potential exposure to MWFs. However, results for bladder cancer were not reported, as in the previous report no excess was found (Eisen *et al*, 1992)**.**

2.2.2   Aromatic Amines

Exposure to aromatic amines (arylamines) occurs in different industrial and agricultural activities. 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 a common contaminant in several working environments, including the chemical and mechanic industries and aluminium transformation. Arylamine-based dyes are used widely, particularly in the textile industry. Arylamines contaminate the ambient air where smokers are present (Maclure *et al*, 1989). Occupational exposures to aromatic amines may explain up to 25% of bladder cancers in some areas of Western countries; these estimates might be higher in limited areas of developing countries (Vineis and Simonato, 1991; Vineis and Pirastu, 1997). Aromatic amines, including 2-naphthylamine (β-naphthylamine), benzidine, 4-aminobiphenyl, chlornaphazine (a derivative of 2-naphthylamine previously used in the treatment of polycythemia), as well as the manufacturing of auramine and magenta dye are well-established causes of bladder cancer, and one of the first carcinogens to be associated with an occupational exposure (Clapp *et al*, 2005; IARC, 1987; Siemiatycki *et al*, 2004; Vineis and Pirastu, 1997). Studies of several other aromatic amines including ortho-toluidine and aniline have demonstrated elevated risks associated with bladder cancer.

However, some of the exposures have ceased (Swerdlow *et al*, 2001). Exposures to carcinogenic intermediates in the dyestuffs industry decreased from about 1935 and especially after 1945, and the use of 1- and 2-naphthylamine in the rubber industry stopped in 1949. A year later in 1950 the use of 2-naphthylamine was banned (Carcinogenic Substances Regulation) (IARC, 1974), as was the use of benzidine in about 1962. The only plant making α-naphthylamine and one making benzidine in Britain were closed in 1965. Carcinogenic arylamines such as 2-naphthylamine have been banned in other Western countries after 1969 (OSHA, 1973).

A cohort study by Ouellet-Hellstrom and Rench (1996) investigated a plant that produced a variety of chemicals, including arylamines, but not benzidine. Cancer incidence was investigated in a cohort of 700 workers employed at a US chemical plant between mid-1965 and 1989. The SIR for bladder cancer was 8.3 (95%CI=3.3-17.1) based on seven cases. The risk increased with increasing exposure to arylamines from zero at no exposure, to 5.5 at <2.5 annual cumulative exposure score, to 16.4 at 2.5+. The association was present whether exposure was less than or over 5 years' duration.

In a review of the cancer risk of aromatic amines Vineis and Pirastu (1997) reported considerable increased bladder cancer risk in workers exposed to 2-naphthylamine, benzidine, and 4-aminobiphenyl, but found that some studies were poorly designed and/or based on very small numbers (Vineis and Simonato, 1991; Vineis and Pirastu, 1997). Kogevinas *et al.* (2003) analysed combined data from 11 case-control studies from six European countries. They concluded that about 5-10% of bladder cancers in European men could be attributed to occupational exposures, including but not specifically aromatic amines, and that the results indicated improvement in working conditions during the last decades in Western Europe have been effective in preventing a significant part of bladder cancer cases caused by exposure to occupational carcinogens, particularly aromatic amines. Other studies have reported considerable increased risks of bladder cancer in workers exposed to 2-naphthylamine, benzidine, and 4-aminobiphenyl. Table 10 shows a selection of these studies.

Table 10. Arylamines with clear evidence of carcinogenicity to humans

Study	Number of observed (expected) deaths	Ratio of Observed over Expected deaths
2-Naphthylamine		
Case *et al.* (1954)	26 (29.9)	87
Mancuso and El-Attar (1967)	18 (60)	30
Schulte *et al.* (1985)	13 (333.3)	3.9
Rubino *et al.* (1982)	6 (4)	150
Bulbuyan *et al.* (1995)	9 (0.476)	18.9
Benzidine		
Case *et al.* (1954)	10 (71.4)	14
Mancuso and el-Attar (1967)	16 (53.3)	30
Zavon *et al.* (1973)	13 (among 25 workers)	-
Tsuchiya *et al.* (1975)	72 (among 1015 workers)	-
Rubino *et al.* (1982)	5 (6.0)	83
Horton *et al.* (1977)	13	
Meigs *et al.* (1986)	6	130
Bi *et al.* (1992)	9	45.7
Bulbuyan *et al.* (1995)	17	13.2
Hayes (1992)	31 (124)	25
4-Aminobiphenyl		
Melamed (1972)	43	
Melick (1972)	53	
Zack and Gaffey (1983)	9	10

Adapted from Vineis and Pirastu (1997)

4-Aminobiphenyl

In the United States, 4-aminobiphenyl (4-AB) now is used only in laboratory research. It was used formerly commercially as a rubber antioxidant, as a dye intermediate, and in the detection of sulphates. The association between 4-AB and bladder cancer was first documented by a descriptive study in the mid-1950s, where of 171 men exposed between 1935 and 1955, 19 developed bladder tumours (IARC, 1972). In 1955, a surveillance programme was initiated on workers reported to have been exposed to the chemical. During the following 14 years, 541 men were studied and 43 developed histologically confirmed carcinoma of the bladder (Melamed, 1972). In a survey of cancer mortality among workers at a chemical plant producing a variety of chemicals, a ten-fold increase in mortality from bladder cancer was reported (Zack and Gaffey, 1983). All nine cases on which the excess was based had started work in the plant before 1949, and 4-AB was known to have been used from 1941 until 1952. Another epidemiological investigation reported on mortality trends for 1,059 production workers at the same facility noted a marked excess of deaths from bladder cancer (SMR=7.97, 95%CI=4.25-13.6) based on 13 observed cases (Strauss *et al*, 1993). Most or all of this excess could be attributed to exposure to *para*-aminobiphenyl.

Benzidine and benzidine-based dyes

Benzidine has been used for over a century as an intermediate in the production of azo dyes, sulphur dyes, fast colour salts, naphthols, and other dyeing compounds (IARC, 1982b). In the past it has also been used in clinical laboratories for the detection of blood, as a rubber compounding agent, in the manufacture of plastic films, for the detection of hydrogen peroxide in milk, and for quantitative determination of nicotine. Most of these uses have been discontinued because of concerns about its potential carcinogenicity. However, some dyes that may contain benzidine as an impurity are still used

as stains for microscopy and similar laboratory applications (ATSDR, 2001). In a recent review of the evidence on benzidine, IARC reiterated its classification as Group 1 and increased the classification for benzidine-based dyes (Baan *et al*, 2008). An early study of workers in the British Chemical Industry exposed to benzidine observed ten bladder cancer cases whereas 0.54 were expected (SMR=18.5, 95%CI=8.9-34.1) (Case *et al*, 1954).

Zavon *et al.* (1973) followed a cohort of 25 males exposed to benzidine during its manufacture for 13 years. Thirteen developed transitional cell bladder cancer after a mean exposure of 13.6 years and an average latency of 16.6 years. The mean duration of exposure for those who did not develop tumours was 8.9 years. In an update of a historical study of Chinese workers (You *et al.*, 1990; Ma *et al.*, 2003) exposed to benzidine, Bi *et al.* (1992) examined cancer risk to 1981 in a group of 1,972 Chinese workers exposed to benzidine between 1972 and 1977. They noted a 25-fold increase in incidence in exposed workers that was associated with level of exposure from 4.8 at low exposure to 36.2 at medium exposure, to 158.4 for high exposure. Risk was increased for both benzidine producers (SIR=45.7, 95%CI=20.9-86.8) and users (SIR=20.9, 95%CI=12.9-32.0) of benzidine dyes. Adjustment for smoking reduced the risk substantially, but it still remained significant. In both these studies, although the common chemical to which all were exposed was benzidine, exposure to other suspect chemicals could not be entirely discounted.

Decarli *et al.* (1985) assessed bladder cancer risk among 664 workers of an Italian dyestuff factory exposed to aromatic amines from 1922 to 1970. Risk was shown to be greater for workers directly involved in aromatic amine manufacture than for those with only intermittent exposure.

In a study of workers at a US dye and resin manufacture plant, Delzell *et al.* (1989) established a cohort of 2,642 men employed between 1952 through 1985. Workers had a significant excess risk of bladder cancer (SMR=12.0, 95%CI=2.5-35.1). An update of this cohort looked at the risk among 3,266 employed for at least six months through 1995 (Sathiakumar and Delzell, 2000). There were eight deaths (all white males) giving an overall SMR of 1.39 (95%CI=0.60-2.72) (SMR=1.45, 95%CI=0.63-2.87). The majority of these cases (n=7) were amongst 'ever' hourly workers (SMR=2.01, 95%CI=0.81-4.15). Half of the cases occurred at one facility (SMR=5.15, 95%CI=1.40-13.18) among hourly workers (SMR=6.25, 95%CI=1.70-16.00). Men who had worked more than five years were at a significant excess risk.

One of the most important industrial facilities in Europe for benzidine production was in Leverkusen, Germany, where 92 of 331 workers ever exposed to benzidine production before 1967 suffered from bladder cancer (Golka *et al*, 1996; Lewalter and Miksche, 1992).

In a recent report of US workers exposed to benzidine and dichlorobenzidine, similar excesses were observed (Rosenman and Reilly, 2004). The cohort consisted of 538 workers employed at a single chemical manufacturing facility between 1960 and 1977, and was followed until 2001 for mortality and 2002 for cancer incidence. A total of 22 bladder cancer cases were identified, with three individuals having bladder cancer as the underlying cause of death. As a result mortality was significantly increased (SMR=8.34, 95%CI=1.72-24.38). All three deaths were in individuals who started work before 1973 and had more than five years employment; diagnosis occurred more than 15 years since they started work. The SIR for bladder cancer was 6.85 (95%CI=4.30-10.40), with an average duration of 10 years and average latency from first exposure of 22 years (Rosenman and Reilly, 2004).

2-Naphthylamine

2-Naphthylamine is now used only in laboratory research. It was formerly used commercially as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthylamine. Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or present as an impurity in other compounds, causes bladder cancer, and

its use has subsequently been banned. Studies of dyestuff workers and of chemical workers exposed mainly to 2-naphthylamine found increased risks of bladder cancer.

The carcinogenicity of 2-naphthylamine was demonstrated clearly in the 1950s in a large epidemiologic investigation of British chemical workers. Case *et al.* (1954) were able to obtain from the chemical industry nominal rolls for all workers, including information on job titles and the chemicals they manufactured. Overall, 4,622 men in 21 firms were enrolled, and mortality from bladder cancer was ascertained. The observed deaths exceeded by far those expected among exposed workers (SMR=87.0). In another UK study of chemical dye workers 2-naphthylamine was given as the most probable cause of a significantly increased bladder risk (Boyko *et al*, 1985). In a US study a significantly increased incidence was found (SIR=3.94, 95%CI=2.10-6.74) (Schulte *et al*, 1985). Two reports on one occupational population at a dyestuffs plant in Italy documented a very high bladder cancer risk linked specifically to 2-naphthylamine production (SMR=150, 95%CI=55-326) and a clear exposure-response relationship of the risk to exposures in the plant (Decarli *et al*, 1985; Rubino *et al*, 1982).

4-Chloro-ortho-toluidine

4-Chloro-ortho-toluidine (4-CoT) started commercial production in Germany in 1924 and was first reported in the US in 1939. It has been used commercially to produce azo dyes for cotton, silk, acetate, and nylon, and as an intermediate in the production of various pigments. Between the 1960s and 1980s it was used in the manufacture of acaricides and insecticides that are believed to be no longer produced or used worldwide. In 1999 IARC reaffirmed its evaluation as "probably carcinogenic to humans" (Group 2A).

Stasik (1988) conducted a study of 335 German men employed before 1970 in 4-CoT production and processing plants and followed them through 1986 but recorded no bladder cancer deaths. However, after completion of the study, bladder cancers were recorded in eight of the employees; all had been employed in the 4-CoT production plant before hygiene improvements in 1970. The SIR for bladder cancer in the 4-CoT sub-cohort (n=116) was 73 times higher than expected (SIR=72.7, 95%CI=31.4-143.3).

In a cohort of 49 Germans involved in the manufacture of the insecticide chlordimeform from 4-CoT from 1965, seven bladder cancer cases were identified between 1982 and 1990 (Popp *et al*, 1992). In comparison to national rates the SIR was 89.7 (95%CI=35.6-168.6), and was only slightly lower when compared to local population rates (SIR=53.8, 95%CI=21.3-101.1).

ortho-Toluidine

ortho-Toluidine is used in the production of dyes, pigments and rubber chemicals, and as a biological stain. IARC (2003) noted that there was limited human evidence for the carcinogenicity of *o*-toluidine and stated it was probable carcinogenic to human (Group 2A). However, in a recent review of its carcinogenicity IARC reclassified it as carcinogenic to humans (Group 1) (Baan *et al*, 2008). Five cohort studies of dye and rubber workers have evaluated the risk of bladder cancer among exposed workers.

In Italy, Rubino *et al.* (1982) studied 906 men involved in dyestuff production and first employed 1922-1970, and followed then from 1946 to 1973. In this cohort there were 36 bladder cancer deaths with an SMR of 29.3 (95%CI=20.5-40.5). Among a sub-cohort of 53 who were exposure to *ortho*-toluidine, five deaths were observed giving an SMR of 62.5 (95%CI=20.3-145.6). However, these were also exposed to MOCA, magenta, and *ortho*-nitrotoluene.

Ott and Langner (1983) followed 275 men employed during 1940-1958 in dyestuff production until 1975. However, no cases of bladder cancer were observed.

In a study of workers involved in the production of rubber chemicals, 1,749 (1,643 men) employed between 1946 and 1988 have been studied (Markowitz and Levin, 2004; Prince *et al*, 2000; Ward *et al*, 1991). In the initial analysis 13 incident cases were observed (SIR=3.6, 95%CI=1.92-6.2). In a sub-cohort of 708 exposed to *o*-toluidine, seven cases were observed giving an SIR of 6.5 (95%CI=2.6-13.3), with a significant exposure-response relationship between risk and duration of exposure. In a second analysis the follow-up was extended to 1994 (Prince *et al*, 2000) but showed no significant elevation in mortality in the total cohort. No results were given for *o*-toluidine exposure. In the most recent analysis of the cohort Markowitz and Levin (2004) followed 1,749 workers until 2004. A total of 28 cases were identified, nearly half of whom died aged between 50 and 59 years. A third had 11-20 and 21-30 years of exposure respectively, and half had their first exposure between 1950 and 1959, with four since 1970. The authors state that the timing of onset of exposure to *o*-toluidine of numerous cases after 1968, and especially 1975, suggests that potentially confounding occupational exposures other than *o*-toluidine were not responsible for the observed excess bladder cancer.

Sorahan and colleagues have studied a group of workers exposed to several aromatic amines, including *o*-toluidine, in a factory manufacturing chemicals for the rubber industry in the UK (Sorahan and Pope, 1993; Sorahan, 2008; Straughan and Sorahan, 2000). All subjects had at least six months employment between 1955 and 1984. In the latest report cancer mortality (1955-2005) and morbidity (1971-2005) of a cohort of 2,160 male production workers were investigated. A total of 611 subjects were potentially exposed to at least one of the four chemicals, including *o*-toluidine, with 11 deaths from bladder cancer (SMR=2.78, 95%CI=1.39-4.97). There was no excess mortality in the remaining 1,555 workers. 53 workers were exposed to *o*-toluidine, among whom three bladder cancer deaths were observed, whereas 0.27 were expected (SMR=11.16, 95%CI=2.30-32.61). In this group four incidence cases were observed when 0.72 were expected (SRR=5.56, 95%CI=1.51-14.22). A significant exposure-response relationship was observed with duration of exposure to *o*-toluidine.

2.2.3   Magenta manufacture

IARC (1987) have stated that there is inadequate evidence for the carcinogenicity of magenta. However, they have stated that the manufacture of magenta entails exposures that are carcinogenic (Group 1). The responsible carcinogens are not known; however, the process of manufacturing magenta has involved condensation of ortho-toluidine and formaldehyde in the presence of nitrotoluene, resulting mainly in the production of magenta III. Magenta I is prepared by the reaction of a mixture of aniline, *ortho*- and *para*-toluidine and their hydrochlorides with nitrobenzene or a mixture of nitrobenzene and *ortho*-nitrotoluene in the presence of ferrous chloride, ferrous oxide and zinc chloride. Most risk estimates come from studies of Western countries; however the major producers of magenta are now India, Mexico and Brazil, where production is increasing.

Case and Pearson (1954) studied men who had been employed for at least six months between 1920 and 1952 in the manufacture of magenta in the UK. Among 85 subjects who had been engaged in magenta manufacture, five cases of bladder cancer were observed, and three deaths, with 0.13 expected (SMR=23.08, 95%CI=4.76-67.4). In a study of 53 Italian workers employed in the manufacture of magenta III between 1922 and 1970 (Rubino *et al.* 1982), five deaths from bladder cancer were observed, while 0.08 were expected (SMR=62.50, 95%CI=20.3-146.0). In both studies there was evidence of ortho-toluidine and 4,4'-methylene-bis(2-methyl aniline) exposure and these were implicated in the excess mortality.

2.2.4   Aluminium production

There have been occurrences of clusters of people experiencing excess risk of bladder cancer, where the causative agent is unknown or at least unproven, for example, high risks of bladder cancer among workers in the aluminium industry (IARC, 1987). Workplace inhalation exposure is to aluminium dust or fumes for chronic conditions, and most workers were concurrently exposed by inhalation to other

known carcinogens, such as tobacco smoke or polycyclic aromatic hydrocarbons (PAH) from coal tars. Epidemiological studies have indicated an increased risk of urinary bladder cancer among workers exposed to coal tar pitch volatiles for long periods in the aluminium industry (Armstrong *et al*, 1994, Spinelli *et al*, 1991, Tremblay *et al*, 1995). PAH exposure in the aluminium industry originates mainly from the evaporation of carbon electrode materials used in the electrolysis process. Anodes and the lining materials are usually made from coal tar pitch and coke, with PAH exposure being particularly high (typical benzo(*a*)pyrene levels in the range of 1-10 mg/m^3) (IARC, 1984a; IARC, 1984b; IARC, 1984c). Large epidemiological studies of aluminium workers have been conducted in Canada, Norway, France and the United States.

In Norway, 1,790 men were employed for more than 5 years at a reduction plant between 1953 and 1995 (Romundstad *et al*, 2000b). There were 23 incident bladder cancer cases observed, resulting in an SIR of 1.3 (95%CI=0.8-1.9). Poisson regression analysis of risk of bladder cancer by cumulative exposure to PAHs did not show a positive relationship either overall or in different departments. In another Norwegian study Romundstad *et al.* (2000a) investigated risk among 5,627 workers employed for more than six months over the same time period. There were 41 incident bladder cancers observed (SIR=1.26, 95%CI=0.90-1.70), the risk being greater in those with >3 years of employment (SIR=1.37, 95%CI=0.96-1.90). The SIRs for bladder cancer showed no exposure-response relationship with PAH exposure, and also showed no increase with increasing lag time, with the exception of the highest exposure category (>2,000μg/m^3-years), where allowing for a 30 years lag period showed a significant excess SIR of 4.08 (95%CI=1.32-9.51). Poisson regression analysis with a 30-year lag period in the model (plus age and smoking) indicated a non-significant increasing trend.

In France, Moulin *et al.* (2000) included all men employed at a single plant for at least one year between 1950 and 1994. Seven bladder cancer deaths were observed giving a SMR of 1.77 (95%CI=0.71-3.64). Mortality did not show any relationship with time since first employment or duration of employment. No clear pattern was observed with regard to the different workshops. Although non-significant, the SMR of workers considered as exposed to PAHs (SMR=2.15) contrasted with that of non-exposed (SMR=0.85), and a non-significant trend was observed according to duration of exposure, with an SMR of 2.54 (95%CI=0.82-5.92) for workers exposed for more than 10 years.

In Canada a number of papers have been published on a cohort of Quebec aluminium smelter workers (Armstrong *et al*, 1988; Armstrong *et al*, 1994; Armstrong *et al*, 1986; Gibbs and Sevigny, 2007a; Gibbs and Sevigny, 2007b; Gibbs *et al*, 2007; Lavoue *et al*, 2007; Theriault *et al*, 1990; Tremblay *et al*, 1995). An early case-control study among blue collar workers who had worked more than one year between 1950 and 1979, identified 138 cases diagnosed between 1970 and 1980 (Tremblay *et al*, 1995). Each case was matched with three controls and the risk for each year of exposure to BaP at a concentration of 1μg/m^3 increased by 1.7% (0.8%-3.2%). In a recent analysis the study populations were: (A) 5,285 men with more than one year of seniority employed at plant A on 1.1.1950; (B) 529 men with more than one year of seniority employed at plant B on 1.1.1951; (C) 163 men with more than one year of seniority employed at plant C on 1.1.1951; and (D) 610 persons with more than one year of seniority (Gibbs and Sevigny, 2007b). All cohorts were followed up for cancer incidence to 1999. A total of 230 incidence bladder cancer cases were observed giving an SMR of 1.82 (95%CI=1.59-2.07). A highly statistical significant excess incidence was observed in all cohorts hired before 1950 and in the post-1950 cohort C, and in the post-1951 cohort B the SIR was almost double that expected. The incidence of bladder cancer was observed to be decreasing since at least 1980. Bladder cancer incidence was shown to be significantly related to coal tar pitch volatiles as represented by cumulative BaP exposure.

Mortality analysis (to 1999) of the cohorts indicated a total of 83 bladder cancer deaths (SMR=2.03, 95%CI=1.62-2.52). However, this excess was due to the significant excess among those employed before 1950 (SMR=2.24, 95%CI=1.77-2.79) (post-1950: SMR=0.85, 95%CI=0.28-1.98) (Gibbs and Sevigny, 2007a; Gibbs *et al*, 2007). For men with more than 20 years of potential latency, there was a statistically significant downward trend in bladder cancer mortality with year of hire. It was evident

that there was an increased risk in the higher categories of exposure and statistically significant trend based on small numbers, with the risk in the highest exposure category (320+µg/m^3 BaP) being 6.52 (95%CI=0.16-36.33). In an analysis of the cohorts hired on or before 1.1.1951 the risks were significantly greater and the exposure-response trend highly significant (Gibbs *et al*, 2007).

In another Canadian study of a plant in British Columbia all men with over three years employment between 1954 and 1997 were studied (Spinelli *et al*, 2006). A total of 6,423 workers were enrolled in the cohort, with 662 diagnosed with cancer. A total of 12 bladder cancer deaths were observed giving an SMR of 1.39 (95%CI=0.72-2.43). There were also 90 incident cases resulting in an SIR of 1.80 (95%CI=1.45-2.21). Poisson regression of cancer incidence in relation to benzo(a)pyrene (BaP) exposure showed a highly significant exposure-response relationship, the risk at 80+ BaP years of exposure being 1.92 (95%CI=1.02-3.65), and 2.12 (95%CI=1.11-4.06) after adjustment for smoking.

In a UK case-control study of 80 urothelial cancer cases Sorahan *et al.* (1998) observed 41 cases were involved in aluminium refining/smelting, compared to 62 controls. This resulted in a significant RR of 1.90 (95%CI=1.25-2.88).

2.2.5 Auramine manufacture

Auramine is a diarylmethane dye used as a fluorescent stain. It is an arylamine and its manufacture has been classified by IARC as Group 1, although the single responsible carcinogens are not known. IARC mention one epidemiological study, which indicates that the open manufacture of auramine presents an occupational bladder cancer risk (IARC, 1972). The presence of aromatic amines with different degrees of evidence of carcinogenicity is documented in some cosmetic products, such as auramine (2B) in brilliantines, CI Disperse Blue 1 (2B) and HC Blue No. 1 in semi-permanent hair dyes used in the past (Vineis and Pirastu, 1997).

IARC mention the study of Case and Pearson (1954) of dyestuff workers in the UK. Among the cohort of 1,555, there were six deaths from bladder cancer among 238 workers with auramine contact, where 0.45 were expected (SMR=13.3, 95%CI=4.9-29.0).

2.2.6 Boot and shoe manufacture and repair

There are several studies which suggest that excess risks of urothelial cancer are associated with textile and leather work (IARC, 1981; IARC, 1987; IARC, 1990; Marret *et al*, 1986). The relevant exposures have not been identified confidently, but exposure to dyes (including some benzidine-based dyes) is a likely explanation (Sorahan *et al*, 1998). Studies have revealed that inert azo dyes can be cleaved to their toxicologically relevant amino components, which have been used to synthesise the respective azo dye. Several professions in which azo dyes based on carcinogenic aromatic amines have been used have revealed increased bladder cancer risks in different studies (Golka *et al*, 2004). Among these, due to intensive dermal contact and inhalation exposure, have been dyers in the textile and leather industries (Frumin *et al*, 1990). IARC (1981) report that in England and Wales, SMRs for 'leather workers' in 1961 and for 'leather' in 1971 were 122 (based on 8 cases) and 151, respectively. An association between work in the leather industry and bladder cancer is supported by three US case-control studies, with relative risks in the order of 2-6 (1981). However, there were weaknesses in all these studies.

Marret *et al.* (1986) undertook a case-control study of 2,982 cases and 3,782 matched controls, and investigated the risk in relation to leather work. The OR of bladder cancer associated with leather work in white subjects was 1.4 (95%CI=1.0-1.9) after adjustment for sex, age and smoking. The risk was highest in those first employed in a leather job before 1945, although no exposure-response relationship with duration of exposure was observed.

In a mortality study of 2,926 male tannery workers, five bladder cancer deaths were observed (Costantini *et al*, 1989). This resulted in an SMR of 1.50 (95%CI=0.48-3.49).

Fu *et al.* (1996) investigated mortality at two shoe manufacturing sites in England and Italy. The English cohort consisted of 4,215 workers and the Italian cohort 2,008 workers, and was followed through 1991. There were 34 deaths seen among the English cohort compared to three among the Italian, which related in SMRs 0.84 (95%CI=0.58-1.17 and 0.86 (95%CI=0.18-5.69), respectively.

Sorahan *et al.* (1998) investigated the occupational histories of 803 patients diagnosed with bladder cancer between 1991 and 1993, and compared them with 2,135 matched controls. Conditional logistic regression indicated leather work was a significant risk for urothelial cancer (RR=2.53, 95%CI=1.48-4.32), even after adjustment for smoking (RR=2.51, 95%CI=1.44-4.35). Cases with more than 20 years exposure of leather work also demonstrated a significant excess risk (RR=3.30, 95%CI=1.16-9.40).

Stern (2003) undertook a study of 9,352 chrome leather tannery workers employed between 1940 and 1980, and followed them through 1993. Overall the risk of bladder cancer was reduced at 0.62 (95%CI=0.28-1.18).

In a study of the Swedish leather tanning industry a cohort of 2,027 workers employed for at least one year between 1900 and 1989 was investigated (Mikoczy and Hagmar, 2005). Cancer incidence was monitored between 1958 and 1999. In total 24 bladder cancers were diagnosed (SIR=0.96, 95%CI=0.61-1.42), 14 before 1990 (SIR=1.07, 95%CI=0.59-1.80) and 10 after 1990 (SIR=0.83, 95%CI=0.40-1.53). In an analysis with a 20-year latency period, the overall risk increased to 1.22 (95%CI=0.77-1.83), with the SIR of cases before 1990 being 1.25 (95%CI=0.68-2.09), after 1990 1.18 (95%CI=0.54-2.24).

In another study from Italy Iaia *et al.* (2006) investigated mortality in leather tanners from Tuscany. The cohort consisted of 4,874 (4,150 men, 724 women) who were followed through 1998. There were only six bladder cancer cases observed, two each among finishers, chrome tanners and vegetable tanners; the SMR was not significantly increased.

2.2.7 Coal gasification

Town gas and industrial gases derived from the destructive distillation of coal are produced in thousands of plants throughout the world. Substantial exposures to airborne polynuclear aromatic compounds have been measured in retort houses (a place where gas is manufactured by heating coal in the absence of air) (IARC, 1984c). PAHs from coal tar are the most plausible explanation for the increased risk of bladder cancer among coal gasification workers (Boffetta *et al*, 1997), in particular, those employed in coal distillation and purification using old types of gasifiers such as horizontal, vertical and continuous vertical retorts.

In Doll's studies of gas workers (Doll, 1952; Doll *et al*, 1965; Doll *et al*, 1972) employed in UK gas boards an increase in bladder cancer risk was noted. In the first analysis nine deaths were observed (SMR=1.55, 95%CI=0.71-2.95). In the second analysis a cohort of 11,499 was assembled and followed through 1961. A total of 14 deaths were observed and 14 expected. The risk, however, among those with heavy exposure (defined in the study as class A workers) (coal carbonising process workers), was increased at 1.70 (95%CI=0.55-3.97), more than triple that of individuals with minimal exposure (defined as Class C) (SMR=0.48, 95%CI=0.10-1.40). In the final report the cohort was followed up an extra four years to 1965. Over the whole study period (1953-1965) the annual death rate for bladder cancer among class A workers was more than double that of the England and Wales population, whereas class C workers the rate was three-quarters that of the national population. Four additional boards were added to the original study and analysis of mortality between 1957 and 1965 showed similar results to the original four boards. The bladder cancer rate in men with heavy exposure

was just over one and half times that of the national population, whereas in those with minimal exposure the rate was less than half.

Gustavsson and Reuterwall (1990) examined cancer risk among 295 workers at a Swedish gas production company, employed for at least one year between 1965 and 1972, following them up from 1966 to 1986 for mortality and to 1983 for incidence. There were only two deaths resulting in an SMR of 2.85 (0.34-10.31). There were also only two incident cases resulting in an SIR of 1.19 (95%CI=0.14-4.31).

In a review Bosetti *et al.* (2007) summarised the results from five cohort studies. However, only two studies, those above, gave results for bladder cancer and the pooled RR was 2.39 (95%CI=1.36-4.21).

2.2.8   Coke production

Coke is a solid carbonaceous residue derived from low-ash, low-sulphur bituminous coal. The volatile constituents of the coal (including water, coal-gas and coal-tar) are driven off by baking in an airless oven at temperatures as high as 1,000 degrees. Coke is used as a fuel. Substantial airborne exposure to PAHs has been measured in various occupations in coke production (IARC, 1984c). Exposure to PAHs is highest in coke oven operations, in particular at the top of the oven. The most important epidemiological study to date on coke oven workers has been conducted since the 1960s in the US and Canada (Costantino *et al*, 1995, Lloyd *et al*, 1970), although no excess of bladder cancer has been found.

Reid and Buck (1956) reviewed the occupational histories of all men dying while still on the books of National Coal Board coking plants during the period 1944-54. During this period the average number of men employed was about 8,000. They observed four deaths from bladder cancer whereas five were expected, based on national rates. Davies (1977) studied 610 coke oven personnel in two south Wales integrated steelworks between 1954 and 1965. During this time 82 had died, 26 from cancer (SMR=1.11). Three deaths from bladder and kidney cancers were observed compared to 1.19 expected (SMR=2.52, 95%CI=0.52-7.37).

In a mortality study of 11,399 coke plant workers in the Netherlands, 5,639 had worked in the coke plant for at least six months between 1945 and 1969, whilst the other 5,740 had worked in another plant and were non-exposed (Swaen *et al*, 1991). Among the non-exposed group 11 bladder cancer deaths were observed (SMR=0.66). In contrast the SMR among coke oven workers was 0.98 (95%CI=0.39-2.02), based on seven deaths. However, mortality due to bladder cancer among by-product workers was non-significantly raised at 1.34. In a French study of 536 retired coke oven plants followed between 1963 and 1987 only one bladder cancer death was observed (Chau *et al*, 1993). This person had worked near the ovens.

In a UK case-control study by Sorahan *et al.* (1998) 35 cases were employed in gasworks and coke ovens, whereas 55 controls were not. This resulted in a RR of 1.98 (95%CI=1.26-3.11), which reduced to 1.91 (95%CI=1.20-3.02) when adjusted for smoking.

In a review by Boffetta *et al.* (1977) no evidence of an increased risk of bladder cancer was found in any study. In addition, a quantitative review by Bosetti *et al.* (2007) concluded that there was no increased risk of bladder cancer in any of the studies.

2.2.9   Polycyclic aromatic hydrocarbons

PAHs are formed by the incomplete combustion of carbon-containing fuels such as wood, coal, diesel, fat, or tobacco. Workers are exposed by inhalation, ingestion and skin contact, the main route of exposure being inhalation. PAHs are produced in a number of occupational settings including coal gasification, coke production, coal-tar distillation, chimney sweeping (soots), coal tar and pitches, creosotes, and others (IARC, 1984a; IARC, 1984b; IARC, 1984c; IARC, 1985), most of which have

been classified by IARC as Group 1 carcinogenic situations (creosote is Group 2A) (IARC, 2008). Because PAHs are common in many occupational exposures, including soot and tar, untreated and mildly treated mineral oils, coke or iron steel foundries, findings of an association should be considered to be indirect evidence of the carcinogenic effects of PAHs (IARC, 1987; Mastrangelo *et al*, 1996).

Occupations in which PAH exposure is associated with an excess bladder cancer risk include painters, machinists, aluminium process, other metal workers, workers in the textile industry, leather workers and shoemakers, printers, hairdressers and transport workers (Kogevinas *et al*, 2003). A number of epidemiological studies have documented an increased risk of bladder cancer among workers exposed to petrochemicals and combustion products in different industries suggesting an association with PAHs and to their nitro-derivatives as well as diesel exhausts (Pirastu *et al*, 1996, Siemiatycki *et al*, 2004). An increase of bladder cancer risk, although inconsistent, is also found among industries with high exposure to PAHs from coal tars and pitches (Boffetta *et al*, 1997; Clapp *et al*, 2005).

Bonassi *et al.* (1989) investigated the association between occupational exposure to PAHs and bladder cancer development in an Italian population-based case-control study. A total of 121 male cases and 342 matched controls were assessed for PAH and aromatic amine (AA) exposure using a job-exposure matrix (JEM) constructed for the study. Logistic regression analysis suggested an increased risk with both possible and definite exposure to PAH. The risk associated with possible exposure to PAHs was not affected by adjustment for smoking, whereas it was greatly reduced after adjustment for AA exposure. For definite exposure to PAH there was little change in the OR estimates when the analysis was adjusted for smoking and AA. The risk was also relatively constant irrespective of the level of AA exposure.

In their meta-analysis, Kogevinas *et al.* (2003) examined which occupations and industries are currently at high risk of bladder cancer in men. They combined data from 11 case-control studies conducted between 1976 and 1996 in six European countries. The study comprised 3,346 incident cases and 6,840 controls. A number of occupations with known exposure to PAHs showed an increased risk of bladder cancer. A JEM was applied to evaluate exposure to PAHs. In the JEM, prevalence of exposure and average levels of exposure were evaluated for each occupation in different time periods. Overall exposure was defined as the product of these two continuous variables, and exposed subjects were classified in tertiles of maximum achieved exposure during their job history. Bladder cancer risk was shown to increase with higher exposure to PAHs with an OR for the highest exposure tertile of 1.23 (95%CI=1.07-1.4). In the lowest tertile the risk was just above one. The risk attributable to occupation ranged from 4.2 to 7.4%, with an estimated 4.3% for exposure to PAHs.

Bitumen fumes, coal tar and related products

Burstyn *et al.* (2007) investigated the risk of bladder cancer among workers exposed to PAHs during asphalt paving. A cohort of 7,298 men first employed between 1913 and 1999 in companies in Denmark, Norway, Finland and Israel was studied. Forty-eight incident bladder cancer cases were identified, the majority of whom were from Denmark (n=27). The rates were also greatly different: Denmark - 57.2, Norway – 18.7, Finland – 6.1, Israel – 46.6. Cumulative exposure did not appear to be associated with the risk of bladder cancer, in analyses that were unlagged or that were lagged 15 years. Similar results were seen for average exposure, although higher categories (>126ng BaP/m^3) of average exposure indicated approximately 40% excess in risk. When a 15-year lag was considered the association became stronger.

In a quantitative review by Bosetti *et al.* (2007) a pooled RR of 1.02 (95%CI=0.85-1.23) was estimated from two cohorts of asphalt workers (Boffetta *et al*, 2003; Hansen, 1989).

A French study examined bladder cancer risk among 658 male cases compared to 658 matched controls (1984-1987) (Clavel *et al*, 1994). For each subject, each occupation/time period was assigned a PAH value, and cumulative exposure summed across all occupations/time periods. No occupation

showed a significant risk for bladder cancer. However, individuals exposed to PAHs showed a significant excess risk whether the OR was unadjusted (OR=1.4, 95%CI=1.1-1.8) or adjusted for smoking and coffee consumption (OR=1.3, 95%CI=1.0-1.7), or these plus AAs (OR=1.3, 95%CI=1.0-1.7). A significant exposure-response relationship was observed with maximum exposure to PAH, average exposure, and cumulative exposure. Risk also increased with duration and time since starting exposure.

Foundry workers

Foundry workers are known to be exposed to PAHs. Boffetta *et al.* (1997) showed that in studies that assessed the risk of bladder cancer the risk was around 1.0-1.1, but one study from Denmark gave a risk of 9.0. However, an update of this study observed 19 urothelial cancers (SMR=1.41, 95%CI=0.85-2.20) (Hansen, 1997). In a Norwegian study there was no sign of an increased risk associated with exposure to PAHs within an iron, steel and coke plant (Grimsrud *et al*, 1998).

The reports of bladder cancer risk in foundry workers have generally been inconsistent, and because of this Gaertner and Theriault (2002) undertook a meta-analysis review of the epidemiological literature. Summary risk estimates (SRE) were calculated from 40 systematically extracted results. The SRE for all studies was 1.11 (95%CI=1.04-1.18) when the high results from Hansen (1991) were excluded. A similar SRE was observed when only studies with better quality exposure information were analysed (SRE=1.11, 95%CI=1.01-1.21). In studies that considered risk in relation to duration of exposure the SRE increased significantly. Within the industry the greatest risk was seen among moulders (SRE=1.47), casters (SRE=1.48) and general labourers (SRE=1.43), compared to furnace men (SRE=1.15), rolling mill operators (SRE=1.15) and fettlers/finishers (SRE=0.93).

The quantitative review by Bosetti *et al.* (2007) estimated from seven cohorts of iron and steel foundry workers a pooled RR of 1.29 (95%CI=1.06-1.57).

Carbon black manufacture

Carbon black is a commercial product of fine particulate soot, which is manufactured mainly by gas combustion and used for printing inks, rubber products, paints, and in photocopying machines. A US study followed up to 2003 5,011 employees in the industry employed for at least one year since the 1930s at 18 facilities. There were eight deaths from urinary organ cancers other than kidney (SMR=0.93, 95%CI=0.47-1.87). Risk did not show a positive relationship with duration of employment or time since hire.

In a study of German carbon black workers, 1,535 men with at least one year employment between 1960 and 1998 were followed (Wellmann *et al*, 2006). However, only one death from bladder cancer was observed.

In a UK study of 1,147 male workers were followed between 1951 and 1996, six bladder cancer deaths were observed (Sorahan *et al*, 2001c). This resulted in an SMR of 1.73 (95%CI=0.64-3.77).

Carbon and graphite electrode manufacture

A number of studies have investigated mortality among carbon electrode workers; four have given SMRs/SIRs ranging from 0 to 8.3 (Donato *et al*, 2000; Gustavsson *et al*, 1995; Merlo *et al*, 2004; Moulin *et al*, 1989). The quantitative review by Bosetti and colleagues (2007) obtained a pooled estimate of 1.35 (95%CI=0.83-2.20).

In an early review, Mastrangelo and co-workers (1996) reported that after 40 years of exposure to 0.2 mg/m^3 benzene soluble matter (which indicated PAH exposure), there was a relative risk of 2.2 for bladder cancer, which was not confounded by smoking.

2.2.10 Diesel engine exhaust

Diesel engine exhaust (DEE) comprises a particulate and gaseous phase, the former being important for a possible carcinogenic effect. Exposure to DEE occurs in many occupational settings, and it is often difficult to separate this agent from other combustion fumes, notably gasoline engine emissions. Levels of PAHs are highest in emissions from heavy-duty diesel engines, lower (and comparable) in emissions from light-duty diesel engines and from gasoline engines without catalytic converters (Boffetta *et al*, 1997). Professional drivers, mechanics, and other professions are exposed to elevated levels of emissions from combustion engines. An effect of DEE on bladder cancer is plausible because metabolites of PAH present in DEE are concentrated in the urine and may interact with the urothelium of the bladder (Silverman *et al*, 1986).

Drivers are an important group of workers exposed to DEE although results of studies on bus drivers do not consistently show an excess of lung and bladder cancer. Mortality from bladder cancer does not increase in studies of railroad workers and no pattern of excess of bladder cancer risk emerges from cohort studies of workers exposed to DEE (Boffetta *et al*, 1997). Olsen and Jensen (1987) observed an elevated risk only after exposures for more than 20 years. Golka (2004) surmises that it is doubtful that exposures to combustion exhausts are nowadays a significant risk of human bladder cancer.

Several studies have found an elevated risk of bladder cancer and DEE. Guo *et al.* (2004) investigated the risk of bladder cancer among Finnish workers born between 1906 and 1945 exposed to DEE, and diagnosed between 1971 and 1995. Occupational history of 8,110 cases was assessed for their exposure to DEE. There was a slight elevation of RR for bladder cancer risk at the lowest exposure level of DEE. The only significant excess was seen among bus drivers (RR=1.29, 95%CI=1.02-1.62).

Colt *et al.* (2004) examined bladder cancer risk in a population-based case-control study in New Hampshire, USA. Occupational histories among 424 cases and 645 controls were assessed, and they observed an elevated risk for male drivers of tractors/trucks (OR=2.4, 95%CI=1.4-4.1), with a significant positive trend in risk with increasing duration of employment (P_{trend} = 0.0003). This was higher than among drivers of other types of trucks and there was no increase for taxicab or bus drivers.

Soll-Johanning *et al.* (2003) investigated risk in Danish bus drivers and tramway employees in a nested case-control study of 84 cases and 606 controls from a cohort of 18,174 employees, employed between 1900 and 1994. However, no differences were seen in rates of bladder cancer even after 20 years of employment. However, after introducing a lag period of 10 years there was a tendency for an increase in risk with increasing time of employment, although there was no positive trend.

Finally, a population based, case-control study in Iowa, USA assessed the association between occupation and bladder cancer of 1,452 incident cases and 2,434 matched controls (Zheng *et al*, 2002). They reported an excess risk for mechanics in the automobile industry (OR=1.6, 95%C=1.0-2.6) and in railroad transportation and mechanics.

In contrast to the studies above, Boffetta *et al.* (2001), in a study of occupational exposure to DEE and cancer risk in Sweden found no increased risk of bladder cancer in either gender from exposure to diesel emissions in a cohort from the Swedish Cancer Environment Register.

In their meta-analysis of studies of workers exposed to DEE, Boffetta and Silverman (2001) identified 35 relevant studies, but did not perform an overall meta-analysis because of the heterogeneity between studies. Results for railroad workers suggested an increased occurrence of bladder cancer but a meta-analysis was not conducted. The SRR among truck drivers was 1.17 (95%CI=1.06-1.29) and that among bus drivers was 1.33 (95%CI=1.22-1.45). There were ten studies that considered DEE exposure based on a JEM or similar approach, and the SRR for these studies was 1.13 (95%CI=1.00-1.27). Within these studies a meta-analysis of high exposure to DEE resulted in a SRR of 1.23 (95%CI=1.12-1.36) for any exposure and 1.44 (95%CI=1.18-1.76) for high DEE exposure. Their

review suggested that exposure to DEE may increase the occurrence of bladder cancer but the effects of misclassification, publication bias and confounding could not be fully taken into account.

2.2.11 Intermediates in plastics and rubber manufacturing

Intermediates used in the manufacture of plastics and rubber include styrene-7,8-oxide and 4,4'-methylene bis(2-chloroaniline). There is independent support for the hypothesis that working with plastics may present excess risks of bladder cancer. In a case-control study of 75 cases and 142 controls Najem *et al.* (1982) noted significantly more cases worked in the plastics industry (risk ratio = 3.4, 95%CI=1.3-9.3). The risk was significantly greater among never smokers than ex-smokers and current smokers. However, if urothelial carcinogens have been or are being used in this industry it does not follow that they will have been used in all parts of the industry (Sorahan *et al*, 1998).

Zahm and co-workers (1987) conducted a case-control study using data from the US National Bladder Cancer Study looking at employment in the chemical industry. The study looked at 2,982 incident cases, of which 190 had ever been employed in the chemical industry. Women who had worked in the plastics industry had a 3.3-fold increased bladder cancer risk. Within the plastics and rubber industry, increased risks were found for men in mixing, filtering, grinding, and other dusty operations (OR=4.6, 95%CI=0.5-15.3) and men in heat-associated operations (OR=2.8, 95%CI=0.5-15.3).

In the US, NIOSH maintains the National Occupational Mortality Surveillance (NOMS) database of death certificate data with coded occupation and industry information[2]. PMR analyses of the NOMS data are used to identify industries with high proportions of deaths due to selected cancers. The results reported are restricted to cancer causes of death in the US manufacturing industries. For deaths between 1984 and 1990 the highest PMR for bladder cancer was in plastics, synthetics and resins with a PMR of 1.7 (95%CI=1.0-2.6) for men and was the highest for women (PMR=2.8, 95%CI=1.0-6.0) (Ward *et al*, 1997). However, in the most recent information published online mortality was not presented by individual industries.

Styrene-7,8-oxide

Styrene-7,8-oxide (SO) is used as a chemical intermediate in the production of styrene glycol and its derivatives, cosmetics, surface coatings, and agricultural and biological chemicals. It is also used as a reactive diluent for epoxy resins and in cross-linked polyesters and polyurethanes. Occupational exposure to SO occurs most often to workers in the fabricated rubber products, paints and allied products. Evidence for SO (1,2-epoxyethylbenzene) to be considered a human carcinogen is based on evidence of carcinogenic activity at multiple tissue sites in multiple species of experimental animals (IARC, 1994). However, no adequate human studies of the relationship between exposure to SO and human cancer have been reported. Wong *et al.* (1994) investigated mortality in exposed workers in the US reinforced plastics and composites industry. The cohort consisted of 15,826 employees employed between 1948 and 1977. There were five deaths from urothelial cancers whereas 6.3 were expected (SMR=0.79, 95%CI=0.26-1.85). Three occurred with <10 years latency (SMR=2.53), and four occurred in employees exposed to 30-99.9 ppm-years styrene exposure.

Kolstad *et al.* (1995) investigated 36,620 workers in reinforced plastics companies and 14,293 not exposed to styrene from similar industries from 1970 to 1990. Among exposed workers there were 117 bladder cases (SIR=1.16, 95%CI=0.96-1.39), whereas there were 45 among non-exposed (SIR=1.00, 95%CI=0.73-1.33). The risk did not show any association with years of and time since first employment and duration of employment.

In a study of the styrene-butadiene industry no excess of bladder cancer was observed (Matanoski *et al*, 1990) which was re-affirmed in more recent follow-ups (Delzell, 2006; Sathiakumar *et al*, 2005).

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[2] http://www.cdc.gov/niosh/topics/surveillance/NOMS/

In the UK cases-control study of Sorahan *et al.* (1998), 68 cases reported working in the manufacture of rubber and rubber products and 50 in the manufacture of plastics, resulting in RRs of 1.89 (95%CI=1.34-2.60) and 1.73 (95%CI=1.17-2.55), respectively.

4,4'-Methylene bis(2-chloroaniline)

4,4'-Methylene bis(2-chloroaniline) (MOCA) has been primarily used as a curing agent for polyurethane pre-polymers in the manufacture of castable urethane rubber products such as shock absorption pads and conveyor belting. IARC had evaluated MOCA as "probably carcinogenic to humans " (Group 2A) (IARC, 1993); however, recently it has been re-evaluated as "carcinogenic to humans" (Group 1), based on studies of experimental animals and toxicological studies (Baan *et al*, 2008), because its chemical structure is similar to that of a known human bladder carcinogen, benzidine, and to that of a potent animal carcinogen 3,3'-dichloro-benzidine. Two early studies found small excesses, and in a review, a higher than expected incidence was reported among workers in a UK plant manufacturing MOCA (Cartwright, 1983), 13 new cases had occurred within a period of a few years, far more than it was believed should have been expected. However, an earlier study of manufacturing workers in the USA, who were followed up for less than 16 years, failed to reveal any bladder tumour (Osorio *et al*, 1990; Ward *et al*, 1990). This study had very little statistical power to detect any excess.

2.3   OCCUPATIONS

2.3.1   Painters

The profession of a painter and varnisher was classified as an occupation associated with sufficient evidence of carcinogenicity (IARC, 1989b). Many chemicals are used in paint products 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 (IARC, 1989b). Titanium dioxide and chromium and iron compounds are used widely as paint pigments. Between 2002 and 2004 the LFS estimates gave an average 24,906 workers employed as vehicle spray painters and 138,212 as painters and decorators [3].

However, paint technology has changed over the last 50 years, as has exposure. Since the introduction of water-based-paints, the inhalation of solvents (i.e. toluene, xylene, ketones, alcohols, esters and glycol ethers) has been reduced. Bladder cancer risk for painters and varnishers is also very dependent on the individual exposure, which is determined by a broad spectrum of working materials and techniques. Due to these differences in past exposure conditions it is understandable that a number of studies did not show a significant bladder cancer risk for painters (IARC, 1989b).

In a review of the evidence of bladder cancer risk in painters Bosetti *et al.* (2005) identified 27 papers published between 1989 and 2004 (7 cohort, 19 case-control, 1 pooled analysis of 11 case-control studies of which 6 were published before 1989). All the studies were from Europe, USA and two from Canada. Overall the pooled RR was 1.17 (95%CI=1.11-1.23). There was a slight difference between cohort incidence studies (PRR=1.10, 95%CI=1.03-1.18), cohort mortality studies (PRR=1.23, 95%CI=1.11-1.37) and case-control studies (PRR=1.35, 95%CI=1.19-1.53). No heterogeneity was observed between studies, but there was significant heterogeneity between study types.

In the UK regional case-control study of urothelial cancers by Sorahan *et al.* (1998), out of 803 cases 86 were in occupations (ever employed in) specified as manufacturing or professional use of paints compared to 127 controls giving a significant RR of 1.91 (95%CI=1.41-2.59). In an analysis with

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[3] http://www.statistics.gov.uk/StatBase/tsdataset.asp?vlnk=429&More=Y

respect to occupations followed in 1971 ("Were you employed in 1971, if yes, what was your occupation?"), the RR for painters and decorators was 1.16 (95%CI=0.61-2.22).

In a large combined European case-control study of 3,346 incident cases and 6,840 controls, Kogevinas *et al.* (2003) observed 116 incident cases among painters. This resulted in an OR of 1.17 (95%CI=0.91-1.50). In workers involved in the manufacture of paints, varnishes and lacquers there were 22 cases, giving a significant OR of 2.94 (95%CI=1.48-5.84).

In the USA Steenland and Palu (1999) undertook a study of a large cohort of 57,000 painters, based on union records, and non-union members. Vital status was followed through 1994, and 18,259 painters and 4,247 non-painters were known to have died. Among non-painters there were 22 bladder cancer deaths giving an SMR of 0.74 (95%CI=0.46-1.11). In painters 166 deaths were observed giving a significantly increased SMR of 1.23 (95%CI=1.05-1.43). Mortality among painters 20 years since first union membership was also significantly raised (SMR=1.25, 95%CI=1.06-1.47). Poisson regression analysis comparing painters and non-painters indicated the rate ratio was significantly raised (SMR ratio=1.77, 95%CI=1.13-2.77), although it was reduced to 1.55 (95%CI=0.96-2.51) after 20 years since joining the union.

Chen and Seaton (1998) undertook a meta-analysis of published papers referring to painters and mortality. Between 1966 and 1995 58 papers were identified from which they selected 17 follow-up studies published in Europe, Canada, USA, New Zealand and one from China. For bladder cancer the combined SMR for painters was 1.30 (95%CI=1.14-1.50). In occupational cohort studies the combined SMR was 1.26 (95%CI=0.98-1.62).

In a Swedish study using data from the 1960 and 1970 censuses, cases were identified from the Swedish Cancer Register between 1971 and 1989 (Brown *et al*, 2002). A total of 42,433 men were classified as painters during either of the censuses, among which there were 4,475 tumours of which 344 were bladder cancer. This resulted in an SIR of 1.1 (95%CI=1.0-1.2). Among lacquerers there was no difference between metal or wood lacquerers; overall the SIR was 1.2 (95%CI=0.9-1.4). Among male pictorial artists the SIR was significantly increased at 1.5 (95%CI=1.2-1.9), based on 71 cases. For male workers in the paint and varnish industry the SIR was 1.2 (95%CI=0.8-1.5).

In a population based, case-control study in Iowa, USA, Zheng *et al.* (2002) identified 1,452 incident bladder cancer cases and 2,434 matched controls between 1986 and 1989. Of the cases 11 were among painters in construction and maintenance, whereas among controls there were six. This gave a significantly increased OR of 2.7 (95%CI=1.0-7.7).

Another case-control study by Jensen and co-workers in Denmark of 371 cases and 771 controls (Jensen *et al*, 1987) found an association for employment in trades undertaking painting (RR=1.4 for 10 years employment) and a significant trend emerged for duration of employment.

However, it has been suggested that any increased risk would have been greater for exposures in the past.

2.3.2 Rubber industry

Antioxidants containing 2-naphthylamine were used in the rubber and electric-cable manufacturing industries in Great Britain. Beta-naphthylamine was also used in the British rubber industry up to the end of 1949, when it was withdrawn because it was deemed to have caused an excess of bladder tumours both in product manufacture and use in the industry (IARC, 1982a; Veys, 2004a). In addition, since the 1970s, further health and safety measures have been widely applied in the rubber industry by substituting some chemical agents and controlling exposure to others (Kromhout *et al*, 1994).

Some epidemiological studies showed strong evidence that demonstrated workers in the rubber industry had elevated risks for bladder cancer (Clapp *et al*, 2005; Kogevinas *et al*, 1998; Siemiatycki *et al*, 1994; Ward *et al*, 1997). In 1982, IARC evaluated the strength of available evidence regarding cancer excesses in the rubber industry (IARC, 1982a), concluding the evidence was sufficient for excess occurrence of bladder cancer. There have been numerous studies conducted in the industry, and studies have reported that occupational bladder cancer in (former) rubber workers is still an issue (Golka *et al*, 2004).

In GB the hazard of occupationally induced urothelial cancer in the rubber industry was highlighted by Case and Hosker (1954) although they did not determine the level of the risk. The risk appeared to persist over the next few years and so mortality studies were undertaken by both the British Rubber Manufacturer's Association (Parkes, 1969; Parkes *et al*, 1982; Sorahan *et al*, 1989) and by the Health and Safety Executive (Baxter and Werner, 1980), plus in a number of factories (Veys, 1969). A detailed study of one of the BRMA factories was also established because of inadvertent exposure of some workers to β-naphthylamine (Veys, 1969; Veys, 1981; Veys, 1992; Veys, 1996; Veys, 2004a). In the most recent analysis 2,090 at-risk men, employed 1945-1949, and 3,038 men, first employed only after January 1950, when β-naphthylamine was removed, were followed until 1995. In the whole cohort there were 115 incident bladder cancer cases diagnosed (SRR=1.23, 95%CI=1.02-1.48). Of these, 58 occurred in the at-risk men employed 1946-1949 (SRR=1.71, 95%CI=1.30-2.21), whereas 39 occurred in men first employed 1950-1960 (SRR=1.02, 95%CI=0.72-1.39). There were 36 deaths (SMR=0.85, 95%CI=0.60-1.18), 16 among at-risk men (SMR=0.97, 95%CI=0.55-1.57) and 15 in men first employed after 1950 (SMR=0.94, 95%CI=0.53-1.56).

Dost *et al.* (2007) monitored cancer in a recently defined cohort of UK rubber workers employed for at least one year between 1982 and 1991. A total of 8,651 men and women from 41 UK factories were followed until 2004. Among women only two incident cases were observed (SRR=3.08, 95%CI=0.37-11.11). However, among men there were three deaths (SMR=1.28, 95%CI=0.26-3.75) and 12 incident cases (SRR=1.25, 95%CI=0.65-2.19).

In an analysis of workers at a UK tyre factory that started production in 1929, 6,454 men had worked between 1946 and 1960 and were followed to 1985 (Veys, 2004b). There were 26 bladder cancer deaths observed, compare to 15.5 expected based on national rates (SMR=1.03, 95%CI=0.67-1.51).

A review of the epidemiological literature concerning the association between bladder cancer and working in the rubber industry published since 1982 identified 14 cohort, six administrative cohorts, and 19 case-control studies (Kogevinas *et al*, 1998). These included the British Rubber Manufactures Association (BRMA) study (Sorahan *et al*, 1986; Sorahan *et al*, 1989) (34,000 workers), the Health and Safety Executive study (Baxter and Werner, 1980) (40,000 workers), and the Veys study (Veys, 2004a) (14,000 workers), thus presenting a picture of 80 years of cancer experience in the industry, which is not the same as the situation that exists today (Straughan, 1998). Excess risk was found in 11 cohorts/sub-cohorts either for the whole cohort or for workers employed in specific departments. Excess risks with ORs ranging from 1.5 to 5.7, after adjustment for potential confounding factors, were found in 11 case-controls studies

An Italian study of 6,629 workers employed from 1906 to 1981 in a rubber tyre factory showed 16 bladder cancer deaths occurred (Negri *et al*, 1989). There was no difference in the risk between those first employed before 1939 or after. Those who started work before the age of 30 years were at a significant excess risk (SMR=2.47, 95%CI=1.13-4.71). There was a negative association between risk and duration of exposure and period since first exposure. In the cohort as a whole the SMR was significantly increased at 1.83 (95%CI=1.05-2.96). Another study of 4,917 males workers who first started work in a large rubber factory between 1962 and 1972 were followed to 1983 (Bernardinelli *et al*, 1987). Only one death was observed but the SMR was 1.37 (95%CI=0.03-7.63). In a more recent study Ietri *et al.* (1997) studied mortality among 925 workers involved in the manufacture of rubber and plastics products between 1950s and 1989, but failed to observe any bladder cancer deaths.

Alder *et al.* (2006) carried out a systematic review and meta-analysis of cohort studies of workers in the rubber-producing industry. Studies were identified from computerised databases through 2003. For bladder cancer mortality 21 studies were identified, which resulted in a pooled estimate of 1.15 (95%CI=0.94-1.39), with significant heterogeneity. The pooled estimate for incidence was slightly higher at 1.33 (95%CI=0.92-1.93) based on seven studies. When only studies that were exclusively producing tyres (n=6) were considered the pooled estimate was 0.97 (95%CI=0.58-1.63).

A study of cancer incidence in 2,448 Norwegian rubber workers employed for at least 18 months and with at least eight years observation time, recorded seven cases where 7.74 were expected (Norseth *et al*, 1983). A small excess was seen in the footwear department (n=4; SIR=1.42, 95%CI=0.39-3.64).

In 1993, Bolm-Audorff *et al.* (1993) reported elevated bladder cancer risks, adjusted for smoking, for "rubber manufacturing and curing" in a German cohort, results that were subsequently confirmed by Straif *et al.* (1998). In this study 11,633 male workers were followed up for mortality from 1981 to 1991. Cohort members were active (n=7,536) or retired (n=4,127) on January 1 1981 and had been employed for at least one year in one of five plants producing tyres or technical rubber goods. A total of 27 deaths were observed (SMR=1.08, 95%CI=0.71-1.57). The distribution of these cases was**:**

Activity	Number of deaths	SMR	95% CI
Preparation of materials	7	1.19	0.48-2.46
Technical rubber goods	9	1.01	0.46-1.92
Tyres	3	0.46	0.09-1.36
Storage, dispatch	6	2.53	0.93-5.51
Maintenance	12	1.59	0.82-2.79
Others	4	0.80	0.22-2.06

Among storage/dispatch workers the highest SMRs were found among workers who had accumulated one to nine years of employment (SMR=5.18, 95%CI=1.68-12.07) and among workers who were hired after 1960 (SMR=5.06, 95%CI=0.61-18.26).

In the population-based, case-control study in Iowa, USA, (Zheng *et al*, 2002) 1,452 incident cases and 2,434 matched controls were identified between 1986 and 1989. Of the cases 12 were among employed in the rubber and miscellaneous plastics products industry, giving an OR 3.1 (95%CI=1.2-8.5). There were six cases involved in manufacture of tyres and inner tubes (OR=2.7, 95%CI=0.7-9.6), with all cases occurring after 10 years in the industry (OR=3.4, 95%CI=0.8-14.1).

2.3.3   Hairdressers and barbers

Elevated risk of bladder cancer has been observed in association with occupational exposure to hair dyes in hairdressers, barbers, beauticians and cosmetologists (Alderson and Rattan, 1980; Czene *et al*, 2003; Gago-Dominguez *et al*, 2003; Huncharek and Kupelnick, 2005; La Vecchia and Tavani, 1995; Skov *et al*, 1990; Skov and Lynge, 1994; Takkouche *et al*, 2005; Teta *et al*, 1984). Since the early twentieth century, hairdressers have made use of a wide range of products, including hair colourants and bleaches, shampoos and conditioners. Many chemicals are found in formulations of these products. Hair colourants are classified as permanent (primarily aromatic amines and aminophenols with hydrogen peroxide), semi-permanent (nitro-substituted aromatic amines, aminophenols, aminoanthraquinones and azo dyes), and temporary (high-molecular-weight or insoluble complexes and metal salts, such as lead acetate). The numerous individual chemicals used in hair colourants have varied over time. Only permanent and semi-permanent hair colourants are used to a significant extent by hairdressers (IARC, 1993).

In 1993, IARC categorised the profession of hairdressers in group 2A (IARC, 1993) despite debates of the risk of bladder cancer due to exposure to hair dyes. There is however, also evidence of occupational exposure to permanent hair dyes and bladder cancer.

In a Danish cohort hairdressers had a RR of 2.05 (men) and 1.75 (women) in 1970-1980 and RR = 1.17 (men) and RR = 0.88 (women) in 1981 – 1987 (Skov and Lynge, 1994). A statistically significant increase risk for bladder cancer was found among male hairdressers in Norway and Sweden using collaborative data from Sweden, Norway and Finland (Skov et al, 1990).

In a UK case-control study of 803 urothelial tumours, 11 were observed in hairdressing (RR=2.00, 95%CI=0.89-4.48) (Sorahan et al, 1998). In the European combined case-control study by Kogevinas et al. (2003), 37 cases were hairdressers compared to 62 controls giving an OR of 1.09 (95%CI=0.70-1.70).

In a large US population-based case-control study there were 1,514 incident cases and an equal number of matched controls (Gago-Dominguez et al, 2001). In total 20 cases and 13 controls had ever held a job as a hairdresser or barber, giving an adjusted OR of 1.5 (95%CI=0.7-3.2). The OR for those with more than 10 years of working was significantly elevated at 5.1 (95%CI=1.3-19.2), whereas for those with <10 years employment the OR was 0.6 (95%CI=0.2-1.6). Subjects applying permanent hair dyes at least once a month for more than 15 years were at an increased risk (OR=3.3, 95%CI=1.3-8.4).

La Vechia and Tavani (2001) reviewed the evidence and concluded that the estimated relative risks, as well as the overall pooled estimates, are only moderately above unity, and hence compatible with potential errors and biases, such as not controlling for smoking.

A follow-up study of a cohort of 38,866 female and 6,824 male hairdressers from Sweden was followed from 1960 to 1998 (Czene et al, 2003). Risk was increased in male hairdressers at any census (SIR=1.22, 95%CI=0.98-1.51), but was greater in those at the 1960 census (SIR=1.25, 95%CI=1.01-1.55). Among female hairdressers the risk was slightly increased in those at any census (SIR=1.09, 95%CI=0.81-1.43) but was slightly reduced in those at the 1960 census (SIR=0.95, 95%CI=0.65-1.34). In males registered at the 1960 census the risk was highest in the first decade (1960-1969) of follow-up with an SIR of 2.56 (95%C.I=1.36-4.39) and decreased with the follow-up time. This suggests that modern hair dyes are less likely to be associated with bladder cancer.

Lamba et al. (2001) evaluated bladder cancer mortality in 24 US states from 1984 to 1995. Of the 38,721 deaths among white and black hairdressers and barbers of both sexes, 6,924 were from cancer, with 109 from cancer of the bladder, urethra and other urinary organs. For hairdressers, among white women (n=88) the mortality odds ratio (MOR) was significantly raised at 1.36 (95%CI=1.10-1.68), and non-significantly raised in black women at 1.19 (95%CI=0.72-1.98). It was not elevated among men. In male barbers the MOR for white men was not raised (MOR=0.98, 95%CI=0.78-1.23), whereas in black men it was non-significantly raised (MOR=1.48, 95%CI=0.77-2.5).

However, most estimates are based on occupational exposures from decades ago, when the control of carcinogenic substances in hair dyes and the working processes was less strict. Huncharek and Kuopelnick (2005) carried out a meta-analysis of the personal use of hair dyes and the risk of bladder cancer. Several studies were included in the analysis with ORs ranging for 0.6 to 1.8. The pooled RR was 1.01 (95%CI=0.92-1.11), suggesting no association between hair dye use and bladder cancer development. However, sensitivity analysis examining the influence of hair dye, type and colour, and study design gave statistically significant RRs ranging from 1.22 (95%CI=1.11.1.51) to 1.50 (95%CI=1.30-1.98), suggesting there might be an increased risk. However, an analysis by Takkouche et al. (2005) found no association.

In a more recent meta-analysis Kelsh et al. (2008) included 11 case-control studies and one cohort study in their article. They found no causal association between any personal use of hair dye and

bladder cancer among women or men, for use of permanent hair dye, duration of use (any type or permanent) and lifetime applications of any hair dye.

2.3.4 Petroleum Refining

Approximately 3000 million tonnes of petroleum fuels, solvents, lubricants, bitumens and other products are produced annually from crude oil. Process operators and maintenance workers may be exposed to a large number of substances, which occur in crude oil, process streams, intermediates, catalysts, additives and final products (IARC, 1989a). A large number of epidemiological studies of workers in the petroleum industry have been conducted to address the issue of carcinogenicity of petroleum chemicals. Because exposure to petroleum chemicals have been steadily reduced over the years, historical exposures were much higher (e.g. before 1950) when compared to current exposures.

Wong and Raabe (2000) critically reviewed the cancer epidemiological literature concerning petroleum workers, and carried out a meta-analysis. Studies from the US, UK, Canada, Finland, Sweden and Italy were included in the investigation resulting in a cohort of more than 350,000. All the SMRs were below 1, with the exception of two small North American studies. The pooled SMR for bladder cancer was 0.78 (95%CI=0.71-0.85) which included distribution as well as refinery workers. The pooled-SMR for bladder cancer for US refineries was 0.71 (95%CI=0.62-0.81), compared to the pooled-SMR for non-US refineries of 0.87 (95%CI=0.73-1.03).

In contrast to these results, recent results from an Australian petroleum industry cohort have shown an excess of bladder cancer (Gun *et al*, 2004; Gun *et al*, 2006). The cohort consisted of 16,547 males and 1,356 females, and was followed to 2001 for mortality and 2000 for cancer incidence (Gun *et al*, 2006). There were 477 cancer deaths, which resulted in an SMR of 0.84 (95%CI=0.76-0.91) for bladder cancer. Among males there were 60 incidence cases (SIR=1.17, 95%CI=0.89-1.50) and nine deaths (SMR=0.81, 95%CI=0.37-1.53) observed. These estimates were lower than those observed in a previous study where the incidence was significantly increased (Gun *et al*, 2004). In this report risk was broken down by workplace type and showed the risk among refinery workers was non-significantly increased at 1.48 (95%CI=0.92-2.26). However, greater risks were seen amongst airport (SIR=2.85) and offshore production (SIR=1.61) workers.

In the UK a cohort of 34,569 refinery workers have been followed for a number of years (Rushton and Alderson, 1981; Rushton, 1993; Sorahan *et al*, 2001a; Sorahan *et al*, 2001b; Sorahan *et al*, 2002; Sorahan, 2007). In the latest update 28,555 workers were studied for cancer mortality (1951-2003) and incidence (1971-2001). There were 3,492 cancer deaths in total, of which 135 were bladder, giving an SMR of 1.00 (95%CI=0.84-1.18). There were 4,631 incident cancers, 353 due to bladder cancer. This resulted in an SIR of 1.02 (95%CI=0.91-1.13). These results confirm those of the previous studies.

2.4 OTHER EXPOSURES

2.4.1 Environmental Tobacco Smoke

Cigarette smoking is well established as a cause of bladder cancer, although the association is not as strong as that observed between smoking and several other cancers (Silverman *et al*, 2006). However, no increased risk has been associated with environmental tobacco smoke (ETS) in two case-control studies (Burch *et al*, 1989; Sandler *et al*, 1985) and one cohort study (Zeegers *et al*, 2002).

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

The substances considered in the estimation of the attributable fraction (AF) for bladder cancer are those outlined in Table 11.

Table 11 Substances considered in the estimation of the attributable fraction for bladder cancer

Agents, Mixture, Circumstance	AF calculated	Strength of evidence	Comments
Group 1: Carcinogenic to Humans			
Agents, groups of agents			

Aromatic amine dyes
    4-aminobiphenyl
    Benzidine
    2-naphthylamine
	Y	Strong	

Coal tars and pitches	N	Suggestive	Included with PAHs
Polyaromatic hydrocarbons: Benzo[a]pyrene	Y	Suggestive	
Mineral oils, untreated and mildly treated	Y	Suggestive	
Exposure circumstances			
Aluminium production	N	Strong	Included with PAHs
Auramine manufacture	N	Strong	Included in aromatic amine
Magenta manufacture	N	Strong	Included in aromatic amine
Rubber industry	N	Strong	Risk confined to pre 1950 in UK
Boot and shoe manufacture and repair	N	Suggestive	Exposure up to 1962 included with aromatic amines
Coal gasification	N	Strong	Included with PAHs
Coke production	N	Suggestive	Included with PAHs
Painters	Y	Suggestive	
Group 2A: Probably Carcinogenic to Humans			
Agents and groups of agents			

Polyaromatic hydrocarbons:
    Dibenz[a,h]anthracene
    Cyclopenta[cd]pyrene,
    dibenzo[a,l]pyrene
	Y	Suggestive	Included with PAHs – benzo[a]pyrene above

Diesel engine exhaust	Y	Suggestive	

Intermediates in plastics and rubber manufacturing
    4,4'-methylene bis(2-chloroaniline)
    Styrene-7,8-oxide
	N	Suggestive	No human evidence

Aromatic amine dyes
    Benzidine-based dyes
    4-Chloro-ortho-toluidine
    Ortho-Toluidine
	Y		Included in aromatic amine

Exposure circumstances			
Hairdressers and barbers	Y	Suggestive	
Petroleum refining	N	Suggestive	Included with PAHs

Data Relevant to the Calculation of AF

The two data elements required are an estimate of relative risk (RR), and either (1) an estimate of the proportion of the population exposed (Pr(E)) from independent data for Great Britain, or (2) an estimate of the proportion of cases exposed (Pr(E|D)) from population based study data.

The RR chosen from a 'best study' source is described for each exposure, with justification of its suitability. Information on the 'best study' and independent data sources for the proportion of the population exposed are also summarised for each exposure in the appropriate section below. In the absence of more precise knowledge of cancer latency, for solid tumours a latency of up to 50 years and at least 10 years has been assumed for all types of solid cancer. Therefore it is assumed that exposure at any time between 1956 and 1995 (the Risk Exposure Period, REP) can result in a cancer being recorded in 2004 as a registration or in 2005 as an underlying cause of death. Although strictly speaking the REP for cancer registrations recorded in 2004, the year for which estimation has been carried out, would be 1955-1994, for simplification the years 1956 to 1995 have also been used, as for deaths, as the proportion exposed will not be affected. For an independent estimate of the proportion of the population exposed, numbers of workers ever exposed during this period are estimated by extrapolating from a point estimate of exposed workers taken from the period. If this is from CAREX relating to 1990-93, an adjustment is made to take account of gross changes in employment levels which have occurred particularly in manufacturing industry and the service sector across the REP. Otherwise a point estimate that represents numbers employed as close as possible to about 35 years before the target year of 2005 is used, as this is thought to represent a 'peak' latency for the solid tumours, and is also close to the mid-point of the REP for estimating numbers ever exposed across the period (for which a linear change in employment levels is implicitly assumed). Where the Census of Employment is used, the point estimate data are for 1971. Where the LFS is used, the first year available and therefore used is 1979. A turnover factor is applied to estimate numbers ever exposed during the REP, determined mainly by the estimate of staff turnover per year during the period. For each exposure therefore, if an AF has been based on independent estimates of numbers exposed, the table of results includes the point estimate of numbers employed, the adjustment factor for CAREX if applicable, the staff turnover estimate, and the resulting estimate of numbers ever exposed during the REP. Other estimates used in the calculations that remain constant across exposures (unless otherwise stated) are given below:

- Number of years in REP = 40

- Proportion in the workplace ever exposed is set to one, i.e. all are assumed to be exposed, in the absence of more detailed information. Where sources other than CAREX are used for the point estimate of numbers exposed, such as the LFS or Census of Employment, a precise as possible definition of workers exposed is sought.

- Numbers ever of working age during the target REP = 19.4 million men, 21.0 million women. This is the denominator for the proportion of the population exposed, and is based on population estimates by age cohort in the target year.

- Total deaths from cancer of the bladder in GB in 2005 = 3039 for men aged 25+ (2758 England and Wales and 281 Scotland), 1603 for women aged 25+ (1427 England and Wales and 176 Scotland).

- Total registrations for cancer of the bladder in GB in 2004 = 7020 for men aged 25+ (5799 England, 663 Wales and 558 Scotland), 2858 for women aged 25+ (2333 England, 252 Wales and 273 Scotland).

Attributable numbers are estimated by multiplying the AF by the total number of cancers in GB. Only cancers, which could have been initiated during the risk exposure period are counted, taking normal

retirement age into account. Therefore for solid tumour cancers, total deaths or registrations recorded at all adult ages (25+) are used to estimate attributable numbers, and for short latency cancers, deaths and registrations for ages 15-84 for men and 15-79 for women are used.

For each agent where data on worker numbers are only available for men and women combined (CAREX data), the assumed percentage of men is given in addition to the numbers exposed. The allocation to high and low, and occasionally negligible, exposure level categories, or division into separate exposure scenarios, is also included in these tables. Where no separate estimate of relative risk is available for the low exposure level category, an estimate is based on an average of the high/low ratios for cancer-exposure pairs for which data were available.

Full details of the derivation of the above factors and the methods of calculating AF are published separately. Unless otherwise stated, Levin's method is used for estimates using independent estimates of numbers exposed, and Miettinen's method is used for study based estimates. A summary of the methodology is given in the Statistical Appendix.

3.2 MINERAL OILS

(a) Risk estimate

NIOSH conclude in their review (NIOSH, 1998) that the association between bladder cancer and metalworking fluids exposure is well supported by one large and well designed case-control study (Silverman *et al*, 1989a, Silverman *et al*, 1989b) as well as several other studies conducted in different geographical locations, all of which controlled for smoking. Although none of the cohort studies found a significant increased risk, it has been observed that mortality studies may not be suitable for detecting elevated risks for cancers with high survival rates (Schulte *et al*, 1985, Steenland *et al*, 1988).

A recent case-control study of bladder cancer cases in Spain did not support an increased risk in the textile industry (Serra *et al*, 2000). A meta-analysis of epidemiological studies for industry workers published after 1990 indicated that, after inclusion of more recent studies the PRR for bladder cancer remained significant only in dyers (Mastrangelo *et al*, 2002). IARC have concluded there is limited evidence that working in the textile manufacturing industry entails a carcinogenic risk, the evaluation being based mainly on findings among dyers (IARC, 1990). However, these workers may be exposed to mineral oils and other bladder carcinogens in dyes.

Tolbert (1997) reviewed the relationship between mineral oil and cancer, covering metal machining, print press operating, and cotton and jute spinning. He noted a number of case-control studies that showed a positive association between bladder cancer and work as a machinist. An overall RR for bladder cancer from exposure to mineral oils (taken as a weighted average across the case-control and population based studies from Tolbert's review), which reflected incidence as well as mortality due to bladder (plus other urinary organ) cancers (Annex 1), is 1.39 (95%CI=1.20-1.61). This assumed a random effects model due to significant heterogeneity across study results (using the test for heterogeneity Q = 98.24, p < 0.0001). In the present study this estimate has been used for the high exposure to MWF categories. Due to the absence of sufficient dose-response data the risk estimate for low exposure was based on a harmonic mean of the high/low ratios across all other cancer-exposure pairs in the overall project where data were available. As this was less than 1 the RR for low exposure has been set to 1.

Numbers exposed

NIOSH list the following industries as having the largest number of exposed workers in the US, with their SIC codes: 35-Machinery (except electrical), 34-Fabricated metal products, 37-Transportation equipment. The numbers of machinists exposed to mineral oils (metal working fluids) in Great Britain are shown in Table 12. Exposure level (H) indicates jobs with known exposure to soluble MWF in large droplet form. As noted above any risk for textile workers is limited to dyers exposed to aromatic amines, covered under that exposure. Increases in printing workers due to mineral oils have also been

identified in several studies (Tolbert 1997). However, Tolbert suggested that the primary constituent that distinguishes newspaper printing ink from metalworking fluids is carbon black, which is known to be contaminated with benzo(a)pyrene and other polycyclic aromatic hydrocarbons. Printing workers have thus been excluded from any estimation. In addition, industry sectors where most of the exposure to MWF is thought to be dermal have also been excluded (motor mechanic (auto engines), maintenance fitters (aircraft engines) and office machinery mechanics and their foremen).

Table 12. Numbers of workers exposed to mineral oils according to LFS 1979

SIC code	Description	Male	Female	Total	Exposure Level
LFS 1979					
111.1	Foremen of Press and Machine Tool Setters	2,164	-	2,164	L
111.2	Foremen of other Centre Lathe Turners	736	-	736	L
111.3	Foremen of Machine Tool Setter Operators	581	-	581	L
111.4	Foremen of Machine Tool Operators	8,947	252	9,199	L
111.5	Foremen of Press Stamping and Automatic Machine Operators	1,498	-	1,498	L
111.6	Foremen of Metal Polishers	265	-	265	L
111.7	Foremen of Fettlers Dressers	-	-	-	L
111.8	Foremen of Shot Blasters	-	-	-	L
112.1	Press and Machine Tool Setters	64,157	740	64,897	H
112.2	Other Centre Lathe Turners	49,774	-	49,774	H
112.3	Machine Tool Setter Operators	10,818	232	11,050	H
112.4	Machine Tool Operators	335,097	50,424	385,521	H
113.1	Press Stamping and Automatic Machine Operators	34,002	18,281	52,283	H
113.2	Metal Polishers	11,112	1,425	12,537	L
113.3	Fettlers Dressers	12,391	1,619	14,010	L
114.1	Foremen of Toolmakers Tool Fitters Markers-Out	4,319	-	4,319	L
114.2	Foremen of Precision Instrument Makers and Repairers	969	-	969	L
114.3	Foremen of Watch and Chronometer Makers and Repairers	-	-	-	L
114.4	Foremen of Metal Working Production Fitters and Fitter/Machinists	27,544	-	27,544	L
115.0	Toolmakers Tool Fitters Markers-Out	92,886	510	93,396	H
116.1	Precision Instrument Makers and Repairers	28,071	1,667	29,738	L
116.2	Watch and Chronometer Makers and Repairers	6,527	225	6,752	L
117.0	Metal Working Production Fitters and Fitter/Machinists	546,544	6,933	553,477	L
131.8	Shot Blasters	6,049	-	6,049	L
160.5	Labourers and Other Unskilled Workers in Foundries in Engineering	15,469	567	16,036	L
160.6	Labourers and Other Unskilled Workers in Engineering and Allied Trades	21,276	259	21,535	L
TOTAL: excluding dermal exposure only (114.5, 114.6, 114.7, 118.1, 118.2, 119.0)		**1281196**	**83134**	**1364330**	

(b) **AF calculation:** For bladder cancer related to exposure to mineral oils the estimated total (male and female) attributable fraction is 2.81% (95%CI= 1.47-4.31), which equates to 131 (95%CI=68-200) deaths, and 296 (95%CI=155-452) registrations. The estimated AF for men is 3.92%% (95%CI=2.05-5.98) resulting in 119 (95%CI=62-182) deaths and 275 (95%CI=144-420) registrations; and for women the AF is 0.73% (95%CI=0.38-1.13) resulting in 12 (95%CI=6-18) deaths and 21 (95%CI=11-32) registrations (Table 13).

Table 13 Summary results for occupational exposure to mineral oils

	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
										AF	LL	UL	AN	LL	UL	AR	LL	UL
Men	Tolbert (1997)	B	C-E	1	29817	1.4	0.09	103019	0.0053	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	All		29817			103019	0.0053	0.0000	0.0000	0.0000	0	0	0	0	0	0
		H	C-E	1.39	586734	1.4	0.09	2027188	0.1045	0.0392	0.0205	0.0598	119	62	182	275	144	420
		H	All		586734			2027188	0.1045	0.0392	0.0205	0.0598	119	62	182	275	144	420
		L	C-E	1	664645	1.4	0.09	2296374	0.1184	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		664645			2296374	0.1184	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		1281196			4426581	0.2282	0.0392	0.0205	0.0598	119	62	182	275	144	420
Women	Tolbert (1997)	B	C-E	1	3044	1.5	0.14	17072	0.0008	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	All		3044			17072	0.0008	0.0000	0.0000	0.0000	0	0	0	0	0	0
		H	C-E	1.39	70187	1.5	0.14	393639	0.0187	0.0073	0.0038	0.0113	12	6	18	21	11	32
		H	All		70187			393639	0.0187	0.0073	0.0038	0.0113	12	6	18	21	11	32
		L	C-E	1	9903	1.5	0.14	55540	0.0026	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		9903			55540	0.0026	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		83134			466252	0.0222	0.0073	0.0038	0.0113	12	6	18	21	11	32

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.3   AROMATIC AMINES

(a) Risk estimate

There are several studies that suggest that excess risks of urothelial cancer are associated with textile and leatherwork. Their relevant exposures have not been identified confidently, but exposure to dyes (including some benzidine-based dyes) is a likely explanation. Sorahan *et al.* (1998) investigated the role of occupational exposures in the risk of developing urothelial cancer, in a hospital based case-control study in the West Midlands. Smoking-adjusted RRs of >2.0 were obtained for seven occupations. The groups are shown in Table 14. The RRs used for four are: manufacture of dyestuffs (D) RR=2.61 (95%CI=0.98-7.00), leather work (L) RR=2.51, (95%CI=1.44-4.35), cable manufacturing industry (C) RR=2.46 (95%CI=1.20-5.04), textile printing and dyeing (T) RR=2.32, (95%CI=0.98-5.45). In the present study, Sorahan's RR estimates for the manufacture of rubber products (R) RR=1.89 (95%CI=1.34-2.66), plastics (P) RR=1.73 (95%CI=1.17-2.55) and organic chemicals (O) RR=1.70 (95%CI=1.05-2.76) are used for industrial exposure to MOCA.

Sorahan *et al.* (1998) also gave an estimate of RR for medical and nursing occupations (MN) R=1.62 (95%CI=1.03-2.55) and laboratory technicians (LT) RR=1.05 (95%CI=0.60-1.86) and these figures have been used for the lower level exposures in the CAREX data (Table 14).

(b) Numbers exposed

The number exposed to benzidine-based dyes and 2-Naphthylamine, benzidine, chloro-ortho-toluidine and MOCA, substances covered by CAREX, are shown in Table 14. The estimated proportions of men to women in the CAREX data for the service industry sectors is taken as that for 'associate professional and technical occupations' in the 1991 Census. Workers in the manufacturing industries can be assumed to be "Blue collar" Skilled trades, shop floor and transport operatives: SOC groups 5, 8 and 9.

Table 15 shows the number of people employed in the cable, dyestuffs, textile and leather industries where there is historical exposure to aromatic amines. These occupations were identified by Sorahan and colleagues (1998). Exposure in the rubber industry, painters, hairdressers and barbers are addressed separately below. For the calculation of AF, CAREX numbers exposed are used for the limited remaining industrial exposures (to MOCA and benzidine based dyes), and for laboratory technicians and medical and nursing occupations, and employment estimates from the 1971 Census of Employment for the other historical exposures in manufacturing industry. It has been assumed that exposure in manufacturing industry for chemicals not covered in CAREX ceased in 1962, when industrial use of benzidine was banned in the UK (Quinn *et al*, 2005), so that the number exposed is estimated for 1955-1962 only. 2-naphthylamine was banned in 1949.

Table 14. Numbers of workers exposed to benzidine-based dyes and 2-Naphthylamine, benzidine, chloro-ortho-toluidine and MOCA according to CAREX in 1990-1993

Industry	CAREX Data 1990-1993			
	Number Exposed	Number in Industry	% Male	RR used
Benzidine-based dyes				
Other manufacturing industries	18	59,375	76%	D
Research and scientific institutes	1,760	91,100	44%	LT
2-Naphthylamine				
Education services	244	1,455,875	44%	LT
Research and scientific institutes	88	91,100	44%	LT
Medical, dental, other health and veterinary services	67	1,435,675	44%	MN
Benzidine				
Education services	609	1,455,875	44%	LT
Research and scientific institutes	352	91,100	44%	LT
Medical, dental, other health and veterinary services	247	1,435,675	44%	MN
Para-Chloro-ortho-toluidine and its strong acid salts				
Education services	30	1,455,875	44%	LT
Research and scientific institutes	22	91,100	44%	LT
Medical, dental, other health and veterinary services	30	1,435,675	44%	MN
4,4'-Methylene bis(2-chloroaniline) (MOCA)				
Manufacture of industrial chemicals	13	130,000	76%	O
Manufacture of rubber products	221	53,025	76%	R
Manufacture of plastic products not elsewhere classified	202	136,900	76%	P
Research and scientific institutes	88	91,100	44%	LT
Total	**3,991**			

Table 15. Number of workers employed in jobs exposing them to aromatic amines for 1971 (source Census of Employment), 1979 and 2003 (source LFS)

SIC Code	Description	Numbers			
		Men	Women	Total	Exposure level, RR used
1971					
362	Insulated wires and cables	34,325	12,132	46,457	C
277	Dyestuffs and pigments	16,576	3,138	19,714	D
893	Dry cleaning, job dyeing etc	7,665	24,295	31,960	D
412-429	Textile industry	276,964	265,804	542,768	
423	Textile finishing	35,584	15,317	50,901	T
429	Other textile industries	17,258	6,365	23,623	T
431	Leather (tanning and dressing)	16,449	4,364	20,813	L
	Total	**127,857**	**65,611**		

(c) AF calculation

It is acknowledged that applying relative risk from a population-based study to the LFS numbers exposed may underestimate the AF for these exposures. However, the numbers affected and therefore AFs are small and alternative industry-based studies were not available for all the relevant industry sectors or for the large number employed in relevant manufacturing areas but not considered according to CAREX to be exposed. For the purposes of this study as the use of benzidine ceased in 1962, the

relevant exposure period in the cable manufacturing, dyestuffs, textile printing and dyeing and leatherwork industries is taken to be from 1955-1962 only; for the other exposures included in the CAREX data the period 1956-1995 was used.

For bladder cancer related to exposures to aromatic amines the estimated total (male and female) attributable fraction is 0.67% (95%CI=0.30-1.49), which equates to 31 (95%CI=14-69) deaths, and 66 (95%CI=30-147) registrations. The estimated AF for men is 0.70% (95%CI=0.34-1.51) resulting in 21 (95%CI=10-46) deaths and 49 (95%CI=24-106) registrations; and for women the AF is 0.60% (95%CI=0.24-1.44) resulting in 10 (95%CI=4-23) deaths and 17 (95%CI=7-41) registrations (Table 16).

Table 16 Summary results for occupational exposure to aromatic amines

	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	AF	LL	UL	AN	LL	UL	AR	LL	UL
				Data		**Calculations**				**Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval**			**Attributable Deaths**			**Attributable Registrations**		
Men	Sorahan et al. (1998)	A	C-E	1.7	10	1.4	0.09	48	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		A	All		10			48	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	C-E	1.89	168	1.4	0.09	812	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		B	All		168			812	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		C	C-E	1.73	154	1.4	0.09	743	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		C	All		154			743	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		D	C-E	2.61	14	1.4	0.09	66	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		D	All		14			66	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		E	G-Q	1.05	1405	0.9	0.11	5283	0.0003	0.0000	0.0000	0.0002	0	0	1	0	0	2
		E	All		1405			5283	0.0003	0.0000	0.0000	0.0002	0	0	1	0	0	2
		F	G-Q	1.62	151	0.9	0.11	569	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		F	All		151			569	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		G	C-E	2.46	34325	1.4	0.09	25271	0.0013	0.0019	0.0003	0.0052	6	1	16	13	2	37
		G	All		34325			25271	0.0013	0.0019	0.0003	0.0052	6	1	16	13	2	37
		H	C-E	2.61	24241	1.4	0.09	17847	0.0009	0.0015	0.0000	0.0054	4	0	16	10	0	38
		H	All		24241			17847	0.0009	0.0015	0.0000	0.0054	4	0	16	10	0	38
		I	C-E	2.32	52842	1.4	0.09	38904	0.0020	0.0026	0.0000	0.0088	8	0	27	18	0	62
		I	All		52842			38904	0.0020	0.0026	0.0000	0.0088	8	0	27	18	0	62
		J	C-E	2.51	16449	1.4	0.09	12110	0.0006	0.0009	0.0003	0.0021	3	1	6	7	2	15
		J	All		16449			12110	0.0006	0.0009	0.0003	0.0021	3	1	6	7	2	15
		All	All		129758			101654	0.0052	0.0070	0.0034	0.0151	21	10	46	49	24	106
Women	Sorahan et al. (1998)	A	C-E	1.7	3	1.5	0.14	26	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		A	All		3			26	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0

Table 16 Summary results for occupational exposure to aromatic amines

Risk Estimate Reference	Exposure	Main Industry Sector[1]	Data RR[2]	Data Ne[3]	Calculations Carex adj[4]	Calculations TO[5]	Calculations NeREP[6]	PrE[7]	Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval AF	LL	UL	Attributable Deaths AN	LL	UL	Attributable Registrations AR	LL	UL
	B	C-E	1.89	53	1.5	0.14	446	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	B	All		53			446	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	C	C-E	1.73	48	1.5	0.14	408	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	C	All		48			408	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	D	C-E	2.61	4	1.5	0.14	36	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	D	All		4			36	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
	E	G-Q	1.05	1788	0.8	0.15	8562	0.0004	0.0000	0.0000	0.0003	0	0	1	0	0	1
	E	All		1788			8562	0.0004	0.0000	0.0000	0.0003	0	0	1	0	0	1
	F	G-Q	1.62	193	0.8	0.15	922	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
	F	All		193			922	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
	G	C-E	2.46	12132	1.5	0.14	15490	0.0007	0.0011	0.0001	0.0029	2	0	5	3	0	8
	G	All		12132			15490	0.0007	0.0011	0.0001	0.0029	2	0	5	3	0	8
	H	C-E	2.61	27433	1.5	0.14	35025	0.0017	0.0027	0.0000	0.0099	4	0	16	8	0	28
	H	All		27433			35025	0.0017	0.0027	0.0000	0.0099	4	0	16	8	0	28
	I	C-E	2.32	21682	1.5	0.14	27682	0.0013	0.0017	0.0000	0.0058	3	0	9	5	0	17
	I	All		21682			27682	0.0013	0.0017	0.0000	0.0058	3	0	9	5	0	17
	J	C-E	2.51	4364	1.5	0.14	5572	0.0003	0.0004	0.0001	0.0009	1	0	1	1	0	3
	J	All		4364			5572	0.0003	0.0004	0.0001	0.0009	1	0	1	1	0	3
	All	All		67701			94170	0.0045	0.0060	0.0024	0.0144	10	4	23	17	7	41

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.4 PAINTERS

(a) Risk estimate

Bosetti *et al.* (2005) systematically reviewed all epidemiological studies on bladder cancer in painters published since the IARC (1989b) monographs, after which paint technology and its exposure has changed. They reviewed all original cohort and case-control investigations on bladder cancer risk in painters between 1989 and 2004 from Europe and the USA, including one from the UK. Four cohort studies on the incidence of bladder cancer among painters, had a pooled RR of 1.10 (95%CI=1.03-1.18), based on 893 cases observed. For mortality, the pooled RR was 1.23 (95%CI=1.11-1.37), based on 370 deaths. The pooled RR from 14 case-control studies and a pooled-analysis of other 11 case-control studies was 1.35 (95%CI=1.19-1.53) based on 465 cases exposed. Overall, the RR from all epidemiological studies was 1.17 (95%CI=1.11-1.27). Thus, recent epidemiological evidence indicates a moderate excess risk for bladder cancer in painters. This overall RR is used for the estimation of AF in the present study.

(b) Numbers exposed

The number of painters employed in the UK according to the LFS is given in Table 17.

Table 17. Numbers of workers employed as painters in the UK according to the Labour Force Survey (1979 and 2003)

SIC Code	Description	Numbers			
		Men	**Women**	**Total**	**Grand total**
1979					
1332.2	Foremen of Coach Painters (So Described)	0	0	0	
132.3	Foremen of Other Spray Painters	1,219	0	1,219	
132.4	Foremen of Painters & Decorators	5,066	277	5,343	
133.2	Coach Painters	5,131	0	5,131	
133.3	Other Spray Painters	44,660	3,027	47,687	
133.4	Painters & Decorators	194,706	2,291	196,997	
138.12	Painting Assembling & Related Occupations, Nec	10,346	17,524	27,870	
Total					**284,247**
2002-2004					
5234	Vehicle Spray Painters	25,272	325	25,597	
5323	Painters & Decorators	144,429	2,562	146,991	
24.301&3	Paint, Varnish, Mastic, Sealant Manufacture	15,452	4,255	19,707	
Total					**192,295**

(c) AF calculation

For bladder cancer related to work as a painter the estimated total (male and female) attributable fractions is 0.67% (95%CI=0.44-0.91), which equates to 31 (95%CI=20-42) deaths, and 71 (95%CI= 47-97) registrations. The estimated AF for men is 0.97% (95%CI=0.64-1.32) resulting in 30 (95%CI= 19-40) deaths and 68 (95%CI= 45-92) registrations; and for women the AF is 0.11% (95%CI= 0.07-0.14) resulting in 2 (95%CI=1-2) deaths and 3 (95%CI=2-4) registrations (Table 18).

Table 18 Summary results for occupational exposure as a painter

	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
							Data / **Calculations**			AF	LL	UL	AN	LL	UL	AR	LL	UL
Men	Bosetti *et al.* (2005)	H	C-E	1.17	61356	1.4	0.09	211987	0.0109	0.0018	0.0012	0.0025	6	4	8	13	8	18
		H	F	1.17	199772	1	0.12	906826	0.0467	0.0079	0.0052	0.0107	24	16	33	55	36	75
		H	All		261128			1118813	0.0577	0.0097	0.0064	0.0132	30	19	40	68	45	92
		All	All		261128			1118813	0.0577	0.0097	0.0064	0.0132	30	19	40	68	45	92
Women	Bosetti *et al.* (2005)	H	C-E	1.17	20551	1.5	0.14	115259	0.0055	0.0009	0.0006	0.0013	1	1	2	3	2	4
		H	F	1.17	2568	0.67	0.15	15371	0.0007	0.0001	0.0001	0.0002	0	0	0	0	0	0
		H	All		23119			130630	0.0062	0.0011	0.0007	0.0014	2	1	2	3	2	4
		All	All		23119			130630	0.0062	0.0011	0.0007	0.0014	2	1	2	3	2	4

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.5   RUBBER INDUSTRY

(a) Risk estimate

Veys (2004a) followed a composite cohort of 6,450 men employed at a large tyre factory either during inadvertent exposure to the human bladder carcinogen beta-naphthylamine, or just after it. A statistically significant elevated risk of bladder cancer for the exposed workforce was evident, but this reversed when the carcinogen was removed from processing in October 1949.

The Kogevinas *et al.* study (1998) is more recent as it reviews studies published after 1982, including 12 cohort studies in nine countries that examined distinct populations of workers in the rubber industry, seven industry-based nested case-control studies, 48 community-based case-control studies in 16 countries, and 23 studies based on administrative data that reported risks for employment in the rubber industry. An excess risk of bladder cancer was found in seven cohort studies (Bernardinelli *et al*, 1987; Gustavsson *et al*, 1986; Holmberg *et al*, 1983; Negri *et al*, 1989; Norseth *et al*, 1983; Solionova and Smulevich, 1993; Szeszenia-Dabrowska *et al*, 1991; Weiland *et al*, 1996). Risk of workers first employed after the 1960s was examined in three studies. A twofold excess risk was found in the largest study (SMR=2.14, 95%CI=1.07-3.84; 11 deaths). Excess risks with ORs ranging from 1.5 to 5.7, after adjustment for potential confounding factors such as smoking, were found in 11 case-control studies.

A cohort of 2160 male production workers at a UK factory manufacturing chemicals for the rubber industry (Sorahan *et al*, 2000) found significant excess mortality from cancer of the bladder in the 605 study subjects potentially exposed to one or more of four pre-specified chemicals investigated (SMR=2.77, 95%CI=1.27-5.26). However, interpretation is difficult because of small numbers in the exposed sub-cohort, relatively crude measures of exposure assessment for the four chemicals under study, and presence of unconsidered potential chemical confounders.

(b) Numbers exposed

The number of workers employed in the UK rubber industry according to the Census of Employment and the LFS is given in Table 19.

Table 19. Numbers of workers employed in rubber industry in the UK according to the Census of Employment (1971) and the Labour Force Survey (1979 and 2003)

SIC Code	Description	Numbers			
		Men	**Women**	**Total**	**Grand total**
1971					
	Rubber	86,882	28,883	115,765	
2002-2004					
24.17	Primary synthetic rubber	734	53	787	
25.11	Rubber tyres etc manufacture	9,012	1,764	10,776	
25.12	Rubber tyres retreading etc	2,021	343	2,364	
25.13	Other rubber products manufacture	18,741	4,489	23,230	
8115	Rubber process operatives	11,531	1,995	13,526	
					50,683

(c) AF calculation

The evidence suggests that the risk ceased in the UK rubber industry after 1950. Therefore no AF has been calculated.

3.6   POLYCYCLIC AROMATIC HYDROCARBONS (PAH):

(a) Risk estimate

In their population-based case-control study, Bonassi *et al.* (1989) created a job-exposure matrix to assess potential lifetime occupational exposure to PAH. This grouped occupations based on IARC (IARC, 1984a; IARC, 1984b; IARC, 1984c; IARC, 1985) and Lindstedt's review (1982) of occupational exposure to PAH that were considered as sharing a definite exposure to PAH. The occupations were coke worker (general), mechanic, railroad worker (machinist), glass worker (foundry), road mender, stoker (in distillery), welder, coalman, and mason (in a kiln). Therefore, based on this, the PAH risk estimate includes workers employed in coal tars and pitches, aluminium production, coal gasification, and coke production. Their findings suggested a clear confounding effect associated with occupational exposure to aromatic amines and a weak confounding effect due to differences in smoking habits. Subjects considered as sharing a "definite exposure to PAH" showed an increased risk even after adjustment for cigarette smoking and exposure to aromatic amines (OR=2.14, 95%CI=0.82-5.60). No elevation in risk was found for the category "possible exposure to PAH" (OR=1.05, 95%CI=0.45-2.44), thus indicating that PAH is a risk factor for bladder cancer.

Kogevinas *et al.* (2003) combined data from 11 case-control studies conducted between 1976 and 1996 in six European countries. They ranked occupations according to their occupation. Industries entailing a high risk included salt mining, manufacture of carpets, paints, plastics and industrial chemicals. An increased risk was found for exposure to PAHs (OR for highest exposure tertile=1.23, 95%CI=1.07–1.4, just above 1 in the lowest exposure tertile).

Boffetta *et al.* (1997) reviewed the cancer risk from occupational and environmental exposure to PAHs, in aluminium production, coal gasification, coke production, iron and steel foundry, diesel engine exhaust exposure, and workers exposed to coal tars and related products, which included 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 diesel exposure (for which AFs are calculated separately), and coke production (for which no evidence was found for a raised risk of bladder cancer), have been used to calculate an inverse variance weighted combined estimate of RR (random effects model; Q test indicated significant heterogeneity, Q = 48.75, p <0.0001). In the present study we have estimated the resulting RR based on 26 studies as 1.44 (95%CI=1.2-1.7), which is used for the 'high exposed' group in manufacturing industry from the CAREX data. The combined RR for only those studies (10) where incident cases were taken into account was lower, at 1.3 (95%CI=1.1–1.6). The RR based on mortality plus incidence studies has been used. It is not stated whether the review RRs were adjusted for smoking.

Estimates of a combined OR from population based case control studies covered in the same review (again excluding diesel exposures and drivers, and mineral oils (cutting fluids)) result in lower relative risks for broader based definitions of workplace exposure, 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 random effects model). The RR for the 'low exposed' group has been set to 1 to reflect these results, and the lowest tertile group from Kogevinas *et al.* (2003).

(b) Numbers Exposed

Table 20 gives the numbers of workers exposed to PAHs by industry according to CAREX for 1990-1993. Numbers are allocated between men and women in construction and in jobs in the service sector assuming that all the exposed were employed in "blue collar" occupations (SOC major groups 5, 8 and 9).

Table 20. Numbers of workers exposed to PAH according to CAREX in 1990-1993

Industry	CAREX Data 1990-1993		
	Number Exposed	Number in Industry	Exposure Level
Crude petroleum and natural gas production	888	53,300	L
Metal ore mining	103	1,225	L
Other mining	217	28,150	L
Food manufacturing	970	414,150	L
Tobacco manufacture	102	9,950	L
Manufacture of wearing apparel, except footwear	8,444	189,500	L
Manufacture of leather and products of leather or of its substitutes	214	16,825	L
Manufacture of footwear	130	38,500	L
Manufacture of wood and wood and cork products, except furniture	515	132,975	L
Manufacture of paper and paper products	289	119,050	L
Printing, publishing and allied industries	105	354,750	L
Manufacture of industrial chemicals	1,006	130,000	H
Petroleum refineries	536	18,075	L
Manufacture of miscellaneous products of petroleum and coal	82	1,125	H
Manufacture of rubber products	3,848	53,025	L
Manufacture of pottery, china and earthenware	1,362	54,450	L
Manufacture of glass and glass products	818	43,275	L
Manufacture of other non-metallic mineral products	2,073	70,875	H
Iron and steel basic industries	4,913	48,425	H
Non-ferrous metal basic industries	1,626	79,325	H
Manufacture of fabricated metal products, except machinery and equipment	6,108	292,200	L
Manufacture of machinery except electrical	4,106	692,275	L
Manufacture of transport equipment	9,292	456,900	L
Electricity, gas and steam	4,996	140,975	L
Construction	4,511	1,753,450	L
Wholesale and retail trade and restaurants and hotels	4,855	4,459,525	L
Land transport	9,348	671,050	L
Water transport	171	68,175	L
Services allied to transport	692	180,725	L
Public administration and defence	250	1,557,875	L
Sanitary and similar services	9,442	274,225	L
Personal and household services	24,273	686,750	L
Total	**106,285**	**13,091,075**	
Main Industry Sector		**% Male**	
Agriculture, hunting and forestry; fishing High	0		
Low	0		
Mining/quarrying, electricity/gas/steam, High	9700	76%	
manufacturing industry Low	43043		
Construction High	0		
Low	4511	99%	
Service industries High	0		
Low	49031	65%	

(c) AF calculation

Workers employed in 'manufacture of wearing apparel, except footwear' in the period 1955 – 1962 have been excluded from the estimate of numbers ever exposed to avoid overlap with aromatic amines to which they may also have been exposed during this period (see Section 3.3).

For bladder cancer related to exposure to PAHs **t**he estimated total (male and female) attributable fraction is 0.07% (95%CI= 0.03-0.11), which equates to 3 (95%CI 1-5) deaths, and 7 (95%CI=3-11) registrations. For men the estimated AF is 0.08% (95%CI= 0.04-0.13) resulting in 2 (95%CI=1-4) deaths and 6 (95%CI= 3-9) registrations; and for women the AF is 0.04% (95%CI= 0.02-0.07) resulting in 1(95%CI= 0-1) death and 1(95%CI=1-2) registration (Table 21).

Table 21 Summary results for occupational exposure to PAHs

	Risk Estimate Reference	Exposure	Main Industry Sector[1]	Data RR[2]	Data Ne[3]	Calc Carex adj[4]	Calc TO[5]	Calc NeREP[6]	Calc PrE[7]	Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval AF	LL	UL	Attributable Deaths AN	LL	UL	Attributable Registrations AR	LL	UL
Men	Boffetta *et al.* (1997)	H	C-E	1.44	7372	1.4	0.09	35659	0.0018	0.0008	0.0004	0.0013	2	1	4	6	3	9
		H	All		7372			35659	0.0018	0.0008	0.0004	0.0013	2	1	4	6	3	9
		L	C-E	1	32783	1.4	0.09	158574	0.0082	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	F	1	4466	1	0.12	20272	0.0010	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	31870	0.9	0.11	119835	0.0062	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		69119			298680	0.0154	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		76491			334339	0.0172	0.0008	0.0004	0.0013	2	1	4	6	3	9
Women	Boffetta *et al.* (1997)	H	C-E	1.44	2328	1.5	0.14	19585	0.0009	0.0004	0.0002	0.0007	1	0	1	1	1	2
		H	All		2328			19585	0.0009	0.0004	0.0002	0.0007	1	0	1	1	1	2
		L	C-E	1	10260	1.5	0.14	86313	0.0041	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	F	1	45	0.67	0.15	181	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	17161	0.8	0.15	82173	0.0039	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		27466			168667	0.0080	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		29794			188252	0.0090	0.0004	0.0002	0.0007	1	0	1	1	1	2

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.7   DIESEL ENGINE EXHAUST

(a) Risk estimate

Boffetta and Silverman (2001) reviewed 35 epidemiological studies from Europe, USA and Canada published between 1977 and 1998, which provided information on bladder cancer occurrence associated with exposure to DEE. Various types of exposure to DEE have been investigated, ranging from groups of highly exposed workers, such as drivers to workers who were probably exposed. The study concentrated on five occupational groups: railroad workers, garage maintenance workers, truck drivers, and drivers and operators of heavy machines in ground and road construction. They also considered studies providing a classification of exposure to DEE based on a job-exposure matrix or on experts' assessment of individual occupational histories. All but one of the 7 cohort studies included did not control for smoking, all but two of the 16 case-control studies controlled for smoking, and all the 6 studies based on routinely collected data were assumed to have adjusted for smoking. They did not carry out an overall meta-analysis because of the heterogeneity of the results, mainly due to the different definitions of exposure used in the studies. The summary RR for ten studies that considered DEE exposure based on a job exposure matrix or a similar approach was 1.13 (95%CI=1.00-1.27). A positive exposure-response relation was suggested by 10 of the 12 studies that provided relevant information. The summary RR for high DEE exposure was 1.44 (95%CI=1.18-1.76); the summary RR was 1.23 (95%CI=1.12–1.36) for any exposure in the subset of studies from which the high DEE exposure estimate was obtained.

For our estimate of a suitable RR for the calculation of AF, an overall inverse variance weighted average of all RRs from the studies included in Boffetta and Silverman's review that were based on cancer incidence, excluding those for overlapping categories, was calculated as 1.24 (95%CI=1.10-1.41) (random effects model, Q=48.3, p=0.002), which is the value used for the 'high exposed' group. Although Boffetta and Silverman did not offer an overall summary RR, due to the heterogeneity between studies with different definitions of DEE exposure, in the present study the value calculated for all studies (RR=1.18, 95%CI=1.08–1.28) is in line with their observation of an overall RR in the range 1.1–1.3. For the low exposure group, Boffetta and Silverman's meta-analysis RR for the 10 studies that classified exposure according to a JEM or similar was used. They note that although there were a few positive results (three above RR=1.1), most were close to unity. An attempt to reproduce their result from the data provided gave a summary RR (fixed effects model) of 1.04 (95%CI=0.9–1.2) rather than 1.13, and of 1.03 (95%CI=0.84-1.26) when only the 6 incidence studies were taken into account. This latter result was used for the low exposure group.

Two of the 45 results contributing to the overall RRs were for women, and a further 4 were for men and women combined. The overall RR however will be applied to women as well as men.

(b) Numbers exposed

The numbers of workers exposed to DEE according to CAREX in 1990 to 1993 are given in Table 22. Numbers are allocated between men and women in mining and manufacturing and in construction, and in low exposed jobs in the service sector, assuming that all the exposed were employed in 'blue collar' occupations (SOC major groups 5, 8 and 9). However for the service sector, as the large numbers exposed at a high level are all in land transport and its allied services, the numbers have been allocated between men and women only on the basis of those employed as plant and machine operatives (SOC major group 8), which specifically covers those employed as road and other transport operatives.

Table 22. Numbers of workers exposed to diesel engine exhaust according to CAREX in 1990-1993

Industry	CAREX Data 1990-1993		
	Number Exposed	Number in Industry	Exposure Level
Crude petroleum and natural gas production	7,530	53,300	L
Metal ore mining	645	1,225	H
Other mining	14,075	28,150	H
Food manufacturing	3,860	414,150	L
Beverage industries	4,660	88,100	L
Tobacco manufacture	12	9,950	L
Manufacture of textiles	1,009	182,000	L
Manufacture of wearing apparel, except footwear	1,120	189,500	L
Manufacture of wood and wood and cork products, except furniture	4,016	132,975	L
ufacture of furniture and fixture, except primary of metal	504	144,325	L
Manufacture of paper and paper products	1,144	119,050	L
Printing, publishing and allied industries	595	354,750	L
Manufacture of industrial chemicals	1,587	130,000	L
Manufacture of other chemical products	1,387	175,175	L
Petroleum refineries	826	18,075	L
Manufacture of miscellaneous products of petroleum and coal	39	1,125	L
Manufacture of plastic products nec	293	136,900	L
Manufacture of glass and glass products	105	43,275	L
Manufacture of other non-metallic mineral products	11,613	70,875	L
Iron and steel basic industries	957	48,425	L
Non-ferrous metal basic industries	2,653	79,325	L
Manufacture of fabricated metal products, except machinery and equipment	3,920	292,200	L
Manufacture of machinery except electrical	3,156	692,275	L
Manufacture of electrical machinery, apparatus, appliances and supplies	1,224	473,750	L
Manufacture of transport equipment	2,574	456,900	L
Manufacture of instruments, photographic and optical goods	154	86,225	L
Other manufacturing industries	326	59,375	L
Electricity, gas and steam	3,795	140,975	L
Water works and supply	4,095	45,175	L
Construction	106,658	1,753,450	H
Wholesale and retail trade and restaurants and hotels	13,487	4,459,525	L
Land transport	158,534	671,050	H
Water transport	12,993	68,175	L
Air transport	6,772	95,700	L
Services allied to transport	14,778	180,725	H
Communication	6,277	459,425	L
Public administration and defence	2,504	1,557,875	L
Sanitary and similar services	4,229	274,225	L
Personal and household services	68,956	686,750	L
Total	473,062	14,874,425	
Main Industry Sector		**%Male**	
Agriculture, hunting and forestry; fishing — High	0		
Low	0		
Mining/quarrying, electricity/gas/steam, — High	14,720	76%	
manufacturing industry — Low	62,197	76%	
Construction — High	106,658	99%	
Low	0		
Service industries — High	173,312	88%	
Low	115,218	65%	

(c) AF calculation

Workers employed in 'manufacture of textiles' and 'manufacture of wearing apparel, except footwear' in the period 1955 to 1962 have been excluded from the estimate of numbers ever exposed to avoid overlap with aromatic amines to which they may also have been exposed during this period (see Section 3.3).

For bladder cancer related to exposure to diesel engine exhaust the estimated total (male and female) attributable fraction is 1.00% (95%CI=0.17-2.03), which equates to 47 (95%CI=8-94) deaths, and 106 (95%CI=18-214) registrations. The estimated AF for men is 1.45% (95%CI=0.26-2.83) resulting in 44(95%CI=8-86) deaths and 102 (95%CI=18-198) registrations; and for women the AF is 0.17% (95%CI=0.00-0.54) resulting in 3 (95%CI=0-9) deaths and 5 (95%CI=0-15) registrations (Table 23).

Table 23 Summary results for occupational exposure to diesel engine exhaust

	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	AF	LL	UL	AN	LL	UL	AR	LL	UL
					Data			Calculations		Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
Men	Boffetta and Silverman (2001)	H	C-E	1.24	14426	1.4	0.09	69777	0.0036	0.0009	0.0002	0.0016	3	1	5	6	1	11
		H	F	1.24	105591	1	0.12	479312	0.0247	0.0058	0.0012	0.0112	18	4	34	41	8	79
		H	G-Q	1.24	152515	0.9	0.11	573469	0.0296	0.0070	0.0014	0.0134	21	4	41	49	10	94
		H	All		272532			1122558	0.0579	0.0137	0.0028	0.0262	42	9	80	96	20	184
		L	C-E	1.03	47997	1.4	0.09	232164	0.0120	0.0004	0.0000	0.0031	1	0	9	2	0	22
		L	G-Q	1.03	74892	0.9	0.11	281600	0.0145	0.0004	0.0000	0.0037	1	0	11	3	0	26
		L	All		122889			513764	0.0265	0.0008	0.0000	0.0068	2	0	21	5	0	48
		All	All		395420			1636322	0.0843	0.0145	0.0026	0.0283	44	8	86	102	18	198
Women	Boffetta and Silverman (2001)	H	C-E	1.24	294	1.5	0.14	2477	0.0001	0.0000	0.0000	0.0001	0	0	0	0	0	0
		H	F	1.24	1067	0.67	0.15	4277	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		H	G-Q	1.24	20797	0.8	0.15	99586	0.0047	0.0011	0.0002	0.0022	2	0	4	3	1	6
		H	All		22158			106340	0.0051	0.0012	0.0002	0.0023	2	0	4	3	1	7
		L	C-E	1.03	15157	1.5	0.14	127510	0.0061	0.0002	0.0000	0.0016	0	0	3	1	0	5
		L	G-Q	1.03	40326	0.8	0.15	193098	0.0092	0.0003	0.0000	0.0024	0	0	4	1	0	7
		L	All		55483			320609	0.0153	0.0005	0.0000	0.0040	1	0	6	1	0	11
		All	All		77642			426949	0.0203	0.0017	0.0000	0.0054	3	0	9	5	0	15

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

3.8   HAIRDRESSERS AND BARBERS

(a) Risk estimate

Czene *et al.* (2003) conducted a follow-up study of a cohort of 45,690 hairdressers from Sweden and analysed all of their malignancies over a period of 39 years (1960-1998). As the formulations of hair dye products have changed over the course of time, it is difficult to assess whether modern hair dyes or gels are still related to some excess risk or whether the elimination of carcinogenic compounds has reduced or eliminated any such risk. The study reports that the highest risk was an SIR of 2.56 for urinary bladder cancer in male hairdressers working in 1960 and followed up during 1960 to 1969. The risk decreased to 1.25 when these hairdressers were followed for the whole period of 1960 to 1998. The decrease of risk over time in men together with no association with urinary bladder cancer in women suggests that the use of brilliantine was the likely cause as noted by others (Guberan and Raymond, 1985; Skov and Lynge, 1994). The SIR for men recorded as a hairdresser at any decennial census between 1960 and 1990 was 1.22 (95%CI=0.98-1.51), and that for women was 1.09 (95%CI=0.81-1.43), not adjusted for smoking. These are the estimates used in the present study to calculate AF.

(b) Numbers exposed

The numbers of hairdressers and barbers according to the LFS for 2003 are given in Table 24.   The numbers for 1979 are used in the estimate of AF.

Table 24. Number of workers employed as hairdressers and barbers in 1979 and in 2002-2004 (source LFS)

Description	Male	Female	Number
1979			
Hairdressers and barbers managers	487	2080	2567
Hairdressers Barbers	22,501	103,498	125,999
Total			128,566
2002-2004			
Hairdressers & beauty salon managers/proprietors			29,558
Hairdressers & barbers			150,974
Hairdressing other beauty treatment			223,084
Total			403,616

(c) AF calculation

For bladder cancer related to work as a hairdresser and barber the estimated total (male and female) attributable fractions is 0.16% (95%CI=0.00-0.63), which equates to 8 (95%CI=0-29) deaths, and 15 (95%CI=0-56) registrations. The estimated AF for men is 0.11% (95%CI=0.00-0.25) resulting in 3 (95%CI=0-8) deaths and 8 (95%CI=0-18) registrations; and for women the AF is 0.27% (95%CI=0.00-1.34) resulting in 4 (95%CI=0-21) deaths and 8 (95%CI=0-38) registrations (Table 25).

Table 25 Summary results for occupational exposure as a hairdresser or barber

|	Risk Estimate Reference	Exposure	Main Industry Sector[1]	RR[2]	Ne[3]	Carex adj[4]	TO[5]	NeREP[6]	PrE[7]	Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
					Data			Calculations		AF	LL	UL	AN	LL	UL	AR	LL	UL
Men	Czene *et al.* (2003)	H	G-Q	1.22	22988	0.9	0.11	96041	0.0050	0.0011	0.0000	0.0025	3	0	8	8	0	18
		H	All		22988			96041	0.0050	0.0011	0.0000	0.0025	3	0	8	8	0	18
		All	All		22988			96041	0.0050	0.0011	0.0000	0.0025	3	0	8	8	0	18
Women	Czene *et al.* (2003)	H	G-Q	1.09	105578	0.8	0.15	631937	0.0301	0.0027	0.0000	0.0134	4	0	21	8	0	38
		H	All		105578			631937	0.0301	0.0027	0.0000	0.0134	4	0	21	8	0	38
		All	All		105578			631937	0.0301	0.0027	0.0000	0.0134	4	0	21	8	0	38

1. Specific scenario or main industry code – (Table A1)
2. Relative risks selected from the best study
3. Numbers exposed, allocated to men/women
4. CAREX adjustment factor to mid-REP (Table A1)
5. Staff turnover (TO, Table A1)
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

4   OVERALL ATTRIBUTABLE FRACTION

4.1   EXPOSURE MAP

The exposure map (Figure 1) gives an indication of how exposures overlap in the working population. It illustrates the potential for double counting of the exposed population to occur when an overall AF is calculated, and facilitates strategies to avoid this. For a given cancer, the map entries consist of either an agent (or group of agents such as PAHs), or an exposure scenario (i.e. an industry or occupation in which such exposure occurs). Agents are in plain type, exposure scenarios in italics, from Table 8. Lines joining boxes then indicate where overlap would occur were all the entries in the map simply considered separately – for example, if PAHs and coal tars/pitches were considered separately overlap would occur within foundries and steel mills (these exposure scenarios are indicated in the smaller print, again based on information in Table 8). For substances and occupations shown in dotted boxes a separate AF has not been estimated, as these exposure scenarios are included with another exposure (see Table 11). In addition a separate AF has not been estimated for substances and occupations shown not in bold as these exposure scenarios are included within another exposure.

Figure 1: Bladder cancer exposure map.
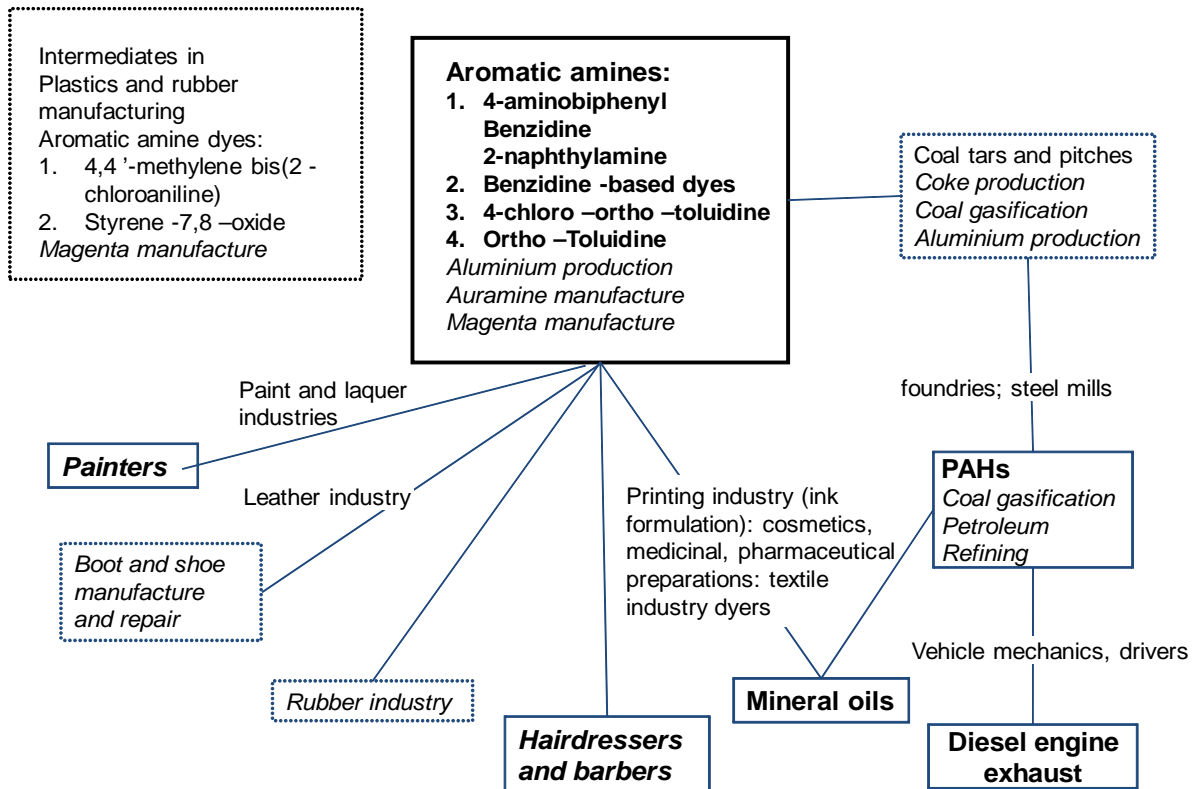
4.2 SUMMARY OF RESULTS

The results are summarised in Table 26 and 27

Table 26 Summary of RR used to calculate AF

Agent	Exposure	RR	LL	UL
Aromatic amines	Cable manufacture	2.46	1.2	5.04
Aromatic amines	Manufacture of dyestuffs	2.61	0.98	7
Aromatic amines	Manufacture of organic chemicals	1.7	1.05	2.76
Aromatic amines	Manufacture of rubber products	1.89	1.34	2.66
Aromatic amines	Laboratory technicians	1.05	0.6	1.86
Aromatic amines	Medical and nursing occupations	1.62	1.03	2.55
Aromatic amines	Textile printing and dyeing	2.32	0.98	5.45
Aromatic amines	Leather work	2.51	1.44	4.35
Aromatic amines	Manufacture of plastics	1.73	1.17	2.55
Diesel engine exhaust	High	1.24	1.01	1.41
Diesel engine exhaust	Low	1.03	0.84	1.26
Hairdressers and barbers	High	1.22	0.98	1.51
Hairdressers and barbers	Low	1.09	0.81	1.43
Mineral oils	Low	1	1	1
Mineral oils	Background	1	1	1
Mineral oils	High	1.39	1.2	1.61
PAHs	High	1.44	1.2	1.74
PAHs	Low	1	1	1
Painters	High	1.17	1.11	1.23

Table 27 Results

Agent	Numbers of Men Ever Exposed	Numbers of Women Ever Exposed	Proportion of Men Ever Exposed	Proportion of Women Ever Exposed	AF Men	MCLL Men	MCUL Men	AF Women	MCLL Women	MCUL Women	Attributable Deaths (Men)	Attributable Deaths (Women)	Attributable Registrations (Men)	Attributable Registrations (Women)
Aromatic amines	101654	94170	0.0052	0.0045	0.0070	0.0034	0.0151	0.0060	0.0024	0.0144	21	10	49	17
Diesel engine exhaust	1636322	426949	0.0843	0.0203	0.0145	0.0026	0.0283	0.0017	0.0000	0.0054	44	3	102	5
Hairdressers and barbers	96041	631937	0.0050	0.0301	0.0011	0.0000	0.0025	0.0027	0.0000	0.0134	3	4	8	8
Mineral oils	4426581	466252	0.22282	0.0222	0.0392	0.0205	0.0598	0.0073	0.0038	0.0113	119	12	275	21
PAHs	334339	188252	0.0172	0.0090	0.0008	0.0004	0.0013	0.0004	0.0002	0.0007	2	1	6	1
Painters	1118813	130630	0.0577	0.0062	0.0097	0.0064	0.0132	0.0011	0.0007	0.0014	30	2	68	3
Totals*					**0.0706**	**0.0457**	**0.0975**	**0.0189**	**0.0128**	**0.0386**	**215**	**30**	**496**	**54**

*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.

4.3 EXPOSURES BY INDUSTRY/JOB

Table 28 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent

Table 28 Industry/occupation codes by agent

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
		1956-62 only							
Aromatic amines	Dyestuffs and pigments	12,204	4,006	7	3	1	0	8	4
Aromatic amines	Insulated wires and cables	25,271	15,490	13	6	3	2	16	7
Aromatic amines	Textile finishing	26,198	19,556	12	5	3	2	16	7
Aromatic amines	Other textile industries	12,706	8,127	6	3	1	1	7	3
Aromatic amines	Leather (tanning and dressing)	12,110	5,572	7	3	1	1	8	3
Aromatic amines	Dry cleaning, job dyeing etc	5,643	31,019	3	1	7	4	10	5
Aromatic amines	**Total**	**101,654**	**94,170**	**49**	**21**	**17**	**10**	**66**	**31**
DEE	Construction	479,312	4,277	41	18	0	0	41	18
DEE	Land transport	524,570	91,095	45	19	3	2	48	21
DEE	Manufacture of other non-metallic mineral products	42,691	23,447	0	0	0	0	1	0
DEE	Other mining	66,720	2,368	6	2	0	0	6	3
DEE	Personal and household services	168,533	115,566	2	1	0	0	2	1
DEE	Services allied to transport	48,899	8,492	4	2	0	0	4	2
DEE	**Total**	**1,636,322**	**426,949**	**102**	**44**	**5**	**3**	**106**	**47**
Hairdressers and barbers	Hairdressers and barbers	94,007	619,487	7	3	8	4	15	7
Hairdressers and barbers	**Total**	**96,041**	**631,937**	**8**	**3**	**8**	**4**	**15**	**8**
Mineral oils	Press and machine tool setters	221,665	4,150	30	13	0	0	30	13
Mineral oils	Other centre lathe turners	171,971	0	23	10	0	0	23	10
Mineral oils	Machine tool setter operators	37,377	1,301	5	2	0	0	5	2
Mineral oils	Machine tool operators	1,157,773	282,800	157	68	15	8	172	76
Mineral oils	Press stamping and automatic machine operators	117,478	102,528	16	7	5	3	21	10

Table 28 Industry/occupation codes by agent

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
Mineral oils	Toolmakers tool fitters markers-out	320,925	2,860	44	19	0	0	44	19
Mineral oils	**Total**	**5,805,643**	**581,140**	**275**	**119**	**21**	**12**	**296**	**131**
Mineral oils	Metal Workers	3,811,384	432,528	231	100	21	12	252	112
Mineral oils	Precision instrument and tool makers (Manufacture of instruments, photographic and optical goods)	436,181	12,210	44	19	0	0	44	19
PAHs	Iron and steel basic industries	18,061	9,920	3	1	1	0	3	2
PAHs	Manufacture of industrial chemicals	3,698	2,031	1	0	0	0	1	0
PAHs	Manufacture of miscellaneous products of petroleum and coal	301	166	0	0	0	0	0	0
PAHs	Manufacture of other non-metallic mineral products	7,621	4,185	1	1	0	0	1	1
PAHs	Non-ferrous metal basic industries	5,977	3,283	1	0	0	0	1	1
PAHs	**Total**	**334,339**	**188,252**	**6**	**2**	**1**	**1**	**7**	**3**
painters	Foremen of coach painters (so described)	0	0	0	0	0	0	0	0
painters	Foremen of other spray painters	4,212	0	0	0	0	0	0	0
Painters	Foremen of painters and decorators	22,996	1,658	1	1	0	0	1	1
Painters	Coach painters	17,728	0	1	0	0	0	1	0
Painters	Other spray painters	154,302	16,977	9	4	0	0	10	4
Painters	Painters and decorators	883,830	13,713	54	23	0	0	54	23
Painters	Painting assembling and related occupations, nec	35,746	98,282	2	1	2	1	4	2
Painters	**Total**	**1,118,813**	**130,630**	**68**	**30**	**3**	**2**	**71**	**31**
Painters	Construction painters	906,826	15,371	55	24	0	0	56	24
Painters	Other painters	211,987	115,259	13	6	3	1	16	7

5 BIBLIOGRAPHY

Alder N, Fenty J, Warren F, Sutton AJ, Rushton L, Jones DR, Abrams KR (2006) Meta-Analysis of Mortality and Cancer Incidence among Workers in the Synthetic Rubber-Producing Industry. *Am J Epidemiol* **164**: 405-420

Alderson MR and Rattan NS (1980) Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. **37**: 85-89

Armstrong B, Tremblay C, Baris D, Theriault G (1994) Lung cancer mortallity and polynuclear aromatic hydrocarbons - a case-cohort study of aluminium production workers in Arvida, Quebec, Canada. *Am J Epidemiol* **139**: 250-262

Armstrong B, Tremblay C, Theriault G (1988) Compensating bladder cancer victims employed in aluminum reduction plants. *J Occup Med* **30**: 771-775

Armstrong BG, Tremblay CG, Cyr D, Theriault GP (1986) Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. *Scand J Work Environ Health* **12**: 486-493

ATSDR (2001) Toxicological Profile for Benzidine.

Baan RA, Straif K, Grosse Y, Secretan MB, El Ghissassi F, Bouvard V, Benbrahim-Talla L, Cogliano VJ (2008) Carcinogenicity of some aromatic amines, organic dyes, and related exposures. *Lancet Oncol* **9**: 322-323

Baxter P and Werner JB (1980) Mortality in the British rubber industries, 1967-76.

Bernardinelli L, de Marco R, Tinelli C (1987) Cancer mortality in an Italian rubber factory. *Br J Ind Med* **44**: 187-191

Bi W, Hayes RB, Feng P, Qi Y, You X, Zhen J, Zhang M, Qu B, Fu Z, Chen M (1992) Mortality and incidence of bladder cancer in benzidine-exposed workers in China. *Am J Ind Med* **21**: 481-489

Boffetta P, Burstyn I, Partanen T, Kromhout H, Svane O, Langard S, Jarvholm B, Frentzel-Beyme R, Kauppinen T, Stucker I, Shaham J, Heederik D, Ahrens W, Bergdahl IA, Cenee S, Ferro G, Heikkila P, Hooiveld M, Johansen C, Randem BG, Schill W (2003) Cancer mortality among European asphalt workers: an international epidemiological study. I. Results of the analysis based on job titles. *Am J Ind Med* **43**: 18-27

Boffetta P, Dosemeci M, Gridley G, Bath H, Moradi T, Silverman D (2001) Occupational exposure to diesel engine emissions and risk of cancer in Swedish men and women. *Cancer Causes Control* **12**: 365-374

Boffetta P, Jourenkova N, Gustavsson P (1997) Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* **8**: 444-472

Boffetta P and Silverman D (2001) A meta-analysis of bladder cancer and diesel exhaust exposure. *Epidemiol* **12**: 125-130

Bolm-Audorff U, Jöckel K, Kilguss B, Pohlabeln H, Siepenkothen T (1993) Bösartige Tumoren der ableitenden Harnwege und Risiken am Arbeitsplatz. Wirtshaftsverlag NW, Bremerhaven. Forschung: Dortmund

Bonassi S, Merlo F, Pearce N, Puntoni R (1989) Bladder cancer and occupational exposure to polycyclic aromatic hydrocarbons. *Int J Cancer* **44**: 648-651

Bosetti C, Boffetta P, La Vecchia C (2007) Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. *Annals Oncol* **18**: 431-446

Bosetti C, Pira E, La Vecchia C (2005) Bladder cancer risk in painters: a review of the epidemiological evidence, 1989-2004. *Cancer Causes Control* **16**: 997-1008

Boyko RW, Cartwright RA, Glashan RW (1985) Bladder cancer in dye manufacturing workers. *J Occup Med* **27**: 799-803

Boyle P and Ferlay J (2005) Cancer incidence and mortality in Europe, 2004. *Ann Oncol* **16**: 481-488

Bray F, Sankila R, Ferlay J, Parkin DM (2002) Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* **38**: 99-166

Brown LM, Moradi T, Gridley G, Plato N, Dosemeci M, Fraumeni Jr JF (2002) Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. *J Occup Environ Med* **44**: 258-264

Brownson RC, Chang JC, Davis JR (1987) Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health* **77**: 1298-1300

Burch JD, Rohan TE, Howe GR, Risch HA, Hill GB, Steele R, Miller AB (1989) Risk of bladder cancer by source and type of tobacco exposure: A case-control study. *Int J Cancer* **44**: 622-628

Burstyn I, Kromhout H, Johansen C, Langard S, Kauppinen T, Shaham J, Ferro G, Boffetta P (2007) Bladder cancer incidence and exposure to polycyclic aromatic hydrocarbons among asphalt pavers. *Occup Environ Med* **64**: 520-526

Calvert GM, Karnik J, Mehler L, Beckman J, Morrissey B, Sievert J, Barrett R, Lackovic M, Mabee L, Schwartz A, Mitchell Y, Moraga-McHaley S (2008) Acute pesticide poisoning among agricultural workers in the United States, 1998-2005. *Am J Ind Med* **51**: 883-898

Calvert GM, Ward E, Schnorr TM, Fine LJ (1998) Cancer risks among workers exposed to metalworking fluids: a systematic review. *Am J Ind Med* **33**: 282-292

Cartwright RA (1983) Historical and modern epidemiological studies on populations exposed to n-substituted aryl compounds. *Environ Health Perspect* **49**: 13-19

Cartwright RA (1982) Occupational bladder cancer and cigarette smoking in West Yorkshire. *Scand J Work Environ Health* **8**: 79-82

Case RAM and Hosker ME (1954) Tumour of the urinary bladder as an occupational disease in the rubber industry in England and Wales. *Br J Prev Soc Med* **8**: 39-50

Case RAM, Hosker ME, McDonald DB, Pearson JT (1954) Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part I. The role of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. *Br J Ind Med* **11**: 75-104

Case RAM and Pearson JT (1954) Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part II. Further

consideration of the role of aniline and of the manufacture of auramine and magenta (fuchsine) as possible causative agents. *Br J Ind Med* **11**: 213-216

Chau N, Bertrand JP, Mur JM, Figueredo A, Patris A, Moulin JJ, Pham QT (1993) Mortality in retired coke oven plant workers. *Br J Ind Med* **50**: 127-135

Chen R and Seaton A (1998) A meta-analysis of painting exposure and cancer mortality. *Cancer Detection Prev* **22**: 533-539

Clapp RW, Howe GK, Jacobs MM (2005) Environmental and Occupational Causes of Cancer.

Claude JC, Frentzel-Beyme RR, Kunze E (1988) Occupation and risk of cancer of the lower urinary tract among men. A case-control study. *Int J Cancer* **41**: 371-379

Clavel J, Mandereau L, Limasset J-, Hemon D, Cordier S (1994) Occupational exposure to polycyclic aromatic hydrocarbons and the risk of bladder cancer: a French case-control study. *Int J Epidemiol* **23**: 1145-1153

Coggon D, Harris EC, Brown T, Rice T, Palmer KT (2009) Occupational mortality in England and Wales, 1991-2000. Office of Public Sector Information, London

Coggon D, Pannett B, Acheson ED (1984) Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. *J Natl Cancer Inst* **72**: 61-65

Cohen SM, Shirai T, Steineck G (2000) Epidemiology and etiology of premalignant and malignant urothelial chenages. *Scand J Urol Nephrol* **205**: 105-115

Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Esteve J (2004) Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer* **90**: 1367-1373

Colt JS, Baris D, Stewart PA, Schned AR, Heaney JA, Mott LA, Silverman D, Karagas M (2004) Occupation and bladder cancer risk in a population-based case-control study in New Hampshire. *Cancer Causes Control* **15**: 759-769

Cooper N and Cartwright RA (2005) Bladder. In Cancer Atlas of the United Kingdom and Ireland 1991-2000. Quinn M, Wood H, Cooper N and Rowan S (eds) pp 39-50. Office for National Statistics: London

Costantini AS, Paci E, Miligi L, Buiatti E, Martelli C, Lenzi S (1989) Cancer mortality among workers in the Tuscan tanning industry. *Br J Ind Med* **46**: 384-388

Costantino JP, Redmond CK, Bearden A (1995) Occupationally related cancer risk among coke oven workers: 30 years of follow-up. *J Occup Environ Med* **37**: 597-604

Czene K, Tiikkaja S, Hemminki K (2003) Cancer risks in hairdressers: assessment of carcinogenicity of hair dyes and gels. *Int J Cancer* **105**: 108-112

Davies GM (1977) A mortality study of coke oven workers in two south Wales integrated steelworks. *Br J Ind Med* **34**: 291-297

De Braud F, Maffezzini F, Vitale V, Bruzzi P, Gatta G, Hendry WF, Sternberg CN (2002) Bladder cancer. *Crit Rev Oncol Hematol* **21**: 89-106

Decarli A, Peto J, Piolatto G, La Vecchia C (1985) Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. *Br J Cancer* **51**: 707-712

Decoufle P (1978) Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. *J Natl Cancer Inst* **61**: 1025-1030

Delzell E (2006) An Update Study of Mortality Among North American Synthetic Rubber Industry Workers. **HEI Research Report 132**

Delzell E, Macaluso M, Cole P (1989) A follow-up study of workers at a dye and resin manufacturing plant. *J Occup Med* **31**: 273-278

Delzell E, Macaluso M, Honda Y, Austin H (1993) Mortality patterns among men in the motor vehicle manufacturing industry. *Am J Ind Med* **24**: 471-484

Doll R (1952) The causes of death among gas-workers with special reference to cancer of the lung. *Br J Ind Med* **9**: 180-185

Doll R, Fisher RE, Gammon EJ, Gunn W, Hughes GO, Tyrer FH, Wilson W (1965) Mortality of gasworkers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. *Br J Ind Med* **22**: 1-12

Doll R and Peto R (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* **66**: 1191-1308

Doll R, Vessey MP, Beasley RWR (1972) Mortality of gas-workers - final report of a prospective study. *Br J Ind Med* **29**: 394-406

Donato F, Monarca S, Marchionna G, Rossi A, Cicioni C, Chiesa R, Colin D, Boffeta P (2000) Mortality from cancer and chronic respiratory diseases among workers who manufacture carbon electrodes. *Occup Environ Med* **57**: 484-487

Dost A, Straughan JK, Sorahan T (2007) A cohort mortality and cancer incidence survey of recent entrants (1982-91) to the UK rubber industry: findings for 1983-2004. *Occup Med* **57**: 186-190

Dresler CM, Leon ME, Straif K, Baan RA, Secretan MB (2006) Reversal of risk upon quitting smoking. **368**: 348-349

Drever F (1995) Occupational Health Decennial Supplement. HMSO: London
Dreyer L, Andersen A, Pukkala E (1997) Avoidable cancers in the Nordic countries. Occupation. *APMIS Suppl* **76**: 68-79

Eisen EA, Bardin J, Gore R, Woskie SR, Hallock MF, Monson RR (2001) Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. *Scand J Work Environ Health* **27**: 240-249

Eisen EA, Tolbert PE, Monson RR, Smith TJ (1992) Mortality studies of machining fluid exposure in the automobile industry. I: a standardized mortality ratio analysis. *Am J Ind Med* **10**: 803-815

Fellows JL, Trosclair A, Adams EK (2002) Annual smoking-attributable mortality, years of potential life lost, and economic costs - United States, 1995-1999. *MMWR* **51**: 300-303

Ferlay J, Bray F, Pisani P, Parkin DM (2001) GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide. (1.0) No. 5.

Frumin E, Velez H, Bingham E, Gillen M, Brathwaite M, LaBarck R (1990) Occupational bladder cancer in textile dyeing and printing workers: six cases and their significance for screening programs. *J Occup Med* **32**: 887-890

Fu H, Demers PA, Costantini AS, Winter P, Colin D, Kogevinas M, Boffetta P (1996) Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. *Occup Environ Med* **53**: 394-398

Gaertner RRW and Theriault G (2002) Risk of bladder cancer in foundry workers: a meta-analysis. *Occup Environ Med* **59**: 655-663

Gago-Dominguez M, Bell DA, Watson MA, Yuan JM, Castelao JE, Hein DW, Chan KK, Coetzee GA, Ross RK, Yu MC (2003) Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. *Carcinogenesis* **24**: 483-489

Gago-Dominguez M, Castelao JE, Yuan JM, Yu MC, Ross RK (2001) Use of permanent hair dyes and bladder-cancer risk. *Int J Cancer* **91**: 575-579

Gibbs GW, Armstrong B, Sevigny M (2007) Mortality and cancer experience of Quebec aluminium reduction plant workers. Part 2: Mortality of three cohorts hired on or before January 1, 1951. *J Occup Environ Med* **49**: 1105-1123

Gibbs GW and Sevigny M (2007a) Mortality and cancer experience of Quebec aluminium reduciton plant workers. Part 3: Monitoring the mortality of workers first employed after January 1, 1950. *J Occup Environ Med* **49**: 1269-1287

Gibbs GW and Sevigny M (2007b) Mortality and cancer experience of Quebec aluminium reduction plant workers. Part 4: Cancer incidence. *J Occup Environ Med* **49**: 1351-1366

Golka K, Prior V, Blaszkewicz M, Bolt HM (2002) The enhanced bladder cancer susceptibility of NAT2 slow acetylators towards aromatic amines: a review considering ethnic differences. *Toxicol Lett* **128**: 229-241

Golka K, Prior V, Blaszkewicz M, Cascorbi I, Schops W, Kierfeld G, Roots I, Bolt HM (1996) Occupational history and genetic N-acetyltransferase polymorphism in urothelial cancer patients of Leverkusen, Germany. *Scand J Work Environ Health* **22**: 332-338

Golka K, Wiese A, Assennato G, Bolt HM (2004) Occupational exposure and urological cancer. *World J Urol* **21**: 382-391

Gonzalez CA, Lopez-Abente G, Errezola M, Escolar A, Riboli E, Izarzugaza I, Nebot M (1989) Occupation and bladder cancer in Spain: a multi-centre case-control study. *Int J Epidemiol* **18**: 569-577

Greene MH, Hoover RN, Eck RL, Fraumeni Jr JF (1979) Cancer mortality among printing plant workers. *Environ Res* **20**: 66-73

Grimsrud TK, Langseth H, Engeland A, Andersen A (1998) Lung and bladder cancer in a Norwegian municipality with iron and steel producing industry: population based case-control studies. *Occup Environ Med* **55**: 387-392

Guberan E and Raymond L (1985) Mortality and cancer incidence in the perfumery and flavour industry of Geneva. *Br J Ind Med* **42**: 240-245

Gun RT, Pratt N, Ryan P, Roder D (2006) Update of mortality and cancer incidence in the Australian petroleum industry cohort. *Occup Environ Med* **63**: 476-481

Gun RT, Pratt NL, Griffith EC, Adams GG, Bisby JA, Robinson KL (2004) Update of a prospective study of mortality from cancer incidence in the Australian petroleum industry. *Occup Environ Med* **61**: 150-156

Guo J, Kauppinen T, Kyyronen P, Heikkila P, Lindbohm ML, Pukkala E (2004) Risk of esophageal, ovarian, testicular, kidney and bladder cancers and leukemia among finnish workers exposed to diesel or gasoline engine exhaust. *Int J Cancer* **111**: 286-292

Gustavsson P, Bellander T, Johansson L, Salmonsson S (1995) Surveillance of mortality and cancer incidence among Swedish graphite electrode workers. *Environ Res* **70**: 7-10

Gustavsson P, Hogstedt C, Holmberg B (1986) Mortality and incidence of cancer among Swedish rubber workers, 1952-1981. *Scand J Work Environ Health* **12**: 538-544

Gustavsson P and Reuterwall C (1990) Mortality and incidence of cancer among Swedish gas workers. *Br J Ind Med* **47**: 169-174

Hansen ES (1997) A cohort mortality study of foundry workers. *Am J Ind Med* **32**: 223-233

Hansen ES (1991) Cancer mortality among Danish molders. *Am J Ind Med* **20**: 401-409

Hansen ES (1989) Cancer incidence in an occupational cohort exposed to bitumen fumes. *Scand J Work Environ Health* **15**: 101-105

Hayes RB (1992) Biomarkers in occupational cancer epidemiology: considerations in study design. *Environ Health Perspect* **98**: 149-154

Holmberg B, Westerholm P, Maasing R, Kestrup L, Gumaelius K, Holmlund L, Englund A (1983) Retrospective cohort study of two plants in the Swedish rubber industry. *Scand J Work Environ Health* **9**: 59-68

Horton AW and Bingham EL (1977) Risk of bladder tumors among benzidine workers and their serum properdin levels. *J Natl Cancer Inst* **58**: 1225-1228

Howe GR and Lindsay JP (1983) A follow-up of a ten-percent sample of the Canadian labor force. I. Cancer mortallity in males, 1965-73. *J Natl Cancer Inst* **70**: 37-44

Huncharek M and Kupelnick B (2005) Personal use of hair dyes and the risk of bladder cancer: results of a meta-analysis. *Public Health Rep* **120**: 31-38

Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, Scotto di Carlo A, Porru S (2004) GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. *Int J Cancer* **110**: 598-604

Iaia TE, Bartoli D, Calzoni P, Comba P, De Santis M, Dini F, Farina GA, Valiani M, Pirastu R (2006) A cohort mortality study of leather tanners in Tuscany, Italy. *Am J Ind Med* **49**: 452-459

IARC (2008) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Polycyclic Aromatic Hydrocarbons.* Volume 92. International Agency for Research on Cancer, Lyon

IARC (2003) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Industrial Chemicals.* Volume 77. International Agency for Research on Cancer, Lyon

IARC (1994) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Industrial Chemicals.* Volume 60. International Agency for Research on Cancer, Lyon

IARC (1993) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants, some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines.* Volume 57. International Agency for Research on Cancer, Lyon

IARC (1990) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some flame retardants and textile chemicals and exposures in the textile manufacturing industry.* Volume 48. International Agency for Research on Cancer, Lyon

IARC (1989a) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Occupational Exposure in Petroleum Refining; Crude Oil and Major Petroleum Fuels.* Volume 45. International Agency for Research on Cancer, Lyon

IARC (1989b) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting.* Volume 47. International Agency for Research on Cancer, Lyon

IARC (1987) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* Supplement No. 7 Volume 63. International Agency for Research on Cancer, Lyon

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Polynuclear Aromatic Hydrocarbons, Part 4: Bitumens, Coal-Tars and Derived Products, Shale-Oils and Soots.* Volume 35. International Agency for Research on Cancer, Lyon

IARC (1984a) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Polynuclear Aromatic Hydrocarbons, Part 1: Chemical, Environmental and Experimental Data.* Volume 32. International Agency for Research on Cancer, Lyon

IARC (1984b) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Polynuclear Aromatic Hydrocarbons, Part 2: Carbon Blacks, Mineral Oils (Lubricant Base Oils and Derived Products) and Some Nitroarenes.* Volume 33. International Agency for Research on Cancer, Lyon

IARC (1984c) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Polynuclear Aromatic Hydrocarbons, Part 3: Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding.* Volume 34. International Agency for Research on Cancer, Lyon

IARC (1982a) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: The Rubber Industry.* Volume 28. International Agency for Research on Cancer, Lyon

IARC (1982b) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs.* Volume 29. International Agency for Research on Cancer, Lyon

IARC (1981) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Wood, Leather and Some Associated Industries.* Volume 25. International Agency for Research on Cancer, Lyon

IARC (1974) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds*

and Miscellaneous Alkylating Agents. Volume 4. International Agency for Research on Cancer, Lyon

IARC (1972) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds and Natural Products.* Volume 1. International Agency for Research on Cancer, Lyon

IARC (1986) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoking, Vol. 38. International Agency for Research on Cancer: Lyon

Ietri E, Belli S, Comba P, Gerosa A, Raffi GB, Pirastu RM (1997) Cohort mortality study of rubber and plastics product makers in Italy. *Occup Med* **47**: 417-422

ISD (2008) *ISD Cancer Information Programme*. Available at http://www.isdscotland.org.

Jarvholm B and Lavenius B (1987) Mortality and cancer morbidity in workers exposed to cutting fluids. *Arch Environ Health* **42**: 361-366

Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL (1987) The Copenhagen case-referent study on bladder cancer. Risks among drivers, painters and certain other occupations. *Scand J Work Environ Health* **13**: 129-134

Kazerouni N, Thomas TL, Petralia SA, Hayes RB (2000) Mortality among workers exposed to cutting oil mist: Update of previous reports. *Am J Ind Med* **38**: 410-416

Kelsh MA, Alexander DD, Kalmes RM, Buffler PA (2008) Personal use of hair dyes and risk of bladder cancer: a meta-analysis of epidemiologic data. *Cancer Causes Control* **19**: 549-558

Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S (1998) Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occup Environ Med* **55**: 1-12

Kogevinas M, t Mannetje A, Cordier S, Ranft U, Gonzalez CA, Vineis P, Chang-Claude J, Lynge E, Wahrendorf J, Tzonou A, Jockel KH, Serra C, Porru S, Hours M, Greiser E, Boffetta P (2003) Occupation and bladder cancer among men in Western Europe. *Cancer Causes Control* **14**: 907-914

Kolstad HA, Juel K, Olsen J, Lynge E (1995) Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry. *Occup Environ Med* **52**: 320-327

Kromhout H, Swuste P, Boleij JS (1994) Empirical modelling of chemical exposure in the rubber-manufacturing industry. *Ann Occup Hyg* **38**: 3-22

Kvam BMN, Romundstad P, Boffetta P, Andersen A (2005) Cancer in the Norwegian printing industry. *Scand J Work Environ Health* **31**: 36-43

La Vecchia C and Tavani A (2001) Hair dyes and bladder cancer: an update. *Eur J Cancer Prev* **10**: 205-208

La Vecchia C and Tavani A (1995) Epidemiological evidence on hair dyes and the risk of cancer in humans. *Eur J Cancer Prev* **4**: 31-43

Lamba AB, Ward MH, Weeks JL, Dosemeci M (2001) Cancer mortality patterns among hairdressers and barbers in 24 US States, 1984 to 1995. *J Occup Environ Med* **43**: 250-258

Lavoue J, Gerin M, Cote J, Lapointe R (2007) Mortality and cancer experience of Quebec aluminium reduction plant workers, part I: The reduction plants and coal tar pitch volatile (CTPV) exposure assessment. *J Occup Environ Med* **49**: 997-1008

Leon DA, Thomas P, Hutchings S (1994) Lung cancer among newspaper printers exposed to ink mist: A study of trade union members in Manchester, England. *Occup Environ Med* **51**: 87-94

Lewalter J and Miksche l (1992) Empfehlungen zur arbeitsmedizinischen Prävention expositions- und dispositions-bedingter Arbeitsstoff-Beanspruchungen. **31**: 135-139

Lilienfeld AM and Lilienfeld DE (1980) Foundations of Epidemiology. Oxford University Press: Oxford

Lindstedt G and Sollenberg J (1982) Polycyclic aromatic hydrocarbons in the occupational environment: with special reference to benzo(a)pyrene measurements in Swedish industry. *Scand J Work Environ Health* **8**: 1-19

Lloyd JW, Lundin F.E. J, Redmond CK, Geiser PB (1970) Long-term mortality study of steelworkers. IV. Mortality by work area. *J Occup Med* **12**: 151-157

Ma Q, Lin G, Qin Y, Lu D, Golka K, Geller F, Chen J, Shen J (2003) GSTP1 A1578G (Ile105Val) polymorphism in benzidine-exposed workers: an association with cytological grading of exfoliated urothelial cells. *Pharmacogenetics* **13**: 409-415

Maclure M, Katz RB, Bryant MS, Skipper PL, Tannenbaum SR (1989) Elevated blood levels of carcinogens in passive smokers. *Am J Public Health* **79**: 1381-1384

Malker HSR and Gemne GA (1987) A register-epidemiology study on cancer among Swedish printing industry workers. *Arch Environ Health* **42**: 73-82

Mancuso TF and el-Attar AA (1967) Cohort study of workers exposed to betanaphthylamine and benzidine. *J Occup Med* **9**: 277-285

Markowitz SB and Levin K (2004) Continued epidemic of bladder cancer in workers exposed to ortho-toluidine in a chemical factory. *J Occup Environ Med* **46**: 154-160

Marret L, Hartge P, Meigs J (1986) Bladder cancer and occupational exposure to leather. *Br J Ind Med* **43**: 96-100

Mastrangelo G, Fadda E, Marzia V (1996) Polycyclic aromatic hydrocarbons and cancer in man. *Environ Health Perspect* **104**: 1166-1170

Mastrangelo G, Fedeli U, Fadda E, Milan G, Lange JH (2002) Epidemiologic evidence of cancer risk in textile industry workers: a review and update. *Toxicol Ind Health* **18**: 171-181

Matanoski GM and Elliott EA (1981) Bladder cancer epidemiology. *Epidemiol Revs* **3**: 203-229

Matanoski GM, Santos-Burgoa C, Schwartz L (1990) Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Health Perspect* **86**: 107-117

Matsumoto K, Irie A, Satoh T, Kuruma H, Arakawa T, Baba S (2005) Occupational bladder cancer: from cohort study to biologic molecular marker. *Med Sci Mon* **11**: RA311-RA315

Meigs JW, Marrett LD, Ulrich FU, Flannery JT (1986) Bladder tumor incidence among workers exposed to benzidine: a thirty-year follow-up. *J Natl Cancer Inst* **76**: 1-8

Melamed MR (1972) Diagnostic cytology of urinary tract carcinoma. A review of experience with spontaneous and carcinogen induced tumors in man. *Eur J Cancer* **8**: 287-292

Melick WF (1972) Bladder carcinoma and xenylamine. *New Engl J Med* **287**: 1103

Merlo DF, Garattini S, Gelatti U, Simonati C, Covolo L, Ceppi M, Donato F (2004) A mortality cohort study among workers in a graphite electrode production plant in Italy. *Occup Environ Med* **61**: e9-e15

Mikoczy Z and Hagmar L (2005) Cancer incidence in the Swedish leather tanning industry: updated findings 1958-99. *Occup Environ Med* **62**: 461-464

Mirer F (2003) Updated epidemiology of workers exposed to metalworking fluids provides sufficient evidence for carcinogenicity. *Appl Occup Environ Hyg* **18**: 902-912

Moulin JJ, Clavel T, Buclez B, Laffitte-Rigaud G (2000) A mortality study among workers in a French aluminium reduction plant. *Int Arch Occup Environ Health* **73**: 323-330

Moulin JJ, Wild P, Mur JM, Lafontaine M, Lefer M, Mercier-Gallay M, Villemot P, Whebi V, Coulon JP (1989) Risk of lung, larynx, pharynx and buccal cavity cancers among carbon electrode manufacturing workers. *Scand J Work Environ Health* **15**: 30-37

Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, Fernicola AR (1982) Life time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. *Int J Epidemiol* **11**: 212-217

Negri E, Piolatto G, Pira E, Decarli A, Kaldor J, La Vecchia C (1989) Cancer mortality in a northern Italian cohort of rubber workers. *Br J Ind Med* **46**: 624-628

NIOSH (1998) Occupational Exposure to Metalworking Fluids. DHHS (NIOSH) Publication No. 98-102

Norseth T, Andersen A, Giltvedt J (1983) Cancer incidence in the rubber industry in Norway. *Scand J Work Environ Health* **9**: 69-71

Olsen JH and Jensen OM (1987) Occupation and risk of cancer in Denmark. An analysis of 93,810 cancer cases, 1970-1979. *Scand J Work Environ Health* **13**: 1-91

ONS (2007a) *Cancer Statistics: Registrations*, Available at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843.

ONS (2007b) *Mortality statistics: Cause*, Available at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=618.

ONS (2006) Mortality Statistics: Cause. Series DH2 No. 32

ONS (2004) Cancer Survival in England by Strategic Health Authority.

OSHA (1973) Carcinogens.: Fed Register No. 38:10929. Standard No. 1910.93, doi:http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FEDERAL_REGISTER&p_id=11718

Osorio AM, Clapp D, Ward E, Wilson HK, Cocker J (1990) Biological monitoring of a worker acutely exposed to MBOCA. *Am J Ind Med* **18**: 577-589

Ott MG and Langner RR (1983) A mortality survey of men engaged in the manufacture of organic dyes. *J Occup Med* **25**: 763-768

Ouellet-Hellstrom R and Rench JD (1996) Bladder cancer incidence in arylamine workers. *J Occup Environ Med* **38**: 1239-1247

Parkes HG (1969) Epidemiology and etiology of human bladder cancer: occupational bladder cancer in the British rubber industry. *J Natl Cancer Inst* **43**: 249-252

Parkes HG, Veys CA, Waterhouse JA, Peters A (1982) Cancer mortality in the British rubber industry. *Br J Ind Med* **39**: 209-220

Parkin DM (1994) Cancer in developing countries. *Cancer Surv* **19-20**: 519-561

Parkin DM and Muir CS (1992) Cancer Incidence in Five Continents. Comparability and quality of data. *IARC Sci Publ* **120**: 45-173

Parkin DM, Vizcaino AP, Skinner ME, Ndhlovu A (1994) Cancer patterns and risk factors in the African population of southwestern Zimbabwe, 1963-1977. *Cancer Epidemiol Biomarkers Prev* **3**: 537-547

Pelucchi C, Bosetti C, Negri E, Malvezzi M, La Vecchia C (2006) Mechanisms of disease: The epidemiology of bladder cancer. *Nature Clin Pract Urol* **3**: 327-340

Pirastu R, Iavarone I, Comba P (1996) Bladder cancer: a selected review of the epidemiological literature. *Ann Ist Super Sanita* **32**: 3-20

Popp W, Schmieding W, Speck M, Vahrenholz C, Norpoth K (1992) Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-o-toluidine while synthesising chlordimeform. *Br J Ind Med* **49**: 529-531

Prince MM, Ward EM, Ruder AM, Salvan A, Roberts DR (2000) Mortality among rubber chemical manufacturing workers. *Am J Ind Med* **37**: 590-598

Quinn M, Babb P, Brock A, Kirby L, Jones J (2001) Cancer Trends in England and Wales 1950-1999.

Quinn M, Wood H, Cooper N, Rowan S (2005) Cancer Atlas of the United Kingdom and Ireland 1991-2000.

Rehn L (1895) Blasengeschwuelste bei Fushsin-arbeitern. **50**: 588-600

Reid DD and Buck C (1956) Cancer in coking plant workers. *Br J Ind Med* **13**: 265-269

Reulen RC, Kellen E, Buntinx F, Brinkman M, Zeegers M (2008) A meta-analysis on the association between bladder cancer and occupation. *Scand J Urol Nephrol* **42**: 64-78

Romundstad P, Haldorsen T, Andersen A (2000a) Cancer incidence and cause specific mortality among workers in two Norwegian aluminum reduction plants . *Am J Ind Med* **37**: 175-183

Romundstad P, Haldorsen T, Andersen A (2000b) Lung and bladder cancer among workers in a Norwegian aluminium reduction plant. *Occup Environ Med* **57**: 495-499

Rosenman KD and Reilly MJ (2004) Cancer mortality and incidence among a cohort of benzidine and dichlorobenzidine dye manufacturing workers. *Am J Ind Med* **46**: 505-512

Ross R, Paganini-Hill A, Henderson B (1988) Epidemiology of bladder cancer: In Diagnosis and Management of Genitourinary Cancer. W.B. Saunders & Co.: Philadelphia. pp. 32-39

Rousseau M-, Straif K, Siemiatycki J (2005) IARC carcinogen update. *Environ Health Perspect* **113**: A580-A581

Rubino GF, Scansetti G, Piolatto G, Pira E (1982) The carcinogenic effect of aromatic amines: an epidemiological study on the role of o-toluidine and 4,4'-methylene bis (2-methylaniline) in inducing bladder cancer in man. *Environ Res* **27**: 241-254

Rushton L (1993) Further follow-up of mortality in a United Kingdom oil refinery cohort. *Br J Ind Med* **50**: 549-560

Rushton L and Alderson MR (1981) An epidemiological survey of eight oil refineries in Britain. *Br J Ind Med* **38**: 225-234

Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. *Am J Epidemiol* **121**: 37-48

Sathiakumar N and Delzell E (2000) An updated mortality study of workers at a dye and resin manufacturing plant. *J Occup Environ Med* **42**: 762-771

Sathiakumar N, Graff J, Macaluso M, Maldonado G, Matthews R, Delzell E (2005) An updated study of mortality among North American synthetic rubber industry workers. *Occup Environ Med* **62**: 822-829

Schifflers E, Jamart J, Renard V (1987) Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. *Int J Cancer* **39**: 287-292

Schulte PA, Ringen K, Hemstreet GP, Altekruse EB, Gullen WH, Patton MG, Allsbrook WC, Crosby JH, West SS, Witherington R, Koss L, Bales CE, Tillet S, Rooks SCF, Stern F, Stringer W, Schmidt VA, Brubaker MM (1985) Risk assessment of a cohort exposed to aromatic amines. *J Occup Med* **27**: 115-121

Serra C, Bonfill X, Sunyer J, Urrutia G, Turuguet D, Bastus R, Roque M, Mannetje A, Kogevinas M (2000) Bladder cancer in the textile industry. *Scand J Work Environ Health* **26**: 476-481

Siemiatycki J, Dewar R, Nadon L, Gerin M (1994) Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol* **140**: 1061-1080

Siemiatycki J, Dewar R, Nadon L, Gerin M, Richardson L, Wacholder S (1987) Associations between several sites of cancer and twelve petroleum-derived liquids. *Scand J Work Environ Health* **13**: 493-504

Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, Rousseau M-, Boffetta P (2004) Listing occupational carcinogens. *Environ Health Perspect* **112**: 1447-1459

Silverman DT, Devesa SS, Moore LE, Rothman N (2006) Bladder Cancer. In Cancer Epidemiology and Prevention, Schottenfeld D and Fraumeni Jr JF (eds) pp 1101-1127. Oxford University Press: Oxford

Silverman DT, Hoover RN, Albert S, Graff KM (1983) Occupation and cancer of the lower urinary tract in Detroit. *J Natl Cancer Inst* **70**: 237-245

Silverman DT, Hoover RN, Mason TJ, Swanson GM (1986) Motor exhaust-related occupations and bladder cancer. *Cancer Res* **46**: 2113-2116

Silverman DT, Levin LI, Hoover RN (1989a) Occupational risks of bladder cancer in the United States: II Nonwhite men. *J Natl Cancer Inst* **81**: 1480-1483

Silverman DT, Levin LI, Hoover RN, Hartge P (1989b) Occupational risks of bladder cancer in the United States: I. White men. *J Natl Cancer Inst* **81**: 1472-1480

Silverstein M, Park R, Marmor M, Maizlish N, Mirer F (1988) Mortality among bearing plant workers exposed to metal-working fluids and abrasives. *J Occup Med* **30**: 706-714

Skov T, Andersen A, Malker H, Pukkala E, Weiner J, Lynge E (1990) Risk for cancer of the urinary bladder among hairdressers in the Nordic countries. *Am J Ind Med* **17**: 217-223

Skov T and Lynge E (1994) Cancer risk and exposures to carcinogens in hairdressers. *Skin Pharmacol* **7**: 94-100

Solionova LG and Smulevich VB (1993) Mortality and cancer incidence in a cohort of rubber workers in Moscow. *Scand J Work Environ Health* **19**: 96-101

Soll-Johanning H, Bach E, Jensen SS (2003) Lung and bladder cancer among Danish urban bus drivers and tramway employees: a nested case-control study. *Occup Med* **53**: 25-33

Sorahan T (2008) Bladder cancer risks in workers manufacturing chemicals for the rubber industry. *Occup Med* **58**: 496-501

Sorahan T (2007) Mortality of UK oil refinery and petroleum distribution workers, 1951-2003. *Occup Med* **57**: 177-185

Sorahan T, Hamilton L, Jackson JR (2000) A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-B-naphthylamine and *o*-touluidine. *Occup Environ Med* **57**: 106-115

Sorahan T, Hamilton L, van Tongeren M, Gardiner K, Harrington JM (2001c) A cohort mortality study of U.K. carbon black workers, 1951-1996. *Am J Ind Med* **39**: 158-170

Sorahan T, Hamilton L, Wallace DM, Bathers S, Gardiner K, Harrington JM (1998) Occupational urothelial tumours: a regional case-control study. *Br J Urol* **82**: 25-32

Sorahan T, Nichols L, Harrington JM (2002) Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998. *Occup Med* **52**: 333-339

Sorahan T, Nichols L, Harrington JM (2001a) Mortality of United Kingdom Oil Refinery Workers, 1951-98.

Sorahan T, Nichols L, Harrington JM (2001b) Mortality of United Kingdom Petroleum Distribution Workers, 1951-98.

Sorahan T, Parkes HG, Veys CA, Waterhouse JA (1986) Cancer mortality in the British rubber industry: 1946-80. *Br J Ind Med* **43**: 363-373

Sorahan T, Parkes HG, Veys CA, Waterhouse JA, Straughan JK, Nutt A (1989) Mortality in the British rubber industry 1946-85. *Br J Ind Med* **46**: 1-10

Sorahan T and Pope D (1993) Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry. *Br J Ind Med* **50**: 528-536

Spinelli JJ, Band PR, Svirchev LM, Gallagher RP (1991) Mortality and cancer incidence in aluminum reduction plant workers. *J Occup Med* **33**: 1150-1155

Spinelli JJ, Demers PA, Le ND, Friesen MD, Lorenzi MF, Fang R, Gallagher RP (2006) Cancer risk in aluminium reduction plant workers (Canada). *Cancer Causes Control* **17**: 939-948

Stasik MJ (1988) Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort. *Int Arch Occup Environ Health* **60**: 21-24

Steenland K, Burnett C, Osorio AM (1987) A case-control study of bladder cancer using city directories as a source of occupational data. *Am J Epidemiol* **126**: 247-257

Steenland K and Palu S (1999) Cohort mortality study of 57000 painters and other union members: a 15 year update. *Occup Environ Med* **56**: 315-321

Steenland K, Schnorr T, Beaumont J, Halperin W, Bloom T (1988) Incidence of laryngeal cancer and exposure to acid mists. *Br J Ind Med* **45**: 766-776

Stern FB (2003) Mortality among chrome leather tannery workers: an update. *Am J Ind Med* **44**: 197-206

Straif K, Weiland SK, Werner B, Chambless L, Mundt KA, Keil U (1998) Workplace risk factors for cancer in the German rubber industry: Part 2. Mortality from non-respiratory cancers. *Occup Environ Med* **55**: 325-332

Straughan JK (1998) Cancer risk in the rubber industry: a review of recent epidemiological evidence. *Occup Environ Med* **55**: 646-647

Straughan JK and Sorahan T (2000) Cohort mortality and cancer incidence survey of recent entrants (1982-91) to the United Kingdom rubber industry: preliminary findings. *Occup Environ Med* **57**: 574-576

Strauss ME, Barrick ED, Bannister RM (1993) Mortality experience of employees exposed to 2-mercaptobenzothiazole at a chemical plant in Nitro, West Virginia. *Br J Ind Med* **50**: 888-893

Swaen GMH, Slangen JJM, Volovics A, Hayes RB, Scheffers T, Sturmans F (1991) Mortality of coke plant workers in The Netherlands. *Br J Ind Med* **48**: 130-135

Swerdlow AJ, dos Santos Silva I, Doll R (2001) Cancer Incidence and Mortality in England and Wales: Trends and Risk Factors. Oxford University Press: New York

Szeszenia-Dabrowska N, Wilczynska U, Kaczmarek T, Szymczak W (1991) Cancer mortality among male workers in the Polish rubber industry. *Pol J Occup Med Environ Health* **4**: 149-157

Takkouche B, Etminan M, Montes-Martinez A (2005) Personal use of hair dyes and risk of cancer: a meta-analysis. *J Am Med Assoc* **293**: 2516-2525

Talaska G (2003) Aromatic amines and human urinary bladder cancer: exposure sources and epidemiology. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* **21**: 29-43

Tolbert PE (1997) Oils and cancer. *Cancer Causes Control* **8**: 386-405

Teta MJ, Walrath J, Wister-Meigs J, Flannery JT (1984) Cancer incidence among cosmetologists. *J Natl Cancer Inst* **72**: 1051-1057

Theriault GP, Tremblay CG, Armstrong BG (1990) Bladder cancer screening among primary aluminum production workers in Quebec. *J Occup Med* **32**: 869-872

Tolbert PE (1997) Oils and cancer. *Cancer Causes Control* **8**: 386-405

Tremblay C, Armstrong B, Theriault G, Brodeur J (1995) Estimation of risk of developing bladder cancer among workers exposed to coal tar pitch volatiles in the primary aluminum industry. *Am J Ind Med* **27**: 335-348

Tsuchiya K, Okubo T, Ishizu S (1975) An epidemiological study of occupational bladder tumours in the dye industry of Japan. *Br J Ind Med* **32**: 203-209

Vena JE, Sultz HA, Fiedler RC, Barnes RE (1985) Mortality of workers in an automobile engine and parts manufacturing complex. *Br J Ind Med* **42**: 85-93

Veys CA (2004a) Bladder tumours in rubber workers: a factory study 1946-1995. *Occup Med* **54**: 322-329

Veys CA (2004b) A study of mortality patterns at a tyre factory 1951-1985: a reference statistic dilemma. *Occup Med (Lond)* **54**: 330-335

Veys CA (1996) Bladder cancer in rubber workers: a phenyl beta-naphthylamine (PBNA) exposed workforce. *Prog Rubber Plast Technol* **12**: 258-273

Veys CA (1992) Bladder cancer as an occupational disease in the British rubber industry: an in-depth factory study to show the past extent of the risk and confirmation of its subsequent disappearance. *Prog Rubber Plast Technol* **8**: 1-14

Veys CA (1981) Bladder cancer in rubber workers: the story reviewed and updated. *Plast Rubber Process Appl* **1**: 207-212

Veys CA (1969) Two epidemiological inquiries into the incidence of bladder tumors in industrial workers. *J Natl Cancer Inst* **43**: 219-226

Vineis P and Magnani C (1985) Occupation and bladder cancer in males: a case-control study. *Int J Cancer* **35**: 599-606

Vineis P and Martone T (1996) Molecular epidemiology of bladder cancer. *Ann Ist Super Sanita* **32**: 21-27

Vineis P and Pirastu R (1997) Aromatic amines and cancer. *Cancer Causes Control* **8**: 346-355

Vineis P and Simonato L (1991) Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. *Arch Environ Health* **46**: 6-15

Ward E, Carpenter A, Markowitz S, Roberts D, Halperin W (1991) Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. *J Natl Cancer Inst* **83**: 501-506

Ward E, Halperin W, Thun M, Grossman E, Fink B, Koss L, Osorio AM, Schulte P (1990) Screening workers exposed to 4,4'-methylene bis(2-chloroaniline) for bladder cancer by cystoscopy. *J Occup Med* **32**: 865-868

Ward EM, Burnett CA, Ruder A, Davis-King K (1997) Industries and cancer. *Cancer Causes Control* **8**: 356-370

WCISU (2008) *Cancer Incidence in Wales.* Available at http://www.wales.nhs.uk.

Weiland SK, Mundt KA, Keil U, Kraemer B, Birk T, Person M, Bucher AM, Straif K, Schumann J, Chambless L (1996) Cancer mortality among workers in the German rubber industry: 1981-91. *Occup Environ Med* **53**: 289-298

Wellmann J, Weiland SK, Neiteler G, Klein G, Straif K (2006) Cancer mortality in German carbon black workers 1976-98. *Occup Environ Med* **63**: 513-521

Wong O and Raabe GK (2000) A critical review of cancer epidemiology in the petroleum industry, with a meta-analysis of a combined database of more than 350,000 workers. *Regul Toxicol Pharmacol* **32**: 78-98

Wong O, Trent LS, Whorton MD (1994) An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* **51**: 386-396

You XY, Chen JG, Hu YN (1990) Studies on the relation between bladder cancer and benzidine or its derived dyes in Shanghai. *Br J Ind Med* **47**: 544-552

Zack JA and Gaffey WR (1983) A mortality study of workers employees at the Monsanto Company plant in Nitro, West Virginia. *Environ Sci Res* **26**: 575-591

Zahm SH, Hartge P, Hoover R (1987) The National Bladder Cancer Study: employment in the chemical industry. *J Natl Cancer Inst* **79**: 217-222

Zavon MR, Hoegg U, Bingham E (1973) Benzidine exposure as a cause of bladder tumors. *Arch Environ Health* **27**: 1-7

Zeegers MPA, Goldbohm RA, Van den Brandt PA (2002) A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control* **13**: 83-90

Zheng T, Cantor KP, Zhang Y, Lynch CF (2002) Occupation and bladder cancer: a population-based, case-control study in Iowa. *J Occup Environ Med* **44**: 685-691

Zoloth SR, Michaels DM, Villabi JR, Lacher M (1986) Patterns of mortality among commercial pressmen. *J Natl Cancer Inst* **76**: 1047-1051

6 STATISTICAL APPENDIX

Formulae used in the estimation of AF

Levin's equation

$$AF = Pr(E)*(RR-1)/\{1+Pr(E)*(RR-1)\} \tag{1}$$

where   RR = relative risk, Pr(E) = proportion of the population exposed

A common denominator is used across exposure levels and industries for each exposure

Miettinen's equation

$$AF = Pr(E|D)*(RR-1)/RR \tag{2}$$

where   Pr(E|D) = proportion of cases exposed (E = exposed, D = case)

Turnover equation to estimate numbers ever employed during the REP

$$N_{e(REP)} = \sum_{i=a}^{i=b} l_{(adj15)i} * n_0/(R-15)\}$$

$$+ \sum_{k=0}^{k=(age(u)-age(1))} \sum_{j=c+k}^{j=d+k} \{l_{(adj15)j} *n_0 * TO /(age(u)-age(l)+1)\} \tag{3}$$

where $N_{e(REP)}$ = numbers ever employed in the REP

n_0 =   numbers employed in the exposed job/industry at a mid-point in the REP

TO =   staff turnover per year

R   =   retirement age (65 for men, 60 for women)

$l_{(adj15)i}$ = the proportion of survivors to age i of those alive at age 15 (from GB life tables)

a to b = age range achieved by the original cohort members by the target year (2004)
(e.g. 65 to 100 for the solid tumour REP)

c to d = age range achieved by the turnover recruited cohort members by the target year
(25 to 64 for the solid tumour REP)

age(u) and age(l) = upper and lower recruitment age limits (24 and 15)

The derivation and assumptions underlying this formula are described in the methodology technical report, available on the HSE website. The equation can be represented as a single factor acting as a multiplier for n_0, calculated by setting n_0 to 1 in the above equation, so that the factor varies only with TO see Table A1 below.

Equation to estimate the proportion of the population exposed

$$Pr(E) = N_{e(REP)} / N_{p(REP)} \tag{4}$$

where $N_{p(REP)}$ = numbers ever of working age during the REP from population estimates for the relevant age cohorts in the target year

Equation for combining AFs where exposed populations overlap but are independent and risk estimates are assumed to be multiplicative:

$$AF_{overall} = 1- \Pi_k(1-AF_k) \text{ for the k exposures in the set} \tag{5}$$

Table A1 Employment level adjustment and turnover factors used in the calculation of AF

		Main Industry Sector	Adjustment factor for change in employment levels*	Turnover per year
Men	A-B	Agriculture, hunting and forestry; fishing	1	7%
	C-E	Mining and quarrying, electricity, gas and water; manufacturing industry	1.4	9%
	F	Construction	1	12%
	G-Q	Service industries	0.9	11%
		Total	1	10%
Women	A-B	Agriculture, hunting and forestry; fishing	0.75	10%
	C-E	Mining and quarrying, electricity, gas and water; manufacturing industry	1.5	14%
	F	Construction	0.67	15%
	G-Q	Service industries	0.8	15%
		Total	0.9	14%

* Applied to CAREX data for the solid tumour REP only. Exposed numbers are obtained for a mid-point year in the REP where national employment data sources have been used (the LFS or CoE).

7 ANNEX 1: SUMMARY OF RESULTS FOR MINERAL OIL-EXPOSED POPULATIONS

Results for bladder and urinary organ cancer from epidemiologic studies of mineral oil-exposed populations (Taken from Tolbert, 1997)

Author, Year	Location	Type of study/ analysis	No. of exposed cases	RR (95%CI)	Study population
Cohort-based studies					
Decoufle (1978)	Michigan, USA	SMR	6	1.2 (NS)	Workers at metal machining plant, 5+yrs exposure to oil mist, White
Jarvholm & Lavenius (1987)	Sweden	SIR	7	1.0 (0.4-2.2)	Grinders and turners at bearing ring plant
Leon et al. (1994)	England, UK	SMR	6	1.2 (0.5-2.7)	Unskilled rotary press operators
Coggon et al. (1984)	England, UK	SMR	5	5.0 (1.0-25.6)	Men, high exposure to printing inks
Delzell et al. (1993)	Michigan & Ohio, USA	SMR	63	1.0 (0.7-1.2)	Automotive manufacturing workers, White
			12	0.8 (0.4-1.4)	Automotive manufacturing workers, Black
Proportional mortality studies					
Silverstein et al. (1988)	Connecticut, USA	PMR	14	1.3 (0.8-2.2)	Ball bearing plant workers, White
Vena et al. (1985)	New York, USA		7	7.3 (p<0.05)	Based on U.S. mortality, White
Greene et al. (1979)	USA	PMR	17	1.4 (0.9-2.2)	Men in general printing
Zoloth et al. (1986)	USA	PMR	11	1.1 (0.6-2.0)	Men in general printing
Case-control studies/Population based studies					
Silverman et al. (1989b)	USA	OR	102	1.3 (1.0-1.7)	Ever machinist ≥6 months
			51	1.4 (0.9-2.1)	Ever drill press operator ≥6 months
			26	1.1 (0.6-1.9)	Ever metal machinery workers
			37	0.8 (0.5-1.2)	Ever printers
Siemiatycki et al. (1987)	Montreal, Canada	OR	47	1.2 (1.0-1.6)[1]	Ever exposed to cutting oils
Claude et al. (1988)	Germany	OR	18	2.3 (1.0-5.6)	Ever turner
			43	0.8 (0.5-1.3)	Ever metal worker
Gonzalez et al. (1989)	Spain	OR	21	0.8 (0.5-1.1)	Ever toolmaker ≥6 months
			NA	1.9 (1.2-2.8)	Ever machinery adjuster, assembler or mechanic ≥6 months
Steenland (1987)	Ohio, USA	OR	11	2.0 (NS)	Ever grinding machine operator
			45	0.7 (p<0.05)	Ever machinist
Vineis & Magnani (1985)	Italy	OR	16	1.5 (0.7-3.3)	Ever employed in machine tools ≥6 months
Schifflers et al. (1987)	Belgium	OR	34	2.5 (1.3-4.7)	All metal workers
			8	2.6 (0.9-7.2)	Turners
Howe & Lindsay (1983)	Canada	OR	NA	2.7 (1.1-7.7)	Ever metal machinist
Coggon et al. (1984)	England, UK	OR	52	1.3 (0.9-1.9)	Ever had an occupation with potential cutting oil exposure
			21	1.5 (0.8-2.8)	Ever had an occupation with potential high cutting oil exposure
Malker et al. (1987)	Sweden		322	1.2 (p<0.01)	Toolmaker or machinist in 1960
Silverman et al. (1983)	Detroit, MI, USA		137	1.1 (0.8-1.5)	All metal machinists
			32	1.5 (0.9-8.9)	Tool & die workers
Brownson et al. (1987)	Missouri, USA		7	3.1 (1.1-8.9)	Printing machine operators
Cartwright (1982)	England, UK		18	3.1 (1.4-6.8)	Workers exposed to ink from high-speed presses

[1] 90%CI

The burden of occupational cancer in Great Britain

Bladder cancer

The aim of this project was to produce an updated estimate of the current burden of cancer for Great Britain resulting from occupational exposure to carcinogenic agents or exposure circumstances. The primary measure of the burden of cancer was the attributable fraction (AF) being the proportion of cases that would not have occurred in the absence of exposure; and the AF was used to estimate the number of attributable deaths and registrations. The study involved obtaining data on the risk of the cancer due to the exposure of interest, taking into account confounding factors and overlapping exposures, as well as the proportion of the target population exposed over the relevant exposure period. Only carcinogenic agents, or exposure circumstances, classified by the International Agency for Research on Cancer (IARC) as definite (Group 1) or probable (Group 2A) human carcinogens were considered. Here, we present estimates for cancer of the bladder that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

The estimated total (male and female) AF, deaths, and registrations for bladder cancer related to overall occupational exposure is 5.28% (95% Confidence Interval (CI)= 3.43-7.72), which equates to 245 (95%CI=159-358) attributable deaths and 550 (95%CI=357-795) attributable registrations.

RR865