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Health and Safety Executive

The burden of occupational cancer in Great Britain

Liver cancer

Prepared by the **Institute of Environment and Health**, the **Institute of Occupational Medicine** and **Imperial College London** for the Health and Safety Executive 2012

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Research Report

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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 liver 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 liver cancer related to overall occupational exposure is 0.18% (95% Confidence Interval (CI)= 0.11-0.29), which equates to 5 (95%CI= 3-8) attributable deaths and 5 (95%CI=3-8) 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 liver that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

Ionising radiation, arsenic, vinyl chloride monomer (VCM) and aflatoxin have been classified by the IARC as definite human carcinogens for liver cancer and polychlorinated biphenyls (PCB) and trichloroethylene have been classified by IARC as probable human carcinogens. Occupational exposure to ionising radiation affects nuclear industry workers, disaster clean-up workers, radiologists, technologists, miners, aircrew and military personnel. Arsenic exposure can occur in smelting, manufacture and use of arsenical pesticides, sheep-dip compounds, and wood preservatives, and in the manufacture of glass and nonferrous alloys. VCM has been used since the 1930s to manufacture polyvinyl chloride (PVC) resin. Aflatoxin exposure can occur in handling contaminated food stuffs such as grain. PCBs were widely used in a range of industrial products including heat transfer fluids, hydraulic fluids, as lubricants, in plasticizers; surface coatings, inks and adhesives; their use was eliminated in the UK in 2000. Occupational exposure to trichloroethylene also occurred in the dry cleaning industry until the 1950s but has now been largely replaced by other solvents. The widest use of trichloroethylene is in metal degreasing in manufacturing industries.

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 1661 total deaths in men aged 25+ and 1133 in women aged 25+ from liver cancer; in 2004 there were 1670 total registrations for liver cancer in men aged 25+ and 1128 in women aged 25+.

The estimated total (male and female) attributable fractions, deaths and registrations for liver cancer related to occupational exposure is 0.18% (95% Confidence Interval (CI)=0.11-0.29), which equates to 5 (95%CI=3-8) attributable deaths and 5 (95%CI=3-8) attributable registrations. Results for individual carcinogenic agents for which the attributable fraction was determined are as follows:

- **Ionising radiation:** The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to ionising radiation is 0.01% which equates to 0 attributable deaths and 0 attributable registrations

- **Trichloroethylene**: The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to trichloroethylene is 0.06% (95%CI 0.02-0.11), which equates to 2 (95%CI 1-3) attributable deaths and 2 (95%CI 1-3) attributable registrations.

- **Vinyl chloride monomers**: The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to VCM is 0.11% (95%CI=0.05-0.20), which equates to 3 (95%CI=2-6) attributable deaths and 3 (95%CI=2-6) attributable registrations.

- **Other agents**: Available studies are considered inadequate to support the derivation of an attributable burden for arsenic, aflatoxin and PCBs.

CONTENTS

1 INCIDENCE AND TRENDS

The liver is a common site of metastasis for many cancer types, leading to the formation of *secondary* liver tumours. However, this review is concerned only with *primary* liver tumours i.e. those that originate in the liver.

Liver cancers are the third most common cause of cancer deaths in men and the sixth most common in women (Parkin *et al,* 2001b), accounting for more than 600,000 deaths worldwide in 2002 (WHO, 2002). There are a number of *primary* liver cancers, which are classified according to their specific histology and comprise hepatocellular carcinoma (liver cell carcinoma; ICD-10 C22.0), cholangiocarcinoma (intrahepatic bile duct carcinoma; ICD-10 C22.1), hepatoblastoma (ICD-10 C22.2) and angiosarcoma (ICD-10 C22.3). The majority of liver cancers (75 – 90%) are hepatocellular carcinomas (HCC), which are particularly prevalent in the developing countries of Asia and Africa, where 80% of all cases and deaths from HCC occur. Incidence of HCC is also increasing in developed countries, but remains relatively uncommon (El-Serag and Mason, 1999). Intrahepatic cholangiocarcinoma (ICC) occurs with a much lower, but still significant, frequency with 1 to 2 cases per 100,000 of the population per year in the US. Angiosarcoma is a rare form of liver cancer, occurring with a frequency of around 25 cases per year in the US and hepatoblastoma most commonly occurs in childhood, with an incidence of around 1.5 million cases per year (worldwide).

Due to the age-related incidence of hepatoblastoma this form of liver cancer is unlikely to be caused through occupational exposures and therefore will not be considered further in this report. When used here, the term 'Liver Cancer' refers to malignant neoplasms of both the liver and intrahepatic bile duct, with the terms HCC, ICC and ASL referring to 'hepatocellular carcinomas', 'intrahepatic cholangiocarcinoma' and angiosarcoma of the liver specifically.

In the UK, approximately 2800 people are diagnosed with liver cancer each year accounting for around 1% of new cancer cases (Cancer Research UK, 2007) with a higher incidence overall in males than females (average of 1.6:1.0 for period 1992-2005). Table 1 details the trend in liver cancer registrations in England during the period 1995-2005 (ONS, 2008). The number of cases diagnosed has steadily increased over the past 13 years, with 27,232 cases being reported between 1992 and 2005, giving an average crude incidence rate of 4.8 per 100,000 males and 3.1 per 100,000 females.

During the period 1995-2005, the rate (crude rate per 100,000 population) of liver cancer registrations has increased by 40% in men (3.9 and 6.5 for 1995 and 2005 respectively) and by over 30% in women (2.5 and 3.8 for 1995 and 2005 respectively). This is supported by data from a recent study examining longer-term trends in the incidence of liver cancer in England and Wales during the period 1971-2001 (West *et al*, 2006). The authors reported an overall increase of 56% in the incidence of liver, gallbladder and biliary tract cancers in males and 27% in females between 1971-1973 and 1999-2001. In terms of specific liver cancers, ICC was found to be rare in both males and females (European age standardised rates of 0.11 and 0.09 per 100,000 population respectively) during the initial study period (1971-1973). However, incidence rates were seen to be approximately twelve times higher by the end of the period (1999-2001; 1.33 and 1.06 per 100,000 population respectively) in both males and females. Over the same period, the rate of HCC increased by 46% (95% CI 31-60%) in males (1.84 to 2.68 per 100,000 population), and although an 8% rise in incidence rates was also noted in females (0.84 to 0.91 per 100 000 population) this was not found to be significant (95% CI -9 to +26%).

In their longitudinal study on trends in the incidence of liver cancer, West *et al*., (2006) additionally reported differences in age-specific incidence rates of HCC and ICC (males only

studied). For HCC, a gradual increase in rates over the study period (1971-2001) was noted for all except the oldest age groups (80-84 and 85+ years); the rate of ICC however, was seen to increase slowly up to the1990s, followed by a rapid increase in incidence rate that levelled in the mid/late 1990s in all age groups under 75 years.

Table 1 Number of liver cancer[1] registrations in England for 1995-2005.

	Men				Women			
Year	**Total Registrations***	**Registrations**	**%Total**	**Crude Rate /100,000**	**Total Registrations***	**Registrations**	**%Total**	**Crude Rate /100,000**
1995#	103986	948	0.91	3.9	105151	627	0.59	2.5
1996#	104103	1046	1.00	4.3	105461	740	0.70	3.0
1997#	104335	1059	1.01	4.4	107289	777	0.72	3.1
1998#	106745	1149	1.08	4.7	109957	782	0.71	3.1
1999#	108827	1146	1.05	4.7	112237	730	0.65	2.9
2000#	111543	1309	1.17	5.5	112066	860	0.77	3.4
2001#	112516	1242	1.10	5.1	112134	883	0.79	3.5
2002#	112579	1357	1.20	5.6	111210	891	0.80	3.5
2003#	112732	1368	1.21	5.6	114740	833	0.73	3.3
2004#	117805	1385	1.18	5.6	115816	947	0.82	3.7
2005#	119625	1599	1.34	6.5	119352	985	0.83	3.8
Average	**110407**	**1170**	**1.05**	**4.8**	**111409**	**775**	**0.69**	**3.1**

*all ages; [and] England and Wales; [#] England only. [1]- ICD-9 155 (1992-2000) ICD-10 C22 (2001-2005); Source: ONS MB1 Series (ONS 2008)

Numbers of deaths from liver cancer during the period 1999-2005 are detailed in **Table 2** (ONS, 2006). On average, 2174 people per year (1274 males and 903 females) died from liver cancer during this period, accounting for around 1:200 deaths in males and 1:300 deaths in females. The age standardised rate (per 1,000,000 of the population) was seen to rise steeply between 2000 and 2001 for both males and females; thereafter, in males the rate remained fairly constant up to 2004; however, for females a decline in rate was evident between 2002-2003.

Table 2 Number of deaths from liver cancer[1] in England and Wales 1999-2005.

	Men				Women			
Year	**Total Deaths***	**Deaths**	**%Total**	**Rate (Age-Standardised) /1,000,000**	**Total Deaths***	**Deaths**	**%Total**	**Rate (Age-Standardised) /1,000,000**
1999	264299	1134	0.43	17	291819	818	0.28	5
2000	255547	1128	0.44	20	280117	863	0.31	5
2001	252426	1178	0.47	43	277947	877	0.32	33
2002	253144	1245	0.49	45	280383	934	0.33	34
2003	253852	1365	0.54	44	284402	872	0.31	20
2004	244130	1370	0.56	44	268411	951	0.35	22
2005	243324	1480	0.61	46	269368	1008	0.37	23
Average	**252389**	**1271**	**0.51**	**36**	**278921**	**903**	**0.32**	**20**

* all causes, all ages. [1]- ICD-9 (1999-2000) ICD-10 C22 (2001-2005); Source: ONS DH2 Series (ONS 2006)

A breakdown of the total number of liver cancer deaths by specific tumour type in England and Wales during the period 1999-2005 is given in Table 3 (ONS, 2006). In males, mortality from HCC increased by approximately 40% during this period but in females, numbers

remained fairly consistent. Numbers of deaths from ICC were increased in both males and females during the same period, with a 25% and 35% rise for males and females respectively. Mortality from hepatoblastoma and angiosarcoma of the liver remained extremely low. The number of liver cancers remaining unspecified at post-mortem decreased in both males and females, possibly reflecting improved histological classification during this period.

Table 3 Number of deaths from defined liver cancers in England and Wales 1999-2005.

Year	Total Deaths from Liver Cancer	Deaths (% of total)				
		C22.0 Hepatocellular Carcinoma	C22.1 Intrahepatic bile duct carcinoma	C22.2 Hepatoblastoma	C22.3 Angiosarcoma of the liver	C22.9 Unspecified
MALES						
1999	1134	491	415	n/a	n/a	228
2000	1228	572	435	n/a	n/a	221
2001	1178	476	460	n/a	n/a	241
2002	1245	564	447	4	3	227
2003	1365	634	492	2	5	232
2004	1370	674	514	2	3	177
2005	1480	721	560	2	3	194
Average	**1286**	**590**	**475**	**2.5**	**3.5**	**217**
FEMALES						
1999	818	205	451	n/a	n/a	162
2000	863	164	509	n/a	n/a	190
2001	877	170	543	n/a	n/a	164
2002	924	198	555	1	2	178
2003	872	174	548	2	-	148
2004	951	196	615	2	2	136
2005	1008	187	687	1	1	132
AVERAGE	**902**	**185**	**558**	**1.5**	**1.7**	**159**

Source: ONS DH2 Series (ONS 2006); n/a – not available as separate figures

For patients diagnosed with primary liver cancer between 1991-1995 in England and Wales, the population-based five-year relative survival rate is very low, with rates of 3.5% (95% C.I. of 2.8-4.2) and 4.3% (95% C.I. of 3.5-5.2) for males and females respectively. The corresponding one-year relative survival rate for patients diagnosed during this period is 14.2% (95% C.I. of 13.0-15.4) in males and 16.3% (95% C.I. of 14.6-18.0) in females. For patients diagnosed during the period 1996-1999, the five-year relative survival rate is slightly higher, with rates of 5.1% (95% C.I. of 4.2-6.1) for males and 5.7% (95% C.I. of 4.4-7.0) for females. This trend was repeated for the one-year relative survival rates, which increased to 19.6% (95% C.I. of 18.2-20.9) in males and 20.3% (95% C.I. of 18.6-22.1) in females. In both sexes, the one- and five-year survival rates decline steeply with age. For patients diagnosed between 1991-1995, the one-year relative survival rate in the youngest age group (15-49) was 25% (95% C.I. of 20-31) in males and 39% (95% C.I. of 32-47) in females, however in the oldest age group (70-99) this rate declines to 11% for both sexes (95% C.I. of 9-12 and 9-13 for males and females respectively). A similar decline is seen with age for the five-year survival rates, with 9% (95% C.I. of 6-13) and 15% (95% C.I. of 10-21) survival in the youngest age group for males and females respectively which declines to 2% (95% C.I. of 1-3 for males and females) for both sexes in the oldest age groups. Although overall one-and

five-year survival rates are higher for patients diagnosed between 1996-1999, the same declining trend with age is still apparent (ONS, 2005)

Worldwide, primary liver cancer is the fifth most commonly diagnosed cancer and is the third most common cause of death from cancer (Parkin, 2001a). IARC estimates the age-standardized world-wide incidence rate of primary liver cancer among males is 8.7 per 100,000 population in developed countries and 17.4 per 100,000 population in underdeveloped countries (Ferlay *et al*, 2001). More than 80% of liver cancer cases occur in either sub-Saharan Africa or in Eastern Asia, with around 50% of those cases in China alone. North and South America, Northern Europe and Australia are considered as having low-rates for primary liver cancer with typical rates for males and females of 3.2 and 1.1 per 100,000 population in Canada, 3.6 and 1.0 in Australia, 2.2 and 1.1 in the UK and 7.5 and 5.5 in Spain. Although Eastern Asia and sub-Saharan Africa continue to have a high prevalence of liver cancer, in some high rate areas incidence rates have been declining (McGlynn *et al*, 2001).

In most countries, 75-90% of liver cancers are HCC with ICC accounting for between 10 and 25% of cases (Okuda *et al*, 2002); incidence and mortality figures for liver cancer therefore generally reflect those for HCC. The exception to this is Thailand, which has an exceptionally high incidence of ICC (88 and 35.4 per 100 000 in males and females respectively). The highest incidence rates for HCC are reported for Qidong in China, with rates of 72.1 and 29.6 per 100,000 population in males and females respectively.

Survival rates for primary liver cancer remain poor across both high and low rate areas. IARC estimates that the age-standardised worldwide mortality rates for males are 8.1 and 16.8 per 100,000 population in developed and underdeveloped countries respectively, indicating very little difference between incidence and survival in low and high rate areas (Ferlay *et al*, 2001).

2 OVERVIEW OF AETIOLOGY

The four types of primary liver cancer, hepatocellular carcinoma (HCC), intrahepatic bile duct carcinoma (ICC), hepatoblastoma (HE) and angiosarcoma (ASL) are most reliably diagnosed histologically. The most common form of liver cancer, HCC (75-90% of all liver cancers) is a malignant tumour of liver hepatocytes. There is a predominance of HCC in males (M:F=3-5:1) and is generally associated with chronic infection with hepatitis B or C viruses, exposure to mycotoxins, alcohol or androgens (London and McGlynn, 2006). ICC occurs with a much lower, but still significant, frequency and also has a slight predominance in males (M:F=1.5:1). Ninety percent of ICCs are tumours of epithelial cells lining bile ducts and 10% of squamous cells, and the tumour is associated with inflammatory bowel disease, primary sclerosing cholangitis, α 1-antitrypsin deficiency and Thorotrast (thorium dioxide) exposure. In S.E. Asia, ICC is also associated with chronic infestation with liver flukes (London and McGlynn, 2006). ASL is a rare type of liver cancer that originates in the blood vessels of the liver and has a male predominance of 3:1. It is associated with exposure to Thorotrast, arsenicals and vinyl chloride monomer. HEs are the most common form of liver cancer in childhood being more prevalent in males than females (M:F=1.5-2.0: 1) and in people of white origin (White : Black = 5:1). These tumours are associated with Beckwith-Wiedeman syndrome, hemihypertrophy, familial adenomatous polyposis and precocious puberty (London and McGlynn, 2006).

Development of liver cancer was first linked with chronic virus infections of the liver in the 1950s (Edmondson and Steiner, 1954; Edmondson, 1958; Higginson *et al*, 1957). Edmondson (1958) noted that 3-10% of US males with cirrhosis of the liver went on to develop liver cancer, whereas in Africa and Asia the figures were much higher at 5-50%. Liver cirrhosis in Western Countries was regarded as being mainly due to alcohol abuse, but as alcoholism is relatively uncommon in Africa and Asia it was concluded that another factor was responsible for the cirrhosis. It is now recognised that overall 77% of HCC cases worldwide are attributable to infection with either hepatitis B (HBV) or hepatitis C (HCV). IARC has classified HBV and HCV as carcinogenic to humans (IARC 1994). The latency period (time from first exposure to initial diagnosis) for development of HCC linked to HBV infection has been estimated as between 10 and 20 years (Poovorawan *et al*, 2002) and HCC linked to HBC infection as between 15 and 25 years (Hassoun and Gores, 2003).

Latency periods for other types of liver cancer have also been reported. The development of ICC has been most accurately defined through the study of patients given Thorotrast, an X-ray contrast agent, during the period 1920 and 1950 (see section 2.1). The resulting internal exposure to constant ionising radiation resulted in a high incidence of ICC, with latency periods of up to 53 years being reported (Zhu *et al*, 2004). The mean latency period for ASL has been estimated as around 22 years and although most cases occur between 15 to 29 years after first exposure, substantial numbers have been occurring after 30 years or more (Kielhorn *et al*, 2000; Lelbach, 1996).

The Occupational Health Decennial Supplement examined mortality (1979-1980, 1982-1990) and cancer incidence (1981-1987) in males and females aged 20-74 years in England (Drever, 1995). For liver cancer it was found that risk was greatest for males employed as cooks and kitchen porters, as reflected by the elevated PRRs (Proportional Registration Ratio) and PMRs (Proportional Mortality Ratio) shown in Table 4. Statistically elevated PRRs and PMRs were seen for other occupations also associated with a high proportional current drinking ratio (PCDR) including lawyers, doctors, caterers, publicans and bar staff (Drever, 1995). In addition, workers employed in materials processing (metals, electrical, and other materials) were found to have a significant PRR or PMR. No occupationally related rise in PRRs and PMRs were noted for females.

Table 4 Job codes with significantly high PRRs and PMRs for liver cancer. Both sexes aged 20-74 years, England, 1979-90.

Job Group		Registrations	PRR *	95% CI	Deaths	PMR#	95% CI
SIC code	Description	(1981 – 1987)			(1979 – 1980 and 1982 – 1990)		
		Males				Males	
001	Lawyers				32	212	145-300
005	Computer programmers	5	387	126-904			
015	Doctors	18	178	106-282	40	190	136-259
024	Literary and artistic occupations				60	134	102-172
036	Seafarers				46	154	113-206
045	Publicans and bar staff	38	202	143-278	112	162	134-195
046	Caterers	17	227	133-364	56	193	146-251
059	Cooks and kitchen porters	17	215	126-345	70	273	213-345
083	Glass formers and decorators	4	372	101-953			
118	Annealers, hardeners, temperers (metal)	3	649	134 -1898			
146	Metal plate workers				29	159	106-228
159	Other spray painters				19	176	106-275
163	Assemblers (vehicles and other metal goods)				25	157	102-232
173	Mains and service layers	6	289	106-631			
		Female				Female	
		No statistically significant PRRs			No statistically significant PMRs		

*p<0.05 based on at least 3 registrations; adjusted for age, social class and registration region; #p<0.05 05 based on at least 3 registrations; adjusted for age, social class and registration region; Source: Drever (1995) Occupational Health Decennial Supplement

The recent numbers for the Occupational Health Decennial Supplement examined mortality for the period 1991-2000 in males and females aged 20-74 years in England (Table 5). For liver cancer in males, it was found that the risk continued to be greatest for those employed as cooks and kitchen porters, with other catering-related occupations having an increased PMR in comparison to the previous supplement. Publicans and bar staff were the only occupation that re-appeared with a lower PMR and one new category of chemical workers (075) has been added. For females, significantly raised PMRs were listed for workers employed in food, drink and tobacco processing (078) and as welfare workers (013).

Table 5 Job codes with significantly high PMRs for liver cancer. Men and women aged 20-74 years, England

Job Group		Deaths	Expected deaths	PMR	Lower 95% CI	Upper 95% CI
SIC code	Description	1991 - 2000				
Men						
036	Seafarers	60	38.7	154.9	118.2	199.4
045	Publicans and Bar Staff	125	81.8	152.7	127.1	182.0
046	Caterers	102	44.7	228.1	185.9	276.9
059	Cooks and Kitchen Porters	100	38.1	262.5	213.5	319.2
075	Chemical workers	56	41.0	136.7	103.2	177.5
124	Machine Tool Operatives	181	148.0	122.3	105.1	141.5
Women						
013	Welfare workers	48	34.4	139.7	103.0	188.1
078	Other Food, Drink and Tobacco Process Operatives	25	14.9	167.8	109.0	247.8

Source: Coggon *et al* (2009) Occupational mortality in England and Wales, 1991-2000.

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 liver cancer are given in Table 6. From the information included in the IARC assessments (Siemiatycki *et al*, 2004) further classified the evidence as 'strong' or 'suggestive', which can also be found in Table 6. There is 'strong' evidence to support a link between exposure to the definite (Group 1) human carcinogens, ionising radiation and aflatoxin, and development of liver and biliary tract cancer and 'suggestive' evidence of a link between the probable (Group 2A) human carcinogens, polychlorinated biphenyls and trichloroethylene. Additionally, there is 'strong' evidence linking exposure to vinyl chloride (Group 1 carcinogen) and development of ASL a specific form of liver cancer, and 'suggestive' evidence of a link with HCC. There is also only 'suggestive' evidence linking exposure to arsenic and arsenic compounds (Group 1 carcinogens) with the development of ASL

Table 6 Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Vols 1-77 (IARC, 1972-2001), into Groups 1 and 2A, which have the liver 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				
Ionising radiation and sources, notably X-rays, gamma rays, neutrons and radon gas.	Radiologists; technologists; nuclear workers; radium-dial painters; underground miners; plutonium workers; clean-up workers following nuclear accidents; aircraft crew.	Sufficient	Strong	Bone, Leukaemia, Lung, Thyroid, Others.
Arsenic and arsenic compounds	Nonferrous metal smelting; production, packaging and use of arsenic-containing pesticides; sheep-dip manufacture; wool fiber production; mining of ores containing arsenic.	Sufficient	Suggestive (Angiosarcoma)	Skin, Lung
Monomers – Vinyl Chloride	Production: production of polyvinyl chloride and co-polymers; refrigerant before 1974; extraction solvent; in aerosol propellants.	Sufficient	Strong (Angiosarcoma) Suggestive (Hepatocellular)	None
Aflatoxin	Feed production industry; workers loading and unloading cargo; rice and maize processing.	Sufficient	Strong	none
Exposure circumstances				
None identified				
Group 2A: Probably Carcinogenic to Humans				
Agents & groups of agents				
Chlorinated hydrocarbons – Polychlorinated biphenyls,	Production – electrical capacitor manufacturing	Limited	Suggestive	none
Chlorinated hydrocarbons – trichloroethylene	Production – dry cleaning, metal degreasing	Limited	Suggestive	Non-Hodgkin lymphoma; Renal cell
Exposure circumstances				
None identified				

* Evidence according to the IARC monograph evaluation; [$] taken from Siemiatycki *et al*., (2004)

2.1 EXPOSURES

2.1.1 Ionising Radiation

'Ionising radiation' is radiation that has sufficient energy to remove electrons from atoms, which may result in production of negatively-charged free electrons and positively charged ionised atoms and hence is capable of interacting through various mechanisms with DNA.

There are two major classes of ionising radiation, both of which may arise from natural sources (e.g. from naturally occurring radioactive atoms, i.e. radionuclides) or from anthropogenic activity:

- photonic radiation which has no mass or charge, and includes X- and gamma- (γ) radiation.
- particulate radiation which has mass but may either be charged (such as alpha (α) - and beta- (ß) particles) or uncharged (such as neutrons).

The various forms of radiation possess different energies and penetrating power. Thus, α-particles have very low penetrating power being unable to penetrate even the dead keratinised skin cell layers, and are therefore only likely to be a biological hazard if absorbed either orally or by inhalation. Beta (β)-particles are able to penetrate up to 2 cm of human tissue. Neutron radiation is very penetrating but can indirectly produce proton radiation and high linear energy transfer (LET) recoil atoms through collisions, for example, with the hydrogen nuclei of water molecules. Both X- and the more powerful γ-radiations are highly penetrative being capable of passing through the human body, though they may also be absorbed by tissues and cell molecules. The quoting of dosages in terms of ionising radiation all relate to the damage inflicted and can be defined in various ways, including, absorbed, equivalent, effective or collective (see Box 1).

Definitions of Radiation Dose

- ***Absorbed Dose*** – radiation energy absorbed per unit mass of an organ or tissue. The unit or measurement is the gray (Gy).
- ***Equivalent Dose –*** confers the biological effectiveness of α-particles, electrons and photons. Obtained by weighting the 'absorbed dose' by a 'radiation weighting' factor (W_R) as set by the ICRP[1]. Unit of measurement is the Sievert (Sv).
- ***Effective Dose*** – confers the overall biological insult by taking into account variations in equivalent dose due to differences in the radiosensitivity of organs and tissues using a 'tissue weighting' factor (W_T) as set by ICRP. Unit of measurement is the Sievert (Sv).
- ***Collective Dose*** – Used to compare the effects of several sources of radiation and reflects both dose and number of people exposed. Calculated as the product of the mean dose of an exposed group and the number of individuals exposed. Unit of measurement is the 'man-Sievert'.

Box 1 Definitions of Radiation Dose (IARC, 2000 and 2001; NTP, 2005). [1] – International Commission on Radiological Protection.

IARC considered ionising radiation in the forms of X- and γ-radiation and neutrons in 2000 (IARC, 2000) and internally deposited radionuclides (the sources of α- and ß-particles) in 2001 (IARC, 2001). The IARC Working Groups considered that there is *sufficient evidence* in humans and experimental animals for the carcinogenicity of X- and γ-radiation, while for neutrons, there was considered to be *inadequate evidence* in humans but *sufficient evidence* in experimental animals. Thus, IARC concluded overall that X- and γ-radiation and neutrons were all *carcinogenic to humans (Group1).* The extent of evidence on the carcinogenicity in humans or experimental animals for the various radionuclides varied from *inadequate* to *sufficient* but, overall, the Working Group concluded that internalised radionuclides that emit α- or ß-particles are *carcinogenic to humans (Group 1).* Siemiatycki *et al*., (2004) also noted that ionizing radiation and its sources (including X- and γ-radiations, neutrons and radon gas) were definite (Group 1) human carcinogens and associated with cancer of several tissues including the liver, for which evidence was considered to be strong.

Strong non-occupational evidence of the carcinogenic potential of ionising radiation includes the 'Life Span Study', an ongoing study (45+ years) of the long-term health of survivors of the atomic bomb detonations at Hiroshima and Nagasaki (Japan) in 1945 (Pierce *et al*, 1996; UNSCEAR, 2000). For this cohort (n = 86,572), Thompson *et al*., (1994) reported an association with liver cancer, with an estimated excess relative risk at 1 Sv[1] (ERR_{1Sv}) of 0.49 (95% CI 0.16-0.92) and an excess absolute risk (EAR per 10 000 person-year Sv) of 1.6 (95% CI 0.54-2.9) for the period 1958-1987. Pierce *et al*., (1996) reported mortality rates from cancers in the same cohort for 1950-1990. Study findings therefore provide evidence of significant excess risk associated with both the incidence of and mortality from liver cancer following external exposure to radiation. Convincing evidence linking internal exposure to ionising radiation with development of liver cancer also comes from studies on patients injected with Thorotrast, an X-ray contrast medium containing thorium dioxide, an α-particle emitter), widely used between 1930 and 1950. It was found that approximately 59% of the dose injected accumulated in the liver. Sharp (2002) in a review of four studies on Thorotrast exposure in Germany (van Kaick *et al*, 1998), Denmark (Andersson *et al*, 1994), Portugal (da Silva Horta *et al*, 1978) and Japan (Mori and Kato, 1991), demonstrated positive associations with the development of HCC, ICC and, predominantly, ASL (Table 7).

Table 7 Relationship of internally deposited thorium and development of liver cancer[1]

Location of Study	Reference	Odds Ratio by Liver Cancer Subtype (95% confidence interval)		
		HCC	ICC	ASL
Germany	van Kaick *et al* 1998	1.00 (0.31-3.22)	3.16 (1.08-9.28)	60.6 (9.32-394)
Denmark	Andersson *et al* 1994	1.28 (0.39-4.11)	1.45 (0.41-5.1)	33.7 (3.52-324)
Portugal	de Silva *et al* 1978	0.02 (0.001-0.29)	0.23 (0.19-2.78)	14.9 (0.29-757)
Japan	Mori *et al* 1991	0.02 (0.015-0.03)	0.64 (0.54-0.69)	16.6 (15.4-17.9)

[1]. Sharp (2002); HCC – hepatocellular carcinoma; ICC – cholangiocarcinoma; ASL - angiosarcoma

The other sources of radiation considered here all relate to occupational exposure scenarios.

Radium Dial Painters:

Paints made fluorescent by the addition of small amounts of radium salts were widely used in the manufacture of instruments, clocks and watches, particularly during 1915 to 1930 and 1940 to 1954, and this was subsequently identified as a cause of neoplasia and a range of non-neoplastic health effects in several tissues, including the liver (IARC, 2001, Siemiatycki *et al*, 2004). However, as use of radium salts in dial painting had essentially ceased worldwide by 1974, this occupational scenario is not considered further.

***Radiologists and Radiologic Technologists*:**

Various radiation sources are used in medicine for diagnostic and therapeutic purposes, with workers in diagnostic radiology, dental radiology, nuclear medicine and radiotherapy being externally exposed. Diagnostic X-rays are the most frequently used source of ionising radiation in health care and medical radiation workers are typically exposed to low doses and rates of radiation.

Yoshinaga *et al*., (2004) reviewed epidemiologic studies of cancer risk among radiologists and radiologic technicians. The authors identified 8 major worker cohorts, including 3 from the US (Doody *et al*, 1998; Matanoski *et al*, 1984) cohort updated by (Miller and Jablon, 1970; Mohan *et al*, 2003) and one each from the UK (Berrington *et al*, 2001), Denmark

(Andersson *et al*, 1991), China (Wang *et al*, 2002), Japan (Yoshinaga *et al*, 1999) and Canada (Ashmore *et al*, 1998; Sont *et al*, 2001). The combined cohort comprised 270,000 medical radiologic workers exposed over several decades. Of the 8 cohort studies reviewed, only one, a cohort of 27,011 medical diagnostic X-ray workers in China during the period 1950-1995, estimated a SIR for liver cancer (Wang *et al*, 2002). An average cumulative dose of 551 mGy was estimated for workers employed before 1970 and an average 82 mGy for those employed after 1970. A significantly elevated risk (SIR = 1.2; $P< 0.05$) for liver cancer was reported for the cohort as a whole, and for workers employed before 1970 (SIR = 1.39; $P<0.05$). However, no elevated risk was found in workers employed post-1970 (SIR 0.85).

Mortality risk associated with liver cancer was estimated in 3 studies (Doody *et al*, 1998; Matanoski *et al*, 1984; Yoshinaga *et al*, 1999). The study of US radiologists reported by Matanoski *et al*., (1984) comprised a cohort of 6500 male US radiologists (radiation-exposed group) who joined the Radiological Society of North America between 1920 and 1969. Risk of incidence and mortality from cancer in this cohort was assessed in comparison with a group of other non-radiation exposed physician specialists, and for those radiologists employed between 1920 and 1939, a SMR = 1.45 was found for liver cancer; no such effect was seen in radiologists employed between 1940 and 1969 (SMR 0.56). One of the largest cohort studies of radiologic technicians was reported by Doody *et al*., (1998), where mortality risk following chronic exposure to low-levels of ionising radiation was evaluated in 146,000 workers in the US. No excess risk was noted for liver cancer with a SMR = 0.73 (95% CI, 0.51-1.02). Yoshinaga *et al*., (1999) carried out an assessment of mortality in a cohort of 12,000 Japanese male radiologic technicians registered up to 1975 and born before 1950. Mortality rates were compared with those for Japanese men and no excess risk of mortality from liver cancer was found (SMR = 0.83 and 0.81 for birth years of 1897-1933 and 1934-1950 respectively).

In their study of British radiologists, Berrington *et al*., (2001) assessed patterns of mortality in radiologists registered after 1920. Evidence of an increasing trend in risk of mortality from cancer was shown, with radiologists employed for more than 40 years having a 41% excess risk (SMR = 1.41, 95% CI 1.03-1.90); no evidence of an increased risk was found in radiologists employed after 1954. However, this study did not consider mortality from liver cancer in isolation.

***Nuclear Industry Workers*:**

Workers employed at the Mayak nuclear complex in Russia in the early years of production have been the focus of a number of studies as these employees are considered to have been potentially exposed to high levels of external γ-radiation and internal exposure through deposited plutonium. Working conditions at the Mayak facility, levels of exposure to radiation and some health effects on workers employed between 1948 and 1958 were first reported by (Nikipelov *et al*, 1990). In a later study, Gilbert *et al*., (2000) estimated liver cancer mortality rates from available incidence rates (assuming these to be equivalent) for a cohort of approximately 11,000 workers at this site employed between 1948 and 1958. Of the cohort, 2207 workers were found to have detectable body burdens of plutonium (mean dose 0.60 Gy). Excess liver cancer mortality was reported (SMR = 2.8, 95% CI, 1.9-3.9) for workers in the plutonium plant with body burdens >7.4 kBq. This was twice as high in women as in men (SMR = 3.0, 95% CI 1.9-4.6 and 1.5, CI 1.1-2.0, respectively); IARC (2001) attributed this to larger plutonium burdens and lower baseline risk in women than men. Histological typing of around 70% of the liver tumours showed 55% to be HCC, 18% ICC, 23% ASL and 4% unclassified. All ASL's occurred in workers with detectable body burdens of plutonium, with 80% being women. Liver cancers attributable to plutonium within the Mayak cohort of Russian nuclear industry workers have also been reported by Koshurinikova *et al*., (1998, 1999 and 2000).

In a recent 15-country multi-national retrospective cohort study, Cardis *et al*., (2007) estimated cancer-risk for nuclear industry workers exposed to low-level ionising radiation over a protracted period. The study included all cohorts from the UK NRRW study (Muirhead *et al*, 1999) and the 3-country combined study (Cardis, 1994; Cardis *et al*, 1995) with the overall cohort comprising 407,391 nuclear industry workers from 154 facilities who had been employed in at least one of the facilities for a minimum of 1 year. All subjects had been monitored individually for external radiation exposure to X- and γ-radiation (range 100 – 300 keV), and observed and expected numbers of deaths were calculated using an internal comparison population. Liver cancer rate was not significantly raised (ERRSv 6.47; 90% CI <0-27.0) and the RR (at 100mSv) was 1.65. There was no significant trend in liver cancer with cumulative dose. A number of other cohort-studies have also evaluated the risk of liver cancer following protracted exposure to ionising radiation and specific nuclides (e.g. tritium and plutonium) in nuclear workers in the UK (Carpenter *et al*, 1994; Carpenter *et al*, 1998; Muirhead *et al*, 1999; Omar *et al*, 1999) and US (Gilbert *et al*, 1993; Wilkinson *et al*, 1987). None have reported excess risk of liver cancer.

Studies of workers at the Mayak nuclear facility in Russia have shown a consistent association between internal plutonium exposure and development of ASL. However, studies on UK and US cohorts show consistently negative findings, identifying no excess risk of liver cancer associated with exposure to low levels of ionising radiation or radionuclides (including plutonium). This apparent contradiction is probably a reflection of differences in levels of exposure, particularly to plutonium. In the UK and US studies, only a small proportion of workers showed body burdens of plutonium >1 kBq whereas at the Mayak facility levels were >3 kBq in a significant number of workers.

***Miners*:**

Approximately 5 million workers worldwide are currently thought to be exposed to natural sources of ionising radiation at levels above those of background. Of those it has been estimated that around 75% are coal miners and a further 13% work in other underground mines (e.g. uranium ore; UNSCEAR, 2000), with exposure being both external and internal. The largest source of internal exposure in (coal) miners is through inhalation of radon progeny (Thoron) and dust containing long-lived alpha-particle emitters of uranium and thorium series. In general, good ventilation in mines is known to reduce exposure, and this is a legal requirement in the UK and therefore exposure to radon gas is generally low. In 1991, the average effective exposure dose (external and internal) for UK coal miners was estimated to be 0.6 mSv, with only around 70 miners being exposed to doses of more than 5 mSv, and 10 being exposed to doses greater than 15 mSv (UNSCEAR, 2000). Exposure of uranium miners (not a UK industry) to ionising radiation (external and internal) is at a higher level than for coal miners. In 1995, the annual exposures of German uranium miners were estimated to be between 1-6 mSv for approximately 1250 workers and between 6-20 mSv, for around 230 workers. Assessment of effects due solely to external radiation exposure in miners is often compromised by concurrent internal exposure, occurring as a consequence of inhalation of radon gas and radon decay progeny. Discussion is therefore restricted below to studies that have considered internal exposures only.

An important study is that of Darby *et al*., (1995), who undertook a pooled analysis of 11 - national studies of underground miners. The cohort comprised miners from 7 Uranium mines (Tomášek *et al*, 1994a; Tomášek *et al*, 1994b), Czech Republic; (Howe *et al*, 1986; Howe *et al*, 1987; Kusiak *et al*, 1993; Morrison *et al*, 1988; Muller and Kusiak, 1988), Canada; (Hornung and Meinhardt, 1987; Samet *et al*, 1991; Waxweiler *et al*, 1981), USA and (Tirmarche *et al*, 1993), France, 2 Tin mines (Hodgson and Jones, 1990; Xuan *et al*, 1993), China) 1 Fluorospar mine (Morrison et al 1988, Canada) and one Iron (Radford and Renard, 1984, Sweden). The overall cohort considered comprised 64,209 men employed in mines for an average of 6.4 years (range 1.7 to 18.4 years). Exposure to radon progeny was estimated as

working-level months (WLM) with the overall average final cumulative exposure being 155 WLM. Mortality rates were compared to expected numbers of deaths, calculated from national or regional data. Observed (O) and expected (E) deaths from liver cancer were sub-divided according to employment start dates, using cumulative radon exposure and a 5-year lag to allow for the latency period. Mortality from liver cancer was significantly higher in miners with an O/E ratio of 1.73 (95% CI 1.29-2.28). The O/E ratio was higher in those workers employed for ≥ 10 years (1.78; 95% CI 1.31-2.37) compared with those employed for less than 10 years (1.19; 95% CI 0.24-3.47). Interestingly, the higher mortality rate from liver cancer in the miners employed for greater than 10 years did not correlate with cumulative radon exposure and it was therefore considered by the authors and the IARC Working Group (2001) that radon exposure alone was unlikely to be the cause of the excess risk for liver cancer; rather the discrepancy in findings may reflect confounding by lifestyle factors, such as a high alcohol consumption or from miss-diagnosis of some secondary cancers as primary liver tumours.

***Aircraft Crew*:**

Aircraft pilots and cabin crews are exposed to cosmic radiation (gamma-radiation and neutrons) with duration (short and long haul) and extent of exposure varying with the route of travel. Annual exposure to ionising radiation worldwide for aircraft crew has been estimated to be 3 mSv/person, resulting in a world-wide total effective dose in 1985-1989 of approximately 800 person-Sv (UNSCEAR, 1993). The extent of exposure of aircrew to neutrons is less well defined but estimated as around 0.1 mSv per transatlantic flight (Schalch and Scharmann, 1993).

Mortality from cancer amongst male aircraft cockpit crew was assessed in a cohort study from 9 European countries (Blettner *et al*, 2003) which comprised 28,000 males identified from airline personnel records in Finland, Germany, Great Britain, Greece, Iceland, Italy and Sweden with an estimated average annual exposure of 2-6 mSv. Observed and expected deaths for the period 1960-1997 were compared with the respective national mortality rates; adjustment for period and duration of employment was included in the analysis. No evidence of an increased risk of liver /biliary tract cancer was seen in the cohort (SMR = 0.86; 95% CI 0.55-1.33). The influence of duration of employment on SMR was not, however, considered for liver cancer in isolation.

2.1.2 Arsenic and Arsenic Compounds

Arsenic occurs in organic and inorganic forms, and is capable of eliciting various neoplastic and non-neoplastic toxicities in a range of tissues and organ systems, depending on route of exposure. Inorganic arsenic has been known to be carcinogenic since the late 1960's, with extensive evidence of associations between inhalation and oral ingestion of inorganic arsenic and cancers of the lung and skin (ATSDR, 2007). Arsenic and arsenic compounds were first reviewed by IARC in 1973, with updates published in 1980 and 1987 (IARC 1980, 1987,). The evaluations by IARC concluded that there is *sufficient* human but *limited* animal evidence of carcinogenicity and that arsenic and arsenic compounds are *carcinogenic* to humans (Group 1). Siemiatycki *et al*., (2004) also considered the evidence, and concluded that it was suggestive for liver angiosarcoma (ASL).

Historically, the main occupations with high levels of exposure to arsenic have included hot copper smelters, manufacturers of arsenical pesticides and sheep-dip compounds, fur handlers and vineyard workers and some miners (Hayes, 1997, IARC, 1987). Arsenic is currently still used in a variety of industrial processes, including the manufacture of glass and nonferrous alloys, and of insecticides and herbicides, although not now in high quantities. Gallium arsenide is an important semiconductor material used in integrated circuits. Arsenic is also used in wood preservatives (chromated copper arsenate, CCA); however, many countries, including EU member states, have restricted the use of CCA containing preservatives.

Exposure to arsenic may also occur during the smelting of copper, lead, and zinc, and during its mining. The regulatory history for arsenic began after the initial IARC review, when a UK occupational exposure limit (OEL) of 0.2 mg/m^3 (8-hr time weighted average (TWA) was set. This was reduced to 0.1 mg/m^3 (8-hr TWA) in 1989, and was established as the workplace limit in 2005 (Pritchard, 2007). The CAREX database estimates that around 25,000 GB workers were exposed to arsenic between 1990-1993, with the highest percentage exposure found in workers in non-ferrous metal basic industries (see Section 3.3).

Although most occupational exposure to arsenic will occur through inhalation, there is some non-occupational evidence linking ingestion of arsenic and arsenic compounds with the development of liver cancer. These include a series of case studies of patients with arsenic-induced skin cancer who were also reported to have developed liver tumours (ATSDR, 2007). However, it is not certain if the cases described in these studies represent *primary* or *secondary* liver tumours. The findings from case studies are supported by a number of large-scale epidemiological studies, where associations and/or dose-response trends were detected for tumours of various internal organs, including the liver (ATSDR, 2007). Chen *et al,* (1985; 1986; 1988, 1992) reported on the association between high-arsenic artesian well water and cancers in an area of Taiwan where Blackfoot disease (BFD), a unique peripheral vascular disease related to continuous arsenic exposure, was endemic. In comparison with the general population in Taiwan, both the SMR and cumulative mortality rate were significantly higher in the study cohort, with a SMR for liver cancer of 1.70 (95% CI 1.51-1.89) in males and 2.29 (95% CI 1.92-2.66) in females. In addition, a positive dose-response was reported between the SMR for liver cancer and black-foot prevalence (Chen *et al*, 1985). In a further study, the age-sex adjusted ORs for developing liver cancer in subjects who had ingested well water over minimum of 40 years was found to be 2.67 (Chen *et al*, 1986). Differences in cancer risk between males and females was also assessed and a potency index for developing liver cancer due to an intake of 10 micrograms kg day of arsenic was reported as 4.3 x 10^{-3} for males and 3.6 x 10^{-3} for males (Chen *et al*, 1992). A significant dose response relationship was also identified. The multivariate-adjusted regression coefficient (indicating increase in age-adjusted mortality per 100,000 person-years for every 0.1 ppm increase in arsenic level of well water) was reported as 6.8 for cancer of the liver (Chen and Wang, 1990).

In contrast, no significant excess risk of liver cancer was found in a cohort exposed to chronic consumption of arsenic contaminated drinking water in the US. SMR for cancer of the liver and biliary tract was found to be 0.85 (95% CI, 0.18-2.48) in males and 1.42 (95% CI, 0.57-2.98) in females (Lewis *et al*, 1999). The apparent difference in these findings compared with those from the Taiwan cohort is most probably due to differences in levels of arsenic-contamination, with levels of exposure in the US cohort being considerably lower (<200 ppb) than in the Taiwan cohort (approximately 2000 ppb).

An increased risk of liver cancer, and in particular ASL, has also been associated with ingestion of the arsenic-containing medicine, Fowler's Solution (Lander *et al*, 1975; Regelson, 1968).

The other sources of arsenic considered here all relate to occupational exposure scenarios.

Metal Smelters:

Exposure of workers to arsenic and arsenic compounds during the smelting of nonferrous metal is potentially high due to the wide use of arseniferous ores. A prospective study of copper smelter workers in Japan who had potentially been exposed to arsenic compounds was reported by Tokudome and Kuratsune (1976). Mortality rates from cancer were assessed amongst a cohort of 2675 male workers employed at a metal refinery in Japan between 1949 and 1971, and compared with the national average for Japanese males. A significant excess was noted for liver (primary, secondary and unspecified) and biliary tract cancer (SMR =

3.37) within a sub-cohort of copper smelters (n=839). However the authors report that, for the majority of these deaths, the type of tumour was not adequately diagnosed and therefore considered that their findings required further validation.

Pesticide Production and Application:

The link between exposure to inorganic arsenic and development of ASL was initially reported by Roth in 1957 who noted a high incidence of ASL development in a group of vineyard workers in Germany and France. These workers had been heavily exposed to arsenical insecticides by inhalation of copper arsenate dust and through the consumption of a wine made from contaminated grape skins (Galy *et al*, 1963; Latarjet *et al*, 1964; Liebegott, 1952).

Incidence of cancer was evaluated in a large, prospective cohort study of pesticide applicators in the US (Alavanja *et al,* 2005). Overall cancer risk was assessed in commercial applicators, farmer applicators and spouses of farmers. Although the median period of use was 16 years and 7.3 years in farmers and commercial applicators, a high proportion of farmers had used pesticides for >20 years (37 %) and may therefore have been exposed to arsenic containing pesticides. Incidence of liver cancer was not found to be increased in either the commercial applicators (O/E of 0, 95% CI 0f 0-4.20), the farmers (O/E of 0.98, 95% CI 0.68-1.37) or farmers spouses (O/E of 0.86, 95% CI of 0.17-2.51).

Giordano *et al* (2006) reported on the most recent follow-up of a cohort of 168 urban pesticide applicators employed in Rome in 1946. An earlier analysis of mortality up to 1987 had shown a significant excess in mortality from liver cancer within the cohort. In the update study, mortality was followed to 2005 and the significantly increased risk of liver cancer was still apparent, with a SMR = 5.96 (90% CI 2.04-13.65). The SMR for liver cancer was higher in workers exposed prior to a ban of arsenic-containing pesticides in 1978, however, no association was found between risk and duration of exposure.

2.1.3 Vinyl Chloride

Vinyl chloride monomer (VC) has been commercially available since the 1920s and has been used since the 1930s to manufacture polyvinyl chloride (PVC) resin. In 2000, production of VC was estimated to be 27 million tons per year worldwide, double the production of 1980, and occurs in most industrialised countries, including the UK, which currently has 2 producers of PVC.

Vinyl chloride is not known to occur naturally and exposure is predominantly occupational. The highest exposure is known to occur during the cleaning of the reactors in which VC is polymerized to make PVC, a process that traditionally was done manually by workers who would have sustained exposures to VC as high as 1000 ppm (2600 mg/m3; (Anderson et al, 1980, Barnes, 1976, Purchase et al, 1987, Xu et al, 1996).

Vinyl chloride has very specific effects and is strongly associated with the development of angiosarcomas (Creech and Johnson, 1974, Popper et al, 1978). The report by Creech and Johnson (1974) detailed cases of the usually rare form of liver cancer termed ASL, among workers exposed to vinyl chloride and led to the identification of a causal association between VC exposure and risk of developing this type of cancer. As a consequence, in 1975 many countries reduced occupational VC exposure levels to <1-5ppm (<2.2-13 mg/m^3) while, in 1974, the Association of Plastic Manufacturers in Europe were prompted to set up a register to record all cases of ASL resulting from exposure to VC worldwide. In a study of this register, Forman et al (1985) concluded that in the UK during the decade 1975-1984, the increased number of cases of ASL represented a rise of between 10% and 35% for that period.

IARC Working Groups have considered VC in 1974, 1979 and 1987. Most recently, IARC (1987) considered that there is *sufficient* evidence in both humans and experimental animals for the carcinogenicity of VC, and concluded that VC is *carcinogenic to humans* (Group 1). Although there have been many case reports, cohort studies and other epidemiologic studies that have attempted to assess the effects on health and mortality of VC exposure in workers from many countries, information on occupational exposure levels for the period prior to the mid-1970s is, in many cases, inadequate to allow accurate assessment of exposure-response relationships.

Exposure to VC was suggested to be a causal factor in the development of ASL by Baxter *et al,* (1980) who reported findings of the annual occurrence of ASL in Britain during the period 1963 – 1977. Although an increased risk of ASL was suggested in the electrical and plastics fabrication industry, exposure information was too limited to identify specific chemicals as causal agents. Indeed, of the 35 cases of ASL reported for the 14-year period, only 2 could be attributed to heavy exposure to VC.

In a review by Kielhorn *et al*., (2000), epidemiologic studies of mortality amongst VC/PVC workers from several countries were combined (summarised in Table 8). The authors reported a 5-fold excess of liver cancer amongst workers that was primarily due to an excess risk of ASL, with a 45-fold increase in ASL being seen in workers exposed to >10,000 ppm-years compared with workers exposed to <2000 ppm years.

Table 8 Summary of findings for liver cancer[1] from epidemiologic studies on workers exposed to VC[2].

Liver Cancer[2]	European Cohort	US Cohort	German Cohort	Russian Cohort	Canadian Cohort	French Cohort	All Studies
Ref	Simonato *et al* (1991)	Wong *et al* (1991)	Weber *et al* (1981)	Smulevich *et al* (1988)	Theriault & Allard (1981)	Laplanche *et al* (1992)	-
O/E	24/8.4	37/5.77	12/0.9		8/0.14	3/0	81/19.21
SMR	2.86	6.41	15.23	0/n.a	57.14	3 ASL	5.33
CI	1.83-4.25[a]	4.5-8.84[b]			8 ASL[c]		4.23-6.62

[1] Including ASL
[2] Adapted from Kielhorn *et al*., (2000)
n.a – not available
[a] of 17 liver cancers confirmed histologically, 16 were ASL.
[b] 15 cases of ASL from death certificates and 21 from international register.
[c] plus 2 undiagnosed ASL cases.

The WHO International Programme on Chemical Safety Task Group (IPCS 1999) reported that "there is a 5-fold excess risk for liver cancer observed among workers exposed to VC", which can largely be attributed to excess risk for ASL. An association between occupational VC exposure and other forms of liver cancer is less well defined. In an updated study of mortality and cancer incidence among 12,700 Europeans working in the vinyl chloride industry an excess of liver cancer was observed (SMR=2.4; 95%CI=1.8-3.1), as in earlier studies (Ward *et al*, 2001). A strong exposure-response relation was reported for angiosarcomas where time since first exposure, duration of employment, and cumulative exposure were all associated with extremely high risks ranging from 7.9 (95%CI=1.7-37.3), to 15.7 (95%CI=5.6-44.0) and 88.2 (95%CI=26.4-295), respectively. However, the study

included only a small number of HCC cases and confounding factors, such as alcohol consumption and viral infection, were not adjusted for.

In addition, Wong *et al*., (2003) have suggested a possible interaction between VC exposure and HBV infection in the development of liver cancer. Similar suggestions have been made by Mastrangelo *et al*., (2004); these authors noted that VC exposure appears to be an independent risk factor for HCC that synergistically interacts with alcohol consumption and additively with viral hepatitis infection. With regards to the risk posed by VC exposure on development of HCC, the Industrial Injury Advisory Council (2005) concluded that there was insufficient evidence to support an increased risk other than for ASL, but advised monitoring of the situation to assess new evidence as it became available.

A meta-analysis, based on four studies, obtained a meta-SMR of 2.52 (95%CI=1.56-4.07) (Boffetta *et al*, 2003). However, the authors noted that this might have been higher because of under-diagnosis of angiosarcoma of the liver.

A follow-up mortality analysis was carried out on a previous UK study cohort of 1700 male workers exposed to PVC during or prior to 1979 (IOM, 2006). The period of follow-up was from Jan 1st 1979 to December 31st 2003 and mortality details were obtained from the Office for National Statistics (ONS). Individual exposures up to 1979 were based on estimates of dust concentrations in 1979 and time accumulated in exposed jobs up to that date. No exposure information was available after that date. Over the 20+ year follow-up adopted in the study, 6 cases of liver cancer were reported within the cohort, of which 2 were ASL. The number of expected cases of liver cancer during the same period was noted as 2.2; however an SMR (± 95% CI) was not calculated.

A recent Policy Watch report (Grosse *et al*., 2007) summarises the findings of an IARC working group, formed to re-assess the carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride and vinyl bromide. It was concluded that exposure to vinyl chloride substantially increased the relative risk for development of ASL, which increased further with duration of exposure. The Working Group also concluded that an increased risk of HCC was associated with cumulative exposure to vinyl chloride.

The carcinogenicity of vinyl fluoride and vinyl bromide was also considered by the Working Group. It was concluded that the available animal studies demonstrated a "consistently parallel response between these chemicals and vinyl chloride", including development of ASL, however, the effects of human exposure to vinyl fluoride and vinyl bromide have not been adequately assessed. Both chemicals were classified as *probably carcinogenic to humans* (Group 2A) and the Working Group advised that they should be considered to "act similarly to the human carcinogen, vinyl chloride". These conclusions are now available in the published report. (IARC 2008).

2.1.4 Aflatoxin

Aflatoxins are naturally occurring fungal products (i.e. mycotoxins) produced by *Aspergillus* species such as *A. flavus* and *A. parasiticus*. There are four principal aflatoxins, B_1, B_2, G_1, G_2, and a metabolite (M_1) of aflatoxin B_1, that can be present in some human foodstuffs such as grains, through contamination before harvesting or during storage; presence in milk and dairy products is as a result of animals consuming feed contaminated with aflatoxins (Applebaum *et al*, 1982). The aflatoxin-producing *Aspergillus* species are ubiquitous in countries with hot and humid climates, including sub-Saharan Africa and Southeast Asia and contamination of foodstuffs in these regions is widespread; European populations become exposed through the importing of contaminated crops. An extensive review of aflatoxin levels in commodities from North America, South America, Europe, Asia and Africa was carried

out by IARC (1993) and the most pronounced contamination was seen in maize, peanuts, cottonseed and tree nuts.

Aflatoxins have been considered in IARC monographs in 1972, 1976, 1987, 1993 and, most recently, 2002. The IARC Working Group (1993) considered that there was *sufficient evidence* in humans for the carcinogenicity of naturally occurring mixtures of aflatoxins with *sufficient evidence* in humans being noted specifically for aflatoxin B_1 but *inadequate evidence* for aflatoxin M_1. The extent of animal data was also noted to vary between the individual compounds, such that it was considered that there was *sufficient evidence* in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins and aflatoxins B_1, G_1 and M_1 but *limited evidence* for aflatoxin B_2 and *inadequate evidence* for aflatoxin G_2. Overall the Working Group concluded that naturally occurring aflatoxins are *carcinogenic to humans (Group 1)* and that aflatoxin M_1 is *possibly carcinogenic to humans (Group 2B)*. The conclusions for naturally occurring aflatoxin mixtures were reaffirmed at the most recent IARC review (2002). In an attempt to reduce exposure of humans and animals to aflatoxins, regulatory limits and a worldwide monitoring programme have been established. In 1998, the EU regulated the permissible aflatoxin content of all raw commodities and processed foods and of aflatoxin M_1 in milk (European Commission, 1998). The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has, since 1981, recommended that aflatoxin levels in food be reduced to the lowest levels technologically practicable. The legal limit for aflatoxin B_1 in cereals, including rice, is 2 µg / kg or 2 ppb.

A large number of descriptive, cohort and case-control studies have assessed the potential link between non-occupational exposure to aflatoxins and risk of liver cancer and are summarised in IARC (2002). The more recent of the studies have improved study design, particularly in relation to cohort size and accuracy of exposure measurements to both aflatoxin and hepatitis viruses, both of which are known to play key roles in developing liver cancer (see section 2.0). Increased risk of liver cancer following exposure to aflatoxin (generally measured as aflatoxin-albumin adducts) has been reported for cohorts in Shanghai (RR = 1.6, 95% CI, 0.8-3.1; Qian et al 1994), Taiwan (OR of 5.5, 95% CI 1.2-505, Chen et al 1996; OR of 1.6, 95% CI, 0.4-5.5, Wang et al, 1996; OR of 2.0, 95% CI, 1.1-3.7, Sun et al 2001) and Qidong (OR of 3.5, 95% CI 1.3-10.0, Lu et al, 1998); these studies incorporated various measures of aflatoxin exposure and, therefore, to enable inter-study comparison, only the risk values for afltoxin-albumin adduct exposure measures have been presented. It should, however, be noted that these estimates may be conservative, with risk values being generally higher when other metrics are used, particularly when exposure is expressed as aflatoxin metabolite-DNA adducts, AFB_1-*N*7-guanine (which is thought to be the precursor to mutations induced by aflatoxin B_1; IARC, 2002).

While considerable attention has been given to assessing the risk associated with consumption of contaminated foodstuffs, the risk associated with occupational exposure to aflatoxin through inhalation of contaminated foodstuffs has been less well defined. The highest occupational exposures to aflatoxins are likely to occur in the food production industry, during loading and unloading of cargo and during rice and maize processing. Estimates of exposure have been attempted in a number of studies. Aflatoxin B_1 was found at levels of 300 ng/m^3 during the unloading of ships (Lafontaine *et al*, 1994). Autrup *et al*., (1993) estimated the average daily intake of aflatoxin B_1 to be 64ng/kg body weight in employees at an animal feed processing plant in Denmark. Airborne (respirable) aflatoxin levels of 26 pg/m^3 were measured in rice and maize processing plants in India (Ghosh *et al*, 1997), while air samples taken during the handling of animal feed in factories in Thailand were estimated to contain levels of between 1.55 and 6.25 ng/m^3, compared with control samples of 0.99 ng/m^3 (Nuntharatanapong *et al,* 2001).

Prior to the recognition in 1965 of the hazards associated with exposure to aflatoxins, levels of contamination of food commodities and subsequent levels of exposure were potentially high. Many occupational studies therefore relate to workers employed before this date. A significantly elevated risk of liver cancer was reported in a cohort of Swedish grain millers employed during the period 1961 to 1979, with a SIR = 2.38 (95% CI 1.14-4.38; Alavanja *et al*., 1987). In a further study Alavanja, *et al*., (1990) examined cause-specific mortality of a cohort of 22,938 males who were members of the American Federation of Grain Millers during the period 1955 to 1985. In addition, a nested case-control study was carried out for individuals within the cohort for whom complete employment information was available (numbers not specified by authors) to relate occupational factors and exposure information with specific causes of death. The observed and expected numbers (US white males) of deaths from liver cancer were recorded and were found not to be significantly raised for workers in flour mills (SMR = 0.69) and workers in other grain industries (manufacture and processing of animal feed, beet sugar, potatoes; SMR = 0.19). As no increased risk was found for liver cancer amongst the cohort; further case-control analysis was not carried out by the authors.

Olsen *et al*., (1988) assessed occupational cancers among male employees at 241 livestock feed processing companies in Denmark dating back to 1964 with past exposures to aflatoxins equivalent to 170 ng/day. The risk of liver cancer and cancers of the biliary tract within the cohort were increased significantly (2-3 times) after a 10 year lag period (SPIR of 1.41, 95% CI 57-293). In a nested case-control study (Dossing *et al*, 1997) the employment histories (beginning in 1964) of 973 cases of histologically verified HCC, ICC or combined HCC/ICC were assessed against 15,348 controls. Men from 35 industrial branches, women from 7 branches and men and women from 3 branches had an excess risk of liver cancer, with an OR>1.0; of these, 29 industrial branches had an OR>3.0. The authors proposed that the increased risk seen in warehouse and storage workers (n= 71,920; OR 4.02, 95% CI 1.7-9.33 after a 10 year lag period) and oil mill workers (n= 31,251; 3.52, 95% CI 1.7-2.3 after a 10 year lag period) was attributable to aflatoxin exposure.

It should be noted that for many of the studies described above, exposure to aflatoxin is only estimated or inferred, rather than measured, and adjustment for confounding factors (such as alcohol consumption) appears not to have been generally attempted.

2.1.5 Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a class of organic compounds with varying numbers of chlorine atoms (1 to 10) attached to biphenyl (2 benzene rings) that have specific chemical and physical properties that have been widely utilised by industry, including exceptional thermal stability, resistance to oxidation, acids, bases and other chemical agents and excellent insulating properties.

Commercial use of PCB mixtures began in 1929 and they were produced in large quantities, reaching 38.5 million kg/annum by 1970. Many countries were producers of PCBs including: Great Britain; Austria; former Federal Republic of Germany; France; Italy; Japan; Spain; USSR and USA. The total global production of PCBs to date has been estimated as around 1.5 million tons, with the US being the largest manufacturer with over 600,000 tons produced between 1930 and 1977, while European production to 1984 is thought to have been in the region of 450,000 tons. Due to their physiochemical properties, PCBs were widely used in a range of industrial products including: heat transfer fluids; hydraulic fluids; as lubricants (closed applications); in plasticizers; surface coatings; inks; adhesives; pesticide extenders; and for microencapsulation of dyes for carbonless duplicating paper (open systems).

Although the toxic and environmental impacts of PCBs were recognised as early as 1937 (Drinker *et al*, 1937), few regulations were imposed on use until concerns focused, in the

1970's, on their marked physical stability and persistence and the consequent recognition of their status as a persistent organic pollutant (POP). In 1973 the use of PCBs in open systems was stopped, although PCBs were still permitted for use in closed systems such as capacitors and transformers. By 1974, US production had dropped to 18.4 million kg and by 1977 US domestic production of PCBs was banned. In the UK, the use of PCBs in new 'closed-use' equipment was banned in 1981 by which time the majority of production had also ceased. However, the use of PCBs in existing 'closed-use' equipment was not eliminated until December 2000.

IARC Working Groups have considered PCBs in 1974, 1978 and 1987. IARC (1987) considered that there was *limited* evidence in humans but *sufficient* evidence in animals to classify PCBs as *probably carcinogenic to humans* (Group 2A). Evidence of the toxic nature of PCBs has been highlighted by a number of non-occupational exposure incidents. For example, mass poisonings occurred in western Japan in 1968 and central Taiwan in 1979 following ingestion of rice oils contaminated with polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQ). The exposed populations – approximately 1800 in Japan and 1700 in Taiwan – showed a range of non-neoplastic clinical signs, most obviously acne-like dermal changes, of varying severity and persistence. The exposed populations of these incidents (which are generally referred to as the Yusho and Yu-Cheng accident, respectively) have been subject to follow-up in a number of studies. In a comprehensive study following 887 male Yusho patients to 1983, a statistically significant increased mortality from liver cancer was reported (OR of 5.6 [3.9 using local expected rates]). However, adjustment for other potential confounders that might explain the effect was not possible (Kuratsune *et al*, 1986). Also, an autopsy series on 10 Yusho patients reported the presence of adenocarcinomas (HCC or ICC) in two patients, but no causal association could be made with PCBs (Kikuchi, 1984).

Other retrospective cohort mortality studies have considered exposed workers from manufacturing or the use of capacitors. In a review of the available evidence, Knerr and Schrenk (2006) noted that most occupational cohorts have also been exposed to other chemicals and that commercial PCB mixtures are likely to have been contaminated with chlorinated dibenzofurans and various concentrations of dioxin-like PCBs (DL-PCBs). A further limitation identified was that retrospective estimation of exposure may not adequately describe durations or rates of exposure, which may be important factors in determining carcinogenic outcome. In 1959, maximum atmospheric PCB levels in several plants in the US were 0.2-10.5 mg/m^3 (Elkins, 1959). Blood levels of PCBs in workers at a capacitor factory in Finland in 1973 were also found to be greatly increased (50 times) over those of an unexposed control group (0.07-1.9µg/g and 0.003-0.012µg/g; Karppanen and Kolho, 1973). Since PCB production and distribution was banned, occupational exposure has been mainly limited to work on the maintenance and repair of electrical transformers and capacitors and the disposal of material containing PCBs. The UK TWA has been set at 0.1 mg/m^3 over an 8 hr period (HSE-EH40, 2005).

A retrospective cohort mortality study of 2500 US workers exposed to a mixture of PCBs during manufacture of electrical capacitors prior to 1950 and followed up to 1976 was reported by Brown (1981), with an additional analysis of the cohort up to 1982 reported in 1987 (Brown, 1987). Although excess mortality was noted for liver and biliary tract cancer (SMR = 2.80, 95% CI 0.58-8.20) in the 1981 study, the increase was not significant. With an additional 2 cases being reported in the 1987 follow-up study, the SMR (2.63) was statistically significant. However, the study findings were limited by small numbers and possible misclassification of the cause of death (Brown and Jones, 1981; Brown, 1987). Mortality from liver and bile duct cancer was also increased in a cohort of workers in a capacitor manufacturing facility in Sweden. Employees were exposed between 1965 and 1978 to PCBs of 42% chlorine content, with average exposure duration of 6.5 years; airborne levels of PCB exposure at the facility were measured as 0.1 mg/m^3 in 1973. SMR for liver and

biliary tract cancer combined for the entire cohort was reported as 1.96 (95% CI 0.05-10.9). However, in workers categorised as having 'high-exposure', the SMR was 6.67 (95% CI, 0.16-37.1). The authors highlighted several limitations in the study findings including limited cohort size and small number of liver cancer cases. In addition they noted that the case distribution did not correlate with exposure (Gustavsson and Hogstedt, 1997). Bertazzi *et al*., (1987) also reported an increase in mortality from cancer of the digestive system (SMR = 3.46, 95% CI 141-721) which included the liver and biliary tract, in 2100 workers in an Italian capacitor manufacturing plant employed during the period 1946 and 1987. Airborne PCB levels at the plant had been measured and ranged from 5.2 and 6.8 mg/m^3 in 1954 to 0.048 and 0.275 mg/m^3 in 1977. The obvious limitation of this study however, is that liver and/or liver and biliary tract cancers were not categorised separately.

In cohorts of 3588 capacitor manufacturing workers and 38,925 electric utility workers (Loomis *et al*, 1997, Sinks *et al*, 1992a), no increases in cancer mortality were noted for either group (Capacitor manufacturing workers - SMR = 1.1, 95% CI 0.0-6.4; Electric utility workers - SMR = 0.73, 95% CI 0.57-0.93). Kimbrough *et al*., (1999b) carried out retrospective cohort mortality study of 7075 workers employed in two US capacitor manufacturing/repair plants between 1945 and 1977. No significant excess of liver cancer was found amongst the cohort. In a later paper, Kimbrough *et al*., (1999a) consider that the earlier study was subject to several limitations, including, the misclassification of some exposure levels, insufficient difference in dose between exposed and control groups and lack of statistical power due to low numbers of deaths for some cancers.

2.1.6 Trichloroethylene

Trichloroethylene (TCE) is a chlorinated hydrocarbon commonly used as an industrial solvent for a variety of organic materials. Historically, TCE has been widely used as a degreaser for metal parts, and although since the 1950s its demand for this purpose declined, there has been a recent resurgence in its use. Five main industrial groups use TCE in vapour or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electrician equipment, transport equipment, and miscellaneous manufacturing industries (IARC, 1995). TCE can be used as an extraction solvent for natural fats and oils, spices and hops and for the decaffeination of coffee (Linak *et al*, 1992). In addition it is used as a chemical intermediate, as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides and cold metal cleaners (ATSDR, 1997) and during the period 1930 to 1960 it was also used as a volatile anaesthetic.

The IARC working group most recently considered TCE in 1995 and stated there was *limited evidence* in humans but *sufficient evidence* in experimental animals for the carcinogenicity of TCE and that it is *probably carcinogenic to humans* (Group 2A; IARC, 1995). This overall evaluation was made from the findings of a number of animal and human epidemiologic studies. Several animal studies showed significant increases in benign and malignant liver tumours, and incidence of lymphomas in mice, following oral and inhalatory exposure to TCE (Henschler *et al*, 1995; Maltoni *et al*, 1986; Maltoni *et al*, 1988; NTP, 1990). Of the human epidemiologic cohort and case-control studies, IARC considered the most important findings were those showing an elevated risk for cancer of the liver and biliary tract, and a slightly elevated risk for non-Hodgkins lymphoma (Anttila *et al*, 1995; Axelson *et al*, 1994; Spirtas *et al*, 1991). In 1996 the UK's Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) reviewed TCE and concluded that there was limited epidemiological evidence for a carcinogenic effect in humans but that it should still be regarded as a potential human carcinogen (Department of Health, 1998). In GB, the current 8-hour TWA Workplace Exposure Limit has been set at 100 ppm (550 mg/m^3) and with a STEL (15 min) of 150 ppm (820 mg/m^3; EH40, HSE, 2005)

Epidemiological studies on TCE have included occupational cohort studies, nested and population-based case-controls studies which have mainly focused on metal degreasing and aircraft/aerospace maintenance or manufacturing work. Other industries identified as involving potential exposure to TCE through use as a degreaser and as a general solvent, include: iron/steel industries; painting; electronics industry; chemical industry; printing; shoe manufacturing; and jewellery manufacturing. However in few, if any, studies have workers been exposed to TCE exclusively.

Evidence of a potential association between occupational exposure to solvents, including TCE, and development of liver cancer was found in several case-control studies (Hardell *et al*, 1984; Hernberg *et al*, 1984; Hernberg *et al*, 1988), where ORs were increased for primary liver cancer in solvent exposed workers (OR of 2.3, 95% CI 0.8-7.0; OR of 0.6, 95% CI 0.3-1.4 [males] and 3.4, 95% CI 1.1-10 [females]; OR of 1.8, 95% CI 0.99-3.4 respectively). The IARC working group (IARC, 1995) also evaluated excess risk of cancer associated specifically with TCE using a number of cohort studies of three occupational groups: dry cleaners; workers who had undergone biological monitoring for exposure to trichloroethylene; and employees in miscellaneous manufacturing industries (Anttila *et al*, 1995; Axelson *et al*, 1994; Garabrant *et al*, 1988; Spirtas *et al*, 1991). Data from these studies consistently indicated an excess risk for cancer of the liver and biliary tract (Anttila *et al*, 1995; Axelson *et al*, 1994; Spirtas *et al*, 1991). The main findings for liver cancer are summarised in Table 9.

Table 9 Studies of trichloroethylene and liver cancer

Reference	Industry/ product	Country	Design	Study size	Results[#]
Garabrant *et al*., (1988)	Aircraft manufacture (1958-1982)	USA	Cohort	14,067 (male and female)	SMR=0.94 (95% CI 0.40-1.9, 8 obs.)
Spirtas *et al*., (1991)	Aircraft manufacture (1953-1982)	USA	Cohort	7282 (male and female)	SMR=1.9 (95% CI 0.91-3.5, 10 obs.) *SMR=1.1 (95% CI 0.14-4.0, 2 obs) **SMR=2.2 (95% CI 0.96-4.4, 8 obs.)
Axelson *et al*., (1994)	TCE use – biological monitoring (1958-1987)	Sweden	Cohort	1421 (male only)	SIR=1.4 (95%CI 0.38-3.6, 4 obs.)
Anttila *et al*., (1995)	TCE use – biological monitoring (1967-1992)	Finland	Cohort	3089 (male and female)	SIR=1.9 (95% CI 0.86-3.6, 9 obs.) *SIR=2.3 (95% CI 0.74-5.3, 5 obs.) **SIR=1.6 (95% CI=0.43-4.0, 4 obs.)

#considered to be liver and biliary tract cancer unless otherwise specified.
***** Primary liver cancer
****** Biliary tract cancer

Wong and Morgan (1990A) described a cohort study of 20,535 workers in a US aircraft manufacturing company employed between 1950 and 1993. No increased risk from liver and biliary tract cancer combined was seen for the cohort as a whole, with SMR = 0.94 (95% CI 0.47-1.19). A sub-cohort of 5000 workers identified as having direct or routine exposure to TCE also showed no increased risk of mortality from liver and biliary tract cancer with SMR = 0.98 (95% CI 0.36-2.13). Additionally, there was no significant trend with duration of employment within the sub-cohort.

Since the IARC (1995) assessment, the available epidemiological information has been comprehensively reviewed by Wong (2004), and reassessed in one cohort study (Raaschou Nielsen *et al*, 2003) and two major meta-analyses (Alexander *et al*, 2007; Wartenberg *et al*, 2000).

Raaschou-Nielson *et al*., (2003) reported on cancer risk in a cohort of 40,049 workers in Danish companies that used TCE between 1968 and 1997. A significant excess risk for primary liver cancer was reported for females (SIR=2.8, 95% CI 1.13-5.80). However, no consistent exposure-related trend was observed and the SIR was not significantly elevated in

males (SIR=1.1, 95% CI 0.74-1.64). The authors report that findings were limited by the lack of accurate assessment of TCE exposure.

Wartenberg *et al*., (2000) has reviewed evidence for an association between cancer and TCE – used as a degreasing agent and solvent - based on all identified cohort and case-control studies up to the year 2000. These studies relate predominantly to the iron and steel industry and dry cleaning, and the review assigns the various cohort studies to three tiers based on the specificity of exposure information. Tier I studies were those that determined exposures using urinary biomarkers (Anttila *et al*, 1995; Axelson *et al*, 1994; Tola *et al*, 1980), job exposure matrices (Blair *et al*, 1998; Boice *et al*, 1999; Morgan *et al*, 1998; Ritz, 1999; Spirtas *et al*, 1991), and job histories (Henschler *et al*, 1995). Tier II studies included those that evaluated mortality in cohorts using job titles and other general information to assess TCE exposure (Blair *et al*, 1989; Blair, 1980; Dubrow and Gute, 1987; Garabrant *et al*, 1988; Shannon *et al*, 1988; Shindell and Ulrich, 1985; Sinks *et al*, 1992a, b). Tier III studies are those relating to dry cleaning and laundry workers, where exposures were assessed on job title only (Blair *et al*, 1979; Blair *et al*, 1990; Brown and Kaplan, 1987; Duh and Asal, 1984; Katz and Jowett, 1981; Lynge and Thygesen, 1990; Lynge, 1994; McLaughlin *et al*, 1987; Ruder *et al*, 1994).

For the Tier I studies, there was evidence of an excess of incidence of, and mortality from, primary liver cancer, with average RR = 1.9 (95% CI, 1.0-3.4) and 1.7 (95% CI, 0.2-16.2) respectively (SIR based on cohort studies from Anttila *et al*, 1995; Axelson *et al*., 1994; Blair *et al*, 1998; total cohort size of 12,020; SMR based on cohort study from Blair *et al*, 1998; total cohort size of 7204). For liver and biliary tract cancer combined, there was a slightly raised SIR (1.1, 95% CI 1.0-3.4; based on Blair *et al*., 1998, total cohort of 7204) and SMR (1.1, 95% CI 0.7-1.7; based on studies from Blair *et al*, 1998, Boice *et al,* 1999; Henschler *et al*, 1995; Morgan *et al,* 1998; Ritz, 1999, total cohort of 17,374). Of the Tier II studies (Blair *et al*, 1989; Blair, 1980; Dubrow and Gute, 1987; Garabrant *et al*, 1988; Shannon *et al*, 1988; Shindell and Ulrich, 1985; Sinks *et al*, 1992a), three reported RR>1 for liver or biliary cancer incidence with average RR for primary liver cancer of 2.0 (95% CI 1.3-3.3) and, for liver and biliary tract cancer combined, a RR = 1.3 (95% CI, 1.0-1.8). The mortality rate was also higher for primary liver cancer (RR = 2.0, 95% CI, 1.3-3.3) than for liver and biliary tract cancer combined (RR = 1.3, 95% CI 1.0-1.8). Tier III studies (Blair *et al*, 1979; Blair *et al*, 1990; Brown, 1987; Duh and Asal, 1984; Katz and Jowett, 1981; Lynge and Thygesen, 1990; Lynge, 1994; McLaughlin *et al*, 1987; Ruder *et al*, 1994) gave more ambiguous findings with increased incidence of primary liver cancer (average RR = 3.3, 95% CI 1.6-6.90) and liver and biliary tract cancer combined (RR = 1.8, 95% CI 1.1-2.9) but no increased mortality for liver and biliary cancer combined (RR = 0.7, 95% CI of 0.4-1.3). The authors suggest that these apparent anomalies may reflect the limited robustness of the exposure assessments and concluded that the evidence overall was suggestive of an increased risk of liver cancer following occupational exposure to TCE.

In a recent meta-analysis, Alexander *et al*., (2007) assessed the risk of primary liver cancer and liver and biliary tract cancer combined for 14 cohort studies and 1 case-control study of TCE exposed workers. Inclusion criteria were (i) cohort or case-control study design (ii) evaluation of occupational exposure (iii) TCE exposure specifically identified and (iv) reported results for liver and/or liver/biliary tract cancers, with results expressed as relative risk estimate with CI or such that these could be calculated. Studies varied by geographical location (US and Europe), type of industry, type of cancer endpoint (primary liver, biliary tract, combined), type of study outcome (incidence and mortality) and exposure assessment classification. Using similar criteria to Wartenberg *et al*., (2000) 9 cohort studies were classified as Group I (Antilla *et al*., 1995; Axelson *et al*, 1994; Hansen *et al*, 2001; Raaschou-Nielkson *et al*, 2003; Boice *et al*, 1999, 2006; Morgan 1998; Blair *et al,* 1998; Ritz *et al*, 1999) as they specifically identified TCE as a work place exposure and, of these, a sub-cohort (definite exposure of workers to TCE) of 8 studies was identified. Group II studies (n=5) were those that either mentioned TCE but provided little or no documentation of actual/potential

exposure, or where workers were presumed to have been exposed to TCE (Garabrant, *et al*, 1988; Costa *et al*, 1989; Blair *et al*, 1989; Chang *et al*, 2003; Seldon and Ahlborg 1991). Group II studies were considered as more limited for evaluating the relationship between TCE exposure and liver cancer. Summary relative risk estimates (SRRE) were calculated for Group I and Group II studies combined, for the total Group I cohort and the Group I sub-cohort. For liver and biliary tract cancer, the combined summary relative-risk estimate (SRRE) for all 15 studies was slightly elevated (RR=1.08; 95% CI, 0.91-1.29). For Group I studies only (n=9) the combined SRRE was reported as 1.14 (95% CI, 0.93-1.39) with five studies reporting an elevated SRRE (1.37, 95% CI 1.04-1.79) for primary liver cancer and four studies for biliary tract cancer (SRRE = 1.35, 95% CI 1.03-1.78). For the Group II studies, the combined SRREs for primary liver cancer and liver and biliary tract cancer were not elevated (0.87, 95% CI 0.55-1.38). In the TCE-exposed sub-cohort of Group I studies, a combined SRRE of 1.30 (95% CI of 1.09-1.55) was reported for liver and biliary tract cancer; this was slightly stronger but less precise for primary liver cancer only (SRRE=1.41, 95% CI 1.06-1.87).

The authors concluded that, overall, a positive SRRE was seen between occupational exposure to TCE and liver/biliary cancer. However, the authors suggested that, due to inconsistencies of findings across study location, occupational groups and incidence versus mortality endpoints, this interpretation should be treated with some caution and that the available epidemiological data did not support a causal relationship between occupational exposure to TCE and liver/biliary tract cancer.

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

The substances considered in the estimation of the attributable fraction (AF) for cancer of the liver are those outlined in Table 10.

Table 10 Substances considered in the estimation of the attributable fraction for cancer of the liver

Agents, Mixture, Circumstance	AF calculation	Strength of evidence	Comments
Group 1: Carcinogenic to Humans			
Agents, group of agents			
Ionising radiation and sources thereof	Yes	Strong	Radiologists and Radiologic technologists with pre-1970 exposure.
Arsenic and arsenic compounds	No	Suggestive (Angiosarcoma)	Angiosarcoma only considered with vinyl chloride
Vinyl chloride	Yes	Strong (Angiosarcoma) Suggestive (Hepatocellular)	Angiosarcoma only
Aflatoxin	No	Strong	
Exposure circumstances			
None identified			
Group 2A: Probably Carcinogenic to Humans			
Agents, group of agents			
Polychlorinated biphenyls	No	Suggestive	
Trichloroethylene	Yes	Suggestive	
Exposure circumstances			
None identified			

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. The latency period for development of HCC linked to HBV infection has been estimated as between 10 and 20 years (Poovorawan *et al*, 2002), HCC linked to HBC infection as between 15 and 25 years (Hassoun and Gores, 2003) and up to 43 years following exposure to Thorotrast (Frank *et al*., 1996); latency periods of up to 53 years have been reported for ICC (Frank *et al*., 1996; Zhu, 2004) and the mean latency period for ASL has been estimated as around 22 years although some cases have occurred 30 years or more after first exposure (Kielhorn *et al*, 2000; Lelbach, 1996). A latency of up to 50 years and at least

10 years has thus been assumed for all types of liver 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 is therefore 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 liver cancer (HCC and ICC) in GB in 2005 = 1661 for men (1472 England and Wales and 189 Scotland), 1133 for women (1002 England and Wales and 131 Scotland).

- Total registrations from liver cancer (HCC and ICC) in GB in 2004 = 1670 for men (1366 England, 104 Wales and 200 Scotland), 1128 for women (934 England, 76 Wales and 118 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 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 IONISING RADIATION

(a) Risk estimate:
A significantly elevated risk (SIR = 1.2; P< 0.05) for liver cancer was found for a cohort of 27,011 radiologists and radiologic technologists in China working during the period 1950-1995 (Wang *et al*., 2002). Employees working prior to 1970 had an increased risk (SIR = 1.39; P<0.05) in comparison to those employed post-1970 (SIR = 0.85); this probably reflects improvements in protection procedures from that time. The SMR for liver cancer was found to be raised in a cohort of US radiologists employed prior to 1940 (SMR = 1.45) and risk of mortality from cancer in a cohort of British Radiologists following 40 years of employment was also significantly raised (SMR = 1.41, 95% CI 1.03-1.90).

Gilbert *et al*., (2000) reported a significant excess risk of liver cancer (in particular ASL) in plutonium workers employed between 1948 and 1958 at the Mayak facility in Russia, but no such effect has been identified in a series of cohorts of US and UK nuclear industry workers. The difference in response is probably a consequence of the marked differences in exposure between the Western and Russian plants.

No excess risk of liver cancer has been found for workers in other nuclear industries, underground (coal or uranium) miners or air-craft crew.

An increased risk of liver cancer is apparent following exposure of radiologists and radiologic technicians employed prior to 1970 to ionising-radiation. An AF calculation is therefore warranted. Although a cancer mortality study has been reported for a cohort of UK radiologists (Berrington, 2001), liver cancer as a specific end-point was not considered in isolation and therefore the study is not appropriate for use in calculating an AF. The study of choice for AF calculation is that reported by Wang *et al*., (2002) as it specifically addresses liver cancer as an end-point, has a large cohort size and exposure levels were measured during both high (pre-1970) and low (post-1970) exposure periods. In addition, a follow-up period of 45 years was employed in the study, which allows for the different latency periods associated with the various types of liver cancer.

The UNSCEAR model
Airline cockpit crews are occupationally exposed to ionising radiation (IR) of cosmic origin. Radiation workers in the nuclear industry and medical and laboratory staff are the other principal group exposed. The relative risks for occupational exposure to ionising radiation were obtained from UNSCEAR, 2006, using models of excess relative risk (ERR) per unit of radiation dose, estimated as RR=1+ERR. Details of the model used are described below.

From the UNSCEAR report (2006) see Table 50, the generalized ERR incidence model is based on a linear dose response:

ERR(a) = α . D

where α= 3.95106 × 10^{-1} Sv^{-1}
From Table D8: Model Deviance = 5,370.978, df = 42,690

ERR is obtained as average ERR(a), averaged over a = 25-100 (long latency REP 1956-1995).

Dose was assumed to be an individual's cumulative dose received over the risk exposure period (REP) for each cancer (1956-1995 for the solid tumours). For workers exposed to ionising radiation, doses were estimated using data from the Central Index of Dose Information (CIDI, see below). To estimate lifetime dose from the CIDI data, the following procedure was used. Data on collective doses for the years 1990 to 2004 were used to estimate total collective dose for the REP, by assuming a constant 1990 rate prior to 1990 for the 1956-1995 REP. The estimated REP collective dose was then divided by an estimate of the numbers ever exposed to ionising radiation during the REP. These estimates were obtained by multiplying the CIDI point estimates of IR exposed workers (see below) by the employment turnover factors in Table A1 and by the number of years in the REP (40 for the solid tumours).

For aircrew who are not covered by the CIDI data, an estimate of lifetime dose from Langner *et al*, 2004 was used. In a large seven country European cohort of airline pilots employed from the earliest days of air transport (1921, Finland to 1965, Italy) up to between 1994 and 1997, the mean total lifetime radiation dose per pilot for all pilots in the cohort was 15.3 mSv, (median 10.7 mSv, maximum 78.5 mSv). The annual mean dose rate of all active pilots was 2.96 μSv per block hour flying time, for an average of 7,031 block hours. Pilots in the cohort were employed for an average 14.6 years. The lifetime dose estimate of 15.3 mSv per worker is used to estimate ERR for aircrew.

ERR(a) was estimated for ages (a) that could be attained by workers in 2005 who had been exposed during the REP between the ages of 15 and 65 (an even distribution of ages from 15 to 65 in the exposed cohorts was assumed). ERR (all ages) was then obtained as the average across these ages.

Standard errors were not available from the UNSCEAR data so no confidence intervals are given.

The RR estimate is 1.01 for men and women for ionising radiation exposed workers (excluding aircrew) (with an estimated average lifetime dose of 15.3 mSv) and the same for aircrew (also with an estimated average lifetime dose of 15.3 mSv).

(b) Number exposed:
Data from the HSE's Central Index of Dose Information (CIDI, 1998) indicates that there were 43,805 people exposed above 0.1mSv in GB in 1990. The data exclude aircrew. A breakdown by occupation is in Table 11 below. Estimated numbers exposed over 0.1mSv are split between men and women in proportion to the proportion of men (93%) with recorded doses between 1997 and 2004. Estimates of numbers of aircraft flight deck officers and male travel and flight attendants estimated from the LFS for 1979, are also given in Table 11. CIDI data from 1990 and LFS data from 1979 are used as a best available point estimate for numbers exposed in the 'solid tumour' REP, 1956-1995.

For female air stewardesses, full data of numbers employed since 1958 was available from the British Airways Stewards and Stewardesses Union (for women only). Noting that in 2003 the number of women stewardesses employed by BA (11,479) was 48% of the LFS 'air travel assistants' total (23,890), and 55% of the CAA 'cabin attendants' total (20,761), doubling the

BA numbers of new starters during the REP gives an appropriate estimate of stewardesses 'ever employed' in the period (13,902 in 1956-95). These 'ever exposed' numbers for air stewardesses are given in Table 11, and are used in the estimation of AF for this part of the exposed population (bypassing the usual turnover equation estimate).

Table 11: Numbers of workers exposed to >0.1mSv ionising radiation in GB in 1990, from CIDI, numbers of aircrew in 1979, from LFS data, and air stewardesses from BA union data

	Industry/occupation	***Numbers exposed >0.1 mSv***			
	REP 1956-95	***M***	***F***	***Total***	***%male***
	CIDI 1990				
C-E	Nuclear Power	13414	1010	14424	93%
C-E	Nuclear Fuel Fabrication/ Reprocessing	7376	555	7931	93%
C-E	General Industry	7489	564	8053	93%
C-E	Industrial Radiography	2614	197	2811	93%
C-E	Non-coal Mining	264	20	284	93%
C-E	Radiation Protection	2407	181	2588	93%
C-E	Waste Treatment	1202	90	1292	93%
C-E	Nuclear Industry Misc.	683	51	734	93%
C-E	Other	4275	322	4597	93%
	Sub-total	***39724***	***2990***	***42714***	
G-Q	Medical/Dental	408	31	439	93%
G-Q	Transport	179	13	192	93%
G-Q	Academic	428	32	460	93%
	Sub-total	***1015***	***76***	***1091***	
	CIDI Total >0.1 mSv	***40739***	***3066***	***43805***	
	LFS 1979				
G-Q	Aircraft Flight Deck Officers	6915	-	6915	
G-Q	Supervisors of Travel Stewards and Attendants	258			
G-Q	Travel Stewards and Attendants	6248			
	BA stewards and stewardesses union data				
	Air stewardesses, number employed 1956-1995		13,902		
	Aircrew Total	***13421***			

(c) AF calculation:

Ionising radiation: The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to ionising radiation is 0.01% which equates to 0 attributable deaths and 0 attributable registrations (Table 12).

Table 12 Summary results for occupational exposure to ionising radiation

				Data		Calculations				Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval		Attributable Deaths				Attributable Registrations		
	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
Men	UNSCEAR 2006	H	C-E	1.01	39724	1.4	0.09	192147	0.0099	0.0001			0			0		
		H	G-Q	1.01	1015	0.9	0.11	3816	0.0002	0.0000			0			0		
		H	All		40739			195964	0.0101	0.0001			0			0		
		L	G-Q	1.01	13421	0.9	0.11	56071	0.0029	0.0000			0			0		
		L	All		13421			56071	0.0029	0.0000			0			0		
		All	All		54160			252035	0.0130	0.0001			0			0		
Women	UNSCEAR 2006	H	C-E	1.01	2990	1.5	0.14	25154	0.0012	0.0000			0			0		
		H	G-Q	1.01	76	0.8	0.15	364	0.0000	0.0000			0			0		
		H	All		3066			25518	0.0012	0.0000			0			0		
		L (Aircrew)	G-Q	1.03	-			13902	0.0007	0.0000			0			0		
		L (Aircrew)	All					13902	0.0007	0.0000			0			0		
		All	All		3066			39420	0.0019	0.0000			0			0		

1. Specific scenario or main industry code (Table 11)
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 ARSENIC AND ARSENIC COMPOUNDS

(a) Risk estimate:

Tokudome and Kuratsune (1976) reported a significant excess in risk of liver cancer amongst Japanese copper smelters employed between 1949 and 1971, with an SMR = 3.37. However, due to limitations with regard to tumour diagnosis, this finding is not considered reliable.

A few other studies have reported a significant association between exposure to arsenical pesticides and development of liver cancer, in particular ASL (e.g. Roth *et al*., 1957; Giordano *et al*., 2006). The findings reported by Roth *et al*., (1957) are however of limited use as direct exposure measurements to arsenic were not carried out amongst the cohort of vineyard workers (Roth *et al*., 1957). In addition, although exposure estimates were included in the study of pesticide applicators by Giordano *et al*., (2006), no association was found between risk of liver cancer and duration of exposure.

(b) AF calculation:

There is limited evidence to suggest an association between ingestion of arsenic and arsenical compounds, and the development of liver tumours, in particular ASL. Although ASL has a latency period of between 15 and 29 years some cases have been reported 30 years following exposure. As arsenic and arsenical compounds have been eliminated from the workplace for only 30 years, it is still feasible that cases of ASL reported between 1999 and 2005 are due to occupational exposure. However, the available studies are considered inadequate to support the derivation of an AF, and therefore a formal AF calculation is omitted.

3.4 VINYL CHLORIDE

a) Risk estimate:

Occupational exposure to VC has been shown to be associated with an increased risk of ASL. However, it is known that elevated risk of ASL is particularly associated with high exposures over long periods of time. There are only 2 producers of PVC in the UK that use VC in large quantities who are subject to tight regulatory controls; it is therefore unlikely that there is now any substantial risk to workers in these plants.

The review by Kielhorn *et al*., (2000) provides a robust summary and analysis of epidemiologic studies on workers exposed to VC in several countries, including studies of workers employed pre-1975 prior to the introduction of occupational exposure level. The authors reported a 5-fold excess of liver cancer following occupational exposure to VC, reporting an SMR = 5.33 (95% CI, 4.32-6.62) for all studies combined; this increase was, reported as being primarily due to an excess of ASL (45-fold excess risk) and not HCC. However, it is not clear how the authors calculated the 'all studies' SMR which could be heavily influenced by that reported for the Canadian cohort (SMR = 57.14). We therefore suggest that the European cohort (Simonato *et al*., 1991) included in the review by Kielhorn *et al*., (2000) is most relevant for comparison with workers in Great Britain exposed to VC. In the study by Simonato *et al*., (1991) a significantly raised excess of liver cancer was observed (SMR = 2.86, 95% CI 1.83 – 4.25) with a significant exposure-response relationship ($p<0.001$) being demonstrated. In addition, histological analysis was performed and 16 of the 24 cases of liver cancer in the study cohort were verified as ASL.

The SMR for liver and biliary tract cancer for workers in the European cohort was found to be 2.86 (95% CI, 1.83 – 4.25) and will be used for AF calculation. It should be noted however that only between 2 and 5 deaths from ASL have occurred in England and Wales between 1999 and 2005 (Table 3), which, as noted by Baxter *et al*. (1980) and IOM (2006), will not all be occupationally linked. Due to the absence of sufficient dose-response data specific to

VCM an RR = 1.89 has been estimated for the low exposure level category. This was based on a harmonic mean of the high/low ratios across all other cancer-exposures pairs in the overall project for which data were available

(b) Number exposed:

The numbers of workers exposed to VC in various industries according to CAREX for 1990-93 are given in Table 13 and have been estimated to be 4211. Exposures in the manufacture of industrial chemicals and chemical products and manufacture of plastic products were allocated to the 'higher' exposure category. Workers in the manufacturing industries can be expected to be predominantly male but those in the service industries will include a high proportion of women.

Table 13 Numbers of workers exposed to vinyl chloride according to CAREX in 1990-1993.

Sector	Industry	CAREX Data 1990-1993			
		Number Exposed	Number in Industry	% Exposed	Exposure Level
C-E	Food manufacturing	4	414150	0.001	L
C-E	Manufacture of wearing apparel, except footwear	8	189500	0.004	L
C-E	Manufacture of industrial chemicals	1324	130000	1.018	H
C-E	Manufacture of other chemical products	1388	175175	0.792	H
C-E	Petroleum refineries	77	18075	0.426	L
C-E	Manufacture of plastic products not elsewhere classified	1010	136900	0.738	H
C-E	Manufacture of other non-metallic mineral products	2	70875	0.003	L
C-E	Non-ferrous metal basic industries	33	79325	0.042	L
C-E	Manufacture of instruments, photographic and optical goods	2	86225	0.002	L
G-Q	Water transport	59	68175	0.087	L
G-Q	Air transport	2	95700	0.002	L
G-Q	Services allied to transport	180	180725	0.100	L
G-Q	Education services	122	1455875	0.008	L
G-Q	Research and scientific institutes	88	91100	0.097	L
	TOTAL	**4211**	**3191800**		
	Main Industry Sector		%Male		
C-E	**Mining/quarrying, electricity/gas/water; manufacturing industry** **High**	3722	76%		
	Low	126			
G-Q	**Service Industries** **High**	0	36%		
	Low	401			

(c) AF calculation:

Vinyl chloride monomers: The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to VCM is 0.11% (95%CI=0.05-0.20), which equates to 3 (95%CI=2-6) attributable deaths and 3 (95%CI=2-6) attributable registrations. The estimated AF for men is 0.14% (95% CI=0.07-0.24) resulting in 2 (95%CI= 1-4) attributable deaths and 2 (95%CI= 1-4) attributable registrations; and for women the AF is 0.07% (95%CI=0.04-0.14) resulting in 1 (95%CI= 0-2) attributable deaths and 1 (95%CI= 0-2) attributable registrations (Table 14).

Table 14 Summary results for occupational exposure to vinyl chloride

				Data		Calculations				Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
	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
Men	Simonato *et al*, (1991)	H	C-E	2.86	2829	1.4	0.09	13683	0.0007	0.0013	0.0006	0.0024	2	1	4	2	1	4
		H	All		2829			13683	0.0007	0.0013	0.0006	0.0024	2	1	4	2	1	4
	Estimated	L	C-E	1.89	96	1.4	0.09	463	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	G-Q	1.89	162	0.9	0.11	610	0.0000	0.0000	0.0000	0.0002	0	0	0	0	0	0
		L	All		258			1074	0.0001	0.0000	0.0000	0.0003	0	0	1	0	0	1
		All	All		3087			14756	0.0008	0.0014	0.0007	0.0024	2	1	4	2	1	4
Women	Simonato *et al*., (1991)	H	C-E	2.86	893	1.5	0.14	7515	0.0004	0.0007	0.0003	0.0012	1	0	1	1	0	1
		H	All		893			7515	0.0004	0.0007	0.0003	0.0012	1	0	1	1	0	1
	Estimated	L	C-E	1.89	30	1.5	0.14	254	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	G-Q	1.89	289	0.8	0.15	1382	0.0001	0.0001	0.0000	0.0004	0	0	0	0	0	0
		L	All		319			1637	0.0001	0.0001	0.0000	0.0004	0	0	1	0	0	1
		All	All		1212			9151	0.0004	0.0007	0.0004	0.0014	1	0	2	1	0	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

3.5 AFLATOXIN

(a) Risk estimate:

Overall the evidence from both occupational and non-occupational studies supports a role for aflatoxin in the development of liver cancer. In the UK, occupational exposure is most likely to occur during the handling of aflatoxin contaminated food commodities. Estimation of the increased risk associated with development of liver cancer is considered to be equivalent to that reported by Dossing *et al*., (1997) for a cohort of Danish workers employed in warehouse and storage operations. The study design incorporates a large cohort size, a long period of follow-up (over 30 years) that allows for the latency period associated with liver cancers, and the use of histologically verified cases of liver cancer only. However, the study does not include any direct measurement or assessment of exposure to aflotoxins, estimates being only inferred from job histories. Additionally, the impact of confounding factors (such as alcohol consumption, smoking and other potential co-exposures) on the risk of liver cancer was not considered.

Although an OR of 4.02 (95% CI of 1.7-9.33) was developed in the study for risk of liver cancer associated with aflatoxin exposure (Dossing *et al,* 1997), given the limitations associated with the study design, the robustness of this value cannot be confirmed.

(b) AF calculation:

As the dataset is inadequate, it is considered inappropriate to proceed with an AF calculation.

3.6 POLYCHLORINATED BIPHENYLS

(a) Risk estimate:

Although there are some studies suggestive of an elevated risk of liver and biliary tract cancer amongst workers in capacitor manufacture and maintenance (Brown 1981; Brown 1987; Gustavsson *et al,*1986; Gustavsson and Hogstedt 1997; Bertazzi *et al*., 1987; Tironi *et al*., 1996), these studies have a number of limitations including small cohort size, apparent lack of exposure-response relationship, and concurrent exposure to various other chemicals.

The best available study is that reported by Gustavsson and Hogstedt (1997) for a cohort of Swedish capacitor manufacturing workers employed between 1965 and 1978. Incidence of mortality from liver cancer was seen to be raised with an SMR = 1.96 (95% CI 0.05-10.9) for the cohort as a whole, and for workers considered as having a 'high' exposure to PCBs, the SMR was increased further (6.67, 95% CI 0.16-37.1). However, the authors note several limitations of the study design, including low cohort size and case numbers, and liver cancer cases were not found to be correlated with exposure to PCBs.

A robust study can therefore not be recommended for AF calculation.

(b) AF calculation:

The evidence to support a positive association between occupational exposure to PCBs and development of liver cancer is only *suggestive*. The total number of workers in the UK exposed to PCBs is low (1860) with only 54 of those estimated to have a 'high' exposure level. The AF calculation is therefore omitted.

3.7 TRICHLOROETHYLENE

(a) Risk estimate:

A number of cohort and case-control studies have evaluated the association between TCE exposure in occupations involving use of TCE as a dry cleaning agent and as a metal degreasant (in aerospace, cardboard and other industries) and incidence of/mortality from liver cancer. Wartenberg and co-workers (Wartenberg *et al*, 2000) evaluate many of these studies, including 20 cohort and 40 case-control studies, dividing the cohort studies into three tiers based on the specificity of the exposure information. Tier 1 studies are those that provide the best characterisation of TCE exposure through the use of biomarkers and job-exposure matrices. Across the Tier 1 studies, for *primary* liver cancer an average standardised incidence ratio (SIR) of 1.9 (95%CI=1.0-3.4) and an average standardised mortality ratio (SMR) of 1.7 (95%CI=0.2-16.2) were obtained. For liver and biliary tract cancer combined, a SIR = 1.1 (95% CI 0.3-4.8) and SMR = 1.1 (95% CI 0.7-1.7) was reported.

In the meta-analysis reported by Alexander *et al* (2007), incidence of and mortality from liver cancer in workers exposed to TCE was assessed across 14 occupational cohort studies. Ecologic studies of TCE in drinking water and studies of dry cleaners and laundry workers (included as Tier III studies in Wartenberg *et al* 2000) were excluded due to exposure assessment limitations and use of proportionate mortality estimates (PMR) that limits the ability to make causal links. In contrast to the meta-analysis from Wartenberg *et al*., (2000), studies were divided into 2 Groups; however, Group I studies were again those that provided the most accurate estimate of TCE exposure through biomonitoring. Across the Group I studies, a SRRE of 1.41 (95% CI of 1.06-1.87) and of 1.30 (95% CI of 1.09-1.55) were obtained for primary liver cancer and liver and biliary tract cancer combined.

For both meta-analyses discussed above, the RR estimates were derived from studies identified as the best quality cohort studies with sufficient follow-up periods (17-38 years). The Wartenberg meta-analysis included four Tier I studies (Henschler *et al*, 1995; Spirtas *et al*, 1991; Tola *et al*, 1980; Wong and Morgan, 1990) that were not considered by Alexander et al (2007). However, the latter meta-analysis included three more recent Group I studies (Hansen, Raaschou-Nielson, Boice [updated from 1999]). It should be noted however, that no adjustment has been made for confounders in either meta-analysis; this is a common limitation in many of the cohort studies evaluating the association between TCE exposure and liver cancer as there is considerable difficulty in separating TCE exposure from general organic solvent exposure amongst workers. As such, it is perhaps more accurate to define the exposure as being to organic solvents including TCE. Other confounding variable such as smoking, alcohol consumption and other "lifestyle" confounders are rarely considered by any of the studies included by Wartenberg *et al*., and Alexander *et al*., which again does not make one risk estimate more accurate than the other.

The choice of meta-analysis and estimate of RR for attributable fraction (AF) calculation will therefore be dependent upon selection of cohorts, and especially those included as Tier I or Group I studies. Of the four studies unique to Tier I of the Wartenberg meta-analysis, one was subject to methodological constraints with only a limited interpretation of results possible and one other study did not specifically identify liver cancer as an end point (Henschler *et al*, 1995; Tola *et al*, 1980). In contrast, all three of the studies unique to Group I of the Alexander meta-analysis were of relevance for assessing risk of liver cancer following occupational exposure to TCE and their inclusion provided the most up to date analysis of epidemiologic data. For these reasons the meta-analysis from Alexander at al (2007) is the one most suitable for use in the AF calculation. Although the authors emphasised the limitations of their findings at present, it is considered that, due to the raised SRRE for both primary liver cancer and liver and biliary tract cancer in the TCE-exposed Group I sub-cohort, an AF calculation is warranted.

The SRRE for liver and biliary cancer combined, as calculated by Alexander *et al*., (2007) for the Group I sub-cohort that had the most accurate information on TCE exposure, was 1.30 (95%CI=1.09-1.55), and this value for liver and biliary cancer combined will be used in the AF calculation. 'Low exposures' have been set to 1 to reflect the scarcity of exposure-response data and, where data exist, the frequent absence of an exposure-response relationship (Wartenberg et al. 2000; Blair et al. 1998).

(a) Numbers exposed:

The numbers of workers exposed to TCE in various industries according to CAREX for 1990-93 are given in Table 15 and have been estimated to be 10,819. Exposures in the textile/clothing industries and in the manufacture of finished metal products were allocated to the 'higher' category, as it was assumed that within these occupations the use of TCE as a metal degreasant was more likely. The textile industry may also have been exposed to TCE as a spot-cleaning agent, along with dry cleaners who were considered to fall in the personal and household services category. TCE used in dry cleaning until 1950s/1960s when predominant use was as a metal degreasant. Use as a solvent for oils/resins is less common. Despite declining popularity during early part of current burden assessment (1956-1996), high exposures have been allocated to dry cleaners.

Workers in the metal manufacturing industries can be expected to be predominantly male but clothing manufacture will include a high proportion of women. However, as only 117 workers were recorded as being exposed to TCE in clothing manufacture, it can be assumed that 99% of workers in the manufacturing industries are male. It has been assumed that 65% of service workers were male as applies to "blue collar" workers in SOC major groups 5, 8 and 9. These data were used to estimate Pr(E) for Levin's calculation of AF.

Table 15 Numbers of workers exposed to trichloroethylene according to CAREX in 1990-1993.

Sector	Industry	CAREX Data 1990-1993			
		Number Exposed	Number in Industry	%Exposed	Exposure Level
C-E	Beverage industries	92	88100	0.104	L
C-E	Tobacco manufacture	40	9950	0.402	L
C-E	Manufacture of wearing apparel, except footwear	117	189500	0.062	H
C-E	Manufacture of leather and products of leather or of its substitutes	8	16825	0.048	L
C-E	Manufacture of glass and glass products	130	43275	0.300	L
C-E	Manufacture of other non-metallic mineral products	50	70875	0.071	L
C-E	Manufacture of fabricated metal products, except machinery and equipment	2139	292200	0.732	H
C-E	Manufacture of machinery except electrical	3041	692275	0.439	H
C-E	Manufacture of electrical machinery, apparatus, appliances and supplies	1852	473750	0.391	H
C-E	Manufacture of transport equipment	2949	456900	0.645	H
G-Q	Sanitary and similar services	117	274225	0.043	L
G-Q	Education services	122	1455875	0.008	L
G-Q	Research and scientific institutes	88	91100	0.097	L
G-Q	Recreational and cultural services	74	534600	0.014	L
G-Q	Personal and household services	5517	686750	0.803	H
	TOTAL	**10819**	**5376200**		
	Main Industry Sector		%Male		
C-E	**Mining/quarrying, electricity/gas/water; manufacturing industry** **High** **Low**	10 098 320	76%		
G-Q	**Service Industries** **High** **Low**	5517 401	36%		

(c) AF calculation:

Trichloroethylene: The estimated total (male and female) attributable fraction for liver cancer associated with occupational exposure to trichloroethylene is 0.06% (95%CI=0.02-0.11), which equates to 2 (95%CI=1-3) attributable deaths and 2 (95%CI=1-3) attributable registrations. The estimated AF for men is 0.07% (95%CI= 0.02-0.12) resulting in 1 (95%CI= 0-2) attributable death and 1 (95%CI 0-2) attributable registration; and for women the AF is 0.06% (95% CI=0.02-0.11) resulting in 1 (95%CI= 0-1) attributable death and 1 (95%CI= 0-1) attributable registration (Table 16).

Table 16 Summary results for occupational exposure to trichloroethylene

				Data		Calculations				Attributable Fraction (Levins[8]) and Monte Carlo Confidence Interval			Attributable Deaths			Attributable Registrations		
	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
Men	Alexander *et al*., (2007)	H	C-E	1.3	7674	1.4	0.09	37122	0.0019	0.0006	0.0002	0.0011	1	0	2	1	0	2
		H	G-Q	1.3	1379	0.9	0.11	5186	0.0003	0.0001	0.0000	0.0001	0	0	0	0	0	0
		H	All		9054			42308	0.0022	0.0007	0.0002	0.0012	1	0	2	1	0	2
		L	C-E	1	243	1.4	0.09	1176	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	100	0.9	0.11	377	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		343			1553	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		9397			43861	0.0023	0.0007	0.0002	0.0012	1	0	2	1	0	2
Women	Alexander *et al*., (2007)	H	C-E	1.3	2424	1.5	0.14	20388	0.0010	0.0003	0.0001	0.0005	0	0	1	0	0	1
		H	G-Q	1.3	4138	0.8	0.15	19813	0.0009	0.0003	0.0001	0.0005	0	0	1	0	0	1
		H	All		6561			40201	0.0019	0.0006	0.0002	0.0011	1	0	1	1	0	1
		L	C-E	1	77	1.5	0.14	646	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	301	0.8	0.15	1440	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		378			2086	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		6939			42288	0.0020	0.0006	0.0002	0.0011	1	0	1	1	0	1

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

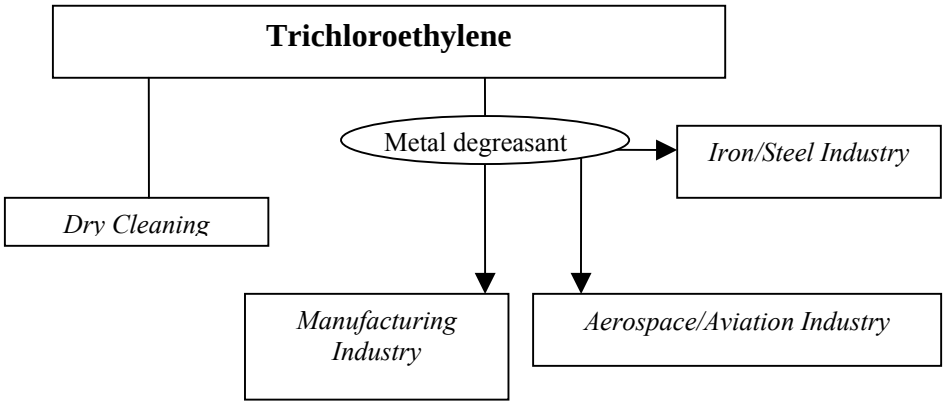

Figure 1 Liver cancer exposure map

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) or an exposure scenario (i.e. an industry or occupation in which such exposure occurs). Certain exposures, such as PCBs and arsenic and arsenical compounds have not been included in the exposure map due to uncertainty of the link between exposure and liver cancer. AF has been calculated for the agent and exposure scenario shown in Figure 1.

4.2 SUMMARY OF RESULTS

The results are summarised in Tables 17& 18

Table 17: Summary of RR used to calculate AF

Agent	Exposure	RR	LL	UL
Ionising radiation	L	1.01		
Ionising radiation	H	1.01		
Trichloroethylene	H	1.3	1.09	1.55
Trichloroethylene	L	1	1	1
Vinyl chloride	H	2.86	1.83	4.25
Vinyl chloride	L	1.89	0.32	3.96

Table 18: Summary of 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)
Ionising radiation	252035	39420	0.0130	0.0019	0.0001			0.0000			0	0	0	0
Trichloroethylene	43861	42288	0.0023	0.0020	0.0007	0.0002	0.0012	0.0006	0.0002	0.0011	1	1	1	1
Vinyl chloride	14756	9151	0.0008	0.0004	0.0014	0.0007	0.0024	0.0007	0.0004	0.0014	2	1	2	1
Totals*					**0.0021**	**0.0013**	**0.0033**	**0.0013**	**0.0008**	**0.0021**	**4**	**2**	**4**	**1**

*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 19 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent.

Table 19 Industry/occupation codes by agent

Agent	Industry	Number of men Ever Exposed over REP	Number of Women Ever Exposed over REP	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
Ionising Radiation	**Total**	**252,035**	**39,420**	**0**	**0**	**0**	**0**	**0**	**0**
Trichloroethylene	**Total**	**43,861**	**42,288**	**1**	**1**	**1**	**1**	**2**	**2**
Vinyl chloride	Manufacture of industrial chemicals	4,867	2,673	1	1	0	0	1	1
Vinyl chloride	Manufacture of other chemical products	5,103	2,802	1	1	0	0	1	1
Vinyl chloride	Manufacture of plastic products not elsewhere classified	3,713	2,039	1	1	0	0	1	1
Vinyl chloride	**Total**	**14,756**	**9,151**	**2**	**2**	**1**	**1**	**3**	**3**

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6 STATISTICAL APPENDIX

Formulae used in the estimation of AF

Levin's equation

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

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

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

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

Turnover equation to estimate numbers ever employed during the REP

$$N_{e(REP)} = \sum_{i=a}^{i=b} l_{(adj15)i} * n_0/(R-15)\} + \sum_{k=0}^{k=(age(u)-age(1))} \sum_{j=c+k}^{j=d+k} \{l_{(adj15)j} * n_0 * TO /(age(u)-age(l)+1)\} \quad (3)$$

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

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

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:

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

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).

HSE

Health and Safety Executive

The burden of occupational cancer in Great Britain

Liver 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 liver 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 liver cancer related to overall occupational exposure is 0.18% (95% Confidence Interval (CI)= 0.11-0.29), which equates to 5 (95%CI= 3-8) attributable deaths and 5 (95%CI=3-8) attributable registrations.

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