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Health and Safety Executive

The burden of occupational cancer in Great Britain

Leukaemia

Prepared by the **Health and Safety Laboratory**, 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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Leukaemia

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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 leukaemia 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 leukaemia related to overall occupational exposure is 0.74% (95% Confidence Interval (CI)= 0-3.86), which equates to 23 (95%CI= 5-120) attributable deaths and 38 (95%CI= 8-198) 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 leukaemia that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

Benzene, ionising radiation, ethylene oxide/ ethylene dichloride, formaldehyde,1,3 butadiene, boot and shoe manufacture and repair, work in petroleum refining and work in the rubber industry have been classified by the IARC as definite human carcinogens for leukaemia. Non-arsenical insecticides have been classified by IARC as probably carcinogenic to humans. Other suspected occupations included electricity workers (& electromagnetic fields), chemists and painters but there is as yet insufficient evidence to consider them as occupational causes of leukaemia.

Benzene is a constituent of petrol (gasoline) and a by-product of coke production and many other combustion processes including cigarette smoke, and has been extensively used in the chemical industry and in the past in the shoe and boot manufacturing industry. Occupational exposure to ionising radiation can affect nuclear industry workers, disaster clean-up workers, radiologists, technologists and military personnel, aircrew and during underground mining, working with plutonium, reactor fuel manufacture and radium-dial painting. Ethylene oxide is used widely as a sterilising agent, disinfectant, and pesticide and is an intermediary in the chemical synthesis of ethylene glycol (antifreeze), non-ionic surfactants, resins and films. Formaldehyde exposure occurs during production, in pathology and embalming and in the plastics, plywood and textile industries. 1,3-butadiene is used mainly in the production of synthetic rubbers and other synthetic elastomers for the manufacture of tyres, latex adhesives, hoses, gaskets, and other rubber products. Occupational exposure to non-arsenical insecticides occurs in farming, forestry and horticulture, in the flour and grain milling industry and during pesticide manufacture.

Due to assumptions made about cancer latency and working age range, only cancers in ages 15-84 for men and 15-79 in 2005/2004 could be attributable to occupation. For Great Britain in 2005, there were 2001 total deaths in men aged 15-84 and 1101 in women aged 15-79 from leukaemia; in 2004 there were 3333 total registrations for leukaemia in men aged 15-84 and 1869 in women aged 15-79.

The estimated total (male and female) attributable fractions, deaths and registrations for leukaemia related to occupational exposure is 0.74% (95% Confidence Interval (CI)=0-3.86), which equates to 23 (95%CI=5-120) attributable deaths and 38 (95%CI=8-198) attributable registrations. Results for individual carcinogenic agents for which the attributable fraction was determined are as follows:

- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to benzene is 0.25% (95%CI=0.00-4.65), which equates to 4 (95%CI=0-78) attributable deaths and 7 (95%CI=0-128) attributable registrations.
- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to 1,3-butadiene is 0.01% (95%CI=0.00-0.06) which equates to 0 (95%CI=0-2) attributable deaths and 0 (95%CI=0-3) attributable registrations.
- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to ionising radiation is 0.02% (no CI available) which equates to 0 attributable deaths and 1 attributable registration.
- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to ethylene oxide is 0.01% (95%CI=0.00-0.21) which equates to 0 (95%CI=0-7) attributable deaths and 1 (95%CI=0-11) attributable registration.
- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to formaldehyde is 0.20% (95%CI=0.05-0.48) which equates to 6 95%CI=2-15) attributable deaths and 10 (95%CI=3-25) attributable registrations.
- The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to non-arsenical insecticides is 0.38% (95%CI=0.09-0.68), which equates to 12 (95%CI=3-21) attributable deaths and 19 (95%CI=5-35) attributable registrations.

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1 INCIDENCE AND TRENDS

Leukaemias (ICD-9: 204-208; ICD-10: C91-C96) account for less than 3% of all cancers in the UK, but grouped together are the 10th most common form of cancer in men and the 9th in women[1]. In 2004, there were around 6,388 new cases diagnosed in GB, over 90% occurring in people aged over 15 years and just under 58% of which were in males[2]. Based on mortality information, almost a half of all cases are acute myeloid leukaemia (AML) with a further quarter chronic lymphoid leukaemia (CLL). Chronic myeloid (CML) and acute lymphoid (ALL) leukaemias each account for just over 5% of cases. Monocytic leukaemia and other specified leukaemias each account for only 0.5% of cases; and 7% are other or unspecified forms of leukaemia[3]. The age-standardised incidence rates in 2004 for males and females were 13.5 and 9.5 per 100,000, respectively, and have fluctuated around 5 to 7 for females and between 8 and 12 for males since the 1970s (Swerdlow *et al*, 2001). Leukaemia shows a bimodal peak in incidence, the childhood peak of the disease is greater and occurs at a slightly older age in boys than in girls (Swerdlow *et al*, 2001). At subsequent ages there is modest excess in males up to about age 50 years, and a widening gap between the sexes at older age. Mortality from leukaemia increased throughout the 1950s but levelled off between the late-1960s and mid-1970s, and since has declined slightly. Little change has been seen in the incidence and mortality among men and women under the age of 65 years. There are no consistent geographical patterns worldwide in either incidence or mortality, although rates tend to be higher in developed countries (USA, Australia, Europe), and is particularly low in India (Linet *et al*, 2006). In Scotland, leukaemia mortality has increased by 16.4% over the past ten years (1994-2004).

One-year relative survival from all leukaemias was around 57% and five-year survival was around 30% for patients diagnosed in the period 1996-1999 in England and Wales (ONS, 2004). Survival (1-, 5-, 10-year) from leukaemia has steadily increased since the 1980s, more so in men (Rachet *et al*, 2008). However, rates differ between the subtypes of leukaemia. For example, less than 10% of those diagnosed with AML will survive five years compared with half those diagnosed with CLL.

Table 1 shows the leukaemia registration trends for 1994-2004, for all leukaemias and all lymphoid and all myeloid leukaemias, for men and women in England and England/Wales. Table 2 gives the number of registrations by country with GB for 2004. Table 3 shows the leukaemia mortality trend for 1999-2005, for all leukaemias and all lymphoid and all myeloid leukaemias, for men and women. Table 4 shows the numbers of leukaemia sub-types by country in GB and crude incidence rate 2005.

[1] http://info.cancerresearchuk.org/cancerstats/types/leukaemia/incidence/ (accessed May 2009)
[2] http://www.statistics.gov.uk/downloads/theme_health/MB1_35/MB1_No%2035_2004.pdf; http://www.isdscotland.org/isd/1538.html; http://www.wales.nhs.uk/sites3/page.cfm?orgid=242&pid=18135
[3] http://www.statistics.gov.uk/downloads/theme_health/Dh2_32/DH2_No32_2005.pdf

Table 1. Leukaemia registration trends for England

		All Leukaemia		Lymphoid		Myeloid	
Year	Total Registrations[1]	Cancer Registrations	Rate /100000	Cancer Registrations	Rate /100000	Cancer Registrations	Rate /100000
Males							
1994	112,145	3,053	12.1	1,482	5.9	1,401	5.5
1995	103,986	3,040	12.7	1,540	6.4	1,348	5.6
1996	104,103	2,787	11.6	1,491	6.2	1,145	4.7
1997	104,335	2,798	11.5	1,346	5.6	1,304	5.4
1998	106,745	2,994	12.3	1,515	6.2	1,324	5.4
1999	108,827	3,040	12.4	1,579	6.4	1,290	5.3
2000	111,543	3,268	13.7	1,707	7.2	1,376	5.8
2001	112,516	3,159	13.1	1,632	6.8	1,368	5.7
2002	112,579	3,143	12.9	1,635	6.7	1,342	5.5
2003	112,732	3,310	13.6	1,653	6.8	1,509	6.2
2004	117,805	3,306	12.7	1,688	6.5	1,462	5.6
Average	**109,756**	**3,082**	**12.6**	**1,570**	**6.4**	**1,352**	**5.5**
Females							
1994	112,175	2,506	9.5	1,130	4.3	1,210	4.6
1995	105,151	2,364	9.5	1,078	4.3	1,149	4.6
1996	105,461	2,272	9.1	1,044	4.2	1,096	4.4
1997	107,289	2,271	9.1	959	3.8	1,164	4.6
1998	109,957	2,423	9.6	1,068	4.3	1,171	4.7
1999	112,237	2,479	9.8	1,102	4.4	1,216	4.8
2000	112,066	2,396	9.5	1,144	4.5	1,116	4.4
2001	112,134	2,439	9.7	1,163	4.6	1,137	4.5
2002	112,210	2,465	9.7	1,125	4.4	1,193	4.7
2003	114,740	2,431	9.6	1,087	4.3	1,222	4.8
2004	115,816	2,414	8.9	1,071	4.0	1,213	4.5
Average	**110,840**	**2,405**	**9.5**	**1,088**	**4.3**	**1,172**	**4.6**

[1]Total registrations exclude non-melanoma skin cancers.
SOURCE: Office for National Statistics, Series MB1

Table 2. Cancer registrations in England, Wales and Scotland in 2004

	England		Wales		Scotland	
	Men	Women	Men	Women	Men	Women
Specified leukaemias (C91-C95)	3,306	2,414	290	213	357	278
Unspecified leukaemias (C96)	18	17	1	2	2	0

Table 3. Leukaemia mortality trends for England and Wales.

		All Leukaemia		Lymphoid		Myeloid	
Year	Total Deaths[1]	Number of Deaths	Rate (/100000)	Number of Deaths	Rate (/100000)	Number of Deaths	Rate (/100000)
Males							
1999	264,299	1,946	7.2	661	2.5	1,123	4.2
2000	255,347	1,964	7.1	625	2.4	1,194	4.7
2001	252,426	2,108	7.6	750	3.0	1,214	4.8
2002	253,144	2,100	7.6	750	3.0	1,228	4.9
2003	253,852	2,232	7.5	726	2.9	1,300	5.1
2004	244,130	2,126	6.7	730	3.0	1,266	5.2
2005	242,057	2,165	8.3	753	2.9	1,256	4.8
Average	**252,179**	**2,092**	**7.4**	**714**	**2.8**	**1,226**	**4.8**
Females							
1999	291,819	1,734	6.4	503	1.7	1,077	3.7
2000	280,117	1,606	5.9	469	1.7	992	3.5
2001	277,947	1,673	6.2	510	1.8	1,053	3.8
2002	280,383	1,811	6.6	568	2.0	1,098	3.9
2003	284,402	1,684	3.9	524	1.8	1,024	3.6
2004	268,411	1,702	4.0	511	1.9	1,056	3.9
2005	268,408	1,694	6.2	497	1.8	1,058	3.9
Average	**278,784**	**1,701**	**5.6**	**512**	**1.8**	**1,051**	**3.8**

[1]Total deaths exclude non-melanoma skin cancers

SOURCE: Office for National Statistics, Series DH1 and DH2; Note rate for all leukaemias in age-standardised, rates for lymphoid and myeloid leukaemias are crude rates.

Table 4. Numbers of deaths of leukaemia sub-types in 2005 (Source: ONS & ISD)

Site	England & Wales	Scotland
Acute lymphoid	244 (130:114)	20 (12:8)
Acute myeloid	1880 (1015:865)	175 (87:88)
Chronic lymphoid	978 (599:379)	85 (52:33)
Chronic myeloid	206 (109:97)	29 (16:13)
Total:	**3308 (1853:1455)**	**309 (167:142)**

2 OVERVIEW OF AETIOLOGY

2.1 INTRODUCTION

The aetiology of leukaemia is not well understood and involves a number of factors (Linet *et al*, 2006). Ionising radiation has been recognised as a cause of leukaemia for many years; however, it only accounts for a small proportion of cases, 10% in some communities, and appears to have no effect on the risk of CLL (Higginson *et al*, 1992). Other agents that are accepted as causal risk factors are occupational exposure to benzene and certain drugs used for cancer chemotherapy including alkylating agents (Linet *et al*, 2006). Chemical-related cases account for probably less than 1% of the total. It has also long been thought that leukaemia may be induced by viruses, including human T-cell lymphotropic virus, bovine leukaemia virus, Epstein-Barr virus and Hepatitis B virus (Dalgleish, 1991). Recently, an association with smoking has been observed in a number of studies for both myeloid and lymphoid types of acute leukaemia (Linet *et al*, 2006).

The Occupational Health Decennial Supplement (OHDS) for 1981-1990 did not show any clear patterns with regards to the possible exposures encountered during employment that would increase the risk of leukaemia (Drever, 1995) (Table 5). However, increases were seen in butchers who may be more exposed to animal viruses. Similarly, farmers were at an increased risk, maybe because of their increased contact with animals but also potential exposure to pesticides. Leather and shoe workers, historically, were exposed to high levels of benzene and plastic goods makers are exposed to numerous toxic chemicals. Teachers, both in schools and higher education were at a greater risk, excesses which again are consistent with an aetiological role of infections acquired as an adult through frequent contact with large numbers of young people. Leukaemias contributed around 2% of all registrations in the 20-74 year age group, AML being the most common in both males (35%) and females (45%).

The OHDS for 1991-2000 also did not show any clear patterns with some of the increases seen during the 1981-1990 period not being observed (Table 6) (Coggon *et al,* 2009).

Table 5. Job codes with significantly high PRRs and PMRs for leukaemia. Men and women aged 20-74 years, England, 1979-80, 1982-90.

Job group			PRR	95%CI	PMR	95%CI
SIC code	**Description**					
Men						
003	Personnel managers	Other			303	122-623
006	Sales managers	ALL			161	99-246
007	Government inspectors	CLL	234	107-445		
010	Teachers in higher education	CLL			184	105-298
011	Teachers	AML			130	104-161
		CML	155	100-229	143	102-194
027	Chemical engineers & scientists	CLL	270	109-557		
042	Butchers	CLL	175	104-278		
047	Farmers	All	117	102-134		
		CLL	127	100-160		
051	Launderers & dry cleaners	Other	675	139-1974		
059	Cooks & kitchen porters	CLL	203	108-348		
068	Leather & shoe workers	All	159	106-230		
		AML	222	119-381		
093	Plastic goods makers	ALL			574	211-1250
095	Printing plate preparers	AML			426	171-878
098	Tailors & dressmakers	CLL			234	107-445
101	Upholsterers	CLL			222	102-422
124	Machine tool operators	ALL			144	99-203
		AML			125	107-146
129	Toolmakers	CML			181	110-279
130	Precision instrument makers	All	190	101-325		
142	Other electronic maintenance	All	277	167-434		
	engineers	AML	293	127-579	179	104-287
		CML			242	116-445
		CLL	408	133-954		
148	Scaffolders	AML			214	110-373
150	Riggers	CML	484	132-1239		
159	Other spray painters	Other	404	110-1035		
163	Assemblers (vehicles/ metal goods)	ALL	520	108-1522		
169	Builders	AML			125	100-155
171	Road construction workers	ALL			323	119-703
		CML			211	105-377
173	Mains & service layers	CML	450	146-1052		
174	Construction workers	Other			184	111-288
177	Railway guards	CLL	319	104-745		
180	Railway engine drivers	AML	223	102-425		
183	Lorry drivers	AML			203	113-334
Women						
012	Vocational trainers	CML			350	129-762
020	Physiotherapists	CML			399	109-1021
026	Biological scientists	AML	1244	339-3188		
038	Production & maintenance	All	290	107-632		
	managers	AML	500	162-1168		
161	Electrical, electronic assemblers	CML			269	108-555
		All	320	138-632		
182	Bus & coach drivers	AML	584	159-1497		

Source: Drever *et al.* (1995) Occupational Health Decennial Supplement

Table 6. Job codes with significantly high PMRs for leukaemia. Men and women aged 16-74 years, England and Wales, 1991-2000.

Job group			PMR	95%CI
SIC code	**Description**			
Men				
021	Other health professions	AML	193	118-298
031	Draughtspersons	All	394	128-920
049	Police	AML	154	115-202
057	Sales representative	ALL	176	109-269
058	Security workers	CML	158	110-218
062	Ambulance staff	ALL	419	114-1074
063	Railway station staff	AML	186	112-290
065	Forestry workers	AML	255	122-469
078	Other food, drink & tobacco process operatives	AML	163	111-230
		Other	269	116-530
079	Paper manufacturers	ALL	571	156-1462
083	Glass product & ceramic finishers & decorators	CLL	555	151-1420
124	Machine tool operators	ALL	166	108-246
132	Production fitters	CLL	134	108-164
142	Other electronic maintenance engineers	CML	187	114-289
143	Electrical engineers	CLL	176	110-267
190	Storekeepers & warehousemen/women	ALL	154	101-226
Women				
003	Personnel managers, etc.	AML	178	102-289
017	Nurses	ALL	151	100-218
041	General & office managers	AML	145	104-196
054	Postal workers, mail sorters	ALL	569	185-1327
059	Cooks & kitchen porters	AML	133	103-169
074	Other textile processing operators	Other	945	257-2419
113	Rollers	AML	3980	101-22176

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 leukaemogenic are given in Table 7. Siemiatycki *et al.* (2004) and Rousseau *et al.* (2005) summarise the strength of evidence used in the classification of these agents and substances as strong and suggestive and this is also given in Table 7. In addition to these a number of other occupations have been suspected of entailing exposure to leukaemogenic chemicals, including painters, chemists and electricity workers (non-ionising radiation).

Table 7. Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Vols 1-90 (IARC, 1972-2001), into Groups 1 and 2A, which have leukaemia as the target disease.

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				
Benzene	Production, Boot & shoe industry, chemical, pharmaceutical & rubber industries, printing, petrol additive	Sufficient	Strong	
Ionising radiation	Radiologists, technologists, nuclear workers, air craft crews; underground miners;	Sufficient	Strong	Bone Lung Liver Thyroid
1,3-Butadiene	Chemical & rubber industries	Sufficient	Suggestive*	
Ethylene oxide	Production, chemical industry, sterilising agent (hospitals, spice fumigation)	Sufficient	Strong	
Formaldehyde	Production, pathologists, medical laboratory technicians, plastics, textile & plywood industry	Sufficient	Suggestive	Sino-nasal Nasopharynx
Exposure circumstances				
Boot and shoe manufacture and repair	Benzene & other solvents		Strong	
Petroleum refining	Benzene		Suggestive	
Rubber industry	Solvents		Suggestive	
Group 2A: Probably Carcinogenic to Humans				
Agents & groups of agents				
Non-arsenical insecticides	Production, pest control & agricultural workers, flour and grain mill workers	Limited	Suggestive	Brain Lung Myeloma NHL
Exposure circumstances				
None identified				

$ Taken from IARC monographs; § Taken from Siemiatycki *et al.* (2004), Rousseau *et al.* (2005); * for lymphohaematopoietic

2.2 EXPOSURES

2.2.1 Benzene

Benzene, the simplest aromatic solvent, occurs naturally in petroleum, is a constituent of petrol, and used extensively as a synthetic building block in the chemical industry. It is a by-product of coke production and virtually any combustion process including cigarette smoke,

and has been extensively used in the shoe and boot manufacturing industry. Occupational benzene exposure has been demonstrated to cause leukaemia (Hayes *et al*, 2001, Lynge *et al*, 1997, Siemiatycki *et al*, 2004). In 1982 the IARC concluded that benzene was aetiologically related to the development of acute non-lymphocytic leukaemia (ANLL) (IARC, 1982). However, various reviews of leukaemia sub-types associated with benzene exposure have come to different conclusions. Lamm *et al*. (1989) concluded that the evidence simply supported a causal connection between AML and benzene, but that evidence linking ALL, CML, and CLL to benzene was lacking. In contrast Savitz and Andrews (1997) concluded that the overall pattern did not indicate an association limited to AML, and concluded their evidence linking lymphocytic leukaemia to benzene was similar to that for myeloid leukaemia.

Hayes *et al.* (1997) studied a cohort of 74,828 Chinese benzene-exposed and 35,805 unexposed workers from 1972 through 1987. The workers were from a variety of industries and occupations, including painting, printing and the manufacture of footwear, paint and other chemicals. Among exposed workers the mean exposure was 22.5 parts per million (ppm) over an average of 9.3 years. Exposure was greater in those first employed before 1972 (24.9ppm) compared to those after 1972 (19.2ppm). Workers involved in the rubber industry (53.5ppm) had more than double the average exposure compared to other industries (coatings - 21.5ppm; chemical – 24.8ppm; shoe – 21.8ppm; other – 17.4ppm). The relative risk (RR) for all lymphohaematopoietic cancers combined among exposed workers was 2.6 (95% confidence interval (CI)=1.4-4.7) based on 58 cases (13 cases among controls). There were 38 deaths from leukaemia among exposed workers, which resulted in a RR of 2.5 (95%CI=1.2-5.1), with an RR for ANLL of 3.0 (95%CI=1.0-8.9). The risk appeared to be greater in those first hired after 1972 compared to those first hired before 1972, 3.4 compared to 2.4 for all leukaemias, and 5.1 compared to 2.6 for ANLL. For all leukaemias the RR was greatest among chemical workers (RR=3.6) as it was for ANLL (RR=4.5). For both leukaemias and ANLLs significant exposure-response relationships were seen for average exposure and cumulative exposure, and for those always exposed at indicated levels.

Rushton & Romaniuk (1997) investigated the association between leukaemia and exposure to benzene in petroleum marketing and distribution workers in the UK by a case-control study. From a large cohort, 91 leukaemia cases were identified through a death certificate or cancer registration. These were matched with controls (four per case). There was no significant increase in risk for all leukaemias with high cumulative exposure to benzene or with intensity of exposure, although risk was consistently doubled in subjects employed in the industry for more than ten years. All occurred in workers who started work after the age of 30 years, employed after 1950, worked for a short duration and experienced low cumulative exposure. For AML and acute monocytic leukaemia duration of employment was the variable most closely related to risk, it being increased to an odds ratio (OR) of 2.8 (95%CI=0.8-9.4) for a cumulative exposure between 4.5 and 45ppm-years compared with <0.45ppm-years. For mean intensity between 0.2 and 0.4ppm an OR of 2.8 (95%CI=0.9-8.5) was found compared with <0.02ppm. Risk did not increase with any other measure of exposure.

Lewis *et al.* (2000) investigated mortality among a cohort of 34,560 Canadian petroleum workers, employed from 1964-83. A total of 6,760 deaths were observed (men: 6,254, Standardised Mortality Ratio (SMR)=0.86, 95%CI=0.84-0.88; women: 506, SMR=0.80, 95%CI=0.73-0.88). Among men there were 1,611 cancer deaths (SMR=0.89, 95%CI=0.85-0.94), and among women there were 198 cancer deaths (SMR=0.96, 95%CI=0.83-1.11). There were 56 leukaemia deaths among men (SMR=0.89, 95% CI=0.67-1.16) and six among women (SMR=0.86, 95%CI=0.32-1.88). Among men there were 23 cases of ANLL (SMR=1.53, 95%CI=0.97-2.30) and 19 from AML (SMR=1.38, 95%CI=0.83-2.16). Workers involved in marketing and distribution showed a non-significant excess of all leukaemias, ANLL and AML; however, office workers also showed an excess of ANLL and AML.

Guenel *et al.* (2002) investigated leukaemia mortality in a case-control study nested in a cohort of gas and electric utility workers. A total of 72 leukaemia cases were matched with 285 controls, and exposure was assessed by a job-exposure matrix. Leukaemia risk was increased in workers with an estimated cumulative exposure to benzene ≥16.8ppm-years (OR=3.6, 95%CI=1.1-11.7) with indication of a significant exposure-response. For all acute leukaemias the OR at cumulative exposure of ≥16.8ppm-years was 4.6 (95%CI=1.2-17.4) with again a significant exposure-response relationship. The risk of AML at an exposure of ≥5.5ppm-years was 2.4 and that for ALL was 3.3, although no exposure-response relationship was observed. For all leukaemias significant exposure-response relationships were observed with duration of exposure, mean intensity, and cumulative-exposure; these were also seen when taking into account latencies of two, five or ten years respectively. The authors suggested that exposures older than ten years at diagnosis might play a more important role in leukaemia causation.

Collins *et al.* (2003) examined mortality among 4,417 benzene exposed chemical workers. There were 22 leukaemia deaths in the cohort as a whole (19.7 expected; SMR=1.12, 95%CI=0.70-1.69)). Among exposed workers there were 12 deaths with 9.3 expected (SMR=1.29, 95%CI=0.67-2.25). There was no exposure-response relationship, although the SMR in workers with cumulative exposure 6ppm-years was 1.7 (95%CI=0.6-3.8). There was also no exposure-response for ANLL with the risk in the highest exposure category being 2.2 (95%CI=0.3-8.1). When peak exposures over 100ppm for 40 or more days were considered, the observed number of all leukaemias (SMR=2.7, 95%CI=0.8-6.4) and ANLL (SMR=4.1, 95%CI=0.5-14.9) were greater than expected.

Glass *et al.* (2003) examined leukaemia risk among Australian petroleum workers exposed to low levels of benzene. In a case-control study 79 cases were identified between 1981 and 1999, and matched with five controls. Matched analysis indicated leukaemia risk was increased at cumulative exposures above 2ppm-years, with the risk at >16ppm-years being 98.2 (95%CI=8.8-10.90), and with intensity of exposure of highest exposed job over 0.8ppm. At a cumulative lifetime benzene exposure >8ppm-years the risk for ANLL was 7.17 (95%CI=1.27-40.4) and for CLL was 4.52 (95%CI=0.89-22.9), and for CML was 0.91 (95%CI=0.08-9.8). The risk of leukaemia was not associated with start date or duration of employment.

Rinsky *et al.* (2002) followed a previously studied (Infante *et al*, 1977, Rinsky *et al*, 1981, Rinsky *et al*, 1987) cohort of rubber hydrochloride workers between 1940 and 1996, the Pliofilm production study. A cohort of 1,845 individuals was assembled and by the end of follow-up, 976 had died. Among males exposed to at least 1ppm-day of benzene the all-cause mortality was 0.99 and all-cancer mortality was 1.05. There were 15 deaths from leukaemia resulting in a SMR of 2.56 (95%CI=1.43-4.22). Leukaemia risk by exposure category showed a significant exposure-response as seen in the table below. Cox proportional hazards modelling showed the relationship between benzene exposure and leukaemia mortality risk was best described by a linear function of cumulative exposure with no lag. There was also no relationship between exposure and leukaemia cell type (Table 8).

Table 8. SMRs for leukaemia in white males exposed to benzene by exposure category (source: Rinsky *et al.*, 2002)

Cumulative exposure (ppm-years)	SMR (95%CI)	Number of cases
<40	1.45 (0.53-3.31)	6
40-<200	3.21 (0.86-8.89)	4
200-<400	5.55 (0.62-24.08)	2
400+	23.96 (4.82-78.51)	3

Costantini *et al.* (2003) studied leukaemia risk among benzene-exposed workers in an Italian shoe factory. The cohort consisted of 1,687 persons employed after 1950 and followed through 1999. Exposure was assessed with a job-exposure matrix constructed using models developed for each job category from limited measurements of benzene. Mean cumulative exposure was 58.4ppm-years (71.8 for men, 43.4 for women) with a range of 0-522.5ppm-years. For men and women combined there were 11 deaths from leukaemia (9 men, 2 women), giving an overall SMR of 2.48 (95%CI=1.24-4.44). The risk of leukaemia was elevated in all categories of cumulative exposure with the exception of the lowest (<40ppm-years). In the highest category (≥200ppm-years) the risk was 5.1 (95%CI=1.4-13.0), and for men only it was 7.0 (95%CI=1.9-18.0). For both men and men/women combined the risk of leukaemia showed an exposure-response relationship with categories of peak exposure with the risk being 4.5 (95%CI=1.1-9.9) for men and 3.5 (95%CI=1.3-7.6) for men/women in the highest category (≥30ppm).

Bloemen *et al.* (2004) assessed mortality in a cohort of 2,266 chemical workers exposed to benzene in various manufacturing processes since 1935 and followed them through 1996. All-cause mortality (SMR=0.90) was significantly reduced, although all-cancer mortality (SMR=0.97) was not. There were 12 leukaemia deaths giving a SMR of 1.14 (95%CI=0.59-1.99). Leukaemia risk by cumulative exposure and average intensity showed an exposure-response relationship (Table 9).

Table 9. Leukaemia SMRs by benzene exposure measures in US benzene exposed chemical workers (source: Bloemen *et al.*, 2004)

Cumulative exposure (ppm-years)	**SMR – 0 lag**	**SMR – 15yr lag**
<340	0.60	0.69
28.3-79.1	2.00	1.71
79.1+	2.16	2.55
Average intensity (ppm)		
<5	0.75	0.95
5-14	1.57	2.96
15+	1.19	--

A review of the literature showed high and significant risks with positive dose-response relationships across study designs, particularly in the well conducted cohort studies and especially in more highly exposed workers in rubber, shoe, and paint industries (Schnatter *et al*, 2005). Risks for CLL tended to show elevations in nested case-control studies, with possible exposure-response relationships. However, risks for CLL were not elevated in cohort studies. Data for other subtypes of leukaemia are sparser. In the decennial supplement male leather and shoe workers had a high risk of leukaemia (PRR: 159, 95%CI=106-230), as did male chemical engineers (PRR: 117, 95%CI=66-193) and female chemical workers (PRR: 305, 95%CI=181-483), although the last two may or may not have been exposed to benzene (Drever, 1995).

2.2.2 Ionising Radiation

Ionising radiation (IR) is a well-established cause of leukaemia and has been classified as a Group 1 carcinogen by IARC (2000). The causal relation between IR and leukaemia was first demonstrated during the follow-up of the Nagasaki and Hiroshima atomic-bomb survivors with a high incidence of AML (UNSCEAR, 2000, Yardley-Jones and Gray, 2001). A study of men who participated in the UK atmospheric nuclear weapons tests and experimental programmes also found significant excess RRs (Darby *et al*, 1988a, Darby *et al*, 1988b, Darby *et al*, 1993a, Darby *et al*, 1993b, Muirhead *et al*, 2003, Muirhead *et al*, 2004). In the cohort 21,357 participants were followed to 1998. Among the cohort 4,902 were known to have died.

All-cause (SMR=0.89) and all-cancer (SMR=0.93) mortality were both significantly reduced among test participants (Muirhead *et al*, 2003). There were 45 deaths from leukaemia giving a SMR of 0.98 (95%CI=0.72-1.31) and compared to the controls (Ministry of Defence employees not involved in tests) this SMR was 45% higher (SMR ratio=1.45, 95%CI=0.96-2.17). The corresponding RR for leukaemia incidence was 1.33 (95%CI=0.97-1.84). After excluding CLL, which is not believed to be radiation inducible, the RR for leukaemia mortality increased to 1.83 (95%CI=1.15-2.93). Analysis of subgroups of participants with greater potential for exposure provided little evidence of increased risks, although the numbers involved were small. The RR, excluding CLL, up to the end of 1990 was shown to be 1.84 and very similar in the subsequent eight years at 1.81. Over both periods the SMRs for test participants were close to national rates.

Airline pilots and flight engineers are occupationally exposed to IR of cosmic origin, the highest doses occurring in jet flights in high altitude and on polar routes (Blettner *et al*, 2003). A study of British Airways (BA) crew members, 6,209 male pilots and 1,153 male flight engineers employed for at least one year between 1950 and 1992, were followed up and compared with the national population (Irvine and Davies, 1999). At the end of the study period, 592 pilots and 127 flight engineers were known to have died. For pilots and flight engineers the all cause and all cancer mortality were significantly reduced. Only four leukaemia deaths were observed among pilots whereas 7.84 were expected (SMR=0.51, 95%CI=0.14-1.31). For flight engineers only two leukaemia deaths were observed with 1.75 expected (SMR=1.14, 95%CI=0.14-4.12). Cancer risk was greater among pilots and flight engineers on long haul flights compared to short haul but there were too few deaths to make a detailed comparison. A European-wide study of crews from nine countries, including an update of the BA cohort (7,770 employed between 1950 and 1997), found 30 leukaemia deaths (32.1 expected) giving a SMR of 1.05 (95%CI=0.69-1.50) (Blettner *et al*, 2003) for all leukaemias and 1.12 (95%CI=0.67-1.70) for all leukaemias, excluding CLL. Poisson regression analysis of risk by duration of exposure showed a significant trend of rate ratios of 1.0, 1.02, 0.3, 0.77 for duration of <10, 10-<20, 20-<30, 30+ years, respectively. The typical annual exposure of aircraft crew in this study was between 2 and 6mSv.

In a large European cohort of 19,184 male pilots cancer mortality was investigated on the basis of individual effective dose estimates (Langner *et al*, 2004). Mean annual doses were in the range of 2-5mSv and cumulative lifetime doses did not exceed 80mSv. Follow-up varied between countries from which cohort members came from but was either 1996 or 1997. There were a total of 1,234 deaths, giving a SMR for all causes of 0.70 (95%CI=0.67-0.75), with 338 cancers (SMR=0.67, 95%CI=0.60-0.75). There were 19 deaths from leukaemia, which resulted in a SMR of 1.14 (95%CI=0.69-1.78), and 14 non-CLL leukaemias (SMR=1.39, 95%CI=0.76-2.34). The SMRs for leukaemia sub-types were all slightly increased (not significantly) in all categories of cumulative dose but did not show a clear pattern with radiation dose or block hours. The increase was more pronounced when CLL was excluded from the analysis.

Physicians joining the British radiological society before 1921 experienced an excess leukaemia risk. March (1944) showed an excess risk among early radiologists, evidence that predates the atomic bombings. An update by Smith and Doll (1981) showed that they had a six-fold leukaemia mortality excess. Recently, Berrington *et al.* (2001) presented the results of 100 years of observation of British radiologists. Those who had registered between 1897 and 1979 were followed-up through 1997. Mortality risk from all cancers was 0.73 (95%CI=0.64-0.83) when compared to the national population, whereas when compared to other medical practitioners it was 1.16 (95%CI=1.02-1.32). Since 1920 there were eight deaths from leukaemia (20+ years after registration), compared to 4.26 expected giving an SMR of 1.88 (95%CI=0.81-3.70). When compared to rates for medical practitioners the SMR was 2.40 (95%CI=1.04-4.73). Risk in those first registered in 1897-1920 (2.50) was lower than in those first registered in 1921-1935 (2.70) but has subsequently declined (1936-54:

1.75; 1955-79: 1.16). However, the occupational health decennial supplement has failed to show any excess in this occupational group (Drever, 1995).

Nuclear industry workers provide an opportunity to investigate an effect of internally deposited radionuclides. Smith and Douglas (1986) investigated the mortality of all 14,327 people who were known to have been employed at the Sellafield plant of British Nuclear Fuels (BNFL) at any time between 1947 and 1975, and followed to 1983. A total of 2,277 were known to have died, 572 from cancer (SMR=0.95, 95%CI=0.87-1.03). Among all workers 11 deaths were from leukaemia giving a SMR of 0.63 (95%CI=0.32-1.14) based on national rates and 0.68 based on local rates. Ten of these deaths were among radiation workers resulting in a SMR of 0.82 (95%CI=0.39-1.51). Among radiation workers a non-significant trend was observed with radiation dose lagged 15-years. A subsequent report obtained similar results (Douglas *et al*, 1994). In the most recent study Omar *et al.* (1999) assessed the health of 14,319 workers and followed them to 1992, for cancer incidence. A total of 3,854 (men: 3,411; women: 445) were known to have died, 2,682 among radiation workers (1,345 plutonium workers, 1,337 other radiation workers) and 1,172 among other workers. There were 738 cancer deaths resulting in a SMR of 0.96 (95%CI=0.89-1.03) compared to the national population and 0.97 (95%CI=0.90-1.04) compared to the local population. Table 10 gives the leukaemia mortality among different workers.

Table 10. Leukaemia mortality among different workers within the UK nuclear industry (source: Omar *et al.*, 1999)

	Number observed/expected	SMR	
		Compared to national population	Compared to local population
All workers	20/28.14	0.71	0.75
Radiation workers	16/20.03	0.80	
Plutonium	7/9.86	0.71	
Other	9/10.17	0.88	
Non-radiation	4/8.1	0.49	
Plutonium vs Other		0.79	
Radiation vs Non-radiation		1.27	

A significant exposure-response relationship was observed between leukaemia risk and external radiation dose with no lag and a two-year lag. However, no trend was seen with plutonium dose.

A total of 489 incident cancers were observed (254 among plutonium workers and 235 other radiation workers). A total of 13 leukaemia cases observed (SRR=0.90, 95%CI=0.48-1.54), with three among plutonium workers (SRR=0.40, 95%CI=0.08-1.17) and 10 among other radiation workers (SRR=1.44, 95%CI=0.69-2.65). An exposure-response relationship was not estimated for leukaemia because of small numbers; however, a significant relationship was observed between all lymphohaematopoietic cancers and cumulative plutonium plus external radiation doses.

Prior to the most recent analysis, the Sellafield cohort was combined with cohorts from the UK Atomic Energy Authority (UKAEA) and the Atomic Weapons Establishment (AWE) (Carpenter *et al*, 1994, Carpenter *et al*, 1998). The first study looked at mortality among all 75,006 employees of the three establishments between 1946 and 1988. A total of 13,505 were known to have died, with 3,745 cancer deaths (men: 3,077; women: 668) resulting in a SMR of 0.84 (95%CI=0.82-0.87). There were 116 leukaemia deaths among all workers

(SMR=1.00, 95%CI=0.83-1.20), with 60 among monitored workers (SMR=0.99, 95%CI=0.75-1.27) and 56 among other workers (SMR=1.02, 95%CI=0.77-1.32). Mortality in relation to cumulative whole body dose was significantly related to leukaemia risk for exposure lagged 10-years and unlagged. A much stronger trend was observed for leukaemia excluding CLL. For leukaemia (excluding CLL) with a two-year lag period the absolute risk estimate was 2.10 deaths per 10^4-person-years per sievert (Sv) and the excess relative risk was +4.18 per Sv. This positive exposure-response relationship was confined to Sellafield, associations for UKAEA and AWE being negative. The second paper examined the monitored workers in more detail. In individuals ever monitored for tritium, plutonium or other radionuclides, the SMR was well below unity (maximum 0.62), whereas that for individuals not monitored the SMR was 1.17 (n=43). As before a significant exposure-response trend was observed between leukaemia risk and cumulative whole-body lagged 10-years and unlagged.

In an extension to the analysis, the National Registry for Radiation Workers (NRRW) was set up (Kendall *et al*, 1992, Little *et al*, 1993, Muirhead *et al*, 1999). The initial analyses included workers from AWE, BNFL, Ministry of Defence, Nuclear Electric, and the then UKAEA. The most recent study included workers from Central Laboratory of the Research Councils, the Medical Research Council Radiobiology Unit, the National Radiological Protection Board, Nycomed Amersham plc, Rolls-Royce and Associates Ltd., and Scottish Nuclear Ltd. In total there were 124,743 workers with a range of exposures and a mean dose of 30.5mSv. There was a total of 12,765 deaths (SMR=0.82, 95%CI=0.81-0.84), and 3,598 cancer deaths (SMR=0.82, 95%CI=0.79-0.85). There were 108 leukaemia deaths (SMR=0.91, 95%CI=0.75-1.10) and 90 excluding CLL (SMR=0.94, 95%CI=0.75-1.15). In a lagged analysis (10-years) the SMRs were slightly higher. No exposure-response relationship was observed, and the excess relative risk (ERR) per Sv was 1.20 for all leukaemias and 2.55 for leukaemia excluding CLL.

In an IARC sponsored analysis, the three UK cohorts were combined with three from the USA and one from Canada (Cardis *et al*, 1995). This resulted in a mortality analysis on 95,673 workers (85.4% men) monitored for external exposure to IR and employed for at least six months. There were a total of 15,825 known deaths, 3,976 from cancer. There were 146 leukaemia deaths with 145.9 expected (SMR=1.00, 95%CI=0.85-1.18). There were 27 deaths from CLL (SMR=1.00, 95%CI=0.66-1.45), 119 from all except CLL (SMR=1.00, 95%CI=0.83-1.20), and 63 from acute leukaemias (SMR=1.00, 95%CI=0.77-1.28). Leukaemia mortality by cumulative radiation exposure approached significance for all types (p=0.076) and was significant for all leukaemias except CLL (p=0.046). The excess relative risk (ERR) estimate for leukaemia excluding CLL was 2.18 per Sv (95%CI=0.1-5.7) which corresponds to a RR of 1.22 for a cumulative protracted dose of 100mSv compared to 0mSv. The ERR for men was 2.21 whereas it was -2.67 for women. For individual facilities the highest (and highly significant) ERRs were for Sellafield (43.50) and the Canadian site (48.40).

In an update of this study a further 12 countries were included in the analysis with a total of 154 facilities included (Cardis *et al*, 2005). There were a total of 407,391 workers, with over 5 million person-years. There were a total of 24,158 deaths, 6,519 cancer deaths (excluding leukaemia), and 196 leukaemia deaths excluding CLL. The ERR for leukaemia excluding CLL was 1.93 per Sv (95%CI=<0-8.47), which gives a RR of 1.19 for a dose of 100mSV.

Many studies in the nuclear industry, nuclear weapons production workers and nuclear shipyard workers have reported no increases of leukaemia or only small non-significant excesses (Linet *et al*, 2006). However, a study of 95,217 UK radiation workers found a positive dose-response relationship associated with leukaemia risk (Kendall *et al*, 1992), as did a study of workers employed between 1947 and 1975 at the Sellafield plant of British Nuclear Fuels, although the overall risk was significantly reduced (Omar *et al*, 1999). A

mortality study of workers at the Sellafield plant of British Nuclear Fuels, followed up to the end of 1983, initially observed a significant deficit of leukaemia amongst radiation and other workers (Smith and Douglas, 1986). Further follow-up to the end of 1992 still observed a deficit of cases (Omar *et al*, 1999). Among all radiation workers, there was a significant positive association between accumulated external radiation dose and leukaemia mortality. Analysis of trends in lymphohaematopoietic neoplasm incidence showed significant increases in risk with cumulative plutonium plus external radiation doses for 0-, 10- and 20-year lag periods. A study of these workers plus employees of the UK Atomic Energy Authority and the Atomic Weapons Establishment found no increase in risk for leukaemia as a whole (Carpenter *et al*, 1994). A positive association was observed with cumulative external radiation, assuming a two-year lag between external radiation and increasing risk of death. Estimates of excess relative risk per Sv were estimated as +4.18 for leukaemia (95%CI +0.4-+13.4).

A meta-analysis of seven UK and US studies estimated a significantly elevated relative risk of 1.8 for mortality in workers who received a cumulative dose of 10-50mSv compared to those exposed to less than 10mSv (Wilkinson and Dreyer, 1991). Another study of nuclear industry workers obtained a similar figure (Cardis *et al*, 1995). A combined analysis of workers in the US, the UK and Canada resulted in a RR of 1.22 for leukaemia excluding CLL for a cumulative protracted dose of 100mSV compared to 0mSv (Cardis *et al*, 1995). However, further follow-up of the three UK industries did not see any excess of leukaemia (Carpenter *et al*, 1998), and studies of UK Atomic Energy Authority employees have shown no association between measured radiation dose and leukaemia mortality (Fraser *et al*, 1993, Smith and Douglas, 1986).

2.2.3 Ethylene oxide/Ethylene dichloride

Ethylene oxide (EO) is used widely as a sterilising agent, disinfectant, and pesticide. It is also an intermediary in the chemical synthesis of ethylene glycol (antifreeze), non-ionic surfactants, resins and films, and other derivatives in smaller quantities. Human exposure occurs in hospitals, in the production of certain chemicals and in the manufacture of plastics and drugs. Although the epidemiological evidence is limited, it has been classified by IARC as carcinogenic to humans (Group 1) based primarily upon sufficient evidence in animals and genotoxic considerations (IARC, 1994).

The initial concern about the health risk of EO was raised by studies in Sweden when a cluster of cases was observed among EO-exposed workers (Hogstedt *et al*, 1979). The study investigated mortality and cancer incidence in a cohort of workers employed by a company producing EO since the 1940s. The cohort consisted of 241 men and was followed up between 1961 and 1977. A total of nine cancers were observed (SMR=2.65, 95%CI=1.12-5.02), of which two were from leukaemia (SMR=14.3, 95%CI=1.71-51.6), were seen among full-time exposed workers. Among maintenance workers there was one leukaemia death (SMR=7.69, 95%CI=0.20-42.9). No cases were seen among unexposed workers. Updates of the cohort increased its size to 733 exposed workers (Hogstedt *et al*, 1986, Hogstedt, 1988). In this analysis eight cases of leukaemia were observed, with 0.8 expected. This resulted in a SMR of 10.0 (95%CI=4.32-19.7).

Since these studies were published EO research increased and in 1993 Shore and colleagues published a meta-analysis of a number of cohorts (Shore *et al*, 1993), and obtained a meta-SMR of 1.06 (95%CI=0.73-1.48), based on 31 leukaemia deaths among 29,800 workers. In 1999 Teta and her colleagues (1999) published an update of this meta-analysis, including 17 studies of ten unique cohorts of nearly 33,000 exposed workers with more than 800 cancers (mostly deaths, but some incident cases) (Teta *et al*, 1999). The cancer meta-SMR was 0.94 (95%CI=0.85-1.05), and that for leukaemia (based on 35 observed cases) was 1.08 (95%CI=0.61-1.93). However, for leukaemia, if the Swedish studies of Hogstedt were

removed then the meta-SMR was reduced to 0.95 (95%CI=0.64-1.35). The Hogstedt study was excluded in the second analysis because it accounted for the large amount of heterogeneity in leukaemia risk.

In an extended follow-up of the British cohort included in the meta-analysis, Coggon *et al*. (2004) investigated cancer risk among 2,876 men and women with definite or potential exposure to EO in the chemical industry or in hospital sterilising units. The cohort was ascertained after 1956 from 12 different locations (four industrial manufacturers and eight sterilising units), and followed-up to the end of 2000. There were a total of 188 cancer deaths observed (SMR=1.02, 95%CI=0.88-1.18), 120 among chemical manufacturers (SMR=1.11, 95%CI=0.92-1.32) and 68 among hospitals (SMR=0.90, 95%CI=0.70-1.14). There were only five leukaemia deaths (SMR=1.08, 95%CI=0.35-2.51), four among chemical manufacturers (SMR=1.41, 95%CI=0.39-3.62) and one in hospitals (SMR=0.55, 95%CI=0.01-3.06). Among the chemical workers all of the deaths were workers with definite exposure to EO (SMR=2.29, 95%CI=0.62-5.85), and those in hospital were among workers with continual exposure (SMR=1.08, 95%CI=0.03-5.99). This study indicates there is a low risk particularly at the levels of occupational exposure that have occurred in GB over recent decades and concluded it may reflect the capacity of human cells to repair DNA damage caused by the chemical, which is a potent genotoxin and carcinogen in animals.

In an update of the largest cohort, 18,235 workers were followed-up through 1998 (Steenland *et al*, 2004). In total there were 2,852 deaths, 860 from cancer (SMR=0.92, 95%CI=0.86-0.98). There were a total of 29 leukaemia deaths resulting in an SMR of 0.99 (95%CI=0.71-1.36). A definite negative exposure-response relationship was observed as seen in Table 11.

Table 11. Leukaemia risk among US workers exposed to ethylene oxide (source: Steenland *et al.*, 2004)

Cumulative exposure (ppm-days)	SMR (95%CI)
0-1199	1.15 (0.55-2.11)
1200-3679	1.06 (0.39-2.31)
3680-13499	0.93 (0.34-2.02)
13500+	0.43 (0.09-1.26)

However, internal analyses found positive trends for lymphohaematopoietic cancers, which were limited to males (15-year lag); the trend was driven by lymphoid tumours (non-Hodgkin's lymphoma, myeloma, lymphocytic leukaemia).

2.2.4 Formaldehyde

IARC classified formaldehyde as a probable human carcinogen based on animal studies with neoplastic lesions at the point of contact, the nasal cavity, and limited evidence of human respiratory tract carcinogenicity (IARC, 1995). Increased leukaemia rates have been observed in some studies of anatomists, pathologist and embalmers who often have formaldehyde exposure, but industrial workers have not consistently reported increased leukaemia rates (Blair *et al*, 1990). A recent IARC review concluded that there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde (Cogliano *et al*, 2005).

Two recent studies of industrial workers exposed to formaldehyde found a positive association between exposure and leukaemia risk (Hauptmann *et al*, 2003, Pinkerton *et al*, 2004). Hauptman *et al.* (2003) studied a cohort of 25,619 industrial workers, who were thought to have high exposures, first employed at one of 20 industrial plants before 1st January 1966 and followed-up through to 1994. A total of 8,486 deaths were observed, 827 among unexposed workers (SMR=0.77, 95%CI=0.72-0.83) and 7,059 among exposed

(SMR=0.95, 95%CI=0.93-0.97). There was a total of 69 leukaemia deaths, four among unexposed (SMR=0.38, 95%CI=0.14-1.00) and 65 among exposed workers (SMR=0.85, 95%CI=0.67-1.09). A significant exposure-response trend was observed between leukaemia risk and peak exposure ($p<0.01$), although for average intensity, cumulative exposure and duration of exposure the trend was non-significant. RRs particularly increased with formaldehyde exposure for myeloid leukaemia (30 deaths).

Pinkerton *et al.* (2004) evaluated the mortality experience of 11,039 workers in three US garment plants exposed to formaldehyde for at least three months. The cohort was assembled after formaldehyde was first introduced into the production process, 1955 at one plant and 1959 at the other two. The cohort was followed-up through 1998, when 2,206 were known to have died (SMR=0.92, 95%CI=0.88-0.96). A total of 608 cancers were seen over the total study period (1955-1998), giving an SMR of 0.89 (95%CI=0.82-0.97). There were 24 leukaemia deaths resulting in an SMR of 1.09 (95%CI=0.70-1.62). The greatest risk was for myeloid leukaemia (n=15; SMR=1.44, 95%CI=0.80-2.37) compared to lymphocytic (n=3; SMR=0.60, 95%CI=0.12-1.75) and other types (n=6; SMR=0.92, 95%CI=0.34-2.00). No trend was observed with leukaemia risk and duration of exposure, although individuals with 10+ years of exposure had an SMR of 1.53, compared to an SMR of 0.96 among those with <3-years exposure. However, a non-significant exposure-response trend was observed for myeloid leukaemia, the SMR for <3-years, 3-9 years and 10+ years exposure being 0.83, 1.26 and 2.19 respectively. A similar trend was seen for acute myeloid leukaemia. No trend was observed with time since first exposure, although the risk in those 20+ years since they were first exposed was more than double that in those <10-years since first exposure, suggesting risk was greatest among workers first exposed in the earliest years when exposures were presumably higher. A similar result was also found comparing the risk for those first exposed prior to 1963 (1.23 for leukaemia and 1.61 for myeloid leukaemia) with those first exposed after 1971 (risk for leukaemia 0.56 and for myeloid leukaemia 1.02).

Coggon *et al.* (2003) investigated mortality among 14,014 men employed after 1937 at six British factories where formaldehyde was produced or used, followed-up to 2000. During this time 5,185 deaths were recorded (SMR=1.04, 95%CI=1.02-1.07), 1,511 cancers (SMR=1.10, 95%CI=1.04-1.16). There were 31 deaths in the total cohort between 1941 and 2000 (SMR=0.91, 95%CI=0.62-1.29), and between 1990 and 2000 there were 12 deaths (SMR=0.91, 95%CI=0.47-1.59). In men with high exposure, greater than 2ppm, there were eight leukaemia deaths over the whole study period (SMR=0.71, 95%CI=0.31-1.39). Thus, in exposure situations that occur in British industry no association was found.

A recent review and meta-analysis of 18 studies of exposed workers published between 1975 and 2004, resulted in the study of 287 leukaemia deaths (Collins and Lineker, 2004). Table 12 highlights the risk in different job types, a small increase was observed among embalmers and pathologists/anatomists. Industrial workers, who have been reported to have the highest exposure, had a risk below unity. They concluded that the data do not provide consistent support for a relationship between formaldehyde exposure and leukaemia risk. However, Blair and Kazerouni (1997) suggest the failure to observe any excess, and the lack of absorption of formaldehyde beyond the site of contact suggests that the excesses among professionals may be due to bias or some other exposures.

Table 12. Leukaemia risk in different types of job (source: Collins &Lineker, 2004)

Job type	Number of leukaemia deaths	SMR (95%CI)
Industrial	164	0.9 (0.8-1.0)
Embalmers	78	1.6 (1.2-6.0)
Pathologists/Anatomists	45	1.4 (1.0-1.9)

2.2.5 1,3-Butadiene

IARC have classified 1,3-butadiene (BD) as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans of an increased risk for leukaemias (Grosse *et al*, 2007), whereas previously it was classed as probably carcinogenic to humans (Group 2A) (IARC, 1999). It is used mainly in the production of synthetic rubbers and other synthetic elastomers, the major end-use products being tyres, latex adhesives, hoses, gaskets, various rubber products, nylon carpet backings, paper coatings, paints, pipes, vehicle parts and luggage. BD is also used in the manufacture of the fungicides, captan and captafol (IARC, 1992) and is also a by-product of combustion and is ubiquitous in the environment at lower concentrations. Workplace concentrations in Canada, the USA, and Western Europe, are generally below $2mg/m^3$, but can be higher in countries that use older technologies. A UK control limit of 10ppm (8-hr TWA) was established in 1988, which became a MEL (Maximum Exposure Limit) with the introduction of COSHH (Control of Substances Hazardous to Health regulations) and subsequently a workplace exposure limit (WEL). Epidemiological studies of BD have focused mainly on its production and its use in the styrene-BD rubber industry (SBRI).

In the first study at a BD production plant built during World War II in Texas to supply BD to two adjacent rubber manufacturing facilities workers were enrolled into a cohort. Workers employed for at least six months after 1943 were included in the study. The cohort has been the subject of a number of reports (Divine, 1990, Divine *et al*, 1993, Divine and Hartman, 1996, Divine and Hartman, 2001, Downs *et al*, 1987). The earlier reports found a statistically significant deficit for all causes of death, and deficits for many leading causes of death including all cancers, hearts disease, lung cancer and gastrointestinal cancer. A statistically significant excess of death from all lymphohaematopoietic cancer (LHC) was due to non-significant increases in several specific LHCs. Only a slight elevation for leukaemia mortality was observed with SMRs of 1.12 (95%CI=0.56-2.00) and 1.13 (95%CI=0.60-1.93), which was concentrated in a group of workers employed less than five years (Divine *et al*, 1993, Divine and Hartman, 1996). In the most recent analysis, 2,800 male workers employed at least six months between 1943 and 1996 were followed up to 1999. Overall, a total of 1,422 deaths were observed, resulting in a significantly reduced all cause mortality (SMR=0.89, 95%CI=0.84-0.94). For all cancers the SMR was 0.90 (95%CI=0.81-1.86). The SMR for all LHCs was significantly raised (SMR=1.41, 95%CI=1.05-1.86), although the risk was raised in those employed less than five years (SMR=1.36, 95%CI=0.62-2.59) and more than 20-years (SMR=1.51, 95%CI=0.61-3.12). All the leukaemia deaths (n=18) occurred in men first employed before 1950 (SMR=1.52, 95%CI=0.90-2.40). The majority of the deaths (n=13) occurred in those workers with the potential for BD exposure on a routine basis (SMR=1.65, 95%CI=0.88-2.81), the risk being slightly greater in those employed less than five years (SMR=1.89) than those over five years (SMR=1.36).

The second study consisted of employees of eight SBRI plants in the United States and Canada (Delzell *et al*, 1995, Delzell *et al*, 1996, Delzell *et al*, 2001, Delzell, 2006, Graff *et al*, 2005, Macaluso *et al*, 1996, Sathiakumar *et al*, 1998). Workers employed for at least one-year after 1943 were enrolled into the cohort. In early studies in which subjects were followed to the end of 1991 (Delzell *et al*, 1996, Macaluso *et al*, 1996, Sathiakumar *et al*, 1998) subjects had lower than expected mortality from all causes combined and from most major causes of death. Leukaemia mortality was statistically significantly increased in hourly workers with 10+ years of employment in the industry and with 20+ years since hire. Leukaemia excesses were also observed among workers in plant areas with potentially high BD exposure. Irons and Pyatt (1998) hypothesised that another risk factor must be correlated with BD exposure and suggested dimethyldithiocarbamate (DMDTC) as a possible risk factor. In the most recent analysis 13,130 workers employed between 1943 and 1991 at six of the plants (two did not contain work area/job information) were followed-up (Delzell *et al,* 2001). A total of 3,892 deaths were observed, with 59 (49 confirmed) from leukaemia. Poisson regression analysis

was carried out to obtain the maximum likelihood relative rate for the worker group in a particular agent/exposure category compared to the worker group unexposed or having low exposure to that agent. Table 13 indicates that the RR was statistically significant only for the highest exposure category when looking at BD exposure only. Multiple-agent analysis indicated that after adjusting for styrene and DMDTC exposure as well as age and years since hire, BD exposure was associated only weakly with leukaemia. Analysis also showed that DMDTC was an independent risk factor for leukaemia, but that the association between DMDTC and leukaemia was not as strong as that for BD and leukaemia because the relative mortality rate for DMDTC did not increase linearly with cumulative exposure to DMDTC.

Table 13: Leukaemia relative rate (95%CI) for cumulative exposure to BD (source: Delzell *et al.*, 2001)

BD ppm-years	L/PY[a]	Single agent model[b]	Model 1[c]
0	7/48,139	1.0	1.0
<86.3	17/97,623	1.0 (0.5-3.0)	1.3 (0.4-4.3)
<362.2	18/60,114	2.0 (0.8-4.8)	1.3 (0.4-4.6)
362.2+	17/28,540	3.8 (1.6-9.1)	2.3 (0.6-8.3)

[a] number of leukaemias and person-years; [b] Adjusted for age, years since hire; [c] Adjusted for age, years since hire, styrene and DMDTC exposure

A recent meta-analysis of the styrene-butadiene rubber industry (SBRI) identified 36 published articles reporting information on 31 different cohort groups. A pooled meta-SMR of 1.31 (95%CI=1.03-1.43) was estimated for mortality and 1.16 (95%CI=0.67-2.03) for incidence (Alder *et al*, 2006). No significant increase was found for those workers exclusively manufacturing tyres or tyres and other goods, but was found for those exclusively making other goods (1.70, 95%CI=1.14-2.54).

2.2.6 Non-arsenical Insecticides

Investigations have shown some negative, but mainly positive associations between farming and leukaemia (Linet *et al*, 2006). Leukaemia types linked with farming include ALL (Donham *et al*, 1980), CLL (Blair and White, 1985, Blair *et al*, 1992, Brown *et al*, 1990, Swaen *et al*, 1992), AML (Pearce *et al*, 1986) and CML (Blair and White, 1981) and pesticide exposure has been suggested as the cause. Exposures to specific pesticides including mancozeb, toxaphane, carbon disulphide, phosphine and methyl bromide have been associated with excess mortality from leukaemia (Alavanja *et al*, 1990, Mills *et al*, 2005). In addition, evidence from a few studies of workers exposed to DDT provides limited support for an association with leukaemia, notably CLL (Brown *et al*, 1990, Flodin *et al*, 1988). Exposure to dichlorvos and other pesticides like nicotine and pyrethrins gave, after a 20-year latency, significant excesses of leukaemia (Brown *et al*, 1990).

Donham *et al*. (1980) noted excess ALL in males living in rural areas, especially where cattle and pigs were raised. Blair and White (1985) studied the risk of specific histologic types of leukaemia among farmers using mortality records from Nebraska for the years 1957-1974. Farmers were shown to be at a significantly increased risk of CLL (OR=1.67), and non-significantly increased risks from ALL (OR=1.34), AML (OR=1.94) and acute unspecified leukaemia (OR=2.36). Brown *et al.* (1990) noted significant elevation in the risk for leukaemia (OR=1.2) and CLL (OR=1.4) for farmers compared to non-farmers, with significant risk seen for exposure to a number of animal insecticides.

Pearce *et al*. (1986) carried out a registry-based case-control study of 546 cases. An excess risk was found for leukaemia for the occupation category involving agriculture and forestry (OR=1.24, 95%CI=0.95-1.61), with the greatest risk being for livestock farmers (OR=3.00, 95%CI=1.23-7.32). The risk was greatest for AML (OR=1.55, 95%CI=0.90-2.67) or acute

monocytic leukaemia (OR=10.38, 95%CI=1.99-54.29). Blair and White (1981) studied the risk leukaemia among US farmers between 1968 and 1976. A comparison of occupation as noted on the death certificate for 1,499 cases and a like number of matched controls revealed a slight (OR=1.10), but statistically non-significant, excess risk of leukaemia among farmers.

In a study of LHCs in farm workers between 1988 and 2001, Mills *et al.* (2005) observed 51 cases of leukaemia (men: 35; women: 16), with 23 lymphocytic and 20 granulocytic leukaemias. Multivariate analysis of leukaemia risk by chemical found a significant excess risk among those with high exposure to mancozeb (OR=2.35, 95%CI=1.12-4.95) and toxaphane (OR=2.20, 95%CI=1.04-4.65) compared to those with low exposure. Flodin and colleagues (1988) carried out a case-control study of CLL, with 111 cases and 431 controls. Crude rate ratios were raised for exposure to DDT (CRR=6.1, 95%CI=1.9-19.0) and farmers as an occupation (CRR=1.8, 95%CI=1.0-3.1). After adjustment for confounding exposures there was still a significant excess risk with exposure to DDT (RR=6.0, 95%CI=1.5-23.0).

Studies of pesticide applicators have generally shown no excess risk (Cantor and Silberman, 1999, Figa-Talamanca *et al*, 1993, Swaen *et al*, 2004, Zahm, 1997). Figa-Talamanca *et al.* (1993) examined the mortality of 2,310 Italian men licensed to handle pesticides between 1973 and 1979, and followed them to 1988. Only two leukaemia deaths were observed, and risk was reduced when compared to the provincial population (SMR=0.52, 95%CI=0.06-1.88) and the national population (SMR=0.60, 95%CI=0.07-2.15). Zahm (1997) studied mortality in a cohort of 32,600 employees of a lawn care company; however, mortality from leukaemia was not increased. Cantor and Silberman (1999) examined mortality of 9,861 male aerial pesticide applicators between 1965 and 1988. Fourteen deaths from leukaemia were observed, resulting in a rate of 8.3, whereas in flight instructors (n=4) the rate was 2.5, giving a rate ratio of 3.35 (95%CI=1.3-8.5). The SMR for leukaemia among aerial applicators was 1.18 (95%CI=0.64-1.98) compared to 0.34 (95%CI=0.09-0.86) for flight instructors. There was no trend between risk and number of flight hours of applicators.

Swaen *et al.* (2004) investigated mortality in a cohort of 1,341 Dutch licensed herbicide applicators followed-up to 2001. Only three leukaemia deaths were observed giving a SMR of 1.30 (95%CI=0.26-3.74).

In a meta-analysis of 27 studies of the risk of leukaemia among farmers, Acquavella *et al.* (1998) obtained a RR of 1.10 (95%CI=1.02-1.18), although the risk estimate varied between study type (follow-up: 1.00; PMR studies: 1.17; case-control: 1.11). The overall risk was the same as that obtained by Blair *et al.* (1992) of 1.1 (95%CI=1.0-1.12).

In an analysis of mortality of 52,393 private and 4,916 commercial pesticide applicators as part of the US Agricultural Health Study, follow-up was for 1994-2000 (Blair *et al*, 2005). All cause and all cancer mortality was significantly reduced at 0.5 (95%CI=0.4-0.6) and 0.6 (95%CI=0.5-0.6), respectively. There were 27 leukaemia deaths observed giving a SMR of 0.8 (95%CI=0.5-1.1) and there was no excess mortality in relation to type of farm and exposure. Cancer incidence within the cohort was studied up to 2002 (Alavanja *et al*, 2005). Overall incidence was significantly decreased among private applicators and non-significantly decreased among commercial applicators. For leukaemia there were 70 observed cases (SIR=0.91, 95%CI=0.71-1.15) among private applicators and four among commercial applicators (SIR=0.92, 95%CI=0.25-2.36).

Findings from studies of occupationally exposed pesticide production/manufacturing workers, including studies among phenoxy or chlorophenol production and manufacturing workers (Burns *et al*, 2001, Coggon *et al*, 1991, Hooiveld *et al*, 1998, Mannetje *et al*, 2005), triazine manufacturing workers (MacLennan *et al*, 2002, Sathiakumar *et al*, 1996), and alachlor manufacturing workers (Acquavella *et al*, 2004) have generally also been mixed.

Coggon *et al.* (1991) investigated mortality among 2,239 male workers at four phenoxy-herbicide manufacturing factories in GB between 1963 and 1985 and followed them to 1987. However, they reported no cases of leukaemia. Hooiveld *et al.* (1998) followed up a Dutch cohort of workers exposed to phenoxy herbicides, chlorophenols and contaminants (dioxins). The cohort consisted of 562 exposed workers and 567 non-exposed, followed between 1955 and 1991. However, only one death was observed (SMR=1.01, 95%CI=0.0-5.7). Burns *et al.* (2001) investigated mortality among chemical workers exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) between 1945-94. The cohort consisted of 1,517 exposed male workers and 50 female. Among men there were four leukaemia deaths observed (SMR=1.30, 95%CI=0.35-3.32), all of them 20 years since recruitment (SMR=1.39, 95%CI=0.38-3.56). In a study of phenoxy herbicide producers (n=1,025) and sprayers (n=703) in New Zealand, followed up from 1969 and 1973 respectively to 31 December 2000, Mannetje *et al.* (2005) observed only one death from leukaemia (myeloid) among sprayers (SMR=1.16, 95%CI=0.03-6.44).

Sathiakumar *et al.* (1996) examined mortality among 5,417 workers at two triazine herbicide manufacturing plants (2,683 definite/probable exposures; 2,234 possible exposures). The cohort was followed to 1987. Only two leukaemia deaths were observed (one from CML and one from AML), compared to 1.8 expected (SMR=1.33, 95%CI=0.16-4.82). MacLennan *et al.* (2002) investigated mortality among 2,213 workers employed for at least six months in operations related to the manufacture or formulation of atrazine and other triazine herbicides in USA between 1970 and 1997. However, there was only one death from leukaemia with 0.7 expected. (SMR=1.43, 95%CI=0.04-7.96).

Acquavella *et al.* (2004) examined mortality and cancer incidence among alachlor manufacturing workers between 1968 and 1999. Among a total workforce of 1,391 (men: 1,091; women: 300), 1,206 (men: 966; women: 240) had some exposure to alachlor. In total there were 48 deaths. There were only two deaths from leukaemia among those with any exposure (SMR=2.23, 95%CI=0.27-8.04), both cases occurring in individuals with high exposure (SMR=2.75, 95%CI=0.33-9.94). There was also only two incident cases among individuals with any exposure (SIR=1.76, 95%CI=0.21-6.36), again both had high exposure (SIR=2.06, 95%CI=0.25-7.44) and both cases were CML.

In a recent study Jones *et al.* (2009) carried out a systematic review and meta-analysis of crop protection production manufacturing workers that assessed leukaemia risk. The study included a number of studies from Europe, USA and China and obtained a summary risk estimate of 1.08 (95%CI=0.81-1.44). In a sub-group of 20 cohorts of workers involved in the manufacture of phenoxy-herbicides the summary risk estimate was 1.02 (95%CI=0.71-1.46).

In the flour and grain industry there is a problem with controlling insects, which can cause serious losses. All areas of the industry are therefore treated with insecticides to minimise these losses (including grain elevators, mills and processing plants). A cohort study of 22,938 members of the American Federation of Grain Millers followed from 1955 to 1985 observed 25 deaths amongst workers in flourmills (SMR=1.36, 95%CI=0.88-2.01) and 11 among workers in other and unidentified grain industries (SMR=0.71, 95%CI=0.36-1.28) (Alavanja *et al*, 1990). No significant trend was observed between duration of follow-up and leukaemia risk, unadjusted and adjusted for age. A significant increased risk was observed in workers in the maintenance department (OR=8.1, 95%CI=1.4-47.7). Workers in the grain industry as a whole showed no increased risk of leukaemia (Observed=36, Expected=33.8; SMR=1.07, 95%CI=0.75-1.47).

2.3 OCCUPATIONS

2.3.1 Boot and shoe manufacture and repair

In 1980, and again in 1987, IARC concluded that the boot and shoe manufacturing and repair industry entails exposures that are carcinogenic to humans (IARC, 1981, IARC, 1987). However, a number of PMR and cohort studies have shown no excess mortality from leukaemia (Decoufle and Walrath, 1983, Garabrant and Wegman, 1984, Walker *et al*, 1993, Walrath *et al*, 1987). Relative risks well in excess of ten-fold have been reported from studies in England and Italy (Acheson *et al*, 1982, Merler *et al*, 1986). People who worked in the dustiest operations were found to be at the greatest risk suggesting a role for exposure to leather dust. Another study of Italian workers, where benzene-containing glues had been used from 1953-60 observed an excess of leukaemia (Paci *et al*, 1989). A further study of over 5,000 men in three UK towns showed a significant risk to those in the 'lasting and making' department (Pippard and Acheson, 1985). Workers in this department handled glues, and had potential exposure to solvents including benzene.

2.3.2 Oil refinery/Petrochemical workers

Workers in the oil refinery and petroleum industry are potentially exposed to a variety of petrochemicals, including benzene or benzene-containing liquids, and other aromatic hydrocarbons and organic solvents. An increased risk in mortality from AML has been observed in some studies of these workers (Divine *et al*, 1999b, Sathiakumar *et al*, 1995).

Divine *et al.* (1999a, 1999b) presented results on a cohort of employees of Texaco employed for five years or more employed as refiners, researchers and petrochemical workers from 1943-1993. 28,840 people were included in the cohort, with a total of 9,575 deaths, 2,144 from cancer. There were 97 leukaemia deaths (93 among white men and four among women). For the white men the SMR was 1.01 (95%CI=0.81-1.23). There was no pattern with duration of employment; however, the risk among men first employed before 1950 (SMR=1.13) was more than double that of those first employed after 1950 (SMR=0.50). The risk was greatest for men employed in the fluid catalytic cracking unit (SMR=1.42, 95%CI=0.61-2.80), as a pipefitter or boilermaker (SMR=1.60, 95%CI=0.88-2.69), or in motor oil units (SMR=1.21, 95%CI=0.33-3.10). In an analysis of leukaemia by cell type the risks for AML (SMR=1.29, 95%CI=0.78-1.99), CML (SMR=1.05, 95%CI=0.54-1.83), acute unspecified leukaemia (SMR=2.76, 95%CI=1.54-4.55) and cell type unspecified leukaemia (SMR=2.31, 95%CI=1.29-3.81) were raised. For all of these cell types, except acute unspecified leukaemia (AUL), the risk in those employed before 1950 was well above 1.00, whereas in those employed in 1950 and after, the risk was below 1.00. For AUL the risk in both groups was about that for all people.

In a case-control study among active and retired employees of a large petroleum company, 69 leukaemia cases were matched with 284 controls (Sathiakumar *et al*, 1995). Workers employed in production-related work in the oil and gas division were particularly at risk of myelogenous leukaemia (OR=2.0, 95%CI=0.97-4.2) and AML in particular (OR=2.8, 95%CI=1.1-7.3). The risk of AML was greatest in the highest category of duration of employment (32+ years) (OR=8.7, 95%CI=2.0-37.0), and with a significant exposure-response relationship (p=0.01). Individuals who worked in refining exhibited no risk for leukaemia.

In the UK a large study of the oil industry has been carried out (Rushton, 1993a, Rushton, 1993b, Sorahan *et al*, 2002). In the oil distribution part of the study, 23,306 workers employed for at least one year were initially followed to 1989 (Rushton, 1993a). A total of 8,743 workers were known to have died, giving a SMR of 0.91 (95%CI=0.89-0.93). There were 61 deaths from leukaemia observed (SMR=1.08, 95%CI=0.83-1.40), although the risk increased

with time since first employment and there was no clear pattern by year of entry. No one type of leukaemia showed appreciably increased mortality. Mortality was raised among drivers (SMR=1.25, 95%CI=0.83-1.81). Nearly 75% of all leukaemia deaths occurred at one company. In the oil refinery part of the study, 34,569 workers were followed with 10,193 known to have died (Rushton, 1993b). There were 68 leukaemia deaths giving a SMR of 0.97 (95%CI=0.76-1.24). Only two cell types showed raised mortality overall, other myeloid (SMR=6.78, 95%CI=2.73-13.97) and monocytic (SMR=2.21, 95%CI=0.89-4.35).

Further work of the UK cohort, extended the follow-up period of 28,630 oil refinery workers and 16,480 petroleum distribution workers to 1998 (Sorahan *et al*, 2002). In this time 9,341 deaths occurred among refinery workers (SMR=0.88, 95%CI=0.86-0.90) and 6,083 among distribution workers (SMR=0.94, 95%CI=0.92-0.97). In the two groups there were 2,862 and 1,913 cancer deaths, respectively. Table 14 below gives the risk of leukaemia in the cohort, indicating a small excess of myeloid leukaemia in both groups and a large excess (non-significant) of monocytic leukaemia in refinery workers.

Table 14. Leukaemia mortality among UK oil refinery and petroleum distribution workers (source: Sorahan *et al.*, 2002)

	Refinery Workers		Distribution Workers	
	Number	**SMR (95%CI)**	**Number**	**SMR (95%CI)**
Leukaemia	80	1.08 (0.86-1.35)	57	1.30 (0.98-1.68)
Lymphoid	21	0.98 (0.61-1.05)	20	1.56 (0.95-2.40)
Myeloid	44	1.08 (0.79-1.45)	29	1.19 (0.80-1.71)
Monocytic	5	2.16 (0.70-5.05)	1	0.75 (0.02-4.19)
Other	10	1.06 (0.51-1.96)	7	1.32 (0.53-2.72)

There was no trend between leukaemia risk and time since commencing employment or year of hire in either group. The greatest leukaemia risk was observed among pipefitters (SMR=2.28, 95%CI=0.92-4.70), fire and safety workers (SMR=1.96, 95%CI=0.64-4.58), operators (SMR=1.36, 95%CI=0.90-1.96) and riggers (SMR=1.57, 95%CI=0.32-4.59) in refineries; and operators (SMR=1.59, 95%CI=0.93-2.54), general manual workers (SMR=1.43, 95%CI=0.46-3.33), supervisors (SMR=1.76, 95%CI=0.48-4.51) and administration/clerical workers (SMR=1.56, 95%CI=0.57-3.40) in the distribution sector.

In a critical review of cancer epidemiology in the refining industry Wong and Raabe (2000) investigated mortality in 350,201 workers (266,616 refinery workers, 56,576 distribution workers, 27,009 crude oil workers) from seven countries. A meta-analysis of the findings from individual studies resulted in a SMR of 0.86 (95%CI=0.85-0.88) for all cancers, but did not present any results for leukaemia. In a previous analysis, Wong and Raabe (1995) studied 208,741 UK and US workers with 56,411 deaths. There were 327 leukaemia deaths (148 AML, 62 CML, 34 ALL, and 83 CLL). Meta-analysis of AML risk in the whole cohort gave a SMR of 0.96 (95%CI=0.81-1.13) with no difference between US (0.90) and UK (0.95) cohorts. Similar findings were seen for CML. However, for ALL the combined SMR was 1.16 (95%CI=081-1.61) (US=1.23; UK=0.99). The combined risk for CLL was 0.84 (US=0.79; UK=0.94). Similar patterns were observed for refinery workers. AML showed a significant exposure-response relationship with cumulative exposure (Table 15).

Table 15. AML risk by cumulative benzene exposure among US and UK petroleum workers (source: Wong & Raabe, 1995)

Cumulative exposure (ppm-years	SMR		95%CI	
<40	1.19	} 0.91	0.03-6.63	} 0.02-5.11
40-200	0		0-14.75	
200-400	27.21		3.29-98.24	
400+	98.37		20.28-287.65	

2.3.3 Rubber industry work areas

Workers employed in the industry before 1950 have a high risk of bladder cancer, probably associated with exposure to aromatic amines. Leukaemias have been associated with exposure to solvents (including and excluding benzene) and with employment in areas such as back processing, tyre curing, synthetic rubber production tyre cutting, then synthetic rubber production and vulcanisation (Alder *et al*, 2006).

A study of 15,649 US synthetic rubber workers, employed for at least one year between 1943 and 1991, observed 48 deaths from leukaemia, whereas 36.6 were expected (SMR=1.31, 95%CI=1.74) (Sathiakumar *et al*, 1998). The majority of these cases (n=45) occurred amongst workers who had an hourly job (SMR=1.43, 95%CI=1.04-1.91). In this group those with more than 10-years employment and 20+ years since hire, the risk of leukaemia was more than doubled (SMR=2.24, 95%CI=1.49-3.23). In an update of these workers, the cohort was increased to 17,924 and follow-up extended to 1998 (Sathiakumar *et al*, 2005). This time there were 71 leukaemia deaths giving a SMR of 1.16 (95%CI=0.91-1.47), again those ever hourly employed being at a greater risk (SMR=1.23, 95%CI=0.94-1.57). The risk was concentrated in hourly paid subjects with 20-29 years since hire and 10 or more years of employment in the industry (SMR=2.58, 95%CI=1.56-4.03). Those employed in polymerisation (SMR=2.04, 95%CI=1.21-3.22), coagulation (SMR=2.31, 95%CI=1.11-4.25), maintenance labour (SMR=3.26, 95%CI=1.78-4.56) and laboratory operations (SMR=3.26, 95%CI=1.78-5.46) had the greatest risk.

However, a review of the literature found moderate increases in leukaemia risk in a number of studies and no excesses in others (Kogevinas *et al*, 1998). Of those studies reviewed that could examine exposure to specific agents benzene was most associated with the increased risk. A recent meta-analysis among workers in the synthetic rubber-producing industry examined cancer mortality/incidence from 36 published studies of 31 different cohort groups (Alder *et al*, 2006). The pooled SMR for leukaemia (based on 16 studies) was 1.21 (95%CI=1.03-1.43), whereas for incidence (four studies) the pooled SIR was 1.16 (95%CI=0.67-2.03). In cohorts of tyre workers the risk was 1.03, compared to 1.12 among those manufacturing tyres and other goods, and 1.70 exclusively manufacturing other goods.

2.4 OTHER SUSPECTED EXPOSURES AND OCCUPATIONS

2.4.1 Electricity Workers and Electromagnetic fields

Leukaemia has been linked to exposure to low frequency non-ionising electromagnetic fields, especially in electrical occupations (Linet *et al*, 2006). In the decennial supplement, leukaemia mortality was non-significantly elevated in a number of electrical occupations, including: electrical and electronic engineers and production fitters; telephone fitters; electrical engineers; and other electronic maintenance engineers (Drever, 1995). However, the PRR was only elevated for other electronic maintenance engineers. In the most recent analysis

a significantly excess risk was observed for electrical engineers and other electronic maintenance engineers (Coggon *et al.*, 2009).

In an early review of the health effects of living near or working with electricity generation and transmission equipment 11 studies showed variable results with an overall excess risk of 1.18 (95%CI=1.09-1.29) (Coleman and Beral, 1988). Among men occupationally exposed risk decreased from 1949-54 (1.22) to 1970-72 (0.82), and then increased again in 1979-80 and 1982-83 (1.42). A similar pattern was seen among married women occupationally exposed. The increased risk was primarily related to a 46% excess in AML (SMR=1.46, 95%CI=1.27-1.65). However, another meta-analysis that included an adjustment for heterogeneity reported a lower 95% confidence interval closer to unity (Shore, 1988). The authors suggest that the evidence for an association is marginal.

A further meta-analysis of 39 papers pertaining to occupational exposure to EMFs, including low frequency and extremely low frequency fields, and leukaemia observed a pooled RR of 1.18 (95%CI=1.12-1.124) for the fixed-effect model and the same for the random-effect model (95%CI=1.11-1.26) (Kheifets *et al*, 1997). The pooled results were significantly increased) for both AML (SMR=1.40, 95%CI=1.16-1.69) and CLL (SMR=1.55, 95%CI=1.10-2.19), but non-significantly increased for ALL and CML.

However, a study of UK electricity generation and transmission workers found no excess risk (Harrington *et al*, 2001, Nichols and Sorahan, 2005). The most recent study examined the mortality experience of a cohort of 83,923 former employees who had worked for at least six months between 1973 and 1982, followed up to 2002. Overall mortality was significantly reduced in both men (n=18,773) and women (n=1,122). All cancer mortality was significantly reduced in men (SMR=0.93, 95%CI=0.91-0.95) but not for women (SMR=0.97, 95%CI=0.89-1.06). There were 141 leukaemia deaths (men: 128; women: 13). For men the SMR was significantly reduced at 0.77 (95%CI=0.64-0.92) and slightly increased in women at 1.07 (95%CI=0.57-1.83). In men the risk among power station workers was significantly reduced (SMR=0.74, 95%CI=0.59-0.92) but not among substation and transmission workers (SMR=0.94, 95%CI=0.38-1.94). In women power station workers the SMR was 0.43 (95%CI=0.05-1.56).

Nevertheless, the problem with assessing any link between leukaemia and EMF is the wide variability in field exposures among different types of electrical workers and over time (Bowman *et al*, 1988, Gamberale *et al*, 1989). The apparent lack of a clear pattern of exposure to EMF and risk of leukaemia substantially detracts from the hypothesis that measured magnetic fields in the work environment are responsible for the observed excess of leukaemia.

2.4.2 Chemists

Studies of chemists have found excesses of leukaemia in a number of countries (Hoar and Pell, 1981, Li *et al*, 1969, Maher and Defonso, 1986, Milham, 1976, Walrath *et al*, 1985). A study of 14,884 members of the Royal Society of Chemists observed a significant excess leukaemia, especially AML (Hunter *et al*, 1993). However, chemists are known to handle large numbers of chemicals, in small quantities, therefore identifying any specific one as the major risk factor would prove difficult.

2.4.3 Painters

IARC have evaluated occupational exposure as a painter to be carcinogenic (Group 1) (IARC, 1989). Painters are exposed to numerous chemicals that IARC have also classified as Group 1 and 2A carcinogens, and also Group 2B. These include solvents, the main ones being petroleum solvents, toluene, xylene, ketones, alcohols, esters and glycol ethers. Chlorinated

hydrocarbons are used in paint strippers and less frequently in paint formulations. Benzene was used as a paint solvent in the past but is currently found in only small quantities in some petroleum solvent-based paints. Titanium dioxide, chromium and iron compounds are used widely as paint pigments. The IARC evaluation was based on the findings of large cohorts of painters from Denmark (Englund, 1980), the United States (Matanoski *et al*, 1986) and Sweden (Olsen and Jensen, 1987). However, findings since the evaluation have been inconsistent.

Matanoski and colleagues (1986) examined the mortality experience of 57,175 current and former trade union members in four US states across the country between 1975 and 1979. No excess mortality was observed overall based on 5,313 deaths, and there were 44 deaths from leukaemia, although 47.2 were expected (SMR=0.93, 95%CI=0.68-1.25). When the analysis was confined to painters there was still no excess mortality (3,811 deaths) although mortality was mainly due to an excess of lung cancer. There were 37 leukaemia deaths whereas 31.8 were expected (SMR=1.16, 95%CI=0.82-1.60).

However, a large study of 42,170 painters and 14,316 non-painters, an update of the Matanoski cohort, were followed up to 1994, resulting in 18,259 deaths among painters and 4,247 among non-painters (Steenland and Palu, 1999). Among painters there were 138 leukaemia deaths, giving a SMR of 0.92 (95%CI=0.78-1.11). However, SMR results for leukaemia 20-years since first union membership was higher at 1.11 (95%CI= 0.74-1.80).

Blair *et al.* (2000) conducted a large population-based case-control in two US states. All cases of leukaemia (men >30 years) diagnosed between 1980 and 1983 (n=513) were matched with controls (n=1,087). Men involved in painting, plastering and waterproofing were at a significant risk of ALL (SMR=8.4, 95%CI=1.4-51.3; two cases) and non-significant risk of AML (SMR=1.9, 95%CI=0.6-5.9; 22 cases). Risk of leukaemia by intensity of exposure indicated that individuals with high paint exposure had a more than double the risk of ALL than those with low exposure (OR=2.3 *cf* 1.0). However, for other histologic subtypes those with low exposure tended to have the greater risk.

In a similar study in Italy, Costantini *et al.* (2001) collected information on all incident cases 20-74 years of age from 12 areas, between 1991 and 1993. There were a total of 653 leukaemia cases (men: 383; women: 269) that were matched with controls. Twenty cases were classified as painters giving an OR of 1.2 (95%CI=0.6-2.4).

Brown *et al.* (2002) examined leukaemia risk associated with employment in painting trades and paint manufacturing in Sweden for 1971 to 1989. A total of 115 cases were identified resulting in a SMR of 0.9 (95%CI=0.8-1.1). Non-significant risks were associated between non-lymphocytic leukaemia and lacquers,

In a meta-analysis of 17 studies the combined meta-SMR was 1.87 (95%CI=1.15-3.07) (Chen and Seaton, 1998). Restricting the analysis to occupational cohort studies resulted in a higher SMR of 2.21 (95%CI=0.95-5.13), although there was significant heterogeneity. However, when data were excluded where known benzene exposure was high the SMR of leukaemia was reduced to 1.18 (95%CI=0.99-1.35), indicating the high risk may have been mainly from benzene exposure, usually mixed with painting solvents in the past.

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

Table 16 shows the substances and exposure circumstances considered in the estimation of the attributable fraction (AF) for leukaemia.

Table 16. Substances considered in the estimation of the attributable fraction for leukaemia.

Agents, Mixture, Circumstance	AF calculation	Strength of Evidence	Comments
Group 1: Carcinogenic to Humans			
Agents, groups of agents			
Benzene	Y	Strong	
1,3-Butadiene	Y	Suggestive	
Ionising radiation	Y	Strong	
Ethylene oxide	Y	Strong	
Formaldehyde	Y	Suggestive	
Exposure circumstances			
Boot and shoe manufacture and repair	N	Strong	Considered within overall estimation for benzene
Petroleum refining	N	Suggestive	Considered within overall estimation for benzene
Rubber industry	N	Suggestive	Considered within overall estimation for benzene
Group 2A: Probably Carcinogenic to Humans			
Agents & groups of agents			
Non-arsenical insecticides	Y	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. In the absence of more precise knowledge of cancer latency, for haematopoietic malignancies a latency of between 0 and 20 years has been assumed for all types of the cancer. Therefore it is assumed that exposure at any time between 1986 and 2005 (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 1985-2004, for simplification the years 1986 to 2005 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 counted using a

point estimate of exposed workers taken from the period. A point estimate is used that is as close as possible 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). 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. Where the LFS is used, the 1991 survey is used. 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 = 20. The 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 = 23.0 million men, 23.1 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 leukaemia, Great Britain, 2005 = 2001 for men aged 15-84 (1836 in England and Wales, 165 in Scotland), 1101 for women aged 15-79 (999 in England and Wales, 102 in Scotland).

- Total registrations for leukaemia, Great Britain, 2004 = 3333 for men aged 15-84 (2782 in England, 243 Wales, 308 in Scotland), 1869 for women aged 15-79 (1494 in England, 150 Wales, 225 in Scotland).

The association of the substances considered in the AF estimation with the subtypes of leukaemia often tend to point to acute leukaemias having a stronger relationship than other sub-types. However, analyses are not always carried out separately for the sub-types and many studies only consider total leukaemia because of limited numbers. Taking into account the uncertainties in the nature of the relationship between these substances and different leukaemia sub-types it was decided to use a precautionary approach and to assume a causal relationship for all types, i.e. leukaemia in aggregate. Deaths coded to ICD-10 C91 to C95 are included, except for (i) benzene for which only acute myeloid and monocytic leukaemias C92.0, C92.4, C92.5 and C93.0 are included; including for deaths Great Britain, 2005 = 1,017 for men aged 15-84 (928 in England and Wales, an estimated 89 in Scotland), 664 for women aged 15-79 (609 in England and Wales, an estimated 55 in Scotland) and for registrations Great Britain, 2004 = an estimated 1,807 for men aged 15-84, 1,013 for women aged 15-79; and (ii) ionising radiation for which chronic lymphatic leukaemia C91.1 is excluded; including for deaths Great Britain, 2005 = 1496 for men aged 15-84 (1367 in England and Wales, an estimated 129 in Scotland), 935 for women aged 15-79 (855 in England and Wales, an estimated 80 in Scotland).and for registrations including Great Britain, 2004 = 2612 for men aged 15-84, 1465 for women aged 15-79. Figures for acute myeloid and monocytic leukaemias, and for CLL, were estimated for Scotland (deaths) and for GB as a whole (registrations) as 50% and 25% of total leukaemias respectively, based on deaths for these sub-types for men and women in England and Wales in 2005. Ages 15 and upwards only are included (separate numbers of deaths are not available for 16 and upwards in the national mortality statistics) as childhood leukaemias are excluded as not work-related.

Attributable numbers are estimated by multiplying the AF by the total number of cancers in GB. Only cancers, which could have been initiated during the risk exposure period are counted, taking normal retirement age into account. Therefore for solid tumour cancers, total deaths or registrations recorded at all adult ages (25+) are used to estimate attributable numbers, and for short latency cancers, deaths and registrations for ages 15-84 for men and 15-79 for women are used.

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

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

3.2 BENZENE

3.2.1 Risk Estimate

Exposures levels: A review of exposure to benzene in different industries and occupations in the US and Europe is given by Capleton & Levy (2005). Between 1948 and 1977 a Threshold Limit Value (TLV) of 25ppm in the workplace was set for the US, reducing to 10ppm in 1977 and down to 0.5pmm in 1997. In the UK the Maximum Exposure Limit (MEL) was 5ppm in 1988, reduced to 3ppm in 2000 and 1ppm in 2003. Benzene levels have thus been greatly reduced over time. Capleton and Levy (2005) give estimates of both long term and short term exposure levels in the mid 1980s and 1990s for those occupations where exposure has been measured, including the petrochemical industry (values for many tasks and jobs within this), service station attendants, the coke oven industry, motor mechanics, aviation workers and urban workers. A typical arithmetic mean (AM) value for long-term exposure is around 0.3mg/m^3, approximately 0.1ppm (1ppm = 3.25mg/m^3), although values vary between much lower for urban workers such as traffic police and bus drivers (0.20mg/m^3), to much higher for workers in coke plants (1.79mg/m^3). An average cumulative exposure, assuming 30 or 40 years at 0.1ppm level would be between 3 and 4ppm-years. Intermittent and short term exposures can be much higher than the average long term exposures in several industries, with several jobs having AMs over 2mg/m^3 and some having maximum short-term exposure levels over 10mg/m^3 (3ppm). These types of workers might thus have had cumulative exposures between 5-10ppm-years. Historically it is thought that some workers in the 1960s and 1970s might have been accumulating exposures much higher than this, up to 100ppm-years. The industries and occupations highlighted in Capleton and Levy's review have been used alongside those under CAREX in the estimation of the population proportion exposed – see below.

Choosing risk estimate values: Schnatter *et al*. (2005) review the literature on the relationship between benzene exposure and leukaemia subtypes. The evidence for high and significant risks of AML with positive dose-response relationships is strong across different study designs. The evidence for a relationship with CLL is more equivocal, with elevations and possible dose-response relationships in nested case-control studies but not in cohort studies. Schnatter *et al*. (2005) point out that data for CML and ALL are sparse and inconclusive. Savitz and Andrews (1997) are also of the opinion that, although the risk for AML is established, the few studies of specific histologic types of leukaemia do not indicate larger or more consistent elevations in risk of AML compared to other leukaemia cell types. Risk estimates for total leukaemia for the total populations studied vary widely from below one to about seven (Savitz and Andrews, 1997), as do the dates when these studies were carried out, the industries studied, the proportion of the populations exposed and the levels to which they were exposed. However, in the oil and chemical industries risk estimates are around two or above.

Several studies have carried out quantitative estimation of benzene exposure and the risks associated at different levels of cumulative exposure. The results from these are summarised in Table 17. For workers in the industries considered by Capleton and Levy (2005) lifetime cumulative exposures could potentially be from 3 and 4ppm years up to 10ppm years or above, depending on the job and the frequency and duration of exposure. The risk estimates in Table 8 in this range of cumulative exposures range from about 1.5 to 2.5. The upper value is approximately the same as the overall risk estimate from the study by Rinsky *et al.* (2002) (RR=2.47, 95%CI=1.38-4.07). This estimate is also similar to that in Hayes *et al.* (2001), of 2.5 (95%CI=1.8-3.4) for all leukaemias.

Crump (1994, 1996) gives a risk estimate for the acute non-lymphocytic leukaemias (ANLL, defined as acute myelogenous or acute monocytic leukaemia) for the same US pliofilm cohort

as reported on by Rinsky *et al.* (2002) (RR=5.0, 95%CI=2.5-10.0, based on eight leukaemias of known type). It should be noted that this estimate was for males and females and for all races. The RR estimate from the Chinese cohort of Hayes *et al.* (1997) for ANLL was 3.0 (95%CI=2.0-4.6), based on a broader range of exposure levels. However it is not possible from the CAREX data to identify any GB workers who would have equivalent exposures to the US Pliofilm industry. The majority of the high exposed (82%) are in land transport. A cohort mortality study in a large Canadian petroleum company (Lewis *et al*, 2000) gave an RR estimate of 1.32 (95%CI=0.49-2.88) for ANLL for workers in marketing and distribution, an appropriate RR to apply to this group (H2 in Table 19). For workers in industrial chemical manufacturing, the mortality study of Collins *et al.* (2003) of men and women in a US chemical plant gives a RR estimate of 2.17 (95%CI=0.9-5.2) for ANLL for workers with recorded exposure to benzene, which is therefore used as the risk estimate for this industry group (H1 in Table 19).

The excess risk for cumulative exposures below 1 or 2ppm-years is uncertain but probably greater than zero. The levels of exposure in those industries designated as 'low' in Table 18 are likely to be below 1ppm. Average benzene exposures have been estimated to be below 1ppm for refinery workers, although higher for distribution workers (Runion, 1988, Schnatter *et al*, 2005). A meta-analysis of petroleum workers (Wong and Raabe, 1989) found a meta-SMR of 1.10 (95%CI=0.95-1.35) for all leukaemia, although meta-analysis of a subset of these studies in the US and UK found an SMR of 0.96 (95%CI=0.81-1.13) for AML only (Wong and Raabe, 1995). As this appears to be inconsistent with the observations of higher risks for ANLL than for leukaemia as a whole at the lower dose levels in Table 17, Bloemen *et al.* (2004) overall RR of 1.11 (95%CI=0.3-2.83) for the ANLLs has been chosen instead for those industry groups where benzene exposure is known to occur at low levels, i.e. the 'low' category (L in Table 19)**.**

It should be noted that in the Global Burden study the risk estimates for leukaemia were 2 for low and 4 for high exposures with countries such as the UK assumed to have 90% at the low level and 10% at the high level (Driscoll *et al*, 2005).

Table 17. Leukaemia relative risks (95% confidence intervals) by cumulative exposure

Cumulative Exposure (ppm-years)	Study (Industry)				
	Collins *et al.* (2003); (US chemical plant)	**Rinsky *et al.* (2002) & Crump (1996) (US Rubber Industry)**	**Bloemen *et al.* (2004) (US Chemical plant)**	**Glass *et al.* (2003) (Australian Petroleum Industry)**	**Rushton & Romaniuk (1997) (Petroleum distribution)**
Overall (All leukaemia) Overall (ANNL)		2.47 (1.38,4.07) 5.0 (2.5,10.0)	1.14 (0.59,1.99) 1.11 (0.3,2.83)	2.00 (1.3,2.9)	
0 (All leukaemia) 0 (ANNL)	1.00 (0.5,1.8) 0.8 (0.1,2.8)				
< 0.45 (All leukaemia) <0.45 (ANNL)					1.00 1.00
<1 (All leukaemia) <1 (ANNL)	0.7 (0.1,2.5) 1.4 (0.1,5.1)			1.00	
>1 – 2 (All leukaemia)				3.9 (0.9,17.1)	
>2 – 4 (All leukaemia)				6.1 (1.4,26.0)	
0.45 – 4.5 (All leukaemia) 0.45 - 4.5 (ANNL)					1.42 (0.77,2.61) 2.17 (0.77,6.09)
1-6 (All leukaemia) 1-6 (ANNL)	1.4 (0.4,3.6) 2.7 (0.3,9.9)				
<=4 (ANNL)				1.0	
>4 – 8 (All leukaemia) >4 – 8 (ANNL)				2.4 (0.4,13.6) 0.52 (0.05,5.0)	
>6 (All leukaemia) >6 (ANNL)	1.7 (0.6,3.8) 2.2 (0.3,8.1)				
1 – 39 (All leukaemia)		1.45 (0.53,3.31)			
0 – 45 (All leukaemia)		0			
4.5 – 45 (All leukaemia) 4.5 – 45 (ANNL)					2.48 (0.73,3.00) 2.82 (0.82,9.38)
>8 (All leukaemia) >8 (ANNL)				11.3 (2.85,45.1) 7.17 (1.27,40.4)	
< 28.3 (All leukaemia) <28.3 (ANNL)			0.60 (0.16,1.54) 0.87 (0.11,3.13)		
28.3 – 79.1 (All leukaemia) 28.3 – 79.1 (ANNL)			2.00 (0.54,5.11) 1.47 (0.04, 8.17)		
> 45 (All leukaemia) >45 (ANNL)					1.35 (0.14,12.8) 0
> 79.1 (All leukaemia) >79.1 (ANNL)			2.16 (0.59,5.53) 1.61 (0.04, 8.95)		
40 – 399 (All leukaemia)		5.5 (0.62,24.08)			
45 – 400 (ANNL)		2.0 (0.3,14.2)			
> 400 (All leukaemia)		23.96 (4.82,78.51)			
400-1000 (ANNL)		9.1 (2.3,36.4)			
>1000 (ANNL)		82.8 (34.5,198.9)			

3.2.2 Numbers Exposed

CAREX has been used to identify the numbers exposed in 1990-3. These are given in Table 18 together with the classification as higher or lower.

Table 18. Numbers of workers exposed to benzene according to CAREX in 1990-1993.

Industry		CAREX Data 1990-1993		Exposure Level
		Number Exposed	Number in Industry	
Crude Petroleum and Natural Gas Production		508	5330	L
Beverage industries		2	88100	L
Manufacture of industrial chemicals		1234	130000	H1
Manufacture of other chemical products		1674	175175	L
Petroleum refineries		497	18075	L
Manufacture of miscellaneous products of petroleum		44	1125	L
Manufacture of plastic products nec		1516	136900	L
Iron and steel basic industries		754	48425	L
Non-ferrous metal basic industries		14	79325	L
Wholesale and retail trade and restaurants and hotels		51654	4459525	L
Land transport		7828	671050	H2
Water transport		585	68175	L
Air transport		64	95700	L
Services allied to transport		8	180725	L
Sanitary and similar services		741	274225	L
Education services		1219	1455875	L
Research and scientific institutes		440	91100	L
Personal and household services		228935	686750	L
Total		**297717**		
Main Industry Sector			**% Male**	
Agriculture, hunting and forestry; fishing	High	0		
	Low	0		
Mining/quarrying, electricity/gas/steam, manufacturing industry	High	1234	100%	
	Low	5009	100%	
Construction	High	0		
	Low	0		
Service industries	High	7828	65%	
	Low	283646	37%	

Exposure to benzene in the boot and shoe and rubber industries and for painters is thought to have ceased by 1985, other than as a trace contaminant. This is the beginning of the relevant exposure period for currently occurring leukaemias. Therefore these industries are not included for the count of numbers exposed.

The studies chosen as a source of estimates of relative risk only considered male workers exposed to benzene, in the rubber and chemical and petroleum industries. It has therefore been assumed that all the exposed workers in the mining/quarrying, electricity/gas/steam and manufacturing sectors were men. The ranges of industries in the service sectors however indicate that women are also likely to have been exposed to benzene at work in these areas. The CAREX estimate of numbers exposed for the service industries have therefore been split between men and women assuming that the highly exposed, mostly in land transport, are predominantly in blue collar occupations (skilled trades, shop floor and transport operatives in SOC major groups 5, 8 and 9, 65% male), and the low exposed are predominantly in personal service and 'other' occupations (standard occupational classification (SOC) major groups 6 and 9, 37% male). The allocations are based on identifying the SOC major occupation groups

that account for at least 20% of workers in industries accounting for the most workers in the CAREX list.

3.2.3 AF estimation

Both the 'high' and 'low' exposure risk estimates were for AML only, so attributable numbers have been calculated by applying the estimated AF to estimated numbers of AML (ICD code C92.0), acute promyelocytic leukaemia (C92.4) acute myelomonocytic leukaemia (C92.5), and acute monocytic leukaemia (C93.0).

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to benzene is 0.25% (95% Confidence Interval (CI)=0.00-4.65), which equates to 4 (95%CI=0-78) attributable deaths and 7 (95%CI=0-128) attributable registrations. The AF estimate for men is 0.19% (95%CI=0-3-38) (Table 19) resulting in 2 (95%CI=0-33) attributable deaths and 3 (95%CI=0-59) attributable registrations. For women the estimated AF is 0.34 (95%CI=0-6.76) resulting in 2 (95%CI=0-45) attributable deaths and 3 (95%CI=0-68) attributable registrations.

Table 19: Summary results for occupational exposure to benzene

				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	Collins *et al.* (2003)	H1	C-E	2.17	1234	1	0.09	3170	0.0001	0.0002	0.0000	0.0006	0	0	1	0	0	1
		H1	All		1234			3170	0.0001	0.0002	0.0000	0.0006	0	0	1	0	0	1
	Lewis *et al*. (2000)	H2	G-Q	1.32	5088	1	0.11	15084	0.0007	0.0002	0.0000	0.0014	0	0	1	0	0	3
		H2	All		5088			15084	0.0007	0.0002	0.0000	0.0014	0	0	1	0	0	3
	Bloemen *et al.* (2004)	L	C-E	1.11	5009	1	0.09	12869	0.0006	0.0001	0.0000	0.0013	0	0	1	0	0	2
		L	G-Q	1.11	104949	1	0.11	311113	0.0135	0.0015	0.0000	0.0311	2	0	32	3	0	56
		L	All		109958			323982	0.0141	0.0015	0.0000	0.0323	2	0	33	3	0	58
		All	All		116280			342236	0.0149	0.0019	0.0000	0.0328	2	0	33	3	0	59
Women	Lewis *et al* (2000)	H2	G-Q	1.32	2740	1	0.15	10638	0.0005	0.0001	0.0000	0.0010	0	0	1	0	0	1
		H2	All		2740			10638	0.0005	0.0001	0.0000	0.0010	0	0	1	0	0	1
	Bloemen *et al.* (2004)	L	G-Q	1.11	178697	1	0.15	693836	0.0300	0.0033	0.0000	0.0674	2	0	45	3	0	68
		L	All		178697			693836	0.0300	0.0033	0.0000	0.0674	2	0	45	3	0	68
		All	All		181437			704474	0.0305	0.0034	0.0000	0.0676	2	0	45	3	0	68

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

3.3 IONISING RADIATION

3.3.1 Risk estimate

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 (2008), 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 Table 46 in the UNSCEAR report (UNSCEAR, 2008), the linear-quadratic dose response mortality model was used,

$ERR(a) = (\alpha . D + \beta . D^2) . \exp(\kappa_1 . \ln(a))$,

where $\alpha = 864.552\ Sv^{-1}$
$\beta/\alpha = 1.180\ 92\ Sv^{-1}$
$\kappa_1 = -1.647$
D = mean lifetime dose /worker (Sv)
a = attained age;

From Table D3: Model Deviance = 2,136.589, df = 31,412

ERR is obtained as average ERR(a), averaged over a = 15-84 years (short latency REP 1986-2005).

Dose was assumed to be an individual's cumulative dose received over the REP for each cancer (1986-2005 for leukaemia). For workers exposed to IR, doses were estimated using data from the Central Index of Dose Information (CIDI) (HSE, 1998) (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 was used to estimate total collective dose for the REPs, by linear extrapolation forward and back from the year 1994 to obtain estimates for 1986-89 and 2005 respectively for the 1986-2005 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 by the employment turnover factors in Table A1 and by the number of years in the REP (20 for leukaemia).

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 15.3mSv, (median 10.7mSv, maximum 78.5mSv). The annual mean dose rate of all active pilots was 2.96μSv 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. Figure 1 in Langner *et al.* (2004) shows how average radiation doses have changed over time up to 2000. It indicates an almost continuous increase of the 10-year moving average of dose per block, with a steep increase at the beginning of the jet era around 1960. The lifetime dose estimate of 15.3mSv 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 and therefore confidence intervals could not be estimated from the UNSCEAR data.

The RR estimate is 1.027 for IR exposed workers (with an estimated average lifetime dose of 11.5 mSv) and 1.036 for aircrew (with an estimated average lifetime dose of 15.3 mSv), for men and women.

3.3.2 Numbers exposed

Data from the HSE's CIDI (HSE, 1998) indicates that there were 43,805 people exposed above 0.1mSv in GB in 1990, and 30,289 in 1995. The data exclude aircrew. A breakdown by occupation is in Table 20 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 and 1991, are also given in Table 20. CIDI data from 1995 and LFS data from 1991 are used as a best available point estimate for numbers exposed in the 'short latency' REP for leukaemia, 1986-2005.

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 (22,980 in 1986-2005). These 'ever exposed' numbers for air stewardesses are given in Table 20, and are used in the estimation of AF for this part of the exposed population (negating the use of the usual turnover equation estimate).

Table 20. Numbers of workers exposed to >0.1mSv ionising radiation in GB in 1995, from CIDI, numbers of aircrew in 1991, from LFS data, and air stewardesses from BA union data

Grouped main industry sector	Industry/occupation	Numbers exposed >0.1 mSv			
	REP 1986-2005	**M**	**F**	**Total**	**% Male**
	CIDI 1995				
C-E	Nuclear Power	8575	645	9220	93%
C-E	Nuclear Fuel Fabrication/ Reprocessing	6258	471	6729	93%
C-E	General Industry	4185	315	4500	93%
C-E	Industrial Radiography	1549	117	1666	93%
C-E	Non-coal Mining	244	18	262	93%
C-E	Radiation Protection	1618	122	1740	93%
C-E	Waste Treatment	931	70	1001	93%
C-E	Nuclear Industry Misc.	690	52	742	93%
C-E	Other	3718	280	3998	93%
	Sub-total	27768	2090	29858	
G-Q	Medical/Dental	130	10	140	93%
G-Q	Transport	89	7	96	93%
G-Q	Academic	181	14	195	93%
	Sub-total	401	30	431	
	CIDI Total >0.1 mSv	**28169**	**2120**	**30289**	
	LFS 1991				
G-Q	Aircraft Flight Deck Officers	14630	766	15396	
G-Q	Travel and flight attendants	11495			
	BA Stewards and Stewardesses Union data				
	Air stewardesses, numbers employed 1986-2005		22,980		
G-Q	Aircrew Total	26125			

3.3.3 AF calculation:

The total of leukaemias excluding CLL is used for the estimate of attributable numbers.

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to ionising radiation is 0.02% which equates to 0 attributable deaths and 1 attributable registration.

The AF estimate for men is 0.02% (Table 21) resulting in 0 attributable deaths and 1 attributable registrations. For women the estimated AF is 0.01% resulting in 0 attributable deaths and 0 attributable registrations.

Table 21 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	1.03	27768	1	0.09	71340	0.0031	0.0001			0			0		
		H	G-Q	1.03	401	1	0.11	1188	0.0001	0.0000			0			0		
		H	All		28169			72529	0.0032	0.0001			0			0		
		L	G-Q	1.04	26125	1	0.11	77446	0.0034	0.0001			0			0		
		L	All		26125			77446	0.0034	0.0001			0			0		
		All	All		54294			149974	0.0065	0.0002			0			1		
Women	UNSCEAR (2006)	H	C-E	1.03	2090	1	0.14	7699	0.0003	0.0000			0			0		
		H	G-Q	1.03	30	1	0.15	116	0.0000	0.0000			0			0		
		H	All		2120			7816	0.0004	0.0000			0			0		
		L	G-Q	1.04	766[9]	1	0.15	2974	0.0001	0.0000			0			0		
		L	All		766			2974	0.0001	0.0000			0			0		
		L (Aircrew)	G-Q	1.03	-			22980	0.0010	0.0000			0			0		
		L (Aircrew)	All					22980	0.0010	0.0000			0			0		
		All	All		2886			33770	0.0015	0.0001			0			0		

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
9. Excludes air stewardesses from the BASSA data

3.4 ETHYLENE OXIDE

3.4.1 Risk estimate

A series of reports by Hogstedt and colleagues (1979, 1986) raised concern about the health risk of a cluster of ethylene oxide (EO) exposed workers. Since then there have been studies varying in size and quality in several countries. No clear association between EO exposure and any cancer has been observed (Blair and Kazerouni, 1997). A meta-analysis by Shore *et al.* (1993) found no excesses of any cancer. This was updated by Teta *et al.* (1999) with similar results, and no trend with duration or intensity of exposure or latency. An updated analysis of the largest cohort (Steenland *et al*, 2004) found only a slight trend with cumulative exposure. A study of British EO workers observed 5 cases of leukaemia with 4.6 expected (Coggon *et al*, 2004) (Table 22). However, all five deaths were in a subset of subjects with the greatest potential for exposure to EO, but even in this group the excess of deaths was small (2.6 expected). The most recent meta-analysis obtained a meta-SMR of 0.95 (95%CI=0.64-1.35) after ignoring the initial work of Hogstedt (SMR=1.08, 95%CI=0.61-1.93, when included). For the AF calculation the figure of 0.95 will be used for those at low risk (1.00 in practice, as it is unrealistic to work with a 'protective' effect for ethylene oxide), 1.08 for medical workers (H2 in Table 23) and 2.29 for the others (H1 in Table 23).

Table 22. SMRs (95%CI) for leukaemia among a cohort of ethylene oxide workers in UK (Source: Coggon *et al*., 2004).

	Chemical Manufacturers	**Hospitals**	**All**
All	1.41 (0.39-3.62)	0.55 (0.01-3.06)	1.08 (0.35-2.51)
Highest exposure category	2.29 (0.62-5.86)	1.08 (0.03-6.02)	

3.4.2 Numbers exposed

According to CAREX there were an estimated 3,064 workers exposed to EO, most of these (61%) in hospitals (Table 23).

Table 23: Numbers of workers exposed to ethylene oxide according to CAREX in 1990-1993.

Industry		**CAREX Data 1990-1993**		**Exposure Level**
		Number Exposed	**Number in Industry**	
Crude petroleum and natural gas production		353	53300	H1
Food manufacturing		97	414150	H1
Manufacture of other chemical products		540	175175	H1
Education services		122	1455875	L
Research and scientific institutes		88	91100	H2
Medical, dental, other health and veterinary services		1864	1435675	H2
Main Industry Sector			**Male**	**Female**
Mining/quarrying, electricity/gas/steam manufacturing industry	Higher (H1) Lower	990	990 (100%)	
Service industries	Higher (H2) Lower	1952 122	878 (45%) 55 (45%)	1074 (55%) 67 (55%)

3.4.3 AF calculation

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to ethylene oxide is 0.01% (95%CI=0.00-0.21) which equates to 0 (95%CI=0-7) attributable deaths and 1 (95%CI=0-11) attributable registration.

The AF estimate for men is 0.02% (95%CI=0-0.19) (Table 24) resulting in 0 (95%CI= 0-4) attributable deaths and 1 (95%CI=0-6) attributable registration. For women the estimated AF is 0.00 (95%CI=0-0.26) resulting in 0 (95%CI=0-3) attributable deaths and 0 (95%CI=0-5) attributable registrations.

Table 24 Summary results for occupational exposure to ethylene oxide

				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	Coggon *et al.* (2004)	H1	C-E	2.29	990	1	0.09	2543	0.0001	0.0001	0.0000	0.0007	0	0	1	0	0	2
		H1	All		990			2543	0.0001	0.0001	0.0000	0.0007	0	0	1	0	0	2
		H2	G-Q	1.08	878	1	0.11	2604	0.0001	0.0000	0.0000	0.0016	0	0	3	0	0	5
		H2	All		878			2604	0.0001	0.0000	0.0000	0.0016	0	0	3	0	0	5
	Teta *et al.* (1999)	L	G-Q	1	55	1	0.11	163	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		55			163	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		1923			5310	0.0002	0.0002	0.0000	0.0019	0	0	4	1	0	6
Women	Coggon *et al.* (2004)	H2	G-Q	1.08	1074	1	0.15	4169	0.0002	0.0000	0.0000	0.0026	0	0	3	0	0	5
		H2	All		1074			4169	0.0002	0.0000	0.0000	0.0026	0	0	3	0	0	5
	Teta *et al.* (1999)	L	G-Q	1	67	1	0.15	261	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		67			261	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		1141			4429	0.0002	0.0000	0.0000	0.0026	0	0	3	0	0	5

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 FORMALDEHYDE

3.5.1 Risk estimate

A meta-analysis of 18 epidemiological studies of workers exposed to formaldehyde where leukaemia rates were reported found a small increase in risk for embalmers (meta-RR (mRR)=1.6, 95%CI=1.2-2.0) and pathologists/anatomists (mRR=1.4, 95%CI=1.0-1.9) (Collins and Lineker, 2004). Industrial workers, who have been reported to have the highest cumulative formaldehyde exposures, had an mRR of 0.9 (95%CI=0.8-1.0). Collins & Lineker (2004) suggest that the failure to observe excesses of leukaemia among industrially exposed workers, across job types and exposure groupings, and the difficulty of getting formaldehyde beyond the site of contact suggests a lack of biological plausibility, and that excesses among professionals is due to bias or some other exposures. The long latency for leukaemia deaths observed in the two industrial cohorts that reported an increased risk was not consistent with exposure to a chemical carcinogen such as benzene. In the large industrial studies an exposure-response relationship was observed based on peak exposure and to a lesser extent, on average intensity of exposure (Hauptmann *et al*, 2003). In a study of garment workers excess mortality was found among workers with a longer duration of exposure and follow-up (Pinkerton *et al*, 2004). However, the trend analysis of peak exposures was shown to be sensitive to different cut points (Collins and Lineker, 2004), and the updated study of UK industrial workers, which had more workers with higher exposures than the other studies did not find an excess mortality, even in the highest exposure categories (Coggon *et al*, 2003).

For the AF estimation the decision was made to use the meta-RR for embalmers above (RR =1.6 95%CI=1.2-2.0) for medical, dental, other health and veterinary services, and research and scientific institutes (H in Table 26); a mRR of 1.2 (95%CI=0.8-1.8) for high peak exposures for industries manufacturing and textiles (L in Table 26) taken from Collins and Lineker (2004); and 1.0 for background (B in Table 26).

3.5.2 Number exposed

The number of workers exposed to formaldehyde in 1990-1993 according to CAREX is given in Table 25. Embalmers and related professions are considered to be included in the 'personal and household services' category based on the SOC 'personal service occupations' (SOC major group 6 and minor group 629). According to the British Institute of Embalmers (BIOE), there are currently 1400 registered embalmers in the UK and Ireland, 100 of whom work overseas (BIOE, Pers. Comm.). However, not all registered embalmers will be working at one time, with many retired or employed elsewhere. As the occupation is unregulated, there is no requirement for workers to qualify and hence register, and there may be many more employed in the embalming services than current estimates allow (BIOE, Pers. Comm.). It is also uncertain how many embalmers were employed in the past although it is thought that numbers are increasing. In the AF estimate the CAREX figure for personal and household services has thus been used.

In order to split the CAREX exposed numbers between men and women, it is assumed that all the exposed occupations in manufacturing and in construction were in skilled trades, shop floor and transport operatives (SOC major groups 5, 8 and 9), and that the exposed occupations in the service sector were in professional, associated professional and technical and personal and protective service occupations (SOC groups 2, 3 and 6), except workers employed in personal and household services. For this industry, it assumes that workers are mainly embalmers and according to BIOE, 78% are male. These data were used to estimate Pr(E) for Levin's calculation of AF, as an alternative to the European population based studies.

Table 25: Numbers of workers exposed to formaldehyde according to CAREX in 1990-1993.

Industry		CAREX Data 1990-1993 Number Exposed	Number in Industry	Exposure Level
Crude Petroleum and Natural Gas Production		656	53300	B
Beverage industries		881	88100	B
Manufacture of textiles		4730	182000	H
Manufacture of wearing apparel, except footwear		17992	189500	H
Manufacture of wood and wood and cork products, except		12430	132975	L
Manufacture of furniture and fixture, except primary of		39772	144325	L
Manufacture of paper and paper products		722	119050	B
Manufacture of industrial chemicals		1006	130000	L
Manufacture of other chemical products		360	175175	L
Manufacture of plastic products nec		2021	136900	L
Manufacture of glass and glass products		278	43275	H
Manufacture of other non-metallic mineral products		585	70875	L
Iron and steel basic industries		1870	48425	L
Non-ferrous metal basic industries		1254	79325	L
Manufacture of fabricated metal products, except		535	292200	L
Manufacture of machinery except electrical		760	692275	L
Construction		4511	1753450	L
Education services		122	1455875	H
Research and scientific institutes		176	91100	H
Medical, dental, other health and veterinary services		2796	1435675	H
Recreational and cultural services		74	534600	B
Personal and household services		276	686750	H
Total		**93807**		
Main Industry Sector			**Male**	**Female**
Agriculture, hunting and forestry; fishing	High	0		
	Low	0		
Mining/quarrying, electricity/gas/steam, manufacturing industry	High	2300060593	17480 (76%)	5520 (24%)
	Low	2259	46051 (76%)	14542 (24%)
	Back.		1717 (76%)	542 (24%)
Construction	High	0		
	Low	4511	4466 (99%)	45 (1%)
Service industries	High	3370	1608 (45%)	1762 (55%)
	Background	74	33 (45%)	41 (55%)

3.5.3 AF calculation

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to formaldehyde is 0.20% (95%CI=0.05-0.48) which equates to 6 95%CI=2-15) attributable deaths and 10 (95%CI=3-25) attributable registrations.

The AF estimate for men is 0.24% (95%CI=0.06-0.60) (Table 26) resulting in 5 (95%CI=1-12) attributable deaths and 8 (95%CI=2-20) attributable registrations. For women the estimated AF is 0.12 (95%CI=0.04-0.27) resulting in 1 (95%CI=0-3) attributable death and 2 (95%CI=1-5) attributable registrations.

Table 26 Summary results for occupational exposure to formaldehyde

				Data		Calculations				Attributable Fraction (Levins[8]) & 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	Collins & Lineker, 2004	H	C-E	1.6	17480	1	0.09	44909	0.0020	0.0012	0.0007	0.0032	2	1	6	4	2	11
		H	G-Q	1.6	1608	1	0.11	4766	0.0002	0.0001	0.0000	0.0002	0	0	0	0	0	1
		H	All		19088			49675	0.0022	0.0013	0.0008	0.0034	3	2	7	4	3	11
		L	C-E	1.2	46051	1	0.09	118312	0.0051	0.0010	0.0000	0.0033	2	0	7	3	0	11
		L	F	1.2	4466	1	0.12	14121	0.0006	0.0001	0.0000	0.0005	0	0	1	0	0	2
		L	All		50517			132433	0.0058	0.0011	0.0000	0.0038	2	0	8	4	0	13
		B	C-E	1	1717	1	0.09	4411	0.0002	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	G-Q	1	33	1	0.11	99	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	All		1750			4510	0.0002	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		71354			186617	0.0081	0.0024	0.0006	0.0060	5	1	12	8	2	20
Women	Collins & Lineker, 2004	H	C-E	1.6	5520	1	0.14	20334	0.0009	0.0005	0.0003	0.0014	1	0	2	1	1	3
		H	G-Q	1.6	1762	1	0.15	6843	0.0003	0.0002	0.0001	0.0003	0	0	0	0	0	1
		H	All		7282			27177	0.0012	0.0007	0.0004	0.0018	1	0	2	1	1	3
		L	C-E	1.2	14542	1	0.14	53570	0.0023	0.0005	0.0000	0.0015	1	0	2	1	0	3
		L	F	1.2	45	1	0.15	175	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		14587			53745	0.0023	0.0005	0.0000	0.0015	1	0	2	1	0	3
		B	C-E	1	542	1	0.14	1997	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	G-Q	1	41	1	0.15	158	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		B	All		583			2155	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		22453			83078	0.0036	0.0012	0.0004	0.0027	1	0	3	2	1	5

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

3.6 1,3-BUTADIENE

3.6.1 Risk estimate

A study by Delzell *et al.* (2001) was carried out of workers employed at 8 styrene-butadiene plants in the USA and Canada and gave risk estimates for butadiene adjusted for exposure to styrene and dimethyldithiocarbamate. The highest adjusted risk estimate from Delzell *et al*, (2001) (RR=2.30, 95%CI=0.6-8.3) has been selected for the AF calculation for the highly exposed using a precautionary approach, and RR of 1.30 (95%CI=0.4-4.3) has been selected for the low exposure group. All the exposed workers are assumed to be men.

3.6.2 Numbers exposed

BD is used very little in GB and the CAREX estimated only 2,871 workers 1990-93 potentially exposed (Table 27). To allocate the CAREX numbers between men and women, it has been assumed that those exposed in the manufacturing sectors (C-E) are in blue collar jobs, and those exposed service sector workers are in professional, associate professional and technical and personal service occupations (SOC major groups 2, 3 and 6).

Table 27. Numbers of workers exposed to 1,3-Butadiene according to CAREX in 1990-1993.

Industry		**CAREX Data 1990-1993**		**Exposure Level**
		Number Exposed	**Number in Industry**	
Manufacture of paper and paper products		2	119050	L
Manufacture of industrial chemical		744	130000	L
Manufacture of other chemical products		254	175175	L
Petroleum refineries		118	18075	L
Manufacture of rubber products		318	53025	H
Manufacture of plastic products nec		1212	136900	L
Education services		122	1455875	L
Research and scientific institutes		88	91100	L
Medical, dental, other health and veterinary services		13	1435675	L
Total		**2871**		
Main Industry Sector			**% Male**	
Agriculture, hunting and forestry; fishing	High	0		
	Low	0		
Mining/quarrying, electricity/gas/steam, manufacturing industry	High	318	76%	
	Low	2330		
Construction	High	0		
	Low	0		
Service industries	High	0		
	Low	223	45%	

3.6.3 AF calculation

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to 1,3-butadiene is 0.01% (95%CI=0.00-0.06) which equates to 0 (95%CI=0-2) attributable deaths and 0 (95%CI=0-3) attributable registrations.

The AF estimate for men is 0.01% (95%CI=0-0.08) (Table 28) resulting in 0 (95%CI=0-2) attributable deaths and 0 (95%CI=0-3) attributable registrations. For women the estimated AF is 0.00 (95%CI=0-0.04) resulting in 0 (95%CI=0-0) attributable deaths and 0 (95%CI=0-1) attributable registrations.

Table 28 Summary results for occupational exposure to 1,3-butadiene

				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	Delzell *et al.* (2001)	H	C-E	2.3	242	1	0.09	621	0.0000	0.0000	0.0000	0.0002	0	0	0	0	0	1
		H	All		242			621	0.0000	0.0000	0.0000	0.0002	0	0	0	0	0	1
		L	C-E	1.3	1771	1	0.09	4549	0.0002	0.0001	0.0000	0.0006	0	0	1	0	0	2
		L	G-Q	1.3	100	1	0.11	297	0.0000	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		1871			4847	0.0002	0.0001	0.0000	0.0007	0	0	1	0	0	2
		All	All		2113			5468	0.0002	0.0001	0.0000	0.0008	0	0	2	0	0	3
Women	Delzell *et al.* (2001)	H	C-E	2.3	76	1	0.14	281	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		H	All		76			281	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	C-E	1.3	559	1	0.14	2060	0.0001	0.0000	0.0000	0.0003	0	0	0	0	0	1
		L	G-Q	1.3	123	1	0.15	476	0.0000	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	All		682			2536	0.0001	0.0000	0.0000	0.0004	0	0	0	0	0	1
		All	All		758			2817	0.0001	0.0000	0.0000	0.0004	0	0	0	0	0	1

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

3.7 NON-ARSENICAL INSECTICIDES

3.7.1 Risk estimate

Acquavella *et al*. (1998) conducted a meta-analysis of 37 studies to assess whether farmers were at greater risk of any cancer. A total of 27 of these examined the risk of leukaemia. The studies were based in the US, UK and one from New Zealand. A meta-RR of 1.10 was obtained using a random effects model, with 95%CI of 1.02-1.18, and with a high significance for heterogeneity. This figure compares with PRRs of 1.17 (95%CI=1.02-1.34) for all leukaemias (ALL: PRR=1.28, 95%CI=0.68-2.19; CLL: PRR=1.27, 95%CI=1.00-1.60; AML: PRR=1.14, 95%CI=0.89-1.46; CML: PRR= 1.12, 95%CI=0.77-1.59) for farmers in the decennial supplement (Drever, 1995).

Dich *et al*. (1997) showed a wide range of RRs for leukaemia in farmers in studies published after 1992, the greater risks being associated with exposure to insecticides particularly organochlorines and organophosphates. There are also an increasing number of studies, particularly from the US AHS, linking particular chemicals with an increased risk of leukaemia. These include:

- Diazinon: RR=3.36, 95%CI=1.08-10.49 (Beane-Freeman *et al*, 2005)
- Mancozeb: RR=2.35, 95%CI=1.12-4.95 (Mills *et al*, 2005)
- Toxaphane: RR=2.20, 95%CI=1.04-4.65 (Mills *et al*, 2005)
- Alachlor: RR=2.83, 95%CI=0.74-10.9 (Lee *et al*, 2004)

It is difficult to identify the proportion of the population exposed to these specific chemicals. For the AF estimation the meta-RR of 1.10 (95%CI=1.02-1.18) from Acquavella (1998) will be applied to farm and other agricultural workers, gardeners, pest control workers and workers in pesticide manufacturing (H in Table 30).

The result of the meta-analysis of crop protection product manufacturing workers of Jones *et al*. (2009) will be used for workers employed in pesticide manufacturing (meta-RR=1.08, 95%CI=0.81-1.44) (L in Table 30). The analysis included 26 studies from around the world, USA, Europe and one from New Zealand.

The estimate for workers in the grain industry will be taken from the cohort study of 22,938 members of the American Federation of Grain Millers followed from 1955 to 1985, SMR=1.07 (95%CI=0.75-1.47) (Alavanja *et al*, 1990) (B in Table 30).

3.7.2 Numbers exposed

The numbers of workers employed in the occupations above are given below in Table 29 and were obtained from the LFS.

Table 29. Numbers of workers in different industries with potential for exposure to pesticides in 2003.

SIC Code	Job Title	Number employed		Total
LFS 1991		Men	Women	
	Farm owners & managers, horticulturalists	206,038	29,240	23,5278
	Other managers, farm hort. forest & fishing	11,066	6,497	17,563
	Gardeners, groundsmen, groundswomen	131,964	7,459	139,423
	Horticultural trades	17,816	12,555	30,371
	Farm workers	100,734	41,772	142,506
	Agricultural machinery drivers & ops	20,233	358	20,591
	Other occupations in farming & related	17,271	19,345	36,616
	Forestry workers	19,254	709	19,963
	Total	**524,376**	**117,935**	**64,2311**
Industry				
2568	Formulated pesticides	1,343	1,084	2,427
4160	Grain milling	6,187	1,197	7,384

source: Labour Force Survey

According to the Agricultural and Horticultural Census, there were 528,000 employed in 1987 compared to 478,000 employed in 1997, in full-time or part-time employment (not including seasonal or casual labour). The LFS estimate based on occupation, of about 483,000 employed in farming and horticulture (excluding the category described as gardeners and groundsmen and forestry workers), is broadly in line with these estimates which are the most reliable source for agricultural employment. To calculate AF therefore we have used the estimate of numbers employed in farming and horticulture in 1991 from the LFS, plus the 1991 LFS estimate for non-agricultural exposed workers (gardeners and groundsmen/women, forestry workers and those employed in the industries described as 'formulated pesticides' and 'grain milling'). This gives an estimate of 650,000 workers exposed in the early 1990s.

3.7.3 AF calculation

The estimated total (male and female) attributable fraction for leukaemia associated with occupational exposure to non-arsenical insecticides is 0.38% (95%CI=0.09-0.68), which equates to 12 (95%CI=3-21) attributable deaths and 19 (95%CI=5-35) attributable registrations.

The AF estimate for men is 0.50% (95%CI=0.12-0.91) (Table 30) resulting in 10 (95%CI=2-18) attributable deaths and 17 (95%CI=4-30) attributable registrations. For women the estimated AF is 0.15% (95%CI=0.04-0.27) resulting in 2 (95%CI=0-3) attributable deaths and 3 (95%CI=1-5) attributable registrations.

Table 30 Summary results for occupational exposure to non-arsenical insecticides

				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	Acquavella (1998)	H	A-B	1.1	524376	1	0.07	1139943	0.0496	0.0049	0.0011	0.0090	10	2	18	16	4	30
		H	All		524376			1139943	0.0496	0.0049	0.0011	0.0090	10	2	18	16	4	30
	Jones *et al.* (2009)	L	C-E	1.08	1343	1	0.09	3450	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	All		1343			3450	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
	Alavanja *et al*, 1990	B	C-E	1.07	6187	1	0.09	15895	0.0007	0.0000	0.0000	0.0003	0	0	1	0	0	1
		B	All		6187			15895	0.0007	0.0000	0.0000	0.0003	0	0	1	0	0	1
		All	All		531906			1159288	0.0504	0.0050	0.0012	0.0091	10	2	18	17	4	30
Women	Acquavella (1998)	H	A-B	1.1	117935	1	0.1	340563	0.0147	0.0015	0.0003	0.0027	2	0	3	3	1	5
		H	All		117935			340563	0.0147	0.0015	0.0003	0.0027	2	0	3	3	1	5
	Jones *et al.* (2009)	L	C-E	1.08	1084	1	0.14	3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		L	All		1084			3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
	Alavanja *et al*, 1990	B	C-E	1.07	1197	1	0.14	4409	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		B	All		1197			4409	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		All	All		120216			348966	0.0151	0.0015	0.0004	0.0027	2	0	3	3	1	5

1. Specific scenario or main industry code (Table A1)
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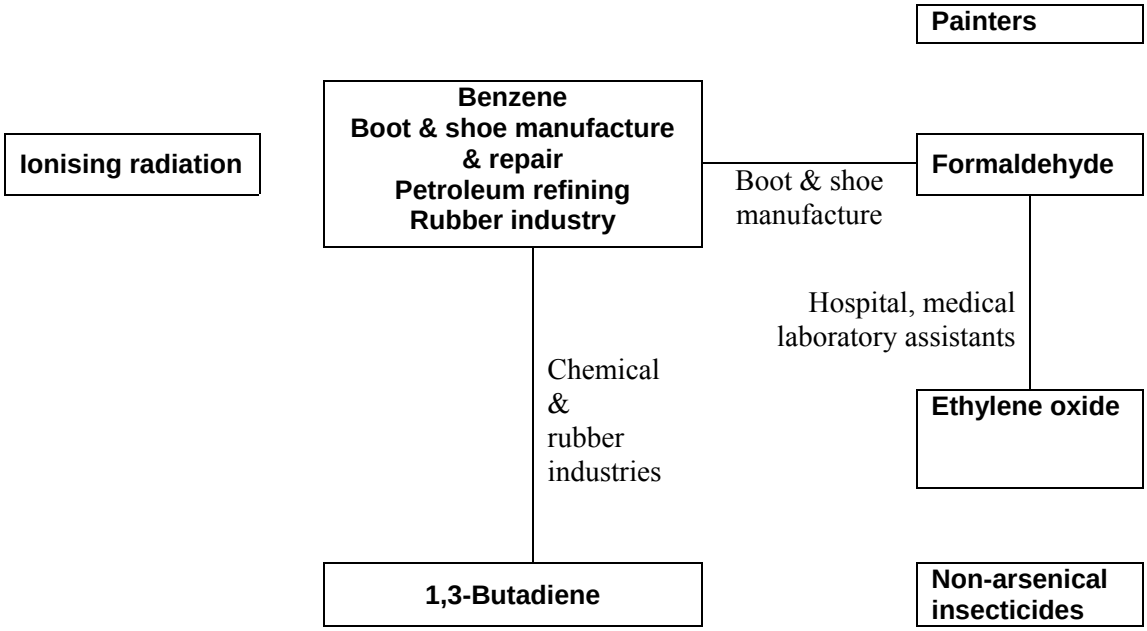
6. Number ever exposed during the REP (Statistical Appendix equation 3)
7. Proportion of the population exposed (Pr(E), Statistical Appendix equation 4)
8. Statistical Appendix equation 1

4 OVERALL ATTRIBUTABLE FRACTION

4.1 EXPOSURE MAP

The exposure map (Figure 1) gives an indication of how exposures overlap in the working population. It illustrates the potential for double counting of the exposed population to occur when an overall AF is calculated, and facilitates strategies to avoid this. For a given cancer, the map entries consist of either an agent (or group of agents such as PAHs), or an exposure scenario (i.e. an industry or occupation in which such exposure occurs). Agents are in plain type, exposure scenarios in italics, from Table 6. Lines joining boxes then indicate where overlap would occur were all the entries in the map simply considered separately – for example, if benzene and formaldehyde were considered separately overlap would occur in boot and shoe manufacture (these exposure scenarios are indicated in the smaller print, again based on information in Table 6).

Figure 1. Leukaemia exposure map



4.2 SUMMARY OF RESULTS

The results are summarised in Table 31.

Table 31 Summary of RR used to calculate AF

Agent	Exposure	RR	LL	UL
1,3-Butadiene	High	2.3	0.6	8.3
1,3-Butadiene	Low	1.3	0.4	4.3
Benzene	Manufacture of industrial chemicals	2.17	0.9	5.2
Benzene	Land transport	1.32	0.49	2.88
Benzene	Low	1.11	0.3	2.83
Ethylene oxide	High	2.29	0.64	6.02
Ethylene oxide	Research and medical	1.08	0.03	6.19
Ethylene oxide	Low	1	0.64	1.35
Formaldehyde	High	1.6	1.2	2
Formaldehyde	Low	1.2	0.8	1.8
Formaldehyde	Background	1	1	1
Ionising radiation	High	1.03	1.03	1.03
Ionising radiation	Low	1.04	1.04	1.04
Non-arsenical insecticides	High	1.1	1.02	1.18
Non-arsenical insecticides	Low	1.08	0.81	1.44
Non-arsenical insecticides	Background	1.07	0.75	1.47

Table 32: 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)
1,3-Butadiene	5468	2817	0.0002	0.0001	0.0001	0.0000	0.0008	0.0000	0.0000	0.0004	0	0	0	0
Benzene	342236	704474	0.0149	0.0305	0.0019	0.0000	0.0328	0.0034	0.0000	0.0068	2	2	3	3
Ethylene oxide	5310	4429	0.0002	0.0002	0.0002	0.0000	0.0019	0.0000	0.0000	0.0026	0	0	1	0
Formaldehyde	186617	83078	0.0081	0.0036	0.0024	0.0006	0.0060	0.0012	0.0004	0.0027	5	1	8	2
Ionising radiation	149974	33770	0.0065	0.0015	0.0002			0.0001			0	0	1	0
Non-arsenical insecticides	1159288	348966	0.0504	0.0151	0.0050	0.0012	0.0091	0.0015	0.0004	0.0027	10	2	17	3
Totals*					**0.0088**	**0.0020**	**0.0353**	**0.0048**	**0.0008**	**0.0045**	**18**	**5**	**30**	**9**

*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.

- **EXPOSURES BY INDUSTRY/JOB**

Table 33 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
1,3-Butadiene	**Total**	**5468**	**2817**	**0**	**0**	**0**	**0**	**0**	**0**
Benzene	Manufacture of industrial chemicals	3170	0	0	0	0	0	0	0
Benzene	Land transport	15084	10638	0	0	0	0	1	0
Benzene	Personal and household services	251104	560005	2	1	3	2	5	3
Benzene	Wholesale and retail trade and restaurants and hotels	56656	126353	0	0	1	0	1	1
Benzene	**Total**	**342236**	**704474**	**3**	**2**	**3**	**2**	**7**	4
Ethylene oxide	**Total**	**5310**	**4429**	**1**	**0**	**0**	**0**	**1**	0
Formaldehyde	Manufacture of wood and wood and cork product. except furniture	24270	10989	1	0	0	0	1	1
Formaldehyde	Manufacture of textiles	9236	4182	1	0	0	0	1	1
Formaldehyde	Manufacture of wearing apparel. except footwear	35131	15907	3	2	1	0	4	2
Formaldehyde	Medical, dental, other health and veterinary services	3730	5971	0	0	0	0	1	0
Formaldehyde	Manufacture of furniture and fixtures, except primary use of metal	77657	35162	2	1	1	0	3	2
Formaldehyde	**Total**	**186617**	**83078**	**8**	**5**	**2**	**1**	**10**	**6**
Ionising radiation	**Total**	**149974**	**34475**	**1**	**0**	**0**	**0**	**1**	**0**
Non-arsenical insecticides	Farm workers	218986	120626	3	2	1	1	4	2
Non-arsenical insecticides	Horticultural trades	38730	36255	1	0	0	0	1	1

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
Non-arsenical insecticides	Forestry workers	41856	2047	1	0	0	0	1	0
Non-arsenical insecticides	Gardeners, Groundsmen, groundswomen	286877	21539	4	2	0	0	4	3
Non-arsenical insecticides	Farm owners & managers, horticulturalists	447907	84437	6	4	1	0	7	4
Non-arsenical insecticides	Agricultural machinery drivers & operators	43985	1034	1	0	0	0	1	0
Non-arsenical insecticides	Other occupations in farming and related	37545	55863	1	0	0	0	1	1
Non-arsenical insecticides	**Total**	**1159288**	**348966**	**17**	**10**	**3**	**2**	**19**	**12**

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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 (2005) (e.g. 35 to 84 (men, 79 women) for the short latency REP)

c to d = age range achieved by the turnover recruited cohort members by the target year (15 to 34 for the short latency 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).

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The burden of occupational cancer in Great Britain

Leukaemia

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 leukaemia 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 leukaemia related to overall occupational exposure is 0.74% (95% Confidence Interval (CI)= 0-3.86), which equates to 23 (95%CI= 5-120) attributable deaths and 38 (95%CI= 8-198) attributable registrations.

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