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Health and Safety Executive

The burden of occupational cancer in Great Britain

Multiple myeloma

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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Multiple myeloma

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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 multiple myeloma 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 multiple myeloma related to overall occupational exposure is 0.30% (95%Confidence Interval (CI)= 0.00-0.64), which equates to 6 (95%CI= 0-12) deaths and 10 (95%CI= 0-21) 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 multiple myeloma that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

Non-arsenical insecticides have been classified by the IARC as a probable human carcinogen for multiple myeloma. 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 1065 total deaths in men aged 15-84 and 704 in women aged 15-79 from multiple myeloma; in 2004 there were 1863 total registrations for multiple myeloma in men aged 15-84 and 1143 in women aged 15-79.

The estimated total (male and female) attributable fraction for multiple myeloma associated with occupational exposure overall and to non-arsenical insecticides is 0.30% (95%Confidence Interval (CI)= 0.00-0.64), which equates to 6 (95%CI=0-12) deaths and 10 (95%CI=0-21) registrations.

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1 INCIDENCE AND TRENDS

Multiple myeloma (ICD-10 C90; ICD-9 203) is a form of cancer that affects plasma cells in the bone marrow. Plasma cells normally produce antibodies that the body requires to fight infection. In myeloma a single cell becomes malignant and produces a very large number of identical cells. In patients very large quantities of a single type of antibody are produced. This form of antibody is called a paraprotein and it is present in the blood and/or urine in about 99% of cases. Normal antibody levels are almost always reduced in myeloma which, combined with a reduction in neutrophil number, can lead to a susceptibility to life-threatening infections.

Internationally, the reported incidence varies substantially; the highest rates have been reported for African-Caribbeans; Europeans and North American Caucasians have intermediate rates; generally low rates have been reported for Asians living in Asia and the US (de Roos *et al*, 2006). The reasons why rates are higher in African-Caribbeans are not understood but seem to suggest an underlying variation at the population level in the probability of developing the condition. In the UK in the 1990s myeloma accounted for about 1.3% of all cases of cancer per year in males and 1.2% in females (Adamson, 2005). Myeloma is a disease of the elderly, being virtually unknown in childhood and very uncommon in young adults. Only about 2% of cases in the UK occur in people under the age of 40 years (LRF, 2006)**.** The highest rate is seen in people in their 70s and 80s and age-specific rates in men are markedly higher than those in women. From the 1970s to the mid-1990s incidence increased substantially in both sexes, after which it slowed down in males and levelled off in females in the 1990s. Overall rates in males have increased by about 80% over this time period, and about 70% in females, due mainly to large increases in those aged 75 and over.

Over the 10 years from 1995 to 2005 there was an average of over 2900 new cases (registrations) each year in England[1] (Table 1), with about 280 in Wales[2] and 320 in Scotland[3]. In GB the age standardised incidence rate per 100,000 person years is substantially greater in Wales[4] (Men: 8.2; Women: 5.3) than England (Men: 6.9; Women: 5.5) and Scotland (Men: 5.9; Women: 3.8). Within England above average rates are seen in the South West for males and females, and South East and Trent for males only (Adamson, 2005). Myeloma accounts for and average of over 2,900 deaths in England and Wales (Table 2) each year, with an average additional 280 in Scotland. In males it accounts for 1.5% of all cancer deaths, whereas it is 1.7% in females. Age-specific mortality followed the same pattern as for incidence, with the highest rates in those aged over 85 years, with higher rates in men than women.

The temporal pattern for mortality is similar to that of incidence, with steep increases in rates up to the 1980s, and at ages 50 and above there have been large increases in recorded mortality (Swerdlow *et al*, 2001). The male:female ratio for mortality in England and Wales is approximately 1.06:1, whereas for Scotland it is 1.09:1. The age-standardised rates are similar in all three[1,2,3] countries, and are not dissimilar at the health authority level (Adamson, 2005).

The five-year relative survival rate for multiple myeloma has increased consistently over the past 30 years from approximately 10% in 1971-1975 to about 30% in 2000-2001 (Adamson, 2005). However, there has been little or no improvement in long-term (>10-years) survival. Until recently the survival rates were greater for women than men. For individuals diagnosed

[1] http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=618
[2] http://www.wales.nhs.uk/sites3/home.cfm?OrgID=242
[3]http://www.isdscotland.org/isd/cancer-statistics.jsp?pContentID=183&p_applic=CCC&p_service=Content.show&

between 15 to 39 years the five-year survival rate is greater than 50%, compared to less than 10% in those aged 80 to 99 years.
The cancer mortality to incidence ratios (numbers) is 0.61 for males and 0.70 for females.

Table 1 Number of multiple myeloma registrations in England, Scotland and Wales 1994-2003[5]

	Men				Women			
Year	**England**	**Scotland**	**Wales**	**Total**	**England**	**Scotland**	**Wales**	**Total**
1995	1381 (5.8)	162 (6.2)	n/a		1370 (5.5)	169 (4.3)	n/a	
1996	1347 (5.6)	166 (6.3)	n/a		1267 (5.1)	144 (3.9)	n/a	
1997	1320 (5.4)	133 (5.0)	n/a		1204 (4.8)	140 (3.6)	n/a	
1998	1554 (6.4)	139 (5.2)	n/a		1384 (5.5)	169 (4.2)	n/a	
1999	1508 (6.1)	139 (5.1)	n/a		1381 (5.5)	153 (3.9)	n/a	
2000	1580 (6.6)	177 (5.1)	139 (7.8)	1896	1498 (6.0)	163 (4.0)	106 (4.6)	1767
2001	1528 (6.3)	189 (6.6)	177 (9.7)	1894	1331 (5.3)	153 (3.8)	136 (5.9)	1620
2002	1567 (6.5)	176 (6.1)	153 (8.3)	1896	1361 (5.4)	159 (3.7)	115 (4.8)	1635
2003	1657 (6.8)	174 (6.1)	162 (8.7)	1984	1404 (5.5)	154 (3.7)	133 (5.2)	1691
2004	1691 (6.9)	174 (5.9)	156 (8.2)	2021	1394 (5.5)	159 (3.8)	131 (5.5)	1684
2005	1739 (7.0)		130 (6.9)		1504 (5.9)		122 (4.7)	
Average 1995-2005	**1534 (6.3)**	**163 (5.8)**	**153 (8.3)**	**1850**	**1373 (5.5)**	**156 (3.9)**	**124 (5.1)**	**1653**

Table 2 Number of multiple myeloma deaths in England, Wales, and Scotland 1999-2004 (Source: ONS DH2 Series[6])

	Men			Women		
	England & Wales	**Scotland**	**Great Britain**	**England & Wales**	**Scotland**	**Great Britain**
Year	**Number (Crude Rate, /100000)**	**Number (Crude Rate, /100000)**	**Number**	**Number (Crude Rate, /100000)**	**Number (Crude Rate, /100000)**	**Number**
1999	1107 (4.4)	94 (3.4)	1201	1058 (4.0)	105 (2.6)	1163
2000	946 (3.7)	85 (3.0)	1031	1042 (4.0)	127 (2.9)	1169
2001	1133 (4.4)	112 (3.9)	1245	1090 (4.1)	115 (2.8)	1205
2002	1209 (4.7)	116 (4.0)	1325	1114 (4.2)	109 (2.5)	1223
2003	1199 (4.6)	105 (3.5)	1304	1134 (4.3)	127 (2.9)	1261
2004	1208 (4.7)	110 (3.7)	1318	1071 (4.0)	90 (1.9)	1161
2005	1129 (4.3)	102 (3.4)	1231	1065 (4.0)	119 (2.5)	1184
2006	1210 (3.6)	125 (4.1)	1335	1091 (2.4)	114 (2.4)	1205
Average 1999-2006	**1143 (4.3)**	**106 (3.6)**	**1249**	**1083 (3.9**	**113 (2.9)**	**1196**

[5] http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=8843&Pos=&ColRank=1&Rank=240; http://www.wales.nhs.uk/sites3/home.cfm?OrgID=242; http://www.isdscotland.org/isd/cancer-statistics.jsp?pContentID=183&p_applic=CCC&p_service=Content.show&

[6] http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=618; http://www.isdscotland.org/isd/cancer-statistics.jsp?pContentID=183&p_applic=CCC&p_service=Content.show&

2 OVERVIEW OF AETIOLOGY

There are no clearly defined risk factors for multiple myeloma (LRF, 2006). Elevated relative risks for the association between obesity and myeloma have been reported in a few epidemiological studies (Alexander *et al*, 2007). Intake of several meats and fats, butter and total seasoning fats have been associated with an increased risk (de Roos *et al*, 2006), whereas fresh fruit and vegetables and fish intake were associated with a decreased risk. Studies of the relation between alcohol intake and risk of myeloma have found no apparent association (Boffetta *et al*, 1989b, Brown *et al*, 1992b, Tavani *et al*, 1997) as have studies investigating tobacco use (Boffetta *et al*, 1989b, Brown *et al*, 1992a, Miligi *et al*, 1999).

A number of prior medical conditions and treatments have been suspected to increase the risk of myeloma, either through chronic immune stimulation or another biologic mechanism (de Roos *et al*, 2006). Numerous studies have shown an increased risk with autoimmune disease (including: rheumatoid arthritis; systemic lupus erythmatous; pernicious anaemia; and psoriasis), asthma, allergies and allergy treatment, bacterial infections (including rheumatic and scarlet fever, tuberculosis, urinary tract infections and gonorrhoea), viral infections (e.g., chicken pox, hepatitis, infectious mononucleosis, mumps and shingles), and other chronic (diabetes, colitis) and acute (blood transfusion, tonsillectomy) conditions (de Roos *et al*, 2006).

Because myeloma is a relatively rare cancer, cohort studies of the relation between occupational exposures and myeloma have generally provided limited information. The only studies with large numbers of myeloma cases have been those population-based death certificate studies like the Occupational Health Decennial Supplement (Drever, 1995), where job title is generally the only occupational variable that could be evaluated. Studies have observed increased risk of myeloma in those involved in/exposed to agricultural work and pesticides, rubber and plastics manufacturing, paint-related occupations, wood products industries, asbestos, engine exhaust, metals and others (de Roos *et al*, 2006).

The Occupational Health Decennial Supplement (Drever, 1995) observed that the risk was raised in farmers and forestry workers who could be exposed to pesticides (Table 3). The latter, along with carpenters and cabinet-makers (also had elevated PMRs), are exposed to wood products. Results also indicate a consistently elevated risk in electrical occupations. The increased risk among teachers, both in schools and higher education, are consistent with an aetiological role of infections acquired as an adult through frequent contact with large numbers of young people. In the more recent supplement the risk amongst farmers, forestry workers and electrical occupations was not observed (Table 4) (Coggon *et al*, 2009). However, there was still an increased risk for teachers.

Similar studies of cancer registration in the Nordic countries (Andersen *et al*, 1999) and Switzerland (Bouchardy *et al*, 2002) observed an excess myeloma risk amongst farmers and gardeners/related workers, and carpenters. The Swiss study also observed an increased risk amongst social work and teaching professions.

Table 3 Job codes with significantly high PRRs and PMRs for multiple myeloma. Men and women aged 20-74 years, England, 1981-87 (Source: Drever et al. (1995).

Job group		Registrations			Deaths		
SIC code	**Description**	**Observed**	**PRR**	**95%CI**	**Observed**	**PMR**	**95%CI**
Men							
010	Teachers in higher education				38	148	105-204
011	Teachers, nec	60	144	111-187	107	133	109-160
029	Electrical and electronic engineers (professional)				24	167	107-249
047	Farmers	120	126	105-151			
049	Police				47	140	103-186
065	Foresters	7	322	130-664			
104	Carpenters				125	120	100-143
105	Cabinet makers				23	204	129-307
124	Machine tool operators				204	117	102-134
130	Precision instrument makers	9	284	130-540			
136	Electrical and electronic production fitters				7	121	48-248
137	Electricians	43	143	104-193	97	120	97-146
138	Electrical plant operators				17	155	96-248
139	Telephone fitters				33	113	78-159
140	Electric cable and line workers				10	134	64-247
142	Other electronic maintenance engineers				13	134	71-228
143	Electrical engineers (so described)				47	141	103-187
185	Bus conductors and drivers' mates	10	220	106-405	24	201	129-300
Women							
003	Personnel managers etc.	5	473	154-1105			
010	Teachers in higher education				7	161	65-332
011	Teachers, nec				95	125	101-153

Table 4 Job codes with significantly high PRRs and PMRs for multiple myeloma. Men and women aged 20-74 years, England, 1991-2000.

Job group		Deaths		
SIC code	**Description**	**Observed**	**PMR**	**95%CI**
Men				
010	Teachers in higher education	61	134	102-172
011	Teachers, nec	100	135	110-164
038	Production & maintenance managers	165	118	101-138
087	Synthetic fibre makers	4	430	117-1101
103	Other workers in fabrics	7	265	106-545
124	Machine tool operatives	172	122	105-142
153	Coach & vehicle body builders	13	213	114-365
169	Builders, building contractors	113	132	109-158
Women				
011	Teachers, nec	161	135	114-157
142	Other electrical/electronic trades	5	418	136-975

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. IARC have classified one occupational agent as a Group 2A carcinogen for multiple myeloma (Table 5). Siemiatycki *et al*, (2004) summarised the evidence used in the classification of these agents and substances as suggestive. Other exposures and industries/occupations thought to be associated with an increased risk of myeloma include exposure to ionising radiation, benzene and other organic solvents, asbestos, engine exhaust and metals, and work in petroleum refining and distribution, rubber and plastics manufacturing, paint-related occupations and wood products industries.

Table 5 Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Vols 1-98 (IARC, 1972-2007), into Groups 1 and 2A, that have the multiple myeloma as the target organ.

Agents, Mixture, Circumstance	**Main industry, Use**	**Evidence of carcinogenicity in humans***	**Strength of evidence$**	**Other target organs**
Group 1: Carcinogenic to Humans				
Agents, groups of agents				
None identified				
Exposure circumstances				
None identified				
Group 2A: Probably Carcinogenic to Humans				
Agents & groups of agents				
Non-arsenical insecticides	Production; pest control & agricultural workers; flour & grain mill workers	Limited	Suggestive	Brain Leukaemia Lung NHL
Exposure circumstances				
None identified				

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

2.1 EXPOSURES

2.1.1 Non-arsenical insecticides

Many epidemiological studies, both cohort and case-control, have investigated the relationship between agricultural work and myeloma (Alexander *et al*, 2007, de Roos *et al*, 2006). They have consistently found that workers, specifically farmers, have lower all-cause and lower all-cancer mortality rates than the general population (Acquavella *et al*, 1998, Blair *et al*, 1992). Those studies that have reported a risk for myeloma have reported estimates exceeding 1.0 with overall or for specific subgroups (Blair *et al*, 2005, Blair *et al*, 2007, Boffetta *et al*, 1989b, Cantor and Blair, 1984, Cuzick and De Stavola, 1988, Demers *et al*, 1993, Franceschi *et al*, 1993, Heineman *et al*, 1992, Keller and Howe, 1994, La Vecchia *et al*, 1989, Lee *et al*, 2002, Miligi *et al*, 1999, Pearce and Howard, 1986, Pottern *et al*, 1992, Pukkala and Notkola, 1997, Reif *et al*, 1989, Ronco *et al*, 1992, Semenciw *et al*, 1993, Wiklund and Dich, 1987).

However, interpretation of the results from studies examining the link between farming and myeloma is limited by the broad exposure classification of farming as an occupational group. In addition, besides pesticides, farmers are exposed to many other things including paints, solvents, etc. (Blair *et al*, 1985, Pearce *et al*, 1989).

A number of meta-analyses have been carried out on papers that have assessed the association between farmers as an occupational group and cancer. In one that included 12 studies published between 1977 and 1990, relative risk estimates (RR) ranged from 0.4 to 2.5, with a summary RR of 1.12 (95%CI=1.04-1.21) (Blair *et al*, 1992). In a second analysis, (Khuder and Mutgi, 1997) of 32 studies published between 1981 and 1996, a random-effects summary RR of 1.23 (95%CI=1.14-1.32) was obtained. In a third analysis of 22 studies (16 follow-up; 11 PMR; 7 case-control, and 1 other) published through 1994 a summary RR of 1.09 (95%CI=0.99-1.19) was recorded (Acquavella *et al*, 1998). White male farmers were shown to have a significant risk (SMR=1.10, 95%CI=1.01-1.21), and the risk was greater than 1.0 irrespective of the study design. No heterogeneity was observed. The authors also re-analysed the information using the studies examined by Blair et al (1992), and obtained a summary RR of 1.10 (95%CI=1.01-1.21). A recent study of 13 case-control studies that examined pesticide-related occupations observed a non-significant increase in myeloma risk (OR=1.16, 95%CI=0.99-1.36) (Merhi *et al*, 2007). However, although there was no sign of heterogeneity there was an indication that publication bias existed. The authors undertook a process to correct for this with the result of a decrease in the OR to 1.12 (95%CI=0.96-1.30). Nevertheless, this study only included two studies in their analysis.

Individuals involved in the production of insecticides may also be exposed. Jones et al. (2009) have carried out a systematic review and meta-analysis in 25 studies of crop protection production manufacturing workers. The study included a number of studies from Europe, USA and China. The summary risk estimate for myeloma was 1.26 (95%CI=0.89-1.77). In a sub-group of 20 cohorts of workers involved in the manufacture of phenoxy herbicides the summary risk estimate was 1.24 (95%CI=0.82-1.86).

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 22938 members of the American Federation of Grain Millers were followed from 1955 to 1985 observed six deaths amongst workers in flour mills (SMR=0.98, 95%CI=0.36-2.13) and four among workers in other grain industries (SMR=1.01, 95%CI=0.28-2.59) (Alavanja *et al*, 1990).

2.1.2 Other Exposures

Ionising Radiation:

Early studies of survivors of the Hiroshima and Nagasaki atomic bombs have shown a dose-response risk (Shimizu *et al*, 1990) between ionising radiation (IR) and myeloma; however, more comprehensive analyses have shown no relationship (Preston *et al*, 1994). Similarly, early studies of occupational groups, including nuclear and radiology workers suggested an increased risk (Cuzick, 1981). However, more recent studies at the United Kingdon Atomic Energy Authority (UKAEA) (SMR=0.88, 95%CI=0.63-1.20) (Atkinson *et al*, 2004), Sellafield (Douglas *et al*, 1994), nuclear and medical radiation industries (Unlagged: SMR=0.74, 95%CI=0.53-1.01; Lagged: SMR=0.76, 95%CI=0.53-1.06) (Muirhead *et al*, 1999) observed no relationship. A combined analysis of mortality in three UK nuclear industry workforces showed a modest association between external radiation dose and risk of myeloma (SMR=1.08, 95%CI=0.70-1.60) (Carpenter *et al*, 1994).

Benzene and other organic solvents

The risk of myeloma from exposure to benzene is not convincing, some studies showing an increased risk (Ireland *et al*, 1997, Rinsky *et al*, 2002), whilst others have not (Hayes *et al*, 1997, Heineman *et al*, 1992, Linet *et al*, 1987). Two meta-analyses of different industries with probable exposure to organic solvents have shown different results, one a slightly increased risk

(SMR=1.1, 95%CI=0.8-1.6) (Chen and Seaton, 1996) the other a slightly decreased risk (Meta-OR=0.7, 95%CI=0.6-0.9) (Sonoda *et al*).

Petroleum Refining and Distribution

Petroleum workers are exposed to PAHs and various solvents that historically may have included benzene. A meta-analysis of cohort studies found that workers were at no increased risk of death from myeloma (SMR=0.9, 95%CI=0.8-1.1) (Wong, 1995). However, an incidence study of an Australian cohort found a 2.2-fold (95%CI=0.6-5.6) increased risk in men employed five years or longer (Christie *et al*, 1991a, Christie *et al*, 1991b). Results from case-control studies have varied, some risk being increased and others decreased (Cuzick and De Stavola, 1988, Demers *et al*, 1993, La Vecchia *et al*, 1989, Linet *et al*, 1987).

Rubber and Plastics Manufacturing

Rubber workers can be exposed to organic solvents, plastic monomers, rubber additives, and asbestos, and again historically benzene. Greater than expected numbers of deaths from multiple myeloma were observed in a number of studies (Divine and Hartman, 2001, Wilczynska *et al*, 2001), whereas no association was found in a British rubber worker cohort (SMR=0.73, 95%CI=0.45-1.11) (Sorahan *et al*, 1989) or a North American cohort (SMR=0.95, 95%CI=0.62-1.40) (Sathiakumar *et al*, 2005). A meta-analysis of case-control studies also found no association (OR=1.1, 95%CI=0.9-1.3) (Sonoda *et al*).

Paint-Related Occupations

Painters are exposed to dyes and pigments, aromatic and aliphatic hydrocarbons, and low molecular weight solvents such as trichloroethylene and methylethyl ketone. Many studies, both cohort (Lundberg, 1986, McLaughlin *et al*, 1988) and case-control (Cuzick and De Stavola, 1988, Demers *et al*, 1993) have shown an increased risk (ranging from 1.6 to 5.5) of myeloma and a history of paint-related occupations; others have found decreased risk (ORs ranging from 0.7 to 1.0) (La Vecchia *et al*, 1989, Pottern *et al*, 1992). In one study duration of employment was shown to increase the risk of myeloma, and dyes and inks were said to be associated (<10 years: OR=1.4, 95%CI=0.6-2.8; more than 10 years: OR=4.1, 95%CI=1.8-10.0) (Demers *et al*, 1993). A meta-analysis of 17 studies reporting printing exposure and cancer mortality obtained a combined SMR of 1.73 (95%CI=0.82-3.67) (Chen and Seaton, 1998).

Wood Products Industries

Work in these industries may involve exposure to wood dust, chemicals used to treat wood, adhesives, paints and stains. Studies of workers have been inconsistent. A pooled analysis of cohort studies have suggested an increased risk ((SMR=1.3, 95%CI=0.9-1.9) (Demers *et al*, 1995), whereas case-control studies suggest little or no altered risk (Cuzick and De Stavola, 1988, La Vecchia *et al*, 1989, McLaughlin *et al*, 1988, Pottern *et al*, 1992).

Asbestos

Early case reports suggested a link between asbestos exposure and an increased risk of myeloma, however, a recent meta-analysis of case-control studies from the US and Europe observed only a slightly increased myeloma risk associated with asbestos exposure (OR=1.2, 95%CI=1.0-1.4) (Becker *et al*, 2001).

Engine Exhaust

Numerous studies, both cohort and case-control, have observed an increased myeloma risk with a history of occupational exposure to diesel engine exhaust (Boffetta *et al*, 1989a, Boffetta *et al*, 1989b, Hansen, 1993, Pottern *et al*, 1992). A meta-analysis of studies found a slightly elevated

summary odds ratio of 1.34 (95%CI=1.14-1.57) (Sonoda *et al*), based on self-reported exposure or exposure inferred from job titles.

Metals

A number of studies have found an increased myeloma risk in workers exposed to metals (Cuzick and De Stavola, 1988, Gallagher and Threlfall, Teta and Ott, 1988), although there is limited information about exposure to specific metals in relation to the disease. Other studies have found no relation (La Vecchia *et al*, 1989, Pottern *et al*, 1992).

Others

Studies have found an increased risk of myeloma amongst fire-fighters, welders, embalmers, funeral directors and fishermen (de Roos *et al*, 2006).

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

Table 6 shows substances considered in the estimation of the attributable fraction (AF) for multiple myeloma.

Table 6 Substances considered in the estimation of the attributable fraction for multiple myeloma

Agents, Mixture, Circumstance	AF calculation	Strength of evidence	Comments
Group 1: Carcinogenic to Humans			
Agents, groups of agents			
None identified			
Exposure circumstances			
None identified			
Group 2A: Probably Carcinogenic to Humans			
Agents & groups of agents			
Non-arsenical insecticides	Yes	Suggestive	
Exposure circumstances			
None identified			

Data Relevant to the Calculation of AF

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

The RR chosen from a 'best study' source is described for each exposure, with justification of its suitability. Information on the 'best study' and independent data sources for the proportion of the population exposed are also summarised for each exposure in the appropriate section below. 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 forms 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 estimated by extrapolating from a point estimate of exposed workers taken from the period. If this is from CAREX relating to 1990-93, an adjustment is made to take account of gross changes in employment levels, which have occurred particularly in manufacturing industry and the service sector across the REP. 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 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 multiple myeloma, Great Britain, 2005 = 1065 for men aged 15-84 (978 in England and Wales, 87 in Scotland), 704 for women aged 15-79 (642 in England and Wales, 62 in Scotland)

- Total registrations for multiple myeloma, Great Britain, 2004 = 1863 for men aged 15-84 (1560 in England, 140 Wales, 163 in Scotland), 1143 for women aged 15-79 (954 in England, 85 Wales, 104 in Scotland).

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

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

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

3.2 NON-ARSENICAL INSECTICIDES

3.2.1 Risk estimate

Flour and grain mill workers will be considered to have very low risk, as demonstrated by Alavanja *et al.* (1990); the following risk estimate from this paper will be used for this industry 1.01 (95%CI=0.50-1.81).

Acquavella and colleagues (1998) conducted a meta-analysis of 37 studies that assessed whether farmers were at a greater risk of any cancer. A total of 22 of these studies examined the risk of multiple myeloma. The studies were based in Canada, USA, Europe and one from New Zealand. A meta-RR of 1.09 (95%CI=0.99-1.19) was obtained using a random-effects model. The meta-RR for follow-up studies (1.04, 95%CI=0.84-1.28), PMR studies (1.13, 95%CI=1.06-1.22) and case-control studies (1.10, 95%CI=0.90-1.33) were all similar, the latter two showing no significant heterogeneity. The overall meta-RR will be applied to farm and other agricultural workers, gardeners, pest control workers.

The summary risk estimate of Jones *et al.* (2009) will be used in the AF calculation for those involved in pesticide production. This is a large meta-analysis of 25 studies from Europe, USA and elsewhere. The RR is 1.26 (95%CI=89-.77).

3.2.2 Numbers exposed

The number of workers employed in the occupations above is given below in Table 7 and were obtained from the LFS.

Table 7 Numbers of workers in different industries with potential for exposure to non-arsenical insecticides (Source: Labour Force Survey).

SIC code	Job title	Number Employed		
LFS 1991		**Men**	**Women**	**Total**
A-B	Farm owners & managers, horticulturalists	206038	29240	235278
	Other managers farming, horticulture, forestry & fishing	11066	6497	17563
	Farm workers	100734	41772	142506
	Agricultural machinery drivers & operators	20233	358	20591
	Other occupations in farming and related	17271	19345	36616
	Forestry workers	19254	709	19963
	Horticultural trades	17816	12555	30371
	Gardeners, Groundsmen, groundswomen	131964	7459	139423
		524376	**117935**	**642311**
C-E	Formulated pesticides	1343	1084	2427
C-E	Grain milling	6187	1197	7384

3.2.3 AF calculation

The estimated total (male and female) attributable fraction for multiple myeloma associated with occupational exposure to non-arsenical insecticides is 0.30% (95%CI= 0.00-0.64), which equates to 6 (95%CI=0-12) deaths and 10 (95%CI=0-21) registrations.

The estimated AF for men is 0.45% (95%CI=0.0%-0.97%) resulting in 5 (95%CI=0-10) and 8 (95%CI=0-18) attributable deaths and registrations respectively, and for women is 0.14% (95%CI=0.00-0.29), resulting 1 (95%CI=0-2) and 2 (95%CI=0-3) attributable deaths and registrations respectively (Table 8).

Table 8 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 *et al.* (1998)	Farming, forestry and horticulture	A-B	1.09	524376			1139943	0.0496	0.0044	0.0000	0.0096	5	0	10	8	0	18
			All		524376			1139943	0.0496	0.0044	0.0000	0.0096	5	0	10	8	0	18
	Alavanja *et al.* (1990)	Flour, grain milling	C-E	1.01	6187	1	0.09	15895	0.0007	0.0000	0.0000	0.0006	0	0	1	0	0	2
			All		6187			15895	0.0007	0.0000	0.0000	0.0006	0	0	1	0	0	2
	Jones *et al.* (2009)	Pesticide manufacture	C-E	1.26	1343	1	0.09	3450	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
			All		1343			3450	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		All	All		531906			1159288	0.0504	0.0045	0.0000	0.0097	5	0	10	8	0	18
Women	Acquavella *et al.* (1998)	Farming, forestry and horticulture	A-B	1.09	117935	1	0.1	340563	0.0147	0.0013	0.0000	0.0029	1	0	2	2	0	3
			All		117935			340563	0.0147	0.0013	0.0000	0.0029	1	0	2	2	0	3
	Alavanja *et al.* (1990)	Flour, grain milling	C-E	1.01	1197	1	0.14	4409	0.0002	0.0000	0.0000	0.0002	0	0	0	0	0	0
			All		1197			4409	0.0002	0.0000	0.0000	0.0002	0	0	0	0	0	0
	Jones *et al.* (2009)	Pesticide manufacture	C-E	1.26	1084	1	0.14	3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
			All		1084			3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		All	All		120216			348966	0.0151	0.0014	0.0000	0.0029	1	0	2	2	0	3

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

4 OVERALL ATTRIBUTABLE FRACTION

4.1 EXPOSURE MAP

No exposure map is given since there is only one exposure substance.

4.2 SUMMARY OF RESULTS

The results are summarised in Tables 9 and 10.

Table 9 Summary of relative risks used to calculate AF

Agent	Exposure	RR	LL	UL
Non-arsenical insecticides	Flour, grain milling	1.01	0.5	1.81
Non-arsenical insecticides	Farming, forestry and horticulture	1.09	0.99	1.19
Non-arsenical insecticides	Pesticide manufacture	1.26	0.89	1.77

Table 10 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)
Non-arsenical insecticides	1159288	348966	0.0504	0.0151	0.0045	0.0000	0.0097	0.0014	0.0000	0.0029	5	1	8	2

4.3 EXPOSURES BY INDUSTRY/JOB

Table 11 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent.

Table 11 Industry/occupation codes by agent

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)
Non-arsenical insecticides	Farm owners & managers, horticulturalists	206038	29240	3	2	0	0
Non-arsenical insecticides	Farm workers	100734	41772	2	1	1	0
Non-arsenical insecticides	Other occupations in farming and related	17271	19345	0	0	0	0
Non-arsenical insecticides	Gardeners, Groundsmen, groundswomen	131964	7459	2	1	0	0
Non-arsenical insecticides	Total	531906	120216	8	5	2	1

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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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HSE

Health and Safety Executive

The burden of occupational cancer in Great Britain

Multiple myeloma

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 multiple myeloma 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 multiple myeloma related to overall occupational exposure is 0.30% (95%Confidence Interval (CI)= 0.00-0.64), which equates to 6 (95%CI= 0-12) deaths and 10 (95%CI= 0-21) registrations.

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