Health and Safety Executive

The burden of occupational cancer in Great Britain

Cancer of the larynx

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Research Report

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Cancer of the larynx

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

The estimated total (male and female) attributable fractions, deaths and registrations for cancer of the larynx related to occupational exposure is 2.61% (95% Confidence Interval (CI)=0.83-4.32), which equates to 20 (95%CI=5-101) attributable deaths and 56 (95%CI=8-101) attributable registrations.

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EXECUTIVE SUMMARY

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

Asbestos, mustard gas, and strong inorganic mists containing sulphuric acid have has been classified by IARC as a definite human carcinogen for laryngeal cancer and work in the rubber industry has been classified by IARC as a probable human carcinogen. Historical exposure to asbestos occurred in manufacture of, insulation, among cement workers, vermiculite workers, miners and millers, railroad car construction workers, shipyard workers, and asbestos textile workers. Current exposure occurs particularly in the construction industry. Workers exposure to strong inorganic acid mists can occur during production of isopropanol and ethanol, steel pickling, battery manufacture and sulphuric acid production, and manufacture of soaps and detergents. Mustard gas exposure occurred to workers employed in manufacture before the Second World War. As very few workers have been exposed since no estimation has been carried out for this carcinogen. Other exposures that have been considered as possible risk factors for cancer of the larynx include metal working fluids and wood dusts.

Due to assumptions made about cancer latency and working age range, only cancers in ages 25+ in 2005/2004 could be attributable to occupation. For Great Britain in 2005, there were 605 total deaths in men aged 25+ and 161 in women aged 25+ from laryngeal cancer; in 2004 there were 1748 total registrations for laryngeal cancer in men aged 25+ and 364 in women aged 25+.

The estimated total (male and female) attributable fractions, deaths and registrations for cancer of the larynx related to occupational exposure is 2.61% (95% Confidence Interval (CI)=0.83-4.32), which equates to 20 (95%CI=5-101) attributable deaths and 56 (95%CI=8-101) 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 cancer of the larynx associated with exposure to asbestos is 0.37% (95%CI=0.17-0.60), which equates to 3 (95%CI=1-5) deaths and 8 (95%CI=4-13) registrations.

The estimated total (male & female) attributable fraction for cancer of the larynx associated with occupational exposure to strong inorganic acid mists is 2.13% (95%CI=0.77-4.76), which equates to 16 (95%CI=6-36) attributable deaths and 46 (95%CI=17-102) attributable registrations of laryngeal cancer.

The estimated total (male & female) attributable fraction for cancer of the larynx associated with work in the rubber industry is 0.12% (95%CI=0.00-0.44), which equates to 1 (95%CI=0-3), attributable death and 3 (95%CI=0-10) attributable registrations of laryngeal cancer.

CONTENTS

1. INCIDENCE AND TRENDS

Laryngeal cancer (ICD-9 161; ICD-10 C32) is the eighteenth worldwide most common cancer with an estimated 159,000 new cases (about 2% of the total world cancer cases) and 90,000 deaths in the year 2002 (Parkin *et al*. 2005). In the UK, 2,166 (1,789 males and 377 females) new cases and 786 (620 males and 166 females) deaths have been reported for the year 2004. It is usually squamous and arises in three locations: glottic (vocal cords), supraglottic, and subglottic. Most laryngeal cancers originate in the glottis (ICD-9 161.0; ICD-10 C32.0). Supraglottic cancers are relatively rare (ICD-9 161.1; ICD-10 C32.1), and subglottic tumours are least frequent (ICD-9 161.2; ICD-10 C32.2). This disease is markedly more frequent in males than in females (Rafferty *et al,* 2001) and there is a large geographic variability in disease frequency.

In the UK and Ireland in the 1990s, laryngeal cancer accounted for around 1 in 70 diagnosed cases of cancer. Overall, the age-standardized incidence rate (using the European standard population) was 6.3 per 100,000 males and 1.2 per 100,000 females (Quinn *et al,* 2005). Moreover, cancer of the larynx is a disease that mainly affects elderly people. Incidence was considerably lower than the overall rate in those aged under 50, and then rose rapidly to peak in those aged 75-79 (29.4 per 100,000 males in 2004, Cancer Research UK, 2007). Within the countries of the UK, the highest incidence rates for cancer of the larynx occurred in Scotland, where the age-standardized incidence in males was 57% higher than the average (8.3 versus 5.3) in 2004. Incidence rates were closer to the average in the other constituent countries. However, Quinn *et al.* (2005) observed a large variability within England, where there was a very clear North-South divide (with incidence rates being higher than average in the North West, and Northern and Yorkshire regions), as well as between the health authorities within a country or region. The geographical variations in incidence are likely to reflect the corresponding variation in the historical patterns of prevalence of smoking and alcohol consumption, both of which are established risk factors. Patterns of mortality across the UK and Ireland were similar to those of incidence: the highest mortality rate was seen in Scotland.

Time trends in incidence and mortality are presented in Tables 1 and 2, respectively. There was a little apparent variation in the incidence among males with a peak in 2000 (6.6 per 100,000 males). After 2000, it seems to decrease with an incidence rate of 5.8 in 2004. Among females, the rate was relatively stable.

Table 1: Laryngeal cancer registration trends in England and Wales for 1992-1994, in England only for 1995-2004 (source: Office of National Statistics, 2007)

Year	Males				Females			
	Total*	Laryngeal cancer	% total	Rate** /100,000	Total*	Laryngeal cancer	% total	Rate** /100,000
1992[&]	109,336	1,681	1.5	6.7	112,247	365	0.3	1.4
1993[&]	109,414	1,597	1.5	6.3	109,891	398	0.4	1.5
1994[&]	112,145	1,714	1.5	6.8	112,175	362	0.3	1.4
1995[#]	103,986	1,449	1.4	6.0	105,151	345	0.3	1.4
1996[#]	104,103	1,471	1.4	6.1	105,461	328	0.3	1.3
1997[#]	104,335	1,482	1.4	6.1	107,289	330	0.3	1.3
1998[#]	106,745	1,461	1.4	6.0	109,957	329	0.3	1.3
1999[#]	108,827	1,451	1.3	5.9	112,237	318	0.3	1.3
2000[#]	111,543	1,578	1.4	6.6	112,066	325	0.3	1.3
2001[#]	112,516	1,477	1.3	6.1	112,134	328	0.3	1.3
2002[#]	112,579	1,374	1.2	5.7	112,210	300	0.3	1.2,
2003[#]	112,732	1,380	1.2	5.7	114,740	318	0.3	1.2,
2004[#]	117,805	1,424	1.2	5.8	115,816	269	0.2	1.1
Average	**109,697**	**1,503**	**1.4**	**6.1**	**110,875**	**332**	**0.3**	**1.3**

* all cancers excluding non-melanoma skin cancer (nmsc), all ages

** crude rate per 100 000 population of newly diagnosed cases, all ages

[&] England and Wales

[#] England only

Table 2 Laryngeal cancer mortality trends in England and Wales for 1999-2005 (source: Office of National Statistics, 2007)

Year	Males				Females			
	Total*	Laryngeal cancer	% total	Rate** /1,000,000	Total*	Laryngeal cancer	% total	Rate** /1,000,000
1999	264,299	584	0.22	22	291,819	156	0.05	6
2000	255,547	570	0.22	21	280,117	139	0.05	5
2001	252,426	612	0.24	22	277,947	142	0.05	5
2002	253,144	584	0.23	21	280,383	148	0.05	5
2003	253,852	571	0.22	18	284,402	150	0.05	4
2004	244,130	534	0.22	17	268,411	136	0.05	3
2005	243,324	524	0.22	17	269,368	136	0.05	3
Average	**252,389**	**568**	**0.23**	**19.7**	**278,921**	**144**	**0.05**	**4.4**

* number of deaths, all causes, all ages

** crude rate per 1,000,000 population

Survival from cancer of the larynx in England and Wales is moderately good. Based on male patients diagnosed in 2000-2001, the age-standardized 1-year relative survival rates was 85% and after 5 years of 65%. Survival was poorer for females than males (Quinn *et al*, 2005).

Incidence data available from population-based registries on five continents vary considerably (Parkin et *al*, 2005). The disease is markedly more frequent in males than in females with a male:female ratio of 12:1 and 6:1 in developing and developed countries, respectively. For men, high-risk countries were found in Southern Europe (France, Italy and Spain, with an age-adjusted incidence rate of 10.8, 10.2 and 12.8 respectively for the year 2002), Eastern Europe (Russia, Ukraine, and Poland), South America (Uruguay, Argentina, and Brazil) and Western Asia (Turkey, Iraq). In comparison, incidence rates for men were lower than 5 per 100,000 in most registries in Africa, China, Japan, Northern Europe, UK, and Canada. Among females, the age-adjusted incidence rates are usually less than 1 per 100,000 and vary a little. Mortality rates from laryngeal cancer are prone to error due to difficulty in distinguishing between larynx and hypopharynx, but similar patterns emerge to those of incidence (Bray *et al*, 2002).

2. OVERVIEW OF AETIOLOGY

2.1 INTRODUCTION

The main risk factors for cancer of the larynx are tobacco and alcohol, each of which has a multiplicative effect (Altieri *et al*, 2005, IARC 2004, Pelucchi *et al*, 2006).

Case-control and cohort studies have consistently reported an elevated risk of laryngeal cancer in current smokers compared with people who have never smoked. Moreover, these studies found that the increase in RR was directly related to the numbers of cigarettes smoked and the duration of smoking (IARC, 2004). A pattern of decreasing risk with increasing time since smoking cessation has been reported. Tobacco smoking is estimated to cause two-thirds of all cases in men (Pelucchi *et al*. 2006). A recent Italian case-control study, including 527 cases and 1,297 hospital controls, found that 90% of cases could be attributable to tobacco (Altieri *et al,* 2002).

A meta-analysis of 20 case-control studies of laryngeal cancer (Bagnardi *et al*, 2001), including 3,759 cases, reported a strong direct relationship between alcohol consumption and risk of laryngeal cancer with a significant trend: people who consumed 25, 50 or 100g of alcohol per day had RRs of 1.38 (95%=1.32-1.45), 1.94 (1.78-2.11), 3.95 (3.43-4.57), respectively. When restricted to studies that reported adjustment for tobacco, a pooled RR of 2.8 (2.4-3.3) for 100g of alcohol per day was found. Despite the dose-response pattern with amount of drinking, studies have not found a clear trend of increasing duration with increasing risk. After stopping drinking, some fall in risk becomes apparent in the long term (more than 20 years) (Altieri *et al,* 2002, Altieri *et al,* 2005)). The supraglottis is more closely related to alcohol consumption, as compared to the glottis/subglottis.

In summary, tobacco is the best-described and most important risk factor for laryngeal cancer (Olshan, 2006). The reported effect estimates have been generally strong, consistent, and show a pronounced dose-response relationship. The etiologic role of alcohol is less clear, but evidence suggests both a weaker dependant and a joint effect with tobacco. From these findings, tobacco and alcohol should be controlled when assessing epidemiologic evidence for associations between occupational exposures and laryngeal cancer.

The Occupational Health Decennial Supplement (Drever, 1995) examined mortality (1979-1980, 1982-1990) and cancer incidence (1981-1987) in men and women aged 20-74 years in England and differences in mortality between job groups appeared to be determined mainly by non-occupational influences. Table 3 gives the significantly high PRRs and PMRs for laryngeal cancer, by job group and gender. The high proportional registration risk (PRR) among men employed as publicans and bar staff, and possibly also seafarers, may reflect drinking and smoking habits of individuals in these occupations. A high proportional mortality risk is also found for publicans and bar staff. The PRRs for petrol pump attendants and coach painters may also be worth noting (risks based on few numbers of registrations).

Table 3 Job codes with significantly high PRRs and PMRs for laryngeal cancer. Men and women aged 20-74 years, England

Job group		Registrations	PRR*	95% CI	Deaths	PMR**	95% CI
SIC code	**Description**	**(1981-87)**			**(1979-1980 and 1982-90)**		
Men							
036	Seafarers	33	173	119-243	67	242	188-307
043	Fishmongers and poultry	9	219	100-417			
045	Publicans and bar staff	75	194	153-244	119	262	217-314
051	Launderers and dry cleaners	8	233	101-461			
055	Petrol pump attendants	6	368	135-801			
066	Fishing and related workers				14	279	152-467
120	Other metal manufacturers	27	154	102-225	40	153	109-208
146	Metal plate workers				37	205	144-283
147	Steel erectors				21	182	112-278
150	Riggers				12	219	113-383
158	Coach painters	5	365	119-853			
173	Mains and service layers				16	224	128-364
183	Lorry drivers				249	132	116-150
194	Boiler operators				34	166	115-232
Women							
124	Machine tool operators	5	325	204-6080			

Source: Drever *et al.* (1995) Occupational Health Decennial Supplement
* $p<0.05$, based on at least 3 registrations. Adjusted for age, social class and region of registration
** $p<0.05$, based on at least 3 registrations. Adjusted for age and social class

The recent Occupational Health Decennial Supplement examined mortality for the period 1991-2000 in men and women aged 20-74 years in England (Table 4) (Coggon *et al*, 2009). For laryngeal cancer several of the jobs identified in the earlier supplement occur again, e.g. seafarers, publicans, fishermen and metal plating workers. Both supplements identify jobs within construction although the exact job groups vary. In the recent supplement painters, plasterers, roofers, other construction workers and crane drivers are highlighted for men. Publicans are identified for women as well as men in the recent supplement.

Table 4: Job codes with significantly high PMRs for cancer of the larynx. Men and women aged 20-74 years, England.

Job Group		**Deaths**	**Expected deaths**	**PMR**	**Lower 95% CI**	**Upper 95% CI**
SIC code	**Description**	**1991 - 2000**				
Men						
017	Nurses	16	8.5	188	108	306
036	Seafarers	61	24.1	253	194	325
045	Publicans and Bar Staff	100	36.1	277	225	337
046	Caterers	37	21.8	169	119	234
066	Fishing and related workers	12	4.7	257	133	449
146	Metal Plate Workers, Shipwrights, Riveters	31	14.3	216	147	307
160	Painters and decorators	95	74.4	128	103	156
167	Plasterers	30	14.9	202	136	288
168	Roofers and Glaziers	23	14.2	162	103	243
174	Other Construction workers	151	106.6	142	120	166
187	Crane Drivers	29	17.5	166	111	238
Women						
044	Retailers and Dealers	34	20.5	166	115	231
045	Publicans and Bar Staff	14	6.9	204	112	343
185	Bus Conductors and Driver's Mates	4	0.9	445	121	1139

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. Table 5 shows agents and exposure circumstances classified as Group 1 or 2A for laryngeal cancer. Siemiatycki *et al*. (2004) summarised the evidence used in the classification of these agents and substances as strong or suggestive and this is also given in Table 5. There is strong evidence that the following are occupational carcinogens: isopropanol manufacture, strong acid process; strong inorganic-acid mists containing sulfuric acid; and mustard gas. There is suggestive evidence that exposure to asbestos and the rubber industry is associated with an increased risk of work-related laryngeal cancer (Siemiatycki *et al*, 2004). A number of other chemicals, not classified group 1 or 2A laryngeal carcinogens, may be associated with laryngeal cancer, including metalworking fluids, e.g. straight oil metal working fluids (MWFs) (Calvert *et al*, 1998), Tolbert (1997) and wood dust (Ward *et al*, 1997).

Table 5 Occupational agents, groups of agents, mixtures, and exposure circumstances classified by the IARC Monographs, Vols 1-77 (IARC, 1972-2001), into Groups 1 and 2A, which have the larynx as target

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				
Asbestos	Mining and milling; by-product manufacture; insulating; shipyard workers; sheet-metal workers; asbestos cement industry	Sufficient	Suggestive	Lung Mesothelioma GI tract
Mustard gas	Production; used in research laboratories; military personnel	Sufficient	Strong	Lung Pharynx
Strong inorganic-acid mists containing sulfuric acid	Pickling operations; steel industry; petrochemical industry; phosphate acid fertilizer manufacturing	Sufficient	Strong	Lung
Exposure circumstances	**Suspected substance**			
Isopropanol manufacture, strong-acid process	diisopropyl sulfate; isopropyl oils; sulfuric acid	Sufficient	Strong	Paranasal sinuses Lung
Rubber industry	Aromatic amines; solvents	Sufficient	Suggestive	Bladder Stomach Leukaemia Lung
Group 2A: probably carcinogenic to humans				
None identified				

2.2 EXPOSURES

2.2.1 Asbestos

According to CAREX, approximately 95,000 workers were exposed to asbestos in Great Britain, primarily in the construction industry (48.5%), and also in personal and household services (23.2%) and other mining (14.8%). Exposure to asbestos is via inhalation or ingestion. All forms of asbestos, serpentine (chrysotile) and amphiboles (crocidolite, amosite, tremolite, etc.) are carcinogenic to humans, although the potency of chrysotile might be lower than that of other types (IARC (1987). However, the role of asbestos in causing laryngeal cancer remains controversial (Siemiatycki *et al*, 2004). Recent reviews (Browne and Gee, 2000, Edelman, 1989, Griffiths and Molony 2003, Wight *et al*, 2003) concluded that the evidence does not indicate that asbestos exposure increases the risk of laryngeal cancer; positive results are probably due to a missing or sufficient adjustment for alcohol and tobacco consumption. For case-control studies, associations were significant without adjustment for smoking and alcohol consumption, or borderline significant with these adjustments. Among cohort studies, no associations were found.

Goodman *et al*. (1999) reviewed 69 asbestos-exposed occupational cohorts, 42 in Europe, 22 in North America and the remainder elsewhere. The results of the study are therefore portable. The earliest study was published in 1967 and the most recent in 1997. The studies covered a variety of occupations, including: asbestos products manufacture (22%); cement workers (20%); shipyard workers (12%); asbestos miners and millers (10%); and textile workers (10%). The pooled analysis had 4 cohorts that provided results with latency and 27 without. Overall, the meta-SMR for laryngeal cancer, without taking into account latency and confounding factors (tobacco and alcohol), was 1.33 (95% CI=1.14-1.55), with a very high degree of homogeneity (p=0.99). In addition, a proxy of dosage exposure (using deaths from mesothelioma) showed no dose-response in laryngeal cancer. A weak association between laryngeal cancer and asbestos was concluded.

Browne and Gee (2000) reviewed 22 cohort studies including observed and expected numbers of laryngeal cancer deaths. The summary of all cohorts showed a mean SMR for laryngeal cancer of 1.08 (O=114, E=105.8); among these 22 studies, 17 are common with the meta-analysis by Goodman *et al*. (1999). In addition, 17 case-control studies were also reviewed (9 with adjustment for smoking and alcohol, 4 with adjustment for only smoking and 4 without adjustment): of the 17 studies, 8 showed no increase in relative risk; of the remaining nine, the increase in seven was not significant and the significance was only borderline in the 2 remaining (RR=1.8, 95% CI=1.0-3.4 (Olsen *et al,* 1984); RR=2.4, 95% CI=1.0-5.9 (Blot *et al*, 1980). The mean RR for 7 of the 9 case-control studies with adjustment for smoking and alcohol was 1.25. Two studies were not included in the meta-analysis: Elwood *et al*, 1984 did not give figures and mentioned that no indication of any substantial relationship was found; Zagraniski *et al*. (1986) used two methods, one based on self-reported exposure and the other one based on occupations but only the last one was retained.

Gustavsson *et al*. (1998) conducted a population-based case-control study in Sweden during 1988-1990, including 161 male cases of laryngeal cancer and 641 male controls. The study subjects were interviewed about several lifestyle factors (alcohol consumption and smoking habits) and a life history of occupations and work tasks; an occupational hygienist coded the exposure to 17 specific agents. After adjusting for alcohol and tobacco consumption, exposure to asbestos was associated with an increased risk of laryngeal cancer: the RR was 1.69 (95% CI=1.05-2.74) for the group of workers ever exposed to asbestos. In addition, a significant dose-response relation was present (ranging from RR=1.16 (1.02-1.32) for the lower class of exposure to RR=1.82 (1.08-3.04) for the highest class of exposure, p-value=0.02).

Marchand *et al*. (2000) conducted a hospital-based case-control study in France between 1989 and 1991. This study involved 315 male cases of laryngeal cancer and 315 male controls. The subjects' past occupational exposures to asbestos were evaluated based on their job history, with the aid of a job-exposure matrix. Exposure to asbestos resulted in a non-significant increase in the risk of laryngeal cancer (OR=1.24, 95% CI=0.83-1.90, adjustment for alcohol and tobacco consumption).

In the most recent cohort (Purdue *et al*, 2006), including 307,799 male workers followed during 1971-2001 in the Swedish construction industry, asbestos exposure was related to an increased laryngeal cancer incidence, with a RR of 1.9 (95% CI=1.2-3.1) for workers ever exposed to asbestos (adjustment for smoking). This association was stronger for workers with a moderate exposure level (RR=2.3, 95% CI=1.4-3.8); however, there were only two laryngeal cancers in the high-exposure group.

2.2.2 Mustard Gas

Mustard gas was used in chemical warfare during the First World War (but not in the Second World War). Currently, this chemical is not produced anymore, except in military research. The main routes of potential human exposure to mustard gas are inhalation and dermal contact; however, the general population is typically not exposed.

Based on the studies of manufacturers, mustard gas is clearly carcinogenic in humans (Blair and Kazerouni, 1997, IARC 1987). Laryngeal cancer among workers engaged in the manufacture of mustard gas has been studied in Japan (Nishimoto *et al*, 1988) and in England (Easton *et al*, 1988).

Nishimoto *et al*. (1988) studied 1,632 workers employed at a mustard gas factory between 1929 and 1945 and followed through 1980. There appeared to be an excess of cancer of the larynx but the SMR was not presented.

In a cohort study of 2,498 men and 1,032 women in England (Easton *et al*, 1988) followed up from 1945 to 1984, a significant increased mortality from laryngeal cancer (SMR=273, $p<0.001$) was found in workers employed in the manufacture of mustard gas during the second world war, compared with national death rates. The effect of smoking could not be controlled for. The SMR for laryngeal cancer was higher in workers employed for 3 or more years than in those employed for less than 3 years by a factor of 1.4 (323 versus 238); the difference in SMR was not significant. Moreover, no consistent relation with time since first exposure was found. In a previous study in this same manufacture, including 511 workers, Manning *et al*. (1981) reported a significant excess of laryngeal cancer (7 cases compared with 0.75 expected, $p<0.001$).

However, in the UK, manufacture of mustard gas ceased in the 1940s, and it is unlikely that attributable cases now occur in any number (Coggon, 1999). Indeed, CAREX estimated there were only 213 workers possibly exposed to this chemical in 1990-1993. The industries involved are education services (57%), research and scientific institutes (21%) and medical, dental, other health and veterinary services (22%).

2.2.3 Strong inorganic-acid mists containing sulfuric acid

An increased risk has been suggested in workers exposed to strong inorganic acid, e.g. sulfuric acid, in a number of industries, including production of isopropanol and ethanol, steel pickling, battery manufacture and sulfuric acid production, and manufacture of soaps and detergents, and treatment of metals. IARC, on the basis of numerous epidemiological studies, have stated the association with laryngeal cancer is sufficient (IARC, 1987) and the evidence of carcinogenicity was considered as strong by Siemiatycki *et al*. (2004). In 1997, a review of literature (Blair & Kazerouni (1997), based on 12 studies (6 cohort, 4 case-control, 1 PMR and 1 geographic correlation studies), considered that the risk of laryngeal cancer was consistently raised among exposed workers. Epidemiologic studies of cancer and sulfuric acid exposures, with adjustment for smoking and alcohol, are summarized in Table 6. Brown *et al*. (1988) failed to find an association; their study dichotomized exposure into “ever versus never exposed” and thereby reduced its ability to detect “high-level exposure” effects. Risks for laryngeal cancer rose to fourfold or more in heavily exposed workers and over longer periods (Soskolne *et al*, 1984, Soskolne *et al*, 1992); results were similar with and without adjustments for tobacco and alcohol. However, the most recent case-control study (Shangina *et al*, 2006) did not find an association between laryngeal cancer and exposure to inorganic acid mists.

According to CAREX, approximately 42,000 workers are exposed to strong inorganic acid mists in Great Britain, mainly in the manufacture of industrial chemicals (26.9%), fabricated metal products (13.0%), electrical machinery (11.3%) and in nonferrous metal basis industries (10.1%).

Table 6 Selected epidemiologic studies of sulfuric acid and laryngeal cancer (with adjustments for tobacco and alcohol)

Reference	**Industry /product**	**Country**	**Design**	**Study size Period**	**Exposure assessment**	**Results**
Cohort studies						
Steenland *et al*. (1988)	Metal treatment	US	Industry	1,156 M workers employed 1940-65 follow-up 1985-94	Duration	SIR=2.2 (1.2-3.7) CSIR=2.5 (O=14, E=5.6)
Case-control studies						
Brown *et al*. (1988)	Job history	US	Hospital	183 M cases diagnosed 1980-81 250 M controls	Industrial hygienist estimation	RR=0.76 (0.42-1.35) CRR=0.69 (Ca=22, Co=42)
Soskolne *et al*. (1984)	Chemical workers	US	Industry	30 M cases diagnosed 1944-80 175 M controls	Average level	Moderate level: OR=4.6 (0.83-25.4), p<0.10 High level: OR=13.4 (2.08, 86.0), p<0.05
Soskolne *et al*. (1992)	Job history	Canada	Population	204 cases diagnosed 1977-79 204 controls	Level, frequency, probability	OR=2.90 (1.62-5.20), p<0.001 Low: OR=1.91 (0.97-3.78) High: OR=4.28 (2.13-8.58), p<0.001
Shangina *et al*. (2006)	Job history	Romania Poland Russia Slovakia	Hospital	316 M cases diagnosed 1999-2002 728 M controls	Industrial hygienist estimation	OR=0.94 (0.60, 1.49)

Abbreviations: M, male; CRR/CSIR: crude RR/SIR

2.3 EXPOSURE CIRCUMSTANCES

2.3.1 Isopropanol manufacture, strong-acid process

Manufacture of isopropanol by the strong acid process has been linked with increased of laryngeal cancer (IARC, 1987). Currently, only one British company is thought to use this process, with a few relatively few workers involved (Coggon, 1999). Only one study reported results on the association between laryngeal cancer and “working in isopropanol production” (Teta *et al*, 1992). The authors observed excesses of laryngeal cancer, based on two cases only.

2.3.2 Rubber industry

The evidence of a carcinogenic risk in the rubber industry has been reviewed by IARC in 1982 (IARC, 1982) and in summary form in 1987 (IARC, 1987). They concluded that there was sufficient evidence that employment in this industry entails a carcinogenic risk for laryngeal cancer. The strength of the evidence was considered ‘suggestive’ by Siemiatycki *et al*. (2004). Kogevinas *et al*. (1998), Ward *et al*. (1997) and Wight *et al*. (2003) reviewed the literature and concluded that there was an excess risk, not significant but consistent between studies (Table 7). In a recent meta-analysis of mortality among workers in the synthetic rubber-producing industry (Alder *et al*, 2006), a meta-SMR for laryngeal cancer was 1.19 (95% CI=0.88-1.60), based on 13 cohort studies, with a high level of heterogeneity (p=0.01). In addition, they calculated a pooled estimate of 1.39 (95% CI=0.75-2.59) for incidence (3 studies).

Table 7 Epidemiological studies of rubber industry and laryngeal cancer

Reference	Country	Study size Period	Exposure assessment	Results
Industry-based cohorts (no adjustment for tobacco and alcohol)				
Bernardinelli *et al*. (1987)	Italy	4,917 M workers employed 1962-1972 follow-up 1962-1983	Job history	SMR=129 (O=2)
Negri *et al*. (1989)	Italy	6,629 M workers employed 1946-81 follow-up 1946-81	Job history	SMR=1.26 (0.67-2.16)
Solionova & Smulevich (1993)	Russia	3,670 workers employed 1979-83 follow-up 1979-88	Job history	SIR=88 (O=2, E=2.2) all M workers Production subgroup SIR=121 (O=2, E=1.6) Non production subgroup SIR=0 (O=0, E=0)
Last update: Sorahan *et al*. (1989)	UK	36,691 M workers employed 1946-60 job history 1976-85 mortality 1946-85	Job history	SMR=119 (O=33, E=27.8)
Weiland *et al*. (1998)	Germany	11,663 M workers employed 1910-91 mortality 1981-91	Job history	SMR=129 (69-221) Preparation of materials SMR=253 (93-551) Technical rubber goods SMR=106 (29-271) Tyres SMR=146 (40-373) Storage-dispatch SMR=0 (O=0) Maintenance SMR=154 (42-394) Others SMR=73 (O=1)
Straughan & Sorahan (2000) Last update:Dost *et al*. (2007)	UK	7,561 M workers employed 1982-91 follow-up 1983-2004	Job history	SMR=103 (3-574), O=E=1
Hospital-based case-control studies (with adjustment for tobacco and alcohol)				
Muscat & Wynder (1992)	US	194 M cases diagnosed 1985-90 184 M controls	Self-exposure assessment	RR=6.4 (0.8-7.9)
Zagraniski *et al*. (1986)	US	92 M cases diagnosed 1975-80 181 M controls	Job history	OR=2.0 (0.7-6.1)
Meta-analysis				
Alder *et al*. (2006)	World	16 cohorts (3 cancer incidence) 1966-2003		meta-SMR=1.19 (0.88-1.60) heterogeneity: p=0.01, 13 studies meta-SIR=1.39 (0.75-2.59) heterogeneity: p=0.58, 3 studies

2.4 OTHER EXPOSURES

The following occupational exposures are not included in IARC classification but some studies found that they are possible risk factors for laryngeal cancer.

Metalworking fluids

Mineral oils (mineral oils include metalworking fluids) are known to be human carcinogens based on sufficient evidence of carcinogenicity that exposure to these types of mineral oils causes cancer. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of untreated and mildly treated mineral oils in humans (IARC, 1984, IARC , 1987). Metalworking fluids (MWFs) are commonly used in variety of industrial machining and grinding operations. CAREX did not estimate the number of workers exposed to mineral oils or MWFs. According to Labour Force Survey (LFS), some 1.7 million workers (95% males) were exposed to mineral oils in 1979.

Several studies suggest that MWFs may be associated with laryngeal cancer (Calvert *et al*, 1998). In particular, the studies by Eisen *et al*. (1992), Eisen *et al*. (1994) and Tolbert *et al*. (1992) found that laryngeal cancer is associated with exposure to straight oil MWFs. Zagraniski *et al*. (1986) found that workers ever employed as a metal grinder or as a machinist had an elevated risk with OR of 2.1 (1.0,4.7) and 2.5 (1.2,5.2) respectively.

Wood dust

An IARC review of wood dust concluded that it was not a laryngeal carcinogen (IARC, 1995). However, occupations related to working with wood have been found to affect risk of laryngeal cancer (Ward *et al,* 1997) in case-studies, while cohort studies have not found excess mortality from laryngeal cancer. The most important association was found by Pollan and Lopez-Abente (1995): Workers in wood-related occupations (wood-workers and furniture workers) exposed over 20 years showed elevated risk (OR=5.63, 95% CI=1.15-6.64 for wood-workers; OR=6.67, 95% CI=1.05-42.57 for furniture workers subgroup) in a case-control study conducted in Madrid.

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

The substances considered in the estimation of the attributable fraction (AF) for cancer of the larynx are those outlined in Table 8.

Table 8 Substances considered in the estimation of the attributable fraction for cancer of the larynx

Agents, mixture, circumstance	AF calculation	Strength of evidence	Comments
Group 1: carcinogenic to humans Agents, groups of agents			
Asbestos	Y	Suggestive	
Mustard gas	N	Strong	Few workers possibly exposed
Strong inorganic-acid mists containing sulfuric acid	Y	Strong	
Exposure circumstances			
Isopropanol manufacture, strong-acid process	N	Strong	Number of workers not be identified clearly
Rubber industry	Y	Suggestive	

Data Relevant to the Calculation of AF

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

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

- Number of years in REP = 40

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

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

- Total deaths from cancer of the larynx in GB in 2005 = 605 for men aged 25+ (524 England and Wales and 81 Scotland), 161 for women aged 25+ (136 England and Wales and 25 Scotland).

- Total registrations for cancer of the larynx in GB in 2004 = 1748 for men aged 25+ (1424 England, 91 Wales and 233 Scotland), 364 for women aged 25+ (269 England, 24 Wales and 71 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 ASBESTOS

(a) Risk estimate

Goodman *et al*. (1999) reviewed 69 asbestos-exposed occupational cohorts, 42 in Europe, 22 in North America and the remainder elsewhere. The earliest study was published in 1967 and the most recent in 1997. The studies covered a variety of occupations, including: asbestos products manufacture (22%); cement workers (20%); shipyard workers (12%); asbestos miners and millers (10%); and textile workers (10%). The pooled analysis had 4 cohorts that provided results with latency and 27 without. Overall, the meta-SMR for those studies, without taking into account latency and confounding factors (tobacco and alcohol), was 1.33 (95% CI=1.14-1.55), with a very high degree of homogeneity (p=0.99). In addition, no evidence of a dose-response was observed. The disadvantage of this meta-analysis is that the most common cited occupations appear not to be included in the list of industries (see Table 9) in which workers are exposed to asbestos in Great Britain (CAREX, 1990-1993)

It might be more appropriate to use the RR from the case-control studies because CAREX numbers are probably more comparable with population-based case-control studies. Moreover, most case-control studies took into account confounding factors as tobacco and alcohol consumption. To improve information and precision from case-control studies the research team carried out a meta-analysis, and the details of this are summarised in Appendix 1.

The meta-analysis included 9 case-control studies (8 population based and 1 industry based) with adjustments for tobacco and alcohol consumption; of the 9 studies, 6 were included in the review by Browne and Gee (2000) and the 3 remaining studies were added after reviewing literature. Six studies were conducted in Europe and 3 in US. The results of these studies are therefore portable in UK. The earliest study (Olsen *et al,* 1984) was published in 1984 and the most recent (Dietz *et al*, 2004) in 2004. The case-control studies ranged in size from 92 cases (Zagraniski *et al*, 1986) to 326 cases (Olsen *et al,* 1984) of laryngeal cancer. The earliest year of diagnosis was 1975 (Zagraniski *et al*, 1986) and the latest was 2000 (Dietz *et al*, 2004). The pooled analysis for laryngeal cancer gave a meta-SIR of 1.38 (95% CI= 1.17-1.63) with homogeneity across studies (p-value=0.94). Four of the case-control studies presented results for larynx in relation to dose levels. The meta-SIR from the combined analysis of the highest category of exposure from these 4 studies was 1.48 (95% CI=1.10-1.97; test for heterogeneity: p = 0.65); for the lowest level of exposure the meta-SIR was 1.16 (95% CI=1.02-1.31; test for heterogeneity: p = 0.99). However, all four studies used different measures of exposure and cut-offs for categorization, and were carried out in 3 different countries and across different industries and jobs. It is questionable therefore whether these can be combined. Therefore, for the present study the figure from the overall meta-analysis (meta-SIR=1.37, 95% CI=1.17-1.60) was used to calculate the AF for the high exposure level. The relative risk for low exposure was based on a harmonic mean of the high/low ratios across all other cancer-exposures pairs in the overall project for which data were available. As this was less than 1 the RR for low exposure has been set to 1.

(b) Numbers exposed

Table 9 gives the number of workers exposed to asbestos by industry for the period 1990-1993 according to CAREX. For asbestos, it has been assumed that only men have been exposed in the high exposure level categories. The low exposed numbers in the service industries (category G-Q) have however been split between men and women, in the proportions of numbers employed at the 1991 Census in associate professional, technical, personal and customer service occupations (Standard Occupational Classification Major Groups 3, 6 and 7). The low exposed numbers in the SIC Main Industry Sector C-E have been split between men and women in the proportion of men employed in this main industry sector at the 1991 Census.

Table 9 Number of workers exposed to asbestos according to CAREX in 1990-1993, Great Britain

Main industry sector	Industry	Carex Data 1990-1993		Exposure level
		Number exposed	Number in industry	
C-E	Other Mining	14,075	28,150	L
	Manufacture of paper and paper products	577	119,050	H
	Manufacture of industrial chemicals	1,006	130,000	H
	Manufacture of other chemical products	1,077	175,175	H
	Petroleum refineries	588	18,075	H
	Manufacture of transport equipment	1,792	456,900	H
	Electricity, gas and steam	304	140,975	H
F	Construction	46,096	1,753,450	H
G-Q	Wholesale and retail trade and restaurants and hotels	4,046	4,459,525	L
	Land transport	2,660	671,050	H
	Sanitary and similar services	824	274,225	L
	Personal and household services	22,066	686,750	L
	Total	***95,111***	***8,913,325***	

	Main industry sector		% Male	
A-B	Agriculture, hunting and forestry; fishing			
	High	0		
	Low	0		
C-E	Mining/quarrying, electricity/gas/steam, manufacturing industry			
	High	5,344	100%	
	Low	14,075	71%	
F	Construction			
	High	46,096	100%	
	Low	0		
G-Q	Service industries			
	High	2,660	100%	
	Low	26,936	38%	

(c) AF calculation:

The estimated total (male and female) attributable fraction for cancer of the larynx associated with exposure to asbestos is 0.37% (95%Confidence Interval (CI)=0.17-0.60), which equates to 3 (95%CI=1-5) deaths and 8 (95%CI=4-13) registrations. The estimated AF for men is 0.47% (95%CI=0.22-0.76) resulting in 3 (95%CI=1-5) attributable deaths and 8 (95%CI=4-13) attributable registrations; and for women the AF is 0% resulting in 0 attributable deaths and 0 attributable registrations (Table 12).

Table 10 Summary results for occupational exposure to asbestos

				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	Meta-analysis (Appendix 1)	H	C-E	1.37	5344	1.4	0.09	25849	0.0013	0.0005	0.0002	0.0008	0	0	0	1	0	1
		H	F	1.37	46096	1	0.12	209244	0.0108	0.0040	0.0018	0.0065	2	1	4	7	3	11
		H	G-Q	1.37	2660	0.9	0.11	10002	0.0005	0.0002	0.0001	0.0003	0	0	0	0	0	1
		H	All		54100			245095	0.0126	0.0047	0.0022	0.0076	3	1	5	8	4	13
		L	C-E	1	13794	1.4	0.09	66720	0.0034	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	10236	0.9	0.11	38487	0.0020	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		24029			105207	0.0054	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		78129			350302	0.0181	0.0047	0.0022	0.0076	3	1	5	8	4	13
Women	Meta-analysis (Appendix 1)	L	C-E	1	282	1.5	0.14	2368	0.0001	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	G-Q	1	16700	0.8	0.15	79968	0.0038	0.0000	0.0000	0.0000	0	0	0	0	0	0
		L	All		16982			82336	0.0039	0.0000	0.0000	0.0000	0	0	0	0	0	0
		All	All		16982			82336	0.0039	0.0000	0.0000	0.0000	0	0	0	0	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

3.3 MUSTARD GAS

(a) Risk estimate

A strong association was found between laryngeal cancer and exposure to mustard gas in three studies. However, subjects were workers employed in manufactures before the Second World War, period where mustard gas was still produced and used**.**

(b) Numbers exposed

According to CAREX, only 213 workers were exposed to mustard gas for the period 1990-1993. This number exposed in the GB over the risk exposure period is therefore very small.

(c) AF calculation

The AF calculation is therefore omitted.

3.4 STRONG INORGANIC-ACID MISTS CONTAINING SULFURIC ACID

(a) Risk estimate

An industry-based case-control study in US (Soskolne *et al*, 1984)) and a cohort study of US male workers in pickling operations in the steel industry (Steenland *et al*, 1988)) found an excess of laryngeal cancer, even after adjusting for smoking and alcohol. These two studies were based on specific workers (chemical workers and metal treatment), with very high exposure level to sulfuric acid that does not represent all workers exposed to strong inorganic-acid mists. Brown *et al*. (1988) did not find any association with exposure to sulfuric acid (RR=0.76, 95% CI=0.42-1.35); with adjustment for smoking and alcohol, estimations were the same or increased. Shangina *et al*. (2006) evaluated many exposures and were not able to separate out risk for sulfuric acid; moreover, this study was conducted in four countries in Eastern Europe and the main results were found only in Poland then exposures could not be portable in Great Britain.

Soskolne *et al*. (1992) conducted a population-based case-control study in Canada, including 183 male laryngeal cases diagnosed between 1977 and 1979, and 183 male controls. Although it is based on the general population, exposure assessment was excellent. From the questionnaires, each work experience was extracted (including period, occupation, job title and employer) and a retrospective assessment of exposure to sulfuric acid for each job held by all the study subjects (blind of case or control status). No measurements were carried out for this study; however, discussions with various local hygiene and engineering experts were carried out to assist authors to assess the specificity of the local situation. The estimates reported by Soskolne *et al*. (1992) were adjusted for both alcohol and tobacco consumption. The exposure distribution of all of the study subjects is as following: 133 male cases and 94 male controls were exposed to sulfuric acid; among the exposed cases, 60 were classified with a low exposure level and 73 with a high exposure level. The study-based estimate of the proportion of exposed male cases was 73%; for exposed male controls, this proportion was estimated at 51%. The study was restricted to the men, then the proportions were not calculated for the women. A strong association was found with exposure to sulfuric acid (OR=2.90, 95% CI=1.62-5.20), with a dose-response relationship (low exposure: OR=1.91, 95% CI=0.97-3.78; high exposure: OR=4.28, 95% CI=2.13-8.58); this one was stronger for duration of exposure above 10 years (low exposure: OR=2.23, 95% CI=1.07-4.64; high exposure: OR=5.24, 95% CI=2.48-11.10) and after a lag period of 5 years. In the present study, figures from the dose-response relationship and without lag period were chosen for the RRs; for low exposure: OR=1.91, 95% CI=0.97-3.78; for high exposure: OR=4.28, 95% CI=2.13-8.58.

(b) Number exposed

The numbers of workers exposed to strong inorganic-acid mists containing sulfuric acid, according to CAREX and for the period 1990-1993, are given in Table 11. For this agent, the exposed numbers have been divided between men and women on the assumption that the CAREX exposed numbers were "blue-collar" workers (SOC Major Groups 5, 8 and 9) with low exposure level in the service industries

(SIC Major Industry Sector G-Q). It has also been assumed that workers in the SIC Major Industry Sector C-E were only exposed at high exposure level.

Table 11: Numbers of workers exposed to strong inorganic-acid mists containing sulfuric acid according to CAREX in 1990-1993

Main industry sector	Industry	CAREX Data 1990-1993		Exposure level
		Number exposed	Number in industry	
C-E	Crude Petroleum and Natural Gas Production	1,429	53,300	L
	Manufacture of leather and products of leather or of its	760	16,825	H
	Manufacture of paper and paper products	2,994	119,050	H
	Manufacture of industrial chemicals	5,186	130,000	H
	Manufacture of other chemical products	6,200	175,175	H
	Manufacture of pottery, china and earthenware	14	54,450	L
	Iron and steel basic industries	2,378	48,425	H
	Non-ferrous metal basic industries	4,293	79,325	H
	Manufacture of fabricated metal products, except machinery and equipment	5,502	292,200	H
	Manufacture of machinery except electrical	3,990	692,275	H
	Manufacture of electrical machinery, apparatus, appliances and supplies	4,766	473,750	H
	Manufacture of transport equipment	3,690	456,900	H
G-Q	Air transport	1,131	95,700	L
	Total	***42,333***	***2,687,375***	

	Main industry sector	,	% Male	
A-B	Agriculture, hunting and forestry; fishing			
	High	0		
	Low	0		
C-E	Mining/quarrying, electricity/gas/steam, manufacturing industry			
	High	39,759	71%	
	Low	1,443	71%	
F	Construction			
	High	0		
	Low	0		
G-Q	Service industries			
	High	0		
	Low	1,131	65%	

(c) AF calculation

The estimated total (male & female) attributable fraction for cancer of the larynx associated with occupational exposure to strong inorganic acid mists is 2.13% (95%CI=0.77-4.76), which equates to 16 (95%CI=6-36) attributable deaths and 46 (95%CI=17-102) attributable registrations of laryngeal cancer. The estimated AF for men is 2.29% (95%CI=0.83-5.11) resulting in 14 (95%CI=5-31) attributable deaths and 40 (95%CI= 15-89) attributable registrations; and for women the AF is 1.52% (95% CI= 0.55-3.41) resulting in 2 (95%CI=1-5) attributable deaths and 6 attributable registrations (95%CI=2-12) (Table 12).

Table 12: Summary results for occupational exposure to strong inorganic-acid mists containing sulfuric acid

				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	Soskolne *et al*. (1992)	H	C-E	4.28	28229	1.4	0.09	136545	0.0070	0.0226	0.0079	0.0507	14	5	31	39	14	89
		H	All		28229			136545	0.0070	0.0226	0.0079	0.0507	14	5	31	39	14	89
	Soskolne *et al*. (1992)	L	C-E	1.91	1025	1.4	0.09	4956	0.0003	0.0002	0.0000	0.0007	0	0	0	0	0	1
		L	G-Q	1.91	735	0.9	0.11	2764	0.0001	0.0001	0.0000	0.0004	0	0	0	0	0	1
		L	All		1760			7720	0.0004	0.0004	0.0000	0.0011	0	0	1	1	0	2
		All	All		29989			144265	0.0074	0.0229	0.0083	0.0511	14	5	31	40	15	89
Women	Soskolne *et al*. (1992)	H	C-E	4.28	11530	1.5	0.14	96999	0.0046	0.0149	0.0052	0.0339	2	1	5	5	2	12
		H	All		11530			96999	0.0046	0.0149	0.0052	0.0339	2	1	5	5	2	12
	Soskolne *et al*. (1992)	L	C-E	1.91	418	1.5	0.14	3520	0.0002	0.0002	0.0000	0.0005	0	0	0	0	0	0
		L	G-Q	1.91	396	0.8	0.15	1895	0.0001	0.0001	0.0000	0.0002	0	0	0	0	0	0
		L	All		814			5416	0.0003	0.0002	0.0000	0.0007	0	0	0	0	0	0
		All	All		12344			102415	0.0049	0.0152	0.0055	0.0341	2	1	5	6	2	12

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 ISOPROPANOL MANUFACTURE, STRONG-ACID PROCESS

(a) Risk estimate

Only one suitable epidemiological study was identified to obtain a risk estimate: Teta *et al*. (1992) observed an excess of laryngeal cancer, but it was based on only two cases.

(b) Number exposed

The number of workers involved in the isopropanol manufacture by strong-acid process could not be identified for GB.

(c) AF calculation

The AF calculation is therefore omitted.

3.6 RUBBER INDUSTRY

(a) Risk estimate

Kogevinas *et al*. (1998) reviewed studies published after 1982, including 7 cohort studies in 6 countries that examined distinct populations of workers in the rubber industry, and 2 case-control studies that reported risks for employment in the rubber industry. Low or moderate excess risks were found in all seven studies reporting results on laryngeal cancer, although 95% CIs were wide. The highest risks were found for workers in Russia (Solionova & Smulevich (1993) and Poland (Szeszenia-Dabrowska *et al*, 1991). However, estimates were based on few numbers of cases and exposures did not seem to be portable in GB.

A recent meta-analysis of the synthetic rubber-producing industry calculated a pooled estimate of 1.19 (95% CI=0.88-1.60) for mortality, with a high level of heterogeneity (p-value=0.01), and 1.39 (95% CI=0.75-2.59) for incidence (Alder *et al*, 2006). These figures were based on 13 and 3 studies for mortality and incidence, respectively. The goods produced were tyres only for 4 studies, other non-tyre products (manufacture of footwear, general rubber goods, and plastics) for 4 studies, and both for 5 studies. The 13 studies had been carried out in Europe (7, 54%), North America (5, 38%) and Russia (1, 8%), published during the time period 1976-2001. The study size range varied from 1,972 to 36,691 workers. The earliest follow-up period started in 1910 and the latest period ended in 1995.

Mortality and cancer morbidity in workers employed in the rubber industry were investigated in UK through two cohorts (Dost *et al*, 2007, Sorahan *et al*, 1989, Straughan and Sorahan (2000). Sorahan *et al*, (1989) followed 36,691 male rubber workers from 13 factories during 1946-85. A weak excess mortality from laryngeal cancer (SMR=1.19, based on 33 observed cases) was found. A prospective cohort of 9,031 workers who began work at 42 rubber factories in the period 1982-1991 (Straughan and Sorahan, 2000) found an excess mortality for males for the period 1983-1998 (SMR=2.13, not significant, based on 1 observed case) from cancer of the larynx. A recent update, from 1983 to 2004 (Dost *et al*, 2007), showed a SMR of 1.03 (based on 1 observed case).

The cohorts by Sorahan *et al*. (1989) and Straughan & Sorahan (2000) were included in the meta-analysis by Alder *et al*. (2006). SMRs provided by Straughan & Sorahan (2000) (and therefore Dost *et al*, 2007) were different from the meta-SMR; the findings should be treated with caution because they are related to a later period of exposure (average follow-up for males: 17.6 years). Both, the meta-SMR and SMR from Sorahan *et al*. (1989) were similar. Figures from the British cohort study were used to calculate the AF as this study was thought to be representative of workers throughout the UK rubber industry; the meta-analysis by Alder *et al*. (2006) included studies of the rubber industry from many different countries using several different processes and substances.

Sorahan *et al*. (1989) conducted a mortality study in the British rubber industry during 1946-1985, including 36,691 male rubber workers. The latter were employed in any of the 13 factories in the period 1946-1960, for at least 12 months. Most of subjects were employed in the tyre factories in

England and only 15% of all subjects were engaged in manufacturing general rubber goods. Detailed job histories (defined in terms of 10 broad occupational groups) were recorded for each subject. The mean duration of exposed employment in the rubber industry was 10.5 years. The number of deaths was compared with the expected number calculated from the mortality rates applicable to the male population of England and Wales. The SMR reported was 1.19 (observed cases: 33, expected cases: 27.8) and this was used in the present study. A confidence interval was not provided for this estimate and therefore we used the Byar's approximation proposed in Breslow and Day (1987) to calculate it: 95% CI=0.82-1.62.

(b) Number exposed

The number of workers in the rubber industry is given in Table 13 according to the Labour Force Survey (1979 and 2003), those for 1979 being used as a point estimate in the calculations. The figures from LFS 2003 show the stability of the number of workers in the rubber industry in Great Britain.

Table 13: Numbers of workers employed in rubber industry in the UK according to the Labour Force Survey (1979 and 2003)

Main industry sector	SIC Code	Description	Numbers		
			Men	Women	Total
	LFS 1979				
C-E	95.4	Foremen of rubber process workers moulding machine operators tyre builders	0	0	0
	95.9	Foremen of rubber	3,710	228	3,938
	97.1	Rubber process workers moulding machine operators tyre builders	13,273	1,959	15,232
	107.1	Rubber	21,955	6,050	28,005
	136.4	Foremen inspectors viewers examiners of rubber goods	236	0	236
	138.4	Inspectors viewers examiners of rubber goods	3,109	2,860	5,969
		Total	***42,283***	***11,097***	***53,380***
	LFS 2003				
C-E	24.17	Primary synthetic rubber	734	53	787
	25.11	Rubber tyres etc manufacture	9,012	1,764	10,776
	25.12	Rubber tyres retreading etc	2,021	343	2,364
	25.13	Other rubber products manufacture	18,741	4,489	23,230
	8115	Rubber process operatives	11,531	1,995	13,526
		Total	***42,039***	***8,644***	***50,683***

(c) AF calculation

The estimated total (male & female) attributable fraction for cancer of the larynx associated with work in the rubber industry is 0.12% (95%CI=0.00-0.44), which equates to 1 (95%CI=0-3), attributable death and 3 (95%CI=0-10) attributable registrations of laryngeal cancer. The estimated AF for men is 0.14% (95%CI=0.00-0.50) resulting in 1 (95%CI=0-3) attributable death and 2 (95%CI=0-9) attributable registrations; and for women the AF is 0.06% (95%CI=0.00-0.20) resulting in 0 attributable deaths and 0 attributable registrations (Table 14).

Table 14: Summary results for workers employed in rubber industry

				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	Sorahan *et al*, (1989)	H	C-E	1.19	42283	1.4	0.09	146089	0.0075	0.0014	0.0000	0.0050	1	0	3	2	0	9
		H	All		42283			146089	0.0075	0.0014	0.0000	0.0050	1	0	3	2	0	9
		All	All		42283			146089	0.0075	0.0014	0.0000	0.0050	1	0	3	2	0	9
Women	Sorahan *et al*, (1989)	H	C-E	1.19	11097	1.5	0.14	62237	0.0030	0.0006	0.0000	0.0020	0	0	0	0	0	1
		H	All		11097			62237	0.0030	0.0006	0.0000	0.0020	0	0	0	0	0	1
		All	All		11097			62237	0.0030	0.0006	0.0000	0.0020	0	0	0	0	0	1

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

4. OVERALL ATTRIBUTABLE FRACTION

4.1 EXPOSURE MAP

No overlap occurs between the substances and carcinogens relevant for laryngeal cancer and so no exposure map is presented.

4.2 SUMMARY OF RESULTS

The results are summarised in Tables 15 and 16.

Table 15: Summary of relative risks used to calculate AF

Agent	Exposure	RR	LL	UL
Asbestos	H	1.37	1.17	1.6
Asbestos	L	1	1	1
Rubber industry	H	1.19	0.82	1.62
Strong inorganic-acid mists containing sulfuric acid	H	4.28	2.13	8.58
Strong inorganic-acid mists containing sulfuric acid	L	1.91	0.97	3.78

Table 16: 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)
Asbestos	350302	82336	0.0181	0.0039	0.0047	0.0022	0.0076	0.0000	0.0000	0.0000	3	0	8	0
Rubber industry	146089	62237	0.0075	0.0030	0.0014	0.0000	0.0050	0.0006	0.0000	0.0020	1	0	2	0
Strong inorganic-acid mists containing sulphuric acid	144265	102415	0.0074	0.0049	0.0229	0.0083	0.0511	0.0152	0.0055	0.0341	14	2	40	6
Totals*					**0.0288**	**0.0138**	**0.0569**	**0.0157**	**0.0060**	**0.0348**	**17**	**3**	**50**	**6**

*Totals are the product sums and are not therefore equal to the sums of the separate estimates of attributable fraction, deaths and registrations for each agent. The difference is especially notable where the constituent AFs are large.

4.3 EXPOSURES BY INDUSTRY/JOB

Table 17 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent.

Table 17 Industry/occupation codes by agent

Agent	Industry	Number Ever Exposed over REP (Men)	Number Ever Exposed over REP (Women)	Attributable Registrations (Men) (2004)	Attributable Deaths (Men) (2005)	Attributable Registrations (Women) (2004)	Attributable Deaths (Women) (2005)	Attributable Registrations (Total) (2004)	Attributable Deaths (Total) (2005)
Asbestos	Construction	209,244	0	7	2	0	0	7	2
Asbestos	Total	350,302	82,336	8	3	0	0	8	3
Rubber	Rubber	75,855	33,931	1	0	0	0	1	0
Rubber	Rubber process workers moulding machine operators tyre builders	45,859	10,987	1	0	0	0	1	0
Rubber	Manufacture of rubber products (Total)	146,089	62,237	2	1	0	0	3	1
Strong inorganic acid mists	Iron and steel basic industries	8,167	5,802	2	1	0	0	3	1
Strong inorganic acid mists	Manufacture of electrical machinery, apparatus, appliances and supplies	16,368	11,627	5	2	1	0	5	2
Strong inorganic acid mists	Manufacture of fabricated metal products, except machinery and equipment	18,896	13,423	5	2	1	0	6	2
Strong inorganic acid mists	Manufacture of industrial chemicals	17,810	12,652	5	2	1	0	6	2
Strong inorganic acid mists	Manufacture of leather and products of leather or of its substitutes	2,610	1,854	1	0	0	0	1	0
Strong inorganic acid mists	Manufacture of machinery except electrical	13,703	9,734	4	1	1	0	5	2
Strong inorganic acid mists	Manufacture of other chemical products	21,293	15,126	6	2	1	0	7	3
Strong inorganic acid mists	Manufacture of paper and paper products	10,282	7,304	3	1	0	0	3	1
Strong inorganic acid mists	Manufacture of transport equipment	12,673	9,002	4	1	1	0	4	1
Strong inorganic acid mists	Non-ferrous metal basic industries	14,743	10,474	4	1	1	0	5	2
Strong inorganic acid mists	Total	144,265	102,415	40	14	6	2	46	16

5. BIBLIOGRAPHY

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6. STATISTICAL APPENDIX

Formulae used in the estimation of AF

Levin's equation

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

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

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

Turnover equation to estimate numbers ever employed during the REP

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

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

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

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

TO = staff turnover per year

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

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

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

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

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

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

Equation to estimate the proportion of the population exposed

$Pr(E) = N_{e(REP)} / N_{p(REP)}$ (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:

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

APPENDIX 1: META-ANALYSIS FOR ASBESTOS

We identified 14 case-control studies that provide data on association between risk of laryngeal cancer and exposure to asbestos (or any employment in an occupation or industry where asbestos exposure was known to occur) and that control for tobacco and alcohol consumption: 7 were included in the review by Browne & Gee (2000) and 7 were added after reviewing literature. The details of the design aspects as well as the findings of those studies are summarized in Table 18.

The aim of this meta-analysis was to provide a meta-SIR associated to asbestos exposure that could be used for CAREX data. Five studies were excluded from this analysis for the following reasons: in Ahrens *et al*. (1991), the asbestos exposure assessment was only based on a self-reported exposure; Berrino *et al*. (2003) combined cancers of the larynx and the hypopharynx; the 3 other studies (De Stefani *et al*, 1998, Elci *et al*, 2002, Shangina *et al,* 2006) were conducted in countries where the exposure to asbestos does not seem portable in Great Britain. The characteristics of the 9 case-control studies included in the meta-analysis are as follows. Six studies were conducted in Europe and 3 in US. The earliest study (Olsen *et al,* 1984) was published in 1984 and the most recent (Dietz *et al*, 2004) in 2004. The earliest year of diagnosis was 1975 (Zagraniski *et al*, 1986) and the latest was 2000 (Dietz *et al,* 2004)). The studies involved between 92 cases (Zagraniski *et al*, 1986) to 326 cases (Olsen *et al*, 1984). Except for 3 studies, all subjects were male; among these 3 studies, two studies (Dietz *et al*, 2004), Olsen *et al,* 1984) gave only results for men. Wortley *et al*. (1992) present results only in relation to exposure level. However, no dose-response was observed; a pooled estimate of the RRs for the three exposure levels has been calculated for use in our meta-analysis giving an overall RR: meta-SIR=1.22, 95% CI=0.86-1.72; test for heterogeneity: p=0.91. Gustavsson *et al*. (1998) presented results for high or low exposure to asbestos (versus never exposed); the figure from the high exposure to asbestos was used for our meta-analysis. Among the 9 studies, four studies also gave risk estimates without adjustment for tobacco and alcohol consumption. In Dietz *et al*. (2004) and Muscat & Wynder (1992), the association between asbestos exposure and laryngeal cancer was weakened by controlling for other covariates; in Brown *et al*. (1988) and Olsen *et al*. (1984), the estimates were the same with or without adjustment for tobacco and alcohol consumption.

Figure 1 provides the RR or OR estimates associated with reporting “any” exposure to asbestos in 9 case-control studies that compared subjects with any occupational exposure to those with no exposure to asbestos. The meta-analysis, combining 9 studies and using the inverse weighted variance method, found an RR of 1.37 (95% CI= 1.17-1.60) associated with any exposure to asbestos (test for heterogeneity: p=0.94). Four of the case-control studies (Gustavsson *et al*, 1998), Imbernon *et al*, 1995), Marchand *et al*, 2000), Wortley *et al*, 1992) presented results on the dose-response relationships. The meta-SIR from the combined analysis of the highest category of exposure from these 4 studies was 1.48 (95% CI=1.10-1.97; test for heterogeneity: p = 0.65); for the lowest level of exposure the meta-SIR was 1.16 (95% CI=1.02-1.31; test for heterogeneity: p = 0.99). However, all four studies used different measures of exposure and cut-offs for categorization. It is questionable therefore whether these can be combined.

To assess the influence of each of the 9 studies a sensitivity analysis has been carried out by recalculating the meta-SIR and removing each study in turn. The results for the 9 combinations are presented in Figure 2. The association persisted with or without the inclusion of a study: the meta-SIRs vary from 1.33 (without the study 8) to 1.41 (without the study 5). In addition, a high degree of homogeneity is observed (from 0.90 to 0.96).

The influence of removal of the five case-control studies without dose-response results has also been assessed. The association between risk of laryngeal cancer and exposure to asbestos is weakened (meta-SIR of the 14 studies =1.28, 95% CI=1.13-1.44) and the homogeneity across studies is smaller (p=0.62).

Figure 1: RR and 95% CI for the 9 case-control studies and the meta-SIR

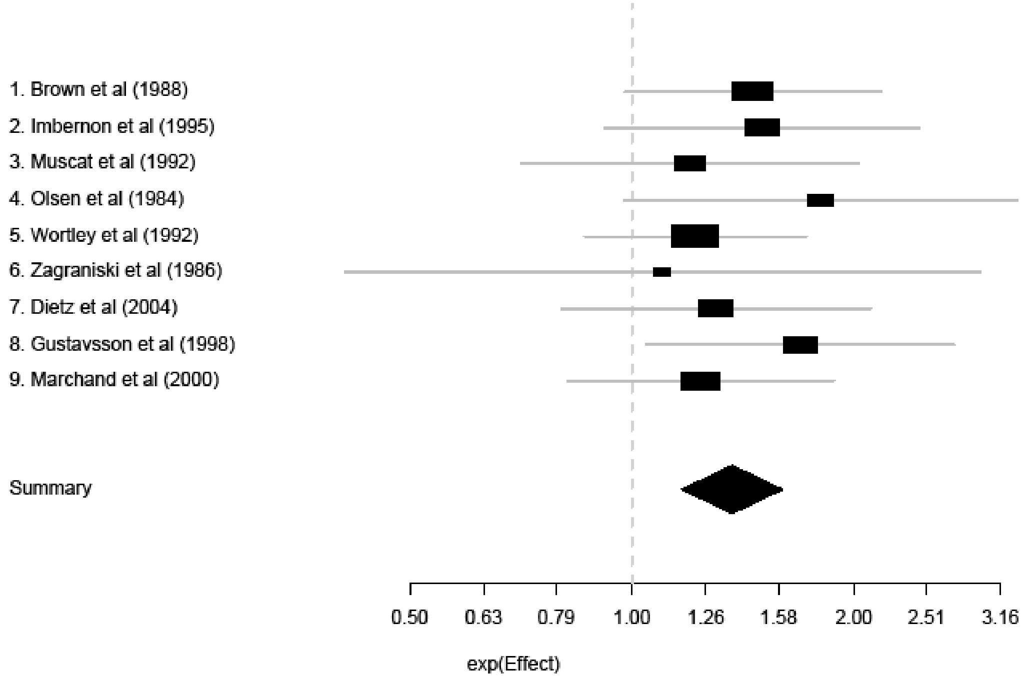

Figure 2: Sensitivity analysis: meta-SIR and 95% CI for all 9 studies (red) and for all combinations of 8 studies (black). The p-value for the test of heterogeneity are given between brackets

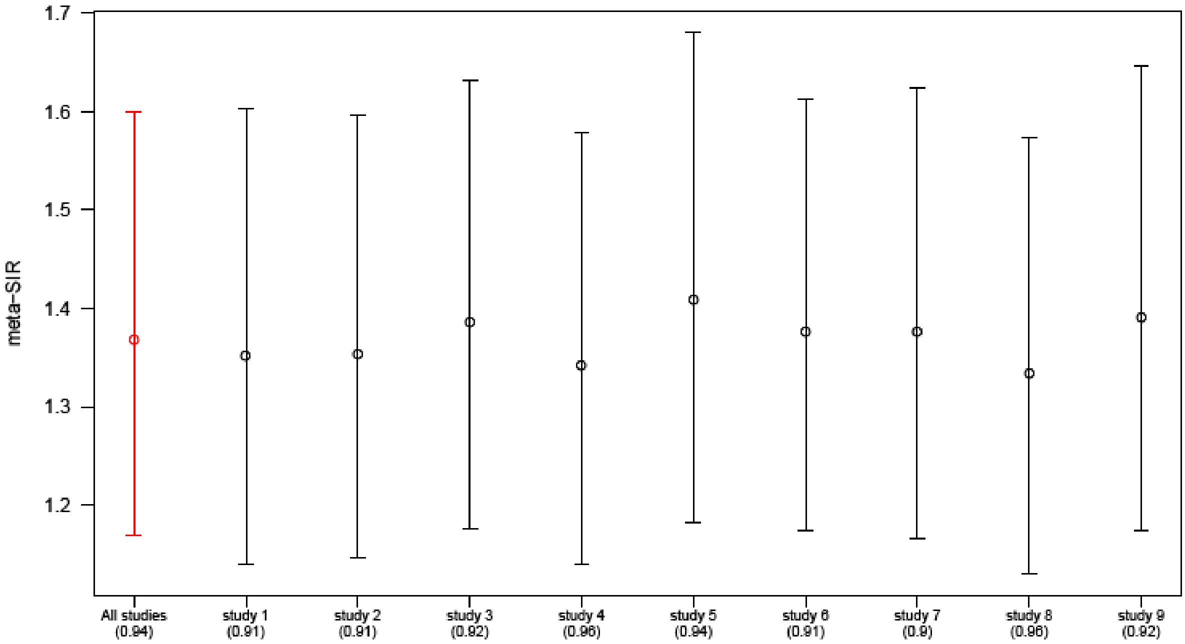

Table 18: Laryngeal cancer and exposure to asbestos, case-control studies with adjustment for tobacco and alcohol consumption

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment	Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
						Ever versus never exposed	**Dose-response relationships**				
1. Brown *et al*. (1988)	12 industries 8 occupational categories Job titles 12 chemicals (asbestos)	US	Ho	183 M Ca 250 M Co 1975-1980	Jobs held at least 6 months, after 1939 Industrial hygienist classified job titles for exposure to specific exposures	Exposed: 88 Ca, 99 Co RR=1.46 (0.98-2.18) CRR=1.46	Not studied	HQ	Y	Y	
2. Imbernon *et al*. (1995)	Cohort of workers in the electricity and gas industry	France	In	116 M Ca 457 M Co 1978-1989	All jobs in the company EDF JEM Industrial hygienist	Exposed: 38 Ca, 107 Co Adj for **SES** OR=1.5 (0.9-2.4)	Asbestos exposure, cumulative (all subjects) (fibers/cm3) Quartile1: RR=1.1 (0.5-2.8) (8 Ca, 30 Co) Quartile 2: RR=1.3 (0.5-3.3) (7 Ca, 23 Co) Quartile 3: RR=2.1 (0.9-4.3) (14 Ca, 31 Co) Quartile 4: RR=1.6 (0.7-3.7) (9 Ca, 23 Co)	-	Y	Y	Case-control study nested within the cohort of 170,000 workers. They did not have information about smoking and alcohol consumption. They used socioeconomic status (smoking habits vary considerably in relation to SES)
3. Muscat *et al*. (1995)	Exposures (asbestos) Occupations	US	Ho	194 M Ca 184 M Co 1985-1990	1. 6 jobs held at least 1yr occupation and linkage system applied to determine exposure probability and intensity 2. Self-reported exposure (at least 8hrs per week)	1. Occupation Exposed: 63 Ca, 48 Co RR=1.2 (0.7-2.0) CRR=1.3 2. Self-reported exposure to asbestos Exposed: 15 Ca, 13 Co RR=0.8 (0.3-1.9) CRR=1.1	Not studied	HQ	Y	Y	Use RR from the analysis using occupations and not this one with the self-reported exposure: 3 Ca of 15 Ca did not work in occupations classified as asbestos related
4. Olsen *et al.* (1984)	Exposures (asbestos)	Denmark	Ho	326 Ca (276 M, 50 W) 1134 Ca (1134 M, 163 W) 1980-1982	Questions about their exposure to specific chemicals and physical agents	only men Exposed: 17 Ca, 34 Co OR=1.8 (1.0-3.4) COR=1.8	Not studied	LQ	Y	Y	

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment	Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
						Ever versus never exposed	**Dose-response relationships**				
5. Wortley *et al*. (1992)	Exposures (asbestos) Occupations	US	Po	235 Ca 547 Co 1983-1987	Job history Industrial hygienist performed JEM exposure assignments	NS but results not shown Meta-SIR=1.22 (0.86-1.72)	Highest exposure code for subject (code 0: never exposed, 1-3=L-M-H) Low: OR=1.2 (0.6-7.1) (3 Ca, 6 Co) Medium: OR=1.3 (0.8-2.0) (57 Ca, 94 Co) High: OR=1.1 (0.6-1.9) (30 Ca, 54 Co)	-	Y	Y	No overall RR for subjects ever exposed to asbestos. However, no significant dose-response relationship. Combined analysis of the RRs for the 3 levels: meta-SIR=1.22 (0.86-1.72), test for heterogeneity: p=0.91 in agreement with authors' comment: suggestion of increased risk associated with asbestos
6. Zagraniski *et al*. (1986)	Industries Occupations (asbestos workers)	US	Ho	92 M Ca 181 M Co 1975-1980	1. Job history (all jobs) 2. Self-reported exposure (at least 20hrs per week for 6 months or more)	1. Asbestos workers Exposed: 11 Ca, 18 Co OR=1.1 (0.4-2.9) 2. Self reported exposure to asbestos: Exposed: 10 Ca, 24 Co OR=0.8 (0.4-1.7)	Not studied	HQ	Y	Y	Use the RR from the analysis using occupations
7. Dietz *et al*. (2004)	Cement dust related occupational groups	Germany	Po	257 Ca (236 M, 21 F) 769 Co (702 M, 67 F) 1998-2000	1. Jobs held at least 6 months 2. Quantification using job-specific supplementary questionnaires validated for asbestos	Only men Exposed: 59 Ca, 104 Co 2. NS but results not shown High exposed group (>1000hrs) OR=1.3 (0.8-2.1) COR=2.1	Not studied	HQ	N	Y	

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment	Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
						Ever versus never exposed	**Dose-response relationships**				
8. Gustavsson *et al*. (1998)	17 specific substances	Sweden	Po	157 M Ca 641 M Co 1988-1990	Jobs held at least 1yr Occupational hygienist assigned exposure intensity Probability to 17 specific occupational exposures	1. > median of cumulative dose among exposed Co Exposed: 34 Ca RR high=1.69 (1.05-2.74) 2. < median of cumulative dose among exposed Co Exposed: 28 Ca RR low=1.21 (0.73-2.02)	Cumulative exposure distribution among exposed Co (exposure intensity*prob of exposure *duration of exposure) Quartile1: RR=1.16 (1.02-1.32) (13 Ca, 43 Co) Quartile 2: RR=1.35 (1.04-1.74) (15 Ca, 45 Co) Quartile 3: RR=1.56 (1.06, 2.30) (16 Ca, 44 Co) Quartile 4: RR=1.82 (1.08-3.04) (18 Ca, 45 Co)	-	N	Y	No overall RR for subjects ever exposed to asbestos, only RR for subjects ever exposed to high/low level of asbestos Use the RR for high exposure to asbestos
9. Marchand *et al*. (2000)	Asbestos Man-made vitreous fibers	France	Ho	296 M Ca 295 M Co 1989-1991	1. Job history (all jobs) 2. Job-exposure matrix (JEM): prob of exposure, concentration, frequency	Exposed: 216 Ca, 185 Co OR=1.24 (0.83-1.90)	Cumulative exposure distribution (exposure intensity*prob of exposure*duration of exposure) Low: OR=1.10 (0.66-1.82) (67 Ca, 67 Co) Intermediate: OR=1.20 (0.73-1.99) (72 Ca, 67 Co) High: OR=1.47 (0.87-2.46) (77 Ca, 51 Co)	HQ	N	Y	
10. Ahrens *et al*. (1991)	21 industries 31 occupations Job titles 19 substances (asbestos)	Germany	Ho	85 M Ca 100 M Co 1984-1986	Jobs held at least 6 months Self-reported exposure	Self-reported exposure to asbestos Ca and Co exposed: 36 (19.5%) OR=1.1 (0.5-2.4) COR=1.2	Not studied	LQ	Y	N	Not included in the meta-analysis because only self-reported exposure
11. Berrino *et al*. (2003)	Job titles	France Italy Spain Switzerland	Po	315 Ca (215 larynx) 819 Co 1979-1982	All jobs held for at least 1 year after 1944 JEM Industrial hygienists, occupational physicians (probability of exposures to specific agents)	Exposed: 215 Ca, 380 Co OR=1.6 (1.0–2.5)	Not studied	-	N	N	Not included in the meta-analysis because combined analysis with 100 Ca of hypopharyngeal cancer (ICD-10 C13)

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment	Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
						Ever versus never exposed	**Dose-response relationships**				
12. De Stefani *et al*. (1998)		Uruguay	Ho	112 M Ca 352 M Co 1993-1995	1. Jobs held at least 1yr 2. Specific questions concerning use of several substances	Exposed: 23 Ca, 70 Co OR=1.8 (0.9-3.2)	Not studied	LQ	N	N	This study was conducted in Uruguay. Exposure might be not portable in GB
13. Elci *et al*. (2002)		Turkey	Ho	940 M Ca 1519 M Co 1979-1980	Job history Industrial hygienist performed JEM exposure assignments	Exposed: 150 Ca OR=1.0 (0.8-1.3)	Not studied	HQ	N	N	This study was conducted in Turkey. Exposure might be not portable in GB
14. Shangina *et al*. (2006)	43 agents	Romania, Poland, Russia, Slovakia	Ho	316 M Ca 728 M Co (cancers) 1999-2002	Jobs held at least 1yr - 13 specific jobs, 73 agents - intensity, frequency, confidence IH estimation	Exposed: 26 Ca, 65 Co OR=0.86 (0.51-1.45)	Not studied	-	N	N	This study was conducted in East Europe. Results were mainly observed for Poland. Exposure might be not portable in GB

Ca: case, Co: control

* Ho: hospital-based study, In: industry-based study, Po: population-based study

1 Exposure assessment method from the book "Asbestos: Selected Cancers", 2006. HQ: high quality, LQ: low quality

2 studies included in the review by Browne & Gee (2000): Y: yes, N: no

3 studies included in the meta-analysis: Y: yes, N: no

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The burden of occupational cancer in Great Britain

Cancer of the larynx

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

The estimated total (male and female) attributable fractions, deaths and registrations for cancer of the larynx related to occupational exposure is 2.61% (95% Confidence Interval (CI)=0.83-4.32), which equates to 20 (95%CI=5-101) attributable deaths and 56 (95%CI=8-101) attributable registrations.

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