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Health and Safety Executive

The burden of occupational cancer in Great Britain

Soft tissue sarcoma

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Research Report

Health and Safety Executive

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Soft tissue sarcoma

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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 soft tissue sarcoma 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 soft tissue sarcoma related to overall occupational exposure (to dioxins) is 2.27% (95%Confidence Interval (CI)= 0.0-7.73), which equates to 13 (95%C= 0-45) deaths and 27 (95%CI= 0-90) 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 soft tissue sarcoma that have been derived using incidence data for calendar year 2004, and mortality data for calendar year 2005.

Dioxins been classified by the IARC as a definite human carcinogen for soft tissue sarcoma. Occupational exposure to dioxins can occur in the production and handling or certain chlorinated phenols, in production or handling of chlorinated pesticides, in pulp and paper manufacturing, operation of municipal solid waste or hazardous waste incinerators and during hazardous waste clean-up operations. 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 317 total deaths in men aged 15-84 and 240 in women aged 15-79 from soft tissue sarcoma; in 2004 there were 662 total registrations for soft tissue sarcoma in men aged 15-84 and 401 in women aged 15-79.

The estimated total (male and female) attributable fraction for soft tissue sarcoma associated with occupational exposure overall and for occupational exposure to dioxins (TCCD) is 2.27% (95%Confidence Interval (CI)=0.0-7.73), which equates to 13 (95%CI=0-45) deaths and 27 (95%CI=0-90) registrations.

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1 INCIDENCE AND TRENDS

Soft tissue sarcomas (STS) are a rare heterogeneous group of tumours that show a broad range of differentiation that may reflect distinct aetiologies (Berwick, 2006, Toro *et al*, 2006). They occur in approximately one to two of every 100,000 individuals worldwide and account for about 0.1% of all cancer cases and 0.7% of all cancer deaths in the US (Howe *et al*, 2001). STS include malignancies of a range of different tissues (Table 1). In the US 1978-2001 Surveillance, Epidemiology and End Results program observed 26,758 STS cases (Toro *et al*, 2006). Of these leiomysarcomas accounted for 23.9%, malignant fibrous histiocytomas 17.1%, liposarcomas 11.5%, dermatofibrosarcomas 10.5%, rhabdomyosarcomas 4.6% and angiosarcomas 4.1%. Almost half (47.9%) arose in the soft tissues, 14.0% in the skin and 7.0% in the uterus. It is difficult for the International Classification of Diseases (ICD) system to classify STS in a meaningful way as they can occur in any anatomical site. A category exists for tumours of the connective and soft tissue (C49); however, sarcomas occurring in the visceral organs are often assigned the site code for the organ, rather than to the connective tissue code, and therefore substantial numbers of these tumours may not be coded to the ICD site code for STS (Swerdlow *et al*, 2001).

Table 1 Major types of soft tissue sarcomas in adults (Source: NC I (2008))

Tissue of origin	Type of cancer	Usual location in the body
Fibrous tissue	Fibrosarcoma Malignant fibrous histiocytoma Dermatofibrosarcoma	Arms, legs, trunk Legs Trunk
Fat	Liposarcoma	Arms, legs, trunk
Muscle – Striated	Rhabdomyosarcoma	Arms, legs
Muscle – Smooth	Leiomyosarcoma	Uterus, digestive tract
Blood vessels	Haemangiosarcoma Kaposi sarcoma	Arms, legs, trunk Legs, trunk
Lymph vessels	Lymphangiosarcoma	Arms
Synovial tissue	Synovial sarcoma	Legs
Peripheral nerves	Neurofibrosarcoma	Arms, legs, trunk
Cartilage & bone-forming tissue	Extraskeletal chondrosarcoma Extraskeletal osteosarcoma	Legs Legs, trunk (not involving the bone)

Source: NCI (2008)

The highest rates for connective tissue tumours in the world are in South African whites, being twice those in any other country (Parkin *et al*, 2002). The incidence of Kaposi sarcoma (KS) in Uganda is extremely high, 37.7 per 100,000 among males (20.5 among females), five times the rate seen in the US (Parkin *et al*, 2002). However, HIV infection is driving the rates of KS in these areas. In England and Wales incidence has increased at all adult ages since 1970, whereas in children there were decreases. In the UK STS is reported to account for about 1% of all malignant neoplasms (Storm, 1994) and generally the incidence increases with age (NICE, 2006). There are approximately 1000 new cases diagnosed each year in England (Table 2), with a male:female ratio of 1.4:1 (Swerdlow *et al*, 2001). In Wales there are about 100 new cases each year and about 120 in Scotland. In addition there are about 67 men and 16 women in England diagnosed with KS each year, with a total of about five in Wales and Scotland. For consistency between ICD-9 (171) and ICD-10 the category C47 (peripheral and autonomic nerves) should be included, of which there are just under 100 each year. In 2004 there were a total of 97 KS in GB (83 men and 14 women), and 1364 STS (772 men and 592 women).

There are about 600 deaths from STS every year (20 from cancer of peripheral and autonomic nerves), with a 1.1:1 male:female ratio (Table 3). In addition there are about six men and two women who die from KS each year. With the exception of an unchanged rate in young women, there have been substantial increases in recent decades in the recorded incidence of STS in adults, changes that have not been attributed to changes in known risk factors, and may be due in part to the changes in reporting and coding (Swerdlow *et al*, 2001). In 2005 there were nine deaths from KS and 718 from STS.

Table 2 Number (age-standardised rate, per 100,000) of soft tissue sarcoma registrations in England, Scotland and Wales 1995-2005.

	Men				Women			
Year	England	Scotland	Wales	Total	England	Scotland	Wales	Total
1995	446 (1.9)	64 (2.6)			419 (1.7)	62 (1.9)		
1996	528 (2.2)	92 (3.6)			439 (1.8)	57 (1.8)		
1997	500 (2.1)	67 (2.5)			429 (1.7)	51 (1.6)		
1998	603 (2.5)	44 (1.7)			410 (1.6)	45 (1.4)		
1999	546 (2.2)	54 (2.1)			475 (1.9)	45 (1.4)		
2000	589 (2.5)	75 (2.8)	45 (2.8)	709	451 (1.8)	49 (1.6)	41 (2.2)	541
2001	536 (2.2)	59 (2.2)	57 (3.3)	652	469 (1.9)	44 (1.5)	35 (1.7)	548
2002	555 (2.3)	71 (2.7)	62 (3.6)	688	427 (1.7)	55 (1.6)	33 (1.8)	515
2003	553 (2.3)	83 (3.1)	52 (3.1)	688	458 (1.8)	51 (1.5)	39 (2.0)	548
2004	619 (2.5)	66 (2.4)	41 (2.4)	726	454 (1.8)	28	40 (2.0)	522
2005	657 (2.7)		61 (3.6)		377 (2.1)		53 (2.8)	
Average	**557 (2.3)**	**68 (2.6)**	**53 (3.1)**	**693**	**437 (1.8)**	**46 (1.5)**	**40 (2.1)**	**535**

Table 3 Number of soft tissue sarcoma deaths in England/Wales and Scotland 1999-2006

	Men			Women		
Year	England & Wales	Scotland	Great Britain	England & Wales	Scotland	Great Britain
	Number (Crude Rate, /100000)	Number (Crude Rate, /100000)	Number	Number (Crude Rate, /100000)	Number (Crude Rate, /100000)	Number
1999	319 (1.2)	32 (1.2)	351	315 (1.2)	37 (1.1)	352
2000	325 (1.2)	43 (1.6)	368	333 (1.2)	18 (0.5)	351
2001	282 (1.1)	33 (1.2)	315	265 (1.0)	33 (1.0)	298
2002	308 (1.2)	29 (1.1)	337	281 (1.1)	35 (1.0)	316
2003	284 (1.1)	18 (0.6)	302	276 (1.0)	30 (0.9)	306
2004	291 (1.1)	28 (1.1)	319	301 (1.1)	40 (1.2)	341
2005	325 (1.2)	37 (1.4)	362	297 (1.1)	34 (0.9)	341
2006	351 (1.3)	29 (1.0)	380	298 (1.1)	24 (0.5)	322
Average	**311 (1.2)**	**31 (1.2)**	**342**	**296 (1.1)**	**31 (0.9)**	**327**

The five-year survival rate is between 50% and 60% for STS as a group (Storm and Hat, 1998). However, there is a wide variation depending on anatomical site and histological features of the tumours. For example, the five-year disease specific actuarial survival for localised extremity STS has been reported as 79% (Weitz *et al*, 2003), whereas the rate for retroperitoneal sarcoma has been reported as 50% (Mendenhall *et al*, 2005). The prognosis for patients with limb and trunk STS is based on five factors: the patient's age, the presence of metastases at the time of presentation, the size of the tumour, its depth and its histological grade (Weitz *et al*, 2003).

2 OVERVIEW OF AETIOLOGY

It is difficult to study the aetiology of STS because of the relatively low incidence and inherent misclassification of histology (Berwick, 2006). In addition, because of the rarity, any study usually groups all the different histological subtypes into one, resulting in a loss of specificity and possibly masking the behaviour of the different subtypes. It has been suggested that occupational risk factors are not uniform across subtypes (Hoppin *et al*, 1999).

A number of factors have been implicated in the aetiology of STS. Viruses have long been suspected as causal in the development, and the association of KS and AIDS is supportive of this hypothesis. Tobacco use has been inconsistently associated with STS (Berwick, 2006), and diet has been little studied. The role of therapeutic radiation in inducing STS is well established (Berwick, 2006, Swerdlow *et al*, 2001) although the incidence is too low to have affected population trends appreciably. Several studies of women with breast cancer treated with radiation have shown an increase risk of STS (Blanchard *et al*, 2002, Cozen *et al*, 1999, Huang and Mackillop, 2001).

The Occupational Health Decennial Supplement for the 1980s did not show any distinctive pattern for exposures/occupations, the highest mortality was for launderers and artistic occupations for women (Table 4) (Drever, 1995). The latter also showed an increased PRR in men. Even fewer excesses were seen in the more recent supplement (Table 5) (Coggon *et al*, 2009). Similar studies in Switzerland (Bouchardy *et al*, 2002) and Nordic countries (Andersen *et al*, 1999) only found excesses among sales agents, nurses and related occupations and economically inactive women.

Table 4 Job codes with significantly high PRRs and PMRs for cancers of the soft tissues. Men and women aged 20-74 years, England, 1981-87.

Job group		Registrations			Deaths		
SIC code	**Description**	**Observed**	**PRR**	**95%CI**	**Observed**	**PMR**	**95%CI**
Men							
005	Computer programmers				11	203	101-363
024	Literary & artistic occupations	20	170	104-263			
038	Production & maintenance managers	20	173	106-268			
051	Launderers				7	415	167-855
052	Hairdressers				0	0	0-94
093	Plastic goods makers				6	275	101-599
124	Machine tool operators	60	134	103-173	65	129	99-164
150	Riggers				6	282	104-615
Women							
024	Literary & artistic occupations				13	218	116-373

Table 5 Job codes with significantly high PMRs for cancers of the soft tissues. Men and women aged 20-74 years, England, 1991-2000.

Job group		Deaths		
SIC code	**Description**	**Observed**	**PMR**	**95%CI**
Men				
104	Carpenters & Joiners	54	146	110-191
108	Woodworking machine operators	9	225	103-428
139	Telephone Fitters	12	219	113-383
Women				
161	Assemblers/Lineworkers (electrical/electronic)	12	196	101-343

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

IARC have assessed the carcinogenicity of a number of substances and occupational circumstances with those classified as Group 1 having sufficient evidence in humans and those classified as Group

2A having limited evidence in humans. Those classified as causing STS are given in Table 6. In addition, exposures and occupations/industries that have been associated with an increased risk of STS include radiation.

Table 6 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, which have the soft tissue 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				
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)	Production; use of chlorophenols & chlorophenoxy herbicides; waste incineration; PCB production; pulp & paper bleaching	Sufficient	Suggestive	All sites Lung NHL
Exposure circumstances				
None identified				
Group 2A: Probably Carcinogenic to Humans				
Agents & groups of agents				
None identified				
Exposure circumstances				
None identified				

2.1 EXPOSURES

2.1.1 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)

Dioxins, or chlorinated dibenzo-*p*-dioxins, are a class of structurally similar chlorinated hydrocarbons. Dioxin is a term used interchangeably with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or TCDD), the most toxic form of dioxins. They are not intentionally produced and have no known use. They are the by-products of various industrial processes (i.e. bleaching paper pulp, and chemical and pesticide manufacture) and combustion activities (i.e. burning household rubbish, forest fires, and waste incineration). The defoliant Agent Orange, used during the Vietnam War, contained dioxins. Dioxins are found at low levels throughout the world in air, soil, water, sediment (the bottom of rivers, streams, and lakes), and in foods such as meats, dairy, fish, and shellfish. The highest levels are usually found in soil, sediment, and in the fatty tissues of animals. Much lower levels are found in air and water. Dioxins are not manufactured commercially, except on a small scale for use in chemical and toxicological research. Dioxins enter the physical environment by release during: combustion; metal smelting and refining; manufacturing of chlorinated chemicals; paper bleaching; natural biological and photochemical processes; mobilisation from environmental sources (e.g. stirred sediments). With regards to occupation, people who perform the following types of work can be exposed to dioxins: production and handling or certain chlorinated phenols (such as 2,4,5-trichlorophenol or pentachlorophenol (PCP)); production or handling of chlorinated pesticides, such as 2,4-dichlorophenoxyacetic acid (2,4-D) and other herbicides; Chlorinated pesticide application; pressure treatment of wood with PCP and handling of PCP-treated wood; production of chlorinated paper at pulp and paper mills; operation of municipal solid waste or hazardous waste incinerators; and hazardous waste clean-up operations. There are also rare cases of high-level exposures through industrial accidents such as occurred in Seveso, Italy.

In 1997 IARC classified TCDD as a Group 1 human carcinogen (IARC, 1997), based largely on four highly exposed industrial cohorts that showed an excess of all cancers combined (Becher *et al*, 1996, Fingerhut *et al*, 1991, Hooiveld *et al*, 1996, Ott and Zober, 1996). However, the UK Committee on Carcinogenicity (CoC) concluded that there was insufficient epidemiological and toxicological data on TCDD to conclude a causal link with cancer in humans, but that it would be prudent to consider TCDD as a "probable weak human carcinogen" (COC, 2001). Reviews of epidemiological studies published since 1998 have come to different conclusions. The CoC review concluded that updates of the industrial cohorts provided evidence for an excess total cancer mortality in exposed individuals in these cohorts of 13%-15%, and that the dose-response was significant indicating a causal interpretation could be considered credible although bias and confounding could not be ruled out. However, another review concluded that the evidence does not support the IARC's classification of TCDD as a Group 1 carcinogen, and that the evidence indicates that TCDD is not carcinogenic at low levels and that it may not be carcinogenic even at high levels (Cole *et al*, 2003). Steenland *et al.* (2004) also reviewed the new evidence and stated that it generally supports the 1997 IARC classification.

Numerous studies have examined occupational groups and those accidentally exposed to TCDD, but as it is a contaminant of industrial processes, it is difficult to measure exposures from these processes. In the summer of 1976 the contents of a reactor vessel in the trichlorophenol production department of a chemical plant near the town of Seveso, Italy, were vented directly into the atmosphere due to the failure of a safety device. Several thousand people were exposed to substantial quantities of TCDD. A follow-up study to 2001 of the population exposed observed no excess risk from all cancers in those who lived in both the high exposed zone (SMR=1.03, 95%CI=0.76-1.39) and low exposed zone (SMR=0.92, 95%CI=0.81-1.05). No cases of STS were observed over the 25-year period (Consonni *et al*, 2008).

A case-control study of 172 STS cases, diagnosed between 1990 and 1996, in Northern Italy observed the risk of developing sarcoma was 3.3 times higher (95%CI=1.24-8.76) among subjects with the longest exposure period and the highest exposure level (Zambon *et al*, 2007).

There continues to be conflicting evidence of an association between TCDD exposure and STS, risks ranging from 0 to over 10 (Berwick, 2006). Of the four studies assessed by IARC, only one had any STS cases and showed a non-significant increase. A retrospective mortality cohort study among 5172 workers at 12 plants in the US that produced chemicals contaminated with TCDD observed a non-significant excess of STS (Fingerhut *et al*, 1991). Further follow-up of the cohort identified no new STS deaths (four in total) but the risk remained high (SMR=2.32, 95%CI=0.63-5.93) (Steenland *et al*, 1999). In a study of 2479 male German workers exposed to phenoxy herbicides and dioxins no cases of STS were found (Becher *et al*, 1996). Similarly, in a Dutch study of 1167 workers exposed to phenoxy herbicides, chlorophenols and contaminants, no STS cases were found (Hooiveld *et al*, 1996, Hooiveld *et al*, 1998). A cohort mortality study of 243 men exposed to high doses of TCDD after a 1953 reactor accident also resulted in no cases of STS (Ott and Zober, 1996).

Coggon *et al.* (1991) studied 1222 men employed during 1963-1985 at one of four chemical plants and observed no STS cases.

A study of 1025 phenoxy herbicide producers and 703 sprayers followed-up between 1969 and 2000, found 813 producers and 699 sprayers were classified as exposed to dioxins (Mannetje *et al*, 2005). No STS deaths were seen among production workers and only one among sprayers (SMR=4.28, 95%CI=0.11-23.8).

In the late 1980s IARC developed an International Register of Workers Exposed to Phenoxy Herbicides and their contaminants. In 1997 the study consisted of 21863 male and female workers in 36 cohorts in 12 countries (Kogevinas *et al*, 1997). The cohorts included the four reviewed by IARC for their 1997 evaluation. Among workers exposed to TCDD or higher chlorinated solvents mortality from STS (six deaths) was higher than expected when compared with national mortality rates (SMR= 2.03, 95%CI= 0.75-4.43). Workers not exposed to TCDD or higher chlorinated dioxins had a SMR of 1.35 (95%CI= 0.16-4.88; two deaths). For individuals with 10-19 years of exposure the SMR (6.52) was significantly increased (95%CI= 1.35-19.06).

A study of 2187 male chemical production workers previously exposed to substantial levels of TCDD were followed-up between 1940 and 1995 observed a SMR of 2.4 (95%CI=0.3-8.6) based on only two cases (Bodner *et al*, 2003).

A previous meta-analysis of studies published between 1979 and 1987 concerning the associations between phenoxy acid herbicides and chlorophenols and the occurrence of STS did not provide strong support for an association (Johnson *et al*, 1990). The study compared the total number of deaths due to STS (N=169) in cohort studies compared to those expected, calculated using US SEER registry data. This resulted in a proportional mortality ratio (PMR) of 3.53 (95%CI=0.73-10.31). The summary OR for case-control studies was 1.1 (95%CI=0.9-1.4). A more recent meta-analysis of STS mortality in crop protection production manufacturing workers (including the IARC studies) included 22 studies results in a pooled SMR of 1.13 (95%CI=0.75-1.70) (Jones *et al*, 2009). In a sub-group of 20 cohorts of workers involved in the manufacture of phenoxy herbicides the summary risk estimate was 0.96 (95%CI=0.62-1.49).

A meta-analysis studies that investigated cancer risk in farmers published up to 1994 identified only six that published data on STS (Acquavella *et al*, 1998). From these studies a summary RR of 1.03 (95%CI=0.90-1.17) was obtained, with no difference between the type of study and no significant heterogeneity.

A recent analysis of cancer incidence in the US Agricultural Health Study was carried out (Alavanja *et al*, 2005). This is a large prospective cohort study of 89,658 pesticide applicators and their spouses, and was followed up to 2002. Only 13 STS cases were observed, 10 among private applicators (SIR=0.65, 95%CI=0.31-1.20) and three among their spouses (SIR=0.48, 95%CI=0.40-1.41), with none among commercial applicators. A study of mortality followed up to 2000 observed four deaths among private applicators (SMR=0.7, 95%CI=0.2-1.8) and three among their spouses (SMR=1.4, 95%CI=0.3-4.1) (Blair *et al*, 2005).

Among forestry workers, farmers and pesticide applicators and producers, in population case-control studies, exposure to phenoxy herbicides and chlorophenols has been associated with increased risk of STS (Eriksson *et al*, 1981, Eriksson *et al*, 1990, Hardell, 1977, Hardell and Ericksson, 1988a,b, Kogevinas *et al*, 1995, Wingren *et al*, 1990). A study of 1222 male forestry workers at a public electrical utility company in Canada who had worked for six months or more during 1950-1982 and had routine exposure observed no STS cases (Green, 1991). A case-control study of 19904 male patients diagnosed with cancer during the period 1980-1984 observed an increased risk for STS (OR=3.24) in forestry workers which was confined to men less than 60 years of age at registration (>20 years of age) (Reif *et al*, 1989). A case-control study of 96 STS cases also observed an excess risk among gardeners (OR=4.1, 95%CI=1.0-14.0) (Wingren *et al*, 1990). Hansen *et al*. (1992) followed a cohort of 4015 employed gardeners from 1975 to the end of 1984 for cancer incidence. Among male gardeners a significantly increased incidence was seen for STS (SIR=5.26, 95%CI=1.09-15.38).

Studies of cancer risk in the pulp and paper industry have reported no overall increase in cancer (Langseth and Andersen, 2000, McLean *et al*, 2006, Rix and Lynge, 1997, Rix *et al*, 1998). In a cohort of 23,718 male workers employed continuously for at least one year between 1920 and 1993 in Norway no cases of STS were reported (Langseth and Andersen, 2000). A cohort of 20,953 men and 4,415 women who worked in Danish paper mills between 1943 and 1990 and followed up to 1993 observed a SIR of 2.7 (95%CI=1.5-4.5) among women (based on 14 cases) but no increase among men (Rix and Lynge, 1997). A subsequent study by the same authors, and probably the same cohort, of cancer incidence in 14,362 workers also observed an increased risk in women (SIR=2.33, 95%CI=1.06-4.43) and no increase in men (SIR=0.95, 95%CI=0.26-2.43) (Rix *et al*, 1998). A recent international collaborative study of workers employed between 1920 and 1996 in 11 countries consisted of 60,468 workers (including the above two studies) (McLean *et al*, 2006). The study observed 12 deaths among workers ever exposed to volatile organochlorines (SMR=1.13, 95%CI=0.59-1.98), and four deaths among those with high exposure (SMR=1.75, 95%CI=0.48-4.48). Among those exposed to non-volatile organochlorine compounds four deaths from STS were observed (SMR=0.80, 95%CI=0.22-2.04). A total of 30 deaths from STS were seen among workers in the industry (SMR=1.12, 95%CI=0.76-1.60).

A population-based case-control study of STS among 357 Canadian men diagnosed between 1991 and 1994 observed 18 cases worked in the pulp and paper industry (Hossain *et al*, 2007). This resulted in a non-significant OR of 1.77 (95%CI=0.98-3.21). In a multivariate conditional logistic regression model, work in the industry remained significantly associated with an increased risk of STS (OR=2.01, 95%CI=1.09-3.71).

Polychlorinated biphenyls (PCBs) were widely used as a capacitor filling fluid due to its electrical isolation properties, as well as fire resistancy and very slow degradation. They have also been used as plasticizers in furnishers, in building construction, in paints, in self-carbonising copy paper and as lubricants. These lipophilic chemicals tend to persist in the environment, have long biological half-lives, and bioaccumulate in the food chain. As a result, exposure of the general population to these chemicals has occurred primarily through diet and through employment in certain occupations. PCBs are carcinogenic to experimental animals, and are classified as probably carcinogenic to humans by IARC (IARC, 1987). Recent reviews of the carcinogenicity of PCBs reported no excess risk of STS among exposed cohorts (Golden *et al*, 2003, Knerr and Schrenk, 2006).

2.1.2 Other Exposures

Radiation

Radiation exposure has been associated with STS in radium dial painters (Aub *et al*, 1952, Brues and Kirsh, 1977, Polednak *et al*, 1978, Rowland, 1975); however, this occupation has not existed for many decades. Workers in the nuclear industry have not shown any excess risk for STS, SMRs ranging from 0.45 to 1.11 (Atkinson *et al*, 2004, Cardis *et al*, 1995, Carpenter *et al*, 1994, Carpenter *et al*, 1998, Muirhead *et al*, 1999, Omar *et al*, 1999).

3 ATTRIBUTABLE FRACTION ESTIMATION

3.1 GENERAL CONSIDERATIONS

Substances and Occupations

Table 7 shows the substances considered in the estimation of the attributable fraction (AF) for soft tissue sarcoma.

Table 7 Substances considered in the estimation of the attributable fraction for soft tissue sarcoma.

Agents, Mixture, Circumstance	AF calculation	Strength of evidence	Comments
Group 1: Carcinogenic to Humans			
Agents, groups of agents			
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)	Y	Suggestive	
Exposure circumstances			
None identified			
Group 2A: Probably Carcinogenic to Humans			
Agents & groups of agents			
None identified			
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. A latency of between of around 20 years has been assumed for soft tissue sarcoma based on studies of farmers and insecticide exposure (Zahm *et al*, 1988). 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). Where the LFS is used, 1991 is used. A turnover factor is applied to estimate numbers ever exposed during the REP, determined mainly by the estimate of staff turnover per year during the period. For each exposure therefore, if an AF has been based on independent estimates of numbers exposed, the table of results includes the point estimate of numbers employed, the adjustment factor for CAREX if applicable, the staff turnover estimate, and the resulting estimate of numbers ever exposed during the REP. Other estimates used in the calculations that remain constant across exposures (unless otherwise stated) are given below:

- Number of years in REP = 20. The proportion in the workplace ever exposed is set to one, i.e. all are assumed to be exposed, in the absence of more detailed information. Where sources other than CAREX are used for the point estimate of numbers exposed, such as the LFS or Census of Employment, a precise as possible definition of workers exposed is sought.

- Numbers ever of working age during the target REP = 23.0 million men, 23.1 million women. This is the denominator for the proportion of the population exposed, and is based on population estimates by age cohort in the target year

- Total deaths from soft tissue sarcoma, Great Britain, 2005 = 317 for men aged 15-84 (283 in England and Wales, 34 in Scotland), 240 for women aged 15-79 (217 in England and Wales, 23 in Scotland)

- Total registrations for soft tissue sarcoma, Great Britain, 2004 = 662 for men aged 15-84 (562 in England, 41 Wales, 59 in Scotland), 401 for women aged 15-79 (336 in England, 28 Wales, 37 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 TCDD

3.2.1 Risk estimate

Berwick (2006) summarised a large number of studies that have studied the relationship between various exposures (reviewed in section 2) and the risk of STS. What is evident is that all types of study have been employed and that in the majority of studies, especially cohort, only a few STS cases/deaths have occurred. The cohorts also are not appropriate populations for GB, because of whom they investigated, e.g. Vietnam veterans, rice workers, and individuals exposed as a result of an accident. Therefore, as STS is rare, meta-analyses of a large number of studies have been chosen.

The summary risk estimate (SMR=1.03, 95%CI=0.90-1.17 (A in Table 8)) from the meta-analysis of Acquavella et al. (Acquavella *et al*, 1998) will be used to calculate the AF for workers in farming, horticultural trades and agriculture/fishing (not elsewhere classified), and gardeners and groundsmen, forestry workers and pest control workers. For workers involved in the manufacture of pesticides the summary risk estimate from meta analysis by Jones *et al.* (2009) (SMR=1.13, 95%CI=0.75-1.70 (J in Table 8)). This estimate will be used and not the one for phenoxy herbicide cohorts because the number of workers specifically involved in the manufacture of these pesticides in GB cannot be identified.

For workers in pulp manufacture the risk estimate (SMR=1.13, 95%CI=0.59-1.98 (M in Table 8)), based on 12 cases, from the international collaborative study of 60,468 workers employed between 1920 and 1996 in 11 countries will be used (McLean *et al*, 2006). This study included one from Scotland that investigated mortality in 4242 workers between 1955 and 1992 but did not report any STS cases (Coggon *et al*, 1997).

IARC has established a register of workers exposed to phenoxy-acid herbicides and chlorophenols, substances that are known to be contaminated with dioxins (especially TCDD) and furans (Kogevinas *et al*, 1997). The risk estimate of 2.03 (95%CI=0.75-4.43 (K in Table 8)) will be used for industries where exposure may occur but levels of exposure are unknown. The risk estimate from the Kogevinas study was chosen instead of that by Bodner et al. (2003) because it studied over 21,000 workers and observed six deaths from STS among exposed workers, whereas the latter investigated 2,187 workers and observed only two STS cases.

3.2.2 Numbers exposed

A range of industrial processes operating in the UK for the potential to release dioxins were screening and a short-listed of 23 were identified for consideration as potential emitters (Eduljee and Dyke, 1996). They include the combustion of coal (industrial/commercial, power generation), waste oil, municipal waste, wood, straw, tyres, landfill gas, chemical waste, clinical waste and sewage sludge. Other processes included industries involved in treated wood, gas production, sinter plants iron and steel, non-ferrous metals, manufacture of cement, lime, glass and ceramics, halogenated chemicals, carbon regeneration, asphalt mixing and PCP in timber processes, and pesticide production. According to this study pesticide production had an emission factor of 0.01-0.025 µg I-TEQ of dioxin per tonne of product produced. They estimated about 12,950 tonnes of product were produced in a year, which equated to between 130 and 325 µg I-TEQ of dioxin. On the basis of emission factors the occupations with the potential for exposure to dioxins greater than those in pesticide production are given in the lower half of table 8 were assigned a level of exposure compared to pesticide production.

Table 8 Number of workers in different industries with potential for exposure to TCDD in 1991 (Source: Labour Force Survey)

SOC/SIC Code	Job Title	Number employed			Risk Estimate[$]
1991		Men	Women	Total	
A-B	Agriculture & horticulture	421820	118624	540444	A
	Forestry	19012	4318	23330	A
	Gardeners & Groundsmen	131962	7459	139421	A
C-E	Formulated pesticides	1343	1084	2427	J
C-E	Pulp manufacture	40620	12579	53199	M
C-E	Wood sawmill planning impregnation	9191		9191	K
	Organic chemical manufacture	5472	1172	6644	K
	Flat glass manufacture	15158	3881	19039	K
	Glass containers	5489	2559	8048	
	Other glass products	20647	6531	27178	K
	Refractory goods	7731	1113	8844	K
	Ceramic goods	24447	18338	42785	K
	Cement, lime, & plaster manufacture	9434	1195	10629	K
	Iron & steel industry	90164	9395	99559	K
	Steel tubes	30233	3612	33845	K
	Steel wire & wire products	15225	2989	18214	K
	Other drawing cold rolling forming of steel	8146	799	8945	K
	Aluminium & aluminium alloys	19969	3704	23673	
	Copper, brass & other copper alloys	9228	4467	13695	K
	Other non-ferrous metals & their alloys	6863	657	7520	K
	Scrap dealers & metal merchants	7152		7152	K

$ A=Acquavella estimate; J=Jones estimate; M=McLean estimate; K=Kogevinas estimate

3.2.3 AF calculation:

The estimated total (male and female) attributable fraction for soft tissue sarcoma associated with occupational exposure to dioxins (TCCD) is 2.27% (95%CI=0.0-7.73), which equates to 13 (95%CI= 0-45) deaths and 27 (95%CI=0-90) registrations. The estimated AF for men is 3.38% (95%CI=0-11.37) resulting in 11 (95%CI=0-36) deaths and 22 (95%CI=0-75) attributable registrations; and for women the AF is 1.06% (95%CI=0.00-3.76), resulting in 3 (95%CI=0-9) deaths and 4 (95%CI=0-15) attributable registration respectively (Table 9).

Table 9 Summary results for occupational exposure to TCDD

				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	Jones *et al*. (2009)	J	C-E	1.13	1343	1	0.09	3450	0.0002	0.0000	0.0000	0.0001	0	0	1	0	0	0
		J	All		1343			3450	0.0002	0.0000	0.0000	0.0001	0	0	1	0	0	0
	McLean *et al*, (2006)	M	C-E	1.13	40620	1	0.09	104359	0.0045	0.0006	0.0000	0.0046	0	0	1	0	0	3
		M	All		40620			104359	0.0045	0.0006	0.0000	0.0046	0	0	1	0	0	3
	Kogevinas *et al*, (1997)	K	C-E	2.03	284549	1	0.09	731053	0.0318	0.0316	0.0000	0.1113	10	0	35	21	0	74
		K	All		284549			731053	0.0318	0.0316	0.0000	0.1113	10	0	35	21	0	74
	Acquavella *et al*, (1998)	A	A-B	1.03	572794	1	0.07	1245199	0.0541	0.0016	0.0000	0.0090	0	0	3	1	0	6
		A	All		572794			1245199	0.0541	0.0016	0.0000	0.0090	0	0	3	1	0	6
		All	All		899306			2084061	0.0906	0.0338	0.0000	0.1137	11	0	36	22	0	75
Women	Jones *et al*. (2009)	J	C-E	1.13	1084	1	0.14	3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
		J	All		1084			3993	0.0002	0.0000	0.0000	0.0001	0	0	0	0	0	0
	McLean *et al*, (2006)	M	C-E	1.13	12579	1	0.14	46338	0.0020	0.0003	0.0000	0.0021	0	0	1	0	0	1
		M	All		12579			46338	0.0020	0.0003	0.0000	0.0021	0	0	1	0	0	1
	Kogevinas *et al*, (1997)	K	C-E	2.03	60412	1	0.14	222542	0.0096	0.0098	0.0000	0.0365	2	0	9	4	0	15
		K	All		60412			222542	0.0096	0.0098	0.0000	0.0365	2	0	9	4	0	15
	Acquavella *et al*, (1998)	A	A-B	1.03	130401	1	0.1	376562	0.0163	0.0005	0.0000	0.0028	0	0	1	0	0	1
		A	All		130401			376562	0.0163	0.0005	0.0000	0.0028	0	0	1	0	0	1
		All	All		204476			649435	0.0281	0.0106	0.0000	0.0376	3	0	9	4	0	15

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

4 OVERALL ATTRIBUTABLE FRACTION

4.1 SUMMARY OF RESULTS

The results are summarised in Tables 10 and 11.

Table 10 Summary of relative risks used to calculate AF

Agent	Exposure	RR	LL	UL
TCDD	A	1.03	0.9	1.17
TCDD	J	1.13	0.75	1.7
TCDD	M	1.13	0.59	1.98
TCDD	K	2.03	0.75	4.43

Table 11 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)
TCDD	2084061	649435	0.0906	0.0281	0.0338	0.0000	0.1137	0.0106	0.0000	0.0376	11	3	22	4

4.2 EXPOSURES BY INDUSTRY/JOB

Table 12 shows for industry categories from CAREX and job categories from LFS, attributable registrations in 2004 and attributable deaths in 2005 by agent.

Table 12 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)
TCDD	Agriculture & horticulture	421820	118624	1	0	0	0
TCDD	Pulp manufacture	40620	12579	0	0	0	0
TCDD	Wood sawmill planning impregnation	9191	0	1	0	0	0
TCDD	Flat glass manufacture	15158	3881	1	1	0	0
TCDD	Glass containers	5489	2559	0	0	0	0
TCDD	Other glass products	20647	6531	2	1	0	0
TCDD	Refractory goods	7731	1113	1	0	0	0
TCDD	Ceramic goods	24447	18338	2	1	1	1
TCDD	Cement, lime, & plaster manufacture	9434	1195	1	0	0	0
TCDD	Iron & steel industry	90164	9395	7	3	1	0
TCDD	Steel tubes	30233	3612	2	1	0	0
TCDD	Steel wire & wire products	15225	2989	1	1	0	0
TCDD	Other drawing cold rolling forming of steel	8146	799	1	0	0	0
TCDD	Aluminium & aluminium alloys	19969	3704	1	1	0	0
TCDD	Copper, brass & other copper alloys	9228	4467	1	0	0	0
TCDD	Other non-ferrous metals & their alloys	6863	657	1	0	0	0
TCDD	Scrap dealers & metal merchants	7152	0	1	0	0	0
TCDD	**Total**	**899306**	**204476**	**22**	**11**	**4**	**3**

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6 STATISTICAL APPENDIX

Formulae used in the estimation of AF

Levin's equation

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

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

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

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

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

HSE

Health and Safety Executive

The burden of occupational cancer in Great Britain

Soft tissue sarcoma

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 soft tissue sarcoma 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 soft tissue sarcoma related to overall occupational exposure (to dioxins) is 2.27% (95%Confidence Interval (CI)= 0.0-7.73), which equates to 13 (95%C= 0-45) deaths and 27 (95%CI= 0-90) registrations.

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