# SOFT TISSUE SARCOMA, NON-HODGKIN LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA IN WORKERS EXPOSED TO PHENOXY HERBICIDES: EXTENDED FOLLOW-UP OF A UK COHORT

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**Abstract**

*Objectives:* To provide further information on the possible carcinogenicity of phenoxy herbicides, and in particular their relationship to soft tissue sarcoma (STS), non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia (CLL).

*Methods:*  We extended follow-up to December 2012 for 8,036 men employed at five factories in the UK which had manufactured phenoxy herbicides, or in a contract spraying business. Mortality was compared with that for England and Wales by the person-years method. Nested case-control analyses compared men with incident or fatal STS (n=15) or NHL/CLL (n=74) and matched controls (up to 10 per case).

*Results:* 4,093 men had died, including 2,303 since the last follow-up. Mortality from all causes and all cancers was close to expectation, but an excess of deaths from NHL was observed among men who had worked for ≥ 1 year in jobs with more than background exposure to phenoxy herbicides (19 deaths, standardised mortality ratio 1.85, 95% confidence interval (CI) 1.12-2.89). Four deaths from STS occurred among men potentially exposed above background (3.3 expected). In the nested case-control analyses, there were no significantly elevated risks or consistent trends across categories of potential exposure, for either STS or NHL/CLL. The highest odds ratio (for STS in men who had worked for ≥1 year in potentially exposed jobs) was only 1.30 (95%CI 0.30-5.62).

*Conclusions:* Our findings are consistent with the current balance of epidemiological evidence. If phenoxy herbicides pose a hazard of either STS or NHL then any absolute increase in risk is likely to be small.

## Key words

Phenoxy, MCPA, 2,4-D, soft tissue sarcoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, cohort, mortality, incidence

## What this paper adds

## Previous studies have suggested an increased risk of soft tissue sarcoma and non-Hodgkin lymphoma in workers exposed to phenoxy herbicides, but evidence has been inconsistent and the existence of a hazard remains controversial

* In extended follow-up of a large British cohort of chemical manufacturers and pesticide sprayers, we found little indication that exposure to phenoxy herbicides increases the risk of either disease
* If phenoxy herbicides pose a hazard of either STS or NHL then any absolute increase in risk is likely to be small.

## Introduction

The phenoxy herbicides are a class of selective weed-killers, which since their first commercial production in the 1940s have been widely used in agriculture, forestry, parks and gardens. They include, among others, the compounds 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-methyl-4-chlorophenoxyacetic acid (MCPA). 2,4,5-T is liable to contamination during manufacture by 2,3,7,8-tetrachlorodibenzodioxin (TCDD) [1] which is an established human carcinogen [2], and products containing 2,4,5-T are no longer approved for use in the European Union or the USA. TCDD is not found in other phenoxy herbicides, although some of them may contain traces of other, less toxic, dioxin congeners [3].

Phenoxy acids and their salts and esters are not genotoxic, and have not been found to cause cancer when tested in laboratory animals [3-5]. However, early case-control studies in Sweden suggested associations with soft tissue sarcoma (STS) [6,7] and non-Hodgkin lymphoma (NHL) [8], with odds ratios for occupational use in excess of five. Since then, extensive epidemiological research has failed to confirm either hazard, and currently chlorophenoxy acids are classified by the International Agency for research on Cancer (IARC) only as possibly carcinogenic to humans (Group 2B) [9]. However, some studies have produced positive results, and recent systematic reviews have concluded that because of statistical uncertainties, it is not possible to rule out an increased risk of these cancers [10, 11]. In particular, the single most robust and informative investigation, which was a case-control analysis nested within a large international cohort study coordinated by IARC, found an odds ratio of 10.3 (95% confidence interval 1.2-91) for STS in workers exposed to any phenoxy herbicide [12].

The 36 sub-cohorts that contributed to the IARC study included employees at five factories in the UK which had manufactured phenoxy herbicides, together with a group of contract pesticide sprayers who had worked for one of the same companies [13,14]. The last published follow-up of these workers was as part of the IARC study [15], and covered a period up to 1990/91.

To provide further information on the possible carcinogenicity of phenoxy herbicides, and in particular their relationship to STS, NHL and chronic lymphocytic leukaemia (CLL) (which is now considered a form of NHL [16,17]), we extended follow-up of the six British sub-cohorts to December 2012.

## Methods

The definition of the cohort and potential exposures of cohort members are summarised in Table 1. All of the sub-cohorts were engaged in the manufacture, formulation or application of a range of phenoxy herbicides, as well as other products, although not all of the compounds listed in Table 1 were handled throughout the entire period during which subjects might have worked. Further information about this, and about the manufacturing processes, has been reported previously [13,14]. 2,4,5-T was produced at one factory (sub-cohort A) during 1968-78, and at times was formulated at each of the other factories (sub-cohorts B-E). However, it was virtually never used by the sprayers (sub-cohort F).

At each company, cohort members were identified from personnel, wages or other plant records, and demographic information was abstracted together with job histories. The latter were then used to classify subjects according to the timing and duration of their potential exposure to phenoxy compounds. This classification was based on dates of starting and finishing relevant jobs. Because products were manufactured and formulated in campaigns, and sprayers applied other products as well as phenoxy herbicides, exposures would have been intermittent. The classification took into account that sprayers would not use phenoxy herbicides during the autumn and winter months, but beyond this, we did not have information on the dates of exposures within jobs. Thus, it was only possible to determine periods when an individual was liable to be exposed. Some jobs (e.g. clerical staff, sales workers and managers who did not normally enter production areas) were classed as having only background exposure. Most individuals who worked for longer than a year in other jobs would have experienced exposures substantially above background. In sub-cohorts E and F, we further distinguished between jobs with high potential for exposure (principally chemical process workers, certain laboratory occupations and spray operatives) and others in which average exposures over the long term were likely to be lower (e.g. maintenance staff, workers in chemical stores and transport). For a few men in sub-cohorts E and F, job title was available for only the most recent of several jobs that had been held at the company, and it was assumed that earlier jobs had similar exposure to the one that was recorded.

The cohort was traced through the Health and Social Care Information Centre (HSCIC – previously the National Health Service Central register) to the end of 2012, with supplementary information in a few cases from national insurance records. Information was obtained about all deaths and cancer registrations, and also about loss to follow-up from emigration or for other reasons. Underlying and contributing causes of death were coded to the ninth revision of the International Classification of Diseases (ICD 9) for deaths up to December 2000, and the tenth revision (ICD 10) for those that occurred subsequently. For subjects with registered cancers, we obtained information about the type of cancer and date of registration.

Statistical analysis was carried out with Stata (Version 13) software (StataCorp LP, College Station, Texas). The person-years method was used to compare the mortality of the cohort by underlying cause of death with that in the national population of England and Wales. The reference rates were for five-year age bands and five-year calendar periods (except for deaths during 2010-2012, for which rates during 2005-2012 were used). A worker was considered to be at risk from the later of: a) the date from which he met the criteria for entry to the cohort; and b) the date when he first entered the relevant exposure category. He then remained at risk until the earliest of: a) exit from the relevant exposure category; b) death; c) loss to follow-up for other reasons; or d) 31 December 2012. Men who could not be traced at the HSCIC or through the National Insurance Index were treated as lost to follow-up at their last known date of employment. Results were summarised as standardised mortality ratios (SMRs) with 95% confidence intervals (95%CIs).

In addition to the person-years analysis, we carried out a nested case-control study of STS and for the combination of NHL and CLL. For this, we identified cases not only from underlying causes of death, but also from cancer registrations (which included information about histology) and from contributing causes on death certificates. We then applied a prescribed algorithm to match each case with up to 10 controls from the same sub-cohort, who had the same year of birth to within two years, and were under follow-up at the time when the case was first recorded as having STS or NHL/CLL. Associations with duration of potential exposure to phenoxy herbicides (lagged by five years) were assessed by conditional logistic regression, and summarised by odds ratios (ORs). These analyses excluded a small number of subjects (22) whose date of first potential exposure for at least one year was unknown.

## Results

Table 1 shows the numbers of men who were included in the analysis by sub-cohort, and also the numbers who were classed as having potential for exposures above background. In total, the cohort comprised 8,036 subjects, including 54 who belonged to both of sub-cohorts E and F, and whose occupational histories from the two categories of employment were merged. Most men (6,168, 76.8%) had worked in jobs entailing greater than background exposure to phenoxy acids, including 2,653 (33.0%) with potential for such exposure over a year or longer. In sub-cohorts E and F, a total of 1,669 workers had been employed for at least a year in jobs with potential for high exposure.

Over the full period of study there were 4,093 deaths, including 2,303 since the last follow-up in 1990/91. One hundred and thirty six subjects could not be traced at HSCIC or through National Insurance records, and were followed only to their last known date of employment. A further 772 were lost to follow-up subsequently, including 297 because of emigration.

Table 2 summarises the mortality of the cohort from major categories of disease. In comparison with national rates, mortality was close to expectation for all causes, all cancers, and each of circulatory and respiratory disease, both in the cohort as a whole, and in the subset of workers with potential exposure to phenoxy acids above background (SMRs 0.94 to 1.02). However, there was a significant excess of deaths from injury and poisoning (187 deaths, SMR 1.26, 95%CI 1.08-1.45 overall; 141 deaths, SMR 1.26, 95%CI 1.06-1.49 in those with potential for more than background exposure), and from digestive diseases among men potentially exposed above background (120 deaths, SMR 1.20, 95%CI 1.00-1.44). Most of the deaths from injury and poisoning (103/187) occurred when workers were no longer employed at the participating companies, and they were largely in sub-cohort F. None of the deaths during employment was from accidental poisoning by pesticides.

Table 3 shows the mortality of cohort members from specific categories of cancer, overall and by duration of potential for exposure above background. There was an excess of deaths from NHL among men who had worked for a year or longer in exposed jobs (19 deaths, SMR 1.85, 95%CI 1.12-2.89), but no other significant associations were observed. There were four deaths from STS (3.3 expected) among men potentially exposed above background, including three (1.5 expected) in those who had done such work for at least a year.

Supplementary Tables S1 to S6 show separate findings for each sub-cohort on mortality from major causes of death and from the more common cancers (>10 deaths observed or expected in the full cohort) among workers potentially exposed above background. Results are presented both for the entire follow-up period, and also for the period since the cohort was last analysed as part of the IARC collaborative study [15]. Three sub-cohorts (A, B and D) had significantly elevated total mortality (SMRs of 1.58, 1.47 and 1.28 respectively), which was driven mainly by excesses of deaths from respiratory and digestive disease, and in sub-cohort A, also from circulatory disease (136 deaths, SMR 1.80, 95%CI 1.51-2.13). In these three sub-cohorts mortality from lung cancer was also higher than expected (SMRs of 1.46, 1.66 and 1.76 based on 26, 8 and 27 deaths respectively). In contrast, patterns of mortality in sob-cohorts C, E and F were unremarkable.

In addition to the four deaths from STS that were included in the person-years analysis summarised in Table 3, we identified a further 11 cases from scrutiny of death certificates and cancer registrations, giving a total of 15 (Table 4), who were matched with 150 controls. Twenty nine cases of NHL and 12 of CLL were recorded as underlying causes of death, and a further 20 and 13 respectively were ascertained from contributing causes of death and cancer registrations (Supplementary Table S7). This gave a total of 74 cases of NHL/CLL, who were matched with 719 controls. Table 5 summarises the associations of STS and NHL/CLL with duration and level of potential for exposure above background. There were no significantly elevated risks or consistent trends across categories of potential exposure, for either group of cancers. The highest odds ratio (for soft tissue sarcoma in men who had worked for at least one year in jobs with potential exposure) was only 1.30 (95%CI 0.30-5.62).

## Discussion

Our extended follow-up added substantially to the information that was previously available for the six sub-cohorts studied, with an additional 2,303 deaths available for analysis. Comparison of mortality with that in the national population suggested a possible risk of NHL. However, that was not supported by a nested case-control analysis which included cases with non-fatal as well as fatal disease, and also men with CLL, which is now thought to be classified most appropriately with solid non-Hodgkin lymphomas [16,17]. Nor did we find an increased risk of STS, either in person-years or nested case-control analyses.

Apart from its size, a major strength of our study was the high exposures that are likely to have been incurred by many of the subjects in comparison with those studied in community-based case-control investigations. Furthermore, the assessment of exposure did not rely on subjects’ personal recall, which is often liable to differential error in case-control studies, leading to spurious overestimation of risk. On the other hand, because the production and application of phenoxy herbicides was intermittent, the individual exposures of our cohort members could not be ascribed with certainty. We think it unlikely that many men classed as having only background exposure would in fact have had higher exposures – for example, because they were still employed at the time when the sub-cohorts were assembled and later moved to other jobs at the same companies (it was not practical to update occupational histories for such workers). However, it may be that some men classed as potentially exposed above background did not in fact experience such exposure, especially if they were only in relevant jobs for short periods. Any such error will have tended to bias risk estimates towards the null.

Another challenge was reliable and complete ascertainment of the cancers of main interest. Survival rates for STS and NHL are relatively high, meaning that cases will not necessarily be picked up from death certificates. Moreover, deaths from STS are often coded as cancers of the anatomical site at which they occur (along with more numerous carcinomas) rather than as STS specifically. These problems were addressed by ascertaining cases also from cancer registrations (which include a separate histology code) and from contributing causes on death certificates. Because in the past the completeness of cancer registration in England and Wales varied by region, there were no suitable comparator rates for a person-years analysis of cancer incidence. Instead, therefore, we carried out nested case-control analyses in which controls were matched to cases by sub-cohort as well as approximately by year of birth.

The nested case-control study of STS included 15 cases and 150 controls, and as such was the largest such analysis to date. A previous case-control study nested within the IARC international cohort study was based on 11 cases of STS and 55 controls [12]. That study found an OR of 10.32 (95%CI 1.18-90.56) for exposure to any phenoxy herbicide, with only one of 11 cases classed as unexposed. In contrast, risk estimates in our study were much lower (ORs 1.30, 95%CI 0.30-5.62, for potential exposure over ≥1 year; and 0.95, 95%CI 0.19-4.88, for potential high exposures in sub-cohorts E and F). While misclassification of exposures may have caused a little bias towards the null, these results suggest that any increase in risk for this rare group of tumours is at most small, and substantially less than was suggested by early case-control studies, which may have been prone to important recall bias [6,7].

While we did find a significant excess of deaths from NHL in our person-years analysis (SMR 1.85, 95%CI 1.12-2.89), we consider that greater weight should be given to the nested case-control analysis, which included non-fatal as well as fatal cases, and men with CLL as well as solid lymphomas. That analysis found no significant elevation of risk with exposure to phenoxy herbicides, the highest risk estimate (for those with potential for high exposure in sub-cohorts E and F) being 1.22 (95%CI 0.61-2.46). This is consistent with the findings of a recent systematic review, which examined results for NHL from 13 cohort and 20 case-control studies, and found little evidence of in support of a hazard [11].

Although our findings for STS and NHL gave little indication of a hazard, three of the sub-cohorts exhibited notably elevated mortality from all causes, respiratory disease, digestive disease, lung cancer, and in the case of sub-cohort A, also circulatory disease. The excess of circulatory disease in sub-cohort A was noted when the cohort was first analysed in 1991 [14]. At that time, a nested case-control analysis did not suggest an association with work in any specific department, and it was concluded that the elevated mortality might be attributable to a combination of smoking and other non-occupational causes. A confounding effect of smoking (about which we did not have data) would be consistent with the increased mortality from respiratory disease and lung cancer, which was found also in sub-cohorts B and D. It seems unlikely that the excesses of these diseases were caused by phenoxy herbicides, since they did not extend to the other three sub-cohorts. Nor has a relationship to these diseases been suggested by other cohort studies of phenoxy herbicide workers. For example, in the IARC international cohort of workers exposed to phenoxy herbicides and chloropohenols, the SMRs for circulatory disease, respiratory disease and lung cancer in men were 0.91 (95%CI 0.87-0.95), 0.82 (95%CI 0.72-0.92) and 1.09 (95%CI 0.98-1.20) [15]. The factories at which sub-cohorts A, B and D worked were all located in relatively deprived industrial areas, whereas sub-cohorts C, E and F were based in more affluent places.

Overall, the results of our extended follow-up are consistent with the current balance of epidemiological evidence in not pointing clearly to a hazard of either STS or NHL. Given the rarity of these cancers, the findings suggest that if there is a hazard, then any absolute increase in risk is likely to be small.

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**Table 1 Definition of cohort and potential exposures**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sub-cohort** |  | **Activity** |  | **Phenoxy herbicides produced, formulated or applieda** |  | **Other chemicals produced, formulated or applied** |  | **Definition of cohort** |  | **No. of men** |  | **Number potentially exposed to phenoxy acids above background** |
| **Ever** | **For ≥ 1 year** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| A |  | Manufacture and formulation |  | 2,4,5-T; 2,4-D: 2,4-DP: 2,4-DB; MCPA; MCPP; MCPB, PCPA; PAA |  | Picric acid; dinitro-o-butyl phenol; dinitro-o-cresol; simazine; aminotriazole; oxynils |  | All manual employees during April 1975-October 1985 |  | 1,146 |  | 934 | 462 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| B |  | Manufacture and formulation |  | 2,4,5-T; 2,4-D; 2,4-DP; 2,4-DB; MCPA; MCPP; MCPB |  | Dithiocarbamates; organophosphorus compounds; carbamates; dinocap; toluidine compounds; urea herbicides; imidazole compounds; phthalimide compounds  |  | All weekly paid employees during March 1969-November 1985 |  | 272 |  | 272 | 86 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C |  | Manufacture and formulation |  | 2,4,5-T; 2,4-D; MCPB; PBA |  | Aminophylline; metronidazole; sulphonamides; oxynils; dinocap; asulam; sodamide; diflufenican |  | All process workers on phenoxy plant during January 1963-December 1984; all formulators and packers during January 1982-December 1984; All maintenance workers during July 1967-December 1984  |  | 345 |  | 345 | 185 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| D |  | Manufacture and formulation |  | 2,4,5-T; 2,4-D; 2,4-DP; MCPA; MCPP |  | Metallic soaps; plasticiser esters; naphthenic acid; alkyl phenols; phthalate esters; 2,4,6-trichlorophenol |  | All weekly paid employees during April 1969-December 1985 |  | 520 |  | 511 | 251 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| E |  | Manufacture and formulation |  | MCPA; 2,4,5-T; and others |  | Copper oxychloride; dinitro orthocresol; organophosphorus compounds; chlortriazine herbicides |  | All men employed during January 1947-December 1975 |  | 2,738 |  | 1,544 | 848 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| F |  | Contract spraying |  | MCPA; others but virtually never 2,4,5-T |  | Copper oxychloride; dinitro orthocresol; organophosphorus compounds; chlortriazine herbicides |  | All men employed during January 1947-December 1975 |  | 3,015 |  | 2,562 | 821 |

a2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4-DP = 2,4-dichlorophenoxypropionic acid; 2,D-B = 2,4-dichlorophenoxybutyric acid; MCPA = 2-methyl-4-chlorophenoxyacetic acid; MCPP = 2-methyl-4-chlorophenoxypropionic acid; MCPB = 2-methyl-4-chlorophenoxybutyric acid; PCPA = parachlorophenoxyacetic acid; PAA = phenoxyacetic acid; PBA = phenoxybutyric acid

bIncludes 24 men who subsequently worked also in cohort F

cIncludes 30 men who subsequently worked also in cohort E

**Table 2 Mortality of cohort from major disease categories, 1947-2012**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cause of death** | **ICD Codes** |  | **All workers** |  | **Workers potentially exposed to phenoxy acids above background** |
|  |  |
|  | **ICD 9** | **ICD 10** |  | **Deaths observed** | **Deaths expected** | **SMR** | **(95% CI)** |  | **Deaths observed** | **Deaths expected** | **SMR** | **(95% CI)** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| All cancers | 140-208 | C00-C97 |  | 1,205 | 1,213.8 | 0.99 | 0.94-1.05 |  | 900 | 880.7 | 1.02 | 0.96-1.09 |
| Circulatory disease | 390-459 | I00-I99 |  | 1,737 | 1,793.0 | 0.97 | 0.92-1.02 |  | 1,227 | 1,263.2 | 0.97 | 0.92-1.03 |
| Respiratory disease | 460-519 | J00-J99 |  | 454 | 484.7 | 0.94 | 0.85-1.03 |  | 323 | 335.7 | 0.96 | 0.86-1.07 |
| Digestive diseases | 008-009, 520-579 | K00-K93 |  | 156 | 136.4 | 1.14 | 0.97-1.34 |  | 120 | 99.7 | 1.20 | 1.00-1.44 |
| Injury and poisoning | 800-999 | U509, V01-Y89 |  | 187 | 148.6 | 1.26 | 1.08-1.45 |  | 141 | 111.5 | 1.26 | 1.06-1.49 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| All Causes | 001-999 | A00-R99, U5009, V01-Y89 |  | 4,093 | 4,084.0 | 1.00 | 0.97-1.03 |  | 2,974 | 2,911.7 | 1.02 | 0.99-1.06 |

**Table 3 Mortality of cohort from specific cancers, 1947-2012**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cancer** | **ICD Codes** |  | **All workers** |  | **Workers potentially exposed to phenoxy acids above background** |  | **Workers potentially exposed to phenoxy acids above background for ≥ 1 yearc** |
|  |  |
|  |  |
| **ICD 9** | **ICD 10** |  | **Obs** | **Exp** | **SMR** | **95%CI** |  | **Obs** | **Exp** | **SMR** | **95%CI** |  | **Obs** | **Exp** | **SMR** | **95%CI** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lip | 140 | C00 |  | 0 | 0.3 | 0.00 | 0.00-11.53 |  | 0 | 0.2 | 0.00 | 0.00-17.45 |  | 0 | 0.1 | 0.00 | 0.00-35.84 |
| Tongue | 141 | C01-C02 |  | 8 | 4.2 | 1.93 | 0.83-3.80 |  | 5 | 3.1 | 1.63 | 0.53-3.80 |  | 3 | 1.4 | 2.16 | 0.45-6.32 |
| Moutha | 143-145 | C03-C06 |  | 2 | 3.8 | 0.53 | 0.06-1.90 |  | 1 | 2.8 | 0.36 | 0.01-1.99 |  | 0 | 1.3 | 0.00 | 0.00-2.89 |
| Pharynxa | 146-149.1 | C09-C14.2 |  | 4 | 8.2 | 0.49 | 0.13-1.25 |  | 4 | 6.1 | 0.66 | 0.18-1.68 |  | 0 | 2.7 | 0.00 | 0.00-1.34 |
| Oesophagus | 150 | C15 |  | 55 | 55.8 | 0.99 | 0.74-1.28 |  | 46 | 41.6 | 1.11 | 0.81-1.48 |  | 17 | 19.0 | 0.89 | 0.52-1.43 |
| Stomach | 151 | C16 |  | 66 | 84.3 | 0.78 | 0.61-1.00 |  | 43 | 58.8 | 0.73 | 0.53-0.99 |  | 21 | 28.0 | 0.75 | 0.46-1.15 |
| Small intestinea | 152 | C17 |  | 4 | 2.4 | 1.67 | 0.46-4.28 |  | 4 | 1.8 | 2.26 | 0.62-5.80 |  | 2 | 0.8 | 2.48 | 0.30-8.96 |
| Large intestine | 153 | C18 |  | 77 | 79.1 | 0.97 | 0.77-1.22 |  | 50 | 57.3 | 0.87 | 0.65-1.15 |  | 23 | 26.8 | 0.86 | 0.54-1.29 |
| Rectum | 154 | C19-C21 |  | 39 | 51.5 | 0.76 | 0.54-1.04 |  | 31 | 37.1 | 0.84 | 0.57-1.19 |  | 14 | 17.3 | 0.81 | 0.44-1.36 |
| Liverb | 155.0-155.1 | C22 |  | 20 | 16.2 | 1.24 | 0.76-1.91 |  | 14 | 12.3 | 1.14 | 0.62-1.91 |  | 4 | 5.5 | 0.72 | 0.20-1.85 |
| Gall bladderb | 156 | C23-C24 |  | 2 | 4.7 | 0.43 | 0.05-1.55 |  | 1 | 3.3 | 0.30 | 0.01-1.68 |  | 0 | 1.6 | 0.00 | 0.00-2.35 |
| Pancreas | 157 | C25 |  | 54 | 52.0 | 1.04 | 0.78-1.35 |  | 39 | 38.0 | 1.03 | 0.73-1.40 |  | 13 | 17.6 | 0.74 | 0.39-1.26 |
| Nose and nasal sinuses | 160 | C30-C31 |  | 3 | 1.7 | 1.80 | 0.37-5.26 |  | 3 | 1.2 | 2.50 | 0.52-7.31 |  | 0 | 0.6 | 0.00 | 0.00-6.66 |
| Larynx | 161 | C32 |  | 7 | 10.7 | 0.66 | 0.26-1.35 |  | 7 | 7.7 | 0.91 | 0.36-1.87 |  | 3 | 3.6 | 0.84 | 0.17-2.44 |
| Lung | 162 | C33-C34 |  | 392 | 388.7 | 1.01 | 0.91-1.11 |  | 298 | 278.7 | 1.07 | 0.95-1.20 |  | 138 | 131.4 | 1.05 | 0.88-1.24 |
| Bone | 170 | C40-C41 |  | 4 | 2.5 | 1.60 | 0.44-4.09 |  | 3 | 1.8 | 1.67 | 0.35-4.89 |  | 1 | 0.8 | 1.27 | 0.03-7.07 |
| Soft tissue sarcomaa | 171 | C46, C47, C49 |  | 4 | 4.3 | 0.92 | 0.25-2.36 |  | 4 | 3.3 | 1.22 | 0.33-3.13 |  | 3 | 1.5 | 2.05 | 0.42-5.98 |
| Melanomaa | 172 | C43 |  | 7 | 10.7 | 0.66 | 0.26-1.35 |  | 6 | 8.2 | 0.73 | 0.27-1.59 |  | 2 | 3.6 | 0.55 | 0.07-2.00 |
| Other skina | 173 | C44 |  | 4 | 3.5 | 1.15 | 0.31-2.93 |  | 2 | 2.5 | 0.81 | 0.10-2.91 |  | 0 | 1.2 | 0.00 | 0.00-3.15 |
| Prostate | 185 | C61 |  | 120 | 108.8 | 1.10 | 0.91-1.32 |  | 89 | 77.9 | 1.14 | 0.92-1.41 |  | 43 | 37.3 | 1.15 | 0.83-1.55 |
| Testisa | 186 | C62 |  | 5 | 2.5 | 2.00 | 0.65-4.67 |  | 4 | 1.9 | 2.10 | 0.57-5.37 |  | 3 | 0.7 | 4.03 | 0.83-11.78 |
| Other genitala | 187 | C63 |  | 2 | 1.2 | 1.60 | 0.19-5.79 |  | 2 | 0.9 | 2.30 | 0.28-8.31 |  | 1 | 0.4 | 2.42 | 0.06-13.49 |
| Bladdera | 188 | C65-C68 |  | 44 | 48.0 | 0.92 | 0.67-1.23 |  | 30 | 34.3 | 0.87 | 0.59-1.25 |  | 16 | 16.3 | 0.98 | 0.56-1.59 |
| Kidneya | 189 | C64 |  | 23 | 26.4 | 0.87 | 0.55-1.31 |  | 16 | 19.7 | 0.81 | 0.46-1.32 |  | 11 | 9.0 | 1.22 | 0.61-2.19 |
| Brain and nervous system | 191,192 | C71-C72 |  | 33 | 28.7 | 1.15 | 0.79-1.62 |  | 25 | 21.8 | 1.15 | 0.74-1.70 |  | 10 | 9.6 | 1.04 | 0.50-1.92 |
| Thyroid | 193 | C73 |  | 3 | 1.9 | 1.56 | 0.32-4.57 |  | 3 | 1.4 | 2.15 | 0.44-6.28 |  | 2 | 0.6 | 3.11 | 0.38-11.22 |
| Hodgkin’s disease | 201 | C81 |  | 3 | 5.7 | 0.53 | 0.11-1.55 |  | 3 | 4.2 | 0.72 | 0.15-2.11 |  | 3 | 1.8 | 1.71 | 0.35-4.99 |
| Non-Hodgkin lymphomaa | 200.202.0, 202.1,202.8 | C82-C85 |  | 29 | 30.2 | 0.96 | 0.64-1.38 |  | 26 | 22.6 | 1.15 | 0.75-1.68 |  | 19 | 10.3 | 1.85 | 1.12-2.89 |
| Multiple myelomaa | 203.0 | C90 |  | 18 | 17.3 | 1.04 | 0.62-1.64 |  | 15 | 12.8 | 1.18 | 0.66-1.94 |  | 6 | 5.9 | 1.01 | 0.37-2.20 |
| Leukaemia | 204-208 | C91-C95 |  | 40 | 31.6 | 1.27 | 0.91-1.73 |  | 30 | 23.2 | 1.29 | 0.87-1.84 |  | 11 | 10.6 | 1.04 | 0.52-1.86 |
| Myeloid leukaemiaa | 205 | C92 |  | 22 | 18.1 | 1.21 | 0.76-1.84 |  | 15 | 13.5 | 1.11 | 0.62-1.83 |  | 6 | 6.1 | 0.98 | 0.36-2.13 |

Obs = deaths observed; Exp =Deaths expected

aBecause of changes in disease classification, the earliest follow-up for these cancers was from 1950

bBecause of changes in disease classification, the earliest follow-up for these cancers was from 1958

cTheanalysis for potential exposure to phenoxy acids above background for ≥ 1 year excluded 22 men whose date of first completing a year in potentially exposed jobs was unknown

**Table 4 Cases of soft tissue sarcoma and sources of diagnostic information**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sub-cohort** |  | **Diagnosis** |  | **Source(s) of informationa** |
|  |  |  |  |  |
| A |  | Dermatofibrosarcoma |  | CR |
| A |  | Chondrosarcoma |  | CR |
| C |  | Leiomyosarcoma of small intestine |  | CR |
| D |  | Soft tissue sarcoma |  | UC |
| E |  | Haemangiosarcoma |  | CR |
| E |  | Liposarcoma |  | CR |
| E |  | Malignant neurilemoma of bone/articular cartilage |  | CR |
| E |  | Chondrosarcoma |  | CR, UC |
| E |  | Spindle cell sarcoma |  | CR |
| E |  | Fibromyxosarcoma |  | CR, UC |
| F |  | Myxosarcoma |  | CR |
| F |  | Leiomyosarcoma peritoneum |  | CR |
| F |  | Round cell liposarcoma |  | CR |
| F |  | Spindle cell sarcoma |  | CR, UC |
| F |  | Sarcoma |  | CR |

aCR = cancer registration; UC = underlying cause of death on death certificate

**Table 5 Associations of soft tissue sarcoma and non-Hodgkin lymphoma/chronic lymphocytic leukaemia with duration and level of potential exposure to phenoxy herbicides above background**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Potential exposure to phenoxy acids above backgrounda** |  | **Number of exposed cases** |  | **Number of exposed controls** |  | **Odds ratio** | **95% CI** |
|  |  |  |  |  |  |  |  |
| **Soft tissue sarcoma** |  |  |  |  |  |  |  |
|  None |  | 3 |  | 30 |  | Baseline |  |
|  <1 year |  | 6 |  | 75 |  | 0.77 | (0.17, 3.50) |
|  ≥1 year |  | 6 |  | 45 |  | 1.30 | (0.30, 5.62) |
|  |  |  |  |  |  |  |  |
|  None |  | 3 |  | 27 |  | Baseline |  |
|  Low |  | 5 |  | 32 |  | 0.79 | (0.16, 3.89) |
|  High |  | 3 |  | 51 |  | 0.95 | (0.19, 4.88) |
|  |  |  |  |  |  |  |  |
| **Non-Hodgkin lymphoma/chronic lymphocytic leukaemia** |  |  |  |  |  |  |  |
|  None |  | 16 |  | 150 |  | Baseline |  |
|  <1 year |  | 28 |  | 331 |  | 0.77 | (0.39, 1.53) |
|  ≥1 year |  | 30 |  | 238 |  | 1.11 | (0.57, 2.18) |
|  |  |  |  |  |  |  |  |
|  None |  | 14 |  | 139 |  | Baseline |  |
|  Low |  | 17 |  | 154 |  | 0.67 | (0.32, 1.40) |
|  High |  | 28 |  | 285 |  | 1.22 | (0.61, 2.46) |

aSubjects were classified according to their exposure status 5 years before the date when they or their matched case were first recorded as having the relevant cancer. Analyses by level of potential exposure above background were limited to sub-cohorts E and F.