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PHENOXY HERBICIDES, SOFT TISSUE SARCOMA AND NON-HODGKIN LYMPHOMA: A SYSTEMATIC REVIEW OF EVIDENCE FROM COHORT AND CASE-CONTROL STUDIES

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Abstract

Background—Phenoxy herbicides have been used widely in agriculture, forestry, parks and domestic gardens. Early studies linked them with soft tissue sarcoma (STS) and non-Hodgkin lymphoma (NHL), but when last reviewed by the International Agency for Research on Cancer in 1986, the evidence for human carcinogenicity was limited.

Sources of data—We searched Medline and Embase, looking for cohort or case-control studies that provided data on risk of STS and/or NHL in relation to phenoxy herbicides, and checked the reference lists of relevant publications for papers that had been missed.

Areas of agreement, areas of controversy—The extensive evidence is not entirely consistent, and a hazard of STS or NHL cannot firmly be ruled out. However, if there is a hazard, then absolute risks must be small.

Growing points, areas timely for developing research—Extended follow-up of previously assembled cohorts may be the most efficient way of further reducing uncertainties.

Keywords

2,4-D; 2,4,5-T; MCPA; MCPP; epidemiology; cancer

Introduction

Phenoxy herbicides are synthetic analogues of auxin plant growth hormones. They include the compounds 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2-methyl-4-chlorophenoxyacetic acid (MCPA) and methylchlorophenoxypropionic acid (MCPP), all of which have a similar molecular structure comprising an aromatic ring with a carboxylic side chain. Since their first commercial production in the 1940s, they have been used widely in agriculture, forestry,

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Authors' contributions

Nimeshi Jayakody and Clare Harris each helped to design the study, abstracted most of the reports reviewed, and helped to revise the draft paper.

David Coggon oversaw the design of the study, abstracted a minority of the reports, and prepared the first draft of the paper.

parks and domestic gardens. In addition, a mixture of 2,4-D and 2,4,5-T, known as Agent Orange, was used as a defoliant during the Vietnam war.

2,4,5-T, which is no longer approved for use in European Union (EU) countries or the USA, can be contaminated during its manufacture by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is the most toxic of the dioxin congeners, and has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC) [1]. Other phenoxy herbicides, some of which may contain traces of less toxic dioxins [2], are still in use in the EU and elsewhere.

Experimental studies have not indicated that 2,4-D, 2,4,5-T or MCPA are mutagenic or cause cancer in laboratory animals [2-4]. However, during 1979-81, a series of case-control studies from Sweden linked occupational exposure to phenoxy herbicides with an increased risk of soft tissue sarcoma (STS) and non-Hodgkin lymphoma (NHL) [5-7]. This prompted further epidemiological research using both cohort and case-control designs, but results were inconsistent. Thus when phenoxy herbicides were last reviewed by IARC in 1986, there was judged to be only “limited evidence” that they are carcinogenic in humans [2].

Since 1986, further epidemiological evidence has accumulated, and it is therefore timely to re-evaluate the suggested association of phenoxy herbicides with STS and NHL. To this end, we conducted a systematic review of the epidemiological data that are currently available from cohort and case-control studies.

Methods

We carried out a systematic search of the entire Medline and Embase databases up to 21.02.14, looking for all reports of cohort or case-control studies that provided data on the risk of STS and/or NHL (including chronic lymphocytic leukaemia (CLL)) in relation to one or more phenoxy herbicides. This was achieved using terms for relevant exposures (phenoxy herbicide, 2,4-D, 2,4,5-T, MCPA or MCPP) in combination with terms that would embrace the outcomes of interest (STS, NHL, CLL or cancer). Publications that did not have either an abstract or main text in English were excluded.

After removal of duplicates and papers which, on the basis of title or abstract, were clearly not relevant, remaining publications were retrieved, and those that met our inclusion criteria were abstracted onto standardised pro-formas – one for cohort studies and one for case-control studies. In addition, we scanned their reference lists for further reports that might have been missed by the electronic search. These too were retrieved, and if appropriate, abstracted. Reviews that only included data from previously published research were not abstracted, but their reference lists were checked for additional papers that had not previously been picked up. Where the results in one paper were totally subsumed by those in another (e.g. a later report of extended follow-up of the same cohort), only the latter were abstracted. The selection and abstraction of relevant papers was carried out independently in duplicate by two members of the study team (in most cases NJ and ECH), and any differences were resolved by consensus.

The data abstracted included: the type of study; time period covered; sources and numbers of subjects; exposures assessed; risk estimates for relevant outcomes; and (where reported) the numbers of exposed cases on which risk estimates were based and their associated confidence intervals (CIs). For cohort studies, risk estimates generally took the form of standardised mortality or incidence ratios, which collectively were denoted risk ratios (RRs). Risk estimates from case-control studies were presented as odds ratios (ORs).

Many papers reported separate risk estimates for different categories of exposure, sometimes with differing adjustment for potential confounders. Where results were presented for all phenoxy herbicides and separately for individual compounds, we gave preference to the former, since associations with individual compounds were liable to be mutually confounded. However, if separate results were given for exposure exclusively to phenoxy herbicides uncontaminated by TCDD and other higher chlorinated dioxins, they were noted. When risk estimates were reported for different levels of exposure, we focused on the highest level for which results were statistically informative. If analyses had been carried out with differing adjustment for potential confounders, we gave priority to the most fully adjusted results.

We did not attempt to score the quality of papers according to standardised criteria, but we noted the main limitations of each individual study, and took these into account when evaluating the overall pattern of results.

Results

After removal of duplicates, the computerised literature search yielded 555 potentially relevant papers, of which 469 were excluded following a check of titles and abstracts. The 86 remaining papers were retrieved and scrutinised, and 64 were found to meet our specified inclusion criteria, as did an additional 11 publications that were identified from their reference lists or those of earlier reviews. Among the 75 papers that satisfied the inclusion criteria, 32 were subsumed by other publications (mostly early reports of cohort studies that were subsequently reanalysed with extended follow-up), leaving 43 papers that provided at least partially unique information on risks STS or NHL.

Sixteen of the papers related to 13 cohort studies, either of pesticide manufacturers (three studies), people exposed in pesticide application (eight studies) or both (two studies) (Table 1). Four studies were carried out in Sweden, three in the USA, two in the Netherlands and three in other countries. In addition, a large study coordinated by the International Agency for Research on Cancer (IARC) included cohorts of manufacturers and sprayers from 12 countries [22]. Findings from this study partially overlapped with those in two later reports [31, 36], but the exact extent of the overlap was unclear. There were some uncertainties about the completeness of follow-up in one investigation of chemical manufacturers in the USA [38], but in general the quality of the cohort studies was good.

The other papers described 27 case-control studies (Table 2). One of these [61] was nested within the IARC multinational cohort, and partially overlapped with cohort analyses reported elsewhere [22,31,36]; one was nested in a US cohort of agricultural workers [72];

and a third was conducted among US Vietnam veterans [57]. The other 24 were based in the general population, and were carried out in Sweden (7), USA (7), Italy (3), New Zealand (2), Australia (2), Canada (2) and France (1). Seven focused on STS, 17 on NHL (of which four included CLL), and three on both STS and NHL.

Table 3 summarises results from the cohort studies that provided information about STS. In the investigation with by far the largest number of cases (331), there was no increased risk of STS (RR 0.9, 95%CI 0.8-1.0) [10]. However, only about 15% of the cohort were thought to have been exposed to phenoxy herbicides. In a smaller study by the same group, the probability of exposure was rather higher (~72%), but again, no excess of STS was observed (RR 0.9, 95%CI 0.4-1.9) [14]. Most informative was the IARC multi-national study, in which there was a total of nine deaths from STS (RR 2.00, 95%CI 0.91-3.79), the excess risk occurring mainly among workers potentially exposed to TCDD or higher chlorinated dioxins [22]. This observation was supported by results from a Danish investigation [31] in which four cases of STS were identified with 2.47 expected, although one of the four cases may also have been recorded in the IARC investigation. A study in New Zealand found one case of STS with 0.4 expected [36]. No cases were recorded in the other five cohort investigations [8,16,18,21,35], the total expected number across the four studies being in the order of 1.5.

The findings from case-control studies of STS are summarised in Table 4. Two early investigations in Sweden indicated ORs in excess of five [5,6]. In contrast, other more recent studies based in the general population found only weak associations or none at all. The highest OR (2.70 based on four exposed cases) was in an Italian investigation [46], but otherwise, ORs were all 1.3 or less [43,44,47,50,59,75]. It should be noted, however, that the exposures considered in these studies were not always definite, and were often relatively low (in some cases perhaps only on a single day). In the nested case-control study by Kogevinas et al [61], the OR for high cumulative exposure to phenoxy acids (relative to exposure for <1 day) was higher (11.96, 95%CI 1.03-701.9), although based on only five exposed cases.

Table 5 shows risk estimates for NHL from cohort studies. No statistically significant associations were observed in any of the 12 investigations. The IARC multi-national cohort study found a risk ratio of 1.27 (95%CI 0.88-1.78), the increased risk being limited to workers exposed to TCDD or higher chlorinated dioxins [22]; a similar risk estimate was obtained in an analysis of cancer incidence among 2,4-D manufacturers in the USA [38]; a study of lawn applicators in the USA found three deaths from NHL with 1.8 expected [21]; and in a small study of lumberjacks in Sweden, there were two cases of NHL with 0.86 expected [33]. Otherwise, risk estimates were all close to, or less than, one.

Among the case-control studies of NHL (Table 6), the highest ORs were observed in two investigations based in the general population – one in Sweden (OR 5.2, 95%CI 1.6-17) [60], and one in the USA (OR 2.2, 95%CI 1.2-4.1) [44] – and in a third study among a population of Californian agricultural workers (OR 3.58, 95%CI 1.02-12.56) [72]. In the two US studies, exposures were principally to 2,4-D. A second Swedish study [65] found an OR of 2.6 (95%CI 1.1-6.1), but the index of exposure (occupational use of herbicides in farming

or forestry) was crude. In all other studies, associations were non-significant, most risk estimates lying between 0.8 and 1.5. These included the case-control study nested within the IARC international cohort (OR 1.36, 95%CI 0.46-4.03) [61].

Discussion

The body of epidemiological evidence on risks of STS and NHL in relation to phenoxy herbicides has grown substantially since the compounds were last reviewed by IARC in 1986. However, it remains unclear whether there is a hazard. In part, this uncertainty reflects the difficulties in discriminating small relative risks for rare health outcomes from exposures that are also fairly uncommon.

We elected to restrict our review to cohort and case-control studies, since we expected that these would provide the best information about any hazard of relevant tumours. However, even with this restriction, assessment of the evidence base posed a number of challenges. Published studies related to different combinations of phenoxy herbicides and differing levels of exposure. There was a possibility that associations might vary according to whether there was coincident exposure to TCDD, since this is a known carcinogen, albeit not an established cause of STS or NHL specifically. Beyond that, however, there was no *a priori* toxicological reason to expect a higher risk from one phenoxy compound than any other. Moreover, subjects were often exposed to multiple phenoxy herbicides, and risk estimates reported for one phenoxy compound generally did not adjust for co-exposure to others. Therefore, we focused principally on associations with exposures to phenoxy herbicides as a group, but for each study noted the specific compounds to which exposures most frequently occurred. In addition, where separate risk estimates were recorded for exposures other than to TCDD and higher chlorinated dioxins, these were abstracted. Furthermore, because our main objective was the assessment of hazard, and not quantitative characterisation of exposure-response relationships, when risk estimates were presented for several different levels of exposure, we gave priority to the highest category of exposure for which results were statistically meaningful.

The studies that were identified employed a variety of methods with differing potentials for bias. We did not attempt to grade the quality of studies according to a standardised scoring scheme, since that approach, although relatively objective and reproducible, may not adequately capture the potential impacts of bias (both in magnitude and direction) from different sources. Instead, we identified the main limitations of each study, highlighted any major deficiencies in their design, and took their shortcomings into account when weighing the overall balance of evidence.

The quality of most studies was good, but many suffered from generic weaknesses inherent in their design. In the cohort studies, exposures were inferred from job title, which may have led to some uncertainty or misclassification, the effects of which would normally be to bias risk estimates towards the null. Nevertheless, it seems safe to conclude that exposures will generally have been substantially higher than in the reference populations with which the cohorts were compared.

A bigger problem is that health outcomes, although sometimes ascertained from cancer registrations, were usually determined from death certificates. The latter are known to suffer from inaccuracies [80], and there are particular problems with STS, which in some cases may have been miscoded according to the site rather than the type of cancer (e.g. classification of gastric leiomyosarcoma as cancer of the stomach). Such misclassification would normally be non-differential with respect to exposure, tending to bias risk estimates towards the null and to obscure any true associations that were present.

Another concern in the cohort studies that compared death rates with those in the general population is the possibility of bias because unhealthy workers were selectively excluded from employment. In theory this might spuriously reduce risk estimates. However, such healthy worker effects tend to have greatest impact on diseases in which death is preceded by prolonged disability (e.g. chronic obstructive pulmonary disease), and are less of a problem for cancers.

Diagnostic information in the case-control studies should have been reasonably accurate, but there was greater potential for bias from error in the ascertainment of exposures, particularly when it depended on recall over many years. Job histories may be remembered fairly accurately, but inference of exposures from job titles in the general population (as opposed to job title in a particular company) is often unreliable. And where participants were asked to recall exposures to specific chemicals, errors can be expected, especially if the exposures were only of short duration and some years in the past. If resultant inaccuracies were non-differential with respect to health outcome, risk estimates will have been biased towards the null. However, if cases remembered their past exposures more completely than controls, perhaps because they were more motivated or had been primed by media publicity about a possible hazard, risk estimates will have been spuriously inflated. Such bias may be less when controls are patients with other diseases than when they are selected from the general population.

Confounding is a possible concern in both cohort and case-control studies. However, apart from sex and age, the known causes of STS and NHL are rare or have only weak effects. Given that all of the reviewed studies took account of sex and age, confounding therefore seems unlikely to have been an important problem.

Another consideration in systematic reviews is the possibility that positive results have been reported selectively. This can be because small, non-positive investigations are not considered worthy of publication, or because the published reports of studies focus on the most interesting findings, and omit null results. This may have occurred in some case-control studies, but is less likely to have been a problem in the cohort investigations, all of which were undertaken against a background of prior concern about risks of STS and NHL. Nevertheless, expected numbers of STS and NHL were not always presented in the smaller cohort studies in which no cases occurred, and could only be inferred approximately from the total number of deaths or cancers expected.

Among the studies of STS, the results from two early case-control investigations in Sweden [5,6] stand out from those generated more recently. This might be because the exposures

differed, but recall bias seems a more likely explanation, especially as in cohort studies, which were less prone to bias and in which cumulative exposures are likely in general to have been higher, risk estimates were lower. A caveat, however, is that because STS is so rare, the cohort studies had low statistical power, and it is notable that in the case-control analysis nested within the IARC multinational cohort, the OR for high cumulative exposure to phenoxy acids was 11.96, albeit based on only five exposed cases [61]. Aside from this finding, and the overlapping results from the main analysis of the IARC cohort [22] and a sub-cohort from Denmark [31], risk estimates from other studies since the initial Swedish case-control investigations have been close to unity and non-significant. Thus, there is no strong evidence of a hazard, although a small absolute elevation of risk cannot be ruled out.

As regards NHL, the risk estimate from an early case-control study in Sweden [7,60] was again much higher than those from other investigations. This study, was by the researchers who found unusually high odds ratios for STS, increasing the concern that there may have been important unrecognised bias, although in a later study by the same group [64], the odds ratio was lower (1.5).

The cohort studies reviewed found little to support a hazard of NHL, the highest RR being 1.39 (95% CI 0.89-2.06) for workers in the IARC multinational cohort who were also exposed to TCDD and higher chlorinated dioxins [22]. On the other hand, the same study found no elevation of risk among workers exposed to phenoxy acids in the absence of higher chlorinated dioxins.

Aside from the study by Hardell [60], four other case control investigations have found significant elevations of risk for NHL. In one of these [65], the OR of 2.6 was for occupational use of any herbicides in farming or forestry, and not for phenoxy herbicides specifically. In the other three, the ORs were 1.45 (95% CI 1.13-1.87) [77], 2.2 (95% CI 1.2-4.1) [44] and 3.58 (95% CI 1.02-12.56) [72]. Across the remainder, risk estimates were mostly between 0.9 and 1.5. Again, it is not possible to exclude a hazard, but if there is an increased risk then it must be small in absolute terms.

In summary, extensive epidemiological evidence is now available on the relationship of phenoxy herbicides to STS and NHL. Although this does not clearly indicate that such herbicides cause either disease, findings have not been entirely consistent, and the possibility of a hazard cannot be confidently ruled out. If there is a hazard, however, then the absolute increases in risk must be small. This conclusion accords with those of another systematic review that was published while ours was in progress [81]. Extended follow-up of previously assembled cohorts may be the most efficient way of reducing the uncertainties that remain.

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Table 1
Cohort studies that provided information on soft tissue sarcoma or non-Hodgkin lymphoma

Reference	Country	Description of cohort	Follow-up period	Outcome	Comparator	Comments
Axelsson et al 1980 [8]	Sweden	348 railroad workers	1957-78	Mortality	National death rates	Subsumes Axelsson and Sundell 1974 [9], which indicates that 207 were exposed to phenoxy herbicides.
Wiklund and Holm 1986 [10] Wiklund et al 1988 [11]	Sweden	354,620 men employed in agriculture or forestry at 1960 census An estimated 15% exposed to phenoxy herbicides (principally MCPA, 2,4,5-T and 2,4-D)	1961-79	Cancer incidence	1,725,845 men employed in other industries	Subsume Wiklund et al 1987 [12].
Wiklund et al 1987 [13] Wiklund et al 1988 [14]	Sweden	20,245 licensed pesticide applicators An estimated 72% exposed to phenoxy herbicides including MCPA, MCPP, 2,4-DP, 2,4-D and 2,4,5-T	1965-84	Cancer incidence	National registration rates	Follow-up for NHL was only to 1982. Subsume Wiklund et al 1989 [15].
Thomas and Kang 1990 [16]	USA	894 men in Army Chemical Corps units assigned to Vietnam with potential exposure to 2,4-D and 2,4,5-T	1966-87	Mortality	National death rates	Cohort subsequently expanded in Dalager and Kang 1997 [17], but no additional results on STS or NHL.
Asp et al 1994 [18]	Finland	1,909 men who sprayed 2,4-D and 2,4,5-T during 1955-71	1972-89	Cancer incidence	National registration rates	Results are also presented on mortality (no deaths from STS or NHL). Subsumes Riihimäki et al 1982 [19] and Riihimäki et al 1983 [20].
Zahm 1997 [21]	USA	15,576 male lawn applicators who sprayed 2,4-D, MCPP and other pesticides	1969-90	Mortality	National death rates	
Kogevinas et al 1997 [22]	12 countries ^a	21,863 male and female workers exposed to phenoxy herbicides, chlorophenols and dioxins in production or spraying	1939-92	Mortality	National death rates	Subsumes Coggon et al 1986 [23], Ott et al 1987 [24], Fingerhut et al 1991 [25], Saracci et al 1991 [26], Green 1991 [27], Coggon et al 1991 [28], Bueno de Mesquita et al 1993 [29] and Becher et al 1996 [30].
Lynge 1998 [31]	Denmark	2,119 workers at two factories making phenoxy herbicides (mainly MCPA but also 2,4-DP and MCPP) during 1947-81 and 1951-81	1947-93	Cancer incidence	National cancer registration rates	Mortality outcomes for cohort are included in Kogevinas et al 1997 [22]. Subsumes Lynge 1985 [32].
Thörn et al 2000 [33]	Sweden	257 male and female lumberjacks employed at a forestry company during 1954-67 and exposed for >5 days to 2,4,5-T or 2,4-D	1958-92	Cancer incidence	National cancer registration rates	Subsumes Hogstedt and Westerlund 1980 [34].
Swaen et al 2004 [35]	Netherlands	1,341 licensed herbicide applicators	1980-2000	Mortality	National death rates	

Reference	Country	Description of cohort	Follow-up period	Outcome	Comparator	Comments
Van't Manneffe et al 2005 [36]	New Zealand	Phenoxy herbicides accounted for ~9% of all herbicides applied for ~9% of all herbicides applied by weight for 1 month during 1969-84 at a plant making phenoxy herbicides and chlorophenols and 699 sprayers most of whom were exposed to phenoxy herbicides during 1973-84	1969-2000	Mortality	National death rates	Overlaps with Kogevinas et al 1997 [22], but this report adds 10 years follow-up. Results are not presented separately for the additional 10 years.
Burns et al 2001 [37]	USA	1,517 men potentially exposed to 2,4-D during 1945-94 at Dow plant in Michigan	1960-94	Mortality	National death rates	Subsumes Bond et al 1988 [39] and Bloemen et al 1993 [40].
Burns et al 2011 [38]		Sub-cohort of 1,316 men who were alive on 1.1.85	1985-2007	Cancer incidence	Registration rates for Michigan state	Some uncertainties about completeness of follow-up.
Boers et al 2010 [41]	Netherlands	1,021 men employed during 1955-85 at a factory (A) making 2,4,5-T, of whom 539 were classed as exposed 1,037 men employed during 1965-86 at a factory (B) making 2,4-D, MCPA and MCPP, of whom 411 were classed as exposed	1955-2006	Mortality	Internal comparison with non-exposed	Subsumes Hooiveld et al 1998 [42]. Included in Kogevinas et al 1997 [22] with follow-up to 1991.

^a Australia, Austria, Canada, Denmark, Finland, Italy, The Netherlands, New Zealand, Sweden, UK, Germany, United States

Table 2
Case-control studies of soft tissue sarcoma and non-Hodgkin lymphoma

Reference	Country	Cases	Controls	Method of exposure assessment	Comments
Hardell et al 1979 [5]	Sweden	21 living and 31 deceased men aged 26-80 who had been admitted to a hospital with STS during 1970-77	206 men (up to 4 per case) matched for sex, age (± 5 years), vital status and place of residence or death	Self-administered questionnaire completed by subject or next of kin, supplemented by blinded telephone interview	
Eriksson et al 1981 [6]	Sweden	110 patients with STS diagnosed during 1974-78 in 5 counties	219 controls (up to 2 per case) matched by age, municipality, vital status and year of death, and employment within 5 years of case's retirement or death	Self-administered questionnaire completed by subject or next of kin, supplemented by blinded telephone interview	
Greenwald et al 1984 [43]	USA	281 men with STS diagnosed during 1962-80 and registered in New York State, who were aged 18-29 during 1962-71	281 living men from driver's license files, individually matched for 5-year period of birth and area of residence, plus 130 deceased controls for deceased cases	Telephone interview of subject or next of kin, or in-person interview if requested	
Hoar et al 1986 [44]	USA	Men with new STS (133), NHL (170) and Hodgkin's disease (121) during 1976-82 identified from cancer registry for Kansas State	948 men from general population individually matched on age vital status and year of death	Telephone interview of subject or next of kin	Data on NHL later included in pooled analysis by De Roos et al 2003 [45].
Vineis et al 1986 [46]	Italy	68 men and women aged 20 from three provinces with proved or suspected histological diagnosis of STS during 1981-83	122 men and women selected from electoral registers and 36 selected from death records	Inference by blinded experts from job descriptions elicited from subject or next of kin at interview or (for 16 cases and 37 referents) by postal questionnaire	
Smith and Pearce 1986 [47]	New Zealand	133 men with histologically confirmed STS registered during 1976-82	407 men with other registered cancers	Telephone interview of subject or next of kin	Extends Smith et 1984 [48], and subsumes Smith et al 1983 [49].
Woods et al 1987 [50]	USA	Men aged 20-79 in 13 counties of Washington State with STS (128) and NHL (576) diagnosed during 1981-84	694 men from general population, individually matched for vital status and age, identified through random digit dialling, social security records and death records	In-person interview	Subsumes Woods and Pollissar 1989 [51].
Pearce et al 1987 [52]	New Zealand	183 men aged >70 with histologically confirmed NHL registered during 1977-81	338 men with other registered cancers	Telephone interview of subject or next of kin	Subsumes Pearce et al 1986 [53].
Olsson and Brandt 1988 [54]	Sweden	167 men aged 20-81 admitted to oncology department in Lund during 1978-81 with NHL	50 men from population register for same geographical area as cases plus 80 men from different parts of Sweden (originally controls for other studies)	Interview	Second control group inappropriate because from different geographical areas. Interviews not blinded.
Zahm et al 1990 [55]	USA	White men aged 21 from 66 counties of Nebraska with NHL (201), Hodgkin's disease, multiple myeloma or CLL diagnosed during 1983-86	725 white men from general population frequency matched for race, vital status and age, identified through random digit dialling, social security records and death records	Telephone interview of subject or next of kin	Subsumes Weisenberger 1990 [56]. Later included in pooled analysis by De Roos et al 2003 [45].

Reference	Country	Cases	Controls	Method of exposure assessment	Comments
Dalager et al 1991 [57]	USA	201 male Vietnam-era veterans born during 1937-54 with NHL diagnosed and treated in Veterans Affairs hospitals during 1969-85	358 male Vietnam-era veterans who were in-patients at Veterans Affairs hospitals and individually matched for birth date, hospital and year of discharge from hospital	Self-administered questionnaire completed by subject or next of kin, supplemented by telephone interview	
Cantor et al 1992 [58]	USA	622 men aged 30 from Iowa and parts of Minnesota with histologically confirmed NHL diagnosed during 1981-83 (Iowa) and 1980-82 (Minnesota)	1,245 white men frequency matched by 5-year age group, vital status and state of residence, selected from random digit dialling, Medicare records and death certificate files	In-person interview with subject or proxy.	Later included in pooled analysis by De Roos et al 2003 [45].
Smith and Christophers 1992 [59]	Australia	30 men aged 30 with STS registered at six Melbourne hospitals during 1982-88 and still alive at time of study	Patients registered with other cancers and people selected from electoral register, individually matched for sex, age and current area of residence	Interview	
Hardell et al 1994 [60]	Sweden	105 men aged 25-85 admitted to an oncology department with NHL during 1974-78	335 men from general population, individually matched for age, place of residence, vital status and year of death	Self-administered questionnaire completed by patient or next of kin and supplemented by telephone interview where necessary.	Subsumes Hardell et al 1981 [7].
Kogevinas et al 1995 [61]	11 countries ^a	11 cases of STS and 32 of NHL identified from death certificates and cancer registrations in an international cohort study	Five controls per case, individually matched for sex, age and country, selected by incidence density sampling (information on exposure missing for 2 controls)	Inferred from employment records by a panel of hygienists blinded to case/control status	Overlaps Kogevinas et al 1997 [22] and Lyngge 1998 [31].
Tatham et al 1997 [62]	USA	1,048 living men born 1929-53 with NHL diagnosed during 1984-88 and registered at one of 8 cancer registries	1,659 men from general population, frequency matched for registry and date of birth (in 5-year bands), identified through random digit dialling	Telephone interview	
Fontana et al 1998 [63]	Italy	180 patients aged 20-74 with NHL, Hodgkin's disease or CLL during 1991-93 at four hospitals	Random sample from general population, frequency matched for sex and age	In-person interview	Methods poorly described.
Hardell and Eriksson 1999 [64]	Sweden	404 men aged 25 years from 7 Swedish counties with NHL diagnosed during 1987-90	741 men from general population, individually matched for age, county, vital status and year of death	Self-administered questionnaire completed by subject or next of kin, supplemented by telephone interview if necessary	
Persson and Fredriksson 1999 [65]	Sweden	199 surviving patients aged 20-79 from 2 regions with NHL registered during 1964-86	479 adults form the same populations, randomly selected from population registers	Postal questionnaire	Subsumes Persson et al 1989 [66] and Persson et al 1993 [67].
Miligi et al 2003 [68]	Italy	1,145 adults aged 20-74 from 11 areas of Italy with newly diagnosed NHL or CLL during 1990-93	1,232 people randomly selected from general population with frequency matching for sex and age	In-person interview of subject or proxy with expert inference of exposure to specific pesticides based on questionnaire data	Miligi et al 2006 [69] is based on same study.
Fritschi et al 2005 [70]	Australia	694 adults aged 20-74 from 2 Australian states with NHL first diagnosed 2000-01	694 adults randomly selected from electoral roll and frequency matched for sex, age and region of residence	Postal questionnaire supplemented by interview in those with relevant jobs	

Reference	Country	Cases	Controls	Method of exposure assessment	Comments
Hartge et al 2005 [71]	USA	1,321 adults aged 20-74 from 3 geographical areas with NHL diagnosed 1998-2000 (excluded a random subset of whites in two areas)	1,057 adults from general population, frequency matched for sex, age, race and area, identified through random digit dialling or Medicare records	In-person interview and measurement of dust samples in home	
Mills et al 2005 [72]	USA	60 cases of NHL incident during 1987-2001 among 139,000 members of a farm workers' union in California	300 controls from same cohort with no history of cancer, matched for sex, age and Hispanic ethnicity	Linkage of job histories to records of pesticide applications by month, county and crop	
Orsi et al 2008 [73]	France	Men aged 20-75 from 6 French centres with recently diagnosed NHL (244) and CLL (77) during 2000-04	456 hospital patients mainly from orthopaedic and rheumatological departments	In-person interview with supplementary telephone interview if needed.	
Eriksson et al 2008 [74]	Sweden	910 patients aged 18-74 from 4 regions with histologically confirmed NHL newly diagnosed during 1999-2002	1,016 adults randomly selected from population registers and frequency matched for sex and age	Postal questionnaire	
Pahwa et al 2011 [75]	Canada	357 men aged 19 years from 6 provinces with STS diagnosed during 1991-94	1,506 men from general population, identified from health insurance records, telephone listings and voters' lists	Postal questionnaire (subject or proxy) supplemented by interview	Subsumes Pahwa et al 2006 [76].
Pahwa et al 2012 [77]	Canada	513 men aged 19 years from 6 provinces with NHL diagnosed during 1991-94	1,506 men from general population, frequency matched for age, identified from health insurance records, telephone listings and voters' lists	Postal questionnaire (subject or proxy) supplemented by interview in subjects with more intensive exposure to pesticides	Subsumes McDuffie et al 2001 [78] and Hohenadel et al 2011 [79].

^a Australia, Austria, Canada, Denmark, Finland, Germany, Italy, the Netherlands, New Zealand, Sweden, UK

Table 3

Findings on soft tissue sarcoma from cohort studies

Reference	Exposure	Cases		Risk ratio	95%CI	Comments
		Observed	Expected			
Axelsson et al 1980 [8]	Phenoxy herbicides	0		0		17.47 deaths expected from all cancers.
Wiklund and Holm 1986 [10]	Potential exposure to phenoxy herbicides (~15% probability)	331		0.9	0.8-1.0	
Wiklund et al 1988 [14]	Potential exposure to phenoxy herbicides (~72% probability)	7	7.7	0.9	0.4-1.9	
Thomas and Kang 1990 [16]	2,4-D and 2,4,5-T	0				6.6 deaths expected from all cancers.
Asp et al 1994 [18]	2,4-D and 2,4,5-T	0	0.99			
Zahm 1997 [21]	2,4-D, MCPP and other pesticides	0				21.2 deaths expected from all cancers.
Kogevinas et al 1997 [22]	All exposure to phenoxy herbicides, chlorophenols or dioxins	9		2.00	0.91-3.79	Pathology review failed to confirm diagnosis in 2 cases. 3 further cases were identified by detailed review of selected causes of death in sub-cohorts from USA.
	TCDD or higher chlorinated dioxins	6		2.03	0.75-4.43	
	No TCDD or higher chlorinated dioxins	2		1.35	0.16-4.88	
Lynge 1998 [31]	Phenoxy herbicides	4	2.47	1.62	0.4-4.1	Only 1 of the 4 cases had died of STS.
Swaen et al 2004 [35]	Potential exposure to phenoxy herbicides (probability uncertain)	0	0.5			
't Mannetje et al 2005 [36]	Phenoxy herbicides	1	0.4			

Table 4

Findings from case-control studies of soft tissue sarcoma

Reference	Exposure	Factors of adjustment	No. of exposed cases	OR	95%CI	Comments
Hardell et al 1979 [5]	Phenoxyacetic acids for >1 day, >5 years before tumour diagnosis		13	5.3	2.4-11.5	Matching dissolved in analysis.
Eriksson et al 1981 [6]	Phenoxy acids for >1 day, >5 years before tumour diagnosis		14	6.8	2.6-17.3	Matching dissolved in analysis.
Greenwald et al 1984 [43]	Agent Orange, dioxin or 2,4,5-T		7	0.70	0.17-2.92	
Hoar et al 1986 [44]	Herbicides (including 2,4-D)	Age	22	0.9	0.5-1.6	
Vineis et al 1986 [46]	"Definite" exposure to phenoxy acids	Age, therapeutic X-rays, smoking	4	2.70	0.59-12.37 (90% CI)	Risk estimate is derived from living women. Among living men, 0 cases and 2 controls were exposed. Controls may not have been fully representative of source population because some municipalities and electoral offices did not respond.
Smith and Pearce 1986 [47]	Probable or definite exposure to phenoxy herbicides for >1 day >5 years before registration	Decade of birth, interview with subject or next of kin, phase of study	23	1.1	0.7-1.8 (90% CI)	
Woods et al 1987 [50]	Phenoxy herbicides (high)	Age		0.89	0.4-1.9	
Smith and Christophers 1992 [59]	Exposure to phenoxy herbicides for 1 day >5 years before diagnosis (for controls, diagnosis of matched case)	Sex, age, area of residence		1.3	0.4-4.1	
Kogevinas et al 1995 [61]	High cumulative exposure to phenoxy acids	Sex, age and country	5	11.96	(1.03-701.9)	Overlaps Kogevinas et al 1997 [22] and Lynge 1998 [31].
Pahwa et al 2011 [75]	Use of phenoxy herbicides at work, in garden or for hobby	Age, province, history of measles, rheumatoid arthritis, infectious mononucleosis, whooping cough or cancer in a first degree relative	80	1.09	(0.81-1.48)	

Table 5

Findings on non-Hodgkin lymphoma from cohort studies

Reference	Exposure	Cases		Risk ratio	95% CI	Comments
		Observed	Expected			
Axelsson et al 1980 [8]	Phenoxy herbicides	0		0		17.47 deaths expected from all cancers.
Wiklund et al 1988 [11]	Potential exposure to phenoxy herbicides (~15% probability)	861		<1		Risk estimates are only reported for 6 sub-cohorts.
Wiklund et al 1987 [13]	Potential exposure to phenoxy herbicides (~72% probability)	21	20.8	1.01	0.63-1.54	
Thomas and Kang 1990 [16]	2,4-D and 2,4,5-T	0				6.6 deaths expected from all cancers.
Asp et al 1994 [18]	2,4-D and 2,4,5-T	1	2.83			
Zahm 1997 [21]	2,4-D, MCPP and other pesticides	3	1.8	1.63	0.33-4.77	2 cases had 3 years employment (SMR 7.11).
Kogevinas et al 1997 [22]	All exposure to phenoxy herbicides, chlorophenols or dioxins	34		1.27	0.88-1.78	
	TCDD or higher chlorinated dioxins	24		1.39	0.89-2.06	
	No TCDD or higher chlorinated dioxins	9		1.00	0.46-1.90	
Lynge 1998 [31]	Phenoxy herbicides	6	5.07	1.10	0.4-2.6	
Thörn et al 2000 [33]	2,4-D and 2,4,5-T	2	0.86			
Swaen et al 2004 [35]	Potential exposure to phenoxy herbicides (probability uncertain)	0	0.3			
't Mannetje et al 2005 [36]	Phenoxy herbicides	2	2.6			
Burns et al 2001 [37]	2,4-D	3	3.0	1.00	0.21-2.92	
Burns et al 2011 [38]	2,4-D	14	10.27	1.36	0.74-2.29	Possibility of some overlap with Burns et al 2001 [37].
Boerts et al 2010 [41]	2,4,5-T	4		0.92	0.19-4.47	Internal comparison with unexposed workers.
	2,4-D, MCPA, MCPP	1	0			Potential overlap with Kogevinas et al 1997 [22].

Table 6
Findings from case-control studies of non-Hodgkin lymphoma and chronic lymphocytic leukaemia

Risk estimates are for NHL unless otherwise stated

Reference	Exposure	Factors of adjustment	No. of exposed cases	OR	95%CI	Comments
Hoar et al 1986 [44]	Phenoxyacetic acids (almost all 2,4-D)	Age	24	2.2	1.2-4.1	Matched analyses gave similar results.
Woods et al 1987 [50]	Phenoxy herbicides (high)	Age		1.24	0.8-1.9	
Pearce et al 1987 [52]	Probable or definite exposure to phenoxy herbicides for 5 days, >10 years before cancer registration	Decade of birth, interview with subject or next of kin	23	0.9	0.6-1.5 (90% CI)	
Olsson and Brandt 1988 [54]	Exposure to phenoxy acids 1 day	Age, solvents, chlorophenols		1.3	0.8-2.1	Control group inappropriate.
Zahn et al 1990 [55]	Mixed or applied 2,4-D	Age	43	1.5	0.9-2.5	
Dalager et al 1991 [57]	Service in Vietnam	Military branch	100	0.91	0.64-1.28	
Cantor et al 1992 [58]	Phenoxy herbicides	Vital status, state, age, smoking, family history of lymphopoeitic cancer, non-farming job related to NHL, hair dyes, other substances associated with NHL in study	118	1.2	0.9-1.6	
Hardell et al, 1994 [60]	Phenoxyacetic acids	Chlorophenols, organic solvents, DDT, asbestos	25	5.2	1.6-17	
Kogevinas et al 1995 [61]	High cumulative exposure to phenoxy acids	Sex, age and country	7	1.36	(0.46-4.03)	Overlaps Kogevinas et al 1997 [22] and Lyngge 1998 [31].
Tatham et al 1997 [62]	Chlorophenoxy herbicides	Cancer registry, date of birth, age at diagnosis, year entered study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviours, use of seizure medication, service in or off coast of Vietnam, smoking	53	0.76	0.52-1.10	
Fontana et al 1998 [63]	Work in rice fields (where phenoxy herbicides were widely used)			1.1 ^a 1.9 ^b	0.1-19.0 0.6-6.0	^a Men ^b Women
Hardell and Eriksson 1999 [64]	Phenoxyacetic acids	Age, county, vital status and year of death (by conditional logistic regression of matched sets)	51	1.5	0.9-2.4	
Persson and Fredriksson 1999 [65]	Occupational use of herbicides in farming or forestry (presumed to include phenoxy herbicides because widely used at time) for at least 1 year, 5-45 years before diagnosis/recruitment	Farming, age, sex, geographical area plus 11 other exposures	16	2.6	1.1-6.1	Crude index of exposure. Potential for exposure to phenoxy herbicides may have changed over time.

Reference	Exposure	Factors of adjustment	No. of exposed cases	OR	95%CI	Comments
Miligi et al 2003 [69]	Medium or high probability of exposure to phenoxy acids	Area, age	18 ^a 11 ^b	1.0 1.3	0.5-2.0 0.5-3.7	^a Men ^b Women Both risk estimates are for NHL including CLL.
Fritschi et al 2005 [70]	Phenoxy herbicides	Sex, age, ethnicity, region of residence	5	1.75	0.42-7.38	
Hartge et al 2005 [71]	50 applications of herbicides with 1000ng/g of 2,4-D in carpet dust	Age, sex, race, geographic location		0.89	0.49-1.59	
Mills et al 2005 [72]	High (v low) cumulative exposure to 2,4-D	Sex, age, length of union affiliation, date of first union affiliation, 15 other chemicals		3.58	1.02-12.56	
Orsi et al 2008 [73]	Phenoxy herbicides	Age, centre	11 ^a 3 ^b	0.9 0.4	0.4-1.9 0.1-1.7	^a NHL ^b CLL
Eriksson et al 2008 [74]	Exposure to phenoxy acids for >45 days at least 2 calendar years before diagnosis	Age, sex, year of diagnosis/enrolment	15	1.27	0.59-2.70	OR 2.83 (95%CI 1.47-5.47) for exposure for 1-44 days.
Pahwa et al 2012 [77]	Phenoxy herbicides 10 hours/year	Age, province, diesel oil, type of respondent (subject or proxy)	129	1.45	1.13-1.87	