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Ejaculation Frequency and Risk of Prostate Cancer: Updated Results with an Additional Decade of Follow-up

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Abstract

Background: Evidence suggests that ejaculation frequency may be inversely related to the risk of prostate cancer (PCa), a disease for which few modifiable risk factors have been identified.
Objective: To incorporate an additional 10 yr of follow-up into an original analysis and to comprehensively evaluate the association between ejaculation frequency and PCa, accounting for screening, clinically relevant disease subgroups, and the impact of mortality from other causes.
Design, setting, and participants: A prospective cohort study of participants in the Health Professionals Follow-up Study utilizing self-reported data on average monthly ejaculation frequency. The study includes 31 925 men who answered questions on ejaculation frequency on a 1992 questionnaire and followed through to 2010. The average monthly ejaculation frequency was assessed at three time points: age 20–29 yr, age 40–49 yr, and the year before questionnaire distribution.
Outcome measurements and statistical analysis: Incidence of total PCa and clinically relevant disease subgroups. Cox models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).
Results and limitations: During 480 831 person-years, 3839 men were diagnosed with PCa. Ejaculation frequency at age 40–49 yr was positively associated with age-standardized body mass index, physical activity, divorce, history of sexually transmitted infections, and consumption of total calories and alcohol. Prostate-specific antigen (PSA) test utilization by 2008, number of PSA tests, and frequency of prostate biopsy were similar across frequency categories. In multivariable analyses, the hazard ratio for PCa incidence for ≥21 compared to 4–7 ejaculations per month was 0.81 (95% confidence interval [CI] 0.72–0.92; $p < 0.0001$ for trend) for frequency at age 20–29 yr and 0.78 (95% CI 0.69–0.89; $p < 0.0001$ for trend) for frequency at age 40–49 yr. Associations were driven by low-risk disease, were similar when restricted to a PSA-screened cohort, and were unlikely to be explained by competing causes of death.
Conclusions: These findings provide additional evidence of a beneficial role of more frequent ejaculation throughout adult life in the etiology of PCa, particularly for low-risk disease.
Patient summary: We evaluated whether ejaculation frequency throughout adulthood is related to prostate cancer risk in a large US-based study. We found that men reporting higher compared to lower ejaculatory frequency in adulthood were less likely to be subsequently diagnosed with prostate cancer.

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1. Introduction

Prostate cancer (PCa) accounts for approximately 15% of all new cancer diagnoses among men worldwide, and the burden of disease continues to increase globally [1]. While diet and physical activity may provide some promise for secondary prevention [2–5], there are no evidence-based recommendations to offer healthy adult men to reduce PCa risk. The few established disease risk factors—age, race, family history, and germline polymorphisms—are not modifiable [6].

Sexual behaviors represent potential modifiable risk factors and may influence PCa development through a variety of specific mechanisms. One biological mechanism involves prostatic accumulation of potentially carcinogenic secretions, which may create more opportunity for PCa development, sometimes referred to as the *prostate stagnation hypothesis* [7,8]. On the basis of this premise, a prospective report from the Health Professionals Follow-up Study (HPFS) cohort published in 2004 found a statistically significant inverse association between monthly ejaculation frequency and PCa risk based on 8 yr of follow-up [8]. Compared to men reporting an average of 4–7 ejaculations per month (EPM), the risk of PCa among men reporting ≥21 EPM in middle age was 50% lower. Although these initial findings were intriguing, the strongest reduction in risk was noted for ejaculation frequency in the time period immediately before questionnaire administration, raising concerns about the potential influence of undiagnosed PCa on the results.

To confirm and build on these results [8], we conducted an updated study within the HPFS cohort with an additional 10 yr of follow-up and 3839 PCa cases, more than double the number included in the original report. This updated analysis allows us to address possible reverse causation, investigate the potential impact of PSA screening, and determine whether the association between ejaculation frequency and PCa differed according to the clinical disease characteristics, as has been observed for other PCa risk factors [9]. Finally, because ejaculation frequency may be an indicator of health status and could be related to mortality from multiple causes, the current analysis considers the impact of competing causes of death on our findings. Thus, this updated analysis represents a comprehensive evaluation of the association between ejaculation frequency and PCa in a large US-based prospective cohort.

2. Patients and methods

2.1. Study population

The HPFS is an ongoing prospective cohort study among 51 529 US male health professionals [8]. In brief, cancer-free, predominantly Caucasian (>91%) health professionals aged 40–75 yr were recruited in 1986 and have been followed with biennial questionnaires on medical history and lifestyle, including known or suspected cancer and chronic disease risk factors, diet, use of supplements, and preventive behaviors. Ejaculation frequency was assessed in the 1992 questionnaire, which was completed by 46 213 men. Men with a diagnosis of cancer before 1992 (excluding non-melanoma skin cancer) were excluded from the analysis, leaving 41 201 men. Of these, 9276 did not complete all three questions on ejaculation frequency, leaving 31 925 men in the study population for the current analysis. Nonresponders who provided information on weight, physical activity, and diet appeared to be similar to the responders. Among participants who were alive in 2010, follow-up was 96% complete. All participants provided informed consent and the study was approved by the human subjects committee of the Harvard T.H. Chan School of Public Health, Boston.

2.2. Exposure and covariate assessment

In 1992, participants were asked the following question: "On average, how many ejaculations did you have per month during these ages?: ages 20–29; ages 40–49; past year." The frequency at each time point was reported in the categories none, 1–3, 4–7, 8–12, 13–20, and >20 EPM. To limit the burden for participants and because the question was designed specifically to address the prostate stagnation hypothesis, no information on the specific type of activity leading to ejaculation was requested. Information on potential confounders was ascertained in the 1992 questionnaire and most were updated on the biennial questionnaires throughout follow-up. PSA testing was first assessed in the 1994 questionnaire; starting in 1994, men were also asked if they had an elevated PSA level and whether they had undergone a prostate biopsy or rectal ultrasound.

2.3. Outcome assessment

For men reporting a diagnosis of PCa, we retrieved medical records and pathology reports to confirm the diagnosis and to obtain information on age at diagnosis, PSA level, and tumor stage and grade. Cases were followed through biennial questionnaires to collect information on the clinical course, including the development of metastases and treatments. Deaths were ascertained through repeated mailings and telephone calls to participants, as well as periodic searches of the National Death Index. Cause of death was assigned following a review of death certificates, information from the family, and medical records.

Total PCa incidence was the primary endpoint of interest. Men diagnosed with stage T1a cancers were excluded from analyses. To determine whether the association between ejaculation frequency and PCa differed according to the clinical disease characteristics, we also used clinical information to group PCa diagnoses into four risk categories according to National Comprehensive Cancer Network (NCCN) guidelines [10]. Locally advanced and metastatic disease categories were combined owing to limited numbers. Men were assigned to the highest category for which they were eligible: low risk = T1/T2 tumor, PSA < 10 ng/ml, Gleason score 6; intermediate risk = T1/T2 tumor, PSA 10–<20 ng/ml, Gleason score 7; high risk = T3 tumor, PSA 20–<50 ng/ml, Gleason score 8; and regional or distant metastases = T4/N1/M1 tumor, PSA ≥50 ng/ml. To more carefully explore differences in risk for indolent and aggressive disease, we also considered the following subgroups as secondary analyses: lethal disease (defined as PCa death or metastases to bone or other organs before the end of follow-up), advanced disease (stage T3b, T4 or N1 or M1 at diagnosis or lethal disease during follow-up), organ-confined disease (low-grade stage T1 or T2 and N0, M0 at diagnosis and no progression to metastasis or death during follow-up); and categories of Gleason score based on prostatectomy or biopsy pathology reports (Gleason ≤ 3 + 4 and Gleason ≥ 4 + 3).

2.4. Statistical analyses

Person-time was calculated from the return date for the 1992 questionnaire to the date of PCa diagnosis, death, or the end of the follow-up period (January 31, 2010). Actuarial curves for PCa-free survival were generated according to the ejaculation frequency category for

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age 40–49 yr using the Kaplan-Meier method. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for total PCa and for each of the clinical subgroups for each ejaculation frequency category. As in the 2004 report [8], 4–7 EPM was selected as the reference category as relatively few men reported an average of 0–3 EPM. The top two categories were combined for some analyses owing to small numbers of men in the ≥21 EPM group. Age-adjusted and multivariable models were evaluated. Age-adjusted models are adjusted for age in months (as the time scale) and for calendar time. Multivariable models were additionally adjusted for: race (Caucasian, African-America, Asian, other ancestry, missing); family history of PCa (yes/no); vigorous physical activity (quintiles); body mass index (BMI, <21, 21–<23, 23–<25, 25–<27.5, 27.5–<30, ≥30 kg/m^2, missing); height (quintiles); diabetes (yes/no); marital status (married, divorced, other); intake of energy, processed meat, tomato sauce, calcium, alcohol, and α-linolenic acid (all quintiles); multivitamin use (yes, no, missing); smoking (never, quit >10 yr ago, quit ≤10 yr ago, current, missing); history of vasectomy (yes/no); and history of PSA testing (yes/no in the previous 2-yr questionnaire cycle). Statistical significance was evaluated based on a p trend estimated by assigning the minimum frequency for each category. The missing indicator method was used for missing data on most covariates [11]. All participants had baseline questionnaire data for food frequency, and missing data on nutrients were carried forward from previous reported values. For activity, missing data were assumed to be in the lowest reference category. For height, missing data were assumed to be in the middle category.

2.5. Sensitivity analyses and effect modification

If men with erectile dysfunction have lower ejaculatory frequency and serious comorbidities associated with a higher risk of premature death from other causes, a spurious association between less frequent ejaculation and reduced risk of PCa could result. To address this issue, we performed a sensitivity analysis that excluded men who reported a history of erectile dysfunction, defined as poor or very poor ability to maintain an erection without treatment during the period 1990–1994, as assessed in the 2000 questionnaire. To eliminate a possible effect of undiagnosed disease on ejaculation frequency reported, we also performed analyses that excluded cases diagnosed within the first 4 yr of follow-up. Finally, to address the fact that diagnostic intensity may vary according to ejaculation frequency, we conducted a sensitivity analysis restricted to a PSA-screened subset of men who reported a PSA test before 1994 with follow-up from 1994 to 2010. Stratified analyses were performed to evaluate potential effect modification by age, BMI, and vasectomy status. The statistical significance of effect modification was tested using likelihood ratio tests to compare models with and without interaction terms between the potential effect modifier and ejaculation frequency. All aforementioned analyses were performed using SAS statistical software (release 9.3; SAS Institute, Cary, NC, USA).

2.6. Competing risks analysis

PCa has a long natural history [12], is very sensitive to diagnostic intensity [13], and is often indolent [14]. Thus, to better understand the interplay between PCa and deaths due to other causes, we modeled these events jointly using a multistate model in a semi-competing risks framework [15], as shown in Supplementary Figure 1. Specifically, we modeled PCa diagnoses as intermediate states and deaths due to PCa or other causes as final states. We grouped men into the four NCCN risk categories described above. Each transition hazard was modeled assuming that hazards are proportional across ejaculation frequency levels. We present results for a simple model using age as the time scale and considering event occurrence by levels of ejaculation frequency reported at age 40–49 yr. We also investigated causes of death across ejaculation frequency categories to better understand the different mortality rates. Analyses were run in R using the *mstate* package [16]. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Ejaculation frequency declined with age. The proportion of men reporting average frequency of ≥13 EPM was 57% at age 20–29 yr but dropped to 32% at age 40–49 yr. The Spearman correlation between ejaculation frequency as an ordinal variable and ages 20–29 and 40–49 yr was 0.66. Some 40% of men were in the same frequency category for ages 20–29 and 40–49 yr, and 47% of men moved down a single category from age 20–29 yr to age 40–49 yr.

The baseline age-standardized characteristics of the study population (n = 31 925) according to average monthly ejaculation frequency at age 40–49 yr are presented in Table 1. Having had a PSA test by 1994 or by 2008 was not monotonically associated with ejaculation frequency at age 40–49 yr, and the total number of PSA tests was similar across frequency categories. Among 17 093 men who reported an initial elevated PSA, the percentage who subsequently reported prostate biopsy was similar across ejaculation categories. Men reporting ≥21 EPM who were subsequently diagnosed with PCa were somewhat less likely to undergo radical prostatectomy and more likely to report radiation compared to men reporting lower frequencies.

Overall, associations between the covariates investigated and ejaculation frequency were similar for frequency at age 20–29 yr and in the year before the questionnaire (Supplementary Tables 1 and 2). Although the associations were not monotonic, there was some evidence that men in the highest ejaculation frequency category in the year before the questionnaire were less likely to have had a PSA screening test by 1994 (45.4% vs 52.6%) and by 2008 (87.5% vs 91.8%). However, the associations between covariates and ejaculatory frequency remained similar to those for the overall cohort when analysis was restricted to the subset of 13 405 screened men who reported having had a PSA test in 1994 (Supplementary Table 3).

3.2. Ejaculation frequency and PCa risk

During 480 831 person-years of follow-up, a total of 3839 incident PCa cases were diagnosed. As shown in Figure 1, PCa was less frequently diagnosed among men in the higher ejaculation frequency categories. The age-adjusted and multivariable-adjusted HRs according to average monthly ejaculation frequency are presented in Table 2. We also present results excluding 10 103 men who reported erectile dysfunction, leaving 21 822 men and 2704 total cases.

Results for total PCa were similar for the age-adjusted and multivariable analyses for all three time points at which ejaculation frequency was assessed, and for the sensitivity analysis excluding men with erectile dysfunction (Table 2).

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Table 1 – Age-standardized characteristics at baseline in 1992 for the 31 925 men from the Health Professionals Follow-up Study according to reported ejaculation frequency at age 40–49 yr[a]

	Ejaculation frequency				
	0–3 EPM	4–7 EPM	8–12 EPM	13–20 EPM	≥21 EPM
Cases (*n*)	1713	7812	12147	7440	2813
Age (yr)	59.9 (10.4)	59.1 (9.6)	58.9 (9.1)	58.5 (8.9)	58.0 (8.9)
Height (cm)	178 (7)	178 (7)	178 (7)	178 (7)	178 (7)
Body mass index in 1992 (kg/m^2)	25.6 (3.6)	25.5 (3.3)	25.8 (3.4)	26.0 (3.4)	26.3 (3.7)
Total activity (MET h/wk)	31 (35)	33 (38)	37 (39)	41 (47)	42 (46)
Total calorie intake (kcal/d)	1847 (583)	1890 (561)	1923 (576)	1968 (590)	2013 (619)
Alcohol intake (g/d)	8.4 (12.9)	9.4 (13.3)	10.4 (14.2)	11.3 (15.3)	12.2 (17.0)
Processed meat intake (servings/d)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Tomato sauce intake (servings/wk)	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	1.0 (1.0)	1.0 (1.0)
Calcium intake (mg/d)	908 (396)	916 (391)	909 (389)	908 (404)	927 (417)
α-Linolenic acid intake (g/d)	1.0 (0.4)	1.1 (0.4)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)
Divorced	4.9	4.1	5.1	7.8	11.8
Smoked in the past 10 yr	33.5	37.5	38.8	39.3	39.6
Self-reported history of syphilis or gonorrhea	1.2	2.6	3	3.3	4.6
Vasectomy history	18.2	25	27.6	27.2	27.9
Race					
White	93.4	96.3	96.7	96.9	96.2
African-American	0.6	0.6	0.8	0.6	0.8
Asian	4	1.7	1.3	1.2	1.1
Other	2.1	1.3	1.2	1.4	2.0
Screening behavior					
Had physical examination in past 2 yr	67.8	71.3	71.1	70.7	68.9
Had rectal examination in past 2 yr	65.4	67.4	68.1	67.1	66.3
Had PSA test by 1994	48.2	54.4	55.6	53.8	50.4
Had PSA test by 2008	90.9	92.7	93.1	92.2	90.6
Total periods with PSA test by 2008 (*n*)[b]	4.6 (2.6)	5.1 (2.5)	5.1 (2.5)	4.9 (2.6)	4.8 (2.6)
Had prostate biopsy after first report of elevated PSA[c]	47.2	47.4	48	46.7	47.2
Primary treatment among 3839 cases					
Cases (*n*)	192	1041	1509	807	290
Radical prostatectomy	38.4	41.8	40.8	41.8	36.2
Radiation therapy	30.2	31.9	34.2	34.3	39.3
Hormone therapy	8.3	5.9	5.7	6.6	8.4
Active surveillance/none	8.4	8.2	8.3	6.7	5.1
Other	2.2	1.6	1.8	2.9	0.7
Missing treatment information	12.6	10.6	9.3	7.7	10.2

EPM = ejaculations per month; MET = metabolic equivalent of task; PSA = prostate-specific antigen.
[a] Data are presented as the age-standardized mean (standard deviation) for continuous variables and the age-standardized percentage for categorical variables. All characteristics except age and primary treatment are age-standardized to the distribution for the full cohort in 1992. Primary treatment is standardized to the age distribution for all prostate cancer cases.
[b] Number of 2-yr questionnaire cycles in which a PSA test was reported in the previous 2 yr (maximum = 8).
[c] Among 17 093 men who reported "elevated PSA"; based only on first report of elevated PSA.

Compared to men with an average monthly frequency of 4–7 ejaculations, men reporting ≥21 EPM at ages 20–29 and 40–49 yr and in 1991 had a significantly lower risk of total PCa, with a multivariable-adjusted HR of 0.81 (95% CI 0.72–0.92), 0.78 (95% CI 0.69–0.89), and 0.76 (95% CI 0.61–0.94), respectively. Trend tests at each time point when excluding men in the lowest ejaculation frequency category, who may be more likely to have serious comorbidities, were similar to results when considering all five categories ($p < 0.0001$ for ages 20–29 and 40–49 yr, $p = 0.06$ for 1991).

The absolute PCa incidence rate for frequency at age 20–29 yr was 6.56 cases/1000 person-years for ≥21 EPM and 8.95 cases/1000 person-years for 4–7 EPM (incidence rate difference [IRD] 2.39 cases/1000 person-years). For frequency at age 40–49 yr, the absolute rate was 6.74 cases/1000 person-years for ≥21 EPM and 8.94 cases/1000 person-years for 4–7 EPM (IRD 2.20 cases/1000 person-years). For frequency in the year before the questionnaire, the rate was 4.49 cases/1000 person-years for ≥21 EPM and 8.35 cases/1000 person-years for 4–7 EPM (IRD 3.89 cases/1000 person-years).

Men who reported an average frequency of ≥21 EPM at both age 20–29 yr and age 40–49 yr experienced the same risk reduction for total PCa as men in the highest EPM category at age 40–49 yr (HR 0.78, 95% CI 0.68–0.90). The association appeared to be driven by frequency at age 40–49 yr when frequency at both time points was included in the same model. Compared to men with 4–7 EPM, the HR for men with ≥13 EPM at age 40–49 yr was 0.85 (95% CI 0.76–0.94; $p = 0.005$ for trend) after adjusting for frequency at age 20–29 yr. The HR for ≥13 EPM compared to 4–7 EPM at age 20–29 yr was 0.95 (95% CI 0.83–1.08; $p = 0.30$ for trend) after adjusting for frequency at age 40–49 yrs. However, the correlation between frequencies at different time points makes it challenging to completely disentangle the associations.

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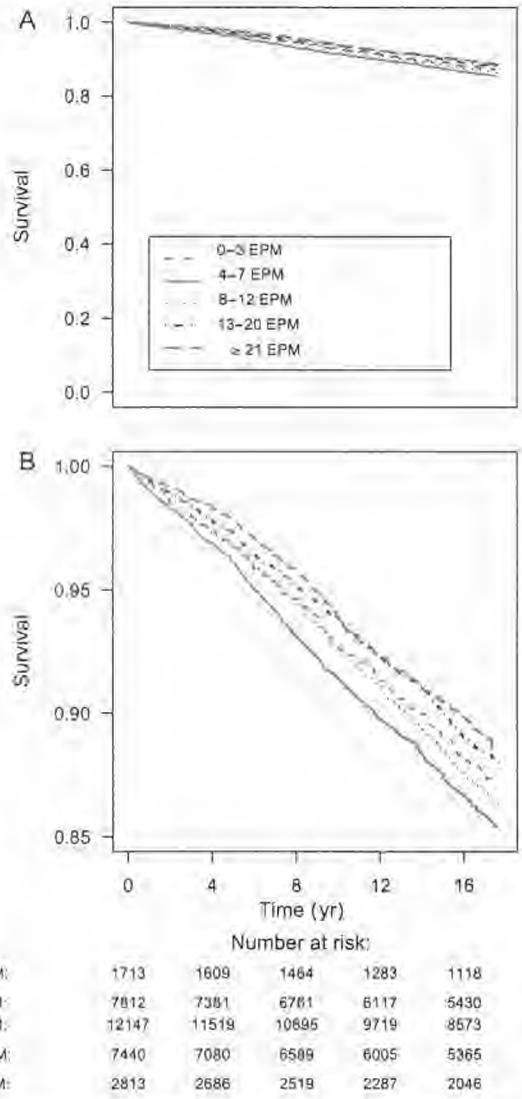

Fig. 1 – Kaplan-Meier curve for prostate cancer–free survival according to ejaculation frequency category for age 40–49 yr (1992–2010). (A) Plot over the full prostate cancer–free survival range. (B) Magnified plot for a restricted survival range. EPM = ejaculations per month.

According to the four NCCN risk groups, 1585 cases had localized low-risk PCa, 1493 had localized intermediate-risk disease, 604 had localized high-risk PCa, and 157 patients had evidence of regional or distant metastases at diagnosis. Information on clinical disease characteristics was missing for 434 (11%) men, who were classified in the two lowest risk categories depending on whether their PCa diagnosis occurred after a PSA test ($n = 336$; 21.2% of the localized low-risk group) or in the absence of a PSA test ($n = 98$; 6.6% of the localized intermediate-risk group). For all three time periods, ≥13 EPM was associated with a significantly lower risk (25–28%) of low-risk PCa in comparison to 4–7 EPM (Table 3). Ejaculation frequency at age 20–29 yr was also significantly associated with intermediate-risk PCa ($p = 0.0003$), with a 27% reduction for ≥13 versus 4–7 EPM. Ejaculation frequency at any time point was not significantly associated with diagnosis of high-risk PCa or regional/distant metastases. However, for age 20–29 yr there was a suggestion of an inverse association between ejaculation frequency and local/distant metastases (HR 0.89, 95% CI 0.68–1.15; $p = 0.07$ for ≥13 vs 4–7 EPM).

The risk of both organ-confined and low-grade PCa was significantly lower for ≥13 compared to 4–7 EPM for all three time periods (Table 4). For high-grade PCa, there was a suggestion of higher risk for men in the lowest frequency category at age 20–29 yr (HR 1.32, 95% CI 0.91–1.92) and age 40–49 yr (HR 1.38, 95% CI 1.03–1.86). However, there was some evidence that higher ejaculation frequency in the year before questionnaire distribution is associated with higher risk of advanced PCa (HR 1.37, 95% CI 1.00–1.86) or lethal PCa (HR 1.48, 95% CI 1.02–2.15), but the trend tests were only marginally significant (p values 0.11 for advanced and 0.05 for lethal PCa). When we excluded men diagnosed within the first 4 yr of follow-up to address the impact of undiagnosed disease or early symptoms on the results, the associations for ≥13 versus 4–7 EPM were attenuated for both advanced PCa (HR 1.15, 95% CI 0.79–1.69; $p = 0.36$ for trend) and lethal PCa (HR 1.19, 95% CI 0.73–1.94; $p = 0.33$ for trend; data not shown).

Sensitivity analyses, including analyses excluding men diagnosed with PCa in the first 4 yr of follow-up and analyses restricted to a screened cohort, produced results similar to the overall findings (Supplementary Material and Supplementary Tables 4 and 5). Several stratified analyses were conducted to explore potential effect modifiers. Results stratified by age at baseline, age at diagnosis, BMI at diagnosis, and history of vasectomy provided no evidence that any of these factors modified the association between ejaculation frequency and PCa risk (data not shown).

3.3. *Competing causes of death*

Because ejaculation frequency may be an indicator of health status, we fitted the multistate model in Supplementary Figure 1 to examine PCa incidence over time across the four NCCN risk groups and the cumulative incidence of lethal PCa in light of other causes of death. None of the ejaculation categories was significantly associated with changes in PCa-specific survival after diagnosis, but categories for the lowest (0–3 EPM) and highest (≥13 EPM) frequency had a higher risk of other-cause mortality (Supplementary Tables 6 and 7). However, the predicted probability of events over time for men who were cancer-free at age 50 yr (Supplementary Fig.) shows that the reduction in PCa risk in the highest category cannot be fully explained by death from other causes. Additional details on the results from this analysis are included in the Supplementary Material.

4. Discussion

The results of this prospective cohort study involving 31 925 men, 18 yr of follow-up, and 3839 PCa cases offer additional evidence of a role for ejaculation frequency in the etiology of PCa, particularly for low-risk disease.

Table 2 – Hazard ratio for incidence of total prostate cancer among 31 925 men in the Health Professionals Follow-up Study according to reported ejaculation frequency in different time periods[a]

	Ejaculation frequency							
	0–3 EPM	4–7 EPM	8–12 EPM	13–20 EPM	≥21 EPM	*p* trend	≥13 EPM	*p* trend
Age 20–29 yr								
Cases (*n*)	137	438	1208	1303	753		2056	
Age-adjusted HR (95% CI)	0.97 (0.80–1.17)	1.00	1.03 (0.92–1.15)	0.92 (0.83–1.03)	0.80 (0.71–0.90)	<0.0001	0.87 (0.79–0.97)	0.0001
Age-adjusted no-ED HR (95% CI)	0.90 (0.70–1.15)	1.00	0.98 (0.86–1.12)	0.89 (0.78–1.01)	0.78 (0.67–0.89)	<0.0001	0.84 (0.75–0.96)	0.0009
MV HR (95% CI)	0.99 (0.81–1.19)	1.00	1.03 (0.92–1.14)	0.92 (0.82–1.02)	0.81 (0.72–0.92)	<0.0001	0.88 (0.79–0.97)	0.0002
MV no-ED HR (95% CI)	0.91 (0.71–1.17)	1.00	0.99 (0.86–1.13)	0.90 (0.78–1.02)	0.80 (0.69–0.92)	<0.0001	0.86 (0.76–0.97)	0.002
Age 40–49 yr								
Cases (*n*)	192	1041	1509	807	290		1097	
Age-adjusted HR (95% CI)	0.87 (0.74–1.01)	1.00	0.91 (0.84–0.98)	0.80 (0.72–0.87)	0.77 (0.67–0.87)	<0.0001	0.79 (0.72–0.86)	<0.0001
Age-adjusted no-ED HR (95% CI)	0.91 (0.75–1.11)	1.00	0.93 (0.85–1.02)	0.80 (0.72–0.89)	0.80 (0.68–0.93)	<0.0001	0.80 (0.72–0.88)	<0.0001
MV HR (95% CI)	0.88 (0.76–1.03)	1.00	0.90 (0.83–0.98)	0.80 (0.73–0.88)	0.78 (0.69–0.89)	<0.0001	0.80 (0.73–0.87)	<0.0001
MV no-ED HR (95% CI)	0.91 (0.75–1.11)	1.00	0.93 (0.84–1.02)	0.81 (0.72–0.90)	0.82 (0.70–0.96)	0.0006	0.81 (0.73–0.90)	0.0002
Year before questionnaire (1991)								
Cases (*n*)	1293	1299	831	322	94		416	
Age-adjusted HR (95% CI)	1.03 (0.95–1.11)	1.00	0.95 (0.87–1.04)	0.90 (0.80–1.02)	0.73 (0.59–0.90)	0.0004	0.86 (0.76–0.96)	0.002
Age-adjusted no-ED HR (95% CI)	1.06 (0.96–1.17)	1.00	0.96 (0.87–1.06)	0.91 (0.80–1.05)	0.71 (0.56–0.90)	0.0005	0.86 (0.76–0.97)	0.002
MV HR (95% CI)	1.05 (0.97–1.13)	1.00	0.96 (0.87–1.05)	0.93 (0.82–1.05)	0.76 (0.61–0.94)	0.001	0.89 (0.79–0.99)	0.004
MV no-ED HR (95% CI)	1.07 (0.97–1.19)	1.00	0.96 (0.87–1.06)	0.94 (0.82–1.08)	0.74 (0.58–0.94)	0.002	0.89 (0.78–1.01)	0.007

EPM = ejaculations per month; HR = hazard ratio; CI = confidence interval; ED = erectile dysfunction; MV = multivariate.
[a] Age-adjusted models are adjusted for age in months and calendar time. Multivariate models are additionally adjusted for: race; family history of prostate cancer; vigorous physical activity (quintiles); body mass index (six categories); height (quintiles); diabetes; marital status; intake of energy, processed meat, tomato sauce, calcium, alcohol, and α-linolenic acid (all quintiles); multivitamin use; smoking (never, quit >10 yr ago, quit ≤10 yr ago, current); history of vasectomy; and history of PSA testing. No-ED models exclude men who reported poor or very poor ability to have and maintain an erection in the time period 1990–1994, for which analyses include 21 822 participants and 2704 prostate cancer events.

The absolute difference in PCa rate between ≥21 and 4–7 EPM was 2.39 cases/1000 person-years for frequency at age 20–29 yr, 2.20 cases/1000 person-years for frequency at age 40–49 yr, and 3.89 cases/1000 person-years for frequency in the year before questionnaire distribution.

An initial report published in 2004 for this cohort found that more frequent ejaculation was related to a lower risk of total PCa, with strongest associations for higher frequency in the year before questionnaire distribution [8]. With an additional decade of follow-up, we demonstrate that

Table 3 – Hazard ratio for prostate cancer by disease severity among 31 925 men in the Health Professionals Follow-up Study according to reported ejaculation frequency at different times[a,b]

	0–3 EPM		4–7 EPM		8–12 EPM		≥13 EPM		*p* value
	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	for trend
Age 20–29 yr									
Low-risk disease	40	0.84 (0.59–1.18)	160	1.00 (Ref)	407	0.91 (0.75–1.09)	687	0.75 (0.63–0.89)	0.0006
Intermediate-risk disease	39	0.85 (0.60–1.20)	156	1.00 (Ref)	390	0.88 (0.73–1.06)	664	0.73 (0.61–0.88)	0.0003
High-risk disease	43	0.99 (0.70–1.39)	142	1.00 (Ref)	435	1.13 (0.93–1.36)	775	1.00 (0.84–1.20)	0.46
Regional/distant metastases	28	1.20 (0.77–1.87)	70	1.00 (Ref)	186	1.01 (0.77–1.33)	320	0.89 (0.68–1.15)	0.07
Age 40–49 yr									
Low-risk disease	65	0.95 (0.72–1.23)	347	1.00 (Ref)	502	0.88 (0.77–1.01)	335	0.72 (0.61–0.83)	<0.0001
Intermediate-risk disease	52	0.70 (0.52–0.94)	363	1.00 (Ref)	579	0.99 (0.87–1.13)	401	0.83 (0.72–0.96)	0.11
High-risk disease	39	1.13 (0.80–1.61)	160	1.00 (Ref)	217	0.85 (0.69–1.04)	188	0.89 (0.72–1.11)	0.17
Regional/distant metastases	7	0.61 (0.27–1.35)	44	1.00 (Ref)	55	0.85 (0.57–1.27)	51	0.96 (0.64–1.45)	0.65
Year before questionnaire (1991)									
Low-risk disease	365	1.05 (0.91–1.21)	446	1.00 (Ref)	303	0.94 (0.81–1.09)	135	0.75 (0.62–0.92)	0.002
Intermediate-risk disease	432	1.01 (0.89–1.16)	481	1.00 (Ref)	325	1.00 (0.87–1.15)	157	0.89 (0.74–1.07)	0.27
High-risk disease	232	1.18 (0.96–1.45)	180	1.00 (Ref)	129	1.20 (0.95–1.50)	63	1.12 (0.84–1.51)	0.94
Regional/distant metastases	72	0.94 (0.64–1.38)	48	1.00 (Ref)	15	0.59 (0.33–1.07)	22	1.82 (1.07–3.10)	0.19

EPM = ejaculations per month; MV = multivariate; HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.
[a] Risk groups are based on National Comprehensive Cancer Network guidelines. Men were assigned to the highest category for which they were eligible: low risk = T1/T2 tumor, PSA <10 ng/ml, Gleason score 6; intermediate risk = T1/T2 tumor, PSA 10–<20 ng/ml, Gleason score 7; High risk = T3 tumor, PSA level 20–<50 ng/ml, Gleason score 8; regional or distant metastases = T4/N1/M1 tumor, PSA >50 ng/ml.
[b] Age-adjusted models are adjusted for age in months and calendar time. Multivariate models are additionally adjusted for: race; family history of prostate cancer; vigorous physical activity (quintiles); body mass index (six categories); height (quintiles); diabetes; marital status; intake of energy, processed meat, tomato sauce, calcium, alcohol, and α-linolenic acid (all quintiles); multivitamin use; smoking (never, quit >10 yrs ago, quit ≤10 yrs ago, current); history of vasectomy; and history of PSA testing.

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Table 4 – Multivariable prostate cancer incidence by disease severity among 31 925 men in the Health Professionals Follow-up Study according to reported ejaculation frequency at different times[a]

	Ejaculation frequency								
	0–3 EPM		4–7 EPM		8–12 EPM		≥13 EPM		*p* value
	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	Cases (*n*)	MV HR (95% CI)	for trend
Age 20–29 yr									
Low grade (GS ≤ 3 + 4)	76	0.88 (0.68–1.13)	283	1.00 (Ref)	785	1.00 (0.87–1.15)	1364	0.86 (0.76–0.98)	0.006
High grade (GS ≥ 4 + 3)	39	1.32 (0.91–1.92)	93	1.00 (Ref)	244	1.00 (0.78–1.27)	451	0.93 (0.74–1.16)	0.08
Organ-confined	98	1.04 (0.82–1.30)	309	1.00 (Ref)	877	1.04 (0.91–1.18)	1508	0.89 (0.78–1.00)	0.0008
Advanced	21	0.79 (0.48–1.29)	72	1.00 (Ref)	156	0.87 (0.65–1.15)	268	0.80 (0.62–1.05)	0.23
Lethal	14	0.63 (0.35–1.14)	57	1.00 (Ref)	113	0.83 (0.60–1.14)	200	0.82 (0.60–1.10)	0.71
Age 40–49 yr									
Low grade (GS ≤ 3 + 4)	106	0.76 (0.62–0.93)	689	1.00 (Ref)	1010	0.90 (0.82–0.99)	703	0.76 (0.68–0.85)	<0.0001
High grade (GS ≥ 4 + 3)	57	1.38 (1.03–1.86)	197	1.00 (Re)	318	1.01 (0.85–1.21)	255	0.99 (0.82–1.19)	0.23
Organ-confined	132	0.86 (0.71–1.03)	749	1.00 (Ref)	1126	0.93 (0.84–1.02)	785	0.78 (0.71–0.86)	<0.0001
Advanced	33	0.98 (0.67–1.44)	146	1.00 (Ref)	185	0.83 (0.66–1.03)	153	0.85 (0.67–1.07)	0.16
Lethal	24	0.95 (0.61–1.49)	107	1.00 (Ref)	133	0.83 (0.64–1.08)	120	0.95 (0.73–1.24)	0.78
Year before questionnaire (1991)									
Low grade (GS ≤ 3 + 4)	778	1.04 (0.94–1.15)	869	1.00 (Ref)	587	0.97 (0.87–1.08)	274	0.82 (0.72–0.95)	0.003
High grade (GS ≥ 4 + 3)	284	1.08 (0.91–1.29)	264	1.00 (Ref)	180	1.07 (0.88–1.30)	99	1.13 (0.89–1.43)	0.68
Organ-confined	901	1.08 (0.98–1.18)	852	1.00 (Ref)	648	1.00 (0.90–1.11)	291	0.82 (0.72–0.94)	0.0008
Advanced	211	0.99 (0.79–1.22)	157	1.00 (Ref)	88	0.98 (0.75–1.28)	61	1.37 (1.00–1.86)	0.11
Lethal	169	0.95(0.74–1.22)	114	1.00 (Ref)	60	1.01 (0.74–1.39)	41	1.48(1.02–2.15)	0.05

EPM = ejaculations per month; MV = multivariable; HR = hazard ratio; CI = confidence interval; GS = Gleason score.
[a] Organ-confined disease: stage T1/2N0M0 at diagnosis that did not progress to metastasis or death during the follow-up period. Advanced disease: stage T3b/4 or N1 or M1 at diagnosis or prostate cancer death or distant metastasis during follow-up. Lethal disease: prostate cancer death or metastases to bone or other organs before the end of the follow-up period.

ejaculation frequency at three different time points during adulthood is associated with statistically significant modest reductions in risk of total PCa. The association with frequency at age 20–29 yr became more pronounced with additional follow-up, while the associations with frequency at age 40–49 yr and in the year before the questionnaire remained statistically significant but were somewhat attenuated. Taken together with the fact that strong inverse associations remained after excluding men diagnosed in the first 4 yr of follow-up, the updated results are unlikely to be strongly influenced by the effects of undiagnosed disease on ejaculation frequency.

Importantly, our findings were robust to adjustment for time-varying factors such as BMI, physical activity, and diet that differed with ejaculation frequency and that have also been associated with PCa and its progression [5], as well as other factors associated with PCa risk in this cohort. Because men in the higher ejaculation frequency categories had some exposure patterns that might put them at higher risk of morbidity and mortality due to other causes—higher BMI, greater alcohol consumption, and more frequent history of smoking and sexually transmitted infections—we were concerned that the reduction in PCa risk we observed in this group might be attributable to premature death from other causes among men who may have had undiagnosed PCa. Thus, a strength of our study is the consideration of a model for semi-competing risks. From this model, the increase in risk of death by age 80 yr among men with the lowest ejaculation frequency is 3.8%, while the reduction in PCa risk is 2.2%. By comparison, men reporting ≥13 EPM have an increase of only 1.8% in the risk of dying from other causes by age 80 yr, while their decrease in PCa risk is 3.8%. Thus, in both cases the reduction in PCa risk may be partly explained by premature death due to other causes, but the reduction among men reporting high ejaculation frequency seemingly cannot be explained by this effect alone.

Several important limitations of our study should be noted. Ascertainment of the exposure relied on reporting of sexual activity in the past. This may introduce measurement error, particularly in the reporting of frequency at age 20–29 yr. However, the use of an anonymized questionnaire may have resulted in more accurate reporting of sexual behaviors than a one-on-one interview [17]. Previous studies suggest that the validity of data on sensitive information is further improved by: (1) an understanding among participants that their data will be kept confidential, most likely true in this large ongoing cohort in which men had already responded to at least one and potentially two previous questionnaires; and (2) the avoidance of implying a "normal" response category [18]. Most importantly, however, the data were collected prospectively, preventing differential misclassification (ie, recall bias). Thus, our results can be considered conservative estimates of the true association.

While the utilization of a large prospective study has numerous advantages, the clinical information available for men at the time of their PCa diagnosis is more limited than in clinical settings. Thus, we are not able to distinguish very low-risk disease from low-risk disease in subgroup analyses. The abundance of data on potential confounders

is an advantage of working within the well-annotated HPFS cohort, but we still cannot rule out residual confounding by other lifestyle factors. Furthermore, our cohort consisted primarily of Caucasian men and the frequency of ejaculation may vary across populations. However, the results may still be generalizable to other men, as we would not expect a true biological association between ejaculation frequency and PCa to differ by race or ethnicity.

The literature exploring the role of sexual activity in the etiology of PCa is inconsistent [7,19–30]. Previous studies are primarily retrospective case-control studies, raising concerns about recall bias, especially given that erectile dysfunction, ejaculatory dysfunction, and decreased libido are common consequences of both PCa and its treatment [31,32]. Moreover, few previous studies have considered ejaculation frequency per se, with most utilizing proxies of sexual activity, such as age at first marriage, marital status, number of sexual partners, and number of children. Few previous studies have examined associations according to tumor grade or stage despite their particular importance for PCa; spurious associations with more favorable disease may result from confounding by early detection. We do, in fact, find that the inverse association with overall PCa is driven by low-risk disease, which could indicate that more sexually active men might undergo less screening and follow-up testing. This alternative explanation for our findings is especially plausible given the potential resulting side effects of PCa and its treatment on sexual function. However, PSA screening history and biopsy utilization after elevated PSA were quite similar across the ejaculation frequency categories. Moreover, the results were consistent even when we restricted the analysis to a screened cohort and PSA history was taken into account. Nonetheless, we cannot rule out residual confounding by screening or post-screening biopsy behaviors.

Our results identified suggestive but not statistically significant associations between higher ejaculation frequency in the year before the questionnaire and both advanced and lethal PCa. However, the findings appear to be driven by men diagnosed in the period immediately following the questionnaire. The attenuated association in sensitivity analyses excluding men diagnosed in the first 4 yr of follow-up, together with the fact that these suggestive positive associations were only found for ejaculation frequency in the year before the questionnaire distribution and not at younger ages, is consistent with men with undiagnosed aggressive PCa experiencing symptoms that promoted more frequent ejaculation. While we are not aware of any literature supporting ejaculation for relief of PCa symptoms, it nonetheless seems unlikely that these suggestive associations with advanced and lethal disease reflect causality.

In addition to the prostate stagnation hypothesis [7], a number of mechanisms have been proposed to explain an inverse association between ejaculation frequency and PCa. More frequent ejaculation may influence the function of peripheral-zone epithelial cells, hindering the metabolic switch from citrate secretion to citrate oxidation known to occur early in prostate tumorigenesis [33]. Alternatively, more frequent ejaculation may reduce the development of prostatic intraluminal crystalloids, which have been associated with higher risk of PCa [34,35]. Higher ejaculatory frequency may be linked to lowering of psychological tension and central sympathetic nervous system suppression, which could dampen the stimulation of prostate epithelial cell division [36]. Given the lack of modifiable risk factors identified for PCa to date, the specific biological mechanisms underlying these associations are worthy of further investigation.

5. Conclusions

This large prospective study provides the strongest evidence to date of a beneficial role of ejaculation in prevention of PCa, a disease for which relatively little is understood about etiology generally and knowledge of modifiable risk factors is particularly scant. The results are robust to adjustment for many dietary, lifestyle, and screening behaviors, but additional work on the underlying biological mechanisms should be undertaken to corroborate these findings given the potential for residual confounding. More frequent ejaculation in the absence of risky sexual behaviors could represent an important means of reducing the profound medical costs and physical and psychological side effects of unnecessary diagnosis and treatment of low-risk tumors, even though it appears to be less strongly associated with aggressive disease.

Author contributions: Jennifer R. Rider had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rider, Mucci, Giovannucci.
Acquisition of data: Rider, Wilson, Mucci, Giovannucci.
Analysis and interpretation of data: Rider, Wilson, Sinnott, Mucci, Giovannucci.
Drafting of the manuscript: Rider, Wilson.
Critical revision of the manuscript for important intellectual content: Rider, Wilson, Sinnott, Kelly, Mucci, Giovannucci.
Statistical analysis: Rider, Wilson, Sinnott, Kelly.
Obtaining funding: Giovannucci.
Administrative, technical, or material support: None.
Supervision: Mucci, Giovannucci.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.03.027.

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Supplementary Information

Non–Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta–Analysis

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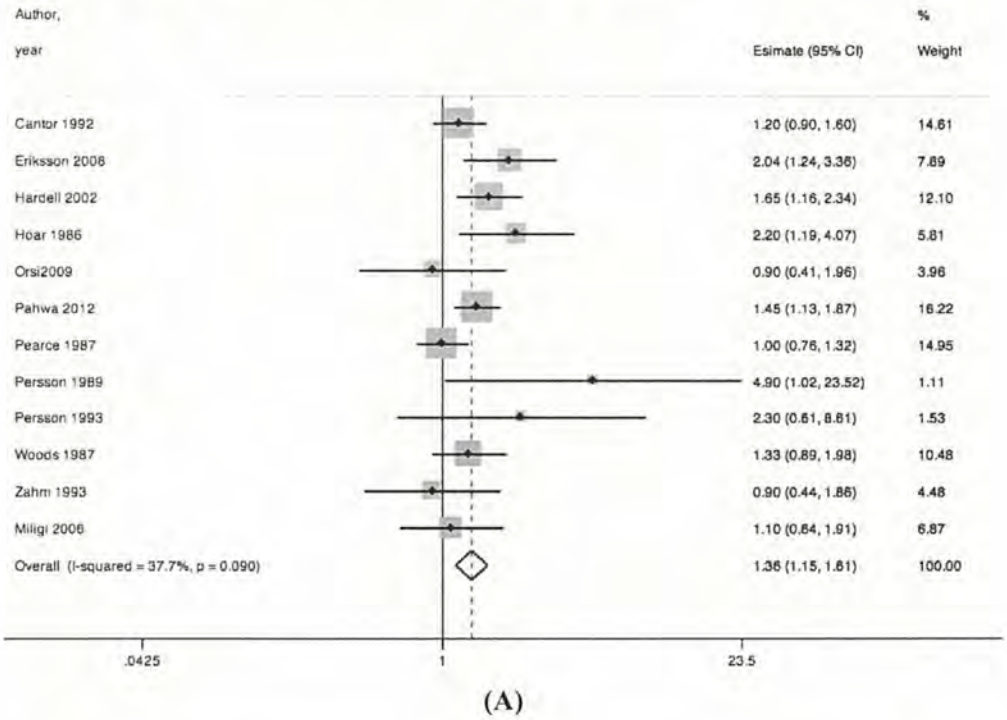
S1. List of terms included in the PubMed literature search.

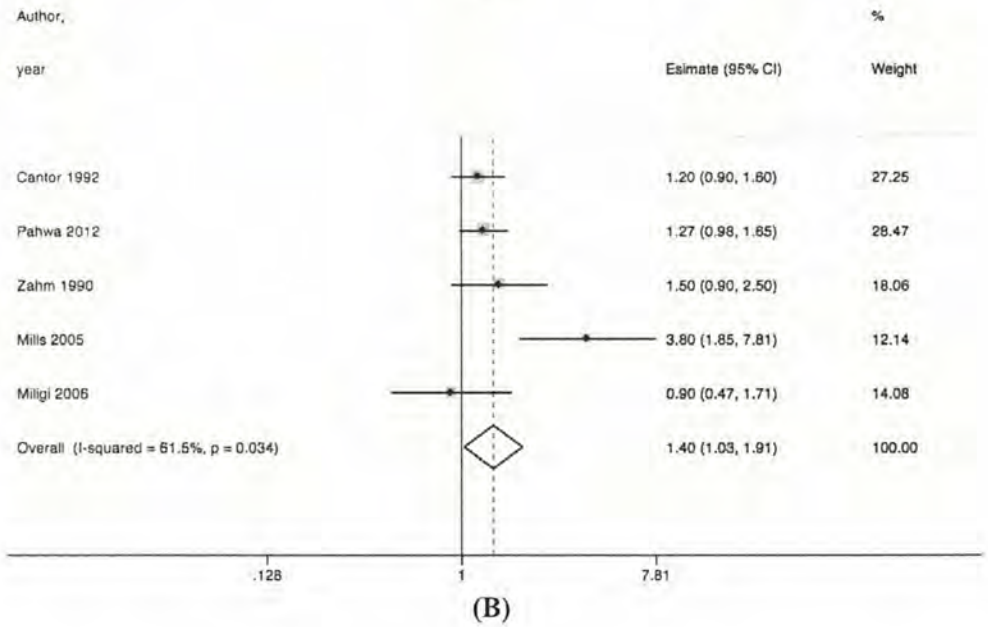
(((((((("agricultural workers' diseases/chemically induced"[MAJR] AND "neoplasms"[MeSH Major Topic] AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) OR ((((("occupational exposure"[MeSH Terms] OR occupational exposure[Title/Abstract]) OR "occupational exposure"[MeSH Terms]) OR occupational exposures[Title/Abstract]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) AND ((((((("lymphoma, non–hodgkin"[MeSH Terms] AND "humans"[MeSH Terms] AND english[la]) OR (non–hodgkin[tiab] OR non–hodgkins[tiab]) AND (lymphoma[tiab] OR lymphomas[tiab])) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) OR "neoplasms"[MeSH Terms]) OR neoplasm[Title/Abstract]) OR cancer morbidity[Title/Abstract]) OR cancer mortality[Title/Abstract]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) AND (((pesticid[tiab] OR pesticidal[tiab] OR pesticidal'[tiab] OR pesticidally[tiab] OR pesticidas[tiab] OR pesticide[tiab] OR pesticide/albumin[tiab] OR pesticide/animal[tiab] OR pesticide/biocide[tiab] OR pesticide/commodity[tiab] OR pesticide/crop[tiab] OR pesticide/environmental[tiab] OR pesticide/fertilizer[tiab] OR pesticide/food[tiab] OR pesticide/fruit[tiab] OR pesticide/fungicide[tiab] OR pesticide/ha[tiab] OR pesticide/heavy[tiab] OR pesticide/herbicide[tiab] OR pesticide/humic[tiab] OR pesticide/m2[tiab] OR pesticide/matrix[tiab] OR pesticide/metabolite[tiab] OR pesticide/metabolites[tiab] OR pesticide/metal[tiab] OR pesticide/mmt[tiab] OR pesticide/neurotoxin/free[tiab] OR pesticide/nitrate[tiab] OR pesticide/oxidation[tiab] OR pesticide/pathogen[tiab] OR pesticide/petroleum[tiab] OR pesticide/polymer[tiab] OR pesticide/product[tiab] OR pesticide/seed[tiab] OR pesticide/soil[tiab] OR pesticide/solvent[tiab] OR pesticide'[tiab] OR pesticide's[tiab] OR pesticideformulating[tiab] OR pesticiderelated[tiab] OR pesticides[tiab] OR pesticides/biocides[tiab] OR pesticides/chemicals[tiab] OR pesticides/commodities[tiab] OR pesticides/consumption[tiab] OR pesticides/contaminants[tiab] OR pesticides/fertilisers[tiab] OR pesticides/fertilizer[tiab] OR pesticides/fertilizers[tiab] OR pesticides/fruit[tiab] OR pesticides/fungicides[tiab] OR pesticides/herbicide[tiab] OR pesticides/herbicides[tiab] OR pesticides/insecticides[tiab] OR pesticides/metabolites[tiab] OR pesticides/metals[tiab] OR pesticides/pesticide[tiab] OR pesticides/petroleum[tiab] OR pesticides/polycyclic[tiab] OR pesticides/sample[tiab] OR pesticides/vasectomy/occupational[tiab] OR pesticides/weedicides[tiab] OR pesticides'[tiab] OR pesticidesatlas[tiab] OR pesticidestargeted[tiab] OR pesticidic[tiab] OR pesticids[tiab])

OR "pesticides"[MeSH Terms] OR pesticides[nm] OR (insecticid[tiab] OR insecticidal[tiab] OR insecticidal/acaricidal[tiab] OR insecticidal/anthelmintic[tiab] OR insecticidal/antifeedant[tiab] OR insecticidal/irritant[tiab] OR insecticidal/larvicidal[tiab] OR insecticidal/narcotic[tiab] OR insecticidal'[tiab] OR insecticidal'b[tiab] OR insecticidally[tiab] OR insecticidation[tiab] OR insecticide[tiab] OR insecticide/acaricide[tiab] OR insecticide/antifeedant[tiab] OR insecticide/ascaricide[tiab] OR insecticide/atrazine[tiab] OR insecticide/fumigant[tiab] OR insecticide/fungicide[tiab] OR insecticide/herbicide[tiab] OR insecticide/kg[tiab] OR insecticide/lipid[tiab] OR insecticide/liter[tiab] OR insecticide/miticide[tiab] OR insecticide/mosquito[tiab] OR insecticide/nematicide[tiab] OR insecticide/nematocide[tiab] OR insecticide/organophosphrus[tiab] OR insecticide/pesticide/herbicide[tiab] OR insecticide/repellant[tiab] OR insecticide/repellent[tiab] OR insecticide'[tiab] OR insecticide's[tiab] OR insecticided[tiab] OR insecticideresistance[tiab] OR insecticideresistant[tiab] OR insecticides[tiab] OR insecticides/acaricides[tiab] OR insecticides/attract[tiab] OR insecticides/larvicides[tiab] OR insecticides/mn[tiab] OR insecticides/pesticides[tiab] OR insecticides/repellents[tiab] OR insecticides'[tiab] OR insecticidetreated[tiab] OR insecticidewise[tiab] OR insecticidial[tiab] OR insecticidic[tiab] OR insecticiding[tiab] OR insecticidity[tiab] OR insecticido[tiab]) OR "insecticides"[MeSH Terms] OR insecticides[nm] OR (herbicidal[tiab] OR herbicidally[tiab] OR herbicide[tiab] OR herbicide/binding[tiab] OR herbicide/dessicant[tiab] OR herbicide/fungicide[tiab] OR herbicide/g[tiab] OR herbicide/humic[tiab] OR herbicide/insect[tiab] OR herbicide/kg[tiab] OR herbicide/micelle[tiab] OR herbicide/ml[tiab] OR herbicide/mutation[tiab] OR herbicide/nematicide[tiab] OR herbicide/outcome[tiab] OR herbicide/pesticide[tiab] OR herbicide/substrate[tiab] OR herbicide/therapeutic[tiab] OR herbicide/tio2[tiab] OR herbicide's[tiab] OR herbicided[tiab] OR herbicideh[tiab] OR herbicideh/phytocide[tiab] OR herbicideinduced[tiab] OR herbicides[tiab] OR herbicides/chlorophenols[tiab] OR herbicides/desiccants[tiab] OR herbicides/fungicides[tiab] OR herbicides/pesticides[tiab] OR herbicides'[tiab] OR herbicidetolerant[tiab] OR herbicidies[tiab] OR herbicidin[tiab] OR herbicidins[tiab] OR herbicidovorans[tiab] OR herbicids[tiab]) OR (herbicides[nm] OR herbicidins[nm]) OR (fungicid[tiab] OR fungicidal[tiab] OR fungicidal/bactericidal[tiab] OR fungicidal/fungistatic[tiab] OR fungicidal/parasiticidal[tiab] OR fungicidally[tiab] OR fungicidals[tiab] OR fungicide[tiab] OR fungicide/algicide[tiab] OR fungicide/antioxidant[tiab] OR fungicide/bactericide[tiab] OR fungicide/disinfectant[tiab] OR fungicide/oomyceticide[tiab] OR fungicide/slimicide[tiab] OR fungicide's[tiab] OR fungicideal[tiab] OR fungicideinsensitive[tiab] OR fungicides[tiab] OR fungicides/herbicides[tiab] OR fungicides'[tiab] OR fungicidial[tiab] OR fungicidic[tiab] OR fungicidicus[tiab] OR fungicidin[tiab] OR fungicidine[tiab] OR fungicidity[tiab] OR fungicido[tiab] OR fungicidy[tiab])) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) NOT News[Publication Type]) NOT Congresses[Publication Type]) NOT Review[Publication Type]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) NOT "child"[MeSH Terms] AND (("1980/01/01"[PDAT] : "2013/12/31"[PDAT]) AND "humans"[MeSH Terms]))

Figure S1. Forest plots showing estimates of association between non–Hodgkin lymphoma and occupational, agricultural exposures to (**A**) phenoxy herbicides, (**B**) 2,4–D, (C) MCPA, (**D**) glyphosate, (**E**) organochlorine insecticides, and (**F**) DDT.

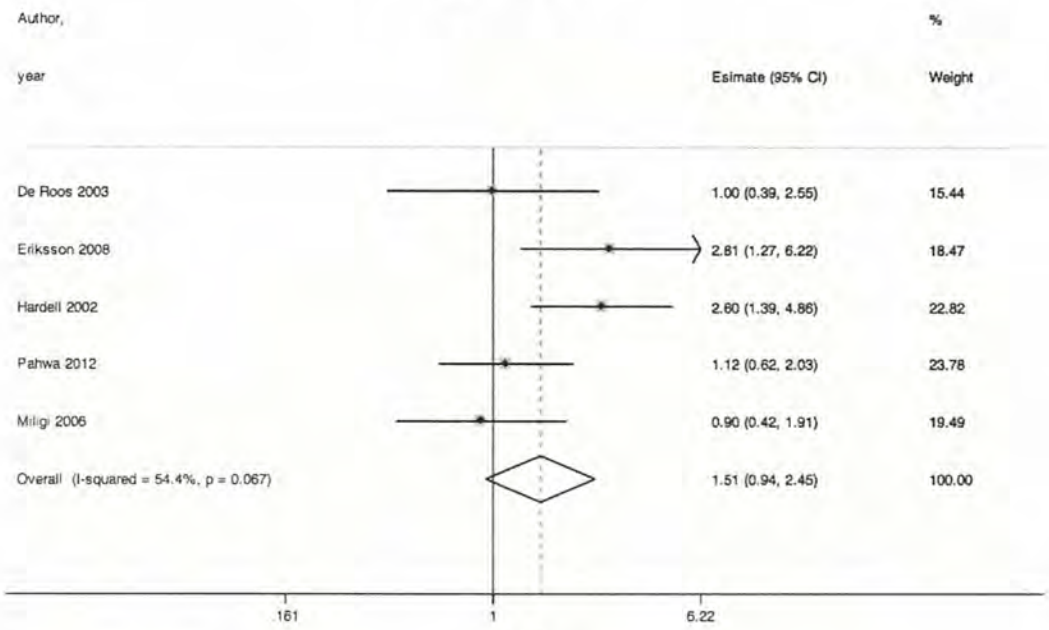


(A)

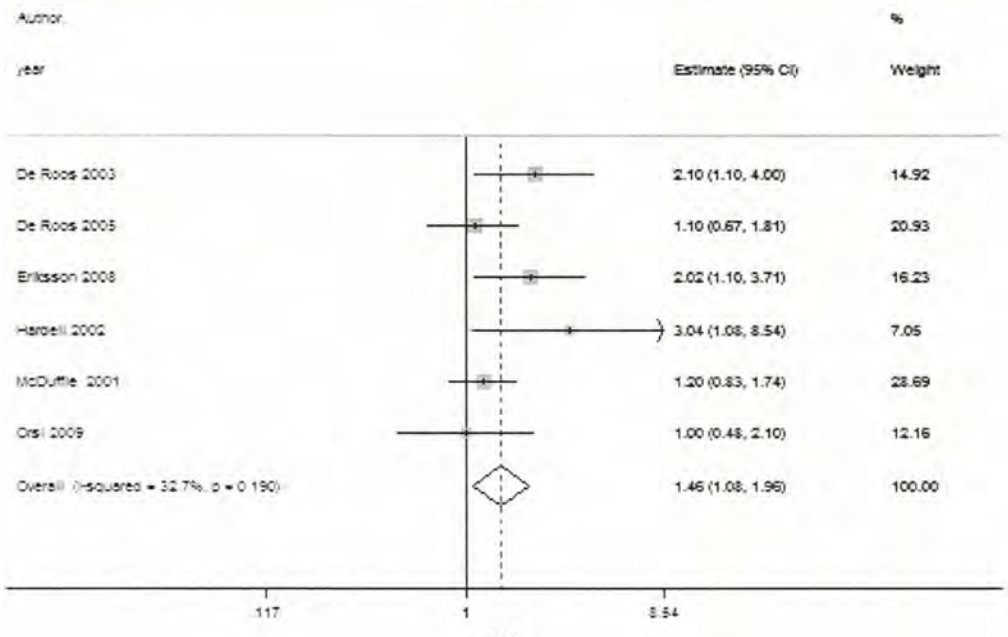


(B)

Figure S1. *Cont.*

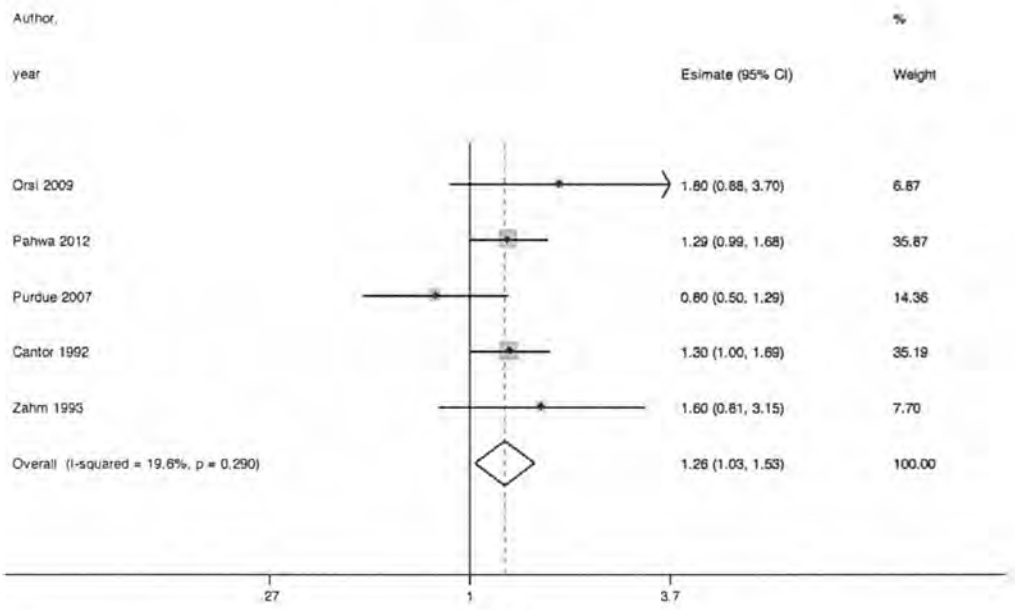


(C)

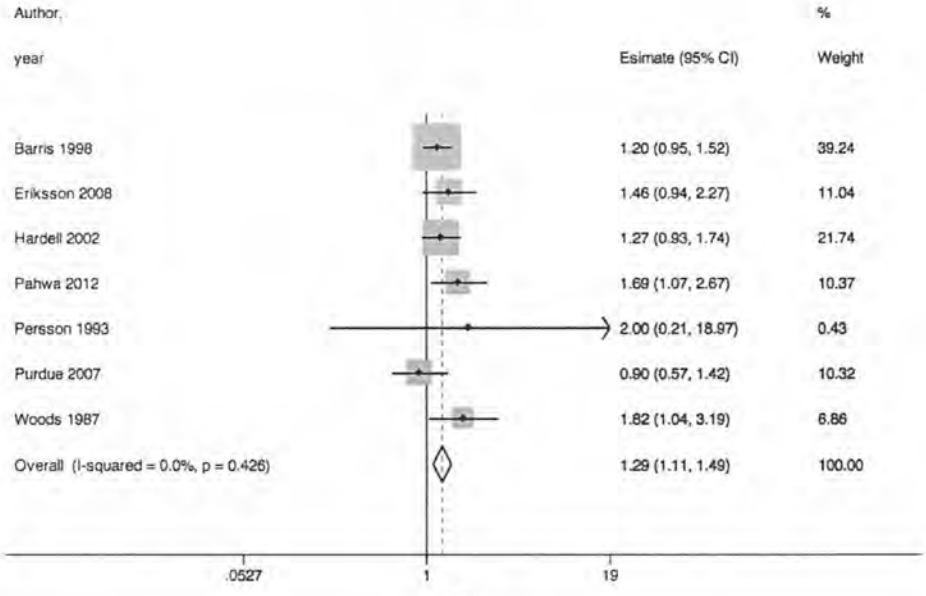


(D)

Figure S1. *Cont.*



(E)



(F)

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; 2,4,5–T, 2,4,5–Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid.

Table S1. Results of the sensitivity analysis of the effects of gender on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta relative risk, 95% CI	I^2	Papers contributing
Male only population			
Amide herbicides	1.7, 0.7–3.8	64.0%	[1,2]
Glyphosate	1.7, 1.0–2.9	52.7%	[3–5]
Phenoxy herbicides	1.4, 1.1–1.6	44.1%	[1,2,4,6–8]
2,4–D	1.3, 1.2–1.5	0.0%	[1,6,9]
MCPA	1.5, 0.8–2.7	56.6%	[3,4,6]
Benzoic acid herbicides	1.3, 0.9–1.9	0.0%	[1,2]
Trifluralin	1.0, 0.6–1.5	0.0%	[3,5]
Triazine herbicides	1.5, 0.70–3.4	73.5%	[1,2]
OP insecticides	1.7, 1.3–2.1	39.2%	[6,10]
Diazinon	1.7, 1.2–2.3	0.0%	[5,10]
Malathion	1.8, 1.4–2.2	0.0%	[6,10]
Carbamate insecticides	1.8, 1.3–2.4	0.0%	[5,11]
OC insecticides	1.3, 1.1–1. 6	0.0%	[1,6]
DDT	1.3, 1.1–1.5	27.3%	[4,6,8,12]
Aldrin	1.4, 0.2–11.1	92.0%	[3,5]
Chlordane	1.3, 0.9–1.7	0.0%	[3,5,8]
Lindane	1.9, 1.2–2.9	38.0%	[5,13,14]
Male and female population			
Phenoxy herbicides	1.6, 1.0–2.5	42.2%	[15–19]
2,4–D	1.8, 0.5–7.5	88.3%	[19,20]
MCPA	1.6, 0.5–4.8	76.0%	[15,19]
OC insecticides	1.2, 0.5–2.5	70.4%	[16,21]
DDT	1.2, 0.8–1.7	18.0%	[15,18,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus.

Table S2. Results of the sensitivity analysis of the effects of study design on the meta–analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides, with contributing estimates restricted to case–control studies.

Chemical	Meta relative risk, 95% CI	I^2	Paper contributing
Glyphosate	1.6, 1.1–2.2	36.6%	[3–5,15,16]
Organochlorine insecticides	1.3, 1.1–1.6	0.0%	[1,6,16,22]
Aldrin	1.4, 0.2–11.1	92.0%	[3,5]
Chlordane	1.3, 0.9–1.7	0.0%	[3,5,8]
DDT	1.3, 1.1–1.6	0.0%	[4,6,8,12,15,18]
Lindane	1.9, 1.2–2.9	38.0%	[5,13,14]

Notes: DDT; dichlorodiphenyltrichloroethane.

Table S3. Results of the sensitivity analysis of the effects of diagnosis period on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta relative risk, 95% CI	I^2	Papers contributing
Diagnosis period 1975–1989			
2,4–D	1.8, 1.0–3.1	76.6%	[1,9,20]
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	2.3, 1.4–4.0	0.0%	[3,4]
MCPA	1.7, 0.7–4.4	63.8%	[3,4]
Phenoxy herbicides	1.4, 1.1–1.7	44.9%	[1,2,4,7,8,17,18,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,23]
Carbamate insecticides	1.6, 1.1–2.4	0.0%	[11,22]
OC insecticides	1.3, 1.0–1.7	0.0%	[1,22]
OP insecticides	1.5, 1.2–1.8	0.0%	[10,22]
Diazinon	1.6, 1.2–2.2	0.0%	[10,20]
Chlordane	1.5, 1.0–2.5	0.0%	[3,8]
Trifluralin	0.9, 0.6–1.3	0.0%	[3,20,22]
Malathion	1.6, 1.3–2.1	0.0%	[10,20]
DDT	1.3, 1.1–1.5	0.0%	[4,8,12,18]
Lindane	2.0, 0.9–4.4	65.0%	[13,14]
Diagnosis period in the 1990s			
2,4–D	1.6, 0.8–3.1	79.3%	[6,19,20]
Glyphosate	1. 5, 1.0–2.1	41.1%	[4,5,15,24]
MCPA	1.6, 0.9–2.9	61.9%	[4,6,15,19]
Phenoxy herbicides	1.5, 1.3–1.8	0.5%	[4,6,15,19]
Trifluralin	1.0, 0.6–1.6	0.0%	[5,20]
Aldrin	1.5, 0.2–10.1	90.0%	[5,21]
Chlordane	0.9, 0.6–1.4	42.2%	[5,21]
Diazinon	1.5, 1.0–2.4	0.0%	[5,20]
DDT	1.3, 1.0–1.6	25.4%	[4,6,15,21]
Lindane	1.9, 1.1–3.2	46.6%	[5,14,21]
Malathion	1.9, 1.5–2.5	0.0%	[6,20]
OC insecticides	1.1, 0.7–1.7	66.2%	[6,21]
Diagnosis period in the 2000s			
Glyphosate	1.3, 0.9–2.0	31.8%	[15,16,24]
Phenoxy herbicides	1.4, 0.7–3.2	66.7%	[15,16]
Lindane	2.0, 0.8–5.0	70.6%	[14, 21]
OC insecticides	1.2, 0.5–2.5	70.4%	[16,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus; [1] The first, second, and third editions of the International classification of diseases for oncology were introduced in 1976, 1990, and 2000, respectively.

Table S4. Results of the sensitivity analysis of the effects of geographic region on the meta-analytic relative risk estimates of association between non Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
Only papers that report results from studies conducted in North America			
Glyphosate	1.3, 1.0–1.8	26.7%	[3,5,24]
Phenoxy herbicides	1.4, 1.1–1.6	12.9%	[1,2,6,8,22]
2,4–D	1.5, 1.1–2.1	66.5%	[1,6,9,20]
MCPA	1.1, 0.7–1.8	0.0%	[3,6]
DDT	1.3, 1.0–1.7	45.1%	[6,8,12,21]
OC insecticides	1.2, 1.0–1.5	24.7%	[1,6,21,22]
OP insecticides	1.6, 1.3–2.0	15.1%	[6,10,22]
Lindane	1.5, 1.2–1.9	0.0%	[5,13,21]
Only papers that report results from studies conducted in the United States			
2,4–D	1.8, 1.0–3.1	76.6%	[1,6,9,20]
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	1.5, 0.8–2.8	58.5%	[3,24]
Phenoxy herbicides	1.3, 1.0–1.7	27.1%	[1,2,8,22]
Trifluralin	0.9, 0.6–1.3	0.0%	[3,20,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,22]
Aldrin	0.5, 0.4–0.8	0.0%	[3,21]
Carbamate insecticides	1.6, 1.1–2.4	0.0%	[22,23]
Chlordane	1.1, 0.7–2.0	55.0%	[3,8,21]
DDT	1.2, 0.9–1.7	44.8%	[8,12,21]

Table S4. *Cont.*

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
Only papers that report results from studies conducted in the United States			
Diazinon	1.6, 1.2–2.2	0.0%	[10,20]
Lindane	1.4, 1.1–1.9	0.0%	[13,21]
Malathion	1.6, 1.3–2.1	0.0%	[10,20]
OC insecticides	1.2, 0.8–1.7	47.5%	[1,21,22]
OP insecticides	1.5, 1.2–1.8	0.0%	[10,22]
Only papers that report results from studies conducted in European countries			
Glyphosate	1.7, 1.0–3.1	42.8%	[4,15,16]
Phenoxy herbicides	1.6, 1.2–2.1	29.1%	[4,15–19]
MCPA	1.9, 0.9–3.8	64.8%	[4,15,19]
Only papers that report results from studies conducted in Sweden			
Glyphosate	2.2, 1.3–3.8	0.0%	[4,15]
MCPA	2.7, 1.6–4.4	0.0%	[4,15]
Phenoxy herbicides	1.9, 1.4–2.4	0.0%	[4,15,17,18]
DDT	1.3, 1.0–1.7	0.0%	[4,15,18]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus

Table S5. Results of the sensitivity analysis of the effects of control source on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides, with contributing estimates restricted to those from population–based case–control studies.

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
HERBICIDES			
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	1.7, 1.2–2.6	39.0%	[3,4,5,15]
Phenoxy herbicides	1.5, 1.2–1.7	20.7%	[1,2,4,6,8,15,17–19,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,22]
INSECTICIDES			
Organochlorine insecticides	1.2, 1.0–1.5	24.7%	[1,6,21,22]
Organophosphate insecticides	1.6, 1.4–1.8	0.0%	[1,6,10,22]

Table S6. Results of the sensitivity analysis of the effects of paper contributing on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides.

Chemical	Meta estimate, 95% CI	I^2	Change	Papers contributing
HERBICIDES				
Alachlor	0.9, 0.6–1.5	69.7%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,25]
Glyphosate	1.3, 1.0–1.7	18.2%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,24]
2,4–D	1.3, 0.8–2.1	82.5%	Use De Roos 2003 [3] instead of Cantor 1992 [1] and Zahm 1990 [9]	[3,6,19,20]
Carbamate herbicides	1.2, 0.5–2.6	24.8%	Use Cantor 1992 [1] and Hoar 1986 [2] instead of Zheng 2001 [11]	[1,2,16,22]
Trifluralin	1.1, 0.7–1.8	40.0%	Use Cantor 1992 [1] and Hoar 1986 [2] instead of De Roos 2003[3]	[1,2,5,20,22]
INSECTICIDES				
OP insecticides	1.7, 1.4–2.0	0.0%	Use Cantor 1992 [1] instead of Waddell 2001 [10]	[1,6,16,22]
Diazinon	1.5, 1.1–2.1	0.0%	Use Cantor 1992 [1] instead of Waddell 2001 [10]	[1,3,5,20]
Diazinon	1.7, 1.2–2.4	0.0%	Use De Roos 2003 [3] instead of Cantor 1992 [1] and instead of Waddell 2001 [10]	[3,5,20]
Dimethoate	1.2, 0.7–2.0	0.0%	Use De Roos 2003 [3] instead of Waddell 2001 [10]	[3,5]
Malathion	1.7, 1.3–2.2	13.5%	Use Cantor 1992 [1] (use of malathion on animals) instead of Waddell 2001 [10] or De Roos 2003 [3]	[1,6,20]
Malathion	1.8, 1.4–2.4	0.0%	Use Cantor 1992 [1] (use of malathion on crops) instead of Waddell 2001 [10] or De Roos 2003 [3]	[1,6,20]
Malathion	1.6, 1.2–2.3	37.2%	Use De Roos 2003 [3] instead of Waddell 2001 [10] and Cantor 1992 [1]	[3,6,20]
Carbaryl	1.9, 1.3–2.9	0.0%	Use Cantor 1992 [1] instead of Zheng 2001 [11]	[1,5]
Carbaryl	1.5, 0.7–3.1	64.7%	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Zheng 2001 [11]	[3,5]
Carbofuran	1.1, 0.7–1.8	0.0%	Use Cantor 1992 [1] instead of Zheng 2001 [11]	[1,5]

Table S6. *Cont.*

Chemical	Meta estimate, 95% CI	I^2	Change	Papers contributing
Carbofuran	1.1, 0.6–2.0	23.0%	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Zheng 2001 [11]	[3,5]
DDT	1.3, 1.1–1. 5	0.0%	Use Cantor 1992 [1] (use of DDT on animals) instead of Baris 1998 [12]	[1,4,6,8,15,18,21]
DDT	1.3, 1.2–1. 6	9.1%	Use Cantor 1992 [1] (use of DDT on crops) instead of Baris 1998 [12]	[1,4,6,8,15,18,21]
Methoxychlor	1.0, 0.8–1.4	0.0%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,5]
Aldrin	1.3, 0.5–2.9	80.2%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,5,21]
Chlordane	1.2, 0.8–1.7	48.7%	Use Cantor 1992 [1] (Use of chlordane on animals) instead of De Roos 2003 [3]	[1,5,8,21]
Chlordane	1.1, 0.8–1.7	42.1%	Use Cantor 1992 [1] (Use of chlordane on crops) instead of De Roos 2003 [3]	[1,5,8,21]
Dieldrin	1.0, 0.4–2.2	50.8%	Use Cantor 1992 [1] instead of De Roos 2003[3]	[1,21]
Heptachlor	1.0, 0.7–1.7	20.5%	Use Cantor 1992 [1] instead of De Roos 2003[3]	[1,21]
Lindane	1.62, 1.16–2.27	30.6%	Use Cantor 1992 [1] (use of lindane on animals) instead of Blair 1998 [13] and De Roos 2003 [3]	[1,5,14,21]
Lindane	1.85, 1.27–2.69	23.30 %	Use Cantor 1992 [1] (use of lindane on crops) instead of Blair 1998 [13]and De Roos 2003 [3]	[1,5,14,21]
Lindane	1.62, 1.08–2.41	39.20 %	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Blair 1998 [13]	[3,5,14,21]
Toxaphene	1.25, 0.72–2.19	23.50 %	Use Cantor 1992 [1] (use of toxaphene on animals) instead of De Roos 2003 [3]	[1,20,21]
Toxaphene	1.50, 0.96–2.33	0.00%	Use Cantor 1992 [1] (use of toxaphene on crops) instead of De Roos 2003 [3]	[1,20,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus.

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Authors	Year	RR	95% CI	Relative weight (%)
De Roos et al. [13]	2003	1.6	0.9–2.8	16.2
De Roos et al. [12]	2005	1.1	0.7–1.9	21.0
Eriksson et al. [14]	2008	1.51	0.77–2.94	11.6
Hardell et al. [15]	2002	1.85	0.55–6.20	3.6
McDuffie et al. [16]	2001	1.20	0.83–1.74	38.1
Orsi et al. [17]	2009	1.0	0.5–2.2	9.5
Meta-RR		1.3	1.0–1.6	

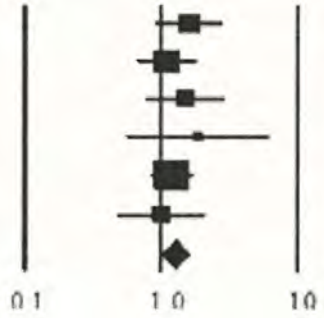

Figure 1. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of non-Hodgkin lymphoma. Meta-RRs were identical in random-effects and fixed-effects models.

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Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers

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ABSTRACT

This systematic review and meta-analysis rigorously examines the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia. Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between any versus no use of glyphosate and risk of NHL (meta-RR = 1.3, 95% confidence interval (CI) = 1.0–1.6, based on six studies) and MM (meta-RR = 1.4, 95% CI = 1.0–1.9; four studies). Associations were statistically null for HL (meta-RR = 1.1, 95% CI = 0.7–1.6; two studies), leukemia (meta-RR = 1.0, 95% CI = 0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). Bias and confounding may account for observed associations. Meta-analysis is constrained by few studies and a crude exposure metric, while the overall body of literature is methodologically limited and findings are not strong or consistent. Thus, a causal relationship has not been established between glyphosate exposure and risk of any type of LHC.

ARTICLE HISTORY
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KEYWORDS
Glyphosate; non-Hodgkin lymphoma; Hodgkin lymphoma; multiple myeloma; leukemia; hematologic malignancies; herbicides; meta-analysis

Introduction

The broad-spectrum herbicide glyphosate (*N*-(phosphonomethyl)glycine), as a constituent of more than 750 products for agricultural, forestry, urban, and residential applications, is the most commonly used herbicide in the world. Therefore, understanding its potential human carcinogenicity has major implications for public health and risk assessment.

In 2014, the German Federal Institute for Risk Assessment (BfR), on behalf of the European Union, reviewed all toxicological studies of glyphosate in laboratory animals, as well as over 30 epidemiological studies in humans, and concluded that "the available data do not show carcinogenic or mutagenic properties of glyphosate" and "there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer."[1,2] This conclusion was consistent with those previously reached by the United States Environmental Protection Agency (U.S. EPA) and the Joint Meeting on Pesticide Residues (JMPR), sponsored by the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO), which concluded that glyphosate was unlikely to be carcinogenic to humans.[3–5]

By contrast, the International Agency for Research on Cancer (IARC) in 2015 classified glyphosate as "probably carcinogenic to humans" (Group 2A). In arriving at this classification, IARC characterized evidence of carcinogenicity in humans as "limited," based on the data available for non-Hodgkin lymphoma (NHL).[6] IARC considered the evidence of carcinogenicity in experimental animals as "sufficient." The latter determination was based on the occurrence of renal tubule carcinoma, hemangiosarcoma, and pancreatic islet-cell adenoma in rodents, as well as mechanistic evidence.

To incorporate the IARC classification into the European Union review of glyphosate, BfR was commissioned by the German government and the European Food Safety Authority (EFSA) to review the IARC assessment.[7] In its subsequent revised assessment report, BfR reached the conclusion that "no carcinogenic risk to humans is to be expected from glyphosate if it is used in the proper manner for the intended purpose."[8] This assessment was supported by all European Union member states except one (Sweden) and by EFSA.[9] The WHO also has established an expert taskforce to re-evaluate the available data on glyphosate and report its findings to JMPR.[10]

In summarizing the epidemiological evidence, IARC stated that "case-control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The [Agricultural Health Study] cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures."[6] A recent meta-analysis conducted by investigators from IARC[11] found a statistically significant positive association between glyphosate use and NHL risk (meta-relative risk [RR] = 1.5, 95% confidence interval [CI] = 1.1–2.0), based on six studies.[12–17] The same meta-analysis also found a significant positive association between

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glyphosate use and risk of B-cell NHL, based on two studies.[14,18]

Although Schinasi and Leon[11] stated that in their meta-analysis, "[i]n an effort to use the most unbiased estimate, [they] extracted the most adjusted effect estimate," two or arguably three of the RR estimates that they selected for inclusion were not the most highly adjusted estimates reported by the original authors.[13–15] Instead, in a personal communication (11 August 2015), Dr. Schinasi indicated that other estimates were selected based on considerations of consistency of estimates across meta-analyses of other pesticides, secondary analyses, and statistical modeling approach.

Meta-analyses are not intended to identify, validate, or dispute causal relationships. Although they can be useful in providing a summary measure of association and identifying heterogeneity among research results, they can obscure important differences in methods and results among studies that can be more thoroughly evaluated in a detailed qualitative review. Schinasi and Leon[11] did not assess study quality and did not specifically address the potential impact of study limitations on the findings for glyphosate, nor did they discuss whether the apparent association between glyphosate and NHL risk is likely to be causal. On the other hand, Mink et al.[19] conducted a qualitative systematic review, without a meta-analysis, of epidemiologic studies of glyphosate and various cancers, including NHL. Taking into account potential sources of error, including selection bias, confounding, and especially exposure misclassification, the authors concluded that they "found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate."

Given the conflicting findings surrounding this issue, we conducted this systematic review and meta-analysis to examine more rigorously the relationship between exposure to glyphosate and risk of NHL, as well as major histopathological subtypes of NHL, in human epidemiologic studies. Because NHL is often considered alongside other lymphohematopoietic cancers (LHC), whose ever-changing classification systems now characterize some leukemias and multiple myeloma (MM) as NHL subtypes,[20] we also included Hodgkin lymphoma (HL), MM, and leukemia in this review. Despite the limitations of quantitative meta-analysis for observational epidemiology,[21,22] we conducted a meta-analysis largely to determine the impact of using RR estimates not used in the meta-analysis by Schinasi and Leon.[11] In addition, we conducted a qualitative evaluation of potential for error and bias. Thus, this article goes beyond previous work by examining all types of LHC, conducting a new meta-analysis, providing a detailed evaluation of study quality and potential for bias, and synthesizing the overall epidemiologic evidence for a causal association between glyphosate and LHC risk.

Methods

Literature search

Sources eligible for inclusion in the meta-analysis were original articles describing epidemiological studies that provided numeric point estimates of the RR (i.e., odds ratio, rate ratio, or prevalence ratio) of LHC, including NHL, HL, MM, leukemia, and any subtypes of these disease entities, associated with individual-level glyphosate exposure, along with corresponding interval estimates (e.g., 95% confidence intervals [CI]) or sufficient raw data to calculate RRs and CIs. Reviews, commentaries, letters to the editor without original data, and non-human studies were excluded, as were articles that did not report quantitative measures of association between glyphosate exposure (e.g., those assessing broadly defined categories of pesticides or herbicides) and risk of LHC (e.g., those assessing other cancers or all malignancies combined).

To identify all potentially relevant articles, we searched MEDLINE via PubMed (Supplementary methods), with additional targeted searches in Web of Science and Google Scholar, along with a review of the bibliographies of recent review articles. Based on a review of titles and abstracts to exclude articles without pertinent information, followed by a review of the full text of relevant articles, 19 articles (as well as one letter to the editor[23] that contained additional results from a study described in another one of the included articles,[24] and one abstract[25] that preceded a full-length article[26]) were ultimately deemed eligible for inclusion (Appendix Fig. A1). Two authors independently reviewed and agreed upon the list of eligible articles.

Of the 19 articles reporting on the association between glyphosate and risk of specific forms of LHC, 12 pertained to NHL or its subtypes (including hairy-cell leukemia, which is a subtype of B-cell NHL),[12–18,24,27–30] 2 pertained to HL,[17,31] 6 pertained to MM,[12,17,26,32–34] and 3 pertained to leukemia.[12,35,36]

Evaluation of study characteristics and quality

From each eligible study, we extracted the following information: first author, publication year, study location, study design, study years, source population, number of subjects, proportion of proxy respondents, exposure assessment method, outcome assessment method, confounders adjusted, number of subjects in each exposure category, and RR estimates with CIs.

In addition to summarizing study characteristics, we qualitatively evaluated the methodological quality of each study in terms of its potential for selection bias, information bias/exposure misclassification, confounding, reporting bias, and other issues affecting validity. Potential for bias was evaluated based on subject identification strategy, participation rates, investigator blinding, assessment methods for exposures, outcomes, and potential confounders, statistical approach, reporting of results, and other considerations.[37–39]

Selection of data for meta-analysis

From each publication, we selected an RR point estimate for inclusion in the meta-analysis based on a set of rules specified *a priori*. First, if unadjusted and adjusted RRs were reported in a publication or across multiple publications from the same study population, the most fully adjusted RR was selected for inclusion. The most fully adjusted RR was defined as the RR estimate that took into consideration, by restriction or statistical adjustment, the most covariates that appeared to be confounders. The rationale for choosing the most fully adjusted RR was

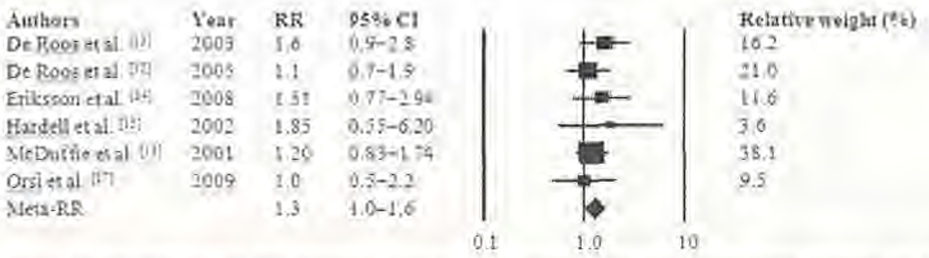

Figure 1. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of non-Hodgkin lymphoma. Meta-RRs were identical in random-effects and fixed-effects models.

based on the assumption that the adjusted covariates were found by the authors to act as confounders by altering the estimate of association (either directly or by acting as a surrogate for another, unmeasured confounder); however, some authors did not explain how confounders were selected, so this assumption may not hold for all studies. If an adjusted RR was not reported, the unadjusted (crude) RR was included as reported by the authors or as calculated from available raw data. Second, if multiple eligible publications were derived from the same study population, the RR from the most recent publication was selected for inclusion unless it was based on a subset of the overall eligible study population, in which case the RR based on the most complete study population was included. Third, subject to the first two rules, the RR for dichotomous exposure with the largest number of exposed cases was selected for inclusion in the meta-analysis. In a few instances where another RR from a given study nearly met these inclusion criteria but was superseded by a more fully adjusted, more recent, or more robust RR, the alternative RR was considered in secondary analyses.

RRs for multiple categories of exposure also were extracted to enable qualitative evaluation of exposure-response trends (based on the assumption, discussed later, that studies were able to distinguish among exposure levels). However, because no two studies used the same set of three or more categories to classify glyphosate exposure, these estimates could not be combined in meta-analysis.

Statistical approach

For associations with at least two independent RR estimates from different study populations, we estimated both fixed-effects and random-effects meta-RRs with 95% CIs. We used comparison of meta-RR estimates from fixed-effects and random-effects models as one approach to the evaluation of the impact of between-study heterogeneity on the meta-RRs. As a quantitative measure of between-study heterogeneity, we calculated I^2, which represents the percentage of between-study variance in RRs that is attributable to study heterogeneity (as opposed to chance).[40] We also tested for statistically significant between-study heterogeneity based on Cochran's Q statistic,[41] although this test has low power to detect modest heterogeneity across a limited number of studies.[42]

In the absence of statistically significant heterogeneity, the presence of at least one statistically significant association, $I^2 <$ 50%, and at least four contributing studies, we evaluated evidence of publication bias (i.e., non-random selection of studies for publication, with a tendency toward submission and publication of studies that report larger, statistically significant associations[43]) by using the linear regression approach of Egger et al.,[44] which measures the degree of funnel plot asymmetry. We also estimated meta-RRs corrected for publication bias by imputing results for missing studies using the trim-and-fill procedure developed by Duval and Tweedie,[45] which iteratively trims asymmetric studies from the overbalanced side of a funnel plot to locate the unbiased effect, and then fills the plot by re-inserting the trimmed studies on the original side of the mean effect, along with their imputed counterparts on the opposite side. Again, we used these approaches with the understanding that they have limited power to detect publication bias based on few studies.[42]

The meta-analysis was conducted using Comprehensive Meta-Analysis Software (Biostat, Inc., Englewood, NJ, USA). All calculated meta-RRs and 95% CIs were confirmed using Episheet (www.krothman.org/episheet.xls).

Sensitivity analysis

To evaluate the robustness of results to various potential sources of heterogeneity, we planned *a priori* to conduct a sensitivity analysis with stratification of studies by study design (case-control vs. cohort), source of controls (population-based vs. hospital-based), gender (males only vs. males and females), geographic region (North America vs. Europe), and time period of cancer diagnosis (1980s, 1990s, or 2000s, with studies contributing to a given stratum if any part of the case diagnosis period was in a given decade).

Overall evaluation

To guide a qualitative assessment of the combined epidemiologic evidence for a causal relationship between glyphosate exposure and risk of LHC, we used Sir Austin Bradford Hill's "viewpoints" as a general framework.[46] Because this review is restricted to the epidemiologic literature, our consideration of the biological plausibility of the association and the coherence of the human, animal, and mechanistic evidence was limited.

Results

Study characteristics and overlap

Studies of NHL and subtypes

Twelve studies from seven independent study populations, including eleven case-control studies and one prospective

cohort study, evaluated the relationship between glyphosate use and risk of NHL and/or its histopathological subtypes.[12–16,24,27–30] Characteristics of these studies are summarized in Table 1. All of the studies considered glyphosate use in agricultural operations or settings, and most evaluated overall NHL as an outcome. The exceptions were Cocco et al.,[18] which analyzed B-cell lymphoma and other NHL subtypes, but not overall NHL, and Nordstrom et al.,[30] which included only hairy-cell leukemia. Eriksson et al.[14] presented results for B-cell lymphoma and other NHL subtypes, as well as for overall NHL, while Orsi et al.[17] included results for overall NHL and several specific NHL subtypes.

De Roos et al.[13] combined data from Cantor et al.[24] with data from two other studies that did not independently report associations between glyphosate use and NHL risk;[47,48] therefore, we did not further consider Cantor et al.[24] as a separate study. Lee et al.[29] was based on Cantor et al.[24] and Hoar Zahm et al.,[48] but not Hoar et al.,[47] and stratified results by asthma status (with no apparent interaction between glyphosate exposure and asthma); therefore, results from De Roos et al.[13] took precedence in our analysis over those from Lee et al.[29] The study by Hardell et al.[15] pooled data from two other studies that reported on glyphosate use and NHL risk.[27,30] Consequently, the latter two studies were not considered further with respect to NHL, although Nordstrom et al.[30] was evaluated separately with respect to hairy-cell leukemia. Based on the same study population as McDuffie et al.,[16] (except for four fewer cases excluded after pathology review), Hohenadel et al.[28] reported associations with use of glyphosate with or without malathion, but not glyphosate overall; therefore, the results from McDuffie et al.[16] were prioritized in our analysis.

The seven independent studies ranged markedly in size with respect to the number of NHL cases classified as exposed to glyphosate (based on reported use): Cocco et al.,[18] 4 B-cell lymphoma cases exposed; Hardell et al.,[15] 8 exposed; Orsi et al.,[17] 12 exposed; Eriksson et al.,[14] 29 exposed; De Roos et al.,[13] 36 exposed; McDuffie et al.,[16] 51 exposed; De Roos et al.,[12] 71 exposed in the total eligible cohort. Four studies were based in Europe[14,15,17,18] and three in North America[12,13,16] (Table 1). Four of the case-control studies were population-based,[12–16] one was hospital-based,[17] and one included a mixture of population-based and hospital-based cases and controls.[18] Four studies were restricted to males,[13,15–17] while the rest included males and females. Two studies conducted at least some case ascertainment during the 1980s,[13,15] five during the 1990s,[12,14–16,18] and four during the 2000s[12,14,17,18] (categories are overlapping). For reference, glyphosate entered the U.S. and European commercial markets in 1974.[49]

Studies of HL

Two case-control studies estimated the OR between glyphosate use and risk of HL.[17,31] Characteristics of these studies are summarized in Table 1. The study by Karunanayake et al.[31] used the same methods and source population as McDuffie et al.,[16] but focused on HL rather than NHL.

As described in the section on NHL studies, Orsi et al.[17] was a hospital-based case-control study set in Europe (France), restricted to males, with case ascertainment in the 2000s, participation rates > 90%, and no proxy respondents. This study classified six HL cases as exposed to glyphosate. Karunanayake et al.[31] was a population-based case-control study set in North America (Canada), restricted to males, with case ascertainment in the 1990s, participation rates of 68% for cases and 48% for controls, and an unspecified proportion of proxy respondents. In this study, 38 HL cases were classified as glyphosate-exposed.

Studies of MM

Six studies from four independent study populations, including four case-control studies and two prospective cohort studies, evaluated the association between glyphosate use and risk of MM.[12,17,26,32–34] These studies are described in Table 1. A cross-sectional analysis within a subset of the Agricultural Health Study Cohort examined the association between glyphosate use and risk of monoclonal gammopathy of unknown significance (MGUS), an MM precursor;[50] this study was not included in the present review.

The studies by De Roos et al.[12] and Sorahan[26] were based on virtually identical datasets from the Agricultural Health Study cohort (except that the dataset used by Sorahan was stripped of data on race, state of residence, and applicator type due to privacy concerns; these differences should not have affected the results substantively). Because the Sorahan[26] study included all eligible cohort members, whereas the De Roos et al.[12] study was based on a restricted subset of the cohort with complete data,[51] the Sorahan[26] results were prioritized in our analysis of MM. Brown et al.[32] employed the same methods and source population as Cantor et al.,[24] which was included in the pooled analysis of NHL by De Roos et al.[13] Pahwa et al.[34] and Kachuri et al.[33] conducted overlapping analyses in the same Canadian source population as McDuffie et al.,[16] Hohenadel et al.,[28] and Karunanayake et al.[31] Pahwa et al.[34] included more controls in their analysis, but these controls were excluded from Kachuri et al.[33] because they were younger than any enrolled MM cases (≤29 years) and thus did not contribute meaningfully to the analysis. Kachuri et al.[33] also controlled for more confounders, and therefore was prioritized in our analysis.

With respect to glyphosate use, the four independent studies of MM included, respectively, 5 exposed cases,[17] 11 exposed cases,[32] 24 exposed cases,[26] and 32 exposed cases.[33] All but one study, which was based in France,[17] were conducted in North America, and all except one[26] were restricted to males. One of the two case-control studies was population-based[32] and the other was hospital-based.[17] Case ascertainment took place during the early 1980s in one study,[32] at least partly during the 1990s in two studies,[26,33] and at least partly during the 2000s in two studies.[17,26]

Studies of leukemia

Two case-control studies and one prospective cohort study investigated the relationship between glyphosate use and risk of leukemia.[12,35,36] Key characteristics of these studies are provided in Table 1. The study by Brown et al.[35] used the same methods

Table 1. Design characteristics of studies of glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Brown et al.[35]	1990	Leukemia (including myelodysplasias)	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa Tumor Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 86% Controls: 77% random digit dialing, 79% Medicare, 77% proxies for deceased Supplemental interview: 93% cases, 96% controls	Cases: 578 Controls: 1,245 Supplemental interview: 86 cases, 203 controls	Cases: 238 (41%) Controls: 425 (34%) Supplemental interview, 63 (73%) cases, 57 (28%) controls
Brown et al.[32]	1993	MM	United States (Iowa)	Population-based case-control	1981–1984	White men aged ≥ 30 years in Iowa	Cases: Iowa Health Registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificates if deceased	Cases: 84% Controls: 78% overall	Cases: 173 Controls: 650	Cases: 72 (42%) Controls: 198 (30%)
Cantor et al.[24]	1992	NHL	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa State Health Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 89% Controls: 77% random-digit dialing, 79% Medicare, 77% proxies for deceased	Cases: 622 Controls: 1245	Cases: 184 (30%) Controls: 425 (34%)
Cocco et al.[18]	2013	B-cell NHL	Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain)	Population- and hospital-based case-control	1998–2004	Persons aged ≥ 17 years in Germany and Italy general populations, and in referral areas of participating hospitals in Czech Republic, France, Ireland, and Spain	Cases: NR Controls: random sampling of population registers in Germany and Italy; recruitment from hospital departments for infectious and parasitic (17.6%), mental and nervous (14.6%), circulatory (8.7%), digestive (7.1%), endocrine and metabolic (4.1%), respiratory (3.9%), and several other conditions (33.2%), excluding cancer, in Czech Republic, France, Ireland, and Spain	Cases: 88% overall; 90% Czech Republic, 91% France, 87% Germany, 90% Ireland, 93% Italy, 82% Spain Controls: 69% overall, 81% hospital-based, 52% population-based; 60% Czech Republic, 74% France, 44% Germany, 75% Ireland, 66% Italy, 96% Spain	Cases: 2348 Controls: 2462	None
De Roos et al.[13]	2003	NHL	United States (Nebraska, Iowa, Minnesota, and Kansas)	Population-based case-control (pooled analysis of 3 studies)	1979–1986	White men aged ≥ 21 years in one of the 66 counties of eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester; white men aged ≥ 21 years in Kansas	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records; University of Kansas Cancer Data Service registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska (93% living, 89% deceased); 89% Iowa and Minnesota; 96% Kansas Controls: 85% Nebraska; 77% random-digit dialing, 79% Medicare, 77% deceased (proxies) Iowa and Minnesota; 93% Kansas Analysis restricted to subjects who lived or worked on a farm before 18 years of age (% NR); analysis of multiple pesticides restricted to subjects with non-missing data (75% cases, 75% controls)	Cases: 650 (in analyses of multiple pesticides) Controls: 1933 (in analyses of multiple pesticides)	Cases: 201 (30.9%) (in analyses of multiple pesticides) Controls: 767 (39.7%) (in analyses of multiple pesticides)
De Roos et al.[12]	2005	LHC, NHL, MM, leukemia	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort: 36,509–49,211 in analyses adjusted for demographics and lifestyle 30,613–40,719 in analyses additionally adjusted for other pesticides	None
Eriksson et al.[14]	2008	NHL, B-cell NHL, SLL/CLL, FL grades I-III, DLBCL, other specified B-cell NHL, unspecified B-cell NHL, T-cell NHL, unspecified NHL	Europe (Sweden)	Population-based case-control	1999–2002	Adults aged 18–74 years in 4 of 7 health service regions in Sweden associated with university hospitals in Lund, Linköping, Örebro, and Umeå	Cases: contact with treating physicians and pathologists Controls: national population registry	Cases: 81% Controls: 65% (92% of initially enrolled controls with 71% participation)	Cases: 995 Controls: 1016	None

Hardell and Eriksson[27]	1999	NHL	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden	Cases: regional cancer registries Controls: national population registry if living, national registry for causes of death if deceased	Cases: 91% (91% living, 92% deceased) Controls: 84% (83% living, 85% deceased)	Cases: 404 Controls: 741	Cases: 177 (44%) Controls: NR (~44%; matched to cases)
Hardell et al.[15]	2002	NHL including hairy-cell leukemia	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden (for NHL) or in the entire country of Sweden (for hairy-cell leukemia)	Cases: regional cancer registries for NHL, national cancer registry for hairy-cell leukemia Controls: national population registry, national registry for causes of death if deceased	Cases: 91% Controls: 84%	Cases: 515 Controls: 1141	Cases: ~35% (NR) Controls: ~29% (NR)
Hohenadel et al.[28]	2011	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 513 Controls: 1506	Cases: 110 (21%) Controls: 220 (15%)
Kachuri et al.[33]	2013	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years (≥ 30 years in analysis) in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1357	Cases: 103 (30%) Controls: 202 (15%)
Karunanayake et al.[11]	2012	HL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 68% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 316 Controls: 1506	Cases: NR Controls: 220 (15%)
Kaufman et al.[36]	2009	Leukemia	Bangkok, Thailand	Hospital-based case-control	1997–2003	Patients aged ≥ 18 years residing in Bangkok proper and suburbs of Nonthaburi, Nakornpathom, Patumthani, Samutprakarn, and Samusakorn, admitted to Siriraj Hospital or Dhonburi Hospital	Cases: hospital records Controls: hospital records for acute infection or inflammation (33%), trauma (22%), acute abdominal emergencies such as appendicitis (27%), or various other diagnoses with elective admission, such as cataract, hernia repair, or cosmetic surgery (17%), excluding head trauma with loss of consciousness or cancer; controls at Dhonburi Hospital (a nearby private hospital) matched to 21 cases admitted to private wards for wealthy patients	Cases: 100% Controls: 100%	Cases: 180 Controls: 756	None
Lee et al.[29]	2004	NHL	United States (Nebraska, Iowa, and Minnesota)	Population-based case-control (pooled analysis of 2 studies)	1980–1986	White men and women aged ≥ 21 years in one of 45 counties in eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska, 89% Iowa and Minnesota Controls: 85% Nebraska, 78% Iowa and Minnesota	Cases: 872 Controls: 2336	Cases: 266 (31%) Controls: 779 (33%)

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Table 1. (*Continued*)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
McDuffie et al.[15]	2001	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 517 Controls: 1506	Cases: ~21% (NR) Controls: 220 (15%)
Nordström et al.[30]	1998	Hairy-cell leukemia	Europe (Sweden)	Population-based case-control	1987–1992 (1993 for one case)	Men living in Sweden	Cases: national cancer registry Controls: national population registry	Cases: 91% Controls: 83%	Cases: 111 Controls: 400	Cases: 4 (4%) Controls: 5 (1%)
Orsi et al.[17]	2009	LHC, NHL, DLBCL, FL, LPS, CLL, hairy-cell leukemia, HL, MM	Europe (France)	Hospital-based case-control	2000–2004	Men aged 20–75 years living in the catchment areas of the main hospitals in Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux, with no history of immunosuppression or taking immunosuppressant drugs	Cases: hospital records Controls: hospital records for orthopedic or rheumatological conditions (89.3%), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue disease (1.8%), and infections (3.0%), excluding patients admitted for cancer or a disease directly related to occupation, smoking, or alcohol abuse	Cases: 95.7% Controls: 91.2%	Cases: 491 LHC, 244 NHL, 104 LPS, 87 HL, 56 MM Controls: 456	None
Pahwa et al.[34]	2012	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1506	Cases: 103 (30%) Controls: 220 (15%)
Sorahan[26]	2015	MM	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort (1): 54,315 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, or missing glyphosate use 49,211 also excluding missing education, smoking, or alcohol 40,719 excluding missing other pesticides Eligible cohort (2): 53,656 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, missing glyphosate use, or missing cumulative exposure days of glyphosateuse 53,304 also excluding missing intensity of glyphosate use Eligible cohort (3): 55,934 excluding subjects with cancer before enrollment, loss to follow-up, or missing age at enrollment	None

Table 1. Continued (additional columns).

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Brown et al.[32]	1990	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, and personal applying/mixing/handling In 1987, supplemental telephone interview to evaluate usual number of days of pesticide use per year among Iowa subjects who had reported agricultural use of specific pesticides	Diagnostic confirmation by regional pathologists; special review of myelodysplasias by one pathologist co-author	No	Adjusted: vital status, age, state, ever used tobacco daily, first-degree family history of LHC, non-farming job related to leukemia risk in this study, exposure to substances (benzene, naphtha, hair dyes) related to leukemia risk in this study	Partial support from National Institute of Environmental Health Sciences	Brown et al.[32]; Cantor et al.[24]; De Roos et al.[13]; Lee et al.[29]
Brown et al.[33]	1993	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation by an expert pathologist	No	Adjusted: vital status, age Considered: smoking, education, other factors found not to be confounders of agricultural risk factors	Partial support from National Institute of Environmental Health Sciences	Brown et al.[32]; Cantor et al.[24]; De Roos et al.[13]; Lee et al.[29]
Cantor et al.[24]	1992	In-person structured interview, including detailed farming and pesticide use history of all subjects who had worked on a farm for ≥ 6 months since age 18 years For each pesticide, evaluated ever use, first and last year of use, method of application, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	No	Adjusted: vital status, state, age, cigarette smoking status, first-degree family history of LHC, non-farming job related to NHL risk in this study, exposure to hair dyes, exposure to other substances associated with NHL risk in this study Considered: pesticides belonging to other chemical families	Partial support from National Institute of Environmental Health Sciences	Brown et al.[32]; Brown et al.[33]; De Roos et al.[13]; Lee et al.[29]
Cocco et al.[18]	2013	In-person structured interview, including detailed farming and pesticide use history for all subjects who reported having worked in agriculture For each agricultural job, reported tasks, crops, size of cultivated area, pests treated, pesticides used, crop treatment procedures, use of personal protective equipment, re-entry after treatment, and frequency of treatment in days per year	Histologically or cytologically confirmed cases with central review of slides of ~20% by an international team of pathologists	No	Adjusted: age, gender, education, study center	European Commission, 5th and 6th Framework Programmes; Spanish Ministry of Health; German Federal Office for Radiation Protection; La Fondation de France; Italian Ministry for Education, University and Research; Italian Association for Cancer Research	None
De Roos et al.[14]	2003	Telephone interview in Nebraska and Kansas; in-person structured interview in Iowa and Minnesota Nebraska: Question about use of any pesticide, followed by prompting for specific selected pesticides, including years of use and average days per year Iowa and Minnesota: Direct question about a selected use of specific pesticides, including first and last years of use Kansas: Open-ended question about use of pesticides, followed by questions on duration of use and days per year for groups of pesticides but not individual pesticides (with validation study)	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists Kansas: Diagnostic confirmation and classification by panel of 3 pathologists	Yes in Nebraska; no in Iowa, Minnesota, and Kansas	Adjusted: age, study site, other individual pesticides with ≥ 20 users in full study Considered: first-degree family history of LHC, education, smoking	NR; assume National Cancer Institute	Brown et al.[32]; Brown et al.[33]; Cantor et al.[24]; Lee et al.[29] (also Hoar et al.[47]; Hoar Zahm et al.[44])
De Roos et al.[12]	2005	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors	Linkage to state cancer registry files, state death registries, and National Death Index	None	Adjusted: age at enrollment, education, cigarette smoking pack-years, alcohol consumption in past year, first-degree family history of cancer, state of residence Considered (adjusted for MM only): 5 pesticides for which cumulative exposure-days were most highly associated with those for glyphosate (i.e., 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, trifluralin), 5 pesticides for which ever/never use was most highly associated with that for glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, diazinon)	National Cancer Institute, National Institute of Environmental Health Sciences, Environmental Protection Agency, and National Institute for Occupational Safety and Health	Sorahan[26]
Eriksson et al.[14]	2008	Self-administered mailed questionnaire with additional telephone interview for missing or unclear answers; evaluated occupational exposure to individual pesticides, including number of years, number of days per year, and approximate length of exposure per day	Diagnostic pathological specimens examined and classified by 1 of 5 Swedish expert lymphoma reference pathologists, if not already initially reviewed by one of them; panel review if classification differed from original report	Yes	Adjusted: age, sex, and year of diagnosis or enrollment; other associated agents (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid and/or 2,4,5-trichlorophenoxyacetic acid, mercurial seed dressing, arsenic, creosote, tar) for NHL only	Swedish Council for Working Life and Social Research; Cancer and Allergy Fund; Key Fund; Örebro University Hospital Cancer Fund	None

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Table 1. (*Continued*)

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Hardell and Eriksson[27]	1999	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed use of pesticides within different occupations, wet contact if not handling the sprayer, brand names of pesticides, years of exposure, and cumulative days of exposure Exposure excluded 1 year prior to diagnosis or index year	Histopathological diagnosis of NHL reported to regional cancer registries, confirmed by review of pathology reports	Yes	Adjusted: age, county, vital status, year of death if deceased, use of phenoxyacetic acids	Swedish Work Environment Fund, Swedish Medical Research Council, Örebro County Council Research Committee, Örebro Medical Center Research Foundation	Hardell et al.[15]
Hardell et al.[15]	2002	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed years and total number of days of occupational exposure to various agents and names of agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Histologically verified NHL; confirmation of hairy-cell leukemia NR	Yes	Adjusted: study, study area, vital status, other associated pesticides (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid + 2,4,5-trichlorophenoxyacetic acid, other herbicides)	Swedish Cancer Research Fund, Swedish Medical Research Council, Örebro County Council Research Committee, Örebro Medical Centre Research Foundation	Hardell and Eriksson[27] Nordström et al.[30]
Hohenadel et al.[28]	2011	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent Considered: diesel exhaust, ultraviolet radiation, farm animals, chemicals such as benzene, first-degree family history of cancer	Health Canada, British Columbia Health Research Foundation, Centre for Agricultural Medicine at University of Saskatchewan	Kachuri et al.[33]; Karunanayake et al.[31]; McDuffie et al.[16]; Pahwa et al.[34]
Kachuri et al.[33]	2013	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent, smoking status, personal history of rheumatoid arthritis, allergies, measles, shingles, or cancer, family history of cancer	Occupational Cancer Research Centre; Cancer Care Ontario; Ontario Workplace Safety and Insurance Board; Canadian Cancer Society, Ontario Division, Mitacs-Accelerate Graduate Research Internship Program	Hohenadel et al.[28]; Karunanayake et al.[31]; McDuffie et al.[16]; Pahwa et al.[34]
Karunanayake et al.[31]	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours/year of cumulative exposure to any combination of herbicides, insecticides, fungicides, fumigants, and algicides Pesticide interview collected information on exposure to individual pesticides, place of pesticide use, year of first use, first year on market, number of years of use, and days per year of use [Note differences from related studies]	Initial diagnosis based on information from cancer registries and hospitals; pathology and tumor tissue slides for 155 of 316 cases reviewed by a reference pathologist who confirmed HL in 150/155 cases, plus 7 cases originally classified as NHL; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, acne, hay fever, or shingles, first-degree family history of cancer	NR; assume same as in related studies	Hohenadel et al.[28]; Kachuri et al.[33]; McDuffie et al.[16]; Pahwa et al.[34]
Kaufman et al.[35]	2009	Interview with nurse to assess occupational and non-occupational exposure to pesticides and other potential risk factors	Histologically confirmed leukemia diagnosed within 6 months before current hospital attendance or admission	No	Considered: age, sex, income, use of cellular telephones, benzene and other solvent exposure, occupational and non-occupational pesticide exposure, pesticides used near home, working with power lines, living near power lines, exposure to X-rays, exposure to certain types of electromagnetic fields, use of hair dyes	Thailand Research Fund and Commission on Higher Education	None
Lee et al.[29]	2004	Telephone interview in Nebraska; in-person structured interview in Iowa and Minnesota Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with years of first and last use	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	Yes in Nebraska; no in Iowa and Minnesota	Adjusted: age, state, vital status Considered: gender, smoking, first-degree family history of LHC, ever having a job correlated with risk of LHC (e.g., painting or welding), use of protective equipment	NR; assume National Cancer Institute	Brown et al.[15]; Brown et al.[32]; Cantor et al.[24]; De Roos et al.[13] (also Hoar Zahm et al.[48])

McDuffie et al.[16]	2001	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours (total = 179 cases, 456 controls with telephone interview) Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, cancer, or allergy desensitization shots, first-degree family history of cancer Considered: pesticide exposure, smoking history	Health Canada, British Columbia Health Research Foundation, Centre for Agricultural Medicine at University of Saskatchewan	Hohenadel et al.[28]; Kachuri et al.[33]; Karunanayake et al.[31]; Pahwa et al.[34]
Nordström et al.[30]	1998	Self-administered mailed questionnaire with supplemental telephone interview for unclear or missing answers; assessed total number of days of occupational exposure to various agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Reported to national cancer registry; further confirmation not described	Yes	Adjusted: age Considered: exposure to animals, herbicides, insecticides, fungicides, impregnating agents, organic solvents, exhausts, or ultraviolet light	Swedish Work Environment Fund, Örebro County Council Research Committee, Örebro Medical Centre Research Foundation.	Hardell et al.[15]
Orsi et al.[17]	2009	Self-administered written questionnaire with lifetime occupational history, followed by in-person structured interview evaluating non-occupational exposure to pesticides and agricultural questionnaire for subjects who had worked as a farmer or gardener for ≥ 6 months during lifetime Agricultural questionnaire collected data on location of all farms where subject had worked for ≥ 6 months, period of occupation and area, farmer's status at each farm, crops and animal husbandry with mean sizes, all pesticides used on each crop during a given period, whether subject had personally prepared, mixed, or sprayed the pesticide, chemical used, brand name, main use, type of spraying equipment used, annual number and duration of applications, and use of pesticides in farm buildings for animals, grain, hay or straw, or to clear lanes and yards All questionnaires reviewed by an occupational hygienist and an agronomist; repeat telephone interviews conducted to clarify information from 95 (56.8%) of 158 subjects who completed the agricultural questionnaire, not completed by 35 (20.8%) who refused (n = 15), died/were in poor health (n = 10), or could not be contacted (n = 15); all chemicals coded using ad hoc system and classified as definite or possible exposure	All diagnoses cytologically or histologically confirmed and reviewed by a panel of pathologists and hematologists	Yes	Adjusted: age, study center, socioeconomic category Considered: all combinations of pesticide families associated with the LHC subtype considered with a p-value ≤ 0.10, rural/urban status, type of housing, educational level, history of mononucleosis, history of influenza immunization, family history of cancer, skin characteristics, smoking status, and alcohol drinking status	Association pour la Recherche contre le Cancer, Fondation de France, AFSSET, Faberge employees (donation)	None
Pahwa et al.[34]	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 h of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 h Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, allergies, arthritis, or shingles, first-degree family history of cancer	Occupational Cancer Research Centre; Cancer Care Ontario; Ontario Workplace Safety and Insurance Board; Canadian Cancer Society	Hohenadel et al.[28]; Kachuri et al.[33]; Karunanayake et al.[31]; McDuffie et al.[16]

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Table 1. (*Continued*)

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Sorahan[26]	2015	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors Missing data classified into "not known/missing" category, with unknown use of 2,4-dichlorophenoxyacetic acid classified with no use and unknown education classified with no education beyond high school due to lack of MM cases in unknown categories	Linkage to state cancer registry files, state death registries, and National Death Index	None	Fully adjusted: age, gender, smoking pack-years, alcohol use in year before enrollment, first-degree family history of cancer, education, use of 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, or trifluralin, ever use of benomyl, maneb, paraquat, carbaryl, or diazinon Intermediate adjusted: age, gender, smoking, alcohol, family history of cancer, education Adjusted in full cohort: age, gender, family history of cancer, education	Monsanto Europe SA/NV	De Roos et al.[12]

CI: confidence interval; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; LHC: lymphohematopoietic cancer; LPS: lymphoproliferative syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; NR: not reported; OR: odds ratio; SLL: small lymphocytic lymphoma.

and source population as Brown et al.,[32] which was described in the section on MM, and Cantor et al.,[24] which was included as part of De Roos et al.[13] in a pooled analysis of NHL.

As described earlier, De Roos et al.,[12] the only prospective cohort study included, was based in North America (Iowa and North Carolina), enrolled both males and females, ascertained cancer incidence in the 1990s and 2000s, and had a 99.5% follow-up rate through 2001. In the total eligible cohort, 43 leukemia cases occurred among glyphosate users. Brown et al,[35] was a population-based case-control study set in North America (Iowa and Minnesota), restricted to white males, with cases identified in 1980–1983, participation rates of 86% for cases and 77–79% for controls, and proxy respondent rates of 41% for cases and 34% for controls. Fifteen leukemia cases in this study were classified as having used glyphosate. The other case-control study of leukemia, by Kaufman et al.,[36] was a hospital-based study set in Asia (Thailand), with males and females, case ascertainment in the 1990s and 2000s, participation rates of 100%, and no proxy respondents for cases or controls.

Meta-analysis

NHL

All relevant RRs and 95% CIs for the association between reported glyphosate use and risk of overall NHL, including those not used in the meta-analysis, such as estimates within subgroups, minimally adjusted estimates, and estimates of exposure-response patterns, are provided in Table 2. The estimates selected from each independent study population for inclusion in the meta-analysis, according to the rules specified in the methods section, are provided in Table 3.

As shown in Table 3 and Fig. 1, the combined meta-RR for overall NHL in association with any use of glyphosate, based on six studies,[12–17] was 1.3 (95% CI = 1.0–1.6). The results were identical in the random-effects and fixed-effects models, suggesting limited between-study heterogeneity in the association. Little heterogeneity also was indicated by the I^2 value of 0.0% and the highly non-significant P-value of 0.84 for Cochran's Q. Given the lack of heterogeneity and at least one statistically significant association, we tested for publication bias using Egger's linear regression approach to evaluating funnel plot asymmetry, and found no significant asymmetry (one-tailed P-value = 0.20). Using Duval and Tweedie's trim-and-fill approach to adjust for publication bias, the imputed meta-RR for both the random-effects and fixed-effects models was 1.2 (95% CI = 1.0–1.6).

In secondary analyses, we replaced the RR estimated by De Roos et al.[13] using a hierarchical (i.e., multistage) regression model with the RR estimated using a more traditional logistic regression model (Table 3). (The hierarchical regression RR was selected for the primary analysis because, as stated by the authors, hierarchical regression models can yield "increased precision and accuracy for the ensemble of estimates" when modeling multiple pesticides simultaneously, and the more conservative prior assumptions specified in these models "seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL.") Using the logistic regression RR did not appreciably affect the results of the meta-analysis (meta-RR = 1.3, 95% CI = 1.0–1.6; identical for random-effects and fixed-effects models).

In another secondary analysis, we replaced the RR reported by McDuffie et al.[16] with the results reported by Hohenadel et al.[28] in the same study population (minus four previously misclassified NHL cases) (Table 3). Because Hohenadel et al.[28] reported two estimates for glyphosate use—one in the absence of malathion use and one in the presence of malathion use—we combined these two estimates into a single estimate (RR = 1.40, 95% CI = 0.62–3.15) using random-effects meta-analysis. Using this alternative estimate also did not appreciably affect the meta-RR (1.3, 95% CI = 1.0–1.7; identical for random-effects and fixed-effects models). Finally, using both the logistic regression RR instead of the hierarchical regression RR from De Roos et al.[13] and the combined RR from Hohenadel et al.[28] instead of the RR from McDuffie et al.[16] slightly but non-significantly increased the meta-RR to 1.4 (95% CI = 1.0–1.8; identical for random-effects and fixed-effects models) (Table 3).

As noted earlier, in their meta-analysis of the association between glyphosate use and NHL risk, Schinasi and Leon[11] included RR estimates from Eriksson et al.[14] and Hardell et al.[15] that were not the most highly adjusted estimates reported by the authors (shown in Table 2 as univariate odds ratios). They also used the logistic regression estimate from De Roos et al.[13] that arguably was not as highly adjusted as the hierarchical regression estimate. When we included these estimates in the meta-analysis, along with the same estimates from De Roos et al.,[13] McDuffie et al.,[16] and Orsi et al.[17] as included in our main meta-analysis, we obtained the same results as reported by Schinasi and Leon:[11] random-effects meta-RR = 1.5, 95% CI = 1.1–2.0 (I^2 = 32.7%, $p_{heterogeneity}$ = 0.19). The fixed-effects meta-RR based on these estimates (not reported by Schinasi and Leon[11]) was 1.4 (95% CI = 1.1–1.8).

NHL subtypes

All reported RRs and 95% CIs for the association between glyphosate use and risk of various NHL subtypes are shown in Table 2. The estimates included in meta-analyses, which were conducted for B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia (i.e., all NHL subtypes for which at least two estimates from independent studies were available), are shown in Table 3. Too few studies of any given NHL subtype were conducted to justify testing for publication bias.

The meta-RR for the association between any use of glyphosate and risk of B-cell lymphoma, based on two studies,[14,18] was 2.0 (95% CI = 1.1–3.6) according to both the random-effects and the fixed-effects model (I^2 = 0.0%, $p_{heterogeneity}$ = 0.58) (Table 3). These results are the same as reported by Schinasi and Leon.[11] The four B-cell lymphoma cases who were classified by Cocco et al.[18] as having used glyphosate consisted of one patient with diffuse large B-cell lymphoma, one with chronic lymphocytic

Table 2. Estimated associations between glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Brown et al.[35]	1990	Non-farmers: 243 cases, 547 controls Ever mixed, handled, or applied glyphosate: 15 cases, 49 controls	Leukemia OR = 0.9	Leukemia 95% CI = 0.5–1.6
Brown et al.[37]	1993	Non-farmers: 62 cases, 272 controls Ever mixed, handled, or applied glyphosate: 11 cases, 40 controls	MM OR = 1.7 Among those who did not use protective equipment, MM OR = 1.9 NHL OR = 1.1	MM 95% CI = 0.8–3.6 Among those who did not use protective equipment, MM 95% CI = NR NHL 95% CI = 0.7–1.9
Cantor et al.[24]	1992	Non-farmers: 226 cases, 547 controls Ever handled, mixed, or applied glyphosate: 26 cases, 49 controls		
Cocco et al.[18]	2013	Unexposed to any pesticides: NR cases, 2262 controls Occupationally exposed to glyphosate: 4 cases (1 DLBCL, 1 CLL, 1 MM, 1 unspecified B-cell NHL), 2 controls	B-cell NHL OR = 3.1	B-cell NHL 95% CI = 0.6–17.1
De Roos et al.[13]	2003	Unexposed to glyphosate: 614 cases, 1892 controls Exposed to glyphosate: 36 cases, 61 controls	Hierarchical regression NHL OR = 1.6 Logistic regression NHL OR = 2.1	Hierarchical regression NHL 95% CI = 0.9–2.8 Logistic regression NHL 95% CI = 1.1–4.0
De Roos et al.[12]	2005	Never used glyphosate: 47 LHC, 21 NHL, 8 MM, 14 leukemia; 13,280 cohort members Ever used glyphosate: 143 LHC, 71 NHL, 24 MM, 43 leukemia; 41,035 cohort members	Fully adjusted LHC RR = 1.1 Age-adjusted LHC RR = 1.1 Fully adjusted NHL RR = 1.1 Age-adjusted NHL RR = 1.2 Fully adjusted MM RR = 2.6 (2.6 in Iowa, 2.7 in North Carolina) Age-adjusted MM RR = 1.1 Fully adjusted leukemia RR = 1.0 Age-adjusted leukemia RR = 1.1	Fully adjusted LHC 95% CI = 0.8–1.6 Age-adjusted LHC 95% CI = 0.8–1.5 Fully adjusted NHL 95% CI = 0.7–1.9 Age-adjusted NHL 95% CI = 0.7–1.9 Fully adjusted MM 95% CI = 0.7–9.4 Age-adjusted MM 95% CI = 0.5–2.4 Fully adjusted leukemia 95% CI = 0.5–1.9 Age-adjusted leukemia 95% CI = 0.6–2.0
		1–20 glyphosate exposure days: 48 LHC, 29 NHL, 8 MM, 9 leukemia 21–56 glyphosate exposure days: 38 LHC, 15 NHL, 5 MM, 14 leukemia 57–2,678 glyphosate exposure days: 36 LHC, 17 NHL, 6 MM, 9 leukemia 0.1–79.5 intensity-weighted glyphosate exposure days: 38 LHC, 24 NHL, 5 MM, 7 leukemia 79.6–337.1 intensity-weighted glyphosate exposure days: 40 LHC, 15 NHL, 6 MM, 17 leukemia 337.2–18,241 intensity-weighted glyphosate exposure days: 43 LHC, 22 NHL, 8 MM, 8 leukemia	Cumulative exposure days, tertiles 2 and 3 vs. 1 LHC RRs = 1.2, 1.2; p-trend = 0.69 NHL RRs = 0.7, 0.9; p-trend = 0.73 MM RRs = 1.1, 1.9; p-trend = 0.27 Leukemia RRs = 1.9, 1.0; p-trend = 0.61 > 108 vs. > 0–9 exposure days, NHL RR = 0.9 Intensity-weighted exposure days, tertiles 2 and 3 vs. 1 LHC RRs = 1.0, 1.0; p-trend = 0.90 NHL RRs = 0.6, 0.8; p-trend = 0.99 MM RRs = 1.2, 2.1; p-trend = 0.17 Leukemia RRs = 1.9, 0.7; p-trend = 0.11 Intensity tertile 3 vs. 1 MM RR = 0.6 Cumulative exposure days, tertiles 1, 2, and 3 vs. never MM RRs = 2.3, 2.6, 4.4; p-trend = 0.09 Cumulative exposure days, quartile 4 vs. never MM RR = 6.6; p-trend = 0.01	Cumulative exposure days, tertiles 2 and 3 vs. 1 LHC 95% CIs = 0.8–1.8, 0.8–1.8 NHL 95% CIs = 0.4–1.4, 0.5–1.6 MM 95% CIs = 0.4–3.5, 0.6–6.3 Leukemia 95% CIs = 0.8–4.5, 0.4–2.9 > 108 vs. > 0–9 exposure days, NHL 95% CI = 0.4–2.1 Intensity-weighted exposure days, tertiles 2 and 3 vs. 1 LHC 95% CIs = 0.6–1.5, 0.7–1.6 NHL 95% CIs = 0.3–1.1, 0.5–1.4 MM 95% CIs = 0.4–3.8, 0.6–7.0 Leukemia 95% CIs = 0.8–4.7, 0.2–2.1 Intensity tertile 3 vs. 1 MM 95% CI = 0.2–1.8 Cumulative exposure days, tertiles 1, 2, and 3 vs. never MM 95% CIs = 0.6–8.9, 0.6–11.5, 1.0–20.2 Cumulative exposure days, quartile 4 vs. never MM 95% CI = 1.4–30.6
Eriksson et al.[14]	2008	No pesticide exposure: NR Glyphosate exposure for ≥ 1 full working day, ≥ 1 calendar year prior to year of diagnosis or enrollment: 29 NHL cases, 18 controls (NHL subtypes NR) Glyphosate exposure for 1 to ≤ 10 days: 12 NHL cases, 9 controls Glyphosate exposure for > 10 days: 17 NHL cases, 9 controls	NHL OR, any glyphosate, multivariate = 1.51 NHL OR, any glyphosate, univariate = 2.02 NHL OR, glyphosate 1 to ≤ 10 days = 1.69 NHL OR, glyphosate > 10 days = 2.36 NHL OR, any glyphosate, latency 1–10 years = 1.11 NHL OR, any glyphosate, latency > 10 years = 2.26 B-cell NHL OR, any glyphosate = 1.87 SLL/CLL OR, any glyphosate = 3.35 FL grades I–III OR, any glyphosate = 1.89 DLBCL OR, any glyphosate = 1.22 Other specified B-cell NHL OR, any glyphosate = 1.63 Unspecified B-cell NHL OR, any glyphosate = 1.47 T-cell NHL OR, any glyphosate = 2.29 Unspecified NHL OR, any glyphosate = 5.63	NHL 95% CI, any glyphosate, multivariate = 0.77–2.94 NHL 95% CI, any glyphosate, univariate = 1.10–3.71 NHL 95% CI, glyphosate 1 to ≤ 10 days = 0.70–4.07 NHL 95% CI, glyphosate > 10 days = 1.04–5.37 NHL 95% CI, any glyphosate, latency 1–10 years = 0.24–5.08 NHL 95% CI, any glyphosate, latency > 10 years = 1.16–4.40 B-cell NHL 95% CI, any glyphosate = 0.998–3.51 SLL/CLL 95% CI, any glyphosate = 1.42–7.89 FL grades I–III 95% CI, any glyphosate = 0.62–5.79 DLBCL 95% CI, any glyphosate = 0.44–3.35 Other specified B-cell NHL 95% CI, any glyphosate = 0.53–4.96 Unspecified B-cell NHL 95% CI, any glyphosate = 0.33–6.61 T-cell NHL 95% CI, any glyphosate = 0.51–10.4 Unspecified NHL 95% CI, any glyphosate = 1.44–22.0
Hardell and Eriksson[27]	1999	No pesticide exposure Glyphosate exposure ≥ 1 year prior to diagnosis or control index year: 4 cases, 3 controls	NHL OR adjusted for phenoxyacetic acids = 5.8 NHL OR unadjusted for phenoxyacetic acids = 2.3	NHL 95% CI adjusted for phenoxyacetic acids = 0.6–54 NHL 95% CI unadjusted for phenoxyacetic acids = 0.4–13
Hardell et al.[15]	2002	No pesticide exposure: NR Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 8 cases, 8 controls	Multivariate NHL OR = 1.85 Univariate NHL OR = 3.04	Multivariate NHL 95% CI = 0.55–6.20 Univariate NHL 95% CI = 1.08–8.52
Hohenadel et al.[28]	2011	Use of neither glyphosate nor malathion: 422 cases, 1301 controls Use of glyphosate only: 19 cases, 78 controls Use of malathion only: 41 cases, 72 controls Use of glyphosate and malathion: 31 cases, 55 controls	NHL OR, glyphosate only = 0.92 NHL OR, malathion only = 1.95 NHL OR, glyphosate and malathion = 2.10 Interaction contrast ratio = 0.23, P-interaction = 0.69	NHL 95% CI, glyphosate only = 0.54–1.55 NHL 95% CI, malathion only = 1.29 –2.93 NHL 95% CI, glyphosate and malathion = 1.31–3.37

Kachuri et al.[33]	2013	Never used glyphosate: 310 cases, 1236 controls (216 cases, 1047 controls without proxy) Ever used glyphosate: 32 cases, 121 controls (23 cases, 108 controls without proxy) Used glyphosate for > 0 to ≤ 2 days per year: 15 cases, 88 controls (11 cases, 78 controls without proxy) Used glyphosate for > 2 days per year: 12 cases, 29 controls (10 cases, 26 controls without proxy)	MM OR, ever glyphosate = 1.19 MM OR, ever glyphosate, no proxies = 1.11 MM OR, glyphosate > 0 to ≤ 2 days per year = 0.72 MM OR, glyphosate > 0 to ≤ 2 days per year, no proxies = 0.70 MM OR, glyphosate > 2 days per year = 2.04 MM OR, glyphosate > 2 days per year, no proxies = 2.11	MM 95% CI, ever glyphosate = 0.76–1.87 MM 95% CI, ever glyphosate, no proxies = 0.66–1.86 MM 95% CI, glyphosate > 0 to ≤ 2 days per year = 0.39–1.32 MM 95% CI, glyphosate > 0 to ≤ 2 days per year, no proxies = 0.35–1.40 MM 95% CI, glyphosate > 2 days per year = 0.98–4.23 MM 95% CI, glyphosate > 2 days per year, no proxies = 0.95–4.70
Karunanayake et al.[61]	2012	Never used glyphosate: 278 cases, 1373 controls Ever used glyphosate: 38 cases, 133 controls	Fully adjusted HL OR = 0.99 Minimally adjusted (age, province) HL OR = 1.14 Crude leukemia OR = 1.40	Fully adjusted HL 95% CI = 0.62–1.56 Minimally adjusted (age, province) HL 95% CI = 0.74–1.76 Crude leukemia 95% CI = 0.15–13.56
Kaufman et al.[36]	2009	No glyphosate use: 179 cases, 753 controls Glyphosate: 1 case, 3 controls		
Lee et al.[29]	2004	Non-farmers, non-asthmatics: 259 cases, 684 controls Non-farmers, asthmatics: 9 cases, 37 controls Exposed to glyphosate, non-asthmatics: 53 cases, 91 controls Exposed to glyphosate, asthmatics: 6 cases, 12 controls	NHL OR, non-farmers, asthmatics = 0.6 NHL OR, glyphosate, non-asthmatics = 1.4 NHL OR, glyphosate, asthmatics = 1.2	NHL 95% CI, non-farmers, asthmatics = 0.3–1.4 NHL 95% CI, glyphosate, non-asthmatics = 0.98–2.1 NHL 95% CI, glyphosate, asthmatics = 0.4–3.3
McDuffie et al.[16]	2001	Never used glyphosate: 466 cases, 1373 controls Ever used glyphosate: 51 cases, 1506 controls Glyphosate use for > 0 to ≤ 2 days per year Glyphosate use for > 2 days per year	Fully adjusted NHL OR, ever glyphosate = 1.20 Minimally adjusted (age, province) NHL OR, ever glyphosate = 1.26 Minimally adjusted NHL OR, glyphosate > 0 to ≤ 2 days per year = 1.00 Minimally adjusted NHL OR, glyphosate > 2 days per year = 2.12 Hairy-cell leukemia OR = 3.1	Fully adjusted NHL 95% CI, ever glyphosate = 0.83–1.74 Minimally adjusted (age, province) NHL 95% CI, ever glyphosate = 0.87–1.80 Minimally adjusted NHL 95% CI, glyphosate > 0 to ≤ 2 days per year = 0.63–1.57 Minimally adjusted NHL 95% CI, glyphosate > 2 days per year = 1.20–3.73 Hairy-cell leukemia 95% CI = 0.8–12
Nordström et al.[30]	1998	No glyphosate exposure: 107 cases, 395 controls Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 4 cases, 5 controls		
Orsi et al.[17]	2009	Never exposed to glyphosate: 464 LHC, 232 NHL, 102 DLBCL, 47 FL, 100 LPS, 75 CLL, 25 hairy-cell leukemia 81 HL, 51 MM, 432 controls Ever exposed to glyphosate: 27 LHC, 12 NHL, 5 DLBCL, 3 FL, 4 LPS, 2 CLL, 2 hairy-cell leukemia, 6 HL, 5 MM, 24 controls	LHC OR = 1.2 NHL OR = 1.0 DLBCL OR = 1.0 FL OR = 1.4 LPS OR = 0.6 CLL OR = 0.4 Hairy-cell leukemia OR = 1.8 HL OR = 1.7 MM OR = 2.4 MM OR = 1.22	LHC 95% CI = 0.6–2.1 NHL 95% CI = 0.5–2.2 DLBCL 95% CI = 0.3–2.7 FL 95% CI = 0.4–5.2 LPS 95% CI = 0.2–2.1 CLL 95% CI = 0.1–1.8 Hairy-cell leukemia 95% CI = 0.3–9.3 HL 95% CI = 0.6–5.0 MM 95% CI = 0.8–7.3 MM 95% CI = 0.77–1.93
Pahwa et al.[34]	2012	Never used glyphosate: 310 cases, 1373 controls Ever used glyphosate: 32 cases, 133 controls		
Sorahan[26]	2015	Never used glyphosate: 8 cases, 13,280 cohort members (of 54,315); 4 cases, 11,881 cohort members (of 49,211); 3 cases, 9809 cohort members (of 40,719) Ever used glyphosate: 24 cases, 41,035 cohort members (of 54,315); 22 cases, 37,330 cohort members (of 49,211); 19 cases, 30,910 cohort members (of 40,719) 1–20 glyphosate exposure days: 10 cases 21–56 glyphosate exposure days: 8 cases 57–2678 glyphosate exposure days: 6 cases 0.1–79.5 intensity-weighted glyphosate exposure days: 6 cases 79.6–337.1 intensity-weighted glyphosate exposure days: 8 cases 337.2–18,241 intensity-weighted glyphosate exposure days: 10 cases Never used glyphosate: 8 cases Ever used glyphosate: 24 Unknown glyphosate use: 2 cases	Fully adjusted MM RR, cohort of 54,315 = 1.24 Age- and sex-adjusted MM RR, cohort of 54,315 = 1.12 Age-adjusted MM RR, cohort of 54,315 = 1.08 Age-adjusted MM RR, cohort of 49,211 = 1.91 Intermediate adjusted MM RR, cohort of 49,211 = 2.07 Age-adjusted MM RR, cohort of 40,719 = 2.21 Fully adjusted MM RR, cohort of 40,719 = 2.79 Cumulative exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM RRs = 1.14, 1.52, 1.38; p-trend = 0.48 using scores, > 0.50 using means Intermediate adjusted MM RRs = 1.13, 1.50, 1.23; p-trend > 0.50 using scores or means Age- and sex-adjusted MM RRs = 1.06, 1.34, 1.08; p-trend > 0.50 using scores or means Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM RRs = 1.00, 1.27, 1.87; p-trend = 0.22 using scores, 0.18 using means Intermediate adjusted MM RRs = 0.99, 1.22, 1.65; p-trend = 0.27 using scores, 0.24 using means Age- and sex-adjusted MM RRs = 0.91, 1.12, 1.44; p-trend = 0.39 using scores, 0.33 using means MM RR, ever glyphosate = 1.18 MM RR, unknown glyphosate = 1.71 Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never MM RRs = 1.11, 1.45, 1.17, 1.19; p-trend > 0.50 using scores or means, excluding unknown Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never MM RRs = 0.95, 1.19, 1.58, 1.04; p-trend = 0.30 using scores, 0.26 using means, excluding unknown	Fully adjusted MM 95% CI, cohort of 54,315 = 0.52–2.94 Age- and sex-adjusted MM 95% CI, cohort of 54,315 = 0.50–2.49 Age-adjusted MM 95% CI, cohort of 54,315 = 0.48–2.41 Age-adjusted MM 95% CI, cohort of 49,211 = 0.66–5.53 Intermediate adjusted MM 95% CI, cohort of 49,211 = 0.71–6.04 Age-adjusted MM 95% CI, cohort of 40,719 = 0.65–7.48 Fully adjusted MM 95% CI, cohort of 40,719 = 0.78–9.96 Cumulative exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM 95% CIs = 0.43–3.03, 0.54–4.34, 0.42–4.45 Intermediate adjusted MM 95% CIs = 0.44–2.88, 0.56–4.05, 0.42–3.58 Age- and sex-adjusted MM 95% CIs = 0.42–2.70, 0.50–3.58, 0.37–3.11 Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM 95% CIs = 0.33–3.00, 0.45–3.56, 0.67–5.27 Intermediate adjusted MM 95% CIs = 0.34–2.86, 0.45–3.28, 0.64–4.24 Age- and sex-adjusted MM 95% CIs = 0.31–2.62, 0.42–3.00, 0.57–3.67 MM 95% CI, ever glyphosate = 0.53–2.65 MM 95% CI, unknown glyphosate = 0.36–8.20 Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never MM 95% CIs = 0.44–2.83, 0.54–3.88, 0.40–3.41, 0.25–5.65 Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never MM 95% CIs = 0.33–2.75, 0.44–3.19, 0.62–4.05, 0.22–4.92

CI: confidence interval; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; LHC: lymphohematopoietic cancer; LPS: lymphoproliferative syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; NR: not reported; OR: odds ratio; RR: relative risk; SLL: small lymphocytic lymphoma.

Table 3. Selected estimates included in meta-analyses and calculated meta-analysis relative risks (meta-RRs) of the association between glyphosate exposure and risk of (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Study *	Authors	Year	Outcome	Number of exposed subjects	RR	95% CI		
1	De Roos et al.[13]	2003	Non-Hodgkin lymphoma	36 cases, 61 controls	a. 1.6 (hierarchical regression) b. 2.1 (logistic regression)	a. 0.9–2.8 (hierarchical regression) b. 1.1–4.0 (logistic regression)		
2	De Roos et al.[12]	2005	Non-Hodgkin lymphoma	71 cases†	1.1	0.7–1.9		
3	Eriksson et al.[14]	2008	Non-Hodgkin lymphoma	29 cases, 18 controls	1.51	0.77–2.94		
4	Hardell et al.[15]	2002	Non-Hodgkin lymphoma	8 cases, 8 controls	1.85	0.55–6.20		
5	Hohenadel et al.[28]	2011	Non-Hodgkin lymphoma	50 cases, 133 controls	1.40 (random effects meta-RR)	0.62–3.15 (random effects meta-CI)		
6	McDuffie et al.[16]	2001	Non-Hodgkin lymphoma	51 cases, 133 controls	1.2	0.83–1.74		
7	Orsi et al.[17]	2009	Non-Hodgkin lymphoma	12 cases, 24 controls	1.0	0.5–2.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Non-Hodgkin lymphoma	1a, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.84
	Model 2		Non-Hodgkin lymphoma	1b, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.59
	Model 3		Non-Hodgkin lymphoma	1a, 2, 3, 4, 5, 7	1.3	1.0–1.7	0.0%	0.85
	Model 4		Non-Hodgkin lymphoma	1b, 2, 3, 4, 5, 7	1.4	1.0–1.8	0.0%	0.63
3	Eriksson et al.[14]	2008	B-cell lymphoma	Not reported	1.87	0.998–3.51		
8	Cocco et al.[19]	2013	B-cell lymphoma	4 cases, 2 controls	3.1	0.6–17.1		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		B-cell lymphoma	3, 8	2.0	1.1–3.6	0.0%	0.58
3	Eriksson et al.[14]	2008	Diffuse large B-cell lymphoma	Not reported	1.22	0.44–3.35		
7	Orsi et al.[17]	2009	Diffuse large B-cell lymphoma	5 cases, 24 controls	1.0	0.3–2.7		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Diffuse large B-cell lymphoma	3, 7	1.1	0.5–2.3	0.0%	0.79
3	Eriksson et al.[14]	2008	CLL/SLL	Not reported	3.35	1.42–7.89		
7	Orsi et al.[17]	2009	CLL/SLL	2 cases, 18 controls	0.4	0.1–1.8		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1, random effects		CLL/SLL	3, 7	1.3	0.2–10.0	83.7%	0.01
	Model 1, fixed effects		CLL/SLL	3, 7	1.9	0.9–4.0		
3	Eriksson et al.[14]	2008	Follicular lymphoma	Not reported	1.89	0.62–5.79		
7	Orsi et al.[17]	2009	Follicular lymphoma	3 cases, 24 controls	1.4	0.4–5.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Follicular lymphoma	3, 7	1.7	0.7–3.9	0.0%	0.73
7	Orsi et al.[17]	2009	Hairy-cell leukemia	2 cases, 18 controls	1.8	0.3–9.3		
9	Nordström et al.[30]	1998	Hairy-cell leukemia	4 cases, 5 controls	3.1	0.8–12		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Hairy-cell leukemia	7, 9	2.5	0.9–7.3	0.0%	0.63
7	Orsi et al.[17]	2009	Hodgkin lymphoma	6 cases, 24 controls	1.7	0.6–5.0		
10	Karunanayake et al.[31]	2012	Hodgkin lymphoma	38 cases, 133 controls	0.99	0.62–1.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Hodgkin lymphoma	7, 10	1.1	0.7–1.6	0.0%	0.36
2	De Roos et al.[12]	2005	Multiple myeloma	19 cases†	2.6	0.7–9.4		
7	Orsi et al.[17]	2009	Multiple myeloma	5 cases, 24 controls	2.4	0.8–7.3		
11	Brown et al.[32]	1993	Multiple myeloma	11 cases, 40 controls	1.7	0.8–3.6		
12	Kachuri et al.[33]	2013	Multiple myeloma	32 cases, 121 controls	a. 1.19 (with proxies) b. 1.11 (without proxies)	a. 0.76–1.87 (with proxies) b. 0.66–1.86 (without proxies)		
13	Pahwa et al.[34]	2012	Multiple myeloma	32 cases, 133 controls	1.22	0.77–1.93		
14	Sorahan[26]	2015	Multiple myeloma	24 cases	1.24	0.52–2.94		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Multiple myeloma	7, 11, 12a, 14	1.4	1.0–1.9	0.0%	0.63
	Model 2		Multiple myeloma	2, 7, 11, 12a	1.5	1.0–2.1	0.0%	0.48
	Model 3		Multiple myeloma	7, 11, 12b, 14	1.4	0.9–1.9	0.0%	0.58
	Model 4		Multiple myeloma	7, 11, 13, 14	1.4	1.0–2.0	0.0%	0.66
	Model 5		Multiple myeloma	2, 7, 11, 13	1.5	1.0–2.1	0.0%	0.52
2	De Roos et al.[12]	2005	Leukemia	43 cases†	1.0	0.5–1.9		
16	Brown et al.[33]	1990	Leukemia	15 cases, 49 controls	0.9	0.5–1.6		
17	Kaufman et al.[26]	2009	Leukemia	1 case, 3 controls	1.4	0.15–13.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Leukemia	2, 16, 17	1.0	0.6–1.5	0.0%	0.92

*Number of exposed cases is provided for the total cohort of 54,315 subjects; the number of exposed cases in the analytic cohort of 49,211 subjects is not stated.
†Number of exposed cases is provided for the analytic cohort of 40,719 subjects, as reported by Sorahan.[26]
CI: confidence interval; CLL: chronic lymphocytic leukemia; RR: relative risk; SLL: small lymphocytic lymphoma.

leukemia, one with unspecified B-cell lymphoma, and one with MM. Eriksson et al.[14] did not report the number of exposed cases, but overall the B-cell lymphomas in their study comprised 29% diffuse large B-cell lymphoma, 24% chronic lymphocytic leukemia/small lymphocytic lymphoma, 20% follicular lymphoma grades I–III, 16% other specified B-cell lymphoma, and 11% unspecified B-cell lymphoma; MM cases were not included.

The meta-RR for the association between any use of glyphosate and risk of diffuse large B-cell lymphoma, based on two studies,[14,17] was 1.1 (95% CI = 0.5–2.3) using both the random-effects and the fixed-effects models (I^2 = 0.0%, $p_{heterogeneity}$ = 0.79) (Table 3).

Based on the same two studies,[14,17] the meta-RR for the association between any use of glyphosate and risk of chronic lymphocytic leukemia/small lymphocytic lymphoma was 1.3 (95% CI = 0.2–10.0) according to the random-effects model and 1.9 (95% CI = 0.9–4.0) according to the fixed-effects model, with significant heterogeneity between the two included estimates (I^2 = 83.7%, $p_{heterogeneity}$ = 0.01) (Table 3).

Results for follicular lymphoma from these two studies,[14,17] by contrast, were not significantly heterogeneous (I^2 = 0.0%, $p_{heterogeneity}$ = 0.73), with a meta-RR of 1.7 (95% CI = 0.7–3.9) in both the random-effects and the fixed-effects models (Table 3).

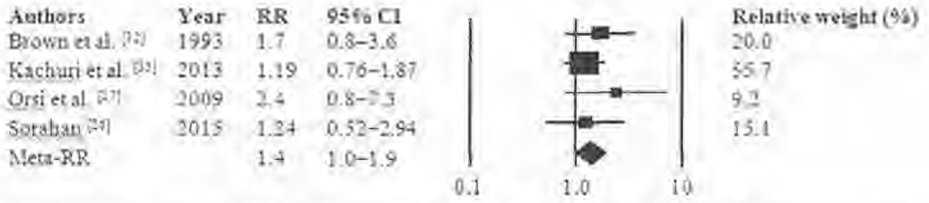

Figure 2. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of multiple myeloma. Meta-RRs were identical in random-effects and fixed-effects models.

Finally, the two studies that reported associations between any glyphosate use and risk of hairy-cell leukemia[17,30] yielded a meta-RR of 2.5 (95% CI = 0.9–7.3) in the random-effects and fixed-effects models ($I^2 = 0.0\%$, $p_{heterogeneity} = 0.63$) (Table 3).

HL

Both of the published, fully adjusted RRs and 95% CIs for the association between any glyphosate use and HL risk (Table 2) were included in the meta-analysis (Table 3). Based on two studies,[17,31] the meta-RR was 1.1 (95% CI = 0.7–1.6) in both the random-effects and the fixed-effects models, with $I^2 = 0.0\%$ and $p_{heterogeneity} = 0.36$ (Table 3). Publication bias was not evaluated due to the availability of only two studies of HL.

MM

All relevant RRs and 95% CIs for the association between glyphosate use and risk of MM, including estimates that did not contribute to the meta-analysis, are shown in Table 2. The independent estimates selected for inclusion in the meta-analysis are shown in Table 3.

The combined meta-RR for the association between any glyphosate use and risk of MM, based on four studies,[17,26,32,33] was 1.4 (95% CI = 1.0–1.9) according to the random-effects and fixed-effects models (Table 3, Fig. 2). On the basis of the I^2 value of 0.0% and the *P*-value of 0.63 for Cochran's Q statistic, between-study heterogeneity was not evident. Egger's linear regression approach yielded no significant evidence of publication bias (one-tailed *P*-value for asymmetry = 0.10), while the imputed meta-RR using the trim-and-fill procedure to adjust for publication bias was 1.3 (95% CI = 0.9–1.8).

Several secondary analyses were conducted for MM by replacing RRs in the primary meta-analysis with alternative estimates (Table 3). When the RR reported by De Roos et al.,[12] who excluded cohort members with missing data from their analysis, was substituted for the one reported by Sorahan,[26] who included such subjects by creating a separate category for missing or unknown data, the meta-RR was slightly increased to 1.5 (95% CI = 1.0–2.1) and was the same for random-effects and fixed-effects models. When the main RR from Kachuri et al.[33] was replaced with the RR from the same study after exclusion of data reported by proxy respondents, the meta-RR was not appreciably different from the original estimate (alternative meta-RR = 1.4, 95% CI = 0.9–1.9 in random-effects and fixed-effects models). Another secondary analysis included the RR reported by Pahwa et al.,[34] who adjusted for a slightly different (and smaller) set of confounders than Kachuri et al.[33] and also retained controls who were too young to have any age-matched MM cases in this Canadian study. This change had minimal impact on the meta-RR (1.4, 95% CI = 1.0–2.0; same for random-effects and fixed-effects models). When both the De Roos et al.[12] and the Pahwa et al.[34] substitutions were made, the resultant meta-RR was the same as that when only De Roos et al.[12] was used (meta-RR = 1.5, 95% CI = 1.0–1.2 in random-effects and fixed-effects models).

Leukemia

Of the four published RRs and 95% CIs for the association between any use of glyphosate and risk of leukemia (Table 2), three (excluding one age-adjusted RR in favor of a more fully adjusted RR from De Roos et al.[12]) were included in the meta-analysis (Table 3). The meta-RR based on three studies[12,35,36] was 1.0 (95% CI = 0.6–1.5) using the random-effects model and the fixed-effects model ($I^2 = 0.0\%$, $p_{heterogeneity} = 0.92$) (Table 3). Publication bias was not assessed because only three studies of leukemia were available.

Sensitivity analysis

A sensitivity analysis was conducted for overall NHL only (Table 4), because other outcomes had an insufficient number of studies for stratification. In all strata, the random-effects and fixed-effects meta-RRs were identical and I^2 was 0.0%. Results did not differ substantially from the main meta-RR (1.3, 95% CI = 1.0–1.6) when the analysis was restricted to case-control studies (meta-RR = 1.3, 95% CI = 1.0–1.7) or those with population-based controls (meta-RR = 1.4, 95% CI = 1.0–1.8). Meta-analysis could not be conducted for cohort studies or studies with hospital-based

Table 4. Sensitivity analysis of the association between glyphosate exposure and risk of non-Hodgkin lymphoma (NHL).

Stratum	Number of studies	Meta-RR*	95% CI
All	6	1.3	1.0–1.6
Case-control	5	1.3	1.0–1.7
Cohort	1	NR	
Population controls	4	1.4	1.0–1.8
Hospital controls	1	NR	
Males only	4	1.3	1.0–1.7
Males and females	2	1.2	0.8–1.8
North America	3	1.2	1.0–1.6
Europe	3	1.3	0.8–2.1
Sweden	2	1.6	0.9–2.8
Cases in 1980s	2	1.6	1.0–2.7
Cases in 1990s	4	1.2	1.0–1.6
Cases in 2000s	3	1.2	0.8–1.7

*All meta-RRs were identical in random-effects and fixed-effects models.
CI: confidence interval; meta-RR: meta-analysis relative risk; NR: not reported, when only one study was available.

controls because only one of each of these study types was available. No major differences were detected between studies restricted to males (meta-RR = 1.3, 95% CI = 1.0–1.7) and those that included males and females (meta-RR = 1.2, 95% CI = 0.8–1.8) or between those conducted in North America (meta-RR = 1.2, 95% CI = 1.0–1.6) and those conducted in Europe (meta-RR = 1.3, 95% CI = 0.8–2.1). Prompted by Schinasi and Leon,[11] we also conducted a stratified meta-analysis of the two studies conducted in Sweden[14,15] and found a stronger, albeit statistically non-significant, association in these particular studies (meta-RR = 1.6, 95% CI = 0.9–2.8). The estimated meta-RR declined somewhat from studies that ascertained cases in the 1980s (meta-RR = 1.6, 95% CI = 1.0–2.7) to those conducted in the 1990s (meta-RR = 1.2, 95% CI = 1.0–1.6) to those conducted in the 2000s (meta-RR = 1.2, 95% CI = 0.8–1.7).

Exposure-response trends

NHL and subtypes. Three studies evaluated exposure-response trends between glyphosate use and NHL risk, with exposure classified as cumulative lifetime[12,14] or annual[16] days of glyphosate use (Table 2). Two studies detected some evidence of a positive exposure-response trend (statistical significance not reported),[14,16] whereas the other did not.[12] All of these studies relied wholly or in part on evaluating days of glyphosate use in an attempt to quantify exposure; however, this metric has been shown to be a poor indicator of actual glyphosate dose received.[52]

In a model adjusted for age, sex, and year of diagnosis or enrollment, Eriksson et al.[14] found that the RR of NHL was higher with > 10 days of lifetime glyphosate use (RR = 2.36, 95% CI = 1.04–5.37) than with ≤ 10 days (RR = 1.69, 95% CI = 0.70–4.07), compared with no pesticide use. Also, the RR of NHL was higher after more than 10 years since first use of glyphosate (RR = 2.26, 95% CI = 1.16–4.40) than after 1–10 years (RR = 1.11, 95% CI = 0.24–5.08). Statistical tests for trend were not performed, and exposure-response analyses adjusted for other potential confounders (i.e., 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and/or 2,4-dichlorophenoxyacetic acid (2,4-D), mercurial seed dressing, arsenic, creosote, and tar) were not presented, even though adjustment for these characteristics attenuated the RR for overall glyphosate use from 2.02 to 1.51.

McDuffie et al.[16] reported that the RR for more than two days of glyphosate use per year (RR = 2.12, 95% CI = 1.20–3.73) was higher than that for up to two days per year (RR = 1.00, 95% CI = 0.63–1.57), compared with never use, adjusting for age and province of residence. Tests for a significant exposure-response trend were not performed, and results were not reported after adjustment for other potential confounders (i.e., personal medical history and family history of cancer; adjustment for these characteristics attenuated the RR for overall glyphosate use from 1.26 to 1.20) or significantly associated pesticides (i.e., aldrin, dicamba, and mecoprop) in this study population.

The most detailed analysis of glyphosate-NHL exposure-response trends was performed by De Roos et al.,[12] who examined tertiles of cumulative lifetime days of glyphosate use (1–20, 21–56, or 57–2,678 days) and tertiles of intensity-weighted cumulative days of use (i.e., years of use × days per year × intensity level, where intensity was defined as (mixing status + application method + equipment repair status) × personal protective equipment use). In analyses adjusted for age, education, smoking, alcohol, family history of cancer, and state of residence, no significant trend was detected for NHL risk in association with increasing cumulative days of glyphosate use (RRs for tertiles 1, 2, and 3, respectively = 1.0 (referent), 0.7 (95% CI = 0.4–1.4), and 0.9 (95% CI = 0.5–1.6); $p_{trend} = 0.73$) or intensity-weighted cumulative exposure days (RRs = 1.0 (referent), 0.6 (95% CI = 0.3–1.1), and 0.8 (95% CI = 0.5–1.4); $p_{trend} = 0.99$).

Exposure-response trends between glyphosate use and risk of specific NHL subtypes were not evaluated in any of the included studies.

HL. No studies assessed exposure-response trends between glyphosate use and risk of HL.

MM. Three studies reported exposure-response trends between glyphosate use and MM risk, including the two analyses based on the same Agricultural Health Study cohort dataset[12,26] and the Canadian case-control study[33] (Table 2). The case-control study found mixed evidence of a positive trend (statistical significance not reported), while a positive trend was detected in one analysis of the cohort data[12] but not the other.[25]

The Canadian case-control study found a lower risk of MM among those who used glyphosate for up to two days per year than those who had never used glyphosate (RR = 0.72, 95% CI = 0.39–1.32).[33] However, risk was higher in those with more than two days of glyphosate use per year (RR = 2.04, 95% CI = 0.98–4.23), adjusting for age, province of residence, proxy status, smoking, personal medical history, and family history of cancer. Results were similar after exclusion of data reported by proxy subjects. The authors did not conduct statistical tests for exposure-response trends.

Based on the 55% of Agricultural Health Study cohort members who had available exposure and covariate data, De Roos et al.[12] reported a positive, albeit statistically non-significant, trend between MM risk and increasing tertiles of cumulative days of glyphosate use (RRs for tertiles 1, 2, and 3, respectively = 1.0 (referent), 1.1 (95% CI = 0.4–3.5), and 1.9 (95% CI = 0.6–6.3); $p_{trend} = 0.27$) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.2 (95% CI = 0.4–3.8), and 2.1 (95% CI = 0.6–7.0); $p_{trend} = 0.17$). These estimates were adjusted for age, education, smoking, alcohol, family history of cancer, state of residence, the five pesticides for which cumulative-use variables were most highly associated with glyphosate cumulative use days (i.e., 2,4-D, alachlor, atrazine, metolachlor, and trifluralin), and the five pesticides that were most highly associated with ever use of glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, and diazinon). When intensity alone was analyzed in association with MM risk, the RR for the highest versus the lowest tertile was 0.6 (95% CI = 0.2–1.8), indicating that the suggested trend was due only to total days of use. When subjects who never used glyphosate were set as the reference group, the RRs for tertiles 1, 2, and 3 of cumulative days

of use were 2.3 (95% CI = 0.6–8.9), 2.6 (95% CI = 0.6–11.5), and 4.4 (95% CI = 1.0–20.2); $p_{trend} = 0.09$. When cumulative use was categorized into quartiles, the RR for the highest quartile versus never use was 6.6 (95% CI = 1.4–30.6); $p_{trend} = 0.01$.

In contrast to De Roos et al.,[12] Sorahan[26] included more than 53,000 eligible cohort members in the analysis (excluding only those with a history of cancer before enrollment, loss to follow-up, missing data on age at enrollment, or missing data on glyphosate use) by creating separate categories for missing or unknown exposure and covariate data. Adjusting for age, sex, education, smoking, alcohol, family history of cancer, and the same 10 pesticides as De Roos et al.,[12] the RRs for each tertile of cumulative days of glyphosate use, compared with never use, were 1.14 (95% CI = 0.43–3.03), 1.52 (95% CI = 0.54–4.34), and 1.38 (95% CI = 0.42–4.45); $p_{trend} = 0.48$ using category scores of 1–4, $p_{trend} > 0.50$ using mean exposures within categories. RRs for increasing tertiles of intensity-weighted days of use versus never use were 1.00 (95% CI = 0.33–3.00), 1.27 (95% CI = 0.45–3.56), and 1.87 (95% CI = 0.67–5.27); $p_{trend} = 0.22$ using scores, $p_{trend} = 0.18$ using means. When Sorahan[26] expanded the eligible cohort to 55,934 subjects to include those with unknown use of glyphosate, he again detected no significant exposure-response trends with respect to either cumulative days of use (for tertiles 1, 2, and 3 and unknown use versus never use, respectively, RRs = 1.11 (95% CI = 0.44–2.83), 1.45 (95% CI = 0.54–3.88), 1.17 (95% CI = 0.40–3.41), and 1.19 (95% CI = 0.25–5.65); $p_{trend} > 0.50$ across categories of known use using scores or means, excluding unknown) or intensity-weighted cumulative days of use (RRs = 0.95 (95% CI = 0.33–2.75), 1.19 (95% CI = 0.44–3.19), 1.58 (95% CI = 0.62–4.05), and 1.04 (95% CI = 0.22–4.92); $p_{trend} = 0.30$ using scores, $p_{trend} = 0.26$ using means, excluding unknown).

Leukemia. The De Roos et al.[12] study based on the Agricultural Health Study cohort was the only study that reported exposure-response trends between glyphosate use and risk of leukemia (Table 2). No significant trend was observed between increasing tertiles of cumulative days of glyphosate use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.5), and 1.0 (95% CI = 0.4–2.9) for tertiles 1, 2, and 3, respectively; $p_{trend} = 0.61$) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.7), and 0.7 (95% CI = 0.2–2.1); $p_{trend} = 0.11$), adjusting for demographic and lifestyle factors as well as other pesticides.

Evaluation of bias

Selection bias

All studies of the association between glyphosate exposure and risk of LHC were case-control studies except for the Agricultural Health Study, the prospective cohort study that served as the basis for the studies by De Roos et al.[12] and Sorahan.[26] In case-control studies, differences in participation patterns between cases and controls can result in selection bias if participation is related to the exposure of interest. In cohort studies, selection bias can occur if loss to follow-up is related to the exposure and outcome of interest or, less commonly, if baseline participation differs by exposure status and risk of developing the outcome of interest in the future (e.g., based on having a positive family history of an outcome with a genetic susceptibility component). Selection bias in any study also can occur if inclusion in the data analysis, e.g., predicated on data completeness, differs by exposure and outcome status. In general, lower participation, follow-up, or data completeness and large differences in participation between groups increase the potential magnitude of selection bias.

Table 1 shows the reported participation and follow-up proportions in all reviewed studies. Most studies did not report data completeness. The substantial differences in participation between cases and controls in the European multi-center study,[18] the most recent Swedish study,[14] and the Canadian study, which also had relatively low absolute participation proportions of <70% for cases and <50% for controls,[16,28,31,33,34] are of particular concern. However, the smaller discrepancies between case and control participation in other studies also could have produced selection bias. Moreover, even identical participation by cases and controls can obscure differences in reasons for study participation that could result in bias.

Given that several case-control studies were originally designed to evaluate associations between pesticides and risk of LHC,[13–16,28,31–35] it is plausible that cases with a history of agricultural pesticide use were more likely than controls to participate, thereby biasing results toward a positive association for glyphosate as well as other pesticides. It is also possible that certain sources of controls in some of these studies (e.g., residential telephone calls and voter lists) were more likely to identify individuals who were not farmers, again biasing results toward a positive association. Investigators from the Canadian study[16,28,31,33,34] reported that an analysis of postal codes showed that respondents and non-respondents did not differ significantly in terms of rural versus urban residence, but they could not examine differences in occupation or pesticide use.

Although the initial follow-up completion of >99% in the Agricultural Health Study was high,[12,25] the sizeable proportions of subjects with missing data raise concerns about selection bias. Specifically, 88% of the eligible cohort (excluding those who were diagnosed with cancer before enrollment or were lost to follow-up) provided usable data on ever use of glyphosate and key demographic and lifestyle covariates, 73% additionally provided data on use of other pesticides, 65–66% contributed to analyses of cumulative days of glyphosate use (with or without intensity weighting), and 55% contributed to analyses of cumulative use additionally adjusted for other pesticides. Questionnaire completion could conceivably have varied by demographic and lifestyle factors that are associated with LHC risk, thereby producing bias. Neither analysis accounted for missing data using methods such as multiple imputation or inverse probability weighting.

Differential data completeness by disease status is more likely to occur in case-control studies, such as the pooled Midwestern U.S. study conducted by De Roos et al.[15] In this study, the analysis of multiple pesticides excluded 25% of cases and 25% of controls who lacked complete data. Although the overall frequency of missing data was the same between cases and controls, this exclusion could have led to selection bias if subjects'

reasons for providing complete data, and thus being included in the analysis, differed by disease status and were related to glyphosate exposure status. The authors also excluded subjects who had lived or worked on a farm before age 18 years. If glyphosate use was more common in such subjects, then RR estimates would have been biased upward if a childhood farm environment was inversely associated with NHL risk[53] and biased downward if the association was positive.[54]

Exposure misclassification

All of the included studies assessed use of glyphosate and other pesticides based on self-reported information (Table 1), which is prone to various types of error, such as better recall by cases than controls and by subjects than proxies, inaccurate recall of specific pesticides and amounts used, and a lack of the best measure of biological dose received.[55] Thus, probable exposure misclassification is a key limitation of all of these studies. The degree of misclassification may vary by mode of data collection, for example, by written questionnaire, telephone interview, or in-person interview.[56] The extent of misclassification also may depend on questionnaire structure, for example, whether subjects were asked in an open-ended manner to report use of any pesticides or whether they were prompted to report use of specific pesticides based on a prepared list.[57] Some authors did not clearly describe the structure of their study's questions on pesticide use.

Of the eight independent study populations included in this review (seven studies of NHL with or without other types of LHC and one study of leukemia), three provided information on validation of their exposure assessment methods: the Canadian case-control study,[16,28,31,33,34] the Agricultural Health Study,[15,26] and the Kansas case-control study[47] that contributed to the pooled Midwestern U.S. study by De Roos et al.[13] Overall, these studies do not establish the validity of self-reported information on glyphosate use; rather, the limited results suggest considerable error and inconsistency in such data.

Specifically, in the Canadian study, Dosman et al.[58] reported on the results of a validation pilot study of 21 volunteer farmers whose self-reported pesticide use was compared with written records of pesticide purchases through their local agrochemical supplier. Of the 21 farmers, 17 (81%) had a supplier who had retained written records; the remaining four transactions were conducted with cash. Based on the written records, 146 (65%) of 226 chemicals reported by farmers were verified; 50 of the unverified reports were potentially explained by aerial applications, home and garden use, use more than five years in the past (i.e., during 1958–1984), or use outside of Canada. In 32 instances (for 25 chemicals) the suppliers' records indicated a purchase of chemicals that was unreported by the farmer; 2 of these were for glyphosate. Detailed self-reported exposure (e.g., frequency, intensity, and duration of use of specific pesticides) could not be validated in this pilot study.

Likewise, Hoar et al.[47] reported that suppliers for 110 subjects in the Kansas study (out of 130 sought) were located and provided information on the subjects' crops and herbicide and insecticide purchases as "corroborative evidence" of self-reported pesticide use. The authors observed that suppliers usually reported less pesticide use than subjects; that agreement on specific years of use was better for insecticide use than herbicide use; that the differences between agreement for cases and controls were not consistent; and that agreement between suppliers and subjects was better for pesticide use within the last 10 years than for earlier use. Quantitative results on concordance were not provided by Hoar et al.,[47] but in a summary of this study shared with Dosman et al.[58] the authors stated that reports on herbicide use agreed 59% of the time, with little variation by crop type, and that reports on insecticide use also agreed 59% of the time, but differed by crop type.

In the Agricultural Health Study, the reliability of the question on ever having mixed or applied glyphosate was evaluated by comparing responses to two questionnaires completed one year apart by 3,763 pesticide applicators.[59] Agreement on a positive response to the question was 82%, and the kappa statistic value for inter-rater agreement was moderate (0.54, 95% CI = 0.52–0.58). For more detailed questions about glyphosate use, including years mixed or applied, days per year mixed or applied, and decade first applied, the percentage with exact agreement ranged from 52% to 62% and kappa ranged from 0.37 to 0.71. These metrics evaluated only the reliability (i.e., reproducibility) of self-reported glyphosate use, not its accuracy.

Subsequent exposure validation studies for other pesticides in the Agricultural Health Study, based on comparisons between exposure intensity estimated from an expert-derived algorithm using self-reported or directly observed exposure data and pesticide biomarker levels measured in urine, yielded Spearman correlation coefficients between 0.4 and 0.8, depending on the type of pesticide.[60,61] Correlations with urinary biomarker levels were poorer for self-reported determinants of pesticide exposure such as kilograms of active ingredient, hours spent mixing and applying, and number of acres treated, with correlation coefficients of −0.4 to 0.2, but application method and use of personal protective equipment were found to be important determinants of exposure intensity. However, the latter factors were evaluated in the study questionnaire only for pesticides or pesticide classes in general, not for glyphosate or other individual pesticides;[62] thus, limitations remain in the assessment of specific pesticide exposures.

Several studies included a sizeable proportion of surveys that were completed by proxy respondents for deceased or otherwise unavailable cases and controls (Table 1). The use of exposure data reported by surrogates most likely resulted in even poorer accuracy of exposure information in these studies. Although some exposure misclassification may have been nondifferential by disease status, such error does not inevitably result in underestimated exposure-disease associations unless additional strict conditions are met, such as independence from other classification errors.[63,64]

Furthermore, differential exposure misclassification in case-control studies can readily result in overestimated associations. Reasonable scenarios include more accurate and/or detailed recollection of past exposures by cases, who are more motivated than controls to try to understand the potential causes of their disease; false recollection by cases, who are more aware of scientific hypotheses or media reports that a certain exposure has been linked to their disease; and unconscious influence by study investigators who are aware of causal hypotheses and subjects' case-control status. Only the authors of the Swedish

studies,[14,15] the French study,[17] and the Nebraska component of the pooled Midwestern U.S. study[18] specifically stated that investigators were blinded to case-control status. In reality, such blinding is often difficult to achieve in studies that collect interview data.

Others have discussed in detail the problems of estimating individual subjects' exposure to glyphosate from responses to interviews and questionnaires asking about days of use, mixing and application procedures, use of personal protective equipment, and other work practices.[19,52] Acquavella et al.[52] reported that any given day of pesticide use can entail highly variable amounts of pesticides used and numbers of mixing operations, and that urine concentrations of glyphosate were poorly correlated with lifetime average exposure intensity scores derived from data self-reported by farmers using this agent. Although recall bias between cases and controls generally might be anticipated to affect all specific pesticides (including glyphosate) equally, variation in the degree of misclassification due to these and other factors affecting usage and exposure could result in different pesticide-specific associations.

Most of the case-control studies did not use procedures to exclude glyphosate exposure that might have occurred after disease onset. The Swedish studies omitted glyphosate use within one year prior to diagnosis or the index date in controls,[15,30] or within the same calendar year or the year before.[14] In some cases, however, these restrictions may not have been sufficient to exclude exposure that occurred during the latency period between disease onset and diagnosis. Inclusion of any such post-disease exposure would have led to misclassification.

Finally, exposure misclassification resulting from the crude dichotomization of glyphosate use as ever versus never is an important limitation of most of the included studies. This classification conflates individuals with considerably different frequencies, intensities, and durations of glyphosate use, and precludes potentially informative analyses of any gradient in LHC risk with increasing glyphosate exposure. As described earlier in the section on exposure-response trends, only three independent studies reported on glyphosate use in more than two (ever vs. never) categories, and only the Agricultural Health Study evaluated more than three exposure categories.

Confounding

As shown in Table 1, the degree of control for confounding varied widely among the reviewed studies. Although several studies considered potential confounding by other pesticides or pesticide families, only a minority[12–15,26,28] reported RR estimates for the association between glyphosate use and LHC risk adjusted for use of other pesticides. Given that Schinasi and Leon[11] found significant associations between NHL risk and several other types of pesticides, including carbamate insecticides, organophosphorus insecticides, lindane, and MCPA, and numerous other associations of specific pesticides with LHC risk have been reported in the literature (e.g.,[65,66])—and because most people who use pesticides occupationally are exposed to multiple pesticides—it is important to control for confounding, whether direct or indirect (if pesticides are surrogates for other risk factors), by these agents.

None of the studies controlled for potential confounding by agricultural exposures other than pesticides, such as other agricultural chemicals, farm animals, allergens, and infectious agents. These exposures have been hypothesized, and in some studies shown, to be associated with risk of NHL, HL, MM, or leukemia,[67–73] and they are probably correlated with glyphosate use, making them potential confounders of associations between glyphosate and LHC risk. Medical history, certain infections, diet, alcohol consumption, and obesity also may be associated with risk of these malignancies[74–77] and could vary by glyphosate use, again making them possible confounders. Even in studies where numerous confounders were included in multivariable regression models, crude categorization or other misclassification of confounders could have enabled residual confounding of observed associations. The direction and magnitude of confounding depend on the relationships of each factor with glyphosate use and LHC risk, and are therefore difficult to predict.

Other Issues

Additional issues related to the design, conduct, and reporting of the included studies also could have affected study results and their interpretation. For instance, Hardell et al.[15] enrolled some prevalent rather than incident cases, since eligible NHL cases were diagnosed in 1987–1990 but interviewed in 1993–1995.[27] The relatively long time interval between diagnosis and interview may have hampered recollection of past exposures, thereby undermining the accuracy of self-reported exposure data in this study. The delay between diagnosis and interview also almost certainly increased the proportion of cases and matched controls who were deceased (43%) and had proxy interviews, leading to further exposure misclassification.

In the studies by De Roos et al.[13] and Brown et al.,[32,33] LHC cases were diagnosed in 1979–1986, 1980–1983, and 1980–1984, respectively. With glyphosate having come to market in 1974, the cases in these studies would have had a relatively short potential induction time since first use of glyphosate. However, few studies to date have considered the issue of induction time. The Agricultural Health Study collected information on decade of first use of glyphosate in the baseline questionnaire for private pesticide applicators,[62] but did not use this information in the published analysis.[12] If glyphosate is a cause of LHC, the actual induction time is unknown because the mechanism of carcinogenesis is not established.

Orsi et al.,[17] Kaufman et al.,[36] and four of the six study centers included in Cocco et al.[18] enrolled hospital-based rather than population-based cases and controls. Given that farmers have lower hospitalization rates than non-farmers,[78] hospital-based controls may be less likely than population-based controls to report agricultural occupational exposures, including pesticides, thereby resulting in overestimated RRs for pesticide use. On the other hand, occupational injuries are more common in agriculture than in general private industry,[79] possibly leading to oversampling of farmers from hospital trauma/emergency and orthopedics departments, which might result in underestimated RRs. We did not observe any meaningful change in the meta-RR after restriction to population-based case-control studies.

As noted in Table 1, many possible analyses were not conducted or not reported by authors. De Roos et al.[13] specifically acknowledged that they did not report results for pesticide combinations that were analyzed but yielded statistically null

associations for joint effects, and Hohenadel et al.[28] likewise did not show results for pesticide combinations without evidence of joint effects. Most other authors did not explicitly state when null results were not reported, but the Methods sections of several papers suggested that certain analyses were performed, yet not shown. Given the widespread predilection for emphasizing statistically significant associations in published research articles,[80] unreported results probably are usually statistically null. The omission of null results is a form of reporting bias that favors positive associations.

Other evidence suggests that statistically null associations between glyphosate and LHC risk have been underreported in the epidemiologic literature. For example, two of the studies that contributed to the pooled analysis conducted by De Roos et al.[13] apparently collected information on glyphosate use, yet associations between glyphosate and NHL risk were not reported in the original publications.[47,48] In an analysis of interactions between pesticide use and asthma, allergies, or hay fever diagnosis in relation to NHL risk in the Canadian case-control study,[81] results were reported for several specific pesticides, but not glyphosate, even though information was available for glyphosate use. The most probable scenario in each of these cases is that no significant association was detected between glyphosate use and NHL risk. The omission of such results from the published literature represents a distortion of the body of epidemiologic evidence.

The largest number of studies included in any of the meta-analyses described here was six (in the analysis of NHL), and the majority of meta-analyses (of HL, B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia) included only two studies. The small number of available studies limits the robustness of the estimated meta-RRs, as well as the ability to perform informative sensitivity analysis and evaluation of heterogeneity and publication bias. Even with 10 contributing studies (which we lacked), the statistical power to detect modest heterogeneity using Cochran's Q statistic is "low."[42] The small number of studies also provides little opportunity to qualitatively investigate possible sources of heterogeneity by subject characteristics or study design. Thus, the results of the meta-analyses and related statistical tests reported here should be interpreted cautiously in light of the sparse and possibly selectively published literature, as well as the high potential for bias and confounding in most of the available studies.

Overall evaluation

The validity of the meta-RRs for glyphosate use and LHC risk reported here and by others[11] is uncertain because systematic error due to bias and confounding cannot reasonably be ruled out as explanations for the observed associations (including both positive and null associations). In addition, an evaluation of the association between glyphosate exposure and risk of LHC based on the Bradford Hill viewpoints[46] does not favor a causal relationship with NHL, any NHL subtype, HL, MM, or leukemia. These nine viewpoints are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.

To evaluate the strength of the association between glyphosate use and risk of each type of LHC, we considered the magnitude of study-specific RRs and the corresponding meta-RRs. In individual studies, estimates of the association between glyphosate use and risk of NHL ranged between 1.0 and 2.1, and estimates of the association with NHL subtypes ranged between 0.4 and 3.35 (Table 3). For HL, the two estimates of association were 0.99 and 1.7. For MM, RRs ranged between 1.0 and 2.4, and those for leukemia ranged between 0.9 and 1.40. Most study-specific estimates were between 1.0 and 1.5. The estimated meta-RRs for all LHC outcomes, including those calculated in secondary and sensitivity analyses, ranged between 1.0 (for leukemia) and 2.5 (for hairy-cell leukemia). The meta-RRs calculated based on at least four studies ranged between 1.3 and 1.4. These associations are not of sufficient magnitude to exclude modest bias or confounding as reasonable explanations for the observed results.

Results were not consistent between case-control studies of NHL and the one prospective cohort study of NHL, which reported no association.[12] Even among the six studies that contributed to the meta-analysis of NHL, RR point estimates varied by more than two-fold, only one statistically significant positive association was observed, and results from some studies were internally inconsistent (Table 3). Another, arguably more appropriately adjusted RR (from a hierarchical regression model) that was 24% lower and statistically non-significant was reported in the same study that found a significant association.[13] The lack of statistically significant heterogeneity among studies of NHL, based on an underpowered statistical test, does not indicate consistency of results. For NHL subtypes, RR estimates also were variable, except for diffuse large B-cell lymphoma, for which both estimates were close to 1.0. Only one statistically significant positive association was detected (for chronic lymphocytic leukemia/small lymphocytic lymphoma),[14] and this result was contradicted by a non-significant inverse association in the other study of this outcome.[17] No significant associations with ever use of glyphosate were detected for HL, MM, or leukemia, and for MM the RR point estimates varied by more than two-fold. Results for MM in the Agricultural Health Study were internally inconsistent;[12,26] and the positive association with cumulative glyphosate exposure probably was due largely to selection bias.

Numerous associations have been hypothesized between glyphosate exposure and diverse health outcomes, and between various exposures and risk of NHL, NHL subtypes, HL, MM, or leukemia. Thus, the putative associations are not specific to either the exposure or any of the outcomes. As noted by Bradford Hill,[46] "diseases may have more than one cause" and "one-to-one relationships are not frequent"; therefore, a lack of specificity does not detract from a causal hypothesis.

In case-control studies, where exposure assessment was retrospective, a temporal sequence was not definitively established with glyphosate use preceding the time of disease onset. Although some studies attempted to exclude use close to the time of case diagnosis (or enrollment, for controls),[14,15,30] in practice individuals may not accurately recall the timing of use. Only the prospective Agricultural Health Study[12,26] was designed to collect information on glyphosate use prior to cancer ascertainment. However, the authors did not exclude malignancies diagnosed close to

(e.g., within one year of) study enrollment, nor did they report the distribution of diagnoses with respect to time since first use of glyphosate. Thus, some preclinical cancers may have existed prior to study entry and, possibly, prior to at least some reported glyphosate use.

As discussed in detail earlier, in the three studies of NHL with information on frequency, intensity, and/or duration of glyphosate use,[12,14,16] a positive biological gradient was not consistently demonstrated and was notably lacking in the Agricultural Health Study,[12] which had the most detailed exposure information (Table 2). One case-control study[33] and one prospective cohort study[12] of MM reported results suggesting a positive biological gradient with glyphosate use, but the alternative analysis of the Agricultural Health Study data[26] did not demonstrate such a trend. No data were available to evaluate exposure-response trends between glyphosate and risk of NHL subtypes or HL, and the single study with such data for leukemia found no apparent trend.[12]

Inhalation exposure to glyphosate from agricultural or residential uses is likely to be slight due to glyphosate's extremely low vapor pressure.[82] Although dermal contact can be considerable, the very low skin penetrability of glyphosate[83] should result in minimal, if any, biologically absorbed dose. A study of farm families with a lower limit of detection of 0.001 μg/mL (1 ppb) found that 40% of glyphosate applicators had undetectable urinary glyphosate, which reflects all routes of exposure (dermal, inhalation, and oral).[84] Among those with detectable urinary glyphosate, the distribution of concentrations was right skewed, with a peak geometric mean concentration of 0.0032 μg/mL (3.2 ppb) on the day of application and declining thereafter. A review of seven human biomonitoring studies of glyphosate (including[84]) yielded the conclusion that "no health concern was revealed because the resulting exposure estimates were by magnitudes lower" than the science-based acceptable daily intake and the acceptable operator exposure level proposed by EFSA.[85] Glyphosate is usually applied in agricultural operations only a few days per year. Given the low biological dose of glyphosate that is expected to be sustained, along with the lack of information on the mechanism of carcinogenesis that may exist in humans, the biological plausibility of LHC development due to typical glyphosate exposure has not been established.

IARC recently determined based on their process that there is "sufficient" evidence of carcinogenicity of glyphosate in experimental animals and mechanistic evidence of genotoxicity and oxidative stress.[6] By contrast, U.S. EPA,[86] JMPR,[3] BfR,[1] EFSA,[9] and others[87,88] concluded that glyphosate does not have genotoxic, mutagenic, or carcinogenic effects in *in vivo* animal and *in vitro* studies, and that the negative findings constitute evidence against carcinogenicity. Given these widely divergent opinions, one cannot unambiguously conclude whether the scientific evidence is coherent with the hypothesis that glyphosate causes any or all LHC.

No true experimental evidence exists regarding the association between glyphosate exposure and risk of LHC in humans. However, positive associations between farming and risk of LHC were detected prior to 1974, when glyphosate was first commercially marketed.[89,90] Thus, if the apparent associations between farming and risk of LHC are due to causal agricultural exposures, they cannot be explained only by glyphosate exposure. Likewise, the recent worldwide increase (followed by a plateau or decline) in NHL incidence began before the 1970s[91,92]—although any impact of glyphosate on NHL incidence trends might be obscured by stronger risk factors. No marked increase in the incidence of HL, MM, or leukemia has been observed in parallel with the introduction and expansion of glyphosate use.[93–96]

Finally, numerous analogies exist to support or oppose the hypothesis of a causal link between glyphosate exposure and risk of LHC. On balance, such analogies do not strengthen or weaken a conclusion of causality.

In summary, although none of the Bradford Hill viewpoints can establish or disprove causality, we did not find compelling evidence in support of causality based on any of the nine viewpoints. Thus, on balance, the existing epidemiologic evidence does not favor a causal effect of glyphosate on NHL, HL, MM, leukemia, or any subtype of these malignancies.

Discussion

Our meta-analysis yielded borderline significant RRs of 1.3 and 1.4 between glyphosate use and risk of NHL and MM, respectively, and no significant association with risk of HL or leukemia. Based on more fully adjusted RRs, our NHL meta-RR of 1.3 (95% CI = 1.0–1.6) was weaker than that reported by Schinasi and Leon[13] (RR = 1.5, 95% CI = 1.1–2.0). The largest meta-RR of 2.5 (for hairy-cell leukemia) and the only meta-RR with a lower 95% confidence limit that excluded 1.0 (for B-cell lymphoma) were based on only two studies each, and the maximum number of studies contributing to any meta-analysis was six. The few studies with available data did not consistently detect positive exposure-response trends between quantitative measures of glyphosate use and risk of any LHC.

Consideration of the available epidemiologic evidence in light of the Bradford Hill viewpoints does not substantiate a causal relationship between glyphosate exposure and risk of any type of LHC. A conclusion in favor of causality also is undermined by the studies' methodological limitations, which could reasonably account for at least part of the observed associations. These limitations include exposure misclassification (which may differ by outcome status especially in case-control studies, which constitute nearly all available studies), selection bias (due to differential enrollment, follow-up, or data completeness), poor adjustment for confounding (by other agricultural exposures, for instance), small numbers (which lead to low statistical power as well as a higher probability that a statistically significant finding is false[97]), and potential reporting and publication bias. Although underpowered statistical tests did not formally detect publication bias, we identified several examples of studies with available data that did not report associations between glyphosate use and LHC risk, and these unreported associations were most likely null.

Underpowered statistical tests also generally did not detect heterogeneity of results among studies, except for chronic lymphocytic leukemia/small lymphocytic lymphoma and MM. Nevertheless, our sensitivity analysis revealed some evidence of stronger associations with NHL risk in studies based in Sweden and those that ascertained cases in the 1980s, whereas the meta-RRs for studies that ascertained cases in the 2000s were

close to the null and statistically non-significant The stronger association with NHL diagnosed in the 1980s raises questions about whether glyphosate, an agent first introduced in 1974 in the United States and Europe, could plausibly cause lymphoma less than a decade later. However, deliberation on the potential induction time requires an understanding of the presumed mechanism of carcinogenesis, which is unknown for glyphosate. The classification system for lymphoid tumors underwent major changes in 1994 and 2001,[20] such that the definition of NHL as a disease entity is not entirely comparable between recent studies and those conducted in the 1980s. Study quality also may have improved over time, for example, due to refinements in survey design, interviewing techniques, data management, and other methods to augment data integrity.

The stronger association in Swedish studies probably is not explained by geographical differences in glyphosate use or effect modifiers related to NHL risk. One possible explanation is that of the six NHL studies, only the two Swedish studies[14,15] compared subjects who used glyphosate with those who did not use any pesticides as the reference group, whereas the other studies defined the reference group as those who did not use glyphosate in particular. Comparisons with subjects who do not use any pesticides are more likely to be confounded by other pesticides and agricultural exposures.

Meta-analysis can be problematic when applied to observational epidemiology.[21,22] Meta-analysis increases statistical precision by combining results from studies that may differ substantially in terms of source population, exposure and outcome assessment and classification, control for confounding, and other key characteristics. In the presence of such heterogeneity, even if not detectable using formal statistical tests, a single summary estimate may not be scientifically meaningful. Additionally, even when studies are statistically homogeneous, meta-analysis may not yield valid results, since this technique cannot overcome problems in the design and conduct of the underlying studies. Instead, given that bias can seldom be ruled out and unmeasured and uncontrolled confounding can never be eliminated from observational epidemiologic studies, modest meta-RRs detected across multiple studies may simply be due to shared biases, rather than a true association.[21] As stated earlier, the purpose of meta-analysis is not to evaluate whether associations are causal. We conducted a meta-analysis primarily for comparison with published findings.

Considering the shortcomings of the existing literature, what can be done to shed further light on whether glyphosate causes LHC in humans? Perhaps the foremost need is better exposure assessment. Self-reported information on use of specific pesticides, unless validated by comparison with sales records (which most likely would need to be collected prospectively, and might not be closely correlated with pesticide use) or other objective documentation, is not sufficiently accurate and reliable to yield credible estimates of association, especially exposure-response trends. Urinary glyphosate levels would provide more accurate and quantitatively detailed information on biological dose of glyphosate received, but would probably have to be measured repeatedly to reflect long-term exposure.

Information about temporal aspects of glyphosate exposure, such as the putative induction time since first use of glyphosate, duration of use, and time since last use, could help to shed light on the exposure-outcome relationship. Results from additional prospective cohort studies are necessary to alleviate concerns about selection and reporting bias in case-control studies.

More specific outcome classification also is needed. Only two studies[14,17] examined associations between glyphosate use and more than one histological subtype of NHL, despite growing evidence of important etiologic heterogeneity among NHL subtypes.[74] Information on NHL subtypes also is available in the Agricultural Health Study,[66] and publication of risk associations with glyphosate is anticipated. Risk factors for HL and leukemia also are known to differ by subtype,[76,77] yet no studies estimated associations with glyphosate separately for subtypes of these tumors. (Chronic lymphocytic leukemia and hairy-cell leukemia, which were analyzed as distinct outcomes, are classified as NHL subtypes.[20]) Large, probably pooled studies with histopathological data can determine whether associations with specific tumor subtypes might be obscured by analyzing overall NHL, HL, MM, or leukemia as a single disease entity.

Conclusion

In conclusion, we found marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL and MM, and statistically null associations with HL and leukemia. A statistically significant positive meta-RR for B-cell lymphoma, but not other NHL subtypes, was calculated based on only two studies. Combining these results with recognition of the methodological weaknesses of the small number of existing studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient, we determined that no causal relationship has been established between glyphosate exposure and risk of NHL, HL, MM, leukemia, or any subtype of LHC.

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Appendix

Literature search methods

The authors conducted a search of MEDLINE via PubMed using the following search string, which includes Chemical Abstracts Service (CAS) Registry Numbers for glyphosate and its salts:

(glyphosat OR glifosat* OR glyfosat* OR gliphosat* OR Roundup OR Round-up OR 1071-83-6 OR 38641-94-0 OR 70901-12-1 OR 39600-42-5 OR 69200-57-3 OR 34494-04-7 OR 114370-14-8 OR 40465-66-5 OR 69254-40-6 OR (aminomethyl w phosphonic*) OR 1066-51-9 OR pesticid* OR herbicid* OR organophosphorus compounds [MeSH] OR pesticides [MeSH] OR herbicides [MeSH]) AND (leukemi* OR leukaemi* OR lymphoma* OR NHL OR lymphopoietic OR hemato* OR hematopoie* or hematolog* OR lymphoid OR myeloid OR myeloma OR leukemia [MeSH] OR lymphoma [MeSH] OR multiple myeloma [MeSH]) AND (cases OR controls OR case-control OR cohort).*

As of June 23, 2015, this search string identified a total of 11,755 articles in PubMed. We conducted additional targeted searches in PubMed, Web of Science, and Google Scholar using simpler keyword combinations such as *(glyphosate AND lymphoma)*, *(pesticides AND lymphoma)*, and *(herbicides AND lymphoma)*. References also were identified from the bibliographies of recent review articles.

Altogether, a total of 12,709 articles were identified from these combined sources (Fig. A1). Based on a review of titles and abstracts, 321 articles were identified as potentially containing estimates of the association between glyphosate exposure and LHC risk, and were obtained for further evaluation. Forty-seven of these articles contained the word "glyphosate" or "Roundup" (or alternative spellings of these terms) in the text; as specified earlier, articles that did not mention glyphosate were ineligible for inclusion. Following a review of the full text of each of the 47 articles mentioning glyphosate, 19 articles were ultimately deemed eligible for inclusion.

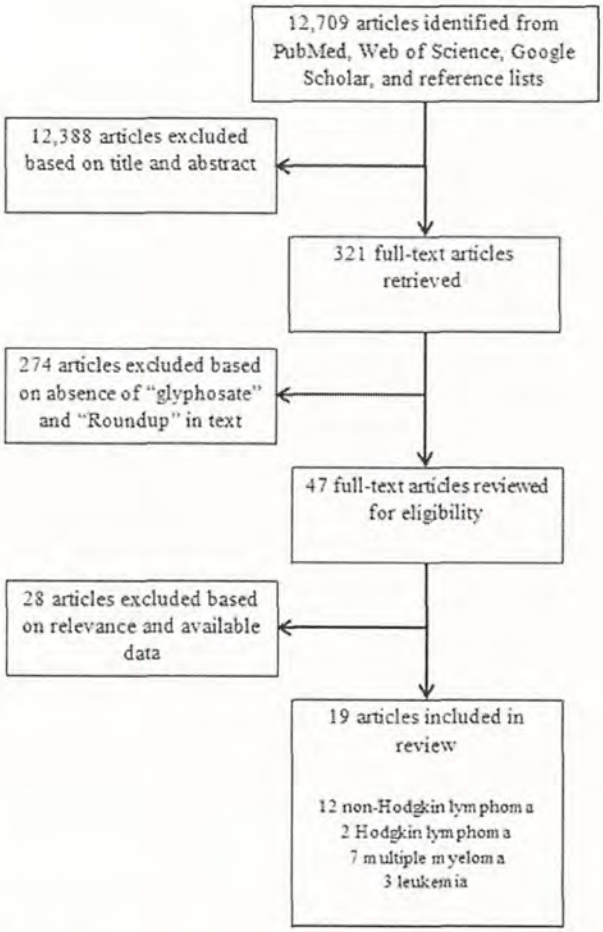

Figure A1. Flow chart of literature identification and selection process.

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Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health[1]

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Abstract

Our objective in the study was to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma [NHL; International Classification of Diseases, version 9 (ICD-9) 200, 202]. We conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study among men in a diversity of occupations using an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 h/year or more, and a 15% random sample of the remainder. Adjusted odds ratios (ORs) were computed using conditional logistic regression stratified by the matching variables of age and province of residence, and subsequently adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization treatment, and a positive history of cancer in first-degree relatives). We found that among major chemical classes of herbicides, the risk of NHL was statistically significantly increased by exposure to phenoxyherbicides [OR, 1.38; 95% confidence interval (CI), 1.06–1.81] and to dicamba (OR, 1.88; 95% CI, 1.32–2.68). Exposure to carbamate (OR, 1.92; 95% CI, 1.22–3.04) and to organophosphorus insecticides (OR, 1.73; 95% CI, 1.27–2.36), amide fungicides, and the fumigant carbon tetrachloride (OR, 2.42; 95% CI, 1.19–5.14) statistically significantly increased risk. Among individual compounds, in multivariate analyses, the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D; OR, 1.32; 95% CI, 1.01–1.73), mecoprop (OR, 2.33; 95% CI, 1.58–3.44), and dicamba (OR, 1.68; 95% CI, 1.00–2.81); to the insecticides malathion (OR, 1.83; 95% CI, 1.31–2.55), 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl (OR, 2.11; 95% CI, 1.21–3.69), aldrin, and lindane; and to the fungicides captan and sulfur compounds. In additional multivariate models, which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives, and exposure to mixtures containing dicamba (OR, 1.96; 95% CI, 1.40–2.75) or to mecoprop (OR, 2.22; 95% CI, 1.49–3.29) and to aldrin (OR, 3.42; 95% CI, 1.18–9.95) were significant independent predictors of an increased risk for NHL, whereas a personal history of measles and of allergy desensitization treatments lowered the risk. We concluded that NHL was associated with specific pesticides after adjustment for other independent predictors.

Introduction

NHL[4] has been epidemiologically associated with farming (1–8), with certain farm practices (9), with pesticide exposure (10–13), and with certain other occupations (14–17). The term pesticide is used to denote a wide variety of chemicals used to destroy weeds (herbicides), insects (insecticides), and mold (fungicides). Such chemicals are widely used in agriculture, horticulture, and forestry, and in the secondary processing of the products of these primary industries. Many of the NHL and pesticide case-control or cohort studies focused either on a small geographical area (1, 2, 4) or on one occupational group (2, 4, 5, 9). Our study encompassed six provinces of Canada with diverse agricultural practices and a number of different types of occupational and nonoccupational exposures to pesticides. Non-Hodgkin's lymphoma incidence rates have been increasing in Canada for the last 25 years reflecting a worldwide trend (18) that has not been explained by improved diagnostic (19) methods or record-keeping (20).

Materials and Methods

Study Population. We conducted a population-based case-control study among men resident in six Canadian provinces to

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[3] Dr. Choi was a collaborator who is now deceased.

[4] The abbreviations used are: NHL, non-Hodgkin's lymphoma; DDT, 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane; STS, soft tissue sarcoma; HD, Hodgkin's disease; MM, multiple myeloma; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPA, 4-chloro-2-methylphenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; OR, odds ratio; OR_{adj}, adjusted OR; 95% CI, 95% confidence interval.

test the pesticide-exposure hypothesis related to four rare tumors. Incident cases among men, ages 19 years or over, with a first diagnosis of STS, HD, NHL [International Classification of Diseases, version 9 (ICD-9), code 200 or 202], or MM diagnosed between September 1, 1991, and December 31, 1994, were eligible. To balance the number of cases by geographical regions, each province was assigned a target number of cases in each tumor category. Each province ceased to ascertain cases when their preassigned target was reached. This report is based solely on cases diagnosed with NHL. Cases were ascertained from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. The Cancer Registries and hospitals provided information, including pathology reports, to confirm the diagnosis. Pathological material was reviewed and classified according to the working formulation by the reference pathologist. Misclassified and ineligible (*e.g.*, Kaposi's sarcoma, known HIV-positive) cases were excluded. Subjects for whom pathological material was unavailable remained in the study. After physician consent was received, postal questionnaires and informed consent forms were mailed to potential cases. Surrogates for deceased cases were not contacted.

Men, ages 19 years and older, selected at random within age constraints from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) were potential controls. The random control subject selection was stratified by age ± 2 years to be comparable with the age distribution of the entire case group (STS, HD, NHL, and MM) within each province. Postal questionnaires and informed consent forms were mailed to potential controls. Surrogates for deceased persons were ineligible as controls. All of the participating control subjects were used in the statistical analyses of each cancer site.

Pilot Study. We conducted a pilot study (21) in each provincial region to test study procedures and to determine an operational definition of pesticide exposure to distinguish between environmental (which includes bystander and incidental) and more intensive exposure. Nonoccupational use of pesticides (home, garden, hobby) was included. There were few individuals who were completely free of being exposed to pesticides. Therefore, we constructed graphs that demonstrated that the most efficient definition of pesticide exposure, which discriminated (*a*) between incidental, bystander, and environmental exposure as compared with more intensive exposure and (*b*) between cases and controls, was a cumulative total of 10 h per year to any combination of pesticides. The screening questions in the postal questionnaire were used to trigger telephone interviews among those with cumulative exposure of ≥10 h/year to any combination of herbicides, insecticides, fungicides, fumigants, and/or algicides. The 68 cases and 103 controls who participated in the pilot study are not included in this report.

Pesticides. Pesticide is a generic term describing a variety of compounds of diverse chemical structures and biological modes of action. In this study, the term pesticide refers primarily to herbicides, insecticides, fungicides, and fumigants.

We conducted a validation pilot study of the modified questionnaires (21). Volunteer farmers ($n = 27$) completed the questionnaires and granted permission for us to access their records of purchases through their local agrochemical supplier. The concordance between the two sources was excellent and discordance was explainable by (*a*) the farmer paid in cash and the supplier discarded the record; (*b*) the farmer purchased the agrochemical in the United States, and, therefore, the local supplier did not have a record; (*c*) the farmer paid for professional ground or aerial spraying, and the account was listed in another name; or (*d*) the supplier had destroyed the records.

Questionnaires. The questionnaires were modified versions of the telephone interview questionnaire that was used in studies of pesticide exposure and rare tumors in Kansas (11) and Nebraska (13). With permission, we modified the questionnaire to create postal and telephone interview questionnaires. To control for the effects of other variables known or suspected to be associated with the development of NHL after conducting an extensive literature review, we used the postal questionnaire to capture demographic characteristics, antecedent medical history, family history of cancer, detailed lifetime job history, and occupational exposure history to selected substances, accidental pesticide spills, and use of protective equipment, as well as details of cigarette smoking history. The telephone questionnaire characterized exposure to individual pesticides. The pesticide data were collected at several levels beginning with the broadest categories (*e.g.*, minimal exposure, occupations with potential pesticide exposure) and progressing sequentially to major classes (*e.g.*, herbicides); to chemical groups (*e.g.*, phenoxy herbicides); and finally to individual compounds (*e.g.*, 2,4-D, MCPA, and 2,4,5-T).

In this report, we focus on lifetime exposure to individual pesticides classified by active ingredients and to major chemical classes of herbicides, insecticides, fungicides, and fumigants. We classified exposure by the number of herbicides, insecticides, fungicides, and fumigants reported by cases and controls as well as by the number of days per year of exposure to individual compounds.

Each subject who reported 10 h per year or more of exposure to pesticides (any combination of compounds) as defined by the screening questions, and a 15% random sample of the remainder was mailed a list of pesticides (both chemical and brand names) and an information letter. Each subject was subsequently telephoned to obtain details of pesticide use.

The listed pesticides were chosen for inclusion (22–25): (*a*) if the compound was ever registered for use in Canada and reviewed by the IARC; (*b*) if the pesticide was recently banned or restricted in Canada by the federal licensing agency; or (*c*) if the pesticide was commonly used in Canada for specific purposes.

To ensure consistency, we developed and distributed manuals for provincial study coordinators, interviewers, and data managers. Before commencing data collection, we held a 2-day workshop with provincial coordinators to review data collection procedures and policies, to practice interviewing skills, and to review SPSS-DE (Statistical Packages for the Social Sciences-Data Entry),[5] the custom data entry program that we used. On receipt of a postal questionnaire, the provincial coordinator reviewed it for internal consistency and completeness. Data were computer-entered and verified in the province of origin, transported to the coordinating center, and rechecked for completeness, after which statistical analyses were performed.

Copies of the questionnaires and additional information on pesticides that were not included in this report are available from the corresponding author.

Pathology Review. Pathologists in participating provinces were requested to send blocks or slides of tumor tissue removed at surgery to the reference pathologist. Ten subjects with Ka-

[5] SPSS-Data Entry II Statistical Package for the Social Sciences: Statistical Data Analysis. SPSS Inc., Chicago, Illinois, 1998.

Table 1 Comparisons of demographic, antecedent personal medical, general pesticide exposures and cigarette smoking history between cases of NHL and control subjects based on the postal questionnaire

	NHL, $n = 517$		Controls, $n = 1506$		OR[a] (95% CI)
	n	%	n	%	
Age, yr					
<30	64	12.4	356	23.6	
30–39	87	16.8	255	16.9	
40–49	111	21.5	238	15.8	
50–59	143	27.7	370	25.6	
>60	112	21.7	287	19.0	
Mean ± SD	57.7 ± 14		55.0 ± 16		
Residence on a farm at any time					
Yes	235	45.5	673	44.7	
No (reference)	279	54.0	828	55.0	1.06 (0.86–1.20)
Missing	3	0.6	5	0.3	
Pesticide exposure (screening question)					
<10 h/yr (reference)	379	73.3	1142	75.8	
≥10 h/yr	138	26.7	364	24.2	1.22 (0.96–1.55)
Smoking History					
Nonsmoker (reference)	160	30.9	526	34.9	
Ex-smoker	254	49.1	648	43.0	1.10 (0.86–1.41)
Current smoker	91	17.6	298	19.8	0.98 (0.72–1.33)
Missing data	12	2.3	34	2.3	
Current or ex-smoker	345	66.7	946	62.8	1.06 (0.86–1.20)
Medical History[b]					
Measles (yes)	251	48.5	888	59.0	**0.64 (0.51–0.79)**
Mumps (yes)	194	37.5	588	39.0	**0.75 (0.60–0.93)**
Previous cancer (yes)	73	14.1	87	5.8	**2.43 (1.71–3.44)**
Skin-prick allergy test	34	6.6	196	13.0	**0.52 (0.34–0.76)**
Allergy desensitization shots (yes)	18	3.5	114	7.6	**0.49 (0.29–0.83)**
Family history of cancer any first-degree relative (yes)	219	42.4	497	33.0	**1.31 (1.05–1.62)**

[a] OR stratified by age and by province of residence.
[b] Also tested and found to be unassociated: acne; asthma; celiac disease; chickenpox; diabetes; hay fever; mononucleosis; rheumatic fever; rheumatoid arthritis; ringworm; shingles; syphilis; tuberculosis; urinary tract infections; whooping cough; allergies; drug treatment for overactive thyroid; treatment for head lice, body lice, or scabies; medical implants; drug treatment for epilepsy; tonsillectomy; positive allergy prick skin test, patch skin test, or positive patch skin test for allergy.

posi's sarcoma were omitted on the basis of the etiological association with HIV infection. Any other known HIV-positive subjects had been previously excluded. Eighty-four % (436 of 517) of the NHL tumors were validated. Because of a change midstudy in some hospitals' policies regarding supplying pathological material without charge, we were unable to obtain the remaining samples.

Statistical Analyses. Data from the postal and telephone interviews were merged by using the identification number. Of the individuals selected randomly for a telephone interview, most had used one or no chemical pesticides. We reviewed these data and decided to include them in the statistical analyses because they might be informative with respect to low levels of exposure to pesticides and their inclusion maximized our sample size with respect to other known or suspected risk factors for NHL. We conducted descriptive analyses of each variable, which included, where applicable, frequencies, ranges, means ± SD, and median values for cases and controls separately.

To evaluate putative risk factors for NHL, conditional logistic regression was used to compute ORs and 95% CIs, stratifying by age groups and province of residence.[6] ORs were calculated for categorical variables related to medical history that were selected based on previous studies (*e.g.*, measles, mumps, previous cancer, allergy desensitization treatment, skin prick allergy test); pesticide exposure (<10 and ≥10 h per year); and smoking history. Using conditional logistic regression, ORs were also calculated for (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; and (*b*) for individual active chemicals. The statistically significant ($P < 0.05$) medical variables were used to adjust the effect of exposure to pesticides classified by major chemical group and by individual active chemical. Given the study sample size and the case-control ratio, *a priori* power calculations indicated that we had sufficient statistical power to detect an OR of 2 when at least 1% of the controls was exposed to a specific pesticide or chemical class of pesticide. Conditional logistic analyses (26) were conducted that retained in the model, all covariates for which the P was ≤.05. The criterion for entry into models was a $P \leq 0.20$ in bivariate age and province stratified analyses.

We created dose-response levels based on days/year of personally mixing or applying selected herbicides, insecticides, fungicides, and fumigants. We reported ORs stratified by age and province of residence. We created exposure categories for exposures to multiple different herbicides, insecticides, fungicides, and fumigants. For these analyses, the unexposed category was specific to the class of pesticide. We also created exposure categories for exposures to combinations of herbicides, insecticides, fungicides, and fumigants for which the reference group did not report exposure to any of those classes of pesticides.

[6] EGRET Intuitive Software for DOS Micros Statistics and Epidemiology Research Corporation, 1993.

Table 2 Herbicides: frequency of exposure to herbicides classified into major chemical classes and as individual compounds

The list includes only those reported by 1% or more of responders.

Major chemical classes	NHL $n = 517$		Controls $n = 1506$		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Phenoxyherbicides,[c] exposed	131	25.3	319	21.2	**1.46 (1.09–1.82)**	**1.38 (1.06–1.81)**
Individual phenoxyherbicides						
2,4-D	111	21.5	293	19.5	1.26 (0.97–1.64)	**1.32 (1.01–1.73)**
Mecoprop	53	10.2	81	5.4	**2.23 (1.38–3.07)**	**2.33 (1.58–3.44)**
MCPA	17	3.3	46	3.1	1.08 (0.59–1.94)	1.10 (0.60–2.00)
Diclofopmethyl	9	1.7	25	1.7	0.96 (0.42–2.20)	0.95 (0.41–2.22)
Phosphonic acid,[d] exposed	63	12.2	147	9.8	1.42 (0.95–1.90)	1.40 (0.94–1.89)
Individual phosphonic herbicides						
Glyphosate (Round-up)	51	9.9	133	8.8	1.26 (0.87–1.80)	1.20 (0.83–1.74)
Thiocarbamates,[e] exposed	21	4.1	49	3.3	1.41 (0.62–2.20)	1.46 (0.82–2.58)
Individual thiocarbamate herbicides						
Diallate (n exposed)	11	2.1	29	1.9	1.26 (0.59–2.67)	1.46 (0.68–3.14)
Phenols: Bromoxynil,[f] exposed	16	3.1	48	3.2	1.05 (0.41 1.69)	1.07 (0.58–1.99)
Dicamba,[g] exposed	73	14.1	131	8.7	**1.92 (1.39–2.66)**	**1.88 (1.32–2.68)**
Individual dicamba herbicides						
Dicamba (Banvel or Target)	26	5.0	50	3.3	1.59 (0.95–2.63)	**1.68 (1.00–2.81)**
Dinitroaniline,[h] exposed	11	2.1	31	2.1	1.17 (0.56–2.41)	1.20 (0.61–2.35)
Individual dinitroaniline herbicides						
Trifluralin	11	2.1	31	2.1	1.17 (0.56–2.41)	1.06 (0.50–2.22)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Phenoxyherbicides include the phenoxyacetic acids (*e.g.*, 2,4-D and MCPA), the phenoxy-2-propionic acids (*e.g.*, mecoprop); the phenoxybutanoic acids (*e.g.*, 2,4-DB) and other phenoxyalkanoic acids (*e.g.*, diclofopmethyl).
[d] Glyphosate is the only phosphonic acid herbicide reported by more than 1% of responders. Round-up, Touchdown, Victor, Wrangler, Laredo do not include dicamba, and Rustler is a mixture of dicamba and glyphosate.
[e] Thiocarbamate herbicides include diallate and triallate.
[f] Bromoxynil is the only phenol herbicide included.
[g] Dicamba as a major chemical class includes Banvel, and Target, and a mixture of dicamba and glyphosate (Rustler), or mixtures of dicamba, 2,4-D, and mecoprop (Dynel DS, Killex).
[h] Dinitroaniline herbicides include ethalfluralin and trifluralin.

Ethics. The protocol, letters of informed consent, questionnaires, and all other correspondence with potential subjects were approved by the relevant agencies in each province. All of the information that could be used to identify individuals remained within the province of origin under the control of the provincial principal investigators.

Results

Data from postal questionnaires based on responses from 517 NHL cases (67.1% of those contacted) and 1506 control subjects (48.0% of those contacted) were analyzed. Similar percentages of potential subjects resident in rural and urban areas responded. There were higher percentages of responders in the middle-age group than at either extreme among both cases and controls. Detailed information related to their pesticide exposure history was obtained by telephone interview from 119 NHL cases and 301 control subjects who indicated pesticide exposure of 10 h per year or more. A 15% random sample of cases and controls who indicated pesticide exposure of less than 10 h/year was also interviewed by telephone, resulting in detailed pesticide exposure information on 60 cases of NHL and on 155 controls. The total telephone interviewed sample consisted of 179 cases of NHL and 456 controls.

A summary of selected demographic, antecedent personal and familial medical history, general pesticide exposure as measured by the screening questions, and cigarette smoking history comparisons of NHL cases and population-based controls is shown in Table 1. Because all of the controls (age-matched for STS, MM, HD, and NHL) were used in the analysis, cases were older than controls. Cases and controls were similar in their smoking patterns. Cases were less likely to have a history of measles or mumps and more likely to have a personal history of a previous primary cancer. Cases were more likely than controls to have a positive family history of cancer, whereas more controls had undergone allergy desensitization injections. A slightly higher proportion of cases than controls indicated cumulative exposure to pesticides of ≥10 h per year.

Table 2 summarizes reported exposure to herbicides classified by major chemical classes (phenoxy, phosphonic acid, thiocarbamates, phenols, dicamba, and dinitroaniline) and by individual compounds for which at least 1% of responders reported exposure. ORs are also shown after adjustment for the statistically significant ($P < 0.05$) variables reviewed in Table 1, which included a history of measles, mumps, cancer, and allergy desensitization shots and a positive history of cancer in a first-degree relative. Cases experienced a significantly higher frequency of exposure to phenoxyherbicides, to dicamba or a mixture including dicamba, to 2,4-D, and to mecoprop.

Table 3 summarizes the insecticide exposure data. Exposure to two major chemical classes, carbamates and organophosphates, was statistically significantly associated with NHL, whereas exposure to organochlorines as a group was not.

Table 3 Insecticides: frequency of exposure to insecticides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Carbamates,[c] exposed	37	7.2	60	4.0	**1.95 (1.25–3.05)**	**1.92 (1.22–3.04)**
Individual carbamate insecticides						
Carbaryl	25	4.8	34	2.3	**2.05 (1.18–3.55)**	**2.11 (1.21–3.69)**
Carbofuran	9	1.7	18	1.2	1.58 (0.68–3.67)	1.64 (0.70–3.85)
Methomyl	6	1.2	13	0.9	1.86 (0.67–5.17)	1.65 (0.54–5.03)
Organochlorine, (1)[d] exposed	50	9.7	134	8.9	1.16 (0.81–1.66)	1.27 (0.87–1.84)
Individual organochlorine (1) insecticides						
Chlordane	36	7.0	105	7.0	1.06 (0.71–1.59)	1.11 (0.74–1.69)
Lindane	15	2.9	23	1.5	**2.05 (1.01–4.16)**	**2.06 (1.01–4.22)**
Aldrin	10	1.9	6	0.4	**3.81 (1.34–10.79)**	**4.19 (1.48–11.96)**
Organochlorine (2) diphenylchlorides[e] exposed	86	16.6	233	15.5	1.24 (0.94–1.65)	1.21 (0.90–1.62)
Individual organochlorine (2) diphenylchlorides						
Methoxychlor	65	12.6	201	13.3	1.08 (0.79–1.47)	1.02 (0.74–1.41)
DDT	32	6.2	59	3.9	**1.63 (1.03–2.57)**	**1.73 (1.08–2.76)**
Organophosphorus,[f] exposed	90	17.4	167	11.1	**1.69 (1.26–2.27)**	**1.73 (1.27–2.36)**
Individual organophosphorus insecticides						
Malathion	72	13.9	127	8.4	**1.77 (1.28–2.46)**	**1.83 (1.31–2.55)**
Dimethoate	22	4.3	50	3.3	1.20 (0.71–2.03)	1.20 (0.70–2.06)
Diazinon	18	3.5	28	1.9	1.72 (0.92–3.19)	1.69 (0.88–3.24)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Carbamate insecticides include carbaryl, carbofuran, and methomyl.
[d] Organochlorine insecticides class one includes aldrin; chlordane; dieldrin; endrin; heptachlor; lindane; and a mixture of lindane, carbathiin, and thiram (Vitavex).
[e] Organochlorine (2) diphenylchloride insecticides include DDT and methoxychlor.
[f] Organophosphorus insecticides include malathion, chlorpyrifos, diazinon, dimethoate, parathion, methidathion, and trichlorfon.

Table 4 Fungicides: frequency of exposure to fungicides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Amide,[c] exposed	30	5.8	58	3.9	**1.69 (1.05–2.73)**	**1.70 (1.04–2.78)**
Individual amide fungicides						
Captan	20	3.9	24	1.6	**2.48 (1.33–4.63)**	**2.51 (1.32–4.76)**
Vitavax	10	1.9	39	2.6	0.88 (0.42–1.85)	0.88 (0.41–1.87)
Aldehyde,[d] exposed	7	1.4	25	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Individual aldehyde fungicides						
Formaldehyde	7	1.4	255	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Mercury Containing,[e] exposed	18	3.5	48	3.2	1.09 (0.61–1.95)	1.28 (0.70–2.27)
Mercury-containing fungicides						
Mercury dust (n exposed)	15	2.9	39	2.6	1.08 (0.57–2.04)	1.23 (0.64–2.35)
Mercury liquid (n exposed)	8	1.5	22	1.5	1.15 (0.49–2.69)	1.40 (0.74–3.22)
Sulphur Compounds	17	3.3	21	1.4	**2.26 (1.16–4.40)**	**2.80 (1.41–5.57)**

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Amide fungicides include captan and a mixture of carbathiin, thiram, and lindane (Vitavax).
[d] Aldehyde fungicides include formaldehyde and a mixture of formaldehyde and iprodione (Rovral Flo).
[e] Mercury-containing fungicides include mercury dusts (Ceresan, Reytosan, and Agrox) and mercury liquids (Panogen, Leytosol, and PMAS).

Among individual carbamate compounds, exposure to carbaryl was statistically significantly associated with NHL. Among organochlorines, exposure to lindane, to aldrin, and to DDT was significantly associated with NHL. Malathion was the only individual organophosphate exposure statistically significantly associated with NHL.

Exposure to fungicides is summarized in Table 4. The fungicides with an amide group (OR_{adj}, 1.70; 95% CI, 1.04–2.78) were associated with NHL, whereas aldehydes and those containing mercury were not. Among individual amide-containing compounds, exposure to captan (OR_{adj}, 2.51; 95% CI, 1.32–4.76) was associated with NHL.

Malathion used as a fumigant was not associated with NHL (Table 5). There were fewer users of malathion as a fumigant compared with its use on crops. Carbon tetrachloride fumigant exposure (OR_{adj}, 2.42; 95% CI, 1.19–5.14) was associated with NHL.

Table 6 shows the results of a conditional logistic regres-

Table 5 Frequency of exposure to fumigants: individual compounds

Individual compounds+	NHL $n = 517$		Controls $n = 1506$		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Malathion[c]	12	2.3	23	1.5	1.49 (0.72–3.11)	1.54 (0.74–3.22)
Carbon tetrachloride[d]	13	2.5	18	1.2	**2.13 (1.02–4.47)**	**2.42 (1.19–5.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative) and with strata for the variables age and province of residence.
[c] Malathion is an organophosphorus insecticide which has been used indoors as a fumigant.
[d] Carbon tetrachloride was used as a grain fumigant.

Table 6 Most parsimonious model: conditional logistic regression analyses that contained major chemical classes of pesticides and important covariates ($P < 0.05$)

Phenoxyherbicides as a group, carbamate, and organophosphate insecticides, amide group containing fungicides, and carbon tetrachloride users/nonusers were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter Estimate ± SE	OR (95% CI)
Measles (yes)	−0.47 ± 0.11	**0.62 (0.50–0.78)**
Previous cancer (yes)	0.79 ± 0.18	**2.20 (1.54–3.15)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.37 (1.10–1.71)**
Allergy desensitization shots (yes)	−0.65 ± 0.27	**0.52 (0.31–0.89)**
Dicamba mixtures (user)	0.67 ± 0.17	**1.96 (1.40–2.75)**

Table 7 Most parsimonious model: conditional logistic regression analyses that contained individual chemical pesticides and important covariates ($P < 0.05$)

Among individual pesticides, carbaryl, lindane, DDT, and malathion insecticides, and captan fungicide user/nonuser were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter estimate ± SE	OR (95% CI)
Measles (yes)	−0.48 ± 0.11	**0.50 (0.45–0.83)**
Previous cancer (yes)	0.80 ± 0.18	**2.23 (1.56–3.19)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.38 (1.11–1.72)**
Allergy desensitization shots (yes)	−0.68 ± 0.27	**0.51 (0.30–0.87)**
Mecoprop (user)	0.80 ± 0.20	**2.22 (1.49–3.29)**
Aldrin (user)	1.23 ± 0.54	**3.42 (1.18–9.95)**

sion model that included major chemical classes of pesticides and all other covariates for which $P < 0.05$. The variables that remained statistically significantly associated with increased risk of NHL were a previous personal history of another malignancy, a history of cancer among first-degree relatives, and exposure to dicamba and mixtures containing dicamba. ORs for a personal history of measles or of allergy desensitization injections were significantly lower than those without this history. Table 7 summarizes a similar model that included individual pesticides and all of the other covariates for which $P < 0.05$ and in which mecoprop and aldrin exposure as well as the same covariates as in Table 6 were associated with NHL.

Table 8 shows the frequency of exposure to selected individual herbicides, insecticides, fungicides, and fumigants, stratified by the average number of days per year of exposure. In general, the results of these dose-response analyses are consistent with the exposed/nonexposed findings. Those compounds for which we found statistically significant case-control differences also have elevated ORs based on strata of the variable "days per year of exposure" (mecoprop, dicamba, malathion, DDT, captan, carbon tetrachloride, and sulfur). The exceptions were 2,4-D, for which there was no dose-response relationship, and glyphosate, which was not significant for exposure but for which we demonstrated a dose-response relationship.

Table 9 compares the frequencies of multiple herbicide, insecticide, fungicide, and fumigant use among cases and controls. Cases are significantly more likely to report exposure to between two and four herbicides or insecticides but not to five and more of either. An elevated OR was found for exposure to two or more fungicides. Table 9 also shows a dose-response relationship in comparisons of subjects who reported no pesticide exposure and those who reported using five or more pesticides.

Discussion

The hypothesis that farming (1–8), agricultural practices (9), and pesticide exposure (10–13, 22–25) are associated with NHL has been tested in a number of occupational studies. Not all of the studies confirm an association (27–29). Pesticides have diverse chemistry and biological modes of action. In addition to the active ingredients, there are emulsifiers, carriers, dispersants, and a variety of agents used to formulate liquids, granular and mists. The major chemical classes of *a priori* interest based on epidemiological studies (10–13, 22–25) were phenoxyherbicides, organophosphorus, organochlorines, aldehydes, and carbon tetrachloride. Occupational exposure to 2,4-D, 2,4,5-T, carbaryl, chlordane, DDT, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene has been reported to be associated with NHL. In addition, our interest focused on pesticides classified as possibly or probably carcinogenic to humans based on evaluations by the IARC expert panels (Refs. 22–25; phenoxyherbicides including 2,4-D, MCPA, and 2,4,5-T as a group, atrazine, chlordane, DDT, dichlorvos, heptachlor, and pentachlorophenol). Our bivariate results for exposure to groups of phenoxyherbicides or dicamba-containing herbicides, for carbamates and organophosphorus insecticides, and for amide fungicides and for carbon tetrachloride were not attenuated when simultaneously adjusted for the important medical covariates (history of measles, mumps, cancer, allergy desensitization shots, and a positive history of cancer in a first-degree relative).

Among individual compounds, our results that related to exposure to 2,4-D, mecoprop, dicamba, malathion, DDT, carbaryl, lindane, aldrin, captan, and sulfur compounds were not attenuated after simultaneous adjustment for the same medical covariates. Clearly, we had few exposed men whose exposure was limited to one pesticide or to one class of pesticides. Our results show elevated risk for exposure to multiple herbicides, insecticides, and fungicides.

Table 8 Frequency of exposure to selected herbicides, insecticides, fungicides, and fumigants stratified by the number of days per year of exposure

Models that included the time variable "days per year" and stratification for age and province of residence were also assessed for the individual herbicide compounds bromoxynil, 2,4-DB, diallate, MCPA, triallate, and treflan. No significant associations were found.

Individual compounds	Days/yr	NHL		Controls		OR[a] (95% CI)
		n	%	*n*	%	
Herbicides						
2,4-D	Unexposed	406	78.5	1213	80.5	1
	>0 and ≤2	55	10.6	160	10.6	1.17 (0.83–1.64)
	>2 and ≤5	36	7.0	82	5.4	1.39 (0.91–2.13)
	>5 and ≤7	9	1.7	20	1.3	1.38 (0.60–3.15)
	>7	11	2.1	31	2.1	1.22 (0.60–2.49)
Mecoprop	Unexposed	464	89.8	1425	94.6	1
	>0 and ≤2	31	6.0	48	3.2	**2.27 (1.40–3.68)**
	≥2	22	4.3	33	2.2	**2.06 (1.17–3.61)**
Phosphonic acid: glyphosate	Unexposed	466	90.1	1373	91.2	1
	>0 and ≤2	28	5.4	97	6.4	1.00 (0.63–1.57)
	>2	23	4.5	36	2.4	**2.12 (1.20–3.73)**
Dicamba	Unexposed	491	95.0	1456	96.7	1
	≥1	26	5.0	50	3.3	1.58 (0.96–2.62)
Insecticides						
Malathion	Unexposed	445	87.0	1379	91.6	1.00
	>0 and ≤2	50	9.7	88	5.8	**1.82 (1.25–2.68)**
	≥2	22	4.3	39	2.6	**1.75 (1.02–3.03)**
DDT	Unexposed	485	93.8	1447	96.1	1.00
	>0 and ≤2	18	3.5	32	2.1	1.75 (0.96–3.21)
	>2	14	2.7	27	1.8	1.50 (0.77–2.91)
Fungicides						
Captan	Unexposed	497	96.1	1482	98.4	1.00
	>0 and ≤2	11	2.1	12	0.8	**2.69 (1.17–6.19)**
	>2	9	1.7	12	0.8	**2.80 (1.13–6.90)**
Sulphur	Unexposed	500	96.7	1485	98.6	1.00
	Exposed ≥1	17	3.3	21	1.4	**2.26 (1.16–4.40)**
Fumigant						
Carbon tetrachloride	Unexposed	504	97.5	1488	98.8	1.00
	>0 and ≤2	13	2.5	18	1.2	**2.13 (1.02–4.47)**

[a] ORs calculated with strata for the variables age and province of residence.

The strength of our results is enhanced by their internal consistency as we applied the strategy of assessing risk by different analytic approaches progressing from exposure to: (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; (*b*) individual compounds within those major chemical classes; and (*c*) individual compounds stratified by days per year of exposure. We constructed models that included potential confounders (*e.g.*, positive history of cancer in a first-degree relative). Generally, the same individual compounds or class of compounds was associated with case status. The risk estimates based on exposure to major chemical classes or to individual compounds tended to be precise, as indicated by the 95% CIs.

Our results confirm previously reported associations of NHL and a personal history of cancer (30, 31), of NHL and a history of cancer among first-degree relatives (32, 33), and of NHL and exposure to selected pesticides (1, 3, 5, 9–13). We were unable to find a previous report suggesting a protective effect of allergy desensitization shots. Koepsell *et al.* reported little association of the number of allergy desensitization shots and MM (34). The relationship between allergy and cancer is complex with well-designed studies reporting opposite results (35–38). Cigarette smoking was not a risk factor overall, confirming one study (39) and contradicting others (40, 41), although certain subtypes (39, 40) of NHL may be associated with cigarette smoking.

The limitations of this study relate to those inherent in the case-control design, specifically the potential for recall bias and for misclassification of pesticide exposure. Hoar *et al.* and Zahm *et al.* (11, 13), as well as others (27–29, 42–45), have dealt extensively with these issues among farmers. We have included individuals in many different occupations as well as home and garden users. These are groups for whom we did not find extensive validation studies. Their inclusion may have biased our dose-response findings toward the null, although the yes/no responses to individual pesticides would be less affected. We reduced the number of surrogate responders by excluding deceased persons from our definition of eligible subjects. This strategy was useful in decreasing the potential for misclassification of exposure.

A second limitation is the less-than-optimal response rates. We continued to recruit subjects in each province until the target numbers were achieved. We compared respondents to nonrespondents using postal codes as an indicator of rural residence, and we did not find a rural bias among respondents.

We reported results for a number of chemical agents and exposures, not all of which were specified in the hypothesis. Therefore, the statistical analyses related to these unspecified agents should be considered exploratory. As a consequence of conducting multiple comparisons, a small number of statistically significant results may be attributable to chance.

The two-tiered study design permitted us to obtain detailed information related to factors other than pesticides that are known or suspected of being etiologically associated with NHL. The mailing of a list of pesticides with both trade and generic chemical names followed by a telephone interview

Table 9 Distribution of numbers of exposures to multiple types of pesticides among cases and controls

	NHL		Controls		OR[a] (95% CI)
	n	%	*n*	%	
Multiple herbicide use					
Unexposed[b]	374	72.3	1148	76.2	1.00
Exposed 1	45	8.7	146	9.7	1.02 (0.70–1.47)
Exposed 2–4	73	14.1	151	10.0	**1.75 (1.27–2.42)**
Exposed ≥5	25	4.8	61	4.1	1.41 (0.84–2.35)
Multiple insecticide use					
Unexposed	370	71.6	1154	76.6	1.00
Exposed 1	44	8.5	127	8.4	1.24 (0.85–1.80)
Exposed 2–4	86	16.6	189	12.6	**1.58 (1.17–2.13)**
Exposed ≥5	17	3.3	36	2.4	1.46 (0.79–2.69)
Multiple fungicide use					
Unexposed	457	88.4	1361	90.4	1.00
Exposed 1	32	6.2	90	6.0	1.08 (0.70–1.67)
Exposed ≥2	28	5.4	55	3.7	1.61 (.99–2.63)
Multiple fumigant use					
Unexposed	487	94.2	1440	95.6	1.00
Exposed ≥1	30	5.8	66	4.4	1.45 (0.91–2.63)
Multiple pesticide use[c]					
Unexposed	357	69.1	1095	72.7	1.00
Exposed 1–4	77	14.9	230	15.3	1.09 (0.81–1.46)
Exposed ≥5	83	16.1	181	12.0	**1.57 (1.16–2.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] With the exception of the variable multiple pesticide use, the "unexposed" referent category is specific to the class of pesticides.
[c] The unexposed referent category contains those who did not report exposure to herbicides, insecticides, fungicides, or fumigants.

allowed the collection of detailed information concerning pesticide exposure. The statistical power of our study was enhanced by the large number of cases and controls. In instances of rare exposures (<1% exposed), we had limited statistical power to detect associations. We restricted our analyses of individual pesticide compounds to those for which at least 1% of respondents indicated exposure.

The study was not restricted to pesticide exposure experienced by a specific occupational group. Occupational exposure was quite diverse; single *versus* multiple pesticides; indoor *versus* outdoor applications. For example, men who work in animal confinement buildings, grain elevators, and pesticide manufacturing have different exposure patterns in comparison with grain farmers and commercial applicators. Because this study encompassed a large geographical area of Canada, there was substantial diversity among agricultural enterprises and in the patterns and types of pesticide exposure.

Delineating the putative relationship between exposure to pesticides and NHL is complicated: (*a*) by the subject's exposure to a variety of different pesticides many of which are not mutagenic, teratogenic, or carcinogenic when tested as a single compound; (*b*) by the complexity of formulations of pesticides, the details of which are privileged proprietary information; (*c*) by the diversity of routes of possible exposure, which include ingestion, dermal, inhalation, and ocular; (*d*) by unexpected interactions among seemingly unrelated exposures, such as the increased permeability of rubber gloves to 2,4-D when exposed simultaneously to the insect repellent DEET and sunlight (46); and (*e*) by the role of differential genetic susceptibility.

Garty *et al.* (47) describe a potential mechanism to explain the relationship between exposure to specific pesticides and an increased risk of developing NHL. They have demonstrated specific chromosomal alterations in the peripheral lymphocytes of pesticide applicators exposed to a variety of pesticide classes. A higher frequency of chromosomal breaks involving band 18q21 was found in men who applied only herbicides compared with nonoccupationally exposed controls. Higher frequencies of rearrangements and breaks involving band 14q32 were found among men who applied herbicides, insecticides, and fumigants compared with controls. Reciprocal translocations between chromosomes 14q32 and 18q21 are frequently found in NHL patients.

Our results support previous findings of an association between NHL and specific pesticide exposures. Our strategy of assessing risk by several different approaches, beginning with general categories (*e.g.*, herbicides), proceeding through cumulative pesticide exposure to specific chemical classes, and proceeding further to specific chemicals, proved effective in delineating complex relationships. In our final models, NHL was associated with a personal history of cancer; a history of cancer in first-degree relatives; and exposure to dicamba-containing herbicides, to mecoprop, and to aldrin. A personal history of measles and of allergy desensitization treatments lowered risk.

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Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies

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Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies

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(In final form 30 October 2001)

Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in univariate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26–2.42), insecticides (OR 1.43, CI 95% 1.08–1.87), fungicides (OR 3.11, CI 95% 1.56–6.27) and impregnating agents (OR 1.48, CI 95% 1.11–1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08–8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40–4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multivariate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above.

Keywords: Non-Hodgkin's lymphoma; Hairy cell leukemia; Pesticides; Phenoxyacetic acids; Glyphosate; Impregnating agents

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is one of the malignant diseases with the most rapidly increasing incidence in the western world [1]. In Sweden, the mean age-adjusted incidence increased yearly by 3.6% in men and 2.9% in women during the time period 1958–1992 [2]. Hairy cell leukemia (HCL) was first described in 1958 and is regarded as a rare subgroup of NHL. HCL is more common in men with 23 male and 9 female patients reported to the Swedish Cancer Register in 1999 for the whole country [3].

The etiology of NHL is regarded to be multifactorial with different environmental exposures being part of it. Certain immunodefective conditions are established risk factors such as immunosuppressive medication after organ transplantation [4,5] and HIV-infection [6]. Also viral genesis, especially regarding Epstein–Barr virus (EBV) and endemic African Burkitt lymphoma has been indicated [7].

Regarding chemicals, exposure to phenoxyacetic acids, chlorophenols and organic solvents were associated with increased risk for NHL in Swedish studies [8–10]. In subsequent studies exposure to phenoxyacetic acids, particularly 2,4-dichlorophenoxyacetic acid (2,4-D), was associated with an increased risk for NHL [11,12]. These associations have been reviewed by us giving reference also to other studies [13].

We have now performed one case-control study on NHL, which did not include HCL [14], and another on HCL, specifically [15]. Both these studies focused interest especially on exposure to pesticides. In the NHL study, we found increased risks for subjects exposed to herbicides or fungicides. Among herbicides, phenoxyacetic acids

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TABLE 1 Number of exposed cases and controls, odds ratio (OR) and 95% confidence interval (CI) for exposure to pesticides and organic solvents

Agent	Number of exposed cases/controls	OR	CI
Herbicides	77/103	1.75	1.26–2.42
Phenoxyacetic acids	64/90	1.65	1.16–2.34
MCPA	21/23	2.62	1.40–4.88
2,4-D + 2,4,5-T	48/70	1.48	0.99–2.20
Glyphosate	8/8	3.04	1.08–8.52
Other	15/13	2.90	1.34–6.37
Insecticides	112/184	1.43	1.08–1.87
DDT	77/138	1.27	0.92–1.73
Mercurial seed dressing	20/33	1.40	0.77–2.47
Pyrethrins	13/27	1.16	0.57–2.25
Fungicides	18/17	3.11	1.56–6.27
Impregnating agents	104/162	1.48	1.11–1.96
Chlorophenols	66/106	1.37	0.98–1.92
Pentachlorophenol	64/101	1.40	0.99–1.98
Arsenic	8/10	1.75	0.66–4.54
Creosote	22/35	1.54	0.87–2.66
Other	40/67	1.35	0.88–2.04
Organic solvents	250/492	1.16	0.93–1.44

dominated. One subclass of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL. For several categories of herbicides, we observed that only exposure during the latest decades before diagnosis of NHL was associated with an increased risk for NHL. In the HCL study, we found increased risk for exposure to different categories of pesticides [15]. However, due to comparatively low number of study subjects, it was not meaningful to make further analyses of the tumor induction period.

Thus, the risk patterns for NHL and HCL in these studies, performed by the same methodology, showed similarities with respect to pesticides. Since the NHL study included patients with many different variants of NHL, it seemed motivated also to include HCL, as nowadays being regarded as a NHL subgroup, in a pooled analysis regarding risks in relation to pesticide exposure. The purpose was to enlarge the study size thereby allowing more precise risk estimates.

MATERIALS AND METHODS

Cases

The NHL study encompassed male cases aged ≥25 years with NHL diagnosed during 1987–1990 and living in the four most northern counties of Sweden and three counties in mid-Sweden [14]. They were recruited from the regional cancer registries and only cases with histopathologically verified NHL were included, in total 442 cases. Of these cases 192 were deceased.

From the national Swedish Cancer Registry, 121 male patients with HCL diagnosed during 1987–1992 were identified from the whole country [15]. One case later turned out to have been diagnosed in 1993, but was included in the study. Only living cases were included.

Controls

For living NHL cases two male controls matched for age and county were recruited from the National Population Registry.

For each deceased case two deceased controls matched also for year of death were identified from the National Registry for Causes of Death. For deceased subjects interviews were performed with the next-of-kin.

Similarly, four male controls matched for age and county were drawn to each case of HCL from the National Population Registry.

Assessment of Exposure

In both studies a similar questionnaire was mailed to the study subjects or next-of-kin for deceased individuals. A complete working history was asked for as well as exposure to different chemicals. If the information was unclear a trained interviewer supplemented the answers over the phone, thereby using written instructions. Years and total number of days for exposure to various agents were assessed. Also names of different agents were carefully asked for. If necessary, the Swedish Chemical Inspectorate was contacted to obtain information on the chemical composition of different brands of pesticides and other agents. A minimum exposure of one working day (8 h) and a tumor induction period of at least one year were used in the coding of chemicals. Thus, total exposure less than one day as well as exposure within one year prior to diagnosis (corresponding time for the matched control) were disregarded. The questionnaires were blinded as to case or control status during the interviews and coding of data.

Statistical Analysis

Conditional logistic regression analysis for matched studies was performed with the SAS statistical program (SAS Institute, Cary, NC). Thereby odds ratios (OR) and

TABLE II Exposure to different types of herbicides with dose-response calculations. High exposure is defined as > median number of days for exposed subjects. Range of exposure in days given within parenthesis

Agent	Total OR (CI)	Median number of days	OR (CI) Low	OR (CI) High
Herbicides	1.75 (1.26–2.42)	33 (1–709)	1.74 (1.10–2.71)	1.79 (1.15–2.79)
Phenoxyacetic acids	1.65 (1.16–2.34)	33 (1–709)	1.65 (1.01–2.66)	1.67 (1.02–2.69)
MCPA	2.62 (1.40–4.88)	25 (1–491)	1.94 (0.79–4.55)	3.61 (1.49–9.05)
2,4-D + 2,4,5-T	1.48 (0.99–2.20)	30 (1–709)	1.87 (1.08–3.20)	1.20 (0.68–2.08)
Other	2.90 (1.34–6.37)	11 (1–220)	2.26 (0.76–6.77)	3.37 (1.08–11)

95% confidence intervals (CI) were obtained. Both univariate and multivariate analyses were done. In this pooled analysis adjustment was made for study, study area and vital status. When risk estimates for different pesticides were analyzed only subjects with no pesticide exposure were taken as unexposed, whereas subjects exposed to other pesticides were disregarded.

RESULTS

The questionnaire was answered by 404 cases (91%) and 741 controls (84%) in the NHL study. Regarding HCL 111 cases (91%) and 400 controls (83%) participated. In the following results are given for the pooled analysis containing 515 cases and 1141 controls.

An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, Table I. Regarding specific agents OR was highest for glyphosate and MCPA.

For herbicides dose-response calculations were also performed by comparing high and low dose exposures divided by the median exposure time in days, Table II. Exposure to MCPA gave a dose-response effect. Also for the group constituting of other herbicides than phenoxyacetic acids the risk was highest in the group with high exposure.

For herbicides in total and phenoxyacetic acids as a group the highest risks were seen when first exposure occurred 10–20 years before diagnosis, Table III. This was also the case for insecticides and impregnating agents. Within the latter group, however, an induction period of 20–30 years gave the highest risk for both creosote and pentachlorophenol.

Time to diagnosis from last exposure to different agents was also used in the calculation of risk estimates, Table IV. For phenoxyacetic acids the OR was highest for exposure 1–10 years prior to diagnosis whereas no increased risk was seen for those with last exposure >20 years from the time of diagnosis.

TABLE III Exposure to phenoxyacetic acids, insecticides, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from first exposure to diagnosis (induction period)

Agent	Induction period, years 1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	1.00 (0.05–11)	2.32 (1.04–5.16)	1.63 (0.87–2.98)	1.70 (1.12–2.58)
Phenoxyacetic acids	–*	2.88 (1.11–7.72)	1.54 (0.85–2.76)	1.50 (0.94–2.37)
MCPA	–*	5.36 (1.57–21)	0.89 (0.20–3.03)	3.77 (1.49–9.99)
2,4-D + 2,4,5-T	–†	2.87 (0.81–11)	1.87 (0.98–3.53)	1.15 (0.67–1.93)
Insecticides	1.20 (0.25–4.70)	2.84 (0.95–8.54)	2.19 (1.14–4.17)	1.31 (0.96–1.77)
DDT	–†	2.64 (0.61–11)	1.63 (0.80–3.26)	1.17 (0.82–1.65)
Impregnating agents	1.20 (0.37–3.49)	2.27 (1.15–4.49)	1.89 (1.07–3.30)	1.23 (0.85–1.75)
Chlorophenols	–†	1.91 (0.82–4.44)	1.90 (0.98–3.65)	1.13 (0.73–1.71)
Pentachlorophenol	–†	1.91 (0.82–4.44)	2.13 (1.07–4.25)	1.13 (0.73–1.72)
Creosote	–*	0.88 (0.04–7.27)	5.33 (1.26–27)	1.34 (0.69–2.49)
Organic solvents	1.51 (0.65–3.37)	1.38 (0.84–2.24)	1.46 (1.00–2.12)	1.02 (0.79–1.30)

* No exposed cases, one exposed control.
† No exposed subjects.

TABLE IV Exposure to phenoxyacetic acids, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from last exposure to diagnosis

Agent	Time span, last exposure-diagnosis, years			
	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	2.53 (1.38–4.64)	1.68 (0.88–3.14)	1.22 (0.66–2.19)	1.84 (0.95–3.51)
Phenoxyacetic acids	3.22 (1.59–6.65)	2.06 (1.03–4.09)	1.01 (0.54–1.81)	1.26 (0.57–2.62)
MCPA	3.52 (1.58–7.99)	2.33 (0.56–9.09)	0.92 (0.13–4.39)	–*
2,4-D + 2,4,5-T	4.31 (1.12–21)	1.85 (0.90–3.78)	1.04 (0.54–1.94)	1.41 (0.65–2.92)
Insecticides	2.37 (1.40–4.02)	0.87 (0.48–1.53)	1.45 (0.85–2.41)	1.46 (0.94–2.24)
DDT	1.45 (0.65–3.10)	1.13 (0.62–1.97)	1.46 (0.83–2.50)	1.20 (0.69–2.02)
Impregnating agents	1.92 (1.30–2.82)	0.79 (0.40–1.46)	1.67 (0.88–3.11)	1.19 (0.61–2.21)
Chlorophenols	–†	1.52 (1.02–2.25)	1.36 (0.61–2.86)	0.84 (0.32–1.96)
Pentachlorophenol	–†	1.59 (1.06–2.37)	1.28 (0.58–2.67)	0.81 (0.29–2.01)
Creosote	2.56 (0.85–7.67)	0.93 (0.13–4.17)	1.17 (0.36–3.43)	1.54 (0.60–3.75)
Organic solvents	1.17 (0.91–1.50)	1.00 (0.66–1.50)	1.39 (0.84–2.25)	0.99 (0.56–1.69)

* one exposed case, one exposed control.
† No exposed case or control.

Furthermore, exposure to phenoxyacetic acids during different decades from the 1940s was analyzed. Increased risk was found during recent decades, Table V.

No statistically significant increased risk was found for the whole group of organic solvents in this pooled analysis, but when the solvents were subgrouped according to specific substances there were increased risks for vanolen (OR = 1.91, CI = 1.03–3.49; $n = 20$ cases) and aviation fuel (OR = 3.56, CI = 1.03–12; $n = 6$ cases).

Multivariate analysis of exposure to phenoxyacetic acids, insecticides, fungicides and impregnating agents is presented in Table VI. An increased risk persisted for exposure to herbicides, fungicides and impregnating agents, however not statistically significant.

A separate multivariate analysis was performed on exposure to herbicides. Lower risk estimates were obtained although all herbicides still constituted risk factors for NHL, Table VII.

DISCUSSION

The cases in this study were identified by using the Swedish Cancer Registry, which is composed by six regional registries. In Sweden, the reporting of malignant diseases to the Cancer Registry is compulsory, which makes it likely that most incident cases in the study area were identified. Controls were selected from the National Population Registry and, in order to minimize recall bias, deceased controls were used for deceased cases in one of the studies [14] which were the basis for this analysis. In the other only living cases were included [15]. Recall bias is always a matter of concern in a case-control study with self-reported exposures. Farmer as occupation did not increase the risk in this pooled analysis (OR = 1.19, CI = 0.95–1.49) which indicates that the risk increase for pesticides was not explained merely by misclassification of exposure. All interviews and coding of data were performed blinded as to case or control status in order to minimize observational bias.

TABLE V Exposure to phenoxyacetic acids during different decades. Note that one subject may occur during several decades

Decade	Cases/controls	OR	CI
1940s	4/6	1.46	0.37–5.23
1950s	35/53	1.44	0.91–2.26
1960s	43/58	1.68	1.10–2.55
1970s	32/33	2.37	1.42–3.95
1980s	16/33	3.25	1.53–7.07

TABLE VI Multivariate analysis of exposure to pesticides

Agent	Univariate		Multivariate	
	OR	CI	OR	CI
Herbicides	1.75	1.26–2.42	1.39	0.96–2.02
Insecticides	1.43	1.08–1.87	1.07	0.78–1.45
Fungicides	3.11	1.56–6.27	2.02	0.97–4.23
Impregnating agents	1.48	1.11–1.96	1.30	0.98–1.72

TABLE VII Multivariate analysis of exposure to herbicides. Odds ratios (OR) and 95% confidence intervals (CI) are given

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
MCPA	2.62	1.40–4.88	1.67	0.77–3.57
2,4-D + 2,4,5-T	1.48	0.99–2.20	1.32	0.88–1.96
Glyphosate	3.04	1.08–8.52	1.85	0.55–6.20
Other herbicides	2.90	1.34–6.37	2.28	1.02–5.15

This study was a pooled analysis of two case-control studies, one on NHL [14] and the other on HCL [15] to provide larger numbers, which would allow more detailed analyses regarding the timing of exposure and adjustment of multiple exposures. This method was justified since HCL is a type of NHL and similar methods and questionnaires were used in both studies. Also the findings regarding pesticide exposure were relatively homogenous for both studies. The smaller HCL study had a somewhat higher prevalence of exposure and therefore has in this pooled analysis more weight than one would expect.

Conditional logistic regression analysis was performed since both studies in this pooled analysis were matched. Heterogeneity in findings was averaged after stratification by study. Since the NHL study included also deceased cases and controls adjustment was made for vital status. Finally, in the HCL study the whole Sweden was included as study base whereas in the NHL study only parts of Sweden were included. Thus, adjustment was made for geographical area for cases and controls, i.e. county.

In the multivariate analysis exposure to herbicides, fungicides and impregnating agents increased the risk although OR was lower than in the univariate analysis. Significantly increased risk remained only for the heterogeneous group of "other herbicides". The results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate. Multivariate analysis is mainly useful to estimate the risk factors that seem to be most important.

Several previous studies have associated exposure to phenoxyacetic acids, primarily 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), with an increased risk for NHL [8–12,16–18]. Concerning MCPA data are sparse although in our first study on NHL, we found an increased risk [9,10].

In this pooled analysis, most subjects were regarding herbicides exposed to phenoxyacetic acids, mostly the combination of 2,4-D and 2,4,5-T. 2,4-D was withdrawn from the Swedish market in 1990 and 2,4,5-T was prohibited in 1977. Also MCPA, the phenoxy herbicide still commonly used in Sweden, increased the risk for NHL. Glyphosate is the herbicide now mostly used in Sweden. In this study, exposure to glyphosate was a risk factor for NHL. Thus, regarding herbicides lymphomagenesis seems not to be depending on contaminating dioxins, i.e. 2,3,7,8-TCDD in 2,4,5-T. A contributing effect of such exposure cannot be excluded, although not supported by mortality results in a cohort of workers exposed to 2,3,7,8-TCDD [19]. IARC classified recently 2,3,7,8-TCDD as a human carcinogen, Group I [20].

In the univariate analysis exposure to insecticides, mostly DDT, increased the risk for NHL. In the multivariate analysis no risk was found. This is in accordance with our previous results [9,10] and a pooled analysis of three case-control studies concluded that DDT is not a risk factor for NHL [21]. Furthermore, analysis of serum DDT/DDE has not given a clear association with NHL [22,24,25].

Regarding fungicides an increased risk for NHL has previously been reported from USA [11]. Our result with increased risk for NHL needs to be further studied since the finding was based on few subjects exposed to several types of fungicides.

Chlorophenols, which are chemically related to phenoxyacetic acids and have been used as e.g. wood preservatives, were banned in Sweden in 1978. An increased risk for NHL was found in this pooled analysis, but also for exposure to arsenic and creosote. Both chlorophenols and creosote have been associated with NHL [26,27].

An association between exposure to organic solvents and NHL has been described [9,10,28–30]. However, such an association was not confirmed now although an influence of tumor induction period can not be ruled out, *c.f.*, below. Another possibility might be that solvents used during later years are less toxic than previously, e.g. water based, and that they are more cautiously handled [31].

To further elucidate mechanisms in lymphomagenesis analysis of tumor-induction period (latency) and also time from last exposure to diagnosis was performed. Thereby the corresponding year for diagnosis was used for the matched control. For 2,4-D, 2,4,5-T and chlorophenols no subject had first exposure during 1–10 years prior to diagnosis due to restrictions in the use of these chemicals in Sweden during that time period. For fungicides such calculations were not meaningful due to low number of exposed subjects.

The highest risk for exposure to herbicides, insecticides and impregnating substances was found for last exposure 1–10 years prior to diagnosis. Correspondingly, in general the lowest risks were found for the longest tumor induction periods.

Do these results cast further light on the etiology of NHL? Certainly, exposure to some chemicals is of significance in lymphomagenesis. Furthermore, bearing in mind that several of these chemicals are immunotoxic, e.g. certain pesticides and chlorophenols [27,32,33] and immunosuppression is an established risk factor for NHL [34] such toxicity might be of importance for chemical agents.

Viruses have been associated with lymphomas in animals [35,36] and more specifically EBV for humans [7,37]. Virus proliferation in lymphocytes is held back by the immune system and immunosuppression may be followed by development of both B-cell and T-cell

lymphoma in animals [38–39]. For renal transplant patients treated with immunosuppressive drugs the risk for NHL is highest during the first years after transplantation and then declines [40].

Timing of exposure in relation to risk of NHL, particularly in regard to higher risk for recent exposures, seemed to be an interesting result regarding lymphomagenesis. Several interpretations are possible such as chance finding, late stage in lymphomagenesis, type of exposure or interaction with other factors. Certainly immunmodulation by pesticides [32,33] is one hypothesis which should be more elaborated on, possibly with interaction with latent virus infection such as EBV. This might explain the short tumor induction period. In fact, results from the included HCL-study showed interaction between EBV-infection and exposure to such chemicals [41,42]. Additionally, polychlorinated biphenyls [22,24,25] and chlordanes [23,24], chemicals that are immunotoxic [43,44], have been associated with an increased risk for NHL.

The etiology of NHL is multifactorial and further studies should consider immunotoxic effects by the studied chemicals as well as tumor induction period and interaction with virus infection, e.g. EBV.

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ELECTRONIC PAPER

Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men

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Background: An increased rate of non-Hodgkin's lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult.

Methods: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable.

Results: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these "potentially carcinogenic" pesticides suggested a positive trend of risk with exposure to increasing numbers.

Conclusion: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.

Farming occupation has been associated with an increased risk of non-Hodgkin's lymphoma (NHL) in the United States and other countries.[1–4] Specific farming exposures contributing to the excess risk have not been clearly discerned, but pesticides have received considerable attention. Associations have been observed between NHL risk and exposure to phenoxyacetic acids, most notably 2,4-dichlorophenoxyacetic acid (2,4-D).[5–10] Organochlorine, organophosphate, carbamate, and triazine pesticides have also been implicated.[8 9 11–14]

There are several analytical challenges in studying health effects of pesticide exposures among farmers. Farmers are typically exposed to multiple pesticides during a lifetime, and pesticides are frequently used together or during the same growing season, posing a challenge for identifying specific risk factors. Although multiple and simultaneous exposures are common in epidemiology and the situation regarding pesticides is not unique, they do require large numbers to successfully identify risks from specific exposures. Many of the past studies of NHL and pesticides had limited power to adjust for potential confounding by associated pesticide exposures. Limited study power has also hindered investigation of the risk associated with common pesticide combinations.

In principle, multiple pesticide exposures should be modelled simultaneously to account for their probable correlation; however, modelling multiple pesticides can lead to imprecise estimates, particularly where exposures are infrequent. In addition, some estimates are expected to be very inaccurate, either due to chance or systematic error (such as recall bias). Hierarchical regression models, also known as multilevel or multistage models, allow the researcher to specify prior distributions for multiple effect parameters of interest (for example, pesticide effects), and to adjust the observed likelihood estimates towards these prior distributions with the objective of obtaining increased precision and accuracy for the ensemble of estimates.[15–17] Although the true prior distributions are rarely known, factors hypothesised to determine or explain the magnitude of the true effects of interest can be used to specify the form of the prior distributions, whose magnitudes are then estimated.[15]

During the 1980s, the National Cancer Institute conducted three population based case-control studies of NHL in Nebraska,[5] Iowa and Minnesota,[11] and Kansas.[7] Each of these studies focused on farming exposure to pesticides, and data from the three studies have been pooled. In the pooled data, certain organophosphate[12] and carbamate[13] insecticides were positively associated with the risk of NHL. Lindane use was associated with slightly increased incidence of NHL,[18] whereas DDT use was not.[19] There was also a slightly increased incidence associated with atrazine exposure.[20]

We used these pooled data to conduct an analysis of exposure to multiple pesticides in farming as risk factors for NHL among men. The larger sample size provided adequate numbers of exposed persons to analyse a set of pesticide exposures simultaneously, using hierarchical regression to adjust estimates based on prior distributions for the pesticide effects. In addition, effects of the number of pesticides used and of common pesticide combinations were explored to assess the risk associated with realistic scenarios of farmers' exposures to multiple pesticides.

METHODS

Study population

The three case-control studies had slightly different methods of subject recruitment. In Nebraska,[5] all cases of NHL diagnosed between July 1983 and June 1986 among white subjects 21 years of age and older, and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals. In Iowa and Minnesota,[11] all newly diagnosed cases of NHL among

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; NHL, non-Hodgkin's lymphoma; OP, organophosphorus

white men aged 30 years or older were ascertained from records of the Iowa State Health Registry from 1981 to 1983, and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1982. In Kansas,[7] a random sample of cases diagnosed between 1979 and 1981 among white men age 21 years or older was selected from the statewide cancer registry run by the University of Kansas Cancer Data Service. Population based controls were randomly selected from the same geographical areas as the cases, frequency matched to cases by race, sex, age, and vital status at the time of interview. Potential controls were identified by random digit dialing and from Medicare records, and for deceased cases, from state mortality files.

Only one study included women; in this pooled analysis we excluded female cases and controls. Those who lived or worked on a farm when younger than 18 years of age, but not after age 18, were not asked about their pesticide use in the Nebraska study; persons with this history from any of the three studies were therefore excluded from analyses of the pooled data. Following exclusions, the study population included 870 cases and 2569 controls.

Interviews

Interviews were conducted with the subjects or their next of kin if the subjects were dead or incapacitated. In each study, detailed questions were asked about the use of agricultural pesticides as well as other known or suspected risk factors for NHL. In Nebraska, information was obtained through questioning about the use of any pesticide, followed by prompting for selected specific pesticides, with details on the total number of years of use and average number of days per year. In Iowa and Minnesota, use was assessed by a direct question about a selected list of specific pesticides. Pesticide users were also asked the first and last year each pesticide was used. In Kansas, use of pesticides was assessed by an open ended question without prompting for specific pesticides, and duration of use and days per year were obtained for groups of pesticides (herbicides, insecticides, and fungicides), but not for each pesticide individually.

Statistical analyses

Each pesticide for which there were data from all three studies, and to which 20 or more persons were exposed, was included in the pooled analysis. The set of pesticides examined included 47 insecticides and herbicides. Exposure to each pesticide was coded as an indicator variable for exposed (1) or not exposed (0). Because these analyses of multiple pesticides modelled the pesticides simultaneously, any subject with a missing or "don't know" response for any one of the 47 pesticides of interest was excluded from all analyses. Following exclusion of subjects with missing data, analyses of multiple pesticides included 650 cases (74.7%) and 1933 controls (75.2%). We employed two approaches to our analyses: standard logistic regression (maximum likelihood estimation) and hierarchical regression, calculating odds ratios to estimate the relative risk associated with each pesticide. All models included variables for age (coded as a quadratic spline variable with one knot at 50 years)[21] and indicator variables for study site. Other factors known or suspected to be associated with NHL, including first degree relative with haematopoietic cancer, education, and smoking, were evaluated and found not to be important confounders of the associations between NHL and pesticides. The standard logistic regression models did not assume any prior distribution of pesticide effects, in contrast to the hierarchical regression modelling.

Hierarchical regression of multiple pesticide exposures

In the first-level model of the hierarchical regression analysis, NHL disease status was regressed simultaneously on the 47 pesticide exposures, age, and study site. The maximum likelihood estimates for the 47 pesticides from the first-level model were regressed in a second-level linear regression model as a function of prespecified prior covariates for each of the pesticides. The second-level model should incorporate what is known about each true effect parameter prior to seeing the study data.[15 22] Information derived from the second-level model was used to adjust the beta coefficient for each pesticide exposure according to its "prior distribution"; the beta for each pesticide was adjusted in the direction of its prior mean, or expected value (from the second-level model), with the magnitude of shrinkage dependent on the precision of its likelihood estimate (from the first-level model) and a prespecified variance of the assumed normal distribution for that parameter. SAS Proc GLIMMIX was used to run the hierarchical models. This program can be adapted for the purpose of hierarchical modelling of multiple exposures, and uses a penalised likelihood function to fit the first- and second-level models by an iterative procedure.[23]

Information on pesticides that would give a priori reason to believe that the true effect parameters for certain specific pesticides would be more or less similar to each other was constructed into a matrix for use in the second level of the hierarchical regression analysis (table 1). The second-level, or prior covariates, were factors hypothesised to determine the magnitude of, or explain some of the variability between, the individual true effects. The covariates were indicators of pesticide class, structure, and toxicity, used to define categories of pesticide effects which would be regarded as "exchangeable", or as draws from a common prior distribution.[15 22] These "categories of exchangeability" included the groupings: insecticides (versus herbicides), organochlorines, organophosphates, carbamates, phenoxyacetic acids, triazines, amides, and benzoic acids (see table 1). In addition to categories of exchangeability, we defined a prior covariate incorporating prior evidence for carcinogenicity of the pesticide. Based on data from the United States Environmental Protection Agency's (US EPA) Integrated Risk Information System (http://www.epa.gov/iris/) and the International Agency for Research on Cancer's Program on the Evaluation of Cancer Risks to Humans (http://monographs.iarc.fr/), carcinogenic probability for any cancer (not limited to NHL), was defined as a continuous variable ranging between 0 and 1 (algorithm for variable definition is included as footnote to table 1).

Another component of each pesticide effect's prior distribution was a value for the residual variance, which captures effects above and beyond those accounted for by the "group" effects of the second-level covariates, and determines the degree of shrinkage of a likelihood estimate toward its prior mean.[15 22] This residual variance was defined as a value relating to a range of probable values for the true effect parameter. We assumed, with 95% certainty, that the rate ratio for each pesticide, after adjusting for the second-level covariates, would fall within a 10-fold range around its prior mean (for example, between 0.5 and 5.0), by defining the prior residual variance as 0.35 (note: for a 10-fold range, residual variance = $((\ln(10))/3.92)^2 \cong 0.35$), assuming normality).

Because our prior covariates were crudely defined, and because there is little information on factors that would be expected to affect the magnitude of the effect of pesticides on NHL incidence, we also performed a hierarchical regression analysis of multiple pesticides using an intercept-only model, in which all pesticide effects were assumed to arise from a common prior distribution, with a prior residual variance of 0.35. In other words, this modelling strategy assumed that there was no a priori reason to believe that any specific pesticide was more likely to be associated with NHL incidence than any other pesticide in the model.

Number of pesticides used

We conducted analyses to estimate NHL incidence associated with the number of pesticides used, out of the total number of

Table 1 Second-level matrix for hierarchical regression analysis, showing values of "prior covariates" for each pesticide of interest*†

Pesticides	Insecticides	Organo-chlorines	Organo-phospates	Carbamates	Phenoxy-acetic acids	Triazines	Amides	Benzoic acids	Carcinogenic probability
Insecticides									
Aldrin	1	1	0	0	0	0	0	0	0.6
Bufencarb	1	0	0	1	0	0	0	0	0.3
Carbaryl	1	0	0	1	0	0	0	0	0.3
Carbofuran	1	0	0	1	0	0	0	0	0.3
Chlordane	1	1	0	0	0	0	0	0	0.8
Copper acetoarsenite'	1	0	0	0	0	0	0	0	1.0
Coumaphos	1	0	1	0	0	0	0	0	0.3
DDT	1	1	0	0	0	0	0	0	0.8
Diazinon	1	0	1	0	0	0	0	0	0.3
Dichlorvos	1	0	1	0	0	0	0	0	0.8
Dieldrin	1	1	0	0	0	0	0	0	0.6
Dimethoate	1	0	1	0	0	0	0	0	0.3
Ethoprop	1	0	1	0	0	0	0	0	0.3
Famphur	1	0	1	0	0	0	0	0	0.3
Fly, lice, tick spray	1	0	0	0	0	0	0	0	0.3
Fonofos	1	0	1	0	0	0	0	0	0.3
Heptachlor	1	1	0	0	0	0	0	0	0.8
Lead arsenate'	1	0	0	0	0	0	0	0	1.0
Lindane	1	1	0	0	0	0	0	0	0.3
Malathion	1	0	1	0	0	0	0	0	0.3
Methoxychlor	1	1	0	0	0	0	0	0	0.3
Nicotine	1	0	0	0	0	0	0	0	0.3
Phorate	1	0	1	0	0	0	0	0	0.3
Pyrethrins	1	0	0	0	0	0	0	0	0.3
Rotenone	1	0	0	0	0	0	0	0	0.3
Tetrachlorvinphos	1	0	1	0	0	0	0	0	0.3
Toxaphene	1	1	0	0	0	0	0	0	0.8
Terbufos	1	0	1	0	0	0	0	0	0.3
Herbicides									
Alachlor	0	0	0	0	0	0	1	0	0.3
Atrazine	0	0	0	0	0	1	0	0	0.3
Bentazon	0	0	0	0	0	0	0	0	0.1
Butylate	0	0	0	1	0	0	0	0	0.3
Chloramben	0	0	0	0	0	0	0	1	0.3
Cyanazine	0	0	0	0	0	1	0	0	0.3
2,4-D	0	0	0	0	1	0	0	0	0.5
Dicamba	0	0	0	0	0	0	0	1	0.3
EPTC	0	0	0	1	0	0	0	0	0.3
Glyphosate	0	0	0	0	0	0	0	0	0.3
Linuron	0	0	0	0	0	0	0	0	0.5
MCPA	0	0	0	0	1	0	0	0	0.3
Metolachlor	0	0	0	0	0	0	1	0	0.5
Metribuzin	0	0	0	0	0	0	0	0	0.3
Paraquat	0	0	0	0	0	0	0	0	0.5
Propachlor	0	0	0	0	0	0	1	0	0.3
Sodium chlorate	0	0	0	0	0	0	0	0	0.3
2,4,5-T	0	0	0	0	1	0	0	0	0.5
Trifluralin	0	0	0	0	0	0	0	0	0.5

*Carcinogenic probability value is created by combining the classifications from the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans and the US EPA Integrated Risk Information System. Assignment of carcinogenic probability by order of priority: 1.0 = classified as a human carcinogen on either assessment; 0.9 = probable human carcinogen in both assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in other assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable in the other; 0.5 = possible human carcinogen in both assessments, or possible human carcinogen in one assessment and not assessed by the other group; 0.3 = not assessed by IARC or US EPA IRIS, or deemed unclassifiable in one or both assessments; 0.1 = evidence for non-carcinogenicity in either assessment.
†Used the IARC assessment for arsenic and arsenic compounds.

86 pesticides reported in all three of the pooled studies (many of these 86 pesticides were not included in the multivariable analysis of the set of 47 specific pesticides because of their infrequent use). The number of pesticides was coded using indicator variables (1 pesticide, 2–4 pesticides, 5 or more pesticides). Similar analyses were conducted for the number of insecticides and herbicides used. For those pesticides showing positive associations with NHL in the hierarchical regression analysis of 47 specific pesticides (nine pesticides total, see table 3), we conducted a similar analysis of the number of pesticides used, restricted to these "potentially carcinogenic" pesticides. In addition to logistic regression analyses, we evaluated the effect of the number of pesticides used by hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating number of pesticides, as well as the 47 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

Combined pesticide exposures

We explored the risk associated with combined pesticide exposures, defined as two pesticides used by the same person, but not necessarily at the same time. For any two pesticides for which more than 75 persons reported use of both (representing the 5% most common of all possible combinations of the 47 pesticides), and at least 20 persons reported use of each of the two individual pesticides not in combination, we evaluated potential superadditivity of pesticide effects on NHL (the appendix contains a list of the pesticide combinations evaluated). Individual and joint effects were first estimated

Table 2 Characteristics of subjects in the study population* and those subjects included in analyses of multiple pesticides†

Characteristics	Pooled study			Included in analyses of multiple pesticides		
	Cases (n=870)	Controls (n=2569)	OR (95% CL)‡	Cases (n=650)	Controls (n=1933)	OR (95% CL)
Study site						
Iowa/Minnesota	520 (60.9%)	1039 (40.4%)	1.0	436 (67.1%)	895 (46.3%)	1.0
Kansas	153 (17.6%)	862 (33.6%)	0.3 (0.3 to 0.4)§	101 (15.5%)	596 (30.8%)	0.3 (0.3 to 0.4)
Nebraska	187 (21.5%)	668 (26.0%)	0.5 (0.4 to 0.7)§	113 (17.4%)	442 (22.9%)	0.5 (0.4 to 0.7)
Respondent status						
Self respondent	545 (62.6%)	1413 (55.0%)	1.0	449 (69.1%)	1166 (60.3%)	1.0
Proxy respondent	325 (37.4%)	1156 (45.0%)	0.7 (0.6 to 0.9)§	201 (30.9%)	767 (39.7%)	0.7 (0.6 to 0.8)
Age (years)						
<40	53 (6.1%)	280 (11.0%)	0.7 (0.5 to 1.0)§	40 (6.2%)	211 (10.9%)	0.7 (0.5 to 1.1)
40–59	196 (22.6%)	493 (19.3%)	1.5 (1.1 to 1.9)§	160 (24.6%)	388 (20.1%)	1.6 (1.2 to 2.1)
60–79	478 (55.1%)	1261 (49.4%)	1.4 (1.1 to 1.7)§	355 (54.6%)	969 (50.1%)	1.4 (1.1 to 1.8)
≥80	141 (16.2%)	521 (20.4%)	1.0	95 (14.6%)	365 (18.9%)	1.0
Educational level						
Less than high school graduation	387 (45.2%)	1126 (44.7%)	1.0	276 (43.0%)	806 (42.4%)	1.0
High school graduation or GED¶	226 (26.4%)	629 (25.0%)	1.0 (0.9 to 1.3)	171 (26.6%)	467 (24.6%)	1.1 (0.9 to 1.3)
Some college or vocational school	151 (17.6%)	457 (18.1%)	1.0 (0.8 to 1.2)	122 (19.0%)	368 (19.4%)	1.0 (0.8 to 1.2)
College graduate or more	93 (10.9%)	308 (12.2%)	1.0 (0.7 to 1.1)	73 (11.4%)	261 (13.7%)	0.8 (0.6 to 1.1)
Ever lived or worked on a farm as an adult						
No	243 (28.1%)	780 (30.4%)	1.0	243 (37.5%)	775 (40.1%)	1.0
Yes	621 (71.9%)	1780 (69.5%)	1.1 (0.9 to 1.3)	405 (62.5%)	1157 (59.9%)	1.1 (0.9 to 1.3)
First degree relative with haematopoietic cancer						
No	792 (92.5%)	2452 (96.8%)	1.0	594 (92.8%)	1863 (96.7%)	1.0
Yes	64 (7.5%)	80 (3.2%)	2.5 (1.8 to 3.5)	46 (7.2%)	63 (3.3%)	2.3 (1.5 to 3.4)
Histological subtype						
Follicular	243 (28.0%)			196 (30.1%)		
Diffuse	334 (38.5%)			233 (35.9%)		
Small lymphocytic	99 (11.4%)			77 (11.9%)		
Other	192 (22.1%)			144 (22.2%)		

*Pooled study population limited to males and following exclusions.
†Any observation with a missing value for any of the 47 multiple pesticides was not included in analyses.
‡Odds ratios (OR) and 95% confidence limits (CL).
§Odds ratios for the matching factors are not interpretable for their relation with NHL, but are presented for comparison to odds ratios for the subgroup included in analyses of multiple pesticides.
¶GED, General Equivalency Diploma.

using logistic regression in models including variables for the joint exposure and two individual exposures, the 45 other specific pesticides, age, and study site. Where the OR for the joint effect was 1.3 or higher, positive interaction on the additive scale was evaluated using the interaction contrast ratio ($ICR = OR_{\text{joint exposure}} - OR_{\text{individual exposure \#1}} - OR_{\text{individual exposure \#2}} + 1$).[23] ICR values above 0.5 were considered indicative of superadditivity, and these pesticide combinations were further analysed using hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating joint and individual exposures to the two pesticides, as well as the other 45 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

RESULTS

Table 2 shows characteristics of men in the pooled studies. In the control population, which was representative of this part of the midwestern United States, approximately 70% of the men had lived or worked on a farm as an adult. There was a 10% increased NHL incidence associated with living or working on a farm as an adult; this increase is similar in magnitude to meta-analyses of farming and NHL mortality and morbidity.[4 23] Cases were slightly more likely than controls to have been directly interviewed, to be between the ages of 40 and 79, and they were more than twice as likely to have a first degree relative with haematopoietic cancer. The subset of subjects included in analyses of multiple pesticides was less likely than those in the overall study population to be from the Kansas or Nebraska studies, to have lived or worked on a farm as an adult, or to have had a proxy respondent, and they were slightly more likely to be more highly educated; however, the relation of these factors with case status did not differ between the overall study and the subset included in the analyses of multiple pesticides.

Use of most specific pesticides was more frequent among cases than controls; however, most of the odds ratios were not increased in the multivariable models (table 3), primarily due to adjustment for study site, since both the frequency of pesticide use and case-to-control ratios differed by study site. The results of the hierarchical regression analysis of 47 pesticides were generally similar to, but had somewhat more narrow confidence intervals than results from the logistic regression model. Only a few pesticides were associated with a possible increased NHL incidence (judged by OR ≥1.3 and lower confidence limit ≥0.8), including the organophosphate (OP) insecticides coumaphos, fonofos, and diazinon, the organochlorine insecticides chlordane and dieldrin, the insecticide copper acetoarsenite, and the herbicides atrazine, glyphosate, and sodium chlorate. There was also a significantly decreased risk associated with aldrin exposure. These suggested effects occurred in both the logistic and hierarchical regression analyses. For pesticides that had wider confidence intervals in the logistic regression model, odds ratios from the hierarchical model were generally closer to the null value, based on a priori assumptions about the probable magnitudes of effect. For example, we assumed that the effect of sodium chlorate would be similar to that of other herbicides and other pesticides for which there was a low carcinogenic probability, and that after accounting for these prior covariates, the rate ratio would likely fall within a 10-fold range around its expected value. Based on these assumptions, a fourfold risk associated with the use of sodium chlorate in the logistic regression analysis was adjusted to a 1.8-fold risk using hierarchical regression. Although unstable estimates were adjusted, results of the

Table 3 Effect estimates for use of specific pesticides and NHL incidence, adjusting for use of other pesticides*

Pesticides	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Insecticides				
Aldrin	47 (7.2%)	115 (5.9%)	0.5 (0.3 to 0.9)	0.6 (0.4 to 1.0)
Bufencarb‡	6 (0.9%)	12 (0.6%)	1.1 (0.3 to 3.7)	1.0 (0.4 to 2.3)
Carbaryl	30 (4.6%)	57 (2.9%)	1.0 (0.5 to 1.9)	1.1 (0.6 to 1.9)
Carbofuran	41 (6.3%)	96 (5.0%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.7)
Chlordane	39 (6.0%)	65 (3.4%)	1.5 (0.8 to 2.6)	1.3 (0.8 to 2.1)
Copper acetoarsenite	41 (6.3%)	68 (3.5%)	1.4 (0.9 to 2.3)	1.4 (0.9 to 2.1)
Coumaphos	15 (2.3%)	22 (1.1%)	2.4 (1.0 to 5.8)	1.7 (0.9 to 3.3)
DDT	98 (15.1%)	226 (11.7%)	1.0 (0.7 to 1.3)	1.0 (0.7 to 1.3)
Diazinon	40 (6.1%)	62 (3.2%)	1.9 (1.1 to 3.6)	1.7 (1.0 to 2.8)
Dichlorvos	16 (2.5%)	37 (1.9%)	0.9 (0.4 to 2.0)	0.9 (0.5 to 1.7)
Dieldrin	21 (3.2%)	39 (2.0%)	1.8 (0.8 to 3.9)	1.4 (0.8 to 2.6)
Dimethoate‡	5 (0.8%)	11 (0.6%)	1.2 (0.3 to 5.3)	1.2 (0.5 to 2.8)
Ethoprop‡	4 (0.6%)	14 (0.7%)	0.7 (0.2 to 2.9)	0.9 (0.4 to 2.1)
Famphur	12 (1.8%)	34 (1.8%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Fly, lice, or tick spray	162 (24.9%)	408 (21.1%)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)
Fonofos	28 (4.3%)	44 (2.3%)	1.8 (0.9 to 3.5)	1.5 (0.9 to 2.7)
Heptachlor	28 (4.3%)	53 (2.7%)	1.1 (0.6 to 2.4)	1.1 (0.6 to 2.0)
Lead arsenate	9 (1.4%)	25 (1.3%)	0.5 (0.2 to 1.2)	0.6 (0.3 to 1.3)
Lindane	59 (9.1%)	109 (5.6%)	1.2 (0.7 to 2.0)	1.2 (0.8 to 1.9)
Malathion	53 (8.1%)	100 (5.2%)	1.1 (0.6 to 1.8)	1.1 (0.7 to 1.7)
Methoxychlor	9 (1.4%)	20 (1.0%)	0.8 (0.3 to 2.1)	0.9 (0.4 to 1.9)
Nicotine	24 (3.7%)	50 (2.6%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.6)
Phorate	28 (4.3%)	67 (3.5%)	0.8 (0.4 to 1.6)	0.9 (0.5 to 1.5)
Pyrethrins‡	6 (0.9%)	12 (0.6%)	1.0 (0.3 to 3.2)	1.0 (0.4 to 2.3)
Rotenone	10 (1.5%)	26 (1.4%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Tetrachlorvinphos‡	3 (0.5%)	11 (0.6%)	0.4 (0.1 to 1.8)	0.8 (0.3 to 1.9)
Toxaphene	17 (2.6%)	34 (1.8%)	1.1 (0.5 to 2.4)	1.1 (0.6 to 2.0)
Terbufos	21 (3.2%)	50 (2.6%)	0.8 (0.4 to 1.8)	0.8 (0.5 to 1.6)
Herbicides				
Alachlor	68 (10.5%)	152 (7.9%)	1.1 (0.7 to 1.8)	1.0 (0.6 to 1.6)
Atrazine	90 (13.8%)	185 (9.6%)	1.6 (1.1 to 2.5)	1.5 (1.0 to 2.2)
Bentazon	22 (3.4%)	58 (3.0%)	0.7 (0.3 to 1.5)	0.8 (0.4 to 1.4)
Butylate	28 (4.3%)	56 (2.9%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.0)
Chloramben	34 (5.2%)	81 (4.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.5)
Cyanazine	37 (5.7%)	96 (5.0%)	0.6 (0.3 to 1.0)	0.6 (0.4 to 1.1)
2,4-D	123 (18.9%)	314 (16.2%)	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.2)
Dicamba	39 (6.0%)	79 (4.1%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.1)
EPTC + protectant	13 (2.0%)	29 (1.5%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Glyphosate	36 (5.5%)	61 (3.2%)	2.1 (1.1 to 4.0)	1.6 (0.9 to 2.8)
Linuron	5 (0.8%)	22 (1.1%)	0.3 (0.1 to 1.2)	0.5 (0.2 to 1.2)
MCPA	8 (1.2%)	16 (0.8%)	1.0 (0.4 to 2.6)	0.9 (0.4 to 2.0)
Metolachlor	13 (2.0%)	37 (1.9%)	0.7 (0.3 to 1.6)	0.7 (0.4 to 1.5)
Metribuzen	20 (3.1%)	53 (2.7%)	0.8 (0.4 to 1.7)	0.8 (0.4 to 1.5)
Paraquat‡	2 (0.3%)	15 (0.8%)	0.1 (0.02 to 0.7)	0.5 (0.2 to 1.2)
Propachlor	20 (3.1%)	50 (2.6%)	1.0 (0.5 to 2.0)	1.0 (0.6 to 1.9)
Sodium chlorate‡	8 (1.2%)	7 (0.4%)	4.1 (1.3 to 13.6)	1.8 (0.8 to 4.1)
2,4,5-T	25 (3.9%)	63 (3.3%)	1.0 (0.5 to 1.9)	0.9 (0.5 to 1.6)
Trifluralin	52 (8.0%)	120 (6.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.4)

*Each estimate is adjusted for use of all other pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).
‡Criteria for inclusion in the models was a pesticide use frequency of ≥20; however, some pesticide use frequencies are <20 in the multivariable models since observations with missing values were dropped.

hierarchical model including prior covariates and those from the hierarchical intercept-only model were virtually identical (results for intercept-only model not shown), indicating that the prior covariates representing pesticide category and carcinogenic probability were not important determinants of the variability between the observed effects, and that adjustment of estimates primarily occurred because of the a priori restriction on their variance. Indeed, a linear regression analysis of the 47 logistic regression beta coefficients for the pesticides regressed on the prior covariates found no statistically significant associations (at a significance level of $p < 0.05$; results not shown).

Among the farmers who used pesticides, the number of total pesticides ever used ranged between 1 and 32, but approximately 50% of farmers reported using only one or two pesticides. There was no association between NHL incidence and either the total number of pesticides or herbicides used (see table 4). There was a 40% increased incidence associated with the use of five or more insecticides; however, there was no apparent exposure-response trend. In an analysis of the number of "potentially carcinogenic" pesticides, NHL incidence increased by the number of pesticides used by the subject. Subjects who reported using any five or more "potentially carcinogenic" pesticides were twice as likely to be NHL cases than controls, compared to those using no pesticides. The results for "potentially carcinogenic" pesticides were highly sensitive to removal of certain pesticides from the count, including dieldrin, atrazine, or glyphosate. For example, removal of glyphosate from the count resulted in a lack of trend for increasing number of "potentially carcinogenic" pesticides (1 pesticide: OR = 1.2; 2–4 pesticides: OR = 1.2; ≥5 pesticides: OR = 1.1).

Table 4 Effect of number of pesticides used on NHL incidence*

Number of pesticides used	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Any pesticide				
0	370	1252	1.0	1.0
1	89 (13.7%)	230 (11.9%)	1.2 (0.8 to 1.8)	1.1 (0.9 to 1.7)
2–4	87 (13.4%)	221 (11.4%)	1.0 (0.6 to 1.6)	1.0 (0.7 to 1.5)
≥5	104 (16.0%)	230 (11.9%)	0.8 (0.4 to 1.9)	1.0 (0.5 to 1.8)
Any insecticide				
0	382	1292	1.0	1.0
1	114 (17.5%)	281 (14.5%)	1.3 (0.9 to 1.9)	1.2 (0.9 to 1.7)
2–4	86 (13.2%)	237 (12.3%)	1.0 (0.5 to 1.8)	0.9 (0.6 to 1.4)
≥5	68 (10.5%)	123 (6.4%)	1.9 (0.6 to 5.7)	1.4 (0.7 to 2.9)
Any herbicide				
0	489	1544	1.0	1.0
1	50 (7.7%)	132 (6.8%)	1.0 (0.6 to 1.9)	1.1 (0.7 to 1.7)
2–4	52 (8.0%)	132 (6.8%)	0.8 (0.4 to 1.9)	1.0 (0.6 to 1.6)
≥5	59 (9.1%)	125 (6.5%)	0.8 (0.2 to 3.3)	1.0 (0.5 to 2.2)
"Potentially carcinogenic" pesticides				
0	496	1632	1.0	1.0
1	74 (11.4%)	168 (8.7%)	1.6 (0.8 to 3.1)	1.1 (0.8 to 1.7)
2–4	68 (10.5%)	123 (6.4%)	2.7 (0.7 to 10.8)	1.3 (0.7 to 2.3)
≥5	12 (1.8%)	10 (0.5%)	25.9 (1.5 to 450.2)	2.0 (0.8 to 5.2)

*Each estimate is adjusted for use of all pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).

The analysis of 48 pesticide combinations in relation to NHL incidence revealed few joint effects of 1.3 or higher that were indicative of superadditivity (table 5). Combined exposures to carbofuran and atrazine, diazinon and atrazine, and alachlor and atrazine had estimated joint effects that were more than additive (ICR ≥0.5), even following shrinkage in hierarchical regression analyses. Other joint pesticide effects which seemed indicative of superadditivity in results from logistic regression analyses, such as that for atrazine and dicamba, were probably misleading due to imprecision of estimates; these results did not hold up following shrinkage in hierarchical regression analyses, according to our prior distribution of complete exchangeability.

DISCUSSION

Incidence and mortality rates for NHL have been generally increasing in the United States and in most industrialised countries for several decades, with an 85–100% increase in

Table 5 Estimated individual and joint effects of pesticide combinations on NHL incidence*†

Individual and joint pesticide exposures	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)‡	Hierarchical regression OR (95% CL)
Chlordane and DDT				
Neither	543	1687	1.0	1.0
Chlordane only	9 (1.4%)	20 (1.0%)	1.1 (0.4 to 2.7)	1.0 (0.5 to 1.9)
DDT only	68 (10.5%)	181 (9.4%)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.2)
Both	30 (4.6%)	45 (2.3%)	1.7 (0.7 to 3.2)	1.3 (0.8 to 2.3)
Carbofuran and atrazine				
Neither	557	1728	1.0	1.0
Carbofuran only	3 (0.5%)	20 (1.0%)	0.2 (0.1 to 1.1)	0.6 (0.3 to 1.3)
Atrazine only	52 (8.0%)	109 (5.6%)	1.4 (0.9 to 2.2)	1.3 (0.9 to 1.9)
Both	38 (5.9%)	76 (3.9%)	1.6 (0.8 to 3.3)	1.5 (0.9 to 2.7)
Diazinon and atrazine				
Neither	551	1730	1.0	1.0
Diazinon only	9 (1.4%)	18 (0.9%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Atrazine only	59 (9.1%)	141 (7.3%)	1.5 (1.0 to 2.3)	1.3 (0.9 to 1.9)
Both	31 (4.8%)	44 (2.3%)	3.9 (1.7 to 8.8)	2.3 (1.2 to 4.2)
Alachlor and atrazine				
Neither	545	1695	1.0	1.0
Alachlor only	15 (2.3%)	53 (2.7%)	0.7 (0.3 to 1.3)	0.7 (0.4 to 1.3)
Atrazine only	37 (5.7%)	86 (4.5%)	1.3 (0.8 to 2.1)	1.2 (0.8 to 1.8)
Both	53 (8.2%)	99 (5.1%)	2.1 (1.1 to 3.9)	1.6 (1.0 to 2.7)
Atrazine and dicamba				
Neither	552	1729	1.0	1.0
Atrazine only	59 (9.1%)	125 (6.5%)	1.5 (1.0 to 2.4)	1.4 (0.9 to 2.0)
Dicamba only	8 (1.2%)	19 (1.0%)	0.9 (0.3 to 2.6)	1.0 (0.5 to 2.0)
Both	31 (4.8%)	60 (3.1%)	2.1 (1.0 to 4.7)	1.6 (0.9 to 2.9)

*Effects of combined pesticide exposures were estimated in models including terms for the joint exposure, two individual exposures, the use of each other pesticide listed in table 2, age, and study site.
†Pesticide combinations considered are listed in the appendix.
‡Odds ratios (OR) and 95% confidence limits (CL).

mortality among whites and non-whites from the late 1940s to the late 1980s,[20] a time period relevant for this study. This increase may be partially attributed to improved diagnosis and in later years to AIDS related lymphomas, but cannot be completely explained by these factors.[20] Environmental factors such as pesticides could play a role in this persistent increase, since their use became more widespread during this time period.[20–22] Several aetiological mechanisms of pesticides in relation to NHL have been proposed, including genotoxicity and immunotoxicity,[11 12] increased cell proliferation,[13] and chromosomal aberrations.[14] In our analysis of multiple pesticides in farming, we found only a small number of the pesticides to be risk factors for NHL, with the highest increased risks among subjects exposed to five or more of these "potentially carcinogenic" pesticides, or those with certain combined pesticide exposures.

The large number of exposed subjects in this pooled analysis allowed adjustment for the use of other pesticides, and hierarchical regression modelling resulted in estimates that were in some instances more stable than those from logistic regression models. However, the effect estimates from the logistic and hierarchical analyses were quite similar overall, with a few standout exceptions. The hierarchical results are more conservative than those from the logistic regressions, given the uninformed nature of the prior distributions we specified, particularly in analyses of the number of pesticides used and combined pesticide exposures. For example, in the hierarchical regression analysis of the number of pesticides used, we assumed that the use of any five or more pesticides was no more likely to be associated with NHL than use of any one pesticide. A less conservative prior distribution could have been specified in which a higher probability would be placed on a positive association for the greater number of pesticides used. However, the uninformed nature of these priors seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL. Both analyses showed increasing odds ratios with the number of "potentially carcinogenic" pesticides used, but the relative risks in the upper category were substantially different—25.9 for the logistic regression and 2.0 for the hierarchical analysis—probably indicating inappropriate use of logistic regression for these sparse data.

Adjustment for multiple pesticides suggested that there were few instances of substantial confounding of pesticide effects by other pesticides. Nevertheless, some previous findings in our data appear to be due to confounding by correlated pesticide exposures. In particular, a previously reported positive association for carbaryl[15] was not replicated in the adjusted analyses. Further analysis here revealed that carbaryl and diazinon use were highly associated ($p < 0.001$), and previously reported associations of different carbaryl measures with NHL were eliminated by adjustment for diazinon, including carbaryl use, personal handling of carbaryl, and use longer than 10 years. In the previous analysis, estimates were adjusted for groups of pesticides, including a group for organophosphate insecticides,[15] but adjustment for specific pesticides here gave different results. Similarly, previous observations of increased NHL risk associated with use of the OP insecticides dimethoate and tetrachlorvinphos[16] were negligible on inclusion of other OP insecticides in the model. These findings underscore the importance of considering correlated pesticide exposures.

Our observation of increased risk associated with the use of certain OP insecticides, including coumaphos, diazinon, and fonofos, is consistent with previous analyses of the pooled data,[15 16] and also corroborates findings of other studies.[7–9] OP insecticides are known to cause cytogenetic damage, and could thereby contribute to NHL aetiology.[23] There are data from in vitro, animal, and human studies that show effects of several OP insecticides on the immune system,[24–40] indicating another potential mechanism. OP compounds may impair immune function through pathways involving cholinergic stimulation,[41] or inhibition of serine esterases found in monocytes, natural killer cells, and cytotoxic T lymphocytes,[42] but it is unknown whether such immune effects might be chemical specific or related to general OP toxicity. Our data do not indicate an aetiological mechanism for NHL common to all OP insecticides, since increased NHL incidence was associated only with certain OPs evaluated.

We observed a possible effect of the organochlorine insecticides chlordane and dieldrin. There is some evidence that chlordane is immunotoxic, causing decreased lymphocyte function in vitro.[43] The concentration of chlordane in adipose tissue was higher among NHL cases than controls in a small case-control study in Sweden,[44] but a larger study in the United States found no such association.[45] Although these chemicals have been banned in the United States, their continued use in some developing countries, and bioaccumulation of their chemical residues in the food chain,[46] justify further research on health effects.

Use of the herbicide atrazine was associated with increased risk of NHL. Increased risk was observed in each of the three pooled studies separately, but a previous analysis of the Nebraska study data found that the risk was diminished on adjustment for use of OP insecticides and 2,4-D.[20] There have been few other epidemiological studies of atrazine in relation to NHL. In a cohort of triazine herbicide manufacturing workers, there was an excess number of deaths from NHL ($n = 3$) among a group of men with definite or probable exposure; however, some of the cases worked in triazine related jobs for short time periods, thus clouding interpretation.[47] A recent NHL study where cases were further distinguished by presence or absence of the t(14;18) chromosomal translocation found that the risk of NHL associated with atrazine use was solely observed among t(14;18) positive cases, suggesting a cytogenetic mechanism.[14] However, there is only very limited evidence for genotoxicity of atrazine, although there are no studies in humans.[48] A small number of studies of atrazine on immune function in rodents and in vitro suggest a decreased lymphocyte count and cytokine production following exposure; however, these effects were not always dose dependent or statistically significant.[17 48–50] In our data, there was an indication of supradditive effects of atrazine in combination with carbofuran, diazinon, or alachlor. This is a factor to consider in future studies of this widely used pesticide.

Glyphosate, commercially sold as Roundup, is a commonly used herbicide in the United States, both on crops and on non-cropland areas.[51] An association of glyphosate with NHL was observed in another case-control study, but the estimate was based on only four exposed cases.[52] A recent study across a large region of Canada found an increased risk of NHL associated with glyphosate use that increased by the number of days used per year.[6] These few suggestive findings provide some impetus for further investigation into the potential health effects of glyphosate, even though one review concluded that the active ingredient is non-carcinogenic and non-genotoxic.[53]

Much attention in NHL research has focused on the herbicide 2,4-D as a potential risk factor, and several studies have observed positive associations with 2,4-D exposure.[4 8 9] Whereas an indicated effect of 2,4-D exposure on NHL was reported in NCI's Nebraska and Kansas studies,[7] this analysis of the pooled data found no association with having ever used 2,4-D. The null association does not result from adjustment for other pesticides, missing data, or from the hierarchical regression modelling approach, but is rather due to pooling data from the Iowa and Minnesota study, in which no association of 2,4-D with NHL incidence was observed, with data from the Nebraska and Kansas studies. The literature on the relation between 2,4-D and NHL is not consistent.[12 54] Some recent studies have reported excess risk among

manufacturers[23] and farmers,[6] while others have not.[31] The study in Nebraska,[7] however, observed that NHL risk increased by number of days per year of 2,4-D use, which we were unable to duplicate in the pooled analysis because of lack of such data from the other two studies. It is possible that a more refined metric incorporating frequency of use better captures relevant exposure. Some recent studies may shed light on potential mechanisms of 2,4-D in relation to NHL. A study of 10 farmers who applied 2,4-D and MCPA observed a significant reduction of several immune parameters, including CD4, CD8, natural killer cells, and activated CD8 cells (expressing the surface antigen HLA-DR), and a reduction in lymphoproliferative response.[34] Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.[35]

This pooled study of multiple agricultural pesticides provided an opportunity to estimate the effect of each specific pesticide and certain pesticide combinations on NHL incidence, adjusted for the use of other pesticides. Overall, few pesticides and pesticide combinations were associated with increased NHL risk; this has several implications. First, it is consistent with results from bioassays where only a few of the pesticides tested have caused cancer in laboratory animals.[35] Although epidemiological data on cancer risks from exposure to specific pesticides are scant, it also suggests that while some pesticides may present a cancer risk to humans, many, maybe even most, pesticides do not. Second, the fact that there were few associations suggests that the positive results we observed are not likely to be due to a systematic recall bias for pesticide exposures, or selection bias for the subgroup included in the analyses of multiple pesticides. Third, although some of the positive results could be due to chance, the hierarchical regression analysis placed some restriction on the variance of estimates, theoretically decreasing the chances of obtaining false positive results. On the other hand, it is possible that the assumptions for the hierarchical regression are too restrictive and that this has increased the number of false negatives.

Certain limitations of our data hinder the inferences we can make regarding specific pesticides in their association with NHL. Our exposure metric of having ever used a pesticide is rather crude, offering no distinctions based on use by the number of years or the number of days per year. Further exploration of observed associations by more refined exposure metrics is warranted. In addition, this analysis provides no information on the timing of pesticide use in relation to disease onset or in conjunction with the timing of other pesticides used. This has particular relevance in our analysis of "combined pesticide exposures", in which two pesticides may or may not have been used at the same time or even during the same year. Lastly, if a study subject had a missing value for any one of the 47 pesticides evaluated, that person was excluded from analyses, resulting in analyses on a limited subset (about 75%) of the pooled study population. Although we have no way to evaluate potential bias due to missing data, some assurances are provided by the fact that cases and controls were equally likely to be included in analyses, and that there were similarities between the entire group of study subjects and subjects included our analyses, in terms of NHL status in relation to demographic factors (table 2). If simultaneous analysis of multiple exposures is to become standard, statistical techniques to impute values for subjects with "don't know" or missing responses should be further developed in order to prevent biased results.

Despite limitations of our study, certain inferences are possible. Our results indicate increased NHL incidence by number of pesticides used, only for the subgroup of "potentially carcinogenic" pesticides, suggesting that specific chemicals, not pesticides, insecticides, or herbicides, as groups, should be examined as potential risk factors for NHL. In addition, argument against an analysis approach focused on classes or groups of pesticides is provided by the fact that our prior covariates of pesticide classes and groups in the hierarchical regression model were not important predictors of the magnitude of observed pesticide effects. A chemical specific approach to evaluating pesticides as risk factors for NHL should facilitate interpretation of epidemiological studies for regulatory purposes. However, the importance of additionally considering multiple correlated exposures is clear.

APPENDIX

Table A1 shows the pesticide combinations considered in analyses of joint and individual exposures.

Table A1 Pesticide combinations considered in analyses of joint and individual exposures

Insecticides	Insecticide and herbicide	Herbicides
DDT and chlordane	Aldrin and alachlor	Alachlor and atrazine
DDT and lindane	Aldrin and atrazine	Alachlor and chloramben
DDT and malathion	Aldrin and 2,4-D	Alachlor and cyanazine
DDT and fly, lice, or tick spray	Aldrin and trifluralin	Alachlor and 2,4-D
DDT and aldrin	Carbofuran and alachlor	Alachlor and dicamba
Lindane and malathion	Carbofuran and atrazine	Alachlor and glyphosate
Lindane and aldrin	Carbofuran and 2,4-D	Alachlor and trifluralin
Malathion and aldrin	Chlordane and 2,4-D	Atrazine and cyanazine
	DDT and alachlor	Atrazine and 2,4-D
	DDT and atrazine	Atrazine and dicamba
	DDT and 2,4-D	Atrazine and glyphosate
	DDT and trifluralin	Atrazine and trifluralin
	Diazinon and atrazine	Chloramben and trifluralin
	Fly, lice, or tick spray and alachlor	Cyanazine and 2,4-D
	Fly, lice, or tick spray and atrazine	Cyanazine and trifluralin
	Fly, lice, or tick spray and 2,4-D	2,4-D and trifluralin
	Fly, lice, or tick spray and trifluralin	
	Lindane and alachlor	
	Lindane and atrazine	
	Lindane and 2,4-D	
	Lindane and trifluralin	
	Malathion and alachlor	
	Malathion and atrazine	
	Malathion and 2,4-D	

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Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis

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We report a population based case–control study of exposure to pesticides as risk factor for non-Hodgkin lymphoma (NHL). Male and female subjects aged 18–74 years living in Sweden were included during December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total 910 (91%) cases and 1016 (92%) controls participated. Exposure to herbicides gave odds ratio (OR) 1.72, 95% confidence interval (CI) 1.18–2.51. Regarding phenoxyacetic acids highest risk was calculated for MCPA; OR 2.81, 95% CI 1.27–6.22, all these cases had a latency period >10 years. Exposure to glyphosate gave OR 2.02, 95% CI 1.10–3.71 and with >10 years latency period OR 2.26, 95% CI 1.16–4.40. Insecticides overall gave OR 1.28, 95% CI 0.96–1.72 and impregnating agents OR 1.57, 95% CI 1.07–2.30. Results are also presented for different entities of NHL. In conclusion our study confirmed an association between exposure to phenoxyacetic acids and NHL and the association with glyphosate was considerably strengthened.
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Key words: phenoxyacetic acids; MCPA; glyphosate; insecticides; impregnating agents; non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies, where new classification systems based on immunohistochemistry, cytogenetics and evolving knowledge in clinical presentation and course has lead to modern classification systems.[1] Today, it is therefore more adequate to discuss NHL as many different diseases, which share some features but also differ in several aspects.

Interest in the etiology of NHL has been strengthened by an observed substantial increase in the incidence of the disease from the 1960's to the 1980's as reported from most countries with reliable cancer registries. However, this increase has clearly leveled off in many countries since the early 1990's, *i.e.*, in Sweden, Denmark and the USA.[2] The established risk factors for development of NHL include different immunosuppressive states, *e.g.*, human immunodeficiency virus (HIV), autoimmune diseases as Sjögren's syndrome and systemic lupus erythematosus (SLE), immunodepressants used after organ transplantation and some inherited conditions, for review see *e.g.*, Ref. 3. However, these causes may only explain a minority of cases, with a possible exception for HIV-related increases among younger persons in certain areas.[4]

It has been shown that Epstein-Barr virus (EBV) plays an essential role in the pathogenesis of lymphomas after organ transplantation.[5] A relation between lymphoma and elevated EBV-titers has been reported in a cohort.[6] Normally, EBV-production is held back by active cellular and humoral immune mechanisms. In immunodeficiency states this balance is disrupted and EBV-infected B-cells begin to proliferate.[7]

During the last decades, research on the etiology of NHL has been directed towards other potential causes such as pesticides, which may explain the impressive increase in the incidence. Today, it is also reasonable to consider the leveling off in incidence as a probable consequence of a reduced carcinogenic influence related to NHL. Furthermore, our emerging knowledge concerning the spectrum of NHL subgroups makes it reasonable to investigate causative agents for these different types of disease.

In 1981, we published results from a case–control study from Sweden, indicating statistically significant increased odds ratios for NHL and Hodgkin lymphoma (HL) in persons who had been exposed to phenoxyacetic herbicides or impregnating chlorophenols.[8] Our study was initiated by a case report.[9] Some of these chemicals were contaminated by dioxins, of which 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been recognised as a complete carcinogen by IARC.[10] Furthermore, these and several other related chemicals are immunotoxic.[11–15] Our results have been confirmed in some other studies, regarding phenoxyacetic herbicides from *e.g.*, Kansas[16] and Nebraska.[17]

Furthermore, in 1999 we reported a new case–control study performed to evaluate more recent exposure to pesticides and other chemicals, and we could thereby confirm our earlier findings regarding a relation with phenoxyacetic herbicides that was related to latency period.[18]

In that study, however, some newer compounds that are widely used today, such as the herbicide glyphosate, were still not very common. During the 1970's certain chemicals, *e.g.*, the phenoxy herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), chlorophenols, and the insecticide dichlorodiphenyltrichloroethane (DDT), were prohibited due to health concerns. Later also the phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was banned in Sweden. Reporting of these agents is therefore nowadays much less likely. It is also probable that the risk pattern has been influenced by protective measures during the last decades.

To further evaluate the relation between exposure to pesticides and other chemicals, focusing also on newer types of compounds, we have performed a new case–control study in Sweden. In our study we have also evaluated exposures in relation to different histopathological subtypes according to the most recent classification.[1]

Material and methods

The study covered 4 out of 7 health service regions in Sweden, associated with the University Hospitals in Lund, Linköping, Örebro and Umeå, and was approved by the ethics committees. Data were collected during December 1, 1999, to April 30, 2002, which was the time period for diagnosis of the cases. Regarding recruitment of cases and controls collaboration was established with another research group, which at the same time performed a parallel study on NHL in Sweden and Denmark.

Cases

All consecutive patients aged 18–74 years with newly diagnosed NHL, identified through physicians treating lymphoma and through pathologists diagnosing the disease, were approached if their physician did not judge this as less appropriate by ethical rea-

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sons. This was done regardless of whether the person had accepted to participate in the parallel study with which we collaborated in the recruitment procedure. If they accepted to participate they were included as potential cases, and went through the data assessment procedure described below. No cases were excluded because of specific conditions potentially associated with NHL, but no cases with *e.g.*, HIV or postransplantation NHL occurred. All the diagnostic pathological specimens were scrutinised by 1 out of 5 Swedish expert lymphoma reference pathologists, if they had not been initially judged by one of these 5. About 70% of all included cases were reviewed, whereas the remaining had been previously classified by one of the reference pathologists. If there was a disagreement from the original report the sample was reviewed by a panel of these pathologists. Therefore, some potential cases could later be excluded if a NHL diagnosis was not verified, and in those occasions all collected exposure information was disregarded. The pathologists also subdivided all NHL cases according to the WHO classification,[1] to enable etiological analyses also for the different diagnostic NHL entities. Since all lymphoma treating clinics and all lymphoma pathologists in the involved regions were covered by the study, it may well be regarded as population based, although the possibility of some individuals not reported through the case ascertainment system used.

Controls

From the population registry covering whole Sweden, randomly chosen controls living in the same health service regions as the cases were recruited during several occasions within the study period. The controls were frequency-matched in 10 years age and sex groups to mirror the age and sex distribution of the included cases, and to increase efficacy in the adjusted analyses. If they accepted to participate, they were included as controls.

Assessment of exposure

All subjects who accepted to participate received a comprehensive questionnaire, which was sent out shortly after the subjects had been telephone interviewed by the other research group we had collaboration with as stated earlier. Their interview, however, did not focus on work environment or chemical exposure, but rather dealt with other life style factors and diseases. Our questionnaire included a total work history with in depth questions regarding exposure to pesticides, organic solvents and several other chemicals. For all pesticides not only numbers of years and numbers of days per year, but also approximate length of exposure per day were questioned. Since most work with pesticides was performed in an individualized manner, no job-exposure matrix was judged to be applicable. Furthermore, the questionnaire also included questions on *e.g.*, smoking habits, medications, leisure time activities and proximity from home to certain industrial installations, but data on these factors are not included in this article.

Specially trained interviewers scrutinized the answers and collected additional exposure information by phone if important data were lacking, incomplete or unclear. These interviewers were blinded with regard to case/control status. All exposures during the same calendar year as the diagnosis and the year before were disregarded in the cases. Correspondingly, the year of enrolment and the year before were disregarded for the controls. As in our previous lymphoma studies we used a minimum criterion of one full day exposure to be categorized as exposed.[8,18]

Statistical methods

Unconditional logistic regression analysis (Stata/SE 8.2 for Windows; StataCorp, College Station, TX) was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis (cases) or enrolment (controls). In the univariate analysis, different pesticides were analyzed separately and the unexposed category consisted of subjects that were unexposed to all included pesticides. When analyzing subgroups of NHL all controls were used in the separate analyses. In the dose-response calculations made for agents with at least 20 exposed subjects, median number of days of exposure among controls was used as cut-off. Latency period calculations and multivariate analyses included agents with statistically significant increased OR, or with an OR > 1.50 and at least 10 exposed subjects.

TABLE I – NON-HODGKIN LYMPHOMA CASES DIVIDED ON HISTOPATHOLOGICAL SUBTYPES ACCORDING TO WHO CLASSIFICATION.

WHO diagnosis	Number of cases
B-cell lymphomas, total	819
Lymphocytic lymphoma/B-CLL (SLL/CLL)	195
Follicular, grade I–III (FL)	165
Diffuse large B-cell lymphoma (DLBCL)	239
Other specified B-cell lymphoma	131
Unspecified B-cell lymphoma	89
T-cell lymphomas	53
Unspecified non-Hodgkin lymphoma	38
Total	910

Results

In total, 1,163 cases were reported from the participating clinics. Of these, 46 could not participate because of medical conditions, 88 died before they could be interviewed. Since these were primarily excluded by the reporting physicians we had no information on *e.g.*, final WHO categories on these cases. Three NHL cases were not diagnosed during the study period, 1 lived outside the study area and 30 were excluded not being NHL (HL 20, acute lymphoblastic leukaemia 1, other malignancy 7 and unclear diagnosis 2). Of the finally included 995 cases with NHL, 910 (91%) accepted to participate and answered the questionnaire. Of these, 819 were B-cell, 53 T-cell and 38 unspecified lymphomas, Table I.

Among the 1,108 initially enrolled controls 92 did not respond to the mail questionnaire, resulting in 1,016 (92%) controls to be included in the analyses.

The medium and median age in cases was 60 and 62 years, and in controls it was 58 and 60 years, respectively. Of the cases, 534 were males and 376 females, and of the controls the corresponding numbers were 592 and 424.

This report presents exposure data regarding different types of pesticides.

Herbicides

Exposure to herbicides gave for all NHL OR 1.72 (95% CI 1.18–2.51), Table II. Exposure to phenoxyacetic acids yielded OR 2.04 (95% CI 1.24–3.36). This group was further subdivided in 3 categories; (*i*) 4-chloro-2-methyl phenoxyacetic acid (MCPA), which is still on the market and not known to be contaminated by dioxins; (*ii*) 2,4,5-T and/or 2,4-D which often were used together and were potentially contaminated with different dioxin isomers; (*iii*) other types. MCPA seemed to give the most pronounced increase in OR. Exposure to other herbicides, regardless if they also had been exposed to phenoxyacetic acids or not, also gave a statistically significant OR 1.82 (95% CI 1.08–3.06). In this category the dominating agent was glyphosate, which was reported by 29 cases and 18 controls, which produced OR 2.02 (95% CI 1.10–3.71). If both phenoxyacetic acids and glyphosate were excluded, exposure to other herbicides (37 different agents reported, but no one by more than 6 subjects at most) gave a nonsignificant OR of 1.22 (95 % CI 0.63–2.39).

Dose-response analyses regarding herbicides in total and glyphosate yielded an increased OR in the higher exposed group, Table II. For phenoxyacetic acids, however, no such association was demonstrated.

Regarding phenoxy herbicides and glyphosate an analysis was made taken the latency period for exposure into account. For the

latency period 1–10 years no exposed cases were found for MCPA and 2,4,5-T and/or 2,4-D. Regarding glyphosate OR 1.11 (95% CI 0.24–5.08) was obtained. Latency period >10 years yielded for MCPA OR 2.81 (95% CI 1.27–6.22), for 2,4,5-T and/or 2,4,-D OR 1.72 (95% CI 0.98–3.19), and for glyphosate OR 2.26 (95% CI 1.16–4.40).

When different NHL entities were analysed separately, the OR for the subtype small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) was increased for both phenoxy herbicides and, especially, glyphosate, Table III. The entity diffuse large B-cell lymphoma (DLBCL) was significantly associated with exposure to phenoxyacetic acids, but not to other herbicides. On the other hand, the group follicular lymphoma was not clearly associated with phenoxyacetic acids, and only nonsignificantly with glyphosate. The category "other specified B-cell lymphoma" (*e.g.*, mantle cell lymphoma, marginal zone lymphoma) was significantly associated with exposure to phenoxyacetic acids, and an increased risk was also indicated for glyphosate. T-cell lymphomas seemed to be associated with all types of herbicides, but no statistically significant ORs were found due to relatively few exposed subjects. The least numerous categories ("unspecified NHL") yielded high and statistically significant ORs for phenoxy herbicides and glyphosate.

TABLE II – EXPOSURE TO VARIOUS HERBICIDES

Agents	Cases/controls	OR	CI
Herbicides, total	74/51	1.72	1.18–2.51
≤20 days	36/27	1.58	0.95–2.65
>20 days	38/24	1.87	1.10–3.18
Phenoxyacetic acids	47/26	2.04	1.24–3.36
≤45 days	32/13	2.83	1.47–5.47
>45 days	15/13	1.27	0.59–2.70
MCPA	21/9	2.81	1.27–6.22
≤32 days	15/5	3.76	1.35–10.5
>32 days	6/4	1.66	0.46–5.96
2,4,5-T and/or 2,4-D	33/21	1.61	0.87–2.97
≤29 days	21/11	2.08	0.99–4.38
>29 days	12/10	1.33	0.57–3.13
Other	7/7	1.21	0.42–3.48
Herbicides except phenoxyacetic acids	38/26	1.82	1.08–3.06
≤24 days	20/13	1.91	0.93–3.89
>24 days	18/13	1.73	0.84–3.60
Glyphosate	29/18	2.02	1.10–3.71
≤10 days	12/9	1.69	0.70–4.07
>10 days	17/9	2.36	1.04–5.37
Other herbicides	18/18	1.22	0.63–2.39
≤32 days	12/9	1.64	0.68–3.96
>32 days	6/9	0.80	0.28–2.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. Adjustment was made for age, sex and year of diagnosis or enrolment.

Insecticides

In our study no overall increased OR was demonstrated for exposure to insecticides, OR 1.28 (95% CI 0.96–1.72), Table IV. The most reported insecticide DDT yielded OR 1.46 (95% CI 0.94–2.28). Increased risk was shown for mercurial seed dressing, OR 2.03 (95% CI 0.97–4.28).

In the dose-response analysis, OR 1.47 (95% CI 0.99–2.16) was found for the high category of insecticide exposure, Table IV. Similar trends were found for DDT and mercurial seed dressing.

Different NHL entities were analysed separately, Table V. Hereby, certain exposures seemed to be associated with subtypes of NHL. Thus, the group follicular lymphoma was associated with DDT, OR 2.14 (95% CI 1.05–4.40) and mercurial seed dressing, OR 3.61 (95% CI 1.20–10.9). Furthermore, exposure to DDT increased the risk also for T-cell lymphoma, OR 2.88 (95% CI 1.05–7.95).

Fungicides and rodenticides

Exposure to fungicides was not a risk factor in our study, neither in total, OR 1.11 (95% CI 0.56–2.23), Table IV, nor for different subtypes of NHL, Table VI. Furthermore, there were no single substances among 24 reported that significantly differed between cases and controls. Also for rodenticides no increased risk was found, Table IV.

Impregnating agents

Exposure to impregnating agents yielded a statistically significant OR 1.57 (95% CI 1.07–2.30), Table IV. In a dose-response calculation OR increased further in the high exposure group. Creosote showed a statistically significant OR for high exposure, OR 3.33 (95% CI 1.20–9.27).

Table VI presents results for different NHL entities. An increased risk for SLL/CLL was associated with exposure to impregnating agents in total, and most pronounced for creosote,

TABLE III – EXPOSURE TO VARIOUS HERBICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Herbicides, total	Phenoxyacetic acids (ph)	MCPA	2,4,5-T and/or 2,4-D	Herbicides except ph	Glyphosate	Other
B-cell lymphomas, total (n = 819)	1.68 1.14–2.48	1.99 1.20–3.32	2.59 1.14–5.91	1.69 0.94–3.01	1.72 1.003–2.94	1.87 0.998–3.51	1.14 0.57–2.31
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	2.27 1.28–4.01	2.11 0.995–4.47	2.57 0.74–8.97	1.93 0.85–4.41	2.56 1.17–5.60	3.35 1.42–7.89	1.39 0.45–4.31
Follicular, grade I–III (n = 165) (FL)	1.78 0.88–3.59	1.26 0.42–3.75	–[1]	1.21 0.35–4.22	2.32 0.96–5.60	1.89 0.62–5.79	1.48 0.42–5.23
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.44 0.81–2.59	2.16 1.08–4.33	3.94 1.48–10.5	1.65 0.71–3.82	1.20 0.51–2.83	1.22 0.44–3.35	1.00 0.33–3.03
Other specified B-cell lymphoma (n = 131)	1.62 0.82–3.19	2.60 1.20–5.64	3.20 0.95–10.7	2.21 0.90–5.44	1.38 0.51–3.73	1.63 0.53–4.96	1.15 0.33–4.03
Unspecified B-cell lymphoma (n = 89)	1.09 0.41–2.89	1.14 0.33–3.95	1.35 0.16–11.2	0.88 0.20–3.92	1.52 0.44–5.27	1.47 0.33–6.61	0.71 0.09–5.53
T-cell lymphomas (n = 53)	1.64 0.55–4.90	1.62 0.36–7.25	2.40 0.29–20.0	1.02 0.13–7.95	1.57 0.35–6.99	2.29 0.51–10.4	2.24 0.49–10.3
Unspecified non-Hodgkin lymphoma (n = 38)	2.86 1.001–8.18	3.75 1.16–12.1	9.31 2.11–41.2	3.21 0.85–12.1	5.29 1.60–17.5	5.63 1.44–22.0	1.88 0.23–15.4

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases

OR 2.91 (95% CI 1.01–8.33). Regarding follicular lymphomas and DLBCL, increased risks were also noted after creosote exposure, and for the latter subtype this was also the case for all impregnating agents together. T-cell lymphomas were also associated with impregnating agents, and it seemed to be specifically chlorophenols. In the group of patients whose lymphomas were not possible to classify histopathologically, increased risks were indicated for all types of impregnating agents.

TABLE IV – EXPOSURE TO VARIOUS OTHER PESTICIDES

Agents	Cases/controls	OR	CI
Insecticides, total	112/101	1.28	0.96–1.72
≤40 days	44/51	1.03	0.68–1.57
>40 days	65/50	1.47	0.99–2.16
DDT	50/37	1.46	0.94–2.28
≤37 days	20/19	1.17	0.62–2.22
>37 days	30/18	1.76	0.97–3.20
Mercurial seed dressing	21/11	2.03	0.97–4.28
≤12 days	7/6	1.27	0.42–3.83
>12 days	14/5	2.93	1.04–8.25
Pyretrine	15/10	1.74	0.78–3.91
≤25 days	8/5	1.86	0.60–5.75
>25 days	6/5	1.36	0.41–4.51
Permetrine	9/9	1.23	0.48–3.14
Other insecticides	28/26	1.25	0.72–2.16
≤33 days	9/14	0.79	0.34–1.85
>33 days	18/12	1.67	0.79–3.51
Fungicides	16/18	1.11	0.56–2.23
≤37 days	9/9	1.29	0.51–3.31
>37 days	7/9	0.94	0.35–2.57
Impregnating agents	70/51	1.57	1.07–2.30
≤45 days	27/25	1.23	0.71–2.16
>45 days	43/24	2.04	1.21–3.42
Chlorophenols	40/36	1.24	0.77–1.98
≤33 days	23/18	1.46	0.78–2.74
>33 days	17/17	1.08	0.54–2.15
Arsenic	7/5	1.63	0.51–5.20
Creosote	19/10	2.10	0.96–4.58
≤39 days	4/5	0.87	0.23–3.29
>39 days	15/5	3.33	1.20–9.27
Tar	8/5	1.84	0.59–5.69
Other impregnating agents	27/20	1.55	0.85–2.81
≤7 days	4/10	0.44	0.14–1.42
>7 days	22/10	2.55	1.19–5.47
Rodenticides	5/4	1.67	0.44–6.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. In some subjects, number of days was not known (excluded in dose-response calculations). Adjustment was made for age, sex and year of diagnosis or enrolment.

Multivariate analysis

Since mixed exposure to several pesticides was more a rule than an exception, and all single agents were analyzed without adjusting for other exposure, a multivariate analysis was made to elucidate the relative importance of different pesticides. Criteria for agents to be included in this analysis are defined in Statistical Methods above. As seen in Table VII increased ORs were found but in general lower than in the univariate analysis.

Discussion

This was a population based case–control study on NHL, which is a strength of the investigation. Only living cases and controls were included, which was of advantage in comparison with interviewing next-of-kins. The study covered all new cases of NHL during a specified time. Pathologists in Sweden that were experts in lymphoma diagnosis confirmed all diagnoses. Thus, a main advantage compared with the earlier studies was the possibility to study the different NHL entities, classified according to the recently developed WHO classification system. The histopathological subgroups may well be regarded as separate in etiology and pathogenesis, as well as they are known to be different regarding course, prognosis and best treatment.

The frequency matching on age groups, gender and health service regions increased the efficacy of the study and ensured exposure conditions for the controls representative for the population in the included geographical areas. We achieved a high response rate among cases and controls, which is another advantage. A motivating introduction letter that was sent out with the questionnaire and with reminders if needed may explain this.

Exposures were assessed by questionnaires with information supplemented over the phone. Thereby use of different pesticides could be checked by information in *e.g.*, receipts and bookkeeping. However, no registries exist in Sweden on such individual use, which is a weakness in the assessment of exposure. Exposure to pesticides may be difficult to assess, and some misclassification regarding quantity of exposure has probably occurred, but such misclassification would most probably be nondependent of case/control status, and therefore only weaken any true risks. Use of protective equipment was not asked for which might have been a disadvantage of the study. However, such use would dilute the exposure and thus bias the result towards unity.

We have earlier published the results from 2 Swedish case–control studies on lymphomas, the first one on NHL and HL[8,19] and later on NHL.[18] These studies showed an increased risk for lymphomas as a result of exposure to herbicides belonging to the class phenoxyacetic acids. In the first study we also found correlation with chlorophenols and organic solvents. Several other studies,

TABLE V – EXPOSURE TO VARIOUS INSECTICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Insecticides, total	DDT	Mercurial seed dressing	Pyretrine	Other
B-cell lymphomas, total (n = 819)	1.19	1.32	1.81	1.68	1.08
	0.88–1.61	0.83–2.10	0.84–3.93	0.73–3.86	0.60–1.94
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	1.46	1.39	0.75	2.40	1.57
	0.91–2.35	0.69–2.83	0.16–3.47	0.73–7.89	0.66–3.75
Follicular, grade I–III (n = 165) (FL)	1.37	2.14	3.61	2.60	0.28
	0.79–2.38	1.05–4.40	1.20–10.9	0.79–8.51	0.04–2.11
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.23	1.24	2.20	1.25	1.31
	0.78–1.93	0.61–2.49	0.79–6.12	0.34–4.61	0.58–2.97
Other specified B-cell lymphoma (n = 131)	1.32	1.33	2.39	1.49	1.42
	0.77–2.27	0.57–3.10	0.73–7.81	0.32–6.94	0.53–3.80
Unspecified B-cell lymphoma (n = 89)	0.42	0.23	–[1]	–[1]	0.42
	0.15–1.18	0.03–1.75			0.06–3.18
T-cell lymphomas (n = 53)	1.61	2.88	2.08	2.20	1.59
	0.72–3.60	1.05–7.95	0.25–17.1	0.27–17.8	0.36–7.02
Unspecified non-Hodgkin lymphoma (n = 38)	1.91	2.39	5.43	3.14	4.70
	0.79–4.62	0.77–7.42	1.34–22.0	0.37–26.3	1.48–14.9

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VI – EXPOSURE TO FUNGICIDES AND IMPREGNATING AGENTS DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Fungicides	Impregnating agents, total	Chlorophenols	Creosote	Other
B-cell lymphomas, total (n = 819)	1.01	1.41	1.12	2.09	1.51
	0.48–2.09	0.95–2.11	0.69–1.84	0.94–4.64	0.82–2.78
Lymphocytic lymphoma/B-CLL (n = 195)	1.33	1.71	1.35	2.91	2.23
	0.43–4.12	0.94–3.11	0.64–2.85	1.01–8.33	0.97–5.13
Follicular, grade I–III (n = 165)	–[1]	1.49	0.91	2.56	1.80
		0.70–3.19	0.31–2.66	0.68–9.68	0.59–5.48
Diffuse large B-cell lymphoma (n = 239)	1.26	1.70	1.40	1.75	1.51
	0.45–3.47	0.97–2.96	0.70–2.78	0.54–5.74	0.62–3.67
Other specified B-cell lymphoma (n = 131)	1.56	1.24	0.95	2.58	1.09
	0.51–4.76	0.58–2.63	0.36–2.51	0.78–8.55	0.31–3.78
Unspecified B-cell lymphoma (n = 89)	–[1]	0.41	0.54	–[1]	0.54
		0.10–1.75	0.12–2.32		0.07–4.19
T-cell lymphomas (n = 53)	1.10	3.26	2.39	–[1]	2.07
	0.14–8.70	1.39–7.63	0.78–7.28		0.45–9.53
Unspecified non-Hodgkin lymphoma (n = 38)	3.73	2.52	2.02	4.94	1.40
	0.77–18.0	0.88–7.19	0.56–7.31	0.97–25.2	0.17–11.2

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex, and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VII – MULTIVARIATE ANALYSES INCLUDING AGENTS ACCORDING TO SPECIFIED CRITERIA, SEE TEXT

Agents	Univariate		Multivariate	
	OR	CI	OR	CI
MCPA	2.81	1.27–6.22	1.88	0.77–4.63
2,4,5-T and/or 2,4-D	1.61	0.87–2.97	1.24	0.68–2.26
Glyphosate	2.02	1.10–3.71	1.51	0.77–2.94
Mercurial seed dressing	2.03	0.97–4.28	1.58	0.74–3.40
Arsenic	1.63	0.51–5.20	1.17	0.34–4.02
Creosote	2.10	0.96–4.58	1.70	0.73–3.98
Tar	1.84	0.59–5.69	1.39	0.43–4.48

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.

but not all, from different research groups have supported our results, as reviewed,[20] and also confirmed later, *e.g.*, Ref. 21.

Furthermore, other groups have demonstrated associations between NHL and other classes of pesticides, especially different types of insecticides, *e.g.*, organophosphates,[22] carbamate,[23] lindane[24] and chlordane,[25] but also other groups of herbicides as atrazine.[26] Some case–control studies have found associations between several classes of pesticides, *e.g.*, Ref. 27 or merged groups of pesticides as in one recent study,[28] which demonstrate a significantly increased risk for NHL associated with exposure to "nonarsenic pesticides." These authors discuss the fact that several pesticides are chemically related and may exert their effects on humans through a similar mechanism of action, which may explain the wide range of pesticides that have been related to NHL over time in different countries and with different exposure conditions.

Several factors urged for a third Swedish study on the relation between pesticides, other chemicals and NHL, and the present study also used a somewhat changed methodology, which also may be of interest.

Thus, the use of phenoxyacetic herbicides, which earlier were dominating both as weed killers in agriculture and against hard wood in forestry, have substantially decreased during the last decades. 2,4,5-T, which was contaminated by TCDD, was prohibited in Sweden 1977, and 2,4-D was withdrawn from the market in 1990. MCPA, even if still used, has been largely substituted by other agents, among which glyphosate has been clearly dominating. This change of herbicide practice along with successively strengthened protection instructions has prompted our new study, reflecting also later years of exposure.

Furthermore, the changing trend of the incidence of NHL in many countries with reliable cancer registries, *e.g.*, Sweden, with a substantial and steady increase during the 1960's through 1980's but a leveling off or even slight decrease after that, makes it important to find etiological factors contributing to this shift in trend. Chlorinated compounds in the environment, which have been regulated during the 1970's and 1980's, may at least partly explain this trend, as discussed by us.[2] Phenoxyacetic herbicides with potential contaminating dioxins are examples of such substances. However, the prohibition of common environmental pollutants as polychlorinated biphenyls (PCB) and the following decline in the environment is probably more important to explain the leveling off of the incidence.[2]

In contrast to our 2 former case–control studies on NHL, this study included both genders and only consecutive living cases and living controls. In our earlier studies we have only studied male lymphoma cases, making the results of this study more representative for the whole population. To facilitate comparisons with our earlier results we also made additional analyses of herbicide exposure by gender. Only few women were exposed and separate analyses for both sexes still yielded an increased risk for NHL. Thus, in the total material herbicide exposure gave OR = 1.72, 95% CI 1.18–2.51 (n = 74 cases, 51 controls), whereas for men only OR = 1.71, 95% CI = 1.15–2.55 (n = 68 cases, 47 controls) and for women only OR = 1.82, 95% CI = 0.51–6.53 (n = 6 cases, 4 controls) were calculated.

In our study lymphocytic lymphoma/B-CLL was significantly associated with herbicides with highest OR for glyphosate but also creosote. Follicular lymphoma was significantly associated with DDT and mercurial seed dressing, diffuse large B-cell lymphoma with MCPA, and T-cell lymphoma with DDT and impregnating agents overall. Unspecified NHL was significantly associated with MCPA, glyphosate and mercurial seed dressing. It should be noted that several ORs were increased for herbicides, insecticides and impregnating agents but the calculations were hampered by low numbers of exposed cases and controls.

Our earlier results of exposure to phenoxyacetic herbicides as a risk factor for NHL were confirmed in our study. As in our previous lymphoma studies exposure to MCPA seemed to yield the highest OR among the different phenoxyacetic acids. This is of interest because MCPA is known not to be contaminated by dioxins, as 2,4-D and 2,4,5-T. At the same time MCPA is the only phenoxyacetic acid still in wider use in Sweden and many other countries.

Glyphosate is a broad-spectrum herbicide, which inhibits the formation of amino acids in plants.[29] The US Environmental Protection Agency[30] and the World Health Organization[31] have concluded that glyphosate is not mutagenic or carcinogenic. Since then, however, some experimental studies indicate genotoxic, hormonal and enzymatic effect in mammals, as reviewed.[32] Of particular interest is that glyphosate treatment of human lymphocytes *in vitro* resulted in increased sister chromatid exchanges,[33] chromosomal aberrations and oxidative stress.[34,35]

Glyphosate was associated with a statistically significant increased OR for lymphoma in our study, and the result was strengthened by a tendency to dose-response effect as shown in Table II. In our former study[18] very few subjects were exposed to glyphosate, but a nonsignificant OR of 2.3 was found. Furthermore, a meta-analysis combining that study with an investigation on hairy-cell leukaemia, a rare NHL variant, showed an OR for glyphosate of 3.04 (95% CI 1.08–8.52).[36] Recent findings from other groups also associate glyphosate with different B-cell malignancies such as lymphomas and myeloma.[32,37,38]

Glyphosate has succeeded MCPA as one of the most used herbicides in agriculture, and many individuals that used MCPA earlier are now also exposed to glyphosate. This probably explains why the multivariate analysis does not show any significant ORs for these compounds.

Exposure to insecticides was associated with a slightly increased OR, Table IV. In some other studies on the relation between pesticides and NHL, insecticides seem to be of some importance as causative agents.[27,37,38] Especially, different organophosphates were indicated as risk factors in those studies, with a Canadian study[37] showing statistical significant ORs for malathion and diazinon. In our study, only few subjects were exposed to different organophosphates, but we found a nonsignificant OR of 2.81 (95% CI 0.54–14.7) for malathion based on 5 exposed cases and 2 controls, not shown in Table.

The organochlorine DDT has shown suggestive but rarely significant association with NHL in some studies.[8,19,38–40] Our study showed a moderately but not significant increased OR for exposure to DDT.

Fungicides were not associated with the risk for NHL in our study, but few subjects were exposed to a wide range of different agents. In some earlier studies increased risks have also been noted for this group of pesticides.[16,18]

Exposure to impregnating agents produced a significant OR with a dose-response relation, Table IV. The highest risk was found for high exposure to creosote, which gave a significant OR. This finding was in contrast to our previous results on NHL,[18] but another Swedish study also found an association between creosote and NHL.[41] Chlorophenols have been the most common group of impregnating agents in Sweden, but were banned in 1977. In our first NHL study, reflecting exposures mainly during the time these substances were used, we found a strong association with NHL. As in the present study, however, no association was found in our second study on NHL.[18]

In conclusion, this study, which mirrors pesticide exposure during later years than in our previous studies, confirmed results of an association between exposure to phenoxyacetic herbicides and NHL. Furthermore, our earlier indication of an association between glyphosate and NHL has been considerably strengthened.

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ORIGINAL ARTICLE

Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

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ABSTRACT

Objectives We investigated the role of occupational exposure to specific groups of agrochemicals in the aetiology of lymphoma overall, B cell lymphoma and its most prevalent subtypes.

Methods In 1998–2003, 2348 incident lymphoma cases and 2462 controls were recruited to the EPILYMPH case-control study in six European countries. A detailed occupational history was collected in cases and controls. Job modules were applied for farm work including specific questions on type of crop, farm size, pests being treated, type and schedule of pesticide use. In each study centre, industrial hygienists and occupational experts assessed exposure to specific groups of pesticides and individual compounds with the aid of agronomists. We calculated the OR and its 95% CI associated with lymphoma and the most prevalent lymphoma subtypes with unconditional logistic regression, adjusting for age, gender, education and centre.

Results Risk of lymphoma overall, and B cell lymphoma was not elevated, and risk of chronic lymphocytic leukaemia (CLL) was elevated amongst those ever exposed to inorganic (OR=1.6, 95% CI 1.0 to 2.5) and organic pesticides (OR=1.5, 95% CI 1.0 to 2.1). CLL risk was highest amongst those ever exposed to organophosphates (OR=2.7, 95% CI 1.2 to 6.0). Restricting the analysis to subjects most likely exposed, no association was observed between pesticide use and risk of B cell lymphoma.

Conclusions Our results provide limited support to the hypothesis of an increase in risk of specific lymphoma subtypes associated with exposure to pesticides.

What this paper adds

- Inconsistent opinions exist about the evidence linking occupational exposure to pesticides with lymphoma risk.
- The complex array of chemicals comprised in the pesticide definition and the heterogeneity of the pathological diagnoses included in the lymphoma or non-Hodgkin's lymphoma definitions might contribute to the controversy.
- We used the WHO classification of lymphoma to identify specific lymphoma entities, and state of the art retrospective exposure assessment for occupational exposure to chemical classes of pesticides and specific agrochemicals in a population-based case-control study.
- Our results provide limited evidence of an increase in risk of chronic lymphocytic leukaemia associated with exposure to organophosphates, and no association for other lymphoma subtypes.

INTRODUCTION

Among hundreds of agents and groups of agents examined in 35 years of International Agency for Research on Cancer (IARC) Monographs (volumes 1–99)[1] pesticides account for two dozens; only a few of those are still in use worldwide, some are obsolete but still in use in developing countries, and most have been banned or abandoned for some decades. Only arsenic and arsenical pesticides are group 1 human carcinogens, while occupational exposure in the spraying and application of non-arsenical insecticides overall is included in group 2A, because of limited evidence from epidemiological studies. Group 2A also includes two active ingredients, namely the fungicide captafol, which uses have been restricted in the USA and most world countries from 1999,[2] and ethylene dibromide, which is used as a grain fumigant. As for the rest, the insufficient evidence from human studies is coupled with the sufficient, limited or unavailable evidence from experimental animal studies. Nowadays, thousands of chemicals are available to farmers to treat plant diseases and protect their crops; their use changes year by year, across countries and within each country, and by type of crop and type of disease being treated: the difficulty of conducting epidemiological studies of the long term effects of agrochemicals is reflected in the poor information on their human carcinogenicity and the absence of evaluation by international scientific and regulatory agencies.

Reviews of the scientific literature reported inconsistent opinions about the association between occupational exposure to pesticides and non-Hodgkin's lymphoma (NHL).[3 4] In fact, while several meta-analyses have come to positive conclusions on NHL risk,[5–10] particularly for prolonged exposures,[11–13] or for exposure in the years

relatively close to the diagnosis,[14] risk has been shown to vary by gender,[15] or specific jobs,[16] and by specific chemicals.[17] Besides, the causal link is not always recognised,[18] and negative studies have also been published.[19-24] In some instances, interpretation of findings is limited by imprecise definition of either exposure or disease entity[22] or a small study size.[25] Geographical variation in NHL mortality has also been reported in relation to the prevalent type of crop, and therefore the pesticide used.[26-28] For instance, NHL mortality in the female population was elevated in an area of Minnesota where wheat, corn and soy crops were prevalent.[28]

METHODS

The EPILYMPH study, a multicentre case-control study on environmental exposures and lymphoid neoplasms, was conducted in Czech Republic, France, Germany, Italy, Ireland and Spain from 1998 to 2004. Details about the study have been described elsewhere.[29] Briefly, cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres. The diagnosis was classified according to the 2001 WHO classification of lymphoma,[30] and slides of about 20% of cases from each centre were reviewed centrally by a panel of pathologists, coordinated by MM. Controls from Germany and Italy were randomly selected by sampling from the general population, matched to cases on gender, 5-year age-group, and residence area. The rest of the centres used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases and immunodeficient diseases. Approval by the relevant Ethics Committees was obtained in all centres. Informed consent was obtained for the 2348 lymphoma cases and 2462 controls who participated to the study. Overall, the participation rate was 88% in cases, 81% in hospital controls and 52% in population controls.

Trained interviewers conducted in person interviews with cases and controls, using the same structured questionnaire translated into the local language. Questions sought information on sociodemographic factors, lifestyle, health history and a list of all full time jobs held for 1 year or longer. Industrial hygienists in each participating centre coded the occupations and industries using the 5-digit 1968 International Labour Office International Standard Classification of Occupations[31] and the 4-digit codes of the 1996 European Statistical Classification of Economic Activities, revision 1 (NACE, rev. 1).[32] Study subjects who reported having worked in agriculture were given a job-specific module inquiring in detail into the following: detailed description of the tasks; kind of the crops and size of the cultivated area; type of pests being treated; pesticides used, and procedures of crop treatment; use of personal protective equipment; re-entry after treatment; frequency of the treatment in days/year.

Occupational exposure assessment

With the support of a local agronomist, and the support of a crop-exposure matrix, created by LM, to supplement the available information, industrial hygienists and occupational experts in each participating centre reviewed the general questionnaires and job modules to assess exposure to pesticides classified into inorganic (mainly sulphur and arsenic salts) and organic (carbamates, organophosphates, organochlorines, triazines and triazoles, phenoxyacids, and chlorophenols). Exposure was classified according to the following exposure metrics:

confidence, representing the industrial hygienist's degree of certainty that the worker had been truly exposed to the agent, based upon two criteria: 1. a summary evaluation of the probability of the given exposure (1= possible, but not probable; 2=probable; and 3=certain); and 2. the proportion of workers exposed in the given job (1≤40%; 2=40–90%; 3≥90%);

intensity of exposure, expressed in relation to the circumstances of use (personal preparation of the pesticide mixture, use of hand pump or tractor, size of the area being treated, re-entry after treatment) and use of personal protective equipment. Semiquantitative estimates of exposure were derived from the publicly available EUROPOEM programme,[33] and then categorised on a 4-point scale (0=unexposed; 1=low; 2=medium; 3=high);

frequency of exposure, expressed in annual days of pesticide use reported in the questionnaire or estimated based on the type of plant disease and the size of the crop or the livestock being treated (low≤50 days/year; medium 51–100 days/year; high≥101 days/year).

A cumulative exposure score was calculated for each pesticide group as follows: $C_i = S(y_j \times f_j/3)^{x_j}$ where C is the cumulative exposure score; i the study subject; j the jth job in the work history of study subject i; y the duration of exposure (in years); x the exposure intensity level f the exposure frequency level.

Cumulative exposure scores for each pesticide group were then categorised by tertiles of their distribution among the exposed (cases and controls combined).

Consistency in the occupational coding and exposure assessments was optimised through several meetings of the industrial hygienists.

Statistical methods

We assessed risk of B cell lymphoma, and its most prevalent subtypes, diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukaemia (CLL), associated with ever exposure to inorganic and organic pesticides (all types), and the organic pesticide groups listed in table 1. The analysis was led by PC, supported by GS, SD, MP and TN, both on all exposed subjects, and after restriction to subjects whose exposure was assessed with high confidence. Linear trends in all exposure metrics were also estimated. The OR was calculated using unconditional logistic regression, adjusted for age, gender, education and centre. Two-tailed 95% CI for the OR were estimated using the Wald statistics ($e^{\beta} \pm (z_{\alpha/2} \times se_{\beta})$). Subjects unexposed to any pesticide comprised the reference category used for all the analyses. Trends in the ORs were assessed using the Wald test for trend.

Role of the funding sources

The private and public institutions that sponsored this study did not influence or intervene in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

Details on the study size, number of cases and controls by participating centre, and their frequency distribution by selected variables of interest in the occupational analyses were reported elsewhere.[34] Table 1 shows the frequency distribution of exposure to pesticide groups for which exposure was assessed in the EPILYMPH study, by country. In a footnote, the active ingredients within each group are reported, selected among those reported by study subjects or suggested by the collaborating agronomists. Overall, the prevalence of exposure to pesticides in our study was low, with only 3.7% of participants exposed to inorganic pesticides and 6.4% exposed to organic pesticides,

Table 1 Prevalence of exposed to the individual pesticide groups by country in the EPILYMPH study

Pesticide groups*	Spain N=1222	France N=574	Germany N=1413	Italy N=598	Ireland N=409	Czech republic N=594	Total N=4810
Inorganic pesticides	88 (7.2)	14 (2.4)	28 (2.0)	31 (5.2)	14 (3.4)	6 (1.0)	181 (3.8)
Arsenicals	30 (2.4)	0 (0.0)	9 (0.6)	0 (0.0)	3 (0.7)	0 (0.0)	42 (0.9)
Organic pesticides	127 (10.4)	38 (6.7)	86 (6.1)	48 (8.2)	38 (9.4)	5 (0.8)	342 (7.1)
Carbamates	3 (0.2)	4 (0.7)	11 (0.8)	15 (2.5)	2 (0.5)	0 (0.0)	35 (0.7)
Organophosphates	7 (0.6)	4 (0.7)	11 (0.8)	16 (2.7)	14 (3.4)	1 (0.2)	53 (1.1)
Organochlorines	22 (1.8)	8 (1.4)	22 (1.6)	13 (2.2)	5 (1.0)	0 (0.0)	70 (1.5)
Triazines and triazoles	0 (0.0)	3 (0.6)	2 (0.1)	13 (2.2)	0 (0.0)	2 (0.3)	20 (0.4)
Phenoxyacids	2 (0.2)	4 (0.7)	10 (0.7)	5 (0.8)	4 (1.0)	0 (0.0)	25 (0.5)
Chlorophenols	46 (3.7)	9 (0.9)	31 (2.0)	19 (3.0)	10 (2.0)	0 (0.0)	115 (2.4)

For each country, the total number of participants is provided upon which the percentage of exposed (in brackets) is calculated.
*Note: Inorganic pesticides include: sulphur, arsenic, fluorine, zinc, mercury derivatives and other; arsenicals include: ammonium, calcium, sodium and potassium arsenate; organic pesticides include carbamates (aldicarb, carbaryl, mancozeb, methomyl, propoxur and other), organophosphates (acephate, diazinon, dimethoate, glyphosate, malathion, parathion and other), organochlorines (aldrin, DDT, chlordane, endrin, lindane, metoxychlor, endosulfan and other), triazines and triazoles (atrazine, propazine, terbutryn and other), phenoxyacids (2,4 dichlorophenoxyacetic acid, 2,4,5 T, methylchloro-phenoxyacetic acid, mecoprop and other), chlorophenols (2 chlorophenol, pentachlorofenol and other).

and it was lowest for triazines and triazoles and phenoxy acids. The prevalence of exposed was highest in Spain and lowest in the Czech Republic. The prevalence of exposure to the specific groups of pesticides varied by country. Use of inorganic pesticides was widespread, but it mainly consisted of copper sulphide or other sulphur compounds as reported by study subjects, indicated by the agronomist or by the crop-exposure matrix. Arsenicals were mainly used in Spain and, to a smaller extent, in Ireland. Among organic pesticides, chlorophenols were most frequently represented, and their prevalence was highest in Spain, Italy and Germany. Organophosphates were the most prevalent group of organic pesticides in Ireland. The most variegate pattern of pesticide use was described in Italy.

Table 2 shows risk of lymphoma overall, B cell lymphoma, DLBCL and CLL, amongst those ever exposed to each type of pesticide considered in this study. No excess risk of lymphoma (all types), B cell lymphoma and DLBCL was observed in association with ever exposure to inorganic or organic pesticide, nor to any of the organic pesticide groups assessed in this study. Risk of CLL was significantly associated with ever exposure to

Table 2 Risk of lymphoma and major subtypes associated with ever exposure to pesticide groups in the Epilymph study

	Lymphoma (all types)			B cell lymphoma			Diffuse large B cell lymphoma			Chronic lymphocytic leukaemia		
Pesticide group	Cas/cont	OR	95% CI	Cas/cont	OR	95% CI	Cas/cont	OR	95% CI	Cas/cont	OR	95% CI
Inorganic pesticides												
Any confidence level	100/81	1.3	0.9 to 1.7	81/81	1.2	0.8 to 1.6	13/81	0.7	0.4 to 1.3	28/81	1.6	1.0 to 2.5
High confidence	57/46	1.3	0.9 to 2.0	42/46	1.1	0.7 to 1.8	7/46	0.7	0.3 to 1.6	15/46	1.6	0.8 to 2.9
Arsenicals												
Any confidence level	18/24	0.8	0.4 to 1.4	14/24	0.7	0.4 to 1.3	2/24	0.4	0.1 to 1.6	6/24	1.1	0.4 to 2.7
High confidence	4/5	0.8	0.2 to 3.1	2/5	0.5	0.1 to 2.6	0/5	0.0	–	0/5	0.0	–
Organic pesticides												
Any confidence level	180/162	1.2	0.9 to 1.4	148/162	1.2	0.9 to 1.5	28/162	0.8	0.5 to 1.2	45/162	1.5	1.0 to 2.1
High confidence	101/91	1.1	0.8 to 1.5	79/91	1.1	0.8 to 1.5	13/91	0.7	0.4 to 1.2	23/91	1.4	0.8 to 2.2
Carbamates and thiocarbamates												
Any confidence level	16/19	0.9	0.5 to 1.7	9/19	0.7	0.3 to 1.5	1/19	0.2	0.0 to 1.8	3/19	1.1	0.3 to 3.8
High confidence	4/8	0.5	0.2 to 1.7	3/8	0.5	0.1 to 2.0	0/8	0.0	–	1/8	0.9	0.1 to 7.2
Organophosphates												
Any confidence level	32/21	1.6	0.9 to 2.8	23/21	1.4	0.8 to 2.6	5/21	1.1	0.4 to 2.9	9/21	2.7	1.2 to 6.0
High confidence	11/7	1.6	0.6 to 4.2	7/7	1.4	0.5 to 3.9	1/7	0.6	0.1 to 5.3	1/7	0.9	0.1 to 7.7
Organochlorines												
Any confidence level	33/37	0.9	0.6 to 1.5	27/37	0.9	0.5 to 1.4	5/37	0.6	0.2 to 1.6	10/37	1.2	0.6 to 2.5
High confidence	12/12	1.0	0.5 to 2.3	11/12	1.1	0.5 to 2.6	2/12	0.7	0.2 to 3.3	5/12	1.9	0.6 to 5.6
Triazines and triazoles												
Any confidence level	8/12	0.7	0.3 to 1.7	6/12	0.7	0.2 to 1.7	2/12	0.8	0.2 to 3.4	2/12	0.9	0.2 to 4.1
High confidence	5/6	0.9	0.3 to 2.8	3/6	0.6	0.2 to 2.5	1/6	0.8	0.1 to 6.4	1/6	0.8	0.1 to 6.9
Phenoxy acids												
Any confidence level	14/11	1.3	0.6 to 2.9	12/11	1.4	0.6 to 3.1	4/11	1.7	0.5 to 5.2	2/11	0.9	0.2 to 4.1
High confidence	5/5	1.0	0.3 to 3.6	4/5	1.1	0.3 to 4.1	2/5	1.9	0.4 to 9.9	0/5	0.0	–
Chlorophenols												
Any confidence level	59/56	1.1	0.8 to 1.6	49/56	1.1	0.7 to 1.6	13/56	1.1	0.6 to 2.0	13/56	1.1	0.6 to 2.2
High confidence	32/27	1.2	0.7 to 2.1	25/27	1.1	0.6 to 2.0	6/27	1.0	0.4 to 2.5	5/27	1.0	0.4 to 2.6

Results are presented for all confidence levels combined and limited to study subjects with high confidence of exposure.

Table 3 Chronic lymphocytic leukaemia risk and intensity of exposure to pesticide groups (all levels of confidence)

	Unexposed			Low			Medium			High		
Pesticide groups	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI
Inorganic pesticides	362/2262	1.0	–	14/33	2.2	1.1 to 4.2	10/34	1.2	0.6 to 2.5	3/11	1.2	0.3 to 4.3
Organic pesticides	362/2262	1.0	–	21/81	1.4	0.8 to 2.3	18/55	1.6	0.9 to 2.8	6/26	1.2	0.5 to 3.0
Carbamates*	362/2262	1.0	–	0/10	–	–	3/9	1.8	0.5 to 6.9			
Organophosphates*	362/2262	1.0	–	5/13	2.7	0.9 to 7.8	4/8	2.6	0.7 to 9.2			
Organochlorines*	362/2262	1.0	–	5/15	1.8	0.6 to 5.0	5/20	1.0	0.4 to 2.8			
Phenoxy acids*	362/2262	1.0	–	0/7	–	–	2/4	2.4	0.4 to 13.8			
Chlorophenols	362/2262	1.0	–	7/27	1.2	0.5 to 2.6	5/18	1.4	0.4 to 3.9	1/11	0.5	0.1 to 4.2

*Medium and high intensity categories combined.

organic pesticides and particularly to organophosphates (OR=2.6, 95% CI 1.2 to 6.0). An elevated risk of CLL was also associated with ever exposure to inorganic pesticides (OR=1.6, 95% CI 1.0 to 2.5), but not with arsenical pesticides. Because of the a priori hypothesis of an association, we cite the moderate excess risk of B cell lymphoma associated with ever exposure to phenoxyacids (OR=1.4, 95% CI 0.6 to 3.1). No excess risk was observed in association with ever exposure to the other pesticide groups. The results did not change when exploring risk for NHL, thus excluding CLL and multiple myeloma, but including T-cell lymphomas. Further adjustment for ever exposure to solvents or contact with livestock did not virtually change the risk estimates.

Table 3 shows risk of CLL by intensity of exposure. The excess risk associated with ever exposure to inorganic pesticides was limited to the lowest category of intensity of exposure. Risk for medium-high intensity of exposure to organophosphates showed a 2.6-fold excess (CI 95% 0.7 to 9.2), matching that observed for the low intensity category; however, the CI was wide at either level, and there was no trend in risk (Wald test for trend=0.14; p=0.44).

Risk of B cell lymphoma associated with ever exposure to organophosphates did not vary according to whether exposure started before 1980 or from 1980 onwards and it did not increase by cumulative exposure tertiles (Wald test for trend p=0.09). Instead, CLL risk was highest when exposure started from 1980 onwards (OR=4.0, 95% CI 0.9 to 16.6), and it increased significantly by increasing cumulative exposure tertile (Wald test for trend p=0.02).

Only a few individual agrochemicals were represented by a sizable number of study subjects, and the exposed cases of DLBCL, CLL and even B cell lymphoma overall were too few for any meaningful inference to be drawn. Exposure to the three most frequently identified individual organophosphate pesticides, namely dimethoate and parathion, among the most commonly used agricultural insecticides, and glyphosate, an organophosphorous herbicide, was more prevalent among B cell lymphoma cases, while exposure to 2,4 dichlorophenoxyacetic acid (2,4 D) was not (table 4). Four cases and no controls had been exposed to methylchloro-phenoxyacetic acid (MCPA) (p=0.13); these were one case of diffuse large B cell lymphoma, one case of follicular lymphoma and two cases of unspecified non-Hodgkin's lymphoma. Three cases and one control to other phenoxy herbicides (p=0.28) not shown in the tables.

When limiting the analysis to the only study subjects whose exposure was assessed with a high degree of confidence, numbers became smaller and CIs wider. The excess risk of CLL associated with exposure to organophosphates and that of B cell lymphoma associated with exposure to phenoxyacids were no longer observed. Risk was not significantly elevated for the B cell lymphomas overall among study subjects with high confidence of exposure to organophosphates, and CLL risk was moderately increased among study subjects with high confidence of exposure to organochlorines . Overall, these results were not interpretable because of the small number of cases and the rarity of the exposed.

Table 4 Risk of B cell lymphoma and occupational exposure to selected specific active ingredients of pesticides

	B cell lymphoma		
Pesticide	Ca/Co	OR	95% CI
Mancozeb	2/4	0.6	0.1 to 3.5
Methomyl	0/4	–	
Dimethoate	3/2	1.8	0.3 to 10.6
Glyphosate	4/2	3.1	0.6 to 17.1
DDT	3/3	1.2	0.2 to 5.9
Endosulfan	0/4	–	
2,4-dicholorophenol	2/4	0.6	0.1 to 3.5
Methylchloro phenoxyacetic acid	4/0	∞	

DDT, dichloro-diphenyl-trichloro-ethane.

DISCUSSION

Our results provide limited support to the hypothesis of an association between occupational exposure to organophosphorous pesticides and risk of CLL. We did not find evidence of an association with lymphoma overall, B cell lymphoma as a group of different subtype entities and DLBCL. The low prevalence of exposed in our community based study did not allow to explore the association with other less prevalent lymphoma subgroups, nor to detect unquestionable associations with specific agrochemicals. Also, we were unable to confirm the repeatedly reported association between exposure to phenoxyacids and lymphoma. It is worth reporting, however, that while we did not observe any indication of a higher prevalence of exposure to 2,4 D among cases in respect to controls, four B cell lymphoma cases and no controls were identified as exposed to MCPA.

Organophosphate insecticides were introduced for agricultural use in Europe mainly in the early 1970s, when insect resistance to organochlorines became manifest. Their use was associated with an almost twofold increase in risk of NHL in a Nebraska case-control study;[35] women appeared to be at greater risk.[15] Similar findings were reported in Italy and China.[36 37] An increase in NHL risk was also reported in Australia for exposures defined as substantial, although no increasing trend in risk was observed with frequency, intensity level, probability, duration and period of exposure.[38] Specific organophosphates were investigated in several studies. Malathion, one the most frequently used organophosphorous insecticide, showed an association in a Canadian case-control study,[39] and in another study conducted

the household insecticides, did not allow the use of such information. We cannot exclude that bias might have resulted, although it seems unlikely that it would have acted only on the specific association between occupational exposure to organophosphates and CLL.

Caution is therefore required in interpreting our findings. Among pesticides considered in the IARC Monographs for their potential human carcinogenicity,[1] subjects in our study mentioned having used arsenicals, DDT, chlorophenols and phenoxyacids. In most instances, the use of these chemicals date to early periods in the work histories of study subjects, while the limited evidence of an association with CLL risk was related to still popular organophosphorous insecticides and phenoxy herbicides that did not undergo specific IARC evaluations thus far. The lack of consistent dose response trends with all the exposure metrics might support chance as the explanation for the observed associations, or it might imply some mechanism different from a direct intervention in the carcinogenic process. For instance, dimethoate was shown to have the lowest cytotoxic and genotoxic potential in cultured cells, compared to other three organophosphates and the organochlorine endosulfan;[30] however, its administration in experimental female mice caused a decrease in total immunoglobulins and IgM and in the number of plaque forming cells;[31] the same effects were observed over three generations following repeated administration of low doses dimethoate in outbred Wistar rats.[32] Functional activity of Th1 lymphocytes, immune reactions associated with these cells, and interferon-γ production were impaired after subacute malathion intoxication in albino rats,[33] while thymic atrophy and reduction in splenic germinal centres followed methylparathion administration in rabbits.[34] Such immunosuppressive effects do not seem related to acetylcholinesterase inhibition, the typical toxicological mechanism of organophosphate poisoning, and cover a large number of pesticides, including organochlorines, organophosphates, carbamates and pyrethroids.[35 36] It is unclear whether the typically toxicological criterion of dose-response in establishing causal association would apply also in mechanisms involving the immune system.

In conclusion, our analysis of a large European data set provides no support to a role of occupational exposure to several specific agrochemicals in the aetiology of B cell lymphoma, and limited support in the aetiology of CLL. Further multicentre studies in international settings coupling state of the art exposure assessment in farm work and availability of detailed pathological diagnoses with a larger study size might provide the proper setting to further test the hypothesis.

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Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

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Review

Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis

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Abstract: This paper describes results from a systematic review and a series of meta-analyses of nearly three decades worth of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to agricultural pesticide active ingredients and chemical groups. Estimates of associations of NHL with 21 pesticide chemical groups and 80 active ingredients were extracted from 44 papers, all of which reported results from analyses of studies conducted in high-income countries. Random effects meta-analyses showed that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL. In a handful of papers, associations between pesticides and NHL subtypes were reported; B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure. Despite compelling evidence that NHL is associated with certain chemicals, this review indicates the need for investigations of a larger variety of pesticides in more geographic areas, especially in low- and middle-income countries, which, despite producing a large portion of the world's agriculture, were missing in the literature that were reviewed.

Keywords: pesticides; insecticides; herbicides; fungicides; lymphoma; non-Hodgkin; occupational; agricultural

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1. Introduction

Striking increases in the incidence of non-Hodgkin lymphoma (NHL) cancer have occurred in the last 30 years [1,2], and interest in identifying environmental and occupational exposures associated with this cancer has accompanied this trend. Several environmental exposures have been proposed and investigated as potentially important—pesticides, dioxins, solvents, oils, and viruses, among others [3,4]. Farmers experience low overall mortality but high rates of some cancers; this suggests that some or several agricultural exposures may be key determinants [5,6]. Indeed, positive associations between NHL and farm related exposures, including pesticides, fertilizers, chemicals, animals, viruses, and endotoxin, have been observed previously [3,5,7]. However, the wide variety of chemical and microbial exposures that occur simultaneously in agricultural production makes disentangling the effects of these factors challenging. Of the many exposures experienced in farm settings, pesticides have drawn particular attention, especially since the increased incidence of NHL in the mid- to late-1900s followed widespread use of synthetic organic pesticides [4]. Also, several epidemiologic studies have reported positive associations between NHL and pesticide exposure in occupational manufacturing settings [8,9].

The United States Environmental Protection Agency defines pesticides as substances intended to prevent, destroy, repel, or mitigate a pest [10]. Within this broad category, pesticides are often grouped according to the type of pests that they control; for example, fungicides are used to kill fungi, insecticides to kill insects, and herbicides to kill weeds and plants. In addition to function, pesticides vary in terms of structure, and they are sometimes grouped according to chemical relationships. Furthermore, applicators often use a variety of pesticides simultaneously. These characteristics make designing and conducting epidemiologic studies of their health effects both challenging and expensive.

Because pesticides are thought to have different toxicologic and immunologic effects, identifying the chemicals and chemical groups that are most dangerous to humans and non-target living organisms is important [11]. From a research perspective, the decision about what chemicals to investigate has implications for disease prevention, and it impacts the information that is available to policy makers and the public.

These challenges and needs motivated us to systematically review the published epidemiologic literature of relationships of NHL with occupational exposures to agricultural pesticide chemical groups and active ingredients. The primary objectives of this paper were to investigate the depth of the literature on the relationship between specific pesticide chemicals and NHL, to identify gaps in this area of research, and to elucidate pesticide chemical groups and active ingredients that have shown particularly strong relationships with NHL. To help us to achieve these objectives, we conducted a series of meta-analyses of associations of individual pesticide chemicals with NHL.

2. Methods

2.1. Article Identification

We performed a search of literature on associations between occupational pesticide exposure and NHL. We restricted our search to articles published since 1980. This time period is consistent with that used in previous meta-analyses of farming exposures [5], and it captured the epidemiologic literature

that has not been reviewed by early IARC monograph evaluations of pesticides [12]. The search used combinations of the following words: occupational exposure, pesticides, insecticides, herbicides, fungicides, neoplasms, cancer, lymphomas, non-Hodgkin lymphoma, cancer mortality, agricultural workers' diseases/chemically induced, and humans. We entered combinations of these terms into PubMed and Web of Science. Details of the search are given in Supplementary file S1.

2.2. Article Selection

To identify eligible studies, we reviewed the titles and abstracts of papers. When it was unclear from the abstract and title whether the paper fit these criteria, the full text of the paper was reviewed. We included estimates from papers with the following characteristics:

(1) Written and published in English;
(2) Reported results of analyses of case control or cohort epidemiology studies;
(3) Reported results of studies that used interviews, questionnaires, and/or exposure matrices to assess exposure;
(4) Reported associations of NHL with occupational, agricultural pesticide exposures;
(5) Reported quantitative associations of NHL overall and/or NHL subtypes with specific individual active ingredients or chemical groups.

We excluded papers with the following characteristics:

(1) Written in a language other than English;
(2) Did not report on associations with NHL;
(3) Were a commentary, letter to the editor, or monograph;
(4) Did not report associations with individual pesticide active ingredients or chemical groups; we excluded papers that reported associations with only the broadly defined categories of pesticide, insecticide, herbicide, or fungicide;
(5) Reported results of analyses of ecologic studies;
(6) Reported results of analyses of data from studies that were not case control or cohort in design;
(7) The exposure definition/classification was ambiguous;
(8) The exposure route was not occupational;
(9) The exposure route was not agricultural;
(10) Reported only associations within unique subpopulations (e.g., HIV positive patients);
(11) Reported analyses of manufacturing cohorts;
(12) Reported associations with NHL as a second primary;
(13) Reported results of studies in which exposure was assessed using biological markers.

2.3. Data Extraction

We extracted the following information from the full text of each eligible paper:

- author;
- publication year;
- study location;

- study design (case-control or cohort);
- source population for the controls in case-control studies;
- whether case-control studies were matched, and if so, the matching factors;
- diagnosis period if a case-control study or cancer follow-up period if a cohort study;
- number of cohort participants or number of cases and controls;
- cancer definition or ICD codes used to identify the cancers;
- method of assessing exposure;
- exposure metrics and definitions;
- referent categories used in the analysis;
- active ingredient(s) and/or chemical group(s) studied;
- covariates entered into the model to adjust for confounding;
- type of effect estimate reported;
- number of exposed participants;
- effect estimates and confidence interval limits; and
- gender restrictions, if any.

We also identified papers that were related to each other (e.g., pooled analyses that used data that were analyzed and reported on previously, papers that reported on different analyses from the same study, studies that were follow up analyses of the same population). In cases of related papers, we used a specific set of rules to decide which effect estimate to report and use in the meta-analyses; this rule is described in Section 2.5.

2.4. Chemical Group Classification

We reported results for all chemical groups for which there was information from the available literature. We did not consider exposures to chlorophenols in this paper, since much of the exposure to this chemical group comes from non-agricultural settings. We classified pesticide active ingredients into chemical groups based on Alan Wood's classification system [13].

2.5. Reporting of Results for the Systematic Review

From every relevant paper, we extracted an effect estimate for each active ingredient and/or chemical group. We extracted results for associations with NHL, and when available, for associations with subtypes of NHL.

We used the following algorithm to determine which effect estimates to use:

(1) For related papers that examined the same exposure/outcome association, we used the results from the most complete and updated analysis with the greatest number of participants;

(2) If more than one exposure definition was considered and reported, we used the definition that best represented agricultural exposures (e.g., we selected results for farmers who worked with phenoxy herbicides, instead of results for herbicide applicators, gardeners, or landscapers);

(3) The various papers used different confounder adjustment sets, which were selected based on different criteria. In an effort to use the most unbiased estimate, we extracted the most adjusted effect estimate;

(4) Most papers defined exposure dichotomously. Papers that reported results according to more than two categories used a variety of definitions for the exposure metrics, including duration of use, days/year of use, time since first exposure, and cumulative days of exposure. Because the definitions and metrics used to define categories varied, it was not possible to combine estimates based on multiple categories of exposure in formal meta-analyses. Therefore, for the meta-analyses, we used the result for the dichotomously defined exposure with the greatest number of exposed cases. To assess dose-response relationships, we qualitatively examined results in association with multiple categories;

(5) Some papers only reported results in association with multiple categories of exposure. We extracted these results for the systematic review, since they can be used to qualitatively evaluate trends in association of NHL with active ingredient or chemical group and are important for identifying dose-response relationships;

(6) Some studies only reported estimates of association between pesticide exposures and subtypes of NHL. We abstracted these estimates for presentation and analysis of association of pesticide exposures with NHL subtypes.

We present results from the systematic review sorted by chemical group and, within chemical group, by active ingredient.

2.6. Meta Analysis

2.6.1. Grouping

When possible, we conducted separate meta-analyses for each chemical group and active ingredient. We conducted meta-analyses for associations of these pesticides with NHL and NHL subtypes. Although we abstracted results according to dichotomous exposure and multiple levels of exposure, we conducted formal meta-analyses for dichotomously categorized exposures only.

2.6.2. Analytic Methods

Because we identified a variety of sources of heterogeneity between papers, we decided a priori to calculate meta- risk ratio (RR) estimates and 95% confidence intervals (CIs) using random effect models, allowing between study heterogeneity to contribute to the variance [14,15]. We report I^2 values, which represent the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency [15]. We did not perform formal heterogeneity tests; Cochran's Q statistic has been shown to have low power to detect true heterogeneity across studies, especially in meta-analyses that include a small number of papers [15]. Following recommendations for meta-analyses of observational studies, we also identified possible sources of heterogeneity and used sensitivity analyses to evaluate these, as described in Section 2.6.3 [16]. We evaluate the meta- estimates of association based on the magnitude of the point estimate and interpret the associated 95% CIs as indicators of precision. To aid this interpretation, we have calculated and reported confidence limit ratios (CLRs), which are the ratio of the upper to the lower CI limit [17]. We also present forest plots for meta-analyses to which five or more papers contributed.

2.6.3. Sensitivity Analysis

We conducted sensitivity analyses to evaluate robustness of our results to the following sources of heterogeneity: study design (case-control versus cohort), gender (male only versus both genders), geographic area, decade of cancer diagnosis, and source of the controls in case-control studies (population-based versus hospital).

One paper presented results of analyses of women only [18]. Thus, we were not able to conduct a sensitivity analysis for analyses of women; we were able to conduct sensitivity analyses using papers that reported results for men and for men and women. Only two papers reported estimates of association from studies in which controls were drawn from hospitals, and these two studies reported associations of NHL with different pesticides. Therefore, our sensitivity analysis of the control source in case-control studies was restricted to controls drawn from the population. Data from only one cohort study contributed to our meta-analyses. Therefore, we could not restrict meta-analyses to cohort studies only.

The geographic areas that we investigated separately in sensitivity analyses were North America, the United States, Europe, and Sweden. We selected these because there was more than one study within each area that investigated associations of NHL with a particular pesticide. In addition to maintaining Sweden and the United States in sensitivity analyses of Europe and North America, respectively, we analyzed results from Sweden separately from the rest of Europe, and results from the United States separately from Canada. We conducted these separate analyses because more than one paper reported effect estimates of association with a pesticide from each of these countries, and because we believed effects might be different when separated from the rest of the continent. Although we identified papers from Australia and New Zealand we were not able to analyze these separately because there was not more than one effect estimate of association with an individual pesticide from either country.

We investigated the following diagnosis periods: 1975–1989, 1990–1999, and year 2000 and later. If any part of the diagnosis period overlapped these periods, we included the estimate from the paper in the sensitivity analysis. We selected these periods based on the periods that appeared in the papers that we reviewed and on the different editions of the ICD coding systems [1].

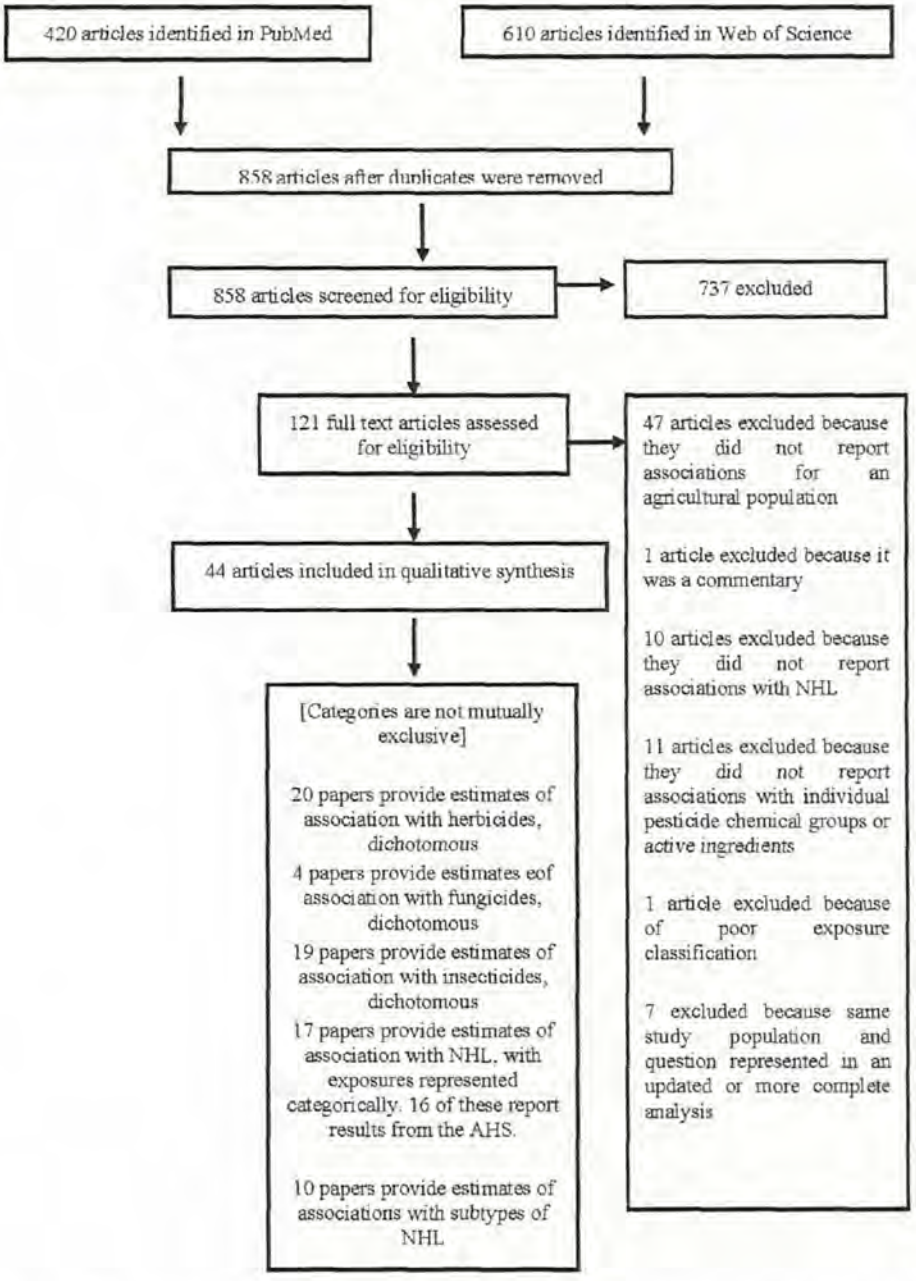
After performing meta-analyses for each active ingredient or chemical group, we repeated analyses, removing studies that differed from the others based on the above-described characteristics. In cases when results from individual studies were also represented in papers that analyzed these data pooled with data from other studies, we performed sensitivity analyses by replacing the results from the pooled analyses with the individual studies, or the individual studies with the results from the pooled analyses.

3. Results

3.1. Systematic Review

The PubMed and Web of Science searches yielded 858 unique articles (Figure 1). After screening the abstracts and titles, we excluded 737 articles. Of the remaining 121 articles, 47 were excluded because they reported results within a non-agricultural population. We decided to exclude non-agricultural populations because the nature of exposure they receive is different compared to agricultural groups. Because of contamination and production of multiple chemicals simultaneously, it is difficult to determine the exact chemical to which manufacturing cohort participants have been exposed.

Figure 1. Flow chart showing the articles that were included and excluded in the systematic review, with reasons for the exclusions.



After excluding 27 additional articles because they did not meet one or more of the inclusion criteria described in the methods section, we included 44 papers in our qualitative synthesis. Of these, 20 papers provided estimates of association with herbicide chemical groups or active ingredients, four papers provided estimates of association with fungicides, and 17 with insecticides.

3.2. Summary of Studies from Which Estimates were Extracted

A summary of the 44 papers from which effect estimates were abstracted is presented in Table 1.

Table 1. Summary of papers from which effect estimates were extracted.

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Barry 2012 [19] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	53,588	Self-administered questionnaire completed during enrollment and interviewer administered follow-up questionnaire	Referent: No exposure Intensity weighted lifetime exposure days, 15 year lag Intensity weighted lifetime exposure days, no lag	No	Age, gender, race, state of residence, applicator type, enrollment year, cigarette smoking, alcohol consumption, education, family history of cancer, 5 most correlated pesticides	Methyl bromide	No
Baris 1998 [20] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, and vital status at the time of interview, year of death for controls matched to deceased cases	Dx period [1]: 1979–1983	993 cases/2, 918 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Used *vs.* did not use on crops and animals , Used *vs.* did not use on crops, Used *vs* did not use on animals Duration of use, in years (1-4, 5-9, ≥10) Days/year of use (≤5, >5)	Yes	Age, state of residence	DDT	Yes
Beane Freeman 2005 [21] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	23,106	Two self-administered questionnaires	Referent: No exposure Lifetime exposure days Intensity weighted exposure days	Yes	Age, smoking, education, family history of cancer, state of residence, total days of any pesticide application	Diazinon	No
Beane Freeman 2011 [22] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2007	36,357	A self-administered questionnaire	Referent 1: No exposure Referent 2: Lowest quartile of exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, state, license type, gender, smoking status, alcohol consumption, education, use of most highly correlated pesticides	Atrazine	Yes

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Blair 1998 [23] Iowa, Kansas, Minnesota, Nebraska, USA	CC	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	987 cases/2,895 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: nonfarmer Farmers who ever used Days/year of use (≤4 days, ≥5 days) First lindane use (≥20 years ago, <20 years ago)	Yes	Age, proxy/direct interview, state of residence	Lindane	Yes
Bonner 2010 [24] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2005	44,624	Self-administered questionnaires	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Intensity weighted lifetime exposure days	No	Age, gender, education, family history of cancer, smoking, alcohol, year of enrollment, state of residence, correlated pesticides	Terbufos	No
Bonner 2005 [25] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	49,877	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days Intensity weighted lifetime exposure days	No	Age, gender, education, family history of cancer, smoking, alcohol, year of enrollment, state of residence, exposure to correlated pesticides	Carbofuran	No
Bonner 2007 [26] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	19,717	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, gender, smoking, alcohol, education, family history of cancer, year of enrollment, state of residence	Malathion	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Cantor 1992 [27] Iowa and Minnesota, USA	CC	Population	Matched by 5-year age group, vital status at time of interview, and state of residence	Dx period [1]: 1979–1983	622 cases/1,245 controls	In-person interviews	Referent: Non-farmers Ever handled, Handled prior to 1965 Handled without protective equipment	Yes	Age, vital status, state, cigarette smoking, family history of lymphohematapoeitic cancer, high risk occupations, high risk exposures	2,4-D, 2,4,5-T, alachlor, atrazine, aldrin, bentazon, butylate, carbofuran, carbaryl, chlordane, chloramben, copper acetoarsenate, cyanazine, coumaphos, diazinon, dicamba, dichlorvos, DDT, famphur, Flyspray, fonofos, glyphosate, heptachlor, lindane, malathion, methoxychlor, metribuzen, nicotine, phorate, popachlor, rotenone, toxaphene, trifluralin, turbufos,	No
Cocco 2013 [28] Multicentre; Czech Republic, France, Germany, Italy, Ireland, Spain	CC	Population (German and Italian centers), Hospital (Czech Republic, French, Irish, Spanish centers)	Matched by gender, 5-year age group, and residence area	1998–2004	2,348 cases/2,462 controls	Structured in-person interviews conducted by trained interviewers, jobs were coded by industrial hygienists; industrial hygienists and occupational experts reviewed the questionnaires and job modules to assess exposures to pesticides (with the help of a crop exposure matrix)	Referent: Never exposed Ever exposed, by level of industrial hygienists's degree of confidence that the participant was truly exposed to the agent: Any level of confidence High confidence	No	Age, gender, education, study center	Carbamates, OPs, OC, Triazines and triazoles, phenoxy acids, chlorophenols, mancozeb, methomyl, dimethoate, glyphosate, DDT, endosulfan, 2,4-D, MCPA	Only reported for subtypes
Delancey 2009 [29] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	23,072	Two self-administered questionnaires	Referent: Lowest tertile of exposure Lifetime exposure days Intensity weighted lifetime exposure days	Yes	Age, smoking, alcohol consumption, education, family history of cancer, state of residence, exposure to all pesticides	Metribuzin	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
de Roos 2003 [30] Iowa, Kansas, Minnesota, Nebraska, USA	CC	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	650 cases/1,933 controls	Telephone interviews (Kansas and Nebraska, USA). In-person interviews (Iowa and Minnesota)	Referent: Not exposed Exposed	Yes	Age, study site, use of all other pesticides	Aldrin, bufencarb, carbaryl, carbofuran, chlordane, copper acetoarsenite, coumaphos, DDT, diazinon, dichlorvos, dieldrin, dimethoate, ethoprop, famphur, fly/tick/lice spray, fonofos, heptachlor, lead arsenate, lindane, malathion, methoxychlor, nicotine, phorate, pyrethrins, rotenone, tetrachlorvinphos, toxaphene, terbufos, alachlor, atrazine, bentazon, butylate, chloramben, cyanazine, 2,4-D, dicamba, EPTC, glyphosate, linuron, MCPA, metolachlor, metribuzin, paraquat, propachlor, sodium chlorate, 2,4,5-T, trifluralin	No
de Roos 2005 [31] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	54,315	Self-administered questionnaire	Referent 1: Never used Referent 2: Lowest tertile of exposure Ever used Cumulative exposure days Intensity weighted exposure days	No	Age at enrollment, education, cigarette smoking, alcohol consumption, family history of cancer, state of residence, other pesticides	Glyphosate	No
Eriksson 2008 [32] Sweden	CC	Population	Matched in 10 year age and gender groups to mirror the age and gender distribution of the cases	Dx period: 1999–2002	1,163 cases/1,016 controls	Telephone interview on life style factors and diseases; Self-administered questionnaire on work history and chemical exposures; follow up telephone interviews to collect incomplete data	Referent: Never exposed Ever exposed, Days of exposure (categorized at the median of the exposure distribution),	No	Age, gender, year of Dx/enrollment	Phenoxyacetic acids, MCPA, 2,4,5-T and/or 2,4-D, glyphosate	Yes

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Hardell 2002 [33] Sweden	CC, pooled analysis of two studies, one of hairy cell lymphoma and one of NHL	Population	Matched by age and county	Dx period: 1987–1990 (NHL); 1987–1992 (hair cell lymphoma)	515 cases/1,141 controls	Self-administered questionnai-re supplement-ed by telephone interviews by a trained interviewer when information was unclear	Referent 1: Not exposed Ever exposure, High exposure (>median number of days for exposed participants) Low exposure (<median number of days for exposed participants) Years between first exposure and diagnosis: Referent 2: 1-10years, >10-20 years, >20-30 years, >30 years Years between last exposure and diagnosis: Referent 3: 1-10 years, >10-20 years, >20-30 years, >30 years Decade of exposure	Yes	Study, study area, vital status, age	Phenoxy acids, MCPA, 2,4-D + 2,4,5-T, glyphosate, DDT, mercurial seed dressing, pyrethrins, arsenic	No
Hoar 1986 [34] Kansas, USA	CC	Population	Matched by age and vital status	Dx period: 1976–1982	170 cases of NHL/948 controls (no. included in NHL analysis unclear)	Telephone interviews, with questions on years living/ working on a farm, and herbicides/insecticides used.	Referent: Non-farmers Ever use, Duration of use (years), Frequency of use (days/year), First year of use	Yes	Age	Phenoxyacetic acids, Triazine herbicides, Amide herbicides, Benzoic herbicides, Carbamate herbicides, Trifluralin herbicides, Uracil herbicides	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Kang 2008 [35] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,127	Self-administered questionnai-res completed during enrollment and interviewer administered follow-up questionnaires	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age at enrollment, education, cigarette smoking, alcohol consumption, family history of cancer, state of residence, top five most highly correlated pesticides	Trifluralin	No
Koutros 2009 [36] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,398	Self-administered questionnaire	Referent: Nonexposed Intensity weighted lifetime exposure days	No	Age, year of enrollment, race	Imazethapyr	No
Koutros 2008 [37] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,762	Self-administered questionnaire	NA	No	Not applicable, since an adjusted effect estimate for an association with NHL was not reported	Dichlorvos	No
Lee 2004 [38] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2001	54,383	Self-administered questionnaire	Referent 1: Nonexposed Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, gender, alcohol consumption, smoking history, educational level, family history of cancer, year of enrollment, state of residence, use of 4 correlated pesticides	Chlorpyrifos	No
Lee 2004 [39] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2000	49,980	Self-administered questionnaire	Referent 1: Nonexposed Exposed, Referent 2: Lowest quartile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, sex, alcohol, smoking, education, family history of cancer, enrollment year, state of residence, 5 correlated pesticides	Alachlor	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Lynch 2009 [40] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	19,655	Self-administered questionnaire	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age at enrollment, gender, race, smoking status, education, family history of cancer, atrazine, 5 most correlated pesticides	Butylate	No
Lynch 2006 [41] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,800	Self-administered questionnaire	Referent: Lowest tertile of exposure[1] Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, race, gender, alcohol consumption, smoking status, education level, family history of cancer, state of residence, 5 most correlated pesticides	Cyanazine	No
Mahajan 2007 [42] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2003	21,416	Self-administered questionnai-re	Referent 1: Nonexposed Referent 2: Lowest tertile of exposure Lifetime exposure days, Intensity weighted lifetime exposure days	No	Age, smoking, gender, state of residence, use of 4 correlated pesticides	Carbaryl	No
McDuffie 2001 [43] Six Canadian provinces	CC	Population	Frequency matched by age and province of residence	Dx period: 1991–1994	517 cases/1,506 controls	Self-administered postal questionnai-re followed by telephone interview with participants who had 10 or more hours of pesticide use in lifetime plus a 15% random sample of those with fewer than 10 hours pesticide use	Referent: Not exposed Exposed, Frequency of exposure (days/year)	Yes	Age, providence of residence	2,4-D, mecoprop, MCPA, DiclofopmethylGlyphosate, phosphonic acids, phenoxy herbicides, thiocarbamates,diallate, dicamba, dinitroaniline, trifluralin, carbaryl, carbofuran, methomyl, carbamate insecticides, organochlorine insecticides, chlordane, lindane, aldrin, methoxychlor, DDT, Captan, vitavax, aldehyde, formaldehyde, mercury dust, mercury liquid, malathion, carbon tetrachloride	

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Miligi 2006 [44] Italy	CC	Population	Stratified by gender and 5-year age groups	Dx period: 1991–1993	1,145 cases/1,232 controls	In-person interviews, including questions on crops grown and whether pesticides were used combined with exposure matrix	Reference: Those who never worked in agriculture Overall exposure, Probability of use >low and lack of protective equipment	No	Age, gender, area	Phenoxy herbicides, 2,4-D, MCPA	No
Mills 2005 [45] California	CC	Same source as the cases (United Farm Workers of America cohort)	Matched by gender, hispanic ethnicity and +/− one year of birth	Dx period: 1988–2001	60 cases/300 controls	Work histories combined with exposure matrix	Reference: Low use High use	No	Age, gender, length of union affiliation, date of first union affiliation	Methyl bromide, diazinon, malathion, dichloro-propane, captan, simazine, chlrothalonil, mancozeb, methyl parathion, nitrofen, propyzamide, toxaphene, trifluralin, 2,4-D, maneb	No
Orsi 2009 [46] France	CC	Hospital	Matched by center, age +/− 3 year, gender	2000–2004	244 cases/436 controls	Self-administered questionnai-res, followed by face to face interviews with trained staff, and review of interviews by experts to verify logical consistency with pesticide product availability, geographic location, *etc.*	Reference: Nonexposed Exposed	No	Age, center, socioeconomic characteristic (white collar vs blue collar)	Organochlorine insecticides, organophosphorus insecticides, pyrethrin, carbamate fungicides, imide fungicides, triazole fungicides, phenoline herbicides, phenoxy herbicides, picoline herbicides, triazine herbicides, amide herbicides, urea herbicides, quaternary ammonium herbicides, glyphosate	Yes
Pahwa M 2012 [47] Six Canadian provinces	CC	Population	Frequency matched by age and province of residence	Dx period: 1991–1994	513 cases/ 506 controls	Self-administered postal questionnaire followed by telephone interview with participants who had 10 or more hours of pesticide use in lifetime plus a 15% random sample of those with fewer than 10 hours pesticide use	Reference: No use Use	Yes	Age, province of residence, respondent type (self or proxy), diesel oil exposure	OC insecticides, DDT, OP insecticides, malathion, phenoxy herbicides, MCPA, mecoprop, 2,4-D	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Pearce 1987 [48] New Zealand	CC	Cancer registry	Matched by year of cancer registration and age (± 2 years)	Dx period: 1977–1981	183 cases/338 controls	Telephone interviews	Reference: Nonexposed Used any agricultural chemical spray in a farming setting	Yes	Decade of birth, type of interview respondent (self or relative)	Phenoxy herbicides	No
Persson 1989 [49] Sweden	CC	Population	Unmatched	Dx period: 1964–1986	106 cases/275 controls	Self-administered questionnaire	Reference: Not exposed Exposed	No	Age, date of Dx, gender, farming, exposure to fresh wood, other exposures associated with at least a doubled risk for hodgkins disease or NHL	Phenoxy herbicides, DDT	No
Persson 1993 [50] Sweden	CC	Population	Unmatched	Dx period: 1975–1984	93 cases/204 controls	Self-administered questionnaires	Reference: Not exposed Exposed	No	Age, other exposures investigated with OR ≥2 or significantly below unity and with at least 5 exposed subjects	Phenoxy herbicides, DDT	No
Purdue 2007 [51] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	51,011	Self-administered questionnaire	Reference 1: Never use/unexposed Ever use Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, sate, gender, education level, smoking status, alcohol use, family history of cancer, lifetime days of total pesticide application	OC insecticides, aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene	No
Rafnsson 2006 [52] Iceland	CC	Non-cases from cohort of sheep owners	Unmatched	Dx period: 1966–2003	45 cases/221 controls	Records of sheep owned, used as a proxy measure for dermal exposure from sheep dipping; sheep dipping used as a proxy for exposure to hexa-chlorocyclohexane, which is a mixture of different isomers containing around 15% lindane. <100 sheep owned was used to indicate unexposed	Referent: <100 sheep ≥100 sheep , Categories of number of sheep owned: 100-199 sheep, 200-683 sheep	Yes	Age	Hexachlorocyclohexane	No

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Rusiecki 2009 [53] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	49,093	Self-administered questionnaire	Referent: Nonexposed Lifetime days of exposure Intensity weighted	No	Age, gender, race, family history of cancer, cigarette smoking, state of residence, enrollment year	Permethrin	No
Rusiecki 2006 [54] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2002	50,193	Self-administered questionnaire	Referent: Lowest tertile of exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	No	Age, gender, race, smoking, alcohol, applicator status, family history of cancer, sate of residence, most highly correlated pesticides	Metolachlor	No
van Bemmel 2008 [55] Iowa and North Carolina, USA	C (AHS)	NA	NA	1993–2004	48,378	Self-administered questionnaire	Referent: No exposure Lifetime days of exposure Intensity weighted lifetime days of exposure	Yes	Age, race, smoking, alcohol use, applicator type, family history of cancer, state of residence, total days of pesticide use	EPTC	No
Waddell 2001 [56] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, and vital status at the time of interview, year of death for controls matched to deceased cases	Dx period [1]: 1979–1983	748 cases/2,236 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Ever Used First used Years used Days/year of use Protective gear	Yes	Age, state of residence, respondent type (proxy or direct)	OP insecticides, dichlorvos, trichlorfon, dimethoate, diazinon, disulfoton, ethoprop, malathion, phorate, terbufos, chloropyrifos, coumaphos, crufomate, runnel, tetrachlorvinphos, fensulfothion, famphur, fonofos, parathion	Yes

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Woods 1987 [57] Washington state, USA	CC	Population	Matched by vital status and 5-year age group	Dx period: 1981–1984	746 cases/910 controls	In-person interviews about occupational history and self-reported chemical exposure	Referent: No exposure Farming exposures to phenoxy herbicides Any exposure to DDT Any exposure to chlordane Estimated intensity of occupational exposure to phenoxy herbicides: Low/medium/high	Yes	Age	Phenoxy herbicides, DDT, Chlordane	No
Zahm 1990 [58] Nebraska, USA	CC	Population	Matched by race, gender, vital status, age	Dx period: 1983–1986	201 cases/725 controls	In-person interviews about agricultural pesticide use	Referent: Never lived or worked on a farm Mixed or applied Days/year mixing or applying Years used on a farm First year of use	Yes	Age	2,4-D	No
Zahm 1993 [59] Iowa, Kansas, Minnesota, Nebraska, USA	Pooled analysis of 3 CC studies	Population	Matched by race, gender, age, vital status at the time of interview	Dx period [1]: 1979–1983	993 cases/2,918 controls	Telephone interviews (Kansas and Nebraska, USA), In-person interviews (Iowa and Minnesota)	Referent: Non-farmers Used atrazine [1] Personally handled Used but did not handle Duration of use (years) Days/year handled Year of first use	Yes	Age, state	Atrazine	Yes

Table 1. *Cont.*

Author, year, location	Design	Source for controls	Matching	Diagnosis or follow-up period (cancer)	No. Participants	Exposure assessment	Referent category for exposure, exposure definition(s)/metric	Men only	Adjustment set	Pesticides	Reported results by subtype
Zahm 1993 [18] Nebraska, USA	CC	Population	Matched by race, gender, vital status, and age (5 year age groups)	Dx period: 1983–1986	119 cases/471 controls	In-person interviews about agricultural pesticide use	Referent: women who never lived or worked on a farm Used on farm	No (women only)	Age	*Phenoxy herbicides*, triazine herbicides, amide herbicides, benzoic acid herbicides, carbamate herbicides, trifluralin herbicides, chlorinated hydrocarbons, carbamate insecticides, OP insecticides	No
Zheng 2001 [60] Nebraska, USA, Iowa and Minnesota, Kansas	Pooled analysis of 3 CC studies	Population	Matched by gender, age, race, vital status, state of residence	*Dx period* [1]: 1979–1983	985 cases/2,895 controls	In-person interviews about agricultural pesticide use	*Referent: Non-farmers* Used Personally handled Year since first use Years of use Days/year of use	Yes	Age, type of respondent (proxy or direct), state of residence, first-degree family history of cancer, *use of hair dye*, use of private wells, tobacco smoking	Carbaryl, carbamate herbicides, carbamate insecticides	Yes

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; AHS, Agricultural Health Study; C, cohort study; CC, case-control study; DDT, *dichlorodiphenyltrichloroethane*; DX, Diagnosis; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; OC, organochlorine; OP, organophosphorus; [1] Diagnosis period varied by state: July 1983–June 1986 (Nebraska, USA), October 1980–September 1982 (Minnesota), March 1981-October 1983 (Iowa), 1979–1981 (Kansas).

3.2.1. Studies Conducted in the United States

Nineteen papers [19,21,22,24–26,29,31,35,36,38–42,51,53–55] report results from analyses of data from the Agricultural Health Study, which is a prospective cohort study of licensed pesticide applicators and their spouses living in Iowa and North Carolina, USA. Enrollment began in 1993 and the study is still ongoing [61]. The number of participants included in the analyses varied due to exclusions and completeness of exposure data. The last year of follow-up was defined by the last date on which the incident cancers were identified. At enrollment, participants completed a questionnaire in which they provided historical data on exposure to pesticides. They were also given a take home questionnaire to complete. Most analyses of the Agricultural Health Study data classified active ingredient exposures using two metrics: (1) lifetime exposure days, defined as number of years of use x number of days used per year; and (2) intensity-weighted lifetime exposure days, which was defined as years of use x number of days used per year x personal protective equipment use x intensity level, which incorporates factors that modify pesticide exposure, such as mixing status, application method, equipment repair status. Four papers [31,38,39,51] also reported associations using ever/never use categories; we used these estimates in the meta-analyses.

Six papers reported results from pooled analyses of three case-control studies that were conducted by the USA National Cancer Institute [20,23,30,56,59,60], in Iowa and Minnesota, Kansas, and Nebraska. Diagnosis periods for NHL ranged from 1979 to 1986, depending upon the study. In all studies, population based controls were frequency matched to cases by race, sex, age, and vital status at the time of the interview, and lifetime exposure to pesticides was assessed via telephone interviews. Using these pooled data, De Roos *et al.* [30] examined associations of NHL with 47 active ingredients. The authors investigated pesticides for which there was exposure data from all three studies and to which at least 20 participants were exposed. They used standard logistic regression to model the association of NHL with the multiple pesticides, simultaneously. These analyses were restricted to participants with complete information on all of the pesticides. Other papers reported results from analyses of these pooled data. Baris *et al.* [20] examined associations with dichlorodiphenyltrichloroethane (DDT), Blair *et al.* [23] with lindane, Zahm *et al.* [59] with atrazine, Waddell *et al.* [56] with organophosphates, and Zheng *et al.* [60] with carbamates. We also extracted results from analyses of the individual studies. Using data from the study in Iowa and Minnesota, Cantor *et al.* [27] examined associations with multiple pesticides. In Kansas, Hoar *et al.* [34] examined associations with exposures to various herbicides. In Nebraska, Zahm *et al.* [58] examined associations with 2,4-Dichlorophenoxyacetic acid (2,4-D).

In a population based case-control study in western Washington State, USA Woods *et al.* [57], examined associations between phenoxy exposure and NHL. Controls were group matched to cases diagnosed 1981–1984, based on vital status and age. Lifetime occupational histories and self-reported pesticide chemical exposures were ascertained using in-person interviews. The authors reported exposure to phenoxy herbicides by occupational type. We extracted the result for farming exposure to phenoxy herbicides. Exposures to DDT and chlordane were reported as ever/never, but they were not stratified by occupation.

We also extracted results from a USA based case-control study nested in a cohort of primarily Hispanic members of the California farm worker labor union [45]. Cases were diagnosed 1988–2001.

Controls were selected from the same cohort as cases and matched on the basis of gender, Hispanic ethnicity, and year of birth. Pesticide exposure was defined as low *versus* high use, with the category cut-points based on the distribution of use of the top 15 pesticides. To estimate exposure, union job history data that described crops farmed in a given month/year and county was combined with data collected by the California Pesticide Databank that describes pesticides used on a crop in a given county and time period.

3.2.2. Canadian Studies

Two papers reported results from the Cross-Canada Study of Pesticides and Health, which was a case control study conducted in six Canadian provinces [43,47]. Population based controls were frequency matched to NHL cases, diagnosed 1991–1994, based on age and province of residence. Detailed information on specific pesticide use was ascertained by telephone interviews. The questionnaires used for this study were based on the one used in the USA National Cancer Institute led case-control studies [20,23,30,56,59,60] in Nebraska [18,58] and Kansas [34]. McDuffie *et al.* [43] and Pahwa *et al.* [47] present results from some of the same analyses with the same population. When the same analysis was reported in both papers we selected the effect estimate from the paper by Pahwa *et al.* [47] because the authors excluded four NHL cases based on pathology review that occurred subsequent to the analyses reported in McDuffie *et al.* [43].

3.2.3. European Studies

Four papers [32,33,49,50] reported results from distinct case-control studies conducted in Sweden. The papers by Eriksson *et al.* [32] and Hardell *et al.* [33] reported analyses from population based case-control studies; case diagnosis periods were 1999–2002 and 1987–1992, respectively. A complete lifetime occupational and chemical exposure history was ascertained using self-administered questionnaires followed by telephone interviews when clarification was needed. The two studies by Persson *et al.* [49,50] report results from unmatched population based case-control studies; the results reported from the paper published in 1993 [50] were performed in an adjacent region of Sweden to the area represented in the earlier paper [49]. They examined the association of NHL with various occupational exposures, including phenoxy herbicides and DDT. Case diagnosis periods were 1964–1986 and 1975–1984, respectively.

We extracted results from papers that report results from analyses of data collected in France [46], Italy [44], Iceland [52], and multiple European centers that form parts of the EPILYMPH study [28]. All of these studies were case-control in design. In France [46], cases (diagnosed 2000–2004) and controls were recruited in the same hospitals. Exposure was assessed using self-administered questionnaires, followed by face-to-face interviews in which participants reported information about farms on which they worked for a minimum of six months; they reported information about location, period, crops and animals farmed, name of pesticides mixed or sprayed, duration and number of pesticide applications. Pesticide exposure was classified as possible or definite; the referent category included people never exposed to the pesticide. In the Italian study [44], cases were diagnosed from 1991 to 1993. Participants were interviewed about agricultural work, crop diseases, pesticides used to treat diseases, frequency of pesticide treatments, period of treatment, protective equipment used,

means of application, and re-entry tasks. Exposure was classified into low, medium, and high probabilities of use. The Icelandic case-control study [52] was nested in a cohort of male sheep owners. The authors included cases diagnosed 1966–2003. Paper records on sheep dipping in hexachlorocyclohexane, an organochlorine insecticide that contains lindane, were used as a proxy measure for exposure; records were available for the period 1962–1980. Number of sheep owned was used as a surrogate measure for exposure. In the EPILYMPH study [28], in-person interviews were conducted to ascertain detailed job histories, including information about farm size, crops farmed, pests treated, types and frequency of pesticides used, protective equipment, and re-entry tasks. Industrial hygienists classified pesticide exposure as possible, probable, or certain. In analysis, contrasts were made between high confidence of ever lifetime exposure *versus* never exposure, and any level of confidence of ever exposure *versus* never exposure.

3.2.4. Studies from Australia and New Zealand

Only two papers reported results from analyses of studies conducted outside of North America and Europe. Pearce *et al.* [48] reported analyses of data from a New Zealand based case-control study of agricultural exposures. Cases were diagnosed 1977–1981. Telephone interviews were used to ascertain lifetime occupational history and work with chemicals (phenoxy herbicides). In analysis, Pearce *et al.* [48] stratified phenoxy herbicide exposure by occupation (farming, forestry, railway work, *etc.*). We extracted the estimate of association with any phenoxy herbicide exposure in farming occupations. In Australia [62], Fritschi *et al.* enrolled incident NHL cases diagnosed between 2000 and 2001. They matched controls to cases based on age, gender, and region of residence. In structured telephone interviews, participants provided occupational histories. Occupational hygienists reviewed the responses to these questions and, with the help of a pesticide crop matrix, assigned likelihood of exposure to pesticides (probable, possible, no exposure), level of exposure, and frequency of exposure. These assignments were combined to classify participants' lifetime amount of exposure (substantial, meaning the person was probably exposed to the substance at a medium or high level for more than five 8-h days per year for a combined total of five years, nonsubstantial, or none).

3.2.5. Gender

Nineteen of the papers reported results from analyses that were restricted to men only [20,21,23,27–30,33,34,43,47,48,52,55–60]. One paper reported results from an analysis that was restricted to women [18]. The other papers reported results from analyses of study populations with men and women; in the analytic models reported in these papers, gender was treated as a confounder.

3.2.6. Covariates

In all papers, age was included in models to adjust for potential confounding. Location (state of residence, study center) was also a common adjustment factor. Other variables that were included in models as covariates were race, smoking status, alcohol consumption, correlated pesticides, education level, year of study enrollment, family history of cancer (all cancers or lympho-hematopoetic),

other environmental risk factors for NHL (e.g., gasoline exposure), and type of respondent to the interview used for exposure assessment (direct or proxy).

3.2.7. Reference Groups

In the majority of papers reviewed, the reference group contained farmers and non-farmers who were not exposed to the pesticide. However, there were exceptions to this, either because of study design or analytic decisions.

By design, all participants in the Agricultural Health Study were either pesticide applicators or spouses of applicators. Most of the analyses from this cohort contrasted exposed participants with two different referent groups: (1) participants with no exposure to the pesticide; and (2) participants in the lowest category of exposure. Similarly, all of the participants in the California based study reported in Mills *et al.* [45] were farm workers. The referent group in this analysis consisted of those with estimated low use of the pesticide being analyzed. Both cases and controls in the Icelandic study on which Rafnsson *et al.* [52] reported were sheep owners; people who owned <100 sheep made up the reference group.

By contrast, in some papers, the authors defined the reference group as those who neither worked nor lived on a farm. Miligi *et al.* [44] defined the referent group as participants who never worked in agriculture. Similarly, in papers reporting analyses of the case-control studies in Iowa, Minnesota, Nebraska, and Kansas, the referent group was defined as participants who never worked or lived on a farm. The exception to this was the paper by De Roos *et al.* [30]; the authors used pooled data from these case-control studies but defined the referent group as farmers and non-farmers who never used the pesticide being considered.

3.2.8. Exposure Period and Definition

Pesticide exposure periods and definitions varied, also. For the most part, papers investigated associations of NHL with ever lifetime pesticide exposure. However, some were more specific in their definition, and not all papers used the ever lifetime exposure metric.

In the cohort of California based union farm workers, Mills *et al.* [45] assessed pesticide exposure in the two to three year decade period prior to cancer diagnosis or enrollment. In Canada, McDuffie *et al.* [43] and Pahwa *et al.* [47] defined pesticide exposure as ever *versus* never lifetime use of pesticides for at least 10 h. In Sweden, Eriksson *et al.* [32] and Hardell *et al.* [33] required participants to have worked with the pesticide for a minimum of eight hours in a day, and the pesticide exposure was required to have occurred at least one year prior to the time of diagnosis or enrollment. Persson *et al.* [49,50] only classified as exposed those participants who were exposed to the chemical for at least one year, five to 45 years prior to case diagnosis. In the Italian study described by Miligi *et al.* [44], an agricultural pesticide questionnaire was only administered to participants who had worked on a farm for at least six months; presumably, therefore, anyone who had worked with pesticides but worked on a farm for less than six months was excluded from the exposed group. In the Icelandic study that Rafnsson *et al.* [52] described, records on sheep ownership, which were used to estimate lindane exposure, were available for the period 1962–1980; however, the cancer diagnosis period was 1966–2003.

3.3. Individual Effect Estimates and Dose Response Relationships

Table 2 presents effect estimates from studies in which chemical exposures were represented using multiple categories. Strong dose response relationships were generally absent; most analyses that examined associations with multiple categories of exposure derived imprecise estimates with wide confidence intervals. McDuffie *et al.* [43] and Eriksson *et al.* [32] observed increased odds of NHL in association with a greater number of days/year of glyphosate exposure. De Roos *et al.* [31] did not observe a similar relationship in analyses of Agricultural Health Study data. McDuffie *et al.* [43] observed elevated effect estimates in association with exposure to 2,4-D; however, they did not observe a dose-response relationship with days/year exposed. In analyses of Agricultural Health Study data, Lynch *et al.* [40] observed a nearly three-fold increase in the rate of NHL among those with ≥26 lifetime- and intensity-weighted exposure days to butylate, although the rate ratio comparing those with one to 25 lifetime exposure days to non-exposed applicators was close to the null.

Table 2. Effect estimates from studies that investigated associations between non-Hodgkin lymphoma and herbicides, insecticide, and fungicide exposures classified using multiple categories.

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
HERBICIDES				
Amide herbicides				
Lee 2004 [39]	Alachlor	Lifetime exposure days [1]		Rate ratio, 95% CI:
		Quartile 1, 0.1–19.9	5	1.0, Referent
		Quartile 2, 20.0–56.0	4	0.6, 0.1–2.5
		Quartile 3, 56.1–116.0	8	1.5, 0.4–5.4
		Quartile 4, ≥116.1	10	1.1, 0.3–4.4
				P for trend: 0.5
		Intensity weighted exposure days [1]		
		Quartile 1, 0.1–101.9	5	1.0, Referent
		Quartile 2, 102.0–253.1	3	0.6, 0.1–3.4
		Quartile 3, 253.2–710.4	10	2.4, 0.7–8.8
		Quartile 4, ≥710.5	9	1.4, 0.3–6.1
				P for trend: 0.4
Rusiecki 2006 [54]	Metolachlor	Lifetime exposure days [1]		Rate ratio, 95% CI:
		Tertile 1, ≤20	14	1.0, Referent
		Tertile 2, 21–56	11	0.8, 0.3–1.7
		Tertile 3, >56	11	0.7, 0.3–1.7
				P for trend: 0.5
		Intensity-weighted lifetime exposure days [1]		
		Tertile 1, ≤20	13	1.0,Referent
		Tertile 2, 21–56	10	0.7, 0.3–1.7
		Tertile 3, >56	13	1.0, 0.4–2.7
				P for trend: 0.7

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Dinitroaniline herbicides				
Kang 2008 [35]	Trifluralin	Lifetime days of exposure [2]		Rate ratio, 95% CI
		Non-exposed	53	1.0, referent
		Tertile1, 1-24.4	17	0.9, 0.5–1.5
		Tertile 2, 24.5-108.4	23	1.0, 0.6–1.8
		Tertile 3, Lower half, 108.5-224.75	6	0.6, 0.2–1.4
		Tertile 3, Upper half, >224.75	4	0.6, 0.2–1.7
				P for trend: 0.2
		Intensity weighted lifetime days [2]		
		Tertile 1, 0-162.1	15	0.7, 0.4–1.4
		Tertile 2, 162.2-593	20	1.1, 0.8–2.9
		Tertile 3, Lower half, 593.1-1176.0	9	0.9, 0.4–2.0
		Tertile 3, Upper half, >1176.0	4	0.4, 0.1–1.1
				P for trend: 0.1
Glyphosate				
McDuffie 2001 [43] [3]	Glyphosate	Days/year of exposure		OR, 95% CI:
		Unexposed	466 cases/1,373 controls	1.0, Referent
		>0–≤2	28 cases/97 controls	1.0, 0.6–1.6
		>2	23 cases/36 controls	2.1, 1.2–3.7
De Roos 2005 [31] [3]	Glyphosate			
		Lifetime days of exposure [2]		Rate ratio, 95% CI:
		Tertile 1, 1–20	29	1.0, Referent
		Tertile 2, 21–56	15	0.7, 0.4–1.4
		Tertile 3, 57–2678	17	0.9, 0.5–1.6
				P for trend: 0.7
		Intensity weighted exposure days [2]		
		Tertile 1, 0.1–79.5	24	1.0, Referent
		Tertile 2, 79.6–337.1	15	0.6, 0.3–1.1

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, 337.2–1,824.1	22	0.8, 0.5–1.4
				P for trend: 1.0
Eriksson 2008 [32] [3]	Glyphosate			OR, 95% CI:
		Days of exposure [4]		
		>0–≤10 days	12 cases/9 controls	1.7, 0.7–4.1
		>10 days	17 cases/9 controls	2.4, 1.0–5.4
Imidazolinone herbicides				
Koutros 2009 [36]	Imazethapyr	Intensity weighted exposure days [5]		Rate ratio, 95% CI:
		No exposure:	80	1.0, Referent
		Tertile 1, <54.1	15	1.0, 0.6–1.7
		Tertile 2, 54.1–<152.9	13	0.9, 0.5, 1.6
		Tertile 3, lower half, 152.9–<311.9	7	0.8, 0.3–1.8
		Tertile 3, upper half, ≥311.9	11	1.4, 0.8–2.7
				P for trend: 0.4
Phenoxy herbicides				
Fritschi 2005 [62]	Phenoxy herbicides, group	Degree of pesticide exposure [6]		OR, 95% CI:
		None	679 cases/677 controls	1.0, Referent
		Nonsubstantial	10 cases/14 controls	0.7, 0.3–1.7
		Substantial	5 cases/3 controls	1.8, 0.4–7.4
Eriksson 2008 [32] [3]	Phenoxy herbicides, group	Days of exposure [4]		
		>0–≤45 days	32 cases/13 controls	2.8, 1.5–5.5
		>45 days	15 cases/13 controls	1.3, 0.6–2.7
Hardell 2002 [33] [3]	Phenoxy herbicides, group			OR, 95% CI:
		Number of days of exposure		
		Not exposed	NR	1.0, Referent
		Low	NR	1.7, 1.0–2.7
		High	NR	1.7, 1.0–2.7

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.9, 1.1–7.7
		>20–30	NR	1.5, 0.9–2.8
		>30	NR	1.5, 0.9–2.4
		Years between last exposure and diagnosis		
		1–10	NR	3.2, 1.6–6.7
		>10–20	NR	2.1, 1.0–4.1
		>20–30	NR	1.0, 0.5–1.8
		>30	NR	1.3, 0.6–2.6
		Decade of exposure		
		1940s	4 cases/6 controls	1.5, 0.4–5.2
		1950s	35 cases/53 controls	1.4, 0.9–2.3
		1960s	43 cases/58 controls	1.7, 1.1–2.6
		1970s	32 cases/33 controls	2.4, 1.4–4.0
		1980s	16 cases/33 controls	3.3, 1.5–7.1
Eriksson 2008 [32] [3]	MCPA	Days exposed [4]		
		≤32	15 cases/5 controls	3.8, 1.4–10.5
		>32	6 cases/4 controls	1.7, 0.5–6.0
Hardell 2002 [33] [3]	MCPA			OR, 95% CI:
		Number of days of exposure		
		Not exposed	NR	1.0, Referent
		Low	NR	1.9, 0.8–4.6
		High	NR	3.6, 1.5–9.1
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	5.4, 1.6–21

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		>20–30	NR	0.9, 0.2–3.0
		>30	NR	3.8, 1.5–10.0
		Years between last exposure and diagnosis		
		1–10	NR	3.5, 1.6–8.0
		>10–20	NR	2.3, 0.6–9.1
		>20–30	NR	0.9, 0.1–4.4
		>30	NR	-
McDuffie 2001 [43] [3]	Mecoprop	Days/year exposed		
		Unexposed	464 cases/1,425 controls	1.0, Referent
		>0–≤2	31 cases/48 controls	2.3, 1.4–3.7
		≥2	22 cases/33 controls	2.1, 1.2–3.6
Hardell 2002 [33] [3]	2,4-D + 2,4,5-T			OR, 95% CI:
		Number of days of exposure		
		Low	NR	1.9, 1.1–3.2
		High	NR	1.2, 0.7–2.1
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.9, 0.8–11.0
		>20–30	NR	1.9, 1.0–3.5
		>30	NR	1.2, 0.7–1.9
		Years between last exposure and diagnosis		
		1–10	NR	4.3, 1.1–21.0
		>10–20	NR	1.9, 0.9–3.8
		>20–30	NR	0.9, 0.1–4.4
		>30	NR	1.4, 0.7–2.9
Eriksson 2008 [32] [3]	2,4,5-T and/or 2,4-D	Days exposed [4]		OR, 95% CI:
		Non-exposed		1.0, Referent

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		≤29	21 cases/11 controls	2.1, 1.0–4.4
		>29	12 cases/10 controls	1.3, 0.6–3.1
Zahm 1990 [58] [3]	2,4-D			OR, 95% CI:
		Never lived/worked on a farm	54 cases/184 controls	1.0, Referent
		Days/year mixing or applying		
		1–5	16 cases/44 controls	1.2, 0.6–2.4
		6–20	12 cases/25 controls	1.6, 0.7–3.6
		21+	3 cases/4 controls	3.3, 0.5–22.1
		Unknown	12 cases/25 controls	-
				P for trend: 0.1
		Years used on farm		
		1–5	3 cases/12 controls	0.9, 0.2–3.6
		6–15	11 cases/15 controls	2.8, 1.1–7.1
		16–20	3 cases/18 controls	0.6, 0.1–2.1
		21+	13 cases/33 controls	1.3, 0.6–2.7
		Unknown	15 cases/29 controls	-
				P for trend: 0.3
		First year of use		
		Prior to 1945	8 cases/21 controls	1.4, 0.5–3.5
		1946–1955	13 cases/39 controls	1.1, 0.5–2.3
		1956–1965	5 cases/8 controls	2.1, 0.6–7.7
		1965–1986	4 cases/12 controls	1.3, 0.3–4.9
		Unknown year	13 cases/18 controls	-
				P for trend: 0.2
McDuffie 2001 [43] [3]	2,4-D	Days/yr exposed		OR, 95% CI:
		Unexposed	406 cases/1,213 controls	1.0, Referent
		>0–≤2	55 cases/160 controls	1.2, 0.8–1.6
		>2–≤5	36 cases/82 controls	1.4, 0.9–2.1

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		>5–≤7	9 cases/20 controls	1.4, 0.6–3.2
		>7	11 cases/31 controls	1.2, 0.6–2.5
Thiocarbamate herbicides				
Zheng 2001 [60] [3]	Butylate			OR, 95% CI
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	34 cases/56 controls	1.5, 0.9–2.4
		≥20	4 cases/10 controls	1.1, 0.3–3.7
		Years of use		
		<7	21 cases/35 controls	1.5, 0.9–2.8
		≥7	20 cases/37 controls	1.5, 0.8–2.7
		Days/year of use		
		<5	3 cases/5 controls	2.6, 0.6–11.1
		≥5	2 cases/2 controls	4.7, 0.6–34.5
Lynch 2009 [40]	Butylate	Lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	27	1.0, Referent
		Low exposure, 1–25	6	0.9, 0.4–2.0
		High exposure, ≥26	12	2.9, 1.5–5.8
				P for trend: 0.0
		Intensity weighted exposure days [5]		
		No exposure	27	1.0, Referent
		Low exposure, 1–157	5	0.8, 0.3–2.0
		High exposure, ≥158	13	2.9, 1.5–5.5
				P for trend: 0.0
Van Bemmel 2008 [55]	EPTC	Lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	83	1.0, Referent
		Tertile 1, 1–9	10	1.2, 0.6–2.3
		Tertile 2, 10–49	7	1.5, 0.7–3.2

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, 50+	5	0.8, 0.3–2.0
				P for trend:0.7
		Intensity-weighted lifetime exposure days [5]		Rate ratio, 95% CI:
		No exposure	83	1.0, Referent
		Tertile 1, 1–47	8	1.4, 0.7–2.8
		Tertile 2, 48–111	4	0.9, 0.3–2.5
		Tertile 3, 112+	10	1.1, 0.6–2.1
				P for trend:0.9
Zheng 2001 [60] [3]	EPTC + Protectant			OR, 95% CI:
		Non-farmers:		1.0, Referent
		Years since first use		
		<20	19 cases/34 controls	1.7, 0.9–3.1
		≥20	0 cases/1 control	-
		Years of use		
		<7	15 cases/20 controls	2.2, 1.1–4.4
		≥7	7 cases/26 controls	1.0. 0.4–2.4
		Days/year of use		
		<5	7 cases/12 controls	2.2, 0.8–5.8
		≥5	1 case/5 controls	0.9, 0.1–7.7
Triazine herbicides				
Lynch 2006 [41]	Cyanazine	Lifetime exposure days [5]		Rate ratio, 95% CI
		Tertile 1, 1–16	9	1.0, Referent
		Tertile 2, 17–56	18	1.6, 0.7–3.5
		Tertile 3, ≥57	9	1.3, 0.5–3.4
				P for trend: 1.0
		Intensity-weighted exposure days [5]		
		Tertile 1, 1–83	10	1.0, Referent
		Tertile 2, 84–314.35	12	1.3, 0.6–3.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Tertile 3, ≥315.35	13	1.4, 0.6–3.4
				P for trend: 0.5
Zahm 1993 [59] [3]	Atrazine			OR (95% CI not presented)
		No use	445 cases/1507 controls	1.0, Referent
		Years of use		
		1–5	4 cases/14 controls	0.4
		6–15	5 cases/20 controls	0.5
		16–20	5 cases/8 controls	0.6
		≥21	7 cases/11 controls	0.8
		Days/year personally handled		
		1–5	7 cases/20 controls	0.6
		6–20	8 cases/17 controls	0.7
		≥21	1 cases/1 control	1.4
		Year of first use		
		1965 or prior	10 cases/35 controls	0.4
		1966 or later	10 cases/18 controls	1.0
Beane Freeman 2011 [22]	Atrazine	Lifetime days of exposure [5]		Rate ratio, 95% CI
		Quartile 1, >0–20	41	1.0, Referent
		Quartile 2, 21–56	41	1.1, 0.7–1.7
		Quartile 3, >56–178.5	38	0.9, 0.6–1.5
		Quartile 4, >178.5	32	1.0, 0.6–1.6
				P for trend: 0.7
		Intensity weighted lifetime days of exposure [5]		
		Quartile 1, >0–20	38	1.0, Referent
		Quartile 2, 21–56	45	1.2, 0.8–1.9
		Quartile 3, >56–178.5	34	0.9, 0.6–1.5
		Quartile 4, >178.5	34	0.9, 0.6–1.5
				P for trend: 0.5

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Triazinone herbicides				
Delancey 2009 [29]	Metribuzin	Lifetime days of exposure [5]		Rate ratio, 95% CI
		No exposure	39	
		Tertile 1, >0–8.75	5	1.0, Referent
		Tertile 2, 8.76–24.5	6	2.3, 0.6–8.6
		Tertile 3, >24.5	8	2.6, 0.8–9.1
				P for trend: 0.1
		Intensity weighted lifetime exposure days [5]		
		No exposure: 0	39	
		Tertile 1, >0–58.3	4	1.0, Referent
		Tertile 2, >58.3–174.4	6	1.4, 0.3–5.8
		Tertile 3, >174.5	9	2.5, 0.7–9.6
				P for trend: 0.1
FUNGICIDES				
McDuffie 2001 [43] [3]	Captan	Days/year exposed		OR, 95% CI:
		Unexposed	497 cases/1,482 controls	1.0, Referent
		>0–≤2	11 cases/12 controls	2.7, 1.2–6.2
		>2	9 cases/12 controls	2.8, 1.1–6.9
INSECTICIDES				
Carbamate insecticides				
Zheng 2001 [60] [3]	Carbaryl			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	19 cases/44 controls	1.1, 0.6–2.0
		≥20	14 cases/21 controls	1.8, 0.9–3.7
		Years of use		
		<7	16 cases/36 controls	1.1, 0.6–2.1
		≥7	15 cases/26 controls	1.5, 0.8–3.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Days/year of use		
		<5	9 cases/14 controls	2.4, 1.0–5.9
		≥5	2 cases/4 controls	1.8, 0.3–10.0
Mahajan 2007 [42]	Carbaryl	Lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	23	1.0, Referent
		Tertile 1, 1–9	5	0.7, 0.2–1.8
		Tertile 2, 10–56	8	1.2, 0.5–3.0
		Tertile 3, >56	10	1.7, 0.6–4.5
				P for trend: 0.3
Zheng 2001 [60] [3]	Carbofuran			OR, 95% CI:
		Nonfarmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	32 cases/63 controls	1.3, 0.8–2.1
		≥20	15 cases/30 controls	1.6, 0.8–3.1
		Years of use		
		<7	30 cases/48 controls	1.7, 1.0–2.9
		≥7	24 cases/47 controls	1.4, 0.8–2.4
		Days/year of use		
		<5	9 cases/15 controls	2.7, 1.1–6.4
		≥5	12 cases/16 controls	3.1, 1.4–6.8
Bonner 2005 [25]	Carbofuran	Lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	44	1.0, Referent
		Tertile 1, 1–9	6	0.8, 0.3–1.9
		Tertile 2, 10–56	7	1.3, 0.6–2.9
		Tertile 3, >56	7	1.4, 0.6–3.3
				P for trend: 0.4

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Organophosphorus insecticides				
Fritschi 2005 [62]	Organophosphorus insecticides, group	Degree of exposure [6]		OR, 95% CI:
		No exposure	662 cases/660 controls	1.0, Referent
		Nonsubstantial exposure	20 cases/28 controls	0.7, 0.4–1.3
		Substantial exposure	12 cases/6 controls	2.1, 0.8–5.7
Waddell 2001 [56] [3]	Organophosphorus pesticides, group			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	44 cases/94 controls	1.0, 0.7–1.5
		≥20	79 cases/188 controls	1.6, 1.1–2.2
		Years used		
		<10	34 cases/69 controls	1.1, 0.7–1.7
		10–19	44 cases/71 controls	1.4, 0.9–2.1
		20+	39 cases/59 controls	1.5, 1.0–2.4
Lee 2004 [38]	Chlorpyrifos	Lifetime days of exposure [1]		Rate ratio, 95% CI:
		Nonexposed	53	1.0, Referent
		Quartile 1, 0.1–8.8	10	0.6, 0.2–1.5
		Quartile 2, 8.9–24.5	13	1.8, 0.9–3.5
		Quartile 3, 24.6–56.0	5	0.9, 0.4–2.4
		Quartile 4, ≥56.1	9	1.0, 0.4–2.4
				P for trend: 0.7
		Intensity-weighted lifetime days of exposure [1]		
		Nonexposed	53	1.0, Referent
		Quartile 1, 0.1–48.9	6	0.9, 0.3–2.2
		Quartile 2, 49.0–135.9	6	0.6, 0.2–1.8
		Quartile 3, 136.0–417.6	10	1.2, 0.6–2.7
		Quartile 4, ≥417.7	10	1.6, 0.7–3.5
				P for trend: 0.4

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Beane Freeman 2005 [21]	Diazinon			Rate ratio, 95% CI:
		No exposure	26	1.0, Referent
		Lifetime days of exposure [2]		
		Tertile 1, <20	6	1.8, 0.7–4.4
		Tertile 2, 20–38.8	3	1.4, 0.4–4.6
		Tertile 3, >38.8	2	0.9, 0.2–4.1
				P for trend: 1.0
		Intensity-weighted lifetime days of exposure [2]		
		Tertile 1	5	1.9, 0.7–5.1
		Tertile 2	2	0.7, 0.2–3.1
		Tertile 3	4	1.7, 0.6–5.2
				P for trend: 0.4
Waddell 2001 [56] [3]	Diazinon			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	20 cases/34 controls	1.1, 0.6–2.0
		≥20	16 cases/24 controls	1.4, 0.7–2.7
		Years used		
		<10	20 cases/40 controls	0.9, 0.5–1.7
		10–19	10 cases/11 controls	1.8, 0.7–4.4
		20+	1 cases/1 controls	1.9, 0.1–31.6
		Days/year of use		
		<5	6 cases/11 controls	1.3, 0.5–3.9
		≥5	6 cases/6 controls	2.4, 0.7–8.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Waddell 2001 [56] [3]	Fonofos			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	20 cases/36 controls	1.0, 0.6–1.9
		≥20	5 cases/6 controls	1.6, 0.5–5.5
		Years used		
		<10	16 cases/25 controls	1.2, 0.6–2.4
		10–19	7 cases/9 controls	1.5, 0.5–4.1
		20+	2 cases/1 control	4.2, 0.4–47.2
		Days/year of use		
		<5	2 cases/6 controls	0.7, 0.1–3.8
		≥5	9 cases/6 controls	3.4, 1.1–10.3
McDuffie 2001 [43] [3]	Malathion	Days/year of exposure		OR, 95% CI:
		Unexposed	445 cases/1,379 controls	1.0, Referent
		>0–≤2	50 cases/88 controls	1.8, 1.3–2.7
		≥2	22 cases/39 controls	1.8, 1.0–3.0
Waddell 2001 [56] [3]	Malathion			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	22 cases/46 controls	0.9, 0.5–1.6
		≥20	35 cases/39 controls	1.7, 1.1–2.9
		Years used		
		<10	22 cases/39 controls	1.1, 0.6–1.9
		10–19	23 cases/23 controls	1.9, 1.0–3.5
		20+	10 cases/18 controls	1.1, 0.5–2.4
		Days/year of use		
		<5	7 cases/8 controls	2.1, 0.7–6.1
		≥5	5 cases/7 controls	1.5, 0.5–5.2

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Bonner 2007 [26]	Malathion	Lifetime days of exposure [5]		Rate ratio, 95% CI
		No exposure	1.0 Referent	
		Tertile 1, >0–9	0.6, 0.2–1.6	
		Tertile 2, 10–39	0.7, 0.3–1.8	
		Tertile 3, >39	0.8, 0.3–2.0	
		Intensity-weighted lifetime days of exposure [2]		Rate ratio, 95% CI
		No exposure	14	1.0, Referent
		Tertile 1, >0–58	5	0.5, 0.2–1.5
		Tertile 2, 59–245	9	0.7, 0.3–1.8
		Tertile 3, >245	9	0.8, 0.3–2.0
				P for trend: 0.9
Waddell 2001 [56] [3]	Phorate			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	19 cases/43 controls	0.8, 0.4–1.5
		≥20	14 cases/23 controls	1.3, 0.6–2.6
		Years used		
		<10	20 cases/33 controls	1.2, 0.6–2.1
		10–19	9 cases/19 controls	0.9, 0.4–2.1
		20+	4 cases/5 controls	1.5, 0.4–5.9
		Days/year of use		
		<5 days	5 cases/9 controls	1.3, 0.4–4.0
		≥5 days	7 cases/8 controls	2.0, 0.7–5.9
Waddell 2001 [56] [3]	Terbufos			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent
		Years since first use		
		<20	23 cases/51 controls	0.9, 0.5-1.5
		≥20	0 cases/1 control	-

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Years used		
		<10	13 cases/38 controls	0.6, 0.3–1.3
		10–19	6 cases/8 controls	1.5, 0.5–4.4
		20+	0 cases/1 control	-
		<20	23 cases/51 controls	0.9, 0.5–1.5
		≥20	0 cases/1 control	-
		Days/year of use		
		<5	3 cases/8 controls	0.8, 0.2–3.4
		≥5	7 cases/4 controls	4.0, 1.1–14.5
Bonner 2010 [24]	Terbufos	Intensity weighted lifetime exposure days [5]		Hazard ratio, 95% CI
		No exposure	69	1.0, referent
		Tertile 1, >0–107	17	1.3, 0.7–2.3
		Tertile 2, >107–352	24	1.9, 1.2–3.2
		Tertile 3, >352	15	1.2, 0.7–2.2
				P for trend: 0.6
Organochlorine insecticides				
Fritschi 2005 [62]	Organochlorines, group	Degree of exposure [6]		OR, 95% CI:
		None	674 cases/679 controls	1.0, Referent
		Nonsubstantial	14 cases/13 controls	1.1, 0.5–2.3
		Substantial	6 cases/2 controls	3.3, 0.7–16.4
Purdue 2007 [51] [3]	Organochlorines, group	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	16	1.0, Referent
		Tertile 1, 1–110	8	1.2, 0.5–2.8
		Tertile 2, 111–450	10	1.5, 0.6–3.5
		Tertile 3, >450	11	1.5, 0.6–3.8
				P for trend: 0.3

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	16	1.0, Referent
		Tertile 1, 1–110	9	1.3, 0.6–3.1
		Tertile 2, 111–450	7	1.1, 0.4–2.9
		Tertile 3, >450	13	1.7, 0.7–4.2
				P for trend: 0.3
Purdue 2007 [51] [3]	Aldrin	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	38	1.0, Referent
		1–20	5	0.8, 0.3–2.1
		>20	4	0.4, 0.1–1.5
				P for trend: 0.2
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	38	1.0, Referent
		1–20	4	0.6, 0.2–1.9
		>20	5	0.6, 0.2–1.8
				P for trend: 0.4
Purdue 2007 [51] [3]	Chlordane	Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	32	1.0, Referent
		1–9	9	1.6, 0.8–3.6
		>9	6	1.8, 0.7–4.6
				P for trend: 0.2
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	32	1.0, Referent
		1–9	8	1.8, 0.8–4.0
		>9	7	1.6, 0.7–3.9
				P for trend: 0.3
Baris 1998 [20] [3]	DDT			OR, 95% CI:
		Non-farmers	243 cases/775 controls	1.0, Referent

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Days/year of use		
		≤5	12 cases/35 controls	1.0, 0.5–2.1
		>5	11 cases/15 controls	2.1, 0.9–4.9
		Duration of use in years		
		1–4	36 cases/79 controls	1.0, 0.7–1.6
		5–9	31 cases/53 controls	1.4, 0.8–2.2
		≥15	39 cases/64 controls	1.5, 0.9–2.3
McDuffie 2001 [43] [3]	DDT	Days/year of exposure		OR, 95% CI:
		Unexposed	485 cases/1,447 controls	1.0, Referent
		>0–≤2	18 cases/32 controls	1.8, 1.0–3.2
		≥2	14 cases/27 controls	1.5, 0.8–2.9
Hardell 2002 [33] [3]	DDT			OR, 95% CI:
		Never exposed	NR	1.0, Referent
		Years between first exposure and diagnosis		
		1–10	NR	-
		>10–20	NR	2.6, 0.6–11.0
		>20–30	NR	1.6, 0.8–3.3
		>30	NR	1.2, 0.8–1.7
		Years between last exposure and diagnosis		
		1–10	NR	1.5, 0.7–3.1
		>10–20	NR	1.1, 0.6–2.0
		>20–30	NR	1.5, 0.8–2.5
		>30	NR	1.2, 0.7–2.0

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Purdue 2007 [51] [3]	DDT			
		Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	32	1.0, Referent
		1–20	5	0.7, 0.3–1.9
		>20	9	1.2, 0.5–2.8
				P for trend: 0.6
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	32	1.0, Referent
		1–20	6	0.9, 0.3–2.2
		>20	8	1.0, 0.4–2.5
				P for trend: 0.9
Eriksson 2008 [32] [3]	DDT	Days of exposure [4]		
		≤37 days	20 cases/19 controls	1.2, 0.6–2.2
		>37 days	30 cases/18 controls	1.8, 1.0–3.2
Purdue 2007 [51] [3]	Dieldrin			
		Lifetime days of exposure [5]		Rate ratio, 95% CI:
		Unexposed	46	1.0, Referent
		1–20	1	0.6, 0.1–4.2
		>20	1	0.9, 0.1–6.9
				P for trend: 0.8
		Intensity weighted lifetime days of exposure [5]		
		Unexposed	46	1.0, Referent
		1–20	1	0.7, 0.1–5.0
		>20	1	0.7, 0.1–5.5
				P for trend: 0.7

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Purdue 2007 [51] [3]	Heptachlor	Lifetime days of exposure		Rate ratio, 95% CI:
		Unexposed	38	1.0, Referent
		1–9	6	1.5, 0.6–4.1
		>9	4	1.1, 0.4–3.2
				P for trend: 0.8
		Intensity weighted lifetime days of exposure		
		Unexposed	38	1.0, Referent
		1–9	4	1.2, 0.4–3.6
		>9	6	1.4, 0.5–3.7
				P for trend:0.6
Blair 1998 [23] [3]	Lindane			OR, 95% CI:
		Nonfarmer	243 cases/775 controls	1.0, Referent
		Years since first use		
		≥20	59 cases/83 controls	1.7, 1.1–2.5
		<20	18 cases/30 controls	1.3, 0.7–2.4
		Days/ year of use		
		≤4	8 cases/16 controls	1.6, 0.6–4.0
		≥5	5 cases/8 controls	2.0, 0.6–6.4
Rafnsson 2006 [52] [3]	Lindane	Number of sheep owned		OR, 95% CI:
		100–199 sheep	22 cases/71 controls	3.8, 1.6–9.3
		200–683 sheep	15 cases/62 controls	3.4, 1.3–9.0
Purdue 2007 [51] [3]	Lindane	Lifetime days exposed [5]		Rate ratio, 95% CI:
		Unexposed	34	1.0, Referent
		1–22 days	6	1.9, 0.8–4.7
		>22 days	7	2.1, 0.8–5.5
				P for trend: 0.1

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
		Intensity-weighted lifetime days of exposure [5]		
		Unexposed	34	1.0, Referent
		1–22	5	0.9, 0.3–3.0
		>22	8	2.6, 1.1–6.4
				P for trend: 0.04
Purdue 2007 [51] [3]	Toxaphene	Lifetime days exposed [5]		Rate ratio, 95% CI:
		Unexposed	35	1.0, Referent
		1–25 days	10	2.3, 1.1–5.0
		>25 days	2	1.3, 0.3–5.5
				P for trend: 0.8
		Intensity-weighted lifetime days of exposure [5]		
		Unexposed	35	1.0, Referent
		1–25	7	2.3, 1.0–5.4
		>25	5	1.6, 0.5–4.8
				P for trend:0.4
Pyrethroid insecticides				
Rusiecki 2009 [53]	Permethrin	Lifetime days of exposure [5]		Relative rate, 95% CI:
		Nonexposed	94	1.0, Referent
		Tertile 1, ≤8.74	8	0.8, 0.4–1.7
		Tertile 2, 8.75–50.75	5	0.6, 0.3–1.7
		Tertile 3, >50.75	5	0.7, 0.3–1.7
				P for trend: 0.2
		Intensity-weighted lifetime days of exposure [5]		
		Nonexposed	94	1.0, Referent
		Tertile 1, ≤8.74	7	0.8, 0.4–1.8
		Tertile 2, 8.75–50.75	7	0.9, 0.4–2.0
		Tertile 3, >50.75	4	0.5, 0.2–1.3
				P for trend: 0.2

Table 2. *Cont.*

Author, date	Pesticide	Category of exposure	N exposed	Effect estimate, 95% CI
Other insecticides				
Eriksson 2008 [32] [3]	Pyretrine	Days of exposure [4]		OR, 95% CI:
		≤25	8 cases/5 controls	1.9, 0.6–5.8
		>25	6 cases/5 controls	1.4, 0.4–4.5
	Mercurial seed dressing	Days of exposure [4]		
		≤12	7 cases/6 controls	1.3, 0.4–3.8
		>12	14 cases/5 controls	2.9, 1.0–8.3
	Fumigant fungicides			
Barry 2012 [19]	Methyl Bromide	Intensity weighted lifetime days of exposure [5]		Rate ratio, 95% CI:
		Nonexposed	166	1.0, Referent
		Tertile 1, >0–310	21	2.3, 1.4–3.9
		Tertile 2, 311–1519	8	0.7, 0.3–1.6
		Tertile 3, >1519	6	0.6, 0.3–1.5
				P for trend: 0.1
		Intensity weighted lifetime days of exposure, 15 year lag [5]		
		Nonexposed	174	1.0, Referent
		Tertile 1, >0–310	13	1.7, 0.9–3.1
		Tertile 2, 311–1519	6	0.6, 0.3–1.5
		Tertile 3, >1519	8	1.0, 0.5–2.1
				P for trend: 0.7

Notes: CI, confidence interval; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; [1] Categories based on mid-points of the questionnaire category; [2] Categories based on distribution among users; [3] Effect estimates in association with dichotomous exposure were also reported; [4] Categories based on the number of days of exposure among controls; [5] Categories based on the distribution of exposure among cancer cases; [6] Substantial indicates the person was exposed to the substance at a medium or high level for more than five 8-hour days per year for a combined total of more than 5 years. Non-substantial indicates any other combination of exposures; estimates derive from a case-control study.

Table 3. Associations of subtypes of non-Hodgkin lymphoma with herbicides and insecticides.

	Chemical	Number of exposed cases	Risk ratio, 95% CI
B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.9, 1.0–3.5
Phenoxy herbicides			
Cocco 2012 [28]	Phenoxy herbicides	12 cases	1.4, 0.6–3.1
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.0, 1.2–3.3
Fritschi 2005 [62] [1]	Phenoxy herbicides	NR	No exposure: 1.0, Referent Non-substantial exposure: 0.6, 0.3–1.5 Substantial exposure: 1.5, 0.3–6.6
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.7, 0.9–3.0
Cocco 2012 [28]	2,4-D (Phenoxy herbicide)	2 cases	0.6, 0.1–3.5
Cocco 2012 [28]	MCPA (Phenoxy herbicide)	4 cases	Infinity (zero exposed controls)
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	2.6, 1.1–5.9
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	4 cases (small lymphocytic)	1.1, 0.3–3.4
Zheng 2001 [60]	EPTC + Protectant (Thiocarbamate herbicides)	2 cases (small lymphocytic)	1.5, 0.3–7.1
Cocco 2012 [28]	Triazines and triazoles	6 cases	0.7, 0.2–1.7
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticide)	9 cases(small lymphocytic)	2.9, 1.2–7.0
Zheng 2001 [60]	Carbofuran (Carbamate insecticide)	7 cases (small lymphocytic)	1.5, 0.6–3.8
Cocco 2012 [28]	Methomyl (Carbamate insecticide)	0 cases	NR(zero exposed cases)
Cocco 2012 [28]	Mancozeb (Dithiocarbate fungicide)	2 cases	0.6, 0.1–3.5
Cocco 2012 [28]	Glyphosate (OP herbicide)	4 cases	3.1, 0.6–17.1

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Organochlorine (OC) insecticides			
Cocco 2012 [28]	Organochlorines	27 cases	0.9, 0.5–1.4
Fritschi 2005 [62] [1]	Organochlorines	NR	No exposure: 1.0, Referent Nonsubstantial: 1.1, 0.5–2.5 Substantial: 3.5, 0.7–17.3
Baris 1998 [20] [2]	DDT (OC insecticides)	22 cases	1.6, 0.8–2.9
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.3, 0.8–2.1
Cocco 2012 [28]	DDT (OC insecticide)	3 cases	1.2, 0.2–5.9
Cocco 2012 [28]	Endosulfan (OC insecticide)	0 cases	NR, zero exposed cases
Organophosphorus insecticides			
Cocco 2012 [28]	Organophosphates	23 cases	1.4, 0.8, 2.6
Zheng 2001 [60] [2]	Organophosphates	18 cases	1.6, 0.8–3.2
Fritschi 2005 [62] [1]	Organophosphates	NR	No exposure [1]: 1.0, Referent Non-substantial: 0.6, 0.3–1.2 Substantial: 2.1, 0.8–5.7
Cocco 2012 [28]	Dimethoate (OP insecticide)	3 cases	1.8, 0.3–10.6
Waddell 2001 [56] [2]	Fonofos (OP insecticide)	5 cases	2.6, 0.8–8.5
Waddell 2001 [56] [2]	Malathion (OP insecticide)	10 cases	1.9, 0.8–4.7
Waddell 2001 [56] [2]	Diazinon (OP insecticide)	9 cases	2.8, 1.1–7.3
Waddell 2001 [56] [2]	Phorate (OP insecticides)	8 cases	2.3, 0.9–6.0
Waddell 2001 [56] [2]	Terbufos (OP insecticides)	5 cases	2.2, 0.7–7.4
Other insecticides			
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	1.7, 0.7–3.9
Eriksson 2008 [32]	Mercurial seed dressing	NR	1.8, 0.8–3.9

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Mature B cell lymphoma			
Beane Freeman 2011 [22]	Atrazine (Triazine herbicide)	Lifetime days of exposure:	
		Quartile 1, >0–20: 36	1.0, Referent
		Quartile 2, 21–56: 34	1.0, 0.7–1.7
		Quartile 3, >56–178.5: 31	0.9, 0.5–1.4
		Quartile 4, >178.5: 28	0.9, 0.6–1.6
			P for trend: 0.8
		Intensity weighted lifetime days of exposure:	
		Quartile 1, >0–20: 34	1.0, Referent
		Quartile 2, 21–56: 38	1.1, 0.7–1.8
		Quartile 3, >56–178.5: 25	0.8, 0.5–1.3
		Quartile 4, >178.5: 31	0.9, 0.6, 1.5
			P for trend: 0.7
Diffuse large B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicides)	NR	1.2, 0.4–3.4
Phenoxy herbicides			
Cocco 2012 [28]	Phenoxy herbicides	4 cases	1.7, 0.5–5.2
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.2, 1.1–4.3
Fritschi 2005 [62] [1]	Phenoxy herbicides	NR	No exposure [1]: 1.0, Referent
			Nonsubstantial exposure: 0.5, 0.1–2.0
			Substantial exposure: 2.2, 0.4–13.1
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	3.9, 1.5–10.5
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.7, 0.7–3.8

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	15 cases	1.6, 0.9–3.1
Zheng 2001 [60]	EPTC + Protectant (Thiocarbamate herbicides)	10 cases	1.8, 0.8–3.7
Triazine herbicides			
Cocco 2012 [28]	Triazines and triazoles	2 cases	0.8, 0.2–3.4
Beane Freeman 2011 [22]	Atrazine (Triazine herbicides)	Lifetime exposure days:	
		Quartile 1, >0–20: 20	1.0, Referent
		Quartile 2, 21–56: 14	0.8, 0.4–1.6
		Quartile 3, >56–178.5: 14	0.7, 0.4–1.5
		Quartile 4, >178.5: 11	0.7, 0.3–1.6
			p for trend:0.5
		Intensity-weighted lifetime exposure days:	
		Quartile 1, >0–20: 15	1.0, Referent
		Quartile 2, 21–56: 18	1.2, 0.6–2.5
		Quartile 3, >56–178.5: 11	0.8, 0.4–1.7
		Quartile 4, >178.5: 15	1.1, 0.5–2.3
			p for trend:0.96
Zahm 1993 [59]	Atrazine (Triazine herbicides)	66 cases	1.6, 1.1–2.2
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticides)	15 cases	1.5, 0.8–2.8
Zheng 2001 [60]	Carbofuran (Carbamate insecticides)	24 cases	1.6, 1.0–2.7

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Organochlorine insecticides			
Cocco 2012 [28]	Organochlorines	5 cases	0.6, 0.2–1.6
	Organochlorines	NR	No exposure [1]: 1.0, Referent
Fritschi 2005 [62] [1]			Non-substantial exposure: 1.2, 0.4–3.4
			Substantial exposure: 1.6, 0.2–18.1
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.2, 0.6–2.5
Baris 1998 [20]	DDT (OC insecticide)	53 cases	1.2, 0.8–1.7
Organophosphorus insecticides			
Cocco 2012 [28]	Organophosphates	5 cases	1.1, 0.4–2.9
Waddell 2001 [56]	Organophosphates	63 cases	1.8, 1.2–2.6
Fritschi 2005 [62]	Organophosphates	NR	No exposure [1]: 1.0, Referent
			Non-substantial exposure: 0.6, 0.3–1.6
			Substantial exposure: 2.1, 0.6–7.7
Waddell 2001 [56]	Fonofos (OP insecticide)	10 cases	1.3, 0.6–2.7
Waddell 2001 [56]	Malathion (OP insecticide)	19 cases	1.1, 0.6–1.9
Waddell 2001 [56]	Diazinon (OP insecticide)	13 cases	1.2, 0.6–2.4
Waddell 2001 [56]	Phorate (OP insecticide)	10 cases	0.8, 0.4–1.8
Waddell 2001 [56]	Terbufos (OP insecticide)	7 cases	0.8, 0.4–2.0
Other insecticides			
Cocco 2012 [28]	Arsenicals	2 cases	0.4, 0.1–1.6
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	1.3, 0.3–4.6
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.2, 0.8–6.1
Chronic lymphocytic leukemia			
HERBICIDES			
Cocco 2012 [28]	Phenoxy acids	Ever *vs.* never exposed	
		2 cases ever exposed	0.9, 0.2–4.1
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
		Low: 0 cases	
		Medium/high: 2 cases	2.4, 0.4–13.8
Cocco 2012 [28]	Triazines and triazoles	2 cases	0.9, 0.2–4.1
INSECTICIDES			
Cocco 2012 [28]	Arsenicals	15 cases	1.6, 0.8–2.9
Cocco 2012 [28]	Carbamates		
Cocco 2012 [28]	Organochlorines	Ever *vs* never exposed	
		10 cases ever exposed	1.2, 0.6–2.5
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent
		Low: 5 cases	1.8, 0.6–5.0
		Medium/high: 5 cases	1.0, 0.4–2.8
Cocco 2012 [28]	Organophosphates	Ever *vs* never exposed	
		9 cases ever exposed	2.7, 1.2–6.0
		Intensity of exposure	
		Unexposed: 362 cases	1.0, Referent
		Low: 5 cases	2.7, 0.9–7.8
		Medium/high: 4 cases	2.6, 0.7–9.2
Lymphocytic lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	3.4, 1.4–7.9
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.1, 1.0–4.5
Cocco 2013 [28]	Phenoxy herbicides	NR	0.9, 0.2–4.1

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicides)	NR	1.9, 0.9–4.4
Eriksson 2008 [32]	MCPA (Phenoxy herbicides)	NR	2.6, 0.7–9.0
INSECTICIDES			
Organochlorine insecticides			
Eriksson 2008 [32]	DDT (OC insecticides)	NR	1.4, 0.7–2.8
Organophosphorus insecticides			
Fritschi 2005 [62] [1]	Organophosphates	NR	No exposure: 1.0, Referent Non-substantial exposure: 1.1, 0.5–2.3 Substantial exposure: 4.3, 1.4–13.0
Other insecticides			
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.4, 0.7–7.9
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.9, 1.0–8.3
Follicular lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.9, 0.6–5.8
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.3, 0.4–3.8
Fritschi 2005 [62] [1]	Phenoxy herbicides	NR	No exposure: 1.0, Referent Non-substantial exposure: 0.5, 0.1–2.0 Substantial exposure: 1.2, 0.1–11.2
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	1.2, 0.4–4.2
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	No exposed cases
Thiocarbamate herbicides			
Zheng 2001 [60]	Butylate (Thiocarbamate herbicides)	17 cases	1.5, 0.8–2.8
Zheng 2001 [60]	EPTC + Protectant use (Thiocarbamate herbicides)	10 cases	1.7, 0.8–3.8

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Triazine herbicides			
Zahm 1993 [59]	Atrazine (Triazine herbicide)	40 cases	1.3, 0.9–1.9
Beane Freeman 2011 [22]	Atrazine (Triazine herbicide)	Lifetime exposure days, by quartile:	
		Quartile 1, >0–20: 10	1.0, Referent
		Quartile 2, 21–56: 8	0.9, 0.3–2.2
		Quartile 3, >56–178.5: 6	0.6, 0.2–1.7
		Quartile 4, >178.5: 8	1.0, 0.4–2.6
			p for trend: 0.9
		Intensity-weighted exposure days:	
		Quartile 1, >0–20: 10	1.0, Referent
		Quartile 2, 21–56: 10	1.0, 0.4–2.4
		Quartile 3, >56–178.5: 8	0.8, 0.3–2.1
		Quartile 4, >178.5: 4	0.4, 0.1–1.3
			p for trend: 0.07
INSECTICIDES			
Carbamate insecticides			
Zheng 2001 [60]	Carbaryl (Carbamate insecticides)	14 cases	1.3, 0.6–2.4
Zheng 2001 [60]	Carbofuran (Carbamate insecticides)	22 cases	1.4, 0.8–2.4
Organochlorine insecticides			
Fritschi 2005 [62][1]	Organochlorines	NR	No exposure: 1.0, Referent
			Non-substantial exposure: 1.8, 0.7–4.8
			Substantial exposure: 3.5, 0.5–25.2
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.1, 1.1–4.4
Baris 1998 [20]	DDT (OC insecticide)	47 cases	1.3, 0.8–1.9
Organophosphorus insecticides			
Waddell 2001 [56]	OP pesticides, group	50 cases	1.3, 0.9–2.0
Waddell 2001 [56]	Fonofos (OP insecticide)	14 cases	1.2, 0.6–2.4
Waddell 2001 [56]	Malathion (OP insecticide)	29 cases	1.3, 0.8–2.2

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Waddell 2001 [56]	Diazinon (OP insecticide)	17 cases	1.3, 0.7–2.3
Waddell 2001 [56]	Phorate (OP insecticide)	10 cases	0.7, 0.3–1.4
Waddell 2001 [56]	Terbufos (OP insecticide)	9 cases	0.7, 0.3–1.6
Eriksson 2008 [32]	Mercurial seed dressing	NR	3.6, 1.2–10.9
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.6, 0.8–8.5
T cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP insecticide)	NR	2.3, 0.5–10.4
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.6, 0.4–7.3
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicides)	NR	1.0, 0.1–8.0
Eriksson 2008 [32]	MCPA (Phenoxy herbicides)	NR	2.4, 0.3–20.0
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.9, 1.1–8.0
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.1, 0.3–17.1
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	2.2, 0.3–17.8
Unspecified NHL			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP insecticide)	NR	5.6, 1.4–22.0
Phenoxy herbicides			
Eriksson 2009 [32]	Phenoxy herbicides	NR	3.8, 1.2–12.1
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	3.2, 0.9–12.1
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	9.3, 2.1–41.2
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	2.4, 0.8–7.4
Eriksson 2008 [32]	Mercurial seed dressing	NR	5.4, 1.3–22.0

Table 3. *Cont.*

Author, date	Chemical	Number of exposed cases	Risk ratio, 95% CI
Eriksson 2008 [32]	Pyrethrine (Botanical insecticide)	NR	3.1, 0.4–26.3
Other specified B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.6, 0.5–5.0
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	2.6, 1.2–5.6
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	2.2, 0.9–5.4
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	3.2, 1.0–10.7
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	1.3, 0.6–3.1
Eriksson 2008 [32]	Mercurial seed dressing	NR	2.4, 0.7–7.8
Eriksson 2008 [32]	Pyretrine	NR	1.5, 0.3–6.9
Unspecified B cell lymphoma			
HERBICIDES			
Organophosphorus herbicides			
Eriksson 2008 [32]	Glyphosate (OP herbicide)	NR	1.5, 0.3–6.6
Phenoxy herbicides			
Eriksson 2008 [32]	Phenoxy herbicides	NR	1.1, 0.3–4.0
Eriksson 2008 [32]	2,4,5-T and/or 2,4-D (Phenoxy herbicide)	NR	0.9, 0.2–3.9
Eriksson 2008 [32]	MCPA (Phenoxy herbicide)	NR	1.4, 0.2–11.2
INSECTICIDES			
Eriksson 2008 [32]	DDT (OC insecticide)	NR	0.2, 0.0–1.8
Eriksson 2008 [32]	Mercurial seed dressing	NR	No exposed cases

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; NR, Not reported; OC, Organochlorine; OP, Organophosphorus; [1] Substantial indicates the person was exposed to the substance at a medium or high level for more than five 8-hour days per year for a combined total of more than 5 years. Nonsubstantial indicates any other combination of exposures; estimates derive from a case-control study; [2] NHL subtype is labeled small lymphocytic in the paper.

In the Agricultural Health Study, Delancey *et al.* [29] observed a fairly strong dose response relationship between exposure to metribuzin, a triazinone herbicide, and NHL (P for trend: 0.13). Waddell *et al.* [56] observed a dose-response relationship between years of use of the organophosphorus insecticide fonofos and NHL. These authors also observed a strong positive relationship between days/year of exposure to another organophosphorus insecticide, terbufos, and NHL (OR, 95% CI for ≥5 days *vs.* non-farmers: 4.0, 1.1–14.5).

Table 3 shows estimates of association between subtypes of NHL and chemical groups or active ingredients. Table 4 shows the individual effect estimates of associations with herbicides, fungicides, and insecticides, coded dichotomously.

Table 4. Effect estimates from papers that investigated associations between non-Hodgkin lymphoma and herbicide, fungicide, and insecticide exposures, categorized dichotomously.

Author, date	N exposed	Risk ratio, 95% CI
HERBICIDES		
Amide herbicides		
Amide herbicides, group		
Hoar 1986 [34]	8 cases/22 controls	2.9, 1.1–7.6
Cantor 1992 [27]	58 cases/114 controls	1.2, 0.8–1.7
Zahm 1993 [18] [1]	8 cases/34 controls	0.9, 0.4–2.2
Orsi 2009 [46]	5 cases/12 controls	0.9, 0.3–2.8
Alachlor		
De Roos 2003 [30]	68 cases/152 controls	1.1, 0.7–1.7
Lee 2004 [39] [2]	29 cases	0.7, 0.5–1.1
Metolachlor		
De Roos 2003 [30]	13 cases/37 controls	0.7, 0.3–1.6
Propachlor		
De Roos 2003 [30]	20 cases/50 controls	1.0, 0.5–2.0
Propyzamide		
Mills 2005 [45]	NR	0.7, 0.3–1.4
Organophosphorus herbicides		
Glyphosate		
McDuffie 2001 [43]	51 cases/133 controls	1.2, 0.8–1.7
Hardell 2002 [33]	8 cases/8 controls	3.0, 1.1–8.5
De Roos 2003 [30]	36 cases/61 controls	2.1, 1.1–4.0
De Roos 2005 [31] [2]	71 cases	1.1, 0.7–1.9
Eriksson 2008 [32]	29 cases/18 controls	2.0, 1.1–3.7
Orsi 2009 [46]	12 cases/24controls	1.0, 0.5–2.2
Phosphonic acid		
McDuffie 2001 [43]	63 cases/147 controls	1.4, 0.9–1.9
Phenoxy herbicides		
Phenoxy herbicides, group		
Hoar 1986 [34]	24 cases/78 controls	2.2, 1.2–4.1
Pearce 1987 [48]	81 cases/143 controls	1.0, 0.8–1.4
Woods 1987 [57]	NR	1.3, 0.9–2.0
Persson 1989 [49]	6 cases/6 controls	4.9, 1.0–23.5

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Cantor 1992 [27]	118 cases/231 controls	1.2, 0.9–1.6
Persson 1993 [50]	10 cases/14 controls	2.3, 0.2–2.8
Zahm 1993 [18] [1]	14 cases/63 controls	0.9, 0.4–1.7
Hardell 2002 [33]	64 cases/90 controls	1.7, 1.2–2.3
Miligi 2006 [44]	32 cases/28 controls	1.1, 0.6–1.8
Eriksson 2008 [32]	47 cases/26 controls	2.0, 1.2–3.4
Orsi 2009 [46]	11 cases/25 controls	0.9, 0.4–1.9
Pahwa 2012 [47]	129 cases/138 controls	1.5, 1.1–1.9
2,4-D		
Zahm 1990 [58]	43 cases/98 controls	1.5, 0.9–2.5
Cantor 1992 [27]	Ever handled: 115 cases/227 controls	1.2, 0.9–1.6
Cantor 1992 [27] [3]	Handled prior to 1965: 86 cases/153 controls	1.3, 0.9–1.8
Mills 2005 [45]	NR	3.8, 1.9–7.8
Miligi 2006 [44]	17 cases/18 controls	0.9, 0.5–1.8
Pahwa 2012 [47]	110 cases/293 controls	1.3, 1.0–1.7
2,4,5-T		
De Roos 2003 [30]	Ever handled: 25 cases/63 controls	1.0, 0.5–1.9
Cantor 1992 [27] [3]	Handled prior to 1965: 13 cases/18 controls	1.7, 0.8–3.6
2,4,5-T and/or 2,4-D		
Eriksson 2008 [32]	33 cases/21 controls	1.6, 0.9–3.0
Diclofop-methyl		
McDuffie 2001 [43]	9 cases/25 controls	1.0, 0.4–2.2
MCPA		
Hardell 2002 [33]	21 cases/23 controls	2.6, 1.4–4.9
De Roos 2003 [30] [1]	8 cases/16 controls	1.0, 0.4–2.6
Miligi 2006 [44]	18 cases/19 controls	0.9, 0.4–1.8
Eriksson 2008 [32]	21 cases/9 controls	2.8, 1.3–6.2
Pahwa 2012 [47]	17 cases/46 controls	1.1, 0.6–2.0
Carbamate/Thiocarbamate herbicides		
Carbamate/Thiocarbamate herbicides, group		
Zahm 1993 [18] [1]	2 cases/14 controls	0.6, 0.1–2.8
McDuffie 2001 [43]	21 cases/49 controls	1.5, 0.8–2.6
Zheng 2001 [60]	60 cases/108 controls	1.5, 1.1–2.3
Butylate		
Cantor 1992 [27] [3]	Handled prior to 1965: 1 case/6 controls	0.5, 0.1–4.3
Zheng 2001 [60]	45 cases/76 controls	1.6, 1.0–2.4
Diallate		
McDuffie 2001 [43]	11 cases/29 controls	1.5, 0.7–3.1
EPTC + Protectant		
Zheng 2001 [60]	23 cases/49 controls	1.6, 0.9–2.7

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Aromatic acid herbicides		
Benzoic acid herbicides		
Hoar 1986 [34]	1 case/2 controls	4.0, 0.1–62.6
Cantor 1992 [27]	53 cases/98 controls	1.3, 0.9–1.9
Zahm 1993 [18] [1]	4 cases/12 controls	1.2, 0.3–4.4
Chloramben		
Cantor 1992 [27] [3]	Handled prior to 1965: 16 cases/19 controls	2.0, 1.0–4.0
De Roos 2003 [30]	34 cases/81 controls	0.9, 0.5–1.6
Dicamba		
Cantor 1992 [27] [3]	Handled prior to 1965: 7 cases/7 controls	2.8, 1.0–8.1
McDuffie 2001 [43]	26 cases/50 controls	1.6, 1.0–2.6
De Roos 2003 [30]	39 cases/79 controls	1.2, 0.6–2.3
Dinitroaniline herbicides		
Dinitroanilines, group		
Cantor 1992 [27]	46 cases/88 controls	1.2, 0.8–1.8
McDuffie 2001 [43]	11 cases/31 controls	1.2, 0.6–2.4
Trifluralin		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/23 controls	1.5, 0.8–3.1
Zahm 1993 [18] [1]	3 cases/24 controls	0.5, 0.1–1.7
McDuffie 2001 [43]	11 cases/31 controls	1.1, 0.5–2.2
De Roos 2003 [30]	52 cases/120 controls	0.9, 0.5–1.6
Mills 2005 [43,45]	NR	0.9, 0.4–1.8
Triazine herbicides		
Triazine herbicides, group		
Hoar 1986 [34]	14 cases/43 controls	2.5, 1.2–5.4
Cantor 1992 [27]	64 cases/133 controls	1.1, 0.8–1.6
Zahm 1993 [18] [1]	12 cases/38 controls	1.2, 0.6–2.6
Orsi 2009 [46]	17 cases /20 controls	1.9, 0.9–3.8
Atrazine		
Zahm 1993 [59]	130 cases/249 controls	1.4, 1.1–1.8
Cyanazine		
De Roos 2003 [30]	37 cases/96 controls	0.6, 0.3–1.0
Metribuzin		
De Roos 2003 [30]	20 cases/53 controls	0.8, 0.4–1.7
Simazine		
Mills 2005 [45]	NR	1.7, 0.9–3.0
Urea herbicides		
Urea herbicides		
Cantor 1992 [27]	5 cases/18 controls	0.6, 0.2–1.6
Orsi 2009 [46]	5 cases/7 controls	1.8, 0.5–6.0
Linuron		
De Roos 2003 [30]	5 cases/22 controls	0.3, 0.1–1.2

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Other herbicides		
Bentazon		
Cantor 1992 [27]	22 cases/58 controls	0.7, 0.3–1.5
Nitrofen		
Mills 2005 [45]	NR	1.2, 0.6–2.5
Paraquat		
De Roos 2003 [30]	2 cases/15 controls	0.1, 0.2–0.7
Quaternary ammonium compounds, group		
Orsi 2009 [46]	4 cases/12 controls	0.7, 0.2–2.3
Sodium chlorate		
De Roos 2003 [30]	8 cases/7 controls	4.1, 1.3–13.6
Uracil herbicides		
Hoar 1986 [34]	19 cases/114 controls	1.3, 0.7–2.5
FUNGICIDES		
Aldehyde fungicides		
Aldehyde fungicides, group		
McDuffie 2001 [43]	7 cases/25 controls	0.9, 0.4–2.3
Formaldehyde		
McDuffie 2001 [43]	7 cases/25 controls	0.9, 0.4–2.3
Amide fungicides		
Amide fungicides, group		
McDuffie 2001 [43]	30 cases/58 controls	1.7, 1.0–2.8
Captan		
McDuffie 2001 [43]	20 cases/24 controls	2.5, 1.3–4.8
Mills 2005 [45]	NR	0.9, 0.5–1.6
Vitavax		
McDuffie 2001 [43]	10 cases/39 controls	0.8, 0.4–1.9
Carbamate and dithiocarbamate fungicides		
Carbamate fungicides		
Orsi 2009 [46]	15 cases/17 controls	1.8, 0.9–3.7
Maneb		
Mills 2005 [45]	NR	1.1, 0.6–2.1
Mancozeb		
Mills 2005 [45]	NR	0.9, 0.5–1.9
Triazole fungicides		
Triazole fungicides, group		
Orsi 2009 [46]	8 cases/9 controls	1.9, 0.7–5.3
Mecoprop		
Pahwa 2012 [47]	51 cases/81 controls	2.3, 1.5–3.3
Mercury containing fungicides		
Mercury fungicides, group		
McDuffie 2001 [43]	18 cases/48 controls	1.3, 0.7–2.3
Mercury dust		
McDuffie 2001 [43]	15 cases/39 controls	1.2, 0.6–2.4

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Mercury liquid		
McDuffie 2001 [43]	8 cases/22 controls	1.4, 0.7–3.2
Fumigant fungicides		
Methyl bromide		
Mills 2005 [45]	NR	1.5, 0.8–2.7
Dichloro-propane		
Mills 2005 [45]	NR	0.9, 0.5–1.7
Other fungicides		
Chlorothalonil		
Mills 2005 [45]	NR	1.2, 0.6–2.2
Sulfur compounds		
McDuffie 2001 [43]	17 cases/21 controls	2.8, 1.4–5.6
INSECTICIDES		
Arsenicals		
Acetoarcenate		
De Roos 2003 [30]	41 cases/68 controls	1.4, 0.9–2.3
Arsenic		
Hardell 2002 [33]	8 cases/10 controls	1.8, 0.7–4.5
Eriksson 2008 [32]	7 cases/5 controls	1.6, 0.5–5.2
Lead arsenate		
De Roos 2003 [30]	9 cases/25 controls	0.5, 0.2–1.2
Botanical insecticides		
Nicotine		
Cantor 1992 [27]	31 cases/47 controls	1.5, 0.9–2.5
Cantor 1992 [27] [3]	Handled prior to 1965: 28 cases/36 controls	1.8, 1.0–3.0
Pyrethrine		
De Roos 2003 [30]	6 cases/12 controls	1.0, 0.3–3.2
Eriksson 2008 [32]	15 cases/10 controls	1.7, 0.8–3.9
Rotenone		
Cantor 1992 [27]	12 cases/23 controls	0.5, 2.2–1.0
Carbamate insecticides		
Carbamate insecticides, group		
McDuffie 2001 [43]	37 cases/60 controls	1.9, 1.2–3.0
Zahm 1993 [18] [1]	7 cases/17 controls	1.6, 0.6–4.4
Zheng 2001 [60]	89 cases/172 controls	1.6, 1.0–2.4
Bufencarb		
De Roos 2003 [30]	6 cases/12 controls	1.1, 0.3–3.7
Carbaryl		
Cantor 1992 [27] [3]	Handled prior to 1965: 7 cases/4 controls	3.8, 1.1–13.6
De Roos 2003 [30]	30 cases/57 controls	1.0, 0.5–1.9
McDuffie 2001 [43]	25 cases/34 controls	2.1, 1.2–3.7
Carbofuran		
Cantor 1992 [27] [3]	Handled prior to 1965: 28 cases/63 controls	1.0, 0.6–1.7
McDuffie 2001 [43]	9 cases/18 controls	1.6, 0.7–3.9
Zheng 2001 [60]	66 cases/131 controls	1.6, 1.1–2.3

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Methomyl		
McDuffie 2001 [43]	37 cases/60 controls	2.1, 1.2–3.7
Fly spray		
Cantor 1992 [27]	185 cases/394 controls	1.1, 0.9–1.4
Cantor 1992 [27] [3]	Handled prior to 1965: 173 cases/368 controls	1.1, 0.9–1.4
Organochlorine insecticides		
Organochlorine insecticides, group		
Cantor 1992 [27]	150 cases/162 controls	1.3, 1.0–1.7
Zahm 1993 [18] [1]	20 cases/46 controls	1.6, 0.8–3.1
Orsi 2009 [46]	15 cases/17 controls	1.8, 0.9–3.8
Purdue 2007 [51]	58 cases/44 non cases	0.8, 0.5–1.3
Pahwa 2012 [47]	106 cases/276 controls	1.3, 1.0–1.7
Aldrin		
Cantor 1992 [27] [3]	Handled prior to 1965: 34 cases/59 controls	1.3, 0.8–2.1
McDuffie 2001 [43]	10 cases/6 controls	4.2, 1.5–12.0
De Roos 2003 [30]	47 cases/97 controls	1.1, 0.7–1.7
Purdue 2007 [51]	21 cases/79 non-cases	0.6, 0.3–1.0
Chlordane		
Woods 1987 [57]	NR	1.6, 0.7–3.8
Cantor 1992 [27] [3]	Handled prior to 1965: 22 cases/22 controls	2.2, 1.2–4.2
McDuffie 2001 [43]	36 cases/105 controls	1.1, 0.7–1.7
De Roos 2003 [30]	21 cases/26 controls	1.7, 0.9–3.2
Purdue 2007 [51]	27 cases/73 non-cases	0.7, 0.4–1.2
DDT		
Woods 1987 [57]	Not reported	1.8, 1.0–3.2
Cantor 1992 [27] [3]	Handled prior to 1965: 68 cases/123 controls	1.3, 0.9–1.8
Persson 1993 [50]	4 case/3 controls	2.0, 0.2–18.9
Baris 1998 [20]	161 cases/340 controls	1.2, 1.0–1.6
Hardell 2002 [33]	77 cases/138controls	1.2, 0.9–1.7
De Roos 2003 [30]	98 cases/226 controls	1.0, 0.7–1.3
Purdue 2007 [51]	37 cases/63 noncases	0.9, 0.6–1.5
Eriksson 2008 [32]	50 cases/37 controls	1.5, 0.9–2.3
Pahwa 2012 [47]	33 cases/59 controls	1.7, 1.1–2.7
Dieldrin		
Cantor 1992 [27] [3]	Handled prior to 1965: 10 cases/13 controls	1.9, 0.8–4.4
De Roos 2003 [30]	21 cases/39 controls	1.8, 0.8–3.9
Purdue 2007 [51]	7 cases/92 controls	0.6, 0.2–1.3
Heptachlor		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/25 controls	1.3, 0.6–2.6
De Roos 2003 [30]	25 cases/43 controls	1.3, 0.7–2.2
Purdue 2007 [51] [2]	18 cases/82 noncases	0.8, 0.4–1.4
Lindane		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/25 controls	2.2, 1.0–4.7
Blair 1998 [23]	93 cases/151 controls	1.5, 1.1–2.0

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
McDuffie 2001 [43]	15 cases/23 controls	2.1, 1.0–4.2
Rafnsson 2006 [52]	37 cases/133 controls	3.5, 1.4–9.0
Purdue 2007 [51] [2]	24 cases/76 controls	1.3, 0.8–2.1
Methoxychlor		
McDuffie 2001 [43]	65 cases/201 controls	1.0, 0.7–1.4
De Roos 2003 [30]	9 cases/16 controls	1.2, 0.5–2.7
Toxaphene		
Cantor 1992 [27] [3]	Handled prior to 1965: 6 cases/5 controls	2.4, 0.7–8.2
De Roos 2003 [30]	10 cases/13 controls	1.5, 0.6–3.5
Purdue 2007 [51] [2]	24 cases/75 controls	1.5, 0.9–2.5
Organophosphorus insecticides		
Organophosphorus insecticides		
Zahm 1993 [18] [1]	14 cases/43 controls	1.2, 0.6–2.5
Waddell 2001 [56]	158 cases/279 controls	1.5, 1.2–1.9
Orsi 2009 [46]	20 cases/24 controls	1.7, 0.9–3.3
Pahwa 2012 [47]	92 cases/169 controls	1.9, 1.4–2.6
Chlorpyrifos		
Waddell 2001 [56]	7 cases/8 controls	3.2, 1.1–9.2
Lee 2004 [38] [2]	37 participants	1.0, 0.6–1.7
Coumaphos		
Cantor 1992 [27] [3]	Handled prior to 1965: 3 cases/5 controls	1.5, 0.3–6.3
Waddell 2001 [56]	23 cases/37 controls	1.7, 1.0–2.9
Crufomate		
Waddell 2001 [56]	5 cases/8 controls	1.6, 0.5–4.9
Diazinon		
Cantor 1992 [27] [3]	Handled prior to 1965: 14 cases/12 controls	2.6, 1.2–5.9
McDuffie 2001 [43]	18 cases/28 controls	1.7, 0.9–3.2
Waddell 2001 [56]	60 cases/93 controls	1.7, 1.2–2.5
Mills 2005 [45]	NR	1.4, 0.8–2.5
Dichlorvos		
Cantor 1992 [27] [3]	Handled prior to 1965: 12 cases/17 controls	1.8, 0.8–3.9
Waddell 2001 [56]	23 cases/51 controls	1.0, 0.6–1.7
Koutros 2008 [37] [2]	6 exposed cases	NR
Dimethoate		
McDuffie 2001 [43]	22 cases/50 controls	1.2, 0.7–2.1
Waddell 2001 [56]	12 cases/22 controls	1.8, 0.9–3.8
Disulfoton		
Waddell 2001 [56]	7 cases/13 controls	2.0, 0.8–5.3
Ethoprop		
Waddell 2001 [56]	7 cases/17 controls	0.9, 0.4–2.3
Famphur		
Waddell 2001[56]	18 cases/47 controls	1.0, 0.5–1.8
Fensulfothion		
Waddell 2001 [56]	4 cases/4 controls	2.0, 0.5–8.2

Table 4. *Cont.*

Author, date	N exposed	Risk ratio, 95% CI
Fonofos		
Waddell 2001 [56]	43 cases/67 controls	1.7, 1.1–2.6
Malathion		
Cantor 1992 [27] [3]	Handled prior to 1965: 11 cases/9 controls	2.9, 1.1–7.4
Waddell 2001 [56]	91 cases/147 controls	1.6, 1.2–2.2
Mills 2005 [45]	NR	1.8, 1.0–3.2
Pahwa 2012 [47]	72 cases/127 controls	2.0, 1.4–2.7
Methyl parathion		
Mills 2005 [45]	NR	0.6, 0.3–1.2
Parathion		
Waddell 2001 [56]	5 cases/8 controls	2.9, 0.9–9.7
Phorate		
Cantor 1992 [27] [3]	Handled prior to 1965: 9 cases/12 controls	1.8, 0.7–4.5
Waddell 2001 [56]	44 cases/97 controls	1.1, 0.8–1.7
Ronnel		
Waddell 2001 [56]	6 cases/11 controls	1.3, 0.5–3.6
Terbufos		
Waddell 2001 [56]	32 cases/97 controls	1.1, 0.7–1.8
Terrachlorvinphos		
Waddell 2001 [56]	9 cases/17 controls	1.8, 0.7–4.7
Toxaphene		
Mills 2005 [45]	NR	0.9, 0.5–1.9
Trichlorfon		
Cantor 1992 [27] [3]	Handled prior to 1965: 6 cases/5 controls	2.4, 0.7–8.2
Waddell 2001 [56]	7 cases/11 controls	1.8, 0.7–4.7

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; EPTC, S-Ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; NHL, non-Hodgkin lymphoma; NR, Not reported; [1] Only women included in analysis; [2] Cohort study; [3] Effect estimate not included in the meta-analysis; another estimate from the same paper with a larger number of exposed cases was used..

3.4. Meta Analyses

When there was more than one effect estimate for a chemical group or active ingredient, the estimates shown in Tables 3 and 4 were combined to produce meta-analytic summary estimates and 95% CIs (Table 5).

The strongest meta RR estimates were associated with subtypes of NHL. There was a positive association between exposure to organophosphorus herbicide, glyphosate, and B cell lymphoma (2.0, 95% CI: 1.1–3.6, CLR: 3.2). Phenoxy herbicide exposures were associated with B cell lymphoma (1.8, 95% CI: 1.2–2.8, CLR: 2.4), lymphocytic lymphoma (1.8, 95% CI: 0.9–3.5, CLR: 3.8), and diffuse large B-cell lymphoma (DLBCL; 2.0, 95% CI: 1.1–3.7, CLR: 3.3). All these effect estimates were relatively precise, with CLRs < 4.

Table 5. Meta analytic summary estimates of association between herbicides and insecticides with non-Hodgkin lymphoma.

Chemical group or active ingredient	Meta Risk Ratio estimate, 95% CI	I^2	Papers contributing
HERBICIDES			
Amide herbicides			
Amide herbicides	1.3, 0.8–1.9	22.2%	[18,27,34,46]
Alachlor	0.9, 0.6–1.3	43.0%	[30,39]
Aromatic acid herbicides			
Benzoic acid herbicides	1.3, 0.9–1.9	0.0%	[18,27,34,46]
Dicamba	1.4, 1.0-2.1	0.0%	[30,43]
Carbamate/thiocarbamate herbicides			
Carbamate/thiocarbamate herbicides	1.4, 1.1–2.0	0.0%	[18,43,60]
Dinitroanilines			
Dinitroanilines	1.2, 0.8–1.7	0.0%	[27,43]
Trifluralin	0.9, 0.6–1.3	0.0%	[18,30,43,45]
Organophosphorus herbicides			
Glyphosate	1.5, 1.1–2.0	32.7%	[30–33,43,46]
Glyphosate-association with B cell lymphoma	2.0, 1.1–3.6	0.0%	[32,63]
Phenoxy herbicides			
Phenoxy herbicides	1.4, 1.2–1.6	37.7%	[27,32–34,44, 46–50,57,59]
Phenoxy herbicides, association with B cell lymphoma	1.8, 1.2–2.8	0.0%	[32,63]
Phenoxy herbicides, association with DLBCL	2.0, 1.1–3.7	0.0%	[32,63]
Phenoxy herbicides, association with lymphocytic lymphoma	1.8, 0.9–3.5	0.0%	[32,63]
2,4-D	1.4, 1.0–1.9	61.5%	[27,44,45,47,58]
MCPA	1.5, 0.9–2.5	54.4%	[30,32,33,44,47]
Triazine herbicides			
Triazine herbicides	1.5, 1.0, 2.1	38.5%	[18,27,34,46]
Urea herbicides			
Urea herbicides, group	1.0, 0.3–2.9	43.4%	[27,46]
INSECTICIDES			
Arsenicals			
Arsenic	1.7, 0.8–3.6	0.0%	[32,33]
Botanical insecticides			
Pyrethrine	1.4, 0.8–2.8	0.0%	[30,32]
Carbamate insecticides			
Carbamate insecticides, group	1.7, 1.3–2.3	0.0%	[18,43,60]
Carbaryl	1.7, 1.3–2.3	0.0%	[43,60]
Carbofuran	1.6, 1.2–2.3	0.0%	[43,60]
Organophosphorus insecticides			
Organophosphorus insecticides, group	1.6, 1.4–1.9	0.0%	[18,46,47,56]
Chlorpyrifos	1.6, 0.6–4.9	72.0%	[38,56]
Diazinon	1.6, 1.2–2.2	0.0%	[43,45,56]
Dimethoate	1.4, 0.9–2.1	0.0%	[43,56]
Malathion	1.8, 1.4–2.2	0.0%	[45,47,56]

Table 5. *Cont.*

Chemical group or active ingredient	Meta Risk Ratio estimate, 95% CI	I^2	Papers contributing
Organochlorine insecticides			
Organochlorine insecticides, group	1.3, 1.0–1.5	19.6%	[18,27,46,47,51]
DDT	1.3, 1.1–1.5	0.0%	[20,32,33,47,50,51,57]
DDT-association with B cell lymphoma	1.4, 1.0–2.0	0.0%	[20,32,63]
DDT-association with DLBCL	1.2, 0.9–1.7	0.0%	[20,32]
DDT-association with follicular lymphoma	1.5, 1.0–2.4	26.6%	[20,32]
Methoxychlor	1.0, 0.7–1.4	0.0%	[30,43]
Aldrin	1.0, 0.4–2.7	84.6%	[30,43,51]
Chlordane	1.1, 0.8–1.6	32.5%	[30,43,51,57]
Dieldrin	1.1, 0.4–3.1	67.6%	[30,51]
Heptachlor	0.9, 0.6–1.5	0.0%	[30,51]
Lindane	1.6, 1.2–2.2	26.0%	[23,43,51,52]
Toxaphene	1.4, 0.9–2.1	0.0%	[30,45,51]
Amide fungicides			
Captan	1.5, 0.5–4.2	82.5%	[43,45]

Notes: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; EPTC, s-ethyl dipropylthiocarbamate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; OC, Organochlorine; OP; Organophosphorus.

The meta RR estimates (95% CI) of association between phenoxy herbicide exposure and NHL subtypes were more positive than those for NHL overall, although the estimate of association with NHL overall was more precise (meta RR, 95% CI: 1.4, 1.2–1.6, CLR: 1.4). Only two papers contributed to each of the estimates of association between phenoxy herbicide exposures and NHL subtypes, and 12 papers contributed to the meta RR estimates for the relationship between phenoxy herbicide exposure and NHL overall.

There was a positive and relatively precise association between NHL and the phenoxy herbicide 2-methyl-4-chlorophenoxyacetic acid (MCPA) (meta RR, 95% CI: 1.5, 0.9–2.5, CLR: 2.6). Five estimates contributed to this summary estimate; an I^2 value of 54.4% indicates some inconsistency in the effect estimates. The forest plot for the meta-analysis of MCPA, along with plots for meta-analyses of phenoxy herbicicides as a group, the phenoxy herbicide 2,4-D, glyphosate, organochlorine insecticides as a group, and the organochlorine insecticide DDT, are presented in Supplementary Figure S1.

In addition to assessing the association of ever exposure to MCPA with NHL, Hardell *et al.* [33] investigated dose-response relationships between number of days of exposure; they observed increasing odds in association with increased number of days of MCPA exposure (Table 2). In similar analyses, Eriksson *et al.* [32] and Mcduffie *et al.* [43] did not observe dose-response relationship between days/year of MCPA exposure and NHL.

There was a positive but less precise estimate of association between arsenic and NHL (meta RR, 95% CI: 1.7, 0.8–3.6, CLR: 4.4). Meta estimates of association between NHL and carbamate insecticides and carbaryl, a carbamate insecticide, were nearly identical (meta RR, 95% CI: 1.7, 1.3–2.3,

CLR: 1.8) and both were positive and precise. Estimates from three papers contributed to the meta analysis of carbamate insecticides. The I^2 value was 0%, indicating consistency in effect estimates. Carbofuran, another carabamate insecticide, was positively associated with NHL (meta RR, 95% CI: 1.6, 1.2–2.3, CLR: 2.0). However, in two investigations from the Agricultural Health Study that reported estimates of association with tertiles of lifetime days of exposure to carbofuran [25] and carbaryl [42], the relationships were imprecise and there was a lack of a dose-response relationship (Table 2).

There were positive and precise estimates of association between NHL and organophosphorus insecticides (meta RR, 95% CI: 1.6, 1.4–1.9, CLR: 1.4), and the organophosphorus insecticides diazinon (meta RR, 95% CI: 1.6, 1.2–2.2, CLR: 1.8), and malathion (meta RR, 95% CI: 1.8, 1.4–2.2, CLR: 1.5). Although Fritschi *et al.* [62] studied the relationship between organophosphorus insecticides and NHL, we did not include the estimate from their paper in the meta analysis because they investigated the association with exposure in three categories (no exposure, non-substantial exposure, substantial exposure). Fritschi *et al.* [62] reported a positive but imprecise estimate for substantial exposure *versus* no exposure (odds ratio, 95% CI: 2.1, 0.8–5.7, CLR: 7.3). The meta RR estimate of association between NHL and the organophosphorus insecticide chlorpyrifos was positive but imprecise (meta RR, 95% CI: 1.6, 0.6–4.9, CLR: 8.9). There was a positive and precise association with lindane, an organochlorine insecticide (meta RR, 95% CI: 1.6, 1.2–2.2, CLR: 1.8); estimates of association with other organochlorine insecticides were closer to the null.

3.5. Sensitivity Analyses

We conducted sensitivity analyses to examine the effect of gender (Supplementary Table S1), study design (Supplementary Table S2), diagnosis period (Supplementary Table S3), geographic region (Supplementary Table S4), source for controls in case-control studies (Supplementary Table S5) and/or the effect of using alternative papers that represent the same study population (Supplementary Table S6). For the most part, meta-estimates were robust.

3.5.1. Gender

When we subset the analyses of associations between NHL and amide herbicides to the two studies that included men only, the association became more positive but less precise (meta RR, 95% CI: moved from 1.3, 0.8–1.9, CLR: 2.3 to 1.7, 0.7–3.8, CLR: 5.3). Restricting to all male studies moved the summary estimate of the relationship with aldrin up and across the null; however, the estimate in the sensitivity analysis was too unstable to interpret (meta RR, 95% CI: moved from 1.0, 0.4–2.7, CLR: 7.8 to 1.4, 0.2–11.1, CLR: 65.0). Restricting the analysis to studies that included men and women caused the meta RR estimate of association between NHL and 2,4-D to become more positive but less precise; it moved from 1.4, 1.0–1.9, CLR: 1.9 to 1.8, 0.5–7.5, CLR: 16.7. We were not able to conduct sensitivity analyses for female only studies, since only one paper reported results for women only [18].

3.5.2. Study Design

Nearly all of the studies that contribute to the meta estimates were case control in design. The only cohort study was the Agricultural Health Study. In nearly all of the analyses of data from the

Agricultural Health Study, exposure was defined using multiple categories. However, in the papers on glyphosate [31], chlorpyrifos [38], organochlorine insecticides, aldrin, chlordane, dieldrin, lindane, and toxaphene [51], the association with ever/never use of exposure was analyzed. For the most part, restricting analyses to case control studies did not cause the meta estimate to change substantially (Supplementary Table S2). However, the magnitude of the meta RR for aldrin moved up and away from the null, but became more imprecise (it moved from 1.0, 0.4–2.7, CLR: 6.8 to 1.4, 0.2–11.1, CLR: 55.5). For lindane it changed from 1.6, 1.2–2.2, CLR: 1.8 to 1.9, 1.2–2.9, CLR: 2.4.

3.5.3. Diagnosis Period

We also investigated the sensitivity of the meta-analytic estimates to decade of cancer diagnosis (Supplementary Table S3). For the most part, estimates were robust. However, when we subset the meta-analysis of glyphosate to the two papers in which cases were diagnosed from 1975–1989, the meta RR, 95% CI changed from 1.5, 1.1–2.0, CLR: 1.8 to 2.3, 1.4–4.0, CLR: 3.0. Similarly, for the phenoxy herbicide 2,4-D, when we included estimates from the three papers with diagnosis periods from 1975 to 1989, the summary estimate was more positive but less precise (meta RR, 95% CI: 1.8, 1.0–3.1, CLR: 3.2) compared to the full meta-analysis estimate (1.4, 95% CI: 1.0–1.9; CLR: 1.9).

3.5.4. Geographic Area

We investigated the impact of geographic area on the meta-analytic RR estimates (Supplementary Table S4). For glyphosate exposure, including estimates from papers that reported results from Swedish studies caused the estimate to become more positive; it moved from 1.5, 95% CI: 1.1–2.0, CLR: 1.8 to 2.2, 95% CI: 1.3–3.8, CLR: 2.9. Similarly, restricting estimates of the relationship between NHL and phenoxy herbicide exposure to Sweden caused the estimate to become more positive; it changed from 1.4, 95% CI: 1.2–1.6, CLR: 1.4 to 1.9, 1.4–2.4, CLR: 1.7. When we restricted estimates of association with MCPA to those that came from North American studies, the meta RR moved towards the null, from 1.5, 0.9–2.5, CLR: 2.6 to 1.1, 0.7–1.8, CLR: 2.7. In contrast, restricting to European and Swedish studies caused the estimate of association with MCPA to become more positive (meta RR, 95% CI: 1.9, 0.9–3.8, CLR: 4.1 and 2.7, 1.6–4.4, CLR: 2.7 respectively). When we included estimates of association with aldrin that came from studies conducted in the USA, the estimate became more precise but moved down and away from the null (meta RR, 95% CI: 1.0, 95% CI: 0.4–2.7, CLR: 7.8 changed to 0.5, 95% CI: 0.4–0.8, CLR: 2.3).

3.5.5. Source of Controls in Case Control Studies

Only two papers reported results from case control studies in which controls were selected from the hospital [46,48]. The meta-analytic RR estimates remained robust when we restricted the estimates to those resulting from population-based case-control studies (Supplementary Table S5).

3.5.6. Alternative Papers

In several cases, analyses of the same study populations were represented in multiple papers. For the meta-analyses, we included the result(s) that represented the largest number of participants.

In some cases, we selected the result from a pooled analysis instead of the individual, original studies. In other cases, use of effect estimates from the individual studies was preferable because it represented more people. We performed sensitivity analyses to evaluate the impact of replacing results from pooled analyses of multiple studies [23,30,59,60] with the original ones [27,34,58], or the original ones with the pooled analyses (Supplementary Table S6).

When we replaced the estimate of a relationship between carbofuran exposure and NHL reported in Zheng *et al.* [60] by that reported in Cantor *et al.* [27] the relationship became weaker and less precise: the meta RR and 95% CI changed from 1.6, 1.2–2.3, CLR: 2.0 to 1.1, 0.7–1.8, CLR: 2.4. Using the estimate reported in De Roos *et al.* [30] yielded a similar result (meta RR, 95% CI changed to 1.1, 0.6–2.0, CLR: 3.1). For the relationship between aldrin and NHL, we replaced the estimate reported in De Roos *et al.* [30] by that reported by Cantor *et al.* [27]; the estimate moved from a null relationship to a positive one (meta RR, 95% CI changed from 1.0, 0.4–2.7 to 1.3, 0.5–2.9).

4. Discussion

This systematic review and series of meta-analyses show that there is consistent evidence of positive associations between NHL and carbamate insecticides, organophosphorus insecticides, lindane, an organochlorine insecticide, and MCPA, a phenoxy herbicide. Our results represent an important contribution to a growing body of literature on agricultural exposures associated with cancer. Past review papers and meta-analyses have identified positive associations between NHL and farming related exposures, including fertilizers, chemicals, and animals [5], and occupational exposures to pesticides [6].

We extracted estimates of association of NHL with individual pesticide chemical groups or active ingredients from 44 papers that reported analyses of results from 17 independent studies. The studies represented data collected in 12 countries, the majority of which were located in either Europe or North America. Several of the papers that we identified were related to one another; many used data from the same cohort study, the Agricultural Health Study, and several others pooled the same data from individual studies. Thus, although this review identified 44 papers, it also highlights the need for additional epidemiologic studies in a larger variety of geographic locations.

In the papers from which we extracted information, estimates of associations with NHL were reported with 13 herbicide chemical groups and 28 herbicide active ingredients, five fungicide groups and 12 fungicide active ingredients, and three insecticide groups and 40 insecticide active ingredients. More than 1,700 active ingredients are listed in Alan Wood's compendium of pesticide common names, although not all of these are necessarily used in agriculture or currently registered for use in any or all countries [13]. Many chemicals remain for consideration in future epidemiologic analyses of associations between NHL and pesticides. It would be useful to identify pesticides to investigate by ranking, by country, the most commonly used chemicals.

The positive and precise estimate of associations of NHL with carbamate insecticides, organophosphorus insecticides, and lindane were robust to sensitivity analyses of gender, geographic area, and cancer diagnosis period. The positive association between MCPA and NHL was robust to a sensitivity analysis of diagnosis period, but when we restricted the meta-analysis to estimates from studies conducted in North America, the estimate moved to the null.

Consistent with the results from the meta-analysis of lindane exposure, analyses of data from the American cohort, the Agricultural Health Study, revealed a positive dose-response relationship between NHL and intensity weighted lifetime days of lindane exposure, where the referent group consisted of applicators never exposed to pesticide products containing the active ingredient [51]. In this same paper, however, the estimate of association with dichotomously coded exposure to lindane was close to the null and imprecise. This difference in results within the Agricultural Health Study suggests that dichotomous classification of exposure might be too crude; the binary categories could lead to exposure misclassification and attenuated effect estimates. Because of variability in definitions and cut-points across papers, we were unable to conduct formal meta-analyses of exposures classified using multiple categories. When they were available, we reviewed estimates of dose-response relationships from the individual papers. We found that, in most of the papers in which dose-response relationships were investigated, effect estimates were imprecise due to small numbers of exposed cases within categories.

There were positive meta RR estimates of association of NHL with two carbamate insecticides, carbaryl and carbofuran, and the organophosphorus insecticide active ingredients diazinon and malathion. However, results from analyses of Agricultural Health Study data, which were not included in the meta-analyses, did not show dose response relationships between NHL and lifetime days of exposure to carbofuran [25], carbaryl [42], diazinon [29] or malathion [21,26].

Some discrepancies in findings from the Agricultural Health Study compared to the other studies could be due to differences in design (cohort *versus* case-control). Differences could also be the result of different referent category compositions. All participants of the Agricultural Health Study were pesticide applicators; therefore, the referent group generally consisted of applicators who were not exposed to the pesticide active ingredient of interest. In contrast, in the papers contributing to the meta-RR estimate for carbaryl [30,43] and carbofuran [43,60], the referent groups consisted of farmers and non-farmers [30,43], or only of non-farmers [60]. In the papers contributing to the meta-analyses of malathion and diazinon, the referent categories consisted of non-farmers [56], farmers and non-farmers [43,47], and only farm-workers [45]. It is possible that, in studies that included non-farmers in the referent group, confounding by other agricultural exposures, not adjusted for in analysis, caused estimates of association to be higher than results from Agricultural Health Study analyses.

Only a handful of papers reported associations of pesticides with NHL subtypes; this is probably due to small sample sizes. Our meta-analyses of these relationships suggested the need for further studies of this kind, especially since some of the strongest relationships were seen with the most common subtype of NHL, B cell lymphoma and, more specifically, with DLBCL. NHL are a heterogeneous group of malignancies that include multiple subtypes with varied characteristics and possibly diverse etiologies [4]. Consequently, the overall group of neoplasms represented by NHL might be too diverse as a study endpoint to adequately detect associations with pesticide exposures in epidemiologic analyses. Some but not all specific subtypes of lymphoma might be associated with pesticides, and these relationships would only be revealed by analyses of the subtypes. Pooling projects that include cases of the NHL subtypes that have been classified according to the more recent and etiologically specific definitions (B-cell, T-cell, and within these, more refined subtypes of T- and B-cell neoplasms) [65] present the opportunity to perform more sensitive

epidemiologic analyses and identify important relationships that may have been undetected if the cancer outcome was defined broadly as NHL overall. Such projects are particularly attractive for studying rarer subtypes (*i.e.*, T-cell). To this end, a pooling project within the AGRICOH consortium [64] is currently underway to investigate these associations.

There are various sources of heterogeneity across the studies that contributed to these meta-analyses; these include gender, region, cancer diagnosis period, exposure assessment methods, exposure definitions, referent groups, study populations, and/or analysis adjustment sets. Different activity patterns, which might cause differences in exposure, combined with different biological mechanisms, could result in between-gender differences in chemical exposure and disease risk associations. Pesticide use, application, and handling patterns, regulations and legislation, demographics and genetics differ by region, which could contribute to area-specific differences in associations. In the papers that contributed to the meta analyses, a variety of exposure assessment methods were used; these included self-reported chemical exposures, exposure matrices, and approximations based on number of animals raised. Differences in exposure assessment methods could influence the magnitude of effects observed, especially since some methods might be superior to others in terms of reducing the potential for exposure misclassification. Study design (case-control *versus* cohort) and source of controls in case-control studies (hospital *versus* population) could also influence the magnitude of the exposure estimates observed. In case-control studies, exposure is assessed retrospectively, which could lead to recall bias. In contrast, in the Agricultural Health Study, the only cohort included in this review, exposure was assessed when participants were cancer-free. Finally, NHL classification systems have changed over time, reflecting changes in disease definitions [1]. Recently (after year 2000), the definition of NHL has become more comprehensive. The definition now includes disease entities that were excluded from earlier definitions, such as plasma cell neoplasms (*i.e.*, multiple myeloma) and chronic lymphocytic leukemia. These malignancies are also among the most frequently reported sub-types within NHL [65]. Thus, estimates of association between pesticides and overall NHL from studies conducted in earlier periods may not be entirely comparable to estimates from research conducted since the year 2000 that used the updated NHL definition.

We did not conduct a formal test of publication bias; it is unclear if asymmetry tests with funnel plots are useful in meta-analyses of observational studies, and it has been recommended that these tests not be used when fewer than 10 studies contribute to a meta-analysis [66]. For the most part, we believe that our review was systematic and comprehensive.

Nevertheless, we did not identify papers that published results of studies conducted in middle- and low-income countries. It is possible that, in such regions where cancer-follow and exposure ascertainment may be particularly challenging, no studies have investigated the relationship of NHL with pesticide exposures. Restricting our literature search to articles published in English could be another reason that we did not identify studies in lower-income countries. A lack of studies in these areas is potentially alarming, since these regions are responsible for much of the world's agricultural production [67]. Also, lympho-hematopoetic malignancies represent a substantial proportion of cancers in low- and middle-income countries. For example, based on estimates from the World Health Organization's GLOBOCAN 2012, NHL accounted for 37.7% of the estimated prevalent cancer cases diagnosed in the past 5 years, among adults in less-developed regions (Africa, Asia excluding Japan, Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia) [68]. Nevertheless, research results

from higher-income countries could be transferable and have important implications for pesticide regulation and legislation world-wide, especially in low-income countries where protective equipment may be less available and/or used.

There are several mechanisms by which pesticide exposure might be associated with NHL. First, pesticides might cause chromosomal aberrations and genetic mutations. An often studied chromosomal abnormality is the t(14;18) translocation, which is particularly common among cases of follicular lymphoma and diffuse large B-cell lymphoma [69]. In a paper that used data from the Iowa/Minnesota case-control study that contributed to several of the pooled and individual analyses that we reviewed [23,30,59], Schroeder *et al.* [70] investigated the relationship between pesticide exposures and the t(14;18) translocation. Compared with controls, t(14;18) positive NHL cases but not t(14;18) negative cases had a higher odds of exposure to dieldrin, toxaphene, lindane, and atrazine. Chiu *et al.* [69,71] performed a similar analysis using data from the Nebraska-based case-control study and reported positive associations between t(14;18) positive NHL and dieldrin, toxapehen, and lindane. A second mechanism by which pesticide exposure may cause NHL is by altering cell mediated immune function. Indeed, immunological changes have been observed following short-term exposure to phenoxy herbicides (2,4-D and MCPA) among farmers [72].

The IARC Monographs have evaluated the carcinogenicity of a handful of pesticides. Of these, only arsenic and inorganic arsenic compounds have been given a Group 1 rating (carcinogenic to humans) [73]. The fumigant insecticide ethylene dibromide was classified as a group 2A carcinogen based on inadequate evidence for carcinogenicity in humans but sufficient evidence in experimental animals; the overall evaluation was upgraded to 2A (probably carcinogenic to humans) with supporting evidence from other relevant data [74]. In Volume 53 (1991) [75], the fungicide captafol was also classified as a group 2A carcinogen based on sufficient evidence in experimental animals but no available data from human studies. In this same volume, several other pesticides were classified as either group 2B (possibly carcinogenic to humans) or group 3 carcinogens (not classifiable as to its carcinogenicity)—aldicarb chlordane/heptachlor, DDT, deltamethrin, dichlorvos, fenvalerate, permethrin, thiram, ziram, atrazine, monuron, picloram, simazine, and trifluralin. The IARC monographs have classified other pesticides, including heptachlor, chlordane, and toxaphene [76], as group 2B carcinogens; in each of these cases, the 2B classification was based on inadequate evidence in humans but sufficient evidence in experimental animals. Chlorophenoxy herbicides were classified as group 2B carcinogens based on limited evidence for carcinogenicity in humans, and inadequate evidence for carcinogenicity of 2,4-D and 2,4,5-T in animals [77].Similarly, hexachlorocyclohexanes were evaluated as group 2B carcinogens due to inadequate evidence for carcinogenicity to humans, sufficient evidence for carcinogenicity to animals for the technical-grade and the alpha isomers but limited for the beta and gamma (lindane) isomers [77]. Several other pesticides, including malathion and maneb [77] have been classified as group 3 carcinogens. These evaluations took place several decades ago and there is now more epidemiologic literature that can provide information. There also remains a need for further epidemiologic research of certain chemicals, which could help to inform future evaluations. In the current systematic review, we did not observe entirely consistent trends in association for all of the active ingredients within chemical groups. Furthermore, classification of active ingredients into groups is subjective and there is not a consistent and established scheme for doing so. Therefore, evaluations of individual active ingredients rather than chemical groups might be more useful.

Limitations and Strengths

Because of variability in definitions and metrics that were used in published papers, we were not able to consider additional exposure definitions, such as exposure lags, duration of exposure (e.g., number of days/year exposed), or routes of exposure (e.g., application *versus* mixing of pesticides). In an effort to use similar exposure definitions from the various papers, we only included dichotomous definitions in the meta-analyses. Since dose-response relationships could not be summarized, this restricted the strength of our conclusions from an etiologic perspective. Furthermore, we were not able to conduct analyses of certain active ingredients or chemical groups due to a lack of published literature. In other cases, very few papers contributed to the meta-analyses. The largest number of papers contributing to any meta-analysis was 12 for phenoxy herbicides, followed by eight for DDT. Most meta-analyses included estimates from only two to three studies. In most papers, associations with NHL overall, rather than with subtypes of NHL, were investigated. Thus, most of our meta-analyses were of associations with NHL rather than with its subtypes, which are probably more homogeneous disease entities for assessing the relationship with pesticides. It is possible that this led to a dilution of effects, since the various NHL subtypes have diverse etiologies and some might be more strongly associated with certain pesticides than others.

Nevertheless, this systematic review represents a novel contribution to the literature on NHL and pesticide exposure. We identified trends in the relationship of NHL and NHL subtypes with chemical groups and active ingredient groups. To our knowledge, this is the most comprehensive systematic review and meta-analysis to investigate associations with specific agricultural pesticide active ingredients. We observed fairly consistent results for certain pesticide groups and active ingredients. We evaluated the robustness of our meta-analyses by examining the sensitivity of the estimates to gender, study design, region, diagnosis period, control source in case-control studies, and paper that provided the effect estimate.

5. Conclusions

We systematically reviewed more than 25 years' worth of epidemiologic literature on the relationship between pesticide chemical groups and active ingredients with NHL. This review indicated positive associations between NHL and carbamate insecticides, OP insecticides, the phenoxy herbicide MCPA, and lindane. Few papers reported associations with subtypes of NHL; however, based on the few that did, there were strong associations between certain chemicals and B cell lymphomas. Our results show that there is consistent evidence that pesticide exposures experienced in occupational agricultural settings may be important determinants of NHL. This review also revealed clear research needs, including further investigation of some already studied pesticide active ingredients, of additional pesticides that have not yet been investigated in epidemiologic analyses, of the strength of association of pesticide exposures with subtypes of NHL, and of the relationship between NHL and pesticides in middle- and low- income areas.

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Author Contributions

Leah Schinasi conducted the literature search, screened the papers from the search, abstracted data from the papers, conducted the meta-analyses, and led the writing of the manuscript. Maria E. Leon co-defined the scope of the review, the search strategy for the literature search and contributed to the writing of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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