Herbicide use in farming and other jobs in relation to non-Hodgkin’s lymphoma (NHL) risk

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ABSTRACT

Objectives Given mixed evidence for carcinogenicity of current-use herbicides, we studied the relationship between occupational herbicide use and risk of non-Hodgkin’s lymphoma (NHL) in a large, pooled study.

Methods We pooled data from 10 case-control studies participating in the International Lymphoma Epidemiology Consortium, including 9229 cases and 9626 controls from North America, the European Union and Australia. Herbicide use was coded from self-report or by expert assessment in the individual studies, for herbicide groups (eg, phenoxy herbicides) and active ingredients (eg, 2,4-dichlorophenoxyacetic acid (2,4-D), glyphosate). The association between each herbicide and NHL risk was estimated using logistic regression to produce ORs and 95% CIs, with adjustment for sociodemographic factors, farming and other pesticides.

Results We found no substantial association of all NHL risk with ever-use of any herbicide (OR=1.10, 95% CI: 0.94 to 1.29), nor with herbicide groups or active ingredients. Elevations in risk were observed for NHL subtypes with longer duration of phenoxy herbicide use, such as for any phenoxy herbicide with multiple myeloma (>25.5 years, OR=1.78, 95% CI: 0.74 to 4.27), 2,4-D with diffuse large B-cell lymphoma (>25.5 years, OR=1.47, 95% CI: 0.67 to 3.21) and other (non-2,4-D) phenoxy herbicides with T-cell lymphoma (>6 years, lagged 10 years, OR=3.24, 95% CI: 1.03 to 10.2). An association between glyphosate and follicular lymphoma (lagged 10 years: OR=1.48, 95% CI: 0.98 to 2.25) was fairly consistent across analyses.

Conclusions Most of the herbicides examined were not associated with NHL risk. However, associations of phenoxy herbicides and glyphosate with particular NHL subtypes underscore the importance of estimating subtype-specific risks.

INTRODUCTION

Synthetic herbicides were first introduced to the agricultural market for weed control in the 1940s. Today, herbicides are widely applied in farming as well as urban and residential settings, resulting in potential exposure for both applicators and the general public. Several herbicides have been evaluated for human carcinogenicity in recent years by international or national advisory or regulatory bodies; for example, in 2015, the
International Agency for Research on Cancer (IARC) classified 2,4-dichlorophenoxyacetic acid (2,4-D) as a possible carcinogen and glyphosate as a probable carcinogen.\(^1\)\(^2\)

The human (epidemiological) data supporting these assessments were considered inadequate or limited,\(^3\)\(^4\) forcing heavy reliance on the available animal bioassays and mechanistic data for evidence conclusions. Nevertheless, several epidemiologic studies showed positive relationships between exposure to the herbicide active ingredients and risk of non-Hodgkin’s lymphoma (NHL), so research has continued to focus on NHL as a target cancer outcome. Noted limitations of the previous epidemiological research include assessment of simple exposure metrics such as ever-use that did not characterise dose or level of exposure, limited or no adjustment for other pesticides, and small sample sizes. More recent studies have sought to overcome these limitations, primarily through analysis of large study populations and assessment of semi-quantitative exposure metrics including duration, frequency and intensity.

While the evidence linking herbicide exposures to NHL risk is mixed, heavy use of herbicides begs further study. To add new data on the topic, we conducted a pooled analysis of case-control studies participating in the International Lymphoma Epidemiology (InterLymph) Consortium. Our aim was to estimate associations between occupational herbicide use and risk of NHL and its major subtypes in a large study population, with a particular focus on 2,4-D and glyphosate. We also aimed, to the extent possible, to estimate risks for various exposure metrics harmonised across the studies, including duration and lagged use.

**METHODS**

**Study population**

InterLymph formed in 2001 to facilitate intellectual exchange and collaborative research towards identifying preventable risk factors for lymphoid cancers. Individual case-control studies participating in InterLymph were eligible for this pooled analysis if they collected information on occupational chemical use by questionnaire items that implicitly or explicitly elicited reporting of herbicides.

A summary of the 10 participating case-control studies is provided in Table 1.\(^5\)\(^6\)\(^16\) The studies included persons with historically confirmed incident primary diagnosis of NHL during the respective enrolment periods, spanning 1980–2013. Reflecting changes in the pathology classification of lymphomas,\(^17\) the studies used different criteria for inclusion of lymphoma subtypes. Controls were identified from the general population or participating hospitals/clinics and were frequency-matched or pair-matched to the cases by factors including age and sex, and in some studies, region or race. The pooled data included 9626 controls and 9229 cases (1638 chronic lymphocytic leukaemia/small lymphocytic lymphoma/mantle cell lymphoma/prolymphocytic leukaemia (hereafter referred to, collectively, as CLL), 2160 diffuse large B-cell lymphoma (DLBCL), 1587 follicular lymphoma (FL), 1581 other B-cell lymphoma (OBCL), 1355 multiple myeloma (MM), 456 T-cell lymphoma (TCL) and 452 not otherwise specified/unknown (NOS/UNK).

Variables already harmonised for previous InterLymph analyses included age at the reference date (diagnosis date or corresponding date for controls), sex, race/Hispanic ethnicity, socioeconomic status (SES) at the reference date (based on education and/or income),\(^18\) NHL subtype coded according to the 2008 WHO classification\(^19\)\(^20\) and job titles from occupational histories, coded according to the International Standard Classification of Occupations 1968.\(^21\)\(^22\)

**Pesticide exposure coding**

Each study provided data on occupation, farming and pesticide use. Occupational use of pesticides was coded directly from questionnaire responses (ie, self-report) or from reviews conducted by local experts in the individual studies (ie, expert assessment), as described previously (online supplemental material).\(^1\)\(^2\)

Particular herbicides were selected for the pooled analysis based on exposure in at least three studies, and included use of any herbicide, the broad herbicide groups of phenoxy acids (‘phenoxy’ herbicides), triazines and amides, and the active ingredients 2,4-D, glyphosate, atrazine, alachlor, trifluralin, dicamba, pendimethalin and paraquat, as well as grouped ‘other’ (non-2,4-D) phenoxy herbicides (eg, 2,4,5-T, MCPA, mecoprop). For each herbicide group or active ingredient, exposure variables were summarised across all jobs held by a participant. Ever-use and use duration were coded, in addition to lagged versions of these variables that captured use >10 years before NHL diagnosis or the corresponding reference date for controls. Duration variables were categorised based on percentiles (p), in two categories (≤50p, >50p) and three categories (≤50p, >50p to 75p, >75p).

Although a 10-year exposure lag was selected for the main analysis, a priori, variables were also created for lagged exposure windows that covered multiple periods before the case diagnosis or control reference date. These were coded as four indicator variables (>0–5 years, >5–10 years, >10–20 years, >20 years), and participants could be included in one or multiple exposure windows, depending on their years of use. Another set of indicator variables was created to represent decades of use (before 1960, 1960s, 1970s, 1980s, 1990s, 2000 or later).

**Statistical analysis**

**Pooled analysis**

Logistic regression was used to estimate ORs and 95% CIs for associations between herbicide use and risk of NHL. All pooled analyses were conducted using SAS V.9.4 (Cary, North Carolina, USA). Exposure was analysed in separate models as ever-use, duration, 10-year lagged ever-use or duration, lagged exposure windows and decades of use—each with never-use of the particular herbicide as the reference category. The linear trend in NHL risk across categories of duration was evaluated by the p value from modelling the median of each duration category as a continuous variable. Several variables were selected, a priori, to adjust for potential confounding, including (all coded as indicator terms) the study centre (ie, specific city/hospital of data collection), age (<45, 45–54, 55–64, 65–74, ≥75 years), gender, SES (low, medium, high), race/ethnicity (white, non-Hispanic vs non-white or Hispanic) and farming occupation (ever vs never). Covariates were also included to adjust for other pesticide use, as evidence of confounding by other pesticides has been suggested in previous studies of herbicides and NHL.\(^1\)\(^2\) This adjustment included up to five covariates, selected and coded specifically for each herbicide, broadly including indicators for use of organophosphate insecticides, organochlorine insecticides, phenoxy herbicides, glyphosate and any other pesticide (details in online supplemental material 2).

Aetiological heterogeneity was evaluated by fitting polytomous logistic regression models for the NHL subtypes, with estimation of the OR and 95% CI for each subtype-specific association versus a common control group.
Table 1  Case-control studies participating in the International Lymphoma Epidemiology study of herbicides*

| Study abbreviation (citation) | LAMMCC (Nuyujukian et al, 2014) | LANHL (Bernstein et al, 1992) | Italian (Milliggi et al, 2003) | Yale (Zhang et al, 2004, Koutrous et al, 2009) | NCI-SEER (Hartge et al, 2005) | Eplymph (Cocco et al, 2013) | NSW (Fritsch et al, 2005) | ENGEA (Orsi et al, 2009) | Mayo (Cerhan et al, 2011) | BCMM (Weber et al, 2018) |
|------------------------------|----------------------------------|------------------------------|--------------------------------|-----------------------------------------------|-------------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Location(s)                  | USA: Los Angeles County          | USA: Los Angeles County      | Italy: Firenze, Forlì, Impietra, Latina, Novara, Reggio, Siena, Torino, Verona | USA: Detroit, Iowa, Los Angeles County, Seattle | Europe: Czech Republic, France, Germany, Ireland, Italy, Spain | Australia: New South Wales and Australian Capital Territory | France: Bordeaux, Brest, Caen, Lille, Nantes, Toulouse | USA: Minnesota, Iowa, Wisconsin | Canada: British Columbia |
| Case diagnosis years         | 1980–1990                        | 1988–1991                    | 1990–1994                      | 1996–2002                                     | 1998–2000                     | 1998–2003                   | 1999–2001                    | 2000–2004                    | 2002–2012                    | 2009–2013                   |
| Source of controls           | Population                       | Population                   | Population                      | Population or hospital                       | Population                    | Population                  | Hospital                     | Hospital                    | Clinic                      | Population                  |
| Control matching to cases    | Pair-matched by age, sex, race,  | Pair-matched by age, sex,    | Frequency-matched by age, sex,  | Frequency-matched by age, sex, race          | Frequency-matched by age, sex, | Frequency-matched by age,  | Frequency-matched by age,  | Frequency-matched by age, sex, | Frequency-matched by age, sex, | Frequency-matched by age, sex, |
|                             | neighbourhood                    | sex, race, neighbourhood     | sex                            | sex, race                                     | sex, race                     | sex, region                | sex, region                  | region                      | sex, region                  | sex, age                    |
| Participants queried regarding occupational pesticides | All                               | All                           | All                            | All                                           | All                          | All                        | All                          | All                         | All                         | All                         |
| Basis for pesticide use classification | Self-report (closed-ended questions on pesticides exposed to at work) | Self-report (open-ended question on pesticides directly exposed to at work) | Expert-assessment (open-ended questions on products used at work and additional farming questionnaire; responses checked against a crop-exposure matrix) | Self-report (open-ended questions on pesticides handled, with provided list of frequently used pesticides as a prompt) | Expert-assessment (open-ended questions on specific pesticides personally mixed or applied from job-specific questionnaire; responses checked against product availability dates and a crop-exposure matrix, with the support of agronomists) | Expert-assessment (open-ended questions on specific pesticides personally mixed or applied from job-specific module farming questionnaire; responses checked against product availability dates and a crop-exposure matrix) | Self-report (closed-ended questions on pesticides used at work and additional farming questionnaire; responses checked against product availability dates, type and size of crops, geographic location and treatment frequency) | Self-report (open-ended questions about pesticides used at work and additional farming questionnaire) | Self-report (closed-ended questions on pesticides personally applied, mixed or loaded at work or when living on a farm) |

| Included in the pooled study (Ns) | Cases | Controls | Case subtypes (% of all cases) |
|-----------------------------------|-------|----------|--------------------------------|
| Cases                             | 275   | 278      | Chronic lymphocytic          |
|                                   |       |          | leukemia/small lymphocytic   |
|                                   |       |          | lymphoma/mantle cell lymphoma/|
|                                   |       |          | prolymphocytic leukemia     |
|                                    | 368   | 372      | Diffuse large B-cell         |
|                                    | 1243  | 1142     | lymphoma                     |
|                                    | 773   | 706      | Follicular lymphoma          |
|                                    | 1189  | 982      |                                |
|                                    | 2000  | 2462     |                                |
|                                    | 688   | 683      |                                |
|                                    | 404   | 447      |                                |
|                                    | 1898  | 2183     |                                |
|                                    | 391   | 371      |                                |
| Controls                          |       |          | Chronic lymphocytic          |
|                                   | 0%    | 0%       | leukemia/small lymphocytic   |
|                                   | 9.3%  | 8.5%     | lymphoma/mantle cell lymphoma/|
|                                   | 14.2% | 12.3%    | prolymphocytic leukemia      |
|                                   | 7.4%  | 24.3%    | Diffuse large B-cell         |
|                                   | 34.8% | 0%       | lymphoma                     |
|                                   | 0%    | 0%       | Follicular lymphoma          |

continued
### Table 1 continued

| Study abbreviation (citation) | LAMMCC (Nuyujukian et al, 2014) | LANHL (Bernstein et al, 1992) | Italian (Miligi et al, 2003) | Yale (Zhang et al, 2004, Koutros et al, 2009) | NCI-SEER (Hartge et al, 2005) | Epilymph (Cocco et al, 2013) | NSW (Fritschi et al, 2005) | ENGEA (Orsi et al, 2009) | Mayo (Cerhan et al, 2011) | BCMM (Weber et al, 2018) |
|------------------------------|--------------------------------|--------------------------------|----------------------------|---------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Multiple myeloma            | 100%                          | 0%                            | 14.2%                      | 23.2%                                       | 0%                          | 13.8%                       | 0%                          | 13.9%                       | 0%                          | 14.9%                       | 10.2%                       | 100%                       |
| Other B-cell lymphoma        | 0%                            | 27.2%                         | 2.6%                       | 7.6%                                        | 14.8%                       | 17.4%                       | 15.4%                       | 14.9%                       | 0%                          | 10.2%                       | 0%                          | 0%                         |
| T-cell lymphoma              | 0%                            | 0.3%                          | 4.5%                       | 4.4%                                        | 6.2%                        | 6.6%                        | 3.5%                        | 5.2%                        | 4.6%                        | 0%                          | 0%                          | 0%                         |
| NOS-unknown                  | 0%                            | 26.1%                         | 39.9%                      | 14.4%                                       | 9.4%                        | 0.3%                        | 4.2%                        | 3.0%                        | 6.6%                        | 0%                          | 0%                          | 0%                         |

Control characteristics

| Control characteristics | Age in years (mean (SD)) | Male gender (%) | Non-white race or Hispanic ethnicity (%) | Low socioeconomic status (%) | Farming job, ever (%) | Occupational pesticide use, ever (%) | Occupational insecticide use, ever (%) | Occupational herbicide use, ever (%) |
|-------------------------|---------------------------|-----------------|------------------------------------------|----------------------------|----------------------|---------------------------------------|---------------------------------------|--------------------------------------|
| Age in years (mean (SD))| 61.2 (9.0)                | 51.1 (14.4)     | 55.0 (13.7)                              | 61.3 (14.2)                | 58.1 (12.3)          | 56.2 (16.0)                           | 56.3 (12.0)                           | 52.5 (13.5)                          |
| Male gender (%)         | 54.7%                     | 49.2%           | 55.4%                                    | 0%                         | 53.4%                | 53.6%                                 | 57.7%                                 | 100%                                 |
| Non-white race or Hispanic ethnicity (%) | 32.0% | 23.9% | 0% | 8.1% | 21.4% | 1.5%‡ | 12.9% | 0.4% | 2.4% | 9.4% |
| Low socioeconomic status (%) | 46.4% | 32.3% | 57.3% | 36.7% | 37.2% | 45.5% | 33.7% | 27.7% | 23.0% | 29.4% |
| Farming job, ever (%)    | 10.4%                     | 6.5%            | 31.4%                                    | 2.1%                       | 9.5%                 | 17.1%                                 | 15.1%                                 | 18.1%                                |
| Occupational pesticide use, ever (%) | 5.0% | 8.3% | 26.7% | 11.9% | 11.2% | 8.5% | 10.5% | 10.5% | 14.2% | 5.1% |
| Occupational insecticide use, ever (%) | 2.2% | 3.8% | 6.3% | 8.2% | 6.7% | 2.0% | 8.6% | 8.3% | 12.1% | 3.8% |
| Occupational herbicide use, ever (%) | 1.4% | 1.6% | 5.2% | 6.2% | 5.2% | 2.0% | 4.8% | 9.4% | 13.6% | 3.5% |

*Studies are ordered in table by the earliest case diagnosis year.
†The LANHL study included intermediate-grade and high-grade NHL diagnosed in HIV-negative individuals, to correspond to a concurrent study protocol of HIV-related NHL.
‡Assumed non-white race.

BCMM, British Columbia Cancer Agency Study of Multiple Myeloma; ENGEA, L’Étude des Facteurs Environnementaux et Génétique des Lymphomes de l’Adulte; LAMMCC, Los Angeles County Multiple Myeloma Case-Control Study; LANHL, Los Angeles County Study of Non-Hodgkin Lymphoma; NCI-SEER, National Cancer Institute-Surveillance, Epidemiology, and End-Results Program Non-Hodgkin Lymphoma Study; NHL, non-Hodgkin’s lymphoma; NSW, New South Wales Non-Hodgkin Lymphoma Study.
Meta-analysis

Random effects meta-analysis was conducted on study-specific ORs to assess comparability to findings from the pooled analysis, and to test heterogeneity of the estimated effect among studies by the p value for the I² statistic (p value for heterogeneity (p-het)). Meta-analysis was conducted using StataSE V.15 (StataCorp, College Station, Texas, USA).

Sensitivity analysis

Several additional analyses of the pooled data were conducted to assess sensitivity of the main results to: (1) no adjustment for other pesticides; (2) limiting to participants who never used other specific herbicides as an alternative approach to assessing confounding, in analysis of phenoxy herbicides (excluded if used glyphosate), 2,4-D (excluded if used other phenoxy herbicides or glyphosate), other phenoxy herbicides (excluded if used 2,4-D or glyphosate) and glyphosate (excluded if used phenoxy herbicides); (3) limiting exposure to high-frequency (eg, days/year) of use in 6 of the 10 studies (defined as frequency of use above the 25th percentile frequency value for the particular herbicide in each study); herbicide use from the four studies without frequency information were also included in this analysis using the same exposure coding as the main analysis; (4) limiting the population to participants who ever worked on a farm, as this subgroup was more likely to be exposed than the rest of the study population, yet may also have had unmeasured risk factors24; (5) limiting to participants who never worked in farming but ever worked in non-farming jobs considered, a priori, to have relatively high probability of herbicide use, including jobs in forestry and occupation as a gardener/groundkeeper, janitor/cleaner or general labourer; (6) fitting separate models for men and women, as the two genders may have different levels of exposure25; (7) fitting separate models for studies with exposures coded according to expert assessment or self-report; (8) fitting separate models for the largest study with the highest herbicide exposure prevalence (Mayo), and other studies excluding Mayo.

RESULTS

The 10 case-control studies participating in the pooled analysis were conducted in North America, Europe and Australia from 1980 to 2013 (table 1). Controls differed between the studies by history of work in farming, as at least one study exclusively focused on agricultural regions (Italian, 31.4% ever held farming job), other studies included a mix of rural and urban areas (ENELA and Mayo, 15.6%–18.1% farming) and several studies were conducted in large cities (LAMMCC, LANHL and BCMM, 6.5%–10.4% farming). Occupational pesticide use was somewhat reflective of farming history in the studies, ranging from 5% (LAMMCC) to 26% (Italian). Herbicide use ranged somewhat reflective of farming history in the studies, ranging from 5% (LAMMCC) to 26% (Italian). Herbicide use ranged from 1.4% (LAMMCC) to 13.6% (Mayo) and was generally less than the rest of the study population.

We present as our main results, analyses of ever-use of any type of pesticide including insecticides, herbicides, fungicides, fumigants, rodenticides, etc. Controls with occupational herbicide use had frequently worked in farming (70.5%), as gardeners/groundkeepers (7.4%), cleaners/janitors/building maintenance workers (6.1%) and general labourers (6.2%) (not shown). Out of all controls who ever worked in farming, 28.2% had used herbicides (not shown).

Several additional analyses of the pooled data were conducted to assess sensitivity of the main results to: (1) no adjustment for other pesticides; (2) limiting to participants who never used other specific herbicides as an alternative approach to assessing confounding, in analysis of phenoxy herbicides (excluded if used glyphosate), 2,4-D (excluded if used other phenoxy herbicides or glyphosate), other phenoxy herbicides (excluded if used 2,4-D or glyphosate) and glyphosate (excluded if used phenoxy herbicides); (3) limiting exposure to high-frequency (eg, days/year) of use in 6 of the 10 studies (defined as frequency of use above the 25th percentile frequency value for the particular herbicide in each study); herbicide use from the four studies without frequency information were also included in this analysis using the same exposure coding as the main analysis; (4) limiting the population to participants who ever worked on a farm, as this subgroup was more likely to be exposed than the rest of the study population, yet may also have had unmeasured risk factors24; (5) limiting to participants who never worked in farming but ever worked in non-farming jobs considered, a priori, to have relatively high probability of herbicide use, including jobs in forestry and occupation as a gardener/groundkeeper, janitor/cleaner or general labourer; (6) fitting separate models for men and women, as the two genders may have different levels of exposure25; (7) fitting separate models for studies with exposures coded according to expert assessment or self-report; (8) fitting separate models for the largest study with the highest herbicide exposure prevalence (Mayo), and other studies excluding Mayo.

Table 2 Characteristics of cases and controls in the International Lymphoma Epidemiology study of herbicides (n (%))

| Characteristic                      | Controls N=9626 | Cases N=9229 |
|------------------------------------|-----------------|--------------|
| **Age (years)**                    |                 |              |
| <45                                | 1692 (17.6)     | 1306 (14.1)  |
| 45–54                              | 1726 (17.9)     | 1716 (18.6)  |
| 55–64                              | 2472 (25.7)     | 2566 (27.8)  |
| 65–74                              | 2886 (30.0)     | 2849 (30.9)  |
| ≥75                                | 850 (8.8)       | 792 (8.6)    |
| **Gender**                         |                 |              |
| Female                             | 4597 (47.8)     | 4195 (45.4)  |
| Male                               | 5029 (52.2)     | 5034 (54.6)  |
| **Race/Hispanic ethnicity**        |                 |              |
| White                               | 3614 (37.6)     | 3827 (41.5)  |
| Hispanic                           | 3170 (32.9)     | 2754 (29.8)  |
| Black                              | 2762 (28.7)     | 2203 (23.9)  |
| **Socioeconomic status**           |                 |              |
| Low                                | 80 (0.8)        | 445 (4.8)    |
| Medium                             | 1492 (15.5)     | 1526 (16.5)  |
| High                               | 65 (1.0)        | 69 (1.1)     |
| **Job history (ever)**             |                 |              |
| Farming                            | 74 (1.0)        | 93 (1.3)     |
| Forestry                           | 639 (6.6)       | 669 (7.2)    |
| General labourer                   | 596 (6.2)       | 644 (7.0)    |
| **Occupational pesticide use (ever)**|              |              |
| Any†                               | 1201 (12.5)     | 1263 (13.7)  |
| Insecticide                        | 460 (4.8)       | 532 (5.8)    |
| Herbicide                          | 344 (4.8)       | 400 (5.7)    |

*White category includes ‘assumed white’, based on region and/or ethnicity (<2% of study population).
†Occupational use of any type of pesticide including insecticides, herbicides, fungicides, fumigants, rodenticides, etc.
| Exposure | All NHL | CLL | DLBCL | FL | EBCL | MM | TCL | Adjustments for other pesticides |
|----------|---------|-----|-------|----|------|----|-----|----------------------------------|
|          | Controls | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) |
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| October 6, 2023 by guest. Protected by copyright. Occup Environ Med: first published as 10.1136/oemed-2022-108371 on 7 October 2022. Downloaded from http://oem.bmj.com/ on November 6, 2023. To view the Table continued.
| Exposure | Controls | All NHL | CLL | DLBCL | FL | OBCL | MM | TCL |
|----------|----------|--------|-----|-------|----|------|----|-----|
|          | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) | Cases (OR (95% CI)) |
| Atrazine | Never 51 83 5235 | 9.30 (0.61 to 1.40) | 178 174 | 0.85 (0.61 to 1.24) | 67 0.88 (0.53 to 1.46) | 10 0.51 (0.24 to 1.07) | 27 0.90 (0.52 to 1.56) | 290 9.05 (3.33 to 2.15) |
|          | Ever 178 | 1195 | 1076 | 967 | 0.68 (0.43 to 1.06) | 27 | 0.90 (0.52 to 1.56) | 27 | 0.90 (0.52 to 1.56) |
|           | Duration |   |   |   |   |   |   |   |
|          | all years 96 86 | 0.77 (0.53 to 1.17) | 36 | 1.00 (0.59 to 1.70) | 15 | 0.85 (0.46 to 1.55) | 15 | 0.71 (0.42 to 1.20) |
|          | >8 80 | 87 | 0.95 (0.66 to 1.37) | 36 | 0.95 (0.46 to 1.93) | 15 | 0.71 (0.42 to 1.20) | 3 | 0.64 (0.17 to 2.40) |
|          | p-trend=0.88 | p-trend=0.96 | p-trend=0.70 | p-trend=0.71 | p-trend=0.79 | p-trend=0.51 |
| Alachlor | Never 5266 5269 | 1034 | 1132 | 1035 | 270 | OP insecticides, OC insecticides, phenoxy herbicides, glyphosate, any other pesticide |
|          | Ever 171 | 153 | 0.74 (0.55 to 1.00) | 61 | 0.85 (0.55 to 1.31) | 22 | 0.90 (0.33 to 1.39) | 19 | 0.90 (0.33 to 1.39) |
|           | Duration |   |   |   |   |   |   |   |
|          | all years 92 94 | 0.96 (0.66 to 1.34) | 43 | 1.11 (0.64 to 1.92) | 12 | 0.65 (0.33 to 1.37) | 16 | 0.57 (0.31 to 1.07) |
|          | >8 77 | 56 | 0.90 (0.60 to 1.36) | 17 | 0.54 (0.29 to 1.00) | 9 | 0.47 (0.22 to 1.01) | 14 | 0.65 (0.34 to 1.25) |
|          | p-trend=0.01 | p-trend=0.05 | p-trend=0.05 | p-trend=0.00 | p-trend=0.05 | p-trend=0.20 | p-trend=0.30 |
| Dicamba | Never 5919 5919 | 1016 | 1138 | 1229 | 1053 | 742 | 295 | OP insecticides, OC insecticides, phenoxy herbicides, glyphosate, any other pesticide |
|          | Ever 148 | 130 | 0.95 (0.55 to 1.64) | 47 | 0.85 (0.53 to 1.37) | 21 | 0.91 (0.41 to 2.01) | 19 | 0.91 (0.41 to 2.01) |
|           | Duration |   |   |   |   |   |   |   |
|          | all years 87 76 | 0.77 (0.51 to 1.17) | 34 | 0.69 (0.40 to 1.20) | 11 | 0.40 (0.22 to 0.80) | 12 | 0.89 (0.44 to 1.80) |
|          | >8 60 | 50 | 0.67 (0.44 to 1.02) | 13 | 0.63 (0.32 to 1.21) | 11 | 0.81 (0.40 to 1.64) | 7 | 0.79 (0.34 to 1.86) |
|          | p-trend=0.03 | p-trend=0.48 | p-trend=0.48 | p-trend=0.53 | p-trend=0.29 | p-trend=0.97 | p-trend=0.78 |
| Pendimethalin | Never 5602 5607 | 948 | 1337 | 1126 | 1076 | 254 | OP insecticides, OC insecticides, phenoxy herbicides, glyphosate, any other pesticide |
|          | Ever 131 | 120 | 0.79 (0.57 to 1.10) | 49 | 0.87 (0.54 to 1.38) | 16 | 0.60 (0.32 to 1.14) | 25 | 0.64 (0.37 to 1.10) |
|           | Duration |   |   |   |   |   |   |   |
|          | all years 75 71 | 0.79 (0.53 to 1.10) | 35 | 1.04 (0.61 to 1.76) | 10 | 0.98 (0.49 to 1.97) | 16 | 0.92 (0.49 to 1.74) |
|          | >8 54 | 46 | 0.77 (0.49 to 1.21) | 13 | 0.81 (0.30 to 1.22) | 10 | 0.76 (0.33 to 1.74) | 8 | 0.90 (0.43 to 2.14) |
|          | p-trend=0.25 | p-trend=0.35 | p-trend=0.48 | p-trend=0.45 | p-trend=1.00 | p-trend=0.92 |
| Paraquat | Never 1425 1427 | 921 | 982 | 855 | 857 | 230 | OP insecticides, OC insecticides, phenoxy herbicides, glyphosate, any other pesticide |
|          | Ever 57 | 58 | 0.94 (0.61 to 1.44) | 25 | 1.11 (0.63 to 1.94) | 10 | 1.03 (0.48 to 2.21) | 8 | 0.82 (0.21 to 3.35) |
|           | Duration |   |   |   |   |   |   |   |
|          | all years 33 23 | 0.63 (0.35 to 1.14) | 11 | 0.82 (0.38 to 1.76) | 3 | 0.52 (0.25 to 1.02) | 4 | 0.40 (0.14 to 1.25) |
|          | >4 24 | 31 | 1.16 (0.64 to 2.07) | 14 | 1.44 (0.69 to 3.01) | 5 | 1.19 (0.42 to 3.53) | 5 | 0.57 (0.19 to 1.83) |
|          | p-trend=0.97 | p-trend=0.47 | p-trend=0.47 | p-trend=0.45 | p-trend=1.00 | p-trend=0.92 |
| *SIFs and 95% CIs. Observational data, with adjustment for study centre, age, gender, socioeconomic status, smoking, ethnicity, family history and a set of covariates for use of other pesticides.‡Three category duration variable results are shown if there were at least 50 exposed NHL cases in the highest category; otherwise, two-category duration results are shown.§P < 0.05 for a continuous variable with all results set as the mean of each duration category.¶Categories collapsed if included 0 or 1 cases.¶Continuous variable with categories collapsed if there were less than 5 NHL cases in at least one category.¶Non-Hodgkin’s lymphoma, B-cell lymphomas; FL, follicular lymphomas; MM, multiple myelomas; NPC, non-Hodgkin’s lymphoma, B-cell lymphomas; TCL, T-cell lymphomas.
Phenoxy herbicides and 2,4-D, specifically, were associated with non-significantly increased risks of several NHL subtypes. The most consistent associations were observed by increasing duration of use for phenoxy herbicides with MM (≥25.5 years, OR = 1.78, 95% CI: 0.74 to 4.27; p-trend = 0.15) and 2,4-D with DLBCL (≥25.5 years, OR = 1.47, 95% CI: 0.67 to 3.21; p-trend = 0.21). Associations with any phenoxy herbicides and 2,4-D were generally less strong when exposure was lagged by 10 years (online supplemental table 2); likewise, the strongest associations were estimated for exposures within 5 years before diagnosis (table 4 and online supplemental table 2). An association between phenoxy herbicides and TCL (OR = 1.85, 95% CI: 0.98 to 3.48) was explained by an association with other (ie, non-2,4-D) phenoxy herbicides (OR = 2.71, 95% CI: 1.16 to 6.33). Analysis of lagged exposure windows showed the highest ORs for TCL with exposures occurring 10–20 or >20 years before diagnosis, and associations with longer duration were strongest with a 10-year lag (≥6 years, OR = 3.24, 95% CI: 1.02 to 10.2; p-trend = 0.04). The highest increased risks of all NHL were estimated for phenoxy herbicide or 2,4-D use that occurred in the 1960s—a pattern also observed for 2,4-D use in association with DLBCL (use in 1960s, OR = 3.02, 95% CI: 1.50 to 6.09). In contrast, the association between phenoxy herbicide use and MM was strongest for use that occurred in the 2000s or later, based on five exposed cases (OR = 3.60, 95% CI: 0.94 to 13.7). Use of other phenoxy herbicides in the 1980s was associated with increased risk of all NHL (ORs and 95% CIs)*

### Table 4

| Herbicides         | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) | Cases | OR (95% CI) |
|--------------------|-------|-------------|-------|-------------|-------|-------------|-------|-------------|-------|-------------|
| Phenoxy herbicides |       |             |       |             |       |             |       |             |       |             |
| 2,4-D              |       |             |       |             |       |             |       |             |       |             |
| Other phenoxy      |       |             |       |             |       |             |       |             |       |             |

Glyphosate was not associated with all NHL in our main analysis (OR = 1.03, 95% CI: 0.83 to 1.29). An association between glyphosate use and FL was somewhat stronger when lagged by 10 years (OR = 1.48, 95% CI: 0.98 to 2.25, online supplemental table 2) and this association was limited to shorter-duration exposures (≤8 years, OR = 1.80, 95% CI: 1.15 to 2.82; >8 years, OR = 1.00, 95% CI: 0.55 to 1.83). Non-statistically significant risk increases were also estimated for OBCL and TCL in association with mid-level or longest duration categories of glyphosate use. The association between glyphosate use and FL was strongest for use during the 1970s (OR = 1.21, 95% CI: 0.70 to 2.09), whereas the association with all NHL was highest for use in the 2000s or later (OR = 1.24, 95% CI: 0.87 to 1.76).

None of the other herbicide groups or active ingredients examined were associated with increased risk of NHL. Inverse associations, some statistically significant, were estimated for amide herbicides and trifluralin. Some elevated ORs were observed in association with paraquat use, based on small numbers.

Selected meta-analysis forest plots are shown in online supplemental figure 1. Meta-analysis confirmed weak associations of ever-use of any herbicide, phenoxy herbicides or 2,4-D with all NHL, with little or moderate heterogeneity of effect between studies. An association between herbicide use and TCL was slightly stronger in meta-analysis (mOR = 1.69, 95% CI: 1.00 to 2.86, p-het = 0.65) than pooled analysis. The association between glyphosate and all NHL from meta-analysis was stronger for lagged use (mOR = 1.38, 95% CI: 0.79 to 2.42, p-het = 0.07) than ever-use (mOR = 1.02, 95% CI: 0.70 to 1.48, p-het = 0.17), although both analyses revealed moderate heterogeneity between studies. Associations were higher from meta-analysis than pooled analysis and showed little heterogeneity for lagged glyphosate use with NHL subtypes FL (mOR = 2.20, 95% CI: 1.00 to 4.87, p-het = 0.20) and TCL (mOR = 2.58, 95% CI: 0.60 to 11.1, p-het = 0.28), and glyphosate herbicide use duration >8 years with MM (mOR = 2.33, 95% CI: 0.81 to 6.66, p-het = 0.32). Results were similar between meta-analysis and pooled analysis and there was little heterogeneity for longer-duration 2,4-D use (>8 years) in association with DLBCL and OBCL.

Sensitivity analyses (figure 1) revealed generally small (<10% change in OR from main model) or modest (10%–20% change in OR) magnitudes of confounding by other pesticides (online supplemental table 3). Exclusion of participants with potentially confounding exposures to other herbicides typically resulted in stronger associations for phenoxy herbicides and glyphosate in relation to NHL and subtypes, except the association between phenoxy herbicides and MM was diminished. Limiting to relatively high frequency of use in the studies that collected this information had little impact on most results, with exception
Workplace

Figure 1  Sensitivity and alternative analyses of selected associations between occupational herbicide use and risk of non-Hodgkin's lymphoma (NHL) and NHL subtypes (ORs and 95% CIs from logistic regression models, with adjustment for study centre, age, gender, socioeconomic status (SES), race/Hispanic ethnicity, farm work history and a set of covariates for use of other pesticides). NHL subtypes: 2,4-D, 2,4-dichlorophenoxyacetic acid; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; TCL, T-cell lymphoma. Change in OR refers to the change from the main analysis to the alternative/sensitivity analysis.

of slightly lowering ORs for associations of glyphosate with all NHL and FL. Several associations were stronger (higher ORs) when limiting to participants who ever worked on a farm, such as 2,4-D use with all NHL and other phenoxy herbicides with TCL, although associations with glyphosate were diminished. The association between lagged glyphosate use and FL was prominent among participants with non-farming jobs. Notable differences by gender were higher risk estimates among women for NHL associations with any phenoxy herbicide and 2,4-D. In contrast, associations of any herbicide and other phenoxy herbicides with TCL were limited to men. Associations were generally stronger in studies with expert assessment of exposure than with exposure based on self-report.

Associations were generally more strongly positive with exclusion of the Mayo study (figure 1 and online supplemental table 4). These results differ from our main results with more suggestive duration-response trends for any herbicide with TCL and MM, and for phenoxy herbicides and 2,4-D with all NHL and several subtypes. For example, elevated ORs were estimated for 2,4-D use duration >8 years in association with all NHL (OR=1.48, 95%CI: 0.86 to 2.56, p-trend=0.14), DLBCL (OR=2.16, 95%CI: 0.97 to 4.81, p-trend=0.05), FL (OR=2.16, 95%CI: 0.91 to 5.11, p-trend=0.07), OBCL (OR=2.15, 95%CI: 0.88 to 5.26, p-trend=0.12) and MM (OR=2.62, 95%CI: 0.68 to 10.1, p-trend=0.17). Associations with glyphosate lagged use were considerably stronger with exclusion of the Mayo study, for all NHL (OR=1.40, 95%CI: 0.93 to 2.13), FL (OR=2.16, 95%CI: 1.10 to 4.24) and OBCL (OR=1.92, 95%CI: 0.95 to 3.89).

DISCUSSION

In our consortium-based analysis of data pooled from 10 case-control studies, we found no substantial association of any herbicide, herbicide groups or individual active ingredients with risk of all NHL. Elevations in risk by increasing duration of 2,4-D use were observed for all NHL, DLBCL and OBCL, but ORs were generally imprecise. An association between glyphosate use and increased risk of FL was fairly consistent among the studies; this association was particularly elevated in analyses of glyphosate exposure lagged by 10 years and with shorter duration of use. Sensitivity analyses revealed diminished associations for glyphosate in participants with high-frequency herbicide use or among those who ever worked on a farm, and generally stronger associations for 2,4-D and glyphosate among those who worked in non-farming jobs, such as gardening. Results were also sensitive to exclusion of the largest study in the pooled analysis, with higher estimated risks after the exclusion.

Phenoxy herbicides are a widely used group of herbicides, of which 2,4,5-T received much attention because of inherent contamination with the carcinogenic ‘dioxin’, 2,3,7,8-tetrachlorodibenzo-p-dioxin. While 2,4,5-T has been banned in most countries, 2,4-D continues to be used worldwide. As noted in the IARC review, several previous studies reported an association between 2,4-D use and NHL (including the Italian study
in our pooled analysis, although risk estimates were sensitive to adjustment for other pesticides, decreasing confidence in the evidence. More recent studies which adjusted for other pesticides found no association between 2,4-D use and all NHL, including the Agricultural Health Study (AHS) cohort, individually, and as part of a meta-analysis of three prospective agricultural cohorts with exposure assignment using a crop-exposure matrix or self-report (AGRICOH). In our analysis with adjustment for other pesticides, we found weak trends of increasing risk with longer duration of 2,4-D use for all NHL and several B-cell NHL subtypes. This result is in line with a meta-analysis that estimated increased risk from 2,4-D when considering only ‘high’ exposures, based on factors such as duration, frequency and intensity. Our analysis further revealed that these associations were strongest for use in the 1960s, possibly suggesting risk linked with early production of 2,4-D that typically resulted in low levels of dioxin contamination—an issue that was largely resolved by improvement of production methods in the late 1980s. Our novel finding of an association between other (non-2,4-D) phenoxy herbicides and TCL is plausible based on high levels of dioxin contamination in 2,4,5-T, which was severely restricted for use and subsequently banned by regulatory bodies in the countries of our pooled study in the 1970s and 1980s. This timeline corresponds with elevated ORs we observed in association with other phenoxy herbicide use in the 1970s and 1980s for TCL and all NHL (1980s only), and no risk increases with use in later decades.

Our study adds to existing data on the relationship between glyphosate use and risk of NHL with analysis of a large, pooled study population and inclusion of six studies (BCMM, Italian, Mayo, NCI-SEER, NSW, Yale) which did not previously report on glyphosate (as well as two studies which did previously report on the association: ENGELA and Epilymph). We found little evidence of an association between glyphosate use and all NHL, and meta-analysis indicated substantial heterogeneity of effect among the studies. Our findings for all NHL agree with recent, large studies, including an updated analysis of the AHS cohort that reported only small, non-significant increases in NHL risk with higher intensity-weighted lifetime days of use, lagged by 20 years (55 cases, OR=1.12, 95%CI: 0.83 to 1.51 for the highest vs lowest quartile) and the AGRICOH meta-analysis of three cohorts (including the AHS) that found no association between ever-use and all NHL (OR=0.95, 95%CI: 0.77 to 1.18). A pooled analysis of case-control studies conducted in North America (not including studies in our analysis) found no association between glyphosate use and all NHL for ever-use or duration, but estimated increased risk in association with use frequency >2 days/year (30 cases, OR=1.73, 95%CI: 1.02 to 2.94). A meta-analysis that evaluated NHL risk in association with ‘high’ glyphosate exposure—defined according to highest intensity, duration, frequency and/or exposure latency (ie, ‘lag’) assessed in the studies—estimated 17% increased risk of NHL in association with exposure. In contrast, in our study, associations between glyphosate use and all NHL did not increase by duration and diminished with consideration of high-frequency use. We did find somewhat stronger associations with exposure lagged by 10 years, but our analysis of exposure windows revealed no association with exposure lagged by 20 years.

In analyses of NHL subtypes, we found an association between glyphosate use and FL that was somewhat stronger when lagged by 10 years. The association with FL was also stronger with shorter duration, contrary to our general hypothesis of increasing risk with longer duration of exposure to carcinogens. Nevertheless, similar results were reported in a recent case-control study conducted in Italy from 2011 to 2017 (after the Italian study in our analysis), in which higher ORs were estimated in association with shorter duration of glyphosate use (≤16 years in that study) for all NHL, B-cell lymphoma and FL. In subtype analyses of the pooled North American study (referenced above), glyphosate use was not associated with risk of FL, but increased risks were estimated in relation to DLBCL for lower duration and higher frequency. An association with DLBCL was not apparent in our study. No subtype-specific associations were found for glyphosate use in the AHS. We can only speculate on a reason for stronger associations found with shorter duration in our study and others, but such a pattern could occur if participants with fewer years of use had more dense exposures. Changes in glyphosate use patterns include more widespread use (greater use prevalence) and much heavier use (greater amounts applied) in the 1990s and 2000s, compared with the early years of use after market introduction in 1974. More widespread and heavier use in later years could correspond with greater exposure intensity in periods of shorter duration. According to these use patterns and if there was a causal association between glyphosate and NHL, then we would expect to see the highest ORs for use in the later decades, as observed for NHL and some subtypes (small or imprecise elevated ORs) for use in the 2000s. However, the association between glyphosate and FL was only elevated for use in the 1970s.

Our analysis suggested different latencies (lags) for the various herbicide exposures and NHL subtypes. While associations between glyphosate and FL were strongest for the herbicide use 10–20 years before diagnosis, more recent exposures appeared relevant for other subtypes including DLBCL and TCL (based on small numbers)—and such different latencies could account for discrepant results among studies. Associations with 2,4-D were generally strongest for recent use within 5 years of diagnosis, suggesting possible carcinogenicity through a late-stage biological mechanism. However, longer latencies were found to be most relevant for the ‘other’ (non-2,4-D) phenoxy herbicides, perhaps suggesting a different mechanism than 2,4-D.

A strong influence of the Mayo study was evident in our analysis. The Mayo population was the largest examined, and the reported use of herbicides was higher than other studies (consistent with extensive agriculture in the upper Midwest and similar to other published reports from the region)—amounting to more than half of the exposed participants in many pooled analyses. While associations observed in the Mayo study were in line with the other studies, they tended to be lower, as evidenced by our sensitivity analysis excluding this study that generally produced higher ORs than the main analysis. Future investigation of heterogeneity of effect among the studies, seen for some associations (eg, glyphosate and all NHL), may shed light on regional exposure differences to consider in future analyses. A major strength of our study is the large pooled sample, from which we characterised a broad spectrum of occupational herbicide use, in both farming and non-farming jobs. Nevertheless, assessment of pesticide exposure is challenging, given the many different pesticide products and the importance of long-term exposure information in studies of cancer—necessitating long, detailed questionnaires to adequately capture the relevant information. Poor reporting is a particular issue when exposure data are collected retrospectively via questionnaire, as for the case-control studies in our pooled analysis, due to concern of biased recall (ie, enhanced recall of exposure by cases, leading to falsely elevated risk estimates). We do not believe recall bias greatly affected our results, as none of the herbicides examined were significantly associated with increased risk of all NHL.
However, open-ended questionnaire items to elicit self-reported exposures have been found to elicit more biased responses,37 and this suggests a greater possibility of recall bias from some studies than others—namely, those with open-ended elicitation of exposures in any job (Yale, NCI-SEER), compared to studies with questionnaire items on specific exposures (LACCMM, Mayo) or questionnaires that were designed for and administered only to participants in certain jobs like farming (ENGELA, Italian, Epilymph, NSW, BCMM). A higher risk of reporting or recall bias may also be suspected for the Yale study because participants were asked about exposures at work or at home, in one questionnaire item. Such a bias may be reflected in the strong association between phenoxy herbicides and all NHL in the Yale study, but does not appear to have globally affected results, given no association in the Yale study for any herbicide use in relation to all NHL (online supplemental figure 1). Our pooled study is also susceptible to selection bias that may have occurred in the individual studies, given that participation in the studies was low to moderate (generally between 40% and 70%).38 Differential selection/participation of subjects by both NHL status and pesticide exposures could bias results in either direction, for example, possibly causing the inverse associations (ORs <1.0) we observed for some pesticides.

We capitalised on our pooling strategy to harmonise herbicide variables across the individual studies, including ever-use, duration, decades of use and lagged exposures. We also considered use frequency (eg, days/year) in the studies that assessed it. Although duration was consistently available across the studies, it is only one component of cumulative exposure that does not necessarily correspond with exposure intensity. Unfortunately, the level of detail and types of information available in the studies was not optimal for harmonising a measure of exposure intensity across studies. Another advantage of pooling is that the approach enabled consistent adjustment for other pesticides across the studies and adequately powered subgroup analyses. Our results suggested, at most, modest confounding by other pesticides. Overadjustment is also a concern, although this may be less of an issue in more homogeneous subgroups, such as farmers. Results for subgroups that differed from our main analysis may suggest residual confounding, effect modification or greater exposure intensity within the subgroup.

Our results add to the evidence on cancer risks from herbicide use, with suggested increases of risks for DLBCL with longer duration 2,4-D exposure, and an association between glyphosate use and FL. These findings underscore the importance of estimating subtype-specific risks to clarify associations. Efforts by future studies to collect detailed information necessary for assessment of exposure intensity, frequency and duration will allow estimation of cumulative exposure, which may be most relevant for carcinogenesis. Also, based on our findings, future research should consider lagged exposure windows that may differ between subtypes, as well as decades of exposure to evaluate the coherence of estimated associations with known herbicide use patterns. Although estimated risks in our study were somewhat variable between analyses, the implications are notable because of current widespread use of these herbicides. Our results may contribute to future hazard assessments of herbicides by inclusion in meta-analyses of ever-more detailed associations for the frequently assessed chemicals 2,4-D and glyphosate (such as to hone-in on subtype-specific associations with particular latencies) and by inclusion in simple meta-analyses of ever-use for the chemicals with limited human data (such as paraquat).

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Details of the data collected and coded by the original studies (i.e., by the individual study investigators as part of the conducting the original study) and subsequent exposure assessment/ coding for the InterLymph pooled study are described in this document.

We requested data from each participating study on occupational history, farming, and occupational pesticide use. In addition to the questionnaire data, we requested any variables coded from these data, such as those resulting from expert assessment of pesticide exposures by an industrial hygienist or other exposure expert. Details on the relevant data from each individual study data are listed below.

In summary, five of the studies queried all participants about chemical and/or pesticide use in any type of job, and five of the studies administered questions about pesticides to persons with a history of farming or those who ever worked in other jobs with probable exposure, such as pest control, gardening and forestry. Two questionnaires asked about chemicals without distinguishing between work and home (LACCMM & Yale), although in both of these studies, participants were also queried separately about occupational and/or farming exposures.

Occupational use of pesticides was coded directly from questionnaire responses (i.e., self-report, 6 studies) or from reviews conducted by local experts in the individual studies (i.e., expert assessment, 4 studies), as follows:

**Self-Reported Use** was based on responses to either closed-ended (LAMMCC, Mayo) or open-ended (LANHL, Yale, NCI-SEER, BCMM) questions (detailed above); these were coded as a specific pesticide if either the active ingredient, or a product that contained the active ingredient, was named. One exception is that Agent Orange, a formulation which contained both 2,4,5-T and 2,4-D, was coded in the categories for ‘all phenoxy herbicides’ and ‘other phenoxy herbicides’, but was not coded as ‘2,4-D’ as we wished to distinguish these exposures. Only personal handling of pesticides (i.e., mixed/loaded/applied) was coded as exposed from the questionnaires that provided this level of detail (all except LAMMCC and LANHL, which queried about substances to which the person was ‘exposed’ or ‘directly exposed’). Self-reported responses to open-ended questions were reviewed for this InterLymph analysis (blinded to case status) by the principal investigator (AJD) and an industrial hygienist (TH), and were coded as a broad pesticide class or active ingredient by matching reported pesticide names to information from product labels, EPA registration materials, manufacturer documentation, and pesticide classification databases; discrepancies between AJD and TH were resolved through discussion and reevaluation.

**Expert Assessments** of pesticide exposure were previously conducted by four of the studies – the Italian Multicenter Study (Miligi et al. 2003), New South Wales (Fritschi et al. 2005), ENGELA (Orsi et al. 2009), and Epilymph (Cocco et al. 2013), as described for each study, below. Coded pesticide exposures (ever-use) from these expert assessments were accepted, as is, without recoding. However, specific pesticides coded in the expert assessment were grouped, when appropriate, into broad pesticide categories for the pooled analysis (the converse of coding specific active ingredients from expert-assessed broad pesticide categories was not done).
Following ever/never coding of the pesticides of interest by either self-report or expert assessment, additional data coding and cleaning was conducted to harmonize the data. Duration of use was coded from reported duration or reported years of use, and cross-checks were conducted to make sure these reported items corresponded to each other (if in disagreement then the lower duration value was retained). Reported years of use were also recoded if they exceeded the study reference year (in this case, the year of use was set to the reference year). Finally, years of use were restricted to plausible years after the chemical was registered for use (for example, glyphosate was first marketed for use in 1974; therefore, we did not count reported use during earlier years).

Duration of use for each pesticide was summed across all use periods, for each participant (e.g., across multiple jobs). If reported duration or years of use was not collected in the study or if the data were missing, then duration was calculated from job years for exposures linked to a particular job. The earliest and latest years of use (out of all uses of the pesticide) were used for calculation of lagged exposures, exposure windows prior to diagnosis, and decades of use.

**LACCMM**

**Original study.** An occupational work history included all jobs held for at least two months. All participants were asked about occupational exposures in two different sections of the questionnaire: a) up to 3 unprompted exposures in the occupational history section; b) up to 8 chemical exposures in response to the interviewer reading a list of substances (these exposures seemed to include both workplace and non-workplace exposures, although the participant could link the exposure to a particular job). Each participant's reported exposures were then summarized into codes by the study investigators.

**Pooled study.** Investigators received questionnaire data including coded occupational history (standard job codes) and chemical exposures. Chemical exposures were, in some cases, further grouped for the pooled analysis (e.g., grouping “agent orange” and “2,4,5-T; 2,4-D” as phenoxy herbicides). Exposure years and duration were coded from self-reported exposure years for the prompted exposures and, otherwise, as job years.
LANHL

**Original study.** An occupational work history included all jobs held for 6 months or longer "since the age of 15 up until 12 months ago". Participants were also asked, separately, about work in farming. All participants were asked if they were ever "directly exposed" to particular types of exposures, prompted by the questionnaire, including, for pesticides: a) "Weed killers or herbicides like agent orange or other phenoxy-acids such as MCP, or 2,4-D, 2,4,5-T"; b) "Insecticides or pesticides"; c) "Rodent or vermin poisons". For each reported exposure, the interviewer elicited more details according to the questionnaire on 'what kinds?' of the chemical (e.g., 2,4-D), whether the participant mixed or applied it themselves, ages exposed, length of exposure (years), total (cumulative) hours exposed, and whether the exposure occurred at work, school, or in leisure.

**Pooled study.** Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed if they indicated that they were exposed at work and they mixed or applied the chemical themselves. Exposure years and duration were coded from self-reported exposure ages. If ages were missing then duration was coded from self-reported length of exposure. A measure of frequency was coded from total hours exposed divided by the duration in years, then divided by 8 for estimation of the number of days per year.

**Italian Multicenter**

**Original study.** Data were collected through an in-person interview. Occupational history included every job held for more than 6 months and included basic information such as the job title, type of company or business, job description, and years. A job-specific questionnaire was administered to any participant who had ever worked in farming. The questionnaire was designed explicitly for crops commonly grown in the study areas, and elicited crop-specific information on crop diseases and pesticide use. Detailed data were also collected on the years and frequency of treatment and means of application.

Expert agronomists (one for each agricultural or mixed study area) reviewed information from the job descriptions and agricultural questionnaire in order to assess chemical exposures. To ensure a standardized approach, the assessors were centrally trained prior and during their independent evaluation of questionnaires. Experts examined the information on crop diseases, treatments carried out, field acreage, geographical location, and reported the use of specific pesticides. The agronomists developed a crop exposure matrix (Miligi et al., 1993) that was used as a baseline for the individual exposure assessment and to create a common resource in order to reduce exposure assessment variability among the different experts. The agronomists also based their judgments on their personal local experience, national statistics on pesticide use per year and administrative unit, available records of local pesticide suppliers, records of pesticides purchased by the major farms, and on professional consultants for the different crops. Pesticides were assessed by the type of treatment (e.g., herbicides), chemical families used (e.g., phenoxy acid), and active ingredients (e.g., 2,4-D).

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.
Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Coded exposure and years of use were taken directly from data specified in the expert-assessed data for each exposure. In some instances, exposures coded as mixtures by the experts were coded in a particular category or active ingredient for the pooled analysis (e.g., "MCPA + DICAMBA" expert assessment was coded for the pooled analysis as both ‘phenoxy herbicides’ and ‘other phenoxy herbicides’, and as dicamba use).

Yale

Original study. Questionnaires were administered by an interviewer. An occupational work history included all jobs held for 1 year or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Information on pesticide exposure was collected in two sections of the questionnaire. First, farm and agricultural pesticide use was elicited from participants who had ever lived or worked on a farm. This section asked separately about insecticides and herbicides used on the farm, eliciting details such as the chemical name, years used and total duration, frequency (days/year), personal handling, application methods, and personal protective equipment/clothing. Participants were shown cards with the names of commonly-used insecticides and herbicides to aid in recall. In a separate section of the questionnaire, participants were asked about a list of chemicals to which they may have been exposed at work or at home. They were asked if they "ever had repeated contact for a period of a year or more" with any of the substances listed on the provided prompt cards "apart from exposure on farms". If yes, they were asked for the names of the substances, years exposed, total duration (years), frequency, personal handling, and protective equipment/clothing.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach described above. Participants were coded as exposed only if they reported that they personally handled the chemical. Exposure years, duration, and frequency were coded from the self-reported information.

NCI-SEER

Original study. Questionnaires were administered by telephone using a computer-assisted structured interview. An occupational history section elicited information on all jobs held for 1 year or longer, including the job title, years worked, hours worked, the type of business/industry, job duties, chemicals or materials handled, and tools and equipment used. The question on chemicals asked, specifically, for each job, "What kinds of chemicals or materials, if any, did you handle?" The questionnaire did not contain any questions to specifically elicit occupational pesticide use.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported data on chemicals handled on the job were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Exposure years and duration were coded from the years worked in the job.
Epilymph

Original study. In-person interviews were conducted using a structured questionnaire. Lifetime occupational history was collected, including all full-time jobs held for 1 year or longer. Participants who reported that they had ever worked in farming were given a job-specific module questionnaire to elicit detailed information about tasks and exposures. Occupational physicians and industrial hygienists from each participating center attended several meetings to share and upgrade their expertise in retrospective exposure assessment and to harmonize the exposure criteria. Local agronomists reviewed the available information to identify broad pesticide group (e.g., phenoxy herbicides) and individual formulations (e.g., 2,4-D), whenever possible. Their assessment was based on review of the questionnaire data regarding the type of crop, pest to be treated, frequency of treatments, and exposure circumstances, including personal preparation of the pesticide mix. A crop-exposure matrix was also available to support the assessment (Miligi et al. 2003). Frequency was expressed as days per year.

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.

Pooled study. Investigators received coded questionnaire data including occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years, duration, and frequency were taken directly from that specified in the expert-assessment-coded data.

NSW

Original study. Questionnaires were administered over the telephone by interviewers blinded to case or control status of the subjects. A lifetime occupational history was obtained that included the job title, industry, and years of each job. In addition, job-specific modules with detailed sets of questions were administered for several types of jobs with possible pesticide exposure, including farmers, gardeners, janitors, and laborers. The modules included questions about specific tasks performed in that occupation, and the number of hours per week and weeks per year spent performing each task. The questions in the relevant modules were asked in a customized computer-assisted telephone interview. An occupational hygienist (blind to case status) reviewed the occupational histories and the answers to the module questions and determined exposure to various substances, including organophosphates, organochlorines, phenoxy herbicides, other herbicides, and specific active ingredients (e.g., 2,4-D, glyphosate). Participants were coded as exposed in a particular job, only if they had personally handled (mixed or applied) the chemical. A pesticide-crop matrix was developed for assistance with exposure assessment, that included information on the kinds of pesticides known to be used (or recommended by the Australian Department of Agriculture) for each combination of crop or animal raised and pest type (insect, weed, etc.) (Benke et al. 2001). A table was also prepared for assistance with identification of chemical composition from trade names reported by the subjects. Former Department of Agriculture employees, environmental scientists, and pesticide manufacturers assisted with construction of the matrix. Frequency of exposure was allocated as number of 8-hour days per year and was calculated using responses to the task questions.

Benke G, Fritschi L, Hughes AM, et al. Combining job specific modules (JSMs) and exposure matrices for retrospective ex exposure assessment. In: Hagberg M, Knave B,
Pooled study. Investigators received coded questionnaire data including coded occupational titles (standard job codes) and pesticide exposures per job. Exposure years and duration were based on the years the job was held for farming, janitor, and laborer jobs. Exposure years and duration were based on the reported years of pesticide use for gardener/groundskeeper jobs.

ENGELA

Original study. Data collection was conducted in several phases. First, participants were asked to complete a self-administered questionnaire to collect information on sociodemographics, and residential and work histories. Occupational work history included all jobs held longer than 6 months, for which the participant was asked to report the job title, start and end dates, specific tasks performed and products personally handled. A face-to-face interview was then conducted with each participant to elicit further information on personal and familial medical histories, lifestyle characteristics, leisure activities, and non-occupational exposures. Finally, a specialized questionnaire was administered to each participant who had reported ever working as a farmer or gardener – designed to allow standardized case-by-case pesticide exposure assessment by experts. Participants were asked questions about each farm they had ever worked on, including specific crops and animals, pesticides applied (including whether they had personally prepared or sprayed the chemical), spraying equipment, frequency, and years of use. Repeat interviews for the specialized questionnaire were conducted for more than 80% of the subjects because the reported information was insufficient. All administered interviews were blind to case-control status.

Two persons, one industrial hygienist and one agronomist individually reviewed all the questionnaires to assess pesticide exposures. The experts reviewed the consistency of the subjects' statements with respect to product availability dates, type and size of the crops, geographic location of the farm and frequency of treatment. A database constructed using the annual directories of phytochemicals published by the Association de Coordination Technique Agricole was used to facilitate the process – including recommendations for use of the products (identified by their chemical and brand names) by crop and pest. When information on pesticides was missing or unreliable, the experts allocated a list of chemicals that may have been used based on the crops treated, method of spraying, period and frequency of treatment and pests targeted. Pesticide exposures were primarily coded in broad categories such as organophosphate insecticides, phenoxy herbicides and triazine herbicides, and there was also specific coding for glyphosate. The exposure years and duration were based on the years of pesticide use for each exposure, reported in the specialized questionnaire.

Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years and duration was coded from the years specified in the expert-assessed data.
Mayo

**Original study.** Questionnaires were self-administered. Information was collected on the longest-held job and up to 5 additional jobs held for longer than 5 years, including the job title, age first worked, and the total number of years worked in the job. An additional questionnaire based off the Agricultural Health Study private applicator questionnaires ([https://aghealth.nih.gov/collaboration/questionnaires.html](https://aghealth.nih.gov/collaboration/questionnaires.html)) was given to participants who reported during the enrollment protocol that they ever worked on a farm or with pesticides for longer than 1 year. Participants who ever personally mixed or applied any pesticides as part of their job were asked about use of 48 active ingredients or pesticide groups; they were asked, separately for each pesticide, to report personal handling, duration (years) of use, frequency (days/year), and the year of first use. Other parts of the questionnaire asked about pesticide application methods and additives used, size of the farm, and crops and animals.

**Pooled study.** Investigators received questionnaire data including coded occupational history (standard occupational codes) and responses from the farming questionnaire. Reported pesticide uses were considered exposed if the participant reported personal handling of that specific pesticide. Specific active ingredients were coded directly from the self-reported information, and active ingredients were also grouped to code broad categories of pesticides (such as grouping “atrazine” and “cyanazine”, reported separately, as triazine herbicides). Exposure duration and year of first use also were coded from the questionnaire responses.

BCMM

**Original study.** Questionnaires were self-administered. An occupational work history included all jobs held for 2 years or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Additional questions were given to participants who had ever lived on a farm or worked in agriculture, gardening, parks, golf courses, or forestry. Participants were asked about use of pesticides in these settings, including the name of the product or active ingredient, the target pest, application method, duration of use, and frequency (days/year). Other parts of the questionnaire asked about personal handling of herbicides, insecticides, and fungicides, as broad categories, protective equipment and clothing, and crops and animals.

**Pooled study.** Investigators received questionnaire data including raw text responses from the occupational history and reported pesticides. The investigators coded jobs of a priori interest for possible pesticide exposures including farming, forestry, gardener/groundskeeper, janitor/cleaner, and laborer. Reported pesticides were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed only if they reported personal handling of the corresponding types of pesticide (out of herbicides, insecticides, and fungicides). Exposure years, duration, and frequency were coded from the self-reported information for each pesticide exposure.
Supplemental Material 2 – Adjustment for other occupational pesticide use in the InterLymph pooled analysis of herbicides

Adjustment for other pesticides included up to 5 covariates for each herbicide group or active ingredient, selected and coded specifically for each herbicide. Because of associations we found with insecticide use in our previous pooled analysis, we adjusted for use of organophosphate insecticides and organochlorine insecticides using two separate indicator variables. Because of a priori hypotheses about associations of phenoxy herbicides and glyphosate with NHL, we adjusted for these herbicides using two indicator variables in each model (except for the models estimating associations with those particular herbicides). Estimated effects of 2,4-D and other phenoxy herbicide use were adjusted for each other (i.e., model for 2,4-D included indicator variable for other phenoxy herbicides, and vice versa). Finally, to capture use of any other type of pesticide including other insecticides, herbicides, fungicides, nematicides, etc., we developed an indicator variable tailored to each particular herbicide exposure (leaving that herbicide exposure out).
Supplemental Table 1. Frequency of occupational herbicide use among controls within each of the case-control studies participating in the InterLymph pooled analysis

| Herbicide Type          | BCMM  | ENGELA | Epilymph | Italian | LAMMCC | LANHL  | Mayo  | NCISEER | NSW  | Yale  |
|-------------------------|-------|--------|----------|---------|--------|--------|-------|---------|------|-------|
| Any herbicide           | 13 (3.5%) | 42 (9.4%) | 48 (2.0%) | 59 (5.2%) | 4 (1.4%) | 6 (1.6%) | 296 (13.6%) | 51 (5.2%) | 33 (4.8%) | 44 (6.2%) |
| Phenoxy herbicides      | 5 (1.4%) | 25 (5.6%) | 13 (0.5%) | 29 (2.5%) | 3 (1.1%) | 3 (0.8%) | 239 (11.0%) | 17 (1.7%) | 18 (2.6%) | 18 (2.6%) |
| 2,4-D                   | 4 (1.1%) | -      | 5 (0.2%) | 22 (1.9%) | -      | 1 (0.3%) | 235 (10.8%) | 14 (1.4%) | 6 (0.9%) | -      |
| Other phenoxy herbicides| 2 (0.5%) | -      | 3 (0.1%) | 24 (2.1%) | 3 (1.1%) | 3 (0.8%) | 39 (1.8%) | 6 (0.6%) | 8 (1.2%) | -      |
| Glyphosate              | 5 (1.4%) | 24 (5.4%) | 2 (0.1%) | 9 (0.8%) | -      | -      | 253 (11.6%) | 5 (0.5%) | 14 (2.1%) | 28 (4.0%) |
| Triazine herbicides     | 1 (0.3%) | 20 (4.5%) | 10 (0.4%) | 18 (1.6%) | -      | -      | 161 (7.4%) | 6 (0.6%) | 4 (0.6%) | -      |
| Atrazine                | 1 (0.3%) | -      | -        | 16 (1.4%) | -      | -      | 154 (7.1%) | 5 (0.5%) | 2 (0.3%) | -      |
| Amide herbicides        | -      | 12 (2.7%) | -        | 11 (1.0%) | -      | -      | 141 (6.5%) | 6 (0.6%) | 1 (0.2%) | -      |
| Alachlor                | -      | -      | -        | 4 (0.4%) | -      | -      | 119 (5.5%) | 3 (0.3%) | -      | -      |
| Trifluralin             | 0      | -      | -        | 21 (1.8%) | -      | -      | 112 (5.1%) | 7 (0.7%) | 0      | 8 (1.1%) |
| Dicamba                 | 1 (0.3%) | -      | -        | 5 (0.4%) | -      | 1 (0.3%) | 121 (5.5%) | 2 (0.2%) | 1 (0.2%) | -      |
| Pendimethalin           | -      | -      | -        | 4 (0.4%) | -      | -      | 52 (2.4%) | 1 (0.1%) | -      | -      |
| Paraquat                | 1 (0.3%) | -      | -        | 4 (0.4%) | -      | -      | 17 (0.8%) | 1 (0.1%) | 3 (0.4%) | -      |

* The symbol " - " indicates that the study was not included in analysis of the particular herbicide, due to no exposed cases or controls
Supplemental Figure 1. Meta-analysis forest plots of selected associations between herbicide use and risk of all non-Hodgkin lymphoma (NHL) and NHL subtypes (individual-study estimates are odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models, with adjustment for study center, age, gender, socioeconomic status (SES), race/ethnicity, and set of covariates for use of other pesticides; meta-OR (overall) estimates are from random effects meta-analysis). NHL Subtypes: DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MM=multiple myeloma; OBCL=other B-cell lymphoma; TCL=T-cell lymphoma.

Any herbicide use, all NHL

| Study    | ES (95% CI) | Weight |
|----------|-------------|--------|
| BCM      | 0.99 (0.29, 3.42) | 2.00   |
| ENGELA   | 0.65 (0.28, 1.49)  | 4.35   |
| Epilymph | 1.22 (0.79, 1.87)  | 16.53  |
| Italian  | 1.20 (0.80, 1.82)  | 17.82  |
| LAMHL    | 2.28 (0.81, 6.44)  | 2.83   |
| LAMMCC   | 0.63 (0.13, 3.12)  | 1.19   |
| Mayo     | 1.27 (0.88, 1.84)  | 22.60  |
| NCISEER  | 0.82 (0.50, 1.32)  | 13.19  |
| NSW      | 1.59 (0.87, 2.90)  | 8.44   |
| Yale     | 0.85 (0.50, 1.43)  | 11.04  |
| Overall  | 1.12 (0.94, 1.33)  | 100.00 |

NOTE: Weights are from random effects analysis

Any herbicide use TCL

| Study    | ES (95% CI) | Weight |
|----------|-------------|--------|
| ENGELA   | 6.58 (0.47, 92.11) | 3.91   |
| Epilymph | 2.34 (0.08, 5.77)  | 33.73  |
| Italian  | 0.73 (0.14, 3.90)  | 9.73   |
| Mayo     | 1.65 (0.04, 5.94)  | 21.91  |
| NCISEER  | 1.65 (0.23, 7.06)  | 12.21  |
| NSW      | 3.23 (0.50, 18.80) | 8.85   |
| Yale     | 0.79 (0.15, 4.28)  | 9.65   |
| Overall  | 1.88 (1.00, 3.88)  | 100.00 |

NOTE: Weights are from random effects analysis
Phenoxy herbicide use, all NHL

| Study  | ES (95% CI) | Weight |
|--------|-------------|--------|
| BCMM   | 1.67 (0.40, 6.87) | 3.97   |
| ENGELA | 0.64 (0.26, 1.59)  | 8.35   |
| Epilymph | 1.32 (0.81, 2.05) | 10.68  |
| Italian | 1.16 (0.67, 2.01)  | 16.38  |
| LANHL  | 3.77 (0.94, 15.14) | 4.17   |
| LAMMCC | 0.86 (0.16, 4.74)  | 2.89   |
| Mayo   | 0.90 (0.61, 1.33)  | 21.97  |
| NCISEER| 0.92 (0.43, 1.96)  | 10.64  |
| NSW    | 0.71 (0.31, 1.64)  | 9.51   |
| Yale   | 2.73 (1.30, 5.73)  | 11.25  |
| Overall (I-squared = 31.1%, p = 0.160) | 1.15 (0.85, 1.55) | 100.00 |

NOTE: Weights are from random effects analysis

Phenoxy herbicide use duration >8 years, all NHL

| Study  | ES (95% CI) | Weight |
|--------|-------------|--------|
| BCMM   | 9.95 (0.49, 20.92) | 1.41   |
| ENGELA | 0.57 (0.21, 1.51)  | 10.38  |
| Epilymph | 2.09 (0.80, 5.04) | 11.37  |
| Italian | 1.54 (0.77, 3.08)  | 18.36  |
| LANHL  | 2.79 (0.17, 46.54) | 1.62   |
| LAMMCC | 0.49 (0.02, 12.06) | 1.28   |
| Mayo   | 0.80 (0.50, 1.39)  | 28.90  |
| NCISEER| 0.80 (0.31, 2.05)  | 11.66  |
| NSW    | 1.13 (0.38, 3.27)  | 9.61   |
| Yale   | 3.32 (0.88, 16.05) | 4.84   |
| Overall (I-squared = 18.7%, p = 0.271) | 1.13 (0.78, 1.62) | 100.00 |

NOTE: Weights are from random effects analysis
Phenoxy herbicide use, MM

| Study     | ES (95% CI)       | Weight |
|-----------|-------------------|--------|
| LAMMCC    | 0.84 (0.18, 4.01) | 16.47  |
| Yale      | 0.51 (0.06, 4.18) | 16.68  |
| Italian   | 1.67 (0.40, 6.97) | 10.36  |
| BCMM      | 1.50 (0.32, 7.05) | 0.86 (0.16, 4.74) | 14.53 |
| ENGELA    | 1.35 (0.24, 7.46) | 0.86 (0.16, 4.74) | 14.53 |
| Epilymph  | 1.59 (0.75, 3.36) | 0.51 (0.06, 4.18) | 16.68 |
| Overall   | 1.30 (0.32, 7.05) | 0.86 (0.16, 4.74) | 14.53 |

NOTE: Weights are from random effects analysis

Phenoxy herbicide use duration >8 years, MM

| Study     | ES (95% CI)       | Weight |
|-----------|-------------------|--------|
| LAMMCC    | 2.33 (0.15, 6.96) | 100.00 |
| Yale      | 3.25 (1.02, 10.22) | 23.25  |
| Italian   | 0.49 (0.02, 12.66) | 11.10  |
| BCMM      | 0.49 (0.02, 12.66) | 11.10  |
| ENGELA    | 0.49 (0.02, 12.66) | 11.10  |
| Epilymph  | 0.49 (0.02, 12.66) | 11.10  |
| Overall   | 1.30 (0.32, 7.05) | 0.86 (0.16, 4.74) | 14.53 |

NOTE: Weights are from random effects analysis

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2,4-D use, all NHL

| Study       | ES (95% CI)     | Weight |
|-------------|-----------------|--------|
| BCMM        | 2.47 (0.57, 10.64) | 3.94   |
| Epilymph    | 0.33 (0.05, 2.04)  | 2.49   |
| Italian     | 1.25 (0.08, 2.20)  | 22.38  |
| LANHL       | 7.27 (0.63, 83.30) | 1.42   |
| Mayo        | 0.95 (0.05, 1.40)  | 53.05  |
| NCISEER     | 0.86 (0.37, 2.08)  | 11.00  |
| NSW         | 0.99 (0.27, 3.02)  | 5.70   |
| Overall     | 1.04 (0.79, 1.38)  | 100.00 |

**NOTE:** Weights are from random effects analysis

2,4-D use duration >8 years, all NHL (BCMM excluded due to 0% weight)

| Study       | ES (95% CI)     | Weight |
|-------------|-----------------|--------|
| Epilymph    | 0.60 (0.08, 4.88) | 2.56   |
| Italian     | 1.03 (0.08, 4.34) | 18.45  |
| LANHL       | 2.74 (0.16, 45.00) | 1.60   |
| Mayo        | 0.86 (0.04, 1.37) | 58.46  |
| NCISEER     | 0.87 (0.33, 2.30) | 13.45  |
| NSW         | 2.00 (0.34, 11.74) | 4.04   |
| Overall     | 1.05 (0.74, 1.50) | 100.00 |

**NOTE:** Weights are from random effects analysis
2,4-D use duration >8 years, DLBCL

| Study   | Odds Ratio (95% CI) | Weight |
|---------|---------------------|--------|
| Italian | 2.74 (0.85, 8.78)   | 26.46  |
| LANHL   | 5.66 (2.11, 14.30)  | 4.70   |
| Mayo    | 0.69 (0.30, 1.52)   | 38.54  |
| NCISER  | 1.96 (0.54, 7.11)   | 22.89  |
| NSW     | 1.47 (0.11, 19.17)  | 7.31   |
| Overall | 1.44 (0.69, 2.97)   | 100.00 |

NOTE: Weights are from random effects analysis

Overall (I-squared = 24.4%, p = 0.259)

2,4-D use duration >8 years, OBCL

| Study   | Odds Ratio (95% CI) | Weight |
|---------|---------------------|--------|
| Epilymph| 2.62 (0.10, 68.77)  | 3.82   |
| Italian | 1.89 (0.37, 5.32)   | 38.58  |
| LANHL   | 2.05 (0.10, 42.30)  | 4.80   |
| Mayo    | 1.21 (0.40, 4.07)   | 49.27  |
| NSW     | 1.71 (0.16, 16.60)  | 4.81   |
| Overall | 1.73 (0.91, 3.28)   | 100.00 |

NOTE: Weights are from random effects analysis

Overall (I-squared = 0.0%, p = 0.491)
Glyphosate use, all NHL

| Study   | ES (95% CI) | Weight |
|---------|-------------|--------|
| BCMM    | 0.33 (0.05, 2.11) | 3.67   |
| ENGELA  | 0.71 (0.30, 1.68) | 12.13  |
| Epiympy| 1.12 (0.15, 6.52) | 3.15   |
| Italian | 1.22 (0.40, 3.03) | 11.93  |
| Mayo    | 1.04 (0.73, 1.49) | 30.26  |
| NCISEER | 0.54 (0.26, 1.11) | 18.30  |
| NSW     | 1.02 (0.70, 1.48) | 100.00 |

Overall (I-squared = 32.8%, p = 0.166)

NOTE: Weights are from random effects analysis

Glyphosate lagged-use (10-year lag), all NHL

| Study   | ES (95% CI) | Weight |
|---------|-------------|--------|
| BCMM    | 0.89 (0.38, 1.87) | 17.85  |
| ENGELA  | 2.25 (0.19, 25.83) | 4.42   |
| Epiympy| 1.20 (0.42, 3.76) | 14.24  |
| Italian | 0.99 (0.84, 1.42) | 27.18  |
| Mayo    | 4.40 (1.30, 14.14) | 10.83  |
| NCISEER | 2.79 (0.94, 8.15) | 14.53  |
| NSW     | 6.44 (0.53, 78.75) | 4.35   |
| Yale    | 0.38 (0.79, 1.42) | 100.00 |

Overall (I-squared = 47.1%, p = 0.067)

NOTE: Weights are from random effects analysis
**Glyphosate use, FL**

| Study    | ES (95% CI) | Weight |
|----------|-------------|--------|
| ENGELA   | 1.44 (0.97, 2.23) | 4.52   |
| Italian  | 2.10 (0.23, 18.81) | 3.46   |
| Mayo     | 1.44 (0.83, 2.51)  | 58.26  |
| NCISER   | 1.71 (0.34, 8.56)  | 6.63   |
| NSW      | 2.22 (0.70, 7.07)  | 13.85  |
| Yale     | 1.00 (0.36, 2.60)  | 18.36  |
| Overall  | 1.47 (0.97, 2.23)  | 100.00 |

**NOTE:** Weights are from random effects analysis

**Glyphosate lagged-use (10-year lag), FL**

| Study    | ES (95% CI) | Weight |
|----------|-------------|--------|
| ENGELA   | 1.69 (1.01, 2.81) | 12.50  |
| Mayo     | 1.21 (0.64, 2.27)  | 44.94  |
| NCISER   | 3.39 (1.00, 10.87) | 13.48  |
| NSW      | 2.20 (0.70, 6.57)  | 21.34  |
| Yale     | 20.34 (1.67, 247.13) | 8.64   |
| Overall  | 3.36 (1.00, 10.07) | 160.08 |

**NOTE:** Weights are from random effects analysis
Glyphosate lagged-use (10-year lag) duration ≤8 years, FL (NCISEER excluded due to 0% weight)

| Study      | OR (95% CI)  | Weight |
|------------|--------------|--------|
| ENGELA     | 2.17 (0.74, 6.45) | 10.01  |
| Mayo       | 1.00 (0.06, 3.29)  | 94.79  |
| NSW        | 3.22 (0.84, 10.01)| 23.84  |
| Yale       | 3.06 (1.98, 4.27)  | 11.77  |
| Overall (heterogeneity: I^2 = 30.8%, p = 0.228) | 2.54 (1.00, 6.45) | 100.00 |

NOTE: Weights are from random effects analysis

Glyphosate lagged-use (10-year lag) duration >8 years, FL

| Study      | OR (95% CI)  | Weight |
|------------|--------------|--------|
| ENGELA     | 2.52 (0.30, 21.46) | 10.69  |
| Mayo       | 2.38 (0.30, 18.97) | 66.35  |
| NCISEER    | 0.98 (0.48, 2.00)  | 11.14  |
| NSW        | 1.30 (0.15, 11.58) | 11.82  |
| Overall (heterogeneity: I^2 = 0.0%, p = 0.536) | 0.98 (0.48, 2.00) | 100.00 |

NOTE: Weights are from random effects analysis
Glyphosate lagged-use (10-year lag), DLBCL

| Study   | ES (95% CI)   | Weight |
|---------|--------------|--------|
| ENGELA  | 0.49 (0.11, 2.17) | 13.35  |
| Italian | 0.93 (0.10, 8.28)  | 6.14   |
| Mayo    | 1.12 (0.35, 2.31)  | 58.48  |
| NCSEER  | 5.30 (0.94, 29.96) | 0.77   |
| NSW     | 1.47 (0.32, 6.38)  | 11.28  |
| Yale    | 2.07 (0.11, 58.71) | 2.89   |

Overall (I-squared = 0.0%, p = 0.469)

ES (95% CI) 1.22 (0.71, 2.10) 100.00
Weight % 11.28

NOTE: Weights are from random effects analysis

Glyphosate lagged-use (10-year lag), TCL

| Study   | ES (95% CI)   | Weight |
|---------|--------------|--------|
| ENGELA  | 1.24 (0.35, 4.34) | 64.63  |
| Mayo    | 7.03 (0.27, 183.63) | 17.17  |
| NCSEER  | 13.59 (0.58, 318.49) | 18.20  |
| NSW     | 2.58 (0.60, 11.07)  | 64.63  |

Overall (I-squared = 21.5%, p = 0.280)

ES (95% CI) 2.04 (0.11, 318) 100.00
Weight % 64.63

NOTE: Weights are from random effects analysis
Supplemental Material 1 – Details on pesticide exposure assessment for the InterLymph pooled analysis of herbicides

Details of the data collected and coded by the original studies (i.e., by the individual study investigators as part of the conducting the original study) and subsequent exposure assessment/coding for the InterLymph pooled study are described in this document.

We requested data from each participating study on occupational history, farming, and occupational pesticide use. In addition to the questionnaire data, we requested any variables coded from these data, such as those resulting from expert assessment of pesticide exposures by an industrial hygienist or other exposure expert. Details on the relevant data from each individual study data are listed below.

In summary, five of the studies queried all participants about chemical and/or pesticide use in any type of job, and five of the studies administered questions about pesticides to persons with a history of farming or those who ever worked in other jobs with probable exposure, such as pest control, gardening and forestry. Two questionnaires asked about chemicals without distinguishing between work and home (LACCMM & Yale), although in both of these studies, participants were also queried separately about occupational and/or farming exposures.

Occupational use of pesticides was coded directly from questionnaire responses (i.e., self-report, 6 studies) or from reviews conducted by local experts in the individual studies (i.e., expert assessment, 4 studies), as follows:

- **Self-Reported Use** was based on responses to either closed-ended (LAMMCC, Mayo) or open-ended (LANHL, Yale, NCI-SEER, BCMM) questions (detailed above); these were coded as a specific pesticide if either the active ingredient, or a product that contained the active ingredient, was named. One exception is that Agent Orange, a formulation which contained both 2,4,5-T and 2,4-D, was coded in the categories for ‘all phenoxy herbicides’ and ‘other phenoxy herbicides’, but was not coded as ‘2,4-D’ as we wished to distinguish these exposures. Only personal handling of pesticides (i.e., mixed/loaded/applied) was coded as exposed from the questionnaires that provided this level of detail (all except LAMMCC and LANHL, which queried about substances to which the person was ‘exposed’ or ‘directly exposed’). Self-reported responses to open-ended questions were reviewed for this InterLymph analysis (blinded to case status) by the principal investigator (AJD) and an industrial hygienist (TH), and were coded as a broad pesticide class or active ingredient by matching reported pesticide names to information from product labels, EPA registration materials, manufacturer documentation, and pesticide classification databases; discrepancies between AJD and TH were resolved through discussion and reevaluation.

- **Expert Assessments** of pesticide exposure were previously conducted by four of the studies – the Italian Multicenter Study (Miligi et al. 2003), New South Wales (Fritschi et al. 2005), ENGELA (Orsi et al. 2009), and Epilymph (Cocco et al. 2013), as described for each study, below. Coded pesticide exposures (ever-use) from these expert assessments were accepted, as is, without recoding. However, specific pesticides coded in the expert assessment were grouped, when appropriate, into broad pesticide categories for the pooled analysis (the converse of coding specific active ingredients from expert-assessed broad pesticide categories was not done).
Cocco P, Satta G, Dubois S, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med 2013;70:91-98.

Fritschi L, Benke G, Hughes AM, et al. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. Am J Epidemiol 2005;162:849-857.

Miligi L, Costantini AS, Bolejack V, et al. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study. Am J Ind Med 2003;44:627-636.

Orsi L, Delabre L, Monnereau A, et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009;66:291-298.

Following ever/never coding of the pesticides of interest by either self-report or expert assessment, additional data coding and cleaning was conducted to harmonize the data. Duration of use was coded from reported duration or reported years of use, and cross-checks were conducted to make sure these reported items corresponded to each other (if in disagreement then the lower duration value was retained). Reported years of use were also recoded if they exceeded the study reference year (in this case, the year of use was set to the reference year). Finally, years of use were restricted to plausible years after the chemical was registered for use (for example, glyphosate was first marketed for use in 1974; therefore, we did not count reported use during earlier years).

Duration of use for each pesticide was summed across all use periods, for each participant (e.g., across multiple jobs). If reported duration or years of use was not collected in the study or if the data were missing, then duration was calculated from job years for exposures linked to a particular job. The earliest and latest years of use (out of all uses of the pesticide) were used for calculation of lagged exposures, exposure windows prior to diagnosis, and decades of use.

LACCMM

**Original study.** An occupational work history included all jobs held for at least two months. All participants were asked about occupational exposures in two different sections of the questionnaire: a) up to 3 unprompted exposures in the occupational history section; b) up to 8 chemical exposures in response to the interviewer reading a list of substances (these exposures seemed to include both workplace and non-workplace exposures, although the participant could link the exposure to a particular job). Each participant's reported exposures were then summarized into codes by the study investigators.

**Pooled study.** Investigators received questionnaire data including coded occupational history (standard job codes) and chemical exposures. Chemical exposures were, in some cases, further grouped for the pooled analysis (e.g., grouping “agent orange” and “2,4,5-T; 2,4-D” as phenoxy herbicides). Exposure years and duration were coded from self-reported exposure years for the prompted exposures and, otherwise, as job years.
LANHL

Original study. An occupational work history included all jobs held for 6 months or longer “since the age of 15 up until 12 months ago”. Participants were also asked, separately, about work in farming. All participants were asked if they were ever “directly exposed” to particular types of exposures, prompted by the questionnaire, including, for pesticides: a) “Weed killers or herbicides like agent orange or other phenoxy-acids such as MCP, or 2,4-D, 2,4,5-T”; b) “Insecticides or pesticides”; c) “Rodent or vermin poisons”. For each reported exposure, the interviewer elicited more details according to the questionnaire on ‘what kinds?’ of the chemical (e.g., 2,4-D), whether the participant mixed or applied it themselves, ages exposed, length of exposure (years), total (cumulative) hours exposed, and whether the exposure occurred at work, school, or in leisure.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed if they indicated that they were exposed at work and they mixed or applied the chemical themselves. Exposure years and duration were coded from self-reported exposure ages. If ages were missing then duration was coded from self-reported length of exposure. A measure of frequency was coded from total hours exposed divided by the duration in years, then divided by 8 for estimation of the number of days per year.

Italian Multicenter

Original study. Data were collected through an in-person interview. Occupational history included every job held for more than 6 months and included basic information such as the job title, type of company or business, job description, and years. A job-specific questionnaire was administered to any participant who had ever worked in farming. The questionnaire was designed explicitly for crops commonly grown in the study areas, and elicited crop-specific information on crop diseases and pesticide use. Detailed data were also collected on the years and frequency of treatment and means of application.

Expert agronomists (one for each agricultural or mixed study area) reviewed information from the job descriptions and agricultural questionnaire in order to assess chemical exposures. To ensure a standardized approach, the assessors were centrally trained prior and during their independent evaluation of questionnaires. Experts examined the information on crop diseases, treatments carried out, field acreage, geographical location, and reported the use of specific pesticides. The agronomists developed a crop exposure matrix (Miligi et al., 1993) that was used as a baseline for the individual exposure assessment and to create a common resource in order to reduce exposure assessment variability among the different experts. The agronomists also based their judgments on their personal local experience, national statistics on pesticide use per year and administrative unit, available records of local pesticide suppliers, records of pesticides purchased by the major farms, and on professional consultants for the different crops. Pesticides were assessed by the type of treatment (e.g., herbicides), chemical families used (e.g., phenoxy acid), and active ingredients (e.g., 2,4-D).

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.
Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Coded exposure and years of use were taken directly from data specified in the expert-assessed data for each exposure. In some instances, exposures coded as mixtures by the experts were coded in a particular category or active ingredient for the pooled analysis (e.g., “MCPA + DICAMBA” expert assessment was coded for the pooled analysis as both ‘phenoxy herbicides’ and ‘other phenoxy herbicides’, and as dicamba use).

Yale

Original study. Questionnaires were administered by an interviewer. An occupational work history included all jobs held for 1 year or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Information on pesticide exposure was collected in two sections of the questionnaire. First, farm and agricultural pesticide use was elicited from participants who had ever lived or worked on a farm. This section asked separately about insecticides and herbicides used on the farm, eliciting details such as the chemical name, years used and total duration, frequency (days/year), personal handling, application methods, and personal protective equipment/clothing. Participants were shown cards with the names of commonly-used insecticides and herbicides to aid in recall. In a separate section of the questionnaire, participants were asked about a list of chemicals to which they may have been exposed at work or at home. They were asked if they “ever had repeated contact for a period of a year or more” with any of the substances listed on the provided prompt cards “apart from exposure on farms”. If yes, they were asked for the names of the substances, years exposed, total duration (years), frequency, personal handling, and protective equipment/clothing.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed only if they reported that they personally handled the chemical. Exposure years, duration, and frequency were coded from the self-reported information.

NCI-SEER

Original study. Questionnaires were administered by telephone using a computer-assisted structured interview. An occupational history section elicited information on all jobs held for 1 year or longer, including the job title, years worked, hours worked, the type of business/industry, job duties, chemicals or materials handled, and tools and equipment used. The question on chemicals asked, specifically, for each job, “What kinds of chemicals or materials, if any, did you handle?” The questionnaire did not contain any questions to specifically elicit occupational pesticide use.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported data on chemicals handled on the job were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Exposure years and duration were coded from the years worked in the job.
Epilymph

Original study. In-person interviews were conducted using a structured questionnaire. Lifetime occupational history was collected, including all full-time jobs held for 1 year or longer. Participants who reported that they had ever worked in farming were given a job-specific module questionnaire to elicit detailed information about tasks and exposures. Occupational physicians and industrial hygienists from each participating center attended several meetings to share and upgrade their expertise in retrospective exposure assessment and to harmonize the exposure criteria. Local agronomists reviewed the available information to identify broad pesticide group (e.g., phenoxy herbicides) and individual formulations (e.g., 2,4-D), whenever possible. Their assessment was based on review of the questionnaire data regarding the type of crop, pest to be treated, frequency of treatments, and exposure circumstances, including personal preparation of the pesticide mix. A crop-exposure matrix was also available to support the assessment (Miligi et al. 2003). Frequency was expressed as days per year.

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.

Pooled study. Investigators received coded questionnaire data including occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years, duration, and frequency were taken directly from that specified in the expert-assessment-coded data.

NSW

Original study. Questionnaires were administered over the telephone by interviewers blinded to case or control status of the subjects. A lifetime occupational history was obtained that included the job title, industry, and years of each job. In addition, job-specific modules with detailed sets of questions were administered for several types of jobs with possible pesticide exposure, including farmers, gardeners, janitors, and laborers. The modules included questions about specific tasks performed in that occupation, and the number of hours per week and weeks per year spent performing each task. The questions in the relevant modules were asked in a customized computer-assisted telephone interview. An occupational hygienist (blind to case status) reviewed the occupational histories and the answers to the module questions and determined exposure to various substances, including organophosphates, organochlorines, phenoxy herbicides, other herbicides, and specific active ingredients (e.g., 2,4-D, glyphosate). Participants were coded as exposed in a particular job, only if they had personally handled (mixed or applied) the chemical. A pesticide-crop matrix was developed for assistance with exposure assessment, that included information on the kinds of pesticides known to be used (or recommended by the Australian Department of Agriculture) for each combination of crop or animal raised and pest type (insect, weed, etc.) (Benke et al. 2001). A table was also prepared for assistance with identification of chemical composition from trade names reported by the subjects. Former Department of Agriculture employees, environmental scientists, and pesticide manufacturers assisted with construction of the matrix. Frequency of exposure was allocated as number of 8-hour days per year and was calculated using responses to the task questions.

Benke G, Fritschi L, Hughes AM, et al. Combining job specific modules (JSMs) and exposure matrices for retrospective ex exposure assessment. In: Hagberg M, Knave B,
Lillienberg L, et al, eds. X2001—exposure assessment in epidemiology and practice. Stockholm, Sweden: National Institute for Working Life, 2001:169–171.

Pooled study. Investigators received coded questionnaire data including coded occupational titles (standard job codes) and pesticide exposures per job. Exposure years and duration were based on the years the job was held for farming, janitor, and laborer jobs. Exposure years and duration were based on the reported years of pesticide use for gardener/groundskeeper jobs.

ENGELA

Original study. Data collection was conducted in several phases. First, participants were asked to complete a self-administered questionnaire to collect information on sociodemographics, and residential and work histories. Occupational work history included all jobs held longer than 6 months, for which the participant was asked to report the job title, start and end dates, specific tasks performed and products personally handled. A face-to-face interview was then conducted with each participant to elicit further information on personal and familial medical histories, lifestyle characteristics, leisure activities, and non-occupational exposures. Finally, a specialized questionnaire was administered to each participant who had reported ever working as a farmer or gardener – designed to allow standardized case-by-case pesticide exposure assessment by experts. Participants were asked questions about each farm they had ever worked on, including specific crops and animals, pesticides applied (including whether they had personally prepared or sprayed the chemical), spraying equipment, frequency, and years of use. Repeat interviews for the specialized questionnaire were conducted for more than 80% of the subjects because the reported information was insufficient. All administered interviews were blind to case-control status.

Two persons, one industrial hygienist and one agronomist individually reviewed all the questionnaires to assess pesticide exposures. The experts reviewed the consistency of the subjects’ statements with respect to product availability dates, type and size of the crops, geographic location of the farm and frequency of treatment. A database constructed using the annual directories of phytochemicals published by the Association de Coordination Technique Agricole was used to facilitate the process – including recommendations for use of the products (identified by their chemical and brand names) by crop and pest. When information on pesticides was missing or unreliable, the experts allocated a list of chemicals that may have been used based on the crops treated, method of spraying, period and frequency of treatment and pests targeted. Pesticide exposures were primarily coded in broad categories such as organophosphate insecticides, phenoxy herbicides and triazine herbicides, and there was also specific coding for glyphosate. The exposure years and duration were based on the years of pesticide use for each exposure, reported in the specialized questionnaire.

Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years and duration was coded from the years specified in the expert-assessed data.
Mayo

**Original study.** Questionnaires were self-administered. Information was collected on the longest-held job and up to 5 additional jobs held for longer than 5 years, including the job title, age first worked, and the total number of years worked in the job. An additional questionnaire based off the Agricultural Health Study private applicator questionnaires ([https://aghealth.nih.gov/collaboration/questionnaires.html](https://aghealth.nih.gov/collaboration/questionnaires.html)) was given to participants who reported during the enrollment protocol that they ever worked on a farm or with pesticides for longer than 1 year. Participants who ever personally mixed or applied any pesticides as part of their job were asked about use of 48 active ingredients or pesticide groups; they were asked, separately for each pesticide, to report personal handling, duration (years) of use, frequency (days/year), and the year of first use. Other parts of the questionnaire asked about pesticide application methods and additives used, size of the farm, and crops and animals.

**Pooled study.** Investigators received questionnaire data including coded occupational history (standard occupational codes) and responses from the farming questionnaire. Reported pesticide uses were considered exposed if the participant reported personal handling of that specific pesticide. Specific active ingredients were coded directly from the self-reported information, and active ingredients were also grouped to code broad categories of pesticides (such as grouping “atrazine” and “cyanazine”, reported separately, as triazine herbicides). Exposure duration and year of first use also were coded from the questionnaire responses.

BCMM

**Original study.** Questionnaires were self-administered. An occupational work history included all jobs held for 2 years or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Additional questions were given to participants who had ever lived on a farm or worked in agriculture, gardening, parks, golf courses, or forestry. Participants were asked about use of pesticides in these settings, including the name of the product or active ingredient, the target pest, application method, duration of use, and frequency (days/year). Other parts of the questionnaire asked about personal handling of herbicides, insecticides, and fungicides, as broad categories, protective equipment and clothing, and crops and animals.

**Pooled study.** Investigators received questionnaire data including raw text responses from the occupational history and reported pesticides. The investigators coded jobs of a priori interest for possible pesticide exposures including farming, forestry, gardener/groundskeeper, janitor/cleaner, and laborer. Reported pesticides were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed only if they reported personal handling of the corresponding types of pesticide (out of herbicides, insecticides, and fungicides). Exposure years, duration, and frequency were coded from the self-reported information for each pesticide exposure.
Supplemental Material 2 – Adjustment for other occupational pesticide use in the InterLymph pooled analysis of herbicides

Adjustment for other pesticides included up to 5 covariates for each herbicide group or active ingredient, selected and coded specifically for each herbicide. Because of associations we found with insecticide use in our previous pooled analysis, we adjusted for use of organophosphate insecticides and organochlorine insecticides using two separate indicator variables. Because of a priori hypotheses about associations of phenoxy herbicides and glyphosate with NHL, we adjusted for these herbicides using two indicator variables in each model (except for the models estimating associations with those particular herbicides). Estimated effects of 2,4-D and other phenoxy herbicide use were adjusted for each other (i.e., model for 2,4-D included indicator variable for other phenoxy herbicides, and vice versa). Finally, to capture use of any other type of pesticide including other insecticides, herbicides, fungicides, nematicides, etc., we developed an indicator variable tailored to each particular herbicide exposure (leaving that herbicide exposure out).
### Supplemental Table 1. Frequency of occupational herbicide use among controls within each of the case-control studies participating in the InterLymph pooled analysis

| Herbicide Type       | BCMM | ENGELA | Epilymph | Italian | LAMMCC | LANHL | Mayo | NCISEER | NSW | Yale |
|----------------------|------|--------|----------|---------|--------|-------|------|---------|-----|------|
| Any herbicide        | 13 (3.5%) | 42 (9.4%) | 48 (2.0%) | 59 (5.2%) | 4 (1.4%) | 6 (1.6%) | 296 (13.6%) | 51 (5.2%) | 33 (4.8%) | 44 (6.2%) |
| Phenoxy herbicides   | 5 (1.4%) | 25 (5.6%) | 13 (0.5%) | 29 (2.5%) | 3 (1.1%) | 3 (0.8%) | 239 (11.0%) | 17 (1.7%) | 18 (2.6%) | 18 (2.6%) |
| 2,4-D                | 4 (1.1%) | -      | 5 (0.2%) | 22 (1.9%) | -       | 1 (0.3%) | 235 (10.8%) | 14 (1.4%) | 6 (0.9%) | -    |
| Other phenoxy herbicides | 2 (0.5%) | -      | 3 (0.1%) | 24 (2.1%) | 3 (1.1%) | 3 (0.8%) | 39 (1.8%) | 6 (0.6%) | 8 (1.2%) | -    |
| Glyphosate           | 5 (1.4%) | 24 (5.4%) | 2 (0.1%) | 9 (0.8%) | -       | -     | 253 (11.6%) | 5 (0.5%) | 14 (2.1%) | 28 (4.0%) |
| Triazine herbicides  | 1 (0.3%) | 20 (4.5%) | 10 (0.4%) | 18 (1.6%) | -       | -     | 161 (7.4%) | 6 (0.6%) | 4 (0.6%) | -    |
| Atrazine             | 1 (0.3%) | -      | -        | 16 (1.4%) | -       | -     | 154 (7.1%) | 5 (0.5%) | 2 (0.3%) | -    |
| Amide herbicides     | -     | 12 (2.7%) | -        | 11 (1.0%) | -       | -     | 141 (6.5%) | 6 (0.6%) | 1 (0.2%) | -    |
| Alachlor             | -     | -      | -        | 4 (0.4%) | -       | -     | 119 (5.5%) | 3 (0.3%) | -       | -    |
| Trifluralin          | 0     | -      | -        | 21 (1.8%) | -       | -     | 112 (5.1%) | 7 (0.7%) | 0       | 8 (1.1%) |
| Dicamba              | 1 (0.3%) | -      | -        | 5 (0.4%) | -       | 1 (0.3%) | 121 (5.5%) | 2 (0.2%) | 1 (0.2%) | -    |
| Pendimethalin        | -     | -      | -        | 4 (0.4%) | -       | -     | 52 (2.4%) | 1 (0.1%) | -       | -    |
| Paraquat             | 1 (0.3%) | -      | -        | 4 (0.4%) | -       | -     | 17 (0.8%) | 1 (0.1%) | 3 (0.4%) | -    |

* The symbol " - " indicates that the study was not included in analysis of the particular herbicide, due to no exposed cases or controls.
Supplemental Figure 1. Meta-analysis forest plots of selected associations between herbicide use and risk of all non-Hodgkin lymphoma (NHL) and NHL subtypes (individual-study estimates are odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models, with adjustment for study center, age, gender, socioeconomic status (SES), race/ethnicity, and set of covariates for use of other pesticides; meta-OR (overall) estimates are from random effects meta-analysis). NHL Subtypes: DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; MM=multiple myeloma; OBCL=other B-cell lymphoma; TCL=T-cell lymphoma.

Any herbicide use, all NHL

| Study     | ES (95% CI) | Weight |
|-----------|-------------|--------|
| BCCM      | 0.99 (0.29, 3.42) | 2.00   |
| ENGELA    | 0.65 (0.28, 1.49) | 4.35   |
| Epilymph  | 1.22 (0.79, 1.87) | 16.53  |
| Italian   | 1.20 (0.80, 1.82) | 17.82  |
| LAMCC     | 2.28 (0.81, 6.44) | 2.83   |
| Mayo      | 1.27 (0.88, 1.84) | 22.60  |
| NCISEER   | 0.82 (0.50, 1.32) | 13.19  |
| NSW       | 1.59 (0.87, 2.90) | 8.44   |
| Yale      | 0.85 (0.50, 1.43) | 11.04  |
| Overall   | 1.12 (0.94, 1.33) | 100.00 |

NOTE: Weights are from random effects analysis

Any herbicide use TCL

| Study     | ES (95% CI) | Weight |
|-----------|-------------|--------|
| ENGELA    | 6.58 (0.47, 92.11) | 3.91   |
| Epilymph  | 2.34 (0.08, 5.77) | 33.73  |
| Italian   | 0.73 (0.14, 3.90) | 0.73   |
| Mayo      | 1.65 (0.50, 5.34) | 21.91  |
| NCISEER   | 1.05 (0.23, 4.70) | 12.21  |
| NSW       | 3.23 (0.50, 18.88) | 8.85   |
| Yale      | 0.79 (0.15, 4.28) | 9.65   |
| Overall   | 1.88 (1.02, 3.36) | 100.00 |

NOTE: Weights are from random effects analysis
Phenoxy herbicide use, all NHL

| Study   | ES (95% CI)   | Weight |
|---------|---------------|--------|
| BCMM    | 1.67 (0.40, 6.97) | 3.97   |
| ENGEA   | 0.64 (0.26, 1.59)  | 8.35   |
| Epilymph| 1.32 (0.81, 2.05)  | 10.68  |
| Italian | 1.16 (0.67, 2.01)  | 16.38  |
| LANHL   | 3.77 (0.94, 15.14) | 4.17   |
| LAMMCC  | 0.86 (0.16, 4.74)  | 2.89   |
| Mayo    | 0.90 (0.61, 1.33)  | 21.97  |
| NCISEER | 0.92 (0.43, 1.96)  | 10.64  |
| NSW     | 0.71 (0.31, 1.64)  | 9.51   |
| Yale    | 2.73 (1.30, 5.73)  | 11.25  |
| Overall (I-squared = 31.1%, p = 0.160) | 1.15 (0.85, 1.55) | 100.00 |

NOTE: Weights are from random effects analysis

Phenoxy herbicide use duration >8 years, all NHL

| Study   | ES (95% CI)   | Weight |
|---------|---------------|--------|
| BCMM    | 9.95 (0.49, 202.92) | 1.41   |
| ENGEA   | 0.97 (0.21, 1.51)  | 10.98  |
| Epilymph| 2.09 (0.80, 5.47)  | 11.37  |
| Italian | 1.54 (0.77, 3.08)  | 18.36  |
| LANHL   | 2.79 (0.17, 46.54) | 1.62   |
| LAMMCC  | 0.49 (0.02, 12.06) | 1.26   |
| Mayo    | 0.80 (0.50, 1.39)  | 28.90  |
| NCISEER | 0.80 (0.31, 2.05)  | 11.86  |
| NSW     | 1.13 (0.38, 3.27)  | 9.61   |
| Yale    | 3.32 (0.90, 16.05) | 4.84   |
| Overall (I-squared = 18.7%, p = 0.271) | 1.13 (0.78, 1.62) | 100.00 |

NOTE: Weights are from random effects analysis
### Phenoxy herbicide use, MM

| Study  | ES (95% CI) | Weight |
|--------|-------------|--------|
| BCMM   | 1.59 (0.75, 3.36) | 18.70 |
| ENGELA | 1.67 (0.40, 6.97)  | 16.47 |
| Epilymph | 0.84 (0.16, 4.01) | 16.68 |
| Italian | 0.86 (0.16, 4.79) | 14.53 |
| LAMMCC | 6.10 (1.82, 20.40) | 23.25 |
| Yale   | 0.51 (0.06, 4.18)  | 10.36 |
| Overall: (I-squared = 28.5%, p = 0.221) | 100.00 |

NOTE: Weights are from random effects analysis.

### Phenoxy herbicide use duration >8 years, MM

| Study  | ES (95% CI) | Weight |
|--------|-------------|--------|
| BCMM   | 2.33 (0.81, 6.66) | 11.10 |
| ENGELA | 0.49 (0.02, 12.06) | 30.96 |
| Italian | 1.38 (0.27, 7.16) | 29.21 |
| LAMMCC | 9.95 (0.49, 202.92) | 9.95 |
| Yale   | 1.35 (0.24, 7.46)  | 18.78 |
| Overall: (I-squared = 15.2%, p = 0.318) | 100.00 |

NOTE: Weights are from random effects analysis.
2,4-D use, all NHL

| Study | ES (95% CI) | Weight |
|-------|-------------|--------|
| BCMM  | 2.47 (0.57, 10.64) | 3.94   |
| Epilymph | 0.33 (0.05, 2.04) | 2.49   |
| Italian | 1.29 (0.68, 2.29) | 22.39  |
| LANHL | 7.27 (0.63, 83.30) | 1.42   |
| Mayo  | 0.95 (0.65, 1.40) | 53.05  |
| NCISEER | 0.88 (0.37, 2.09) | 11.00  |
| NSW   | 0.90 (0.27, 3.02) | 5.70   |
| Overall (I-squared = 1.2%, p = 0.415) | 1.04 (0.79, 1.39) | 100.00 |

NOTE: Weights are from random effects analysis

2,4-D use duration >8 years, all NHL (BCMM excluded due to 0% weight)

| Study | ES (95% CI) | Weight |
|-------|-------------|--------|
| Epilymph | 0.60 (0.08, 4.68) | 2.59   |
| Italian | 1.63 (0.86, 3.40) | 19.45  |
| LANHL | 2.74 (0.16, 45.00) | 1.60   |
| Mayo  | 0.90 (0.54, 1.37) | 58.46  |
| NCISEER | 0.87 (0.33, 2.30) | 13.45  |
| NSW   | 2.00 (0.34, 11.74) | 4.04  |
| Overall (I-squared = 1.2%, p = 0.415) | 1.05 (0.74, 1.50) | 100.00 |

NOTE: Weights are from random effects analysis
### 2,4-D use duration >8 years, DLBCL

| Study     | RR (95% CI) | Weight |
|-----------|-------------|--------|
| Italian   | 2.74 (0.85, 8.78) | 26.46 |
| LANHL     | 5.64 (2.21, 14.36) | 4.70 |
| Mayo      | 0.66 (0.30, 1.52)  | 36.54 |
| NCICER    | 1.96 (0.51, 7.17)  | 23.89 |
| NSW       | 1.47 (0.11, 19.17) | 7.31 |
| Overall (I-squared = 24.4%, p = 0.259) | 1.44 (0.69, 2.97) | 100.00 |

**NOTE:** Weights are from random effects analysis.

### 2,4-D use duration >8 years, OBCL

| Study     | RR (95% CI) | Weight |
|-----------|-------------|--------|
| Epilymph  | 2.62 (0.10, 68.71) | 3.82 |
| Italian   | 1.89 (0.47, 6.32)  | 36.58 |
| LANHL     | 2.05 (0.10, 62.39) | 4.60 |
| Mayo      | 1.21 (0.40, 3.87)  | 49.07 |
| NSW       | 1.41 (0.10, 45.76) | 4.61 |
| Overall (I-squared = 0.0%, p = 0.491) | 1.73 (0.81, 3.29) | 100.00 |

**NOTE:** Weights are from random effects analysis.

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## Glyphosate use, all NHL

| Study     | ES (95% CI) | Weight |
|-----------|-------------|--------|
| BCNM      | 0.33 (0.05, 2.11) | 3.87   |
| ENGELA    | 0.71 (0.30, 1.68) | 13.13  |
| Epilymph  | 1.12 (0.15, 8.52) | 3.15   |
| Italian   | 1.22 (0.49, 3.03) | 11.93  |
| Mayo      | 1.04 (0.73, 1.49) | 30.26  |
| NCISSEIR  | 3.10 (1.00, 9.59) | 6.69   |
| NSW       | 1.73 (0.72, 4.17) | 12.87  |
| Yale      | 0.84 (0.26, 2.86) | 16.50  |
| Overall   | 1.02 (0.70, 1.48) | 100.00 |

**NOTE:** Weights are from random effects analysis

## Glyphosate lagged-use (10-year lag), all NHL

| Study     | ES (95% CI) | Weight |
|-----------|-------------|--------|
| BCNM      | 0.33 (0.05, 2.17) | 7.00   |
| ENGELA    | 0.89 (0.38, 1.67) | 17.85  |
| Epilymph  | 2.25 (0.19, 26.83) | 4.42   |
| Italian   | 1.25 (0.42, 3.78) | 14.24  |
| Mayo      | 0.90 (0.64, 1.42) | 27.16  |
| NCISSEIR  | 5.40 (1.30, 22.34) | 10.83  |
| NSW       | 2.76 (0.94, 8.15) | 14.53  |
| Yale      | 6.44 (0.53, 78.78) | 4.35   |
| Overall   | 1.38 (0.79, 2.42) | 100.00 |

**NOTE:** Weights are from random effects analysis
**Glyphosate use, FL**

| Study       | ES (95% CI) | Weight |
|-------------|-------------|--------|
| ENGELA      | 1.44 (0.20, 10.18) | 4.52   |
| Italian     | 2.10 (0.23, 18.61)  | 3.40   |
| Mayo        | 1.44 (0.83, 2.51)   | 58.26  |
| NCISEER     | 1.71 (0.34, 8.56)   | 6.63   |
| NSW         | 2.22 (0.70, 7.07)   | 13.85  |
| Yale        | 1.08 (0.36, 2.80)   | 16.38  |
| Overall (I-squared = 0.0%, p = 0.949) | 1.47 (0.97, 2.23) | 100.00 |

NOTE: Weights are from random effects analysis

**Glyphosate lagged-use (10-year lag), FL**

| Study       | ES (95% CI) | Weight |
|-------------|-------------|--------|
| ENGELA      | 1.40 (0.22, 11.87) | 12.80  |
| Mayo        | 1.21 (0.46, 3.07)   | 44.84  |
| NCISEER     | 3.39 (0.35, 32.74)  | 13.48  |
| NSW         | 2.43 (0.71, 11.21)  | 21.34  |
| Yale        | 20.34 (4.87, 247.13)| 8.64   |
| Overall (I-squared = 32.9%, p = 0.202) | 3.06 (1.67, 5.67) | 100.00 |

NOTE: Weights are from random effects analysis

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Glyphosate lagged-use (10-year lag) duration ≤8 years, FL (NCISEER excluded due to 0% weight)

| Study        | RR (95% CI)  | Weight |
|--------------|-------------|--------|
| ENGELA       | 2.17 (0.74, 6.45) | 18.01  |
| Mayo         | 1.92 (0.79, 3.00)  | 84.76  |
| NSW          | 3.22 (0.86, 11.58) | 23.44  |
| Yale         | 20.34 (1.67, 247.13) | 11.77  |
| Overall (heterogeneity = 0%, p = 0.228) | 2.54 (1.00, 6.45) | 100.00 |

NOTE: Weights are from random effects analysis.

Glyphosate lagged-use (10-year lag) duration >8 years, FL

| Study        | RR (95% CI)  | Weight |
|--------------|-------------|--------|
| ENGELA       | 1.52 (0.79, 2.92) | 100.00 |
| Mayo         | 0.68 (0.28, 1.64) | 10.01  |
| NSW          | 3.22 (0.65, 15.91) | 66.35  |
| Overall (heterogeneity = 0%, p = 0.536) | 0.98 (0.48, 2.00) | 11.77  |

NOTE: Weights are from random effects analysis.
**Glyphosate lagged-use (10-year lag), DLBCL**

| Study  | ES (95% CI)   | Weight |
|-------|---------------|--------|
| ENGELA| 0.49 (0.11, 2.17) | 13.35  |
| Italian| 0.93 (0.10, 8.28)  | 6.14   |
| Mayo  | 1.12 (0.35, 3.81)  | 56.48  |
| NCISEER | 5.30 (0.94, 29.98) | 9.77   |
| NSW   | 1.47 (0.28, 7.38)  | 11.28  |
| Yale  | 2.07 (0.11, 58.71) | 2.69   |
| Overall (I-squared = 0.0%, p = 0.469) | 1.22 (0.71, 2.10) | 100.00 |

NOTE: Weights are from random-effects analysis

**Glyphosate lagged-use (10-year lag), TCL**

| Study  | ES (95% CI)   | Weight |
|-------|---------------|--------|
| ENGELA| 13.08 (2.08, 35.08) | 16.26  |
| Mayo  | 1.30 (0.30, 4.83)  | 66.83  |
| NSW   | 7.49 (0.27, 101.00) | 17.17  |
| Overall (I-squared = 0.0%, p = 0.060) | 2.00 (0.60, 6.24) | 100.00 |

NOTE: Weights are from random-effects analysis