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

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Abstract

In a departure from prior health and regulatory agency classifications, the herbicide glyphosate was recently classified by an international agency as a probable human carcinogen. A recent meta-analysis of epidemiologic data on pesticides including glyphosate and NHL risk did not present an in-depth assessment of research quality or a weight-of-evidence evaluation of causality. Therefore, the present systematic review and meta-analysis examines more rigorously the relationship between exposure to glyphosate and risk of lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia. Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between glyphosate use and risk of NHL (meta-RR=1.3, 95% confidence interval (CI)=1.0–1.6, based on six independent studies) and MM (meta-RR=1.4, 95% CI=1.0–1.9; four studies). Associations were statistically null for HL (meta-RR=1.1, 95% CI=0.7–1.6; two studies), leukemia (meta-RR=1.0, 95% CI=0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). These meta-RRs have uncertain validity because bias and confounding cannot be excluded. Methodological weaknesses include the small number of available studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient. Thus, no valid association, much less a causal relationship, has been established between glyphosate exposure and risk of any type of LHC.

Introduction

The International Agency for Research on Cancer (IARC) recently classified the broad-spectrum phosphanoglycine herbicide glyphosate (*N*-(phosphonomethyl)glycine) as "probably carcinogenic to humans" (Group 2A). In arriving at this classification, IARC characterized evidence of carcinogenicity in humans as "limited," based on the data available for non-Hodgkin lymphoma (NHL) (IARC, 2015). IARC considered the evidence of carcinogenicity in experimental animals as "sufficient." The latter determination was based on induction of renal tubule carcinoma, hemangiosarcoma, and pancreatic islet-cell adenoma in rodents, as well as supportive mechanistic evidence. By contrast, the United States Environmental Protection Agency (U.S. EPA) in 1993 classified glyphosate as showing evidence of non-carcinogenicity for humans (Group E) (U.S. EPA, 1993), and has not subsequently revised this classification. In 2004, the Joint Meeting on Pesticide Residues (JMPR), sponsored by the Food and Agriculture

Organization of the United Nations and the World Health Organization (WHO), concluded based on "the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests" that "glyphosate is unlikely to pose a carcinogenic risk to humans" (JMPR, 2006). WHO has established an expert taskforce to evaluate the available data and report its findings to JMPR (JMPR, 2015).

More recently, the German Federal Institute for Risk Assessment (BfR), on behalf of the European Union, reviewed all toxicological studies of glyphosate in laboratory animals, as well as over 30 epidemiological studies in humans, and concluded that "the available data do not show carcinogenic or mutagenic properties of glyphosate" and "there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer" (BfR, 2014; BfR, 2015). BfR plans to conduct a thorough review of the IARC classification (BfR, 2015). Given that glyphosate, as a constituent of more than 750 products for agricultural, forestry, urban, and residential applications, is the most commonly used herbicide in the world, understanding its potential human carcinogenicity has major implications for public health and risk assessment.

In summarizing the epidemiological evidence, IARC stated that "case-control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The [Agricultural Health Study] cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures" (IARC, 2015). A recent meta-analysis conducted by investigators from IARC (Schinasi and Leon, 2014) found a statistically significant positive association between glyphosate use and NHL risk (meta-relative risk [RR] = 1.5, 95% confidence interval [CI] = 1.1–2.0), based on six studies (De Roos et al., 2005; De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002; McDuffie et al., 2001; Orsi et al., 2009). The same meta-analysis also found a significant positive association between glyphosate use and risk of B-cell NHL, based on two studies (Cocco et al., 2013; Eriksson et al., 2008).

Although Schinasi and Leon (2014) stated that in their meta-analysis, "[i]n an effort to use the most unbiased estimate, [they] extracted the most adjusted effect estimate," two or arguably three of the RR estimates that they selected for inclusion were not the most highly adjusted estimates reported by the original authors (De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002). Instead, in a personal communication (11 August 2015), Dr. Schinasi indicated that other estimates were selected based on considerations of consistency of estimates across meta-analyses of other pesticides, secondary analyses, and statistical modeling approach.

Meta-analyses can obscure important differences in methods and results among studies that can be more thoroughly evaluated in a detailed qualitative review. Moreover, meta-analysis can yield scientifically uninformative results if they inappropriately conflate studies with different settings and methods. The Schinasi and Leon (2014) meta-analysis did not assess study quality, and hence studies contributing to the meta-analysis were not stratified by quality, despite variation in the potential for random and systematic error (i.e., bias) across studies. The authors

also did not specifically address the potential impact of study limitations on the findings for glyphosate, nor did they discuss whether the apparent association between glyphosate and NHL risk is likely to be causal. On the other hand, Mink et al. (2012) conducted a qualitative systematic review, without a meta-analysis, of epidemiologic studies of glyphosate and various cancers, including NHL. Taking into account potential sources of error, including selection bias, confounding, and especially exposure misclassification, the authors concluded that they "found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate."

Given the controversy surrounding this issue, we conducted this systematic review and meta-analysis to examine more rigorously the relationship between exposure to glyphosate and risk of NHL, as well as major histopathological subtypes of NHL, in human epidemiologic studies. Because NHL is often considered alongside other lymphohematopoietic cancers (LHC), whose ever-changing classification systems now characterize some leukemias and multiple myeloma (MM) as NHL subtypes (Swerdlow et al., 2008), we also included Hodgkin lymphoma (HL), MM, monoclonal gammopathy of unknown significance (MGUS, an MM precursor), and leukemia in this review. As part of our review, bearing in mind the limitations of quantitative meta-analysis for observational epidemiology (Shapiro, 1994; Weed, 2010), we conducted a qualitative evaluation of potential for error and bias, as well as a synthesis of the overall weight of epidemiologic evidence for a causal association between glyphosate and LHC risk.

Methods

Literature search

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

To identify all potentially relevant articles, we conducted a search of MEDLINE via PubMed using the following search string, which includes Chemical Abstracts Service (CAS) Registry Numbers for glyphosate and its salts:

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

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

Altogether, a total of 12,709 articles were identified from these combined sources (Figure 1). Based on a review of titles and abstracts, 321 articles were identified as potentially containing estimates of the association between glyphosate exposure and LHC risk, and were obtained for further evaluation. Forty-seven of these articles contained the word "glyphosate" or "Roundup" (or alternative spellings of these terms) in the text; as specified earlier, articles that did not mention glyphosate were ineligible for inclusion. Following a review of the full text of each of the 47 articles mentioning glyphosate, 20 articles (as well as one letter to the editor (Cantor et al., 1993) that contained additional results from a study described in another one of the included articles (Cantor et al., 1992), and one abstract (Sorahan, 2012) that preceded a full-length article (Sorahan, 2015)) were ultimately deemed eligible for inclusion. Two authors independently reviewed and agreed upon the list of eligible articles.

Of the 20 articles reporting on the association between glyphosate and risk of specific forms of LHC, 12 pertained to NHL or its subtypes (including hairy-cell leukemia, which is a subtype of B-cell NHL) (Cantor et al., 1992; Cocco et al., 2013; De Roos et al., 2005; De Roos et al., 2003; Eriksson et al., 2008; Hardell and Eriksson, 1999; Hardell et al., 2002; Hohenadel et al., 2011; Lee et al., 2004; McDuffie et al., 2001; Nordstrom et al., 1998; Orsi et al., 2009); two pertained to HL (Karunanayake et al., 2012; Orsi et al., 2009); seven pertained to MM or MGUS (Brown et al., 1993; De Roos et al., 2005; Kachuri et al., 2013; Landgren et al., 2009; Orsi et al., 2009; Pahwa et al., 2012b; Sorahan, 2015); and three pertained to leukemia (Brown et al., 1990; De Roos et al., 2005; Kaufman et al., 2009).

Evaluation of study characteristics and quality

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

In addition to summarizing study characteristics, we qualitatively evaluated the methodological quality of each study in terms of its potential for selection bias, information bias/exposure misclassification, confounding, reporting bias, and other issues affecting validity. Potential for bias was evaluated based on subject identification strategy, participation rates, investigator blinding, assessment methods for exposures, outcomes, and potential confounders, statistical approach, reporting of results, and other considerations (Higgins and Green, 2011; Woodruff and Sutton, 2014).

To aid in the assessment of whether results varied by study quality, we classified studies into two tiers: tier 1 (higher quality), which included prospective cohort studies with ≥ 80% complete

follow-up and case-control studies with ≥ 80% participation by cases and controls and < 20% proxy respondents; and tier 2 (lower quality), which included all other studies. Due to the limited number and quality of available studies, stricter and more detailed criteria could not be applied.

Selection of data for meta-analysis

From each publication, we selected a RR point estimate for inclusion in the meta-analysis based on a set of rules specified *a priori*. First, if unadjusted and adjusted RRs were reported in a publication or across multiple publications from the same study population, the most fully adjusted RR was selected for inclusion. The most fully adjusted RR was defined as the RR estimate that took into consideration, by restriction or statistical adjustment, the most covariates that appeared to be confounders. The rationale for choosing the most fully adjusted RR was based on the assumption that the adjusted covariates were found by the authors to act as confounders by altering the estimate of association (either directly or by acting as a surrogate for another, unmeasured confounder). If an adjusted RR was not reported, the unadjusted (crude) RR was included as reported by the authors or as calculated from available raw data. Second, if multiple eligible publications were derived from the same study population, the RR from the most recent publication was selected for inclusion unless it was based on a subset of the overall eligible study population, in which case the RR based on the most complete study population was included. Third, subject to the first two rules, the RR for dichotomous exposure with the largest number of exposed cases was selected for inclusion in the meta-analysis. In a few instances where another RR from a given study nearly met these inclusion criteria but was superseded by a more fully adjusted, more recent, or more robust RR, the alternative RR was considered in secondary analyses.

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

Statistical approach

For associations with at least two independent RR estimates from different study populations, we estimated both fixed-effects and random-effects meta-RRs with 95% CIs. In a fixed-effects model, all studies are assumed to be estimating a common effect size, that is, the exposure has a homogeneous effect within groups or levels of the regressors—an assumption that generally is not realistic. To calculate a fixed-effects meta-RR, the weight assigned to an individual study is inversely proportional to the study's variance. In a random-effects model, the effect is assumed to vary among studies due to heterogeneity (modification) and bias that are randomly distributed. In random-effects models, the weight assigned to an individual study is based on the sum of the within-study variance and the between-study variance. To the extent that the heterogeneity in effects or bias across studies is systematic, the random-effects assumption will be invalid. We used comparison of meta-RR estimates from fixed-effects and random-effects models as one approach to the evaluation of the impact of between-study heterogeneity on the meta-RRs.

As a quantitative measure of between-study heterogeneity, we calculated I^2, which represents the percentage of between-study variance in RRs that is attributable to study heterogeneity (as opposed to chance) (Higgins et al., 2003). An I^2 of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. We also tested for statistically significant between-study heterogeneity based on Cochran's Q statistic (Cochran, 1954), although this test has low power to detect modest heterogeneity across a limited number of studies (Ioannidis, 2008).

In the absence of statistically significant heterogeneity, the presence of at least one statistically significant association, $I^2 < 50\%$ and at least four contributing studies, we evaluated evidence of publication bias (i.e., non-random selection of studies for publication, with a tendency toward submission and publication of studies that report larger, statistically significant associations (Dickersin and Min, 1993)) by using the linear regression approach of Egger et al. (1997), which measures the degree of funnel plot asymmetry. We also estimated meta-RRs corrected for publication bias by imputing results for missing studies using the trim-and-fill procedure developed by Duval and Tweedie (2000), which iteratively trims asymmetric studies from the right-hand side of a funnel plot to locate the unbiased effect, and then fills the plot by re-inserting the trimmed studies on the right of the mean effect, along with their imputed counterparts on the left. Again, we used these approaches with the understanding that they have limited power to detect publication bias based on few studies (Ioannidis, 2008).

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

Sensitivity analysis
To evaluate the robustness of results to various potential sources of heterogeneity, we planned *a priori* to conduct a sensitivity analysis with stratification of studies by methodological quality (tier 1 vs. tier 2), study design (case-control vs. cohort), source of controls (population-based vs. hospital-based), gender (males only vs. males and females), geographic region (North America vs. Europe), and time period of cancer diagnosis (1980s, 1990s, or 2000s, with studies contributing to a given stratum if any part of the case diagnosis period was in a given decade).

Weight-of-evidence evaluation
To guide a qualitative assessment of the weight of epidemiologic evidence for a causal relationship between glyphosate exposure and risk of LHC, we used Sir Austin Bradford Hill's "viewpoints" as a general framework (Hill, 1965). Because this review is restricted to the epidemiologic literature, our consideration of the biological plausibility of the association and the coherence of the human, animal, and mechanistic evidence was limited.

Results

Study characteristics and overlap
Studies of NHL and subtypes
Twelve studies from seven independent study populations, including eleven case-control studies and one prospective cohort study, evaluated the relationship between glyphosate use and risk of NHL and/or its histopathological subtypes (Cantor et al., 1992; Cocco et al., 2013; De Roos et

al., 2005; De Roos et al., 2003; Eriksson et al., 2008; Hardell and Eriksson, 1999; Hardell et al., 2002; Hohenadel et al., 2011; Lee et al., 2004; McDuffie et al., 2001; Nordstrom et al., 1998; Orsi et al., 2009). Characteristics of these studies are summarized in Table 1. All of the studies considered glyphosate use in agricultural operations or settings, and most evaluated overall NHL as an outcome. The exceptions were Cocco et al. (2013), which analyzed B-cell lymphoma and other NHL subtypes, but not overall NHL, and Nordstrom et al. (1998), which included only hairy-cell leukemia. Eriksson et al. (2008) presented results for B-cell lymphoma and other NHL subtypes, as well as for overall NHL, while Orsi et al. (2009) included results for overall NHL and several specific NHL subtypes.

De Roos et al. (2003) combined data from Cantor et al. (1992) with data from two other studies that did not independently report associations between glyphosate use and NHL risk (Hoar et al., 1986; Hoar Zahm et al., 1990); therefore we did not further consider Cantor et al. (1992) as a separate study. Lee et al. (2004) was based on Cantor et al. (1992) and Hoar Zahm et al. (1990), but not Hoar et al. (1986), and stratified results by asthma status (with no apparent interaction between glyphosate exposure and asthma); therefore, results from De Roos et al. (2003) took precedence in our analysis over those from Lee et al. (2004). The study by Hardell et al. (2002) pooled data from two other studies that reported on glyphosate use and NHL risk (Hardell and Eriksson, 1999; Nordstrom et al., 1998). Consequently, the latter two studies were not considered further with respect to NHL, although Nordstrom et al. (1998) was evaluated separately with respect to hairy-cell leukemia. Based on the same study population as McDuffie et al. (2001) (except for four fewer cases excluded after pathology review), Hohenadel et al. (2011) reported associations with use of glyphosate without malathion or glyphosate with malathion, but not glyphosate overall; therefore, the results from McDuffie et al. (2001) were prioritized in our analysis.

The seven independent studies ranged markedly in size with respect to the number of NHL cases classified as exposed to glyphosate (based on reported use): Cocco et al. (2013), 4 B-cell lymphoma cases exposed; Hardell et al. (2002), 8 exposed; Orsi et al. (2009), 12 exposed; Eriksson et al. (2008), 29 exposed; De Roos et al. (2003), 36 exposed; McDuffie et al. (2001), 51 exposed; De Roos et al. (2005), 71 exposed in the total eligible cohort. Four studies were based in Europe (Cocco et al., 2013; Eriksson et al., 2008; Hardell et al., 2002; Orsi et al., 2009) and three in North America (De Roos et al., 2005; De Roos et al., 2003; McDuffie et al., 2001) (Table 1). Four of the case-control studies were population-based (De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002; McDuffie et al., 2001), one was hospital-based (Orsi et al., 2009), and one included a mixture of population-based and hospital-based cases and controls (Cocco et al., 2013). Four studies were restricted to males (De Roos et al., 2003; Hardell et al., 2002; McDuffie et al., 2001; Orsi et al., 2009), while the rest included males and females. Two studies conducted at least some case ascertainment during the 1980s (De Roos et al., 2003; Hardell et al., 2002), five during the 1990s (Cocco et al., 2013; De Roos et al., 2005; Eriksson et al., 2008; Hardell et al., 2002; McDuffie et al., 2001), and four during the 2000s (Cocco et al., 2013; De Roos et al., 2005; Eriksson et al., 2008; Orsi et al., 2009) (categories are overlapping). For reference, glyphosate entered the U.S. and European commercial markets in 1974 (Glyphosate Task Force, 2013). Two studies—one a prospective cohort study with an initial follow-up rate of 99.5% (De Roos et al., 2005) and the other a case-control study (albeit hospital-

based) with case and control participation rates > 90% and no proxy respondents (Orsi et al., 2009)—were classified as tier 1 studies, whereas the rest were classified as tier 2.

Studies of HL

Two case-control studies estimated the OR between glyphosate use and risk of HL (Karunanayake et al., 2012; Orsi et al., 2009). Characteristics of these studies are summarized in Table 1. The study by Karunanayake et al. (2012) used the same methods and source population as McDuffie et al. (2001), but focused on HL rather than NHL.

As described in the section on NHL studies, Orsi et al. (2009) was a hospital-based case-control study set in Europe (France), restricted to males, with case ascertainment in the 2000s, participation rates > 90%, and no proxy respondents (tier 1). This study classified 6 HL cases as exposed to glyphosate. Karunanayake et al. (2012) was a population-based case-control study set in North America (Canada), restricted to males, with case ascertainment in the 1990s, participation rates of 68% for cases and 48% for controls, and an unspecified proportion of proxy respondents (tier 2). In this study, 38 HL cases were classified as glyphosate-exposed.

Studies of MM and MGUS

Six studies from four independent study populations, including four case-control studies and two prospective cohort studies, evaluated the association between glyphosate use and risk of MM (Brown et al., 1993; De Roos et al., 2005; Kachuri et al., 2013; Orsi et al., 2009; Pahwa et al., 2012b; Sorahan, 2015), and one prospective cohort study investigated the association between glyphosate and the prevalence of MGUS (Landgren et al., 2009). These studies are described in Table 1.

The studies by De Roos et al. (2005) and Sorahan (2015) were based on virtually identical datasets from the Agricultural Health Study cohort (except that the dataset used by Sorahan was stripped of data on race, state of residence, and applicator type due to privacy concerns; these differences should not have affected the results substantively). Because the Sorahan (2015) study included all eligible cohort members, whereas the De Roos et al. (2005) study was based on a subset of the cohort with complete data, the Sorahan (2015) results were prioritized in our analysis of MM. Landgren et al. (2009) was also based on a subset of the Agricultural Health Study cohort, but had a distinct disease outcome (MGUS). Brown et al. (1993) employed the same methods and source population as Cantor et al. (1992), which was included in the pooled analysis of NHL by De Roos et al. (2003). Pahwa et al. (2012b) and Kachuri et al. (2013) conducted overlapping analyses in the same Canadian source population as McDuffie et al. (2001), Hohenadel et al. (2011), and Karunanayake et al. (2012). Pahwa et al. (2012b) included more controls in their analysis, but these controls were excluded from Kachuri et al. (2013) because they were younger than any enrolled MM cases (≤ 29 years) and thus did not contribute meaningfully to the analysis. Kachuri et al. (2013) also controlled for more confounders, and therefore was prioritized in our analysis.

With respect to glyphosate use, the four independent studies of MM included, respectively, 5 exposed cases (Orsi et al., 2009), 11 exposed cases (Brown et al., 1993), 24 exposed cases (Sorahan, 2015), and 32 exposed cases (Kachuri et al., 2013). The study of MGUS included 27 exposed cases (Landgren et al., 2009). All but one study, which was based in France (Orsi et al.,

2009), were conducted in North America, and all except one (Sorahan, 2015) were restricted to males. One of the two case-control studies was population-based (Brown et al., 1993) and the other was hospital-based (Orsi et al., 2009). Case ascertainment took place during the early 1980s in one study (Brown et al., 1993), at least partly during the 1990s in two studies (Kachuri et al., 2013; Sorahan, 2015), and at least partly during the 2000s in three studies (Landgren et al., 2009; Orsi et al., 2009; Sorahan, 2015). As with the studies of NHL, two were classified as tier 1 studies based on a prospective cohort design with nearly complete follow-up (Sorahan, 2015) or a case-control design with high participation rates and no proxy responses (Orsi et al., 2009). The remaining studies were classified as tier 2, including Landgren et al. (2009), because although the study was based in a prospective cohort, it was a cross-sectional analysis with an unspecified participation rate in the blood draw component.

Studies of leukemia

Two case-control studies and one prospective cohort study investigated the relationship between glyphosate use and risk of leukemia (Brown et al., 1990; De Roos et al., 2005; Kaufman et al., 2009). Key characteristics of these studies are provided in Table 1. The study by Brown et al. (1990) used the same methods and source population as Brown et al. (1993), which was described in the section on MM/MGUS, and Cantor et al. (1992), which was included as part of De Roos et al. (2003) in a pooled analysis of NHL.

As described earlier, De Roos et al. (2005), the only prospective cohort study included in this review, was based in North America (Iowa and North Carolina), enrolled both males and females, ascertained cancer incidence in the 1990s and 2000s, and had a 99.5% follow-up rate through 2001 (tier 1). In the total eligible cohort, 43 leukemia cases occurred among glyphosate users. Brown et al. (1990) was a population-based case-control study set in North America (Iowa and Minnesota), restricted to white males, with cases identified in 1980–1983, participation rates of 86% for cases and 77–79% for controls, and proxy respondent rates of 41% for cases and 34% for controls (tier 2). Fifteen leukemia cases in this study were classified as having used glyphosate. The other case-control study of leukemia, by Kaufman et al. (2009), was a hospital-based study set in Asia (Thailand), with males and females, case ascertainment in the 1990s and 2000s, participation rates of 100%, and no proxy respondents for cases and controls. Although this study would be classified as tier 1 based on our *a priori* criteria, the small number of cases who used glyphosate (n = 1) limited its usefulness for our analysis.

Meta-analysis

NHL

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

As shown in Table 3 and Figure 2, the combined meta-RR for overall NHL in association with any use of glyphosate, based on six studies (De Roos et al., 2005; De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002; McDuffie et al., 2001; Orsi et al., 2009), was 1.3 (95% CI = 1.0–1.6). The results were identical in the random-effects and fixed-effects models, suggesting

limited between-study heterogeneity in the association. Little heterogeneity was also indicated by the I^2 value of 0.0% and the highly non-significant p-value of 0.84 for Cochran's Q. Given the lack of heterogeneity and at least one statistically significant association, we tested for publication bias using Egger's linear regression approach to evaluating funnel plot asymmetry, and found no significant asymmetry (one-tailed p-value = 0.20). Using Duval and Tweedie's trim-and-fill approach to adjust for publication bias, the imputed meta-RR for both the random-effects and fixed-effects models was slightly attenuated to 1.2 (95% CI = 1.0–1.6).

In secondary analyses, we replaced the RR estimated by De Roos et al. (2003) using a hierarchical (i.e., multistage) regression model with the RR estimated using a more traditional logistic regression model (Table 3). (The hierarchical regression RR was selected for the primary analysis because, as stated by the authors, hierarchical regression models can yield "increased precision and accuracy for the ensemble of estimates" when modeling multiple pesticides simultaneously, and the more conservative prior assumptions specified in these models "seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL.") Using the logistic regression RR did not appreciably affect the results of the meta-analysis (meta-RR = 1.3, 95% CI = 1.0–1.6; identical for random-effects and fixed-effects models).

In another secondary analysis, we replaced the RR reported by McDuffie et al. (2001) with the results reported by Hohenadel et al. (2011) in the same study population (minus four previously misclassified NHL cases) (Table 3). Because Hohenadel et al. (2011) reported two estimates for glyphosate use—one in the absence of malathion use and one in the presence of malathion use—we combined these two estimates into a single estimate (RR = 1.40, 95% CI = 0.62–3.15) using random-effects meta-analysis. Using this alternative estimate also did not appreciably affect the meta-RR (1.3, 95% CI = 1.0–1.7; identical for random-effects and fixed-effects models). Finally, using both the logistic regression RR instead of the hierarchical regression RR from De Roos et al. (2003) and the combined RR from Hohenadel et al. (2011) instead of the RR from McDuffie et al. (2001) slightly but non-significantly increased the meta-RR to 1.4 (95% CI = 1.0–1.8; identical for random-effects and fixed-effects models) (Table 3).

As noted earlier, in their meta-analysis of the association between glyphosate use and NHL risk, Schinasi and Leon (2014) included RR estimates from Eriksson et al. (2008) and Hardell et al. (2002) that were not the most highly adjusted estimates reported by the authors (shown in Table 2 as univariate odds ratios). They also used the logistic regression estimate from De Roos et al. (2003) that arguably was not as highly adjusted as the hierarchical regression estimate. When we included these estimates in the meta-analysis, along with the same estimates from De Roos et al. (2003), McDuffie et al. (2001), and Orsi et al. (2009) as included in our main meta-analysis, we obtained the same results as reported by Schinasi and Leon (2014): random-effects meta-RR = 1.5, 95% CI = 1.1–2.0 (I^2 = 32.7%, $p_{heterogeneity}$ = 0.19). The fixed-effects meta-RR based on these estimates (not reported by Schinasi and Leon (2014)) was 1.4 (95% CI = 1.1–1.8).

NHL subtypes

All reported RRs and 95% CIs for the association between glyphosate use and risk of various NHL subtypes are shown in Table 2. The estimates included in meta-analyses, which were

conducted for B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia (i.e., all NHL subtypes for which at least two estimates from independent studies were available) are shown in Table 3. Too few studies of any given NHL subtype were conducted to justify testing for publication bias.

The meta-RR for the association between any use of glyphosate and risk of B-cell lymphoma, based on two studies (Cocco et al., 2013; Eriksson et al., 2008), was 2.0 (95% CI = 1.1–3.6) according to both the random-effects and the fixed-effects model (I^2 = 0.0%, $p_{heterogeneity}$ = 0.58) (Table 3). These results are the same as reported by Schinasi and Leon (2014). The four B-cell lymphoma cases who were classified by Cocco et al. (2013) as having used glyphosate consisted of one patient with diffuse large B-cell lymphoma, one with chronic lymphocytic leukemia, one with unspecified B-cell lymphoma, and one with MM. Eriksson et al. (2008) did not report the number of exposed cases, but overall the B-cell lymphomas in their study comprised 29% diffuse large B-cell lymphoma, 24% chronic lymphocytic leukemia/small lymphocytic lymphoma, 20% follicular lymphoma grades I–III, 16% other specified B-cell lymphoma, and 11% unspecified B-cell lymphoma; MM cases were not included.

The meta-RR for the association between any use of glyphosate and risk of diffuse large B-cell lymphoma, based on two studies (Eriksson et al., 2008; Orsi et al., 2009), was 1.1 (95% CI = 0.5–2.3) using both the random-effects and the fixed-effects model (I^2 = 0.0%, $p_{heterogeneity}$ = 0.79) (Table 3).

Based on the same two studies (Eriksson et al., 2008; Orsi et al., 2009), the meta-RR for the association between any use of glyphosate and risk of chronic lymphocytic leukemia/small lymphocytic lymphoma was 1.3 (95% CI = 0.2–10.0) according to the random-effects model and 1.9 (95% CI = 0.9–4.0) according to the fixed-effects model, with significant heterogeneity between the two included estimates (I^2 = 83.7%, $p_{heterogeneity}$ = 0.01) (Table 3).

Results for follicular lymphoma from these two studies (Eriksson et al., 2008; Orsi et al., 2009), by contrast, were not significantly heterogeneous (I^2 = 0.0%, $p_{heterogeneity}$ = 0.73), with a meta-RR of 1.7 (95% CI = 0.7–3.9) in both the random-effects and the fixed-effects models (Table 3).

Finally, the two studies that reported associations between any glyphosate use and risk of hairy-cell leukemia (Nordstrom et al., 1998; Orsi et al., 2009) yielded a meta-RR of 2.5 (95% CI = 0.9–7.3) in the random-effects and fixed-effects models (I^2 = 0.0%, $p_{heterogeneity}$ = 0.63) (Table 3).

HL

Both of the published, fully adjusted RRs and 95% CIs for the association between any glyphosate use and HL risk (Table 2) were included in the meta-analysis (Table 3). Based on two studies (Karunanayake et al., 2012; Orsi et al., 2009), the meta-RR was 1.1 (95% CI = 0.7–1.6) in both the random-effects and the fixed-effects models, with I^2 = 0.0% and $p_{heterogeneity}$ = 0.36 (Table 3). Publication bias was not evaluated due to the availability of only two studies of HL.

MM and MGUS

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

The combined meta-RR for the association between any glyphosate use and risk of MM, based on four studies (Brown et al., 1993; Kachuri et al., 2013; Orsi et al., 2009; Sorahan, 2015), was 1.4 (95% CI = 1.0–1.9) according to the random-effects and fixed-effects models (Table 3, Figure 3). According to the I^2 value of 0.0% and the p-value of 0.63 for Cochran's Q statistic, between-study heterogeneity was not evident. Egger's linear regression approach yielded no significant evidence of publication bias (one-tailed p-value for asymmetry = 0.10), while the imputed meta-RR using the trim-and-fill procedure to adjust for publication bias was slightly attenuated to 1.3 (95% CI = 0.9–1.8).

Several secondary analyses were conducted for MM by replacing RRs in the primary meta-analysis with alternative estimates or by adding the RR for MGUS from Landgren et al. (2009) (Table 3). The addition of the MGUS RR, which was marginally significantly inverse, lowered the meta-RR to 1.2 (95% CI = 0.8–1.9 in the random-effects model; 95% CI = 0.9–1.6 in the fixed-effects model) and introduced moderate heterogeneity (I^2 = 41.8%, $p_{heterogeneity}$ = 0.14). When the RR reported by De Roos et al. (2005), who excluded cohort members with missing data from their analysis, was substituted for the one reported by Sorahan (2015), who included such subjects by creating a separate category for missing or unknown data, the meta-RR was slightly increased to 1.5 (95% CI = 1.0–2.1) and was the same for random-effects and fixed-effects models. When the main RR from Kachuri et al. (2013) was replaced with the RR from the same study after exclusion of data reported by proxy respondents, the meta-RR was not appreciably different from the original estimate (alternative meta-RR = 1.4, 95% CI = 0.9–1.9 in random-effects and fixed-effects models). Another secondary analysis included the RR reported by Pahwa et al. (2012b), who adjusted for a slightly different (and smaller) set of confounders than Kachuri et al. (2013) and also retained controls who were too young to have any age-matched MM cases in this Canadian study. This change had minimal impact on the meta-RR (1.4, 95% CI = 1.0–2.0; same for random-effects and fixed-effects models). When both the De Roos et al. (2005) and the Pahwa et al. (2012b) substitutions were made, the resultant meta-RR was the same as that when only De Roos et al. (2005) was used (meta-RR = 1.5, 95% CI = 1.0–1.2 in random-effects and fixed-effects models). Finally, when the RR for MGUS from Landgren et al. (2009) was added to this last model with estimates from De Roos et al. (2005) and the Pahwa et al. (2012b), the meta-RR was attenuated to 1.3 (95% CI = 0.8–2.2) in the random-effects model and 1.2 (95% CI = 0.9–1.7) in the fixed-effects model (I^2 = 51.2%, $p_{heterogeneity}$ = 0.08).

Leukemia

Of the four published RRs and 95% CIs for the association between any use of glyphosate and risk of leukemia (Table 2), three (excluding one age-adjusted RR in favor of a more fully adjusted RR from De Roos et al. (2005) were included in the meta-analysis (Table 3). The meta-RR based on three studies (Brown et al., 1990; De Roos et al., 2005; Kaufman et al., 2009) was 1.0 (95% CI = 0.6–1.5) using the random-effects model and the fixed-effects model (I^2 = 0.0%

and $p_{heterogeneity}$ = 0.92) (Table 3). Publication bias was not assessed because only three studies of leukemia were available.

Sensitivity analysis

A sensitivity analysis was conducted for overall NHL only (Table 4), because other outcomes had an insufficient number of studies for stratification. In all strata, the random-effects and fixed-effects meta-RRs were identical and I^2 was 0.0%. Results did not differ substantially from the main meta-RR (1.3, 95% CI = 1.0–1.6) when the analysis was restricted to case-control studies (meta-RR = 1.3, 95% CI = 1.0–1.7) or those with population-based controls (meta-RR = 1.4, 95% CI = 1.0–1.8). Meta-analysis could not be conducted for cohort studies or studies with hospital-based controls because only one of each of these study types was available. No major differences were detected between studies restricted to males (meta-RR = 1.3, 95% CI = 1.0–1.7) and those that included males and females (meta-RR = 1.2, 95% CI = 0.8–1.8) or between those conducted in North America (meta-RR = 1.2, 95% CI = 1.0–1.6) and those conducted in Europe (meta-RR = 1.3, 95% CI = 0.8–2.1). Prompted by Schinasi and Leon (2014), we also conducted a stratified meta-analysis of the two studies conducted in Sweden (Eriksson et al., 2008; Hardell et al., 2002) and found a stronger, albeit statistically non-significant, association in these particular studies (meta-RR = 1.6, 95% CI = 0.9–2.8). The estimated meta-RR declined somewhat from studies that ascertained cases in the 1980s (meta-RR = 1.6, 95% CI = 1.0–2.7) to those conducted in the 1990s (meta-RR = 1.2, 95% CI = 1.0–1.6) to those conducted in the 2000s (meta-RR = 1.2, 95% CI = 0.8–1.7). Some heterogeneity was also observed by study quality, with a weaker association in higher-tier studies (meta-RR = 1.1, 95% CI = 0.7–1.6) than lower-tier studies (meta-RR = 1.4, 95% CI = 1.0–1.8).

Exposure-response trends

NHL and subtypes

Three studies evaluated exposure-response trends between glyphosate use and NHL risk, with exposure classified as cumulative lifetime (De Roos et al., 2005; Eriksson et al., 2008) or annual (McDuffie et al., 2001) days of glyphosate use (Table 2). Two studies detected some evidence of a positive exposure-response trend (statistical significance not reported) (Eriksson et al., 2008; McDuffie et al., 2001), whereas the other did not (De Roos et al., 2005). All of these studies relied wholly or in part on evaluating days of glyphosate use in an attempt to quantify exposure; however, this metric has been shown to be a poor indicator of actual glyphosate dose received (Acquavella et al., 2006).

In a model adjusted for age, sex, and year of diagnosis or enrollment, Eriksson et al. (2008) found that the RR of NHL was higher with > 10 days of lifetime glyphosate use (RR = 2.36, 95% CI = 1.04–5.37) than with ≤ 10 days (RR = 1.69, 95% CI = 0.70–4.07), compared with no pesticide use. Also, the RR of NHL was higher after more than 10 years since first use of glyphosate (RR = 2.26, 95% CI = 1.16–4.40) than after 1–10 years (RR = 1.11, 95% CI = 0.24–5.08). Statistical tests for trend were not performed, and exposure-response analyses adjusted for other potential confounders (i.e., 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and/or 2,4-dichlorophenoxyacetic acid (2,4-D), mercurial seed dressing, arsenic, creosote, and tar) were not presented, even though adjustment for these characteristics attenuated the RR for overall glyphosate use from 2.02 to 1.51.

McDuffie et al. (2001) reported that the RR for more than two days of glyphosate use per year (2.12, 95% CI = 1.20–3.73) was higher than that for less than two days per year (RR = 1.00, 95% CI = 0.63–1.57), compared with never use, adjusting for age and province of residence. Tests for a significant exposure-response trend were not performed, and results were not reported after adjustment for other potential confounders (i.e., personal medical history and family history of cancer; adjustment for these characteristics attenuated the RR for overall glyphosate use from 1.26 to 1.20) or significantly associated pesticides (i.e., aldrin, dicamba, and mecoprop).

The most detailed analysis of glyphosate-NHL exposure-response trends was performed by De Roos et al. (2005), who examined tertiles of cumulative lifetime days of glyphosate use (1–20, 21–56, or 57–2,678 days) and tertiles of intensity-weighted cumulative days of use (i.e., years of use × days per year × intensity level, where intensity was defined as (mixing status + application method + equipment repair status) × personal protective equipment use). In analyses adjusted for age, education, smoking, alcohol, family history of cancer, and state of residence, no significant trend was detected for NHL risk in association with increasing cumulative days of glyphosate use (RRs for tertiles 1, 2, and 3, respectively = 1.0 (referent), 0.7 (95% CI = 0.4–1.4), and 0.9 (95% CI = 0.5–1.6); p_{trend} = 0.73) or intensity-weighted cumulative exposure days (RRs = 1.0 (referent), 0.6 (95% CI = 0.3–1.1), and 0.8 (95% CI = 0.5–1.4); p_{trend} = 0.99).

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

HL

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

MM and MGUS

Three studies reported exposure-response trends between glyphosate use and MM risk, including the two analyses based on the same Agricultural Health Study cohort dataset (De Roos et al., 2005; Sorahan, 2015) and the Canadian case-control study (Kachuri et al., 2013) (Table 2). Both case-control studies found some evidence of a positive trend (statistical significance not reported), while a positive trend was detected in one analysis of the cohort data (De Roos et al., 2005) but not the other (Sorahan, 2012).

The Canadian case-control study found a lower risk of MM among those who used glyphosate for up to two days per year than those who had never used glyphosate (RR = 0.72, 95% CI = 0.39–1.32) (Kachuri et al., 2013). However, risk was higher in those with more than two days of glyphosate use per year (RR = 2.04, 95% CI = 0.98–4.23), adjusting for age, province of residence, proxy status, smoking, personal medical history, and family history of cancer. Results were similar after exclusion of data reported by proxy subjects. The authors did not conduct statistical tests for exposure-response trends.

Based on the 55% of Agricultural Health Study cohort members who had available exposure and covariate data, De Roos et al. (2005) reported a positive, albeit statistically non-significant, trend between MM risk and increasing tertiles of cumulative days of glyphosate use (RRs for tertiles 1,

2, and 3, respectively = 1.0 (referent), 1.1 (95% CI = 0.4–3.5), and 1.9 (95% CI = 0.6–6.3); p_{trend} = 0.27) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.2 (95% CI = 0.4–3.8), and 2.1 (95% CI = 0.6–7.0); p_{trend} = 0.17). These estimates were adjusted for age, education, smoking, alcohol, family history of cancer, state of residence, the five pesticides for which cumulative-use variables were most highly associated with glyphosate cumulative use days (i.e., 2,4-D, alachlor, atrazine, metolachlor, and trifluralin), and the five pesticides that were most highly associated with ever use of glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, and diazinon). When intensity alone was analyzed in association with MM risk, the RR for the highest vs. the lowest tertile was 0.6 (95% CI = 0.2–1.8), indicating that the suggested trend was due only to cumulative days of use. When subjects who never used glyphosate were set as the reference group, the RRs for tertiles 1, 2, and 3 of cumulative days of use were 2.3 (95% CI = 0.6–8.9), 2.6 (95% CI = 0.6–11.5), and 4.4 (95% CI = 1.0–20.2); p_{trend} = 0.09. When cumulative use was categorized into quartiles, the RR for the highest quartile vs. never use was 6.6 (95% CI = 1.4–30.6); p_{trend} = 0.01.

In contrast to De Roos et al. (2005), Sorahan (2015) included more than 53,000 eligible cohort members in the analysis (excluding only those with a history of cancer before enrollment, loss to follow-up, missing data on age at enrollment, or missing data on glyphosate use) by creating separate categories for missing or unknown exposure and covariate data. Adjusting for age, sex, education, smoking, alcohol, family history of cancer, and the same 10 pesticides as De Roos et al. (2005), the RRs for each tertile of cumulative days of glyphosate use, compared with never use, were 1.14 (95% CI = 0.43–3.03), 1.52 (95% CI = 0.54–4.34), and 1.38 (95% CI = 0.42–4.45); p_{trend} = 0.48 using category scores of 1–4, p_{trend} > 0.50 using mean exposures within categories. RRs for increasing tertiles of intensity-weighted days of use vs. never use were 1.00 (95% CI = 0.33–3.00), 1.27 (95% CI = 0.45–3.56), and 1.87 (95% CI = 0.67–5.27); p_{trend} = 0.22 using scores, p_{trend} = 0.18 using means. When Sorahan (2015) expanded the eligible cohort to 55,934 subjects to include those with unknown glyphosate use, he again detected no significant exposure-response trends with respect to either cumulative days of use (for tertiles 1, 2, and 3 and unknown use vs. never use, respectively, RRs = 1.11 (95% CI = 0.44–2.83), 1.45 (95% CI = 0.54–3.88), 1.17 (95% CI = 0.40–3.41), and 1.19 (95% CI = 0.25–5.65); p_{trend} > 0.50 across categories of known use using scores or means) or intensity-weighted cumulative days of use (RRs = 0.95 (95% CI = 0.33–2.75), 1.19 (95% CI = 0.44–3.19), 1.58 (95% CI = 0.62–4.05), and 1.04 (95% CI = 0.22–4.92); p_{trend} = 0.30 using scores, p_{trend} = 0.26 using means).

Landgren et al. (2009) did not investigate the exposure-response relationship between glyphosate use and the prevalence of MGUS.

Leukemia

The De Roos et al. (2005) study based on the Agricultural Health Study cohort was the only study that reported exposure-response trends between glyphosate use and risk of leukemia (Table 2). No significant trend was observed between increasing tertiles of cumulative days of glyphosate use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.5), and 1.0 (95% CI = 0.4–2.9) for tertiles 1, 2, and 3, respectively; p_{trend} = 0.61) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.7, and 0.7 (95% CI = 0.2–2.1); p_{trend} = 0.11), adjusting for demographic and lifestyle factors as well as other pesticides.

Evaluation of bias

Selection bias

All studies of the association between glyphosate exposure and risk of LHC were case-control studies except for the Agricultural Health Study, the prospective cohort study that served as the basis for the studies by De Roos et al. (2005), Sorahan (2015), and Landgren et al. (2009). In case-control studies, differences in participation patterns between cases and controls can result in selection bias if participation is related to the exposure of interest. In cohort studies, selection bias can occur if loss to follow-up is related to the exposure and outcome of interest or, less commonly, if baseline participation differs by exposure status and risk of developing the outcome of interest in the future (e.g., based on having a positive family history of an outcome with a genetic susceptibility component). Selection bias in any study can also occur if inclusion in the data analysis, e.g., predicated on data completeness, differs by exposure and outcome status. In general, lower participation, follow-up, or data completeness and large differences in participation between groups increase the potential magnitude of selection bias.

Table 1 shows the reported participation and follow-up proportions in all reviewed studies. Most studies did not report data completeness. The substantial differences in participation between cases and controls in the European multi-center study (Cocco et al., 2013), the most recent Swedish study (Eriksson et al., 2008), and the Canadian study, which also had relatively low absolute participation proportions of < 70% for cases and < 50% for controls (Hohenadel et al., 2011; Kachuri et al., 2013; Karunanayake et al., 2012; McDuffie et al., 2001; Pahwa et al., 2012b), are of particular concern. However, the smaller discrepancies between case and control participation in other studies could also have produced selection bias. Moreover, even identical participation by cases and controls can obscure differences in reasons for study participation that could result in bias.

Given that several case-control studies were originally designed to evaluate associations between pesticides and risk of LHC (Brown et al., 1990; Brown et al., 1993; De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002; Hohenadel et al., 2011; Kachuri et al., 2013; Karunanayake et al., 2012; McDuffie et al., 2001; Pahwa et al., 2012b), it is plausible that cases with a history of agricultural pesticide use were more likely than controls to participate, thereby biasing results toward a positive association for glyphosate as well as other pesticides. It is also possible that certain sources of controls in some of these studies (e.g., residential telephone calls and voter lists) were more likely to identify individuals who were not farmers, again biasing results toward a positive association. Investigators from the Canadian study (Hohenadel et al., 2011; Kachuri et al., 2013; Karunanayake et al., 2012; McDuffie et al., 2001; Pahwa et al., 2012b) reported that an analysis of postal codes showed that respondents and non-respondents did not differ significantly in terms of rural vs. urban residence, but they could not examine differences in occupation or pesticide use.

The cross-sectional analysis of glyphosate and MGUS in the Agricultural Health Study cohort (Landgren et al., 2009) was based on a sample of the < 44% of all subjects who completed the enrollment questionnaire, the take-home questionnaire, and the five-year follow-up interview, with further restriction to an unknown percentage who provided serum. However, selection bias

is improbable, given that MGUS is usually asymptomatic and therefore would be unlikely to influence study participation.

Although the initial follow-up completion of > 99% in the Agricultural Health Study was high (De Roos et al., 2005; Sorahan, 2012), the sizeable proportions of subjects with missing data raise concerns about selection bias. Specifically, 88% of the eligible cohort (excluding those who were diagnosed with cancer before enrollment or were lost to follow-up) provided usable data on ever use of glyphosate and key demographic and lifestyle covariates, 73% additionally provided data on use of other pesticides, 65–66% contributed to analyses of cumulative days of glyphosate use (with or without intensity weighting), and 55% contributed to analyses of cumulative use additionally adjusted for other pesticides. Questionnaire completion could conceivably have varied by demographic and lifestyle factors that are associated with LHC risk, thereby producing bias.

Differential data completeness by disease status is more likely to occur in case-control studies, such as the pooled Midwestern U.S. study conducted by De Roos et al. (2003). In this study, the analysis of multiple pesticides excluded 25% of cases and 25% of controls who lacked complete data. Although the overall frequency of missing data was the same between cases and controls, this exclusion could have led to selection bias if subjects' reasons for providing complete data, and thus being included in the analysis, differed by disease status and were related to glyphosate exposure status. The authors also excluded subjects who had lived or worked on a farm before age 18 years. If these subjects were more likely than others to have used glyphosate (which seems probable), then RR estimates would have been biased upward if a childhood farm environment was inversely associated with NHL risk (Rudant et al., 2011) and biased downward if the association was positive (Hofmann et al., 2015).

Exposure misclassification

All of the included studies assessed use of glyphosate and other pesticides based on self-reported information (Table 1), which is prone to various types of error, such as better recall by cases than controls and by subjects than proxies, inaccurate recall of specific pesticides and amounts used, and a lack of the best measure of biological dose received (Blair and Zahm, 1990). Thus, probable exposure misclassification is a key limitation of all of these studies. The degree of misclassification may vary by mode of data collection, e.g., by written questionnaire, telephone interview, or in-person interview (Bowling, 2005). The extent of misclassification may also depend on questionnaire structure, e.g., whether subjects were asked in an open-ended manner to report use of any pesticides or whether they were prompted to report use of specific pesticides based on a prepared list (Griffith et al., 1999). Some authors did not clearly describe the structure of their study's questions on pesticide use.

Of the eight independent study populations included in this review (seven studies of NHL with or without other types of LHC and one study of leukemia), three provided information on validation of their exposure assessment methods: the Canadian case-control study (Hohenadel et al., 2011; Kachuri et al., 2013; Karunanayake et al., 2012; McDuffie et al., 2001; Pahwa et al., 2012b), the Agricultural Health Study (De Roos et al., 2005; Landgren et al., 2009; Sorahan, 2015), and the Kansas case-control study (Hoar et al., 1986) that contributed to the pooled Midwestern U.S. study by De Roos et al. (2003). Overall, these studies do not establish the

validity of self-reported information on glyphosate use; rather, the limited results suggest considerable error and inconsistency in such data.

Specifically, in the Canadian study, Dosman et al. (1990) reported on the results of a validation pilot study of 21 volunteer farmers whose self-reported pesticide use was compared with written records of pesticide purchases through their local agrochemical supplier. Of the 21 farmers, 17 (81%) had a supplier who had retained written records; the remaining four transactions were conducted with cash. Based on the written records, 146 (65%) of 226 chemicals reported by farmers were verified; 50 of the unverified reports were potentially explained by aerial applications, home and garden use, use more than five years in the past (i.e., during 1958–1984), or use outside of Canada. In 32 instances (for 25 chemicals) the suppliers' records indicated a purchase of chemicals that were unreported by the farmer; two of these were for glyphosate. Detailed self-reported exposure (e.g., frequency, intensity, and duration of use of specific pesticides) could not be validated in this pilot study.

Likewise, Hoar et al. (1986) reported that suppliers for 110 subjects in the Kansas study (out of 130 sought) were located and provided information on the subjects' crops and herbicide and insecticide purchases as "corroborative evidence" of self-reported pesticide use. The authors observed that suppliers usually reported less pesticide use than subjects; that agreement on specific years of use was better for insecticide use than herbicide use; that the differences between agreement for cases and controls were not consistent; and that agreement between suppliers and subjects was better for pesticide use within the last 10 years than for earlier use. Quantitative results on concordance were not provided by Hoar et al. (1986), but in a summary of this study shared with Dosman et al. (1990), the authors stated that reports on herbicide use agreed 59% of the time, with little variation by crop type, and that reports on insecticide use also agreed 59% of the time, but differed by crop type.

In the Agricultural Health Study, the reliability of the question on ever having mixed or applied glyphosate was evaluated by comparing responses to two questionnaires completed one year apart by 2,379 pesticide applicators (Blair et al., 2002). Agreement on a positive response to the question was 82%, and the kappa statistic value for inter-rater agreement was moderate (0.54, 95% CI = 0.52–0.58). For more detailed questions about glyphosate use, including years mixed or applied, days per year mixed or applied, and decade first applied, the percentage with exact agreement ranged from 52% to 62% and kappa ranged from 0.37 to 0.71. These metrics evaluated only the reliability (i.e., reproducibility) of self-reported glyphosate use, not its accuracy.

Subsequent exposure validation studies for other pesticides in the Agricultural Health Study, based on comparisons between exposure intensity estimated from an expert-derived algorithm using self-reported or directly observed exposure data and pesticide biomarker levels measured in urine, yielded Spearman correlation coefficients between 0.4 and 0.8, depending on the type of pesticide (Blair et al., 2011; Coble et al., 2011). Correlations with urinary biomarker levels were poorer for self-reported determinants of pesticide exposure such as kilograms of active ingredient, hours spent mixing and applying, and number of acres treated, with correlation coefficients of -0.4 to 0.2, but application method and use of personal protective equipment were found to be important determinants of exposure intensity. However, the latter factors were

evaluated only for pesticides or pesticide classes in general, not for glyphosate or other individual pesticides (Agricultural Health Study, 1996); thus, limitations remain in the assessment of specific pesticide exposures.

Several studies included a sizeable proportion of surveys that were completed by proxy respondents for deceased or otherwise unavailable cases and controls (Table 1). The use of exposure data reported by surrogates most likely resulted in even poorer accuracy of exposure information in these studies. Although some exposure misclassification may have been non-differential by disease status, such error does not inevitably result in underestimated exposure-disease associations unless additional strict conditions are met, such as independence from other classification errors (Jurek et al., 2008; Jurek et al., 2005).

Furthermore, differential exposure misclassification in case-control studies can readily result in overestimated associations. Reasonable scenarios include more accurate and/or detailed recollection of past exposures by cases, who are more motivated than controls to try to understand the potential causes of their disease; false recollection by cases, who are more aware of scientific hypotheses or media reports that a certain exposure has been linked to their disease; and unconscious influence by study investigators who are aware of causal hypotheses and subjects' case-control status. Only the authors of the Swedish studies (Eriksson et al., 2008; Hardell et al., 2002), the French study (Orsi et al., 2009), and the Nebraska component of the pooled Midwestern U.S. study (Hoar Zahm et al., 1990) specifically stated that investigators were blinded to case-control status. In reality, such blinding is often difficult to achieve in studies that collect interview data.

Others have discussed in detail the problems of estimating individual subjects' exposure to glyphosate from responses to interviews and questionnaires asking about days of use, mixing and application procedures, use of personal protective equipment and other work practices (Acquavella et al., 2006; Mink et al., 2012). Acquavella et al. (2006) reported that any given day of pesticide use can entail highly variable amounts of pesticides used and numbers of mixing operations, and that urine concentrations of glyphosate were poorly correlated with lifetime average exposure intensity scores derived from data self-reported by farmers using this agent. Although recall bias between cases and controls generally might be anticipated to affect all specific pesticides (including glyphosate) equally, variation in the degree of misclassification due to these and other factors affecting usage and exposure could result in different pesticide-specific associations.

Most of the case-control studies did not use procedures to exclude glyphosate exposure that might have occurred after disease onset. The Swedish studies omitted glyphosate use within one year prior to diagnosis or the index date in controls (Hardell et al., 2002; Nordstrom et al., 1998), or within the same calendar year or the year before (Eriksson et al., 2008). In some cases, however, these restrictions may not have been sufficient to exclude exposure that occurred during the latency period between disease onset and diagnosis. Inclusion of any such post-disease exposure would have led to misclassification.

Finally, exposure misclassification resulting from the crude dichotomization of glyphosate use as ever vs. never is an important limitation of most of the included studies. This classification

conflates individuals with considerably different frequencies, intensities, and durations of glyphosate use, and precludes potentially informative analyses of any gradient in LHC risk with increasing glyphosate exposure. As described earlier in the section on exposure-response trends, only three independent studies reported on glyphosate use in more than two (ever vs. never) categories, and only the Agricultural Health Study evaluated more than three exposure categories.

Confounding

As shown in Table 1, the degree of control for confounding varied widely among the reviewed studies. Although several studies considered potential confounding by other pesticides or pesticide families, only a minority (De Roos et al., 2005; De Roos et al., 2003; Eriksson et al., 2008; Hardell et al., 2002; Hohenadel et al., 2011; Sorahan, 2015) reported RR estimates for the association between glyphosate use and LHC risk adjusted for use of other pesticides. Given that Schinasi and Leon (2014) found significant associations between NHL risk and several other types of pesticides, including carbamate insecticides, organophosphorus insecticides, lindane, and MCPA, and numerous other associations of specific pesticides with LHC risk have been reported in the literature (e.g., (Alavanja et al., 2014; Weichenthal et al., 2010))—and because most people who use pesticides occupationally are exposed to multiple pesticides—it is important to control for confounding, whether direct or indirect (if pesticides are surrogates for other risk factors), by these agents.

None of the studies controlled for potential confounding by agricultural exposures other than pesticides, such as other agricultural chemicals, farm animals, allergens, and infectious agents. These exposures have been hypothesized, and in some studies shown, to be associated with risk of NHL, HL, MM, or leukemia (Fritschi et al., 2002; Keller-Byrne et al., 1995; Khuder et al., 1999; McDuffie et al., 2002; Pahwa et al., 2003; Pearce and McLean, 2005; Perrotta et al., 2008), and they are probably correlated with glyphosate use, making them potential confounders of associations between glyphosate and LHC risk. Medical history, certain infections, diet, alcohol consumption, and obesity also may be associated with risk of these malignancies (Becker, 2011; Glaser et al., 2015; Linet et al., 2006; Morton et al., 2014) and could vary by glyphosate use, again making them possible confounders. Even in studies where numerous confounders were included in multivariable regression models, crude categorization or other misclassification of confounders could have enabled residual confounding of observed associations. The direction and magnitude of confounding depend on the relationships of each factor with glyphosate use and LHC risk, and are therefore difficult to predict.

Other issues

Additional issues related to the design, conduct, and reporting of the included studies could also have affected study results and their interpretation. For instance, Hardell et al. (2002) enrolled some prevalent rather than incident cases, since eligible NHL cases were diagnosed in 1987–1990 but interviewed in 1993–1995 (Hardell and Eriksson, 1999). The relatively long time interval between diagnosis and interview may have hampered recollection of past exposures, thereby undermining the accuracy of self-reported exposure data in this study. The delay between diagnosis and interview also almost certainly increased the proportion of cases and matched controls who were deceased (43%) and had proxy interviews, leading to further exposure misclassification.

In the studies by De Roos et al. (2003) and Brown et al. (1990; 1993), LHC cases were diagnosed in 1979–1986, 1980–1983, and 1980–1984, respectively. With glyphosate having come to market in 1974, the cases in these studies would have had a relatively short potential induction time since first use of glyphosate. However, few studies to date have considered the issue of induction time. The Agricultural Health Study collected information on decade of first use of glyphosate in the baseline questionnaire for private pesticide applicators (Agricultural Health Study, 1996), but did not use this information in the published analysis (De Roos et al., 2005). If glyphosate is a cause of LHC, the actual induction time is unknown because the mechanism of carcinogenesis is not established.

Orsi et al. (2009), Kaufman et al. (2009), and four of the six study centers included in Cocco et al. (2013) enrolled hospital-based rather than population-based cases and controls. Given that farmers have lower hospitalization rates than non-farmers (Stiernstrom et al., 2001), hospital-based controls may be less likely than population-based controls to report agricultural occupational exposures, including pesticides, thereby resulting in overestimated RRs for pesticide use. On the other hand, occupational injuries are more common in agriculture than in general private industry (McCurdy and Carroll, 2000), possibly leading to oversampling of farmers from hospital trauma/emergency and orthopedics departments, which might result in underestimated RRs. We did not observe any meaningful change in the meta-RR after restriction to population-based case-control studies.

As noted in Table 1, many possible analyses were not conducted or not reported by authors. De Roos et al. (2003) specifically acknowledged that they did not report results for pesticide combinations that were analyzed but yielded statistically null associations for joint effects, and Hohenadel et al. (2011) likewise did not show results for pesticide combinations without evidence of joint effects. Most other authors did not explicitly state when null results were not reported, but the methods sections of several papers suggested that certain analyses were performed, yet not shown. Given the widespread predilection for emphasizing statistically significant associations in published research articles (Kavvoura et al., 2007), unreported results are probably usually statistically null. The omission of null results is a form of reporting bias that favors positive associations.

Other evidence suggests that statistically null associations between glyphosate and LHC risk have been underreported in the epidemiologic literature. For example, two of the studies that contributed to the pooled analysis conducted by De Roos et al. (2003) apparently collected information on glyphosate use, yet associations between glyphosate and NHL risk were not reported in the original publications (Hoar et al., 1986; Hoar Zahm et al., 1990). In an analysis of interactions between pesticide use and asthma, allergies, or hay fever diagnosis in relation to NHL risk in the Canadian case-control study (Pahwa et al., 2012a), results were reported for several specific pesticides, but not glyphosate, even though information was available for glyphosate use. The most probable scenario in each of these cases is that no significant association was detected between glyphosate use and NHL risk. The omission of such results from the published literature represents a distortion of the body of epidemiologic evidence.

The largest number of studies included in any of the meta-analyses described here was six (in the analysis of NHL), and the majority of meta-analyses (of HL, B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia) included only two studies. The small number of available studies limits the robustness of the estimated meta-RRs, as well as the ability to perform informative sensitivity analysis and evaluation of heterogeneity and publication bias. Even with 10 contributing studies (which we lacked), the statistical power to detect modest heterogeneity using Cochran's Q statistic is "low" (Ioannidis, 2008). Few studies also provide little opportunity to qualitatively investigate possible sources of heterogeneity by subject characteristics or study design. Thus, the results of the meta-analyses and related statistical tests reported here should be interpreted cautiously in light of the sparse and possibly selectively published literature, as well as the high potential for bias and confounding in most of the available studies.

Weight-of-evidence evaluation

The validity of the meta-RRs for glyphosate use and LHC risk reported here and by others (Schinasi and Leon, 2014) is uncertain because systematic error due to bias and confounding cannot reasonably be ruled out as explanations for the observed associations (including both positive and null associations). In addition, an evaluation of the association between glyphosate exposure and risk of LHC based on the Bradford Hill viewpoints (Hill, 1965) shows that a causal relationship has not been established with NHL, any NHL subtype, HL, MM/MGUS, or leukemia. These nine viewpoints are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.

To evaluate the **strength** of the association between glyphosate use and risk of each type of LHC, we considered the magnitude of study-specific RRs and the corresponding meta-RRs. In individual studies, estimates of the association between glyphosate use and risk of NHL ranged between 1.0 and 2.1, and estimates of the association with NHL subtypes ranged between 0.4 and 3.35 (Table 3). For HL, the two estimates of association were 0.99 and 1.7. For MM, RRs ranged between 1.0 (0.5 for MGUS) and 2.4, and those for leukemia ranged between 0.9 and 1.40. Most study-specific estimates were between 1.0 and 1.5. The estimated meta-RRs for all LHC outcomes, including those calculated in secondary and sensitivity analyses, ranged between 1.0 (for leukemia) and 2.5 (for hairy-cell leukemia). The meta-RRs calculated based on at least four studies ranged between 1.1 (for MM including MGUS) and 1.4 (for several NHL and MM models). These associations are not of sufficient magnitude to exclude modest bias or confounding as reasonable explanations of the observed results.

Results were not **consistent** between case-control studies of NHL and the one prospective cohort study of NHL, which reported no association (De Roos et al., 2005). Even among the six studies that contributed to the meta-analysis of NHL, only one statistically significant positive association was observed (Table 3), and RR point estimates varied by more than two-fold. Another, arguably more appropriately adjusted RR (from a hierarchical regression model) that was 24% lower and statistically non-significant was reported in the same study that found a significant association (De Roos et al., 2003). The lack of statistically significant heterogeneity among studies of NHL, based on an underpowered statistical test, does not indicate consistency of results. For NHL subtypes, RR estimates were also variable, except for diffuse large B-cell

lymphoma, for which both estimates were close to 1.0. Only one statistically significant positive association was detected (for chronic lymphocytic leukemia/small lymphocytic lymphoma) (Eriksson et al., 2008), and this result was contradicted by a non-significant inverse association in the other study of this outcome (Orsi et al., 2009). No significant associations with ever use of glyphosate were detected for HL, MM/MGUS, or leukemia, and for MM the RR point estimates varied by more than two-fold (or nearly five-fold when including the estimate for MGUS). Results for MM in the Agricultural Health Study were internally inconsistent (De Roos et al., 2005; Sorahan, 2015), and the positive association with cumulative glyphosate exposure was probably due in part to selection bias.

Numerous associations have been hypothesized between glyphosate exposure and diverse health outcomes, and between various exposures and risk of NHL, NHL subtypes, HL, MM/MGUS, or leukemia. Thus, the putative associations are not **specific** to either the exposure or any of the outcomes. As noted by Bradford Hill (1965), "diseases may have more than one cause" and "one-to-old relationship are not frequent"; therefore, a lack of specificity does not detract from a causal hypothesis.

In case-control studies, where exposure assessment was retrospective, and in the cross-sectional study of MGUS (Landgren et al., 2009), a **temporal** sequence was not definitively established with glyphosate use preceding the time of disease onset. Although some studies attempted to exclude use close to the time of case diagnosis (or enrollment, for controls) (Eriksson et al., 2008; Hardell et al., 2002; Nordstrom et al., 1998), in practice individuals may not accurately recall the timing of use. Only the prospective Agricultural Health Study (De Roos et al., 2005; Sorahan, 2015) was designed to collect information on glyphosate use prior to cancer ascertainment. However, the authors did not exclude malignancies diagnosed close to (e.g., within one year of) study enrollment, nor did they report the distribution of diagnoses with respect to time since first use of glyphosate. Thus, some preclinical cancers may have existed prior to study entry and, possibly, prior to at least some reported glyphosate use.

As discussed in detail earlier, in the three studies of NHL with information on frequency, intensity, and/or duration of glyphosate use (De Roos et al., 2005; Eriksson et al., 2008; McDuffie et al., 2001), a positive **biological gradient** was not consistently demonstrated and was notably lacking in the Agricultural Health Study (De Roos et al., 2005), which had the most detailed exposure information (Table 2). Two case-control studies of MM reported results suggesting (but not formally testing) a positive biological gradient with glyphosate use (Brown et al., 1993; Kachuri et al., 2013), but the more complete analysis of the Agricultural Health Study data (Sorahan, 2015) did not demonstrate such a trend. No data were available to evaluate exposure-response trends between glyphosate and risk of NHL subtypes, HL, or MGUS, and the single study with such data for leukemia found no apparent trend (De Roos et al., 2005).

Inhalation exposure to glyphosate from agricultural or residential uses is likely to be slight due to glyphosate's extremely low vapor pressure (Acquavella et al., 1999). Although dermal contact can be considerable, the very low skin penetrability of glyphosate (Wester et al., 1991) should result in minimal, if any, biologically absorbed dose. Indeed, a biomonitoring study of tree nursery workers found measurable dermal contact with glyphosate but no detectable glyphosate in urine (with 0.01 µg/mL as the lower limit of detection) (Lavy et al., 1992). Another study of

farm families with a lower limit of detection of 0.001 µg/mL (1 ppb) found that 40% of glyphosate applicators had undetectable urinary glyphosate, which reflects all routes of exposure (dermal, inhalation, and oral) (Mandel et al., 2005). Among those with detectable urinary glyphosate, the distribution of concentrations was right skewed, with a peak geometric mean concentration of 0.003 µg/mL (3 ppb) on the day of application and declining thereafter. Glyphosate is usually applied only a few days per year. Given the low biological dose of glyphosate that is expected to be sustained, along with the lack of information on the mechanism of carcinogenesis that may exist in humans, the **biological plausibility** of LHC development due to typical glyphosate exposure has not been established.

IARC recently determined that there is "sufficient" evidence of carcinogenicity of glyphosate in experimental animals, as well as supportive mechanistic evidence of genotoxicity and oxidative stress (IARC, 2015). By contrast, the U.S. EPA (1993), the WHO and United Nations Food and Agriculture Organization (JMPR, 2006), the BfR (2014), and others (Greim et al., 2015; Kier and Kirkland, 2013) concluded that glyphosate does not have genotoxic, mutagenic, or carcinogenic effects in *in vivo* animal and *in vitro* studies, and that the negative findings constitute evidence against carcinogenicity. Given these widely divergent opinions, one cannot unambiguously conclude whether the scientific evidence is **coherent** with the hypothesis that glyphosate causes any or all LHC.

No true **experimental** evidence exists regarding the association between glyphosate exposure and risk of LHC in humans. However, positive associations between farming and risk of LHC were detected prior to 1973, when glyphosate was first commercially marketed (Fasal et al., 1968; Milham, 1971). Thus, if the apparent associations between farming and risk of LHC are due to causal agricultural exposures, they cannot be explained only by glyphosate exposure. Likewise, the recent worldwide increase (followed by a plateau or decline) in NHL incidence began before the 1970s (Holford et al., 1992; Sandin et al., 2006)—although any impact of glyphosate on NHL incidence trends might be obscured by stronger risk factors. No marked increase in the incidence of HL, MM, or leukemia has been observed in parallel with the introduction and expansion of glyphosate use (Hirabayashi and Katanoda, 2008; Hjalgrim, 2012; Morton et al., 2006; Thygesen et al., 2009).

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

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

Discussion

Our meta-analysis yielded borderline significant RRs of 1.3 and 1.4 between glyphosate use and risk of NHL and MM, respectively, and no significant association with risk of HL or leukemia. The largest meta-RR of 2.5 (for hairy-cell leukemia) and the only meta-RR with a lower 95% confidence limit that excluded 1.0 (for B-cell lymphoma) were based on only two studies each,

and the maximum number of studies contributing to any meta-analysis was six. The few studies with available data did not consistently detect positive exposure-response trends between quantitative measures of glyphosate use and risk of any LHC. Furthermore, consideration of the available evidence in light of the Bradford Hill viewpoints does not substantiate a causal relationship between glyphosate exposure and risk of any type of LHC.

A conclusion in favor of causality is also undermined by the studies' methodological limitations, which could reasonably account for at least part of the observed associations. These limitations include exposure misclassification (which may differ by outcome status especially in case-control studies, which constitute nearly all available studies), selection bias (due to differential enrollment, follow-up, or data completeness), poor adjustment for confounding (by other agricultural exposures, for instance), small numbers (which lead to low statistical power as well as a higher probability that a statistically significant finding is false (Button et al., 2013)), and potential reporting and publication bias. Although underpowered statistical tests did not formally detect publication bias, we identified several examples of studies with available data that did not report associations between glyphosate use and LHC risk, and these unreported associations were most likely null.

Underpowered statistical tests also generally did not detect heterogeneity of results among studies, except for chronic lymphocytic leukemia/small lymphocytic lymphoma and MM including MGUS. Nevertheless, our sensitivity analysis revealed some evidence of stronger associations with NHL risk in studies based on Sweden, those that ascertained cases in the 1980s, and lower-quality studies, whereas the meta-RRs for studies that ascertained cases in the 2000s and higher-quality studies were close to the null and statistically non-significant The stronger association with NHL diagnosed in the 1980s raises questions about whether glyphosate, an agent first introduced in 1974 in the United States and Europe, could plausibly cause lymphoma less than a decade later. However, deliberation on the potential induction time requires an understanding of the presumed mechanism of carcinogenesis, which is unknown for glyphosate.

The classification system for lymphoid tumors underwent major changes in 1994 and 2001 (Swerdlow et al., 2008), such that the definition of NHL as a disease entity is not entirely comparable between recent studies and those conducted in the 1980s. Study quality may also have improved over time, for example, due to refinements in survey design, interviewing techniques, data management, and other methods to augment data integrity. The weaker meta-RR in relatively higher-quality (tier 1) studies, as classified based on criteria indicating lower risk of selection bias and information bias, also suggests that at least some of the observed positive association may be spurious. Our definition of tier 1 and tier 2 studies, however, was based on only a small, incomplete set of criteria due to the limited number and quality of available studies. Ideally, for example, tier 1 studies might have been defined as prospective cohort studies with urinary biomarker data for glyphosate exposure and high follow-up and data completeness rates, but no such studies were available. Therefore, the existing classification by necessity includes in tier 1 studies with major limitations, such as self-reported exposure information (De Roos et al., 2005; Orsi et al., 2009), a sizeable proportion of subjects excluded due to missing data (De Roos et al., 2005), no assessment of exposure-response trends (Orsi et al., 2009), and hospital-based controls (Orsi et al., 2009).

The stronger association in Swedish studies probably is not explained by geographical differences in glyphosate use or effect modifiers related to NHL risk. One possible explanation is that of the six NHL studies, only the two Swedish studies (Eriksson et al., 2008; Hardell et al., 2002) compared subjects with glyphosate use to those who did not use any pesticides as the reference group, whereas the other studies defined the reference group as those who did not use glyphosate in particular. Comparisons with subjects who do not use any pesticides are more likely to be confounded by other pesticides and agricultural exposures.

Meta-analysis can be problematic when applied to observational epidemiology (Shapiro, 1994; Weed, 2010). Meta-analysis increases statistical precision by combining results from studies that may differ substantially in terms of source population, exposure and outcome assessment and classification, control for confounding, and other key characteristics. In the presence of such heterogeneity, even if not detectable using formal statistical tests, a single summary estimate may not be scientifically meaningful. Additionally, even when studies are statistically homogeneous, meta-analysis may not yield valid results, since this technique cannot overcome problems in the design and conduct of the underlying studies. Instead, given that bias can seldom be ruled out and unmeasured and uncontrolled confounding can never be eliminated from observational epidemiologic studies, modest meta-RRs detected across multiple studies may simply be due to shared biases, rather than a true association (Shapiro, 1994).

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

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

More specific outcome classification is also needed. Only two studies (Eriksson et al., 2008; Orsi et al., 2009) examined associations between glyphosate use and more than one histological subtype of NHL, despite growing evidence of important etiologic heterogeneity among NHL subtypes (Morton et al., 2014). Information on NHL subtypes is also available in the Agricultural Health Study (Alavanja et al., 2014), and publication of risk associations with glyphosate is anticipated. Risk factors for HL and leukemia are also known to differ by subtype (Glaser et al., 2015; Linet et al., 2006), yet no studies estimated associations with glyphosate separately for subtypes of these tumors. Large, probably pooled studies with histopathological data can determine whether associations with specific tumor subtypes might be obscured by analyzing overall NHL, HL, MM, or leukemia as a single disease entity.

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

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Figure 1. Flow chart of literature identification and selection process

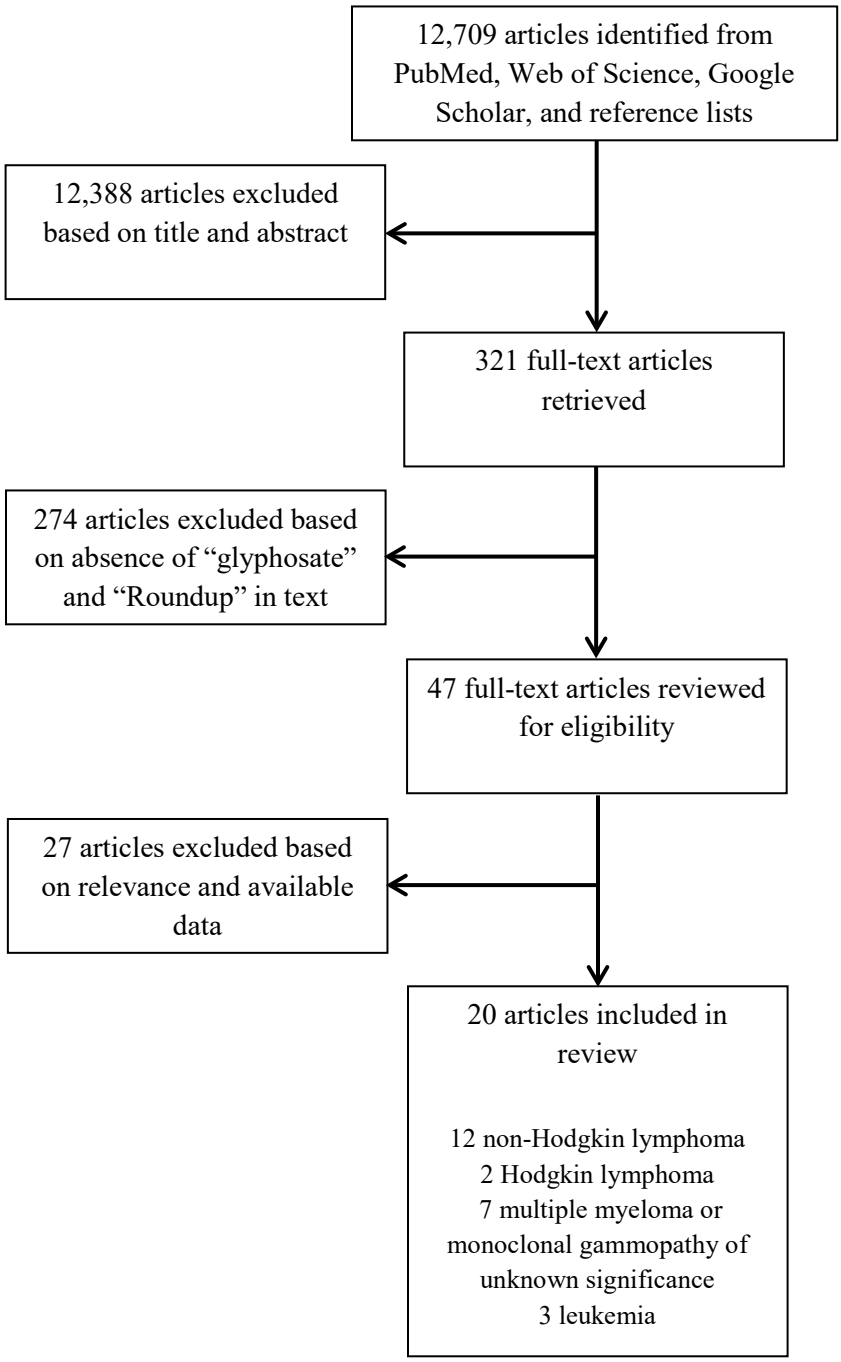

Figure 2. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of non-Hodgkin lymphoma. Meta-RRs were identical in random-effects and fixed-effects models.

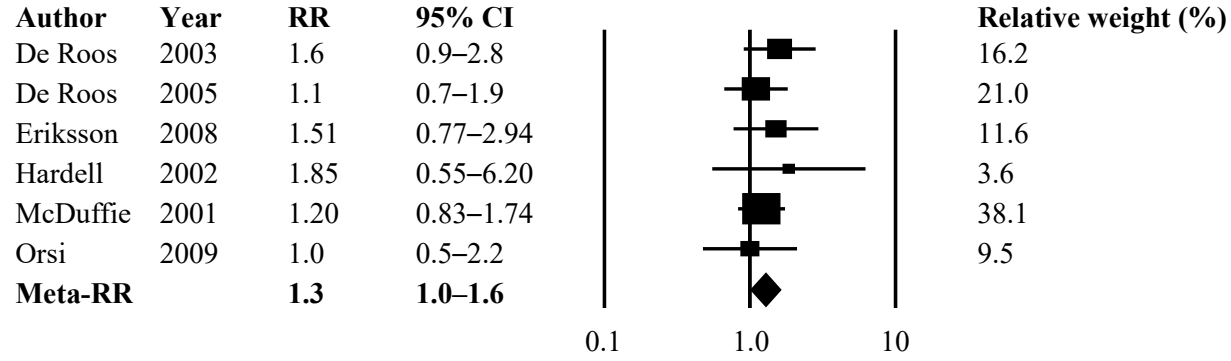

Figure 3. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of multiple myeloma. Meta-RRs were identical in random-effects and fixed-effects models.

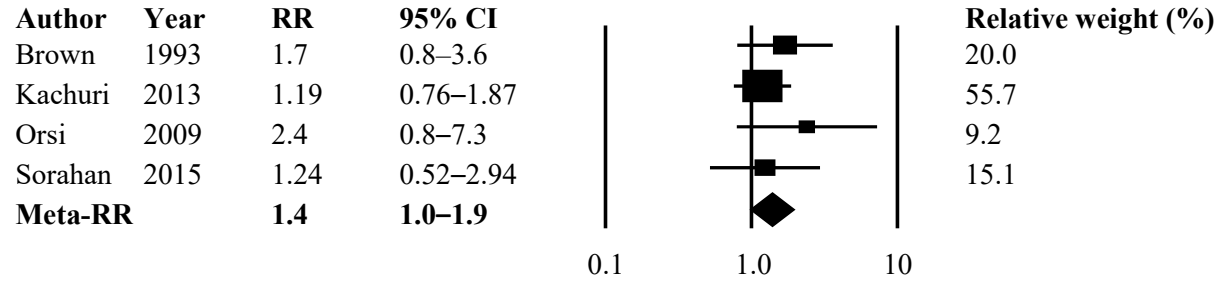

Table 1. Design characteristics of studies of glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Brown et al.	1990	Leukemia (including myelodysplasias)	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa Tumor Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 86% Controls: 77% random digit dialing, 79% Medicare, 77% proxies for deceased Supplemental interview: 93% cases, 96% controls	Cases: 578 Controls: 1245 Supplemental interview: 86 cases, 203 controls	Cases: 238 (41%) Controls: 425 (34%) Supplemental interview, 63 (73%) cases, 57 (28%) controls
Brown et al.	1993	MM	United States (Iowa)	Population-based case-control	1981–1984	White men aged ≥ 30 years in Iowa	Cases: Iowa Health Registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificates if deceased	Cases: 84% Controls: 78% overall	Cases: 173 Controls: 650	Cases: 72 (42%) Controls: 198 (30%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Cantor et al.	1992	NHL	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa State Health Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 89% Controls: 77% random-digit dialing, 79% Medicare, 77% proxies for deceased	Cases: 622 Controls: 1245	Cases: 184 (30%) Controls: 425 (34%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Cocco et al.	2013	B-cell NHL	Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain)	Population- and hospital-based case-control	1998–2004	Persons aged ≥ 17 years in Germany and Italy general populations, and in referral areas of participating hospitals in Czech Republic, France, Ireland, and Spain	Cases: NR Controls: random sampling of population registers in Germany and Italy; recruitment from hospital departments for infectious and parasitic (17.6%), mental and nervous (14.6%), circulatory (8.7%), digestive (7.1%), endocrine and metabolic (4.1%), respiratory (3.9%), and several other conditions (33.2%), excluding cancer, in Czech Republic, France, Ireland, and Spain	Cases: 88% overall; 90% Czech Republic, 91% France, 87% Germany, 90% Ireland, 93% Italy, 82% Spain Controls: 69% overall, 81% hospital-based, 52% population-based; 60% Czech Republic, 74% France, 44% Germany, 75% Ireland, 66% Italy, 96% Spain	Cases: 2348 Controls: 2462	None

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
De Roos et al.	2003	NHL	United States (Nebraska, Iowa, Minnesota, and Kansas)	Population-based case-control (pooled analysis of 3 studies)	1979–1986	White men aged ≥ 21 years in one of the 66 counties of eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester; white men aged ≥ 21 years in Kansas	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records; University of Kansas Cancer Data Service registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska (93% living, 89% deceased); 89% Iowa and Minnesota; 96% Kansas Controls: 85% Nebraska; 77% random-digit dialing, 79% Medicare, 77% deceased (proxies) Iowa and Minnesota; 93% Kansas Analysis restricted to subjects who lived or worked on a farm before 18 years of age (% NR); analysis of multiple pesticides restricted to subjects with non-missing data (75% cases, 75% controls)	Cases: 650 (in analyses of multiple pesticides) Controls: 1933 (in analyses of multiple pesticides)	Cases: 201 (30.9%) (in analyses of multiple pesticides) Controls: 767 (39.7%) (in analyses of multiple pesticides)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
De Roos et al.	2005	LHC NHL MM Leukemia	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort: 36,509–49,211 in analyses adjusted for demographics and lifestyle 30,613–40,719 in analyses additionally adjusted for other pesticides	None
Eriksson et al.	2008	NHL B-cell NHL SLL/CLL FL grades I-III DLBCL Other specified B-cell NHL Unspecified B-cell NHL T-cell NHL Unspecified NHL	Europe (Sweden)	Population-based case-control	1999–2002	Adults aged 18–74 years in 4 of 7 health service regions in Sweden associated with university hospitals in Lund, Linköping, Örebro, and Umeå	Cases: contact with treating physicians and pathologists Controls: national population registry	Cases: 81% Controls: 65% (92% of initially enrolled controls with 71% participation)	Cases: 995 Controls: 1016	None

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Hardell and Eriksson	1999	NHL	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden	Cases: regional cancer registries Controls: national population registry if living, national registry for causes of death if deceased	Cases: 91% (91% living, 92% deceased) Controls: 84% (83% living, 85% deceased)	Cases: 404 Controls: 741	Cases: 177 (44%) Controls: NR (~44%; matched to cases)
Hardell et al.	2002	NHL including hairy cell leukemia	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden (for NHL) or in the entire country of Sweden (for hairy cell leukemia)	Cases: regional cancer registries for NHL, national cancer registry for hairy cell leukemia Controls: national population registry, national registry for causes of death if deceased	Cases: 91% Controls: 84%	Cases: 515 Controls: 1141	Cases: ~35% (NR) Controls: ~29% (NR)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Hohenadel et al.	2011	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 513 Controls: 1506	Cases: 110 (21%) Controls: 220 (15%)
Kachuri et al.	2013	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years (≥ 30 years in analysis) in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1357	Cases: 103 (30%) Controls: 202 (15%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Karunanayake et al.	2012	HL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 68% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 316 Controls: 1506	Cases: NR Controls: 220 (15%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Kaufman et al.	2009	Leukemia	Bangkok, Thailand	Hospital-based case-control	1997–2003	Patients aged ≥ 18 years residing in Bangkok proper and suburbs of Nonthaburi, Nakornpathom, Patumthani, Samutprakarn, and Samusakorn, admitted to Siriraj Hospital or Dhonburi Hospital	Cases: hospital records Controls: hospital records for acute infection or inflammation (33%), trauma (22%), acute abdominal emergencies such as appendicitis (27%), or various other diagnoses with elective admission, such as cataract, hernia repair, or cosmetic surgery (17%), excluding head trauma with loss of consciousness or cancer; controls at Dhonburi Hospital (a nearby private hospital) matched to 21 cases admitted to private wards for wealthy patients	Cases: 100% Controls: 100%	Cases: 180 Controls: 756	None

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Landgren et al.	2009	MGUS	United States (Iowa and North Carolina)	Cross-sectional analysis in prospective cohort	Exposures in 1993–1997 Outcomes in 2006–2008	Male private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides, without history of LHC; analysis restricted to cohort members who completed enrollment questionnaire, take-home questionnaire, and follow-up interview	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire 64% of private applicators and 59% of commercial applicators completed the 5-year follow-up interview Participation in blood draw NR	Cases: 38 Non-cases: 640	None

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Lee et al.	2004	NHL	United States (Nebraska, Iowa, and Minnesota)	Population-based case-control (pooled analysis of 2 studies)	1980–1986	White men and women aged ≥ 21 years in one of 45 counties in eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska, 89% Iowa and Minnesota Controls: 85% Nebraska, 78% Iowa and Minnesota	Cases: 872 Controls: 2336	Cases: 266 (31%) Controls: 779 (33%)
McDuffie et al.	2001	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 517 Controls: 1506	Cases: ~21% (NR) Controls: 220 (15%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Nordström et al.	1998	Hairy cell leukemia	Europe (Sweden)	Population-based case-control	1987–1992 (1993 for one case)	Men living in Sweden	Cases: national cancer registry Controls: national population registry	Cases: 91% Controls: 83%	Cases: 111 Controls: 400	Cases: 4 (4%) Controls: 5 (1%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Orsi et al.	2009	All LHC NHL DLBCL FL LPS CLL Hairy-cell leukemia HL MM	Europe (France)	Hospital-based case-control	2000-2004	Men aged 20–75 years living in the catchment areas of the main hospitals in Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux, with no history of immunosuppression or taking immunosuppressant drugs	Cases: hospital records Controls: hospital records for orthopedic or rheumatological conditions (89.3%), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue disease (1.8%), and infections (3.0%), excluding patients admitted for cancer or a disease directly related to occupation, smoking, or alcohol abuse	Cases: 95.7% Controls: 91.2%	Cases: 491 LHC, 244 NHL, 104 LPS, 87 HL, 56 MM Controls: 456	None

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Pahwa et al.	2012	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1506	Cases: 103 (30%) Controls: 220 (15%)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Sorahan	2015	MM	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort (1): 54,315 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, or missing glyphosate use 49,211 also excluding missing education, smoking, or alcohol 40,719 excluding missing other pesticides Eligible cohort (2): 53,656 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, missing glyphosate use, or missing cumulative exposure days of glyphosate use 53,304 also excluding missing intensity of glyphosate use Eligible cohort (3): 55,934 excluding subjects with cancer before enrollment, loss to follow-up, or missing age at enrollment	None

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

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents

Table 1, continued (additional columns)

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Results not shown	Overlap
Brown et al.	1990	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, and personal applying/mixing/handling In 1987, supplemental telephone interview to evaluate usual number of days of pesticide use per year among Iowa subjects who had reported agricultural use of specific pesticides	Diagnostic confirmation by regional pathologists; special review of myelodysplasias by one pathologist co-author	No	Adjusted: vital status, age, state, ever used tobacco daily, first-degree family history of LHC, non-farming job related to leukemia risk in this study, exposure to substances (benzene, naphtha, hair dyes) related to leukemia risk in this study	ORs for leukemia subtypes (CLL, chronic myelogenous leukemia, acute non-lymphocytic leukemia, acute lymphocytic leukemia, or myelodysplasias); ORs by number of days per year of glyphosate use	Brown et al. 1993, Cantor et al. 1992, De Roos et al. 2003, Lee et al. 2004
Brown et al.	1993	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation by an expert pathologist	No	Adjusted: vital status, age Considered: smoking, education, other factors found not to be confounders of agricultural risk factors	ORs for deceased vs. living subjects; ORs for older vs. younger subjects	Brown et al. 1990, Cantor et al. 1992, De Roos et al. 2003, Lee et al. 2004

Cantor et al.	1992	In-person structured interview, including detailed farming and pesticide use history of all subjects who had worked on a farm for ≥ 6 months since age 18 years For each pesticide, evaluated ever use, first and last year of use, method of application, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	No	Adjusted: vital status, state, age, cigarette smoking status, first-degree family history of LHC, non-farming job related to NHL risk in this study, exposure to hair dyes, exposure to other substances associated with NHL risk in this study Considered: pesticides belonging to other chemical families	ORs for NHL subtypes (diffuse, follicular, small lymphocytic, or other); ORs for glyphosate use among farmers who reported not having used protective equipment; ORs adjusted for other pesticide families	Brown et al. 1990, Brown et al. 1993, De Roos et al. 2003, Lee et al. 2004
Cocco et al.	2013	In-person structured interview, including detailed farming and pesticide use history for all subjects who reported having worked in agriculture For each agricultural job, reported tasks, crops, size of cultivated area, pests treated, pesticides used, crop treatment procedures, use of personal protective equipment, re-entry after treatment, and frequency of treatment in days per year	Histologically or cytologically confirmed cases with central review of slides of ~20% by an international team of pathologists	No	Adjusted: age, gender, education, study center	ORs for overall lymphoma, DLBCL, and CLL; ORs for subjects whose exposure was assessed with a high degree of confidence	None

De Roos et al.	2003	Telephone interview in Nebraska and Kansas; in-person structured interview in Iowa and Minnesota Nebraska: Question about use of any pesticide, followed by prompting for specific selected pesticides, including years of use and average days per year Iowa and Minnesota: Direct question about a selected use of specific pesticides, including first and last years of use Kansas: Open-ended question about use of pesticides, followed by questions on duration of use and days per year for groups of pesticides but not individual pesticides (with validation study)	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists Kansas: Diagnostic confirmation and classification by panel of 3 pathologists	Yes in Nebraska; no in Iowa, Minnesota, and Kansas	Adjusted: age, study site, other individual pesticides with ≥ 20 users in full study Considered: first-degree family history of LHC, education, smoking	ORs showing lack of superadditivity in analyses of joint effects of glyphosate and alachlor or atrazine	Brown et al. 1990, Brown et al. 1993, Cantor et al. 1992, Lee et al. 2004 (also Hoar et al. 1986, Hoar Zahm et al. 1990)

De Roos et al.	2005	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors	Linkage to state cancer registry files, state death registries, and National Death Index	None	Adjusted: age at enrollment, education, cigarette smoking pack-years, alcohol consumption in past year, first-degree family history of cancer, state of residence Considered (adjusted for MM only): 5 pesticides for which cumulative exposure-days were most highly associated with those for glyphosate (i.e., 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, trifluralin), 5 pesticides for which ever/never use was most highly associated with that for glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, diazinon)	RRs for LHC, NHL, or leukemia additionally adjusted for other pesticides (< 20% change) or stratified by state; exposure-response RRs for LHC, NHL, or leukemia using never exposed as referent; RRs for any outcome by quartile or quintile (except highest vs. lowest quintile for NHL and highest vs. lowest quartile for MM)	Landgren et al. 2009, Sorahan et al. 2015
Eriksson et al.	2008	Self-administered mailed questionnaire with additional telephone interview for missing or unclear answers; evaluated occupational exposure to individual pesticides, including number of years, number of days per year, and approximate length of exposure per day	Diagnostic pathological specimens examined and classified by 1 of 5 Swedish expert lymphoma reference pathologists, if not already initially reviewed by one of them; panel review if classification differed from original report	Yes	Adjusted: age, sex, and year of diagnosis or enrollment; other associated agents (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid and/or 2,4,5-trichlorophenoxyacetic acid, mercurial seed dressing, arsenic, creosote, tar) for NHL only	Exposure-response ORs for NHL subtypes; ORs for NHL subtypes and exposure-response ORs adjusted for other agents	None

Hardell and Eriksson	1999	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed use of pesticides within different occupations, wet contact if not handling the sprayer, brand names of pesticides, years of exposure, and cumulative days of exposure Exposure excluded 1 year prior to diagnosis or index year	Histopathological diagnosis of NHL reported to regional cancer registries, confirmed by review of pathology reports	Yes	Adjusted: age, county, vital status, year of death if deceased, use of phenoxyacetic acids	Exposure-response ORs by number of exposure days; ORs by latency period, time since last exposure, or decade of use; ORs for NHL subtypes	Hardell et al. 2002
Hardell et al.	2002	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed years and total number of days of occupational exposure to various agents and names of agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Histologically verified NHL; confirmation of hairy cell leukemia NR	Yes	Adjusted: study, study area, vital status, other associated pesticides (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid + 2,4,5-trichlorophenoxyacetic acid, other herbicides)	Exposure-response ORs by number of exposure days, induction period (time from first exposure to diagnosis/index date), or time from last exposure to diagnosis/index date	Hardell and Eriksson 1999, Nordström et al. 1998

Hohenadel et al.	2011	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent Considered: diesel exhaust, ultraviolet radiation, farm animals, chemicals such as benzene, first-degree family history of cancer	ORs for bromoxynil and glyphosate, carbathin and glyphosate, and mecoprop and glyphosate (i.e., other pesticide pairs with correlation coefficient ≥ 0.4, or correlations with malathion or mecoprop ≥ 0.3); ORs adjusted for additional potential confounders	Kachuri et al. 2013, Karunanayake et al. 2012, McDuffie et al. 2001, Pahwa et al. 2012
Kachuri et al.	2013	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent, smoking status, personal history of rheumatoid arthritis, allergies, measles, shingles, or cancer, family history of cancer	ORs adjusted for other pesticides	Hohenadel et al. 2011, Karunanayake et al. 2012, McDuffie et al. 2001, Pahwa et al. 2012

Karunanayake et al.	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours/year of cumulative exposure to any combination of herbicides, insecticides, fungicides, fumigants, and algicides Pesticide interview collected information on exposure to individual pesticides, place of pesticide use, year of first use, first year on market, number of years of use, and days per year of use [Note differences from related studies]	Initial diagnosis based on information from cancer registries and hospitals; pathology and tumor tissue slides for 155 of 316 cases reviewed by a reference pathologist who confirmed HL in 150/155 cases, plus 7 cases originally classified as NHL; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, acne, hay fever, or shingles, first-degree family history of cancer	ORs stratified by HL histological subtype	Hohenadel et al. 2011, Kachuri et al. 2013, McDuffie et al. 2001, Pahwa et al. 2012

Kaufman et al.	2009	Interview with nurse to assess occupational and non-occupational exposure to pesticides and other potential risk factors	Histologically confirmed leukemia diagnosed within 6 months before current hospital attendance or admission	No	Considered: age, sex, income, use of cellular telephones, benzene and other solvent exposure, occupational and non-occupational pesticide exposure, pesticides used near home, working with power lines, living near power lines, exposure to X-rays, exposure to certain types of electromagnetic fields, use of hair dyes	Adjusted OR	None

Landgren et al.	2009	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors Exposures updated at a 5-year follow-up telephone interview	Serum samples processed and analyzed for MGUS using agarose gel electrophoresis, with agarose strip inspected by a technician and 2 study authors, followed by immunofixation of any serum with a discrete band or thought to have a localized band	All serum samples processed identically (blinding NR)	Adjusted: age, education Considered: 5 pesticides most highly correlated with the pesticide of interest, other pesticides significantly associated with MGUS	Prevalence ratio adjusted for other pesticides	De Roos et al. 2005, Sorahan et al. 2015

Lee et al.	2004	Telephone interview in Nebraska; in-person structured interview in Iowa and Minnesota Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with years of first and last use	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	Yes in Nebraska; no in Iowa and Minnesota	Adjusted: age, state, vital status Considered: gender, smoking, first-degree family history of LHC, ever having a job correlated with risk of LHC (e.g., painting or welding), use of protective equipment	ORs additionally adjusted for other potential confounders; ORs excluding proxy respondents; ORs by state of residence, age at first diagnosis of asthma, or duration of glyphosate use; ORs with unexposed non-asthmatic farmers are reference group	Brown et al. 1990, Brown et al. 1993, Cantor et al. 1992, De Roos et al. 2003, Lee et al. 2004 (also Hoar Zahm et al. 1990)
McDuffie et al.	2001	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours (total = 179 cases, 456 controls with telephone interview) Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, cancer, or allergy desensitization shots, first-degree family history of cancer Considered: pesticide exposure, smoking history	Exposure-response ORs adjusted for additional confounders, including other pesticides;	Hohenadel et al. 2011, Kachuri et al. 2013, Karunanayake et al. 2012, Pahwa et al. 2012

Nordström et al.	1998	Self-administered mailed questionnaire with supplemental telephone interview for unclear or missing answers; assessed total number of days of occupational exposure to various agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Reported to national cancer registry; further confirmation not described	Yes	Adjusted: age Considered: exposure to animals, herbicides, insecticides, fungicides, impregnating agents, organic solvents, exhausts, or ultraviolet light	Multivariate adjusted ORs; ORs with 5-year induction period	Hardell et al. 2002

Orsi et al.	2009	Self-administered written questionnaire with lifetime occupational history, followed by in-person structured interview evaluating non-occupational exposure to pesticides and agricultural questionnaire for subjects who had worked as a farmer or gardener for ≥ 6 months during lifetime Agricultural questionnaire collected data on location of all farms where subject had worked for ≥ 6 months, period of occupation and area, farmer's status at each farm, crops and animal husbandry with mean sizes, all pesticides used on each crop during a given period, whether subject had personally prepared, mixed, or sprayed the pesticide, chemical used, brand name, main use, type of spraying equipment used, annual number and duration of applications, and use of pesticides in farm buildings for animals, grain, hay or straw, or to clear lanes and yards All questionnaires reviewed by an occupational hygienist and an agronomist; repeat telephone interviews conducted to clarify information from 95 (56.8%) of 158 subjects who completed the agricultural questionnaire, not completed by 35 (20.8%) who refused (n = 15), died/were in poor health (n = 10), or could not be contacted (n = 15); all chemicals coded using ad hoc system and classified as definite or possible exposure	All diagnoses cytologically or histologically confirmed and reviewed by a panel of pathologists and hematologists	Yes	Adjusted: age, study center, socioeconomic category Considered: all combinations of pesticide families associated with the LHC subtype considered with a p-value ≤ 0.10, rural/urban status, type of housing, educational level, history of mononucleosis, history of influenza immunization, family history of cancer, skin characteristics, smoking status, and alcohol drinking status	Exposure-response ORs by duration of glyphosate use; ORs with lag times of 10, 20, 30, or 40 years or exposure time windows of 0–10, 10–20, 20–30, or 30–40 years before diagnosis/interview; ORs combining possibly exposed with unexposed subjects; ORs with missing values coded as never used or ever used; conditional ORs restricted to pair-matched case-control samples; ORs sequentially excluding subjects in each center or controls sharing the same category of reason for hospital admission	None

Pahwa et al.	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, allergies, arthritis, or shingles, first-degree family history of cancer	Exposure-response ORs by frequency of use; ORs excluding proxy responses; ORs adjusted for pesticide classes or individual pesticides associated with p-value < 0.10	Hohenadel et al. 2011, Kachuri et al. 2013, Karunanayake et al. 2012, McDuffie et al. 2001

Sorahan	2015	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors Missing data classified into "not known/missing" category, with unknown use of 2,4-dichlorophenoxyacetic acid classified with no use and unknown education classified with no education beyond high school due to lack of MM cases in unknown categories	Linkage to state cancer registry files, state death registries, and National Death Index	None	Fully adjusted: age, gender, smoking pack-years, alcohol use in year before enrollment, first-degree family history of cancer, education, use of 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, or trifluralin, ever use of benomyl, maneb, paraquat, carbaryl, or diazinon Intermediate adjusted: age, gender, smoking, alcohol, family history of cancer, education Adjusted in full cohort: age, gender, family history of cancer, education	RRs by quartile or quintile of cumulative exposure days or intensity-weighted exposure days		De Roos et al. 2005, Landgren et al. 2009

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

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Brown et al.	1990	Non-farmers: 243 cases, 547 controls	OR = 0.9	95% CI = 0.5–1.6
		Ever mixed, handled, or applied glyphosate: 15 cases, 49 controls		
Brown et al.	1993	Non-farmers: 62 cases, 272 controls	OR = 1.7	95% CI = 0.8–3.6
		Ever mixed, handled, or applied glyphosate: 11 cases, 40 controls	Among those who did not use protective equipment, OR = 1.9	Among those who did not use protective equipment, 95% CI = NR
Cantor et al.	1992	Non-farmers: 226 cases, 547 controls	OR = 1.1	95% CI = 0.7–1.9
		Ever handled, mixed, or applied glyphosate: 26 cases, 49 controls		
Cocco et al.	2013	Unexposed to any pesticides: NR cases, 2262 controls	OR = 3.1	95% CI = 0.6–17.1
		Occupationally exposed to glyphosate: 4 cases (1 DLBCL, 1 CLL, 1 MM, 1 unspecified B-cell NHL), 2 controls		
De Roos et al.	2003	Unexposed to glyphosate: 614 cases, 1892 controls	Hierarchical regression OR = 1.6	Hierarchical regression 95% CI = 0.9–2.8
		Exposed to glyphosate: 36 cases, 61 controls	Logistic regression OR = 2.1	Logistic regression 95% CI = 1.1–4.0

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
De Roos et al.	2005	Never used glyphosate: 47 LHC, 21 NHL, 8 MM, 14 leukemia; 13,280 cohort members Ever used glyphosate: 143 LHC, 71 NHL, 24 MM, 43 leukemia; 41,035 cohort members	LHC fully adjusted RR = 1.1 LHC age-adjusted RR = 1.1 NHL fully adjusted RR = 1.1 NHL age-adjusted RR = 1.2 MM fully adjusted RR = 2.6 (2.6 in Iowa, 2.7 in North Carolina) MM age-adjusted RR = 1.1 Leukemia fully adjusted RR = 1.0 Leukemia age-adjusted RR = 1.1	LHC fully adjusted 95% CI = 0.8–1.6 LHC age-adjusted 95% CI = 0.8–1.5 NHL fully adjusted 95% CI = 0.7–1.9 NHL age-adjusted 95% CI = 0.7–1.9 MM fully adjusted 95% CI = 0.7–9.4 MM age-adjusted 95% CI = 0.5–2.4 Leukemia fully adjusted 95% CI = 0.5–1.9 Leukemia age-adjusted 95% CI = 0.6–2.0

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
De Roos et al.	2005	1–20 glyphosate exposure days: 48 LHC, 29 NHL, 8 MM, 9 leukemia 21–56 glyphosate exposure days: 38 LHC, 15 NHL, 5 MM, 14 leukemia 57–2,678 glyphosate exposure days: 36 LHC, 17 NHL, 6 MM, 9 leukemia 0.1–79.5 intensity-weighted glyphosate exposure days: 38 LHC, 24 NHL, 5 MM, 7 leukemia 79.6–337.1 intensity-weighted glyphosate exposure days: 40 LHC, 15 NHL, 6 MM, 17 leukemia 337.2–18,241 intensity-weighted glyphosate exposure days: 43 LHC, 22 NHL, 8 MM, 8 leukemia	Cumulative exposure days, tertiles 2 and 3 vs. 1 LHC RRs = 1.2, 1.2; p-trend = 0.69 NHL RRs = 0.7, 0.9; p-trend = 0.73 MM RRs = 1.1, 1.9; p-trend = 0.27 Leukemia RRs = 1.9, 1.0; p-trend = 0.61 > 108 vs. > 0–9 exposure days, NHL RR = 0.9 Intensity-weighted exposure days, tertiles 2 and 3 vs. 1 LHC RRs = 1.0, 1.0; p-trend = 0.90 NHL RRs = 0.6, 0.8; p-trend = 0.99 MM RRs = 1.2, 2.1; p-trend = 0.17 Leukemia RRs = 1.9, 0.7; p-trend = 0.11 Intensity tertile 3 vs. 1 MM RR = 0.6 Cumulative exposure days, tertiles 1, 2, and 3 vs. never MM RRs = 2.3, 2.6, 4.4; p-trend = 0.09 Cumulative exposure days, quartile 4 vs. never MM RR = 6.6; p-trend = 0.01	Cumulative exposure days, tertiles 2 and 3 vs. 1 LHC 95% CIs = 0.8–1.8, 0.8–1.8 NHL 95% CIs = 0.4–1.4, 0.5–1.6 MM 95% CIs = 0.4–3.5, 0.6–6.3 Leukemia 95% CIs = 0.8–4.5, 0.4–2.9 > 108 vs. > 0–9 exposure days, NHL 95% CI = 0.4–2.1 Intensity-weighted exposure days, tertiles 2 and 3 vs. 1 LHC 95% CIs = 0.6–1.5, 0.7–1.6 NHL 95% CIs = 0.3–1.1, 0.5–1.4 MM 95% CIs = 0.4–3.8, 0.6–7.0 Leukemia 95% CIs = 0.8–4.7, 0.2–2.1 Intensity tertile 3 vs. 1 MM 95% CI = 0.2–1.8 Cumulative exposure days, tertiles 1, 2, and 3 vs. never MM 95% CIs = 0.6–8.9, 0.6–11.5, 1.0–20.2 Cumulative exposure days, quartile 4 vs. never MM 95% CI = 1.4–30.6

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Eriksson et al.	2008	No pesticide exposure: NR	NHL OR, any glyphosate, multivariate = 1.51	NHL 95% CI, any glyphosate, multivariate = 0.77–2.94
		Glyphosate exposure for ≥ 1 full working day, ≥ 1 calendar year prior to year of diagnosis or enrollment: 29 NHL cases, 18 controls (NHL subtypes NR)	NHL OR, any glyphosate, univariate = 2.02	NHL 95% CI, any glyphosate, univariate = 1.10–3.71
			NHL OR, glyphosate 1 to ≤ 10 days = 1.69	NHL 95% CI, glyphosate 1 to ≤ 10 days = 0.70–4.07
			NHL OR, glyphosate > 10 days = 2.36	NHL 95% CI, glyphosate > 10 days = 1.04–5.37
		Glyphosate exposure for 1 to ≤ 10 days: 12 NHL cases, 9 controls	NHL OR, any glyphosate, latency 1–10 years = 1.11	NHL 95% CI, any glyphosate, latency 1–10 years = 0.24–5.08
			NHL OR, any glyphosate, latency > 10 years = 2.26	NHL 95% CI, any glyphosate, latency > 10 years = 1.16–4.40
		Glyphosate exposure for > 10 days: 17 NHL cases, 9 controls		
			B-cell NHL OR, any glyphosate = 1.87	B-cell NHL 95% CI, any glyphosate = 0.998–3.51
			SLL/CLL OR, any glyphosate = 3.35	SLL/CLL 95% CI, any glyphosate = 1.42–7.89
			FL grades I–III OR, any glyphosate = 1.89	FL grades I–III 95% CI, any glyphosate = 0.62–5.79
			DLBCL OR, any glyphosate = 1.22	DLBCL 95% CI, any glyphosate = 0.44–3.35
			Other specified B-cell NHL OR, any glyphosate = 1.63	Other specified B-cell NHL 95% CI, any glyphosate = 0.53–4.96
			Unspecified B-cell NHL OR, any glyphosate = 1.47	Unspecified B-cell NHL 95% CI, any glyphosate = 0.33–6.61
			T-cell NHL OR, any glyphosate = 2.29	T-cell NHL 95% CI, any glyphosate = 0.51–10.4
			Unspecified NHL OR, any glyphosate = 5.63	Unspecified NHL 95% CI, any glyphosate = 1.44–22.0

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Hardell and Eriksson	1999	No pesticide exposure	OR adjusted for phenoxyacetic acids = 5.8	95% CI adjusted for phenoxyacetic acids = 0.6–54
		Glyphosate exposure ≥ 1 year prior to diagnosis or control index year: 4 cases, 3 controls	OR unadjusted for phenoxyacetic acids = 2.3	95% CI unadjusted for phenoxyacetic acids = 0.4–13
Hardell et al.	2002	No pesticide exposure: NR	OR, multivariate = 1.85	95% CI, multivariate = 0.55–6.20
		Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 8 cases, 8 controls	OR, univariate = 3.04	95% CI, univariate = 1.08–8.52
Hohenadel et al.	2011	Use of neither glyphosate nor malathion: 422 cases, 1301 controls	Glyphosate only OR = 0.92	Glyphosate only 95% CI = 0.54–1.55
		Use of glyphosate only: 19 cases, 78 controls	Malathion only OR = 1.95	Malathion only 95% CI = 1.29 –2.93
		Use of malathion only: 41 cases, 72 controls	Glyphosate and malathion OR = 2.10	Glyphosate and malathion 95% CI = 1.31–3.37
		Use of glyphosate and malathion: 31 cases, 55 controls	Interaction contrast ratio = 0.23, P-interaction = 0.69	

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Kachuri et al.	2013	Never used glyphosate: 310 cases, 1236 controls (216 cases, 1047 controls without proxy) Ever used glyphosate: 32 cases, 121 controls (23 cases, 108 controls without proxy) Used glyphosate for > 0 to ≤ 2 days per year: 15 cases, 88 controls (11 cases, 78 controls without proxy) Used glyphosate for > 2 days per year: 12 cases, 29 controls (10 cases, 26 controls without proxy)	Ever glyphosate OR = 1.19 Ever glyphosate OR, no proxies = 1.11 Glyphosate > 0 to ≤ 2 days per year OR = 0.72 Glyphosate > 0 to ≤ 2 days per year OR, no proxies = 0.70 Glyphosate > 2 days per year OR = 2.04 Glyphosate > 2 days per year OR, no proxies = 2.11	Ever glyphosate 95% CI = 0.76–1.87 Ever glyphosate 95% CI, no proxies = 0.66–1.86 Glyphosate > 0 to ≤ 2 days per year 95% CI = 0.39–1.32 Glyphosate > 0 to ≤ 2 days per year 95% CI, no proxies = 0.35–1.40 Glyphosate > 2 days per year 95% CI = 0.98–4.23 Glyphosate > 2 days per year 95% CI, no proxies = 0.95–4.70
Karunanayake et al.	2012	Never used glyphosate: 278 cases, 1373 controls Ever used glyphosate: 38 cases, 133 controls	Fully adjusted OR = 0.99 Minimally adjusted (age, province) OR = 1.14	Fully adjusted 95% CI = 0.62–1.56 Minimally adjusted (age, province) 95% CI = 0.74–1.76
Kaufman et al.	2009	No glyphosate use: 179 cases, 753 controls Glyphosate: 1 case, 3 controls	Crude OR = 1.40	Crude 95% CI = 0.15–13.56
Landgren et al.	2009	Never used glyphosate: 11 cases, 97 non-cases Ever used glyphosate: 27 cases, 543 non-cases	Prevalence ratio = 0.5	95% CI = 0.2–1.0

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Lee et al.	2004	Non-farmers, non-asthmatics: 259 cases, 684 controls Non-farmers, asthmatics: 9 cases, 37 controls Exposed to glyphosate, non-asthmatics: 53 cases, 91 controls Exposed to glyphosate, asthmatics: 6 cases, 12 controls	Non-farmers, asthmatics OR = 0.6 Glyphosate, non-asthmatics OR = 1.4 Glyphosate, asthmatics OR = 1.2	Non-farmers, asthmatics 95% CI = 0.3–1.4 Glyphosate, non-asthmatics 95% CI = 0.98–2.1 Glyphosate, asthmatics 95% CI = 0.4–3.3
McDuffie et al.	2001	Never used glyphosate: 466 cases, 1373 controls Ever used glyphosate: 51 cases, 1506 controls Glyphosate use for > 0 to ≤ 2 days per year Glyphosate use for > 2 days per year	Ever glyphosate OR, fully adjusted = 1.20 Ever glyphosate OR, minimally adjusted (age, province) = 1.26 Glyphosate > 0 to ≤ 2 days per year OR, minimally adjusted = 1.00 Glyphosate > 2 days per year OR, minimally adjusted = 2.12	Ever glyphosate 95% CI, fully adjusted = 0.83–1.74 Ever glyphosate 95% CI, minimally adjusted (age, province) = 0.87–1.80 Glyphosate > 0 to ≤ 2 days per year 95% CI, minimally adjusted = 0.63–1.57 Glyphosate > 2 days per year 95% CI, minimally adjusted = 1.20–3.73
Nordström et al.	1998	No glyphosate exposure: 107 cases, 395 controls Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 4 cases, 5 controls	OR = 3.1	95% CI = 0.8–12

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Orsi et al.	2009	Never exposed to glyphosate: 464 LHC, 232 NHL, 102 DLBCL, 47 FL, 100 LPS, 75 CLL, 25 hairy-cell leukemia 81 HL, 51 MM, 432 controls Ever exposed to glyphosate: 27 LHC, 12 NHL, 5 DLBCL, 3 FL, 4 LPS, 2 CLL, 2 hairy-cell leukemia, 6 HL, 5 MM, 24 controls	LHC OR = 1.2 NHL OR = 1.0 DLBCL OR = 1.0 FL OR = 1.4 LPS OR = 0.6 CLL OR = 0.4 Hairy-cell leukemia OR = 1.8 HL OR = 1.7 MM OR = 2.4	LHC 95% CI = 0.6–2.1 NHL 95% CI = 0.5–2.2 DLBCL 95% CI = 0.3–2.7 FL 95% CI = 0.4–5.2 LPS 95% CI = 0.2–2.1 CLL 95% CI = 0.1–1.8 Hairy-cell leukemia 95% CI = 0.3–9.3 HL 95% CI = 0.6–5.0 MM 95% CI = 0.8–7.3
Pahwa et al.	2012	Never used glyphosate: 310 cases, 1373 controls Ever used glyphosate: 32 cases, 133 controls	OR = 1.22	95% CI = 0.77–1.93

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Sorahan	2015	Never used glyphosate: 8 cases, 13,280 cohort members (of 54,315); 4 cases, 11,881 cohort members (of 49,211); 3 cases, 9809 cohort members (of 40,719) Ever used glyphosate: 24 cases, 41,035 cohort members (of 54,315); 22 cases, 37,330 cohort members (of 49,211); 19 cases, 30,910 cohort members (of 40,719)	Fully adjusted RR, cohort of 54,315 = 1.24 Age- and sex-adjusted RR, cohort of 54,315 = 1.12 Age-adjusted RR, cohort of 54,315 = 1.08 Age-adjusted RR, cohort of 49,211 = 1.91 Intermediate adjusted RR, cohort of 49,211 = 2.07 Age-adjusted RR, cohort of 40,719 = 2.21 Fully adjusted RR, cohort of 40,719 = 2.79	Fully adjusted 95% CI, cohort of 54,315 = 0.52–2.94 Age- and sex-adjusted 95% CI, cohort of 54,315 = 0.50–2.49 Age-adjusted 95% CI, cohort of 54,315 = 0.48–2.41 Age-adjusted 95% CI, cohort of 49,211 = 0.66–5.53 Intermediate adjusted 95% CI, cohort of 49,211 = 0.71–6.04 Age-adjusted 95% CI, cohort of 40,719 = 0.65–7.48 Fully adjusted 95% CI, cohort of 40,719 = 0.78–9.96

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
		1–20 glyphosate exposure days: 10 cases 21–56 glyphosate exposure days: 8 cases 57–2678 glyphosate exposure days: 6 cases 0.1–79.5 intensity-weighted glyphosate exposure days: 6 cases 79.6–337.1 intensity-weighted glyphosate exposure days: 8 cases 337.2–18,241 intensity-weighted glyphosate exposure days: 10 cases	<u>Cumulative exposure days, tertiles 1, 2, and 3 vs. never</u> Fully adjusted RRs = 1.14, 1.52, 1.38; p-trend = 0.48 using scores, > 0.50 using means Intermediate adjusted RRs = 1.13, 1.50, 1.23; p-trend > 0.50 using scores or means Age- and sex-adjusted RRs = 1.06, 1.34, 1.08; p-trend > 0.50 using scores or means <u>Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never</u> Fully adjusted RRs = 1.00, 1.27, 1.87; p-trend = 0.22 using scores, 0.18 using means Intermediate adjusted RRs = 0.99, 1.22, 1.65; p-trend = 0.27 using scores, 0.24 using means Age- and sex-adjusted RRs = 0.91, 1.12, 1.44; p-trend = 0.39 using scores, 0.33 using means	<u>Cumulative exposure days, tertiles 1, 2, and 3 vs. never</u> Fully adjusted 95% CIs = 0.43–3.03, 0.54–4.34, 0.42–4.45 Intermediate adjusted 95% CIs = 0.44–2.88, 0.56–4.05, 0.42–3.58 Age- and sex-adjusted 95% CIs = 0.42–2.70, 0.50–3.58, 0.37–3.11 <u>Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never</u> Fully adjusted 95% CIs = 0.33–3.00, 0.45–3.56, 0.67–5.27 Intermediate adjusted 95% CIs = 0.34–2.86, 0.45–3.28, 0.64–4.24 Age- and sex-adjusted 95% CIs = 0.31–2.62, 0.42–3.00, 0.57–3.67
		Never used glyphosate: 8 cases Ever used glyphosate: 24 Unknown glyphosate use: 2 cases	Ever glyphosate RR = 1.18 Unknown glyphosate RR = 1.71 <u>Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never</u> RRs = 1.11, 1.45, 1.17, 1.19; p-trend > 0.50 using scores or means <u>Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never</u> RRs = 0.95, 1.19, 1.58, 1.04; p-trend = 0.30 using scores, 0.26 using means	Ever glyphosate 95% CI = 0.53–2.65 Unknown glyphosate 95% CI = 0.36–8.20 <u>Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never</u> 95% CIs = 0.44–2.83, 0.54–3.88, 0.40–3.41, 0.25–5.65 <u>Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never</u> 95% CIs = 0.33–2.75, 0.44–3.19, 0.62–4.05, 0.22–4.92

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI

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

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

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI		
1	De Roos et al.	2003	Non-Hodgkin lymphoma	36 cases, 61 controls	a. 1.6 (hierarchical regression) b. 2.1 (logistic regression)	a. 0.9–2.8 (hierarchical regression) b. 1.1–4.0 (logistic regression)		
2	De Roos et al.	2005	Non-Hodgkin lymphoma	71 cases*	1.1	0.7–1.9		
3	Eriksson et al.	2008	Non-Hodgkin lymphoma	29 cases, 18 controls	1.51	0.77–2.94		
4	Hardell et al.	2002	Non-Hodgkin lymphoma	8 cases, 8 controls	1.85	0.55–6.20		
5	Hohenadel et al.	2011	Non-Hodgkin lymphoma	50 cases, 133 controls	1.40 (random effects meta-RR)	0.62–3.15 (random effects meta-CI)		
6	McDuffie et al.	2001	Non-Hodgkin lymphoma	51 cases, 133 controls	1.2	0.83–1.74		
7	Orsi et al.	2009	Non-Hodgkin lymphoma	12 cases, 24 controls	1.0	0.5–2.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Non-Hodgkin lymphoma	1a, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.84
	Model 2		Non-Hodgkin lymphoma	1b, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.59
	Model 3		Non-Hodgkin lymphoma	1a, 2, 3, 4, 5, 7	1.3	1.0–1.7	0.0%	0.85
	Model 4		Non-Hodgkin lymphoma	1b, 2, 3, 4, 5, 7	1.4	1.0–1.8	0.0%	0.63
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
3	Eriksson et al.	2008	B-cell lymphoma	Not reported	1.87	0.998–3.51		
8	Cocco et al.	2013	B-cell lymphoma	4 cases, 2 controls	3.1	0.6–17.1		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		B-cell lymphoma	3, 8	2.0	1.1–3.6	0.0%	0.58
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
3	Eriksson et al.	2008	Diffuse large B-cell lymphoma	Not reported	1.22	0.44–3.35		
7	Orsi et al.	2009	Diffuse large B-cell lymphoma	5 cases, 24 controls	1.0	0.3–2.7		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Diffuse large B-cell lymphoma	3, 7	1.1	0.5–2.3	0.0%	0.79
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
3	Eriksson et al.	2008	CLL/SLL	Not reported	3.35	1.42–7.89		
7	Orsi et al.	2009	CLL/SLL	2 cases, 18 controls	0.4	0.1–1.8		

	Meta-analysis model		Outcome	Studies included	Meta-RR†	95% CI	I^2	$P_{heterogeneity}$
	Model 1, random effects		CLL/SLL	3, 7	1.3	0.2–10.0	83.7%	0.01
	Model 1, fixed effects		CLL/SLL	3, 7	1.9	0.9–4.0		
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
3	Eriksson et al.	2008	Follicular lymphoma	Not reported	1.89	0.62–5.79		
7	Orsi et al.	2009	Follicular lymphoma	3 cases, 24 controls	1.4	0.4–5.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Follicular lymphoma	3, 7	1.7	0.7–3.9	0.0%	0.73
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
7	Orsi et al.	2009	Hairy-cell leukemia	2 cases, 18 controls	1.8	0.3–9.3		
9	Nordström et al.	1998	Hairy-cell leukemia	4 cases, 5 controls	3.1	0.8–12		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Hairy-cell leukemia	7, 9	2.5	0.9–7.3	0.0%	0.63
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
7	Orsi et al.	2009	Hodgkin lymphoma	6 cases, 24 controls	1.7	0.6–5.0		
10	Karunanayake et al.	2012	Hodgkin lymphoma	38 cases, 133 controls	0.99	0.62–1.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Hodgkin lymphoma	7, 10	1.1	0.7–1.6	0.0%	0.36
Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
2	De Roos et al.	2005	Multiple myeloma	19 cases‡	2.6	0.7–9.4		
7	Orsi et al.	2009	Multiple myeloma	5 cases, 24 controls	2.4	0.8–7.3		
11	Brown et al.	1993	Multiple myeloma	11 cases, 40 controls	1.7	0.8–3.6		
12	Kachuri et al.	2013	Multiple myeloma	32 cases, 121 controls	a. 1.19 (with proxies) b. 1.11 (without proxies)	a. 0.76–1.87 (with proxies) b. 0.66–1.86 (without proxies)		
13	Landgren et al.	2009	MGUS	27 cases, 543 non-cases	0.5	0.2–1.0		
14	Pahwa et al.	2012	Multiple myeloma	32 cases, 133 controls	1.22	0.77–1.93		
15	Sorahan	2015	Multiple myeloma	24 cases	1.24	0.52–2.94		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Multiple myeloma	7, 11, 12a, 15	1.4	1.0–1.9	0.0%	0.63
	Model 2, random effects		Multiple myeloma/MGUS	7, 11, 12a, 13, 15	1.2	0.8–1.9	41.8%	0.14
	Model 2, fixed effects		Multiple myeloma/MGUS	7, 11, 12a, 13, 15	1.2	0.9–1.6	"	"
	Model 3		Multiple myeloma	2, 7, 11, 12a	1.5	1.0–2.1	0.0%	0.48
	Model 4		Multiple myeloma	7, 11, 12b, 15	1.4	0.9–1.9	0.0%	0.58
	Model 5		Multiple myeloma	7, 11, 14, 15	1.4	1.0–2.0	0.0%	0.66

	Model 6	Multiple myeloma	2, 7, 11, 14	1.5	1.0–2.1	0.0%	0.52
	Model 7, random effects	Multiple myeloma/MGUS	2, 7, 11, 13, 14	1.3	0.8–2.2	51.2%	0.08
	Model 7, fixed effects	Multiple myeloma/MGUS	2, 7, 11, 13, 14	1.2	0.9–1.7	"	"

Study #	**Author**	**Year**	**Outcome**	**Number of exposed subjects**	**RR**	**95% CI**		
2	De Roos et al.	2005	Leukemia	43 cases‡	1.0	0.5–1.9		
16	Brown et al.	1990	Leukemia	15 cases, 49 controls	0.9	0.5–1.6		
17	Kaufman et al.	2009	Leukemia	1 case, 3 controls	1.4	0.15–13.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR†**	**95% CI**	**I^2**	**$P_{heterogeneity}$**
	Model 1		Leukemia	2, 16, 17	1.0	0.6–1.5	0.0%	0.92

*Number of exposed cases is provided for the total cohort of 54,315 subjects; the number of exposed cases in the analytic cohort of 49,211 subjects was not reported by De Roos et al. (2005).
†All meta-RRs were identical in random-effects and fixed-effects models, unless specifically indicated.
‡Number of exposed cases is provided for the analytic cohort of 40,719 subjects, as reported by Sorahan (2015).
CI: confidence interval; CLL: chronic lymphocytic leukemia; meta-RR: meta-analysis relative risk; MGUS: monoclonal gammopathy of unknown significance; RR: relative risk; SLL: small lymphocytic lymphoma

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

Stratum	Number of studies	Meta-RR*	95% CI
All	6	1.3	1.0–1.6
Case-control	5	1.3	1.0–1.7
Cohort	1	NR	
Population controls	4	1.4	1.0–1.8
Hospital controls	1	NR	
Males only	4	1.3	1.0–1.7
Males and females	2	1.2	0.8–1.8
North America	3	1.2	1.0–1.6
Europe	3	1.3	0.8–2.1
Sweden	2	1.6	0.9–2.8
Cases in 1980s	2	1.6	1.0–2.7
Cases in 1990s	4	1.2	1.0–1.6
Cases in 2000s	3	1.2	0.8–1.7
Tier 1 (higher quality)	2	1.1	0.7–1.6
Tier 2 (lower quality)	4	1.4	1.0–1.8

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