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Glyphosate Epidemiology Review

Final Report

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Summary

In 2015, the International Agency for Research on Cancer (IARC) will convene a working group to review scientific information on glyphosate and to classify this chemical with regard to potential human carcinogenicity. Schinasi and Leon (2014) recently published a review of epidemiologic studies that included data on the relation between agricultural exposure to glyphosate, as well as many other pesticides, and non-Hodgkin lymphoma (NHL). Schinasi and Leon identified a total of seven independent studies of glyphosate and NHL. Their meta-analysis of these studies indicated a positive statistical association between glyphosate and all forms of NHL combined and between glyphosate and B-cell lymphoma, a major subtype of NHL. The present report reviews the study of Schinasi and Leon (2014) and evaluates the possibility that the statistical association between glyphosate and NHL reported by Schinasi and Leon is causal. The report also briefly summarizes epidemiologic data on glyphosate and other forms of lymphatic and hematopoietic cancer (LHC).

Review and Critique of Schinasi and Leon (2014)

The studies of glyphosate and NHL included in the paper by Schinasi and Leon comprised six case-control studies (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Eriksson et al. 2008, Orsi et al. 2009, Cocco et al. 2013) and one prospective cohort study known as the Agricultural Health Study (De Roos et al. 2005). For all forms of NHL combined, Schinasi and Leon identified six studies (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Eriksson et al. 2008, Orsi et al. 2009, De Roos et al. 2005) with results for glyphosate and reported a meta-relative risk (RR) of 1.5 (95% confidence interval [CI] = 1.1–2.0). For glyphosate and B-cell lymphoma, based on data from just two case-control studies (Eriksson et al. 2008, Cocco et al. 2013), the meta-RR was 2.0 (95% CI = 1.1–3.6).

The studies ranged markedly in size with respect to the number of NHL cases exposed to glyphosate: 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. The studies also used diverse methods to estimate exposure to glyphosate from questionnaires and/or interviews and to classify estimated glyphosate exposure for epidemiologic analyses. Only three studies analyzed NHL risk in relation to the number of days exposed to glyphosate in total (De Roos et al. 2005, Eriksson et al. 2008) or annually (McDuffie et al. 2001). The most detailed exposure-response analysis was performed by De Roos et al. (2005). Four of the studies adjusted at least some glyphosate-NHL RR estimates for exposure to other pesticides (Hardell et al. 2002, De Roos et al. 2003, De Roos et al. 2005, Eriksson et al. 2008). However, Schinasi and Leon (2014) did not use RR estimates adjusted for other pesticides from two (Hardell et al. 2002, Eriksson et al. 2008) of the four studies.

Exposure-response data for glyphosate could not be meta-analyzed because exposure classification methods varied considerably among the three studies that conducted such analyses. Qualitative review indicated that two (De Roos et al. 2003, Eriksson et al. 2008) of the

three studies had RR estimates that rose with increasing exposure. In contrast, the large and important Agricultural Health Study (De Roos et al. 2005) found no evidence of such a trend.

Although Schinasi and Leon (2014) included all relevant epidemiologic studies of glyphosate and NHL in their review, they did not provide justification for their selection of four of the six results that they included in their meta-analysis of glyphosate and all forms of NHL combined. The methods of Schinasi and Leon state, "In an effort to use the most unbiased estimate, we extracted the most adjusted effect estimate" (Schinasi and Leon 2014, page 4452). However, the "most adjusted" RRs definitely were not selected from the studies of Hardell et al. (2002) and Eriksson et al. (2008) and arguably were not selected from the studies of McDuffie et al. (2001) and De Roos et al. (2003). All of the four seemingly inappropriate choices of results for inclusion in the meta-analysis produced a higher meta-RR for NHL than would have been obtained if more appropriate selections had been made. In addition, the meta-analysis of B-cell lymphoma was not clearly warranted due to severe limitations of the available data.

When we replaced the RRs extracted by Schinasi and Leon (2014) from McDuffie et al. (2001), Hardell et al. (2002), De Roos et al. (2003) and Eriksson et al. (2008) with alternative, more fully adjusted estimates, the resulting meta-RR was 1.2 (95% CI = 0.9-1.6). An additional meta-analysis replacing the Hardell et al. (2002) and Eriksson et al. (2008) estimates but retaining the other estimates used by Schinasi and Leon yielded a meta-RR of 1.3 (95% CI = 1.0-1.7).

The review by Schinasi and Leon did not assess study quality and did not weight or stratify the studies included in the meta-analysis by quality, despite evidence of considerable variation in quality. Their discussion of research quality was generic and did not specifically discuss the possible impact of study limitations on findings for glyphosate. This is an important deficiency because there is evidence of variation in the potential for random and systematic error among the included studies. Schinasi and Leon also did not comprehensively assess the potential for publication bias, despite some evidence suggesting a tendency toward selective publication of positive results from small studies.

Schinasi and Leon (2014) did not evaluate whether the apparent relationship between glyphosate and NHL is likely to be causal. Their results for glyphosate and NHL indicate an overall statistical association that is not strong and is not observed consistently in all of the relevant studies. Notably, the large, prospective Agricultural Health Study (De Roos et al. 2005) reported that glyphosate was not associated with NHL. Furthermore, effects of bias and confounding on the weak positive associations reported by Schinasi and Leon cannot be ruled out with confidence. Results for NHL do not display consistent evidence of exposure-response, and exposure-response data are not available for B-cell lymphoma. Moreover, biologic plausibility and coherence are lacking for an association between glyphosate and NHL or B-cell lymphoma. On balance, the epidemiologic data on glyphosate and NHL do not warrant a causal interpretation.

Glyphosate and other forms of LHC

None of three studies with information on glyphosate and leukemia (Brown et al. 1990, De Roos et al. 2005, Kaufman et al. 2009) or two studies of glyphosate and Hodgkin lymphoma (Orsi et

al. 2009, Karunanayake et al. 2012) reported a statistically significant association. In addition, none of six studies from four independent settings reported a statistically significant association between glyphosate and multiple myeloma or a related condition, monoclonal gammopathy of undetermined significance (Brown et al. 1993, De Roos et al. 2005, Orsi et al. 2009, Pahwa et al. 2012, Kachuri et al. 2013, Landgren et al. 2009). Although some RRs above 2.0 were reported in the latter studies, these were statistically consistent with no association. A twofold increase in the risk of multiple myeloma associated with glyphosate, reported in an analysis of data from the Agricultural Health Study (De Roos et al 2005), does not appear to be valid, and alternative analyses of the study found that glyphosate was not associated with multiple myeloma (Sorahan 2015).

In summary, there is no convincing evidence that glyphosate is associated causally with other forms of LHC, including leukemia, Hodgkin lymphoma, multiple myeloma and monoclonal gammopathy of undetermined significance.

Introduction

Glyphosate (*N*-(phosphonomethyl)glycine) is a broad-spectrum herbicide that is the most widely used herbicide worldwide. It is the main active ingredient in Roundup, first marketed in 1974. The oral and dermal absorption of glyphosate is low, it does not bioaccumulate in mammals, and it is not carcinogenic in experimental animals (Williams et al. 2000, Greim et al. 2015). The United States Environmental Protection Agency (EPA) and the World Health Organization consider glyphosate as having no evidence of carcinogenicity in humans (EPA Group E, evidence of non-carcinogenicity in humans). The International Agency for Research on Cancer (IARC) plans to convene a working group in 2015 that will review scientific information on this agricultural chemical and classify it with regard to potential human carcinogenicity.

Schinasi and Leon (2014) recently published a review of epidemiologic studies that included data on the relation between agricultural exposure to glyphosate, as well as many other pesticides, and non-Hodgkin lymphoma (NHL). Schinasi and Leon identified a total of seven independent studies of glyphosate and NHL and reported a positive statistical association between glyphosate and all forms of NHL combined and between glyphosate and B-cell lymphoma, a major subtype of NHL. They did not opine on whether or not the observed associations warrant a causal interpretation.

In 2012, Mink et al. published a qualitative systematic review of epidemiologic studies of glyphosate and various cancers, including NHL (Mink et al. 2012). These authors included an in-depth assessment of sources of error in the available studies. In particular, they described potential confounding and selection bias, and they discussed in detail problems with glyphosate exposure estimation. Mink et al. (2012) concluded that, “Our review found no consistent pattern of positive associations indicating a causal relationship between…any site-specific cancer and exposure to glyphosate.” The review of Mink et al. (2012) included five of the seven studies with results for glyphosate and NHL identified by Schinasi and Leon (2014.

The present report includes a review and critique of the study by Schinasi and Leon (2014). In addition to evaluating the Schinasi and Leon study, our review evaluates the epidemiologic evidence pertaining to glyphosate and NHL with respect to causality (i.e., we evaluate the possibility that the association between glyphosate and NHL reported by Schinasi and Leon is causal). Our report also contains a brief summary of epidemiologic data on glyphosate and other forms of lymphatic and hematopoietic cancer (LHC).

Review and Critique of Schinasi and Leon (2014)

The purposes of this critique are to summarize the findings of Schinasi and Leon (2014) with respect to glyphosate and to evaluate the methods, results and interpretation of their review and meta-analysis. We determined if Schinasi and Leon identified all of the relevant studies, selected the most appropriate results to emphasize in their qualitative review and to include in their meta-analysis, adequately assessed the quality (strengths and limitations) of the studies they included and appropriately interpreted their results. Each of the next sections provides our summary evaluation of one of these issues in bold italics at the beginning of the section, followed by an expanded discussion of the topic. We note here that Schinasi and Leon (2014) used random effects models to estimate meta-RRs. This analytic approach is acceptable, given the scope and complexity of their review, and is not discussed further in the current report.

Summary of Results for Glyphosate Reported by Schinasi and Leon (2014)

The studies of glyphosate and NHL included in the Schinasi and Leon review comprised six case-control studies (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Eriksson et al. 2008, Orsi et al. 2009, Cocco et al. 2013) and one prospective cohort study (De Roos et al. 2005). For all forms of NHL combined, six studies (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Eriksson et al. 2008, Orsi et al. 2009, De Roos et al. 2005) reported results for glyphosate, and the meta-RR was 1.5 (95% CI = 1.1-2.0). Schinasi and Leon (2014) also reported a meta-RR of 2.0 (95% CI = 1.1-3.6) for glyphosate and B-cell lymphoma, based on data from just two studies (Eriksson et al. 2008, Cocco et al. 2013).

Of the six case-control studies with data on glyphosate and NHL identified by Schinasi and Leon (2014), all but two (Orsi et al. 2009, hospital-based; Cocco et al. 2013, hospital-based at four of six study sites, population-based at two sites) were population-based. All of the studies considered glyphosate use in agricultural operations or settings. The cases analyzed included all forms of NHL in all studies except the investigation by Cocco et al. (2013), whose analysis of glyphosate exposure was restricted to B-cell lymphoma and other NHL subtypes, but who did not analyze overall NHL (i.e., all NHL subtypes combined). One other study (Eriksson et al. 2008) presented results for B-cell lymphoma and other NHL subtypes, as well as for overall NHL, and another study (Orsi et al. 2009) included results for overall NHL and for several subtypes of B-cell lymphoma, but not for all forms of B-cell lymphoma combined.

The studies ranged markedly in size with respect to the number of NHL cases exposed to glyphosate: 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. The studies also used varying methods to estimate exposure to glyphosate from questionnaires and/or interviews and to classify estimated glyphosate exposure for epidemiologic analyses. Only three studies analyzed NHL risk in relation to the number of days exposed to glyphosate in total (De Roos et al. 2005, Eriksson et al. 2008) or annually (McDuffie et al. 2001). The most

detailed exposure-response analysis was performed by De Roos et al. (2005). Four of the studies adjusted at least some glyphosate-NHL relative risk (RR) estimates for exposure to other pesticides (Hardell et al. 2002, De Roos et al. 2003, De Roos et al. 2005, Eriksson et al. 2008), although, as described in more detail later, Schinasi and Leon (2014) did not use RR estimates adjusted for other pesticides from two (Hardell et al. 2002, Eriksson et al. 2008) of the four studies.

Table 1 displays data on glyphosate and NHL extracted from the report of Schinasi and Leon (2014). For all forms of NHL combined, RR estimates for any versus no exposure to glyphosate ranged from 1.0 (95% confidence interval (CI)) = 0.5-2.2) (Orsi et al. 2009) to 3.0 (95% CI = 1.1-8.5) (Hardell et al. 2002) among the six studies reporting relevant data, and, as mentioned above, the meta-RR was 1.5 (95% CI = 1.1-2.0).

Exposure-response data could not be meta-analyzed because exposure classification methods varied considerably among the three studies that conducted such analyses. Qualitative review indicated that two (De Roos et al. 2003, Eriksson et al. 2008) of the three studies had RR estimates that rose with increasing exposure, but in the third study (De Roos et al. 2005), there was no evidence of such a trend.

Results for B-cell lymphoma were based on two studies (Eriksson et al. 2008, Cocco et al. 2013), one of which did not report the number of B-cell lymphoma cases exposed to glyphosate (Eriksson et al. 2008), and the other of which included only 4 cases and 2 controls exposed to glyphosate (Cocco et al. 2013). RR estimates were 1.9 (95% CI = 1.0-3.5) and 3.1 (95% CI = 0.6-17.1), respectively, in these two studies, and the meta-RR was 2.0 (95% CI, 1.1-3.6). Although not mentioned by Schinasi and Leon (2014), it is of interest to note that, in the study of Cocco et al. (2013), the four glyphosate-exposed cases had clinically diverse diagnoses of multiple myeloma (MM), diffuse large B-cell lymphoma, unspecified B-cell lymphoma and chronic lymphocytic leukemia.

Schinasi and Leon (2014) conducted several sensitivity analyses that considered gender (restriction to male subjects), geography, diagnosis calendar time period, study design (restriction of case-control studies) and extraction of risk estimates from alternative papers. The results pertaining to glyphosate are summarized in Table 2. All meta-RRs for glyphosate and NHL were between 1.3 and 2.3, and most were statistically significant or of borderline statistical significance at the 0.05 probability level. The highest meta-RRs were in analyses restricted to studies conducted in Sweden (Hardell et al. 2002, Eriksson et al. 2008) (meta-RR, 2.2; 95% CI = 1.3-3.8) and to studies with NHL diagnosis years in 1975-1989 (meta-RR, 2.3; 95% CI = 1.4-4.0) (Hardell et al. 2002, De Roos et al. 2003). Meta-RRs declined in studies with NHL diagnosis years in the 1990s (meta-RR=1.5, 95% CI = 1.0-2.1) (Hardell et al. 2002, McDuffie et al. 2001, Eriksson et al. 2008, De Roos et al. 2005) and 2000s (meta-RR=1.3, 95% CI = 0.9-2.0) (Eriksson et al. 2008, De Roos et al. 2005, Orsi et al. 2009).

Identification of Epidemiologic Studies Pertaining to Glyphosate and NHL

The review of Schinasi and Leon (2014) included all relevant epidemiologic studies of glyphosate and NHL.

To assess the completeness of identification of epidemiologic studies of glyphosate and non-Hodgkin lymphoma and to identify studies containing results for glyphosate and other forms of LHC, we conducted a search of MEDLINE via PubMed using the following search string:

(glyphosat OR glifosat* OR glyfosat* OR gliphosat* 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 December 1, 2014, this search string identified a total of 3,370 English-language articles. Based on a review of titles and abstracts, we excluded clinical trials, other treatment studies, prognostic studies, studies of risk factors other than LHC, case reports, animal studies, review articles, and other articles that were not relevant to the potential association between glyphosate and risk of LHC. We then searched the full texts of the remaining 251 articles for the keyword "glyphosate" (including alternative spellings), thereby identifying 41 potentially eligible articles. Based on a review of those 41 articles, 19 papers (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)) were included as containing information on the association between glyphosate and risk of LHC, including NHL, Hodgkin lymphoma (HL), MM, and/or leukemia.

Of the 19 papers, 12 reported on the association between glyphosate and NHL combined (including hairy cell leukemia, which is a subtype of B-cell NHL) (Cantor et al. 1992, Nordstrom et al. 1998, Hardell and Eriksson 1999, McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Lee et al. 2004, De Roos et al. 2005, Eriksson et al. 2008, Orsi et al. 2009, Hohenadel et al. 2011, Cocco et al. 2013). Seven of these 12 papers were included in the main meta-analyses of Schinasi and Leon (2014) (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, De Roos et al. 2005, Eriksson et al. 2008, Orsi et al. 2009, Cocco et al. 2013). Another of the 12 papers, by Cantor et al. (1992), overlapped with the paper by De Roos et al. (2003) and was thus omitted from the main meta-analyses that included the data of De Roos et al. (2003). However, a sensitivity analysis conducted by Schinasi et al. (2014) substituted the study by Cantor et al. (1992) for the study by De Roos et al. (2003) to assess the impact of their decision to include in their main meta-analysis the study of De Roos et al. (2003), rather than the study by Cantor et al. (1992).

Of the four relevant studies that we identified but were not included in the Schinasi and Leon (2014) review, three (Nordstrom et al. 1998, Hardell and Eriksson 1999, Lee et al. 2004) were

included in the Mink et al. (2012) review of epidemiologic studies of glyphosate and cancer. A fourth study (Hohenadel et al. 2011) was not included by either Schinasi and Leon (2014) or Mink et al. (2012). The exclusion of all four of these studies from the Schinasi and Leon (2014) review appears to be justified. The study by Lee et al. (2004) overlaps with the pooled analysis reported by De Roos et al. (2003). The case-control study by Nordstrom et al. (1998), which reported an odds ratio (OR) of 3.1 (95% CI = 0.8–12) for ever use of glyphosate and risk of hairy cell leukemia in Swedish men, and the case-control study by Hardell and Eriksson (1999), which reported an OR of 2.3 (95% CI = 0.4–13) for ever use of glyphosate and risk of NHL in northern Swedish men, were combined by Hardell et al. (2002) in a pooled analysis. The pooled analyses of De Roos et al. (2003) and Hardell et al. (2002) both were included by Schinasi and Leon (2014). The study by Lee et al. (2004) pooled results from two case-control studies conducted in Iowa, Minnesota, and Nebraska, and reported ORs of 1.4 (95% CI = 0.98–2.1) and 1.2 (95% CI = 0.4–3.3) for glyphosate use and risk of NHL among nonasthmatics and asthmatics, respectively. In a pooled analysis by De Roos et al. (2003) that was included by Schinasi and Leon (2014), the findings of Lee et al. (2004) (which in turn incorporated the results of Cantor et al. (1992)), were combined with results from another case-control study conducted in Kansas.

In a case-control study based in six Canadian provinces, Hohenadel et al. (2011) elaborated on the results of McDuffie et al. (2001), which were included by Schinasi and Leon (2014). Evaluating individual and joint associations of malathion and glyphosate with risk of NHL, Hohenadel et al. (2011) reported that the OR (adjusted for age, province, and proxy respondent status) associated with use of malathion without glyphosate was 1.95 (95% CI = 1.29–2.93), the OR associated with use of glyphosate without malathion was 0.92 (95% CI = 0.54–1.55), and the OR associated with use of both glyphosate and malathion was 2.10 (95% CI = 1.31–3.37). These results indicate that, in this study, glyphosate exposure had no effect on the risk of NHL independent of malathion exposure and that the risk of NHL for joint exposure to both pesticides was compatible with the risk associated with exposure to malathion alone.

In summary, among the four additional studies that we identified (Nordstrom et al. 1998, Hardell and Eriksson 1999, Lee et al. 2004, Hohenadel et al. 2011), all contributed results to subsequent pooled analyses that were included by Schinasi and Leon (2014) in their review. Thus, we did not identify any independent findings on the association between glyphosate and NHL risk that were omitted by Schinasi and Leon (2014). However, we note that Schinasi and Leon (2014) identified and described only the study by Cantor et al. (1992) before excluding it from the main meta-analysis because it over-lapped with the study by De Roos et al. (2003). It is not clear if Schinasi et al. (2014) identified the other four articles and chose to exclude them due to study overlap, or if their literature search failed to identify these articles.

Selection of Data for Meta-Analysis

With four exceptions, the selection of results for meta-analysis by Schinasi and Leon (2014) appears to have been appropriate. Schinasi and Leon did not provide justification for these four exceptions, and all of the four seemingly inappropriate choices of results for inclusion in the meta-analysis produced a higher meta-RR for NHL than would have been obtained if

more appropriate selections had been made. The meta-analysis of B-cell lymphoma was not clearly warranted due to severe limitations of the available data.

Hardell et al. (2002) reported a "univariate" OR of 3.04 (95% CI = 1.08–8.52) between ever use of glyphosate and risk of NHL including hairy cell leukemia, and a "multivariate" OR of 1.85 (95% CI = 0.55–6.20). The covariates in the univariate and multivariate analyses were not clearly specified by the authors, but it appears that the univariate analysis adjusted for matching factors (age or age and county, depending on the study), study (Nordstrom et al. 1998 or Hardell and Eriksson 1999), study area, and vital status. The multivariate analysis additionally adjusted for use of other herbicides (2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4-D and 2,4,5-T, or others). Schinasi and Leon included the statistically significant univariate OR, not the statistically nonsignificant and attenuated multivariate OR, in their meta-analysis, despite their assertion, "In an effort to use the most unbiased estimate, we extracted the most adjusted effect estimate" (Schinasi and Leon 2014, page 4452). Thus, the reason for their choice is not clear.

Similarly, for all forms of NHL combined, Eriksson et al. (2008) reported a "univariate" OR of 2.02 (95% CI = 1.10-3.71), adjusted for age, gender and year of diagnosis or enrollment, and a multivariate OR of 1.51 (95% CI = 0.77-2.94), adjusted for age, gender, year of diagnosis or enrollment and, presumably (Eriksson et al. did not adequately describe the multivariable analysis), for exposure to MCPA, 2,4,-D, 2,4,5-T and several other pesticides. Schinasi and Leon (2014) again included the statistically significant univariate OR, not the statistically nonsignificant and attenuated multivariate OR, in their meta-analysis and did not explain their choice of the univariate OR. In their discussion of results for glyphosate and NHL, Eriksson et al. (2008) suggested that the attenuated OR found in their multivariable analysis was due to the fact that co-exposure to glyphosate and other pesticides was common, but this is not adequate justification for selection of the univariate OR for inclusion in the meta-analysis of Schinasi and Leon, especially given their statement that they extracted the most adjusted effect estimate from each study. For B-cell lymphoma, Eriksson et al. (2008) did not report an OR for glyphosate that was adjusted for other pesticides. Therefore, the inclusion of the "univariate" OR for glyphosate and B-cell lymphoma in the meta-analysis by Schinasi and Leon (2014) was necessary, although that OR may be invalid if affected by uncontrolled confounding by exposure to other pesticides.

As mentioned above, Hohenadel et al. (2011), in a further analysis of the study reported earlier by McDuffie et al. (2001), reported an OR of 0.92 (95% CI = 0.54–1.55) for use of glyphosate without malathion, based on 19 exposed cases and 78 exposed controls; an OR of 1.95 (95% CI = 1.29-2.93) for use of malathion without glyphosate, based on 41 exposed cases and 72 exposed controls; and an OR of 2.10 (95% CI = 1.31–3.37) for use of both glyphosate and malathion, based on 31 exposed cases and 55 exposed controls. In the same case-control study population, McDuffie et al. (2001) reported an age- and province-adjusted OR of 1.26 (95% CI = 0.87–1.80) for glyphosate use (with or without malathion) and a multivariate adjusted OR of 1.20 (95% CI = 0.83–1.74), based on 51 exposed cases and 133 exposed controls. The latter OR of 1.20 for glyphosate was not adjusted for exposure to other pesticides. The results from the two papers appear to be reasonably consistent with each other, with one additional glyphosate-exposed case included in the McDuffie et al. (2001) analysis but not the Hohenadel et al. (2011) analysis. (It is possible, for example, that this case had missing data for malathion use and

therefore was excluded from the Hohenadel et al. (2011) analysis.) For their meta-analysis, Schinasi and Leon (2014) selected the multivariate adjusted OR of 1.20 from McDuffie et al. (2001). This is the appropriate estimate for inclusion from *that* study. However, given that the OR of 1.20 was not adjusted for other pesticides and given that much of the (nonsignificantly) increased risk suggested by the OR of 1.20 may have been explained by concomitant malathion use, Schinasi and Leon (2014) should also have considered using the OR of 0.92 (95% CI = 0.54–1.55) for use of glyphosate only, as reported by Hohenadel et al. (2011).

The association between glyphosate and NHL was estimated by De Roos et al. (2003) as OR = 2.1 (95% CI = 1.1–4.0) in a standard logistic regression model and OR = 1.6 (95% CI = 0.9–2.8) in a hierarchical regression model that specified prior distributions for individual pesticides. As described by De Roos et al. (2003), the standard logistic regression model can yield imprecise estimates when modeling multiple pesticides, especially when their use is infrequent and reporting is susceptible to error. To overcome this limitation, they used hierarchical regression models "with the objective of obtaining increased precision and accuracy for the ensemble of estimates." Moreover, De Roos et al. noted that more conservative prior assumptions specified in the hierarchical 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." Thus, the OR from the hierarchical regression model should arguably have been included by Schinasi and Leon (2014) instead of the OR from the logistic regression model, and at a minimum should have been included in sensitivity analyses.

We calculated a meta-RR using the random effects model approach and replacing the RRs extracted by Schinasi and Leon (2014) from McDuffie et al. (2001), Hardell et al. (2002), De Roos et al. (2003) and Eriksson et al. (2008) with the attenuated estimates mentioned above. The result was a meta-RR of 1.2 (95% CI = 0.9-1.6) (Table 3). Additional meta-analyses replacing the Hardell et al. (2002), De Roos et al. (2003) and Eriksson et al. (2008) estimates but retaining the McDuffie et al. (2001) estimate yielded a meta-RR of 1.3 (95% CI = 1.0-1.6), while replacing the Hardell et al. (2002) and Eriksson et al. (2008) estimates but retaining the other estimates used by Schinasi and Leon yielded a meta-RR of 1.3 (95% CI = 1.0-1.7).

The rationale for performing a meta-analysis of the relation between glyphosate and B-cell lymphoma was not convincingly explained by Schinasi and Leon. With only two studies available for analysis, one of which included very few cases and controls exposed to glyphosate, and the other failing to report the number of subjects exposed, meta-analysis of this subtype of NHL may not have been justified. Furthermore, there are data on glyphosate and NHL subtypes other than all B-cell lymphoma available from two studies (Eriksson et al. 2008, Orsi et al. 2009), but Schinasi and Leon did not perform meta-analyses for these other subtypes and did not explain their decision to omit such analyses.

Evaluation of Research Quality

The review by Schinasi and Leon did not include an assessment of study quality and did not weight or stratify the studies included in the meta-analysis by quality, despite evidence of considerable variation in quality. Their discussion of research quality problems, including

limitations of the studies, was generic and did not specifically discuss the possible impact of study limitations on findings for glyphosate. The results for glyphosate are particularly subject to exposure misclassification error.

A critical omission from the Schinasi and Leon (2014) review is an assessment of the quality of each study cited, especially the studies that contributed to the meta-analysis. By not taking into consideration the likelihood of bias in each separate study, Schinasi and Leon (2014) ignored important issues that may invalidate study results and compromise their utility for assessing causality. The quality of each study should have been evaluated systematically to determine if the observed results are more likely to be due to a true causal association, confounding, bias, or chance. Aspects of individual studies that could have been taken into consideration, but were not, include the subject recruitment strategy and participation rates; blinding of investigators to subjects' disease or exposure status; assessment methods for exposures, outcomes, and potential confounders; statistical control of confounding and other statistical approaches; selective reporting of results; and other potential sources of bias (Higgins and Green 2011, Woodruff and Sutton 2014). Some of these issues are discussed below.

Schinasi and Leon (2014) also did not assess the quality of the collective body of epidemiologic research on glyphosate (or any other pesticide evaluated) and NHL risk. The validity of any meta-analysis depends on the quality of the underlying data. Aspects of the overall body of scientific evidence that could have been taken into consideration, but were not, include the risk of bias across all studies, the directness of the evidence for addressing the specific research question of interest, the strength and precision of the observed association, the consistency of findings across study populations, and the detection of an exposure-response gradient (Balshem et al. 2011, Woodruff and Sutton 2014). Some of these considerations are based on the classic Hill guidelines for evaluating whether an epidemiologic association is likely to be causal (Hill 1965). Schinasi and Leon (2014) stated that they considered testing for publication bias across studies, but did not do this because of the small number of contributing studies. Likewise, they were unable to test formally for heterogeneity due to the small number of studies.

All seven of the studies included in the meta-analyses of glyphosate and risk of NHL or B-cell lymphoma (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, De Roos et al. 2005, Eriksson et al. 2008, Orsi et al. 2009, Cocco et al. 2013) have important methodological limitations that raise the probability of bias or otherwise lower the scientific quality of their results. Schinasi and Leon (2014) provided a generic discussion of research limitations but did not include as assessment of individual studies or a discussion of the potential impact of study limitations on results for glyphosate.

Selection bias

As noted earlier, six of the seven studies included in analyses of glyphosate and NHL were case-control studies, and one was a prospective cohort study. 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 (i.e., study attrition) is related to the exposure and outcome of interest. In general, lower participation or follow-up rates and large differences in participation between cases and controls

increase the potential magnitude of selection bias. Table 4 shows the reported participation and follow-up rates in the studies included in the Schinasi and Leon (2014) meta-analysis. The substantial differences in participation rates between cases and controls in the studies by McDuffie et al. (2001) and Cocco et al. (2013) are of particular concern, although the smaller discrepancies between case and control participation rates in other studies could also produce selection bias.

Given that several case-control studies were originally designed to evaluate associations between pesticides and NHL risk (McDuffie et al. 2001, Hardell et al. 2002, De Roos et al. 2003, Eriksson et al. 2008), 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.

Exposure misclassification

Potential for exposure assessment error is a major limitation of all of the included studies. As shown in Table 5, all of the included studies assessed pesticide use based on self-reported data, which is prone to substantial error (Blair and Zahm 1990). The degree of error may vary by mode of data collection, e.g., by written questionnaire, telephone interview, or in-person interview (Bowling 2005). The extent of error may also depend on questionnaire structure, e.g., whether subjects are asked in an open-ended manner to report use of any pesticides or whether they are prompted to report use of specific pesticides based on a prepared list (Griffith et al. 1999). Some studies were not clear about the structure of questions on pesticide use.
Only two of the included studies (McDuffie et al. 2001, De Roos et al. 2005) provided information on validation of their exposure-assessment methods. McDuffie et al. (2001) reported that among 27 volunteer farmers, there was “excellent” concordance between self-reported pesticide use and records of pesticide purchases through their local agrochemical supplier. However, only positive reports of pesticide use appear to have been validated in this pilot study. In the Agricultural Health Study cohort, in which the study by De Roos et al. (2005) was conducted, 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 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 exact agreement ranged from 52% to 62% and kappa ranged from 0.37 to 0.71. Importantly, however, these metrics evaluated only the reliability (i.e., reproducibility) of self-reported glyphosate use, not its accuracy (i.e., validity), which is unknown.

Two of the included studies included a sizeable proportion of surveys that were completed by proxy respondents for deceased cases and controls. 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 be 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. 2005, Jurek et al. 2008). Furthermore, differential exposure misclassification in case-control studies—for example, due to 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; or false recollection by cases, who are more aware of hypotheses or media reports that a certain exposure has been linked to their disease; or unconscious influence by study investigators who are aware of causal hypotheses and subjects' case/control status—can readily result in overestimated associations.

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). Notably, Acquavella et al. (2006) have reported that any given day of pesticide use can entail highly variable amounts of pesticides used and numbers of mixing operations; that urine concentrations of glyphosate were poorly correlated with lifetime average exposure intensity scores derived from self-reports of farmers using this agent; and that type of formulation appeared to be a determinant of urine concentrations in farmers using glyphosate. Type of formulation has not been included in glyphosate exposure estimation algorithms used in epidemiologic studies to date.

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 levels of glyphosate exposure frequency, intensity, and duration, and precludes potentially informative analyses of exposure-response trends. Of the seven included studies, only three (McDuffie et al. 2001, De Roos et al. 2005, Eriksson et al. 2008) reported on glyphosate use in more than two (ever vs. never) categories, and only one (De Roos et al. 2005) had more than three categories (tertiles of cumulative exposure days and tertiles of intensity-weighted exposure days, neither of which showed an exposure-response trend with NHL risk).

Confounding

As shown in Table 6, the degree of control for potential confounding varied among the seven studies included in the meta-analysis by Schinasi and Leon (2014). Several of the studies did not control for exposure to other pesticides, and as noted earlier, two studies included RR estimates adjusted for other pesticide exposure, but Schinasi and Leon did not select those estimates for inclusion in their meta-analysis. The results of the meta-analyses of pesticides other than glyphosate underscore the need to control for certain other herbicides and insecticides. In particular, Schinasi and Leon (2014) concluded that "there is consistent evidence of positive associations between NHL and carbamate insecticides, organophosphorus insecticide, lindane and MCPA." In addition, none of the studies controlled for potential confounding by agricultural exposures other than pesticides, such as farm animals and other agricultural chemicals. All of these exposures have been hypothesized, and in some studies shown, to be associated with NHL risk (Pearce and McLean 2005), and they are probably correlated with glyphosate use, making them potential confounders of the glyphosate-NHL association. Medical

history, certain infections, diet, alcohol consumption, and obesity may also be associated with NHL risk (Alexander et al. 2007) 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.

Other issues

Other issues related to the design, conduct, and reporting of the included studies could also have affected study results and their interpretation. For example, Hardell et al. (2002) enrolled some prevalent rather than incident cases, since eligible NHL cases were diagnosed during 1987–1990 but interviewed during 1993–1995 (Hardell and Eriksson 1999). The relatively long time interval between diagnosis and interview may have further undermined the accuracy of self-reported exposure data in this study.

De Roos et al. (2003) excluded all subjects who had lived or worked on a farm when younger than 18 years of age, but not after age 18, and they also excluded any subject who had a missing or "don't know" response for any one of the 47 pesticides of interest evaluated in their study. Such exclusions could have biased the results if the probability of exclusion differed by exposure and outcome status. De Roos et al. (2003) did not report results for pesticide combinations that were analyzed but yielded statistically null associations for joint effects, such as glyphosate + alachlor and glyphosate + atrazine. If—similar to the results of Hohenadel et al. (2011) for glyphosate plus malathion—an association with NHL risk was detected for glyphosate plus alachlor or atrazine but not glyphosate alone, this null result would have been of interest, since it might have suggested confounding by use of another pesticide. Instead, by omitting null results from their paper, the authors exhibited a form of reporting bias that favors positive associations.

Orsi et al. (2009) and four of the six study centers included in Cocco et al. (2013) enrolled hospital-based cases and controls. Given that hospital-based controls are injured or ill, they may be less likely than population-based controls to report certain occupational exposures, thereby resulting in overestimated associations. Although Schinasi and Leon (2014) conducted a sensitivity analysis in which they restricted results to population-based case-control studies, they only superficially mentioned that results may vary between population-based and hospital-based studies, without discussing the direction of potential bias.

Overall quality of evidence

The inclusion of only six studies in the meta-analysis of glyphosate and NHL risk, and only two studies in the meta-analysis of glyphosate and B-cell lymphoma risk, limited the informativeness of sensitivity analyses and precluded formal evaluation of sources of heterogeneity. For example, in the sensitivity analyses of the NHL association reported in the online supplement to Schinasi and Leon (2014), three studies contributed to the analysis of males, and no analysis was conducted of females; five studies contributed to the analysis of case-control studies, and no analysis was conducted of cohort studies; two studies contributed to the analysis of cases diagnosed in 1975–1989, four to the analysis of cases diagnosed in the

1990s, and three to the analysis of cases diagnosed in the 2000s; three studies contributed to the analysis of North American studies, two to the analysis of U.S. studies, three to the analysis of European studies, and two to the analysis of Swedish studies; and four studies contributed to the analysis of population-based case-control studies, while no analysis was conducted of hospital-based case-control studies. Based on so few studies, there was essentially no opportunity to detect any heterogeneity by subject characteristics or study design. Moreover, each contributing study carries substantial weight in a meta-analysis based on so few studies, such that outlier results can have undue influence on the overall findings.

As stated earlier, due to the small number of available studies, Schinasi and Leon (2014) did not formally evaluate publication bias—that is, the tendency for published studies not to be representative of all valid studies, with a general bias in favor of publishing positive (statistically significant) results. However, a qualitative evaluation reveals that the three highest RR estimates included in the meta-analysis of glyphosate and NHL were reported in relatively small studies (with 8, 29, and 36 glyphosate-exposed NHL cases, respectively) (Hardell et al. 2002; Eriksson et al. 2008; De Roos et al. 2003), whereas the two largest studies (with 71 and 51 exposed NHL cases, respectively) yielded RR estimates closer to the null (De Roos et al. 2005; McDuffie et al. 2001). Although based on few studies, this pattern—which deviates from a symmetric "funnel-shaped" distribution—suggests the possibility of publication bias in favor of positive results from smaller, less precise studies. In any case, the apparent heterogeneity of results by study size requires explanation, but was not investigated by Schinasi and Leon (2014).

Interpretation of the Meta-Analysis

Schinasi and Leon (2014) did not carry out an evaluation of causality with respect to their findings for glyphosate and NHL. The discussion section of their paper does not mention glyphosate. Their conclusions also do not mention glyphosate but indicate that "there were strong associations between certain chemicals and B cell lymphoma." This statement in the conclusions section, combined with the statement in the abstract that "…B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate" could be taken as implying that they found a strong or notable positive association between glyphosate and B-cell lymphoma. Any such interpretation would be unjustified and inappropriate. Results for glyphosate and NHL or B-cell lymphoma do not warrant a causal interpretation for several reasons. The number of studies is small, particularly for B-cell lymphoma (two studies) and particularly for studies that included exposure-response analyses (three studies). Results for glyphosate and NHL are inconsistent across studies, with the large, prospective Agricultural Health Study (De Roos et al. 2005) having convincingly null results for glyphosate and NHL. Biologic plausibility is lacking. Residual confounding by pesticides found in the meta-analysis to be associated with NHL (carbamate insecticides, organophosphorus insecticides, lindane and MCPA) and by other factors is possible. Furthermore, the observed statistical association between glyphosate and B-cell lymphoma is based on an uncertain numbers of exposed subjects (very small in one study, unknown in the other), the two component RRs were not adjusted for other pesticide

exposures, there were other methodological limitations of the two studies, and the meta-RR was only 2.0, indicating a statistical association that is not strong.

The validity of the meta-RRs for glyphosate and NHL and glyphosate and B-cell lymphoma is uncertain because the possibility of systematic error due to bias and confounding cannot be ruled out. Agricultural operations potentially entail exposure to multiple pesticides and other agents, some of which displayed consistent associations with NHL, as reported by Schinasi and Leon (2014) and others. Few studies have controlled adequately for confounding by pesticides other than glyphosate and other agents used in agriculture, nor has the available research attempted to determine if glyphosate is associated with NHL in the absence of exposure to other pesticides associated with NHL. Moreover, a brief evaluation of the association between glyphosate and NHL (or B-cell lymphoma) risk based on the key Hill guidelines (Hill 1965) shows that a causal relationship has not been established. The **strength** of the meta-RRs estimated by Schinasi and Leon (2014) (meta-RR for NHL = 1.5, 95% CI = 1.1–2.0; meta-RR for B-cell lymphoma = 2.0, 95% CI = 1.1–3.6), as well as most of the individual RR estimates reported in the included studies, are not of sufficient magnitude to exclude even modest confounding or bias as likely explanations of the observed associations. Results for all NHL are not **consistent** across studies, with one-half of the available studies reporting null or nearly null results. Numerous associations have been hypothesized with glyphosate and with NHL, such that the putative association between the two is not **specific** to either the exposure or the outcome. In case-control studies, where exposure assessment was retrospective, a **temporal** sequence was not definitively established with glyphosate exposure preceding the time of NHL onset. In the three studies with information on frequency, intensity, and/or duration of glyphosate use (McDuffie et al. 2001, De Roos et al. 2005, Eriksson et al. 2008), a positive **biological gradient** was not consistently demonstrated and was notably lacking in the important Agricultural Health Study, which had the most detailed exposure information of all available studies (De Roos et al. 2005). Given that inhalation exposure to glyphosate from agricultural uses is likely to be minimal, and glyphosate has been shown to have very low skin penetrability, thereby limiting any dermal exposure Acquavella et al. 2004, Niemann et al. 2015), the negligible exposure may render any association with NHL risk **implausible**. The lack of genotoxic, mutagenic, or carcinogenic effects of glyphosate in toxicological studies (Williams et al. 2000, Kier and Kirkland 2013, Kier 2015, Greim et al. 2015) also indicates that scientific evidence is not **coherent** with the hypothesis that glyphosate causes NHL. Thus, taken together, the existing scientific evidence does not support a conclusion that glyphosate causes NHL or B-cell lymphoma.

Epidemiologic Studies of Glyphosate and LHC Other Than NHL

As stated earlier, we identified 19 studies that reported results on the association between glyphosate and LHC other than NHL. Of these, three reported on the association with leukemia (Brown et al. 1990, De Roos et al. 2005, Kaufman et al. 2009), two reported on the association with HL (Orsi et al. 2009, Karunanayake et al. 2012), five reported on the association with MM (Brown et al. 1993, De Roos et al. 2005, Orsi et al. 2009, Pahwa et al. 2012, Kachuri et al. 2013), and one reported on the association with monoclonal gammopathy of undetermined significance (MGUS) (Landgren et al. 2009), a precursor of MM.

Leukemia

In a population-based case-control study of 578 white men with leukemia and 1,245 white male controls in Iowa and Minnesota (the same study setting as in Cantor et al. (1992), discussed above with respect to NHL risk), 15 cases and 49 controls reported having mixed, handled, or applied glyphosate (Brown et al. 1990). The OR for the association between glyphosate and leukemia, adjusting for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures, was 0.9 (95% CI = 0.5–1.6).

In the prospective Agricultural Health Study cohort, the RR for the association between ever vs. never use of glyphosate and leukemia, adjusting for age, demographic and lifestyle factors, and other pesticides, was 1.0 (95% CI = 0.5–1.9), based on 57 incident leukemia cases (75.4% of whom had ever used glyphosate) (De Roos et al. 2005). Compared with the lowest tertile of cumulative exposure days, the RRs for the second and third tertiles, respectively, were 1.9 (95% CI = 0.8–4.5) and 1.0 (95% CI = 0.4–2.9), P_{trend} = 0.61. Compared with the lowest tertile of intensity-weighted exposure days, the RRs for the second and third tertiles, respectively, were 1.9 (95% CI = 0.8–4.7) and 0.7 (95% CI = 0.2–2.1), P_{trend} = 0.11.

In a hospital-based case-control study of 180 leukemia cases and 756 hospitalized controls in Bangkok, Thailand, one case and three controls reported occupational use of glyphosate (Kaufman et al. 2009). The authors did not report the association between glyphosate and leukemia, but the crude (unadjusted) OR can be calculated as 1.4 (95% CI = 0.15–13.6).

None of the above three studies reported a statistically significant association between glyphosate and leukemia. Taken together, these studies do not establish any association, much less a causal relationship, between glyphosate and leukemia.

Hodgkin Lymphoma (HL)

The same French hospital-based case-control study as described above with respect to NHL (Orsi et al. 2009) enrolled 87 males with incident HL and 265 matched male controls. Six cases and 15 controls reported having used glyphosate, resulting in an OR of 1.7 (95% CI = 0.6–5.0), adjusting for age, study center, and socioeconomic category (white collar or blue collar).

In the same Canadian population-based case-control study setting as in McDuffie et al. (2001), 38 of 316 HL cases and 133 of 1,506 controls reported having used glyphosate (Karunanayake et al. 2012). Adjusting for age, province of residence, and statistically significant medical history variables (history of measles, acne, hay fever, or shingles and a positive first-degree family history of cancer), the OR for glyphosate and HL was 0.99 (95% CI = 0.62–1.56).

Neither of these two studies reported a statistically significant association between glyphosate and HL. They do not establish any association, much less a causal relationship, between glyphosate and HL.

Multiple Myeloma (MM) and Monoclonal Gammopathy of Undetermined Significance (MGUS)

The Midwestern United States population-based case-control study described earlier also enrolled 173 white men with MM and 650 controls from the Iowa site only (excluding Minnesota) (Brown et al. 1993). Mixing, handling or applying of glyphosate was reported by 11 cases and 40 controls, resulting in an OR of 1.7 (95% CI = 0.8–3.6), adjusting for age and vital status.

De Roos et al. (2005) evaluated associations between glyphosate use and MM in the prospective Agricultural Health Study cohort. Their analysis of 54,315 pesticide applicators indicated an RR of 1.1 (95% CI = 0.52–2.4), without adjustment for potential confounders, based on 32 incident cases of MM. A further analysis was restricted to the 40,719 cohort members who did not have missing information on demographic and lifestyle factors and pesticide use and included 22 incident cases of MM. The latter analysis found that the RR was 2.6 (95% CI = 0.7–9.4) for ever-use of glyphosate and MM after adjusting for age, demographic and lifestyle factors and other pesticides. No significant exposure-response trend was detected across tertiles of cumulative exposure days (RR for second tertile = 1.1, 95% CI = 0.4–3.5; RR for third tertile = 1.9, 95% CI = 0.6–6.3; P_{trend} = 0.27) or tertiles of intensity-weighted exposure days (RR for second tertile = 1.2, 95% CI = 0.4–3.8; RR for third tertile = 2.1, 95% CI = 0.6–7.0; P_{trend} = 0.17). Sorahan (2015) noted that the RR of 2.6 from the analysis of the restricted cohort by De Roos et al. (2005) differed markedly from the RR of 1.1 in the full cohort analysis, and he conducted an alternative, new analysis of the full cohort that adjusted for age, lifestyle factors and use of other pesticides. The new analysis yielded an RR for glyphosate of 1.24 (95% CI = 0.52–2.94). Sorahan (2015) concluded that the RR of 2.6 reported by De Roos et al. (2005) resulted from the use of restricted data that were not representative of the full cohort and that the results did not constitute valid evidence of a causal association between glyphosate and MM.

MM is usually preceded by MGUS, which progresses to MM at a rate of approximately 1% per year, and the two conditions are likely to have similar causes. Associations with MGUS were examined in a subset of 678 men with serum samples (38 of whom were found to have MGUS) in the Agricultural Health Study cohort (Landgren et al. 2009). Twenty-seven of the 38 MGUS cases reported ever having used glyphosate, resulting in an RR of 0.5 (95% CI = 0.2–1.0), adjusted for age and education level.

In the French hospital-based case-control study described earlier (Orsi et al. 2009), 5 of 56 MM cases and 18 of 313 controls reported having used glyphosate, yielding an OR of 2.4 (95% CI = 0.8–7.3), adjusted for age, study center and socioeconomic category.

The population-based Canadian case-control study described earlier reported associations with MM based on 342 cases and 1,506 controls (Pahwa et al. 2012). Glyphosate use was reported by 32 cases and 133 controls, resulting in an OR of 1.22 (95% CI = 0.77–1.93), adjusted for age, province, and statistically significant medical history variables (history of measles, mumps, allergies, arthritis, or shingles, and a positive first-degree family history of cancer).

The same Canadian study dataset was used to evaluate associations between more detailed pesticide exposures and MM (Kachuri et al. 2013). This analysis included all 342 cases included in the prior analysis (Pahwa et al. 2012), but excluded 52 controls aged <25 years and 97 controls aged 25–29 years with no age-matched MM cases, leaving 1,357 controls. Thirty-two cases were still classified as exposed to glyphosate, compared with 121 controls (OR = 1.19, 95% CI = 0.76–1.87). After excluding proxy respondents (used for 30% of cases and 15% of controls), the OR was 1.11 (95% CI = 0.66–1.86). ORs were higher, but still statistically nonsignificant, for >2 vs. 0 days per year of mixing or applying glyphosate (OR = 2.04, 95% CI = 0.98–4.23 with proxy responses; OR = 2.11, 95% CI = 0.95–4.70 without proxy responses). By contrast, ORs for >0–≤2 vs. 0 days per year were nonsignificantly below 1.0 (OR = 0.72, 95% CI = 0.39–1.32 with proxy responses; OR = 0.70, 95% CI = 0.35–1.40 without proxy responses).

In summary, none of these six studies from four independent settings reported a statistically significant association between glyphosate and MM or MGUS. Although some RRs above 2.0 were reported, these were statistically unstable and therefore also consistent with no association. As a whole, these studies do not establish a causal relationship, between glyphosate use and risk of MM or MGUS.

Conclusions

This review found that the paper by Schinasi and Leon (2014) identified all epidemiologic studies pertaining to glyphosate and NHL. The selection of results for meta-analysis by Schinasi and Leon (2014) included several seemingly inappropriate choices of results that produced a higher meta-RR than would have been obtained if more appropriate selections of more rigorously adjusted RR estimates had been made.

Schinasi and Leon did not include an assessment of study quality and did not weight or stratify the results of the studies included in the meta-analysis by quality. This is an important deficiency because there is evidence of variation in the potential for random and systematic error among the included studies.

Schinasi and Leon also did not carry out an evaluation of causality with respect to their findings for glyphosate and NHL. Results for glyphosate and NHL indicate an overall statistical association that is, at most, moderate in strength and is not observed consistently in all of the relevant studies. Furthermore, effects of bias and confounding on these results cannot be ruled out with confidence. Results for NHL do not display consistent evidence of exposure-response, and exposure-response data are not available for B-cell lymphoma. Moreover, biologic plausibility and coherence are lacking for an association between glyphosate and NHL or B-cell lymphoma. On balance, the epidemiologic data on glyphosate and NHL do not warrant a causal interpretation. There also is no convincing evidence that glyphosate is associated causally with leukemia, HL, MM or MGUS.

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Tables

Table 1. Data on glyphosate and NHL extracted from the main results tables of Schinasi and Leon (2014)			
Analysis and study reference	**N cases/controls exposed to glyphosate[a]**	**RR estimate**	**95% CI**
All NHL, ever vs. never exposed			
McDuffie et al. 2001	51/133	1.2	0.8-1.7
Hardell et al. 2002	8/8	3.0[b]	1.1-8.5
De Roos et al. 2003	36/61	2.1[c]	1.1-4.0
De Roos et al. 2005	71	1.1[c]	0.7-1.9
Eriksson et al. 2008	29/18	2.0[d]	1.1-3.7
Orsi et al. 2009	12/24	1.0	0.5-2.2
META-RR		**1.5**	**1.1-2.0**
All NHL, days exposed			
McDuffie et al. 2001 (days/year)			
Unexposed	466/1,373	1.0	(ref)
>0-=<2	28/97	1.0	0.6-1.6
>2	23/36	2.1	1.2-3.7
De Roos et al. 2005 (lifetime days)			
1-20 (tertile 1 among users)	29	1.0	(ref)
21-56 (tertile 2)	15	0.7[e]	0.4-1.4
57-2,678 (tertile 3)	17	0.9[e]	0.5-1.6
(intensity weighted lifetime days)			
0.1-79.5 (tertile 1 among users)	24	1.0	(ref)
79.6-337.1 (tertile 2)	15	0.6[e]	0.3-1.1
337.2-1,824 (tertile 3, upper half)	22	0.8[e]	0.5-1.4
Eriksson et al. 2008 (total days)			
>0-=<10	12/9	1.7	0.7-4.1
>10	17/9	2.4	1.0-5.4
B-cell lymphoma, ever vs. never exposed			
Eriksson et al. 2008	Not reported	1.9	1.0-3.5[f]
Cocco et al. 2013	4/2	3.1	0.6-17.1
META-RR		**2.0**	**1.1-3.6**
Diffuse large B-cell lymphoma, ever vs. never exposed			
Eriksson et al. 2008	Not reported	1.2	0.4-3.4

Table 1. Data on glyphosate and NHL extracted from the main results tables of Schinasi and Leon (2014)			
Analysis and study reference	**N cases/controls exposed to glyphosate[a]**	**RR estimate**	**95% CI**
Lymphocytic lymphoma/B-cell chronic lymphocytic leukemia, ever vs. never exposed			
Eriksson et al. 2008	Not reported	3.4	1.4-7.9
Follicular lymphoma, grades I-III, ever vs. never exposed			
Eriksson et al. 2008	Not reported	1.9	0.6-5.8
Other specified B-cell lymphoma, ever vs. never exposed			
Eriksson et al. 2008	Not reported	1.6	0.5-5.0
Unspecified B-cell lymphoma, ever vs. never exposed			
Eriksson et al. 2008	Not reported	1.5	0.3-6.6
T-cell lymphoma, ever vs. never exposed			
Eriksson et al. 2008	Not reported	2.3	0.5-10.4
Unspecified NHL, ever vs. never exposed			
Eriksson et al. 2008	Not reported	5.6	1.4-22.0

[a] Only the number of exposed cases is reported because De Roos et al. (2005) was a cohort study.
[b] Hardell et al. (2002) reported that the OR was 1.85 (95% CI = 0.55–6.20) for glyphosate and NHL, after adjustment for exposure to other pesticides including 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4,5-trichlorophenoxyacetic acid and/or 2,4-dichlorophenoxyacetic acid and other herbicides.
[c] RR estimate was adjusted for other pesticides.
[d] Eriksson et al. (2008) reported that the OR was 1.51 (95% CI = 0.77–2.94) for glyphosate and NHL, after adjustment for exposure to 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4,5-trichlorophenoxyacetic acid and/or 2,4-dichlorophenoxyacetic acid, mercurial seed dressing, arsenic, creosote and tar.
[e] Although these RRs were not adjusted for other pesticides, De Roos et al. (2005) indicated that such adjustment changed the rate ratios in their analysis by <20%.
[f] Eriksson et al. (2008) reported that the lower bound of the 95% CI was 0.998.

Table 2. Results of sensitivity analyses glyphosate and NHL extracted from the supplemental tables of Schinasi and Leon (2014)			
Sensitivity analysis	**Studies included[a]**	**Meta-RR**	**95% CI**
Restricted to male subjects	1, 2, 3	1.7	1.0-2.9
Restricted to case-control studies	1, 2, 3, 5, 6	1.6	1.1-2.2
Time period of NHL diagnosis			
1975-1989	2, 3	2.3	1.4-4.0
1990s	1, 2, 4, 5	1.5	1.0-2.1
2000s	4, 5, 6	1.3	0.9-2.0
Geographic location			
North America	1, 3, 4	1.3	1.0-1.8
United States	3, 4	1.5	0.8-2.8
Europe	2, 5, 6	1.7	1.0-3.1
Sweden	2, 5	2.2	1.3-3.8
Restricted to population-based case-control study design	1, 2, 3, 5	1.7	1.2-2.6
Included Cantor et al. 1992 instead of De Roos et al. 2003; United States studies	4, 7	1.3	1.0-1.7

[a] 1, McDuffie et al. 2001; 2, Hardell et al. 2002; 3, De Roos et al. 2003; 4, De Roos et al. 2005; 5, Eriksson et al. 2008; 6, Orsi et al. 2009; 7, Cantor et al. 1992.

Table 3. Results of alternative meta-analyses of data from six studies of glyphosate exposure and non-Hodgkin lymphoma

Study reference	Relative risk (RR) estimates selected for alternative meta-analysis and corresponding meta-RRs			
	Schinasi and Leon 2014	**More fully adjusted/alternative RRs from 4 studies[a]**	**More fully adjusted RRs from 3 studies[a]**	**More fully adjusted RRs from 2 studies[a]**
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
McDuffie et al. 2001	1.2 (0.8–1.7)	*0.92 (0.54–1.55)*[b]	1.2 (0.8–1.7)	1.2 (0.8–1.7)
Hardell et al. 2002	3.0 (1.1–8.5)	*1.85 (0.55–6.20)*	*1.85 (0.55–6.20)*	*1.85 (0.55–6.20)*
De Roos et al. 2003	2.1 (1.1–4.0)	*1.6 (0.9–2.8)*	*1.6 (0.9–2.8)*	2.1 (1.1–4.0)
De Roos et al. 2005	1.1 (0.7–1.9)	1.1 (0.7–1.9)	1.1 (0.7–1.9)	1.1 (0.7–1.9)
Eriksson et al. 2008	2.0 (1.1–3.7)	*1.51 (0.77–2.94)*	*1.51 (0.77–2.94)*	*1.51 (0.77–2.94)*
Orsi et al. 2009	1.0 (0.5–2.2)	1.0 (0.5–2.2)	1.0 (0.5–2.2)	1.0 (0.5–2.2)
Meta-RR	**1.5 (1.1–2.0)**	**1.2 (0.9–1.6)**	**1.3 (1.0–1.6)**	**1.3 (1.0–1.7)**

[a]More fully adjusted estimates used in each analysis are in italics.
[b]Alternative RR estimate is from Hohenadel et al. 2011.

Table 4. Reported participation and follow-up rates in studies included in the Schinasi and Leon (2014) meta-analyses of glyphosate and NHL or B-cell lymphoma			
Study	**Case Participation %**	**Control Participation %**	**Follow-Up %**
McDuffie et al. 2001	67%	48%	---
Hardell et al. 2002	91%	83%	---
De Roos et al. 2003	89% Iowa and Minnesota 91% Nebraska 99% Kansas	78% Iowa and Minnesota 85% Nebraska 94% Kansas	---
De Roos et al. 2005	84% of eligible applicators 44% supplemental applicator questionnaire		99%
Eriksson et al. 2008	91% 81% counting deceased/disabled	92% of initially enrolled	---
Orsi et al. 2009	96%	91%	---
Cocco et al. 2013	88%	81% hospital controls 52% population controls	---

Table 5. Methods for assessing pesticide exposure and percentage of proxy respondents among cases in studies included in the Schinasi and Leon (2014) meta-analyses of glyphosate and NHL or B-cell lymphoma		
Study	**Exposure assessment methods**	**% Proxy respondents (cases)**
McDuffie et al. 2001	Mailed questionnaire + telephone interview on detailed pesticide use	0%
Hardell et al. 2002	Mailed questionnaire + telephone follow-up for insufficient data	44%
De Roos et al. 2003	In-person or telephone interview	37%
De Roos et al. 2005	Written questionnaire	0%
Eriksson et al. 2008	Mailed questionnaire + telephone follow-up for insufficient data	0%
Orsi et al. 2009	Written questionnaire + in-person interview on detailed pesticide use + telephone follow-up for insufficient pesticide data	0%
Cocco et al. 2013	In-person interview	0%

Table 6. Potential confounders considered in studies included in the Schinasi and Leon (2014) meta-analyses of glyphosate and NHL or B-cell lymphoma	
Study	**Confounders considered[a]**
McDuffie et al. 2001	Age, province of residence, statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, first-degree family history of cancer)
Hardell et al. 2002	Age, county, study, vital status, 2-methyl-4-chlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and/or 2,4-dichlorophenoxyacetic acid, other herbicides [b]
De Roos et al. 2003	Age, study site, 46 other pesticides, first-degree family history of hematopoietic cancer, education, smoking
De Roos et al. 2005	Age at enrollment, education, smoking, alcohol consumption, first-degree family history of cancer, state of residence, 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, trifluralin, benomyl, maneb, paraquat, carbaryl, diazinon
Eriksson et al. 2008	Age, sex, year of diagnosis (cases) or enrollment (controls), 2-methyl-4-chlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and/or 2,4-dichlorophenoxyacetic acid, mercurial seed dressing, arsenic, creosote, tar [b]
Orsi et al. 2009	Age, study center, white collar/blue collar occupation
Cocco et al. 2013	Age, sex, education, study center

[a] Confounders considered are those included as covariates in multivariable models or evaluated for inclusion but excluded due to a lack of evidence for confounding.
[b] Although Hardell et al. (2002) and Eriksson et al. (2008) reported odds ratios for glyphosate and NHL that were adjusted for the other pesticides, Schinasi and Leon (2014) selected for inclusion in their meta-analysis only the odds ratios that were not adjusted for other pesticides.