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Critical Reviews in Toxicology

ISSN: 1040-8444 (Print) 1547-6898 (Online) Journal homepage: http://www.tandfonline.com/loi/itxc20

Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

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To cite this article: John Acquavella, David Garabrant, Gary Marsh, Tom Sorahan & Douglas L. Weed (2016) Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma, Critical Reviews in Toxicology, 46:sup1, 28-43, DOI: 10.1080/10408444.2016.1214681

To link to this article: http://dx.doi.org/10.1080/10408444.2016.1214681

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CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 28–43
http://dx.doi.org/10.1080/10408444.2016.1214681

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REVIEW ARTICLE

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Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

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ABSTRACT
We conducted a systematic review of the epidemiologic literature for glyphosate focusing on non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) – two cancers that were the focus of a recent review by an International Agency for Research on Cancer Working Group. Our approach was consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. We evaluated each relevant study according to a priori criteria for study quality: adequacy of study size, likelihood of confounding, potential for other biases and adequacy of the statistical analyses. Our evaluation included seven unique studies for NHL and four for MM, all but one of which were case control studies for each cancer. For NHL, the case-control studies were all limited by the potential for recall bias and the lack of adequate multivariate adjustment for multiple pesticide and other farming exposures. Only the Agricultural Health (cohort) Study met our a priori quality standards and this study found no evidence of an association between glyphosate and NHL. For MM, the case control studies shared the same limitations as noted for the NHL case-control studies and, in aggregate, the data were too sparse to enable an informed causal judgment. Overall, our review did not find support in the epidemiologic literature for a causal association between glyphosate and NHL or MM.

ARTICLE HISTORY
Received 8 April 2016
Revised 25 May 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; non-Hodgkin's lymphoma; multiple myeloma; systematic reviews

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Introduction

The epidemiologic literature for glyphosate was reviewed recently as part of a multi-disciplinary scientific review by the International Agency for Research on Cancer (IARC 2015). In the aftermath of the IARC review and the designation of glyphosate as probably carcinogenic to humans, the Monsanto Company requested expert reviews of the glyphosate literature in several technical areas, including epidemiology. IARC's working group concluded that there was limited epidemiologic evidence[1] in human studies for the carcinogenicity of glyphosate, based on a positive association observed for non-Hodgkin's lymphoma (NHL). The panel also noted that excesses had been observed for multiple myeloma (MM) in three studies, but felt these results were less reliable because of small numbers of cases in the available studies and the

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Table 1. Relevant studies for glyphosate review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

Author, year	Study location(s)	Study design	More recent analysis	Outcome
Cantor et al. 1992	Iowa þ Minnesota	Case-control	De Roos et al. 2003	NHL
Nordstrom et al. 1998	Sweden	Case-control	Hardell et al. 2002	HCL
Hardell & Eriksson 1999	Sweden	Case-Control	Hardell et al. 2002	NHL excluding HCL
McDuffie et al. 2001	Canada	Case-control	n/a	NHL
Hardell et al. 2002	Sweden	Case-control (pooled)	n/a	NHL þ HCL
De Roos et al. 2003	Nebraska Iowa/Minnesota Kansas	Case-control (pooled)	n/a	NHL
De Roos et al. 2005	Iowa, North Carolina	Cohort	n/a	NHL, MM
Eriksson et al. 2008	Sweden	Case-control	n/a	NHL
Orsi et al. 2009	France	Case-control	n/a	NHL, MM
Hohenadel et al. 2011	Canada	Case-control	Extension of McDuffie et al. 2001	NHL
Cocco et al. 2013	Czech Republic, France, Germany, Ireland, Italy, Spain	Case-control	n/a	B-cell lymphoma
Brown et al. 1993	Iowa	Case-control	n/a	MM
Landgren et al. 2009	Iowa North Carolina Minnesota	Prevalence Case-control	n/a	MGUS
Pahwa et al. 2012	Canada	Case-control	Kachuri et al. 2013	MM
Kachuri et al. 2013	Canada	Case-control	n/a	MM
Sorahan 2015	Iowa, North Carolina	Cohort	Reanalysis of De Roos et al. 2005	MM

HCL: hairy cell leukemia; MGUS: monoclonal gammopathy of undetermined significance.

related inability to adjust findings for other pesticide and farming exposures. Lastly, the panel concluded that there was no epidemiologic evidence of a relationship for other cancer sites with respect to glyphosate exposure.

In this epidemiology expert panel review, we focused on the possible relationship between glyphosate exposure and two cancers that were the focus of the IARC epidemiology review: NHL and MM. The focus of our review was qualitative. That is, we evaluated the published evidence according to widely accepted validity considerations and criteria for causality. When there were two or more publications with overlapping populations, we concentrated on the most recent publication noting the relationship to a previous publication(s) (see Table 1). Herein, in succeeding sections, we have presented our evaluation approach, reviewed the key validity issues for epidemiologic studies of pesticides, detailed some statistical considerations pertinent to the glyphosate literature, critically evaluated published studies, and, lastly, provided an overall weight of evidence assessment of the epidemiologic evidence for causality between glyphosate and NHL or MM.

Methods

The approach we took was informed by and consistent with the PRISMA guidelines for systematic reviews (Moher et al. 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau & Seage 2003a,b; Sanderson et al. 2007) and well-recognized interpretative methods – e.g. the criteria-based methods of causal inference (Hill 1965, 1971) – sometimes referred to as "weight of evidence" methods (Weed 2005). With this approach in mind, we address the following questions:

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

Other types of scientific evidence are often evaluated when making causal determinations, including data on human exposure as well as animal studies and studies on mechanism. Since exposure assessment is critical for the validity of occupational epidemiologic studies and biologic plausibility is informed by presumed dose, the former were considered in our overall assessments.

Literature search and included/excluded published papers

A systematic search of the medical literature was performed to identify all analytic epidemiological studies that have examined the possible relationships between exposure to glyphosate and NHL and MM. The aim was to include all such publications – case control studies, cohort studies and pooled analyses – published to the present. In this process, other publications are typically identified, such as reviews, commentaries, methodological investigations, letters to the editor and case reports (or case series). Our primary concern here, however, was the evaluation of the published analytical epidemiological studies of glyphosate and either NHL or MM. To the extent that other types of publications inform our assessment, those papers will be cited in this report. The so-called "gray literature[2]" was not reviewed.

Medline (PubMed) and TOXLINE were searched for English-language publications (with no time constraints) as follows:

a. PubMed: (2 August 2015): search terms: "glyphosate" and "cancer" (n ¼ 31);
b. TOXLINE: (2 August 2015): search terms: "glyphosate" and "cancer" (n ¼ 48);
c. PubMed: (13 August 2015): search terms: "herbicide" and "cancer" and "lymphoma" and "epidemiology" (n ¼ 153);
d. PubMed: (24 August 2015): search: "herbicide" and "cancer" and "multiple myeloma" and "epidemiology" (n ¼ 38);

Table 2. Results for glyphosate: Non-Hodgkin's lymphoma (NHL).

Author, year (study design)	# cases, controls total or exposed	OR/RR (95% CI)	Multivariate adjustments	Outcome
McDuffie et al. 2001	517, 1506 [total]			NHL
(case-control)	51, 133	Any use OR¼1.2 (95% CI 0.8, 1.7)	Age, province, medical conditions	
	28, 97	┐2 days/year OR¼1.0 (95% CI 0.6, 1.6)	Age, province	
	23, 36	>2 days/year OR¼2.1 (95% CI 1.3, 2.7)		
Hardell et al. 2002	515, 1141 [total]			NHL þ HCL
(case-control)	8, 8	Any use OR¼3.0 (95% CI 1.1, 8.5)	None	
	8, 8	Any use OR¼1.9 (95% CI 0.6, 6.2)	Multivariate (unspecified)	
De Roos et al. 2003	650, 1933 [total]			NHL
(case-control)	36, 61	Any use OR¼2.1 (95% CI 1.1, 4.0)	Age, other pesticides, study site	
	36, 61	Any use OR¼1.6 (95% CI 0.9, 2.8)	Age, other pesticides, study site, priors for chemical class and probability of being carcinogenic [hierarchical model]	
De Roos et al. 2005	71 exposed cases	Any use RR¼1.1 (95% CI 0.7, 1.9)	Age, education, smoking, alcohol, family history, state, 10 pesticides	NHL
(cohort, n¼57 311)	21 unexposed cases			
	29 cases	1–20 days RR¼1.0 (referent)	same	
	15 cases	21–56 days RR¼0.7 (95% CI 0.4, 1.4)		
	17 cases	57–2678 days RR¼0.9 (95% CI 0.5, 1.6)		
Eriksson et al. 2008	910, 1016 [total]			NHL
(case-control)	29, 18	Any use OR¼2.0 (95% CI 1.1, 3.7)	Age, sex, year of diagnosis or enrollment	
	17, 9	>10 days OR¼2.4 (95% CI 1.0, 5.4)	Same	
Orsi et al. 2009	244, 436 total			NHL
(case-control)	12, 24	Any use OR¼1.0 (95% CI 0.5, 2.2)	Age, center, socioeconomic category	
Cocco et al. 2013	2348, 2462 [total]			B-cell lymphoma
(case-control)	4, 2	Any use OR¼3.1 (95% CI 0.6, 17.1)	Age, sex, education, study center	

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio; RR: relative risk.

After removal of duplicates and examining the titles and abstracts, 11 publications were identified as relevant. Reasons for exclusions include: not analytical epidemiology, glyphosate not examined, and NHL and/or MM not examined.

An additional seven relevant analytic epidemiological studies were identified after examining reference lists from the publications above, the IARC Monograph 112 (2015) wherein glyphosate and cancer were evaluated, as well as personal collections of relevant papers by the expert panel. Upon further review, two of these references were excluded: Lee et al. (2005) because it did not focus on NHL or MM (only glioma) and the meta-analysis of Schinasi and Leon (2014) because our focus was on the primary literature. A meta-analysis by Chang and Delzell (2016) that was pending publication at the time of our review would have been excluded for the same reason.

The 16 relevant analytical epidemiological studies are listed in Table 1. Data collected from each study included the following: first author, year of publication, study design, number of cases and controls (for case-control studies), number of participants in cohort studies, results (typically in terms of an estimate of the relative risk [RR], e.g. an odds ratio [OR] with accompanying 95% confidence interval [95% CI]), exposure–response (if available), variables adjusted for in the analyses, and outcome (e.g. NHL, MM). See Tables 2 and 3 for details.

Each study was evaluated by the panel for the following key features that relate to study validity: recall bias (likely/unlikely[3]), exposure misclassification (likely/unlikely), exposure–response analyses with a trend test (yes/no), selection bias (likely/unlikely), adjustment for confounding by other (non-glyphosate) pesticides (yes/no), adjustment for confounding from other variables (yes/no), pathological review of cases (yes/no), proxy respondents (%cases/%controls), bias from sparse data (possible/no), blinding of interviews (yes/no/unclear) and consideration of induction/latency (yes/no). See Table 4 for details.

Validity considerations

Selection bias and recall bias

With the exception of one notable cohort study (De Roos et al. 2005), epidemiologists have employed the case control design to investigate glyphosate. Case control and cohort studies are related designs. Both study designs, if conducted with high quality, can produce valid results. In fact, the case control design is best thought of as including the cases that would have been detected in a hypothetical cohort study

Table 3. Results for glyphosate: multiple myeloma (MM).

Author, year (study design)	# cases, controls Total or exposed	OR/RR (95% CI)	Multivariate adjustments	Outcome
Brown et al. 1993	173, 650 [total]			
(case-control)	11, 40	Any use OR¼1.7 (95% CI 0.8, 3.6)	Age, vital status	MM
De Roos et al. 2005	24 exposed cases	Any use RR¼1.1 (95% CI 0.5, 2.4)	Age	MM
(cohort, n¼57 311)	Eight unexposed cases			
	Not specified	Any use RR¼2.6 (95% CI 0.7, 9.4)	Age, education, smoking, alcohol, family history, state, 10 pesticides	
	Eight exposed cases	1–20 days RR¼1.0 (referent)	Age, education, smoking, alcohol, family history, state, 10 pesticides	
	Five exposed cases	21–56 days RR¼1.1 (95% CI 0.4, 3.5)		
	Six exposed cases	57–2678 days RR¼1.9 (95% CI 0.6, 6.3)		
Orsi et al. 2009	56, 313 [total]			MM
(case-control)	5, 18	Any use OR¼2.4 (95% CI 0.8, 7.3)	Age, center, socioeconomic category	
Kachuri et al. 2013	342, 1357 [total]			MM
(case-control)	23, 108	Any use OR¼1.1 (95% CI 0.7, 1.9)	Age, province, smoking, selected medical conditions, family history of cancer	
			Same	
	11, 78	┐2 days/year OR¼0.7 (95% CI 0.4, 1.4)		
	10, 26	>2 days/year OR¼2.1 (95% CI 0.95, 4.7)		
Sorahan 2015	24 exposed cases	Any use RR¼1.1 (95% CI 0.5, 2.5)	Age	MM
	Eight unexposed cases			
Reanalysis of De Roos et al. 2005				
	24 exposed cases	Any use RR¼1.2 (95% CI 0.5, 2.9)	Age, sex, education, smoking, alcohol, family history of cancer, education, 10 pesticides	
	Eight unexposed cases			
	Eight cases	Never used RR¼1.0 (referent)	Age, sex, education, smoking, alcohol, family history of cancer, education, 10 pesticides	
	10 exposed cases	1–20 days RR¼1.1 (95% CI 0.4, 3.0)		
	Eight exposed cases	21–57 days RR¼1.5 (95% CI 0.5, 4.3)		
	Six exposed cases	57–2678 days RR¼1.4 (95% CI 0.4, 4.5)		

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio; RR: relative risk.

1. Reanalysis of De Roos et al. to assess the exclusion of 14 000 with some missing covariate data as the explanation for the difference in RRs adjusted for age (RR¼1.1) versus adjusted for age, education, smoking alcohol, family history, state and 10 pesticides (OR¼2.6).

along with a sample of the source population (Rothman et al. 2008). The purpose of the control group is to determine the relative size of the exposed and unexposed populations that gave rise to the cases, so as to enable valid risk estimates for exposed versus unexposed populations. At times in case control studies, the control population is selected for convenience or practicality in a way that does not allow determining the relative size of the exposed and unexposed populations. For example, hospital controls may be less likely to have strenuous occupations than the general population; hence farmers and/or others with pesticide exposures might be under-represented among hospital controls. Poor or selective participation by potential controls can produce the same result. Both scenarios are examples of selection bias that would almost certainly generate spurious positive associations between farming exposures and cancers.

A particularly important and well-known potential bias in case control studies of pesticides is recall bias. That is, cases tend to be more likely to remember or report exposures than are study participants who have not been diagnosed with cancer. This bias results from the natural self-examination by cases of what might have caused their grievous illness. Recall bias is not a concern in the sole glyphosate cohort study (De Roos et al. 2005) because exposure was determined from study participants at study entry before follow-up began for health outcomes. Recall bias tends to produce spurious positive associations between exposure and disease.

Concern about recall bias also extends to next-of-kin who participate in epidemiologic studies in place of deceased or disabled family members. Analyses of next-of-kin or proxy respondents have been found to produce results similar to those of first-hand study subjects (e.g. Kachuri et al. 2013) or to show results quite different than those based on first-hand responders (e.g. Lee et al. 2005 – ORs for glyphosate and glioma were 0.4 based on primary respondents and 3.1 for proxy respondents); one never knows the impact of having appreciable numbers of next-of-kin respondents without a thorough analysis of data with/without proxy respondents (Johnson et al. 1993). This concern is noteworthy because the case-control studies for glyphosate frequently have a high proportion of next-of-kin participants and many studies did not evaluate the potential bias from next-of-kin responders.

Table 4. Validity considerations for glyphosate studies.

First author, year	Recall bias	Exposure misclassification	Exposure–response and trend test	Selection bias	Adjusted for confounding from other pesticides yes/no	Adjusted for confounding from other variables yes/no	Pathology review of cases	Proxies %cases/%controls	Bias from sparse data	Blinding of interviews	Consideration of latency
Brown et al. 1993	Likely	Moderate ever/never	No	Unlikely	No	Yes	Yes	42% for cases; 30% for controls	No	Unclear	No
McDuffie et al. 2001	Likely	Moderate ever/never; appreciable days of use	Yes, no trend test	Likely	No	Yes and no	Yes	21% cases; 15% controls	No	Unclear	No
Hardell et al. 2002	Likely	Moderate ever/never; appreciable in days of use analysis	No	Unlikely	Yes, but variables not specified	Unclear	Yes for NHL, unclear for HCL	43% NHL cases and controls, 0% for HCL	Possible	Yes	No
De Roos et al. 2003	Likely in original publications	Moderate ever/never	No	Likely, in original publications	Yes	Yes	Yes	31% for cases; 40% for controls	No	Yes	No
De Roos et al. 2005	No	Moderate ever/never; appreciable in days of use analysis	Yes, yes	Unlikely	Yes	Yes	Yes	No	Possible in some analyses	N/A	No
Eriksson et al. 2008	Likely	Moderate ever/never	Yes, no trend test	Unlikely	Yes	Age, sex, year of diagnosis	Yes	No	Possible in some analyses	Yes	Yes
Orsi et al. 2009	Likely	Moderate ever/never	No	Likely	No	Yes	Yes	No	Possible	Yes	No
Cocco et al. 2013	Likely	Likely	No	Likely	No	No	20%	No	Possible	Unclear	No
Kachuri et al. 2013	Likely	Moderate ever/never; appreciable in days of use analysis	Yes, no trend test	Likely	No	Yes	Yes	Excluded	No	Unclear	No

NHL: non-Hodgkin's lymphoma.

Exposure assessment and misclassification

With few exceptions, epidemiologic studies of pesticides assess exposure by questioning participants or their next-of-kin about the prior use of specific pesticides and associated work practices. This practice has limitations compared with other branches of occupational research where epidemiologists often have access to objective documentation about past industrial workplace conditions to aid in exposure assessment (e.g. engineering diagrams, process descriptions, job descriptions, area or personal exposure-monitoring data).

A number of publications provide insights about the validity or reliability of self-reported pesticide information used in epidemiologic studies. In one study, approximately 60% of farmers' self-reports agreed with suppliers' records of purchases for specific pesticides (Hoar et al. 1986). In another article, researchers evaluated the repeatability of self-reported pesticide information on enrollment questionnaires for 4188 licensed pesticide applicators, primarily farmers, who filled out questionnaires in successive years (Blair et al. 2002). The year-to-year reliability for reporting any lifetime use of 11 widely used pesticides varied from 79 to 87%; categorical agreement varied from 50 to 59% for typical days of use per year and from 50 to 77% for years of use. Based on this literature, it is apparent that perhaps 10–20% or more of participants in epidemiologic studies may report incorrectly that they have used a specific pesticide and that reporting on frequency of use and years of use is even less certain.

There seems to be considerable under-appreciation of the implications of the acknowledged degree of exposure misclassification in the pesticide literature. Many consider exposure misclassification to almost always be non-differential (e.g. similar for cases and controls) and, therefore, to bias analyses toward the null (or no association between an exposure and a disease). However, even assuming the misclassification is non-differential overall over multiple analyses, the direction of the resulting bias can be uncertain for any specific analysis. As Rothman and Greenland (1998) pointed out, in any given study, random fluctuations can lead to bias away from the null (towards a positive or negative association) even if the classification method satisfies all the conditions for being non-differential (viz. on average). Hence, in the studies considered in this review, with hundreds of comparisons per study, some fraction of results likely will be biased away from the null even if misclassification is non-differential.

Finally, unlike the five days per week, 50 weeks per year routine for exposures in industrial settings, glyphosate and other pesticide applications are not a frequent occurrence for farmers and applicators. In fact, for most, application of a specific pesticide, like glyphosate, is seasonal and happens only a few days per year. The high exposure category in the glyphosate literature is usually two or more days per year – reflecting extremely infrequent use for the great majority of study subjects and, annually, long periods without exposure. This implies that pesticide exposures are much less frequent than other occupational exposures for those who use pesticides in their occupations and that these other, daily exposures need to be addressed comprehensively in any analysis of infrequently used pesticides.

Biomonitoring studies, implications for exposure assessment

Epidemiologists recognize that there is a difference between exposure (viz. reported use) and dose (the quantity of a substance that is absorbed). In fact, dose is of more interest than exposure in studying potential causal associations. For some chemicals, exposure and dose correlate well. For other chemicals, the correlation is low. Understanding the correlation between exposure and dose is essential for exposure–response analyses – an important indicator for a causal relationship.

The properties of a chemical affect dose. Glyphosate is usually formulated as the isopropylamine salt, which has an extremely low vapor pressure of 1.6×10^{-8} mm Hg (Tomlin 2003). Inhalation of spray droplets was found to be a minor route of glyphosate exposure in a study of glyphosate applicators in Finland (Jauhiainen et al. 1991), leaving dermal contact as the primary route of exposure. Dermal penetration experiments, where glyphosate was left undisturbed on skin surfaces of experimental animals and on human skin in vitro, indicate a percutaneous absorption of less than 2% (Wester et al. 1991).

Biomonitoring studies show results consistent with glyphosate's physical/chemical properties. In a study of 48 farmers in Minnesota and South Carolina during a normal day of glyphosate application on their farms, 60% of applicators were found to have quantifiable glyphosate in urine (the predominant route of excretion), while 40% of farmers did not (Acquavella et al. 2004). The distribution of urinary concentrations was highly skewed, with only a small percentage of values appreciably different than the one part per billion limit of detection. Nine farmers completed applications in excess of 100 acres and did not have detectable values for glyphosate in their urine. Evaluation of different approaches to exposure assessment used in epidemiologic studies has not shown good correlation with biomonitoring data for glyphosate (Acquavella et al. 2006), implying appreciable misclassification in studies that rely on traditional pesticide exposure assessment approaches.

The maximum systemic dose found in a review of all glyphosate biomonitoring studies completed to date is 0.004 mg/kg (Niemann et al. 2015). For comparison, the US Environmental Protection Agency (US EPA)'s reference dose (viz. the daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime) is 500-fold higher at 2 mg/kg/day (US EPA 1993). The geometric mean systemic glyphosate dose for applicators is 0.0001 mg/kg/day.

Statistical considerations

In addition to the potential study biases discussed above, other threats to validity arise from the statistical procedures used (or not used) in the epidemiology studies reviewed for glyphosate. First, glyphosate risk estimates in several studies were based on small numbers of events in the exposure subcategories considered. For example, the case-control studies of NHL reported by Hardell et al. (2002), Cocco et al. (2013), and Eriksson et al. (2008) and of MM reported by Orsi et al. (2009) involved less than 10 exposed cases and/or controls

overall or in specific glyphosate exposure categories. Even the large cohort study of 57 311 pesticide applicators conducted by De Roos et al. (2005) and reanalyzed by Sorahan (2015) included sparse data (viz., 10 or fewer glyphosate-exposed MM cases in each of the three exposure categories considered).

Sparse data not only leads to imprecise risk estimates, but can decrease their validity when analyses are limited to asymptotic procedures (Greenland et al. 2000; Hirji 2006). The phenomenon of a bias away from the null due to small samples or sparse data is termed sparse data bias. It can occur if case-control or cohort studies are analyzed by conventional asymptotic methods such as logistic regression or Poisson regression rather than their counterparts based on exact estimation. For example, in the presence of sparse data, the estimated OR derived from asymptotic conditional logistic regression is substantially overestimated if the true OR is greater than one (Breslow & Day 1980). Sparse data bias also affects estimated CIs and p values (Greenland et al. 2000; Subbiah & Srinivasan 2008). It appears that all studies involving sparse data relied upon asymptotic procedures only, and were thus likely subject to sparse data bias and inflated risk estimates.

As shown in Table 4, with few exceptions, the statistical models used to evaluate NHL or MM risks among pesticide-exposed individuals were deficient at many levels. As all studies were exploratory (viz. not testing a priori hypotheses regarding specific pesticide exposures and NHL or MM risk), they produced a large number of risk estimates along with a high probability of some estimates being statistically significant simply due to chance alone. No attempt was made in any of the studies to adjust p values for these multiple comparisons, though one case control study (De Roos et al. 2003) used a two stage hierarchical modeling approach to adjust risk estimates based on pesticide class characteristics and extant carcinogenic classification to minimize false positives. Also, as shown in Table 4, most studies did not adjust glyphosate risk estimates for potential confounding by other pesticide exposures or relevant medical variables, and only one (Eriksson et al. 2008) considered latency period or the time between first (or last) glyphosate exposure and health outcome. Moreover, only one study (Hohenadel et al. 2011), considered the possible interaction or effect modification between pairs of commonly used pesticides.

Even among the few studies that incorporated potential confounding or effect modifying factors, little if any information was provided about the statistical model selection (e.g. asymptotic or exact), model building strategy (e.g. criteria for including/excluding co-variables) or the diagnostic procedures used to evaluate the fit or robustness of intermediate and final models. Thus, in most studies, reported glyphosate risk estimates remained relatively crude (viz. not fully adjusted) and likely biased due to residual confounding, poor model fit and in some cases, sparse data.

NHL studies

Cantor et al. (1992) conducted a NHL case control study in Iowa and Minnesota to evaluate possible causal factors, including pesticides. The data from this study were pooled with two other US NHL case control studies and subsequently reported by De Roos et al. (2003). We defer consideration to that more recent analysis.

Nordstrom et al. (1998) conducted a population-based case control study in Sweden that included 121 cases of hairy cell leukemia (HCL) and 484 general population controls. The intent of the study was to evaluate occupational exposures and smoking as risk factors for HCL. The data from this study are included with data from the Hardell and Eriksson (1999) study in a later publication (Hardell et al. 2002). We defer consideration of both primary studies to that more recent analysis.

McDuffie et al. (2001) conducted a trans-Canada multi-center case control study to evaluate the relationship between pesticide exposures and NHL. Cases (n¼517) were identified from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. Controls (n¼1506) were selected at random from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario) or voters' lists (British Columbia). Participation was much higher among invited cases (67%) than among invited controls (48%). Pesticide exposure was determined through telephone interviews of study participants or their proxies (21% of cases, 15% of controls). The authors used conditional logistic regression to estimate ORs. The OR for any reported glyphosate use was 1.2 (95% CI 0.8–1.7) controlling for age, province and medical variables associated with NHL. The strongest pesticide associations were with mecoprop (OR¼2.3) and dicamba (OR¼1.9). A subsequent analysis by reported days of use per year (none, ┐2 days/year, >2 days/year) showed glyphosate ORs of 1.0, 1.0 (95% CI 0.6–1.6), and 2.1 (95% CI 1.3–2.7), respectively. This latter analysis did not adjust for medical variables that were controlled in the analysis of any glyphosate use or for the effects of other pesticides.

Assessment: The strengths of this study are the relatively large number of NHL cases and the likelihood that almost all cases were confirmed histologically. The limitations are likely residual confounding in the analysis by days of use by the uncontrolled effects of medical variables and other pesticides, selection bias (differential participation by cases and more proxies for cases), and possible recall bias.

Hardell et al. (2002) reported a pooled analysis of two case control studies; one of NHL and the other of HCL. Both of these studies were previously reported as separate case-control studies (Nordstrom et al. 1998; Hardell & Eriksson 1999). HCL is rare, comprising 2% of lymphoid leukemias, and typically affects middle aged to elderly men (Foucar et al. 2008). It is regarded as a mature B cell neoplasm, as are a high proportion of NHLs. It appears that the authors pooled the two separate studies principally to achieve a larger study size under the assumption that the two neoplasms could be treated as a homogeneous entity for etiologic research. However, the pooled analysis is thereby heavily weighted by HCL cases and the results not representative of NHL more broadly. The 404 NHL cases were males aged 25 and older, diagnosed in 1987–1990, and living in mid- and northern Sweden, drawn from regional cancer registries (viz.

histologically verified). Each case was matched on age and sex to two controls drawn from the National Population Registry. The 111 HCL cases were males diagnosed in 1987–1990, identified from the Swedish Cancer Registry covering the whole country. Each HCL case was matched on age, sex and county to four controls drawn from the National Population Registry. A total of 515 cases and 1141 controls were included in pooled analyses of NHL and HCL. A questionnaire was completed by study subjects or next-of-kin regarding complete working history and exposure to various chemicals. Exposure to each chemical was dichotomized, with at least one working day a year before diagnosis being regarded as positive for exposure. Conditional logistic regression was used to estimate ORs and 95% CIs, adjusted for study (NHL versus HCL), study area, and vital status. In the analyses, only subjects with no pesticide exposure were regarded as unexposed[4], whereas subjects who had not used glyphosate but had used other pesticides were excluded. Analysis for glyphosate, unadjusted for other pesticides, showed a positive association (OR¼3.0, 95% CI 1.1–8.5) based on eight exposed cases and eight exposed controls. Although multivariate analyses were done, it was not stated how variables were selected for inclusion or which variables were included in the multivariate models. The multivariate model for glyphosate indicated appreciable confounding in the unadjusted analysis and a reduced, statistically imprecise, positive association for glyphosate (OR¼1.9, 95% CI 0.6–6.2). Analyses based on increasing days of use were presented for some pesticides, but not for glyphosate.

Assessment: The strengths of this study were that cases were histologically confirmed and controls were population-based. The limitations of this publication were many. First, the investigators found a positive association for every class of pesticide and for every individual pesticide, suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject (inadvertent) unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and precluded being able to control for possible confounding by other pesticides and farming exposures. Third, there seems to be some inconsistency in exposure assessment between the two studies that were pooled in this publication. The prevalence of exposure to glyphosate was three times higher among HCL cases and controls (1.3%) than it was among NHL study subjects (0.4%), even though both studies were contemporaneous and would be expected to have similar exposure prevalences.

De Roos et al. (2003) reported a pooled analysis of three NHL case-control studies of pesticides and other potential causal factors (Hoar et al. 1986; Zahm et al. 1990; Cantor et al. 1992). This analysis was limited to men and excluded cases and controls with a history of living or working on a farm before (but not after) age 18. Cases from the Nebraska study by Zahm et al. (1990) were diagnosed between July 1983 and June 1986 and were identified using the Nebraska Lymphoma Study Group as well as data from area hospitals. Cases from the Kansas study by Hoar et al. (1986) represented a random sample of cases diagnosed between 1979 and 1981 and selected from the Kansas Cancer Data Service. Cases from the study in Iowa and Minnesota by Cantor et al. (1992) were diagnosed between 1981 and 1983 and were identified from the Iowa State Health Registry along with a surveillance system established in Minnesota. Controls for these studies were randomly selected from population databases (e.g. Medicare, random digit dialing, and state mortality files for deceased cases) and frequency matched to cases on race, sex, age and vital status at time of interview. Cases and controls were interviewed (including next-of-kin when necessary) regarding use of pesticides and/or herbicides as well as other known or suspected risk factors for NHL. The final analysis dataset included 650 cases and 1933 controls, after exclusions of individuals for whom there was missing information. Forty-seven pesticides were included in the analysis after excluding pesticides for which there were not at least 20 persons exposed and data available from all three studies. The exposure metric in the analysis was restricted to any reported use of a specific pesticide, with no consideration of extent of use. Two types of statistical models were used to estimate ORs and 95% CIs: (1) standard logistic regression and (2) hierarchical regression, wherein logistic regression estimates were adjusted in a second stage based on expected similarities of effects within pesticide classes and the presumed a priori carcinogenic probability for specific pesticides as determined by external review bodies. For pesticides like glyphosate that were presumed to have a low probability of being carcinogenic, this second stage adjustment tended to draw positive associations toward the null. All analyses were adjusted for age and for the use of 46 other pesticides. Results for glyphosate showed an OR of 2.1 (95% CI: 1.1–4.0) in the logistic regression and a lesser association (OR¼1.6, 95% CI: 0.9–2.8) in the hierarchical regression.

Assessment: The strengths of this analysis were the histological confirmation of NHL cases and the large numbers of cases and controls that enabled simultaneous adjustment of the effects of 47 pesticides. The weaknesses of this study were the reliance on a relatively crude indicator of exposure (ever having used a pesticide with no consideration of the extent of use) and the limitations common to case control studies of pesticides – namely recall bias and, in this case, an appreciably higher proportion of proxy respondents for controls than cases (40% versus 31%).

De Roos et al. (2005) reported glyphosate findings from the Agricultural Health Study (AHS), a large prospective cohort study of health outcomes related to numerous pesticides among more than 53 000 licensed pesticide applicators in North Carolina and Iowa. Analyses for glyphosate considered potential exposure in a number of ways including: ever/never use, estimated cumulative exposure days (CED), and estimated intensity-weighted exposure days (IWED). The statistical approach was Poisson regression and effects were estimated as RRs with 95% CIs. After adjusting for age, findings for ever/never use of glyphosate showed a near null RR of 1.2 for NHL (95% CI 0.7–1.9), based on 92 cases. Further adjustment for education level, pack-years of smoking, alcohol use in last 12 months, family history of cancer, state of residence and 10 other pesticides that were correlated with glyphosate use, and excluding applicators who had missing data for any of these variables, had little effect on findings for NHL (RR 1.1 95% CI 0.7–1.9). Analyses of potential exposure–response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and

excluding the never-users from the analysis, found a slight non-significant negative trend (1–20 days: RR 1.0; 21–56 days: RR 0.7, 95% CI 0.4–1.4; 57–2678 days: RR 0.9, 95% CI 0.5–1.6). These categorical analyses were repeated for IWEDs and findings were little changed. De Roos et al. (2005) qualified their results as being based on small numbers, but concluded: "… the available data provided evidence of no association between glyphosate exposure and NHL incidence."

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the relatively short duration of follow-up for AHS cohort members, the relatively small number of NHL cases, and the likelihood of some degree of exposure misclassification in the various analyses.

Eriksson et al. (2008) reported a population based case control study of NHL in males and females aged 18–74 living in Sweden in 1999–2002. Cases were identified through physicians who diagnosed and treated NHL, and all cases were histologically verified. Controls were randomly chosen from population registries in the same health service regions as the cases, and were frequency matched in 10-year age and sex groups. A total of 910 NHL cases and 1016 controls were included in the analyses. The authors emphasized that, in contrast to their previous studies (Hardell et al. 1981; Hardell & Eriksson 1999), the analyses evaluated newer types of pesticides in relation to different histopathological subtypes of NHL. All subjects received a mailed questionnaire focusing on total work history and exposure to pesticides, solvents and other chemicals. For all pesticides, the number of years, number of days per year and length of exposure per day were questioned. Exposure to each chemical was dichotomized, with at least one working day at least a year before diagnosis being regarded as positive. In the analyses, only subjects with no pesticide exposure were regarded as unexposed[5], whereas subjects with other pesticide exposures were excluded. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, sex, and year of diagnosis. Analyses for individual herbicides showed positive associations for every agent and ORs were elevated for every other pesticide (although not in every analysis by NHL subtype or category of duration of exposure). In the model for glyphosate and all NHL (not adjusted for other exposures), the OR was 2.0, 95% CI 1.1–3.7 for ever/never exposure, based on 29 exposed cases and 18 exposed controls. Exposure to glyphosate for >10 days showed OR¼2.4, 95% CI 1.0–5.4 (not adjusted for other exposures). Analyses of glyphosate exposure and NHL subtypes (not adjusted for other exposures) were positive for every subtype of NHL, and were statistically significant for lymphocytic lymphoma/B-CLL (OR¼3.4, 95% CI 1.4–7.9) and unspecified NHL (OR¼5.6, 95% CI 1.4–22.0). Results for other NHL subtypes were not statistically significant: all B-cell NHL (OR¼1.9, 95% CI 0.998–3.5); follicular NHL (OR¼1.9, 95% CI 0.6–5.8); DLBCL (OR¼1.2, 95% CI 0.4–3.4); other B-cell NHL (OR¼1.6, 95% CI 0.5–5.0); unspecified B-cell NHL (OR¼1.5, 95% CI 0.3–6.6) and T-cell NHL (OR¼2.3, 95% CI 0.5–10.4). Multivariate analysis of glyphosate exposure was stated to include agents with statistically significant increased ORs or with an OR >1.5 and at least 10 exposed subjects. These models excluded subjects with exposure to pesticides that did not meet these conditions. The multivariate model for glyphosate and all NHL showed a non-significant positive association (OR¼1.5, 95% CI 0.8–2.9) for ever/never exposure, indicating substantial confounding in the analysis that were not adjusted for other pesticides.

Assessment: Strengths of the study include histological verification of cases and use of population-based controls. There were, however, a couple of major limitations. First, the investigators found a positive association for every herbicide and for every individual pesticide (although not in every sub-analysis), suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject [inadvertent] unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate for cases and controls and precluded being able to control for possible confounding by other pesticides and farming exposures.

Hohenadel et al. (2011) conducted a reanalysis of data included in the McDuffie publication to evaluate the relationship between exposure to specific pesticide combinations and NHL. The authors used unconditional logistic regression to estimate ORs for the total number of pesticides used by type and carcinogenic potential and for pairwise pesticide combinations (neither, either only or both). Where the OR for joint exposure was higher than the OR for exposure to either pesticide alone, interaction on the additive scale was evaluated using an interaction contrast ratio (ICR). Exposure to glyphosate alone yielded an estimated 8% deficit in NHL risk (OR¼0.92, 95% CI 0.5–1.6), whereas use of malathion only was associated with an elevated NHL risk (OR¼2.0, 95% CI 1.3–2.9). The OR of 2.1 (95% CI 1.3–3.4) for joint exposure to glyphosate and malathion was similar to that for malathion alone and there was no indication of a super additive joint effect (ICR <0.5).

Assessment: The strengths and limitations of this study are similar to those outlined for the related study by McDuffie et al. (2001). The re-analysis was more an exploratory assessment of joint exposures than it was a study of specific pesticides per se and is of limited relevance for a possible association between glyphosate and risk of NHL.

Orsi et al. (2009) reported a hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM) undertaken in France. Incident cases of NHL (n¼244) were identified from six French hospital center catchment areas between 2000 and 2004. A panel of pathologists and hematologists confirmed pathology. Controls (n¼436) were selected from the same hospitals as cases; controls had no history of lymphoid neoplasms and were primarily patients from rheumatology and orthopedic departments. Patients admitted for occupation-related diseases or diseases related to smoking and/or alcohol abuse were not eligible as controls although a past history of such diseases/conditions did not eliminate the control. Controls were matched to cases by center, age (±3 years) and gender. Information on cases and controls

involved a standardized self-administered questionnaire on socioeconomic status, family medical history, and lifelong residential and occupational histories. For additional information (on personal and family history), smoking, alcohol, tea and coffee consumption, use of pesticides (insecticides, fungicides, and herbicides) as well as detailed questions about work on farms, a trained interviewer performed a face-to-face interview with cases and controls. Two exposure definitions were used: definite or possible. Duration of exposure was estimated. ORs and 95% CIs were calculated using logistic regression. Results for any use of glyphosate and NHL showed no association (OR¼1.0, 95% CI: 0.5–2.2) based on 12 exposed cases and 24 exposed controls.

Assessment: A strength of this study is that the NHL cases were confirmed histologically. The limitations are no assessment of potential confounding due to the uncontrolled effects of other pesticides/exposures, possible recall bias and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be under-represented). Scanning the ensemble of hundreds of effect estimates shows that the vast majority of estimates (though not for glyphosate) were greater than one, suggesting systematic error across the various analyses.

Cocco et al. (2013) reported results from the EPILYMPH case control study of NHL in six European countries, conducted in 1998–2004. The study included 2348 incident lymphoma cases and 2462 controls. Approximately 20% of the cases had their tissue slides reviewed by a central panel of pathologists. Controls were population-based in Germany and Italy, matched on gender, age (within five years) and residence area. Hospital controls were used in the Czech Republic, France, Ireland and Spain, excluding patients with diagnoses of cancer, infectious disease, and immunodeficiency. The participation rate was 88% in cases, 81% in hospital controls, but only 52% in population controls in Germany and Italy (Cocco et al. 2010). Trained interviewers conducted in-person interviews with a structured questionnaire regarding full time jobs held for a year or longer. Industrial hygienists coded the occupations to the ISCO, International Labour Office (1968) and the NACE, Statistical Office of the European Communities (1996) classifications. Subjects who reported having worked in agriculture were given a job-specific module inquiring in detail about tasks, kinds of crops, size of cultivated area, pests being treated, pesticides used, procedures of crop treatment, use of personal protective equipment, reentry after application and frequency of treatment in days/year. Hygienists reviewed the job modules to assess exposure to pesticides in categories. Exposure was scored in terms of confidence (probability and proportion of workers exposed), intensity and frequency. A cumulative exposure score was calculated. Subjects unexposed to any pesticide[6] were the referent category for all analyses. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, gender, education and study center. The authors reported a moderate association between glyphosate (ever/never exposure) and B-cell NHL (OR¼3.1, 95% CI 0.6–17.1) in a univariate analysis that was statistically imprecise being based on only four exposed cases and two exposed controls. Clearly, there were too few exposed cases and controls to estimate an OR for glyphosate controlling for other exposures.

Assessment: Glyphosate exposure was so infrequent in this study that it precluded an informative analysis. Were that not the case, there would have been obvious concerns about selection bias (esp. low participation for controls), confounding by other exposures (esp. solvent exposures found to be associated with NHL is a previous analysis of this data (Cocco et al. 2010), and recall bias. In addition, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and would have precluded being able to control for possible confounding by other pesticides and farming exposures had such analyses been attempted.

MM studies

Brown et al. (1993) conducted a re-analysis of the National Cancer Institute Iowa population-based case-control study (Brown et al. 1990; Cantor et al. 1992) to evaluate the relationship between exposure to specific pesticides and MM. Cases (n¼173) were identified from the Iowa Health Registry. Controls (n¼650) were frequency matched to cases by age group and vital status at interview and selected from three sources: random digit dialing (living cases under age 65); Medicare records (living cases aged 65þ) and state death certificate files (for deceased cases). Participation was relatively high and similar among cases (84%) and controls (78%). Pesticide exposure for 34 crop insecticides, 38 herbicides (including glyphosate) and 16 fungicides was determined from in-person interviews with subjects or their proxies. The authors used unconditional logistic regression to estimate ORs for pesticides handled by at least five cases. Subjects who did not farm[7] were the referent exposure category for these analyses. The OR for mixing, handling or applying glyphosate was 1.7 (95% CI 0.8–3.6) adjusted for vital status and age. Failure to use protective equipment (obtained from interviews) did not appreciably increase the risk for glyphosate (OR¼1.9, 95% CI not reported). None of the pesticides considered showed a statistically significant association with MM risk.

Assessment: Strengths of the study were the histological confirmation of cases and the high and similar participation for cases and controls. Study limitations were its exploratory nature (as noted by the authors), lack of control for potential confounding by possibly relevant personal characteristics or by exposure to other pesticides, and possible recall bias. In addition, the definition of unexposed (viz. non-farmers) used in the analysis excluded 64% of cases and 58% of controls, distorted the exposure prevalence for glyphosate, and would have precluded being able to control for possible confounding by other pesticides and farming exposures had the investigators sought to control potential confounding.

De Roos et al. (2005), based on data from the AHS cohort study described previously, estimated the age-adjusted RR for glyphosate and MM to be 1.1 (95% CI 0.5–2.4), based on 32 cases. Further adjustment for education level, pack-years of smoking, alcohol use in the last 12 months, family history of cancer and state of residence, together with the use of 10 other pesticides that were correlated with glyphosate use, and excluding approximately 14 000 applicators and 13 MM cases with missing data for any of these variables, markedly

increased the RR for MM (RR¼2.6, 95% CI 0.7–9.4). Analyses of exposure–response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and excluding the never-users from the analysis, produced a non-significant positive trend (1–20 days: RR¼1.0; 21–56 days: RR¼1.1, 95% CI 0.4–3.5; 57–2678 days: RR¼1.9, 95% CI 0.6–6.3; p values for trend 0.27). This MM CED analysis was based on 19 (of 32) cases, the other 41% of cases being excluded for any missing covariate information. These analyses were repeated for IWED categories and findings were little changed (RRs 1.0, 1.2, and 2.1; p values for trend¼0.17). The authors also repeated the exposure–response analyses for MM, using the never-use group as the baseline category and found a monotonic positive trend (tertile 1: RR¼2.3; 95% CI 0.6–8.9; tertile 2: RR¼2.6; 95% CI, 0.6–11.5; tertile 3: RR¼4.4; 95% CI 1.0–20.2; p values for trend¼0.09). The authors noted that the marked difference between the age adjusted MM findings and the more fully adjusted findings (viz. RR¼1.1 versus 2.6) could have been due to selection bias related to the 14 000 AHS cohort members who were dropped from the more fully adjusted analysis due to missing values for one or more variables.

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the short duration of follow-up for AHS cohort members, the relatively small number of MM cases, the likelihood of some degree of exposure misclassification in the various analyses, and the indications of selection bias affecting RR estimates due to the exclusion of so many cohort members and MM cases from the more fully adjusted analyses (addressed in a subsequent publication by Sorahan 2015).

Orsi et al. (2009) reported a French hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM), described previously. Included were 56 incident cases of MM and 313 controls matched to cases by center, age (±3 years) and gender. ORs and 95% CIs were calculated using logistic regression. Results for glyphosate and MM showed a moderate, but statistically imprecise, association (OR¼2.4, 95% CI: 0.8–7.3) based on five exposed cases and 18 exposed controls.

Assessment: A strength of this study is that the MM cases were confirmed histologically. The limitations are likely residual confounding due to the uncontrolled effects of other pesticides/exposures in the assessment of the OR for glyphosate, possible recall bias, and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be under-represented). Scanning the ensemble of hundreds of ORs shows that the vast majority was greater than 1.0, suggesting systematic error across the various analyses.

Landgren et al. (2009) estimated the age-specific prevalence of monoclonal gammopathy of undetermined significance (MGUS) (a medical condition that is sometimes a precursor to multiple myeloma) among a stratified random sample of 678 AHS participants selected based on lifetime organophosphate use. Subjects in the sample had completed all three phases of the AHS questionnaires, were enrolled into a neurobehavioral study nested within the AHS cohort, and had provided serum for analysis. The authors compared MGUS prevalence for this sample to that for the general population of Olmsted County, Minnesota (due to availability of Mayo Clinic MGUS screening data) and found higher prevalence for AHS participants. Within the AHS sample, associations between MGUS prevalence and pesticide exposures and subject characteristics were assessed in logistic regression models adjusted for age and education level. The prevalence OR for MGUS for glyphosate users versus non-users, adjusted for age and education level, was 0.5 (95% CI 0.2–1.0). None of the herbicides studied showed a strong association with MGUS.

Assessment: This is a small exploratory study of pesticide effects on a medical condition that is sometimes a precursor to MM. Taken at face value, the results provide evidence of a weak inverse association between risk of MGUS and glyphosate, though the exploratory nature of this study, the lack of adjustment for other pesticides in pesticide-specific analyses, the cross-sectional nature of the study, and the implied speculative hypothesis underlying the analysis (that pesticides might cause MM by causing MGUS first) limit conclusions that can be drawn from this work.

Pahwa et al. (2012) reported a trans-Canada, multi-center case control study regarding the relationship between pesticide exposures and MM. The publication is related to the trans-Canada NHL study reported initially by McDuffie et al. (2001) wherein there was a common control group for the study of several lymphopoietic cancers. Pahwa et al. (2012) was updated by Kachuri et al. (2013) and we defer consideration to that more recent publication.

Kachuri et al. (2013) presented a reanalysis and extension of Pahwa et al. (2012) in which they excluded 149 (of 1506) controls who did not have an age match with the MM cases. Kachuri et al. utilized unconditional logistic regression to estimate ORs and presented analyses including and excluding proxy respondents (15% of controls and 30% of cases) and adjusting for smoking, which was associated with MM. They also presented analyses by days of use for individual pesticides. Approximately 9% of cases and controls reported use of glyphosate. ORs adjusted for smoking were 1.2 (95% CI 0.8–1.9) including all cases and controls and 1.1 (95% CI 0.7–1.9) excluding cases and controls who had proxy respondents. ORs excluding proxy respondents for one and two days/year of glyphosate use and for two or more days/year were 0.7 (95% CI 0.4–1.3) in the lower use category and 2.0 (95% CI 0.98–4.2) in the higher use category. However, these results for days of use per year were not adjusted for the potential confounding effects of other pesticides or farm exposures.

Assessment: The strengths of this study are the relatively large number of MM cases, the likelihood that almost all cases were confirmed histologically, and the explicit consideration of proxy respondents in the analysis. The limitations are likely residual confounding in the days of use per year analysis by the uncontrolled effects of other pesticides/exposures, selection bias (58% participation for cases and 48% participation for controls), and possible recall bias.

Sorahan (2015) conducted a re-analysis of data from the AHS to assess the basis for the disparate age-adjusted and

more fully adjusted glyphosate MM findings reported by De Roos et al. (2005). The author used Poisson regression to estimate RRs for MM in relation to glyphosate exposure categorized as ever versus never exposed and by levels of CEDs and IMEDs. Applicators who had missing covariate data were included in the analysis in a "not known" category so that the entire AHS cohort could be maintained. The RR for any glyphosate use adjusted for age and gender was 1.1 (95% CI 0.5–2.5); further adjusting for lifestyle factors and use of 10 other pesticides yielded a similar RR of 1.2 (95% CI 0.5–2.9). RRs for MM tended to increase with increasing CED and IMED reaching a peak RR of 1.9 (95% CI 0.7–5.3; p values for trend ¼ 0.2) in the highest category of IMED in the fully adjusted model; however, none of the trend tests or category-specific RRs was statistically significant. This reanalysis showed that selection bias was associated with inflated MM risk estimates in the paper by De Roos et al. (2005). Those excluded from the analysis included five of eight MM cases in the glyphosate never use category. Sorahan's secondary analysis of this AHS data does not support the hypothesis that glyphosate use is a risk factor for MM and indicates that the practice of restricting analyses to subjects with complete data for all variables can produce appreciable bias.

Assessment: This reanalysis answers some of the questions about the impact of selection bias in the MM analysis by De Roos et al. (2005). Given that there were only 32 MM cases in the original publication, there are obvious limitations to analyses by estimated extent of exposure that can only be addressed with analyses of the AHS cohort using more recent follow-up data.

A special consideration: selection bias in the analysis

According to accepted case control theory (Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate as was done in several studies. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this bias using data from such a glyphosate analysis by Brown et al. (1993).

Brown et al. (1993) analyzed a case control study that had 173 MM cases and 650 controls. Of these, 11 of 173 cases (6%) and 40 of 650 controls (6%) reported use of glyphosate. Hence, there was no difference in exposure prevalence for cases and controls. However, the authors calculated ORs using non-farmers as the referent population with the rationale that they were not exposed to any farm activities. This seemingly well-intentioned modification of the referent population violates a fundamental premise that underlies the validity of case control studies – that controls should be drawn from the population that gave rise to the cases, which, of course, includes individuals with exposure to farm activities. With these exclusions 100 of 173 cases (58%) and 338 of 650 controls (52%), the glyphosate exposure prevalence for cases was increased to 15% (11 of 73 cases) and the glyphosate exposure prevalence for controls was increased a lesser amount to 13% (40 of 312 controls). This created a bias away from the null as illustrated in Tables 5 and 6 in our OR analysis of the Brown et al. data with and without restriction of the referent group to those not exposed to any farm related activities (using Stata version 14).

Table 5. Results as presented by Brown et al. (1993) for glyphosate exposure.

	Case	Control	Total
Exposed	11	40	51
Unexposed	62	272	334
Total	73	312	385

$OR_{unadjusted}$ ¼ 1.2, 95% CI 0.5, 2.6.

Table 6. Results for glyphosate exposure using all the cases and controls from Brown et al. (1993).

	Case	Control	Total
Exposed	11	40	51
Unexposed	162	610	772
Total	173	650	823

$OR_{unadjusted}$ ¼ 1.0, 95% CI 0.5, 2.1.

Ironically, the reason for the clear bias away from the null is that those with exposure to farm related activities and who did not use glyphosate had higher MM risks than farmers who used glyphosate. In addition, by excluding those without exposure to glyphosate and exposure to other farm exposures, the authors would have precluded being able to control fully for confounding had they attempted multivariate analyses of pesticide exposures. Hardell et al. (2002), Eriksson et al. (2008) and Cocco et al. (2013) made similar exclusions, defining their referent population as those not exposed to pesticides (other than glyphosate). The limited data presented in those papers did not permit us to address statistically the direction and extent of the bias as we have for Brown et al. (1993).

In a similar vein, Sorahan's reanalysis of the MM data from the cohort analysis by De Roos et al. (2005) provides another example of selection bias in the analysis that produced an appreciable bias away from the null. In this case, Sorahan (2015) showed that excluding those with any missing covariate data increased the adjusted RR from 1.1 to 2.6, largely by excluding five of eight MM cases from the glyphosate unexposed population.

Weight of evidence evaluation

Descriptive summary

We systematically collected, summarized and critiqued 16 analytical epidemiological publications examining aspects of the possible relationship between reported use of glyphosate and two cancer types: NHL and MM. We excluded redundant publications (Cantor et al. 1992; Nordstrom et al. 1998; Hardell & Eriksson 1999; Pahwa et al. 2012) in favor of more recent published analyses of the same subjects. This resulted in a final evaluative dataset of seven studies of glyphosate exposure and NHL (see Table 2) and four studies of glyphosate exposure and MM (see Table 3), considering the Sorahan publication (2015) as an extension of De Roos et al. (2005).

The descriptive characteristics of each of these studies were examined for the likely presence or absence of validity concerns (see Table 4). It is clear from Table 4 that only one study in the glyphosate literature (highlighted in Table 4) – the AHS cohort study (De Roos et al. 2005) – was designed to minimize selection bias and recall bias, had only firsthand respondents reporting about exposures (viz. no proxy respondents), and conducted analyses that controlled comprehensively for confounding by personal characteristics and occupational exposures. In addition, the AHS cohort study was the only study that attempted to look at exposure–response relationships while controlling for confounding exposures. As such, it deserves the highest weight in our assessment of the literature. The other studies have so many validity concerns that they cannot be interpreted at face value. Indeed, there is evidence in many of these studies that virtually every exposure studied was associated with NHL or MM – a clear indication of widespread systematic bias and the unreliability of any of the reported exposure-disease associations.

We note one potential limitation to our systematic review. Although we were careful to systematically search the existing literature using search terms and secondary sources to identify relevant studies, it is possible that some relevant studies were not identified. Given the focus on glyphosate epidemiology by IARC and the authors of two recent meta-analyses, included among our secondary sources, we think this potential limitation is unlikely to be consequential.

Assessment of causality

The assessment of causality is a complex process that relies upon a family of well-recognized methods: the general scientific method (familiar to all scientists), study design and statistical methods, and research synthesis methods (e.g. the systematic narrative review, meta-analysis and pooled analysis, and the so-called criteria-based methods of causal inference). Of these, the criteria-based methods are often described and considered in causal assessments, with the most familiar having been proposed by Hill (1965) and utilized extensively in the 1964 Surgeon General's Committee on Smoking and Health and the many publications on the topic that dotted the scientific landscape in the late 1950s and early 1960s (Surgeon General 1964; Weed 2005). These "criteria" or "considerations" are substantive components of the stated methodologies of agencies such as the US EPA (2005) and IARC (2015).

At the center of these methods is the fundamental scientific aim of selecting the best explanation from the alternative explanations that exist for any body of scientific observations, however carefully they were obtained. In epidemiological terms, those alternative explanations typically are defined as cause, bias, confounding (a type of bias) and chance. Some studies are better at excluding alternative explanations than others; cohort studies, for example, are typically better at avoiding recall bias than interview based case-control studies, and recall bias affects not only the exposure of interest (here, glyphosate) but also potential confounding factors (e.g. exposure to other pesticides). Similarly, any and all epidemiologic study designs can – and should – control statistically for factors believed to be potential alternative explanations, i.e. known and putative confounders. For example, studying glyphosate and any lymphohematopoietic cancer without controlling for the potential confounding effects of other pesticides and herbicides, as was widely the case for almost all of the case control studies, does not permit one to exclude those confounders as an alternative explanation. And finally, if the results of an epidemiologic study (whether case-control or cohort) fail to achieve conventional levels of statistical significance – whether defined in terms of "p values" or "95% CIs" – then the alternative explanation of chance cannot be excluded. Notably, however, as Greenland (1990) pointed out, interpretation of p values and CIs at face value requires the assumption that a particular OR or RR has been estimated without bias (e.g. recall bias, selection bias, or confounding), elevating the importance of concerns about study validity in the interpretation of results.

In essence, all the causal frameworks in epidemiology focus on whether the observed associations are strong (viz. the size of the OR or RR is appreciably different than 1.0), whether the associations appear to have been estimated without bias, whether the OR or RR increases or decreases with increasing exposure (viz. exposure–response), whether the temporal relationship between exposure and effect is considered appropriate, and whether the results are statistically robust enough to rule out chance as an explanation (Hill 1965; Bhopal 2002; Aschengrau & Seage 2003a, 2003b; Sanderson et al. 2007).

Assessment of the NHL studies

With these considerations in mind, for NHL, it is justified scientifically to rely most on the results of the De Roos et al. (2005) cohort study as those best suited to reveal the existence (or not) of an association between exposure to glyphosate and NHL. This cohort study was the only study where information about pesticide use was collected independently of the participants' knowledge of cancer status, where there were no proxies providing information about pesticide use, where exposure–response was evaluated extensively, and where there was statistical adjustment for other pesticide exposures and personal factors in estimating RRs for glyphosate. As De Roos et al. (2005) concluded "… the available data provided evidence of no association between glyphosate exposure and NHL incidence." On the other hand, all the case control studies had the potential limitation of recall bias, many had clear indications of selection bias (either in terms of subject participation or in the analysis), most had very small numbers of glyphosate exposed cases and controls, none showed evidence of an exposure–response relationship, and most did not control for the potential confounding effects of personal factors or other occupational exposures in their glyphosate risk estimates. We consider the case control studies to be inadequate for the assessment of a relationship between glyphosate and NHL and consider the AHS cohort study as the one reliable evaluation of NHL risk from glyphosate. The two limitations of the AHS study are the relatively small number of NHL cases (n¼92) and that the length of follow-up after enrollment was less than

a decade. Those limitations speak to statistical robustness, not validity.

Assessment for MM

The glyphosate literature for MM is appreciably sparser than the literature for NHL. Again, the AHS cohort study (De Roos et al. 2005) is the best source of evidence when compared with the three available case control studies. The AHS data indicate that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors (factoring in Sorahan's (2015) reanalysis of the fully adjusted MM results from De Roos et al. (2005) to correct the inadvertent selection bias discussed previously). Exposure–response analyses by De Roos et al. (2005) and Sorahan (2015) were relatively uninformative in light of the few MM cases split among exposure categories. More informative analyses await additional follow-up of the AHS cohort to increase the number of MM cases. The three MM case control studies are based on very small numbers, have concerns about recall bias and selection bias, and did not control for confounding by other exposures. Overall, then, we consider this literature inadequate to make an informed judgment about a potential relationship between glyphosate and MM.

Conclusions

The purpose of this literature review was to address two questions:

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

Our review of the glyphosate epidemiologic literature and the application of commonly applied causal criteria do not indicate a relationship with glyphosate exposure and NHL. In addition, we consider the evidence for MM to be inadequate to judge a relationship with glyphosate. Our conclusion for NHL differs from that of the IARC workgroup seemingly because we considered the null NHL findings from the AHS to be more convincing than the case control studies, in aggregate, with their major limitations. We utilized a structured systematic review approach, we formally addressed pre-specified validity criteria for each study, and our weight of evidence assessment employed widely utilized criteria for causal inference.

Notes

1. A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
2. Grey literature publications may include, but are not limited to the following types of materials: reports (pre-prints, preliminary progress and advanced reports, technical reports, statistical reports, memoranda, state-of-the art reports, market research reports, etc.), theses, dissertations, conference proceedings, technical specifications and standards, non-commercial translations, bibliographies, technical and commercial documentation, and official documents not published commercially (primarily government reports and documents) (Alberani et al. 1990).
3. Whether recall bias, exposure misclassification or selection bias was classified as likely or unlikely was based on a consensus after an in person discussion of each study by the authors.
4. According to accepted case control theory (see Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this in the section on selection bias in the analysis using data from such an analysis by Brown et al. (1993). In addition, excluding those with exposure to other pesticides hinders controlling for confounding by other farming exposures and pesticides in multivariate models.
5. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
6. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
7. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.

Acknowledgements

The authors gratefully acknowledge the very useful comments provided by seven reviewers who were selected by the Editor and anonymous to the authors. These comments helped improve the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. This expert panel evaluation was organized and conducted by Intertek Scientific & Regulatory Consultancy. Funding for this evaluation was provided by Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors.

JA worked for Monsanto from 1989 through 2004 and is a consultant on a legal case unrelated to glyphosate that involves a former Monsanto industrial chemical plant. DG serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate, and has consulted on behalf of Bayer Corp. on litigation matters concerning glyphosate and leukemia. GM has no additional declarations. TS has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. In addition, TS has consulted for Monsanto on litigation matters involving glyphosate. DW has consulted on litigation matters concerning Monsanto that did not involve glyphosate.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

Supplemental material

Supplemental material for this article is available online here.

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