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Epidemiologic studies of glyphosate and cancer: A review

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ABSTRACT

The United States Environmental Protection Agency and other regulatory agencies around the world have registered glyphosate as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential, based primarily on results of carcinogenicity studies of rats and mice. To examine potential cancer risks in humans, we reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. We also reviewed relevant methodological and biomonitoring studies of glyphosate. Seven cohort studies and fourteen case-control studies examined the association between glyphosate and one or more cancer outcomes. Our review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. Data from biomonitoring studies underscore the importance of exposure assessment in epidemiologic studies, and indicate that studies should incorporate not only duration and frequency of pesticide use, but also type of pesticide formulation. Because generic exposure assessments likely lead to exposure misclassification, it is recommended that exposure algorithms be validated with biomonitoring data.

1. Introduction

Glyphosate(N-phosphonomethyl glycine; CAS registry #38641-94-0) is the primary active ingredient in Roundup-branded herbicides produced by the Monsanto Company. The United States (US) Environmental Protection Agency (EPA) and other regulatory agencies around the world have registered this chemical as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate-based herbicides, which have been sold in the US since 1974 and marketed under the brand names Roundup®, Roundup Pro®, Roundup PowerMAX™, Roundup WeatherMAX®, and AquaMaster®, are now registered in over 130 countries to control annual and perennial weeds, woody brush, and trees in agricultural, industrial, forestry, greenhouse, rights-of-way and residential areas. Other brands and manufacturers of glyphosate products include but are not limited to Glyfos® (Cheminova), Durango® DMA® (Dow AgroSciences), and Touchdown HiTech® (Syngenta). In the US, glyphosate (isopropylamine salt) herbicides were applied to 31% of all planted corn acres in 2005 (USDA, 2006) and 92% of all planted soybean acres in 2006 (USDA, 2007).

Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential (EC, 2002; US EPA, 1993; WHO/FAO, 2004). US EPA has classified glyphosate as a Group E carcinogen, which is defined as having "evidence of non-carcinogenicity for humans" (US EPA, 1993). This classification was based on "a lack of convincing evidence of carcinogenicity in adequate studies with two animal species, rat and mouse" (US EPA, 1993). Negative results were observed in genotoxicity studies conducted under good laboratory practice conditions and compliant with current regulatory test guidelines (Williams et al., 2000). It was concluded that, in the absence of carcinogenic potential in animals and given the lack of genotoxicity in standard tests, glyphosate is unlikely to pose a carcinogenic risk to humans (WHO/FAO, 2004; Williams et al., 2000). In addition, US EPA has concluded that there is a reasonable certainty that no harm will result to the general population or to infants and children from

Abbreviations: AHS, Agricultural Health Study; CAS, Chemical Abstract Service; CI, confidence interval; FFES, Farm Family Exposure Study; HCL, hairy cell leukemia; IARC, International Agency for Research on Cancer; MGUS, monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin lymphoma; OR, odds ratio; RR, relative risk; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; US EPA, United States Environmental Protection Agency.

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aggregate exposure to residues of glyphosate (US EPA, 2007). Nevertheless, there has been no published comprehensive review of the epidemiologic research on this topic.

We reviewed epidemiologic cohort and case-control studies of glyphosate and cancer to evaluate whether exposure to glyphosate is associated causally with risk of developing cancer in humans. In addition, we reviewed methodological and biomonitoring studies of glyphosate to allow for a more comprehensive discussion of issues related to exposure assessment (including exposure misclassification and information bias) and other interpretation issues as they relate to findings from the epidemiologic studies. We did not consider it appropriate to calculate quantitative summary relative risk estimates across studies evaluating different site-specific cancers (e.g., breast cancer, brain cancer, esophageal cancer, etc.), and therefore did not conduct a meta-analysis.

2. Methods

Studies were included in our review if they met the following criteria: (1) published in a peer-reviewed journal; (2) English language; (3) analytic epidemiologic studies (e.g., cohort, case-control) that evaluated the association between glyphosate and a cancer outcome(s). Analyses of more general categories of "pesticides" or "herbicides" did not meet our criteria. Studies of poisonings or other acute effects of glyphosate were not included.

Multiple search strategies were employed to identify literature related to glyphosate exposure and human cancer outcomes. A PubMed search was conducted using the term "glyphosate," as well as its synonyms, chemical name, and Chemical Abstract Service (CAS) number, in conjunction with various terms related to epidemiology studies (e.g., "cohort," "case-control"). In addition, broader searches for articles regarding epidemiologic studies of organophosphorus compounds used as pesticides or herbicides were conducted, as well as a search for case-control studies of pesticides or herbicides.

A separate search was conducted using the STN search service index, which searches multiple databases simultaneously, including Biosis, EMBASE, Medline, Pascal, and SciSearch. The CAS registry number for glyphosate was searched in combination with epidemiologic terms.

After duplicates were removed, abstracts were reviewed to determine if they met the inclusion criteria. Articles meeting the inclusion criteria were then obtained and reviewed.

Literature searches to identify biomonitoring studies of glyphosate were also performed using PubMed. We searched on the terms "glyphosate" and "Round up OR Roundup" in separate searches. Both searches also included the term "biomonitoring" as well as related terms including "sample," "urine," and "blood." Abstracts identified from these searches were reviewed. For all articles of interest, the "related articles" identified by PubMed were also reviewed. All relevant articles were obtained.

For completeness, we examined the reference sections of the primary epidemiology and biomonitoring publications for additional articles that may not have been identified by the PubMed searches.

3. Results

3.1. Cohort studies

Seven "cohort studies" evaluated the association between glyphosate and cancer (see Table 1). All of these analyses were conducted among participants or family members of the Agricultural Health Study (AHS) cohort. We will describe these as separate "studies" but they are really separate analyses and publications from the same cohort study. One study evaluated multiple pesticides and multiple cancer sites in children (Flower et al., 2004), one study examined glyphosate and multiple cancer sites (De Roos et al., 2005), and five studies evaluated multiple pesticides and site-specific cancers, including prostate (Alavanja et al., 2003), breast (Engel et al., 2005), colon/rectum (Lee et al., 2007), pancreas (Andreotti et al., 2009), and cutaneous melanoma (Dennis et al., 2010). There is some overlap between the cases and person-time reported in the De Roos et al. (2005) analyses of multiple cancer sites and analyses of cancers of the prostate (Alavanja et al., 2003), colon/rectum (Lee et al., 2007), pancreas (Andreotti et al., 2009), and cutaneous melanoma (Dennis et al., 2010) in the AHS. Calendar years of follow-up for each study are shown in Table 1. The AHS is a prospective study of private and commercial applicators in Iowa and North Carolina. Participants were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire.

Results of the cohort studies reporting data on glyphosate and cancer are shown in Table 2. Flower et al. (2004) evaluated associations between pesticide application by parents and cancer among children born to Iowa participants in the AHS. Female applicators and spouses of male applicators were asked to complete a questionnaire to collect data on children born after 1975. This information was used to conduct a linkage with the Iowa Cancer Registry to identify cases of cancer among children age 19 and younger, diagnosed between 1975 and 1998. The linkage identified 50 cases of childhood cancer. Exposure to glyphosate was determined by self-reported responses to questionnaires completed by applicators and spouses. There was no positive association between either maternal (odds ratio [OR] = 0.61; 95% confidence interval [CI]: 0.32–1.16) or paternal (OR = 0.84; 95% CI: 0.35–2.34) use of glyphosate and risk of childhood cancer.

De Roos et al. (2005) evaluated associations between glyphosate exposure and incidence of total and specific cancers in the AHS. There was no statistically significant association between glyphosate and "all cancers" or any cancer site in analyses of ever- versus never-exposed to glyphosate, in analyses of tertiles of cumulative exposure days of glyphosate exposure, or in analyses of tertiles of intensity-weighted exposure days. Results for analyses of tertiles were reported for the models that excluded never-exposed participants and used the lowest-exposed category as the reference group. Intensity levels were estimated based on questionnaire responses using the following algorithm: intensity level = [(mixing status + application method + equipment repair status) × personal protective equipment use] (De Roos et al., 2005). The authors stated that they considered p-values less than 0.10 as being indicative of a trend. There were two p-values that met this criterion, but neither corresponded to monotonic positive patterns of association. In the intensity-weighted analysis of glyphosate and lung cancer, the relative risk for the highest tertile was 0.6 (95% CI: 0.3–1.0) and the corresponding p-value for trend was 0.02. For similar analyses of pancreatic cancer, the relative risk in the highest tertile was 0.5 (95% CI: 0.1–1.9) and the p-value for trend was 0.06. The corresponding relative risk for multiple myeloma was 2.1, but the corresponding 95% confidence interval was wide (0.6–7.0), and the p-value for trend was above the 0.10 threshold ($p = 0.17$). De Roos et al. also reported results of secondary analyses of multiple myeloma using "never exposed" to glyphosate as the referent; the relative risk for the highest tertile was higher but less precise (RR = 4.4; 95% CI: 1.0–20.2) than in analyses using the lowest tertile as the referent. Thus, there was

Table 1
Cohort studies of exposure to glyphosate and cancer outcomes.

Author(s) and year	Location	Study size	Cohort description	Exposure	Comparison population
Total Childhood Cancer					
Flower et al. (2004)	Iowa, US	17,280 children	Agricultural Health Study participants: children born during or after 1975 whose parents were private applicators (fathers only) and applied for a license in Iowa between 1993 and 1997 Total childhood cancer cases (age <19 years) identified from Iowa Cancer Registry Cancer cases ascertained retrospectively and prospectively between 1975 and 1998	Dichotomous exposure variables (ever/never) were used to characterize whether pesticides were ever used by a mother or ever used by the father prior to child's birth	Child's parental exposure: Mothers who never applied the specific pesticides Fathers who were not exposed to the specific pesticides prior to the child's birth
Multiple Cancer Endpoints					
De Roos et al. (2005)	Iowa and North Carolina, US	54,315 eligible licensed pesticide applicators 53,656 had complete glyphosate data	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina Followed from recruitment (1993 to 1997) through 2001 for incident cancer	Three glyphosate exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use (tertiles), intensity-weighted cumulative exposure days (tertiles)	13,280 applicators were not exposed to glyphosate 15,911 applicators in the lowest tertile of exposure to glyphosate
Site-Specific Cancers: Prostate Cancer					
Alavanja et al. (2003)	Iowa and North Carolina, US	55,332 males	Male Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina between 1993 and 1997 with no history of prostate cancer at enrollment Followed through 1999 for incident prostate cancer	Exposure ever/never, frequency, duration, and intensity to individual pesticides was ascertained with a questionnaire A cumulative exposure score for each pesticide was used to evaluate exposure–response trends	Pesticide applicators who never used glyphosate
Site-Specific Cancers: Breast Cancer					
Engel et al. (2005)	Iowa and North Carolina, US	30,454 females	Wives of private pesticide applicators from Iowa and North Carolina enrolled in the Agricultural Health Study with no history of breast cancer at enrollment Followed through 2000 for incident breast cancer	Farmers' wives provided information on ever/never use of individual pesticides, frequency of use of any pesticides, and tasks performed around the farm The farmers provided information via questionnaire on the lifetime pesticide use, frequency, and duration	Farmers' wives who never applied glyphosate Farmers' wives who never used pesticides AND whose husbands did not apply glyphosate
Site-Specific Cancers: Colorectal Cancer					
Lee et al. (2007)	Iowa and North Carolina, US	56,813 eligible licensed pesticide applicators	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of colorectal cancer at enrollment Followed through 2002 for incident colorectal cancer	Pesticide exposure was determined from questionnaire response assessing pesticide use during the year prior to study enrollment, the frequency of use, and the total number of years used Three exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use, intensity-weighted cumulative exposure days 50 specific pesticides were evaluated	Applicators who were not exposed to glyphosate
Site-Specific Cancers: Pancreatic Cancer					
Andreotti et al. (2009)	Iowa and North Carolina, US	52,721 licensed pesticide applicators plus 29,811 spouses	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina with no history of any type of cancer at enrollment Followed through 2004 for incident pancreatic cancer	Pesticide exposure was determined from questionnaire response assessing pesticide use during the year prior to study enrollment, the frequency of use, and the total number of years used Three exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use, intensity-weighted cumulative exposure days 50 specific pesticides were evaluated For spouses, only every/never pesticide use was available	Applicators or spouses who were not exposed to glyphosate
Site-Specific Cancers: Cutaneous Melanoma					
Dennis et al. (2010)	Iowa and North Carolina, US	24,704 eligible licensed pesticide applicators who completed the AHS take-home questionnaire	Agricultural Health Study participants: private and commercial applicators licensed in Iowa or North Carolina without a nonmelanoma cancer diagnosis before Followed through 2005 for incident cutaneous melanoma	Pesticide exposure was determined from questionnaire response assessing pesticide use during the year prior to study enrollment, the frequency of use, and the total number of years used Three exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use, intensity-weighted cumulative exposure days 50 specific pesticides were evaluated	Applicators who were not exposed to glyphosate

Table 2
Summary of findings: Cohort studies of exposure to glyphosate and cancer outcomes.

Author(s) and year	Description	No. of exposed cases	Type of relative risk estimate	Relative risk estimate	95% Confidence interval	Variables included in statistical model
Total Childhood Cancer						
Flower et al. (2004)	Maternal use (ever) of glyphosate	13	OR	0.61	0.32–1.16	Child's age at enrollment
	Paternal use (prenatal) of glyphosate	6	OR	0.61	0.35–2.34	
Multiple Cancer Endpoints						
De Roos et al. (2005)	57–2678 versus 1–20 Cumulative Exposure Days					
	All cancers	358	RR	1.0	0.9–1.1	Age at enrollment, education, pack-years of cigarette smoking, alcohol consumption in the past year, family history of cancer in first-degree relatives, and state of residence
	Lung	26		0.7	0.4–1.2	
	Oral cavity	10		0.8	0.4–1.7	
	Colon	15		0.9*	0.4–1.7	
	Rectum	14		1.1	0.6–2.3	
	Pancreas	7		1.3	0.5–3.6	
	Kidney	9		0.7	0.3–1.6	
	Bladder	17		1.2	0.6–2.2	* Also adjusted for other pesticides
	Prostate	145		1.1	0.9–1.3	
	Melanoma	14		0.9	0.5–1.8	
	All lymphohematopoietic cancers	36		1.2	0.8–1.8	
	Non-Hodgkin lymphoma	17		0.9	0.5–1.6	
	Leukemia	9		1.0*	0.4–2.9	
	Multiple myeloma	6		1.9*	0.6–6.3	
Multiple Cancer Endpoints: Adults						
De Roos et al. (2005)	337.2–18,241 versus 0.1–79.5 Intensity-Weighted Exposure Days					
	All cancers	438	RR	0.9	0.8–1.1	Age at enrollment, education, pack-years of cigarette smoking, alcohol consumption in the past year, family history of cancer in first-degree relatives, and state of residence
	Lung	27		0.6*	0.3–1.0	
	Oral cavity	13		1.0	0.5–2.3	
	Colon	30		1.4*	0.8–2.5	
	Rectum	16		0.9	0.5–1.9	
	Pancreas	3		0.5	0.1–1.9	
	Kidney	10		0.5	0.2–1.0	
	Bladder	13		0.8	0.3–1.8	* Also adjusted for other pesticides
	Prostate	174		1.1	0.9–1.3	
	Melanoma	17		0.7	0.3–1.2	
	All lymphohematopoietic cancers	43		1.0	0.7–1.6	
	Non-Hodgkin lymphoma	22		0.8	0.5–1.4	
	Leukemia	8		0.7*	0.2–2.1	
	Multiple myeloma	8		2.1*	0.6–7.0	
Site-Specific Cancers: Prostate Cancer						
Alavanja et al. (2003)	"[Glyphosate]. . .Did not demonstrate a significant exposure–response association with prostate cancer"	NR	NR	NR	NR	Age, family history of prostate cancer
Site-Specific Cancers: Breast Cancer						
Engel et al. (2005)	Farmers' wives' glyphosate use (all wives in cohort)	82	RR	0.9	0.7–1.1	Age, race, state of residence
	Husbands' use of glyphosate among wives who never used pesticides	109	RR	1.3	0.8–1.9	
Site-Specific Cancers: Colorectal Cancer						
Lee et al. (2007)	Ever versus never exposure among pesticide applicators					
	Colorectal	225	OR	1.2	0.9–1.6	Age, smoking, state, total days of pesticide application among all enrollment applicators
	Colon	151		1.0	0.7–1.5	
	Rectum	74		1.6	0.9–2.9	
Site-Specific Cancers: Pancreatic Cancer						
Andreotti et al. (2009)	Ever versus never exposure among pesticide applicators and spouses	55	OR	1.1	0.6–1.7	Age, smoking, diabetes, applicator type
	Intensity-weighted lifetime exposure days (applicators only)					
	Never	11	OR	1	(ref.)	Age, smoking, diabetes
	<184	29		1.9	0.9–3.8	
	>185	19		1.2	0.6–2.6	
Site-Specific Cancers: Cutaneous Melanoma						
Dennis et al. (2010)	"None of the 22 pesticides[a] detailed on the enrollment questionnaire was associated with melanoma"	NR	NR	NR	NR	NR

Abbreviations: NR: not reported; OR: odds ratio; RR: relative risk.

[a] Glyphosate is one of the 10 herbicides queried on the Agricultural Health Study (AHS) enrollment questionnaire (Dennis et al., 2010, Appendix 1).

no evidence of a statistically significant *positive* association for any of the cancers for which data were reported. Nevertheless, the authors concluded, "a suggested association between glyphosate and the risk of multiple myeloma" (De Roos et al., 2005). Additional follow-up of this cohort may clarify this potential association.

Lash (2007) examined this association further by using Monte Carlo simulation to conduct an analysis to quantify the bias and uncertainty that may be attributable to systematic (non-random) error. De Roos et al. (2005) acknowledged in their paper that over 13,000 subjects were excluded from multivariate analyses because of missing data. In analyses of "ever" versus "never" exposed to glyphosate, the age-adjusted RR was 1.1, whereas the multivariate-adjusted RR was 2.6 (De Roos et al., 2005). Lash's results indicated that adjustment for confounders, which resulted in limiting the data set by 25% because of missing data on the adjustment variables, likely introduced selection bias and produced an estimate that was "substantially biased," and that this bias was likely in the direction away from the null (Lash, 2007).

A recent paper by Landgren et al. (2009) evaluated associations between various pesticides and monoclonal gammopathy of undetermined significance (MGUS) in the AHS. Multiple myeloma is often preceded by MGUS, a premalignant plasma cell disorder. A statistically non-significant decreased risk of MGUS was observed among glyphosate applicators in the AHS, based on 27 exposed MGUS cases and 11 non-exposed cases (OR = 0.5; 95% CI: 0.2–1.0).

Alavanja et al. (2003) evaluated associations between specific pesticides and prostate cancer in the AHS. Glyphosate was listed as one of the herbicides for which information on frequency, duration, intensity, and cumulative exposure was available. In the table of results, however, glyphosate was not listed. The authors stated that pesticides for which "no exposure–response association with prostate cancer was observed" were omitted from the results table to save space. Thus, it can be assumed that there was no significant positive association between glyphosate and prostate cancer in this study.

Engel et al. (2005) evaluated breast cancer risk among wives of farmers in the AHS. The authors analyzed associations of breast cancer incidence with glyphosate use among wives of farmers, and with glyphosate use among husbands of wives who never used pesticides. After adjustment for age, race, and state of residence, there was no statistically significant association in either analysis (Table 2). Although the authors presented additional analyses that stratified on state and on menopausal status, results for glyphosate were not reported.

In their analysis of colorectal cancer and pesticide use, Lee et al. (2007) found no statistically significant association between glyphosate use (ever versus never) and colorectal cancer overall (RR = 1.2; 95% CI: 0.9–1.6), or cancer of the colon (RR = 1.0; 95% CI: 0.7–1.5) or rectum (RR = 1.6; 95% CI: 0.9–2.9). The authors presented analyses of nine pesticides by increasing category of lifetime exposure days, but results for glyphosate were not reported, presumably because there was nothing remarkable to report.

Andreotti et al. (2009) reported no significant association of "ever" use of glyphosate (versus never use) with pancreatic cancer among the combined group of AHS applicators and spouses (OR = 1.1; 95% CI: 0.6–1.07), nor was there evidence of dose–response for increasing category of intensity-weighted lifetime exposure days in analyses limited to applicators (p-trend = 0.85).

Dennis et al. (2010) evaluated associations of 50 pesticides with cutaneous melanoma in the AHS. Specific results for glyphosate were not reported. The authors did state, however, that "None of the 22 pesticides detailed on the enrollment questionnaire was associated with melanoma…" In their Appendix 1, glyphosate is listed among the 22 pesticides on the enrollment questionnaire.

3.2. Case-control studies

Fourteen case-control studies that analyzed glyphosate exposure and cancer were identified and included in this review (Table 3). There is some overlap among these studies, including pooled analyses, as will be described in the following paragraphs. Seven studies evaluated non-Hodgkin lymphoma (NHL) (Cantor et al., 1992; De Roos et al., 2003; Eriksson et al., 2008; Hardell and Eriksson, 1999; Hardell et al., 2002; Lee et al., 2004a; McDuffie et al., 2001), two studies analyzed hairy cell leukemia (HCl) (Hardell et al., 2002; Nordstrom et al., 1998), three studies evaluated gliomas (Carreon et al., 2005; Lee et al., 2005; Ruder et al., 2004), and there was one published study on each of the following: leukemia (adult males) (Brown et al., 1990), multiple myeloma (Brown et al., 1993), and cancer of the stomach and esophagus (Lee et al., 2004b). Main results for these studies are shown in Table 4.

Three case-control studies were conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s, utilizing the same control series for each of the three lymphohematopoietic cancers studied. For each study, male cases and controls reporting glyphosate exposure were considered "exposed" and cases and controls who reported being nonfarmers were considered "unexposed." There was a near null association between glyphosate exposure and leukemia among white males residing in Minnesota and Iowa (OR = 0.9; 95% CI: 0.5–1.6) (Brown et al., 1990). The odds ratio for multiple myeloma was elevated, but not statistically significant, among Iowa farmers reporting ever handling glyphosate (OR = 1.7; 95% CI: 0.8–3.6) (Brown et al., 1993). Cantor et al. (1992) observed an approximately null association between glyphosate exposure and NHL among males from Iowa or Minnesota (OR = 1.1; 95% CI: 0.7–1.9).

Lee et al. (2004a) pooled data from the Iowa and Minnesota NHL case-control study (Cantor et al., 1992) with a similar case-control study conducted in Nebraska that did not publish data on glyphosate (Zahm et al., 1990). In the pooled analysis, results were stratified on asthma status to examine whether asthma may modify potential associations between pesticide exposures and NHL. Associations between NHL and glyphosate use among asthmatics and nonasthmatics were not significantly elevated, nor did they differ significantly from each other (OR for asthmatics = 1.2; 95% CI: 0.4–3.3; OR for nonasthmatics = 1.4; 95% CI 0.98–2.1).

De Roos et al. (2003) conducted a pooled logistic regression analysis and hierarchical regression of NHL (in males) and pesticides, including glyphosate, using data from case-control studies conducted in Iowa and Minnesota, Nebraska, and Kansas. The first-level model of the hierarchical regression analysis included simultaneous adjustment for 47 pesticides in addition to age and study site. The second-level model included incorporated data on "prior covariates" or factors that were hypothesized to be related to the individual "true" effects. These factors included indicators of type of pesticide and toxicity, and values were assigned based on the International Agency for Research on Cancer (IARC) and US EPA classifications. Glyphosate was assigned a zero for all pesticide covariates (e.g., insecticides, organochlorines, organophosphates) and a carcinogenic probability value of 0.3, which corresponded to "not assessed by IARC or US EPA IRIS, or deemed unclassifiable in one or both assessments." The logistic regression analysis produced a statistically significant odds ratio for ever use of glyphosate (OR = 2.1; 95% CI: 1.1–4.0), whereas the estimate was reduced and no longer statistically significant in the hierarchical regression (OR = 1.6; 95% CI: 0.9–2.8). The data available in this study did not permit analyses of duration or frequency of use.

A Canadian population-based case-control study of NHL in men (n = 517 cases) and pesticide exposure found a statistically non-significant positive association between self-reported glyphosate exposure and NHL (multivariate-adjusted OR = 1.20; 95% CI:

Table 3
Case-control studies of exposure to glyphosate and cancer outcomes.

Author(s) and year	Case population	Control population	Enrollment period	Exposure assessment
Leukemia				
Brown et al. (1990)	White male residents of Iowa or Minnesota age 30 years and older diagnosed with leukemia Iowa cases were identified from the Iowa Tumor Registry Minnesota cases were identified from hospital records	White men without lymphatic or hematopoietic cancer selected by: random digit dialing for controls under age 65, from Medicare records provided by the Health Care Financing Administration for controls over age 65, and from state death certificate files for deceased controls, frequency matched by age, vital status, and state	Iowa: Cases were ascertained from March 1981 to October 1983 Minnesota: Cases were ascertained from October 1980 to September 1982 Initial interviews were conducted from 1981–1984 Supplemental interviews (Iowa participants only) were conducted in 1987	Initial interviews with subject or next-of-kin to determine agricultural exposure to specific pesticides, including first and last year used and whether the subject personally mixed or applied the pesticide Supplemental telephone interviews were conducted with Iowa participants to determine the number of days per year pesticides were handled
Multiple Myeloma				
Brown et al. (1993)	White male residents of Iowa age 30 years and older diagnosed with multiple myeloma; identified from Iowa Health Registry	White men without lymphatic or hematopoietic cancer selected by: random digit dialing for controls under age 65, from Medicare records provided by the Health Care Financing Administration for controls over age 65, and from state death certificate files for deceased controls, frequency matched by age and vital status	Cases were ascertained from March 1981 to October 1983 Interviews were conducted from 1981–1984	Interviews with subject or next-of-kin to determine agricultural exposure to specific pesticides, including first and last year used and whether the subject personally mixed or applied the pesticide
Non-Hodgkin Lymphoma				
Cantor et al. (1992)	White male residents of Iowa or Minnesota age 30 years and older diagnosed with NHL Iowa cases were identified from the Iowa State Health Registry Minnesota cases were identified from hospital records	White males without lymphatic or hematopoietic cancer selected by: random digit dialing for controls under age 65, from Medicare records provided by the Health Care Financing Administration for controls over age 65, and from state death certificate files for deceased controls, frequency matched by age, vital status, and state, that were classified as nonfarmers from the initial interview	Iowa: Cases diagnosed between March 1981 and October 1983 Minnesota: Cases diagnosed between October 1980 and September 1982 Interviews were conducted from August 1981 to May 1984	Interviews with subject or next-of-kin to determine agricultural exposure to specific pesticides, including first and last year used and whether the subject personally mixed or applied the pesticide
De Roos et al. (2003)	Nebraska: White male residents of 1 of 66 Nebraska counties age 21 years or older diagnosed with NHL (females were excluded); identified from Nebraska Lymphoma Study Group and hospital records Iowa: White males age 30 years and older diagnosed with NHL; identified from Iowa State Health Registry Minnesota: White males age 30 years or older diagnosed with NHL; identified from hospital records Kansas: White males age 21 years or older diagnosed with NHL; identified from the statewide cancer registry run by the University of Kansas Cancer Data Service	Randomly selected from same geographic area as cases Identified by random digit dialing, Medicare records, and state mortality files Frequency matched by race, sex, age, and vital status	Nebraska: Cases diagnosed between July 1983 and June 1986 Iowa: Cases diagnosed between 1981 and 1983 Minnesota: Cases diagnosed between 1980 and 1982 Kansas: Cases diagnosed between 1979 and 1981	Interviews with subjects or next-of-kin to assess pesticide use Nebraska: Questioning about use of any pesticide and specific pesticides Iowa and Minnesota: Questioning about use of specific pesticides Kansas: Questioning about use of any pesticides and specific groups of pesticides
Hardell and Eriksson (1999)	Male residents of one of four northern or three middle counties in Sweden age 25 years and older diagnosed with NHL; identified regional cancer registries	Two male controls for each case matched by age, year of death if deceased, and county	Diagnosed between 1987 and 1990 Interviews were conducted from 1993 to 1995	Mailed questionnaire was completed by subjects or next-of-kin assessing work history and chemical exposure When answers regarding exposures were unclear, a follow-up telephone interview was conducted A tumor induction period of 1 year were necessary for inclusion; exposures not meeting this criteria were disregarded
Hardell et al. (2002)	NHL: Male residents of one of four northern or three middle counties in Sweden age 25 years and older diagnosed with NHL; identified from regional cancer registries	NHL: Two male controls for each case matched by age, year of death if deceased, and county HCL: Four male controls for each case matched by age and county	NHL: Diagnosed between 1987 and 1990 HCL: Diagnosed between 1987 and 1992	Mailed questionnaire was completed by subjects or next-of-kin assessing work history and chemical exposure When answers regarding exposures

(*continued on next page*)

Table 3 (*continued*)

Author(s) and year	Case population	Control population	Enrollment period	Exposure assessment
	HCL: Living male residents of Sweden age 25 years and older diagnosed with HCl; identified from the Swedish Cancer Registry			were unclear, a follow-up telephone interview was conducted A minimum of 8 h of exposure and a tumor induction period of 1 year were necessary for inclusion; exposures not meeting this criteria were disregarded
Lee et al. (2004a)	Iowa and Minnesota: White males age 30 years and older with newly diagnosed cases of NHL; identified from the Iowa State Health Registry and Minnesota hospitals Nebraska: White male and female residents of 1 of 45 eastern Nebraska counties age 21 years and older diagnosed with NHL; identified from the Nebraska Lymphoma Study Group and area hospitals	Randomly selected from same geographical area Frequency matched by age, gender, race, year of death if deceased, and vital status Identified by random digit dialing for controls under age 65, Medicare records from Health Care Financing Administration for controls over age 65, state death certificates for deceased controls Control:Case ratio for Iowa and Minnesota = 2:1 and for Nebraska = 4:1	Iowa and Minnesota: Diagnosed between 1980 and 1983 Nebraska: Diagnosed between July 1983 and June 1986	Interviews were conducted with subjects or next-of-kin to determine pesticide use, NHL risk factors, and asthma status Iowa and Minnesota: Interviews were conducted in person Nebraska: Interviews were conducted over the telephone
McDuffie et al. (2001)	Male residents of six Canadian provinces age 19 years and older diagnosed with STS, HD, NHL, or MM; this study only evaluated those with NHL Cases were identified from Canadian Cancer Registries; in Quebec, hospital ascertainment was used	Random control subject selection using Health Insurance records, computerized telephone listings, and voters' lists; males 19 years and older from same six Canadian provinces as cases matched by age (within 2 years)	Diagnosed between September 1, 1991 and December 31, 1994	A mailed, self-reported questionnaire was administered to capture lifetime exposure history Participants with 10 or more hours per year of pesticide exposure reported, and 15% of the remainder, had follow–up telephone interviews to determine the details of pesticide exposure
Nordstrom et al. (1998)	Male HCl cases identified from Swedish Cancer Registry	Four controls per case matched for age and county drawn from National Population Registry	Diagnosed between 1987 and 1992	Self-reported questionnaire determining work history, leisure activities, and exposures A follow-up telephone interview was conducted if exposure data was missing from the questionnaire
Eriksson et al. (2008)	Male and female Swedish residents who were newly diagnosed NHL cases aged 18–74 years identified through physicians treating lymphoma and pathologists diagnosing NHL	Random control subject selection was used among Swedish population living in the same health service regions as cases; controls were frequency matched in 10-year age and sex groups	Diagnosed between December 1, 1999 and April 30, 2002	Self-reported questionnaire determining total work history with detailed questions regarding exposure to pesticides, organic solvents, and other chemicals. Questions on pesticide use included the number of years and number of days per year of use, as well as approximate length of exposure per year
Brain Cancer				
Carreon et al. (2005)	Female residents of nonmetropolitan counties (population <250,000) of Iowa, Michigan, Minnesota, or Wisconsin age 18 to 80 years with confirmed cases of glioma Cases identified from medical facilities and neurosurgeon offices	Females with no current diagnosis of glioma frequency matched by state and age (within 10 years); the target was to have 1.5 controls per case Randomly selected, state driver's license/non-driver records for those 18 to 64 years old, Health Care Financing Administration's Medicare data for those 65 to 80 years old	Diagnosed from January 1, 1995 to January 31, 1997	In-person interviews with subjects or proxies to determine lifetime agricultural pesticide exposure through January 1, 1993, for those who ever lived on farms, including ever used and frequency of use and farm activities Proxy respondents were used when study participant was deceased or too impaired to answer the questionnaire
Lee et al. (2005)	White residents of 1 of 66 Nebraska counties age 21 years or older with confirmed adult glioma Cases identified from Nebraska Cancer Registry or from participating hospitals in Lincoln and Omaha, Nebraska	Frequency matched by age, sex, and vital status to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased), and 5-year age groups to the overall case distribution Additional younger controls were brought into the study through	Diagnosed between July 1, 1988 and June 30, 1993 Interviewed between 1992 and 1994	Telephone interviews with subjects; those who lived or worked on a farm were asked about specific pesticide use prior to 1985 Proxy respondents were used when study participant was deceased or too impaired to answer the questionnaire

Table 3 (*continued*)

Author(s) and year	Case population	Control population	Enrollment period	Exposure assessment
		random digit dialing and from death certificates		
Ruder et al. (2004)	Male residents of nonmetropolitan counties of Iowa, Michigan, Minnesota, or Wisconsin age 18 to 80 years with confirmed cases of primary intracranial glioma Cases identified from medical facilities and neurosurgeon offices	Males with no current diagnosis of glioma matched by state and age (within 10 years) Residents of the nonmetropolitan counties of the four states randomly selected based on state driver's license/non-driver records for those 18 to 64 years old, Health Care Financing Administration's Medicare data for those 65 to 80 years old	Diagnosed between January 1, 1995 and January 31, 1997	Interviews with subjects to determine lifetime pesticide exposure Proxy respondents were used when study participant was deceased or too impaired to answer the questionnaire
Lee et al. (2004b)	White residents of 1 of 66 Nebraska counties age 21 years or older with a newly confirmed case of adenocarcinoma of the stomach or Cases identified from the Nebraska Cancer Registry (1988–1990) or from discharge diagnosis and pathology records from 14 Nebraska hospitals (1991–1993)	Frequency matched by age (five-year age groups) and sex to the combined distribution of glioma, stomach, and esophageal cancer cases from a control group from a previous study (1986–1987) that selected controls from the general population by random digit dialing for those under 65 years, Health Care Financing Administration Medicare files for those over 65 years, mortality records for deceased and matched by race, sex, vital status (or year of death if deceased)	Diagnosed between 1988 and 1990 for cases from the Nebraska Cancer Registry and between 1991 and 1993 for cases from discharge diagnosis and pathology records Interviewed between 1992 and 1994	Telephone interviews with subjects; those who lived or worked on a farm were asked about specific pesticide use prior to 1985 Proxy respondents were used when study participant was deceased or too impaired to answer the questionnaire

Abbreviations: HCl: hairy cell leukemia; HD: Hodgkin's disease; MM: multiple myeloma; NHL: non-Hodgkin disease; STS: soft tissue sarcoma.

0.83–1.74) (McDuffie et al., 2001). Hardell et al. (2002) reported results of a pooled analysis of two Swedish case-control studies: one of NHL and one of HCl, which is classified as a type of NHL. The individual studies reported statistically non-significant positive associations between glyphosate and both NHL (OR adjusted for age and country = 2.3; 95% CI: 0.4–13; multivariate-adjusted OR = 5.8; 95% CI: 0.6–54) (Hardell and Eriksson, 1999) and HCl (OR = 3.1; 95% CI: 0.8–12) (Nordstrom et al., 1998). In both studies, estimates were based on few exposed cases ($n = 4$) and confidence intervals were wide (Table 4). The pooled analysis combined NHL and HCl cases ($n = 515$) and, whereas the "univariate" odds ratio was similar to those in the individual studies (OR = 3.04; 95% CI: 1.08–8.52), the multivariate-adjusted odds ratio was attenuated (OR = 1.85; 95% CI: 0.55–6.20) (Hardell et al., 2002).

A recent Swedish case-control study (Eriksson et al., 2008) evaluated the association between glyphosate, including duration of exposure (days) and latency (years), and NHL, including histopathologic type. The statistically significant "univariate" association between glyphosate and NHL (OR = 2.02; 95% CI: 1.10–3.71) was attenuated and no longer significant after adjustment for age, sex, year of diagnosis or study enrollment, and additional pesticides (OR = 1.51; 95% CI: 0.77–2.94). The odds ratios for glyphosate exposure of $\leqslant$10 days and >10 days were 1.69 (95% CI: 0.70–4.07) and 2.36 (1.04–5.37), respectively. In analyses of "latency," the odds ratios for glyphosate were 1.11 (95% CI: 0.24–5.08) and 2.26 (95% CI: 1.16–4.40) for 1–10 years and >10 years latency periods, respectively. In analyses of glyphosate and type of NHL, statistically significant positive associations were observed for small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) (OR = 3.35; 95% CI: 1.42–7.89) and for "unspecified NHL" (OR = 5.63; 95% CI: 1.44–22.0). Odds ratios for the other types (total B-cell lymphomas, follicular (grade I-III), diffuse large B-cell lymphoma, other specified B-cell lymphoma, unspecified B-cell lymphoma, and T-cell lymphomas) were above 1.0, but were not statistically significant.

A case-control study of glioma in Nebraska reported an overall odds ratio of 1.5 (95% CI: 0.7–3.1) for glyphosate exposure (as compared with nonfarmers, who were considered "unexposed") (Lee et al., 2005). The odds ratios differed depending on type of respondent (OR for self-respondents = 0.4; OR for proxy respondents = 3.1), and the authors expressed concern that differential misclassification may explain the positive associations observed for proxy respondents for glyphosate and several other pesticides, perhaps as a result of more accurate reporting of proxies for cases and underreporting by proxies for controls. Sixty-two percent of proxy respondents for cases were spouses compared to 45% of proxy respondents for controls.

The Upper Midwest Health Study, which evaluated brain cancer among rural residents of four Midwestern states, found no material association between gliomas and glyphosate among women (OR = 0.7; 95% CI: 0.4–1.3) (Carreon et al., 2005). The study investigators did not publish the results for analyses of glyphosate and gliomas in men, but stated the following about a group of individual pesticides, which included glyphosate: "We observed no statistically significant associations in analyses including and excluding proxy respondents..." (Ruder et al., 2004).

Lee et al. (2004b) conducted a case-control study of stomach and esophageal adenocarcinomas and pesticide use in eastern Nebraska. There was no material association between self-reported "ever use" of glyphosate and either stomach cancer (OR = 0.8; 95% CI: 0.4–1.5) or esophageal cancer (OR = 0.7; 95% CI: 0.3–1.4).

3.3. Summary of Results from Studies of Glyphosate Exposure and Cancer

All of the epidemiologic studies were observational and are prone to bias, measurement error, and/or confounding. Measurement error is a common problem in observational studies, and it is difficult to estimate the magnitude and direction of any resulting information bias without additional data, which typically is not

Table 4
Summary of findings: case-control studies of exposure to glyphosate and cancer outcomes.

Author(s) and year	Exposure evaluated	Subgroup description	# of exposed cases	# of exposed controls	Odds ratio	95% Confidence Interval	Variables included in statistical model
Leukemia							
Brown et al. (1990)	Agricultural exposure based on ever living or working on a farm	Never farmed	243	547	1.0	Referent	Vital status, age, state of residence, use tobacco daily, family history (parent, sibling, or child) of lymphopoietic cancer, high-risk occupations, and high-risk exposures
		Ever farmed	335	698	1.2	1.0–1.5	
	Specific pesticide exposures (ever mixing, handling, or applying) of Iowa farmers compared to nonfarmers (Iowa and Minnesota)	Glyphosate	15	49	0.9	0.5–1.6	
Multiple Myeloma							
Brown et al. (1993)	Agricultural exposure based on ever living or working on a farm	Never farmed	62	272	1.0	Referent	Vital status and age
		Ever farmed	111	378	1.2	0.8–1.7	
	Individual pesticides that were handled personally (ever mixing, handling, or applying) compared to nonfarmers	Glyphosate	11	40	1.7	0.8–3.6	
Non-Hodgkin Lymphoma							
Cantor et al. (1992)	Agricultural exposure based on ever living or working on a farm	Nonfarmer	266	547	1.0	Referent	Vital status, state, age, smoking, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures
		Farmer	356	698	1.2	1.0–1.5	
	Farmers with specific pesticide exposures (ever mixing, handling, or applying) compared to nonfarmers	Glyphosate	26	49	1.1	0.7–1.9	
De Roos et al. (2003)	Ever exposure to specific pesticide; men only (all 47 pesticides were regressed simultaneously)	Glyphosate (logistic regression)	36	61	2.1	1.1–4.0	Age, study site and other pesticides
		Glyphosate (hierarchical regression)	36	61	1.6	0.9–2.8	Second-level model incorporated what was known about each true effect parameter prior to seeing the study data
Hardell and Eriksson (1999)	Exposure to specific pesticides (ever/never exposed to the specific pesticide versus no exposure to any pesticide)	Glyphosate (conditional logistic regression; univariate analysis)	4	3	2.3	0.4–13	Age and county (matching factors)
		Glyphosate (conditional logistic regression; multivariate analysis)	4	3	5.8	0.6–54	Multivariate variables not listed by authors
Hardell et al. (2002)	Exposure to specific pesticides (ever/never exposed to the specific pesticide versus no exposure to any pesticide)	Glyphosate (conditional logistic regression; univariate analysis)	8	8	3.04	1.08–8.52	Age and county (matching factors);
		Glyphosate (conditional logistic regression; multivariate analysis)	8	8	1.85	0.55–6.20	study, study area (county), and vital status Multivariate variables not listed by authors
Lee et al. (2004a)	Exposure to individual pesticides	Glyphosate use–Nonasthmatics	53	91	1.4	0.98–2.1	Age, state, vital status
		Glyphosate use–Asthmatics	6	12	1.2	0.4–3.3	
McDuffie et al. (2001)	Exposure to individual active chemicals	Glyphosate (Round-Up)	51	133	1.26	0.87–1.80	Strata for age and province of residence
		Glyphosate (Round-Up)	NR	NR	1.20	0.83–1.74	Plus statistically significant medical variables
Nordstrom et al. (1998)	Exposure to specific herbicides, insecticides, and fungicides	Glyphosate	4	5	3.1	0.8–12	Age and county (matching factors)
Eriksson et al. (2008)	Exposure to specific herbicides regardless if they had also been exposed to phenoxyacteic acids or not	Glyphosate	29	18	2.02	1.10–3.71	Age, sex, and year of diagnosis or enrollment
			29	18	1.51	0.77–2.94	Age, sex, and year of diagnosis or enrollment and other pesticides
	Exposure to herbicide stratified by median number of days among exposed controls	Glypohsate ⩽10 days	12	9	1.69	0.70–4.07	Age, sex, and year of diagnosis or enrollment
		Glyphosate >10 days	19	9	2.36	1.04–5.37	
	Exposure to specific herbicides according to different lymphoma entities	Glyphosate:B-Cell lymphomas	NR	NR	1.87	0.998–3.51	Age, sex, and year of diagnosis or enrollment
		Lymphocytic	NR	NR	73.35	1.42–7.89	
			NR	NR	1.89	0.62–5.79	
			NR	NR	1.22	0.44–3.35	
			NR	NR	1.63	0.53–4.96	

Table 4 (*continued*)

Author(s) and year	Exposure evaluated	Subgroup description	# of exposed cases	# of exposed controls	Odds ratio	95% Confidence Interval	Variables included in statistical model
		lymphoma/B-CLL	NR	NR	1.47	0.33–6.61	
			NR	NR	2.29	0.51–10.4	
		Follicular grade I-III	NR	NR	5.63	1.44–22.0	
		Diffuse large B-cell lymphoma					
		Other specified B-cell lymphoma					
		Unspecified B-cell lymphoma					
		T-cell lymphomas					
		Unspecified NHL					
Brain Cancer							
Carreon et al. (2005)	Exposure to the most commonly used individual pesticides by the entire study population compared to those that reported not being exposed to any pesticides (women only)	'Glyphosate (including proxy respondents)	18	41	0.7	0.4–1.3	Age, 10-year age group, education, any other pesticide exposure
		Glyphosate (excluding proxy respondents)	10	41	0.6	0.3–1.2	
Lee et al. (2005)	Adult farming activity and ever-use of specific pesticides compared to non-farmers (men only)	Glyphosate					
		Overall	17	32	1.5	0.7–3.10.	Age, respondent type
		Self respondents	4	17	0.4	1–1.6	Age
		Proxy respondents	13	15	3.1	1.2–8.2	Age
Ruder et al. (2004)	Exposure to individual farm pesticides that most participants were exposed to (men only)	Glyphosate (including proxy respondents)	NR	NR	NS	NS	Age, 10-year age group, education, any other pesticide exposure on the farm, in the house or garden, or on a nonfarm job
		Glyphosate (excluding proxy respondents)	NR	NR	NS	NS	
Esophagus and Stomach Cancer							
Lee et al. (2004b)	Adult farming activity and ever-use of specific pesticides compared to nonfarmers (men only)	Glyphosate[a]					
		Stomach cancer	12	46	0.8	0.4–1.5	Age, gender
		Esophageal cancer	12	46	0.7	0.3–1.4	

Abbreviations: NR: not reported; NS: not significant.

[a] The odds ratios did not differ significantly by respondent type (self versus proxy), as reported in text by the authors.

collected. The issue of exposure measurement and validation is discussed further in Section 3.4. In addition, causality may not be inferred directly from individual observational studies, but requires consideration of all of the relevant literature. Hill (1965) and others have described principles to consider when evaluating a body of literature, including strength of the association, consistency of findings across studies, and dose–response. Unfortunately, many of the potential associations between glyphosate and a given cancer site (or subsite) have been evaluated in only one study and thus a determination of consistency cannot be made.

None of the AHS cohort study analyses reported statistically significant positive findings for glyphosate exposure and total cancer or any site-specific cancer in adults or children. Although the relative risk for multiple myeloma reported by De Roos et al. (2005) was greater than 2.0 (OR = 2.1), formal bias analysis suggested that this estimate was likely spuriously high as a result of bias (Lash, 2007). Brown et al. (1993) reported a statistically non-significant OR of 1.7 in their case-control study of multiple myeloma, but the authors suggested that recall bias and chance may have been contributing factors. De Roos et al. (2003) reported a statistically significant association based on a pooled analysis of case-control studies of NHL and glyphosate, but the pooled odds ratio was not significant in the hierarchical regression. In the pooled analysis of two Swedish case-control studies, Hardell et al. (2002) reported a significant positive univariate association between glyphosate exposure and NHL, but the multivariate-adjusted odds ratio was attenuated and not statistically significant. Similar findings were reported by Eriksson et al. (2008). Odds ratios were above 1.0 for all types of NHL in the case-control study by Eriksson et al. (2008), and were statistically significant for SLL/CLL and "unspecified NHL" types, but the corresponding confidence intervals were wide. In contrast, the prospective AHS did not corroborate the positive association with NHL reported by the Swedish case-control studies. Analyses of increasing category of glyphosate exposure days and incident NHL produced rate ratios that were below the null value of 1.0 (De Roos et al., 2005). Unfortunately, the AHS has not published results of analyses of specific types of NHL and glyphosate (or other pesticides) to date. Lee et al. (2005) observed a significantly elevated odds ratio between gliomas and glyphosate in analyses restricted to proxy respondents, but analyses of self-respondents and self- and proxy-respondents combined were not statistically significant. Thus, there were no consistent patterns of statistically significant positive associations between glyphosate and any cancer. Furthermore, there was only limited evidence of increasing risk with increasing exposure in studies that had data to analyze exposure–response patterns (Eriksson et al., 2008). We support a cautious interpretation of the few positive associations reported and conclude that the epidemiologic data, considered

together, do not support a causal association between glyphosate exposure and cancer.

3.4. Exposure assessment

The validity of epidemiologic studies that evaluate the relationship of exposure to environmental chemicals, including glyphosate, and adverse health effects (e.g., cancer) depends in large part on the ability to correctly quantify and classify an individual's exposure. All of the epidemiologic studies included in this review relied primarily on questionnaires and interviews to characterize participants' past and/or current exposure to glyphosate. Questionnaires are commonly used for characterization of exposure and capture self-reported data on exposure. This is cost-effective and non-invasive, but is subject to misclassification and recall bias. Hoppin et al. (2002) evaluated the accuracy of reported pesticide use from participants of the AHS based on years the pesticide was officially registered and concluded the participants provided plausible information regarding pesticide use when broad definitions of analytic categories were used. In a study by Blair and Zahm (1993), comparing the self-reported use of pesticides with information provided by major suppliers, agreement was found 60% of the time for both cases and controls. Misclassification error is often considered to be non-differential and to result in underestimated relative risk estimates. Neither assumption, however, is necessarily true (Dosemeci et al., 1990; Flegal et al., 1991; Kristensen 1992; Rothman et al., 2008). Differential bias is a general concern because of recall bias in cases, but that was not found in this study (Blair and Zahm, 1993).

Biomonitoring studies can be useful in estimating systemic dose, as well as in validating other exposure assessment tools, such as questionnaires. The algorithm initially developed for the AHS to estimate pesticide exposure intensity scores used information from the questionnaires on mixing, application, repair, and PPE (Dosemeci et al., 2002; Thomas et al., 2010). Exposure determinants and scoring weights used in this algorithm were based on information derived from the available literature and from the Pesticide Handlers Exposure Database. A recent paper by Coble and colleagues (2011) described a revised AHS exposure intensity algorithm. The revised algorithm incorporated information from exposure biomonitoring studies of 2,4-D, chlorpyrifos and captan conducted on AHS participants. Several studies have been conducted to evaluate the AHS pesticide exposure algorithm (Coble et al., 2005; Acquavella et al., 2006; Hines et al., 2008; Thomas et al., 2010); however none specifically addressed glyphosate measurement in the AHS study population. The AHS Pesticide Exposure Study (AHS/PES) was conducted among a subset of 2,4-D and chlorpyrifos applicators in the AHS cohort to assess the pesticide exposure algorithm by comparing algorithm intensity scores with measured exposures, specifically urinary biomarkers, dermal patch, hand wipe, and personal air samples. Correlations between observer and questionnaire intensity scores were high (Spearman's r = 0.92 and 0.84 for 2,4-D and chlorpyrifos, respectively). Correlations between intensity scores from questionnaires for individual applications and post-application urinary biomarker concentrations were moderate for both 2,4-D (Spearman's r = 0.42) and chlorpyrifos (Spearman's r = 0.53) applicators. However, the strength of the correlations varied by method of application among the chlorpyrifos applicators, with higher correlations observed with liquid spray applications (n = 4 applicators) and lower correlations observed with in-furrow granular applications (n = 12 applicators). In a study of captan use (a fungicide) among orchard pesticide applicators in the AHS, Hines et al. (2008) reported that the AHS pesticide exposure intensity algorithm was predictive of thigh and forearm exposures, but not air, hand rinse or urinary THPI (captan metabolite) exposures.

Coble and colleagues (2005) evaluated the initial AHS pesticide exposure algorithm using biomonitoring data from the Canadian Pesticides Exposure Assessment Study (PEAS). In this study, 126 participants completed questionnaires following application of either MCPA or 2,4-D. The concentrations of these chemicals were measured in urine samples colleted prior to application and for two days following application. The authors concluded, "...the algorithm scores, based mostly on PPE use, provide a reasonably valid estimate of exposure intensity for these applicators"(Coble et al., 2005). However, they noted that there was considerable variability in urine concentrations among applicators with similar algorithm scores, and that the algorithm worked less well for MCPA than 2–4,D.

The Farm Family Exposure Study (FFES), a biomonitoring study conducted in South Carolina and Minnesota, evaluated pesticide exposures, including glyphosate, among farmers, spouses of farmers, and their children before, during, and after application (Acquavella et al., 2004; Baker et al., 2005; Mandel et al., 2005). Because epidemiologic studies often rely on self-reported exposure data, this biomonitoring study provided a resource for evaluating models of pesticide exposure and for developing predictors of exposure intensity for future epidemiologic studies. Forty-eight participating farm families had exposure to glyphosate through use or proximity to application (Acquavella et al., 2004). Acquavella et al. (2004) reported 60% of the farmers had detectable levels of glyphosate in their urine on the day of application. The geometric mean was 5-fold higher in applicators reporting not wearing gloves. For children, 12% had detectable levels in their urine; all but one of these helped with the mixing, loading, or application of the pesticide. All of the calculated systemic doses were less than the US EPA reference dose for glyphosate. Mandel et al. (2005) showed that exposure profiles differed for the three chemicals studied (i.e., glyphosate, chlorpyrifos, 2,4-dicholophenoxyacetic acid) and emphasized the importance of chemical-specific considerations when using exposure assessment in biomonitoring studies. Thus, exposure algorithms that rely on average or generic pesticide exposure information and do not take into account specific chemical properties such as vapor pressure or dermal penetration will be limited in their ability to estimate exposure to specific chemicals (Acquavella et al., 2006).

Acquavella et al. (2006) used data from the FFES to evaluate the exposure intensity algorithm used in the AHS. Specifically, Acquavella et al. (2006) evaluated an algorithm used to estimate lifetime average exposure intensity (Dosemeci et al., 2002) based on responses to a questionnaire against measured urinary pesticide concentrations. The study found low to moderate correlations between trained field observers' assessments and urine concentrations for specific pesticides (Spearman correlations ranged from 0.12 to 0.47) and lower correlations with self reported exposures in participants and urine concentrations (Spearman correlations ranged from 0.13 to 0.25). For glyphosate, evaluation of self reported exposures in participants and systemic doses resulted in essentially no correlation (Spearman correlation = 0.04). In addition, this study reported contrasting correlations when evaluating different formulations of the same pesticide to urinary pesticide concentrations. The discussion emphasized the importance of incorporating not only duration and frequency of pesticide use, but also the type of pesticide formulation into exposure characterizations. The specific physical and chemical properties, formulations, and application practices of the individual pesticide lead to different toxicokinetic properties. Thus, generic exposure assessments likely lead to exposure misclassification, and exposure algorithms may be enhanced by validation with biomonitoring data.

Thus, the information from the FFES biomonitoring study indicates that systemic exposure to glyphosate, even among farmer

applicators, was generally low (i.e., less than the US EPA reference dose), and was even smaller among farmers who reported wearing gloves. A limitation common to all of the epidemiologic studies relates to exposure assessment, specifically that all of the studies relied solely on questionnaires and none used biomonitoring or other data to validate self-reported responses. The AHS attempted to take into account duration and intensity of use as well as use of personal protective equipment, but the algorithm was not specific to glyphosate. In fact, it did not correlate with biomonitoring data specific to glyphosate (Acquavella et al., 2006). Results from the biomonitoring studies, considered together, suggest a cautious approach when interpreting results from a "one size fits all" algorithm (Acquavella et al., 2006; Mandel et al., 2005; Coble et al., 2005; Hines et al., 2008; Thomas et al., 2010). Furthermore, Thomas et al. (2010) urge caution in extrapolating findings from the AHS/PES to the larger AHS cohort because participants were not selected to be representative of the larger cohort, only two chemicals were evaluated (2,4-D and chlorpyrifos), and a small number of applications were monitored. We recommend further that data from the FFES specific to glyphosate be considered when interpreting results from the AHS based on "intensity-weighted exposure days" (Acquavella et al., 2006).

Acquavella et al. (2006) suggest that questionnaires appear to be sufficient to distinguish users from nonusers of specific pesticides, and probably can distinguish frequent users from infrequent users. However, the ability of questionnaires alone to collect accurate information regarding frequency, duration and intensity of exposure to specific pesticides has not been established; hence the ability to evaluate exposure–response associations is limited and error-prone (Acquavella et al., 2006).

While data from biological specimens collected from some or all of the study participants can be an important and useful supplement to self-reported exposure information, there are limitations that must also be considered. Personal exposure levels are variable, and biologic specimens collected at one point in time will be less likely to accurately classify individuals than repeat samples (Rothman et al., 2008). Glyphosate formulation is another potential consideration in light of in vitro studies suggesting that product formulation and degree of dilution influence aromatase activity and cell death in cell lines (Richard et al., 2005; Benachour and Seralini 2009). Furthermore, Barr et al. (2006) suggest that if the goal of collecting biomonitoring data is to estimate exposure, additional information such as toxicokinetic data, rate of intake, and rate of uptake may be needed, Similarly, the utility of such data to validate questionnaire data or to use to correct questionnaire data will depend on the accuracy of the biomonitoring data with respect to actual exposure over a defined time period. Specific challenges for using biomonitoring data to validate or correct questionnaire data on glyphosate use and exposure include the fact that glyphosate is cleared rapidly from the body, and thus the timing of collection of biospecimens would need to be considered carefully (Acquavella et al., 2004; Rothman et al., 2008). Finally, costs of such analyses need to be considered and biospecimen may be feasible for only a subset of a study population. Nevertheless, if collected carefully such data may contribute useful information and allow for correction of some misclassification (Barr et al., 2006).

4. Discussion

Our review of the currently available epidemiologic literature on glyphosate and cancer found no evidence of a consistent pattern of positive associations that would be indicative of a causal relationship between any site-specific cancer and exposure to glyphosate. The prospective AHS has evaluated associations between glyphosate and all cancer sites (De Roos et al., 2005), with no statistically significant results. Other studies, including cohort and case-control studies of specific cancers have similarly reported results generally consistent with the null hypothesis. These results are not surprising, given that glyphosate has been classified as a noncarcinogenic and non-mutagenic chemical (WHO/FAO, 2004). The AHS recently revised its exposure intensity algorithm by incorporating biomonitoring data with information from the literature and from the Pesticides Handlers Exposure Database; however, it does not address potential pesticide-specific differences (Coble et al., 2011). Future studies could be improved by more careful attention to validating exposure to glyphosate and other herbicides or pesticides under study. With this in mind, further analyses of the AHS, with additional accrued cases, may be informative regarding associations with specific types of NHL and for more stable estimates of potential associations with multiple myeloma.

Conflict of interest statement

The authors have disclosed the funding source for this research. JSM has served has a paid consultant to Monsanto Company. Final decisions regarding the content of the manuscript were made solely by the four authors.

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