Regulatory Toxicology and Pharmacology 61 (2011) 172–184

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Epidemiologic studies of glyphosate and non-cancer health outcomes: A review

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ARTICLE INFO

Article history:
Received 7 March 2011
Available online 26 July 2011

Keywords:
Glyphosate
Herbicides
Epidemiology
Respiratory health
Reproductive health
Chronic disease

ABSTRACT

The United States (US) Environmental Protection Agency (EPA) 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. To examine potential health risks in humans, we searched and reviewed the literature to evaluate whether exposure to glyphosate is associated causally with non-cancer health risks in humans. We also reviewed biomonitoring studies of glyphosate to allow for a more comprehensive discussion of issues related to exposure assessment and misclassification. Cohort, case–control and cross-sectional studies on glyphosate and non-cancer outcomes evaluated a variety of endpoints, including non-cancer respiratory conditions, diabetes, myocardial infarction, reproductive and developmental outcomes, rheumatoid arthritis, thyroid disease, and Parkinson's disease. Our review found no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease and exposure to glyphosate. Most reported associations were weak and not significantly different from 1.0. Because accurate exposure measurement is crucial for valid results, it is recommended that pesticide-specific exposure algorithms be developed and validated.

1. Introduction

Glyphosate (*N*-phosphonomethyl glycine) 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 have been sold in the US since 1974 and marketed under the brand names Roundup®, Roundup Pro®, Roundup PowerMAX™, Roundup WeatherMAX® and AquaMaster®. Glyphosate-based herbicides 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. 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).

A weight of evidence analysis of glyphosate and Roundup® concluded that they were neither genotoxic nor mutagenic as a result of direct reaction with DNA (Williams et al., 2000). In addition, in multigeneration reproduction and developmental toxicity studies in rats, no adverse effects were observed on the animals' ability to mate, conceive, carry or deliver normal offspring. The US EPA concluded that there is a reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure to glyphosate residues (US EPA, 2007). No evidence of neurotoxicity was observed in any study conducted including specialized neurotoxicity studies (WHO/FAO, 2004).

We reviewed epidemiologic studies of glyphosate and non-cancer health risks to evaluate whether exposure to glyphosate is associated causally with health risks in humans. We follow the presentation of results with a discussion of interpretation issues, including exposure assessment considerations, as they relate to findings from the observational epidemiologic studies. We did not consider it appropriate to calculate quantitative summary relative risk estimates across studies evaluating many different health outcomes ranging from reproductive outcomes to respiratory

Abbreviations: ADD/ADHD, attention deficit disorder/attention deficit hyperactivity disorder; AHS, Agricultural Health Study; CAS, Chemical Abstract Service; CFR, conditional fecundity ratio; CI, confidence interval; FFES, Farm Family Exposure Study; NTD, neural tube defect; OR, odds ratio; PD, Parkinson's disease; RA, rheumatoid arthritis; RR, relative risk; US EPA, United States Environmental Protection Agency.

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doi:10.1016/j.yrtph.2011.07.006

symptoms and conditions to myocardial infarctions. Throughout this review, the term "glyphosate" is used to refer to glyphosate-containing herbicides and not necessarily to the specific chemical itself.

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, cross-sectional) that evaluated the association between glyphosate and a non-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. 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

Although associations between glyphosate and non-cancer outcomes were examined in study cohorts, including the Agricultural Health Study (AHS) cohort, many analyses were based on cross-sectional data and/or prevalent cases (e.g., baseline questionnaire). Studies and results reported under the heading "cohort studies" were limited to analyses of incident cases. The study of pesticides and Parkinson's disease (PD) by Kamel et al. (2007) analyzed both baseline prevalence data as well as incident PD cases identified

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

Author(s) and year	Location	Study size	Study population	Exposure	Comparison group
Diabetes					
Montgomery et al. (2008)	Iowa and North Carolina, US	31,787 licensed pesticide applicators	Licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997 At follow-up, from 1999 to 2003, applicators and spouses were contacted by telephone and interviewed; Participants who self-reported diabetes at baseline were excluded	Two glyphosate exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use based on response to questionnaires	The pesticide applicators who reported never using a specific pesticide
Myocardial infarction					
Dayton et al. (2010)	Iowa and North Carolina, US	22,425 farm women	Female pesticide applicators and female spouses of pesticide applicators enrolled in the Agricultural Health Study who completed the enrollment and follow-up questionnaires and a follow-up phone interview Women who reported an MI before enrollment were excluded	Pesticide exposure was determined from questionnaire response assessing ever use of 50 individual pesticides and overall lifetime use of pesticides	The female pesticide applicators or spouses who reported never using a specific pesticide
Mills et al. (2009)	Iowa and North Carolina, US	Mortality analysis: 54,609	Mortality analysis: all male pesticide applicators who enrolled in the Agricultural Health Study and provided complete data on all covariates	Two glyphosate exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use based on response to questionnaires	The pesticide applicators who reported never using a specific pesticide
		Incidence analysis: 32,024	Incidence analysis: further limited to those who completed follow-up telephone interview and who reported no prior myocardial infarction at enrollment		
Parkinson's disease					
Kamel et al. (2007)	Iowa and North Carolina, US	At enrollment (prevalence) 79,640 pesticide applicators and spouses At follow-up (incidence) 56,009 pesticide applicators and spouses	Licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997 At follow-up, from 1999 to 2003, applicators and spouses were contacted by telephone and interviewed	Two glyphosate exposure metrics were created: ever/never mixed or applied, cumulative lifetime days of use based on response to questionnaires	For the evaluation of prevalence, the comparison population responded negatively to the Parkinson's disease (PD) question during study enrollment For incidence, the comparison population responded negatively during the follow-up interview

during the 1999–2003 follow-up. For simplicity, we reported both the prevalence and incidence findings from this study in the cohort studies section. In addition, one nested case–control study of rheumatoid arthritis (RA) was conducted in the AHS, and is described in the case–control studies section rather than the cohort studies section because it used prevalent rather than incident RA cases. Brief descriptions of each cohort, case–control and cross-sectional study are presented in Tables 1–3, respectively.

3.1. Cohort studies

We identified four reports from cohort studies, with one study each of Parkinson's disease (Kamel et al., 2007) (PD), diabetes (Montgomery et al., 2008, and myocardial infarction (MI) in men (Mills et al., 2009) and women (Dayton et al., 2010). Each analysis was conducted in the AHS (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. Health information was collected as part of this questionnaire as well as on an additional mailed questionnaire and a follow-up telephone interview. 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. All applicators, private and commercial, were given the same set of questionnaires to complete. Spouses of applicators were also invited to participate, and completed a questionnaire at enrollment. All of the analyses reported in the papers summarized in this review were based on dichotomous exposure variables for glyphosate (e.g., ever use vs. never use). In addition, for each published report, glyphosate was one of many pesticides analyzed in association with a given health outcome. There was no evidence that glyphosate was associated with increased risk of diabetes (Table 4); the odds ratio was below 1.0 and the 95% confidence interval excluded the null; (Montgomery et al., 2008). Kamel et al. (2007) observed no association between glyphosate use and self-reported PD in analyses of prevalent PD cases (OR = 1.0; 95% CI: 0.6–1.7) and incident cases (OR = 1.1; 95% CI: 0.6–2.0). There was no material association between glyphosate exposure and fatal or nonfatal MI among male pesticide applicators in the AHS (Mills et al., 2009) or among female spouses of applicators and female applicators in the AHS (Dayton et al., 2010).

3.2. Case–control studies

We identified and reviewed two case–control studies that evaluated glyphosate and reproductive outcomes (Garcia et al., 1998; Rull et al., 2006), one case–control study evaluating PD (Wechsler et al., 1991), and one nested case–control study of RA (De Roos et al., 2005a). Results are summarized in Table 5. Of these studies, two were conducted in agricultural settings (Garcia et al., 1998; De Roos et al., 2005a).

In a case–control study conducted in an agricultural region of Spain, Garcia et al. (1998) observed no significant association between fathers' exposure to glyphosate three months prior to conception or during the first trimester of pregnancy and congenital malformations (OR = 0.94; 95% CI: 0.37–2.34). Rull et al. (2006) pooled data from two California case–control studies that evaluated neural tube defects (NTDs) and residential proximity to areas where agricultural pesticides were applied. In these studies, potential pesticide exposure was estimated based on a linkage of data from pesticide use reports from the California Department of Pesticide Regulation with land use survey maps of crops, which were obtained from the California Department of Water Resources. Analyses of all pesticides, including glyphosate, were based on dichotomous exposure categories. Mothers were considered "exposed" to a particular pesticide if any crop type within a designated radius (1000 m) surrounding her residence was treated with that agent. Results for glyphosate were similar regardless of the statistical model used, and each of the reported 95% confidence intervals included 1.0 (Table 5). In the hierarchical regression model evaluating glyphosate use within 1000 m of maternal residences and NTDs, the odds ratio was 1.4 and statistically nonsignificant (95% CI: 0.8–2.5).

Wechsler et al. (1991) conducted a pilot case–control study of PD. Data on home use "Round-Up" exposure was available for 19 cases (14 exposed) and 22 controls (nine exposed). The unadjusted odds ratio was 4.04, but the corresponding confidence interval was wide and included 1.0 (95% CI: 0.91–19.27). The authors conducted further evaluation, including duration of use, of three home pesticides, but these did not include Roundup®. De Roos et al. (2005a) conducted a nested case–control study of RA within the AHS female cohort. Cases were women with physician-confirmed RA, initially self-reported as part of a 5-year follow-up interview. The authors stated, "Risk of RA was not associated with mixing or applying pesticides overall or with any pesticide class" (De Roos et al., 2005a). Similarly, there was no significant association between glyphosate exposure and RA (OR = 1.2; 95% CI: 0.8–1.8).

3.3. Cross-sectional studies

Brief descriptions of cross-sectional analyses of glyphosate exposure and non-cancer outcomes are presented in Table 3. Six cross-sectional studies evaluated reproductive outcomes (Arbuckle et al., 2001; Curtis et al., 1999; Sathyanarayana et al., 2010; Garry et al., 2002; Saldana et al., 2007; Savitz et al., 1997), eight cross-sectional studies analyzed respiratory conditions in the AHS (Hoppin et al., 2009, 2008, 2007, 2006, 2002a; Slager et al., 2009, 2010; Valcin et al., 2007), and there was one study each of retinal degeneration (Kirrane et al., 2005) and thyroid disease (Goldner et al., 2010). Main results of these studies are shown in Table 6.

Three reports analyzed cross-sectional data from the Ontario Farm Family Health Study. This study identified eligible farm couples and obtained questionnaire data on farm activities and reproductive health. The women in the study were asked to report information on all of their pregnancies. Savitz et al. (1997) evaluated associations between paternal farm activities and pregnancy outcomes. The odds ratios for miscarriages were similar for glyphosate use on crops and on yards, but neither was statistically significant (OR for glyphosate use on crops = 1.5; 95% CI: 0.8–2.7; OR for glyphosate use in the yard = 1.4; 95% CI: 0.7–2.8). The odds ratio for preterm delivery and glyphosate use on crops was 2.4, but the corresponding 95% confidence interval (0.8–7.9) was wide and included 1.0. There were fewer than five preterm delivery cases whose fathers reported using glyphosate on yards and the authors did not analyze these data further. Arbuckle et al. (2001) conducted an "exploratory analysis" to explore the role of exposure timing for pesticides as potential risk factors for spontaneous abortion. The authors reported a borderline significant association between preconception exposure to glyphosate and spontaneous abortion (OR = 1.4; 95% CI: 1.0–2.1), but no significant association with postconception exposure (OR = 1.1; 95% CI: 0.7–1.7). The authors noted many limitations to this study, including likely exposure misclassification and issues with assigning exposures accurately to the preconception or postconception window. Curtis et al. (1999) calculated conditional fecundability ratios (CFR) for several types of pesticides. "Conditional fecundability" is conditional on pregnancy. The CFR estimates the conditional fecundability for the exposed group divided by that of the unexposed group, and a CFR of less than 1.0 indicates a reduced probability of

Table 2
Case–control studies of exposure to glyphosate and non-cancer outcomes.

Author(s) and year	Case population	Control population	Enrollment period	Exposure assessment
Reproductive outcomes: congenital malformations and defects				
Garcia et al. (1998)	Congenital malformations and defects determined *a priori* selected from live births up to the age of 1 year in eight public hospitals in agricultural areas of Comunidad Valenciana, Spain Cases were identified through hospital discharge records	Live births matched by hospital and date of birth (1:1)	1993–1994	Interviews to collect information on potential confounding variables and on activities with potential exposure to pesticides (agricultural work, pesticide application, etc.)
Reproductive outcomes: neural tube defects				
Rull et al. (2006)	Pooled from two case–control studies conducted by the California Birth Defects Monitoring Program	Unmatched, and randomly sampled from all live-born infants during the same sampling time period without structural congenital abnormalities diagnosed before their 1st birthday	First study – delivered between January 1987 and December 1988	Exposures to specific restricted use pesticides were evaluated by linking residential addresses two weeks or more during the periconceptional period, pesticide use reports, and geographic distribution of crops
	Children with a confirmed diagnosis of neural tube defects		Second study – delivered between June 1989 and May 1991	Mothers were interviewed to assess confounders and risk factors experienced during periconceptional period
	First study – children of women in most California counties Second study – children in all California counties except Los Angeles, Ventura, and Riverside			
Parkinson's disease				
Wechsler et al. (1991)	Recruited from two sources: the University Hospital Neurology Clinic at the University of Washington and Seattle area Parkinson's disease support groups	Non-demented individuals with neurological disorders other than Parkinson's that were recruited exclusively from University Hospital Neurology Clinic	Not given	Occupational pesticide exposure was limited to males
	All cases were at least 40 years old	All controls were at least 40 years old		Home pesticides exposure was categorized by "years used" or "days used per year" The frequency of use of specific brand name pesticides was assessed
Rheumatoid arthritis				
De Roos et al. (2005b)	Nested case–control of female participants in the Agricultural Health Study with a physician confirmed diagnosis of rheumatoid arthritis, reported during the 5 year follow-up interview before December 2003 (one case in infancy was excluded)	Controls were selected from the female participants in the Agricultural Health Study that completed the 5-year follow-up interview and matched to each case by birthdate (±1 year) (5:1)	1993–1997	Ever/never personally mixed or applied 49 individual pesticides for use on the farm, in the home or garden, or in commercial application (no designation between uses)
		Women reporting any systemic autoimmune disease were excluded		Data were also collected regarding duration and frequency for all pesticides combined

conception in the exposed group, relative to the unexposed (Curtis et al., 1999). The CFR was less than 1.0, but not statistically significant, for the exposure group in which women reported glyphosate regardless of men's use (CFR = 0.61; 95% CI: 0.30–1.26). For the exposure group in which men reported glyphosate use, but there was no use by women, the CFR was 1.30 (95% CI: 1.07–1.56). Self-reported glyphosate exposure during pregnancy was associated inversely with gestational diabetes (crude OR = 0.61; 95% CI: 0.26–1.48; adjusted odds ratios were presented graphically) in a cross-sectional analysis of data from the AHS (Saldana et al., 2007). Sathyanarayana et al. (2010) evaluated self-reported pesticide exposure and reported birth weight for most recent birth among AHS women. In multivariable linear regression analyses, history of "ever" glyphosate use was associated with a small, statistically non-significant increase in birth weight (beta coefficient = 4 g; 95% CI: −40–48 g). Garry et al. (2002) conducted a cross-sectional study of pesticide applicators and their families. The authors evaluated numerous pesticides and several types of birth defects and adverse developmental outcomes. Parent-reported ADD/ADHD in children was associated positively and significantly with use of glyphosate; six out of 14 children with parent-reported ADD/ADHD had exposure to phosphonamino herbicides (glyphosate, Roundup) (OR = 3.6; 95% CI: 1.35–9.65). The ADD/ADHD diagnoses were not confirmed by a clinician, however.

There were eight published cross-sectional studies of non-cancerous respiratory conditions and glyphosate exposure conducted among participants in the AHS, including two studies of asthma (Hoppin et al., 2009 (males); Hoppin et al., 2008 (females)), two studies of chronic bronchitis (Hoppin et al., 2007 (all applicators); Valcin et al., 2007 (female spouses of applicators)), two studies of rhinitis (Slager et al., 2009 (commercial applicators); Slager et al., 2010 (private applicators)), and two studies of wheeze (Hoppin et al., 2006 (commercial applicators); Hoppin et al., 2002a (private applicators)). Hoppin et al. (2009) evaluated associations between pesticide use and self-reported prevalent adult-onset asthma among male pesticide applicators in the AHS. Self-reported allergy

Table 3
Cross-sectional studies of exposure to glyphosate and non-cancer outcomes.

Author(s) and year	Location	Study size	Study population	Exposure	Comparison group
Reproductive outcomes: spontaneous abortion					
Arbuckle et al. (2001)	Ontario, Canada	2110 farmers' wives	Farm couples living on farms in Ontario selected from the 1986 Canadian Census of Agriculture who lived on the farm year round, the woman was ⩽44 years old, the time interval of the pregnancy was known with certainty, the conception/s occurred at the study farm, and the current husband was the father Three questionnaires were administered from 1991 to 1992	Pesticide unit variables based on reproductive and pesticide exposure history data Analyzed for preconception (3 months prior and month of conception) and postconception (3 month period starting the first month after conception)	Women eligible to participate in the study who were not exposed to the pesticide of interest during the respective exposure time windows
Reproductive outcomes: conditional fecundability ratio (CFR)					
Curtis et al. (1999)	Ontario, Canada	2012 planned pregnancies	Farm couples living on farms in Ontario selected from the 1986 Canadian Census of Agriculture who lived on the farm year round, the woman was ⩽44 years old, the time interval of the pregnancy was known with certainty, the conception/s occurred at the study farm, and the current husband was the father Three questionnaires were administered from 1991 to 1992	Pesticide use on the farm during the month, or prior 2 months, of attempted conception, and on type, amount, and timing of pesticide use by husband, wife, and farm operator (if different)	The exposure group with no use of the pesticide on the farm and no pesticide activities by either the husband or the wife during the exposure window
Reproductive outcomes: birth weight					
Sathyanarayana et al. (2010)	Iowa and North Carolina, US	2246 live births among female spouses of licensed pesticide applicators	Live births to female spouses of licensed pesticide applicators enrolled in the Agricultural Health Study who completed the Female and Family Health Questionnaire for the Agricultural Health Study, from 1993 to 1997 Exclusion criteria included: births that occurred in women >5 years prior to enrollment; multiple births or multiple status unknown; births without birth weight or length of gestation; incomplete information on base model covariates	Four exposure categories were created for the first 3 months of the most recent pregnancy based on data regarding if women had indirect exposure (planting, pruning, weeding, picking, or harvesting); residential exposure (applying pesticides in garden or house); agricultural exposure (mixing or applying pesticides or repairing equipment), or no exposure	The mothers who reported never using a specific pesticide
Reproductive outcomes: attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD)					
Garry et al. (2002)	Red River Valley, Minnesota, US	1532 live births	Randomly selected pesticide applicators licensed between 1991 and 1996 Through compliance, availability, and eligibility, 695 families participated in the study and 536 of these applicators had children Study was conducted between 1997 and 1998	Telephone surveys determined product name, years used, and number of days per year of pesticide use for each pesticide applicator and spouse	Applicators who did not report use of glyphosate
Reproductive outcomes: gestational diabetes mellitus					
Saldana et al. (2007)	Iowa and North Carolina, US	11,273 pregnancies among spouses of licensed pesticide applicators	Female licensed pesticide applicators and female spouses of licensed pesticide applicators who completed the Female and Family Health Questionnaire and the applicator enrollment or Spouse Questionnaires, respectively, for the Agricultural Health Study, from 1993 to 1997 Exclusion criteria included: pregnancies that occurred in women >25 years prior to	Four exposure categories were created based on data regarding if women had ever mixed or applied any of 50 specific pesticides (yes/no) and the average days per year pesticides were mixed or applied	The women who reported never using a specific pesticide

Table 3 (*continued*)

Author(s) and year	Location	Study size	Study population	Exposure	Comparison group
			enrollment; women without age at pregnancy data; women with recorded age <16 or >49 years at the time of pregnancy		
Reproductive outcomes: miscarriages/preterm delivery					
Savitz et al. (1997)	Ontario, Canada	1898 couples 3984 pregnancies	Farm couples living on farms in Ontario selected from the 1986 Canadian Census of Agriculture who lived on the farm year round, the woman was ⩽44 years old, the time interval of the pregnancy was known with certainty, the conception/s occurred at the study farm, and the current husband was the father Three questionnaires were administered from 1991 to 1992	Exposure was classified into one of three categories: chemical activity, nonchemical activity, or no activity based on the man's exposure experience (in the 3 months before conception to the time of conception	Couples with the man's exposure classified as either "no activity" (no activity during the time window of interest) or "nonchemical activity" (no direct chemical exposure during time of interest)
Respiratory outcomes: asthma					
Hoppin et al. (2009)	Iowa and North Carolina, US	19,704 male farmers (licensed private pesticide applicators)	Male licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and had complete information regarding smoking, asthma history, age, BMI and history of pesticide poisoning and high pesticide exposure events	Pesticide exposure was determined from questionnaire response assessing pesticide use, the total years and days per year of pesticide use, and if they had ever experienced a high pesticide exposure event defined as an unusually high personal pesticide exposure Exposure was categorized into ever/never use, and multiple frequency categories based on questionnaire responses 48 specific pesticides were evaluated	The pesticide applicators who reported never using a specific pesticide
Hoppin et al. (2008)	Iowa and North Carolina, US	25,814 female spouses of licensed pesticide applicators	Females spouses of licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and had complete information regarding smoking, asthma history, age and BMI	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 Exposure was categorized into never, currently or former pesticide use based on questionnaire responses 50 specific pesticides were evaluated	The female spouses of commercial pesticide applicators who reported never using a specific pesticide
Respiratory outcomes: chronic bronchitis					
Hoppin et al. (2007)	Iowa and North Carolina, US	20,400 male and 508 female (20,908 total) commercial pesticide applicators (prevalence study)	Licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and a second questionnaire collecting information regarding chronic bronchitis	Pesticide exposure was determined from questionnaire response assessing pesticide use, the total years and days per year of pesticide use, and if they had ever experienced a high pesticide exposure event defined as an unusually high personal pesticide exposure Exposure was categorized into ever/never use over the past year, and six frequency categories based on questionnaire responses 50 specific pesticides were evaluated	The commercial pesticide applicators who reported never having experienced a high pesticide exposure event
Valcin et al. (2007)	Iowa and North Carolina, US	21,541 female spouses of commercial pesticide applicators	Spouses of licensed pesticide applicators enrolled in the Agricultural Health Study, that completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997 and provided	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	The commercial pesticide applicators who reported never using a specific pesticide

(*continued on next page*)

Table 3 (*continued*)

Author(s) and year	Location	Study size	Study population	Exposure	Comparison group
			information regarding chronic bronchitis, smoking, and age	Exposure was categorized into ever/never use over the past year, and five frequency categories based on questionnaire responses 50 specific pesticides were evaluated	
Respiratory outcomes: rhinitis					
Slager et al. (2010)	Iowa and North Carolina, US	21,958 farmers (private pesticide applicators)	Licensed private pesticide applicators enrolled in the Agricultural Health Study who completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997	Pesticide exposure was determined from questionnaire response assessing pesticide use during the year prior to study enrollment. Exposure was categorized into ever/never use over the past year 40 specific pesticides were evaluated	The private pesticide applicators (farmers) who reported never using a specific pesticide
Slager et al. (2009)	Iowa, US	2245 Iowa commercial pesticide applicators	Licensed pesticide applicators enrolled in the Agricultural Health Study who completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997	Pesticide exposure was determined from questionnaire response assessing pesticide use during the year prior to study enrollment. Exposure was categorized into ever/never use over the past year 34 specific pesticides were evaluated	The commercial pesticide applicators who reported never using a specific pesticide
Respiratory outcomes: wheeze					
Hoppin et al. (2006)	Iowa, US	2255 commercial pesticide applicators	Iowa licensed pesticide applicators enrolled in the Agricultural Health Study who completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997 and then returned a more detailed questionnaire on respiratory health	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 Exposure was categorized into never, currently or former pesticide use based on questionnaire responses 40 specific pesticides were evaluated	The commercial pesticide applicators who reported never using a specific pesticide
Hoppin et al. (2002a)	Iowa and North Carolina, US	20,468 farmers (private pesticide applicators)	Licensed private pesticide applicators enrolled in the Agricultural Health Study who completed the enrollment questionnaire and a second mailed questionnaire between 1993 and 1997	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 Exposure was categorized into ever/never use over the past year, and six frequency categories based on questionnaire responses 40 specific pesticides were evaluated	The farmers who reported never using a specific pesticide
Retinal degeneration					
Kirrane et al. (2005)	Iowa and North Carolina, US	31,173 wives of licensed pesticide applicators	Wives whose husbands were farmers and licensed pesticide applicators that worked on their own farm, from Iowa or North Carolina, and were enrolled in the Agricultural Health Study; outcome based on responding yes to the question "Has a doctor ever told you that you had retinal or macular degeneration"	Spouse Questionnaires captured data on whether wives had mixed or applied any of 50 specific pesticides during their lifetime, and on household hygiene factors The Applicator Questionnaire provided information on surrogate exposure measures and husbands' use of pesticides	Female spouses of private applicators, enrolled in the Agricultural Health Study in Iowa or North Carolina that answered no to the question related to doctor diagnosed retinal or macular degeneration
Thyroid disease					
Goldner et al. (2010)	Iowa and North Carolina, US	16,529 wives of licensed pesticide applicators	Female spouses of private applicators enrolled in the Agricultural Health Study who completed both the enrollment questionnaire and a follow-up phone interview and had complete data on all covariates	Spouse Questionnaires captured data on whether wives had mixed or applied any of 50 specific pesticides during their lifetime, duration and frequency of use, and years lived or worked on a farm	The female spouses of private pesticide applicators who reported never using a specific pesticide

Table 4
Summary of findings: cohort studies of exposure to glyphosate and non-cancer outcomes.

Author(s) and year	Description	No. of exposed cases	Type of relative risk estimate	Relative risk estimate	95% confidence limits	Variables included in statistical model
Diabetes						
Montgomery et al. (2008)	Glyphosate use and diabetes incidence	865	OR	0.85	0.74–0.98	Age, state, and BMI
Myocardial infarction						
Dayton et al. (2010)	Glyphosate use and incident nonfatal myocardial infarction (farm women)	46	OR	0.8	0.6–1.2	Age, BMI, smoking, and state
Mills et al. (2009)	Glyphosate use and myocardial infarction mortality	75	Hazard ratio	0.99	0.80–1.23	Age, state, and smoking
	Glyphosate use and nonfatal myocardial infarction incidence	79		1.10	0.93–1.31	Age, state, smoking, and BMI
Parkinson's disease						
Kamel et al. (2007)	Glyphosate use and PD prevalence	45	OR (hierarchical regression)	1.0	0.6–1.7	First-level model: age, state, and applicator or spouse
	Glyphosate use and PD incidence	49		1.1	0.6–2.0	Second-level model: insecticides, herbicides, fungicides, fumigants, organophosphate insecticides, organochlorine insecticides, carbamate insecticides, phenoxyacetate herbicides, and triazine/triazone herbicides

BMI, body mass index.
OR, odds ratio.
NR, not reported.

was used as a surrogate for atopy because there was no clinical measurement of atopy. There were no statistically significant associations with either allergic (OR = 1.37; 95% CI: 0.86–2.17) or non-allergic (OR = 1.15; 95% CI: 0.87–1.51) asthma. In another analysis, Hoppin et al. (2008) evaluated associations between pesticide use and self-reported history of doctor-diagnosed asthma among farm women. Atopic asthma was defined as occurring with eczema and/or hay fever. There was a statistically significant positive association between glyphosate use and atopic asthma (OR = 1.31; 95% CI: 1.02–1.67), but the association with non-atopic asthma was not statistically significant (OR = 1.13; 95% CI: 0.92–1.39), nor was the difference between these two odds ratios statistically significant (p-value for difference = 0.337). The odds ratio for the association between glyphosate and atopy alone (i.e., doctor diagnosis of eczema or hay fever) was similar to that of atopic asthma (OR for atopy alone = 1.31; 95% CI: 1.21–1.42; OR for atopic asthma = 1.35; 95% CI: 1.05–1.73). Hoppin et al. (2007) evaluated associations between pesticides and self-reported doctor-diagnosed chronic bronchitis (after age 19) among farmers, whereas Valcin et al. (2007) evaluated a similar association among non-smoking farm women in the AHS. Both analyses produced odds ratios of approximately 1.0 (or slightly below 1.0) for lifetime exposure to glyphosate (OR for farmers (94% male) = 0.99; 95% CI: 0.82–1.19 (Hoppin et al., 2007); OR for non-smoking farm women = 0.94; 95% CI: 0.76–1.17 (Valcin et al., 2007)). Rhinitis was evaluated in the AHS by the question, "During the past 12 months have you had a stuffy, itchy, or runny nose?" In the analysis of commercial pesticide applicators (Slager et al., 2009), the authors evaluated the association between current rhinitis and 34 pesticides, including glyphosate. With two exceptions, all of the ORs were above 1.0. There was a positive, statistically significant association between use of glyphosate during the past year and current rhinitis (OR = 1.32; 95% CI: 1.08–1.61), however there no evidence of exposure–response. Furthermore, additional analyses showed that the positive association was limited to applicators who used both glyphosate and 2,4-D in the past year; the OR for current use of glyphosate only (and not 2,4-D) was 1.07 (Slager et al., 2009). The association between self-reported current rhinitis and glyphosate use was also significantly elevated (OR = 1.09; 95% CI: 1.05–1.13) in the analyses of private pesticide applicators in the AHS (Slager et al., 2010). Use of glyphosate and 2,4-D was not as strongly correlated in the analysis of private applicators as it was in the analysis of commercial applicators in the AHS. The authors note that their estimate of rhinitis prevalence is high because they were not able to exclude participants with upper respiratory infections. The authors stated that similar results were observed when participants were excluded who reported colds in the past year (79% of participants) and when participants who reported asthma (3–7% of participants) were excluded (Slager et al., 2010). Glyphosate was also a significant predictor of having 13 or more episodes of rhinitis during the previous year. Hoppin et al. (2002a, 2006) evaluated pesticide use and wheeze, which was defined based on responses to the question, "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?" There was no significant association between glyphosate exposure and wheeze in analyses of farmers (OR = 1.05; 95% CI: 0.95–1.17) or commercial applicators (OR = 1.14; 95% CI: 0.83–1.57) (Hoppin et al., 2002a, 2006, respectively).

In an analysis of pesticides and self-reported, doctor-diagnosed retinal or macular degeneration among wives of pesticide applicators in the AHS, Kirrane et al. (2005) observed no association between glyphosate and these conditions (OR = 1.1; 95% CI: 0.8–1.5). The reported associations between glyphosate and self reported history of hyperthyroid, hypothyroid and other thyroid disease among women in the AHS were approximately 1.0 (Goldner et al., 2010).

3.4. Summary of results from studies of glyphosate exposure and non-cancer health outcomes

Four epidemiologic cohort studies of glyphosate and chronic diseases (diabetes, heart disease, PD) reported associations below or close to 1.0 (Montgomery et al., 2008; Dayton et al., 2010; Mills et al., 2009; Kamel et al., 2007). Results for PD and heart

Table 5
Summary of findings: case–control studies of exposure to glyphosate and non-cancer outcomes.

Author(s) and year	Exposure evaluated	Subgroup description	# of exposed cases	# of exposed controls	OR	95% confidence limits	Variables included in statistical models
Reproductive outcomes: congenital malformations and defects							
Garcia et al. (1998)	Father's exposure during the acute risk period (the 3 months preceding conception and/or during the first trimester of pregnancy)	Glyphosate (conditional logistic regression; multivariate analysis)	20	15	0.94	0.37–2.34	Maternal: spontaneous abortions, twins, drug consumption, heavy smoking, education, and occupational situation. Paternal: industrial worker and age >40 years
Reproductive outcomes: neural tube defects							
Rull et al. (2006)	Pesticide application within 1000 m of maternal residences in California, 1987–1991	Glyphosate (logistic regression; single pesticide model)	45	33	1.5	1.0–2.4	Variables included in all models: other pesticides, study population, maternal education, ethnicity, and periconceptional cigarette smoking and vitamin use
		Glyphosate (logistic regression; multiple pesticide model)	45	33	1.5	0.8–2.9	
		Glyphosate (hierarchical logistic regression; multiple pesticide model)	45	33	1.4	0.8–2.5	Second-level of hierarchical model: pesticide physiochemical properties, cholinesterase inhibitors, endocrine disruptors, and developmental toxins
Parkinson's disease							
Wechsler et al. (1991)	Use of pesticides at home	Round-Up	14	9	4.04[a]	0.91–19.27[a]	NR
Rheumatoid arthritis							
De Roos et al. (2005b)	Agricultural pesticide exposure	Ever personally mixed or applied glyphosate	52	222	1.2	0.8–1.8	Birthdate (matching factor) and state

OR, odds ratio.
NR, not reported.

disease (myocardial infarction), for which there were two publications each, are summarized in Figs. 1 and 2, respectively. Epidemiologic case–control and cross-sectional studies of glyphosate and reproductive outcomes evaluated a variety of endpoints and most studies observed no statistically significant positive association, regardless of the outcome evaluated. Garry et al. (2002) conducted multiple analyses and observed a significant positive association between parental use of glyphosate and parent-reported ADD/ADHD in children, but the diagnosis was not confirmed by a clinician. In a series of cross-sectional analyses of data from the AHS, glyphosate exposure was not associated significantly with chronic bronchitis (Hoppin et al., 2007; Valcin et al., 2007), wheeze (Hoppin et al., 2002a, 2006), allergic or non-allergic asthma in men (or non-atopic asthma in women (Hoppin et al., 2008). The positive association with atopic asthma was similar in magnitude to the association with atopy alone (Hoppin et al., 2008). The statistically significant association observed for glyphosate exposure and current rhinitis was limited to applicators who also reported exposure to 2,4-D in the analyses of commercial applicators (Slager et al., 2009), whereas the positive association between glyphosate exposure and current rhinitis did not depend on 2,4-D exposure in the analyses of private applicators (Slager et al., 2010). Finally, there were no statistically significant positive associations with the other health outcomes evaluated, including PD (Wechsler et al., 1991; Kamel et al., 2007), retinal degeneration (Kirrane et al., 2005), RA (De Roos et al., 2005a), or self-reported history of thyroid disease (Goldner et al., 2010). One limitation of many cross-sectional studies is that one cannot determine the temporal sequence of exposure and disease, a key component of causal inference. Another limitation is that prevalent cases do not necessarily represent all cases of a particular disease or condition, hampering the ability to elucidate clues about etiology. In summary, data from epidemiologic studies do not support a causal association between glyphosate and any of the adverse health outcomes evaluated to date.

4. Discussion

The validity of the epidemiologic studies reviewed in this report depends in large part on a valid classification of exposure. All of the studies relied primarily on questionnaires and interviews to characterize exposure to glyphosate. Unfortunately these are subject to misclassification and recall bias. The reports from the AHS evaluated associations with many pesticides in addition to glyphosate, and, despite having collected information on frequency and duration of use, relative risk estimates were reported only for associations with "ever" use of individual pesticides, including glyphosate. Thus, if a true risk exists only at very high exposure levels, it may not have been detected in analyses of a binary exposure variable. Furthermore, there were no data on glyphosate exposure level or "dose" in these observational studies. An earlier publication from the AHS (De Roos et al., 2005b) indicated that a somewhat higher proportion of commercial pesticide applicators (54%) compared to private applicators (45%) were in the "higher" glyphosate exposure group. Private applicators in the AHS were primarily individual farmers, and commercial applicators were professional pesticide applicators. Biomonitoring studies can be useful in estimating systemic dose, as well as in validating other

Table 6
Summary of findings: cross-sectional studies of exposure to glyphosate and non-cancer outcomes.

Author(s) and year	Description	No. of exposed cases	Type of effect estimate	Effect estimate	95% confidence limits	Variables included in statistical model
Reproductive outcomes: spontaneous abortion						
Arbuckle et al. (2001)	Exposure to glyphosate					
	Preconception	33	OR	1.4	1.0–2.1	None
	12–19 weeks only	17		1.7	1.0–2.9	
	Postconception	22		1.1	0.7–1.7	
	Pre- versus post-conception exposure (those with both exposures were excluded)	See above	OR[a]	1.6	0.7–3.4	
Reproductive outcomes: conditional fecundability ratio (CFR)						
Curtis et al. (1999)	Use of glyphosate by women (regardless of men's use)	32	CFR[b]	0.61	0.30–1.26	Woman's age when beginning to try to conceive, recent oral contraceptive use, smoking (men and women), pesticide categories
	Use of glyphosate by men (No use by women)	175		1.30	1.07–1.56	
Reproductive outcomes: birth weight						
Sathyanarayana et al. (2010)	Glyphosate exposure during first 3 months of pregnancy among wives of pesticide applicators	700	Multiple regression estimates of change in birth weight (g)	Coefficient (g): 4	−40–48 g	Site, BMI, BMI squared, parity, maternal height, preterm status, and smoking
Reproductive outcomes: attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD)						
Garry et al. (2002)	Parental use of glyphosate	6	OR	3.6	1.35–9.65	None listed
Reproductive outcomes: gestational diabetes mellitus						
Saldana et al. (2007)	Glyphosate exposure during pregnancy among farmers' wives	19	Crude OR	0.61	0.26–1.48[c]	
			Adjusted OR presented graphically	<1.0	Includes 1.0	BMI at enrollment, mother's age at pregnancy, parity, race, state, commonly used pesticides by women
Reproductive outcomes: miscarriages/preterm delivery						
Savitz et al. (1997)	Male farm activities:					Mother's age, parity, mother's and father's education, per capita income, mother's and father's off farm job, mother's smoking and alcohol use, and conception to interview interval
	No chemical use	102	OR	Referent	–	
	Any chemical use	244		1.1	0.8–1.3	
	Glyphosate use – crops	17		1.5	0.8–2.7	
	Glyphosate use – yard	13		1.4	0.7–2.8	
	Male farm activities:					Mother's age, mother's and father's education, per capita income, mother's off farm job, mother's ethnicity, mother's smoking during pregnancy, mother's caffeine use during pregnancy, primary language, month of conception
	No chemical use	31		Referent	–	
	Any chemical use	80		1.2	0.7–1.9	
	Glyphosate use – crops	5		2.4	0.8–7.9	
	Glyphosate use – yard	<5		NR	–	
Respiratory outcomes: asthma						
Hoppin et al. (2009)	Glyphosate use:					
	Allergic asthma	104	OR	1.37	0.86–2.17	Age, state, smoking, BMI, and high pesticide exposure events
	Non-allergic asthma	247		1.15	0.87–1.51	
Hoppin et al. (2008)	Glyphosate use:					
	Atopic asthma	106	OR	1.31	1.02–1.67	Age, state, smoking status, BMI, and "grew up" on farm
	Nonatopic asthma	148		1.13	0.92–1.39	
Respiratory outcomes: chronic bronchitis						
Hoppin et al. (2007)	Lifetime glyphosate exposure (farmer applicators)	77	OR	0.99	0.82–1.19	Age, state, gender, pack years
Valcin et al. (2007)	Lifetime glyphosate exposure (non-smoking farm women)	33	OR	0.94	0.76–1.17	Age, state, other variables within herbicide category
Respiratory outcomes: rhinitis						
Slager et al. (2010)	Use of glyphosate in the past year (private	6207	OR	1.09	1.05–1.13	Age, race, education, state of residence, BMI, currently working on a farm, years

(*continued on next page*)

Table 6 (*continued*)

Author(s) and year	Description	No. of exposed cases	Type of effect estimate	Effect estimate	95% confidence limits	Variables included in statistical model
	applicators)					mixing pesticides, repairing engines, repairing pesticide equipment, welding, painting, handling stored grain, handling stored hay, working in swine areas, working with hogs, other farm animals, butchering animals, growing cabbage, Christmas trees, field corn, sweet corn, and hay
Slager et al. (2009)	Use of glyphosate in the past year (commercial applicators)	869	OR	1.32	1.08–1.61	Age, education status, and growing up on a farm
Respiratory outcomes: wheeze						
Hoppin et al. (2006)	Use of glyphosate in the past year and current use of glyphosate (commercial applicators)	254	OR	1.38	1.03–1.86	Age, smoking status, asthma/atopy status, and BMI
				1.14	0.83–1.57	+chlorimuron-ethyl
Hoppin et al. (2002a)	Use of glyphosate in the past year (farmer applicators)	2614[d]	OR	1.05	0.95–1.17	Age, state, smoking, and asthma/atopy
Retinal degeneration						
Kirrane et al. (2005)	Ever mixing or applying any of 50 specific pesticides	93[e]	Glyphosate (hierarchical logistic regression; multivariate model (50 pesticides modeled simultaneously)	1.1	0.8–1.5	Age and state of residence Second-stage model: indicators variables for groupings of fungicides, carbamates, organophosphates, and organochlorines
Thyroid disease						
Goldner et al. (2010)	Glyphosate use and hyperthyroid	108	OR	0.98	0.78–1.2	Education, age, smoking, BMI, and hormone replacement therapy
	Glyphosate use and hypothyroid	353		1.0	0.91–1.2	
	Glyphosate use and other thyroid disease	161		0.97	0.81–1.2	

BMI, body mass index.
OR, odds ratio.
NR, not reported.
[a] The odds ratios estimate the risk that exposures to pesticides resulting in a spontaneous abortion occurred in the preconception window, relative to the postconception window (Arbuckle et al., 2001).
[b] CFR = conditional fecundability ratio (~risk/hazard ratio; probability of conception for each month).
[c] Calculated with STATA from data in the paper = 19 (63%) gestational diabetes mellitus cases exposed to glyphosate; 219 (74%) controls without gestational diabetes mellitus exposed to glyphosate.
[d] Calculated from percent exposed.

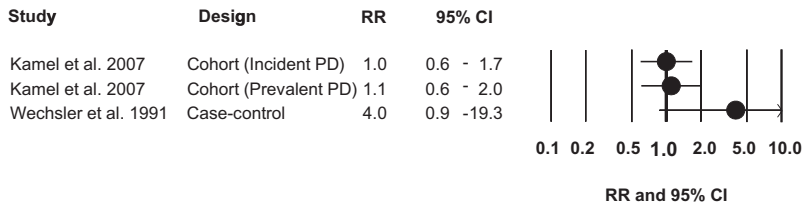

Fig. 1. Studies of glyphosate exposure and Parkinson's disease (PD).

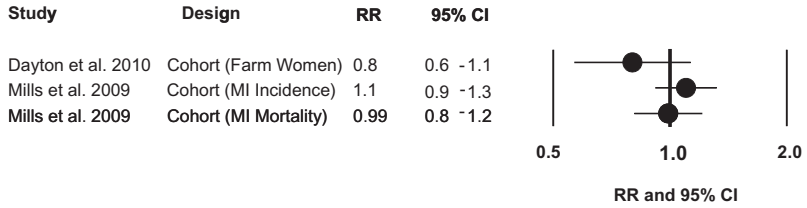

Fig. 2. Studies of glyphosate exposure and myocardial infarction (MI).

exposure assessment tools, such as questionnaires. 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).

One study included in our review (Rull et al., 2006) linked data from pesticide use reports and geographic distribution of crops to residential addresses. Like questionnaires, this method is also cost-effective and non-invasive, but subject to misclassification. Self-reported exposure is subject to recall bias particularly in case–control studies and in cross-sectional studies of prevalent illness and current or past exposures. Hoppin et al. (2002b) 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. Disease (or outcome) misclassification must also be considered, particularly for the studies that did not validate self-reported outcomes. It is probable that there was exposure and disease misclassification in the studies included in this review; unfortunately, we do not have enough information to estimate the likely magnitude or direction of such bias. Because accurate exposure measurement is crucial for valid results, the development and validation of pesticide-specific exposure algorithms would improve researchers' abilities to estimate potential risks associated with pesticide exposure.

Finally, our review relied on observational studies of glyphosate exposure and various health outcomes. As such, results could be biased by uncontrolled or incompletely controlled confounding. Because of the way they are used in practice, it is difficult to study the effect of a particular pesticide in isolation of all others in observational studies. Nevertheless, it is not likely that every pesticide would have a similar effect on human health outcomes. Furthermore, agricultural exposures are myriad and include animals, animal viruses, dust, hay, diesel exhaust, and fertilizers, in addition to different types of pesticides.

Our review of the epidemiologic literature on glyphosate and non-cancer health outcomes found no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease or other adverse health outcome and exposure to glyphosate. There was a general paucity of studies on each specific health outcome, and most of the reports were from the same US agricultural cohort. In conclusion, review of the collection of epidemiologic studies of glyphosate to date does not indicate a causal association with the reproductive, respiratory, or other chronic health outcomes studied.

Conflict of interest statement

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

Acknowledgment

This research was supported by the Monsanto Company, St. Louis, Missouri.

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