



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

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### 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.

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### 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<sup>®</sup>, Roundup Pro<sup>®</sup>, Roundup PowerMAX<sup>™</sup>, Roundup WeatherMAX<sup>®</sup> and AquaMaster<sup>®</sup>. 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<sup>®</sup> 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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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
<i>Diabetes</i>					
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
<i>Myocardial infarction</i>					
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  Incidence analysis: 32,024	Mortality analysis: all male pesticide applicators who enrolled in the Agricultural Health Study and provided complete data on all covariates  Incidence analysis: further limited to those who completed follow-up telephone interview and who reported no prior myocardial infarction at enrollment	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
<i>Parkinson’s disease</i>					
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

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