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PROTOCOL

Glyphosate Exposure and Risk of Non-Hodgkin Lymphoma: A Protocol of Systematic Review and Meta-Analysis

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Abstract

Background: Glyphosate is the most extensively used herbicide worldwide, applied in both agricultural and non-agricultural settings for weed control. Despite its widespread use and perceived safety, concerns have arisen regarding its potential carcinogenicity. Among the health concerns, Non-Hodgkin Lymphoma (NHL) has been the most consistently investigated malignancy potentially associated with glyphosate exposure. Several epidemiological studies have explored this relationship, but results remain inconsistent due to variations in exposure assessment, study design, and confounding control. Therefore, a rigorous systematic review and meta-analysis are warranted to synthesize existing evidence and clarify the potential link between glyphosate exposure and NHL risk in humans. **Method:** The protocol follows the PRISMA 2020 guidelines. A systematic search will be conducted across PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library from inception to the present. Eligible studies will include cohort and case-control designs reporting quantitative estimates of the association between glyphosate exposure and NHL. Two independent reviewers will perform study selection, data extraction, and risk of bias assessment using the Newcastle–Ottawa Scale (NOS). Pooled risk estimates (Odds Ratios, Relative Risks, or Hazard Ratios) will be calculated using a random-effects model. Heterogeneity, subgroup analyses, sensitivity analyses, and publication bias assessments will also be performed. **Results:** The review will summarize the strength, direction, and consistency of the association between glyphosate exposure and NHL risk, identify key sources of heterogeneity, and highlight gaps in current evidence that warrant further research. **Conclusion:** This systematic review and meta-analysis will provide a comprehensive evaluation of existing epidemiological data to clarify whether glyphosate exposure is associated with an increased risk of Non-Hodgkin Lymphoma, thereby informing public health policy, regulatory decision-making, and future research priorities.

Keywords: Glyphosate- Non-Hodgkin Lymphoma- Herbicide- Carcinogenicity- Systematic Review- Meta-Analysis.

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Introduction

Glyphosate [N-(phosphonomethyl)glycine] is currently the world's most widely used herbicidal agent. It was first approved for use in the United States (US) in 1974 [1]. As a non-selective herbicide introduced into an industry built around selective herbicides, it took time for glyphosate to be integrated into agricultural practice. By 1987, glyphosate ranked 17th in pounds applied in the United States and it ranked 5th in that category by 1997 [2]. In 2017, the International Agency for Research on Cancer (IARC) classified glyphosate as a probable human carcinogen (Group 2A), as a result of its unequivocal evidence of carcinogenicity in experimental animals, the limited evidence from epidemiological studies, and the robust evidence of human pertinence of the carcinogenic

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mechanisms identified in cell cultures [3]. Glyphosate is a broad-spectrum herbicide of which the primary mechanism is inhibition of the enzyme 5-enolpyruvoylshikimate 3-phosphate synthase, which is essential for the formation of aromatic amino acids in plants [4]. Occupational studies have demonstrated links between agricultural work and lymphohematopoietic cancers, particularly non-Hodgkin lymphoma (NHL), mostly among male, but also female farmers [5]. Interest in the etiology of NHL has been strengthened by an observed substantial increase in the incidence of the disease from the 1960's to the 1980's as reported from most countries with reliable cancer registries. The established risk factors for development of NHL include different immunosuppressive states, e.g., human immunodeficiency virus (HIV), autoimmune diseases as Sjogren's syndrome and systemic lupus erythematosus (SLE), immunodepressants used after organ transplantation and some inherited conditions. During the last decades, research on the etiology of NHL has been directed towards other potential causes such as pesticides, which may explain the impressive increase in the incidence [6]. There is evidence indicating that pesticide exposure is a risk factor for NHL development. Occupational agricultural exposure has been associated with a higher incidence rate of NHL in multiple studies [7]. The human (epidemiological) data supporting these assessments were considered inadequate or limited, forcing heavy reliance on the available animal bioassays and mechanistic data for evidence conclusions [8]. This systematic review and meta-analysis article will allow for the integration and quantitative evaluation of findings across studies, providing more robust conclusions regarding the association between glyphosate exposure and Non-Hodgkin Lymphoma risk. This work aims to clarify inconsistencies in the literature, assess the quality of existing evidence, and inform regulatory decision-making, occupational health policies, and future research directions.

Rationale

Glyphosate is the most widely used herbicide globally and a key ingredient in many commercial formulations, including Roundup [9]. Despite its extensive use, the potential carcinogenicity of glyphosate remains controversial. In 2017, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A "probable human carcinogen," primarily based on evidence linking it to Non-Hodgkin Lymphoma (NHL) [3, 10, 11]. Given the ongoing debate and emergence of new epidemiological data, a systematic review and meta-analysis are warranted to comprehensively assess the association between glyphosate exposure and the risk of developing NHL.

Methods

1. Inclusion and Exclusion Criteria

The inclusion criteria were developed collaboratively by the review team to ensure alignment with the objectives and research question of this systematic review. The criteria were formulated based on the PRISMA 2020 and Cochrane Handbook for Systematic Reviews of Interventions guidelines to maintain methodological rigor and transparency.

All authors independently reviewed the preliminary draft of the inclusion criteria to verify its comprehensiveness, relevance, and clarity. Discrepancies or differing interpretations were resolved through discussion and consensus. The final version was approved unanimously by all members of the research team prior to the commencement of the screening process.

Any future modifications to these criteria, if necessary, will be documented in an updated version of this protocol, along with a clear rationale for each change. This procedure ensures consistency, reproducibility, and adherence to the principles of systematic review methodology.

2. Search Strategy

A comprehensive search strategy will be developed and executed to identify relevant studies investigating the association between glyphosate exposure and the risk of non-Hodgkin lymphoma (NHL) in three major databases: PubMed, Scopus, and Web of Science. The search will be performed from database inception to the present, with no restrictions on language, and all types of observational studies, including cohort, case-control, and cross-sectional studies, will be considered for inclusion. The search will also incorporate relevant systematic reviews, meta-analyses, and references from eligible articles.

1. PubMed

For PubMed, a comprehensive search strategy will be employed using a combination of Medical Subject Headings (MeSH) terms and keywords. The search strategy will be tailored for PubMed's functionality. The terms used will include:

• "Glyphosate" OR "N-(phosphonomethyl)glycine" OR "Roundup"

• "Non-Hodgkin lymphoma" OR "Non-Hodgkin's lymphoma" OR "NHL" OR "Lymphoma, Non-Hodgkin"

• "Exposure" OR "Risk" OR "Incidence" OR "Epidemiology"

This search will be limited to articles published in English. All study designs that examine the relationship between glyphosate exposure and NHL risk will be included.

2. Scopus

For Scopus, a similar approach will be taken, utilizing both keywords and Boolean operators to refine the search. The following terms will be used:

• "Glyphosate" OR "N-(phosphonomethyl)glycine" OR "Roundup"

• "Non-Hodgkin lymphoma" OR "Non-Hodgkin's lymphoma" OR "NHL" OR "Lymphoma"

• "Exposure" OR "Risk" OR "Incidence" OR "Epidemiology"

The search will be extended to include all document types, with no restrictions on language, to maximize the capture of relevant articles.

3. Web of Science

The search on Web of Science will follow a similar strategy using both keywords and subject-specific terms. The indexing of journals across natural sciences, medical sciences, and social sciences will provide a broad spectrum of relevant literature. The following terms will be used:

• "Glyphosate" OR "Roundup" OR "N-(phosphonomethyl)glycine"

• "Non-Hodgkin lymphoma" OR "NHL" OR "Lymphoma"

• "Exposure" OR "Risk" OR "Incidence" OR "Epidemiology"

The search will not be limited by language and will include studies of all design types related to the exposure-outcome relationship of glyphosate and NHL.

4. Additional Considerations

• Grey Literature: A search for grey literature will be conducted through the reference lists of relevant studies, dissertations, and government or NGO reports to ensure all potential studies are included.

• Language Restrictions: Initially, no language restrictions will be applied. However, if studies in languages other than English are identified, they will be assessed for feasibility of translation and inclusion based on the availability of resources.

• Study Types: All studies investigating the association of glyphosate exposure with NHL will be considered, including cohort studies, case-control studies, and meta- analyses. Interventional studies and studies unrelated to human health will be excluded.

5. Updates and Revisions

The search strategy will be refined during the review process to ensure that the most up-to-date and relevant studies are included. The final search will be conducted prior to the data extraction phase, ensuring the inclusion of all studies published before the protocol's finalization.

3. Study Selection and Data Extraction

The procedures for study selection and data extraction were developed and approved by all members of the review team prior to initiating the systematic review process. Both processes were designed in accordance with the PRISMA 2020 statement and the Cochrane Handbook for Systematic Reviews of Interventions, ensuring methodological transparency, reproducibility, and minimization of selection bias.

All reviewers participated in drafting and refining the study selection criteria, screening protocol, and data extraction form. The inclusion and exclusion criteria, as well as the standardized data extraction template, were pilot-tested on a subset of studies to ensure clarity and consistency in their application. Feedback from all reviewers was incorporated, and revisions were made following group discussion and agreement.

Final approval of the study selection workflow and data extraction strategy was granted unanimously by the principal investigator and co-investigators. Any disagreements arising during the study selection or data extraction phases will be resolved by consensus or, if necessary, through adjudication by a senior reviewer.

All decisions and revisions will be documented to maintain a transparent audit trail for future verification and reproducibility.

4. Quality Assessment

The review team collectively designed and approved the quality assessment framework to ensure consistency, transparency, and methodological rigor throughout the review process. Two independent reviewers will conduct the quality appraisal of each included study using standardized and validated tools appropriate to the study design. Specifically, the Newcastle–Ottawa Scale will be used for cohort and case-control studies, while the Joanna Briggs Institute (JBI) Critical Appraisal Checklist will be applied to cross-sectional studies. These instruments were selected and approved by the research team based on their widespread acceptance, reliability, and suitability for observational epidemiological research.

5. Statistical Analysis

The data synthesis and analysis plan were jointly developed and approved by all members of the review team before the start of data extraction. The team agreed to perform both qualitative and quantitative analyses, using a random-effects meta-analysis model to estimate pooled effect sizes (ORs, RRs, or HRs) with 95% confidence intervals.

Methods for assessing heterogeneity (I^2 statistic and Cochran's Q test), publication bias (funnel plot, Egger's, and Begg's tests), and planned subgroup and sensitivity analyses were also reviewed and approved. All authors endorsed the use of Stata 17 or R for statistical analyses.

Results

The results of this systematic review and meta-analysis will be presented after completion of the study selection, data extraction, and statistical analysis.

In the completed review, findings will be reported in accordance with the PRISMA 2020 guidelines. The PRISMA flow diagram will illustrate the number of studies identified, screened, excluded, and included, along with reasons for exclusion at the full-text stage.

Key characteristics of the included studies such as study design, country, population, exposure assessment method, and outcome definition will be summarized in descriptive tables. The risk of bias assessment results, conducted using the Newcastle–Ottawa Scale or Joanna Briggs Institute checklist, will be presented both narratively and graphically.

If sufficient data are available, a meta-analysis will be performed using a random-effects model to estimate pooled effect sizes (Odds Ratios, Relative Risks, or Hazard Ratios) with corresponding 95% Confidence Intervals. Statistical heterogeneity will be evaluated using Cochran's Q test and the I^2 statistic.

Where appropriate, subgroup and sensitivity analyses

will be undertaken to explore potential sources of heterogeneity. Publication bias will be assessed visually using funnel plots and statistically through Egger's and Begg's tests.

The overall strength and certainty of the evidence linking glyphosate exposure to Non-Hodgkin Lymphoma will be evaluated using the GRADE approach, and the findings will be summarized in a "Summary of Evidence" table.

Discussion

This protocol outlines a systematic and rigorous approach to evaluate the association between glyphosate exposure and the risk of Non-Hodgkin Lymphoma in human populations. By adhering to PRISMA 2020 guidelines and employing comprehensive search strategies, validated quality assessment tools, and robust statistical methods, the planned review will provide a transparent and reproducible synthesis of the existing epidemiological evidence.

The findings are expected to clarify the magnitude and consistency of the potential association between glyphosate and NHL, identify gaps in current research, and inform evidence-based public health policies, regulatory decisions, and future research priorities. Ultimately, this review aims to contribute to a more accurate understanding of glyphosate's potential health risks and support strategies to minimize exposure in at-risk populations.

Acknowledgments

Statement of Transparency and Principals

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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