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## Accepted Manuscript

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PII: S1383-5742(18)30088-7  
DOI: <https://doi.org/10.1016/j.mrrev.2019.02.001>  
Reference: MUTREV 8261

To appear in: *Mutation Research*

Received date: 22 September 2018  
Revised date: 2 February 2019  
Accepted date: 5 February 2019

Please cite this article as: Zhang L, Rana I, Shaffer RM, Taioli E, Sheppard L, Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence, *Mutation Research-Reviews in Mutation Research* (2019), <https://doi.org/10.1016/j.mrrev.2019.02.001>

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## Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence

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### Abstract

Glyphosate is the most widely used broad-spectrum systemic herbicide in the world. Recent evaluations of the carcinogenic potential of glyphosate-based herbicides (GBHs) by various regional, national, and international agencies have engendered controversy. We investigated whether there was an association between high cumulative exposures to GBHs and increased risk of non-Hodgkin lymphoma (NHL) in humans. We conducted a new meta-analysis that included the most recent update of the *Agricultural Health Study* (AHS) cohort published in 2018 along with five case-control studies. Using the highest

exposure groups when available in each study, we report the overall meta-relative risk (meta-RR) of NHL in GBH-exposed individuals was increased by 41% (meta-RR = 1.41, 95% CI, confidence interval: 1.13–1.75). For comparison, we also performed a secondary meta-analysis using high-exposure groups with the earlier AHS (2005), and we determined a meta-RR for NHL of 1.45 (95% CI: 1.11–1.91), which was higher than the meta-RRs reported previously. Multiple sensitivity tests conducted to assess the validity of our findings did not reveal meaningful differences from our primary estimated meta-RR. To contextualize our findings of an increased NHL risk in individuals with high GBH exposure, we reviewed available animal and mechanistic studies, which provided supporting evidence for the carcinogenic potential of GBH. We documented further support from studies of malignant lymphoma incidence in mice treated with pure glyphosate, as well as potential links between GBH exposure and immunosuppression, endocrine disruption, and genetic alterations that are commonly associated with NHL.

Overall, in accordance with evidence from experimental animal and mechanistic studies, our current meta-analysis of human epidemiological studies suggests a compelling link between exposures to GBHs and increased risk for NHL.

(273/300 words)

**Abbreviations:** AHS, Agricultural Health Study; c-NHEJ, canonical non-homologous end joining pathway; CI, confidence interval; EDC, endocrine disrupting chemical; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; ETS, environmental tobacco smoke; GBHs, glyphosate-based herbicides; IARC, International Agency for Research on Cancer; IFN- $\gamma$ , interferon gamma; IL-2, Interleukin-2; JMPR,

Joint Meeting on Pesticide Residues by the Food and Agriculture Organization of the United Nations and World Health Organization; meta-RR, meta-analysis relative risk; mg/kg/day, milligrams per kilogram per day; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio; ppm, parts per million; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RR, relative risk.

**Keywords:** Glyphosate, pesticide, Roundup, Ranger Pro, carcinogenesis, and meta-analysis.

## **1. Background**

### ***1.1 Global Usage of Glyphosate-Based Herbicides***

Glyphosate is a highly effective broad spectrum herbicide that is typically applied in mixtures known as glyphosate-based herbicides (GBHs) and commonly sold under the trade names of *Roundup*® and *Ranger Pro*®. Use of GBHs has increased dramatically worldwide in recent decades. In the United States alone, usage increased nearly sixteen-fold between 1992 and 2009 [1]. Most of this increase occurred after the introduction of genetically modified glyphosate-resistant "Roundup-ready" crops in 1996 [1]. In addition, there have been significant changes in usage. In particular, the practice of applying GBHs to crops shortly before harvest, so-called "green burndown," began in the early 2000s to speed up their desiccation; as a consequence, crops are likely to have higher GBH