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Exposure to glyphosate and risk of non-hodgkin lymphoma: an updated meta-analysis

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Abstract

Objective: *We updated a recent systematic review and meta-analysis of epidemiologic studies to help clarifying the association between exposure to glyphosate and risk of non-Hodgkin lymphoma (NHL).* **Methods:** *We conducted an updated search of the literature, and identified a total of 15 relevant publications, from which we extracted results from six non-overlapping studies. We performed random-effects meta-analyses for ever-exposure to glyphosate, dose-response, and risk of specific NHL subtypes* **Results:** *The meta-RR for ever-exposure to glyphosate was 1.05 (95% confidence interval [CI] 0.90-1.24; I^2 = 0%). The meta-RR for the highest category of exposure was 1.15 (95% CI 0.72-1.83; 3 studies). The meta-RR for diffuse large B-cell lymphoma (DLBCL) was 1.29 (95% CI 1.02-1.63; 4 studies), that for follicular lymphoma was 0.84 (95% CI 0.61-1.17), and that for chronic lymphocytic leukemia/small lymphocytic lymphoma was 1.33 (95% CI 0.65-2.70). There was indication of publication bias.* **Conclusions:** *This updated meta-analysis reinforces our previous conclusion of a lack of an association between exposure to glyphosate and risk of NHL overall, although an association with DLBCL cannot be ruled out.*

In 2020, we performed a meta-analysis of results of epidemiology studies of non-Hodgkin lymphoma (NHL) and occupational exposure to glyphosate, an herbicide and crop desiccant widely used by professional applicators and consumers (1). That study provided evidence of lack of an association between glyphosate exposure and risk of NHL overall, but left open a few questions, including a possible association with diffuse large B-cell lymphoma (DLBCL), a small increase in risk for high exposure, and a possible role of publication bias. Since our results were criticized by Rana et al. (2020) (2) we decided to clarify some aspects and to conduct an updated meta-analysis.

Rana et al. (2020) (2) discussed the reproducibility of our results, the selection of studies and the choice of focusing on the contrast between ever and never exposed to glyphosate. The latter choice was justified by the heterogeneity of exposure measures (i.e. duration, cumulative-exposure, semi-quantitative assessment of exposure etc.) used in the different studies, which prevented us from performing a meta-regression, although we reviewed the results for different exposure groups reported in some of the studies. In addition, if an effect of high-dose exposure were present, we would expect to observe a weaker association for ever-exposure.

With respect to results on diffuse large B-cell lymphoma (DLBCL), we reported the relevant results, but we did not emphasize their interpretation because they concerned a subgroup not selected

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a-priori and would not remain statistically significant after adjustment for multiple comparisons.

To fully address the criticisms of Rana et al. (2020) (2), we extended to December 2020 the literature search and performed a new meta-analysis of results on ever-exposure to glyphosate based on random-effects models (3) to obtain summary RR and its 95% confidence intervals (CIs), using the methodology described in our previous report (1), with the exception of using log-transformed effect measures. Compared to our previous meta-analysis, we identified one additional publication (4), that included a pooled analysis of case-control studies conducted in the 1980s in four US states (Iowa, Kansas, Minnesota, Nebraska), and in the 1990s in six Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Québec, Saskatchewan). Results on glyphosate exposure were previously reported for some of these studies (5-9).

We retained six publications based on non-overlapping populations for the meta-analysis (Table 1); the prevalence of ever-exposure to glyphosate was 46.5% in the only cohort study available (10), and ranged from 0.2% to 6.7% in the case-control studies. The meta-analysis resulted in a meta-RR of 1.05 (95% CI 0.90-1.24; p-value of test for heterogeneity = 0.46; I^2 = 0%) (Figure 1). The studies by Leon et al. (2019) (10) and Pahwa et al. (2019) (4) contributed 56.8% and 30.1% of the total weight in the meta-analysis, respectively. The meta-analysis of case-control studies, excluding the pooled cohort study by Leon et al. (2019) (10), resulted in a meta-RR of 1.21 (95% CI 0.95-1.53; I^2 = 0%). The visual assessment of the funnel plot (Figure 2), the result of the Egger's test (p= 0.04) suggested that publication bias was present in the dataset (11).

The meta-analysis of the results for highest category of exposure in the three studies that reported relevant results (12, 13, 4) yielded in a meta-RR equal to 1.15 (95% CI 0.72-1.83); the corresponding meta-RR for ever-exposure in the same three studies was 1.13 (95% CI 0.77-1.66). Results for types of NHL were reported in four studies (12, 14, 10, 4) and the meta-RR for diffuse large B-cell lymphoma (DLBCL) was 1.29 (95% CI 1.02-1.63).

Taking into account our updated meta-analysis, it is reasonable to conclude that if there is any hazard of NHL from occupational exposure to glyphosate, then the attributable risk in most exposed workers is likely to be small. The evidence of publication bias detracts from a causal interpretation of the combined results. This conclusion is consistent with that of another recent meta-analysis (15).

An interesting finding of our meta-analysis result stems from the comparison of results from case-control and cohort studies. While a pooled analysis of three large cohort studies of pesticide applicators provides no evidence of an association (10), the meta-analysis of case-control studies resulted in a moderately increased risk estimate. Levels of exposure might be very different across studies, and it is plausible that cohorts of professional pesticide sprayers would have higher cumulative exposure than subjects included in case-control studies, who reported exposure to glyphosate under different circumstances, including at their residence. In addition, cohort studies offer better protection from selection bias compared to case-control studies (16), and, although there have been methodological advances in occupational exposure assessment in case-control studies, some of the studies reporting an association between glyphosate exposure and risk of NHL were based uniquely on self-reported information by cases and controls (17, 12).

Our conclusion is based on a larger database than previous reviews and meta-analyses: in particular, the studies included in this meta-analysis comprised a total of 1,878 exposed NHL cases or deaths, compared to 207 (18, 19), 211 (20), or 585 (21).

The results of the analysis of the three main NHL subtypes does not provide evidence of an association with any of them, although the result for DLBCL deserves attention, despite the fact that it would not reach the canonical level of statistical significance once the p-value is adjusted for multiple comparisons. The lack of consistency in the results by subtype is stressed by the fact that, out of four available studies, two identified chronic lymphocytic leukemia/small lymphocytic lymphoma as the type at highest risk, and one each identified DLBCL and follicular lymphoma, respectively. These results stress the need for studying risk factors of specific types of NHL, as illustrated by the pooled analysis conducted by Morton et al. (2014) (22) within the InterLymph Consortium.

Table 1. Studies included in the meta-analysis of glyphosate exposure and risk of NHL

Authors	Country	Study population	Exposure assessment	No. exposed cases	Prev exp	Covariates adjusted for	Participation rate % (ca/co)	Overlap with earlier puublications
Hardell et al., 2002	Sweden	Pooled analysis of two PCC	Questionnaires	8	2.0%	NA	91 /84	Nördstrom et al., 1998 ; Hardell et al., 1999
Eriksson et al., 2008	Sweden	PCC	Questionnaire	29	3.2%	Age, sex, calendar year, pesticides with increased OR	91 / 92	-
Orsi et al., 2009	France	HCC	Questionnaire and expert evaluation	12	4.9%	Age, center, socioeconomic status	95.7 / 91.2	-
Cocco et al., 2013*	6 European countries	Multicentre HPCC	Questionnaires and job modules evaluated by experts, with crop-exposure matrix	4	0.2%†	Age, sex, center, education	88 / 81 (HC), 52 (PC)	-
Leon et al., 2019	France, Norway, USA	Pooled analysis of cohort studies of pesticide applicators (AGRICAN, CNAP, AHS)	AGRICAN and CNAP: crop-exposure matrices. AHS: self-reported use	1131	46.5%	AGRICAN: Age, sex, livestock, retirement status, number of crops with pesticide application CNAP: Age, sex, livestock, selected pesticides AHS: Age, sex, state, livestock, selected pesticides	-	De Roos 2005, Andreotti 2018
Pahwa et al., 2019	USA, Canada	Pooled analysis of PCC	Questionnaire	113	6.7%	Age, sex, state/ province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment, 2,4-D, dicamba, malathion	NA	Cantor et al., 1992 ; McDuffie et al., 2001; De Roos et al., 2003; Lee et al., 2004; Hohenadel et al., 2011

*Cocco et al. (2013) analyzed B-cell lymphoma

†Based on results reported in Cocco et al. (2010)

Prev exp, prevalence of exposure among NHL cases; PCC, population-based case-control study; HCC, hospital-based case-control study; HPCC, hospital- and population-based case-control study; SR, self-report; PR, proxy-report; HC, hospital controls; PC, population controls; NA, not available

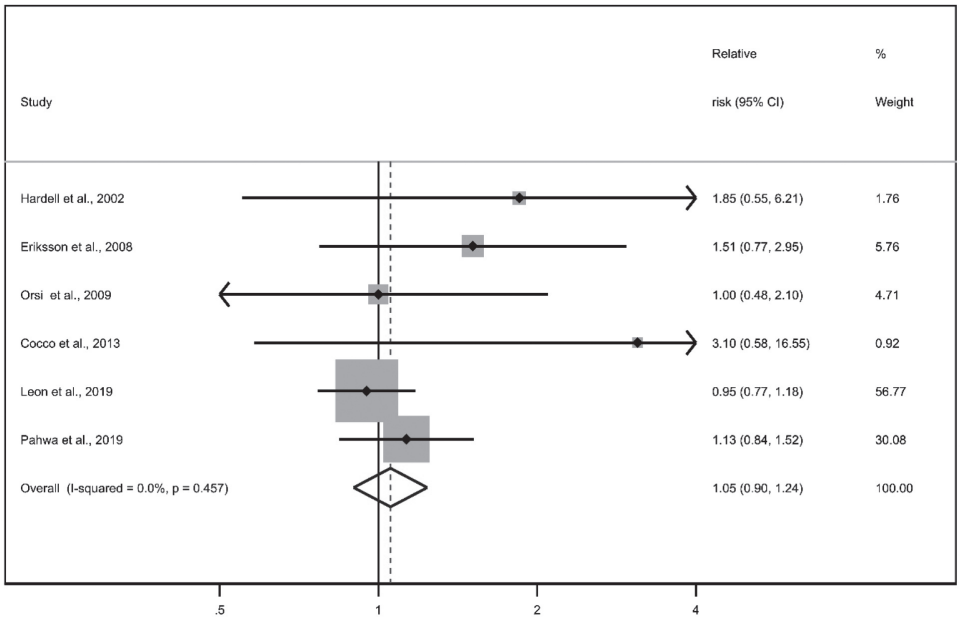

Figure 1. Meta-analysis of studies on glyphosate exposure and risk of NHL.

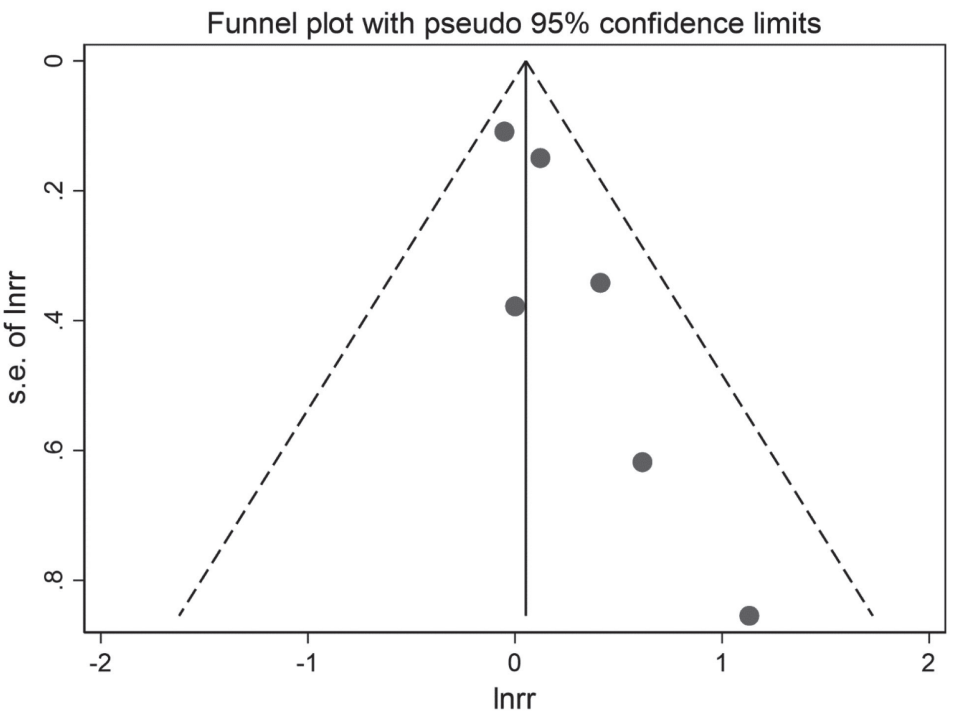

Figure 2. Funnel plot of results on exposure to glyphosate and risk of NHL

Limitations of this meta-analysis refer primarily to those of the underlying studies. Most studies were of case-control design, with potential bias resulting from selection of cases and controls, in particular in hospital-based studies, and from reliance on personal recall and imperfect job-exposure matrices for assessment of glyphosate exposure. Potential residual confounding might also operate, resulting in study-specific bias of unknown direction. In this respect, it is worth noticing that in the recent pooled analysis of case-control studies from the US and Canada (4), adjustment for exposure to other pesticides, including 2,4-D, dicamba and malathion reduced most risk estimates for exposure to glyphosate, even though it did not exclude a possible association. Similarly, in the study by Hohenadel et al. (2011) (9), whose population is included in the pooled analysis by Pahwa et al. (2019) (4), an association was reported for combined exposure to malathion and glyphosate (OR 2.10; 95% CI 1.31-3.37) and malathion alone (OR 1.95; 95% CI 1.29-2.93), but not for exposure to glyphosate alone (OR 0.92; 95% CI 0.54-1.55). Similarly, in the study by Eriksson et al. (2008) (12), adjustment for exposure to other pesticides reduced the OR for ever-exposure to glyphosate from 2.02 (95% CI 1.10-3.71) to 1.51 (95% CI 0.77-2.94).

This updated meta-analysis confirmed our previous conclusion that the association between exposure to glyphosate and risk of NHL originally suggested by results of small studies that may have suffered from bias was not confirmed in larger, better-designed studies. An association with risk of DLBCL cannot be ruled out.

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