

EXHIBIT 7



On recent meta-analyses of exposure to glyphosate and risk of non-Hodgkin's lymphoma in humans

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Received: 13 May 2020 / Accepted: 18 December 2020

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Abstract

Purpose A recent meta-analysis of five case–control studies and one cohort study reported that exposure to glyphosate was associated with increased risk of non-Hodgkin's lymphoma (NHL). The meta-analysis was based on estimates of risk from the included studies at the highest reported exposure level obtained from analyses with the longest lag period. The extent to which the summary estimate depends upon the exposure definitions and assumed latency period is uncertain.

Methods We carried out sensitivity analyses to determine how the definition of exposure and the choice of latency period affect the summary estimate from meta-analyses of the 6 studies included in the recent meta-analysis. We also conducted a meta-analysis of ever-exposure to glyphosate incorporating the most updated results from the case–control studies.

Results The summary estimates of risk varied considerably depending on both the assumptions about exposure level and latency. Using the highest reported exposure levels, evidence of an association between glyphosate and NHL was strongest when estimates from analyses in the cohort study with a 20-year lag [RR = 1.41 (95% CI 1.13–1.76)] and a 15-year lag [RR = 1.25 (95% CI 1.01–1.25)] were included. In our meta-analysis of ever-exposure with no lag period, the summary relative risk with updated estimates was 1.05 (95% CI 0.87–1.28).

Conclusion The results of meta-analyses of glyphosate exposure and NHL risk depend on assumptions made about both exposure level and latency period. Our results for ever-exposure are consistent with those of two recent meta-analyses conducted using somewhat different study inclusion criteria.

Keywords Glyphosate · Non-Hodgkin's lymphoma · Meta-analysis · Latency · Bias

Introduction

Roundup, which contains the active ingredient glyphosate, has been in use for 46 years and is the most popular herbicide worldwide. Risk assessments by numerous international and national health agencies have determined glyphosate to be safe and non-carcinogenic [1]. However, in 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a “probable carcinogen” [2]. The IARC report has been a source of controversy [1, 3] and has provided the basis for tens of thousands of lawsuits against

Roundup's original manufacturer and its successor company [4].

In 2018, following the IARC evaluation, the results of the National Cancer Institute's long-term follow-up of its Agricultural Health Study (AHS) [5] were published, showing no association of glyphosate with more than 20 solid and lymphopietic cancers, including non-Hodgkin's lymphoma (NHL). In addition to this large prospective cohort study of 54,000 pesticide applicators, a number of case–control studies have examined the association of glyphosate and risk of NHL [6–11].

In a recent meta-analysis of studies of human exposure to glyphosate in relation to risk of NHL, Zhang et al. [12] reported that relatively high exposure was associated with a summary relative risk of 1.41 (95% confidence interval [CI] 1.13–1.75). The meta-analysis was based on estimates of risk from the included studies at highest reported exposure level obtained from analyses with the longest lag period. The selection of risk estimates from the 6 studies included in that

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meta-analysis is open to question on a number of grounds: (1) inconsistent definitions of exposure across the studies; (2) evidence of bias in case–control studies; (3) uncertainty about the latency period for NHL; and (4) selection of the highest of available estimates from the AHS [5] and from a pooled analysis of U.S. case–control studies [7].

To address these concerns, we undertook sensitivity analyses based on the five case–control studies and one cohort study included in the Zhang et al. meta-analysis to investigate how substitution of various risk estimates would affect the meta-estimate. We also conducted a meta-analysis of ever-exposure to glyphosate incorporating the most updated results from the case–control studies.

Our re-examination of the Zhang et al. meta-analysis is important for two reasons. First, the question of the carcinogenicity of glyphosate is subject to intense controversy, but has enormous implications for agriculture and the availability of affordable food. Second, in order for a meta-analysis to achieve its objective of providing a more precise and accurate estimate of an association, it is critical to pay attention to the strengths and limitations of the underlying studies and the specific risk estimates selected.

Methods

Criteria for selection of studies

For our meta-analysis of ever exposure, we selected studies reported in articles published in peer-reviewed journals in English that included results from the most recently updated analyses. Only studies with direct assessment of specific pesticide use were included (i.e., studies with pesticide exposure inferred from crops grown using crop-exposure matrices were excluded).

Selection of estimates from the different studies

Estimates for ever exposure to glyphosate, or closely approximating ever exposure, obtained from adjusted analyses were selected for our updated meta-analysis. The AHS reported five different risk estimates for the association of the highest glyphosate exposure level and NHL [5]. For the highest exposure quartile (Q4), the unlagged RR and the RRs for lags of 5, 10, 15, and 20 years were: 0.87, 0.87, 0.83, 0.94, and 1.12, respectively. Zhang et al. selected the 20-year lagged Q4 RR of 1.12 (95% CI 0.83–1.51). RRs for ever exposure to glyphosate were not reported for the AHS [5]. We were unsuccessful in attempts to obtain the ever exposure RRs from AHS investigators, but the RRs for the four quartiles in the unlagged analysis were remarkably consistent (0.83, 0.83, 0.88, and 0.87). Accordingly, we selected the RR from the unlagged analysis for Q4 – 0.87 (95% CI

0.64–1.20)—as an approximation to the RR for ever exposure in the AHS.

Zhang et al. included estimates of 2.12 (95% CI 1.20–3.73) for exposure > 2 days/year from a Canadian case–control study [6] and 2.1 (95% CI 1.1–4.0) for ever-exposure from a pooled analysis of three U.S. case–control studies [7]. The U.S. study also reported an OR of 1.6 (95% CI 0.9–2.8) using an alternate statistical method [7]. We used the more recent NAPP estimate for ever exposure of 1.13 (95% CI 0.84–1.51), that was based on a pooled analysis of the Canadian and the three U.S. case–control studies [11]. The initial pooled analysis of the U.S. studies excluded a number of cases and controls for a variety of reasons, and the analysis of each of 47 pesticides considered was adjusted for exposure to the other 46 pesticides in addition to demographic factors [7]. The larger sample size in the NAPP study (113 exposed cases in Pahwa et al. [11] compared to 87 exposed cases in De Roos et al. [7] and McDuffie et al. [6] combined), and a less complex statistical analysis should result in more stable and precise estimates of risk.

The odds ratio (OR) of 1.85 (95% CI 0.55–6.20) for ever-exposure from Hardell et al. [8] was retained. From the Eriksson et al. study [9], instead of the OR for exposure to > 10 days/year, we selected the OR for ever exposure: 1.51 (95% CI 0.77–2.94) to maintain a consistent exposure definition.

We retained the risk estimate from Orsi et al. [10] for ever exposure of 1.0 (95% CI 0.5–2.2).

Statistical analysis

Meta-analyses using reported ORs or RRs were carried out under both fixed and random effects models. All analyses assumed inverse variance weighting, where weights for fixed effect models used within-study precision as a measure of variance, and weights for random effects models included an additional variance term to account for between-study heterogeneity. Sensitivity analyses, consisting of meta-analyses that omitted one study at a time, or that substituted alternative RR values from specific studies, were carried out to assess the influence of individual studies and RR values. All computations were carried out using Comprehensive Meta-Analysis software, V3 [13].

Results

We reproduced the summary fixed model RR of 1.41 (95% CI 1.13–1.76) when using the estimates included in the Zhang et al. meta-analysis [12]. We then carried out sensitivity analyses for Zhang et al. [12], in order to assess the impact of various RR selections when multiple estimates were available for inclusion in the meta-analysis. If the lower

of two estimates (OR 1.6) from De Roos et al. [7] is selected instead of the higher estimate (OR 2.1), then the summary RR estimate only supported an association between glyphosate exposure and NHL risk when the 20-year lagged estimate for Q4 is included from the AHS: summary RR = 1.38 (95% CI 1.11–1.71). If the larger of two estimates from De Roos et al. [7] is selected, then the summary RR estimate supported an association between glyphosate exposure and NHL only when using the 20-year lagged Q4 estimate [12] or using the 15-year lagged Q4 estimate of 0.94: summary RR = 1.25 (95% CI 1.01–1.55).

The updated meta-analysis of ever glyphosate exposure is summarized in Table 1 and Fig. 1. In all scenarios, the estimated heterogeneity was negligible ($I^2=0$, $\tau^2=0$), and, therefore, the fixed and random estimated RR and associated CI were equal in each case (Table 1). In the meta-analysis including all 5 studies, the summary relative risk was 1.05 (95% CI 0.87–1.28) (Table 1, Fig. 1). In sensitivity analyses excluding one study at a time, the relative risk estimates ranged from 1.00 (95% CI 0.77–1.29) when Pahwa et al. [11] was excluded to 1.19 (95% CI 0.92–1.52) when the AHS [5] was excluded.

As an additional sensitivity analysis for our meta-analysis of ever exposure to glyphosate, we substituted the AHS 20-year lag Q4 estimate of 1.12, which was included in the Zhang et al. meta-analysis, for the unlagged Q4 estimate of 0.87 in our meta-analysis. The average of the RRs for the four quartiles of glyphosate exposure in the 20-year lag analysis is 1.12, so the Q4 RR can be considered an approximation to the ever-exposure RR in the 20-year lag analysis.

Table 1 Individual study results for ever exposure to glyphosate and NHL risk, and summary relative risks for all studies, and from sensitivity analyses excluding one study at a time

	RR	LCL	UCL	Weight (%)
All studies				
1. Andreotti	0.87	0.64	1.19	38.5
2. Eriksson	1.51	0.77	2.95	8.48
3. Hardell	1.85	0.55	6.21	2.59
4. Orsi	1.00	0.45	2.20	6.13
5. Pahwa	1.13	0.84	1.52	44.3
Summary RR*	1.05	0.87	1.28	$Q^\dagger=3.60$
Sensitivity analyses				
Exclude study 1	1.19	0.92	1.52	$Q=1.30$
Exclude study 2	1.02	0.83	1.25	$Q=2.38$
Exclude study 3	1.04	0.85	1.26	$Q=2.75$
Exclude study 4	1.06	0.86	1.29	$Q=3.58$
Exclude study 5	1.00	0.77	1.29	$Q=3.20$

*Because heterogeneity was negligible ($I^2=\tau^2=0$), the fixed effects and random effects summary RRs are identical

[†]If study estimates are homogeneous, Q has a chi-square distribution with $k-1$ degrees of freedom, where k =the number of studies

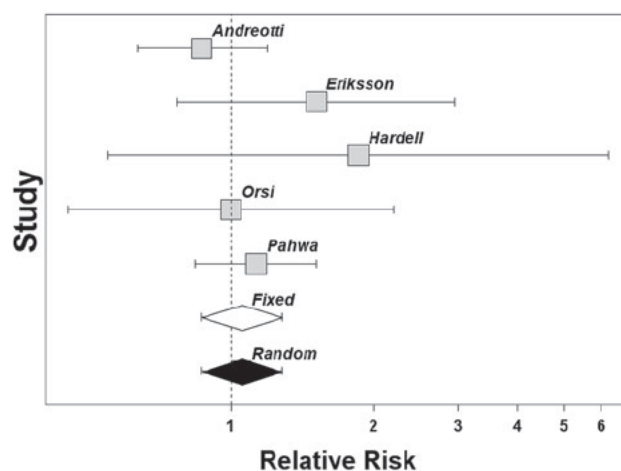


Fig. 1 Forest plot including all 5 studies in meta-analysis of ever exposure to glyphosate

Substituting the AHS 20-year lag Q4 RR of 1.12 for 0.87 resulted in a summary RR of 1.16 (95% CI 0.96–1.40).

Discussion

Our sensitivity analyses of Zhang et al. showed that the strength of evidence for an association between glyphosate and NHL risk is dependent upon the selection of estimates from various studies. In particular, the strength of evidence is greater when estimates from the AHS based on assumptions of long latency are selected.

Using risk estimates for ever exposure from the individual studies, updated data from the NAPP, and an unlagged RR from the AHS, glyphosate exposure was not associated with NHL in the meta-analysis including all 5 five studies. Sensitivity analyses indicated that the AHS had the most influence on the magnitude of the summary risk estimate resulting from the meta-analysis. The influence of the AHS would be somewhat greater if the ever-use RR from the unlagged analysis had been reported and made available for inclusion in the meta-analysis, since it would have been more precise [5].

A recent paper [14] examined the risk of bias in the studies of glyphosate and NHL included in the Zhang et al. meta-analysis [12] by tabulating ORs from case–control studies and RRs from cohort studies for pesticides including glyphosate and those not containing glyphosate. A preponderance of ORs for NHL greater than 1.0 for practically all categories of pesticides was interpreted as suggesting recall bias, possibly exacerbated by selection bias. Crump concluded, “This article provides evidence that at least four of the five case–control studies of glyphosate exposure and NHL are contaminated by statistical bias, likely stemming in the main

from recall bias, exacerbated by selection bias in two of the studies.” Crump’s analysis indicated that the case–control studies by Hardell et al. [6] and Eriksson et al. [7], which contributed the highest odds ratio estimates, might be particularly subject to bias. He also noted that “of the five case-control studies, the study by De Roos et al. (2003) presents considerably less evidence of recall bias” and that the results from the cohort study of Andreotti et al. [5] showed little evidence of statistical bias [14].

Recently, the U.S. Environmental Protection Agency (EPA) issued the results of a meta-analysis of ever exposure to glyphosate using the studies included in the Zhang et al. study [15]. Because the RRs for ever exposure to glyphosate were not reported in the AHS paper [5], the EPA used a fixed effects meta-analysis to combine the 4 quartiles of exposure in the unlagged analysis in the AHS, obtaining an estimated summary relative risk for ever exposure of 0.85 (95% CI 0.73–1.00). Because this estimate was based on the assumption that the RRs for the four quartiles are statistically independent, the confidence interval for this estimate is too narrow. Using this value, which likely gives slightly too much weight to the AHS, in its reanalysis of the six studies included by Zhang et al., EPA obtained a summary relative risk 1.14 (95% CI 0.87–1.50). Because we used the RR of 0.87 for the fourth quartile of exposure as a substitute for the ever exposure RR, our analysis likely gives slightly too little weight to the AHS.

The EPA review also provided empirical evidence that the ORs from two case–control studies were biased and likely overestimated any true relationship between glyphosate and NHL risk [15]. In McDuffie et al. [6], EPA found a pattern of roughly a doubling of the OR for those reporting > 2 days/year compared to ≤ 2 days exposure, for many different pesticides (i.e., not just for glyphosate). The agency considered this indicative of recall bias [15, p. 7, footnote 2]. EPA also noted that the OR estimate of 2.36 (95% CI 1.04–5.37) from Eriksson et al. [9] for more than 10 days of use per year “was based on only 17 cases and 9 controls and was an *unadjusted* effect size.” EPA concluded [15, p. 7, footnote 1] that, “Adjustment for age, sex and year of diagnosis/enrollment would bring about a meaningful decrease in the odds ratio for glyphosate had that statistical adjustment been made.”

Another recent meta-analysis of ever exposure to glyphosate and NHL risk reported a summary RR estimate of 1.03 (95% CI 0.86–1.21) [16]. This meta-analysis included the five case–control studies used by Zhang et al. [12] and the EPA [15], a European case–control study [17], and a pooled analysis of two European cohort studies and the AHS [18]. Pesticide exposure information in the three European studies was inferred from crops grown using crop-exposure matrices (analogous to the use of job exposure matrices to estimate chemical exposures in observational studies of occupation). Because crop-exposure matrices do not provide specific

pesticide exposure information, however, the resulting pesticide use data is of questionable value for epidemiologic studies [19], and we excluded these studies from our analysis.

As noted earlier, we used the 4th quartile of exposure from the AHS as a substitute for ever-exposure, because Andreotti et al. did not publish the RR for ever use of glyphosate [5]. We reasoned that since the RR for the 4th quartile (0.87) was greater than the average of the four quartile RRs (0.83, 0.83, 0.88, and 0.87), this choice was actually conservative as an estimate of the ever-use RR, but provided a reasonable approximation to the ever-use RR.

The Zhang et al. meta-analysis did not assess ever-exposure to glyphosate, but rather purported to examine the hypothesis that relatively heavy exposure to glyphosate was associated with increased NHL risk. Based on their hypothesis they selected the 20-year lagged RR estimate for Q4 to include in their meta-analysis, the only one of the five Q4 RR estimates from the AHS that was greater than 1. The EPA review noted that the largest and highest-quality study—the AHS—failed to support the a priori hypothesis that NHL risk was increased at higher glyphosate exposure levels [15]. Not only was there no evidence of a dose–response for any of the five analyses (with no lag and with four different lag periods), but for the 20-year lag analysis that was preferred by Zhang et al., both the RRs for the first quartile and the second quartile of glyphosate exposure were higher than the fourth quartile RR [5].

We found that the strength of evidence for an association between glyphosate and NHL was greater when estimates from the AHS based on the assumption of long latency were selected. In addition, inclusion of the 20-year lag Q4 RR in our meta-analysis increased the lower confidence bound from 0.87 to 0.96. In order to support their use of the 20-year lag estimate from the AHS in their meta-analysis, Zhang et al. cited a claim by Weisenberger that median latency periods could be 15–20 years for NHL [20]. The Weisenberger estimate was not based on NHL data, however, but rather was a hypothesis based on an early estimate of the latency period for acute leukemia after exposure to benzene [20]. Evidence that NHL risk is associated with benzene exposure remains limited [21, 22]. Furthermore, a recent study indicates that the latency period for acute leukemia after benzene exposure is 10 years or less [23], and a recent review concluded that estimates of latency periods for lymphoma “range from 2 to 10 years” [24]. Long latency periods for NHL cannot be ruled out, but the Zhang et al. preference for a 20-year latency period, like their hypothesis that NHL risk increases with increasing glyphosate level, is open to question.

Meta-analyses are easy to perform and are widely cited, and the number of published meta-analyses cited in PubMed has increased geometrically over the past 30 years [25, 26]. Meta-analysis offers the prospect of obtaining a more

stable and accurate risk estimate by combining a number of smaller studies. However, it is crucial that the studies being combined be of comparable quality and use comparable definitions of exposure. Otherwise, one risks “comparing apples to oranges.” Importantly, meta-analysis cannot improve on the quality of the underlying studies. Rather, if biases are not corrected or compensated for, meta-analysis can simply compound their effects [27]. In addition to biases affecting the constituent studies, investigator bias can influence the selection of studies, the specific risk estimates included in the meta-analysis, and various analytic choices. Such biases can be financial, related to professional advancement, or to finding support for one’s favored hypothesis.

Although the literature on meta-analysis is extensive, questions remain about when to use—and when not to use—the technique. Regarding meta-analysis of clinical studies, the Cochrane training handbook warns that, even for randomized clinical trials, it may be inappropriate to conduct a meta-analysis, particularly in the face of heterogeneity among studies [28]. A recent systematic scoping review of recommendations regarding methods for meta-analysis of observational studies [29] noted that, because meta-analysis was originally developed to synthesize results of randomized clinical trials, there was a need for sound methodological guidance on the conduct of meta-analyses of observational studies, which lack the protection of randomization. Conflicting recommendations were seen on a number of topics, including the combining of different study designs and the use of quality scales to assess bias [29].

There are indications that, in some situations, combining the results of case–control studies with those of cohort studies may not be appropriate. There are numerous examples where an association of a risk factor (dietary fat, vitamin C, induced abortion, red and processed meat, etc.) with cancer is observed in case–control studies but not in cohort studies [30–35], suggesting that recall and selection bias may affect the quality of exposure information obtained in case–control studies. Regarding quality scales to assess bias, although one may use the Newcastle–Ottawa rating score to assess the quality of the included studies, as Zhang et al. did, the application of rating criteria can be subjective. For example, the assignment of scores of 6 or 7 to the case–control studies and a score of 8 to the AHS by Zhang et al. does not, in our opinion, convey the extent of the superiority of the AHS.

One cannot say definitively that any particular meta-analysis is closest to the truth, which is why sensitivity analyses and evaluation of the hypotheses underlying meta-analyses are essential. In view of theoretical concerns about selection and information bias in case–control studies generally, and empirical evidence for the presence of such bias in most case–control studies of glyphosate and NHL, we conclude that formal quantification of risk in meta-analyses combining the AHS with case–control studies is unwise. All such

meta-analyses, including our own, should be interpreted with great caution. The results of the AHS provide the most reliable and precise information regarding the risk of NHL following glyphosate exposure, and combined analyses of the AHS and the case–control studies, rather than enhancing our understanding of the possible association between glyphosate and NHL, may primarily result in diminishing the impact of the AHS.

Acknowledgments Dr. Tarone was deposed in December 2019 as an unpaid fact witness in two January 2020 California trials involving Roundup. The purpose of the deposition was to defend his published papers on the IARC glyphosate classification [3]. Dr. Tarone helped design the Agricultural Health Study and coauthored some early papers based on the study.

Compliance with ethical standards

Conflict of interest All authors declared no potential conflicts of interest. No funding was sought or received for the statistical analyses or for writing the paper.

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