Exposure to glyphosate and risk of non-Hodgkin lymphoma and multiple myeloma: an updated meta-analysis

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Objective: *We carried out a systematic review and meta-analysis of epidemiologic studies on the association between occupational exposure to glyphosate and risk of non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).* **Methods:** *We conducted a systematic search of the literature, and identified 18 relevant publications, from which we extracted results from seven non-overlapping studies of NHL and three of MM. We performed random-effects meta-analyses for ever-exposure to glyphosate, dose-response, and risk of specific NHL subtypes.* **Results**: *The meta-relative risk (RR) of NHL was 1.03 (95% confidence interval [CI] 0.86-1.21), that of MM was 1.04 (95% CI 0.67-1.41). The meta-RR of NHL for highest category of exposure was 1.49 (95% CI 0.37-2.61; 3 studies). The meta-RR for diffuse large B-cell lymphoma (DLBCL) was 1.31 (95% CI 0.93-1.75); that for follicular lymphoma was 0.82 (95% CI 0.93-1.70), and that for chronic lymphocytic leukemia was 0.85 (95% CI 0.20-1.49). There was indication of publication bias for studies on NHL.* **Conclusions**: *Our meta-analysis provided no overall evidence of an increased risk for both NHL and MM in subjects occupationally exposed to glyphosate. In secondary analyses we detected a small increase in risk for the category with highest level of exposure as well as for DLBCL. The evidence of publication bias suggests caution in the interpretation of the results.*

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«*Esposizione al glifosato e rischio di linfoma non Hodgkin e mieloma multiplo: una meta-analisi aggiornata*». **Obiettivo:** *Sono state condotte una revisione sistematica e una meta-analisi degli studi epidemiologici sull'associazione tra esposizione professionale a glifosato e rischio di linfoma non Hodgkin (NHL) e mieloma multiplo (MM).* **Metodi:** *È stata effettuata una ricerca sistematica della letteratura che ha portato all'identificazione di 18 pubblicazioni rilevanti, da cui sono stati estratti i risultati di sette studi indipendenti sul NHL e tre sul MM. È stata effettuata una meta-analisi con modello ad effetti casuali per esposizione a glifosato, inclusi i risultati su dose-risposta e su sottotipi specifici di NHL.* **Risultati:** *Il rischio relativo (RR) della meta-analisi per NHL è risultato pari a 1,03 (intervallo di confidenza al 95% [CI] 0,86-1,21), e quello per MM pari a 1,04 (IC al 95% 0,67-1,41). Il RR per NHL nella più alta categoria di esposizione è risultato pari a 1,49 (IC 95% 0,37-2,61; 3 studi). Il RR per linfoma diffuso a grandi cellule B (DLBCL) è risultato pari a 1,31 (IC 95% 0,93-1,75); quello per il linfoma follicolare pari*

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a 0,82 (IC 95% 0,93–1,70) e quello per la leucemia linfatica cronica pari a 0,85 (IC 95% 0,20–1,49). Si è riscontra–ta un'indicazione di bias di pubblicazione negli studi su NHL. **Conclusioni:** *In generale, questa meta–analisi non ha fornito la prova di un aumento del rischio sia per NHL che per MM in soggetti esposti professionalmente a glifo–sato. In analisi secondarie è stato evidenziato un leggero aumento del rischio per la categoria con il più alto livello di esposizione e per DLBCL. L'evidenza di un bias di pubblicazione suggerisce cautela nell'interpretazione dei risultati.*

INTRODUCTION

Glyphosate is a non-selective herbicide and crop desiccant commonly used worldwide by both professional applicators and consumers. It is a phosphonate agent, and interferes with the synthesis of aromatic amino acids by inhibiting the plant enzyme, 5-enolpyruvylshikimate-3-phosphate synthase, which is responsible for biosynthesis of the aromatic aminoacids phenylalanine, tyrosine, and tryptophan via the shikimate pathway. This mechanism is specific to plants. Glyphosate was first synthesized in 1950 and was introduced in the market as herbicide in 1974; it quickly became one of the most widely used herbicides worldwide; it is used in agriculture and forestry, for weeds in industrial areas, as well as on lawns and gardens. The patent expired in 2000 and the agent is currently produced and sold by various manufacturers (20, 37).

While glyphosate and formulations have been approved by regulatory bodies worldwide, concerns about their effects on humans and the environment have appeared and have grown as the global usage of the agent increased (27).

Glyphosate has been the subject of regular assessments by national and international regulatory agencies (38, 39), which have established that glyphosate has a relatively low toxicity in mammals. In recent years the hypothesis has arisen about the capacity of glyphosate to cause cancer in humans. A 2013 review by the German Federal Institute for Risk Assessment concluded that the available data were contradictory with regard to associations between exposure to glyphosate formulations and risk of various cancers, including non-Hodgkin lymphoma (NHL) (14). In 2015 the International Agency for Research on Cancer (IARC) classified glyphosate as probable human carcinogen (category 2A), based on sufficient evidence for the carcino-genicity of glyphosate in experimental animals, limited evidence of carcinogenicity in humans, based on NHL results, and evidence that exposure to glyphosate is genotoxic and can induce oxidative stress in experimental animals and in humans in vitro (20). The IARC review also noted positive findings for multiple myeloma (MM) in three studies. Also in 2015, a review by the European Food Safety Authority (EFSA) concluded that while carcinogenic glyphosate-containing formulations may exist, studies that look solely at the active substance glyphosate did not show such effect, and glyphosate is unlikely to pose a carcinogenic threat to humans (13). In 2016 the Joint WHO/FAO Meeting on Pesticide Residues considered that glyphosate is not carcinogenic in rats, but the possibility that it is carcinogenic in mice at very high doses could not be excluded, concluding that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet (41). Moreover, the European Chemicals Agency (ECHA) did not find evidence implicating glyphosate as carcinogen, mutagen, or toxic to the reproductive system (12).

The epidemiology data on the association between glyphosate and cancer have been reviewed at different points in time (2, 5, 15, 26, 34). As new results have become available since these reviews, and no overall meta-analyses of the primary results of epidemiologic studies have been conducted in the last years, we have conducted an updated systematic review and meta-analysis of cohort and case-control studies published investigating the association between occupational exposure to glyphosate and risk of NHL and MM.

METHODS

This systematic review and meta-analysis were performed according to the guidelines specified in

the PRISMA-statement (23). The methods were specified and documented in a protocol (available from the authors upon request); the PRISMA checklist is included in Supplementary table 1.

Literature searches and study selection

We conducted comprehensive literature searches of PubMed, Scopus and Embase and, up to 15 May 2019; in addition, PubMed "related article" links and reference lists of key studies and reviews were used to complement the searches. The search included the keywords ("glyphosate" OR "pesticide") AND ("cancer" OR "neoplasm" OR "lymphoma" OR "non-Hodgkin lymphoma" OR "multiple myeloma" OR "lymphohematopoietic cancer").

To be included in the meta-analysis, studies had to fulfill the following criteria: (i) original reports of adults occupationally exposed to glyphosate, (ii) studies in which a measure of association between glyphosate exposure and risk of cancer, expressed either as standardized mortality ratios (SMR), standardized incidence ratios (SIR), proportionate mortality ratio (PMR), relative risk (RR) or odds ratio (OR) was either reported or could be derived from the data reported in the article, (iii) studies written in English, Spanish, German, French or Italian.

Two authors (FD, PB) independently reviewed the list of titles and abstracts, to determine which studies potentially met the inclusion criteria. Duplicates or irrelevant references were eliminated. The final selection was based on the examination of the full text of potentially relevant articles. The search and selection processes are shown in figure 1.

After reviewing the titles of 1452 articles, we eliminated 1289 of them which did not appear to be relevant and reviewed the abstracts of the remaining 163 articles; we further eliminated 110 which did not meet the inclusion criteria, leaving 53 articles for detailed review. We identified one additional article from the lists of references. Thirty-six of the 54 articles were excluded either because results for NHL or MM were not reported, either because they were not epidemiological studies, or because they did not consider glyphosate exposure; among the remaining 18 articles, 13 reported results for NHL and eight reported results for MM. However, some
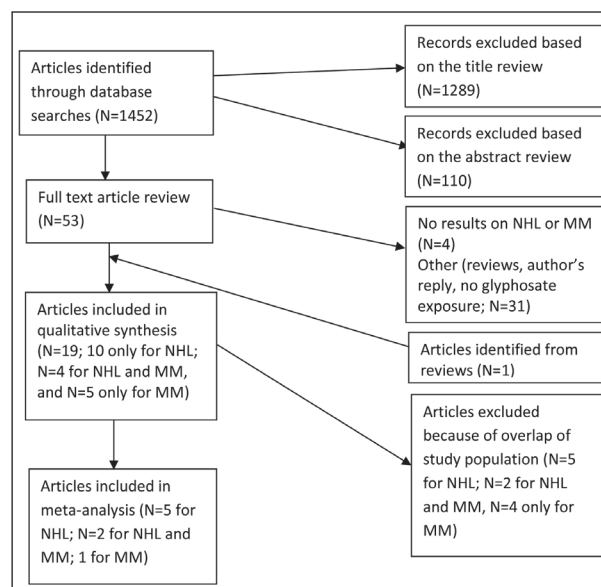
Figure 1 - Flow chart of search and selection of studies included in the review and meta-analysis

of these articles reported results based on the same study population; in such cases, we selected for the meta-analysis the reports with the most complete and updated information (i.e., longest follow-up). For this reason, we eliminated six articles for NHL and two articles for MM, and retained seven articles of non-overlapping studies for NHL, and three for MM. In particular, three articles were based on the Agricultural Health Study (AHS), a large prospective cohort of licensed pesticide applicators from Iowa and North Carolina, United States (1, 8, 35); this study was included in a pooled analysis with two other cohort studies (22), and we excluded the three earlier reports. However, in the dose-response meta-analysis, we used the results reported by Andreotti et al. (1), because these data were not reported in the pooled analysis by Leon et al. (22). Similarly, we selected the article by De Roos et al. (7) which consisted of a pooled analysis of three case-control studies of NHL (4, 7, 21), the article by Hardell et al. (17), which included the data from two Swedish case-control studies of NHL and hairy cell leukemia (HCL) (16, 17, 28). With respect to MM studies, we selected the article by Presutti et al. (33), which combined data from three case-control studies from the United States and Canada (3, 24, 31). We were not aware of potentially relevant stud-

ies published in a language other than the five we selected in our review.

Data extraction and data synthesis

We extracted key characteristics of each of the studies retained for the two main meta-analysis (table 1 and 2). We aimed at investigating NHL (i.e., International Classification of Diseases, version 9 (ICD-9 codes 200, 202 and ICD-10 codes C82, C85) and MM (i.e., International Classification of Diseases, version 9 (ICD-9 code 203 and ICD-10 code C90); however, results from one study were available only for one of the major subgroups of NHL category (6) (see table 1 for details).

If available, we abstracted results for different subgroups defined according to exposure to glyphosate or characteristics of the study populations. When results were reported based on different strategies of adjustment for potential confounders, we included the most adjusted risk estimates.

We conducted meta-analyses separately for NHL and MM, based on random-effects models (9) to obtain summary RR and its 95% confidence intervals (CIs).

We evaluated heterogeneity using the general variance-based method and the I^2 statistics (18). We conducted sensitivity analyses excluding one study at a time from the meta-analysis, and a cumulative meta-regression according to the year of publication of the individual studies. Furthermore, we conducted meta-analyses according to duration of glyphosate exposure and for subtypes of NHL. We assessed the presence of publication bias by reviewing funnel plots and performing the test proposed by Egger et al. (10).

We used the Stata v. 14 commands *metan* (overall, stratified and cumulative meta-analyses), *glst* (meta-regression), and *metafunnel* and *metabias* (publication bias) (30, 32, 36).

RESULTS

The meta-analysis for NHL comprised results reported in seven articles (6, 7, 11, 17, 22, 25, 29) (figure 2), and resulted in a meta-RR of 1.03 (95% CI 0.86-1.21; p-value of test for heterogeneity [p-het] = 0.7; I^2 = 0%). The study by Leon et al. (22) contributed 1131/1271 exposed NHL cases/deaths (89.0%), and 74.1% of the total weight in the meta-analysis. The exclusion of this study resulted in a NHL meta-RR equal to 1.27 (95% CI 0.92-1.61). The exclusion of each of the other studies at a time resulted in meta-RR ranging from 1.00 to 1.03.

The cumulative meta-analysis showed that the meta-RR for NHL ranged between 1992 and 2019 from 0.97 to 1.29 with a decrease in 2018, when the study by Andreotti et al (1) was published (figure 3). The meta-RR never reached the level of statistical significance.

The visual assessment of the funnel plot (figure 4), the result of the Egger's test (p= 0.02) suggested that publication bias was present in the dataset, with negative results of small studies being apparently missing.

Dose-response results were available for three studies (1, 11, 25). McDuffie et al. (25) stratified the results by number of days of exposure per year: the unadjusted OR was 2.12 (95% CI 1.2-3.7) for more than 2 days/year. Eriksson et al. (11) also stratified the results by number of days of exposure per year; the adjusted OR for more than 10 days/year was 1.51 (95% CI 0.77-2.94). Andreotti et al. (1) categorized exposure according to quartiles of lifetime days of glyphosate use, and no excess of risk was identified recognized in any category (RR for the highest quartile, ≥108.5 days, 0.78; 95% CI 0.58-1.05). The meta-analysis of the results for highest category of exposure in these three studies resulted in a meta-RR equal to 1.49 (95% CI 0.37-2.61). In the study by Hohenadel et al. (19), which includes the population studied by McDuffie et al. (25), 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).

Results for NHL subtypes were reported in three studies (12, 22, 29). The meta-RR for diffuse large B-cell lymphoma (DLBCL) was 1.31 (95% CI 0.93-1.7; p-het = 0.85; I^2 = 0); that for follicular lymphoma (FL) was 0.82 (95% CI 0.93-1.70, p-het = 0.63; I^2 = 0), and that for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/

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

Authors	Country	Study population	Exposure assessment	NHL classification	N exposed cases	Covariates adjusted for	Participation rate % (ca/co)	Overlap with other studies
McDuffie et al., (1)	Canada	PCC	Questionnaire	ICD9	51	Age, province of residence, medical history, family history of cancer	67.1 / 48.0	Hohenadel et al. (19)†
Hardell et al, (17)	Sweden	Pooled analysis of two PCC: NHL excluding HCL (16), HCL (28)	Questionnaire	NS	8		91 /84	Nördstrom et al. (28); Hardell et al. (16)
De Roos et al, (7)	USA	Pooled analysis of three PCC: Iowa/Minnesota (4, 21); Kansas; Nebraska (21)	Questionnaire and checklist of pesticides in two studies	NS	36	Age, study site, use of other pesticides	SR 62.6 / 55; PR 37.4 / 45	Cantor et al. (4); Lee et al. (21)
Eriksson et al., (11)	Sweden	PCC	Questionnaire	WHO2001	29	Age, sex, calendar	91 / 92	-
Orsi et al., (29)	France	HCC	Questionnaire and expert evaluation	ICD-O3	12	Age, center, socio-economic status	95.7 / 91.2	-
Cocco et al., (6)*	6 European countries	Multicentre H/PCC	Questionnaire and job modules evaluated by experts, with crop-exposure matrix	WHO2001	4	Age, sex, center, education	88 / 81 (HC), 52 (PC)	-
Leon et al., (22)	France, Norway, USA	Pooled analysis of three cohort studies of pesticide applicators: AGRICAN; CNAP; AHS (8, 1)	AGRICAN and CNAP: crop-exposure matrices. AHS: self-reported use	WHO2001 and ICD-O3	1131	AGRICAN: Sex, livestock, retirement status, number of crops with pesticide application CNAP: Sex, livestock, selected pesticides AHS: Sex, state, livestock, selected pesticides	NA	De Roos et al. (8); Andreotti et al. (1)

* Cocco et al. (6) analyzed B-cell lymphoma
† The study by McDuffie et al. (25) was included in the meta-analysis instead of that by Hohenadel et al. (19) because the latter did not provide results for glyphosate independent of other pesticides.
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; NA, not available; NS, not specified; HCL, hairy cell leukemia

Table 2 - **S**tudies included in the main meta-analysis of glyphosate exposure and risk of MM

Authors	Country	Study population	Exposure assessment	MM classification	N exposed cases	Covariates adjusted for	Participation rate % (ca/co)	Overlap with other studies
Orsi et al., (29)	France	HCC	Questionnaire and expert evaluation	ICD-O3	5	Age, center, socio-economic status	95.7 / 91.2	-
Presutti et al., (33)	USA Canada	Pooled analysis of three PCC: 6 Canadian provinces (31, 24); Iowa (3); Nebraska	Questionnaire, self-reported information.	NS	45	Age, study, use of proxy respondent, medical history	Canada 58 / 48 Iowa 84 / 78 Nebraska 88 / 85	Brown et al., (3); Pawha et al., (31); Kachuri et al., (24)
Leon et al., (22)	France, Norway, USA	Pooled analysis of three cohort studies of pesticide applicators: AGRICAN; CNAP; AHS (8, 1)	AGRICAN and CNAP: crop-exposure matrices. AHS: self-reported use	WHO2001 and ICD-O3	240	AGRICAN: Sex, livestock, retirement status, number of crops with pesticide application CNAP: Sex, livestock, selected pesticides AHS: Sex, state, livestock, selected pesticides	NA	DeRoos et al., (8), Andreotti et al., (1)

PCC, population-based case-control study; HCC, hospital-based case-control study; NA, not available; NS, not specified

SLL) was 0.85 (95% CI 0.20-1.49, p-het = 0.17; I^2 = 44%). The pooled analysis of three cohort studies (22) provided a large proportion of the total weight in these meta-analyses. This latter study reported a RR of 1.36 (95% CI 1.00-1.85) for risk of DLBCL.

The results of the meta-analysis on MM risk, based on three studies, are reported in Figure 5; the meta-RR was 1.04 (95% CI 0.67-1.41; p-het = 0.21; I^2 = 16%). The study by Orsi et al. (29) contributed 1.3% of total weight, while the pooled analysis by Leon et al. (22) contributed 63%. The cumulative MM meta-analysis suggests that the higher cumulative RR was never associated to statistical significance and the cumulative RR of the studies conducted between 1993 and 2019 ranged from 1.04 to 1.87 without a clearly trend over time in the summary RR (details not shown).

Results unadjusted for potential confounders were reported in several studies of NHL (7, 11, 17, 22, 25) and MM (1, 22). The summary RR of meta-analyses including these results instead of the corresponding adjusted results were 1.13 (95% CI 0.88-1.37) for NHL and 1.01 (95% CI 0.84-1.19) for MM.
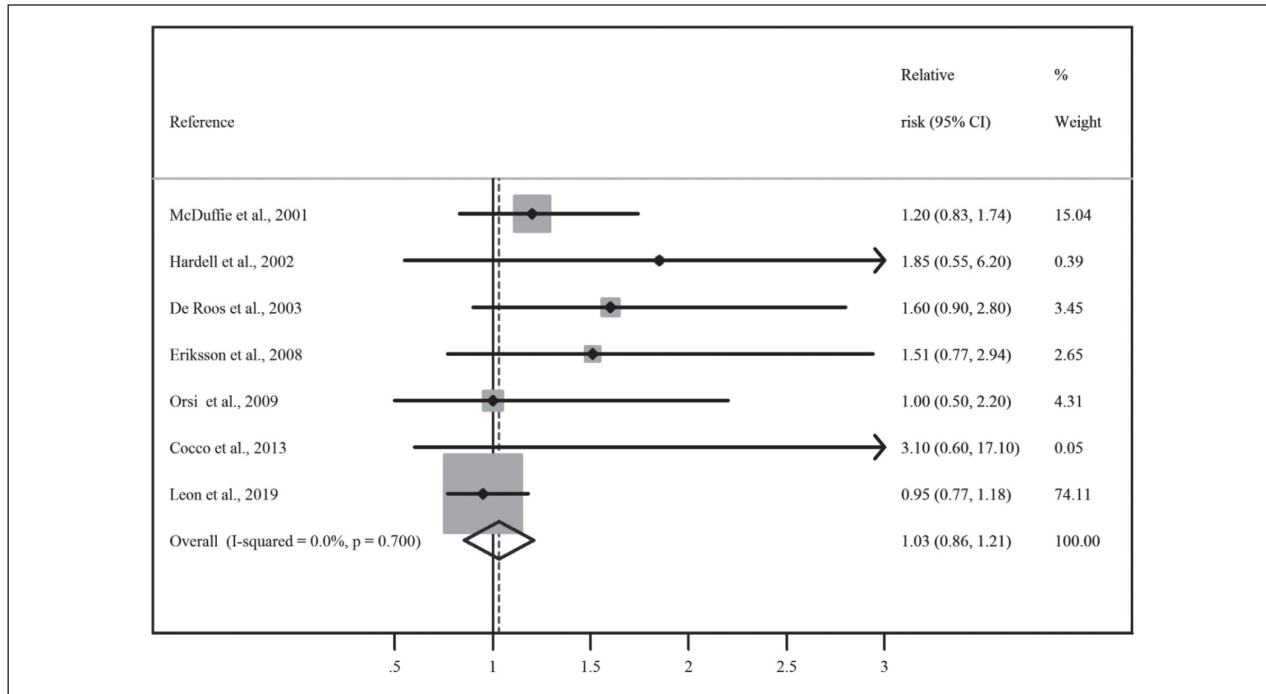
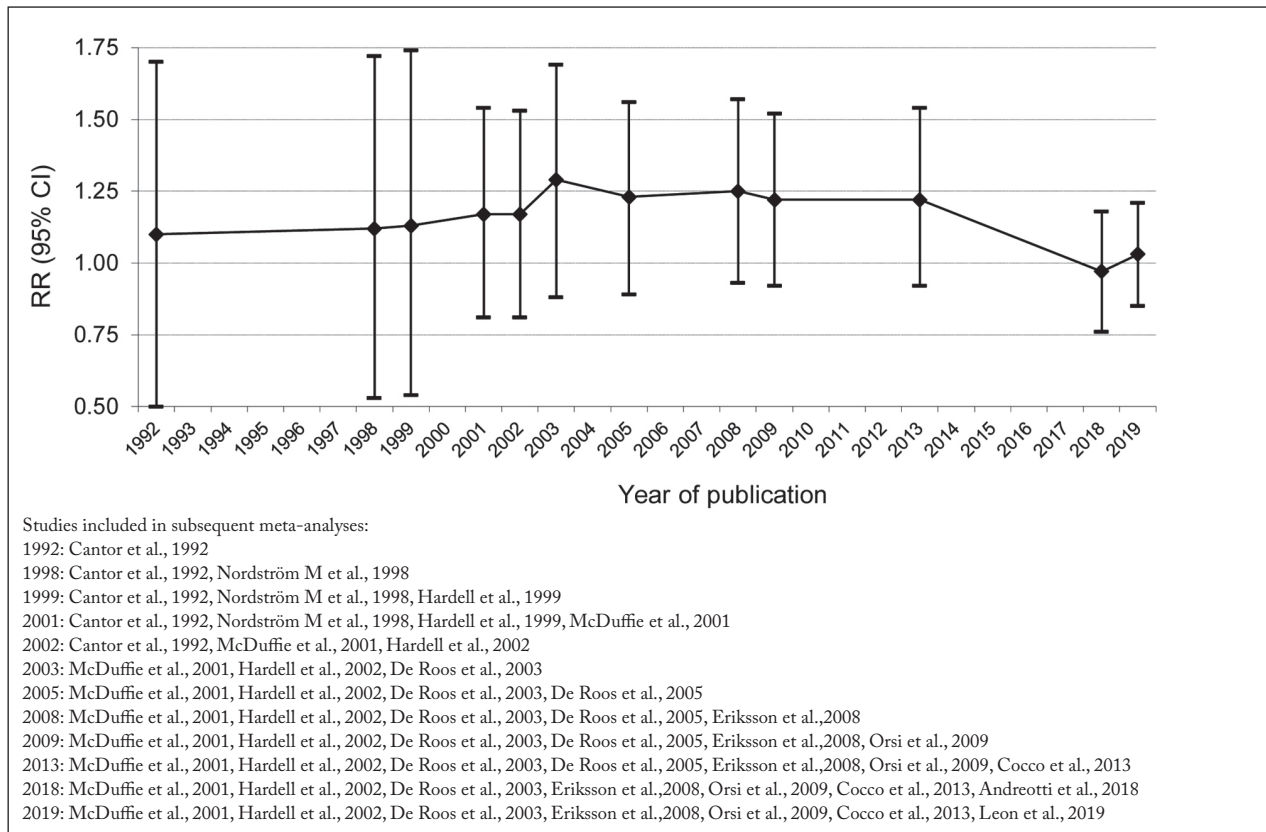**Figure 2** - Meta-analysis of studies on glyphosate exposure and risk of NHL

Studies included in subsequent meta-analyses:
1992: Cantor et al., 1992
1998: Cantor et al., 1992, Nordström M et al., 1998
1999: Cantor et al., 1992, Nordström M et al., 1998, Hardell et al., 1999
2001: Cantor et al., 1992, Nordström M et al., 1998, Hardell et al., 1999, McDuffie et al., 2001
2002: Cantor et al., 1992, McDuffie et al., 2001, Hardell et al., 2002
2003: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003
2005: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, De Roos et al., 2005
2008: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, De Roos et al., 2005, Eriksson et al.,2008
2009: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, De Roos et al., 2005, Eriksson et al.,2008, Orsi et al., 2009
2013: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, De Roos et al., 2005, Eriksson et al.,2008, Orsi et al., 2009, Cocco et al., 2013
2018: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, Eriksson et al.,2008, Orsi et al., 2009, Cocco et al., 2013, Andreotti et al., 2018
2019: McDuffie et al., 2001, Hardell et al., 2002, De Roos et al., 2003, Eriksson et al.,2008, Orsi et al., 2009, Cocco et al., 2013, Leon et al., 2019

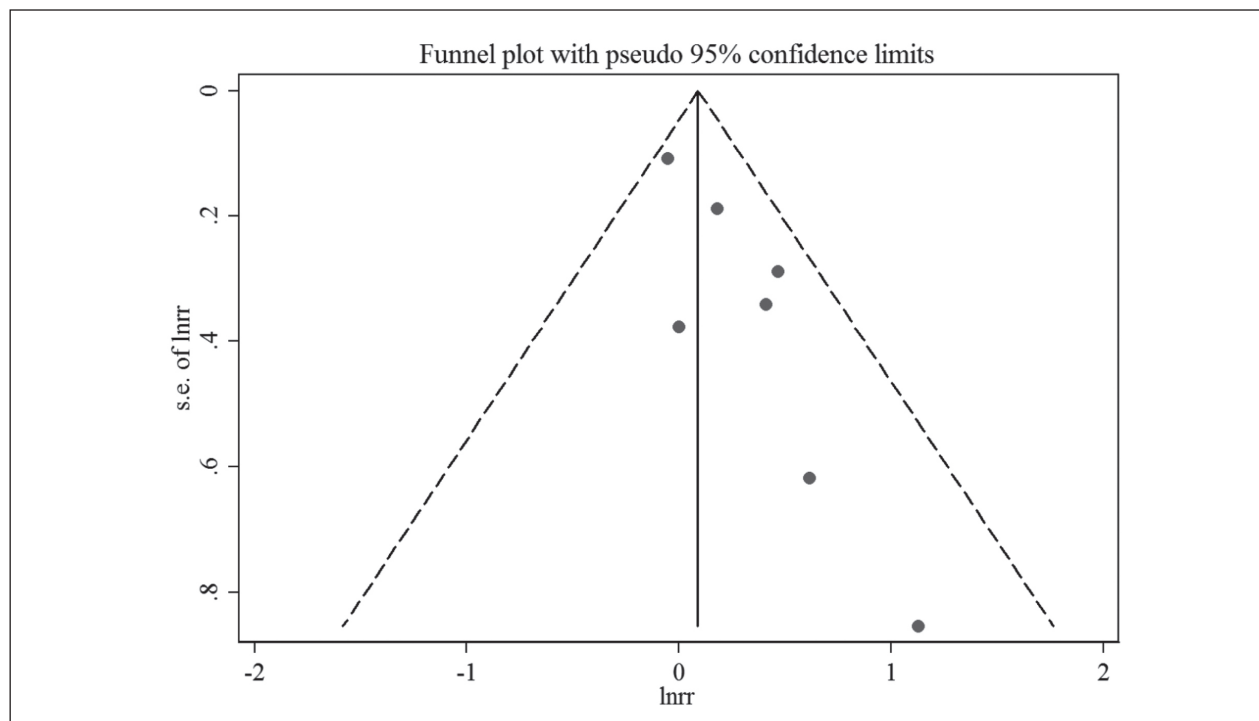**Figure 3** - Cumulative meta-analysis of study on exposure to glyphosate and risk of NHL

Figure 4 - Funnel plot of results on exposure to glyphosate and risk of NHL lnrr, logarithm of relative risk; s.e., standard error
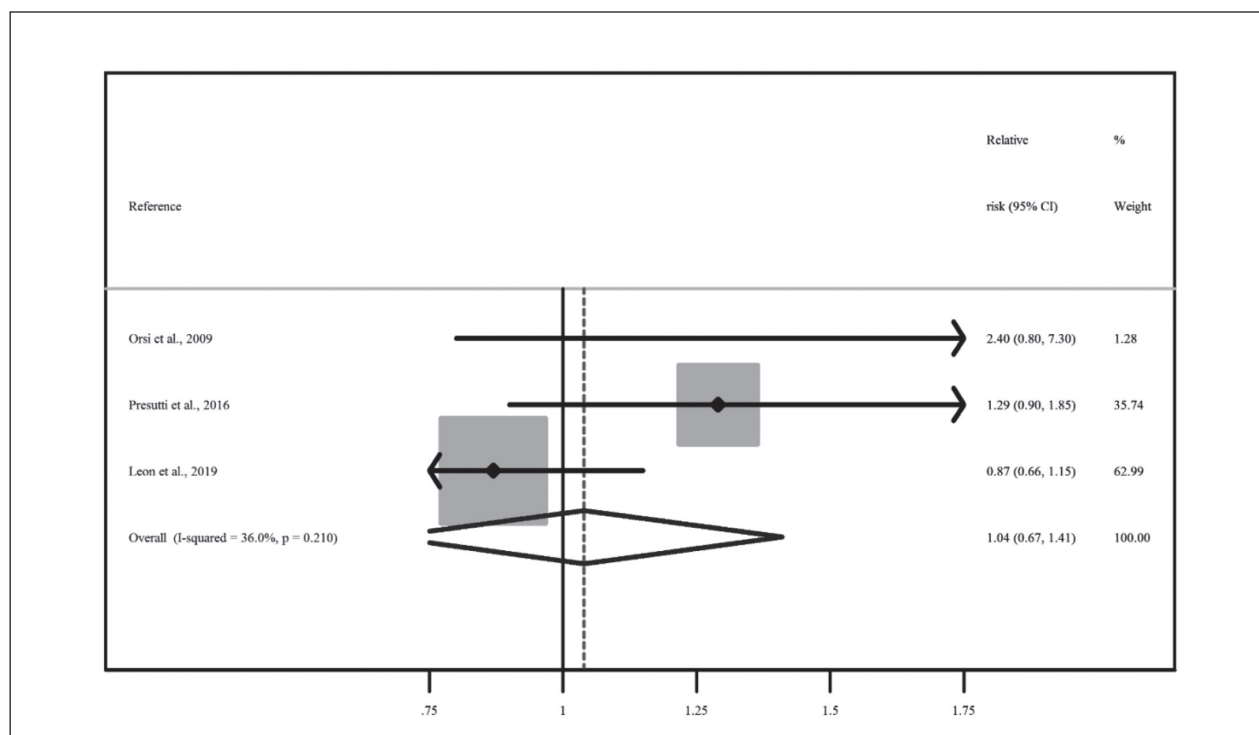

Figure 5 - Meta-analysis of studies on glyphosate exposure and risk of MM

Discussion

We reviewed and summarized all available epidemiologic studies on the association between exposure to glyphosate and NHL or MM incidence in adults; our meta-analysis provided no overall evidence of an increased risk for both NHL and MM in subjects occupationally exposed to glyphosate. The meta-analysis of duration of exposure was based on only three studies; an increase in risk in the category with highest exposure, measured in days/year, was reported in two small case-control study but not in a large cohort, resulting in an overall small, non-significant increase in risk. The secondary analysis of risk of subtypes of NHL, based on three studies, showed no increased risk of FL or CLL/SLL, while a small, non-significant increase was suggested for DLBCL. We found evidence of publication bias for NHL, resulting from lack of reporting of small, non-positive studies.

Although our cumulative meta-analysis showed that at no point in time the results on risk of NHL showed a statistically significant association with glyphosate exposure, they were reduced to the null value since the publication of the results of the Agricultural Health Study (1) and two other cohort studies (22). Cohort studies offer a better protection from selection and information bias compared to case-control studies, and the AHS included a more detailed assessment of exposure to individual pesticides than most other studies. These considerations, and the evidence of publication bias favoring positive studies, provide evidence that risk of NHL is not increased in workers exposed to glyphosate.

Our study was based on a larger database compared to previous reviews and meta-analyses: the studies included in the meta-analysis were based on a total of 1271 cases or deaths from NHL, compared to 211 in the review by IARC (20). Similarly, our meta-analysis of MM included 290 cases or deaths from the disease, compared to 72 in the IARC (20) review.

The suggestion of a possible dose-response relationship is driven by the results of two small case-control studies and were not confirmed by the largest cohort study available. The presence of publication bias in the overall meta-analysis suggest particular caution in interpreting results available from a small subset of studies.

The results of the analysis of the three main NHL subtypes does not provide clear evidence of an association with any of them, although the association with DLBCL detected in the pooled analysis by Leon et al. (22), although it does not reach the canonical level of statistical significance when correction for multiple comparisons is taken into account, deserves attention.

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 lack of comparability of cases and controls, and retrospective assessment of glyphosate exposure. Potential residual confounding might also operate, resulting in study-specific bias of unknown direction. The fact that the meta-analysis for NHL including unadjusted results resulted in higher summary risk estimates than those including adjusted results suggests that confounding is a potentially important issue in the available studies. Heterogeneity in exposure assessment among studies is an additional potential source of bias . Some of the large studies included in the meta-analysis (e.g., Leon et al. (22) and Presutti et al. (33)) consisted of pooled analyses of multiple studies: including such pooled analyses instead of the original studies might have resulted in underestimate of the between-study variance; however, the between study heterogeneity detected in the meta-analyses of both NHL and MM was low, and it is unlikely to be explained only by the inclusion of the pooled analyses. The use of classifications of NHL predating the WHO 2001 classification (40), which established a more valid approach to classify this group of diseases, is an additional limitation of several of the studies included in the meta-analysis. Strengths of the meta-analysis include the relatively large number of events, especially for NHL, the fact that all studies were based on NHL or MM incidence, and the ability to explore, to some extent, heterogeneity of results by period of publication, intensity of exposure, and NHL subtype.

In conclusion, we found no consistent indication of an association between exposure to glyphosate and risk of NHL or MM, even of the data for the

latter neoplasm are limited. The suggestion of an association between glyphosate exposure and risk of NHL came from small studies that suffered from publication and possibly other forms of bias; better-designed studies that were recently reported did not confirm the results of the earlier studies. The weak association with risk of DLBCL reported by Leon et al. (22) deserves replication.

Conflict of interest
PB acted as consultant for glyphosate producers, on matters not related to glyphosate. FD, EP and CC have no potential conflicts to report.

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 1-2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2, 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10, Fig 2, 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Fig. 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14