UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: January 6, 2020

SUBJECT: **Glyphosate**: Epidemiology Review of Zhang et al. (2019) and Leon et al. (2019) publications for Response to Comments on the Proposed Interim Decision

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40 CFR: §180.364

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Glyphosate is currently undergoing Registration Review. As part of the public comment period on the preliminary interim decision (PID) to support Registration Review, open literature studies were identified for the Agency's consideration. Of these, HED's RAB I has requested that TEB review and evaluate two recent review articles involving meta-analyses that were recently published in the scientific literature in 2019. These are:

- **Zhang et al. (2019). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. *Mutation Research/Reviews in Mutation Research* 781:186-206. doi: 10.1016/j.mrrev.2019.02.001.**

- **Leon et al. (2019). Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway, and the USA: a pooled analysis from the AGRICOH consortium. *Int J. Epidemiol.* 48(5):1519-1535. doi: 10.1093/ije/dyz017.**

These summary articles, importantly, both incorporate a recent update on glyphosate and non-Hodgkin's Lymphoma (NHL) published as part of the Agricultural Health Study (AHS) (Andreotti, G., Koutros, S., Hofmann, J.N., Sandler, D.P., Lubin, J.H., Lynch, C.F., Lerro, C.C., De Roos, A.J., Parks, C.G., Alavanja, M.C., Silverman, D.T. 2018. Glyphosate use and cancer incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute*. doi:10.1093/ jnci/djx233). This 2018 AHS publication was previously reviewed by TEB under separate cover (A. Aldridge, DP Barcode D444727, 12/12/2017)[1].

This memorandum provides review and comments on the above two referenced summary review articles to ensure that these are appropriately considered as part of Registration Review for glyphosate. The memorandum is divided into two parts, the first of which covers Zhang et al. (2019) and the second which covers Leon et al. (2019).

PART I. Review of Zhang et al. (2019)

Zhang et al. (2019). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. Mutation Research/Reviews in Mutation Research.
https://doi.org/10.1016/j.mrrev.2019.02.001

This review article summarizes epidemiologic studies published through 2018[2] on the association between exposure to glyphosate and NHL. The authors conducted meta-analyses for the epidemiological studies using an *a priori* hypothesis that the highest exposures to glyphosate-based herbicides (GBHs) will lead to increased risk of NHL in humans. Here, higher exposures corresponded to higher levels, longer durations, and sufficient lags/latencies. Additionally, the article provides a summary of lymphoma prevalence in laboratory animals and cites possible mechanisms, including as immunosuppression, endocrine disruption, genetic alterations, and oxidative stress. This memorandum considers only the epidemiological and meta-analysis content of the Zhang et al (2019) publication and does not review or otherwise evaluate the cited putative mechanisms.

The authors began by conducting their own literature search and identified a total of 909 articles using PRISMA guidelines[3], with 857 of the articles identified through PubMed and 52 through review of the (previously published) US EPA, International Agency for Research on Cancer (IARC), and Joint Meeting on Pesticide Residues (JMPR) reviews and reports. After removing duplicates (n=43) and excluding 850 studies which were either not relevant (animal, para-occupational, or mechanistic studies) or were otherwise inappropriate (generally reports, correspondence, reviews, or documents that did not include the exposure or outcome of interest), a total of 16 full-text articles were assessed. Of these 16, a total of 10 were excluded due to the lack of a risk estimate (n=3), it being an overlapping study (n=6), or containing an uncertain NHL diagnosis (n=1), leaving a total of 6 studies to be included in the meta-analysis. These six studies were the same as the six studies included in the Agency's evaluation of the human carcinogenic potential of glyphosate that was presented to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in 2016.[4] These six articles are listed below:

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[1] Review available at https://beta regulations.gov/document/EPA-HQ-OPP-2009-0361-0074
[2] The article does not indicate when the search years began, but indicated the literature search was done initially in November 2017 and then updated in March 2018 and then again in August 2018.
[3] D. Moher, A. Liberati, J. Tetzlaf, D.G. Altman, and P. Group. *Preferred reporting items for systematic review and meta-analysis, the PRISMA Statement*, 2009. *PLoS Med* **6** e10000097.
[4] See https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel

(1) McDuffie, H.H., Pahwa, P., McLaughlin, J.R., Spinelli, J.J., Fincham, S., Dosman, J.A., Robson, D., Skinnider, L.F., and Choi, N.W. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. *Cancer Epidemiol. Biomarkers Prev* 10(11): 1155-1163.

(2) Hardell, L., Eriksson, M., and Nordstrom, M. (2002). Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma.* 2002 May;43(5):1043-1049.

(3) De Roos, A.J., Zahm, S.H., Cantor, K.P., Weisenburger, D.D., Holmes, F.F., Burmeister, L.F., and Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non- Hodgkin's lymphoma among men. *Occupational and environmental medicine* 60(9): 1-9. doi: 10.1136/oem.60.9.e11.

(4) De Roos, A.J., Blair, A., Rusiecki, J.A., Hoppin, J.A., Svec, M., Dosemeci M., SandlerD.P., Alavanja, M.C. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 113(1): 49-54.

(5) Eriksson, M., Hardell, L., Carlberg, M., and Akerman, M. (2008). Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *International journal of cancer* 123(7):1657-1663. doi: 10.1002/ijc.23589.

(6) Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Marit, G., Soubeyran, P., Huguet, F., Milpied, N., Leporrier, M., Hemon, D., Troussard, X., and Clavel, J. (2009). Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occupational and environmental medicine* 66(5): 291-298.

In addition, the Zhang et al. (2019) authors identified a (then) recent publication on the AHS with updated cohort data for glyphosate and NHL (Andreotti et al., 2018):

> **Andreotti, G., et al. (2018). Glyphosate use and cancer incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute* 110(5): 509–516. doi:10.1093/jnci/djx233**

An earlier AHS publication (De Roos et al., 2005) was considered in the 2016 SAP evaluation and followed that AHS cohort from enrollment in 1993-1997 to December 31, 2001. Andreotti et al. (2018) provides a (post-2016 SAP) AHS update to this publication with an extended follow-up period through 2012/2013 and adds a much larger number of cases. Specifically, the Andreotti et al. (2018) publication updates and supersedes the 2005 De Roos AHS publication and adds 11-12 additional years of follow-up data and considered over five times as many NHL cases (n=575 rather than n=92). TEB prepared an independent review of this AHS study after the 2016 SAP when this publication appeared summarizing the findings (A. Aldridge, DP Barcode D444727, 12/12/2017)[5]. In addition, Andreotti et al. (2018) was also included and addressed in EPA's Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential (DP Barcode D444689, TXR# 0057688, 12/12/2017)[6] which updated the issue paper presented to the FIFRA SAP in 2016. Specifically, the EPA's Revised Glyphosate Issue Paper addressed comments raised by the SAP and incorporated the aforementioned TEB review of Andreotti et al. (2018). Thus, all the data/information summarized and re-interpreted by the Zhang et al. (2019) article have been previously considered by EPA.

[5] Review available at https://beta.regulations.gov/document/EPA-HQ-OPP-2009-0361-0074
[6] See https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=OPP&dirEntryId=337935

The six retained studies retained by the Zhang et al (2019) authors were evaluated, along with the recent AHS updated by Andreotti et al (2018), by quality scores using the Newcastle-Ottawa Scale (NOS)[7] with the two highest scoring studies (7 or 8 points) being the prospective cohort AHS studies (Andreotti et al. (2018) and its progenitor study DeRoos et al. (2005)) and Eriksson et al. (2008), a case-control study. The remaining studies scored either 6 points or 2 points by the NOS, with this latter low score applying only to a case-control study by Orsi et al. (2009). These ratings coincide with the rankings given by EPA in our December 2017 Revised Glyphosate Issue Paper, which ranked De Roos et al. (2005) and Eriksson et al. (2008) as high quality and the remaining four as moderate quality.

Zhang et al (2019) concluded based on their current meta-analysis of human epidemiological studies, using their *a priori* hypothesis that those with higher exposures to GBH will show increased risks of NHL, that GBH exposure was associated with increased risk of NHL in humans. Using the highest cumulative exposures reported, they emphasized in their review article a meta-risk ratio (mRR) of 1.41 (95% CI: 1.13-1.75) using a fixed effect model which included the most recent (Andreotti, 2018) AHS study. They compared this to a mRR estimate of 1.45 (95% CI: 1.11, 1.91) for the fixed effect model using the earlier AHS study (DeRoos et al., 2005) study in place of Andreotti (2019). They reported that a number of sensitivity analyses performed did not reveal substantively different results and concluded that "our current meta-analysis of human epidemiological studies suggests a compelling link between exposures to GBHs and increased risk for NHL."

TEB Evaluation of Zhang et al (2019) Review

TEB was asked to provide an evaluation of the epidemiological summary and meta-analysis performed by Zhang et al (2019) and to update the prior meta-analysis done for our EPA December 2017 Revised Glyphosate Issue Paper. We do this below in two parts: (i) a commentary on the Zhang et al. (2019) review and (ii) a re-analysis/update of the high and moderate quality studies investigating NHL selected by EPA previously, substituting the more recent Andreotti et al. (2018) AHS results for the earlier De Roos et al (2005) results.

(i) TEB Commentary on Zhang et al (2019) Review

As stated above, Zhang et al (2019) performed a meta-analysis of human epidemiological studies to evaluate the *a priori* hypothesis that higher and longer cumulative GBH exposure are likely to yield higher NHL risk estimates than lower and shorter exposures. They reported, depending on the model used, that exposure to glyphosate is associated with a roughly 40 to 60% increase in the incidence of NHL. TEB offers the following points with respect to their analysis:

- Zhang et al (2019) focused their conclusions on the results from a fixed effect meta-analysis on the highest exposure categories presented in each article, including Andreotti et al. (2018). They state that the use of the fixed effect inverse variance method assigns weights to each study that are directly proportional to the study precision which (they appear to believe) is superior to a random effects model where weights are "based on a complex mix of study precision, relative risk (RR), and meta-analysis size." They continue, stating that

> "One benefit of the random effects model is the ability to incorporate between study variance into the summary variance estimate and confidence intervals which may help prevent artificially narrow confidence intervals resulting from use of the fixed effects model in the presence of between study heterogeneity. However, a feature of the random effects model is that study weighting is not directly

[7] G. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-randomized Studies in Meta-Analysis. Ottawa Hospital Research Institute. Ottawa (ON 2009). Available March 2016.

proportional to study precision, and greater relative weight is given to smaller studies which may result in summary estimates that are less conservative than the fixed effects model"

The use of a fixed effect meta-analysis (instead of random) for this kind of data is unusual and the rationale used by the Zhang et al. (2019) authors to justify this use is incorrect. The authors did present the results from the correct (random effects) model but indicated in their publication that they were not emphasizing them.[8] While the results of the random effects model are not substantively different from the fixed effects model (they reported a mRR of 1.56 (95% CI: 1.12, 2.16) using a random effects model incorporating the Andreotti et al (2018) AHS study results), the arguments advanced by the Zhang et al. (2019) authors in support of the fixed effect model contain methodological and logical flaws.[9] The correct meta-analysis method here is a random effects analysis (which tends to give wider and more appropriate confidence intervals).

- The Zhang et al. (2019) authors critiqued Andreotti et al. (2018) for using multiple imputation to account for missing data (Andreotti et al. (2018) had a response rate of only about 63% so 37% of the data needed to be imputed) which Zhang et al. (2019) describe as an "exposure simulation" and provide some technical details about why they have concerns about this. Multiple imputation for missing data is a state-of-the-science practice for dealing with missing data; nevertheless, the Zhang et al. (2019) authors correctly point out that Andreotti et al. (2018) should have included the *outcome* information into the process of imputing missing exposure values. Since the missing data of glyphosate exposure of subjects who did not complete the follow-up questionnaire were imputed based on the available information for factors that related to pesticide use such as demographic, medical history, other farm characteristics, and reported pesticide use at enrollment, it would be expected that the impact of failing to include the NHL information would not be substantial. Importantly, Andreotti et al. (2018) conducted a number of sensitivity analyses that suggest the results of the data analysis of imputed data were reasonable and close to that of data analysis which would have resulted using only complete data. For example: for the association between glyphosate exposure and NHL, an estimated risk ratio for quartile 4 ($RR_{Quartile\ 4}$) = 0.90 (95% CI=0.63 to 1.27) was obtained from the sensitivity analysis using the data of only subjects with complete data vs. an estimated $RR_{Quartile\ 4}$ = 0.87 (95% CI=0.64 to 1.20) from the analysis where the missing data were imputed.[10] Given these minor differences, TEB believes that the Andreotti et al. (2018) analysis is adequate and represents a sufficiently reliable risk ratio (RR) for incorporation into a meta-analysis.

- Zhang et al (2019) also correctly pointed out another difference between the earlier De Roos et al. (2005) AHS study and the updated Andreotti et al. (2018) AHS study with respect to the reference group selected. Specifically, the De Roos et al. (2005) article selected the lowest quartile as the reference group while the later Andreotti et al. (2018) article selected the unexposed as the reference group. Both studies appeared to show differences between the groups

[8] Zhang et al. (2019) reported mRR of 1.56 (95% CI: 1.12, 2.16) using a random effects model and the Andreotti et al (2018) data in addition to the fixed mRR estimate of 1.45 (95% CI: 1.11, 1.91) using the earlier AHS study (DeRoos, 2005) study in place of Andreotti (2019).

[9] See, e.g., various sections in Borenstein, Michael. *Common Mistakes in Meta-analysis and How to Avoid Them*. (Biostat, Inc: Englewood, NJ) 2019. e.g., §8.5 p. 59-63) and Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. *Introduction to Meta-Analysis* (John Wiley and Sons: London) 2008. See also Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. 2010. A basic introduction to fixed effect and random effects models for meta-analysis. *Res. Syn. Meth*. 1:97-111.

[10] $RR_{Quartile\ 4}$ = 0.90 (95% CI: 0.63,1.27) is listed on page 4 of the publication. $RR_{Quartile\ 4}$ = 0.87 (95% CI: 0.64, 1.20) is listed in Table 2 of the publication.

that used glyphosate and those that did not[11] which could mean that the potential exists for residual confounding[12]. It is not clear why Andreotti et al. (2018) did not use the lowest exposed quartile as the reference group, at least as part of a sensitivity analysis, and this appears to be a legitimate critique by Zhang et al (2019). Nevertheless, the (statistically significant) baseline differences between the exposed and unexposed do not appear to be substantive and, in any case, were adjusted for in the Poisson regressions that were performed by both (originally) De Roos et al. (2005) and (subsequently) by Andreotti et al. (2018).

The authors stated that their analyses differ from several earlier meta-analyses by focusing on an *a priori* hypothesis targeting biologically-relevant exposure magnitude and including newly updated AHS information from Andreotti et al (2018). More specifically, the Zhang et al (2019) authors elected with their *a priori* hypothesis to focus on the effect sizes which were associated with and characteristic of high-end exposures to GBHs (where "high" was defined as of greater intensity/magnitude, of longer duration, or of some cumulative combination of the two). For at least Andreotti et al. (2018) -- the largest study and of the highest quality -- this hypothesis does not appear to be supported by initial examination of categorized exposures since there are not statistically significant results, no trend is observed (nor monotonicity), and the confidence interval (CI) around each effect size estimate by categorized exposure overlap considerably. In other words, there is no readily apparent indication of a trend toward higher odds ratios with higher exposures in Andreotti et al (2018) so there appears to be little evidence supporting the authors' stated *a priori* hypothesis. The table below is an excerpt from Andreotti et al. (2018) and it was the RR and its associated 95% CI of 1.12 (95% CI: 0.83, 1.51) from quartile 4 (Q4) and the 20-year lag that was used by the Zhang et al. (2019) authors as part of their meta-analysis (because this reflects the category with the highest exposure/longest lag (Q4, 20-y lag) and thus most likely to display the largest RR if there was indeed an association).

[11] Specifically, De Roos et al. (2005) state that "We compared certain baseline characteristics among the three types of pesticide applicators… [*and*]… the purpose of the comparison was to identify potential confounders of the glyphosate exposure-disease associations for the various analyses we conducted. Differences between the exposure groups were tested using the chi-square statistics and associated p-values." They continue, indicating that "significant differences ($p<0.05$) existed between never exposed and lowest exposed subjects for all of the *[baseline]* characteristics in Table 1. Lowest- and higher- exposures subjects ($p<0.05$) also differed on several factors, the most notable being that higher -exposed subjects were more likely to be commercial applicators, to have consumed greater amounts of alcohol in the past year, and to have used other specific pesticides. However, lowest- and higher-exposed subjects were similar to each other ($p>0.05$) in characteristics including smoking and family history of cancer in a first degree relative. In addition, lowest and higher- exposed subjects were more similar to each other than to their never-exposed counterparts (by qualitative comparison of percentages only) in factors including NC residence, education beyond high school, and use of other pesticides. Because of relative similarities between lowest- and higher-exposed in factors associated with socioeconomic status and other exposures, we decided to conduct some analyses using lowest-exposed rather than never-exposed applicators as the reference group, in order to avoid residual confounding by unmeasured covariates.".

[12] Specifically, if there are systematic differences in observed variables between farmers/applicators that use glyphosate vs. those that don't, these can be adjusted for (i.e., accounted or corrected for) in the statistical modeling. Nevertheless, such differences in observed characteristics between users and non-users of glyphosate may be symptomatic of other (unmeasured) systematic /characteristic differences that *aren't* measured in the study. To the extent that these might affect exposure or disease probabilities, such differences would be 'hidden' from the analysis and be unable to be adjusted for by the analysis and potentially lead to incorrect inferences. Hence, if there are differences between unexposed (e.g., non-users) and exposed (e.g., users) individuals, it can be desirable to use the lowest category of exposure (as opposed to the unexposed) as the reference category.

Table 3. Cancer incidence in relation to lagged intensity weighted lifetime days of glyphosate use in the Agricultural Health Study

		5-y lag			20-y lag		
Cancer sites*	Glyphosate use†	No. of cases	RR (95% CI)‡	P_{trend}‡	No. of cases	RR (95% CI)‡	P_{trend}‡
Non-Hodgkin lymphoma							
	None	150	1.00 (reference)		354	1.00 (reference)	
	Q1	113	0.92 (0.66 to 1.28)		63	1.22 (0.91 to 1.64)	
	Q2	92	0.79 (0.59 to 1.06)		55	1.15 (0.86 to 1.55)	
	Q3	119	1.03 (0.75 to 1.41)		48	0.98 (0.71 to 1.36)	
	Q4	101	0.87 (0.64 to 1.17)	.76	55	1.12 (0.83 to 1.51)	.62

Excerpt copied directly from p. 514 of Andreotti et al (2018)

It seems apparent from the above excerpt, however, that (i) there is no suggestion of a trend toward higher RRs at higher exposures (p_{trend}=0.62), with the Q4 value in fact being only the third highest of the four quartiles value (i.e., one up from the bottom); (ii) none of the RRs associated with any of the quartiles is significant or appear to come close to it; and (iii) all the RRs seem roughly similar at the null RR≅1. Given that, it doesn't appear that extracting only the Q4 value from the RRs here and choosing to move forward with only that selection is necessarily well-supported or justified, particularly since this considerably lowers the sample size (by about two-fold for this 20 year lag and eight-fold compared to an ever/never analysis). This is of particular importance because Andreotti et al. (2018) is a prospective cohort study that is the highest-quality of all the studies selected for meta-analysis. Thus, it seems there is little justification for any *a priori* hypothesis that there is a dose-response phenomenon with higher doses (exposures) leading to increased risks of NHL here and that there is no clear rationale for Zhang et al. (2019) to choose to use only a small subset of the Andreotti et al (2018) data for their meta-analysis.[13]

[13] The subset – as indicated in the text- - was the Q4/20 y lag subset which represents the "high end" exposure to GBHs offered Andreotti et al. (2018) and this RR of 1.12 (95% CI: 0.83, 1.51) was used by Zhang et al. (2018) in place of the earlier De Roos at al. (2005) ever-never estimate of 1.10 (95% CI: 0.7, 1.9). Separate high-end estimates were also provided by Eriksson et al (2008) and McDuffie et al. (2001) representing >10 days/yr. (vs.≤10 days/ yr.) and > 2 days/yr. vs. (vs.≤2 days/yr.), respectively; Zhang et al. (2018) similarly used the high end estimates of 2.36 (95% CI: 1.04, 5.37) and 2.12 (95% CI: 1.20, 3.73), respectively, from these two studies in place of those studies' ever/never estimates. TEB notes two things regarding this substitution:

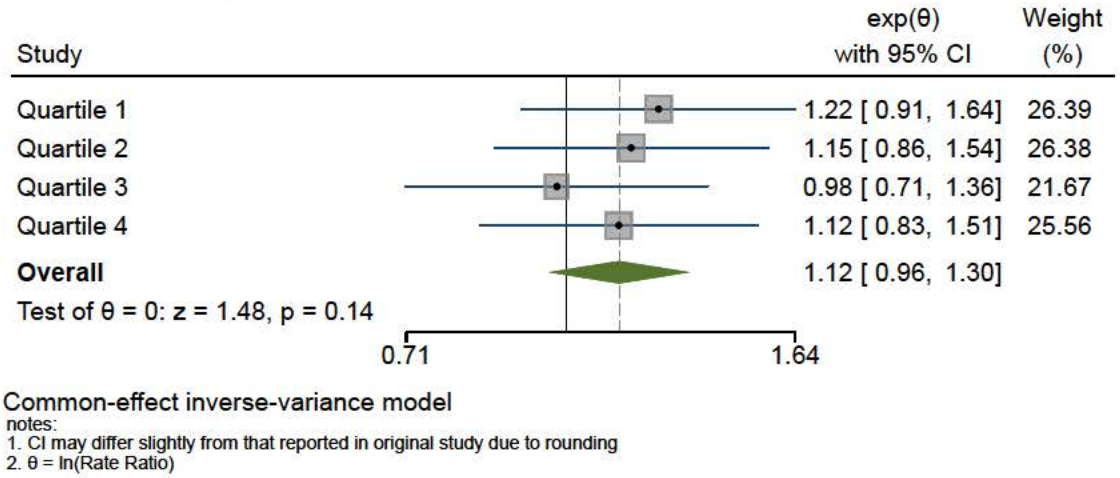
1) the Eriksson et al. (2008)-substituted value of 2.36 (95% CI: 1.04, 5.37) from their Table II was based on only 17 cases and 9 controls and was an ***unadjusted*** effect size because no adjusted effect sizes were provided in the article for the >10 days high end exposure estimate. Table VII in Eriksson et al (2008) suggests that adjustment for age, sex and year of diagnosis/enrolment would bring about a meaningful decrease in the odds ratio for glyphosate had that statistical adjustment been made; this in turn suggests that the > 10 days/yr odds ratio from Ericksson et al (2008) used by Zhang et al. (2018) likely over-estimated any true relationship.

2) McDuffie et al. (2001) reports an odds ratio of 1.00 (95% CI: 1.63, 1.57) and 2.12 (95% CI: 1.20,3.73) for >0 to ≤2 days/yr and >2 days/yr., respectively. Zhang et al uses the odd ratio 2.12 (95% CI: 1.20,3.73) representing the high end (>2 days/yr) exposure estimate in place of the 1.20 (95% CI: 0.83, 1.74) odds ratio value associated with the ever/never estimate. Due to recall bias in case-control studies and its tendency to introduce differential misclassification away from the null, this estimate of 2.12 (95% CI: 1.20,3.73) for the odds ratio is likely to overestimate the true relationship. Support for this is provided in McDuffie et al. (2001) Table 5 wherein it can be seen that substantially higher odds ratios are seen for all nine odds ratios in that table associated with higher end days/yr. exposures. For example, there is no reasonable expectation of any relationship between application of sulfur and NHL, yet Table 5 in McDuffie et al. (2001) suggests that applying sulfur ≥ 1 day per year (vs. 0 days per year) more than doubles the risk of NHL (OR=2.12 (95% CI: 1.20, 3.73). Similar increases are seen for 2,4-D, mecoprop, dicamba, malathion, DDT, captan, and carbon tetrachloride. These are all likely reflective of recall bias, or the tendency of cases (here NHL) to mistakenly overestimate exposures and would consequently lead to odds ratios that likely overestimate true effect sizes. Thus, Zhang et al.'s substitution of the McDuffie et al (2001) odds ratio of 2.12 (95% CI: 1.20,3.73) for glyphosate application of >2 d/yr is likely to overestimate any potential true effect.

As stated earlier, one of the consequences of this choice is that only a small proportion of the results from the largest, most comprehensive, and best designed study among all those examined gets used (specifically, only the 55 exposed cases in Q4 of the 20 year lag analysis vs. 440 exposed cases in all the quartiles for an ever-use analysis). In fact, there is greater justification for combining Q1-Q4 from the 20-year lag analysis into a single 20 year lagged ever/never category for a meta-analysis. Using a fixed effect (aka "common effect") inverse variance meta-analysis a RR close to the null value of 1 (RR = 1.12; 95% CI = 0.96, 1.30) would be obtained that is not statistically significant (p-value =0.14), as shown in Figure 1:

Figure 1

Common Effect Inverse Variance Analysis of 20-year Lag Data from Andreotti et al. (2018)

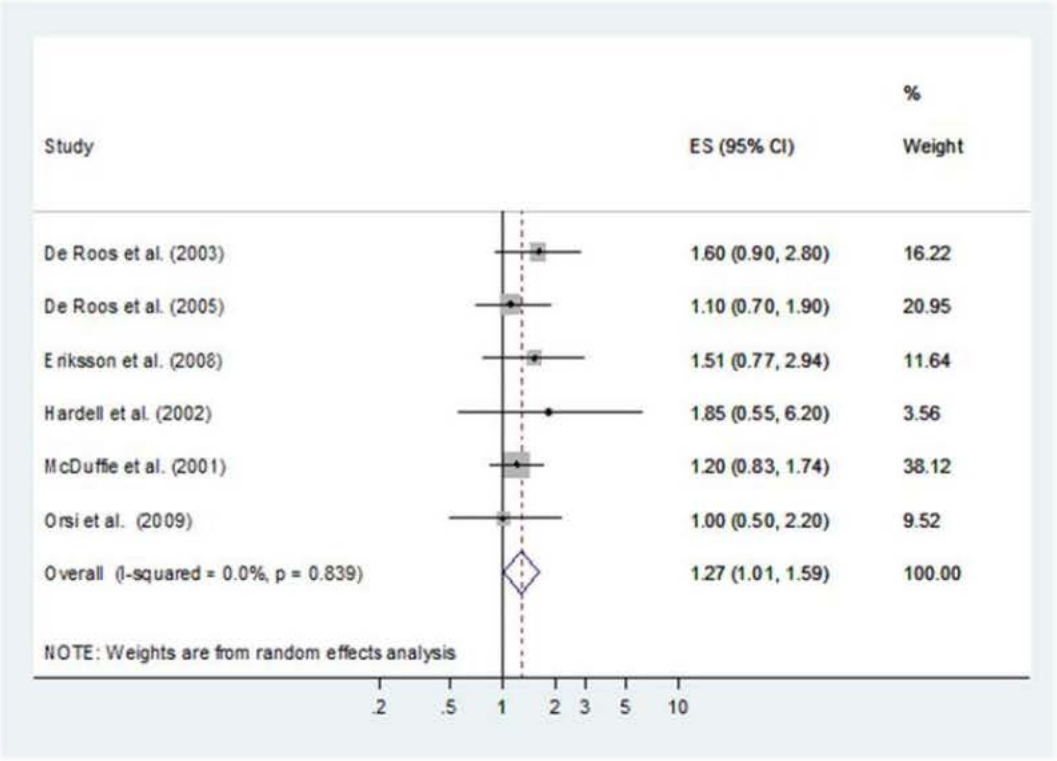


(ii) CEB Update of Revised Estimate:

The EPA's December 2017 Revised Glyphosate Issue Paper used single summary measures (i.e., ever/never effect sizes) from the original six NHL studies identified. The results from Andreotti et al. (2018), which was published online at the time, were not incorporated into the EPA analysis at that time. The meta-estimate of 1.27 (95% CI: 1.01, 1.59) based on this analysis was statistically significant, with the lower limit of the 95% CI just slightly over 1. Figure 2 is the forest plot displaying the meta-analysis results excerpted from the December 2017 EPA Revised Glyphosate Issue Paper.

Figure 2. Forest Plot and Meta-analysis for NHL from EPA's December 2017

Revised Glyphosate Issue Paper



The Andreotti et al. (2018) AHS study updated the De Roos et al (2005) AHS study to include (as indicated above) more recent AHS data: this added 11-12 additional years of follow-up data to De Roos et al (2005) and increased by five-fold the number of NHL cases (n=575 rather than n=92)[14]. TEB has been requested to update its previous meta-analysis (illustrated in Figure 2 above from the EPA Revised Glyphosate Issue Paper) by replacing the earlier AHS data from DeRoos et al (2005) with the updated AHS data from Andreotti et al (2018).

Unlike De Roos et al. (2005) and the other five studies included in the previous EPA meta-analysis, Andreotti et al. (2018) provided risk estimates by exposure *quartile* and did **not** report risk estimates on an ever/never basis as did the earlier De Roos et al. (2005) study and other publications.[15] In order to incorporate the Andreotti et al. (2018) data into the meta-analysis, the ever/never risk estimates were

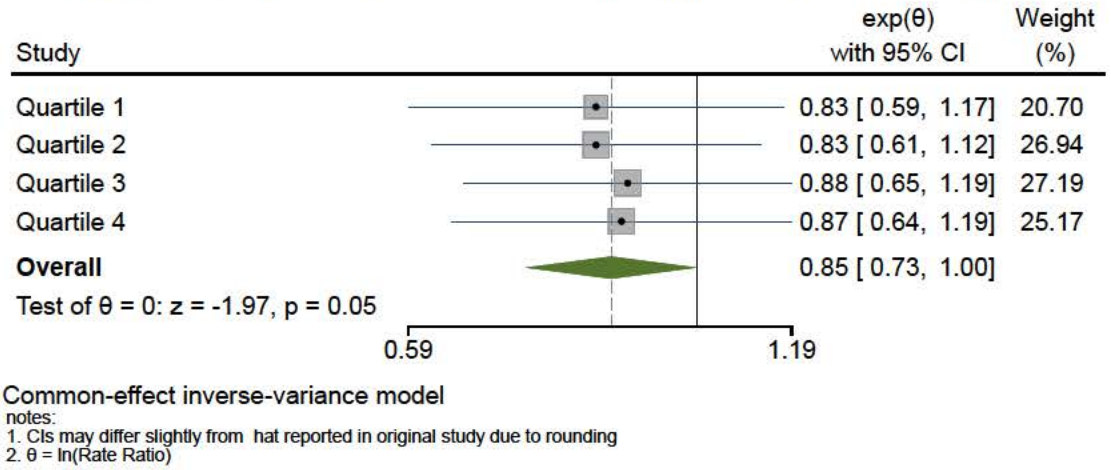
[14] HED prepared an independent review of this AHS study after the 2016 SAP (A. Aldridge, DP Barcode D444727, 12/12/2017). See https://beta.regulations.gov/document/EPA-HQ-OPP-2009-0361-0074.

[15] This may be because the Andreotti et al. (2018) exposed counts were larger than the other studies and thus the authors were able to break this out on a quartile basis. NHL counts for Q1 through Q4 in Andreotti et al. (2018) were 102, 93, 106, and 103, respectively.

calculated from the data expressed in exposure quartiles by Andreotti et al (2018). Specifically, this was done using a fixed effect (aka "common effect") meta-analysis technique which is appropriate when attempting to combine effect size estimates from a *single* study.[16] The resulting estimate for Andreotti et al. (2018) on a comparable ever/never basis is a rate ratio (RR) of 0.85 (95% CI: 0.73, 1.00) as illustrated below in Figure 3.

Figure 3

Ever-Never Re-analysis of Andreotti et al. (2018) Using Common Effect Inverse Variance Method



Using this updated risk estimate and substituting out the (earlier) AHS risk estimate from De Roos et al. (2005) of OR = 1.1 (95% CI: 0.7, 1.9) produces the following set of effect sizes for use in a new meta-analysis that incorporates the newest (updated) AHS NHL study results from Andreotti et al (2018).

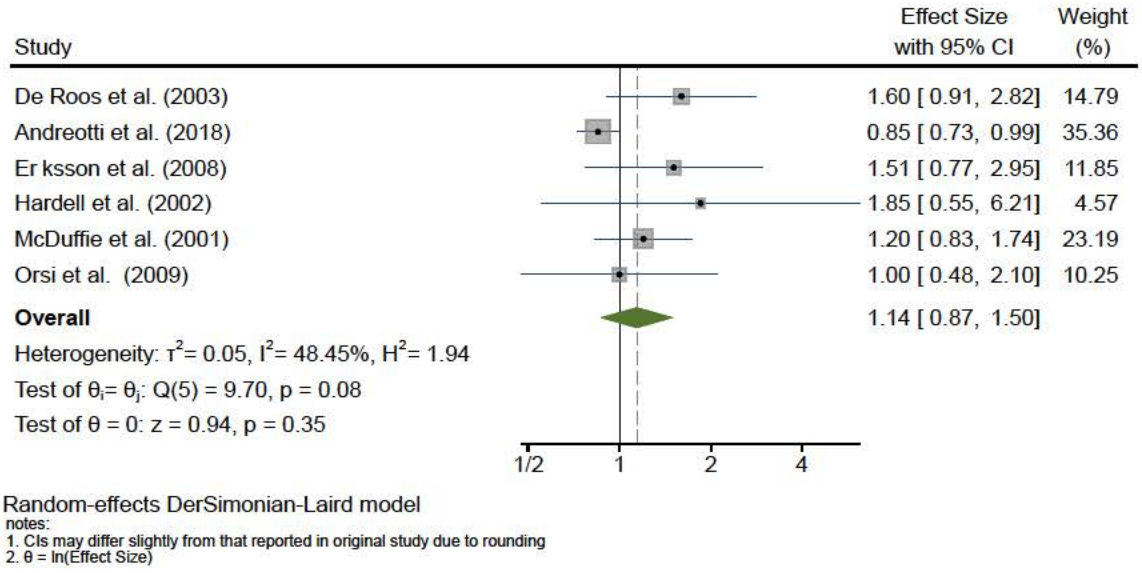
Study	Risk Estimate (OR or RR)	Lower bound of CI	Upper bound of CI
De Roos et al. (2003)	1.60	0.90	2.80
Andreotti et al. (2018)[a]	0.85	0.73	1.00
Eriksson et al. (2008)	1.51	0.77	2.94
Hardell et al. (2002)	1.85	0.55	6.20
McDuffie et al. (2001)	1.20	0.83	1.74
Orsi et al. (2009)	1.00	0.50	2.20
[a]Andreotti et al (2018) substitutes for the earlier De Roos et al. (2005) estimates of 1.1 (95% CI: 0.7, 1.9)			

[16] For this type of analysis, a fixed effect model ***is*** appropriate. See, e.g., various sections in Borenstein, Michael. *Common Mistakes in Meta-analysis and How to Avoid Them*. (Biostat, Inc: Englewood, NJ) 2019 and Borenstein, M. Larry V. Hedges, Julian P.T. Higgins, and Hannah R. Rothstein. *Introduction to Meta-Analysis* (John Wiley and Sons: London) 2008.

Using these data to update the meta-analysis that was originally performed for the December 2017 EPA Revised Glyphosate Issue Paper produces the following forest plot in Figure 4 with a meta-estimate of the effect size of 1.14 (95% CI: 0.87, 1.50).

Figure 4

Updated EPA Meta-analysis Incorporating Andreotti et al. (2018)



Random-effects DerSimonian-Laird model

notes:
1. CIs may differ slightly from that reported in original study due to rounding
2. θ = ln(Effect Size)

As expected, the larger sample size and tighter 95% CI from Andreotti et al. (2018) increased the weight of the AHS cohort study to 35.36% (from 20.95% when using the smaller De Roos et al. (2005) study). The authors of the Zhang et al (2019) review article did not perform this ever-never meta-analysis presumably because Andreotti et al. (2018) reported estimates by quartile and did not provide the ever/never estimates present in and comparable to the original six studies. This updated meta-estimate of 1.14 (95% CI: 0.87, 1.50) compares to EPA's earlier (December 2017) estimate of 1.27 (95% CI: 1.01, 1.59) when the AHS data from De Roos (2005) was included. Therefore, incorporation of the study results from Andreotti et al (2018) yielded a smaller effect size, which is no longer statistically significant.

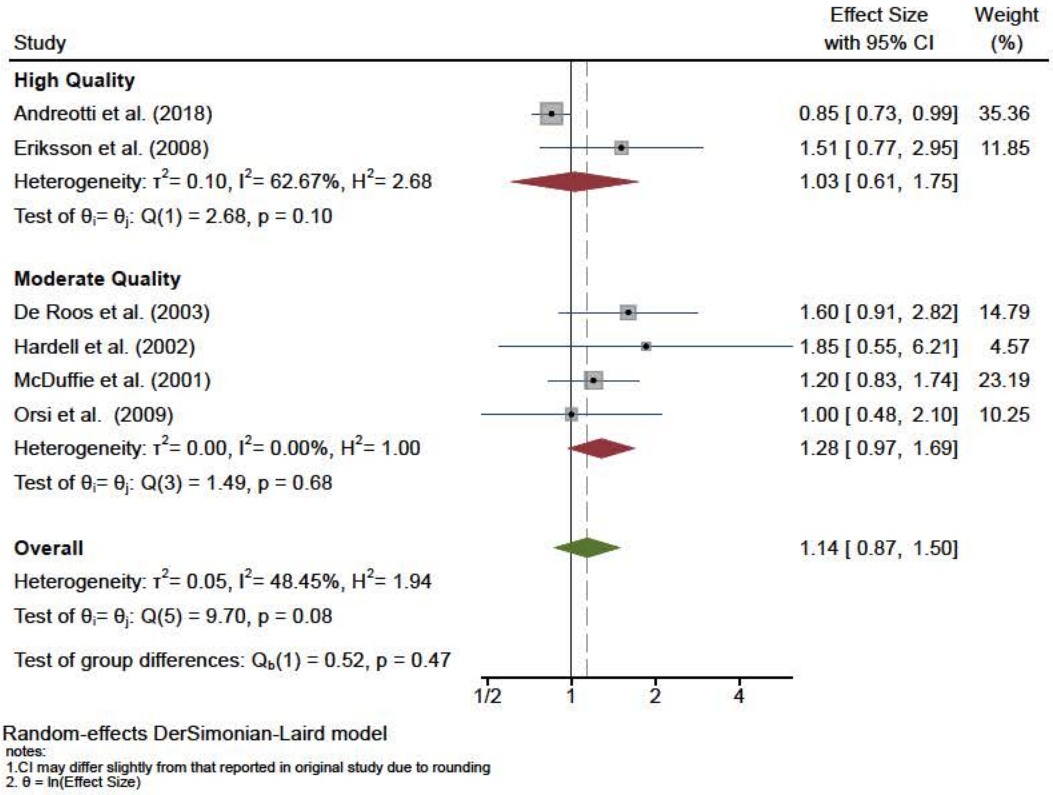
Finally, there has been some interest in the past in performing these analyses after separating the high and moderate quality studies and seeing how they compare. Per the Revised Glyphosate Issue Paper, the following quality ratings were assigned:

Study	Quality Ranking
De Roos et al. (2003)	Moderate
De Roos et al. (2005)	High
Eriksson et al. (2008)	High
Hardell et al. (2002)	Moderate
McDuffie et al. (2001)	Moderate
Orsi et al. (2009)	Moderate

These are the same ratings assigned (independently) by the Zhang et al. (2019) study authors. Substituting the newer (and similarly high ranked) Andreotti et al. (2018) study for the earlier De Roos et al. (2005) high-ranked AHS study produces the following forest plot/meta-analysis (Figure 5):

Figure 5

Updated EPA Meta-analysis Incorporating Andreotti et al. (2018), by Quality Rating



As can be seen, the two high-ranked studies also produce a non-statistically significant meta-estimate of 1.03 (95% CI: 0.61, 1.75) and the four moderately ranked studies produce a similarly non-significant meta-estimate of 1.28 (95% CI: 0.97, 1.69) for the effect size. As expected, the overall meta-estimate of 1.14 in Figure 5 and its confidence interval are the same as shown earlier in Figure 4.

Summary and Conclusions for Zhang et al. (2019):

Overall, HED does not believe Zhang et al. (2019) used appropriate methods to perform their meta-analyses. The supplemental analyses presented here indicates that lower and non-statistically significant meta-estimates would be obtained if the Andreotti et al. (2018) study is more properly incorporated into the meta-analysis done previously and appearing in the EPA 2017 Revised Glyphosate Issue. Specifically, the Andreotti (2018)-updated meta-estimate is 1.14 (95% CI: 0.87, 1.50) and is no longer statistically significant. This meta-analysis represents an update to the one appearing in the December 2017 EPA Revised Glyphosate Issue Paper in which a statistically significant meta-estimate of the effect size of 1.27 (95% CI: 1.01, 1.59) was reported. As expected in the updated random effect meta-analysis presented here, the larger sample size and tighter confidence interval in Andreotti (2018) means that the

weight of this AHS study increases to 35.36% (from 20.95% when the earlier – and smaller - DeRoos (2005) AHS study was used in a similar random effects analysis). The Zhang et al. (2019) authors did not perform this analysis because Andreotti et al. (2018) did not include an ever/never estimate in their AHS update but instead provided estimates by quartile (and also by lagged quartile). The analysis presented here by EPA in the memorandum used a fixed effect (aka "common effect") inverse variance model to combine the Andreotti-generated quartile-based estimates and create an ever-never estimate.

The Zhang et al. (2019) authors conducted their own literature search and used the same six studies that EPA used in its evaluation. Two studies were from the U.S., one was from Canada, two studies were from Sweden, and one study was from France. One of these was a prospective cohort study, with the remainder being case-control. Quality scorings of these studies were performed by Zhang et al. (2019) based on the Newcastle-Ottawa Scale (NOS) with the two highest scoring studies (7 or 8 points) being Andreotti et al. (2018)/DeRoos (2005), the prospective AHS studies, and Ericksson, a case control study. The remaining studies scored either 6 points or 2 points by the NOS, with this latter low score applying only to Orsi et al. (2009). These ratings match the rankings given by EPA in its 2017 Revised Glyphosate Report which ranked DeRoos et al. (2005) and Ericksson et al. (2008) as high and the remainder moderate.

Further regarding the Zhang et al. (2019) publication, the authors state that this study differs from several earlier meta-analyses by focusing on an *a priori* hypothesis targeting biologically-relevant exposure magnitude (using only the risk estimate of the highest exposure and the longest duration of exposure group) and including newly updated AHS information from Andreotti et al (2018). This hypothesis does not appear to be well supported by initial looks at the Andreotti et al. (2018)-categorized 20 year lag rate ratio estimates since there are no statistically significant results, no trend in rate ratios (nor monotonicity), and the confidence intervals around each categorized exposure overlap considerably and cover the null value of 1 for all exposure quartiles. In addition, the authors focused on the results from a fixed effect meta-analysis performed on the effect sizes estimated for highest exposure categories. The use of a fixed effect meta-analyses (instead of random effects) for this kind of data is incorrect. The authors did, nevertheless, perform a random effects analysis and present these results but indicated that they did not emphasize them.

In summary, the *a priori* hypothesis that higher/longer exposures produce larger effect sizes advanced by Zhang et al. (2019) in their analysis does not appear to be supported by the new AHS data from Andreotti et al. (2018) which is the largest, best-designed high quality study examined. EPA has used this Andreotti et al. (2018) AHS data to update its December 2017 meta-analysis by replacing the De Roos et al. (2005) AHS results and revised/updated our meta-estimate to a non-statistically significant 1.14 (95% CI: 0.87, 1.50). This revised estimate incorporates the most recent AHS data from Andreotti et al. (2018) and does not impact the conclusions presented in the EPA Revised Glyphosate Issue Paper which concludes that the strongest support based on the weight-of-evidence is for glyphosate being categorized as "not likely to be carcinogenic to humans".

PART II. EPA Review of Leon et al. (2019)

Leon et al. (2019) published a summary review/meta-analysis investigating pesticide use and the risk of NHL in cohorts from France (Agriculture and Cancer, **AGRICAN**), Norway (Cancer in the Norwegian Agricultural Population, **CNAP**) and the USA (**AHS**) as part of the international AGRICOH consortium (see https://agricoh.iarc.fr). The Leon et al. authors used data from these three large cohort studies to explore the relationship between the use of selected pesticide chemical groups as well as various individual pesticide chemicals -- including glyphosate -- and the risk of NHL overall and four major NHL subtypes; this was done in a combined population of nearly 320,0000 farmers and farmworkers totaling

3.5 million person-years of exposure. The four major NHL subtypes investigated were: (i) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); (ii) diffuse large B-cell lymphoma (DLBC); (iii) follicular lymphoma (FL); and (iv) multiple myeloma/plasma-cell leukemia (MM). More specifically, the **French AGRICAN study** component enrolled 181,747 men in 2005-2007 who met various inclusion criteria including being (i) ≥ 18 y.o.; (ii) affiliated with the national health insurance system of agricultural workers; and (iii) residing in 2005 in one of 11 departments in France covered by population-based cancer registries. The cohort investigated here consisted of active and retired farm owners and farm workers. Members were enrolled after returning self-administered questionnaires that covered historical use information on 13 crops and 5 animal species (first and last year of production) and performance of pesticide treatment tasks (first and last year performed, per crop or animal species). For this study, AGRICAN cohort members were linked with cancer and mortality registries and the French National Death Index through December 2009. The **Norwegian CNAP study** considered owners and non-owners using a farm ("farm holders) and their families that were included in at least one of five national agricultural and horticultural censuses performed during 1969, 1974, 1979, 1985, and 1989 by Statistics Norway (n=147,134). The **US AHS study** has been described previously; briefly, it consisted of 52,394 private pesticide applicators (farmers) and 4916 commercial pesticide applicators registered to apply restricted use pesticides in Iowa and North Carolina. Members of the AHS cohort were enrolled during 1993-97 and completed questionnaires on agricultural practices, crops, and livestock and the use of more than 50 individual pesticide active ingredients, including glyphosate. Applicators completed a second questionnaire approximately five years later that provided details on pesticide use since enrollment. Cohort members have been routinely and regularly linked to the Iowa and North Carolina cancer and mortality registries and the National Death Index through 31 December 2011 for Iowa participants and 31 December 2010 for North Carolina participants. The summary review/meta-analysis performed here by the Leon et al. (2019) study authors considered only farmers (and not commercial applicators) from the US AHS. After additional adjustments[17] , a total of n= 127,282, 137,821, and 51,167 individuals were available for use from the AGRICAN, CNAP, and AHS studies, respectively. Combined, this represents 316,270 individuals and 3,574,815 person-years of follow-up from January 1993 through December 2011, with a median follow-up period of 16 years. During this follow-up a total of 2545 first incident NHL cases were observed (to include both Hodgkins lymphoma and NHL) of which 95.4% were NHL with a median age at diagnosis of 69 years. AGRICAN, CNAP, and AHS contributed 18.1%, 61.6%, and 20.3% of cases to this analysis, respectively.

Study population demographic and other characteristics differed by cohort: for example, AHS cohort members at the start of follow-up were younger than those in CNAP and AGRICAN (median age of 46 years in AHS vs. 51 and 67 years for CNAP and AGRICAN respectively). Half of the AGRICAN cohort consisted of retired farm owners or workers and 44% were female compared with 16% in CNAP and 3% in AHS. Nearly all AHS cohort members (99%) used pesticides (in general, not specifically glyphosate) while only 68% and 63%, respectively did in AGRICAN and CNAP, and of the combined cohort, 63% were classified as ever having been exposed to at least one of the investigated pesticides. Glyphosate in particular was classified as used by 36%, 38%, and 83% of the farmers or farmworkers in the AGRICAN, CNAP, and AHS study cohort populations, respectively.

For the AGRICAN and CNAP studies, data were crossed with country-specific crop-exposure matrices (CEMs) to estimate ever-use of glyphosate and represent *potential* use while for AHS cohort members, self-reported ever-application was used to assess exposure. For AGRICAN, the French PESTIMAT matrix was used to obtain historical use information which incorporated information on the first and last year in which glyphosate was authorized and recommended for use in France on a given crop; potential

[17] Additional adjustments included accounting for emigration or loss to follow-up, prevalent cancer at the start of cancer follow-up, or for being nonfarmers (for AGRICAN), dying before the start of cancer follow-up (for CNAP), and being commercial applicators (for AHS).

exposure in the French AGRICAN was assumed if an individual cultivated a given crop, marked the study questionnaire as having treated the crop with (any) pesticide, and glyphosate was authorized and recommended for use in a given year. In CNAP, matrices were constructed considering in part the first and last year in Norway that glyphosate was authorized for use on each of the selected crops. The French and Norwegian CEMs extended from 1950 until the last year of cancer follow-up. Potential exposure to glyphosate in the Norwegian CNAP was assumed if a farm holder reported cultivating a given crop, owned spraying equipment or spent money on pesticides, and glyphosate was sold in Norway and registered for use on the crop in a given year. As stated before, the AHS cohort members self-reported use of glyphosate and thus no CEM or assumptions regarding potential exposure were needed.

Cox proportional hazards (PH) analysis was done separately for each of the three study cohorts and used to estimate both fully-adjusted and minimally-adjusted hazard ratios (HRs) and their 95% CIs for incident NHL for ever-use of glyphosate assuming time-independence of covariates. The endpoint was the first incident NHL during follow-up, with follow-up beginning on 01 January 1993 corresponding to the date of enrollment for AGRICAN and AHS and (also) 01 January 1993 for CNAP, the earliest year of follow up in the AHS. Follow-up time for the PH assessment was calculated from the start of follow up to the first date of any of the following: (i) first incident cancer (except non- melanoma skin cancer); loss to follow-up or migration out of the cancer registry area; (iii) death: or (v) end of follow-up. Multiple imputation was used for missing data in AGRICAN and AHS for crop, pesticide treatment task, period of production and period of pesticide treatment task for the former survey and for pesticides applied for the latter; no imputation was required for CNAP since exposure data were derived from compulsory agricultural censuses and the information from farm-holders was thus complete. The reference category for the PH analysis consisted of individuals classified as never exposed to glyphosate. All models initially used age at the date of censoring as the time scale and were adjusted for sex and animal production. For AGRICAN, additional covariates included retirement status while for AHS this included state of residence (either Iowa or North Carolina). Subsequently, fully adjusted models were separately constructed for each study cohort. For AGRICAN, adjustment for the number of crops personally treated with pesticides was added as an ordinal variable to approximate increasing opportunity for pesticide exposure. For CNAP, adjustment for pesticide was used instead since similar information was not available. For CNAP and AHS, adjustment was made using a cohort-specific set of active ingredients.

PH models were run first individually for each cohort, with the resulting estimates combined using random effects meta-analysis based on the adjusted results from the three international cohorts. The authors reported no observed association between ever use of glyphosate and NHL (HR=0.95 (95% CI: 0.77,1.18), n=1131 exposed cases) with some evidence of heterogeneity among cohorts (I^2=57%, $p_{heterog}$ = 0.10).

The authors also investigated four NHL subtypes associated with glyphosate and only one – DLBCL at a mHR of 1.36 –was elevated (although not significantly (95% CI: 1.00, 1.85), with n=221). as follows:

- Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL): HR=0.92 (95% CI: 0.69, 1.24), n= 252;
- Diffuse large β-cell lymphoma (DLBCL): HR=1.36 (95% CI: 1.00, 1.85), n= 221[18,19];

[18] The Leon et al (2019) authors state that there was no evidence of heterogeneity among the three cohorts for DLBCL, that cohort-specific CIs were wide, and only the CNAP cohort --accounting for 45% of exposed cases – excluded the null value. Adjusting the CNAP value for ever use of other pesticides (linuron, aldicarb, mancozeb, DDT, lindane, and deltamethrin), the authors state, generated a fully-adjusted HR of ever-use of glyphosate of 1.67 (95% CI: 1.05, 2.65), higher than the minimally adjusted estimate of 1.26 (95% CI; 0.97-1.65) which was driven primarily by adjustment for animal production and DDT use.

[19] For DLBCL, Andreotti et al. (2018) reported ever-never RRs by quartile ranging from 0.94 to 1.13 (n=22-30), and none being statistically significant and a p-for- trend-value of 0.83. The ever-never HR value reported here by Leon et al. (2019) for DLBCL

- Follicular lymphoma (FL): HR=0.79 (95% CI: 0.52, 1.21), n= 105; and
- Multiple Myeloma/plasma-cell leukemia (MM): HR=0.87 (95% CI: 0.66, 1.15), n=240.

Considered individually, only the Norwegian CNAP study excluded the null value for the DLBCL NHL subtype with HR=1.67 (95% CI: 1.05, 2.65) based on 100 cases, with the AHS showing a HR for DLBCL of 1.2 (95% CI: 0.72, 1.98) based on 93 exposed cases and the AGRICAN study showing a HR of 1.06 (95% CI: 0.51, 2.19) with 28 cases.

Summary and Conclusions for Leon et al. (2019):

The Leon et al. (2019) review article used data from three international cohorts – the French AGRICAN study, the Norwegian CNAP study and the US AHS study -- to investigate the putative relationship between a number of pesticides, including glyphosate, and NHL; this was performed for both NHL overall (total) and by NHL broken down into four major subtypes. The study harmonized available exposure data from the three independent agricultural cohorts, thereby increasing the numbers of NHL cases (and exposed cases, particularly) which increases the ability of the combined study to detect associations. In sum, the study cumulated more than 300,000 farmers/farmworkers from France, Norway, and the US which represent more than 3.5 million person-years of exposure follow-up time from 1993 through 2011 with a median follow-up time of 16 years. For glyphosate, no significantly increased risks of NHL overall or of three subtypes were observed; for the DLBCL subtype, a somewhat elevated but non-significant relationship was seen (HR=1.36 (95%CI: 1.00, 1.85; n=221 exposed cases). The corresponding HR for the Leon et al. (2019) analysis of AHS for this NHL subtype is smaller, at HR=1.2 (95% CI: 0.72, 1.98) based on 93 exposed cases and for the AGRICAN study smaller still (HR = 1.06 (95% CI: 0.51, 2.19) with 28 cases).

The Leon et al. (2019) review has a number of strengths. It brings together and combines three very large international prospective cohort studies which increases its ability to detect epidemiological associations. There are, however, also a number of limitations. For example, only one of the two cohorts, the AHS cohort, uses actual exposure information collected by individuals through self-administered questionnaires; the French AGRICAN study and the Norwegian CNAP study instead rely on information from CEMs to derive estimates of ever-exposure to glyphosate (among other pesticides). No actual pesticide exposure measurements were made in in the AGRICAN or CNAP studies nor were specific questions about specific pesticide applications or application practices asked; instead, a variety of very general and very generic assumptions were made which likely lead to what might be a substantial degree of exposure misclassification. In addition, the study protocol was such that exposure misclassifications may have been exacerbated since analysis of the combined cohort did not consider re-entry tasks through which contact with previously applied pesticides may have occurred and which may equal or exceed pesticide exposure through application. An additional complication was that such re-entry work was not evenly distributed through the cohort. For example, 73% of the males and 56% of the females in AGRICAN reported performing re-entry work in vineyards which is a rarely reported crop in the US AHS

is 1.36 (95% CI: 1.00, 1.85). Cohort specific HRs for ever use of glyphosate and DLBCL are as follows: AGRICAN: 1.06 (95% CI: 0.51, 2.19) with n=28 exposed cases; CNAP: 1.67 (95% CI 1.05, 2.65) with n=100 exposed cases; and AHS: 1.20 (95% CI: 0.72, 1.98) with n=93 exposed cases. Leon et al. (2019) reported a number of exposed cases that is lower than that reported by Andreotti (2018) for the AHS study (see p. 513, Table 2 in Andreotti); some reasons for this difference (as reported by the Leon et al. authors) include the fact that that the AHS study included 4619 commercial applicators that were excluded from the Leon et al (2019) analysis and excluded 1620 private users with information on ever use of glyphosate but did not report frequency of use. In addition, the follow up time was longer in the Andreotti et al. (2018) publication (through 2012 and 2013) and thus contained more DLBCL cases (130 vs. 113 cases). Finally, the statistical adjustments that were made were different between the US AHS study and the AGRICOH study examined here: The AGRICOH study did not adjust for cigarette smoking, alcohol intake, or family history of cancer but *did* adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study.

(1%) -- and consisted itself of 97% male farmers. In addition, the cohorts also differed in fundamental ways. For example, AHS cohort members were younger at start of follow-up (median age = 46 years) as compared to those in CNAP (median =51 years) or AGRICAN (median=67 years) with in fact about half of the AGRICAN cohort consisting of retired farm owners and farm workers. Further, 44% of AGRICAN participants were female compared to only 16% in CNAP and 3% in AHS. In the AHS, 99% of participants used pesticides (in general); in AGRICAN and CNAP, the percentages were respectively only 68% and 63%. Further, different statistical adjustments were made depending on what covariates were measured in each of the individual cohorts: The AGRICAN study did not adjust for cigarette smoking, alcohol intake, or family history of cancer as the US AHS did, but did adjust for animal production and for different pesticide active ingredients from those adjusted for and published in the US AHS study. The Leon et al (2019) authors do state that improvements are planned, specifically indicating that the specificity of the exposure assignments will be improved by incorporating the probability of pesticide use and adding parameters reflecting duration, frequency, and use intensity.

In sum, AGRICOH combined three cohorts – one from France (AGRICAN), one from Norway (CNAP) and one from the US (AHS) and did not find a statistically significant relationship between ever-exposure to glyphosate and NHL overall (HR=0.95 (95% CI: 0.77,1.18), n=1131 exposed cases). A somewhat elevated HR was found for one NHL subtype (DLBCL) at a mHR of 1.36, but the 95% confidence interval for this included 1.0. While the AGRICOH analysis benefited from a combined cohort of more than 300,000 farmers and farmworkers from France, Norway, and the USA representing more than 3.5 million person-years of exposure, only one of the three international cohorts used actual measurement instruments (self-administered questionnaire) for glyphosate exposure. Too, the nature and characteristics of the three cohorts differed in substantive ways and is not clear that the statistical adjustment made were necessarily adequate to account for these differences. We conclude that this additional information provided in Leon et al (2019) combining the AGRICAN, CNAP and AHS studies does not impact the conclusions presented in the EPA Revised Glyphosate Issue Paper which itself concludes that the strongest support based on the weight-of-evidence is for glyphosate being categorized as “not likely to be carcinogenic to humans”.

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