UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION

This document relates to:
ALL ACTIONS

SUPPLEMENTAL EXPERT REPORT OF LORELEI A. MUCCI, ScD, MPH

12/21/2017
I. OVERVIEW

In the November 9, 2017 issue of *Journal of the National Cancer Institute*, Andreotti and colleagues published *Glyphosate Use and Cancer Incidence in the Agricultural Health Study*.¹ This article presents updated analyses to the study of De Roos *et al*, 2005², which had been the only published data from a prospective cohort assessing the association between glyphosate-based herbicides and risk of non-Hodgkin's lymphoma (NHL). With extended follow-up for cancer incidence and 575 NHL cases, Andreotti *et al* found no association between glyphosate-based herbicide exposure and NHL risk, no evidence of dose-response across a wide range of exposure levels, and no association when considering a 5-, 10-, 15-, or 20-year latency.

This 2017 publication is significant as its design and methodology directly addresses critiques previously raised by Plaintiffs' Experts about the Agricultural Health Study. Moreover, the study included greater length of follow-up time which increased the number of NHL cases considerably compared to De Roos *et al*, 2005², as well as the draft report of Alavanja *et al*.³ To address potential biases in the study findings, Andreotti *et al* performed a range of sensitivity analyses, all of which supported a null association. Taken together, Andreotti *et al*¹ provides the highest quality epidemiological data on the association between glyphosate-based herbicides exposure and risk of NHL. This 2017 publication provides even further support that there is no evidence of a positive association between glyphosate-based herbicides and NHL risk. Given the totality of the epidemiology literature, my opinion strongly remains that the epidemiological data show no evidence of a causal association between exposure to glyphosate-based herbicides and NHL risk.

II. METHODOLOGIC ISSUES TO ASSESS INTERNAL VALIDITY

In my July 2017 Expert Report, I outlined core epidemiological concepts that are essential in interpreting the epidemiological literature in general, including that of glyphosate-based herbicides and NHL risk. I discussed concepts of study design, as well as bias, confounding, and chance. Specifically, whether an observed association in a study is positive, inverse, or null, it is standard epidemiological practice to first rule out whether the finding could be due to an underlying bias, confounding, or chance. Beyond just considering whether a bias exists, there are complementary approaches that are used in epidemiology to assess the extent to which potential bias and confounding could have impacted the study findings.
Given the finding of Andreotti et al that there is no association between glyphosate-based herbicides and NHL risk, it is important to analyze the types of bias that may arise in the context of a null finding. The association between an exposure and an outcome may be biased if either the exposure or outcome are measured with error. In epidemiological studies, it is standard practice to consider the extent of the measurement error (or misclassification), i.e. whether it is likely small or large, as well as the directionality, i.e. whether it is random/non-differential or differential. In the Agricultural Health Study, the outcome of NHL is determined through state cancer registries, and as such the outcome in this study is measured with little to no error. The exposure, use of glyphosate-based herbicides, is ascertained from participants using questionnaires. Because the questionnaires were completed prior to NHL diagnosis, if there is measurement error in the exposure, it is by definition unrelated to whether or not someone developed NHL and thus is non-differential. This is a well-established important strength of cohort studies. Thus, if misclassification exists in assigning information about glyphosate-based exposures, it would be considered non-differential. When the exposure has only two categories, for example exposed or unexposed, then the direction of bias is easy to predict mathematically such that the relative risk will be biased toward the null value. Thus, if the observed relative risk were 1.2, and there was non-differential misclassification of the exposure, then the true relative risk would be >1.2 (Figure 1) since the misclassification biases the relative risk toward the null value. On the flip side, if the observed relative risk were 0.86, as in the Andreotti study, and there was non-differential misclassification of the exposure, then mathematically the true relative risk would be <0.86.

Sensitivity analyses are a commonly used strategy in epidemiological research to assess whether bias or confounding have influenced the observed study results. Sensitivity analyses involve analyzing the data in different ways in order to test specific assumptions. When the relative risk estimates from different sensitivity analyses are similar, this provides supportive evidence that the results are unbiased. For example, if there is missing data in a study, and the relative risk estimates from different statistical models that account for the missing data in different ways are similar, that provides assurance that there is no bias in the approach to accounting for the missing data. As described below, Andreotti et al undertook several sensitivity analyses to
address potential bias in explaining the null finding. Note, none of the sensitivity analyses indicated that bias led to their finding of no association between glyphosate-based herbicides and NHL risk.

It is important in epidemiology data collection to limit the amount of missing data to the extent possible because of concerns that this missing data could generate bias in the relative risk estimates. In the case of the Agricultural Health Study, missing data occurred in the phase II follow-up questionnaire which sought to collect updated information on exposures including use of glyphosate-based herbicides. The phase II questionnaire was missing for 37% of participants who completed the phase I baseline questionnaire at enrollment. One of the key steps is first to understand the extent to which the missing data is random across study participants such that the probability of missing data is unrelated to the exposure or outcome. Montgomery et al compared the participants who did and did not participate in the phase II questionnaire. They found little difference in the prevalence of NHL or several other covariates in those who did and did not complete the questionnaire.

There are well-established approaches to account for missing data during the analysis phase of a study, including data-driven imputation which was used in Andreotti et al. Multiple imputation is a standard approach used in epidemiological studies. The approach leverages the fact that participants’ covariates co-occur in unique patterns, and that these patterns can then be used to predict missing values. Thus, an important feature of the success of imputation relies on how well the observed data can predict the exposure of interest. In the case of the Agricultural Health Study, the investigators used the covariate patterns from participants who had both Phase I and Phase II data, identified participants who only had the Phase I data but had similar covariate patterns, and derived the exposures. The investigators used a matrix of information on demographics, farm characteristics, medical conditions, and pesticide use to predict exposures for those missing the Phase II questionnaire data. Importantly, Agricultural Health Study investigators evaluated how well the imputation method worked to predict the pesticide exposures in the Phase II, including glyphosate-based herbicides. To do this, they took subsample of 20% of the participants who had actually completed both questionnaires, but imputed data for them using the remaining 80% of participants. Then, they undertook a direct comparison of the actual observed data that was reported by the participant subgroup to that which was imputed. This analysis demonstrated that the imputation method was valid for deriving pesticide exposure including for glyphosate-based herbicides.
study design. this 2017 analysis included 54,251 men and women who were participants in the agricultural health study, a cohort of licensed pesticide applicators from iowa and north carolina. participants were enrolled between 1993 and 1997 when they completed a baseline questionnaire on a range of exposures including use of glyphosate-based herbicides and other pesticides. a follow-up questionnaire was completed between 1999 and 2005 among 63% of participants.

participants were followed prospectively for cancer incidence through linkage with state cancer registries, and for vital status using state mortality files and the national death index. follow-up was through 2012 in north carolina and 2013 in iowa, an additional 11 years beyond which was included in de roos et al. an advantage of this approach is that there is virtually complete follow-up of participants for cancer incidence and death in the agricultural health study and thus selection bias is not a concern.

glyphosate-based herbicides exposure was classified at two time points: on the baseline questionnaire between 1993 and 1997, and a follow-up questionnaire between 1999 and 2005. three different measures of glyphosate-based herbicides exposure were used in the analysis: ever vs. never use, lifetime days of use calculated as days per year * number of years, and intensity-weighted lifetime days which was calculated as lifetime days * intensity scores. since 37% of the cohort did not complete the second questionnaire, the authors used an established procedure to impute the values of pesticide use since enrollment based on a range of participants’ medical and demographic data.

multivariable adjusted relative risks were estimated using poisson regression, adjusting for age, lifestyle factors, occupational exposures, and the five pesticides most strongly associated with glyphosate-based herbicides exposure, as well as the five pesticides that were associated with lymphohematopoietic cancers in prior agricultural health study publications.

as per standard epidemiology practice, the authors undertook a range of additional analyses to assess whether bias may have influenced their study findings. to assess whether the imputation approach induced any bias, the authors undertook two sensitivity analyses: 1-) using only the baseline questionnaire data for the whole population; 2-) limiting the study population to only those who completed both the baseline and follow-up questionnaire. to assess whether changes in pesticide use by study participants after the second phase
questionnaire could influence the relative risk estimates, the authors truncated follow-up to 2005, which is at
the end of when the follow-up questionnaire was given out.

**Results.** This updated analysis in the Agricultural Health Study included 575 incident cases of NHL, more than
6 times greater than the 92 NHL cases in De Roos et al 2005\(^2\) and considerably more than the >300 cases in
the draft report of Alavanja et al\(^3\). Almost 83% of the participants had ever used glyphosate-based herbicides
at baseline or follow-up. There was a considerable range of exposure, with a median 48 lifetime days of use
(interquartile range 20-166 days) and a median 8.5 lifetime years of use (Interquartile range 5-14 years). Such
a broad range of exposure allowed for a meaningful evaluation of the potential dose-response association
between glyphosate-based herbicides and NHL.

A summary of the relative risk estimates of glyphosate-based herbicides and NHL risk are presented in
Table 1. In line with earlier reports from the Agricultural Health Study, Andreotti et al found no association
between ever glyphosate-based herbicides exposure and NHL risk, and no evidence of dose-response. A lack
of association remained in analyses considering a 5-, 10-, 15-, or 20-year lag in exposure to account for
different potential latency periods between glyphosate-based herbicides exposure and subsequent NHL risk.
Moreover, in the sensitivity analyses undertaken to assess potential bias from the exposure imputation or
potential exposures after the Phase II survey, there remained no association between glyphosate-based
herbicides and NHL risk, supporting the validity of the imputation strategy and the lack of any apparent
exposure misclassification (Table 1). Similarly, there was no association between glyphosate-based herbicides
exposure and risk of any of the NHL histologic subtypes. In additional results presented in the supplemental
tables of the report, there was no association between glyphosate-based herbicides exposure of lifetime days
and NHL risk (RR\(_{\text{quartile 4 to never}}\): 0.80, 95% CI 0.60-1.04) nor any associations for lagged analyses using this
metric of exposure.

**Table 1.** Relative risk (and 95% confidence intervals) for association between GBH exposure based on
intensity-weighted lifetime days and NHL risk in the Agricultural Health Study (Andreotti et al, 2017)

<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Overall risk NHL</th>
<th>5-year lag</th>
<th>20-year lag</th>
<th>Exposure at enrollment</th>
<th>Responded to both QQs</th>
<th>Truncated follow-up to 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>0.83 (0.59-1.18)</td>
<td>0.92 (0.66-1.28)</td>
<td>1.22 (0.91-1.64)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.83 (0.61-1.12)</td>
<td>0.79 (0.59-1.06)</td>
<td>1.15 (0.86-1.55)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.88 (0.65-1.19)</td>
<td>1.03 (0.75-1.41)</td>
<td>0.98 (0.71-1.36)</td>
<td>0.82 (0.62-1.80)</td>
<td>0.90 (0.63-1.27)</td>
<td>1.04 (0.70-1.57)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>0.87 (0.64-1.20)</td>
<td>0.87 (0.64-1.17)</td>
<td>1.12 (0.83-1.51)</td>
<td>0.82 (0.62-1.80)</td>
<td>0.90 (0.63-1.27)</td>
<td>1.04 (0.70-1.57)</td>
</tr>
</tbody>
</table>
NR = not reported

**Strengths and limitations.** As I described in my original report, the Agricultural Health Study cohort has several strengths, and the analysis of Andreotti *et al* in particular represents the strongest epidemiological data on glyphosate-based herbicides and NHL risk. First, the prospective assessment of glyphosate-based herbicide exposure information prior to diagnosis of cancer eliminates recall bias. Second, the authors appropriately controlled for lifestyle factors and multiple pesticide exposures in the statistical models, reducing the potential for confounding by other farming exposures associated with NHL. Third, the number of NHL cases was quite large with a broad range of glyphosate-based herbicide exposure, which provided ample statistical power to detect meaningful relative risk estimates. Fourth, the study had virtually complete follow-up of the cohort for cancer incidence and mortality by leveraging the high-quality statewide cancer registries and vital records, which reduces selection bias. Fifth, given the long follow-up of the cohort, the updated exposure information, and the various lagged analyses, the authors were able to explore whether glyphosate-based herbicides may have an association with NHL at different etiologic windows. Finally, the cohort had a sufficient range of exposure to investigate the extremes of exposure in relation to risk of NHL, and at levels much higher than the case-control studies discussed in my initial expert report.

Potential limitations in this study include the possibility of non-differential misclassification of glyphosate-based herbicide exposure. However, validation studies within the Agricultural Health Study show that these licensed applicators have been shown to be able to provide reliable self-reported information in this cohort. Since the observed relative risk for ever vs. never use of glyphosate-based herbicides and NHL risk was ~0.86, if there was misclassification of the exposure, then the true relative risk would be even less than 0.86, which would still provide no evidence of a positive association. Another concern is the potential bias associated with the missing data from participants on the follow-up questionnaire. However, the authors addressed this through the previously described sensitivity analyses, which were concordant with their findings of no association and support the conclusion that bias does not explain the null finding. The authors also adjusted for multiple lifestyle factors as well as concomitant use of different pesticides, substantially reducing the likelihood for unexplained or residual confounding.

In addition to proving the most compelling data to date, the study of Andreotti *et al* in the Agricultural Health Study illustrates the standard approaches used by epidemiologists to assess the quality of the data and
approach. Given the rigorousness of the epidemiological approach, there is no basis to conclude that the observed null association between glyphosate-based herbicides and NHL risk can be explained away by bias, confounding or chance.

IV. META-RELATIVE RISK ESTIMATE

In light of this new data from the Agricultural Health Study, I provide an updated meta-relative risk estimate to summarize findings across studies. I present this figure with the caveat discussed in more detail in my initial report: while meta-analyses can provide increased precision in a summary estimate, they cannot avoid the inherent biases in the original studies.

In this figure, I replace the estimates from De Roos et al, 2005 with these from Andreotti et al, 2017 for the Agricultural Health Study, and replace De Roos et al 2003 and McDuffie et al 2001 with that of Pahwa et al for the studies in the North American Pooled Project. This approach is consistent with the methodologies in the prior meta-analyses in using the most comprehensive and updated epidemiological studies. For Pahwa et al, I used the multivariable relative risk estimates adjusted for pesticides excluding the proxy respondent data. Figure 2 shows the forest plot for the updated meta-analysis relative risk estimate for ever glyphosate-based herbicides exposure and NHL risk, with a meta-relative risk of 0.90 (95% CI 0.78-1.03).

V. ANALYSIS OF PLAINTIFFS’ EXPERT METHODOLOGY IN CRITICIZING THE AGRICULTURAL HEALTH STUDY

As I describe above, it is an established approach in epidemiology to first consider whether an observed association between an exposure and disease is due to bias, confounding, or chance before coming to a conclusion whether any observed association may be causal. In their Expert Reports, Plaintiffs’ experts have
raised multiple critiques about the Agricultural Health Study. Some of their comments were made without relying on standard epidemiological principles, or were unequally applied to the cohort but not the case-control data. As set forth below, none of these critiques are methodologically sound, particularly in light of the new data from Andreotti et al.

- **Sample size of De Roos et al 2005 is small.** With a 6-fold increase in the number of NHL cases, as well as a wide range of exposure (from none to very high), the study by Andreotti et al provides the most powerful analysis of the association between glyphosate-based herbicides and NHL risk. Although the prevalence of exposure is fairly high in this population, there is still 17% of the cohort that is unexposed, and given the size of the cohort it can give meaningful power to look at never vs. ever exposure. Moreover, there is a distribution of participants who had low, moderate, or high exposure, which provides significant power to analyze dose-response. As a corollary, Plaintiffs Experts suggested that the statistical models included too many confounders given the sample size of cases in the De Roos et al publication, a concept known as overparametization or overfitting the statistical model. Given the number of cases in Andreotti et al, this is not a concern for the number of confounders included.

- **Alavanja et al is unpublished.** Plaintiffs’ Experts raised concerns about the appropriateness of relying on data from an unpublished manuscript, and thus discounted the report of Alavanja and colleagues from the Agricultural Health Study. While I do not agree with this statement for the reasons set for in my July 2017 report, and indeed it is standard in epidemiology to rely on reliable unpublished data, the publication of Andreotti et al directly addresses this concern. It is noteworthy that Andreotti et al was published in the *Journal of the National Cancer Institute*, which was initially created by the U.S. National Cancer Institute and is ranked as one of the top tier oncology journals.

- **Missing data and imputation of exposure.** In her report, Dr. Ritz dismissed the use of imputation of the missing data from the follow-up questionnaire. While it is appropriate to raise questions about the potential for bias in using this approach, it is not appropriate to ignore the analyses and studies that actually address such concerns. Indeed, there are established epidemiological strategies to test whether missing data or imputation actually led to a bias as describe above. Addressing this point, Andreotti and colleagues undertook different sensitivity analyses in order to assess the validity of the
imputation approach. As described above, and shown in Table 1, the results of these approaches are similar and suggest that the imputation strategy was valid.

- **Follow-up not long enough to assess long latencies:** Risk factors may have an effect on cancer incidence at different time points, with some having a shorter term or longer-term effects, a concept known as the latency period. A prior critique by Plaintiffs’ Experts is that the follow-up of the Agricultural Health Study was too short to examine longer latency periods. That critique was not valid for the reasons set forth in my July 2017 expert report. Moreover, Andreotti et al had an additional 11 years of follow-up in the cohort beyond De Roos et al, 2005. As such, Andreotti et al was able to consider whether there was any association between glyphosate-based herbicides and NHL risk with 5-, 10, 15- or 20-year latencies. Results from these analyses converged and showed no association considering either shorter or longer-term effects of exposure.

- **Changes in pesticides over time.** Plaintiffs’ Experts state that the Agricultural Health Study results are biased because of the changes in use of glyphosate-based herbicides over time. Andreotti et al covers exposures through 2005, a time period extending past the most recent case-control study. In addition, they raise concerns of exposure misclassification after 2005. This is directly addressed in the truncation analysis described above, where the authors found no association with NHL risk through 2005.

- **Changes in the definition of NHL.** The classification of NHL as a disease has been changed over time by clinical consensus panels, with the addition of multiple myeloma cases to the NHL rubric. Dr. Ritz raised this change as “an important issue”, although her argument for this classification influencing the results of the association between glyphosate-based herbicides and risk in the Agricultural Health Study are unfounded. Andreotti et al (as did Alavanja et al) evaluated the impact of the NHL classification on the findings by undertaking a sensitivity analysis. They found the relative risk estimates were null whether the current (including multiple myeloma) or earlier (excluding multiple myeloma) definition of NHL was used.

**VI. Conclusion:**

In summary, the 2017 publication by Andreotti et al provides the strongest epidemiological evidence to date on the association between glyphosate-based herbicides and NHL risk. The finding in Andreotti et al of no
association converges with that of the prior studies, with a meta-analysis relative risk also showing no association. Taken together, my opinion remains that there is no sound basis upon which to conclude a causal association exists between exposure to glyphosate-based herbicides and NHL risk.

Lorelei A. Mucci, ScD

December 21, 2017

Date
References:

Exhibit A
**Supplemental Materials Considered List – December 21, 2017**


30. Blair, A. et al., Reliability of Reporting on Life-Style and Agricultural Factors by a Sample of Participants in the Agricultural Health Study from Iowa, 13 Epidemiology 94 (2002).


137. Neupane, B. et al., Community controls were preferred to hospital controls in a case-control study where the cases are derived from the hospital, 63 J. Clinical Epidemiology 926 (2010).


152. Portier, C. et al., *Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)*, 70 J Epidemiology Community Health 741 (2016).


