Exhibit 8

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	Case No. 16-md-02741-VC
	MDL No. 2741
This document relates to:	
ALL ACTIONS	

SUPPLEMENTAL EXPERT REPORT OF JENNIFER R. RIDER, ScD.

12/21/2017

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SUPPLEMENTAL EXPERT REPORT OF JENNIFER R. RIDER, SCD, MPH

A. Introduction

At the time of the submission of my expert report dated July 31, 2017, evaluating the epidemiological evidence for a causal association between glyphosate-based herbicides (GBH) and NHL, updated Agricultural Health Study (AHS) findings on GBH and NHL with follow up through 2008 were available in the form of an unpublished draft manuscript [Alavanja *et al*., 2013]. As I explained in my expert report, results included in the draft manuscript were consistent with and even more powerful than the initial published study with follow up through 2001 [De Roos *et al.,* 2005], indicating no evidence of an association between GBH and NHL after adjustment for other pesticides in dose-response analyses based on cumulative exposure or intensity-weighted cumulative exposure. Strengths of the follow-up study included the accrual of 320 NHL cases, a longer latency period and even higher levels of cumulative exposure than in the published 2005 study, as well as analyses of NHL subtypes. Given my own extensive experience as a peer reviewer and the subsequent publication of methods utilized in the 2013 analysis [Alavanja *et al.,* 2014], I determined that the draft manuscript provided important additional data confirming the insufficiency of evidence of GBH acting as a causal factor in NHL.

The subsequent publication of AHS findings with additional follow up through 2012 and 2013 in the *Journal of the National Cancer Institute* [Andreotti *et al.,* 2018] provides even more compelling evidence that the epidemiology does not support a causal association between GBH and NHL. As described below, the Andreotti *et al.* analysis rebuts the plaintiffs' experts' criticisms that aimed to discredit earlier AHS findings, and no meaningful assessment of GBH and NHL can discount the central importance of this new study in the existing body of scientific evidence.

B. Evaluation of Andreotti *et al., 2018*

My evaluation of the Andreotti *et al.* publication follows the same approach for the assessment and interpretation of epidemiologic studies as outlined on pages 10-20 of my initial expert report.

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Study Design. The study design and methods are similar to the AHS report published in 2005 [De Roos *et al.,* 2005], the draft manuscript including GBH data previously reviewed [Alavanja *et al.,* 2013], and the updated publication that omitted GBH and several other chemicals [Alavanja *et al.,* 2014]. The updated GBH analysis includes exposure information from 54,251 pesticide applicators, of whom 44,932 (82.8%) had some level of GBH exposure. A total of 575 cases of NHL were diagnosed during follow up and included in multivariable analyses. As in the 2013 draft manuscript [Alavanja *et al.,* 2013], the primary analysis incorporates exposure information at the time of entry into the study (i.e., baseline) and updated exposure information from a follow-up questionnaire distributed between 1999-2005 that was completed by 63% of the enrolled cohort. Using the same methods described in the draft manuscript [Alavanja *et al.,* 2013] and in the prior peer-reviewed publication that omitted data on GBH and several other chemicals [Alavanja et al., 2014], imputation (i.e., deriving values based upon actual data provided by all participants at baseline and from the responders to the follow-up questionnaire) was used to update more recent exposure values for follow-up survey non-responders. Analyses of all cancer types controlled for age, state of recruitment, education, cigarette smoking status, alcohol intake, family history of cancer, atrazine, alachlor, metolachlor, trifluralin, and 2,4-D. Analyses of the lymphohematopoietic cancers, including NHL, additionally adjusted for the potential confounding effects of occupational exposure to solvents, gasoline, x-ray radiation and engine exhaust, as well as lindane, DDT, diazinon, terbufos, and permethrin because these chemicals were previously associated with cancer lymphohematopoietic cancer risk in the AHS. The authors present information on overall risk of NHL, as well as NHL subtypes. Several sensitivity analyses were conducted to evaluate the impact of the imputed exposure information and potential exposures to GBH in the period after the follow-up survey distribution on the results.

Results.   Higher levels of lifetime use of GBH are apparent in the updated analysis, with 48 median lifetime days (interquartile range 20-166) and 8.5 median lifetime years (interquartile range 5-14 years) of use. The authors focus their presentation of results on intensity-weighted cumulative exposure, which takes into account factors related to use of GBH that impact the intensity of exposure, including how GBH were handled and the

2

Expert Report – Personal and Confidential

use of personal protective
equipment. Compared to cohort
members who did not apply GBH,
the RRs for each increasing
quartile of intensity-weighted
cumulative exposure were 0.83
(95% CI: 0.59-1.18); 0.83 (95%
CI: 0.61-1.12); 0.88 (95% CI: 0.65-

Figure 1. Association between intensity-weighted glyphosate exposure and NHL incidence, AHS, 1993-2013
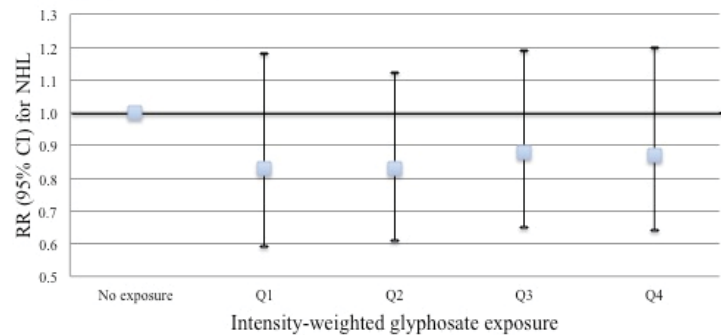
1.19); and 0.87 (95% CI: 0.64-1.20) (**Figure 1**). The intensity-weighted RR estimates
were similar when multiple myeloma was excluded (RR comparing quartile 4 to no
exposure: 0.85; 95% CI: 0.62-1.18). No association was observed between cumulative
exposure or intensity-weighted exposure and any individual NHL subtype. The RR (95%
CI) for the top category of intensity-weighted GBH use compared to no exposure was
0.86 (0.62-1.19) for B-cell lymphoma; 0.87 (0.48-1.58) for chronic lymphocytic
lymphoma/small lymphocytic leukemia; 0.97 (0.51-1.85) for diffuse large B cell
lymphoma; 0.44 (0.09-2.17) for marginal-zone lymphoma; 0.85 (0.36-2.03) for follicular
lymphoma; 0.87 (0.45-1.69) for multiple myeloma; and 1.53 (0.23-10.38) for T cell
lymphoma. Results were similar when the analyses were lagged to include only
diagnoses that predated exposures by 5, 10, 15 and 20 years to remove the influence of
cancers diagnosed too soon after exposure to be etiologically related to outcomes. When
cumulative lifetime days of exposure was considered, the incidence rate ratios (RR) and
95% confidence intervals for NHL for each exposure quartile compared to no exposure
were 0.73 (0.54-0.98); 0.80 (0.60-1.06); 0.86 (0.65-1.15); and 0.78 (0.58-1.05).

Internal validity. Strengths of the updated analysis include the even longer latency
period compared to the 2005 publication, inclusion of a substantial number of additional
cases accrued during follow up between 2001 and 2012 (or 2013 in Iowa), and an even
greater range of exposure levels. In addition, because the RR for all four categories of
intensity-weighted GBH exposure (and cumulative exposure) are *below* the "no
association" null value of 1, non-differential misclassification (i.e., where diseased and
non-diseased persons have the same degree of error in reporting of exposure) could not

3

conceal a positive association between GBH and NHL. Non-differential exposure misclassification can shift the reported RR towards 1.0, often referred to as "biasing towards the null." When reported RR are *above* 1.0, non-differential misclassification could give rise to the validity concern that, if the RR was shifted towards 1.0, it would conceal a positive association. However, whereas here the reported RR are *below* 1.0, non-differential misclassification would push the reported RR higher on the absolute scale, i.e., towards 1.0. Thus, any such misclassification in the Andreotti *et al.* results would mean that the 'true' RR was even lower than reported, i.e., in the direction of a 'protective' effect. When the exposure is grouped into more than two categories, as in the AHS dose-response analyses, it is possible for non-differential misclassification to move the RR for any two categories towards each other [Rothman, Modern Epidemiology, page 142]. While this theoretically could lead to a shift in the RR for any individual category in either direction, because the reported RR in all categories in Andreotti *et al.* results are below 1.0, it is impossible for non-differential exposure misclassification to conceal any positive associations in the data.

It is standard epidemiologic practice to undertake methodological studies and sensitivity analyses to ensure the validity of particular analytic approaches and characterize the potential magnitude of bias on study findings. Numerous methodological studies and sensitivity analyses have been conducted on the AHS data that demonstrate neither selection bias (resulting from non-response to the questionnaire) or exposure misclassification threaten the validity of the Andreotti *et al.* findings. Four different strategies have been employed to test the imputation approach used in Andreotti *et al.* and each supports the validity of that methodology. First, published analyses investigating the AHS population in general, without specific regard to the GBH and NHL association, show that differences in the sample of responders compared to the overall population do not meaningfully alter the evaluated exposure-disease associations [Montgomery *et al.,* 2010]. These results provide evidence that selection bias due to follow-up survey non-response is not necessarily a major concern, though this issue should also be considered with respect to GBH and NHL, specifically. Second, the imputation methodology was validated in a separate AHS publication [Heltshe *et al.,* 2012], which compared the pesticide exposure values obtained from the imputation

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procedure with the actual reported values, in a random sampling of the cohort members who responded to both surveys (i.e., the investigators used imputation to derive values for the sample which was then compared to the sample's actual survey responses). The results demonstrate that imputed and reported pesticide exposure results are similar. The third and fourth methods are sensitivity analyses that restrict the analyses for GBH and NHL solely to the completed survey data and compare the results to those obtained when using imputation; these analyses are reported in the Andreotti *et al.* publication. When the authors included in the analysis exposure information reported from all 54,251 participants collected at enrollment and did not use the follow-up questionnaire to update exposure status, the resulting RR for NHL comparing the highest quartile of intensity-weighted exposure to no exposure was 0.82 (95% CI: 0.62-1.80). This result is similar in magnitude to results using imputation. When the analysis only included the group of participants who provided exposure information on both the baseline and follow-up questionnaires (N=34,698), the RR comparing the highest quartile of intensity-weighted GBH exposure to no exposure was 0.90 (95% CI: 0.63-1.27). This result is also similar to the result from the primary analysis using imputation. In light of the results from these different approaches to the data, there is no basis to conclude that non-response on the follow-up questionnaire or the imputation method used to address non-response by some participants artificially conceals a true association.

The Andreotti *et al.* investigators also implemented another sensitivity analysis to test whether lack of information on exposure after the end of the follow-up questionnaire distribution in 2005 produced misclassification of exposure (i.e., subsequent unmeasured changes in exposure). In order to test this possibility the authors truncated follow up at 2005 to prevent the period for which no updated exposure information was available from influencing the results. The RR comparing the highest quartile of intensity-weighted exposure to no exposure in an analysis that truncated follow-up at 2005 was 1.04 (95% CI: 0.70-1.57), which is also consistent with the primary analysis. Therefore, the additional evidence obtained in sensitivity analyses provides no basis for claims that selection bias resulting from missing data on the follow-up questionnaire nor misclassification of exposure after 2005 produced biased RR estimates.

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Precision. With 575 cases and a wide distribution of exposure histories, the RR estimates for GBH and NHL in the updated AHS publication are by far the most precise in the literature.

Generalizability. The AHS study population includes licensed pesticides applicators. This population was selected for a variety of reasons related to study feasibility, including the ability to accurately recall exposure information and a greater frequency and level of pesticide exposures that would allow for meaningful dose-response analyses. Appropriately, the study design was conceived to maximize internal validity. The wide range of exposure levels and incorporation of the use of personal protective equipment (PPE) in the definition of exposure intensity increases generalizability to all types of users.

C. Evidence synthesis

Table 1 illustrates the current state of the epidemiologic literature on GBH and NHL. The mix of RR and odds ratio (OR) point estimates both below and above the null value of 1.0 are contrary to the results we would expect if GBH was acting as a causal factor in NHL or NHL subtypes. Moreover, all of the confidence intervals cross the null value of 1.0, indicating that the results of all studies are consistent with no association between GBH and NHL or NHL subtypes.

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Table 1. Results from four major epidemiologic studies of GBH with respect to overall NHL and NHL subtypes

Study	RR or OR Estimate	95% Confidence Interval
Overall NHL		
Andreotti 2018	0.87[a]	0.64-1.20
NAPP 2015 (self-respondents)	0.95	0.69-1.32
Eriksson 2008	1.51	0.77-2.94
Orsi 2009	1.0	0.5-2.2
B cell		
Andreotti 2018	0.86[a]	0.62-1.19
Chronic lymphocytic leukemia/Small lymphocytic leukemia		
Andreotti 2018	0.87[a]	0.48-1.58
NAPP 2015	1.79	0.87-3.69
Diffuse large B cell lymphoma		
NAPP 2015	1.23	0.81-1.88
Andreotti 2018	0.97[a]	0.51-1.85
Marginal zone		
Andreotti 2018	0.44[b]	0.09-2.17
Follicular		
NAPP 2015	0.69	0.41-1.15
Andreotti 2018	0.85[c]	0.36-2.03
T cell		
Andreotti 2018	1.53[b]	0.23-10.38

[a] Rate ratio comparing highest intensity-weighted quartile of use to never users
[b] Rate ratio comparing intensity-weighted exposure above the median to never users
c Rate ratio comparing highest intensity-weighted tertile of use to never users

The presentation of results in Table 1 differs from the forest plot on page 14 of the expert report by Dr. Ritz in three important ways. First, Table 1 only includes the four main studies that were conducted in independent populations (i.e., only the most recent findings from a given study population included). The Cocco *et al.,* 2013 and Hardell and Eriksson, 1999 studies are not included because they each include only four exposed cases and, as plaintiffs' experts themselves concede, are far too small to provide any meaningful information. Second, Table 1 only reports adjusted relative risk estimates when available (save for Orsi *et al.,* 2009 overall NHL estimate), rather than a combination of unadjusted and adjusted results from overlapping study populations. Third, the Ritz figure was ordered according to the number of included NHL cases generally, despite the fact that some of the studies with a large number of cases had low power (i.e., wide confidence intervals) due to very small numbers of *exposed* cases, i.e.

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individuals with NHL who are also exposed to GBH. Table 1 is ordered by precision determined by width of the confidence intervals.

As stated in my initial expert report, I do not find the use of meta-analysis appropriate given the lack of internal validity in the individual case-control studies and inability of meta-analysis to account for bias and confounding in underlying studies. However, given plaintiffs' experts' prior reliance on meta-analyses, it is important to note that inclusion of results from the NAPP and the most recent AHS publication on GBH and NHL would likely attenuate the meta-analysis RR to a level at or below the null value.

D. Methodological flaws in plaintiffs' experts' criticisms of AHS

A trained epidemiologist follows a standard approach when interpreting results from epidemiological studies. This process involves placing into context the potential impact of bias, confounding and chance findings on the results. While it is appropriate for epidemiologists to identify the specific potential limitations of population-based studies and weigh the evidence accordingly, this process should be uniformly applied to all of the available evidence and updated when additional studies or new analyses from existing studies become available. Epidemiologists often use sensitivity analyses as a way to test how specific methodological decisions influence the findings. If these analyses reveal that a certain type of bias is unlikely to appreciably impact the study results, it is no longer appropriate to discount the findings based on that particular criticism. The plaintiffs' experts Dr. Ritz and Dr. Neugut downplayed the AHS findings on GBH and NHL in the 2005 and 2013 manuscripts based on a variety of stated limitations. However, based on information available at the time of the 2005 and 2013 analyses or now included in the 2018 publication, there is no scientific basis for the claim that these limitations invalidate the AHS results on GBH and NHL. Specific criticisms of the results published in 2005 and in the 2013 draft manuscript are discussed below with respect to the current state of the evidence.

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De Roos *et al.*, 2005

   Latency period. Dr. Ritz and Dr. Neugut cited inadequacy of the latency period as an important limitation of the 2005 analysis. The latency period of 6.7 years used to support this claim actually represents the median period between enrollment in 1993-1997 and NHL diagnosis. In reality exposure history was captured up to 18 years before enrollment, and participants were followed for NHL through 2001. Accordingly, this claim was unfounded even at the time of the 2005 publication. However, with a substantially longer latency period and a maximum follow-up of 38 years after exposure, the most recent AHS publication eliminates any concerns about latency.

   Number of NHL cases. At time of publication of the 2005 analysis, that study yielded a more precise adjusted estimate than any prior case-control studies. With 575 NHL cases, the Andreotti *et al.* results are even more powerful and represent the most precise estimates of the association between GBH and NHL to date.

   Low exposed as reference group. Dr. Neugut expressed concern about using the lowest quartile of exposure rather than individuals without any exposure as the referent group in dose-response analyses in the 2005 publication. However, this issue was addressed in the 2005 analysis that compared ever versus never use of GBH and found results consistent with no association. Furthermore, both the 2013 draft manuscript and the 2018 publication use unexposed as the referent group in dose-response analyses.

   Non-differential exposure misclassification. Dr. Neugut raised the possibility that because GBH exposure may have increased after 1996, non-differential exposure misclassification could occur as a result of using only exposure information collected during the enrollment period. However, the 2005 AHS publication included dose-response analyses that found that increasing levels of glyphosate exposure had no impact on NHL risk. The 2018 AHS publication further addresses this issue by incorporating updated exposure information obtained during the period of increased use. These analyses continue to find no association between GBH and NHL.

Alavanja *et al.*, 2013

   Peer review/publication status. Dr. Neugut and Dr. Ritz did not consider the 2013 draft manuscript on GBH and NHL in the AHS as making an important contribution to

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the available evidence on GBH and NHL because the manuscript was unpublished, despite the fact that the general methodology used was peer-reviewed and published in Alavanja *et al.,* 2014. In Andreotti *et al.,* the methodology as it was applied specifically to GBH not only endured peer review, but was acceptable for publication in *JNCI*. As measured by its impact factor - a generally accepted measure of a journal's scientific influence - *JNCI* is routinely ranked the top 5% of the most influential scientific journals in the world [Thomson Reuters, 2016 Impact Factor Rankings].

 Imputation/selection bias. Dr. Ritz expressed concern about the imputation strategy implemented to handle missing updated exposure data from non-responders to the follow-up questionnaire. The imputation strategy had been previously validated [Heltshe *et al*. 2012] and used in other publications from the AHS [Alavanja *et al.,* 2014]. As discussed above, sensitivity analyses conducted by the Andreotti *et al.* investigators found that imputation and two other approaches for handling missing exposure data all produced consistent results, providing no basis for the assertion that the imputation method artificially concealed a true association.

 Exposure misclassification after the follow-up questionnaire. Dr. Ritz also cited the lack of information on exposure after the follow-up questionnaire distribution period as a potential source of bias because glyphosate exposure likely increased systematically after this period. Andreotti *et al.* directly addressed this concern by conducting a sensitivity analysis that included follow up only through 2005, the year the follow-up survey distribution period ended. Findings from this sensitivity analysis were consistent with the overall analysis, providing no support for the argument that exposure misclassification after the follow-up survey biased the results.

 Overadjustment for other pesticides. Dr. Ritz argued in her deposition that adjustment for other pesticides in the AHS represented over adjustment; in other words, controlling for other pesticides would wash out the effect of GBH on NHL when these exposures were highly correlated. Problems arising from the inclusion of correlated variables in a regression model primarily are related to precision (i.e., the range of values for the RR that are consistent with the data at a given predetermined threshold of confidence, typically 95%), which, as demonstrated by the width of the confidence intervals compared to the prior case-control studies, was not an issue in the 2013 AHS

10

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analysis or the 2018 AHS analysis. Moreover, adjustment for other pesticides in the AHS population, unlike the case-control populations, had no impact on the findings, eliminating any concerns that adjustment was inappropriately influencing the results.

E. Conclusion

My conclusion based on updated published evidence from the Agricultural Health Study is unchanged: the epidemiologic evidence does not provide a sufficient basis to opine that GBH are causally related to NHL.

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December 21, 2017

11

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