EXHIBIT 22

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

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

SUPPLEMENTAL EXPERT REPORT OF DR. CHRISTOPHER J. PORTIER

SUBMITTED PURUSANT TO PTO #34 and

IN SUPPORT OF GENERAL CAUSATION ON BEHALF OF PLAINTIFFS

This supplemental report addresses a recent publication[1] on the Agricultural Health Study (AHS). The article was published publicly in November 2017, after the submission of my expert and rebuttal reports. My original, revised and rebuttal reports each discussed the initial article from the Agricultural Health Study, which I refer to as De Roos, et al. (2005)[2]. This supplemental report reviews only the newly published manuscript and discusses the implications of the findings in this article on my expert opinion.

Andreotti et al. (2017)[1] reported results on the association of glyphosate and cancer incidence from the AHS, a prospective cohort study in Iowa and North Carolina, which included 57,310 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment. This study is a follow-up to the earlier report by **De Roos et al. (2005)**[2] which includes new cancers identified since the 2005 study and new information on exposure and usage. Recruitment for the AHS occurred between 1993 and 1997, and **Androetti et al. (2017)** used initial enrollment information to conduct their follow-up study. After exclusion of individuals who had a history of cancer at enrollment and those providing no information on glyphosate use, there were 54,251 cohort members available for this follow-up. Cancer incidence in this follow-up were obtained from cancer registry files in North Carolina and Iowa and vital status was identified using National Death Index and state mortality registries. Incident cancers were identified from the date of enrollment until December 31, 2013 in Iowa and until December 31, 2012 in North Carolina. In addition to the original data on glyphosate use from **De Roos et al.** (**2005**), comprehensive use data was obtained by telephone questionnaire that was administered between 1999 and 2005. Only 63% of the cohort responded to the questionnaire so the authors used a multiple imputation procedure to impute glyphosate exposure for the remaining 37% of the cohort[3] prior to 2005. They used three exposure metrics in their analyses: a) ever personally mixed or applied pesticides containing glyphosate; b) cumulative exposure days of use of glyphosate (years of use times days per year); and c) intensity weighted cumulative exposure days (years of use times days per year times intensity of use).

There were 575 cohort members with a diagnosis of non-Hodgkin lymphoma (NHL) during the study period of which 82.8% had ever used glyphosate; no rate ratio[1] (RR) was provided for an ever-never use comparison. The authors grouped cumulative exposure days in exposed individuals into quartiles and provided RRs for each quartile compared to unexposed individuals. The RRs are below 1 but increasing with exposure with values of 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) for quartiles 1,2,3 and 4 respectively controlling for age, smoking, alcohol usage, family history of cancer, state and exposure to pesticides atrazine, alochlor, metolachlor, trifuralin and 2,4D. The authors also grouped intensity-weighted lifetime days in exposed individuals into quartiles and examined RRs using the unexposed group as the reference group. The RRs are again below 1 but increasing with exposure with values of 0.83 (0.59-1.18), 0.83 (0.61-1.12), 0.88 (0.65-1.19) and 0.87 (0.64-1.20) for quartiles 1,2,3 and 4 respectively. Analyses were also done using 5-, 10-, 15- and 20-year lag

[1] The rate ratio (RR) is estimated as the incidence in the exposed population divided by the incidence in the unexposed population. Incidence is calculated as the number of events in a fixed period of time divided by the person's years at risk.

times. No significantly increased RRs were seen in these analyses although the general trend was toward higher RRs in the exposure groups as the lag times increased. Analyses were also presented for individual cancer classifications within the non-Hodgkin lymphoma family including B-cell NHL, chronic and small lymphocytic leukemia, diffuse large B-cell lymphoma, marginal-zone lymphoma, follicular lymphoma, multiple myeloma, and T-cell NHL. The results were similar for the subgroupings as they were for the combined NHL with the exception of T-cell NHL where the RRs for lifetime days of exposure were 3.83 (0.84-17.49) for exposure below the median with no lag, and 2.49 (0.95-6.57) for 20-year lag and for intensity-weighted lifetime days were 4.25 (0.73-24.64) for exposure below the median with no lag, and 2.97 (1.20-7.31) for 20-year lag based on a total of 22 cases. The authors found no association between glyphosate use and NHL.

As noted for the earlier study[2], this is a typical cohort study, but has several limitations in terms of its interpretation. In **De Roos, et al. (2005)**, three-quarters (75.5%) of the subjects in the cohort reported having ever personally mixed or applied products containing glyphosate. Reliability of the answers by subjects on the use of glyphosate between the first and second questionnaire were evaluated in the AHS[4]: 82% agreement for whether they had ever mixed or applied glyphosate, 53% agreement on years mixed or applied, 62% agreement on days per year mixed or applied, and 62% agreement on decade first applied. No such comparison has been provided for this evaluation (the third time the questionnaire is applied), but it is highly likely the same lack of agreement is present. This leads to an increase in non-differential exposure misclassification and reduces the RRs in this study.

Unlike the 2017 AHS publication that compares exposure response to unexposed cohort members, **De Roos, et al. (2005)**, provided risk ratios for exposure response by comparing to the lowest exposure grouping (the exposures were given in tertiles and the exposure-response was compared to the lowest tertile) because the authors felt that never exposed and exposed subjects differed in terms of socio-economic factors and other exposures like smoking[2]. **Andreotti et al. (2017)** did not use this same reasoning, and the article does not discuss why there is a departure from this observation. Since the rate ratio is estimated as the incidence in the exposed population divided by the incidence in the unexposed population, the rate ratio against the lowest exposure would simply be calculated as the rate ratio of each exposed group divided by the rate ratio for the lowest exposed group (cancelling out the unexposed group). This would lead to rate ratios for the quartile analyses of lifetime days of q1=1, q2=1.096, q3=1.118, and q4=1.053 and for intensity q2=1, q3=1.06 and q4=1.048. Thus, unlike the previous study, this study shows increased RRs for NHL relative to the lowest exposure group.

The imputed exposures in this evaluation could also lead to non-differential exposure misclassification. This issue has been discussed before[5, 6]. **Acquavella et al. (2006)**[5] used the method for classifying exposure developed for the AHS[7] to evaluate the agreement between concentrations of glyphosate, 2,4-D and chlorpyrifos using usage data based on field observers and farmer recall. When farmer-based exposure information was used, the Spearman correlation coefficient was below 0.25 for all three compounds indicating a serious lack of agreement. **Blair et al. (2011)**[6] performed a similar analysis on 83 pesticide applicators from

the AHS on 2,4-D and chlorpyrifos. They saw Spearman correlations of 0.4 for 2,4-D (n=64), 0.8 for liquid chlorpyrifos (n=4) and 0.6 for granular chlorpyrifos (n=12). They then demonstrated that for a variety of study sensitivities and underlying RRs, there is substantial attenuation of the RR towards the null when the correlations are in the range they observed. For example, if the true relative risk is 2.0, the spearman correlation coefficient between glyphosate exposure and urinary concentration is 0.4 (close to what was seen in the study by **Acquavella et al. (2006)**, the specificity is 0.7 and the sensitivity is <0.9, the observed RR is expected to be below 1.2. They were also able to show that the misclassification is likely to be non-differential. Thus, when using the farmer's own response to calculate exposure, there is likely to be substantial attenuation to no association. Imputing answers from other farmers' responses to the 37% of the cohort that failed to respond to the questionnaire is likely to magnify the impact of non-differential exposure misclassification.

Glyphosate use in the United States has increased dramatically over the course of the AHS. Using USDA and EPA data, agricultural use in the US was 12,474, 35,720, 71,144 and 106,963 thousand kilograms in 1995, 2000, 2005 and 2010 respectively[8]. Thus, during the critical windows during which exposure histories were being obtained for the most recent questionnaire (1999-2005), agricultural use of glyphosate doubled in the U.S. and from 1999 to 2010 agricultural use tripled, mostly due to the introduction of genetically modified crops that are resistant to glyphosate. Farmers interviewed at the beginning of this time period (1999-2002) are likely to have much smaller exposures than those interviewed toward the end of this period. Using the information over this period as indicative for the entire period will clearly underestimate exposure for the entire period with the underestimation being worse for the early interviewees than for the late interviewees. They then use the information from the 63% that responded to the questionnaire to impute exposures for the remaining 37%; this imputation will compound the problem of exposure misclassification. The algorithm and methods used for the exposure imputation are provided in **Heltshe et al. (2012)**[3]. Of the 38 pesticides they evaluated, 33 had smaller values for prevalence of pesticide use from the 1999-2005 survey in the cohort members who responded as compared to the non-respondents. For glyphosate, the prevalence in respondents was 52.73% whereas for non-respondents it was 45.2%. This suggests either a systematic bias towards imputing no exposure or there is some aspect of non-response that is correlated with cohort members having less exposure during this period. If the bias is systematic, this would lead to a differential exposure misclassification potentially assigning cohort members to the unexposed group when they are really exposed.

Finally, in order to evaluate the accuracy of the imputation procedure, **Heltshe et al. (2012)**[3] withheld a subset of the data from respondents, imputed their responses and compared them using a Brier score. The Brier score is a measurement of the quality of a prediction when the predictions are probabilistic as is the case for the imputed exposures; the smaller the Brier score, the more accurate the imputed exposures. Of the 38 pesticides for which exposures were imputed, glyphosate had the worst Brier score, 0.225; this score, at best, shows a very weak degree of accuracy in the predictions.

The Bradford-Hill approach used in my Expert Report uses all of the relevant data in making a recommendation on whether glyphosate can cause NHL. Epidemiology plays a key role in that evaluation, but the evidence from laboratory studies is also critical to the overall evaluation. **Andreotti et al. (2017)**[1] is one additional piece of information to consider in the overall evaluation. As explained above, the numerous and major weaknesses of this study would certainly decrease the statistical power of the study and would increase the likelihood of no association. Given the size of the database used in my overall evaluation, the weaknesses in this study, as described above, and the likelihood of exposure misclassification, this one study does not change my overall evaluation, which remains: **glyphosate probably causes NHL and, given the human, animal and experimental evidence, I assert that, to a reasonable degree of scientific certainty, the probability that glyphosate causes NHL is high.**

Dr. Christopher Portier

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