EXHIBIT 15

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	

SUPPLEMENTAL EXPERT REPORT OF ALFRED I. NEUGUT, MD, PHD IN SUPPORT OF GENERAL CAUSATION ON BEHALF OF PLAINTIFFS

Supplemental Expert Report on Glyphosate and Non-Hodgkin Lymphoma

Alfred I. Neugut, MD, PhD

I. Introduction

This document is provided as a supplement to my expert report of April 2017, which addressed the issue of the causal association between exposure to glyphosate and the incidence of non-Hodgkin lymphoma (NHL). In this supplement, I specifically address the recent publication of a follow-up study to the Agricultural Health Study (AHS) published online in November 2017 (Andreotti et al. Glyphosate use and cancer incidence in the Agricultural Health Study. JNCI 2018;110:djx233), a cohort study that assessed the association between glyphosate and NHL, but had not previously been presented in a peer-reviewed publication.

As an introduction, I will remind the reader of some key points from my initial report that are crucial to an appreciation of the proper analysis of the epidemiologic aspects of this case:

1. Observational studies (case-control and cohort studies) are most effective and reliable in the setting of high relative risks (the risk in the exposed as compared to the risk in the unexposed). It is no accident that the first major achievement of cancer epidemiology was the finding that cigarette smoking was associated with lung cancer risk, an association where the relative risk is on the order of 10 (i.e., cigarette smokers have a risk of lung cancer that is 10 times that of non-smokers.). For causal associations where the relative risk is modest, such as we are dealing with for glyphosate and NHL, it is much more difficult for these types of studies to demonstrate an increased risk on a consistent basis.
2. As a corollary to this, observational epidemiologic studies are purposefully designed to be conservative, i.e., to be null (a relative risk close to 1), under most circumstances unless there is very strong evidence for a positive association. Most random errors in a study have a conservative impact on the association between the exposure and the outcome, i.e., they attenuate or reduce the observed relative risk. Thus, the observation of a null finding must be interpreted with great caution as the possible result of random errors, *particularly when the true relative risk is modest, inasmuch as it may represent an underestimate of the true relative risk.*

When there is a true large relative risk, such random errors may reduce the observed relative risk, but are less likely to eliminate it entirely.

In this document, I will comment on two issues raised by the recent publication of the follow-up results of the AHS cohort study. The first is whether cohort studies are generally superior to case-control studies for the determination of causality in this context, and the second is whether the AHS study specifically is superior to the group of case-control studies that have found a different conclusion.

II. Are cohort studies superior to case-control studies?

I think that it is common in the world at large to make general statements when comparing choices that *superficially* may indicate that one choice is superior to the other. When my wife and I had small children and we had to choose where to live, many "experts" indicated that we should move to the suburbs where the children would benefit from having backyards and fresh air rather than the congestion of the city. Thus, we ended up in New Jersey – enough said. And while in some simplistic sense this advice and choice may indeed be the superior choice, does that really indicate that the choice of living in the city for children is a poor choice or that children who live there cannot benefit from the advantages of being near museums, theatres, etc? A sophisticated and expert reader will appreciate that both choices may have advantages (and disadvantages) and, more accurately, that context and circumstances dictate the correct choice.

This is the precise situation with the choice between cohort and case-control studies – there may be some true minor advantages to cohort studies that, for the sake of a truism, make it a slightly superior study at least to the elementary student of epidemiology. However, the expert in epidemiology understands that one should look under the surface and examine what are the reasons for the putative advantages (or disadvantages) of each type of study, and whether they apply in the context of glyphosate and NHL.

So what are the specific points that make a cohort or case-control study superior?

1. Temporality – Perhaps the most important advantage of a cohort study in theory is that it can unambiguously unravel the issue of temporality. i.e., the necessity that a cause precede its effect. This is generally a particular issue with a biological or physiological exposure, such as obesity, and an outcome. For example, if one finds in a study a statistical association between obesity and depression, then (assuming confounding is not an issue) is obesity a causal factor for depression or does

depression lead to obesity? In a case-control study, where one may be weighing the individuals in the study at the same time as making the diagnosis of depression, the direction of the causal arrow may be ambiguous. In a cohort study, where the investigators would have recruited and weighed the cohort a few years prior to the diagnosis of depression, the direction of causality is much clearer and unambiguous. This is the BIG advantage of a cohort study since temporality is one of the key criteria in the Bradford-Hill criteria. Clearly, a true cause must precede an outcome.

Having said that, how does that apply in our context of glyphosate and NHL? More generally speaking, temporality is often not at issue. If I find an association between glyphosate and NHL, is there ambiguity as to the direction of the causal arrow? Clearly the glyphosate exposure in all the case-control studies preceded the incidence of NHL, usually by years. Thus, there is no ambiguity as to which came first. Further, we are allowed (and indeed encouraged) to use our common sense. Is it plausible to argue, if there is an association, that NHL led to the use of glyphosate? Obviously not, so overall, this advantage of cohort studies is simply irrelevant in our context.

2. A second advantage of cohort studies over case-control studies is that it permits the evaluation of more than one outcome. In a case-control study of NHL, for example, you collect patients with NHL and controls (people without NHL) and compare the two groups for their exposure to glyphosate. When the study is over, all you know about is the association between glyphosate and NHL. A cohort study (like the AHS study) allows you to evaluate the association between glyphosate and any cancer, and indeed any disease. Again, for the truism that cohort studies have an advantage over case-control studies, this is a real advantage, but specifically for the evaluation of glyphosate and NHL it provides no significant advantage over a case-control study.
3. Cohort studies reduce certain types of bias, such as recall bias, which may or may not be relevant in the case-control studies in our context. On the other hand, they have their own biases, such as follow-up bias (discussed below), so overall this is a mixed bag in terms of advantages or disadvantages over case-control studies.
4. Theoretically, cohort studies are generally preferred for occupational studies (which is what the AHS study is) because the exposures in the occupational setting are

uncommon and cohort studies tend to be better for uncommon exposures (such as pesticide/herbicide exposures, like glyphosate). On the other hand, case-control studies are preferred for uncommon outcomes, like NHL, so each type of study has its pluses and minuses in the context of glyphosate and NHL. Most occupational cohort studies are retrospective and utilize cohorts from unions or factories with exposure data from written records of one type or another. In this way, the studies are able to ascertain fairly valid data on the exposure history of each individual up to the time of the cancer diagnosis.

Unfortunately, because the AHS study is prospective, which might theoretically for some purposes be an advantage, because the usage of glyphosate changed dramatically after the recruitment period, the exposure information for subjects in this particular study is lacking, or at best spotty (discussed in next section). Furthermore, rather than having detailed exposure records as are usually available in occupational cohort studies, the AHS study relied on self-reported exposure histories, another issue which will be discussed below. Thus, the usual advantages of an occupational cohort study were absent in the AHS study.

5. Case-control studies are generally considered superior than cohort studies for the study of uncommon diseases, which NHL is, so from this perspective, the case-control studies would be considered superior. This is exacerbated by the fact that the putative relative risk for the association between glyphosate and NHL is modest.

The bottom line is that most of the "advantages" that cohort studies would potentially be expected to have over case-control studies are either not relevant or not present in the setting of the glyphosate-NHL question. Therefore, at least from a theoretical point of view, the case-control studies are probably at least as good, if not better, than the cohort study as indicators of an association between the exposure and the outcome.

Of course, the quality of the studies themselves is more important than anything. Thus, flaws in either type of study is what truly determines how much reliance you can place on either the cohort (AHS) study or the case-control studies. That is the subject of our next section.

III. Are there specific problems in the AHS study?

1. As mentioned above, one of the problems in the AHS study is the way in which the exposure history was ascertained. As opposed to most occupational cohorts, which rely on recorded exposure data which is usually quite reliable, the AHS study relied on self-report. An example of recorded exposure data would be the employment records of a factory worker, indicating which parts of the plant he worked in and for how long. Since we usually know from industrial hygiene data how much exposure there is to the chemical under study in each part of a plant, such records give us a highly valid estimate of each individual worker's cumulative exposure over time to the chemical being assessed.

Self-report can be reliable, depending on the variable which is being evaluated, e.g., tobacco exposure is generally considered to be reliable as assessed by this methodology. While recall bias (as has been mentioned with regard to case-control studies) would not be a major issue, random misclassification error (subjects in the study randomly getting their exposure wrong) would be enough to spoil the results of the study if there were a substantial amount of such error. As previously noted, random errors such as these are conservative and tend to attenuate the observed relative risk estimates towards the null, *so unbiased misclassification error would lead to an underestimate of the true relative risk.* Thus, if we observe a null effect, we have to take it with a skeptical eye and wonder if the null effect were due to misclassification error.

Specifically in the AHS study, this misclassification error was evaluated to some degree in a paper by Dr. Aaron Blair along with the collaborators on the AHS study, including Dr. Michael Alavanja and Dr. Laura Beane Freeman (Blair et al. Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. Occup Environ Med 2011;68:537-541.) This study found that the reporting of pesticide exposure was comparable to that of other exposures which are measured by questionnaire in epidemiologic studies, i.e., not bad. Nonetheless, "…except in situations where exposure estimation is quite accurate (i.e., correlations of 0.70 or greater with true exposure) and *true relative risks are 3.0 or more,* pesticide misclassification may diminish risk estimates to such an extent that no association is obvious, which indicates false negative findings might be common." (Blair 2011). For the particular pesticides tested in this paper, the correlations were not quite as good as 0.7 (glyphosate was not specifically tested), but even if it were, I remind the reader that with glyphosate and NHL we are in the modest relative risk range of 1.3-1.4 for ever-never use

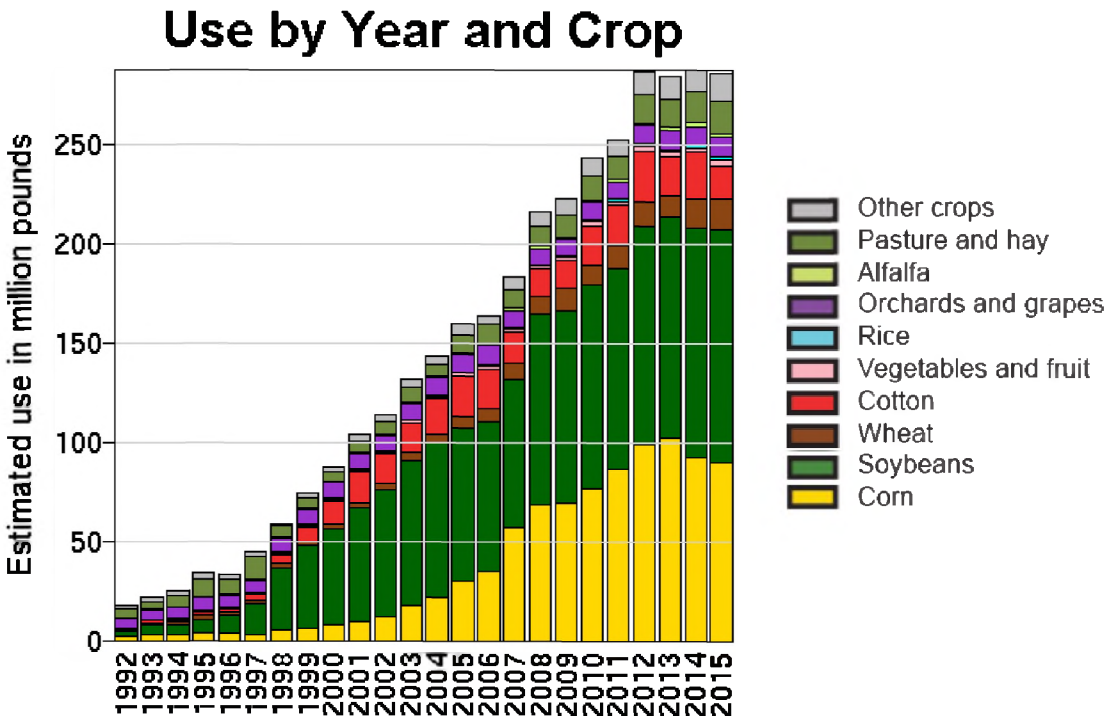
(significantly higher for certain subgroups) rather than 3.0. Thus, even with a correlation of 0.8 or 0.9, a relative risk of that magnitude will almost inevitably be obscured or eliminated by, in effect, a misclassification error of 10%. While the current publication of the AHS follow-up study is actually very poor in describing the weaknesses of the study, it does correctly allude to this particular problem: "…. despite the specific information provided by the applicators about use of glyphosate, some misclassification of exposure undoubtedly occurred. Given the prospective design, however, any misclassification should be nondifferential and lead to attenuated risk estimates." Andreotti et al. Glyphosate use and cancer incidence in the Agricultural Health Study. JNCI 2018;110:djx233

2. While one hears that recall bias is an issue in case-control studies (I don't happen to believe it is a major problem in the studies at play in our glyphosate-NHL context), cohort studies have their own set of biases to worry about. Most salient is follow-up bias. The concern with follow-up bias is that there will be differential follow-up to the diagnosis of the endpoint, in our case lymphoma, which will be dependent on the exposure. This is most likely to occur if, as can occur in a follow-up cohort study, there is significant loss to follow-up. Thus, we may not identify all the cases of the disease under study, and this loss to follow-up may be differential with regard to the original exposure. This usually occurs with diagnoses which are underdiagnosed in the population, such as mental conditions. In the AHS study, and directing our attention to malignancies, this particular problem did not arise – the AHS study took place in two states with excellent tumor registries, and thus it is probable that the vast majority of NHL cases were correctly diagnosed and this particular common problem of follow-up bias did not occur, and the investigators are to be lauded for the quality of the data with this issue. In other words, they probably did correctly ascertain all the NHL cases in the exposed and unexposed groups accurately or pretty accurately.

3. So where does the error in the AHS study occur? Normally we like prospective studies because as mentioned earlier, they give us unbiased assessments of exposure history and can elucidate temporality clearly. This is terrific in the setting of a point exposure, such as the A-bomb explosion in Japan in 1945, when the exposure took place at one millisecond and all you have to do is follow the cohort forward in time and see what happened to each person in terms of where they were in relation to the explosion (in order to estimate their radiation exposure) and what their subsequent history of cancer is.

The problem arises in the setting of an ongoing exposure. Some ongoing exposures tend to be constant – someone smokes two packs per day and does so for extended periods of time without much variation. Thus, even if you collect his exposure history at one point in time and follow him forward for another one to two decades, the degree of error introduced by some people reducing their smoking exposure or quitting does not tend to be drastic. And again, the relative risk for tobacco and lung cancer is on the order of 10, so even if some error is introduced by variability over time in tobacco exposure, leading to an attenuation in the observed relative risk, so we would measure a relative risk of 8 or 9 rather than 10 – the general contour of the risk will be preserved.

But what happened with the glyphosate/NHL association? The subjects were recruited between 1993 and 1997 and at that time underwent a baseline questionnaire which assessed their exposure to glyphosate. In 1996, glyphosate-resistant crops were introduced on a large-scale basis and thus the use of glyphosate increased exponentially after 1996 (see Figure)[1].



[1] https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2012&map=GLYPHOSATE&hilo=H

As a consequence, the glyphosate exposure as estimated from the baseline questionnaire was no longer adequate for estimating the association with the incidence of NHL over the ensuing 15 years. Consequently, the investigators of the AHS study planned a second interview regarding exposure that was to take place between 1999 and 2005. This problem was anticipated even before the follow-up questionnaires were administered in a critical review of the AHS study conducted by multiple nationally renowned experts in environmental epidemiology unrelated to the study (Gray et al. The federal government's Agricultural Health Study: A critical review with suggested improvements. Hum Ecol Risk Assess 2000;6:47-71). This report from Harvard outlined numerous potential issues with the AHS study and suggested potential interventions to ameliorate these flaws. One key flaw that was mentioned was the potential loss to follow-up in the second questionnaire that was anticipated would be administered and I quote the Panel's prophetic remarks on this subject:

> In the prospective cohort study, low response rates to questionnaires designed to obtain information on subject identifiers, exposures, and baseline disease status will clearly diminish statistical power and may create bias. The success of the cohort study also depends upon acceptable response rates to future follow-up surveys of the cohort. Periodic follow-up surveys are necessary to determine how exposures and disease states change as the cohort ages, thereby maintaining the prospective character of the study. If low response rates occur with the follow-up questionnaires, the potential for bias will increase, partly from misclassification of subjects (and person-years) with regard to chemical exposure and partly from residual confounding stemming from inaccurate measurement of risk factors other than pesticides.

Gray (2000)

When this follow-up questionnaire was administered between 1999 and 2005, the response rate was approximately 63%, or 37% did not respond. In the context of cohort studies, this is considered a huge nonresponse rate. Any epidemiologist knows that if this loss to follow-up is differential (i.e., that those who did not respond to the second questionnaire were "different" from those who did respond), that this could have a huge impact on the estimate of the association between the exposure and the outcome. This was what was alluded to in the Harvard Panel's report cited above, with the potential for misclassification error and bias stemming from this large degree of non-response. I will remind the reader that we are

considering an association where the putative true relative risk is modest for ever-never use, so it would not take much differential error to obviate or eliminate this observed risk.

The problem from this differential error would mostly arise from an underestimation of exposure. If the exposure estimate for a study participant was based on the baseline interview conducted between 1993-1997, we would be unaware of how much his exposure could have been increased or expanded by the post-1996 explosion in glyphosate use. Indeed, it would be likely that there were study participants who were unexposed to glyphosate prior to 1996 who would have used glyphosate extensively post-1996 and then developed NHL. Those individuals would be considered unexposed NHL cases in the analyses if they did not participate in the follow-up questionnaire (i.e., nonresponders); even though they could have had extensive glyphosate use prior to their diagnosis of NHL. This illustrates how differential bias or just random non-responder error could have attenuated the observed relative risk because of nonresponse.

I found two studies that addressed differences between the 38% nonresponders and 62% responders. Montgomery et al. (Characteristics of non-participation and potential for selection bias in a prospective cohort study. Am J Ind Med 2010;53:486-496) compared the responders to the nonresponders in the AHS study and found that nonresponders were younger, had less education, lower body mass index, poorer health behaviors, and lower pesticide use at baseline. A more recent evaluation (Rinsky et al. Assessing the potential for bias from nonresponse to a study follow-up interview: an example from the Agricultural Health Study. Am J Epidemiol 2017;186:395-404) found that nonresponse was related to younger and older age, being non-white, having less than a high school diploma, not being married, and heavy drinking, as well as current smokers. These are generally factors that are typically associated with nonresponse, and it does not take much imagination to surmise that they would lead to sufficient differential bias to eradicate a modest relative risk. The impact of loss to follow-up on risk estimation has been well recognized since the classic paper by Greenland in 1977 (Response and follow-up bias in cohort studies. Am J Epidemiol 1977;106:184-187).

4. The AHS investigators were, of course, aware of the large loss to follow-up for the second questionnaire and the necessity of dealing with it in their analyses of the associations between the various pesticides and diseases/outcomes evaluated in the cohort study. In essence, the problem they faced was that they did not know the

pesticide exposure for almost 40% of the cohort for the time frame following the baseline questionnaire.

The solution they employed is known as imputation, which is frequently used for dealing with precisely this same problem in similar situations. The use of pesticides in the second time frame was imputed statistically from answers to various variables for the nonresponders that were available from the baseline questionnaire, which included sex, marital status, farm ownership, farm size, days/year mixing pesticides, percent time personally mixing pesticides, percent time personally applying pesticides, age, education, state of residence, applicator type, and years mixing chemicals. Essentially, based on these variables from the baseline questionnaire, the response of the nonresponders was imputed or assumed using sophisticated statistical multivariate modeling (Heltshe et al. Using multiple imputation to assign pesticide use for nonresponders in the follow-up questionnaire in the Agricultural Health Study. J Expo Sci Environ Epidemiol 2012;22:409-416).

Just how well does this method work? To test its validity, Heltshe et al took a 20% random sample of those who *responded* to the second questionnaire and used the data from the other responders to impute the pesticide usage for this random set of responders (for whom the use of pesticides on the second questionnaire was available). Thus, there was no additional bias from being nonresponders. For the use of glyphosate, the observed percentage use of glyphosate based on the second questionnaire was 52.7%. The imputed use for a 20% sample of responders (n=7269) was 45.4%, 16.0% less, *and this was for a subset of individuals who had all responded to the questionnaire*. Thus, imputation introduced an error of 16% without even taking into account the bias from being a nonresponder versus a responder.

When the investigators then actually calculated the prevalence of use of glyphosate among the responders (n=36,342) versus the nonresponders (n=20,968), they came up with an observed prevalence of use of 51.82% observed for the former versus 43.98% imputed for the latter, a relative difference of 17.8% (similar to the 16% error that was calculated for the imputation methodology) *and this was without taking into account that nonresponders would likely be very different from responders!!!*. Again, it hardly seems worth reiterating that such large differences would easily obfuscate a true modest relative risk of 1.3-1.4 for ever-never use of glyphosate (significantly higher for certain subgroups).

IV. Concluding remarks:

I would conclude by noting two further things. The first is that imputation, the methodology by which the AHS investigators corrected for nonresponse in the AHS study, is essentially the same method by which pollsters in electoral politics adjust for the same problem when faced with the fact that most people do not respond to their pollsters. I note, with only some degree of irony, that based on this methodology, Hillary Clinton won the November 2016 presidential election quite decisively.

More importantly, glyphosate was not the only pesticide evaluated by the AHS study. It evaluated about 30 pesticides and, of these, 5 have been scored by IARC to be at least 2A with regard to their carcinogenicity for non-Hodgkin lymphoma (i.e., probable or definite carcinogens). While we have focused our attention and discussion specifically on glyphosate, it is interesting to note that the AHS study also was insensitive to two other putative lymphoma carcinogens that were recognized for their carcinogenicity through case-control studies. Thus, the fact that the AHS study missed the boat with regard to glyphosate and NHL should not be taken as a singular event, nor as a reason to ignore or obfuscate the preponderance of the rest of the evidence as delineated in the IARC report.

Pesticide	IARC Classification [2]	IARC positive association for NHL	AHS Study (2014) Ever/Never[3]
DDT	2A	Yes	Yes
Diazinon	2A	Yes	No
Malathion	2A	Yes	No
Lindane	1	Yes	Yes
Glyphosate	**2A**	**Yes**	**No[4]**

Dated: 12/20/17

Alfred I. Neugut, MD, PhD.

[2] IARC classifications of carcinogenic agents. Group 1: Carcinogenic to humans; Group 2A: Probably carcinogenic to humans; Group 2B: Possibly carcinogenic to humans; Group 3: Not classifiable as to its carcinogenicity to humans; Group 4: Probably not carcinogenic to humans.
[3] Alavanja et al., Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study, PLoS One, 2014, 9: e109332.
[4] Andreotti et al., JNCI, 2018, 110:ejx233.

Supplemental Reliance List

Alavanja et al., Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study, PLoS One, 2014, 9: e109332.

Andreotti et al. "Glyphosate use and cancer incidence in the Agricultural Health Study." JNCI 2018;110:djx233

Blair et al. "Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study." Occup Environ Med 2011;68:537-541.

Gray et al. "The federal government's Agricultural Health Study: A critical review with suggested improvements." Hum Ecol Risk Assess 2000;6:47-71

Greenland, "Response and follow-up bias in cohort studies." Am J Epidemiol 1977;106:184-187

Heltshe et al. "Using multiple imputation to assign pesticide use for nonresponders in the follow-up questionnaire in the Agricultural Health Study." J Expo Sci Environ Epidemiol 2012;22:409-416

IARC Monograph 112, evaluations of Malthion and Diazon.

IARC Monograph 113, summary of evaluation of Lindand and DDT.

Montgomery et al. "Characteristics of non-participation and potential for selection bias in a prospective cohort study." Am J Ind Med 2010;53:486-496.

Rinsky et al. "Assessing the potential for bias from nonresponse to a study follow-up interview: an example from the Agricultural Health Study." Am J Epidemiol 2017;186:395-404.