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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION THIS DOCUMENT RELATES TO: ALL ACTIONS	MDL No. 2741 Case No. 16-md-02741-VC **PLAINTIFFS' SUPPLEMENTAL BRIEF PURSUANT TO PTO 34** HON. VINCE CHHABRIA

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INTRODUCTION

"[T]he court's job at this stage is not to weigh the evidence, but merely to determine admissibility." *Leite v. Crane Co.*, 868 F. Supp. 2d 1023, 1037 (D. Haw. 2012), *aff'd*, 749 F.3d 1117 (9th Cir. 2014). Nevertheless, despite numerous epidemiological case-control studies, animal bioassays, and geno-toxicological analyses demonstrating that Glyphosate-Based Formulations ("GBFs") cause cancer, *see* Opp. Br. at 24-50 (Dkt. 647), Monsanto asks this Court to do just that and focus exclusively on one negative, seriously flawed study. The Agricultural Health Study ("AHS") is a cohort study investigating health risks associated with pesticides among licensed restricted-pesticide-users in North Carolina and Iowa over several decades. The AHS collects information from the cohort through a series of follow-up questionnaires and phone calls. Unfortunately, due to the number of participants in the AHS, ensuring a full cohort of data has proven difficult. Specifically, in the recently-published AHS analysis (Andreotti 2018[1]), the AHS suffered a 37% membership loss during follow up, prompting the authors to use an imputation model to generate results for the missing data. And, although applying imputation methodology to epidemiologic studies can be appropriate in certain circumstances, here, it created a fatal misclassification bias, where those people deemed "exposed" and "unexposed" were improperly classified—a fact admitted by the authors. Making things worse, this loss to follow up is further compounded by the sudden spike in use of GBFs during and after study enrollment—another problem admitted by the authors. These systematic problems in data collection and classification render the AHS data unhelpful in assessing GBFs and cancer, especially when contrasted against the many reliable, peer-reviewed case control studies showing a statistically significant association between glyphosate use and the development of non-Hodgkin's lymphoma ("NHL") addressed by Plaintiffs' experts' reports and testimony. Accordingly, Andreotti 2018 does not alter or otherwise change the general causation opinions of Plaintiffs' experts.

When the AHS was first announced, Monsanto criticized it as fatally flawed:

[1] This article was published online on November 9, 2017; the official publication will occur in 2018. *See* Exh. 1 Andreotti, et al., *Glyphosate Use and Cancer Incidence in the Agricultural Health Study*, JNCI djx233, https://doi.org/10.1093/jnci/djx233 (hereinafter "Andreotti 2018").

> "The exposure assessment in the AHS will be ***inaccurate.*** … Inaccurate exposure classification can produce spurious results."
>
> -- John Acquavella, **July 22, 1997** (Exh. 2. Acquavella Memo) (emphasis added).
>
> "Many groups have been highly critical of the study as being a flawed study, in fact some have gone so far as to call it junk science. It is small in scope and ***the retrospective question[naire] on pesticide usage … is thought to be unreliable*** ... but the bottom line is scary ... there will be associations identified between glyphosate use and some health effects just because of the way this study is designed."
>
> -- Donna Farmer, **May 31, 1999** (Exh. 3, 1999 Farmer Email) (emphasis added).

This flexibility with science, consistent with Monsanto's storied history of developing cancer-causing agents, speaks volumes about how the Court should review and consider the AHS study, and at the very least raises a triable issue of fact surrounding the reliability of the AHS, compared against the mountain of scientific evidence showing general causation, sufficient to submit general causation to the jury.

AHS BACKGROUND AND MONSANTO'S INCONSISTENT RESPONSES TO IT

The AHS's purpose is to "identify and quantify cancer risks among men and women … associated with direct exposure to pesticides[.]" Exh. 4, Michael Alavanja et al, *The Agricultural Health Study*, 104 ENVIRON. HEALTH PERSP. 4, 362-69, 363 (Apr. 1996). The study enrolled 57,310 individuals between 1993 and 1997 in North Carolina and Iowa, where state regulations require pesticide applicators to "obtain a pesticide applicator license by undergoing training or testing in the safe handling of pesticides." *Id.*; *see* Exh. 1, Andreotti 2018. "At the licensing facility, each pesticide applicator is asked to complete a 21-page, optically scannable enrollment questionnaire." Exh. 4, Alavanja at 363. The AHS planned to follow these participants for decades to assess health outcomes. However, because of its size and duration, there were practical limitations collecting exposure data. *Id.* at 368.

The initial questionnaire asked each participant about his or her detailed use of 22 pesticides and cursory use of 29 other agricultural chemicals. *See* Exh. 5, AHS Com. App. Quest. at 5-14; Exh. 6, AHS Priv. App. Quest. at 7-15. For glyphosate, the questionnaire asked whether the participant had ever used or sprayed "Roundup, Jury or other glyphosate products" and only allowed for a yes or no answer. Exh. 6. at 10. Then, the participant was required to estimate "how many years" they mixed or applied glyphosate and guess "[i]n an average year when you

personally used this pesticide, how many days did you it [sic]?" *Id.* Finally, the participant was asked to state what decade they started using glyphosate. *Id.* Because this questionnaire was administered immediately after a pesticide exam, participants "were not able to review records of past pesticide purchases, ask family members or co-workers to help recall specific use periods and agents, or take time to retrieve necessary information[.]" Exh. 7, Ritz Suppl. Rep. at 2.

Additionally, the AHS questionnaire asked general questions, without distinguishing between the types of pesticide applied or the method of application, and used these answers to determine *specific* exposure information. For example, questions related to personal protective equipment asked participants to report the type of protective gear worn when handling pesticides *generally* but failed to ask the question for each pesticide. Exh. 5, AHS Com. App. Quest. at 15.[2] Exposure metrics were then calculated based upon the type of protective equipment reported generally. So, if someone reported using gloves for pesticides generally, but did not take that precaution with GBFs, their exposure to GBFs would be calculated as if they wore gloves.

Response rate to the supplemental questionnaires was very low, and due to cost, the AHS researchers were not able to conduct follow-up requests for the data. Exh. 4, Alavanja at 364. Because of concerns about data accuracy at enrollment, the AHS investigators conducted a follow-up phone survey after five years, between 1999 and 2005 (Phase 2). Exh. 1, Andreotti 2018 at 2. However, only 63% responded to the Phase 2 survey. *Id.*[3] Consequently, in order to analyze the data, the study authors decided to impute data from the Phase 2 questionnaires to the non-responders.

Before getting the AHS results, Monsanto was highly critical of the AHS study. For example, Dr. John Acquavella, a Senior Fellow of Epidemiology at Monsanto explained:

> (1) the AHS investigators are "inexperienced in agricultural epidemiology"; (2) the study populations "have limited contact with pesticides"; (3) "[t]he exposure assessment in the AHS will be inaccurate" because it "will be based on historical usage as reported by the farmer or applicator on the study questionnaire(s)"; (4) "[i]naccurate exposure classification can produce spurious results" and "obscure exposure disease relationships"; (5) "sophisticated statistical analysis can't correct

[2] This is significant because protective gear and other precautions differ between restricted use pesticides and non-restricted use pesticides, such as GBFs.

[3] In 2010, Phase 3 questionnaires were sent to participants, but a mere 46% responded. Data from Phase 3 was not included in Andreotti 2018. https://aghealth.nih.gov/about/

> for . . .exposure misclassification"; and (6) the AHS investigators had not developed study protocols for any particular analyses, electing to do them "on the fly" which "circumvents some of the scrutiny they might get[.]"

Exh. 2, Acquavella Memo (1997) at 3-5. Similarly, Dr. Donna Farmer, Monsanto's head toxicologist, prepared a presentation in 1999 characterizing the AHS as a "[redacted]" and "[redacted]," and she criticized the AHS because of its "[redacted]" Exh. 8, Farmer Presentation (1999) at 7.[4]

These criticisms prompted the American Crop Protection Association, a Monsanto-sponsored industry group, to commission scientists from the Harvard School of Public Health to review the AHS's design. *See* Exh. 10, George M. Gray, et al, *The Federal Government's Agricultural Health Study: A Critical Review with Suggested Improvements*, 6 HUM. ECOL. RISK ASSESS. 1, 47-70, 69 (2000). Like Dr. Acquavella, the scientists were concerned about the "potentially biased and imprecise exposure assessment … variable rates of subject response to administered surveys" and "limited understanding of the reliability and validity of self-reporting of chemical use[.]" *Id.* at 48. The scientists specifically noted that "[i]f low response rates occur with the follow-up questionnaires, the potential for bias will increase[.]" *Id.* at 52. Both Dr. Acquavella and Dr. Aaron Blair (National Cancer Institute epidemiologist and IARC Monograph 112 Chair) were consulted on the publication. *Id.* at 69.

Monsanto's criticism began to change in 2005 with the publication of AHS data on glyphosate by De Roos and others. Exh. 11, Anneclaire J. De Roos, et al., *Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study*, 113 ENVIRON. HEALTH PERSP. 1, 49-54 (Jan. 2005).[5] De Roos 2005 did not use data from the Phase 2 follow-up and was limited to those participants that had been diagnosed with cancer prior to December 31, 2001. *Id.* Overall, De Roos 2005 was null, meaning it did not demonstrate an association between NHL and glyphosate. *Id.* The researchers noted there were significant socio-economic differences between people who claimed they were never exposed to glyphosate versus people who claimed exposure in the cohort. *Id.* at 51. Because of these differences, the

[4] Indeed, Monsanto was so concerned about exposure assessments in the AHS that it commissioned the Farm Family Exposure Study to "[i]noculate key audiences with messages about epidemiology" and "proactively prepare for the publication of the AHS and its possible negative findings[.]" Exh. 9, Preliminary Communications Plan (2002) at *5.

[5] Dr. Aaron Blair was the second author on the publication.

researchers decided to compare the lower-exposed participants to the higher-exposed participants, rather than compare the higher-exposed to the never/ever exposed. *Id.* The study revealed statistically-significant elevated risks of multiple myeloma in higher-exposed pesticide applicators, RR=2.6[6], but did not reveal any statistically significant elevated risks for other cancers. *Id.* For NHL, there was a slightly elevated risk (RR=1.1), although not statistically-significant. *Id.* De Roos (2005) acknowledged that the AHS results were *different* from the numerous case-control studies that had already been published showing a statistically-significant elevated risk of NHL from GBF exposure. *Id.* at 53 ("These findings conflict with recent studies.").

Following the publication of De Roos (2005), various meta-analyses were done to reconcile the numerous positive findings in the case-control studies with the outlier finding in De Roos (2005). *See* Exh. 34, Ritz Rpt. at 16. Four meta-analyses, including one sponsored by Monsanto, *all* showed statistically-significant elevated risks for NHL. *Id.* at 16-18, 23.

On November 9, 2017, researchers at the National Cancer Institute ("NCI") published an update to the AHS for glyphosate, using imputed data from the Phase 2 follow-up phone questionnaire. Like De Roos (2005), Andreotti (2018) did not show any statistically-significant elevated risks of NHL and GBF exposure.

ARGUMENT

I. The AHS Must Be Considered in the Context of Numerous Epidemiological Studies Showing a Significant Elevated Risk of NHL from GBF Exposure

Multiple, independent, peer-reviewed epidemiological studies show a statistically-significant elevated risk of NHL from glyphosate exposure. *See* Opp. Br. at 22-29 (Dkt. 647) (describing numerous epidemiological studies supporting general causation). That data, itself, is enough to raise a triable issue of fact because a reasonable jury could conclude that exposure to GBFs causes NHL. Contrary to basic scientific principles, Monsanto asks the Court to ignore these

[6] In response to this aspect of the study, Monsanto tasked its consultant, Dr. Tom Sorahan, with writing a critique of the AHS for its observed association between glyphosate and multiple myeloma. Contrary to Monsanto's praise for the study following its initial publication in 2005 regarding other NHL subtypes, privately, it acknowledged that the "[redacted]" of the Sorahan paper was to "[redacted]" Exh. 35, Email Exchanges Re AHS at *5.

studies and rely, exclusively, on AHS data.

"Rule 702 [does] not require, or even permit, the district court to choose between the studies at the gatekeeping stage… [E]xperts [are] entitled to present their views, and the merits and demerits of each study can be explored at trial." *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 432 (7th Cir. 2013); *accord Metabolife Int'l, Inc. v. Wornick*, 264 F.3d 832, 843 (9th Cir. 2001) (reversing district court for picking and choosing studies); *see Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1993) ("[O]pen debate is an essential part of both legal and scientific analyses."). This is particularly true, as here, when various meta-analyses using the original AHS data (before flawed imputation of data) have already been conducted, and they *all* confirm an elevated NHL risk. *See* Opp. Br. at 28-29 (Dkt. 647); *see In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1173–74 (N.D. Cal. 2007); *Mullins v. Premier Nutrition Corp.*, 178 F. Supp. 3d 867, 884 (N.D. Cal. 2016).

The design and failed follow-up in the AHS leading to substantial exposure misclassification warrants particular skepticism in comparison to the case-control studies:

> We believe of the two of the major methodologic issues raised in epidemiologic studies of occupational exposures, that is, confounding and exposure misclassification, the latter is of far greater concern. It is rare to find substantial confounding in occupational studies....[T]the magnitude from relatively small amounts of misclassification can be sufficient to lead to an interpretation of no effect. Thus, interpretation of epidemiologic data and evaluations of epidemiologic studies should be more concerned about exposure assessment than confounding.

Exh. 12, Blair, *et al*. *Methodological Issues Regarding Confounding and Exposure Misclassification in Epidemiological Studies of Occupational Exposures*, 50 AM. J. IND. MED. 199, 199-207 (2006). Conversely, Monsanto's experts, Dr. Mucci and Dr. Rider, focus their attention on hypothetical confounding in case-control studies and minimize the effect of exposure misclassification in the AHS study. This misplaced focus appears to be due to their lack of experience in occupational epidemiology. Exh. 13, Rider Supp. Dep. at 7:21-24 ("I don't do occupational epidemiology"); Exh. 14, Mucci Supp. Dep. at 34:18-22 ("I haven't been involved in studies of occupational based exposures.").

Plaintiffs' experts reviewed and considered De Roos 2005 and Andreotti 2018 in rendering their opinions; the AHS is only *one* study—a study that was never intended to evaluate a specific

pesticide or cancer[7] and is riddled with flaws: "Certainly, the results of one questionable negative study cannot be used to negate the results of multiple positive epidemiological studies." Exh. 16, Weisenburger Supp. Rpt. at 4. Andreotti (2018) even acknowledges that its NHL results conflict with six case-control studies showing "a statistically significant association between glyphosate and NHL[.]" Exh. 1, *Andreotti* at 7. Thus, even if the AHS study did not suffer from misclassification bias and other flaws, it would not negate the multiple positive case control studies.

The role of the Court as a gatekeeper is not to decide whether De Roos 2005 or Andreotti 2018 are "better" or more reliable studies, but whether each of Plaintiffs' experts utilized a reliable methodology in weighing the AHS data in rendering their opinions. *See Kennedy v. Collagen Corp.*, 161 F.3d 1226, 1228-30 (9th Cir. 1998) (reversing district court because it "failed to distinguish between the threshold question of admissibility of expert testimony and the persuasive weight to be accorded such testimony by a jury" and "did not consider all of the data relied upon by" the expert).[8] Each of Plaintiffs' experts considered the AHS data, as it was presented in De Roos (2005), before reaching his or her original opinions, and those opinions did not change upon review of Andreotti 2018. Neither Dr. Neugut nor Dr. Ritz considered Andreotti 2018 to be sufficiently reliable to include in a meta-analysis. Exh. 17, Neugut Supp. Dep. at 40:2-41:1; Exh. 7, Ritz Supp. Rpt. at 9.[9]

II. The AHS Suffers from Significant Bias and Errors, Rendering the Data Unreliable in Assessing whether Glyphosate Causes NHL

[7] Indeed, the AHS has proven unable to detect cancers in other known carcinogens. *See* Exh. 15, Neugut Supp. Rpt. at 12.

[8] *See also In re Bextra*, 524 F. Supp. 2d at 1182 ("While the weight to be given to this evidence can be argued … the Court cannot conclude that expert opinion … is scientifically invalid.").

[9] Likewise, Andreotti (2018) would not have changed IARC's review of glyphosate. In responding to Monsanto's "unprecedented, coordinated efforts to undermine" IARC, which included accusations "that results from the AHS were withheld from the IARC Monograph evaluation and that recent results would have led to a different evaluation," IARC responded:

> For the 2015 classification of glyphosate, several peer-reviewed publications from the AHS were available and included in the evaluation… the latest AHS publication did not report an association between non-Hodgkin lymphoma and glyphosate. However, this null finding did not outweigh the positive associations found in other epidemiological studies.

Exh. 18, Briefing Note for IARC Scientific and Governing Council Members.

Although Plaintiffs' experts considered the AHS in rendering their opinions, none gave it significant weight because the data, as it relates to glyphosate and NHL, is flawed. Indeed, the very criticisms Monsanto raised about the AHS before 2005 apply with equal force today: (A) exposure misclassification; and (B) use of imputed data.

A. Non-Differential Exposure Misclassification

It is well known that non-differential exposure misclassification "tends to produce estimates of the effect that are diluted, or ***closer to the null or no-effect*** value than the actual effect." Exh. 19, Kenneth J. Rothman, *Epidemiology: An Introduction* 100 (2002) (emphasis added); Exh. 15, Neugut Supp. Rpt. at 7; Exh. 13, Rider Supp. Dep. at 22:19-21 ("[I]n general, non-differential misclassification of exposure would bias the results towards the null."). Specifically, non-differential exposure misclassification in the AHS has been observed throughout the course of the study to "reduce the power of the study to detect any genuine cause-effect relationships and…reduce[s] the validity of findings." Exh. 10, Gray at 58; *see* Exh. 20, Blair, *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, 96 (2002) ("The impact of misclassification in ***this range on the relative risks*** can be ***substantial and diminish the opportunity to detect real associations***. It is important to note that nondifferential misclassification…would only diminish estimates of relative risk…in a prospective investigation such as the Agricultural Health Study." (emphasis added)); Exh. 21, Brouwer, *et al*., *Assessment of Occupational Exposure to Pesticides in a Pooled Analysis of Agricultural Cohorts within the AGRICOH Consortium*, 73 OCCUP. ENVIRON. MED. 359, 366 (2016) ("Non-differential exposure misclassification usually leads to a bias of the estimate towards the null, especially … for most pesticide exposures and health effects."). The following types of nondifferential misclassification in the AHS tend to obscure associations.

1. Recall Error at Baseline Creates Non-Differential Exposure Misclassification

The first defect in the AHS stems from the retrospective nature of the questionnaire used to establish each participant's pesticide use. At enrollment, pesticide applicators were asked about prior use of a large number of pesticides. *See* Exh. 5, AHS Commercial Applicator

Questionnaire at 5-14; Exh. 6 AHS Private Applicator questionnaire at 7-15; Exh. 7, Ritz Supp. Rpt. at 2. Thus, measurement error caused by faulty recall of pesticide use was a problem from the outset. Exh. 22, Portier Supp. Rpt. at 3 ("[W]hen using the farmer's own response to calculate exposure, there is likely to be substantial attenuation to no association.").

Misclassification of exposure caused by inaccurate recall of pesticide use is considered non-differential, i.e., "it is as likely for those who remain healthy and those who later develop a disease to make mistakes and not recall and report exposures correctly." Exh. 7, Ritz Supp. Rpt. at 2. Indeed, Monsanto's own Dr. Acquavella, in critiquing the AHS, stated in 1997 that this type of exposure assessment was inaccurate and would likely obscure relationships:

> The exposure assessment in the AHS ***will be inaccurate.*** Exposure assessment will be based on historical usage as reported by the farmer or applicator on the study questionnaire(s)… ***Inaccurate exposure classification can produce spurious results.*** The conventional thinking in epidemiology is that exposure misclassification will most often ***obscure exposure disease relationships.***

Exh. 2, Acquavella Memo (1997) at 3-5 (emphasis added); *see also* Exh. 23, Acquavella, *et al*., *Exposure Misclassification in Studies of Agricultural Pesticides Insights from Biomonitoring*, 17 EPIDEMIOLOGY 69, 73 (2006) ("[G]iven the uncertainty in questionnaire responses … our results suggest that dose-response analyses based on estimated cumulative days of use would have substantial exposure misclassification.").[10] Numerous academics have critiqued this specific defect in the AHS.[11] And, because of this error in the AHS, "substantial exposure misclassification is expected to occur across categories of exposure[.]" Exh. 24, Weichenthal at 1123. The Andreotti 2018 researchers also acknowledge that because of the self-reporting questionnaire "***some misclassification of exposure undoubtedly occurred***" and "any misclassification should … lead to ***attenuated risk estimates.***" Exh. 1, Andreotti at 7 (emphasis added). This error fundamentally undermines the reliability of the AHS data because it is unclear

[10] It has also been stated that "[s]elf-reported exposure information is ***not a true gold standard***. A study among male applicators participating in AHS indicated their ability to produce reliable and reproducible reports of their pesticide use, but the ***validity*** of these reports could not be assessed. Therefore, it remains unclear to what extent the AHS self-reported data may ***underestimate or overestimate*** true pesticide use." Exh. 21, *Brouwer* at 366 (emphasis added).

[11] *See, e.g.*, Exh. 24, Weichenthal, *et al*., *A Review of Pesticide Exposure and Cancer Incidence in the Agricultural Health Study Cohort*, 118 ENVIRON. HEALTH PERSP. 8, 1117-25, 1123 (2010) ("Exposure misclassification undoubtedly had an impact on AHS findings reported to date."); Exh. 10, *Gray* at 57 ("Errors due to misclassification can produce bias towards the null (attenuation of the magnitude of a true positive or inverse association)[.]").

whether the cohort groups accurately reflect exposure.

2. Nonspecific Information Regarding the Use of Protective Equipment Creates Non-Differential Exposure Misclassification

Another source of exposure misclassification derives from the AHS's nonspecific data regarding the type of protective equipment used by participants when applying pesticides. The AHS questionnaire did not inquire about the use of protective equipment with respect to ***each*** pesticide – it only asked a general question about the degree of protection used for ***all*** pesticides. Exh. 6, AHS Private Applicator Questionnaire at 15; Exh. 5, AHS Commercial Applicator Questionnaire at 13; *accord* Exh. 13, Rider Supp. Dep. at 13:6-12; Exh. 25, Ritz Supp. Dep. at 58:12-18. Because the use of personal protective equipment directly affects exposure to glyphosate, *see* Exh. 13, Rider Supp. Dep. at 16:5-10, failure to account for the actual protective equipment worn leads to exposure misclassification because the participants are likely to overstate their use of protective equipment (the participants were seeking a restricted pesticide use license), and thus understate exposure when answering the question for all pesticides. Exh. 25, Ritz Supp. Dep. at 60:4-6.[12]

Specifically, the AHS used an intensity algorithm score ("Dosemeci algorithm") to calculate exposure for each participant. Because the algorithm assigns less exposure to applicators based on the reported use of protective equipment, accuracy of the intensity score necessarily depends upon the correct determination of the type of protective equipment used. And, because the questionnaires only asked participants what protective equipment they used *generally*, it is safe to assume that the intensity scores for GBFs are inaccurate; as noted above, all participants applied restricted use pesticides and were more likely to use protective equipment for pesticides perceived as more toxic but not for GBFs. *Id*. at 182:3-11 ("[Dosemeci]…is really a generic algorithm, meaning that they are using duration and frequency and weighing it according to the exact same weights for every pesticide. So if somebody reports the use of protective equipment,

[12] Importantly, neither Dr. Mucci, nor Dr. Rider, had a basic understanding of restricted use pesticides when they formulated their opinions. See Exh. 14, Mucci Supp. Dep at 38:25-39:3 ("Q. And what is a restricted use pesticide? A. I'm not familiar with that term. I'm not sure what they mean by that specifically."); Exh. 13, Rider Supp. Dep. at 15:24-16:10.

then that protective equipment is presumed to be used for every single pesticide.").[13] This failure to properly assess the type of protective equipment for each pesticide may explain why validation studies of the AHS show "***low to moderate correlations*** between exposure intensity algorithm scores and urinary biomarkers of … glyphosate[.]" Exh. 24, Weichenthal at 1123 (emphasis added); *see also* Exh. 26, Portier Supp. Dep. at 69:23-72:12. In fact, when Blair, *et al*. (2002) (Exh. 20) analyzed the accuracy of the duration and intensity of use scores from the AHS, "the agreement was 53 percent for glyphosate, meaning 47 percent --nearly half -- got it wrong." Exh. 25, Ritz Supp. Dep. at 122:6-10; Exh. 20, Blair (2002) at 96. Such systematic failures in estimating exposure means any analysis from the AHS data is flawed. Indeed, the Andreotti 2018 researchers acknowledge that "changing agricultural practices … and use of personal protective equipment, may impact actual exposure levels." Exh. 1, Andreotti at 7.

3. Dramatic Changes in Glyphosate Use During the AHS Resulted in Non-Differential Exposure Misclassification

GBF use increased substantially following the initial enrollment period of the AHS (1993-1997). *See* Exh. 27, Benbrook, C.M., *Trends in Glyphosate Herbicide Use in the United States and Globally* 28 ENVIRON. SCI. EUR. 1-15, 1, 6 (2016) ("Globally, glyphosate use has risen almost 15-fold since so-called 'Roundup Ready'…were introduced in 1996."). And, glyphosate use continues to increase exponentially. Dr. Ritz explains why this is a problem for the AHS:

> [T]he study would put an applicator into the 'no/low intensity use' group if he applied glyphosate only occasionally or not at all before adopting GMOs/glyphosate use in 1995 as long as he was enrolled and asked to report his use early i.e. in the period 1993-95. The exact same individual would be put into a 'high intensity use' group if asked to report the same use in 1996 or 1997 after he adopted GMOs. It is therefore likely that many high intensity glyphosate users were incorrectly grouped in the no or low intensity use groups.

Exh. 7, Ritz Supp. Rpt. at 5. The original AHS questionnaire was simply not designed to address this sudden increase in glyphosate use, which dramatically compounded the exposure misclassification throughout the AHS study, including Andreotti 2018. Exh. 28, Nabhan Supp. Dep. at 72:19- 73:2; *see* Exh. 15, Neugut Supp. Rpt. at 5.

Furthermore, Andreotti 2018 did not fix this problem by using the Phase 2 follow-up data

[13] This was also echoed by Acquavella (2006): "[The Dosemeci algorithm]…is limited because it ignores important pesticide specific physical; chemical properties that can greatly influence dose such as dermal penetration and vapor pressure." Exh. 23 at 73.

because the Phase 2 interview only asked about exposure *during the last year* of farming, leaving unanalyzed some 9-10 years of glyphosate exposure (between 1993 and 2002). Exh. 7, Ritz Supp. Rpt. at 6-7; Exh. 28, Nabhan Supp. Dep. at 73:3-7 ("So it's not constant. Everything is actually changing, but you're really asking question only for the year before – and you are doing this before the… significant increase in use of glyphosate."); Exh. 29, Weisenburger Supp. Dep. at 49:25-50:18 ("[I]n the first survey they could have been a non-user of glyphosate, and in the second survey they could have become a user of glyphosate, but you wouldn't know when they started using glyphosate."). Thus, people assigned to the "exposed" and "unexposed" groups may be completely inaccurate, injecting randomness into the study and, thus, obscuring associations. The researchers in Andreotti 2018 acknowledge "that these studies have been conducted in different time periods … changing product formulations or ***amounts used*** … may also impact results." Exh. 1, Andreotti at 7 (emphasis added).

B. Imputation Error

The AHS suffers from a large loss to follow up between enrollment and phase 2—20,968 participants (37%) of the cohort did not respond to the Phase 2 questionnaire. In an attempt to mitigate this shortage of data, "a multiple imputation procedure was used to impute pesticide use since enrollment." Exh. 1, Andreotti at 2. The imputation "bases its exposure guesses for non-responders on what is known about exposure levels for responders at both times (enrollment and at follow-up) and what is known about non-responders at enrollment." Exh. 7, Ritz Supp. Rpt. at 7. Apart from the fact that this approach does not cure the substantial misclassification of exposure for the 63% of participants who responded (discussed above), the model is based on assumptions that make it unreliable in the context of imputing results *for glyphosate*.

First, any imputation would use data that is *already* corrupted by virtue of the exposure misclassification, discussed above.

Second, Monsanto's reliance on sensitivity analyses conducted on the imputation method is misguided. *See* Exh. 30, Rider Supp. Rpt. at 4-5. Specifically, Drs. Rider and Mucci cite the

study by Heltshe, *et al*.[14] for the assertion that "imputed and reported pesticide exposure results are similar." Exh. 30, Rider Supp. Rpt. at 5; Exh. 32, Mucci Supp. Rpt. at 4. But, Heltshe, *et al*. merely assessed whether the imputation method properly estimated exposures for those participants that responded to the Phase 2 questionnaire. It did not, and could not, determine whether the exposure data for the 37% non-responders were similar to the 63% who did respond: "[t]hey can only use to predict from data they actually have; so we don't still know anything about the people for whom they don't have the follow-up data. They are just ***assuming that those people behaved in the same way*** as the people they have data for." Exh. 25, Ritz Supp. Dep. at 367:9-15, 368:25-369:1 (emphasis added).[15][16] Moreover, Heltshe, *et al*. revealed that the imputation method actually underestimated the prevalence for glyphosate by 17.8%, meaning the imputation method systematically underestimates exposure. Exh. 15, Neugut Supp. Rpt. at 11; Exh. 16, Weisenburger Supp. Rpt. at 2; Exh. 26, Portier Supp. Dep. at 78:12-14; *see* Exh. 13, Rider Supp. Dep. at 67:5-6 ("[I]t's underreporting the prevalence.").

Third, simply because Andreotti (2018) employed an imputation method previously used to impute data for *other* pesticides does not make it a reliable metric for imputing glyphosate data. This is because "pesticides that are not glyphosate have a very different misclassification structure from glyphosate…this imputation method does not take into account…***dramatically timed varying exposures***." Exh. 25, Ritz Supp. Dep. at 10:1-3, 27:21-24, 155:11-15 (emphasis added); Exh. 29, Weisenburger Supp. Dep. at 96:4-12 ("[F]or glyphosate … the use increased dramatically… It's impossible to capture that kind of information which is critical to a cohort study if you don't have adequate participation in the follow-up[.]").

C. The AHS Study Does Not Demonstrate a Protective Effect of Glyphosate

[14] Exh. 31, *Using Multiple Imputation to Assign Pesticide Use for Non-Responders in the Follow-up Questionnaire in the Agricultural Health Study*, 22 J. EXPO. SCI. ENVIRON. EPIDEMIOL. 409 (2012).

[15] Importantly, the imputation method in the AHS was not only employed to guess the prevalence of glyphosate but also to impute the *amount* used, whereas Heltshe's results, presenting "relative errors of imputed prevalence," only show the accuracy of *prevalence*, not amount. "That's the least you could do and the least piece of information you can have about this method actually working." Exh. 25, Ritz Supp. Dep. at 373:21-24.

[16] Heltshe, *et al* expressly acknowledged this limitation noting that "... missing at random is an untestable assumption without additional data; thus it is possible that no-responders differ from responders in variables we have not measured." Exh. 31 at 8.

Drs. Rider Mucci both claim in their reports that non-differential misclassification exposure in the AHS could not obscure a relative risk greater than 1.0. Exh. 30, Rider Supp. Rpt. at 4; Exh. 32, Mucci Supp. Rpt. at 3. These opinions are based on a faulty assumption that GBHs actually protect against NHL. However, Drs. Rider and Mucci both conceded at deposition that this assumption is not supportable. Exh. 14, Mucci Supp. Dep. at 61:2-8 ("I do not believe that, based on the epidemiological evidence in this study, nor in the totality of the epidemiology evidence, would it suggest either a positive or inverse association."); Exh. 13, Rider Supp. Dep. at 27:2-3 (same). ("I would not regard this as a protective association.").

Drs. Rider and Mucci also fail to account for other real-world conditions in this study (i.e., enormous loss to follow-up, random error, and residual confounding) which combine with nondifferential misclassification error to push the relative risk below 1.0 and obscure the true causal association between GBHs and NHL. Exh. 33, Jurek, *et al*., *Proper interpretation of non-differential misclassification effects: expectations vs. observations*, 34 INT. J. EPID. 680–687, 686 (2005) ("[D]ownward random error could easily combine with downward bias to produce large downward total error" which "can cause an observed relative-risk estimate to be less than one[.]"); *see also* Exh. 25, Dr. Ritz Supp. Dep. at 129:9-132:24; Exh. 17, Neugut Supp. Dep at. 128:15-129:2.

Importantly, in De Roos (2005), the researchers noted that there were significant socio-economic differences between people exposed and unexposed to glyphosate. Exh. 11, De Roos at 51. As these socio-economic differences could account for varying health outcomes, confounding the results, the researchers decided to compare lower exposed to higher exposed participants. *Id.* Andreotti 2018, however, departed from that approach and compared the "exposure response to ***unexposed*** cohort members[.]" Exh. 22, Portier Supp. Rpt. at 2 (emphasis added). This approach resulted in risk ratios below 1.0, suggesting glyphosate was protective against NHL. However, when Dr. Portier reanalyzed the results using the same method employed in De Roos (2005), the resulting risk ratios were all above 1.0. *Id*. ("[T]his study shows increased RRs for NHL relative to the lowest exposure group."); Exh. 26, Portier Supp. Dep. at 29:6-32:7 ("[I]t raises concern on my part about why [Andreotti, *et al*.] changed the

analysis method…There's no mention of a comparison demographically, socio-economically, between the controls and the treated groups[.]"). Dr. Ritz raised similar concerns, noting that the Andreotti (2018) method introduces the risk of residual confounding—the same residual confounding identified in De Roos (2005). Exh. 25, Ritz Supp. Dep. at 166:15-167:22; 83:18-23; *see* Exh. 11, De Roos at 51 ("[W]e 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." (emphasis added)). Both approaches (comparing high vs. low and exposed vs. unexposed) are problematic in the AHS, a fact noted by Dr. Ritz in her original expert report. Exh. 34, Ritz Rpt. at 23. However, the latter method (comparing exposed vs. unexposed) compounds existing exposure misclassification due to the effects of residual confounding, whereas the method employed in De Roos (2005) "reduces any remaining exposure contrasts even further and thus reduces the ability to estimate risks increases with exposure[.]" *Id.* So, regardless of which approach the researchers take, there will be inaccuracies due to the underlying problems with data collection and follow-up—problems neither De Roos (2005) nor Andreotti (2018) can correct. Put simply, the AHS is just too flawed.

CONCLUSION

Each of Plaintiffs' experts reviewed and considered Andreotti (2018), served a supplemental expert report, and sat for a second (or third) expert deposition. In doing so, each expert explained why Andreotti (2018) does not change or otherwise amend their opinion. As it stands, there is considerable reliable scientific evidence and testimony that GBF exposure can cause NHL.

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Respectfully submitted,

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ECF CERTIFICATION

Pursuant to Civil Local Rule 5-1(i)(3), the filing attorney attests that she has obtained concurrence regarding the filing of this document from the signatories to the document.

DATED: February 16, 2018

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

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