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November 14, 2017

Honorable Vince Chhabria
United States District Court
San Francisco Courthouse, Courtroom 4 - 17th Floor
450 Golden Gate Avenue
San Francisco, CA 94102

Re: In Re: Roundup Products Liability Litigation, MDL No. 2741
Response to Pretrial Order No. 33

Dear Judge Chhabria:

Plaintiffs respectfully submit this letter brief in response to Pretrial Order No. 33. Monsanto's defense of the epidemiology in this case asks the Court to ignore numerous studies showing a clear, statistically significant, elevated association between glyphosate exposure and NHL and focus exclusively on the data from the AHS study. Monsanto asks this Court to do this even though internal documents reveal that before the AHS produced the result Monsanto liked, numerous Monsanto employees and researchers roundly criticized AHS's design as being fundamentally flawed. Now, because an updated version of the AHS was published—which changes nothing relevant to the issues of general causation—Monsanto wants to the halt the *Daubert* process. For the reasons set forth below, Plaintiffs believe that (i) there is no basis to adjourn the December 11, 2017 *Daubert* hearing based on the online publication of the article *Glyphosate Use and Cancer Incidence in the Agricultural Health Study*, Journal of the National Cancer Institute[1] (November 2017 AHS Article); (ii) up to two supplemental reports for each party is sufficient to address the November AHS Study; (iii) there is no need for further depositions of those experts who submit supplemental reports as these experts have already been deposed regarding the substantive data in the now published November AHS Article[2]; however, if

[1] Gabriella Andreotti et al., *Glyphosate Use and Cancer Incidence in the Agricultural Health Study*, 110(5) J. NAT'L CANCER INST. (2018).

[2] The November 2017 Article is likely to be one of a series of articles published in the ensuing months that relate to the issues of this MDL. *See, e.g.*, note 2 below. Allowing additional depositions each time additional information is available creates undue burden on experts and unnecessary costs and results in protracted litigation. The Eighth Circuit Court of Appeals recognized that litigation should proceed uninterrupted even when new facts were learned during the trial to support an expert opinion: "that Dr. Ricca learned about [Plaintiff] Tedder's injury

depositions are permitted, they should be capped at one hour and via skype; and (iv) further briefing after the *Daubert* hearing regarding the potential impact of the November 2017 Article is appropriate if the Court requests such briefing necessary or useful. But because new articles are published periodically, litigation cannot be halted every time additional information becomes available.[3]

Finally, Plaintiffs' counsel is available for oral argument on December 20, 2017.

The November 2017 Article Does Not Alter the Experts' General Causation Findings

The November 2017 Article is, in essence, not "new." As a preliminary matter, the initial 2005 AHS publication and the 2013 AHS draft manuscripts show no positive association between glyphosate use and non-hodgkins lymphoma (NHL). The November 2017 Article again shows no association. The AHS's null finding has already been assessed and incorporated in Plaintiffs' expert analyses. Plaintiffs' expert Dr. Ritz set forth in detail the numerous methodological flaws of the AHS study that weaken the weight Monsanto attaches to its null findings; the various iterations of the AHS do not outweigh the studies supporting Dr. Ritz's overall opinion that glyphosate causes NHL. Thus, the November 2017 Article not only does not change Dr. Ritz's opinion, it was anticipated in her rebuttal report. And Monsanto has already questioned Dr. Ritz regarding her criticisms of the AHS study. Accordingly, the *Daubert* hearing should proceed as scheduled on December 11, 2017.[4]

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history at trial rather than from Tedder himself does not render Dr. Ricca's diagnosis unreliable. *See* Fed. R. Evid. 703 (permitting an expert to rely on data that he "has been made aware of" at trial). There is nothing to indicate that Dr. Ricca lacked sufficient time between cross-examination and redirect examination to competently assimilate Tedder's complete injury history into his diagnosis. Indeed, ARI acknowledges that Dr. Ricca modified his diagnosis to account for this new information." *Tedder v. Am. Railcar Indus., Inc.*, 739 F.3d 1104, 1109 (8th Cir. 2014).

[3] Apropos to this very issue, today a new study was released relating to in vitro genotoxicity of human leukocytes, including glyphosate: "Two of them, paraoxon and glyphosate, were found to produce both DSB and the phosphorylation of Ku80, a protein participating in the c-NHEJ recombinational repair pathway. These results are of importance since these effects occurred at low concentrations in an acute treatment to the cells. Effects over longer exposures in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time." Suarez-Larios et al., Screening of Pesticides with the Potential of Inducing DSB and Successive Recombinational Repair, Journal of Toxicology, https://doi.org/10.1155/2017/3574840 at p. 7. The article further states that "[t]his pathway [c-NHEJ] has been demonstrated to be the only one responsible for the formation of chromosomal translocations, of great concern in the development of leukemia, lymphoma, and secondary cancers." *Id.* While relevant to the Daubert hearing, the experts will be available to address the study's significance to their overall general causation opinion at the *Daubert* hearing and, if the Court requests, in post-*Daubert* hearing written submissions.

[4] The Daubert hearing has already been adjourned once before at the request of Monsanto. Curiously, Monsanto's counsel suggested at the November 9 court conference that Plaintiffs requested the earlier adjournment. That is not true: in response to PTO 23 Monsanto insisted, over Plaintiffs' strenuous objection, that the *Daubert* schedule be extended. *See* ECF No. 317. Monsanto should not be allowed to move the hearing once again on invalid grounds.

AHS Background

The AHS was a cohort study, started in 1993, designed to examine licensed restricted use pesticide applicators in two states—North Carolina and Iowa. Scientists criticized its design from its inception—even Monsanto scientists.[5] AHS's multiple flaws, which are not cured by the November 2017 Article, are summarized below and discussed in detail in Plaintiffs' Opposition to Monsanto's Daubert Motion (P. Opp.), ECF No. 647 at 29-35. Principal among those flaws is misclassification of exposure, i.e. miscategorizing participants as exposed to or unexposed to glyphosate, which was exacerbated by not properly accounting for the dramatic increase in Roundup use on genetically modified crops after they entered the market in 1996. *Id.* at 33.

The use of GBFs increased extraordinarily from the inception of the AHS study to the present. At initial enrollment, AHS participants were asked to report glyphosate usein the past decades (i.e. 1970s, 1980s, 1990s). In 1987, farmers and ranchers applied between six (6) and eight (8) million pounds of GBFs annually. *Id*. Ritz Rebuttal Rep. at 3. As of 2007 that number grew to between 180 – 185 million pounds of GBFs used annually. And as of 2014, GBF use had increased even further to 240 million pounds per year. *Id*. Stated another way, before 1996 and the advent of genetically modified seeds, GBFs accounted for 3.8% of total herbicide use by volume but by 2009 accounted for 53.3% of total agricultural use. *Id.* at note 96.

There were two follow up questionnaires to the original AHS questionnaire. Among the AHS cohort members from whom the AHS study requested updated information for the period 1998-2004, ***36% did not respond***. In the second follow-up survey, only 46%—***less than half***—of the study participants responded. Thus, over one-third of all cohort subjects never reported actual exposures or changes in exposures after initial enrollment in 1993 to 1997. *Id*. at 34. The November 2017 Article states that for these non-responders, "a data-driven multiple imputation procedure was used to impute pesticide use since enrollment." *Id*. at 2. Given that GBF use increased by 3,900% from 1993 to at least 2014, imputation of glyphosate use data for non-responders yields irrelevant and unreliable results to the instant litigation. A 2016 Exponent report commissioned by Monsanto and CropLifeAmerica, a pesticide industry group, acknowledged various flaws with the AHS, including that "only 44% of enrolled pesticide applicators completed the detailed take-home questionnaire shortly after enrollment, and participation in follow-up questionnaires was also highly incomplete," and multiple other flaws and biases of the study design. Pl. Opp. at 32. Dr. Ritz explains the flaw of imputation due to the low follow-up response rate of the AHS as follows:

> The AHS researchers attempted to address the loss of active participants with a method called 'imputation' to avoid having large amounts of missing exposure data – for those who did not respond – or generating selection bias (cohort studies may be affected by selection bias due to 'differential' loss to follow-up among the exposed or unexposed cases and controls). . . . This procedure assumes that it is sufficient to use the data in hand to predict/guestimate all future exposures in AHS participants who did not respond; i.e. that the past and current exposures and characteristics of the participants who responded to multiple interviews over time

[5] Monsanto's chief Toxicologist, Dr. Donna Farmer, stated that "[m]any groups have been highly critical of the [AHS] 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 questionnaire on pesticide usage and self reported [sic] diagnoses also from the questioneer [sic] is thought to be unreliable." Pl. Opp. at 31.

would accurately predict the use of those who did not respond. For glyphosate/GBFs with a use pattern change as dramatic as described above, it is a flawed approach to predict who would or would not start using Roundup Ready crops after baseline, and otherwise to predict the use of glyphosate/GBFs.

November 2017 Article

While the November 2017 Article was not published at the time of Dr. Ritz's rebuttal report and thus she was rebutting the unpublished draft AHS manuscripts in response to opinions offered by Monsanto's experts Drs. Rider and Mucci, Dr. Ritz's criticism of the methodology used as it applies to the draft manuscripts applies equally to the November 2017 study. *See* Ritz Rebuttal Rep. at 2-7; Pl. Opp. at 34-36. Specifically, the November 2017 Article does not resolve, or even address, the principal flaw Dr. Ritz identified: exposure misclassification. Monsanto's former lead epidemiologist, Dr. Aquavella, agreed with Dr. Ritz that the AHS would be plagued with exposure misclassification.[6] That flaw is exacerbated by the dramatic increase in GBF use.

In the first follow up with participants, the questionnaire asked a participant's history of use between 1993 and 1997; thus, participants who responded to the questionnaire would have included all GBF use up to the date of questionnaire completion. But for the second follow up with participants, the questionnaire did not ask "since we last asked you about your pesticide use what did you use every year for each identified pesticide." Such an inquiry would have filled the gap between enrollment and follow-up (1999-2005). Instead, the November 2017 Article states that "at follow-up applicators reported the number of days each pesticide was used *in the most recent year farmed*." November 2017 Article at 2. This creates a significant problem for assessing glyphosate exposures for the time between baseline (enrollment time 1993-1997) and the second interview (follow-up time 1999-2004). What is more, this is the very time period when exposures to glyphosate skyrocketed. Reporting only one year leaves unknown GBF use and exposure during up to nine years between baseline and follow-up.

The November 2017 Article applies the same methodology used in the 2014 AHS publication[7] as well as in the two 2013 AHS unpublished draft manuscripts.[8] In all instances, the imputation of data for non-responsive pesticide users follows the multiple imputation technique described in the publication *Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study*.[9] As Dr. Ritz explains in her

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[6] Prior to filing this letter brief, Plaintiffs counsel requested Monsanto's counsel to de-designate this one document by Dr. Aquavella. (MONGLY00885870-874). Monsanto's counsel refused even to engage in a discussion about its de-designation, arguing instead that paragraph 17 of the Court's standing order does not allow exhibits to be attached to letter briefs. Even though Plaintiffs' counsel noted that this submission is not a discovery dispute and thus paragraph 17 does not apply, Monsanto's counsel still refused to respond. To avoid filing this brief under seal, Plaintiffs do not attach the document but will do so if the Court wishes to see the actual document.

[7] Alavanja, M.C., et al., *Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study*, 9 PLOS One 10, October 2014.

[8] Blair Dep. Exs. 19a and 19b.

[9] *See* Heltsche, S., Lubin, J., Koutros, S., Coble, J., Ji, B., Alvanja, M., Blair, A., Sandler, D., Hines, C., Thomas, K., Barker, J., Andreotti, G., Hoppin, J., and Freeman, L., *Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study*, 22 J. EXPOSURE SCIENCE AND E'TAL EPIDEMIOLOGY 409-416 (2012).

rebuttal report (*see* Ritz Rebuttal Rep. at 4-5) and her deposition testimony (*see* Ritz Dep. at 354:24-395:16), application of imputation here is methodologically flawed because there is no adjustment for the significant increased use of glyphosate during the years of imputation. Simply put, use of the multiple imputation technique for glyphosate is improper given the fact that glyphosate saw a dramatic increase in use over the relevant years of the AHS, such that the non-response from 20,000 pesticide applicators substantially affects the imputation calculation.[10]

Dr. Ritz has already provided lengthy explanations for her opinions about the impropriety of imputation under the circumstances of the AHS. At her deposition, she responded to questions by Monsanto's counsel on this specific topic for approximately one hour. That testimony essentially addressed the inappropriateness of the imputation technique in this instance.[11] And as explained above, that testimony would apply equally to the November 2017 Article.

Dr. Blair, one of the principle investigators of the updated AHS study, was also questioned extensively by Monsanto's counsel about the updated AHS study results. Blair Dep. at 164:17-198:15. Dr. Blair acknowledged that the updated AHS study results were below 1.0. *Id.* at 192:19-22. However, he testified the significant problem in the AHS study due to loss of follow-up. *Id.* at 271:14-272:10. Dr. Blair agreed that exposure misclassification is a problem with cohort studies and that it "most likely causes false negatives." *Id.* at 88:16-89:2. In weighing the epidemiological studies, Dr. Blair stated that "I'm not sure I would say [the AHS] was the most powerful study." *Id.* at 285:25-286:25. Further, when comparing the negative AHS study with the multiple positive case-control studies, Dr. Blair concluded that glyphosate is a probable carcinogen associated with NHL. *Id.* at 265:7-25. Dr. Blair maintains this opinion even after considering the updated AHS data, data that is in all relevant respects the same data that appears in the November 2017 Article. *Id.* at 293:6-15.

Thus, because the methodology used in the November 2017 Article is already the subject of an expert rebuttal report and extensive questioning in this litigation, there is no need for a repeat deposition,[12] and there is certainly no basis for an adjournment of the *Daubert* hearing.

Nevertheless, while Plaintiffs believe that further deposition testimony is not necessary, they believe that supplemental reports would be useful to further explain why the November 2017 Article does not alter the general causation opinions of Plaintiffs' experts. Plaintiffs' experts will be able to submit supplemental reports by November 22, 2017. Monsanto's experts should be required to submit supplemental reports by November 30, 2017.

Respectfully submitted,

Robin Greenwald
Michael Miller
Aimee Wagstaff

[10] *See generally*, Ritz Rebuttal Report, 1-7.
[11] *See* Ritz Dep. at 349:6-395:16 (taking 53 minutes of tape).
[12] Similarly, Plaintiffs would not need to re-depose Monsanto's experts on the issue of imputation of data and the low response rate from pesticide applicators of the AHS. Monsanto's expert Dr. Mucci already testified that she finds the imputation method used by AHS studies appropriate. *See* Mucci Dep. at 274:18-275:10 Thus, both experts have offered their opinions, both in reports and in their deposition testimony, regarding the flaws of the AHS.