HOLLINGSWORTH LLP
Joe G. Hollingsworth (*pro hac vice*)
Eric G. Lasker (*pro hac vice*)
Martin C. Calhoun (*pro hac vice*)
Heather A. Pigman (*pro hac vice*)
1350 I Street, N.W.
Washington, DC 20005
Tel: 202-898-5800
Fax: 202-682-1639
Email: jhollingsworth@hollingsworthllp.com
elasker@hollingsworthllp.com
mcalhoun@hollingsworthllp.com
hpigman@hollingsworthllp.com

Attorneys for Defendant
MONSANTO COMPANY

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	**Hearing Date: December 11, 2017** **Time: 9:00 a.m.**

MONSANTO COMPANY'S NOTICE OF MOTION AND *DAUBERT* AND SUMMARY JUDGMENT MOTION BASED ON FAILURE OF GENERAL CAUSATION PROOF

TO ALL PLAINTIFFS AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that beginning on December 11, 2017, at 9:00 a.m., in Courtroom 4 of the United States District Court, Northern District of California, located at 450 Golden Gate Avenue, San Francisco, CA 94102, or as ordered by the Court, Defendant Monsanto Company ("Monsanto") will present its *Daubert* and Summary Judgment Motion Based on Failure of General Causation Proof.

Monsanto seeks an order excluding plaintiffs' general causation expert witnesses (retained and non-retained witnesses) under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and granting summary judgment for Monsanto in all Roundup® lawsuits

pending before this Court based on plaintiffs' failure to present sufficient admissible evidence to prove general causation.

DATED: October 6, 2017

Respectfully submitted,

/s/ Joe G. Hollingsworth

Joe G. Hollingsworth (*pro hac vice*)
(jhollingsworth@hollingsworthllp.com)
Eric G. Lasker (*pro hac vice*)
(elasker@hollingsworthllp.com)
Martin C. Calhoun (*pro hac vice*)
(mcalhoun@hollingsworthllp.com)
Heather A. Pigman (*pro hac vice*)
(hpigman@hollingsworthllp.com)
HOLLINGSWORTH LLP
1350 I Street, N.W.
Washington, DC 20005
Telephone: (202) 898-5800
Facsimile: (202) 682-1639

Attorneys for Defendant
MONSANTO COMPANY

HOLLINGSWORTH LLP
Joe G. Hollingsworth (*pro hac vice*)
Eric G. Lasker (*pro hac vice*)
Martin C. Calhoun (*pro hac vice*)
Heather A. Pigman (*pro hac vice*)
1350 I Street, N.W.
Washington, DC 20005
Tel.: (202) 898-5800
Fax: (202) 682-1639
Email: jhollingsworth@hollingsworthllp.com
elasker@hollingsworthllp.com
mcalhoun@hollingsworthllp.com
hpigman@hollingsworthllp.com

Attorneys for Defendant
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This document relates to: ALL ACTIONS	**Hearing Date: December 11, 2017** **Time: 9:00 a.m.**

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MONSANTO COMPANY'S *DAUBERT* AND SUMMARY JUDGMENT MOTION BASED ON FAILURE OF GENERAL CAUSATION PROOF

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ISSUES TO BE DECIDED

I. Whether plaintiffs have satisfied their burden to present expert testimony that is scientifically reliable and relevant within the meaning of *Daubert* and that is sufficient to prove general causation, *i.e.*, "whether there is sufficient admissible evidence that glyphosate and/or Roundup is capable of causing cancer (specifically, Non-Hodgkin's Lymphoma ["NHL"]) in humans." Pretrial Order 15 (filed Mar. 3, 2017), ECF No. 186.

II. Whether plaintiffs' failure to present sufficient admissible expert testimony to prove general causation entitles Monsanto Company ("Monsanto") to summary judgment in all Roundup® lawsuits pending before this Court.

INTRODUCTION

As Justice Breyer stated, the essential gatekeeping role bestowed on district courts in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), ensures that "the powerful engine of tort liability . . . points toward the right substances and does not destroy the wrong ones." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 148-49 (1997) (Breyer, J., concurring). The *Daubert* trilogy – *Daubert*, *Joiner*, and *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999) – "shift[ed] the focus to the kind of empirically supported, rationally explained reasoning required in science, [which] has greatly improved the quality of the evidence upon which juries base their verdicts." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "Under *Daubert*, the trial court must act as a 'gatekeeper' to exclude junk science that does not meet Federal Rule of Evidence 702's reliability standards by making a preliminary determination that the expert's testimony is reliable." *Ellis v. Costco Wholesale Corp.*, 657 F.3d 970, 982 (9th Cir. 2011).

In this case, plaintiffs' expert witnesses present speculation and self-selected bits of data, offer subjective opinions, and selectively parrot third-party "conclusions" in a transparent effort to side-step their obligations to demonstrate reliable methodologies of their own. Plaintiffs designated six retained experts, with specialties designated by plaintiffs' counsel as follows: Dr. Alfred Neugut ("Epidemiology"), Dr. Beate Ritz ("Epidemiology"), Dr. Christopher Portier ("Toxicology"), Dr. Charles Jameson ("Toxicology"), Dr. Chadi Nabhan ("Oncology and

NHL"), and Dr. Dennis Weisenburger ("Pathology and NHL"). Letter from Robin Greenwald to Heather Pigman (May 16, 2017) (Hollingsworth Decl., Ex. 1) ("5/16/17 Letter"). Plaintiffs also designated Dr. Aaron Blair (epidemiology) and Dr. Matthew Ross (mechanistic data) as non-retained experts. These experts collectively piece together an evidence trail which they say supports their opinion that glyphosate indeed causes NHL in humans.

Plaintiffs' experts' opinions stand in stark contrast to decisions repeatedly and consistently reached over a period of 40 years by regulatory agencies worldwide – including the United States Environmental Protection Agency ("EPA") and those similarly tasked with human health and environmental protection in Canada, Australia, New Zealand, Korea, Japan, and the European Union. ***Every*** major regulatory agency charged with answering the question has, with the benefit of all the available primary data, concluded that glyphosate is ***not*** likely to pose risks of carcinogenicity, including NHL, in humans.[1] Non-regulatory bodies concerned with public health have reached the same conclusions.[2] Plaintiffs' experts endorse the sole outlying assessment reported by a working group of the self-governing International Agency for Research on Cancer ("IARC").[3] This working group: (1) was chaired by Dr. Blair, who admits

[1] *See, e.g.*, EPA Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential* at 140 (Sept. 12, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0094 ("EPA OPP") ("strongest support is for 'not likely to be carcinogenic to humans' at the doses relevant to human health risk assessment"); European Food Safety Authority, *Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate*, 13(11) EFSA J. 4302 at 11 (2015), http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4302/epdf ("EFSA 2015") ("glyphosate is unlikely to pose a carcinogenic hazard to humans"); European Chemicals Agency, *Opinion Proposing Harmonized Classification and Labelling at EU Level of glyphosate (ISO); N-(phosphonomethyl) glycine* at 31 (Mar. 15, 2017), https://echa.europa.eu/documents/10162/2d3a87cc-5ca1-31d6-8967-9f124f1ab7ae ("based on the epidemiological data as well as on data from long-term studies in rats and mice … no hazard classification for carcinogenicity is warranted for glyphosate"); New Zealand EPA, *Review of the Evidence Relating to Glyphosate and Carcinogenicity* at 16 (Aug. 11, 2016), http://www.epa.govt.nz/Publications/EPA_glyphosate_review.pdf ("The overall conclusion is that … glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification … as a carcinogen or mutagen.").

[2] *E.g.*, Joint Management of Pesticide Residues, *Pesticide residues in food – 2004, Joint FAO/WHO Meeting on Pesticide Residues* at 158 (2006), http://apps.who.int/iris/bitstream/10665/43624/1/9241665203_eng.pdf, ("JMPR") ("In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.").

[3] IARC, *Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos, Monograph Vol. 112 on the Evaluation of Carcinogenic Risks*

to hiding epidemiology data that shows no increased risk of NHL attributable to glyphosate; (2) included Dr. Portier, who at the time worked for an environmental activist group opposed to the use of pesticides, Dep. of Christopher Portier 26:9-18 (Sept. 5, 2017) (Hollingsworth Decl., Ex. 2) ("Portier Dep."), and already was engaged by Plaintiffs' counsel in other litigation connected to an IARC review, *id.* 75:14-77:2; and (3) reached its conclusion during a week-long meeting that considered five total compounds, without its members reviewing published primary long-term rodent bioassay data or many of the valid regulatory mechanistic studies.[4]

Monsanto recognizes that neither the extraordinary catalog of regulatory agencies' decisions nor IARC's surprising conclusions can or should substitute for the analysis required by *Daubert*. However, it is clear that in bootstrapping IARC's methodology and then embracing it as their own, each of plaintiffs' experts employ a hazard assessment methodology (which is a "first step" that does not take into account a variety of important scientific factors, such as human relevance, in hypothesizing about causation);[5] this fails *Daubert* because they have applied a "*threshold of proof*" that is "*lower than that appropriate in tort law*." *Johnson v. Arkema, Inc.*, 685 F.3d 452, 464 (5th Cir. 2012) (emphasis in original) (quoting *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996)). Indeed, three of plaintiffs' experts (Drs. Jameson, Neugut, and Nabhan) admit they ***only*** performed hazard assessments;[6] their opinions

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to Humans (2015), http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-10.pdf ("IARC Monograph 112").

[4] *See infra* at n.21 (Dr. Blair's decision to hide data); Portier Dep. 29:23-30:17 (work for Environmental Defense Fund); *infra* at 29 (limitations of IARC review).

[5] IARC intends its hazard assessment methodology to be only a "first step" in assessing the carcinogenic potential of a compound. IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Preamble* at 2 (Jan. 2006), http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf ("IARC Preamble"). A hazard assessment finding that a compound is "probably carcinogenic" in fact has "no quantitative significance." IARC Preamble at 22. Thus, IARC classifies a wide variety of commonly-used substances and exposures as "carcinogenic" or "probably carcinogenic" to humans, including bacon, hot dogs, and red meat; alcoholic beverages; salted fish; shiftwork; frying food; and certain hot beverages. IARC, *Agents Classified by the IARC Monographs, Volumes 1-119*, 1, 16, 29, 30, 31, 35 (June 28, 2017), https://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf; *see* Monsanto Company's Brief Regarding the Relevance of IARC and EPA to General Causation (Feb. 8, 2017), ECF No. 134.

[6] *See, e.g.*, Dep. of Alfred Neugut 254:22-256:14 (Aug. 7, 2017) (Hollingsworth Decl., Ex. 3) ("Neugut Dep.") ("[I] tried to adhere to their [IARC's] criteria and methodologies for establishing, I guess what I would consider to be public policy, as well as judgments with regard

should be excluded on this basis alone. *Id.*

Plaintiffs' experts relied on three categories of evidence (epidemiology studies, rodent carcinogenicity data, and data from mechanism studies), but the general causation opinions that they cobbled together fail to satisfy *Daubert* – no matter what methodology they claim to apply – because the opinions are not the product of reliable science and do not have a valid scientific connection to the pertinent inquiry at issue here. The examples of these flaws are many:

- they rely on epidemiological data that lacks statistical significance and/or is not properly controlled for known confounding variables, which violates bedrock principles of both epidemiology and *Daubert*, *infra* at 15-21;
- they rely on untested statistical methodologies to interpret animal carcinogenicity data, changing such methodologies over time in a blatant results-driven approach, *infra* at 24-29;
- they selectively chose to include or exclude data in any given statistical analysis, thereby ultimately applying different tests in different situations, again solely to achieve a pre-conceived result that supports their opinions, *infra* at 26-27;
- they improperly extrapolate data from animal tests to human risk, without any citation to any literature or support for said extrapolation, *infra* at 21-23, 29-30;
- they completely ignore relevant human exposure levels in their analyses despite recognizing their importance in any risk or causation assessment, *infra* at 5, 29-30, 34-35; and
- their opinions have never been published, tested, peer-reviewed or generally accepted outside the confines of this litigation, confirming they were created solely for litigation, *infra* at 23, 26-28, 35, 38-39.

Any one of these flaws is sufficient to exclude plaintiffs' experts; collectively they demand exclusion. Since plaintiffs' experts' opinions "are no more than educated guesses dressed up in evening clothes," they fail to satisfy *Daubert*. *Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1407 (D. Or. 1996).

BACKGROUND OF GLYPHOSATE AND GLYPHOSATE-BASED HERBICIDES

Glyphosate-based herbicides ("GBHs") became commercially available in 1974 when Monsanto introduced Roundup®, a mixture of glyphosate and surfactants (chemical compounds commonly found in products such as soaps that allow glyphosate to travel on the surface of the weed to growing areas). In the forty years since its initial registration, a robust scientific

to this issue"); Dep. of Chadi Nabhan 257:7-258:22 (Aug. 23, 2017) (Hollingsworth Decl., Ex. 4) ("Nabhan Dep.") (describing application of hazard assessment methodology); Expert Report of Charles Jameson *passim* (Hollingsworth Decl., Ex. 5) ("Jameson Report") (stating that he conducted a hazard assessment at least 15 times); Dep. of Charles Jameson *passim* (Sept. 21, 2017) (Hollingsworth Decl., Ex. 6) ("Jameson Expert Dep.") (describing his methodology as hazard assessment at least 43 times).

database has developed for glyphosate and GBHs, including multiple published human population studies (epidemiology), over a dozen long-term rodent carcinogenicity bioassays, and hundreds of mechanistic studies.[7]

It is undisputed that the bioavailability of glyphosate is extremely low, meaning that very little of the chemical is absorbed and circulated in the human system.[8] Even the heaviest users of GBHs absorb relatively small systemic doses from all possible routes of exposure. For example, the Farm Family Exposure Study evaluated urinary concentrations for farmers and their families, with urine samples taken the day before, the day of, and for three days after a GBH application.[9] The authors found that "the highest estimated systemic dose was 0.004 mg/kg." *Id.* No comparable dose is considered clinically meaningful to human health by any regulatory entity; for example, "[n]one of the systemic doses estimated in this study approached the [EPA] reference dose [which includes a hundred-fold safety factor] for glyphosate of 2 mg/kg/day." *Id.*

Plaintiffs' allegations are based only on dermal exposure. *See* Transcript of Proceedings at 10 (Feb. 24, 2017) (Hollingsworth Decl., Ex. 7). Yet GBHs are "poorly absorbed dermally" and contribute minimally (if at all) to a hypothetical systemic dose. EPA Reregistration Eligibility Decision (RED) Glyphosate at 21 (Sept. 1993), https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf ("EPA RED"). "Dermal penetration has also been shown to be relatively low for human skin (<1%), indicating dermal exposure will only contribute slightly to a systemic biological dose." EPA OPP at 15. Approximately 90% of what remains is eliminated in urine within 6 hours.[10]

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[7] *See* EPA OPP at 130 ("A large database is available for evaluating the carcinogenicity potential of glyphosate."); EFSA 2015 at 10 ("The glyphosate dossier consists of an exceptionally large database, therefore the toxicological evaluation … rel[ies] on a magnitude of valid studies rather than on one 'key study' for each endpoint."). Many of these studies were conducted by independent investigators neither working with nor funded by Monsanto.

[8] *See* EPA OPP at 15 (glyphosate's oral, inhalation, and dermal exposure profile "suggests that there is low potential for a sustainable biological dose following glyphosate exposure.").

[9] *See* J. Acquavella et al., *Glyphosate Biomonitoring for Farmers and Their Families: Results from the Farm Family Exposure Study*, 112 Envtl. Health Persp. 321, 321 (2004).

[10] P. Chan et al., *NTP Tech. Report on Toxicity Studies of Glyphosate Administered in Dosed Feed to F344/N Rats and B6C3F1 Mice*, 16 Toxicity Reports Series at 18 (1992), https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox016.pdf (describing rapid elimination).

BACKGROUND REGARDING NON-HODGKIN'S LYMPHOMA

NHL is a highly diverse group of blood cancers classified into more than 60 distinct subtypes. Collectively, NHL is the seventh most common cancer and adults have approximately a 2.1% chance of developing NHL during their lifetimes. The cause of most NHL cases is not known. There are, however, several established risk factors that may increase a person's likelihood of developing the disease. Aging is an important risk factor. People with autoimmune disease, acquired immunodeficiencies (HIV/AIDS), and organ transplant recipients have an elevated risk for NHL. External factors that suppress the immune system (*i.e.*, chemotherapy or treatments for autoimmune diseases) may contribute to NHL's development. Viral infections, such as Hepatitis C, also play a role.[11]

Farming also has long been considered a potential risk factor for NHL, with several epidemiology studies showing a small but statistically significant increased risk. *See* M. Alavanja et al., *Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study*, 9 PLoS One 1 (2014). Scientists identified this potential risk factor, and many of the studies were undertaken, ***before*** the introduction of GBHs. *See, e.g.*, K. Cantor et al., *Pesticides and Other Agric. Risk Factors for Non-Hodgkin's Lymphoma Among Men in Iowa and Minn.*, 52 Cancer Res. 2447, 2448 Table 2 (1992) (farmers who ceased farming between 1950-69 had a statistically significant increased risk of NHL). Multiple hypotheses, including by some of plaintiffs' experts, have been raised to explain this positive association, including exposure to diesel fumes from farming equipment, farm animals, UV rays, and a range of other pesticides, herbicides, and insecticides.[12]

[11] *See generally* NIH, *Cancer Stat Facts: Non-Hodgkin Lymphoma*, https://seer.cancer.gov/statfacts/html/nhl.html; NIH, Adult NHL Treatment, https://www.cancer.gov/types/lymphoma/patient/adult-nhl-treatment-pdq#section/all; Leukemia & Lymphoma Society, NHL, https://www.lls.org/lymphoma/non-hodgkinlymphoma?src1=20045&src2=.

[12] *See* A. Blair et al., *Epidemiologic Studies of Cancer in Agric. Populations: Observations and Future Directions*, 14 J. Agromedicine 125, 128 (2009). These hypotheses implicate exposure to a plethora of agricultural chemicals other than GBHs, including atrazine, carbaryl, lindane, 2,4-D, and chlorophenols. *See id.* at 127-28; D. Weisenburger, *An Epidemic of Non-Hodgkin's Lymphoma: Comments on Time Trends, Possible Etiologies, and the Role of Pathology*, 5 Mod. Pathol. 481 (1992).

STANDARDS GOVERNING ADMISSIBILITY OF EXPERT TESTIMONY

In *Daubert*, the Supreme Court addressed the admissibility of expert testimony and established "the exacting standards of reliability such evidence must meet." *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000). Even where a party retains an apparently well-credentialed witness, "the trial court's gatekeeping function requires more than simply taking the expert's word for it." Fed. R. Evid. 702 advisory committee's note (2000 amendment). Stated differently, "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Joiner*, 522 U.S. at 146 (rejecting causation opinion based on non-statistically significant epidemiology and animal studies that plaintiffs' experts could not reliably extrapolate to humans). Instead, courts are required to ensure that an expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152. A court resolves a *Daubert* challenge as a "preliminary" admissibility question under Federal Rule of Evidence 104(a), *see Daubert*, 509 U.S. at 592 & n.10 (quoting Rule 104(a)); thus the proponent of the testimony does not benefit from any inferences in its favor. Moreover, the burden is affirmative and cannot be carried by mere attacks on the opposing side. *See, e.g.*, *Caraker v. Sandoz Pharm. Corp.*, 188 F. Supp. 2d 1026, 1034 (S.D. Ill. 2001) ("Plaintiffs' experts' broad criticisms of the existing epidemiological evidence do[] not help them meet their burden," as "plaintiffs' burden is an affirmative one, not served by such attacks.").

As the proponents of the expert testimony at issue here, plaintiffs have the burden of proving that it is admissible under *Daubert* and its progeny. *See, e.g.*, *Daubert*, 509 U.S. at 592 n.10; *Bldg. Indus. Ass'n v. Wash. State Bldg. Code Council*, 683 F.3d 1144, 1154 (9th Cir. 2012). This burden requires plaintiffs to make three kinds of showings.

First, plaintiffs must establish that the witness has the "knowledge, skill, experience, training, or education," Fed. R. Evid. 702, to render an opinion on the specific issue addressed by his testimony. *See Avila v. Willitts Envtl. Remediation Trust*, 633 F.3d 828, 839 (9th Cir. 2011) (affirming exclusion of toxicology opinions of doctor with degrees in chemistry).

Second, plaintiffs must establish scientific reliability – *i.e.*, that the expert's testimony is "ground[ed] in the methods and procedures of science," not "subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 589-90 (quotation marks omitted); *see* Fed. R. Evid. 702 (requiring that expert testimony be "based on sufficient facts or data" and "the product of reliable principles and methods" and that the expert "has reliably applied the principles and methods to the facts of the case"). The *Daubert* Court identified four non-exhaustive factors for courts to consider when evaluating scientific reliability: (1) whether the expert's theory can be and has been tested, because "[s]cientific methodology today is based on generating hypotheses and testing them to see if they can be falsified;" (2) whether the theory "has been subjected to peer review and publication" because "submission to the scrutiny of the scientific community is a component of 'good science;'" (3) the known or potential error rate of the expert's technique; and (4) whether the theory has attained "general acceptance" in the scientific community. *Daubert*, 509 U.S. at 593-94. As the Ninth Circuit stated, "we must determine nothing less than whether the experts' testimony reflects 'scientific knowledge,'" *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1315 (9th Cir. 1995) ("*Daubert II*") (quoting *Daubert*, 509 U.S. at 590), and "something doesn't become 'scientific knowledge' just because it's uttered by a scientist," *id.* at 1315-16. "Under *Daubert*, any step that renders the analysis unreliable . . . renders the expert's testimony inadmissible. This is true whether the step completely changes a reliable methodology or merely misapplies that methodology." *Mitchell v. Gencorp Inc.*, 165 F.3d 778, 782 (10th Cir. 1999) (internal quotation omitted) (ellipsis in original); *Burst v. Shell Oil Co.*, 650 F. App'x 170, 174 (5th Cir. 2016) (same) (quotation omitted).

Third, plaintiffs must satisfy the "fit" requirement by establishing that the expert's testimony assists the trier of fact by having "a valid scientific connection to the pertinent inquiry." *Daubert*, 509 U.S. at 591-92. "*Daubert* stressed the importance of the 'fit' between the testimony and an issue in the case." *Daubert II*, 43 F.3d at 1320. The "fit" requirement is directed to ***scientific*** relevance and "is more stringent than the relevancy requirement of [FRE 402], reflecting the special dangers inherent in scientific expert testimony." *FTC v. Wellness Support Net., Inc.*, Case No. 10-cv-04879-JCS, 2013 WL 5513332, at *9 (N.D. Cal. Oct. 4,

2013) (internal quotation omitted); *see Daubert II*, 43 F.3d at 1321 n.17 (same).

A crucial component of "fit" in product liability litigation is that general causation must be assessed at human-relevant doses. As Judge Breyer has stated, "dose matters" in *Daubert* assessments, particularly where, as here, "all of plaintiffs' experts … agree that there is a dose effect."[13] *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1174 (N.D. Cal. 2007).[14] In *In re Hanford Nuclear Reservation Litigation*, the Ninth Circuit explained fit in the context of the general causation inquiry as "whether exposure to a substance for which a defendant is responsible, such as radiation ***at the level alleged by the plaintiffs***, is capable of causing a particular injury or condition in the general population." 292 F.3d 1124, 1133 (9th Cir. 2002) (emphasis added). Thus, only real-world exposure levels are "relevant to the task at hand," *Daubert*, 509 U.S. at 597 – here, assessing whether exposure to GBHs can cause NHL.

[13] *E.g.*, Amended Expert Report of Christopher Portier at 22-51 (Hollingsworth Decl., Ex. 8) ("Portier Amended Report") (identifying various "dose-related trends"); Jameson Report at 21-29 (same); Expert Report of Beate Ritz at 23 (Hollingsworth Decl., Ex. 9) ("Ritz Report") (dose response observed in epidemiology studies); Expert Report of Chadi Nabhan at 21 (Hollingsworth Decl., Ex. 10) ("Nabhan Report") ("Dose response effect is seen in some case-control studies"); Expert Report of Alfred Neugut at 22 (Hollingsworth Decl., Ex. 11) ("Neugut Report") (epidemiology studies "suggest that there is a dose-response relationship"); Expert Report of Dennis Weisenburger at 4 (Hollingsworth Decl., Ex. 12) ("Weisenburger Report") ("dose-response effect was evaluated" in epidemiology studies).

[14] *See also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (11th Cir. 2005) ("Often low dose exposures – even for many years – will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage.") (quotation marks omitted); *Myers v. U.S.*, No. 02CV1349-BEN, 2014 WL 6611398 at *46 (S.D. Cal. Nov. 20, 2014) (The fact that thallium was present in plaintiff's urine "is a *non sequitur*. It is not the presence of thallium, it is the dose that matters."); *In re Zicam Cold Remedy Mktg., Sales Practices & Prod. Liab. Litig.*, 797 F. Supp. 2d 940, 945-46 (D. Ariz. 2011) ("In order to explain how a pervasive substance is harmful, one must show that at a particular level of exposure, the substance becomes toxic. Without requiring this kind of evidence, the door is open to meritless claims based on generally harmless levels of exposure."); *Young v. Burton*, 567 F. Supp. 2d 121, 128-29 (D.D.C. 2008) (under *Daubert*, "scientific knowledge of the harmful level of exposure to a chemical, plus knowledge that the plaintiff was exposed to such quantities, are minimal facts necessary to sustain the plaintiff's burden in a toxic tort case"); *Pluck v. BP Oil Pipeline Co.*, 640 F.3d 671, 679 (6th Cir. 2011) (same); *Wintz v. Northrop Corp.*, 110 F.3d 508, 513 (7th Cir. 1997) (same); *Allen*, 102 F.3d at 199 (same); *Wright v. Williamette Indus., Inc.*, 91 F.3d 1105, 1106 (8th Cir. 1996) (same).

ARGUMENT

I. PLAINTIFFS HAVE FAILED TO SATISFY THEIR BURDEN OF PRESENTING ADMISSIBLE EXPERT TESTIMONY TO PROVE GENERAL CAUSATION.

To admit plaintiffs' general causation experts' opinions here, the Court "would have to make several scientifically unsupported 'leaps of faith' . . . [but] [t]he *Daubert* rule requires more." *Rider*, 295 F.3d at 1202. Therefore, and as discussed below, the Court should exclude plaintiffs' experts' general causation opinions in each of the three relevant scientific disciplines.

A. Plaintiffs' Experts' Results-Driven Methodologies Do Not And Cannot Reliably Account For The Enormous, Consistent, And Important Body Of Negative Epidemiology That Does Not Support Their General Causation Opinions.

"Epidemiology … is generally considered to be the best evidence of causation in toxic tort actions." *Id*. at 1198; *Lopez .v Wyeth-Ayerst Lab.*, No. C 94–4054 CW, 1996 WL 784566, at *3 (N.D. Cal. Dec. 13, 1996) (citing *Brock v. Merrell Dow Pharm., Inc*., 874 F.2d 307, 313 (5th Cir. 1989), *as modified* 884 F.2d 116 (5th Cir.1989) ("While we do not hold that epidemiologic proof is a necessary element in all toxic tort cases, it is certainly a very important element. This is especially true when the only other evidence is in the form of animal studies of questionable applicability to humans.")), *aff'd*, 139 F.3d 905 (9th Cir. 1998). Epidemiologic studies measure "the strength of an association between exposure and disease" by calculating ratios ("relative risks" or "odds ratios") comparing individuals with or without an exposure in relation to a disease outcome. *Caraker*, 188 F. Supp. 2d at 1031. A risk ratio of 1.0 "suggests that there is no association between a product and the disease." *In re Bextra*, 524 F. Supp. 2d at 1173; *see also Caraker*, 188 F. Supp. 2d at 1031-32. Ratios above 1.0 can suggest a positive association (and below 1.0 can suggest a negative association) but "[b]efore any inferences are drawn about causation, the possibility of other reasons for the association must be examined, including chance, biases . . . , and confounding causes." *Nelson v. Tenn. Gas Pipeline Co.*, 243 F.3d 244, 253 (6th Cir. 2001). In other words, statistical significance and proper controls are key to any epidemiological analysis.

Regarding statistical significance, epidemiologists account for chance by calculating a "confidence interval" around a point estimate of relative risk. As Judge Breyer has explained:

> [I]f a given study show[s] a relative risk of 1.40 (a 40[%] increased risk of adverse events), but the 95[%] confidence interval is .8 to 1.9, we would say that we are 95 [%] confident that the true value, that is, the actual relative risk, is between .8 and 1.9. Because the confidence interval includes results which do not show any increased risk, and indeed, show a decreased risk, that is, it includes values less than 1.0, we would say the study does not demonstrate a "statistically significant" increased risk of an adverse outcome.

In re Bextra, 524 F. Supp. 2d at 1174; *In re Zoloft Prods. Liab. Litig.*, 858 F.3d 787, 793 (3d Cir. 2017) (statistical significance is "an important metric to distinguish between results supporting a true association and those resulting from mere chance"). Regarding proper controls, an epidemiologic study cannot provide evidence of general causation unless "[it] properly accounts for potential confounding factors," *i.e.*, other exposures that might be the true explanation for a reported association. *In re Bextra*, 524 F. Supp. 2d at 1172.[15]

A plaintiff seeking to prove general causation absent statistically significant associations proven through epidemiology, as here, faces "a high bar . . . with respect to the [*Daubert*] reliability requirement." *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001) (excluding epidemiology opinions lacking statistically significant support), *aff'd*, *Rider*, 295 F.3d 1194. Plaintiffs' experts cannot overcome that bar.[16] Indeed, as plaintiffs' expert Dr. Neugut concedes, there is no pesticide-adjusted odds ratio ***anywhere in the***

[15] *See* M. Green et al., *Reference Guide on Epidemiology*, *in Reference Manual on Scientific Evidence* 549, 591-93 (3d ed. 2011), https://www.fjc.gov/sites/default/files/2015/SciMan3D01.pdf ("*Reference Manual*"). Epidemiologists can attempt to control for confounding by conducting statistical analyses. Dep. of Beate Ritz 163:2-17 (Sept. 18, 2017) (Hollingsworth Decl., Ex. 13) ("Ritz Dep.").

[16] Three of plaintiffs' retained experts – Dr. Jameson (chemist/toxicologist), Dr. Portier (toxicologist), and Dr. Nabhan (oncologist) – are not qualified to render epidemiology-based opinions because they do not have the requisite specialized knowledge or experience, *see* 5/16/17 Letter, as a review of their CVs confirms. Dr. Jameson was involved in the IARC Working Group animal subgroup, Fact Dep. of Charles Jameson 139:4-14 (May 3, 2017) (Hollingsworth Decl., Ex. 14) ("Jameson Fact Dep."), but a different subgroup addressed epidemiology, *id*. 138:19-24, and he did not attend those discussions, *id*. 301-21:22. Dr. Nabhan readily admits that he has never been an epidemiologist. Nabhan Dep. 20:25-21:2. Plaintiff's non-retained expert Dr. Ross (chemist and molecular toxicologist) also lacks epidemiology expertise. He does primarily "bench research" on animals – "[i]n test tubes [and] Petri dishes" – which "is not epidemiological research." Dep. of Matthew Ross 12:13-14:19 (May 3, 2017) (Hollingsworth Decl., Ex. 15) ("Ross Dep."). The Court should preclude these four witnesses from presenting epidemiology opinions. *See Avila*, 633 F.3d at 839 (witness excluded because he lacked expertise relevant to opinion that he sought to present); *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 571 (W.D. Pa. 2003) (same).

epidemiologic literature that reports a statistically significant positive association between glyphosate and NHL. Neugut Dep. 158:23-159:6; *see also id.* 45:14-18 (agreeing that one "would not label an exposure as being associated with an outcome unless there is a finding of an increased risk that is statistically significant").[17]

1. The most reliable epidemiology evidence – a major, ongoing prospective cohort study controlling for exposures to other pesticides – does not find any association between exposure to GBHs and NHL.

The glyphosate epidemiologic literature is comprised of cohort (prospective) and case-control (retrospective) studies. As Dr. Neugut explains, cohort studies are "generally preferred," as they are "more naturalistic," "because the people are unbiased at the beginning of the study when you get your data." Neugut Dep. 72:1-10, 73:17-74:9.

Here, powerful prospective cohort epidemiology, the "Agricultural Health Study" ("AHS"), exists – and finds no association between GBHs and NHL. AHS is funded by the U.S. government. Neugut Dep. 121:8-14. A 2005 report presented data for over 50,000 pesticide applicators, including 92 who developed NHL. *See* De Roos 2005 at 49, 51 (Table 2).[18] The authors reported that their data "provided ***evidence of no association between glyphosate exposure and NHL incidence***." *Id*. at 53 (emphasis added); *see id*. at 51 (Table 2) (multi-variable RR for NHL and ever/never use of glyphosate = 1.1 (95% CI 0.7-1.9) (not statistically significant)). Plaintiffs' experts agree that the AHS study shows no association.[19]

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[17] The Ninth Circuit has imposed an even higher bar, explaining that general causation cannot be established unless the epidemiologic data shows a statistically significant doubling of the risk. *Daubert II*, 43 F.3d at 1321 (under *Daubert*'s "fit" requirement, for epidemiology studies to support any general causation opinion, studies must show statistically significant RR in excess of 2.0 because a RR of less than 2.0 "may suggest [an adverse effect], but it actually tends to disprove legal causation, as it shows that [the chemical] does not double the likelihood of [the adverse effect]."); *see Schudel v. Gen. Elec. Co.*, 120 F.3d 991, 996 (9th Cir. 1997) (same), *abrogated on other grounds by Weisgram*, 528 U.S. 440.

[18] A. De Roos et al., *Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study*, 113 Envtl Health Perspectives 49 (2005) ("De Roos 2005"). Although this article uses the term "glyphosate," the study involved formulated products (GBHs), which are what pesticide applicators use. The epidemiology studies at issue in this litigation involve GBHs. Ritz Dep. 52:2-4.

[19] Neugut Dep. 128:1-7 (admitting lack of association in AHS analysis that controlled for other pesticides or other potential confounders); Dep. of Dennis Weisenburger 191:4-15 (Sept. 11, 2017) (Hollingsworth Decl., Ex. 16) ("Weisenburger Dep.") (admitting that De Roos 2005 results "were negative" and that "there was no association found between glyphosate exposure and [NHL]").

This study also reported data from various exposure analyses to account for the most highly exposed populations – "cumulative exposure days" and "intensity-weighted cumulative exposure days" – none of which showed a dose-response relationship between glyphosate exposure and NHL. *See* De Roos 2005 at 52 ("[t]here was ***no association between glyphosate exposure and . . . NHL***, whether the exposure metric was 'ever used,' 'cumulative exposure days,' or 'intensity-weighted cumulative exposure days'" (emphasis added)). Again, plaintiffs' experts acknowledge this is what the AHS data shows. Neugut Dep. 131:2-132:15, 133:4-8 (admitting that AHS reported that subjects with higher durations and higher intensity of glyphosate exposure had lower incidence of NHL than subjects with lower durations and lower intensity of exposure); Dep. of Aaron Blair 155:25-157:21 (Mar. 20, 2017) (Hollingsworth Decl., Ex. 17) ("Blair Dep.") (same).

Plaintiffs' experts also validate the AHS. According to Dr. Blair (one of the AHS co-authors), the AHS was initiated to address some of the limitations of earlier retrospective case-control studies regarding risks of pesticides or other exposures in farmers. *See* Blair Dep. 94:6-95:1, 95:23-96:1; *see also* Neugut Dep. 124:1-4. Unlike the case-control studies discussed below, the AHS results are not skewed by recall bias because information about exposures was collected from the participants before they were diagnosed with cancer.[20] *See* Neugut Dep. 124:1-4 (AHS "was initiated to avoid the problem of recall bias in case-control studies"). In addition, the AHS methodology "appropriately controlled for lifestyle factors and multiple pesticide exposures [*i.e.*, exposures to chemicals other than glyphosate] in the statistical models, reducing the potential for confounding by other farm exposures associated with NHL." Expert Report of Lorelei Mucci at 32 (Hollingsworth Decl., Ex. 18) ("Mucci Report"). Moreover, "the number of NHL cases [in the AHS] was sufficiently large to provide reasonable statistical

[20] In retrospective case-control studies, the quality of the data is determined to a large extent by the participants' ability to accurately recall past exposures. The "recall bias" that occurs when the information provided on exposure differs between the study groups can severely undermine the reliability of the study results. *See Zwillinger v. Garfield Slope Housing Corp.*, No. CV 94-4009(SMG), 1998 WL 623589, at *18 (E.D.N.Y. Aug. 17, 1998). "Research has shown that individuals with disease (cases) tend to recall past exposures more readily than individuals with no disease (controls) …." *Reference Manual* at 585 (footnotes omitted).

power," and the study "had virtually complete follow-up of the cohort for cancer incidence and mortality . . . which reduces selection bias." *Id*. at 32-33.

Discovery in this litigation has brought to light an even more robust and more recent independent analysis of AHS data. This analysis was prepared in 2013. *See* M. Alavanja et al., *DRAFT-Lymphoma risk and pesticide use in the Agricultural Health Study* (Mar. 15, 2013) (unpublished study on file with authors) ("Alavanja 2013"). The analysis was subsequently published as a study in the peer-reviewed literature, but only after the authors – one of whom is Dr. Blair – removed the findings for glyphosate (and other herbicides) and substituted findings for a different category of pesticides. *See* Blair Dep. 259:23-260:15; Mucci Report at 33.

The Alavanja 2013 cohort study likewise finds "***no evidence of association between exposure to glyphosate and NHL***." Blair Dep. 172:11-15. Alavanja 2013 provides an additional seven years of follow-up for NHL cases in the AHS cohort, Blair Dep. 167:21-168:16, and is more than four times larger than De Roos 2005, *id*. 171:21-172:1. Dr. Blair testified that the RR for an "ever/never" analysis of glyphosate and NHL based on the Alavanja 2013 data was below 1.0 – about 0.9. *Id*. 173:6-11. Moreover, "the applicators in highest levels of exposure to glyphosate, both by lifetime days and intensity-weighted lifetime days, had the exact same incidence of [NHL] as applicators with no exposure to glyphosate," so a "***completely null result***." *Id*. 173:12-23.[21]

Of course, despite recognizing certain advantages of the AHS over case-control studies and despite agreeing that the report showed no association, plaintiffs' experts still criticize the AHS data in various ways. But attacking the results of the AHS does not satisfy plaintiffs'

[21] Dr. Blair admitted that the updated findings from the AHS for glyphosate and NHL were not considered by the IARC working group that evaluated glyphosate in March 2015, even though he was the chair of the working group – and even though he had reviewed the data and co-authored a report on it in March 2013. Blair Dep. 176:5-177:25. Dr. Blair did not disclose even the existence of the new information to any of his fellow working group members at IARC. *Id*. 177:13-178:7. Dr. Blair's decision to withhold the finding astonishingly and unfortunately left IARC with a skewed, incomplete set of available data for its glyphosate assessment. *See* Blair Dep. 182:16-183:17 (admitting that 2013 AHS data would have reduced IARC's reported meta-relative risk and probably made it not statistically significant). Thus, to the extent that any of plaintiffs' experts bolster their general causation opinions with the conclusions in the IARC monograph, those opinions are unreliable because the monograph is based on incomplete data and totally undermined by the complete, most recent epidemiological data.

burden of presenting scientifically reliable expert testimony to prove general causation. *See, e.g., Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 886 (10th Cir. 2005) ("Mere criticism of epidemiology cannot establish causation."); *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1213 (10th Cir. 2002) ("[P]laintiffs have the burden of demonstrating the harmful effect of [the drug]. Accordingly, it was not unreasonable for the district court to conclude that [plaintiffs' expert's] attack on the [epidemiology] study did not constitute reliable [general causation] evidence . . ."); *see also Caraker*, 188 F. Supp. 2d at 1034 (same).

2. When properly adjusted for confounding, the case-control studies upon which plaintiffs' experts rely likewise do not find any association between exposures to GBHs and NHL.

With independent, undisputed prospective data failing to lend any support to their hypotheses, plaintiffs' experts accordingly rely instead on cherry-picked, unadjusted epidemiologic data from retrospective case-control studies that previously have been found insufficient to satisfy their *Daubert* burden. *Arias v. DynCorp*, 928 F. Supp. 2d 10, 24-25 (D.D.C. 2013) (excluding expert NHL causation opinion based upon studies at issue here). Case-control studies are generally considered less reliable than cohort studies because they are more prone to biases that can lead to spurious associations. *See* Neugut Dep. 77:12-79:10. But most importantly here, when properly adjusted to avoid confounding by other pesticides, even these studies do not find any association between GBHs and NHL, with non-statistically significant findings and ORs closely surrounding the null value of 1.0.

The case-control studies at issue here can be grouped into three main geographical regions: North America, France, and Sweden. Certain studies overlap with other studies due to pooling of data from the studies. *See* Mucci Report at 37 & Figure 3.

The North American Pooled Project ("NAPP") is a pooled analysis combining original data from three previously-published case-control studies from the United States and Canada. *See id.* 45. In 2015, the NAPP analysis was presented to the International Society for Environmental Epidemiology. *Id.* The NAPP reported non-statistically significant adjusted ORs for GBHs and NHL of 1.13 (95% CI=0.84-1.51) for a group consisting of self-respondents and proxy respondents and an even lower OR of 0.95 (95% CI=0.69-1.32) for what Dr. Neugut

agreed was a more reliable group limited to self-respondents. M. Pahwa et al., *An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project* at Slide 26 (Aug. 31, 2015) (on file with Dr. Blair) ("Pahwa 2015"); Neugut Dep. 263:24-264:17; *see also* Weisenburger Dep. 136:24-137:15 (proxy respondents "are always a concern" and are more likely to give "less reliable" answers regarding pesticide exposure than self respondents); Blair Dep. 140:11-23 (same).

A case-control study from France addresses whether occupational exposure to various pesticides (including glyphosate) is associated with NHL and other lymphoid cancers.[22] The study reported an OR for GBHs of exactly 1.0 (95% CI=0.5-2.2), Orsi 2009 at 295 (Table 3) – *i.e.*, ***a null finding*.**

To the extent relied upon by plaintiffs' experts as a GBH study, a third case-control study from Sweden is undermined by a major methodological flaw because it compares a group of individuals exposed to ***GBHs and other pesticides*** to a group of individuals not exposed to ***GBHs or any other pesticides***.[23] This methodology is "[i]n contrast with a standard epidemiological approach" because it improperly measures the association between a group of pesticides and NHL rather than any association specific to GBHs. *See* Mucci Report at 53; Neugut Dep. 227:6-17 (admitting this "would be a methodological flaw in the study" and "would make it impossible to actually adjust for the potential impact of other exposures"). The results of the study also clearly show the impact of this confounding. The multivariable analyses that attempted to adjust for other pesticides generated a ***non-statistically-significant*** OR (1.5, 95% CI=0.77-2.94) for glyphosate, whereas the analysis that did not adjust for other pesticides (and instead included them in the comparison) had a higher, statistically significant OR (2.02, 95% CI=1.10-3.71) for glyphosate. *See* Eriksson 2008 at 1661 (Table VII). Further, this study reported elevated odds ratios for ***all*** 20 or so different pesticides examined, a finding that Dr. Neugut agrees suggests "systemic bias." Neugut Dep. 283:14-284:24.

[22] L. Orsi et al., *Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study*, 66 Occup. Environ. Med. 291 (2009) ("Orsi 2009").

[23] M. Eriksson et al., *Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis*, 123 Int. J. Cancer 1657, 1658 (2008) ("Eriksson 2008").

Plaintiffs' experts disregard the properly adjusted odds ratios in all case-control studies and instead rely conveniently on odds ratios that are ***not*** adjusted for the confounding effect of other pesticides and that are subject to recall and selection biases. This is litigation advocacy, not sound science generated by a reliable methodology as required by *Daubert*.[24] Whatever their contribution to the public policy debate, the limited scientific value of these data to the general causation question here is summarized by Dr. Blair. He admits that in each case-control study that reported elevated odds ratios between glyphosate and cancer, "***chance, bias and confounding could not be excluded as explanations for the finding***." Blair Dep. 119:18-25.[25] Plaintiffs' experts choose to ignore this chance, bias, and confounding for their litigation opinions – but because they have no "good grounds" to do so, their opinions are the antithesis of reliable science, as explained below.[26]

[24] *See, e.g.*, *In re Bextra*, 524 F. Supp. 2d at 1176 (excluding expert who reached general causation conclusion by "cherry-picking observational studies that support his conclusion," stating that this "is not 'good science'"). For example, Dr. Ritz originally relied upon the NAPP findings in her expert report based upon an abstract that only reported confounded odds ratios. Ritz Report at 15-16. After becoming aware of the data from the same study that was adjusted for other pesticide exposures – and showed no evidence of an association – she sought to distance herself from the study results. *See* Ritz Dep. 305:10-306:17; *see also id.* at 292:11-293:1. Regarding Eriksson 2008, Dr. Weisenburger admits that: (a) the study includes a multivariate analysis that controls for other pesticide exposures and generated an OR that is not statistically significant; (b) the study reports other ORs that were not adjusted for exposure to other pesticides; (c) he does not know whether any of the unadjusted ORs would be statistically significant if they were controlled for other pesticides; (d) like Dr. Neugut, the fact that almost every unadjusted OR for various substances was above 1.0 suggests some kind of bias in the study; and (e) the study does not show a statistically significant association between glyphosate and NHL (or any NHL sub-type) controlled for other pesticides. Weisenburger Dep. 181:4-184:2, 184:24-185:20. Nevertheless, Dr. Weisenburger incredulously claimed that the study showed a statistically significant response. *Id*. 181:20-22; Weisenburger Report at 4-5.

[25] Because chance, bias, and confounding cannot be excluded as explanations for any positive result in the retrospective case-control data, the epidemiology sub-group and the full IARC working group determined that the epidemiology evidence for glyphosate and NHL was "limited," in their hazard assessment parlance. *See* Blair Dep. 118:11-119:17; *see also* Weisenburger Dep. 61:14-62:2 (admitting that a perceived association in an epidemiology study "might be due to a causal association" or due to "confounding or bias or the play of chance").

[26] *See Nelson*, 243 F.3d at 253 ("Before any inferences are drawn about causation, the possibility of other reasons for the association ***must be examined***, including chance, biases . . . , and confounding causes." (emphasis added)); *In re Bextra*, 524 F. Supp. 2d at 1173 ("[t]he downside to observational studies is that . . . it is more difficult to control for confounding factors"). More generally, "[s]howing association is ***far removed*** from proving causation." *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1315 n.16 (11th Cir. 1999) (emphasis added); *see Nelson*, 243 F.3d at 253 ("an association does not mean that there is a cause and effect relationship"); *see also Reference Manual* at 555.

First, plaintiffs' experts rely on epidemiology findings that lack statistical significance. But ruling out chance is a bedrock principle of epidemiology. *See Joiner*, 522 U.S. at 145-47 (affirming *Daubert* exclusion because, *inter alia*, experts relied on epidemiology study that was not statistically significant); *Burst*, 650 F. App'x at 174-75 (same); *Allen*, 102 F.3d at 197 (same); *see also* Neugut Dep. 45:14-18 (requiring statistically significant increased risk before he would conclude that an exposure is associated with an outcome).

Second, plaintiffs' experts rely on epidemiologic findings that fail to adjust for pesticides and other farming exposures that confound the analyses. But as Dr. Blair testified, something is "going on with farmers that appears to be associated with an increased risk of [NHL] that predated glyphosate being on the scene," Blair Dep. 90:15-20, "***that we know for a fact can't be glyphosate***." *Id.* 90:15-91:3. This is classic confounding. *See id*. 91:23-92:4 (to implicate glyphosate exposure in farmers, one wants to ensure that one "can control for those other possible confounders to be sure that [one is] actually studying glyphosate"); *see also* Weisenburger Dep. 179:24-180:5 (admitting that increase of NHL cases in 1950's could not have been caused by glyphosate); *id*. 93:16-23 (admitting other pesticide exposures could be "major confounder for the issue of whether glyphosate can cause [NHL]").

Third, plaintiffs' experts fail to account for recall bias, which artificially increases the odds ratios in case-control studies where, as would be expected, people who have cancer recall more exposures than people who do not have cancer and have not been thinking about their prior exposures. *See* Blair Dep. 95:2-22.

In light of these serious flaws – and Dr. Blair's (correct) admission that the flaws cannot be eradicated when one evaluates the glyphosate-NHL retrospective case-control literature – that literature does not and cannot provide scientifically reliable support for plaintiffs' experts' general causation opinions. *See Joiner*, 522 U.S. at 145-46 (epidemiology cannot provide a scientifically reliable basis for an affirmative causation opinion if it is statistically insignificant or inadequately controlled for bias and other confounders); *Nelson*, 243 F.3d at 252-53 (expert was properly excluded because he failed to account for confounding factors); *In re Bextra*, 524 F. Supp. 2d at 1179 (not scientifically reliable for expert to rely on study that failed to account

for critical confounding factors); *Valentine v. Pioneer Chlor Alkali Co., Inc.*, 921 F. Supp. 666, 678 (D. Nev. 1996) (excluding expert's opinions that failed to account for selection bias, recall bias, and confounding); *see also* Neugut Dep. 39:19-40:1 (conceding that epidemiology evidence alone is not sufficient to show causal relationship between glyphosate and NHL); *id.* 38:4-39:10 (accepting IARC's classification of epidemiology as "limited" and admitting chance, bias, and confounding could not be ruled out); *id.* 61:16-20 (making dispositive concession under *Daubert* that, "looking just at the epidemiological data, bias and confounding cannot be excluded as an explanation for the findings in those studies").[27]

3. Meta-analysis studies also do not provide scientifically reliable support for plaintiffs' experts' epidemiology opinions.

Plaintiffs' experts also rely on two meta-analyses that combine results from some of the glyphosate epidemiological studies.[28] However, these meta-analyses do not provide scientifically reliable support for plaintiffs' experts' general causation opinions.

Combining results of observational studies (as opposed to results from randomized, controlled, experimental trials) into a meta-analysis amplifies and exaggerates the flaws in the underlying studies, such as bias and confounding. This is the "garbage in = garbage out" problem with meta-analyses: "Combining a group of poorly done studies can produce a precise summary result built on a very weak foundation." J. Berlin et al., *The Use of Meta-Analysis in Pharmacoepidemiology*, in Pharmacoepidemiology at 726 (5th ed. 2012). Thus, it is not reasonably disputed that meta-analysis is "of limited value in combining the results of

[27] Drs. Nabhan, Portier, and Jameson agreed that the epidemiology evidence is "limited" as that term was used in the IARC glyphosate review – *i.e.*, that chance, bias, or confounding could not be ruled out with reasonable confidence. Nabhan Dep. 101:16-102:7; Portier Dep. 140:4-141:15; Jameson Report at 9-10, 19. The epidemiology data is "not sufficient by itself to demonstrate causality" between NHL and glyphosate exposure. Portier Dep. 140:4-141:15.

[28] *See* L. Schinasi et al., *Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis*, 11 Int'l J. Envtl. Res. & Public Health 4449 (2014); *see also* IARC Monograph 112 at 30; E. Chang et al., *Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers*, 51 J. Envtl. Sci. & Health 402 (2016). A meta-analysis combines the final results of multiple studies into a combined relative risk and is not dependent upon having access to original study data while a pooled analysis combines the individual data from multiple studies in order to calculate a single risk ratio. Both methods are subject to the various biases inherent to the underlying studies they are based upon.

epidemiologic studies based on observation." *Knight v. Kirby Inland Marine, Inc.*, 363 F. Supp. 2d 859, 866 n.13 (N.D. Miss. 2005); *see In re Bextra*, 524 F. Supp. 2d at 1174 ("[O]ne problem with meta-analysis, ***particularly in meta-analysis of observational studies***, is that the [underlying] studies often use disparate methodologies." (emphasis added)); *Reference Manual* at 607 ("[W]hen meta-analysis is applied to observational studies—either case-control or cohort—it becomes more controversial.").[29]

Dr. Neugut summarized the *Daubert* failings of plaintiffs' experts' reliance on meta-analyses when he acknowledged several of their more well-established problems. He admitted that "meta-analysis is not appropriate" in some cases and that "the results can be misleading." Neugut Dep. 94:5-15. He also conceded that a meta-analysis does not fix "an underlying recall bias," "an underlying selection bias," or "a problem with confounding in any of the underlying studies." *Id*. 99:11-100:4. He acknowledged the misleading results can be further skewed by "publication bias" – where "positive findings may be published and null findings may not be published." *Id*. 104:11-19; *see also* Blair Dep. 202:7-21 (discussing publication bias; admitting that "it's more difficult to get negative findings published" and that "as a result, sometimes negative findings . . . are not published"). And finally, Dr. Neugut testified that "if you haven't included every study, then you . . . have to be concerned that you are biasing the results upward." Neugut Dep. 106:2-8.

Each of these problems exists here, which means that the meta-analyses upon which plaintiffs' experts rely are not scientifically valid support for their opinions. These meta-analyses combine observational studies that used different methodologies (cohort studies versus case-control studies) and that took different approaches towards confounding (controlling versus not controlling for exposures to other pesticides). Moreover, the meta-analyses do not

[29] *See also Reference Manual* at 608 ("The appeal of a meta-analysis is that it generates a single estimate of risk . . . but this strength can also be a weakness, and may lead to a false sense of security regarding the certainty of the estimate."); B. Black et al., *Expert Evidence: A Practitioner's Guide to Law, Science, and the FJC Manual* at 98 (1997) ("[A]ggregation of nonrandomized observational studies [for a meta-analysis] is especially fraught with peril. Such studies often do not have a common research design, and ***controlling for biases is particularly problematic***." (emphasis added)).

fix flaws in the underlying case-control studies like recall bias, selection bias, or confounding. *See supra* at 15-19. "At the heart of meta-analyses . . . is that their validity is completely dependent on the validity in the design and conduct of the original studies," Mucci Report at 58, but – as recognized by IARC and most of plaintiffs' experts – bias and confounding cannot be excluded as explanations for the results of the original studies at issue here. In turn, they cannot be excluded as explanations in any meta-analyses.

Publication bias and the failure to include every study are especially acute and obvious problems here. Neither of the meta-analyses upon which plaintiffs' experts rely included the findings of the 2013 AHS analysis or the NAPP pooling of the North American case-control studies. As Dr. Blair acknowledged in his deposition, if these two studies are included, the meta-relative risk for glyphosate and NHL ***becomes lower and does not show any statistically significant increased risk***. Blair Dep. 182:16-183:17; 189:4-8. Indeed, when the authors of one of the original meta-analyses (Chang & Delzell) updated their meta-analysis using the same methodology and the more current glyphosate/NHL epidemiology data, they calculated a meta-RR of 1.0 (0.86 – 1.2), a completely null finding of no association. Mucci Report at 59-60; *see also* E. Chang et al., *Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma*, Exponent 1, 5 (2017); Ritz Dep. 284:9-285:9 (acknowledging that meta-analysis methodology uses most recent data adjusted for exposure to other pesticides). In short, all of the most reliable epidemiology data fail to support an association between GBHs and NHL, and therefore plaintiffs have failed to meet their burden under *Daubert*.

B. Plaintiffs' Experts Do Not Employ Reliable Scientific Methodologies And Make Unsupported Scientific Leaps In Their Opinions Regarding The Glyphosate Rodent Carcinogenicity Data.

As discussed above, where epidemiology data exists (as it does here), it is the best method to assess causation in humans at the relevant inquiry involving real-world exposure levels. Plaintiffs' toxicology experts – Drs. Portier and Jameson – nevertheless purport to rely on "secondary methodologies, including … animal studies [that] are insufficient proof of general causation." *Chapman v. Proctor & Gamble Distrib., LLC*, 766 F.3d 1296, 1308 (11th

Cir. 2014).[30] Regardless, glyphosate is not even a rodent carcinogen, as regulatory agencies around the world that have reviewed at least 14 long-term studies have concluded. Plaintiffs' experts disagree, yet in doing so, they rely on unreliable methodologies, blatant untested statistical manipulations, and a series of *ipse dixit* conclusions that contradict each other and the actual data.[31] As such, these opinions must be excluded.[32]

As a general matter, plaintiffs' experts admit "the purpose of doing an animal bioassay study is to determine if the chemical can cause cancer *in the experimental animals*," not humans. Jameson Expert Dep. 28:10-12; 28:12-15 ("[an animal bioassay is] not -- not looking to investigate does it form a specific kind of tumor that is the same as found in humans."); Portier Dep. 163:7-23 (rodent models "are not developed for the purpose of identifying tumors

[30] *See also Conde v. Velsicol Chem. Corp.*, 24 F.3d 809, 813-14 (6th Cir. 1994) (rejecting reliance on animal studies where epidemiology does not show risk of alleged injury); *In re Silicone Gel Breast Implants Prod. Liab. Litig.*, 318 F. Supp. 2d 879, 891 (C.D. Cal. 2004) ("Animal studies are not generally admissible where contrary epidemiological evidence in humans exists." (citing *Richardson v. Richardson–Merrell, Inc.*, 857 F.2d 823, 830 (D.C. Cir.1988)).

[31] Although they share some opinions regarding glyphosate (including about the lack of relevance of animal data to human NHL), *see infra*, the methodologies that Drs. Portier and Jameson apply to interpretation of the animal data are so arbitrary and pliable that they reach divergent conclusions with regard to multiple tumor types, one finding statistically significant trends and evidence of carcinogenicity where the other finds none. *See, e.g.*, Jameson Expert Dep. 119:17-19; 123:4-124:6 (statistically significant trend in hemangiosarcomas in male mice according to Jameson, non-statistically significant trend according to Portier); *id.* 142:4-11 (statistically significant increase in lung adenocarcinomas due to glyphosate according to Jameson; lung adenocarcinoma due to chance according to Portier). Dr. Jameson could not explain these discrepancies. *See id.* 124:1-9 ("So if he has a number in his expert report that is different than this, it's probably due to the fact that he did additional analysis or subsequent analysis of the data because being a statistician, they always evaluate and reevaluate the data, so that … But I don't know.").

[32] Six of plaintiffs' experts (Drs. Nabhan, Weisenburger, Neugut, Ritz, Blair, and Ross) are not qualified to render opinions on rodent bioassay data. As plaintiffs' counsel admit, those experts have no specialty experience in toxicology, the branch of science under which analysis of rodent bioassay data falls. *See* 5/16/17 Letter. These admissions are borne out by the experts' CVs, none of which recites any experience in the conduct or interpretation of rodent carcinogenicity bioassay data. Further, mere membership in the IARC working group does not bestow the requisite expertise. *See* Blair Dep. 49:11-13 ("Different subgroups [of the IARC working group] evaluate different components. I'm really familiar with the epidemiology, not so much the other."); Ross Dep. 58:22-59:11 (explaining he did not review the genotoxicity data). Dr. Ritz revealed for the first time at her deposition that she intends to offer opinions on the rodent carcinogenicity bioassays. Ritz Dep. 79:2-16. In addition to her complete lack of qualifications to do so, those opinions must be excluded under Federal Rule of Civil Procedure 26(a)(2)(B) because neither the opinions nor her methodologies are disclosed in her expert report. *See* Ritz Report. Undisclosed opinions must be excluded. *See Nationwide Transp. Fin. v. Cass Info. Sys., Inc.*, 523 F.3d 1051, 1062 (9th Cir. 2008).

that arise in humans from exposure to chemicals.").[33] They further admit "it has always been a challenge to extrapolate from effects observed in experimental animal bioassays to potential effects in humans in order to protect humans from potentially harmful chemical exposures." Portier Dep. 158:14-159:16; Jameson Expert Dep. 9:3-6 ("[T]he fact that something causes a kidney tumor in a mouse, I don't know what that says about causing non-Hodgkin's lymphoma in humans."). Yet they give no reason why extrapolating generally from animals to humans is appropriate in this case notwithstanding: (1) the overwhelmingly negative epidemiology data, (2) the fact that animal dosing is orders of magnitude higher than the plausible human exposure, *see infra* at 29-30, (3) they rely on animal tumors *other than* lymphoma, further improperly skewing their extrapolation of animal data to human risk of NHL, and (4) even with respect to lymphomas in rodents, they cannot explain why extrapolating is appropriate when they agree that the immune systems of rodents and humans have important differences. Portier Dep. 167:8-15; Jameson Expert Dep. 169:16-19.

They cannot cite one article in the published literature that suggests that CD-1 or Swiss Albino mice (the mouse models at issue in this case) are appropriate for assessing the potential for a substance to cause NHL in humans. Portier Dep. 171:21-172:3; Jameson Expert Dep. 27:18-24. Dr. Jameson concedes that both strains have a "high spontaneous incidence" of malignant lymphoma and that actually he is aware of scientific literature *objecting* to the use of mice as a model for evaluating whether a chemical can cause lymphoma precisely "*because* of the high background level . . . ." Jameson Expert Dep. 29:13-30:5, 133:17-134:8. They certainly cannot cite any literature to support the opinion that any of the other tumors at issue in the rodent studies are associated with NHL in people. *See, e.g.*, Portier Dep. 174:24-175:7.

[33] Rodent (mice or rat) carcinogenicity studies start from the hypothesis that the test compound does not cause cancer (a "null hypothesis"). Prior to the study, investigators select which statistical tests they will apply to the data and at what probability level (or "p-value") between 0 and 1 that the data will be considered significant. If the p-value is below the selected level of significance, then further evaluation is needed to assess whether the tumors seen are related to the test compound. If the p-value exceeds the selected level, the null hypothesis holds (*i.e.*, the study is considered to show no compound-related effect).

Plaintiffs' experts' failure to explain how data regarding tumors allegedly induced in rodent models upon which they rely are relevant to NHL in humans is a fatal *Daubert* flaw; without such an explanation, the rodent data cannot "fit" the allegations in this case and must be excluded on that basis alone. *See, e.g.*, *Joiner*, 522 U.S. at 144 (approving exclusion of expert testimony based on "seemingly far-removed" animal studies where expert failed to explain why the extrapolation was scientifically proper).[34] Other factors, such as shifting methodologies and made-for-litigation opinions, amply support that outcome as well.

1. Dr. Portier's result-oriented opinions ignore established scientific principles, violate his own purported methodology, and have not been subjected to scientific scrutiny.

Beyond the broad *Daubert* flaws in his general mouse-to-man methodology, Dr. Portier plays fast and loose with basic statistical principles in a desperate effort to find any calculation to support his predetermined conclusion that glyphosate is carcinogenic in rodents.[35] He has no defined methodology and will discard any data – no matter how credible or whether it appears in his own non-litigation opinions – in an effort to create "proof" of carcinogenicity. He ignores the authors' pre-study protocols for data analysis and their conclusions about that data in favor

[34] *See also O'Hanlon v. Matrixx Initiatives*, No. CV 04-10391AHMJTLX, 2007 WL 2446496, at *2 (C.D. Cal. Jan. 3, 2007) ("[W]hen extrapolating from studies concerning one substance, one species, one dose level or one manner of exposure, it is incumbent upon the expert to explain and demonstrate why the extrapolation is scientifically proper. … [P]ositive results in other animal studies, standing alone, cannot establish positive results for the human claiming the same impact from the drug or chemical element."); *Newkirk v. ConAgra Foods, Inc.*, 727 F. Supp. 2d 1006, 1026 (E.D. Wash. 2010), *aff'd*, 438 F. App'x 607 (9th Cir. 2011) (excluding expert who "offers no explanation for how and why the results of [rat] studies can be extrapolated to humans); *Redfoot v. B.F. Ascher & Co.*, No. C 05-2045 PJH, 2007 WL 1593239, at *11, n.18 (N.D. Cal. June 1, 2007) ("In general, [e]xtrapolations of animal studies to human beings are generally not considered reliable in the absence of a scientific explanation of why such extrapolation is warranted." (internal quotation omitted)); *Siharath*, 131 F. Supp. 2d at 1366-67 ("[E]xtrapolating from animals to humans is difficult because differences in absorption, metabolism, and other factors may result in interspecies variation in responses.") (internal citation omitted); *In re Silicone Gel Breast Implants*, 318 F. Supp. 2d at 891 (same).

[35] Plaintiffs signed Dr. Portier up to assist them in the litigation no later than March 29, 2015, just nineteen days after the IARC Working Group concluded and nine days after their findings became public. (At the time he signed the retainer, he was already working with the same counsel in another litigation connected with a different IARC review.) *See* Portier Dep. 75:14-77:2. Therefore, all of Dr. Portier's post-IARC activities (at least) are those of a "professional plaintiff's witness" and "[i]t is not unreasonable to presume that [his opinion on glyphosate] was influenced by a litigation-driven financial incentive." *Lust v. Merrell Dow Pharm.*, 89 F.3d 594, 597 (9th Cir. 1996) (excluding similar opinion as litigation-driven).

of his *post hoc* made-for-litigation reassessment in which he uses whatever method of calculation best supports the opinion he already reached.[36]

All of these failings in methodology are exemplified in his analysis of renal tumors in the Monsanto 1983 mouse bioassay. Before initiating the study, the original investigators specified which two statistical tests would be used to interpret the data and set a .01 level of significance. *See supra* at n.33 (describing bioassay methodology). When applied upon conclusion of the study, they found no statistically significant increase in incidence in renal tumors in mice exposed to glyphosate. *See* EPA RED at 14. In 1985, a group of independent pathologists reviewed the study and reached the same conclusion using a .05 level of significance and updated tumor data. *Id.* Thirty years later, Dr. Portier embarked on a multi-year quest to find a statistical test that would yield a different result. First, in March 2015 for the IARC Monograph, Dr. Portier applied an "approximate trend" test that achieved a statistically significant result (p-value = .034 (below the .05 level of significance that he used for all of his calculations). Portier Dep. 47:1-17. Some months later, Dr. Portier applied a different test that also achieved a modestly more statistically significant result (p-value = .03).[37] After another well-known biostatistician publicly criticized Dr. Portier's calculation by noting that the test Dr. Portier selected is known to have a large bias toward finding a statistically significant effect,[38] Dr. Portier again changed his statistical method, this time using the more appropriate "exact trend" test and reaching a result (p-value = .063) that was not statistically significant.[39] Presumably unhappy with that turn of events, Dr. Portier unveiled two more novel calculations (the fourth and fifth in his changing methodologies) in his 2017 expert report here,

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[36] Federal courts distrust this type of results-seeking "analysis." *See, e.g. Baker v. Sec'y of HHS*, No. 99-653V, 2003 WL 22416622 at *30 (Fed. Cl. Sept. 26, 2003) ("[t]he validity of this type of 'post-hoc' statistical testing" is "highly questionable"); *Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 82 (3d Cir. 2017) ("researcher who searches for statistical significance in multiple attempts raises the probability of discovering it purely by chance, committing Type I error").

[37] *See* Expert Report of Christopher Portier, Attachments 4 and 5 at Table 4 (Hollingsworth Decl., Ex. 19) ("Portier Report").

[38] *See* Portier Report, Attachment 6 at 1 (commenter noting that Dr. Portier's test statistics "are extremely skewed" due to his use of the approximate trend test).

[39] *See* Portier Report, Attachment 7 at 2 (admitting that switching from approximate to exact test results in a p-value greater than .05).

with one once again finding statistical significance (p-values = .065, .011).[40] This is blatant "p-hacking," an oft-rejected and unscientific process also known as data dredging, in which numerical data is manipulated to generate a statistically significant result and is then used *post hoc* to support a pre-existing scientific conclusion.[41]

Dr. Portier's "willingness to change the pre-specified statistical endpoint – with the effect of turning a 'not significant' study result into a [significant one] – again, demonstrates a lack of objectivity and reliability." *In re Denture Cream Prod. Liab. Litig.*, No. 09-2051-MD, 2015 WL 392021, at *10 (S.D. Fla. Jan. 28, 2015). Stated differently, "[c]oming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method." *Claar v. Burlington N. R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994).[42]

In another "opinion first, data later" made-for-litigation supposition, Dr. Portier developed a novel technique that, he says, permits him to pool, or combine, data from studies done at different laboratories in different animals by different investigators years apart despite his own admission that "there is considerable genetic variability across animal strains both over time and space." Portier Amended Report at 51.[43] Perhaps even worse, Dr. Portier applied his personally developed, untested, non-peer reviewed pooling methodology inconsistently to ensure that he generated a result that supports his predetermined opinions regarding the

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[40] The second p-value is based on a novel statistical test called a "p-hist" test, which itself is unreliable. *See infra*.

[41] *See, e.g.*, R. Nuzzo, *Statistical Errors*, 506 Nature 150, 150-52 (2014).

[42] *See In re REMEC Inc. Sec. Litig.*, 702 F. Supp. 2d 1202, 1273 (S.D. Cal. 2010) (excluding expert who predetermined the "results of his analysis" and applied methodology suited to reach his predetermined result); *Newkirk*, 727 F. Supp. 2d at 1021 (same; citing *Claar*, 29 F.3d at 502-03); *In re Denture Cream*, 2015 WL 392021, at *10 ("'[a] scientist who has a formed opinion as to the answer he is going to find before he even begins his research may be less objective than he needs to be in order to produce reliable scientific results.'" (quoting *Perry v. United States*, 755 F.2d 888, 892 (11th Cir. 1985)); *id.* (excluding under *Daubert* plaintiffs' MDL experts' testimony based on methodologies that are "contrived to reach a particular result") (citing *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1293 n.7 (11th Cir. 2005)).

[43] Dr. Portier developed this novel pooling analysis because "[m]ethods for the combined analysis of multiple animal cancer bioassays are not available in the scientific literature." Portier Amended Report at 21. At deposition, he claimed that pooling disparate data is a peer-reviewed methodology, but could not provide a citation. Plaintiffs failed to respond to a post-deposition request that Dr. Portier identify this source. *See* Ltr. from H. Pigman to R. Greenwald (Sept. 14, 2017) (Hollingsworth Decl., Ex. 20). Any attempt to provide one now must be rejected. *Supra* at n.32.

outcome. For instance, he chose to include three studies in rats (Brammer, Suresh, and Wood) in his pooled analysis for skin keratocanthomas, but then chose to exclude one of those studies (Suresh) for his pooling of hepatocellular adenomas and mammary gland tumors. Portier Dep. 210:6-212:25. He applied a similarly selective pooling technique in assessing tumors in mice. *Id.* 236:17-238:3 (when initial pooled calculations were unhelpful, he recalculated statistics *after* excluding animals in one high-dose group from analysis). When asked how he justified such random, self-serving inclusions and exclusions of data, Dr. Portier testified that ***he included all data when it helped increase his statistically significant result and removed data that defeated statistical significance***. *See id.* 236:24-240:1.[44]

Electing to selectively pool the data ensured that Dr. Portier conjured up statistically significant results, otherwise absent, for a variety of tumors. Such tactics are unscientific p-hacking and must be excluded. *See Lust*, 89 F.3d at 597-98 (excluding expert whose testimony is based on methodology that is unscientific and not accepted). When confronted with the doubtful scientific validity of his methods, Dr. Portier claimed that his pooled data were not a part of his causation assessment. Portier Dep. 238:15-22 ("This is a – this is the pooling evaluation here. There is reason – that's just simply an observation on my part. That is all it is. This is not used as part of my overall evaluation."). However, his expert report and other portions of deposition testimony clearly state otherwise. *See, e.g.*, Portier Amended Report at 33 ("The analysis of the pooled studies yields p_{trend}=0.013 ***supporting the conclusion that glyphosate causes hepatocellular adenomas in Wistar rats*** with similar background responses.") (emphasis added); Portier Dep. 188:19-22 ("Q. You reached your rat causation opinions through the application of a pooling methodology, correct? A. Yes, I did.").

Beyond selective pooling and *post hoc* trend analyses, for certain "rare" rodent tumors, Dr. Portier purported to compare historical control values (as opposed to study-generated control values) to tumor incidences to generate self-described "p-hist" values. Dr. Portier does

[44] Dr. Portier engaged in similar p-hacking by excluding the Lankas rat study from his pooled analysis of adrenal cortical tumors, but then including the Lankas study in his evaluation of other types of tumors, such as testicular tumors. Portier Dep. 214:3-219:23.

not disclose any formal methodology for this work. There is a reason for that: his "p-hist" analysis is novel, untested, unpublished, and created for litigation. Therefore, opinions which rest on it are inadmissible.[45] *See Orrell v. AstraZeneca Pharm. LP (In re Nexium Esomeprazole)*, 662 F. App'x 528, 530 (9th Cir. 2016) (affirming district court's decision to exclude expert opinion on general causation formed for purposes of litigation and that was not subject to peer review) (citing *Daubert II*, 43 F.3d at 1318).

Additionally, as even Dr. Portier recognizes, a potential for a multiple comparison error arises in any of the rodent bioassays because, when making the hundreds of statistical comparisons required in these studies, some statistically significant results will occur by chance alone and are not representative of compound-related effects. Portier Amended Report at 50. Despite peer-reviewed methodology available to do so, Dr. Portier makes no effort to control for these statistical errors. Instead, he decided to draw conclusions based on his self-concocted statistically significant p-values, a methodology that has been rejected by the American Statistical Association ("ASA"), of which Dr. Portier is an elected fellow. *See* R. Wasserstein et al., *Statement on p-values: Context, Process, and Purpose*, 70 Amer. Statistician 129, 132 (2016).

As one would expect, Dr. Portier's Hail Mary attempt at aggregating his inconsistent and disparate methodologies into a single analysis (*e.g.*, Table 15 in his revised expert report) is also irredeemably flawed because the underlying statistics result from inconsistently applied and non-validated methodologies. For example, Dr. Portier claimed to have derived his number of "expected" statistically significant tumor incidences from an estimate prepared by another

[45] Even if the "p-hist" methodology had any indicia of reliability other than Dr. Portier's inadmissible *ipse dixit*, he applies his creation in an inconsistent way that renders opinions based on it inadmissible. *Lust*, 89 F.3d at 598 (courts "should be wary that the [expert's] method has not been faithfully applied"). For instance, Dr. Portier conducted a p-hist evaluation using a historical control database for systemic hemangiosarcomas, but admitted at deposition that he was not sure which hemangiosarcomas to combine for his evaluation and that a pathologist would be more qualified to answer that question. Portier Dep. 246:11-248:20. So he chose the lowest historical control rate possible for hemangiosarcomas in order to generate the most significant possible test statistic. *Compare, e.g.*, Portier Dep. 247:14-17 (admitting there were 29 hemangiosarcomas in historical control data of similar length) *with* 242:24-243:8 (agreeing that he applied a historical control rate based on 0/1424 hemangiosarcomas).

statistician, Portier Dep. 299:17-301:5, but admitted that he had not verified that information. *Id.* 316:23-317:9. He also admitted that in his "observed" statistically significant tumor sites, he included results derived from his novel p-hist test that may or may not have been statistically significant. *Id.* 308:7-311:12; 321:9-323:24. Such methodological hijinks have no basis in the scientific literature, no calculable error rate, and no acceptance in the scientific community, and therefore opinions based on them should be excluded. *See, e.g., Lust*, 89 F.3d at 597-98 (excluding testimony by expert that selectively chose his support from the scientific landscape).

2. Dr. Jameson conducts the wrong scientific assessment and concedes that his opinions add little to the analysis of the risks of NHL in humans.

Like Dr. Portier, Dr. Jameson opines that a variety of tumors seen in long-term rodent bioassays were related to the animals' exposure to glyphosate, notwithstanding contrary opinions offered by regulatory agencies and others. In reaching his opinions, Dr. Jameson used a hazard assessment methodology. *See supra* at 3-4.[46] A hazard assessment is at most a "screening assessment," and more must be done to assess causation under *Daubert*.[47] For example, Dr. Jameson purposely did not take into account whether any carcinogenic effects he allegedly observed would be seen at human relevant doses. Dr. Jameson admits that hazard assessments examine animal carcinogenicity "under the most extreme conditions," and if the compound is an animal carcinogen, "you do additional studies. You do the risk analysis" –

[46] The precise hazard assessment methodology he employed is unclear, even to Dr. Jameson. In his report, Dr. Jameson asserted that his hazard assessment methodology "is the same as defined and characterized by IARC." Jameson Report at 9. At his deposition, Dr. Jameson claimed that his hazard assessment criteria are "very similar" to IARC's, but that he developed his criteria "specifically for this – for my expert report." Jameson Expert Dep. 266:3-16. Whichever version he used, Jameson hides behind it to explain his disagreements with regulators like EPA and EFSA (whom he acknowledges reviewed more data than he did). *See, e.g.*, Jameson Fact Dep. 166:21-167:8 (agencies reviewed more data); Jameson Expert Dep. 207:3-10 ("Again, the EPA was doing their risk assessment, and evidently … these particular tumors did not meet their criteria for inclusion in their risk assessment … [F]or the purpose of the hazard identification I did, these liver tumors -- I consider these liver tumors to be associated with exposure to glyphosate and, therefore, I included them in my report."); *see also id.* 111:4-19; 144:5-145:1; 152:4-20, 180:6-25, 206:5-209:1, 248:21-249:12 (same regarding other tumor types).

[47] *See* Monsanto Co.'s Br. Regarding the Relevance of IARC and EPA to Gen. Causation, ECF No. 134.; *see also* Ltr. from Bernhard Url, Exec. Director, EFSA, to Prof. Christopher J. Portier, Senior Consulting Scientist, Envtl. Def. Fund (Jan. 13, 2016), https://www.efsa.europa.eu/sites/default/files/EFSA_response_Prof_Portier.pdf.

which he did not do – "to see what happens at the human relevant doses." Jameson Expert Dep. 248:6-249:20; *compare, e.g.* EPA OPP at 85 (high dose males in CD-1 mouse study received 4945 mg/kg/day glyphosate) *with supra* at 5 (noting highest estimated systemic dose in farmers of 0.004 mg/kg and EPA reference dose of 2 mg/kg/day). Dr. Jameson also cannot point to any published study or article suggesting that the various tumor findings he identifies in his hazard assessment are associated with or predictive of NHL in humans.[48] Therefore, his opinions do not fit the general causation question here; they do not demonstrate "a valid scientific connection to the pertinent inquiry" in the lawsuit. *Daubert*, 509 U.S. at 591-92.

Dr. Jameson's methodology for evaluating the glyphosate data also differs from methodology he published *prior* to being retained as an expert witness in this litigation. While at the National Toxicology Program, Dr. Jameson co-authored a publication that describes a set of factors that should be considered when interpreting tumor findings in long-term carcinogenicity bioassays.[49] The first of his pre-litigation factors requires assessing whether the results of one study are replicated by "results within the same chemical in other experiments (or elsewhere in the same experiment, if animals of a different sex, strain or species were also studied)." *Id.* For glyphosate, results from at least 12 different experiments by seven different sponsors are available for comparison, which Dr. Jameson concedes is "more than you usually see for a particular compound." Jameson Expert Dep. 32:23-24. Yet for purposes of his expert opinion in this case, Dr. Jameson claims – as he must, in order to advance the opinion he does –

[48] *See, e.g.*, Jameson Expert Dep. 10:16-25 (not aware of any publications or any research that has been done regarding whether renal tumors in mice are predictive of NHL in humans), 27:12-17 (not aware of any research or published papers investigating the association between mouse lymphomas and NHL in humans), 59:24-60:3 (not aware of any studies or published papers investigating the association between lung adenocarcinomas and NHL in humans), 203:11-204:2 (not aware of any data or articles regarding the association between hepatocellular adenomas in rats and NHL in humans); *see generally* H. Morse et al., *B Lymphoid Neoplasms of Mice: Characteristics of Naturally Occurring and Engineered Diseases and Relationships to Human Disorders*, 81 Advances in Immunol. 97, 99 (2003) ("Fundamental differences between mice and men may preclude the exact modeling of any human disease.").

[49] *See* J. Huff & C. Jameson et al., *Carcinogenesis Studies: Results of 398 Experiments on 104 Chemicals from the U.S. National Toxicology Program*, Nat'l Inst. Envtl. Health Sci., Nat'l Toxicology Program at 7 (1988) ("Huff & Jameson") ("[s]cientific judgment must entail full consideration of all the available relevant information together with the statistical findings in an attempt to assess the truth").

that it does not matter whether the tumor findings he identifies are replicated across species, strain, or sex, or even in other experiments with the same strain.[50] Had he attempted the comparison for each of the four tumor types that he claims are replicated, *see* Jameson Report at 29, he would have observed no replication across species, strain, or sex across or within any study.[51]

Where an expert abandons his peer-reviewed pre-litigation methodology in favor of developing new ones just for the litigation, his opinions must be excluded. *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 562 (S.D.N.Y. 2004) (where expert "eschew[ed]" his prior published, peer-reviewed opinion, his opinion was "not based on scientific method but on the expediencies of this particular litigation" and was therefore inadmissible).

C. Plaintiffs' Experts' Opinions Based On The Mechanistic Data Do Not Withstand *Daubert* Scrutiny Because The Data Fails The "Fit" Requirement And Is Not Scientifically Reliable For Such Purposes.

EPA, EFSA, and every other major international regulatory agency, as well as the JMPR of the WHO, have found that glyphosate and GBHs are ***not*** genotoxic based on both the review of the published literature and hundreds of regulatory studies containing primary data.[52] These agencies did not evaluate oxidative stress because "explicit relationships" between oxidative stress and adverse outcomes in the human body "have yet to be defined." *See* EPA, Defining Pesticide Biomarkers: Biomarkers of Effect Categories, https://www.epa.gov/pesticide-science-

[50] *See e.g.*, Jameson Expert Dep. 34:12-35:2 ("not necessary" to see results replicated across species), 48:17-21, 50:25-51:3 (disregarding that kidney tumors and hemangiosarcomas in male mice not replicated in females), 53:25-54:12; 62:7-18 (pancreatic islet cell tumors and interstitial cell tumors in male rats not replicated in any other rat study, in any mouse study, or in female rats in the same study).

[51] Dr. Jameson's pre-litigation publication also emphasized the limitations of statistics for interpreting bioassay results, noting that "[a]lthough *p* values may be helpful in deciding whether or not a substance is carcinogenic, they must not be used inflexibly or given undue weight." Huff & Jameson at 7. Nevertheless, in his evaluation of the tumor data here, Dr. Jameson does just that, giving statistical significance total weight in order to infer causation of otherwise random and disparate findings. *See* Jameson Expert Dep. 23:20-23 ("[T]here was a significant increase in [hemangiosarcomas in male mice], so … it can be said that glyphosate caused the hemangiosarcomas in that particular study."), 59:19-22 ("since [glyphosate] caused a significant increase of lung adenocarcinomas, in this particular study, it's an animal carcinogen").

[52] *See* EPA OPP at 131 ("The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic *in vivo*."); EFSA 2015 at 10 ("Glyphosate did not present genotoxic potential …"); JMPR at 132 ("glyphosate … is devoid of a relevant genotoxic potential.").

and-assessing-pesticide-risks/defining-pesticide-biomarkers. Nevertheless, plaintiffs' experts, most of whom are not qualified to opine on this topic,[53] claim that genotoxicity and the induction of oxidative stress are each mechanisms by which exposure to glyphosate and GBHs can increase the risk of NHL in humans.[54] In support of their assertion, they either rely on IARC or repeat the conclusions of select articles rather than reviewing all of the relevant data as required by *Daubert*. Experts cannot simply parrot the conclusions of others as the basis for their opinions.[55] Further, plaintiffs' experts do not offer a methodology that allows them to leap

[53] Seven of plaintiffs' experts who offer opinions in this area have no qualifications to do so. Drs. Nabhan, Jameson, and Neugut admitted as much. *See* Nabhan Dep. 24:14-25:21 ("Well, I'm not a toxicologist … a toxicologist is able to look at the -- at the evidence when the product or compound is going through the process of being approved through toxicology assays, through animal studies, et cetera. I don't do that. I just look at the literature and review the literature."); Neugut Dep. 305:5-10 (has not conducted an expert analysis of the data and will defer to other experts); Jameson Fact Dep. 90:5-7, 19-20 ("I am not a genetic toxicologist"); *see also id.* 89:5-6, 99:17-19. Two others wrongly seek to appropriate qualifications by imputation of the knowledge of colleagues. Dr. Ritz claims she is in an "interdisciplinary department" and "teaches toxicologists." Ritz Dep. 54:22-55:10. She does not, however, teach them genotoxicology; instead, all of the courses she teaches involve epidemiology. *See* Ritz Report at 14 (CV listing current teaching positions). Similarly, Dr. Weisenburger claims the ability to critically assess mechanistic data by virtue of the fact that his interdisciplinary specialty is human pathology and he has trained himself to do so. Weisenburger Dep. 18:22-19:3. He is mistaken. *See Dura Auto Sys. of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty. That would not be responsible science."); *Washington v. Kellwood Co.*, 105 F. Supp. 3d 293, 311 (S.D.N.Y. 2015) (deeming plaintiffs' expert qualified in one area "does not provide him with carte blance (*sic*) to opine on every issue in the case."); *Castiac Lake Water Agency v. Whittaker Corp.*, No. CV 00-12613 AHM, 2002 WL 34700741, at *5 (C.D. Cal. Oct. 25, 2002) (same). Drs. Blair and Ross are not qualified to opine on the mechanistic data or IARC's conclusions regarding it given their failure to review or analyze it. *See supra* at n. 32.

[54] Cell change due to both genotoxicity (damage to the genetic material of a cell) and oxidative stress (in which oxygen-depleted cells release free radicals into the body) occurs naturally on a daily basis. *See* Weisenburger Dep. 239:11-15; Portier Dep. 345:19-23. All cells are equipped with various protective and repair mechanisms designed to stabilize the cell in the event genotoxicity or oxidative stress occurs. Portier Dep. 344:25-345:6; J. Klaunig et al., *Oxidative Stress and Oxidative Damage in Chemical Carcinogenesis*, 254 Toxicology and Applied Pharmacology 86, 93 (2011). The goal of mechanistic experiments conducted *in vivo* (in cells extracted from exposed living animals or humans) and *in vitro* (cells are exposed in a petri dish) is to identify whether cell change is of a type, amount, or severity that increases the risk that cellular mutations will occur, which in turn may increase the risk of cancer by overriding the body's capacity for cellular repair.

[55] *See, e.g.*, Jameson Report at 30-31 (summarizing genotoxic and oxidative stress studies "[a]s noted in Monograph 112"); Neugut Report at 18-19 (same); Weisenburger Report at 8 (same); Portier Amended Report at 55-62 (same); Nabhan Dep. 149:19-150:16 (IARC is "authoritative" in genotoxicity studies "so I do rely heavily on what the IARC says"); Ritz Report at 24-25 (listing positive findings reported in five mechanistic studies included in IARC as "confirm[ation]" that oxidative stress and genotoxicity are the mechanisms by which glyphosate

in some scientifically valid way from the disparate mechanistic data to NHL in humans.

As an initial matter, this Court need not consider mechanistic data here because it cannot reliably help answer the general causation question. "That [a compound] may have [] effects on living cells or genes is the beginning, not the end of the scientific inquiry and proves nothing ...." *Allen*, 102 F.3d at 198; *see also Richardson*, 857 F.2d at 830 ("*in vivo* and *in vitro* studies may provide a clue signaling the need for further research"); *Merrell Dow Pharm., Inc. v. Havner*, 953 S.W.2d 706, 730 (Tex. 1997) (rejecting expert's reliance on *in vitro* studies to support his general causation opinion; fact that a substance may adversely affect cells *in vitro* proves nothing about causation).[56]

Genotoxicity and carcinogenicity are not synonymous. Some genotoxic compounds are not carcinogens, and some carcinogens are not genotoxic. The same lack of association is true of oxidative stress. Thus, any finding that a chemical has mechanistic capabilities is not even reliably demonstrative of the chemical's carcinogenic potential generally, much less the chemical's potential to cause any specific malignancy, such as NHL.[57] *Allen*, 102 F.3d at 198. To the limited extent it has been considered as a part of the *Daubert* inquiry, courts have found mechanistic data is only relevant in situations where scientifically sound human data is not available.[58] That of course is not the case here.

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cause NHL).

[56] *See also Brock*, 874 F.2d 307 (concluding that *in vitro* studies are speculative and too difficult to extrapolate to whole humans because of the complexities of metabolism and uncertainties of dose equivalents); *Wade-Greaux v. Whitehall Labs.*, 874 F. Supp. 1441 (D.V.I. 1994) (finding that *in vitro* tests are of limited value in understanding the effects of human exposure); *Bourne v. E.I. DuPont De Nemours & Co.*, 189 F. Supp. 2d 482 (S.D. W. Va. 2002) (when experts use *in vitro* tests to show extrapolation to humans, the expert's reliability is viewed with suspicion); *see also* D. Brusick et al., *Genetic Toxicology* in Hayes' Principles and Methods of Toxicology at 1186 (6th ed. 2014) (explaining that *in vitro* experiments are "susceptible to false-positive responses generated by nonphysiological treatment conditions").

[57] *See* Portier Dep. 350:23-351:12 (conceding that the fact that a substance causes genotoxicity or oxidative stress does not establish that it is carcinogenic); D. Eaton, *Scientific Judgment and Toxic Torts – A Primer in Toxicology for Judges and Lawyers*, 12 J.L. & Pol'y 5, 17 (2003) (stating that not all carcinogens increase cancer risk by causing mutation).

[58] *See Monroe v. Zimmer U.S., Inc.*, 766 F. Supp. 2d 1012, 1029-30 (E.D. Cal. 2011) (considering *in vitro* study by plaintiffs' expert because conducting epidemiological research in humans was not feasible); *In re Zicam Cold Remedy Mktg., Sales Practices & Prod. Liab. Litig.*, No. 09-md-2096-PHX-FJM, 2011 WL 798898, at *9-10 (D. Ariz. Feb. 24, 2011) (admitting specific *in vitro* study because of absence of human data).

In addition, mechanistic data is too speculative to extrapolate to disease in humans in a scientifically reliable way because mechanistic experiments do not use routes of exposure that replicate those experienced by humans. For example, many mechanistic studies upon which plaintiffs' experts rely expose rodents to glyphosate or GBHs by intraperitoneal ("IP") injections (injections directly into the body cavity, similar to an intravenous injection).[59] Similarly, plaintiffs' experts rely on studies in which cells sitting in a petri dish were exposed directly to glyphosate or GBHs.[60] No plaintiff in this litigation alleges either route (or even a comparable route) of exposure. Causation opinions based on studies addressing artificial scenarios of exposure are inadmissible, where, as here, the experts offer no methodology for extrapolating from the resulting data to the actual circumstances of the case.[61] Such opinions are particularly untrustworthy where, as here, epidemiology studies utilizing exposure routes that are the same as those alleged by plaintiffs here are available – and show no increased risk.[62]

Similarly, as plaintiffs' experts necessarily concede, the "level of exposure is an important consideration in the formation of NHL from exposure to glyphosate." Jameson Report at 15. But the mechanistic studies test doses far in excess of even the most

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[59] *E.g.*, Portier Amended Report at 58-59, 72 (citing at least 10 IP administration studies); Jameson Report at 30 (citing multiple IP administration studies); Ritz Report at 25 (citing one IP administration study out of the five she discussed).

[60] *E.g.*, Portier Amended Report at 56-61, 70-71 (citing at least 25 *in vitro* petri dish studies); Jameson Report at 30-31 (citing seven); Ritz Report at 25 (citing two); Neugut Report at 19 (citing seven); Weisenburger Report at 9 (citing nine).

[61] *See, e.g., Joiner*, 522 U.S. at 144-45 (holding that district court did not abuse its discretion when it found that animal studies involving mice injected with large doses of alleged toxin were dissimilar to the plaintiffs' situation and thus were unreliable as a basis for expert's opinion as to causation); *Good v. Fluor Daniel Corp.*, 222 F. Supp. 2d 1236, 1244-46 (E.D. Wash. 2002) (finding an expert's methodology unreliable because his *in vitro* testing did not properly account for the different means of absorption in the laboratory instead of the body); *Haim v. HHS*, No. 90-1031V, 1993 WL 346392, at *15 (Fed. Cl. Aug. 27, 1993) (holding expert's testing of chemical on rodents was not analogous to human exposure because he did not explain difference in effect when chemical was injected numerous times directly into brain of rodents as opposed to how chemical affected humans when humans were exposed only to one injection, and not directly into brain).

[62] *See supra* at 10-21; *Lynch v. Merrell-National Labs*, 830 F.2d 1190, 1194 (1st Cir. 1987) (excluding lower-level scientific studies where they stood in the face of significant contrary epidemiological data); *In re "Agent Orange" Prod. Liab. Litig.*, 611 F. Supp. 1223, 1241 (E.D.N.Y. 1985) (excluding lower-level studies of Agent Orange based partly on the court's earlier conclusion that there was significant contrary epidemiological data).

precautionary estimates of human exposure, rendering plaintiffs' experts' use of them invalid.[63] For example, multiple plaintiffs' experts rely on a Bolognesi, et al. 1997 study in rodents. Yet the experimental doses in that rodent study (300 mg/kg (glyphosate) or 900 mg/kg (GBH)) are thousands of times higher than real-world exposures. *Compare* C. Bolognesi et al., *Genotoxic Activity of Glyphosate and Its Technical Formulation Roundup*, 45 J. Agric. & Food Chem. 1957, 1958 (1997) *with supra* at 5 (highest farm worker exposure measured was 0.04 mg/kg and protective EPA reference dose is 2 mg/kg/day). Compounding the lack of scientific fit is the fact that at such high doses, cytotoxicity occurs, meaning that any effect seen is not the result of the compound itself, but of a secondary condition in which the cell is overwhelmed and damaged or destroyed. *See* Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines, Section 4.1.2 (cytotoxicity can lead to "biologically irrelevant positive results"); *Wade-Greaux*, 874 F. Supp. at 1154 (recognizing principle that at some dosage level, virtually any substance, even sugar or salt, can cause malformations).

Certain of the experts' mechanistic opinions are inadmissible for other reasons. Dr. Portier's opinions are derived at least in part by adding up the positive studies and performing more novel statistics instead of actually evaluating the methods and reliability of the studies themselves. *See* Portier Amended Report at 66 (summarizing genotoxicity studies by "Number Positive" and "Number Negative"); *id* at 69-70 (statistical analysis to determine "expected" number of positive studies). An amalgam opinion that lacks verification, general acceptance, or scientific reasoning or standards, is not derived by the scientific method and is inadmissible.[64]

Plaintiffs' experts also rely on two *in vivo* studies (Bolognesi 2009 and Paz-y-Mino 2007) whose methodologies are so flawed that any opinions based on them must be excluded.[65]

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[63] *McClain*, 401 F.3d at 1242 (assessing general causation includes assessment of exposure at human-relevant levels); *In re Zicam*, 797 F. Supp. 2d at 945-46 (same); *Young*, 567 F. Supp. 2d at 133 (excluding expert testimony, noting that without information linking levels of plaintiffs' exposures with known hazardous levels of exposure, the expert's "testimony about the health effects of any such 'exposure' cannot possibly be anything other than conjecture").

[64] *See Young*, 567 F. Supp. 2d at 133; *Allen*, 102 F.3d at 198.

[65] For example, among other methodological flaws, Bolognesi et al. failed to control for exposures to confounding factors that may result in genotoxicity and failed to blind the investigators as to the exposure status (exposed vs. unexposed) of study participants to reduce the risk of bias. C. Bolognesi et al., *Biomonitoring of Genotoxic Risk in Agricultural Workers*

Moreover, the Bolognesi 2009 authors concluded that their study "indicates that the genotoxic risk potentially associated with exposure to [GBH] … is low." *Id.* Dr. Keith Solomon, one of the co-authors, explained that "[w]hen we looked at the differences in the micronuclei between those two groups [exposed and not exposed], we found no difference." *See* R. Arnason, *Toxicologist Pans UN Glyphosate Report*, The Western Producer (Mar. 27, 2015), http://www.producer.com/daily/toxicologist-pans-un-glyphosate-report/. Similarly, the Paz-y-Mino authors have distanced themselves from their 2007 study cited by plaintiffs' experts in a subsequent study[66] that found no evidence of genotoxicity in the same population.[67]

Not surprisingly, both Bolognesi 2009 and Paz-y-Mino 2007 have been deemed low quality by EPA. EPA OPP at 196. Yet plaintiffs' experts reach to interpret data in sweeping ways not supported by the studies and once again disagree with the study authors,[68] lacking any support for doing so other than their own impermissible speculation and *ipse dixit*. Their opinions must be excluded.[69]

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from Five Columbian Regions: Association to Occupational Exposure to Glyphosate, 72 J. Toxicology Envtl. Health, Part A 986 (2009).

[66] Paz-y-Mino and others published another study of the same communities four years later. C. Paz-y-Mino et al., *Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border*, 26 Rev Envtl. Health 45 (2011). The 2011 study reported "no chromosomal alterations in the analyzed individuals" as a result of exposure to GBHs and identified a variety of factors that alone could cause any genotoxicity results discussed in the earlier report. *Id.* at 50.

[67] Flaws in the 2007 study include: (1) a lag time of two weeks to two months between the study subjects' purported aerial exposure to glyphosate and when blood samples were collected, during which the subjects could have encountered any number of chemicals or exposures that confounded the results; (2) a study population that complained of various acute illnesses which could have confounded the results as viral and bacterial infections have been shown to cause DNA damage; (3) a poorly defined control population; (4) freezing of blood samples prior to testing and thus decreasing the reliability of the results; and (5) no indication that a single investigator reviewed the slides in a blinded manner to prevent differences in interpretation or bias in the analysis.

[68] *E.g.*, Portier Dep. 360:17-23 (when questioned regarding the Bolognesi 2009 study investigators' conclusion of "low" genotoxic risk Dr. Portier stated "I don't know how they could possibly come to that conclusion. I can't imagine where they got that from this data.").

[69] *See Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1169 (E.D. Wash. 2009) ("Nothing in *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.") (citation omitted); *In re Accutane Prod. Liab. Litig.*, No. 8:04-MD-2523-T-30, 2009 WL 2496444, at *2 (M.D. Fla. Aug. 11, 2009) ("When an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study."), *aff'd*, 378 F. App'x 929 (11th Cir.

D. Plaintiffs' Experts' Opinions Are Otherwise Inadmissible To Prove General Causation.

Plaintiffs' experts purport to apply the guidelines of epidemiologist Sir Bradford Hill to the relevant glyphosate data as a sum-up of their opinions.[70] First published in 1965, the Bradford Hill guidelines are an oft-cited set of nine "viewpoints" or factors considered by epidemiologists when evaluating whether "the most likely interpretation" of "an association between two variables" is causation. *See* A. Bradford Hill, *The Environment and Disease: Association or Causation?*, 58 Proc. R. Soc. Med. 295, 295 (1965) ("Bradford Hill").[71] It is well-settled, however, that a necessary *predicate* to application of the guidelines is the existence of epidemiology that demonstrates a specific, clear-cut association between the two variables under examination (here, exposure to GBHs and NHL), and any such epidemiological association must be determined by scientifically valid reasoning and methodology. *See, e.g.*, *Daubert*, 509 U.S. at 592-93; Bradford Hill at 295 (criteria applied only where observations "reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance").[72]

No such association exists here. For there to be one warranting application of the Bradford Hill guidelines, epidemiology must eliminate confounding factors and differences between the compared subjects. *See, e.g.*, *Daubert II*, 43 F.3d at 1321 ("an epidemiologist would

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2010).

[70] Whether non-epidemiology experts such as Drs. Portier, Jameson, and Nabhan have the qualifications to apply Bradford Hill is "questionable." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig.*, 174 F. Supp. 3d 911, 933 (D.S.C. 2016).

[71] The nine factors are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Bradford Hill at 295-99. "None of [the] nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*." *Id.* at 299.

[72] *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 569 (W.D. Pa. Jan. 13, 2003) ("The Bradford Hill criteria start with an association demonstrated by epidemiology and then apply such criteria as the temporal sequence of events, the strength of the association, the consistency of the observed association, the dose-response relationship, and the biologic plausibility of the observed association.") (quotation omitted); *Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672, 679 (M.D.N.C. 2003) (noting the "first step in the causation analysis pursuant to Bradford Hill is an epidemiological study that has identified an association between two variables") (citation omitted).

take a sample of the population and compare the frequency of birth defects in children whose mothers took Bendectin with the frequency of defects in children whose mothers did not …"); *Hollander v. Sandoz Pharm. Corp.*, 95 F. Supp. 2d 1230, 1237 (W.D. Okla. 2000) (association cannot be established by studies that are "not controlled … and do not eliminate confounding variables"), *aff'd*, 289 F.3d 1193 (10th Cir. 2002); *Soldo*, 244 F. Supp. 2d at 569 (same). Plaintiffs' experts fail to meet this predicate.

Nor do plaintiffs' experts faithfully apply the guidelines in any event. For example, retroactive case-control studies cannot reliably evaluate *temporality* because the cases were diagnosed with cancer before the study began. *Reference Manual* at 560-561 (where "both exposure and disease are determined in an individual at the same point in time, it is not possible to establish the temporal relationship between exposure and disease … which would be necessary for drawing any casual inference.") Point estimates for associations below a RR of 2.0 would not satisfy the *strength* criterion. *See supra* at 12-21; *Reference Manual* at 612 n.193 ("[S]tudies that find a relative risk less than 2.0 should not be sufficient for causation.") The robust AHS cohort study found no evidence of a *dose response*. *See supra* at 12-14. No *consistent* positive data specific to glyphosate compounds across studies exists. *See* Neugut Dep. 158:23-159:6. And *specificity* is not particularly useful for determining causality in cancer, because there are exposures associated with many cancer types. Fundamentally, plaintiffs' experts' failures cannot be saved with an incantation of purportedly magic words.

Whatever wrap-up methodology they offer, plaintiffs' experts also fail to meet the core *Daubert* factors. For example, as discussed above, many of plaintiffs' experts rely on novel or untested theories – such as Dr. Portier's ever-changing statistical techniques – with unknown error rates. *See supra* at 24-29. In other instances – such as Dr. Jameson's hypothesized extrapolation from rodent data to human NHL – the error rate is simply impermissibly high. *See, e.g.*, Jameson Expert Dep. 304:20-25 (Q. "By the use of the term 'potential,' you mean that if an experimental animal study shows cancer, it has a more than 50 percent likelihood of being a human carcinogen, true? A. I don't know that you can put a percentage on it."). Likewise, many of plaintiffs' experts – again such as Dr. Portier – advance their methodology specifically

for this litigation, meaning that those methods have never been subject to peer review and lack the general acceptance of the scientific community. *See supra* at 24-29. Plaintiffs' experts – such as Drs. Ritz and Weisenburger – also rely on cherry-picked, biased, and confounded data in ways that are far from gaining general acceptance, and in fact have been rejected by the scientific community. *See supra* at n.24. They all miss in every particular instance their obligation to establish "fit." And the proposition that hazard assessments – such as that conducted by Drs. Jameson, Neugut and Nabhan – can be used as surrogates for opinions of a causal relationship also is not accepted in the scientific community. *See supra* at 3 & n.6.

In sum, the methodologies that led to plaintiffs' experts' general causation conclusions have not been published, peer reviewed, generally accepted, or tested and the potential error is unknown or too high to satisfy *Daubert's* exacting standards of reliability.

II. MONSANTO IS ENTITLED TO SUMMARY JUDGMENT BECAUSE PLAINTIFFS HAVE FAILED TO PRESENT ADMISSIBLE EXPERT TESTIMONY TO SATISFY THEIR BURDEN OF PROVING GENERAL CAUSATION.

A district court "shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A "complete failure of proof concerning an essential element of the nonmoving party's case necessarily renders all other facts immaterial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). When ruling on a summary judgment motion, a district court is required to consider only admissible evidence. *See, e.g., Orr v. Bank of America, NT & SA*, 285 F.3d 764, 773 (9th Cir. 2002).

All claims asserted in this toxic tort litigation require plaintiffs to prove general causation. *See Golden v. CH2M Hill Hanford Group, Inc.*, 528 F.3d 681, 683 (9th Cir. 2008); *In re Hanford*, 292 F.3d at 1134; *Daubert II*, 43 F.3d at 1315. Here, general causation is a complex medical and scientific issue that is beyond the knowledge of lay jurors. Accordingly, plaintiffs must present expert testimony to prove general causation. *See Avila*, 633 F.3d at 836; *Hollander*, 289 F.3d at 1214; *In re Mirena IUD Prod. Liab. Litig.*, 202 F. Supp. 3d 304, 310-12 (S.D.N.Y. 2016), *appeal docketed* Nos. 16-2890 & 16-3012 (2d Cir. Aug. 19, 2016).

Plaintiffs have no admissible expert testimony to prove general causation because the opinions of their experts (retained and non-retained) do not satisfy *Daubert*. Thus, Monsanto is entitled to summary judgment as a matter of law. *See, e.g.*, *In re Zoloft*, 858 F.3d at 800 (affirming MDL court's exclusion of general causation opinions and entry of summary judgment in numerous personal injury cases); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig.*, 227 F. Supp. 3d 452, 485, 491 (D.S.C. 2017) (MDL court granting summary judgment in numerous personal injury cases, based on exclusion of general causation opinions); *In re Mirena*, 202 F. Supp. 3d at 327-28 (same); *Arias*, 928 F. Supp. 2d at 24-26 (granting summary judgment in numerous personal injury cases, based on exclusion of general causation opinions regarding glyphosate and NHL).

CONCLUSION

The *Daubert* gatekeeping role requires the Court to "separate[ ] expert opinion evidence based on good grounds from subjective speculation that masquerades as scientific knowledge." *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001) (quotation omitted). In this case, plaintiffs' experts have presented the latter – not the former. This Court should end the masquerade by excluding all of plaintiffs' experts' general causation opinions and entering summary judgment for Monsanto in all Roundup® lawsuits pending in this Court.

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Respectfully submitted,

/s/ Joe G. Hollingsworth

Joe G. Hollingsworth (*pro hac vice*)
(jhollingsworth@hollingsworthllp.com)
Eric G. Lasker (*pro hac vice*)
(elasker@hollingsworthllp.com)
Martin C. Calhoun (*pro hac vice*)
(mcalhoun@hollingsworthllp.com)
Heather A. Pigman (*pro hac vice*)
(hpigman@hollingsworthllp.com)
HOLLINGSWORTH LLP
1350 I Street, N.W.
Washington, DC 20005
Telephone: (202) 898-5800
Facsimile: (202) 682-1639

Attorneys for Defendant
MONSANTO COMPANY