Comments to U.S. Environmental Protection Agency re: Proposed Re-Registration of Glyphosate-Based Herbicides

Submitted by Charles Benbrook, PhD on September 3, 2019

I am submitting these comments on the proposed re-registration of glyphosate-based herbicides by EPA on behalf of Benbrook Consulting Services (BCS). I have not discussed this submission with any past or current BCS clients, and have received no compensation for its preparation. The 31 Attachments cited in these comments will be uploaded in separate submissions: 1-10, 11-20, 21-31. [Attachments are hyperlinked in this text when possible.]

I. Background and Qualifications

My first involvement with glyphosate came in 1982, as the Department Operations, Research, and Foreign Agriculture (DORFA) Subcommittee of the House Committee on Agriculture conducted oversight hearings on pesticides that addressed, among other things, the Industrial BioTest Laboratories (IBT) debacle. I served at that time as the DORFA Subcommittee Staff Director.

Monsanto's Roundup was among the many then-registered pesticides for which essentially the entire chronic toxicology database had been generated by IBT, and found to be either invalid or fraudulent. This placed all existing Roundup registrations and tolerance petitions in jeopardy, and was a major concern among the professionals in Monsanto's Washington D.C. offices. The senior scientist in that office at the time, Dr. Chester Dickerson, visited me regularly to convey Monsanto's views regarding, among many other things, what the EPA should do to existing, Roundup registrations in response to IBT.

Over the last approximate two years, I have served as an expert witness for plaintiffs in the ongoing litigation triggered by Roundup's role in causing, accelerating, or worsening human cases of non-Hodgkin lymphoma (NHL). As part of my work on the litigation, I have filed three expert reports, each about 200 pages in length. I have been deposed six times, producing around 60 hours of sworn, recorded testimony. I have testified in two of the three trials that have been held to date.

The unsealed version of my expert report in the Hardeman case in Federal Court is included in these comments, and is Attachment 1.

As an expert in the litigation, I have had access to the 7 million-plus Monsanto documents that are part of the litigation's discovery record. I have spent about 2,000 of hours tracing the research, analytical work, and actions of Monsanto relative to their internal assessments of glyphosate and Roundup exposures, toxicology, use, and risks, with a special focus on: (a) the information Monsanto shared with the Environmental Protection Agency (EPA), compared to what it knew internally; (b) safety-related communications to users of Roundup herbicides via product labels, and marketing and educational materials; and (c) data, information, and

scientific findings and opinions shared within the scientific community via Monsanto-commissioned peer-reviewed papers, Monsanto-conducted peer reviews of other papers submitted for publication, commentaries, and the participation of Monsanto scientists and consultants at professional meetings.

I have published, as a sole author or co-author, seven peer-reviewed papers on glyphosate and GBHs use, safety, and regulation. Several of my papers address issues critical to EPA's re-registration analysis of glyphosate and the agency's ultimate decision. Two papers have focused on the remarkable growth in GBH use:

- Attachment 2. Benbrook, C. 2012. "Impacts of genetically engineered crops on pesticide use in the U.S. – the first 16 years" *Environmental Sciences Europe*, Vol 24, https://enveurope.springeropen.com/articles/10.1186/2190-4715-24-24).
- Attachment 3. Benbrook, C. 2016. "Trends in glyphosate herbicide use in the United States and Globally" and was published in *Environmental Sciences Europe,* Vol 28:3; DOI 10.1186/s12302-016-0070-0.

Two have addressed public health risk:

- Attachment 4. Meyers, P et al. 2013. "Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement," *Environmental Health* (Volume 15:19; DOI 10.1186/s12940-016-0117-0).
- Attachment 5. Vandenberg, L. N., Blumberg, B., Antoniou, M. N., Benbrook, C. M., Carroll, L., Colborn, T., Everett, L. G., Hansen, M., Landrigan, P. J., Lanphear, B. P., Mesnage, R., Vom Saal, F. S., Welshons, W. V., & Myers, J. P., "Is it time to reassess current safety standards for glyphosate-based herbicides?," *Journal of Epidemiology and Community Health*, 2017, 71(6), 613-618. DOI: 10.1136/jech-2016-208463. https://jech.bmj.com/content/jech/71/6/613.full.pdf.

Three focus on risk assessment and regulatory challenges posed by the rapid adoption of genetically engineered crops, and in particular, glyphosate-tolerant, Roundup Ready crops:

- Attachment 6. Benbrook, C. 2019. "How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?," *Environmental Sciences Europe*, 2019, 31(1). DOI: 10.1186/s12302-018-0184-7. https://enveurope.springeropen.com/articles/10.1186/s12302-018-0184-7.
- Attachment 7. Benbrook, C. 2018. "Why Regulators Lost Track and Control of Pesticide Risks: Lessons From the Case of Glyphosate-Based Herbicides and Genetically Engineered-Crop Technology," Current Environmental Health Reports, 2018, 5(3), 387-395. DOI: 10.1007/s40572-018-0207-y. https://www.ncbi.nlm.nih.gov/pubmed/30003510.
- Attachment 8. Benbrook, C. 2016. "Enhancements Needed in GE Crop and Food Regulation in the U.S," *Frontiers in Public Health*, 2016, 4, 59. DOI: 10.3389/fpubh.2016.00059. https://www.ncbi.nlm.nih.gov/pubmed/27066473.

One paper has discussed critical issues arising from the diversity of GBH formulations and the need for more accurate and full disclosure of what chemicals are in a formulated GBHs sold to the public:

- Attachment 9. Mesnage, R, Benbrook, C, Antoniou M.N. 2019. "Insight into the confusion over surfactant co-formulants in glyphosate-based herbicides," *Food and Chemical Toxicology*, 128:137-145. https://doi.org/10.1016/j.fct.2019.03.053

II. EPA's GBH Re-registration Analysis Largely Ignores Applicator Exposures and the Significant Differences Between Exposures to Technical Glyphosate Versus a Formulated GBH

The human health risk assessment conducted by EPA on glyphosate-based herbicides, and which support the Agency's proposed regulatory decision and actions, is seriously flawed and are out of step with the latest science.

The most serious problem is that the EPA's risk assessment conclusions are, by the Agency's own admission, limited to exposures to technical glyphosate based on routine, expected levels of residues in the diet. The decision by EPA to focus largely on exposures to technical glyphosate via the diet ignores the much higher exposures and risks faced by people applying a glyphosate-based herbicide with handheld, backpack, ATV, or truck-mounted equipment.

Glyphosate-based herbicides are by far -- indeed by about 3-X -- the most heavily applied pesticide in the U.S. and globally in history (see Attachment 3 for details). In addition to frequent use on the majority of farms in the U.S., there are dozens of formulations of GBHs marketed for use around homes, barns, corrals, in and around gardens, and out buildings; along fence lines, irrigation ditches, railroads and powerlines; and, in a diversity of spaces where efforts are made to suppress weed or vegetative growth.

Small-scale application equipment results in much higher exposures per hour of spraying than large-scale commercial application equipment. This is because the applicator walks or rides through the just-sprayed area, and is inevitably exposed to a certain amount of the spray solution. In addition, conditions conducive to much higher exposure episodes are common and essentially unavoidable. These include heavier applications and over-application on hard-to-control, mature weeds; spraying on a windy day; exposures caused by a slow leak in the hand wand, or a valve or tube in the application equipment; and/or exposures when mixing and loading the spray solution into the sprayer, or when cleaning, fixing, or carrying out routine sprayer maintenance.

These risks impact the people carrying out the tens of millions of applications of a GBH made every year in the U.S. with small-scale equipment. In 2001 or early in 2002, Monsanto commissioned a UK consulting firm to conduct a detailed study measuring applicator exposures to glyphosate under major UK-Roundup application conditions (Attachment 10; Pilliod v. Monsanto, Exhibit 0026).

The UK study focused on a number of different Roundup application methods and scenarios including tractor mounted sprayers with and without a cab, and a variety of handheld-wand application methods and scenarios. Exposures were estimated in all scenarios: (a) during mixing and loading operations, (b) as a result of applications, and (c) via inhalation of spray solution. Moreover, exposure estimates were reported by application volumes, and duration of spraying and exposures (typically a work day, or 6 hours of spraying).

Exposures were estimated on the applicator's hands with and without gloves, and on their trunk and legs, with and without impermeable clothing. In the case of a tractor mounted, low-volume spray application, the report estimated dermal exposure at 1,122 mg/day without gloves, and 174 mg/day with gloves -- a reduction greater than six-fold just from wearing gloves.

In section "E. Predicted Exposure" for this application scenario, the report states that the "no gloves" scenario results in applicator exposures of 0.7 mg/kg/day (i.e. 0.7 milligrams of glyphosate per kilogram of the applicator's bodyweight), a level that is 347% of the daily exposure level regarded as acceptable in the UK at that time (0.2 mg/kg/day). But when gloves were worn during mixing and loading and application, estimated exposures drop to 0.12 mg/kg/day, or a level that is 60% of the allowable exposure level. The report highlights this finding "60% AOEL ← OK!".

Scenario 4.2 in the UK report covers a handheld application at a low level of application and low-spray volume, assuming "Gloves at all time + waterproof jacket and trousers + rubber boots" (a high level of PPE). With the listed PPE, exposure is still estimated to be 0.585 mg/kg/day, or 293% of the allowable level.

If the same application scenario were modeled under the PPE provisions listed on a comparable U.S. Roundup label, on which there would be ***NO PPE requirements***, estimated exposures would be far higher, given the PPE "Reduction factor" built into the UK model used to estimate exposures. (Labels for GBHs in the U.S. list wearing long-sleeve shirts and long pants as required PPE, but these are items of clothing, not PPE added to reduce exposure levels). The reduction factors in the UK exposure assessment model include:

- Gloves reduce mixing and loading exposures on the hands to 5% of what they would be without gloves (i.e. a 20-fold reduction), and to 10% of what they would be during application (i.e. 10-fold);
- Impermeable cloths on trunk and legs reduce mixing and loading exposures to 5% of what they would be without such PPE, and 5% during application (20-fold in both cases).

Impact of Wind and Spray Pattern on Exposures

The UK field study also analyzed the impact of spraying with a handheld or backpack sprayer in a pattern parallel to the direction of the wind, versus perpendicular to the wind. When an applicator follows an up-and-back spray pattern that is generally parallel to wind direction, the

wind blows spray solution onto the back of the applicator when walking with the wind, and onto the applicator's front when walking against the wind.

Conversely, when spraying in a pattern that is predominantly perpendicular to the prevailing wind direction, the wind tends to move the spray solution away from the applicator, as opposed to onto his or her front or back.

Tables 3 and 4 in the UK report cover backpack spray applications and report exposure to glyphosate per hour of spraying under a variety of scenarios, including with the wind and perpendicular to the wind (speed 1.95 km/hour). Table 3 reports that spraying perpendicular to the wind reduces estimated exposures per hour by about 35-fold on windy days, and by about 10-fold in the case of an RDA sprayer (a sprayer nozzle that controls droplet size in ways that increase droplet size and reduce drift of spray solution).

The document's Section 6 "General conclusions and proposed actions" states in part: "All studies…except one… showed that contamination of legs represents the major part of exposure." In response, the authors write "Mitigation measures should be proposed to reduce this contamination (???)." And "Field studies…show[n] that the highest contamination of legs occurred when spraying parallel to the wind. ***A mitigation measure could be to recommend spraying perpendicular to the wind***." (Emphasis added)

In addition, the document reports significant uncertainty in the default values for the penetration of glyphosate through clothing in conjunction with PPE, compared to no PPE. Specifically, the authors state that the assumed reduction of glyphosate exposures from impermeable clothing are likely overestimated. This means that UK-regulators, and/or other regulators relying on such models and similar reduction factors to estimate worker exposures, are underestimating actual exposures stemming from mixing and loading and applying Roundup under a variety of scenarios.

EPA Estimates of the Impact of Application Equipment and PPE on Applicator Exposures are Generally Consistent with the UK Findings

The EPA has carried out and refined over several years extremely detailed estimates of the impacts of different application equipment, with and without various combinations of PPE, on typical, expected applicator exposures. The results of EPA's simulations are reported in "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (Attachment 11; November 2016; https://www.epa.gov/sites/production/files/2016-11/documents/handler-exposure-table-2016.pdf).

The surrogate exposure levels are used by registrants and the EPA exposure assessment branch to estimate the need for, and efficacy of worker-safety provisions on pesticide labels. The surrogate values are used to estimate the percent reduction in exposures expected as a result of various new label requirements for PPE, or changes in when and how a pesticide is applied.

In the case of mixer-loader operations with liquids, dermal absorption is estimated as 37.6 ug/lb a.i. with gloves, and 220 ug/lb a.i. without gloves, or a 5.9-fold reduction.
When a pesticide is applied by a backpack or handheld sprayer, dermal absorption is estimated as 29,000 ug/lb a.i. without gloves, and 8,600 ug/lb a.i. with single-layer gloves, a 3.4-fold reduction (the UK analysis was based on an estimated 10-fold reduction, thought by the authors to be high).

Mixer-loader and applicator exposures with a mechanized, pressurized sprayer are estimated by EPA to be 6,050 ug/lb a.i. without gloves, 2,050 with single-layer gloves, and 1,360 with double-layer gloves.

The UK-field study results, coupled with EPA's surrogate tables, show clearly that simply requiring on GBH labels that gloves be worn during all handheld, GBH applications would dramatically reduce exposures from routine spray operations around the home, lawns, and gardens, and in industrial and commercial settings.

Adding a requirement that applicators avoid a spray pattern parallel to the wind would further and markedly reduce exposures. Wearing gloves and spraying a GBH perpendicular to the wind (on windy days) would reduce applicator exposures by well over 10-fold. Wearing gloves and impermeable clothing on legs, and spraying perpendicular to the wind would reduce overall exposures by at least 20-fold.

Yet labels on the vast majority of Roundup and other GBH products sold in the U.S. since 1974 have not included a requirement to wear gloves nor impermeable clothing during applications made with handheld, backpack, ATV, or truck mounted sprayers in order to protect legs, nor a requirement or guidance to spray in a pattern perpendicular to the wind on windy days.

This is a serious deficiency in the newly proposed GBH regulatory decision that the EPA should rectify in its final decision, especially in light of two facts.

First, there are now thousands of individuals suffering from non-Hodgkin lymphoma purportedly caused, or made worse by frequent, multiple applications of Roundup using handheld equipment. The scientific evidence supporting the conclusion that frequent and sometimes heavy applicator exposures to a GBH increase the risk of NHL is strong, especially for individuals that sprayed Roundup or another GBH many times per year, for several hours per day over many years. For a variety of reasons, such individuals almost certainly experience a few to several high-exposure episodes each year. Such exposures are known to increase the risk of NHL compared to comparable levels of exposure spread out over dozens of applications.

Second, in the 1986 Glyphosate Registration Standard, EPA required Monsanto to add to all Roundup labels requirements by mid-1988 a number of worker-safety provisions. These included requirements that: (a) applicators wear gloves, a face shield, and chemical resistant shoes or boots when mixing and loading and applying concentrated glyphosate-based

herbicides; and (b) clothing and PPE worn during spray applications be washed separately, and if heavily contaminated, such clothing should be discarded.

Monsanto objected to the EPA requirement for added PPE as unwarranted and refused to add them to Roundup product labels. In response, the EPA could have initiated a suspension action, possibly leading to cancellation based on failure to fulfill a requirement in a registration standard document. But as a practical matter, the EPA knew it would be challenged and ultimately blocked from cancelling all uses of Roundup over the absence of the PPE called for in its 1986 registration standard document.

Recommended EPA Actions to Address Deficiencies in Glyphosate Applicator Exposure Assessments and Risk Mitigation Measures

Before finalizing the terms for re-registration of GBHs, the EPA should conduct a modern, data-driven assessment of worker-exposure levels. Such an assessment cannot be undertaken until the EPA has a reliable basis for estimating glyphosate's dermal absorption rate when GBH spray solution lands on, or reaches the skin of an applicator, or nearby farm-worker or passerby. In order to resolve the decades-long uncertainty over the amount of glyphosate penetrating the skin of applicators, the EPA should provide funding to independent laboratories to conduct a state-of-the-art re-assessment of the appropriate dermal-absorption rate for formulated GBHs.

Then, taking advantage of the more accurate estimate of glyphosate dermal absorption, the EPA should carry out applicator exposure assessments with formulated GBHs across a range of scenarios, comparable to the scenarios in the EPA's estimates of reference values for exposure as a function of application method, rate, PPE requirements, and application circumstances. The EPA should also provide research funding to independent research teams to validate the updated, EPA applicator-exposure simulation model against actual, measured exposures in carefully controlled and conducted field studies.

For decades, the EPA has incorporated a 3%, "default value" dermal-absorption rate in applicator-exposure assessments. In the EPA's most recent human-health risk assessment, the Agency reduced this rate to 1%, based on highly questionable dermal absorption studies recently submitted to EPA by glyphosate registrants that were conducted by the contract lab DTL. The serious methodological flaws in the DTL method are explained at length in Dr. William Sawyer's expert reports in the ongoing Roundup-NHL litigation (see for example, his Pilliod report; Attachment 12).

A study commissioned in the early 2000s by Monsanto at the contract laboratory TNO reported a 10%, plus or minus 4%, dermal absorption rate following exposure to a concentrated Roundup formulation containing known, high-risk POEA surfactants (Attachment 13). This important TNO study has received significant attention in the ongoing Roundup-NHL litigation because it reports: (a) a dermal absorption rate about three-times higher than EPA's default value of 3; and (b) that the rate of absorption of glyphosate when formulated Roundup lands on skin is around 6-times greater than when technical glyphosate, with no surfactant, falls on

skin. In addition, it is important to note that the TNO report provided to Monsanto should have been submitted to the EPA under the FIFRA Section 6(a)2, but was not.

In summary, EPA's most recent human-health risk assessment, and proposed regulatory decision essentially assumes away, and as a result, then ignores the much higher applicator and occupational exposures and risk faced by people spraying a GBH with small-scale equipment, and predominantly exposed to glyphosate via the dermal and inhalation routes of exposure.

EPA and most GBH registrants are well aware that handheld, backpack, ATV or truck-mounted sprayers lead to far-higher applicator exposures to GBHs per hour of spraying, than exposures experienced by people operating large-scale, modern spray equipment with steel-glass cabs and highly efficient air filtration systems.

Moreover, such occupational and applicator exposures are always to a formulated GBH, not pure, technical glyphosate. Numerous published studies, and Monsanto's own internal studies related to applicator exposures in the field and dermal absorption rates, show clearly that following exposure to Roundup, the glyphosate in the formulation moves through skin faster and to a greater extent compared to technical glyphosate, because of the surfactants in the formulated product.

Moreover, once through skin and inside the body, the POEA surfactants in nearly all U.S.-manufactured GBHs accelerate movement of glyphosate through cell walls, where the chemical can then come into contact with DNA and pose a risk of direct damage to DNA, and/or can trigger oxidative stress that impairs cell function and integrity.

III. EPA's Evaluation of Glyphosate and GBH Genotoxicity

Evidence addressing, and conclusions reached regarding a pesticide's genotoxicity are equivalent to evidence and conclusions regarding a pesticide's mutagenicity. The first round of mutagenicity and genotoxicity studies on glyphosate were commissioned by Monsanto in the 1970s, conducted by IBT, and were found to be invalid and/or fraudulent. The second round was done in the 1980s, and fulfilled the then-existing OPP mutagenicity/genotoxicity data requirements.

Monsanto Seeks Outside Guidance on Glyphosate/Roundup Genotoxicity

Studies published in peer-reviewed journals in the 1990s reported positive evidence of glyphosate's ability to trigger a genotoxic response. Monsanto was deeply concerned that such studies in the scientific literature might lead regulators to take a fresh and deeper look at the genotoxicity of glyphosate and GBHs.

To gauge how serious the threat was, Monsanto hired Dr. James Parry, a leading expert in genotoxicity and genotoxicity testing methods in 1991, to advise the company regarding the

validity of recently published genotoxicity studies. Dr. Parry was a professor in the School of Biological Sciences, University of Wales Swansea, in the UK. Monsanto was considering whether to recruit Parry into their Third Party Network of glyphosate-friendly scientists, but first the company needed to determine if Parry shared Monsanto's critical assessment of published studies reporting a genotoxic response following exposures to glyphosate or Roundup, then the only GBH on the market.

Monsanto hired Parry as a consultant and gave him a first assignment -- reviewing a set of genotoxicity studies reporting one or more positive assays. These included, for example:

- Lioi et al., (1998), Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro, *Mutation Research* 403: 13-20);
- Lioi et al., (1998), Cytogenic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to glyphosate, vinclozolin, atrazine, and DPX-E9636, *Environ. Mol. Mutagenesis* 32: 39-46);
- Bolognesi et al (1997), Genotoxic activity of glyphosate and its technical formulation Roundup, *J. Agric Food Chem* 45: 1957-1962); and
- Clements C, Ralph S, Petras M (1997), Genotoxicity of selected herbicides in *Rana catesbeiana* tadpoles using the alkaline single-cell gel DNA electrophoresis (comet). *Environ Mol Mutagen* 29:277–288.

Parry's first report to Monsanto was dated February 11, 1999 (Attachment 14). This report contained 19 conclusions: (1) six were that certain types of assays showed no evidence of genotoxicity; (2) 6.5 studies/types of assays were positive for evidence of genotoxicity; and (3) 6.5 were equivocal, and would need to be refined and/or repeated.

In the hope of persuading Dr. Parry that the evidence of glyphosate genotoxicity was unreliable, or should be discounted because such evidence was caused by excessive doses or how the glyphosate was administered, Monsanto provided Dr. Parry a more comprehensive set of glyphosate and Roundup genotoxicity studies, including several commissioned by Monsanto for submission to regulators, but never published. All of the Monsanto-commissioned studies provided to Dr. Parry reported no evidence of genotoxicity.

On August 18, 1999, Dr. Parry transmitted his second, and more comprehensive report to Monsanto. At the end of his report, he offered three research recommendations "to clarify the remaining problem..." noted in his analysis. Dr. Parry's third, and most comprehensive report was entitled "Evaluation of the potential genotoxicity of Glyphosate, Glyphosate mixtures and component surfactants." (Attachment 15). The report includes 14 tables, and was based on Parry's review of dozens of genotoxicity studies, including both published and proprietary/unpublished studies.

The report was accompanied by a second document entitled "Key Issues concerning the potential genotoxicity of glyphosate, glyphosate formulations and surfactants: recommendations for future work." In this four-page document, Parry poses eight "Key

Questions"; describes four "Deficiencies in the Data Set"; and, under "Actions Recommended," lists nine areas in need of further research.

Some of Dr. Parry's research recommendations addressed the need for further testing on both technical glyphosate and formulated GBHs, while others were specific to glyphosate technical, formulated GBHs, or the surfactants in GBHs. In this key, third report, Parry states: "I conclude that glyphosate is a potential clastogenic in vitro." (A clastogen is a mutagenic agent which induces disruption or breakages of chromosomes, leading to chromosome deletion , addition , or rearrangement . In short, clastogens damage DNA).

Dr. Parry was unable to draw a conclusion on the clastogenicity of formulated glyphosate-based herbicides because of a lack of studies. He also states that "glyphosate mixtures [i.e. GBHs] may be capable of inducing oxidative damage in vivo [in live animals]."

Monsanto Response to Dr. Parry's Final Report and Research Recommendations

For many months Monsanto continued to discuss internally Parry's recommendations for additional genotoxicity tests, focusing especially on formulated Roundup.

Dr. Parry's final report provided 10 specific recommendations for further research. Depositions with Monsanto scientists in the Roundup-NHL litigation include exhibits and testimony reporting the genotoxicity studies that Monsanto did in response to Dr. Parry's recommendations. The summary table below provides an accounting of Monsanto's actions in response to Parry's genotoxicity research recommendations. This summary table is the result of a detailed analysis I carried out, and reported in my third expert report in the Roundup-NHL litigation (report is still under seal).

Number of Dr. Parry's 10 Specific Recommendations for Additional Genotoxicty Assays that were Acted Upon, Partially Acted Upon, and Not Acted Upon

Fully Acted Upon	Partially Acted Upon	Not Acted Upon
#8	#2	#1
	#5	#3
	#7	#4
	#10	#6
		#9
Total = 1	**Total = 4**	**Total = 5**

In response to Parry's recommendations for additional genotoxicity testing of ***glyphosate technical***:

- 14 assays were recommended in 4 areas (Parry recommendations 1-4)
- Monsanto conducted 1 assay in one area (Parry recommendation #2)
- An adequate number of new assays were conducted in 0 of 4.

In response to Parry's recommendations for additional assays on ***formulated GBHs and GBH surfactants***:

- 70 assays were needed in 6 areas (Parry recommendations 5-10), based on an average of 2 assays on 5 formulations for a given test, and 2 tests in recommendation #4 (mouse liver and mouse kidney),
- Monsanto conducted 26 of the 70 needed assays (37%), including 17 in Parry recommendation #8,
- Zero or 1 assay was carried out in 4 of the 6 areas.

Overall, in response to Dr. Parry's research recommendations, Monsanto carried out 27 of 84 recommended assays (32%), and 0 or 1 assay in 8 of the 10 areas of recommendations.
In addition, Dr. Parry identified six areas of study that were not needed or low-priority. Despite these recommendations, Monsanto carried out 40 assays in these low-priority areas -- considerably more assays than the company conducted in response to Parry's high-priority recommendations (27 assays).

Of the 40 assays done in low-priority areas, 37 were Bacterial reverse mutation assays. In light of the more than two-dozen negative Bacterial reverse mutation regulatory studies that had already been conducted, these additional studies added little to the knowledge base supporting evaluation of glyphosate and GBH genotoxicity.

Monsanto's failure to test formulated Roundup herbicides for genotoxicity, as recommended by Dr. Parry, is a primary reason why the EPA and other regulatory authorities failed for decades to recognize the potential for glyphosate-based herbicides to increase the risk of cancer, including risk of NHL, via genotoxic mechanisms of action.

Dr. Parry's reports arguably triggered an obligation for Monsanto to: (1) submit Dr. Parry's report to the EPA under FIFRA Section 6(a)(2); (2) update Roundup labels to disclose the potential of genotoxicity risk following significant and/or long-term exposures to Roundup; and (3) conduct the various studies proposed by Dr. Parry to further confirm or refute the genotoxicity of formulated GBHs.

Monsanto did not disclose Dr. Parry's reports to EPA, nor has it added a genotoxicity warning on Roundup labels.

EPA and IARC Evaluations of Roundup Genotoxicity

The laboratories conducting Monsanto-sponsored, cell-assay genotoxicity studies on pure glyphosate in the 1980s through 1990s reported no evidence of mutagenic or genotoxic effects. Monsanto concurred with their conclusions and submitted the studies to OPP. Scientists in OPP generally accepted Monsanto's conclusions.

Since the early approvals of Roundup herbicide labels in the 1970s and through multiple re-assessments over the last 40 years, the EPA has stuck with its original determination that glyphosate technical (i.e. nearly pure, 100% glyphosate) is not genotoxic in humans via oral ingestion, at least not at levels of exposure typically expected by EPA in the food supply.

In 1985, the Toxicology Branch in the EPA'S Office of Pesticide Programs (OPP) classified glyphosate as a "possible oncogen" based on the elevated incidence of renal tubular adenomas in male mice in the 1983 Bio/dynamic mouse study. At that time, the Bio/dynamic mouse study was the only valid glyphosate cancer study in the Agency's possession.

Monsanto disagreed vehemently with the Toxicology Branch's determination, and aggressively challenged its scientific basis and the "possible oncogen" classification from the day Monsanto learned of it in 1984 through 1991. In an October 30, 1991 memo entitled "Second Peer Review of Glyphosate," OPP reclassified glyphosate into Group E -- "evidence of non-carcinogenicity for humans." A primary justification for this change in classification cited by EPA was the lack of evidence that glyphosate was genotoxic.

On multiple occasions since the 1980s, the purported absence of evidence of glyphosate genotoxicity has been cited by Monsanto, the EPA, and other regulatory authorities as an important reason to discount other evidence of Roundup toxicity, including more than a dozen elevated rates of tumors in treatment groups reported in the eight valid rat and six mouse oncogenicity studies now available to EPA.

In March 2015, the International Agency for Research on Cancer ("IARC") classified glyphosate and glyphosate-based herbicides as "probable human carcinogens" (Attachment 16). In EPA's September 2016 draft report entitled "Glyphosate Issue Paper: Evaluation of Carcinogenic Potential," the EPA classified glyphosate as "not likely to be carcinogenic to humans."

The most striking differences in IARC's and EPA's assessment of the oncogenic potential of glyphosate and GBHs were in the area of mechanisms and genotoxic potential. Evidence in support of this conclusion is set forth in my 2019, peer-reviewed *ESE* paper "How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides" (Attachment 6).

EPA's and IARC's Evaluation of Glyphosate Genotoxicity

The final version of EPA's key report on glyphosate oncogenicity came out December 12, 2017 and is entitled "Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential." It contains the EPA's assessment of genotoxicity studies conducted on glyphosate technical, and restates the Agency's long-held position -- "The overall weight of evidence indicates there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route." The report makes clear that this conclusion is based on current, labeled uses of GBHs and typical, expected dietary exposures.

EPA'S core conclusion regarding genotoxicity is limited to glyphosate, and does not encompass applicator exposures to GBHs, and is also limited to oral exposures via the diet. These EPA-imposed limits result in the Agency largely ignoring dermal and inhalation exposures to formulated GBHs during and soon after spray applications.

The limited scope and relevance of EPA's genotoxicity evaluation is critical in understanding why EPA and IARC disagree regarding genotoxic risk, and in their differing classifications of glyphosate and GBH oncogenic potential. EPA's conclusion is clearly limited to the general public's average and expected dietary exposures to glyphosate (absent surfactants), whereas IARC's conclusion encompasses all routes of exposure to glyphosate and formulated GBHs, with heavy weight on studies and data reflecting the relatively high human exposures experienced by applicators of GBHs, or by people living in or near areas with heavy GBH use (and hence, people exposed simultaneously to glyphosate and GBH surfactants and co-formulants).

In the September 2016 draft and its 2017 final glyphosate oncogenicity reports, the EPA explains why it's detailed assessment is ***limited to genotoxicity studies on glyphosate technical*** -- the Agency is waiting for the completion of ongoing work by the National Toxicology Program (NTP) on formulated GBH genotoxicity prior to reaching a judgement on differences in the genotoxicity of pure, technical glyphosate, in contrast to GBHs.

Studies Relied Upon by EPA and IARC

IARC's March 2015 classification of glyphosate and GBHs as "probably carcinogenic to humans" was unexpected, and indeed shocking, to most pesticide policy and regulatory experts.

The IARC Working Group that carried out the detailed assessment of glyphosate and GBH toxicity and risk highlighted "strong evidence" of genotoxicity as an important factor supporting its "probable human carcinogen" classification. The basis for IARC's glyphosate classification, and the genotoxicity studies reviewed by the Working Group, are described in detail in the IARC Monograph 112 volume initially released on July 29, 2015 (Attachment 16).

The mutagenicity and genotoxicity studies and assays cited and relied upon by the EPA and IARC differ significantly, as evident in my analysis of the genotoxicity-related tables in the EPA and IARC risk-assessment documents. The data sources and methods used in my analysis are

described in my published paper "How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides." This peer-reviewed paper appeared in *Environmental Sciences Europe* (Attachment 6; Vol. 31, January 14, 2019; https://enveurope.springeropen.com/articles/10.1186/s12302-018-0184-7).

The following discussion focuses on the genotoxicity tables in the September 2016 draft EPA report, because that is the version of EPA's glyphosate oncogenicity report used in my EPA vs. IARC comparison. The genotoxicity-related differences between the September, 2016 and final December 12, 2017 EPA glyphosate oncogenicity report are minor and do not alter any of my empirical findings.

Pages 99-125 of the 2016 EPA glyphosate oncogenic risk assessment discuss studies on "Gene Mutations" involving technical glyphosate. Seven tables in this section identify the specific, mostly regulatory studies on glyphosate technical that were considered by EPA, and reports whether each study presented data positive for one or more genotoxic responses, or were negative for genotoxicity.

The IARC Monograph report has a similar set of tables assessing roughly the same categories of genotoxicity studies addressed in the EPA report, plus four types of studies not considered by EPA (exposed humans, human cells *in vitro* - AMPA, non-human mammals *in vivo* - AMPA, and non-mammalian systems *in vivo* - AMPA; AMPA is the principle metabolite of glyphosate).

Like the EPA report, the IARC Working Group also identifies whether a given study or assay was positive or negative for evidence of genotoxicity. But unlike EPA, the IARC Working Group reviewed mostly studies in peer-reviewed journals on glyphosate technical ***and*** formulated GBHs, whereas EPA focused its review on unpublished, registrant studies on glyphosate technical-- not GBHs.

The data that follow are taken from tables in my "EPA vs IARC Genotox" paper and/or the supplemental tables posted online at the *ESE* website (Attachment 6).

IARC cited 118 genotoxicity studies (number from Table 2). Of these, EPA cited only 51 in its 2016 report, or about 43% of those considered by IARC. Accordingly, IARC considered 67 studies not reviewed by EPA.

The studies cited by IARC, but not EPA included several of the most important *in vivo* studies done in the wake of human exposures to Roundup; these are the type of studies that most scientists, the EPA, and Monsanto regard as most relevant in the evaluation of any chemical's potential to trigger DNA damage in humans.

Of the 118 studies reviewed by IARC, 54 fell in mammalian test categories, and are regarded as more relevant to assessment of glyphosate's potential to trigger human cancer through a genotoxic mechanism of action than studies in non-mammalian organisms.

EPA considered 40 of these mammalian studies/assays, or 74% of the number reviewed by IARC.

Of the five *in vivo* studies on "Exposed Humans" reviewed by the IARC Working Group, three were regarded as positive. These studies were given little or no weight by EPA because they entailed exposures to formulated GBHs, not technical glyphosate (the focus of EPA's review).

IARC reviewed five studies classified as "Oxidative Stress Human Cells *in vitro* - Glyphosate," of which four were positive. EPA considered one of these studies (the positive Mladinic et al [2009b] study).

Results of Registrant-Commissioned Versus Peer-Reviewed Genotoxicity Studies Considered by IARC and EPA

I also conducted an analysis of the outcome of the glyphosate and GBH genotoxicity studies and assays conducted or commissioned by Monsanto or other registrants ("Registrant Studies"), in contrast to studies and assays carried out by scientists not working on behalf of a GBH registrant, and who published their study results in peer-reviewed journals.

All regulatory studies cited in the September 2016 EPA report, or in a Monsanto-commissioned genotoxicity review articles, were analyzed relative to EPA-reported "positive" or "negative" results. Likewise, all studies published in peer-reviewed journals that were cited by EPA and/or the IARC Working Group were identified and analyzed, along with whether they reported "positive" or "negative" genotoxicity results.

Genotoxicity studies/assays in the 2019 *ESE* paper are listed in the seven categories the EPA used to organize its assessment of the glyphosate-technical genotoxicity database. The results of Registrant Studies in each category were compared to the results of studies published in peer-reviewed journals (public literature).

A total of 104 studies on glyphosate technical were identified. Of these, 52 were Registrant Studies and 52 were published in science journals (Table 1).

Of the 52 Registrant Studies assessing the genotoxicity of glyphosate technical, only one reported a positive result (an *in vivo* bone marrow micronucleus study), while 35 of the public-literature studies reported positive evidence of genotoxicity (67% positive).

In the case of studies assessing the genotoxicity of formulated GBHs, registrants conducted 43 studies cited by the EPA and/or in a Monsanto-commissioned review article, and another 65 were published in science journals, for a total of 108.

Across the total 108 genotoxicity studies on formulated GBHs, none of the Registrant Studies reported evidence of a genotoxic response, compared to 49 (75%) of the public-literature studies.

Of the total 95 assays conducted by registrants on glyphosate technical and formulated GBHs, 51 were bacterial reverse mutation studies (54%), only one of which was positive.

The EPA's pesticide testing requirements call for only one bacterial reverse mutation studies on technical glyphosate (see "Table -- Toxicological Data Requirements," page 60976, Federal register, Vol. 72, No. 207, October 26, 2007).

Supplemental Table 11 in Attachment 17 reports the number of assays considered by IARC, but not by EPA, and number considered by EPA, but not IARC.

Across all categories of genotoxicity assays, IARC considered 67 assays not considered by EPA, of which 55 reported one or positive result (82%).

EPA considered 109 mostly Registrant Studies that IARC did not, of which seven reported a positive genotoxic response (6%).

Significant Impact Evident of the Year When Studies were Completed

A review of the results and date when Registrant Studies were conducted, compared to when public literature studies using the same, or similar assay systems, is revealing.

In terms of *in vivo* chromosomal aberration studies on glyphosate technical, the most recent registrant study cited in EPA's September 2016 report was completed in 1994, while two of three public literature studies were done in 2012. In the case of the same type of study on formulated GBHs reported in public literature, seven of eight assays were completed in 2005-2011 (five positive), while no such study/assays on GBHs have been carried out by registrants.

The 15 *in vivo* micronuclei assays carried out by registrants on GBHs were done during or before 2011, all negative. Five of 16 public literature studies were done from 2011 through 2013 (all positive).

In terms of glyphosate technical assays exploring DNA damage in humans, only two registrant studies were completed, one in 1978 and the other in 1982, both of which were reported as negative.

The public literature contains studies reporting the results of 20 DNA damage assays conducted since 2004, 18 of which reported one or more positive result.

Table 4 in my "EPA vs IARC Genotox" paper reports the results of 27 genotoxicity studies published in scientific journals since completion of IARC's glyphosate monograph and the writing of the EPA glyphosate oncogenicity report.

All 11 of these newer studies on glyphosate technical reported positive evidence of a genotoxic response, while 18 out of 19 studies on formulated GBHs reported one or more positive assay result.

The genotoxicity assays designed to detect direct damage to DNA in humans following exposure to a ***formulated GBH*** are the most important in evaluating glyphosate and GBH genotoxicity, and oncogenic potential. In 2001, Monsanto conducted one direct DNA damage study on a GBH formulation, MON 35050. It reported no evidence of oxidative stress in liver or kidney cells.

The public literature reports the results of 32 direct DNA-damage assays since 2005, of which 27 have reported one or more positive responses.

Based on the above analysis, the dramatic differences in the results of genotoxicity assays reported in Registrant Studies, in contrast to assay results appearing in peer-reviewed journals, arise at least in part from advances in genotoxicity testing methods. It is also clear that the EPA's limited assessment of genotoxicity data on formulated GBHs is a major factor explaining why IARC identified "strong evidence" of genotoxicity and EPA expressed no concern over the mutagenicity of glyphosate technical following typical levels of dietary exposure.

In summary, there are two fundamental flaws in EPA's assessment of Roundup genotoxicity. First, the EPA'S near-sole focus on generally old genotoxicity assays testing pure, glyphosate technical. Second, the absence of serious consideration and/or dismissal of dozens of published, positive assay results on formulated GBHs, the herbicide products actually sprayed, and to which people are exposed.

The December 2016 Scientific Advisory Panel (SAP) meeting probed for hours the reasons why OPP dismissed so many genotoxicity studies reporting a positive genotoxic response. An exchange on page 258 of the SAP meeting transcript captures a sentiment expressed many times over the course of the meeting in reference to OPP's dismissal of positive genotoxicity and tumor incidence data:

> "**Dr. Eric Johnson** [member of the SAP]: Yes…[using certain statistical tests and criteria, most genotoxicity studies are negative]. But for some of the other ones like some of the mammalian in vivo tests, I come away with that there's something there, but every time there's something, you're [OPP] saying that well, there's something deficient about it because of so, so, so, so. And then you went further towards the end of your summary and you said, you're ignoring certain in vitro tests because they were not consistent with in vivo tests, meaning in vivo tests being all negative. When, really, some of them were substantial evidence of something going on."
>
> "I just come away with the fact that you are downplaying some of the genotoxicity tests, especially the in vivo ones…And every time there was something positive there you said there's something wrong with this study."

IV. EPA's Glyphosate Cancer Classification

Three primary bodies of evidence are available to determine the contribution of Roundup use and resulting glyphosate exposures to human cancer: genotoxicity studies assessing the possible mechanisms through which exposure to Roundup/glyphosate might trigger or promote damage to DNA and cancerous growths; two-year animal bioassays, also referred to as chronic feeding studies; and, epidemiological studies in exposed versus not-exposed (or lesser-exposed) human populations.

Clear Evidence Supports the Conclusion Glyphosate and GBHs Pose Human Cancer Risks Through At Least Two Mechanisms of Action

In its December 12, 2017 final glyphosate oncogenicity report, EPA clearly did not take into account a significant share of the genotoxicity studies relevant to the evaluation of glyphosate and GBHs. In particular, EPA's inexplicable decision to essentially ignore the studies most relevant to human dermal and inhalation exposures during spray operations -- human and other mammalian *in vivo* assays with formulated GBHs -- renders the EPA's genotoxicity analysis and conclusions as unfinished, unreliable, and inappropriately narrow in scope.

As explained in the previous section, EPA's genotoxicity assessment was limited to studies focused on glyphosate technical, and only typical, expected exposures to glyphosate via the diet (i.e. the "oral route"). Hence, the EPA analysis and conclusions do not apply to other routes of exposure to formulated GBHs, nor to higher-than-typical exposures.

In many accounts of the EPA's analysis and conclusions regarding glyphosate and GBH oncogenicity and genotoxicity, the narrow EPA conclusions that glyphosate poses neither genotox or oncogenic risk via typical levels of dietary exposure are stated generically in ways that seemingly cover all routes of exposure to both glyphosate and formulated GBHs. Certain officials in the Office of Pesticide Programs and the EPA press office are among those failing to assure that public statements about the EPA's glyphosate re-registration analysis remain true to the content of its detailed reports, and grounded in well-supported analytical work.

Any EPA official asserting that the OPP evaluation of glyphosate genotoxicity and oncogenicity applies equally to all routes of exposure, including applicator exposures to GBHs, is stating a personal opinion, and not a finding backed up by credible OPP risk assessments.

In the 216-page final report on glyphosate's carcinogenic potential (EPA, December 12, 2017), about one-third of a page (p. 28) discusses applicator and residential exposures. Another one-third of a page discusses exposure-measurement methodologies in general (section 3.2.2). There is no discussion of the much higher exposures experienced by applicators using handheld, backpack, ATV, and truck-mounted sprayers, nor assessment of how individuals applying a GBH via such equipment for several hours a day, for many days during several months in a year, and over many years face heightened risk of exposure possibly sufficient to trigger genotoxic damage to DNA and elevated risk of certain cancers.

The ORD Evaluation

Gina McCarthy was the Administrator of EPA during the period when the conflicting IARC and OPP glyphosate oncogenicity classification decisions were announced in 2015. In light of the detailed scientific and risk assessment issues in dispute, Administrator McCarthy asked the EPA Office of Research and Development (ORD) to assess the differences in the two analyses and conclusions, in order to advise her office regarding possible steps to resolve or narrow scientific issues and controversies.

The individuals in ORD assigned to carry out this task quickly put together an ad hoc committee of ORD scientists including toxicologists, epidemiologists, and cancer risk assessment experts. Each member appointed to this committee was sworn to secrecy, and instructed that they should not disclose to anyone their participation on the committee, the nature and scope of the committee's scientific work, nor its conclusions. One of the individuals involved in this process told me that the assignment and conditions of participation were highly unusual, but not unexpected given the highly sensitive subject matter.

This committee carried out a comparative assessment of the IARC Working Group's report, and the then-current, draft OPP oncogenicity evaluation report. It carried out an internal meta-analysis of published epidemiological studies assessing the association between GBH use and non-Hodgkin lymphoma (NHL).

The existence of this internal, ORD meta-analysis was briefly mentioned during the December 13-16, 2016 meeting of OPP's SAP. The below passage is quoted from the official SAP meeting transcript:

> "DR. LIANNE SHEPPARD: Yeah. Not statistically significant is different from conflicting, right? Do you agree with that?
> DR. MONIQUE PERRON: So, and that's what I mean. So back to my first statement that we were trying to characterize it a little bit differently so people could see more than just the bottom line. And maybe that got lost in what you're trying to say. And we can take that back in our characterization and improve it in that way.
> DR. LUOPING ZHANG: Luoping Zhang. If I remember correctly actually, EPA yourself, you come back to the meta-analysis, as well. And it has come out positive and statistically significant, as well.
> DR. MONIQUE PERRON: So we have not conducted the meta-analyses for these. No.
> DR. LUOPING ZHANG: I thought I read somewhere --
> DR. MONIQUE PERRON: No.
> DR. LUOPING ZHANG: Just that, you know, in-house analysis or --
> DR. MONIQUE PERRON: No. We don't have access to any of the data. Oh, the meta-analyses. Yes.
> DR. LUOPING ZHANG: Yeah. Meta analysis. Yeah.

> DR. MONIQUE PERRON: ***And we could reproduce probably using the effect estimates. Yes, the meta-analyses. But I don't believe we actually included them in the paper.*** I think that that figure only shows the effect estimates. We could do it. Yes. And it would probably come out exactly the same as some of the ones that you've already seen. In particular, if you look at Chang and Delzel. I think we talked about earlier where they replace effect estimates depending on the study, and they all kind of come out about the same regardless of the study."

In the above, highlighted passage, the word "them" refers to the internal, ORD meta-analysis, and possibly other internal OPP meta-analyses, or alternatively, OPP reviews of published meta-analyses. In the interest of transparency, prior to issuing a final decision on glyphosate re-registration, the OPP should submit to the glyphosate re-registration docket the ORD and any other internal-EPA meta-analyses documents, including those referred to in the above quote from Dr. Monique Perron (an EPA scientist).

The results of the ORD assessment of the conflicting OPP versus IARC assessments of glyphosate oncogenicity and genotoxicity were transmitted to the Office of the Administrator in a four-page memo entitled "Summary of ORD Comments on OPP's glyphosate cancer assessment" and dated December 14, 2015 (Attachment 18). The focus of the ORD assessment was, according to the memo "…was to consider the [OPP] characterization of glyphosate as 'not likely to be carcinogenic to humans,' given IARC's recent decision and looking at the totality of the available cancer database."

Point #3 states that ORD scientists generally concur with the IARC Working Group's conclusion that there is "limited evidence" of carcinogenicity to humans.

Point #5 addresses OPP's assessment of the mechanistic and genotoxicity data. According to the ORD memo:

> "A thorough evaluation of the mutagenic potential of glyphosate was not included in the [OPP] assessment and was not conducted as a part of this review. This aspect of the assessment is important because ***if there is evidence of mutagenic potential or if a mutagenic potential has not been adequately ruled out, then characterization of glyphosate as 'not likely to be carcinogenic' could be problematic for this reason alone, given the lack of a high-quality negative epidemiology study***." (Emphasis added)

Point #6 states that "According to the [EPA] cancer guidelines, characterizing a chemical as either 'carcinogenic to humans' or 'not likely to be carcinogenic to humans' has a high bar with phrases such as 'strong evidence' and 'robust data' included in these descriptors."

The balance of the ORD memo points out several ways in which the glyphosate cancer database does not rise to the level required to support OPP's "not likely to be carcinogenic to humans" classification. In several places, the ORD memo explains, albeit sometimes obliquely, that the glyphosate cancer database is more consistent with a "possible human carcinogen"

classification under EPA cancer guidelines. For example, in the **Summary** section of the memo, ORD notes OPP and IARC agreement that the evidence does not support a "carcinogenic to humans" classification, but then writes:

> "One level down the [classification] continuum puts you at 'suggestive evidence.' For this descriptor, one could argue that the evidence is not strong enough for the 'likely' descriptor but it cannot be dismissed. The positive association (i.e. limited evidence) of carcinogenicity in humans could arguably rule out the last cancer category ('not likely to be carcinogenic to humans')."

So, accordingly to ORD's analysis, the strong evidence of genotoxicity and the limited epidemiological evidence would each, alone, rule out the "not likely" classification chosen by OPP.

ORD also addresses the unusually large glyphosate animal bioassay data. Point #4 in its memo states:

> "A wide range of tumors have been observed in these studies, including adenomas, hemangiosarcoma, lymph, mammary glands, kidney and lung. However, the tumor incidences were generally not statistically significant in pair-wise comparisons and were generally within the range of historical controls. Most tumor types were only observed in one study despite repeat studies within the same strain and similar doses at or above the limit dose. The tumors found in more than one study were in the pancreas and liver, and were observed in 2 of 4 studies in Sprague Dawley (SD) rats. A positive trend was found for male combined renal tubule adenomas and carcinomas in one CD-1 mouse study [Monsanto's 1983 Bio/dynamic study]…The OPP evaluation concluded that all of the tumors were not treatment-related."

ORD then explains a key difference between the EPA's cancer guidelines and IARC's evaluation criteria. In determining whether a given tumor type was "treatment related," OPP insisted on statistical significance using both pair-wise ***and*** trend statistical tests of significance, whereas the EPA cancer risk-assessment guidelines and the IARC Working Group regard a tumor as "treatment related" if its incidence is statistically significant using either a pair-wise ***or*** trend test for significance.

Using either a pair-wise or trend-test to determine whether a given tumor type is "treatment related," or insisting that both be positive is of enormous consequence in the current controversy over OPP's "not likely" classification decision. OPP's insistence that both be positive is clearly not consistent with the clear language on this point in EPA cancer risk guidelines, and is a major reason why the December 2016 SAP concluded unanimously that OPP deviated from EPA cancer guidelines in its evaluation of the glyphosate animal bioassay database.

Epidemiological Data

Following the pattern already described in the first two major categories of the glyphosate cancer database -- genotoxicity and animal bioassays -- the OPP also dismisses multiple,

published epidemiological studies reporting significant associations between the frequency of GBH use and exposures, and risk of non-Hodgkin lymphoma (NHL). There have now been eight published epidemiological studies, seven of which report a positive association.

Likewise, OPP apparently remains unmoved by meta-analyses grouping multiple cohorts, all of which report an association between relatively frequent use of glyphosate and NHL. These include a new, highly refined GBH-NHL meta-analysis conducted in accord with protocols recommended to EPA by the Science Advisory Panel in its final report stemming from the December 2016 SAP meeting.

This definitive, and most recent meta-analysis of the GBH-NHL epidemiological database was conducted by a team of epidemiologist that included three individuals that served on the December 2016 SAP Panel: Dr. Louping Zhang, Dr. Emanuela Taioli, and Dr. Lianne Sheppard.

The results of their analysis are reported in the paper "Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence" (Zhang, L, Rana, I, Shaffer, RM, Taioli, E, Sheppard, L. *Mutation Research/Reviews in Mutation Research*, July-September 2019, pages 186-206; Attachment 19).

The major meta-analysis conclusion stated in the Zhang et al. paper provides valuable new insights that EPA must take into account in finalizing the glyphosate and GBH re-registration process. The abstract summarizes their meta-analysis findings:

> "We conducted a new meta-analysis that includes the most recent update of the Agricultural Health Study (AHS) cohort published in 2018 along with five case-control studies. Using the highest exposure groups when available in each study, we report the overall meta-relative risk (meta-RR) of NHL in GBH-exposed individuals was increased by 41% (meta-RR = 1.41, 95% confidence interval, CI: 1.13–1.75)."

Zhang et al also conducted an assessment of the animal bioassay data and genotoxicity database in determining the mechanisms and plausibility of their reported, meta-analysis results. The last two sentences of the paper's abstract states:

> "We documented further support from studies of malignant lymphoma incidence in mice treated with pure glyphosate, as well as potential links between glyphosate/GBH exposure and immunosuppression, endocrine disruption, and genetic alterations that are commonly associated with NHL or lymphomagenesis. Overall, in accordance with findings from experimental animal and mechanistic studies, our current meta-analysis of human epidemiological studies ***suggests a compelling link between exposures to GBHs and increased risk for NHL***." (Emphasis added)

On June 27, 2019, another important new, pooled epidemiological study was released. The paper was entitled "Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project" (Pahwa, M Freeman LEB, Spinelli, JJ et al. *Scand J Work Environ Health*; Attachment 20).

The critical finding of the Pahwa et al paper aligns with the Zhang et al paper's focus on the risks of NHL among applicators spraying a GBH multiple times per year. The authors state:

> "After adjustment for other pesticides, the OR for NHL overall with "ever use" was 1.13 (95% CI 0.84–1.51), with a statistically significant association for handling glyphosate >2 days/year (OR 1.73, 95% CI 1.02–2.94, P-trend=0.2). In pesticide-adjusted sub-type analyses, the ordinal measure of lifetime-days was statistically significant (P=0.03) for SLL, and associations were elevated, but not statistically significant, for ever years or days/year of use. Handling glyphosate >2 days/year had an excess of DLBCL (OR 2.14, 95% CI 1.07–4.28; P-trend=0.2). However, as with the other sub-types, consistent patterns of association across different metrics were not observed."

Consequences of EPA's 1985 Classification of Glyphosate as a "Possible Oncogen"

Glyphosate-related documents in the discovery record date back to the early 1970s and provide clear evidence why Monsanto was so determined to convince the EPA to change the Toxicology Branch's 1985 classification of glyphosate as a possible human carcinogen -- a classification that remained in place into the fall of 1991.

If that classification had been retained, EPA would have been compelled by law and its regulations through the late 1990s to take several regulatory actions that would have dramatically curtailed growth in Roundup sales.

The most important such action would have been EPA denials of dozens of Monsanto Section 409 food tolerance petitions submitted in the 1980s and early 1990s covering residues of glyphosate in certain processed foods and food ingredients (for a thorough explanation why, see the relevant sections in Attachment 1, my expert report filled as part of the Hardeman case tried in Federal Court in San Francisco earlier this year).

Had EPA continued to regard glyphosate as a possible oncogen, the Agency would have been blocked by the Delaney Clause from approving any Section 409 tolerances. Such denials, in turn, would have blocked EPA from approving the new Roundup registrations and labels needed to allow use of Roundup herbicides on fields planted to genetically engineered (GE), so-called "Roundup Ready" (RR) crops. In addition, denial of all Section 409 tolerances would have blocked the EPA from approving any Roundup label amendments sanctioning pre-harvest desiccation uses of Roundup, uses that are clearly the major source of dietary exposure to glyphosate today.

Classification as a possible, probable, or proven oncogen would have also required that all concentrated Roundup products would have been classified for "restricted use" only. Monsanto knew, as did all pesticide manufacturers, that restricted use classification reduces marketing opportunities and market share. (Under EPA regulations and policy, a "concentrated" pesticide product contains 10% or more of active ingredient by weight).

The vast discovery record in this litigation includes thousands of emails among Monsanto scientists and regulatory officials in which they discuss: (a) the results and implications of the company's internal research and analysis; (b) what information to provide or convey to the EPA; and, (c) Monsanto's responses when independent scientists have published scientific studies raising new, or reinforcing existing hazards associated with exposure to Roundup.

Participation in this litigation has provided me with in-depth understanding of what Monsanto knew, and was concerned about relative to Roundup human health risks, compared to what Monsanto conveyed to the EPA, and other regulators, in hundreds of submissions, letters, petitions, meetings, and campaigns. The discovery record also lays out clearly the multiple, systematic steps Monsanto has taken over the last 40 years to manipulate peer-reviewed scientific literature on core Roundup safety issues.

The company has done so by commissioning outside scientists (internally referred to as its "Third-Party Network" of "glyphosate-friendly" scientists), consulting and PR firms, and a diversity of organizations to publish supposedly independent papers, reports, and commentaries. Such papers and communications were, in fact, largely or partially ghost-written by Monsanto scientists, employees, or consultants, and restate the company's positions and arguments to EPA regarding the validity of published findings raising new Roundup risk concerns. My expert report (Attachment 1) summarizes numerous, such ghost-written papers published in peer-reviewed journals stating that glyphosate, and/or glyphosate-based herbicides (GBHs) pose no genotoxic risk and no oncogenic risk.

The serious ethical deficiencies in the disclosures published as part of multiple, peer-reviewed papers commissioned and controlled by Monsanto are a matter of public record, and are now known to the EPA.

It is important to stress that about a dozen Monsanto-funded and ghost-written scientific publications are frequently cited by the OPP in its glyphosate human-health risk assessment documents, and identified as supporting the OPP's own assessment of core glyphosate genotoxicity, exposure, epidemiology, and oncogenicity studies.

Over the last several decades, it is clear that whenever any scientist or a team of scientists, or a scientific organization like the International Agency for Research on Cancer (IARC) publishes a scientific report raising new or reinforcing existing risk concerns associated with exposure to glyphosate or a GBH, Monsanto immediately produces a detailed critique that typically challenges methods, the data considered, statistical analyses, and the reputation of the scientists.

Monsanto then shares its critique widely through the pesticide industry and allied organizations, and through its Third Party Network of scientists (many of whom are on contract as paid consultants, and bill for any hours they invest in responding to a new study). Depending on the level of concern over a newly published study or report, Monsanto then also shares its critique with its PR firms and consultants, urging them to draw upon the company's critique and

arguments in any and all opportunities to discuss the new science within the scientific community, with media, or in interactions with regulators.

Periodically, Monsanto integrates all such critiques and arguments in a given area -- glyphosate genotoxicity, the results of animal bioassays, glyphosate metabolism and exposure, glyphosate oncogenicity -- in review articles purportedly authored by independent scientists, but which in reality, simply refine and recycle critiques of individual papers and studies initially written by Monsanto scientist and consultants.

Unfortunately, EPA scientists and risk assessors are not aware of, nor have access to, the vast majority of the internal Monsanto communications and documents in the discovery record of the ongoing glyphosate-HNL litigation, including the many documents where Monsanto officials plot their strategies for convincing the EPA to align with the company's views on key science and risk assessment issues.

V. Reproductive, Developmental, and Other Risks Stemming from Exposure to Glyphosate and GBHs

The existing OPP human-health risk assessment of glyphosate is almost exclusively focused on cancer and damage to DNA. There is nearly no analysis of several other possible human health effects from use of and exposure to GBHs that the EPA should assess more deeply prior to completion of the glyphosate re-registration process.

GBH Use Associated with Autism in California

A sophisticated epidemiological study was published by a team of UCLA scientist in 2019 entitled "Prenatal and infant exposure to ambient pesticides and autism spectrum disorders in children: population based case-control study" (von Ehrenstein OS, Ling C, Cui X et al. British Medical Journal 2019; 364 http://dx.doi.org/10.1136/bmj/.1962; Attachment 21).

The paper's unexpected and key finding relative to glyphosate/GBH re-registration is stated in the abstract:

> "Risk of autism spectrum disorder was associated with prenatal exposure to glyphosate (odds ratio 1.16, 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13, 1.05 to 1.23), diazinon (1.11, 1.01 to 1.21), malathion (1.11, 1.01 to 1.22), avermectin (1.12, 1.04 to 1.22), and permethrin (1.10, 1.01 to 1.20). For autism spectrum disorder with intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure to glyphosate (1.33, 1.05 to 1.69)…"

The finding that prenatal exposures to GBHs were the most strongly pesticide exposures associated with the more extreme forms of autism is surprising and warrants further, more in-depth studies.

Given that this high-quality epidemiological study raises a possible linkage between prenatal exposures to GBHs and autism, the EPA should impose the 10-fold added safety factor in adjusting downward the chronic Reference Dose governing acceptable exposures to glyphosate. Such an adjustment is mandatory under the 1996 Food Quality Protection Act (FQPA) when credible evidence suggests that pregnant women, infants and children are more vulnerable to pesticide exposures than other population cohorts.

The lack of reliable residue data quantifying levels of glyphosate in the American food supply and diet is also a major weakness in the EPA's human-health risk assessment of glyphosate/GBHs. Such data are urgently needed to conduct sophisticated glyphosate dietary exposure assessments. The lack of such vital exposure-related data should, by itself, compel OPP to impose the FQP's added 10-fold safety factor.

Absence of reliable dietary exposure data, coupled with the autism findings just published, should compel the EPA to impose the FQPA's added 10-fold safety factor. This action will lower the glyphosate chronic Reference Dose to 0.1 mg/kg/day, in the absence of other adjustments. As a result, several population cohorts would be ingesting levels of glyphosate via the diet that routinely exceed the EPA's "level of concern," and will therefor require the Agency to take steps to reduce dietary exposures.

Liver and Kidney Damage

A worrisome paper published in July 2019 is entitled "Effects of chronic glyphosate exposure to pregnant mice on hepatic lipid metabolism in offspring" (Ren et al, *Environmental Pollution* Vol 254; Attachment 22). The authors report that:

> "The results showed a significant decrease in the body weight and obvious hepatic steatosis with excessive lipid droplet formation in offspring. Moreover, the concentrations of lipids such as triglycerides (TGs), total cholesterol (T-CHO), and low-density lipoprotein cholesterols (LDL-C) increased to a significant extent in both the serum and livers. Furthermore, there were significant differences in the expression levels of the genes SREBP1C, SREBP2, Fasn, Hmgcr, Hmgcs and PPARa, which are related to lipid biosynthesis or catabolism in the liver. ***These results demonstrate that chronic prenatal exposure to glyphosate can result in lipid metabolism disruption in the offspring of mice, as glyphosate exerts a negative influence on the expression of lipogenesis genes***." (Emphasis added)

More than a dozen papers have now been published linking exposures to glyphosate as a risk factor accounting for some of the tens of thousands of cases of fatal chronic kidney disease of unknown origin plaguing male farm workers in hot, humid climates around the world. Attachments 23 and 24 are among the important papers explaining glyphosate's possible contribution to this serious new affliction.

Several papers have been published by a team at Kings College London linking relatively low levels of exposure to glyphosate to non-alcoholic fatty liver disease, a serious health problem

impacting millions of Americans, as well as disruptions in the human GI tract microbiome. A 2017 paper by the team is entitled "Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide" (Attachment 25; Mesnage et al. *Scientific Reports*, January 9, 2017). The team concludes that:

> "The impairment of liver function by low environmentally relevant doses of glyphosate-based herbicides (GBH) is still a debatable and unresolved matter. Previously we have shown that rats administered for 2 years with 0.1 ppb (50ng/L glyphosate equivalent dilution; 4ng/kg body weight/day daily intake) of a Roundup GBH formulation showed signs of enhanced liver injury as indicated by anatomorphological, blood/urine biochemical changes and transcriptome profiling. Here we present a multiomic study combining metabolome and proteome liver analyses to obtain further insight into the Roundup-induced pathology…"
>
> "Overall, metabolome and proteome disturbances showed a substantial overlap with biomarkers of non-alcoholic fatty liver disease and its progression to steatohepatosis and thus confirm liver functional dysfunction resulting from chronic ultra-low dose GBH exposure."

A team based at UC-San Diego published a paper April 2019 entitled "Glyphosate Excretion is Associated with Steatohepatitis and Advanced Liver Fibrosis in Patients With Fatty Liver Disease" (Mills et al., *Clin Gastroenterology and Hepatology* 2019; Attachment 26). According to this paper:

> "Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease in developed countries. Patients with nonalcoholic steatohepatitis (NASH) are considered to be at a higher risk of fibrosis progression and development to cirrhosis and hepatocellular carcinoma."

The authors studied a population of people with NAFLD and write:

> "We report that glyphosate excretion is significantly higher in patients with NASH compared with patents without NASH. In addition, we also report a significant dose-dependent increase of glyphosate exposure with increase in fibrosis stages. For individuals not working in the agricultural or horticultural industries, the primary route of glyphosate exposure is through ingestion of Roundup-treated genetically modified foods and/or non–genetically modified crops such as wheat and oats. Glyphosate excretion was elevated in women, which presumably reflected an increased exposure to glyphosate."

Ramazzini Institute Studies

The most important set of toxicological studies conducted by an independent laboratory on glyphosate and GBHs are currently underway at the Ramazzini Institute in Bologna, Italy. The Ramazzini team has published three papers reporting the results of their 90-day rat pilot study. These papers explore glyphosate's impacts on the GI tract microbiome and glyphosate/GBH genotoxicity (Attachment 27, 28, 29). An additional Ramazzini Powerpoint reports the results of

a recent genotoxicity study (Attachment 30) using both glyphosate and a formulated GBH that confirms the findings of a 1997 paper by Bolognesi and colleagues (Attachment 31)

In October 2019, the Ramazzini Institute will begin the largest and most sophisticated two-year animal bioassay ever conducted on glyphosate and GBHs. The team will test the oncogenic response in rats to low-doses of glyphosate, Roundup BioFlow, and Ranger Pro.

Roundup BioFlow is the EU-reference formulation being used for a variety of studies in conjunction with the ongoing EU reassessment of GBHs. Roundup BioFlow is one of the several new Roundup formulations containing the polyoxylated quaternary ammonium surfactant, as opposed to higher risk, older POEA surfactants.

As originally designed, the Ramazzini bioassay was not going to include a U.S. formulation of Roundup containing a POEA surfactant, rendering the results of the new bioassay not directly relevant to EPA's assessment of glyphosate and GBH oncogenicity. A team of scientists in the U.S. have agreed to collaborate with the Ramazzini Institute's ongoing glyphosate/GBH work, and will provide the funding required to add Ranger Pro to the new bioassay at the same glyphosate-equivalent doses tested in the case of Roundup BioFlow and technical glyphosate.

Ranger Pro is a concentrated GBH developed and registered by Monsanto for non-agricultural applications. It contains one of the common mixtures of tallowamine POEA surfactants used for years in many of the most widely used agricultural and non-agricultural Roundup products in the U.S.

The results from the expanded bioassay will be exceedingly valuable to the EPA, and other regulators around the world, in addressing a number of long-term uncertainties in the evaluation of glyphosate and GBHs:

- The dosage rates are far lower than the doses used in any of the existing animal bioassays;
- The study will include technical glyphosate and formulated GBHs, allowing a direct comparison of toxicity between technical glyphosate and formulated GBHs; and,
- The study will provide data valuable in determining the health benefits that Europeans can expect in the years ahead as a result of the switch from POEA-based GBHs to the much safer, quaternary ammonium surfactant-based GBHs.

VI. Steps Needed to More Accurately Project and Mitigate Now-Proven and Possible GBH Human Health Risks

Prior to a final GBH re-registration decision, the EPA should take necessary steps to calculate more accurately the dermal absorption rate when a formulated GBH lands on human skin. The uncertainty embedded in this key worker-risk assessment parameter is significant and highly consequential, especially for those people applying a GBH as part of their jobs on several days per year for several hours, year after year.

OPP should revert back to the default dermal absorption rate of 3%, until more accurate and independent studies are carried out and submitted to the Agency.

Between now and a final re-registration decision, meaningful steps should be taken to reduce applicator exposures and risk, especially for lawn, garden, industrial and other non-agricultural uses of GBHs. At a minimum:

1. Labels for all products that contain more than 2% glyphosate should include the additional worker-safety provisions called for the in 1986 Glyphosate Registration Standard: gloves, face and eye protection, chemical resistant shoes or boots, and either a double layer of clothing protecting legs, or a chemical-resistant suit.
2. New warning language should be added to product labels stating: (a) Recurrent exposures to this product may increase the risk of damage to DNA and certain cancers, and (b) Extra caution should be exercised to minimize exposures among people applying this, or other glyphosate-based herbicides several days per week for several hours each day during the herbicide spray season.

In addition to the above, commonsense label changes, the EPA should give serious consideration to the risk-mitigation benefits possible through adding new language on all GBH labels focused on the health conditions that may increase an individual's risk of NHL or other lymphatic cancers, following repeated and/or heavy exposures to a GBH. Known, cancer-related risk factors for those applying GBHs include, for example:

- A compromised immune system, or use of medication impairing immune system function;
- Overweight or a history of smoking;
- A previous lymphatic cancer, or a history of cancer in the family; and/or
- Hepatitis B or C.

GBH registrants will likely object to adding such provisions on GBH labels, pointing out accurately that: (a) the Agency does not require such warning language on any other pesticide labels, (b) such warnings are not required by FIFRA, and (c) adding such warnings to all pesticide labels would be an enormous undertaking, raising costs on registrants, pesticide users, and the EPA.

However, the EPA has ample discretion under FIFRA to impose such a requirement only on pesticide products that are widely applied by members of the public, and known to pose some risk of adverse health consequences. Glyphosate-based herbicides are by far the most heavily applied pesticide in the history of the U.S. Vastly more people are involved with applying a GBH every year in the U.S. than the case with all other past, and currently used pesticides. Millions of people annually are exposed to GBHs and glyphosate via the dermal, inhalation, and dietary routes of exposure. There are more instances each year of high, and very-high GBH exposure episodes than the case with any past or currently registered pesticide.

For these reasons, the EPA would be justified in taking such an admittedly unprecedented step to reduce exposures and risks to the full extent possible. The growing list of worrisome,

relatively recent studies suggesting possible, new glyphosate/GBH risk concerns further justifies such EPA action. The simplest, low-cost way to do so would be to provide GBH users information on product labels laying out when, and for whom special precautions are warranted to minimize exposures whenever applying a GBH.

Such contraindications are required on all pharmaceutical products, and for the same reason GBH users should be provided information about pre-existing conditions, or other factors that might enhance their risk of an adverse health outcome from exposures to a GBH.

Need to Reformulate all GBHs

In order to reduce applicator and environmental risks, European regulators forced Monsanto-Europe to phase out all POEA-based surfactants in GBHs. The reformulation of all agricultural and non-agricultural Roundup brands was carried out across Europe in 2012-2014. POEA-based surfactants were replaced by propoxylated quaternary ammonium surfactants known to be 50-100 times less toxic to aquatic ecosystems and human cells.

At the same time, European regulators either cancelled all existing POEA-based GBH registrations, or allowed them to lapse. As a result, by 2015, the majority of GBHs sold and applied in Europe were 50-fold or more less toxic than the GBHs sold previously in Europe, and sold to this day in the U.S.

In the litigation in the U.S. brought by plaintiffs alleging their use of Roundup contributed to their NHL, three cases have gone to the jury. A total of $2.33 billion in punitive damages were awarded, or $582.5 million per person (the Pilliod case involved a husband and wife who both contracted NHL). This is, I believe, the highest per-person, average punitive damage award in litigation involving multiple plaintiffs and three or more trials in the history of U.S. jurisprudence. (Each of the three punitive damage awards were reduced by judges in accord with State and U.S. Supreme Court guidance on the relationship between compensatory and punitive damage awards. After the reductions, the sum of the four punitive damage awards is $81.2 million, or more than $20 million per plaintiff).

One of the factors driving these juries to impose such large punitive damage awards was the evidence presented at trial regarding why Monsanto-Europe reformulated all its Roundup brands in the 2012-2014 period, making them unarguably much safer than the previously sold, POEA-based formulations, and the Roundup ***still sold in the U.S.***

These undisputed facts are, in effect, confirmed by a Monsanto-Europe scientist in an email dated January 25, 2010 sent to senior Monsanto officials in St. Louis. The scientist was discussing pressure placed on Monsanto-Europe to reformulate Roundup in Europe by replacing POEA surfactants with propoxylated quaternary ammonium surfactants. The Monsanto scientist asks his colleagues "…there are non-hazardous formulations so why sell a hazardous one?"

Preharvest Desiccation Uses of GBH

Most Americans are now exposed daily through their diet to glyphosate. This is why 90% or more of the people tested for glyphosate in their urine test positive. While there is remarkably scant data on glyphosate residues in food given the intensity of GBH use and recent biomonitoring test results, the available data shows clearly that pre-harvest desiccation uses of GBHs are the use pattern accounting for the majority of dietary exposures in the U.S. and worldwide.

Based on my ongoing research on GBH use and residues in food, I project that preharvest uses of GBHs that account for less than 5% of agricultural use are responsible for at least 85% of typical dietary exposures for most Americans. Moreover, there is widespread agreement that the economic benefits of pre-harvest GBH applications are marginal. Typically, a grain farmer using a GBH as a harvest aid in northern Montana, North Dakota, or northern Minnesota over a decade can expect to profit from the application in 2-3 years out of 10, loss money in 3-5 years, and about break even in other years.

Such pre-harvest uses of GBHs might meet the basic standard in FIFRA calling for a pesticide's benefits to exceed the risks if there were essentially no risks stemming from dietary exposures to glyphosate. But given recent science raising concerns over glyphosate and GBH contributions to cancer, DNA damage, reproductive problems, autism and other neuro-developmental impacts, and adverse impacts on the human microbiome, it is unlikely that the EPA can defend a determination that exposure to glyphosate and GBHs pose essentially no risk.

For this reason, the EPA should revoke the markedly elevated tolerances approved in order to cover residues of glyphosate in crops treated preharvest with a GBH, and phase out all labels allowing such uses. This step alone will significantly reduce exposures to the general public, and risks stemming from chronic dietary exposures will also markedly fall as a result.