Nos. 19-16636, 19-16708

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

EDWIN HARDEMAN,
Plaintiff-Appellee/Cross-Appellant,

v.

MONSANTO COMPANY,
Defendant-Appellant/Cross-Appellee.

On Appeal from the United States District Court for the Northern District of California, Nos. 16-cv-00525 & 16-md-027451 (Chhabria J.)

ENVIRONMENTAL WORKING GROUP AMICUS CURIAE BRIEF IN SUPPORT OF PLAINTIFF-APPELLEE

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CORPORATE DISCLOSURE STATEMENT

In accordance with Federal Rule of Appellate Procedure 26.1, amicus curiae Environmental Working Group certifies that it is a nonprofit organization that has no parent or subsidiary entities. It has no stock, and therefore, no publicly held company owns 10 percent or more of its stock.

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INTEREST OF AMICUS CURIAE[1]

The Environmental Working Group ("EWG") is a nonprofit, nonpartisan organization with a mission to empower people to live healthier lives in a healthier environment.[2] For more than two decades, EWG has strived to protect human health and the environment through breakthrough research and education, driving consumer choice and civic action. This includes substantial work to support safe, sustainable agriculture, educating consumers on pesticide exposure through food, and advocating for science-backed researched at government agencies.

EWG has a substantial interest in this case due to the widespread use of the probable carcinogen glyphosate, the main ingredient in Monsanto's Roundup, on farms across the nation, which makes its presence on processed foods containing oats, beans, wheat and barley.

EWG has a long history of research on pesticide safety. In particular, EWG has on multiple occasions urged the Environmental Protection Agency ("EPA") to review all evidence linking glyphosate to increased human cancer risk and other

[1] All parties have consented to the filing of this brief. No party's counsel authored this brief in whole or in part, and no party or party's counsel made a monetary contribution to fund the preparation or submission of this brief. No person or entity other than Environmental Working Group made a monetary contribution to the preparation or submission of this brief.

[2] *See* EWG, www.ewg.org.

adverse health effects in human and animal studies. In 2018, along with eight food companies, EWG petitioned the EPA to reduce the tolerance level for glyphosate in oats from 30 parts per million, or ppm, to 0.1 ppm, and to require glyphosate containing product labels to explicitly prohibit the use of glyphosate as a pre-harvest desiccant on oats. In 2019, EWG also commented on the EPA's Proposed Interim Registration Review Decision for Glyphosate, asking the agency to assess the full body of research indicating Monsanto's herbicide Roundup can increase the risk of cancer. In light of these potential hazards, EWG urged the EPA to take action to restrict applications to food crops, and protect applicators and bystanders from harmful exposures.

EWG submits this amicus curiae brief because defendant-appellant Monsanto's arguments that Roundup is safe run contrary to the substantial science in International Agency for Research on Cancer's ("IARC") "probable carcinogen" finding and body of independent research showing a strong connection between glyphosate, including glyphosate-based formulations, and cancer in humans.

INTRODUCTION AND SUMMARY OF ARGUMENT

This appeal raises questions about the reliability of various official assessments of the carcinogenicity of the chemical glyphosate, which is the active ingredient in Monsanto's Roundup. Monsanto relies heavily on EPA's assessment of glyphosate as non-carcinogenic, contending this shows the jury was wrong in finding that Roundup caused Plaintiff Edwin Harden's cancer. In so arguing, Monsanto also tries to discredit the finding of the International Agency for Research on Cancer's ("IARC") that glyphosate *is* a probable carcinogen, saying that EPA's assessment was far more credible than IARC's.

First, EPA's assessment relied heavily on Monsanto-sponsored, often unpublished, studies, whereas IARC considered only peer-reviewed scientific studies. This difference is significant and sheds light on how EPA disregarded established science in favor of the pesticide manufacturer registrants. Notably, of the 95 registrant-conducted genotoxicity studies EPA considered, only one reported a positive association of glyphosate and cancer. By contrast, of the 211 publicly available studies considered by either IARC or the EPA, 156 reported at least one positive association between glyphosate and glyphosate-based formulations, or GBFs.

Second, IARC looked at both glyphosate alone and GBFs like Roundup, whereas EPA's assessment narrowly focused on glyphosate alone. Moreover,

many glyphosate-based formulations like Roundup are more toxic than glyphosate alone. No herbicide products contain glyphosate alone, and therefore, GBFs account for all commercial uses and human exposures. EPA's narrow focus on glyphosate alone fails to capture the real and urgent risks from glyphosate.

Third, IARC considered hazards from multiple routes of exposure, including occupational, whereas EPA largely limited its assessment to dietary risks in the general population from residues in food from legal applications of glyphosate. Accordingly, EPA's assessment failed to properly evaluate the much-higher levels of exposure to people who actually apply GBFs through handheld or hand-directed applicator wands many days per year or hours per day. Applying a GBF many days per year, for several hours per day, likely leads to much higher exposures than dietary exposure.

IARC's assessment is also complete, accurate, and reliable, because it does not have a bias or policy preference to classify chemicals as probably or possibly carcinogenic. Of the more than 1,000 chemicals IARC has evaluated, only 120 are classified as "known human carcinogens" and only 83 chemicals are classified as "probable human carcinogens."

Finally, the EPA's own independent Office of Research and Development ("ORD") recognized the shortcoming of EPA's analysis and scientific support and strongly suggested a different result was warranted. In pointing out the many

deficiencies in the studies EPA relied upon, ORD ultimately recommended EPA should expand the discussion of cancer data, include a detailed discussion as to why EPA differed from IARC's assessment, and directly address IARC's findings.

Upon reviewing the scientific deficiencies in EPA's methods and findings, Monsanto's heavy reliance on EPA's assessment to cast doubt on the jury's finding that Roundup caused Plaintiff's cancer is misplaced because EPA's findings are unreliable and untrustworthy.

ARGUMENT

I. EPA'S ASSESSMENT IS UNTRUSTWORTHY BECAUSE IT FAILED TO LOOK AT GLYPHOSATE-BASED FORMULATIONS, OCCUPATIONAL AND DIETARY EXPOSURE, AND PEER-REVIEWED, INDEPENDENT STUDIES.

a. EPA's determination glyphosate is "not likely to be carcinogenic" is unreliable and untrustworthy.

At trial and on appeal, Monsanto trivializes the science supporting IARC's assessment that glyphosate is "probably carcinogenic to humans" and attempts to bolster the EPA while ignoring the lack of science behind EPA's conclusion glyphosate is "not likely to be carcinogenic to humans." Despite convincing the district court to exclude evidence of Monsanto's aggressive attempt to discredit the IARC's assessment, Monsanto now argues the court erred in excluding evidence that numerous regulatory bodies have rejected IARC's conclusion and refusing "to allow Monsanto to elicit EPA's full explanation for rejecting IARC's conclusion." (Monsanto Brief ("MB") 28). In support of this argument, Monsanto contends the EPA and other international regulatory bodies have conducted a more thorough review of glyphosate than IARC.

IARC is a subdivision of the World Health Organization and was established in 1965 for the purpose of "identify[ing] the causes of human cancer."[3] In 1970, IARC adopted a resolution to "provid[e] government authorities with expert, independent, scientific opinion on environmental carcinogenesis" and "prepare monographs on the evaluation of carcinogenic risk of chemicals to man."[4] The monographs initially assessed cancer risk from chemicals but have subsequently been expanded to include "evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations."[5] IARC refers to the entities or circumstances subject to an evaluation in a monograph as "agents."[6] IARC selects agents for review based on two factors: (a) there is evidence of human exposure, and (b) there is some evidence or suspicion of carcinogenicity.[7]

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[3] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 8 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[4] *Id*.

[5] *Id*.

[6] *Id* at 10.

[7] *Id* at 11.

International working groups composed of independent scientists prepare the monographs, which are qualitative in nature.[8] Invited specialists, representatives of national and international health agencies, and observers with relevant scientific credentials also participate in the process.[9] Importantly, IARC's monographs "do not overstate the strengths of available evidence" but are "conservative in nature."[10]

In 2015, a working group of 17 experts from 11 countries assembled for IARC to review existing data from epidemiological studies in people and research on laboratory animals on the toxicity of glyphosate and glyphosate-based formulations ("GBF"). Upon the conclusion of IARC's working group's assessment, IARC classified the chemical as "probably carcinogenic to humans" ("IARC Assessment").[11] PSER 509-10. In reaching its finding, IARC found that there was sufficient evidence of carcinogenicity in animal studies and strong

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[8] *Id* at 1.

[9] *Id*. at 11-12.

[10] Int'l Agency for Research on Cancer, *IARC Response to criticism of the Monographs and the glyphosate evaluation*, January 2018, https://www.iarc.fr/wp-content/uploads/2018/07/IARC_response_to_criticisms_of_the_Monographs_and_the_glyphosate_evaluation.pdf.

[11] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 398 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

evidence that glyphosate effects cellular changes in ways characteristic of known carcinogens.[12] IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans, in vitro and studies in experimental animals" and strong evidence of "oxidative stress" in "humans in vitro."[13]

IARC made its "probably carcinogenic to humans" finding while glyphosate was undergoing a re-registration review at EPA, which is required every 15 years under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). *See* 7 U.S.C. § 136a(g). As part of that process, EPA's Office of Pesticide Program ("OPP") released an issue paper on the carcinogenicity of glyphosate in September 2016 ("EPA's 2016 Issue Paper"). EPA's 2016 Issue Paper found that "[t]he strongest support is for 'not likely to be carcinogenic to humans' at doses relevant to human health risk assessment for glyphosate."[14] In December 2016, EPA's Scientific Advisory Panel (SAP) reviewed EPA's 2016 Issue Paper and issued a

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[12] *Id*.

[13] *Id*. at 306.

[14] EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 140 (Sept. 12, 2016), https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

report in March 2017 ("SAP Report"). PSER 487. The SAP Report had "conflicting views on how to interpret the overall results for NHL." PSER 487-88. Some reviewers also thought "its conclusion of 'not likely to be carcinogenic to humans'" should be rejected. PSER 572-74. Nonetheless, EPA revised its 2016 EPA Assessment in December 2017, concluding again in an issue paper ("EPA 2017 Issue Paper") that the "strongest support is for 'not likely to be carcinogenic to humans.'"[15]

On the same day EPA's 2017 Issue Paper was released, EPA also released a Draft Human Health Risk Assessment in Support of Reregistration Review.[16] EPA then issued a Proposed Interim Registration Review Decision in April 2019[17] and an Interim Registration Review Decision in January 2020.[18] In each of these

[15] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 143 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073.

[16] EPA, Office of Pesticide Programs, *Health Effects Division, Glyphosate: Draft Human Health Risk Assessment in Support of Registration Review*, at 12 (Dec. 12, 2017) (EPA 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0068.

[17] EPA, *Glyphosate: Proposed Interim Registration Review Decision*, Docket EPA-HQ-OPP-2009-0361-2344 (Apr. 2019), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-2344.

[18] EPA, *Glyphosate: Interim Registration Review Decision*, Docket EPA-HQ-OPP-2009-0361 (Jan. 2020), https://www.epa.gov/sites/production/files/2020-01/documents/glyphosate-interim-reg-review-decision-case-num-0178.pdf.

papers, despite IARC's Assessment, EPA continued to assert that glyphosate was "not likely to be carcinogenic to humans."

b. EPA placed significant weight on unpublished registrant studies, whereas IARC focused on independent, peer-reviewed studies.

IARC and EPA relied on different sets of studies to reach their respective cancer determinations. As a matter of course and in the interest of full transparency, IARC depends only on published peer-reviewed papers or publicly available data contained in government agency reports when it assesses the carcinogenicity of an agent.[19] This is in part because peer-reviewed publications and reports contain detail on the studies, materials and methods used in the publication so that anyone reading the report can independently evaluate the study, co-funders, and potential biases. [20] Unlike IARC, EPA's glyphosate assessments relied heavily on unpublished data submitted by pesticide manufacturer registrants or summarized in review articles sponsored by registrants.[21]

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[19] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 12 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[20] United States. Cong. House. Committee on Science. *Hearing on the International Agency for Research on Cancer* (IARC), Feb. 6, 2018. 115th Cong. (statement of Jennifer Sass, Ph.D., Natural Resources Defense Council), https://science.house.gov/imo/media/doc/Sass%20Testimony.pdf.

[21] *Id*.

Moreover, the EPA's criteria for considering a study in its assessments is vague.[22] In the 2017 EPA Issue Paper states that studies are "considered based on their relevance to answer specific questions" and that relevant studies are then "further considered for their usefulness."[23] The EPA does not explain what it considers "relevant" or "useful."[24]

As a result of these different policies, IARC and EPA relied on different studies in their cancer hazard assessments. For example, IARC excluded two peer-reviewed articles that EPA heavily relied on because the data was not publicly available.

The 2017 EPA Issue Paper states, "data and summaries provided in Greim et al. (2015) and Kier and Kirkland (2013) were relied upon for the current evaluation."[25] Importantly, both the Greim et al. (2015) and Kier and Kirkland

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[22] *Id*.

[23] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 20 (December 12, 2017) (OPP 2017), https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=OPP&dirEntryId=337935.

[24] *Id.*

[25] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 22 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073,

(2013) summaries were *Monsanto-sponsored* and the underlying data in Kier and Kirkland was not made available to the EPA. This forced EPA to rely instead on summaries included in both review articles.[26] Because Monsanto sponsored these studies, EPA could not independently review or verify the study.[27]

Because IARC relies on publicly available sources only, it determined that it could not use the Kier and Kirkland (2013) review article because it "did not meet the criteria for data inclusion as laid out in the Preamble to the IARC Monographs," as the original studies were not publicly available.[28] IARC also looked at the Greim et al review article and found that of the five studies included, only two were public. IARC did consider the findings from the two publicly available underlying studies but was unable to assess the remaining three in the Greim et al. article because "the information provided in the review article and its supplement was insufficient (e.g., information was lacking on statistical methods,

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[26] United States. Cong. House. Committee on Science. *Hearing on The International Agency for Research on Cancer* (IARC), Feb. 6, 2018. 115th Cong. (statement of Jennifer Sass, Ph.D., Natural Resources Defense Council), https://science.house.gov/imo/media/doc/Sass%20Testimony.pdf.

[27] *Id*.

[28] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 365 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture.)."[29]

The inclusion and exclusion of different kinds of studies, and the weight given to those studies, starkly impacted the outcome of each agency's cancer analysis. This is particularly true with regard to the genotoxicity studies. A comparison of the IARC Assessment and EPA's 2016 Issue Paper found that 95 of the 151 genotoxicity studies cited in EPA's risk evaluation were from registrant studies, including Monsanto studies, *whereas 100% of IARC's genotoxicity studies were public literature sources*.[30] Of the 95 registrant-conducted genotoxicity studies EPA considered, only one reported a positive result.[31] By contrast, among the 211 publicly available studies considered by either IARC or the EPA, 156 reported at least one positive result.[32] Overall, EPA cited 109 total studies that

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[29] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 354 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[30] C.M. Benbrook, *How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?*, 31 Envtl. Scis. Europe 1 (2019), at 6 https://hygeia-analytics.com/wp-content/uploads/2019/01/MASTER_ESE_Genotox-SUPP-TABLES_01-05-19.pdf (Table S11).

[31] *Id*.

[32] *Id*.

were not included in the IARC report, 95 of which were registrant studies, and only one of the registrant studies showed a positive association between glyphosate and genotoxicity.[33] IARC relied on 67 publicly available studies that were excluded by EPA, 55 of which reported a positive association between glyphosate and genotoxicity.[34]

As discussed above, EPA largely relied on Monsanto-sponsored summaries of Monsanto-sponsored data. In fact, EPA admits in its assessment that all review articles except one "were funded and/or linked to Monsanto Co. or other registrants."[35] This is a clear example of EPA ignoring published scientific data in favor of industry. Most startling are the now publicly known communications and collusions between Monsanto and Jess Rowland, who led the EPA Cancer Assessment Review Committee for glyphosate. Monsanto internal emails show that Rowland told a Monsanto employee in 2015 that he would try to prevent the Department of Health and Human Services ("DHHS") from releasing its own

[33] *Id*.

[34] *Id*.

[35] EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 22 (Sept. 12, 2016) (OPP2016), https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

glyphosate hazard assessment.[36] Additionally, in a 2015 email, a Monsanto regulatory employee remarked in an email that Rowland "could be useful as we move forward with ongoing glyphosate defense."[37] Monsanto worked with EPA staff to encourage the Agency for Toxic Substances and Disease Registry ("ATSDR") – a federal public health agency within the DHHS charged with investigating environmental health threats – to delay or shelve its toxicity assessment on glyphosate.[38] Similarly, on June 21, 2015, Monsanto scientist Eric Sachs sent a text message to former EPA toxicologist Mary Manibusan stating,

[36] E-mail from Daniel J. Jenkins, US Agency Lead, Regulatory Affairs, Monsanto Company, to William Heydens and Jennifer Listello, of Monsanto Company (April 28, 2015, 09:33 AM) https://drive.google.com/file/d/0B-pJR4cGo9ckcE0ydmtFZ2FfYUE/view.

[37] E-mail from Daniel J. Jenkins, US Agency Lead, Regulatory Affairs, Monsanto Company, to Tracey Reynolds, David Heering Ty Vaughn, Tracy McKay, Susan Maritno-Catt, Michael Dykes, Melissa Agustini, Daniel Hegger, and Stacey Starter, of Monsanto Company (Sept. 3, 2015, 01:23 PM), https://drive.google.com/file/d/0B-pJR4cGo9ckSEtrNEE4OHpwb3c/view.

[38] Email from Michale Dykes, of Monsanto Company, to Jim Jones, of EPA (May 19, 2015. 3:28:05 PM), https://usrtk.org/wp-content/uploads/2017/08/May-2015-discussion-ATSDR-EPA.pdf; Email from Jack Housenger, EPA, to James Stephens, ASTDR, and Patrick Breysse, CDC (June 6, 2015, 8:44:00 AM), https://usrtk.org/wp-content/uploads/2017/08/June-6-2015-EPA-ATSDR.pdf.

"we're trying to do everything we can to keep from having a domestic IARC occur with this group. May need your help."[39]

These concerns of collusion compelled Representative Ted W. Lieu to request the EPA's Office of Inspector General to investigate reports that an EPA employee may have colluded with Monsanto to conduct a biased review of glyphosate.[40] In response, the EPA Inspector General opened an investigation that is still ongoing.[41]

Ultimately, ATSDR released its own Toxicological Profile on glyphosate in April 2019 supporting IARC's Assessment.[42] Specifically, ATSDR found that a possible association between exposure to glyphosate and risk of non-Hodgkin lymphoma could not be ruled out, explaining:

> The carcinogenic potential of glyphosate has been evaluated in three meta-analyses (Chang and Delzell 2016; IARC 2017; Schinasi and

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[39] Text Message from Eric Sachs, Scientist, Monsanto Company to Mary Manibusan, former EPA toxicologist (June 21, 2015, 22:39:14 (UTC)), https://usrtk.org/wp-content/uploads/2017/08/Text-Messages.pdf.

[40] Letter from Arthur A. Elkins Jr, EPA, Inspector General (May 31, 2017), https://www.documentcloud.org/documents/3853786-EPA-OIG-Letter-to-Ted-Lieu.html.

[41] *Id*.

[42] Department of Health and Human Services, *Toxicological Profile for Glyphosate: Draft for Public Comment*, at 86 (Apr. 2019), https://www.atsdr.cdc.gov/toxprofiles/tp214.pdf.

> Leon 2014) and a number of case-control and cohort epidemiology studies (see Section 2.19 for detailed information and specific citations). The metanalyses reported positive associations between glyphosate use and selected lymphohematopoietic cancers.[43]

The ATSDR report also found it could not rule out that "risks to children's health."[44] Based on the foregoing, EPA's dependency on non-public, registrant sponsored data and studies cast doubt on the trustworthiness of the EPA's determinations.

c. EPA's evaluation considered glyphosate alone and ignored evidence of risk from glyphosate-based formulations.

IARC evaluated the cancer risks from both glyphosate alone and GBFs, acknowledging that people are rarely exposed to glyphosate alone, and thus it is important to assess the cancer risks from exposures to GBFs.[45] By contrast, EPA's 2016 Issue Paper is focused solely on the active ingredient glyphosate and failed to consider the risks from GBFs like Roundup.[46]

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[43] *Id*.

[44] *Id*.

[45] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 137, 160-63 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[46] EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 19 (Sept. 12, 2016) (OPP 2016),https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

No herbicide products contain only glyphosate, and therefore, GBFs account for all commercial uses and human exposures. Accordingly, EPA's narrow focus on glyphosate alone fails to capture the real and urgent risks from glyphosate for three reasons: (1) co-formulants in GBF can significantly alter the absorption, distribution, metabolism, excretion and possibly the toxicity of the glyphosate in formulated GBFs, (2) Monsanto has known of the danger of formulated GBFs but has failed to study the health effects, and (3) multiple studies report that formulated GBFs are more toxic than glyphosate alone.

First, glyphosate in GBFs are more toxic than the same amount of glyphosate alone due to co-formulants, which are additional ingredients – other than the active glyphosate ingredient – present in a GBF like Roundup. Surfactants are one type of co-formulant that can increase the absorption of a pesticide.[47] By design, surfactants can augment glyphosate toxicity in a synergistic way by accelerating glyphosate's movement into cells.[48] In fact, many co-formulants are

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("Although there are studies available on glyphosate-based pesticide formulations, the agency is soliciting advice from the FIFRA SAP on this evaluation of human carcinogenic potential for the active ingredient glyphosate only at this time.").

[47] Mesnage R, Bernay B, Séralini GE (2013). *Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity*. Toxicology, 313(2–3):122–8, https://www.ncbi.nlm.nih.gov/pubmed/23000283.

[48] C.M. Benbrook, *How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?*, 31 Envtl. Scis.

more toxic than glyphosate alone.[49] EPA acknowledged this shortcoming, but still failed to consider GBFs in its risk assessment, stating that "glyphosate formulations are hypothesized to be more toxic than glyphosate alone. . . However, the focus of this section is the genotoxic potential of glyphosate technical."[50]

Second, Monsanto has been aware since the 1990s about the increased risk from GBFs but has refused to study the toxic effects of GBFs – sometimes even against the recommendations of its own scientific advisors. In the 1990s, several published studies concluded that glyphosate *and* Roundup are genotoxic. In response, Monsanto retained Dr. James Parry, an expert in genotoxicity, to review these independent studies. Parry noted that Roundup produced a genotoxic response at a 10 times lower concentration than glyphosate alone. PSER 215. He found that another study observed effects from Roundup in mouse kidneys that were not produced from glyphosate alone, which "suggests a synergistic effect of some components of the mixture." PSER 219.

Europe 1, at 8 (2019), https://enveurope.springeropen.com/track/pdf/10.1186/s12302-018-0184-7.

[49] *Id*. at 8-9 (Table 3).

[50] EPA, *Office of Pesticide Programs, Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 99 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073

Another study Parry reviewed found that Roundup could induce DNA adducts in mice, whereas equivalent amounts of glyphosate did not, indicating that "any in vivo activity of Glyphosate may be potentiated by other components of the Roundup mixture." PSER 219-220. Parry concluded that the studies taken together suggested that "Glyphosate is capable of producing genotoxicity, both in vivo and in vitro, by a mechanism based upon the production of oxidative damage." PSER 220. As a result, Parry recommended eight experiments to further study Roundup's genotoxicity to consider the "possibility of susceptible groups within the human population." PSER 235-237. Dr. William Heydens, another Monsanto scientist, responded to Parry's analysis in an internal email:

> However, let's step back and look at what we are really trying to achieve here. We want to find/develop someone who is comfortable with the genotoxic profile of glyphosate/Roundup and who can be influential with regulators and Scientific Outreach operations when genetox issues arise. My read is that Parry is not currently such a person, and it would take quite some time and $$$/studies to get him there. *We simply aren't going to do the studies Parry suggests*.

PSER 239 (emphasis added).

In 2002, Heydens also acknowledged that GBFs might pose risks, stating in an email to Monsanto toxicologist Dr. Donna Farmer, "we are in pretty good shape with glyphosate but vulnerable with the surfactants. . . Glyphosate is OK but the formulated product (and thus the surfactant) does the damage." PSER 283. Farmer also told John Combest, another Monsanto employee in the Public Affairs

Department, that "you cannot say that Roundup does not cause cancer . . . we have not done carcinogenicity studies with Roundup." PSER 244.

Despite scientists' warning of Monsanto's toxicity and urging Monsanto to test thoroughly, Monsanto never researched the toxicity of formulated Roundup or the surfactants in the formulated Roundup product used by consumers. PSER 17-18.

Third, multiple studies report that formulated GBFs are more toxic than glyphosate alone. Several of the studies reviewed by Parry for Monsanto in the 1990s discussed *supra* suggested that GBF is more toxic than glyphosate alone. More recent studies have affirmed the findings that GBF is more toxic than glyphosate alone, in some cases by a large margin.[51] For example, a 2013 study, Mesnage et al. compared the toxicity of nine different GBFs to glyphosate alone found that "all formulations are more toxic than glyphosate."[52]

IARC referenced the 2013 Mesnage et al. study and four others in its analysis of "cell proliferation and death" in finding that "GBFs induced apoptosis

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[51] C.M. Benbrook, *How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?*, 31 Envtl. Scis. Europe 1 (2019),at 11 https://enveurope.springeropen.com/track/pdf/10.1186/s12302-018-0184-7.

[52] Mesnage R, Bernay B, Séralini GE (2013). *Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity*. Toxicology, 313(2–3):122–8, https://www.ncbi.nlm.nih.gov/pubmed/23000283.

in HepG2 cells, whereas glyphosate alone was generally without effect or showed effects only at considerably higher concentrations."[53] EPA's 2017 Issue Paper, however, found that the Mesnage et al. study was "[n]ot Relevant to the current fit for purpose review" and did not include it in its cancer assessments.[54] The EPA also found that both Gasnier studies were "[n]ot Relevant to the current fit for purpose review" and excluded them as well.[55] EPA labeled both the Chaufan and Coalova studies as studies showing "Effects on cellular processes" but did not mark either as "relevant" to its cancer assessment.[56]

IARC considered 85 different studies from the public literature on GBF formulas, 82% of which reported a positive association between GBF exposure and genotoxicity.[57] By contrast, EPA looked at 43 different registrant-produced GBF

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[53] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 392 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[54] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 179 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073

[55] *Id*. at 70.

[56] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 158 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073.

[57] C.M. Benbrook, *How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?*, 31 Envtl. Scis.

studies and 25 GBF studies from the public literature, only 25% of which reported a positive association in studies of GBF exposure and genotoxicity.[58] Notably, all studies provided by the glyphosate manufactures did not report glyphosate genotoxicity.[59] The majority of registrant-produced GBF studies – 65% – were bacterial reverse mutation studies and did not use other types of genotoxicity testing that are able to detect genotoxic effects of GBFs.[60] Other kinds of genotoxic tests are more likely to show a positive association between GBFs and genotoxicity.[61] In comparison, IARC only considered two reverse mutation studies.[62] Overall, IARC considered 41 studies on GBFs that were excluded by EPA, 34 of which (83%) found a positive association.[63]

Europe 1 (2019), https://hygeia-analytics.com/wp-content/uploads/2019/01/MASTER_ESE_Genotox-SUPP-TABLES_01-05-19.pdf (Table S10).

[58] *Id*.

[59] *Id*.

[60] *Id*. at 9.

[61] *Id*.

[62] *Id*. at Table S11.

[63] *Id*.

d. In reviewing glyphosate, IARC considered occupational, residential and dietary exposures to glyphosate, and EPA largely considered dietary exposure.

Critical to the issue of whether Hardeman's exposure to Roundup contributed to his cancer is the extent to which repeat use of glyphosate and GBF in occupational and residential settings contribute to cancer. The IARC Assessment considered occupational, community, dietary, and household exposures to glyphosate in making its cancer determination.[64] EPA largely ignored them. Instead, the EPA focused its hazard analysis and risk calculations on risks from dietary exposure in the general population.

EPA's 2016 Issue Paper of the data led it to conclude that glyphosate was "not likely to be carcinogenic to humans at doses relevant for human health risk assessment."[65] EPA appears to consider "doses relevant for human health risk assessment" to mean residues in food from legal applications of a GBF to crops because that is the exposure pathway EPA emphasizes in both its 2016 and 2017

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[64] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 112, at 40, Table 1.2 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[65] EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 140 (Sept. 12, 2016) (OPP 2016), https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

Issue Paper.[66] EPA purports to "consider all of the anticipated exposure pathways as part of their evaluation for human health."[67] However, EPA's memorandum on EPA's 2017 Draft Human Health Risk Assessment states that "a quantitative occupational risk assessment was not conducted."[68] The memorandum also states that "a quantitative risk assessment was not completed" for residential handlers.[69]

Accordingly, EPA's assessment failed to properly evaluate the much-higher levels of exposure to people who actually apply GBFs through handheld or hand-directed applicator wands.[70] Applying a GBF many days per year, at times for

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[66] *Id*.; *see also* EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 70, 99 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073.

[67] EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 15 (Sept. 12, 2016) (OPP 2016),https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf.

[68] EPA, Office of Pesticide Programs, *Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, at 26 (December 12, 2017) (OPP 2017), https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0361-0073.

[69] *Id*. at 22.

[70] C.M. Benbrook, *How did the US EPA and IARC reach diametrically opposed conclusions on the genotoxicity of glyphosate-based herbicides?,* 31 Envtl. Scis. Europe 1 (2019), https://enveurope.springeropen.com/track/pdf/10.1186/s12302-018-0184-7.

several hours per day, likely leads to much higher, cumulative exposures.[71] People who apply GBFs may also be subject to incidents during which much higher exposures occur because of a leaky hose or valve, wind conditions, a spill or other unforeseen circumstance. EPA knows this. For example, between 2002 and 2008, EPA compiled total of 271 incident reports from these greater than normal exposures to GBFs causing neurological symptoms, dermal irritation, rash or hives, and respiratory duress.[72] EPA's failure to consider occupational and residential exposures raises meaningful questions as to the extent its assessment can be relied upon.

II. IARC's findings are complete, accurate, and reliable.

IARC's Assessment is complete, accurate, and reliable. First, in IARC's Assessment, it classified glyphosate as a "Group 2A" agent, meaning IARC

[71] Alavanja MC, Bonner MR. *Occupational pesticide exposures and cancer risk: a review*. J Toxicol Environ Health B Crit Rev. 2012;15(4):238–263. doi:10.1080/10937404.2012.632358, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6276799/ ("[T]his review will only evaluate occupational exposures to pesticides because workers in certain occupational environments have higher cumulative exposures than do individuals in the general environment.").

[72] EPA, Health Effects Division, *Updated Review of Glyphosate (103601) Incident Reports*, at 3 (Feb. 26, 2009), https://hygeia-analytics.com/wp-content/uploads/2019/01/RUP-EPA-archives-2009-2-26-review-of-incident-reports-lots-of-DERMAL.pdf.

considers that it is "probably carcinogenic to humans."[73] IARC classifies an agent as a Group 2A carcinogen "when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals."[74] Something may also be classified as a Group 2A carcinogen based in part on "strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans," or so-called mechanistic data.[75]

On appeal, Monsanto attempts to trivialize IARC's classification of glyphosate as a Group 2A probable carcinogen by pointing out that "very hot beverages, shift work, and red meat" are also considered Group 2A carcinogens. (MB at 7). However, the vast majority of IARC evaluations have *not* classified agents as "known" or "probable" carcinogens.[76]

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[73] Int'l Agency for Research on Cancer, *Agents Classified by the IARC Monographs, Volumes 1- 125*, https://monographs.iarc.fr/agents-classified-by-the-iarc/.

[74] *Id*.

[75] *Id*.

[76] *Id*.

TABLE OF IARC GROUP FINDINGS[77]

Group	**Group 1**	**Group 2A**	**Group 2B**	**Group 3**	**TOTAL**
Classification	"Known Human Carcinogens"	"Probably carcinogens"	"Possibly carcinogenic to humans"	"Not classifiable"	
Total Number	120	83	314	500	1,017
Percentage	11.7%	8.2%	31%	49.1%	

Accordingly, only 203 agents – 19.9% – fall within the strongest two group.[78] Instead, the vast majority of substances reviewed by IARC fall in either Group 2B, or Group 3.[79] Notably, Group 3 has far more entries than any other group; even more than Group 1 and 2A combined.[80] This data establishes IARC does not have a bias or practice of classifying chemicals in the strongest two groups.

Second, IARC's Assessment is a "hazard identification" and asked whether glyphosate "is capable of causing cancer under some circumstances."[81] Monsanto

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[77] *Id*.

[78] *Id*.

[79] *Id*.

[80] *Id*.

[81] Int'l Agency for Research on Cancer, *Some Organophosphate Insecticides and Herbicides. In: IARC Monographs on the Evaluation of Carcinogenic Risks to*

contends IARC's Assessment "does not amount to a conclusion that glyphosate actually poses a risk of cancer in humans." (MB at 7). However, a hazard identification identifies whether a substance is capable of causing cancer but does not take the additional step of quantifying how much cancer risk increases under different exposure scenarios.[82] In IARC's Assessment, it looked at exposure, cancer data from humans, cancer data from experimental animals, and mechanistic data. As part of its exposure assessment, IARC looks to "production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposure."[83]

Notwithstanding, Monsanto characterizes IARC's Assessment as an "incomplete" finding because it is a hazard identification and does not calculate precise cancer risk levels based on exposure. (MB at 7). Hazard characterization is an essential part of chemical risk assessment. However, Monsanto relies on EPA's 2017 Issue Paper finding that glyphosate is "not likely to be carcinogenic" without

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Humans, Volume 112, at 10, 11 (IARC 2017), https://monographs.iarc.fr/wp-content/uploads/2018/07/mono112.pdf.

[82] National Research Council (US) Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology. *Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*. National Academies Press (US); 2007,vhttps://www.ncbi.nlm.nih.gov/books/NBK10201/.

[83] *Id*. at 25.

acknowledging that "not likely to be carcinogenic" is *also* a hazard determination. (MB at 7). EPA reached that hazard determination, in part, by choosing to ignore risks to residential and occupational applicators of glyphosate. To the extent EPA's issue papers and subsequent risk assessment and interim registration review decisions do calculate glyphosate risk thresholds, EPA's analysis is largely limited to dietary exposure in the general population. Thus, EPA's analysis is incomplete because it disregards the risks from the higher-exposure, repeat use, residential application of glyphosate and GBFs like Roundup that Hardeman alleges caused his cancer.

III. AN INDEPENDENT EPA OFFICE CRITICIZED OPP'S FINDINGS, METHODOLOGY, AND FAILURE TO COMPLY WITH ESTABLISHED EPA CANCER TESTING GUIDELINES.

The EPA's Office of Research and Development, or ORD, ("ORD") conducted an expedited review of OPP's conclusion that glyphosate was "not likely to be carcinogenic to humans."[84] ORD is an independent scientific research arm of EPA staffed by independent scientists. ORD is charged with conducting the research for EPA that provides the foundation for credible decision-making to safeguard human health and ecosystems from environmental pollutants. After its

[84] EPA, *Summary of ORD comments on OPP's glyphosate cancer assessment*, at 1 (Dec. 14, 2015) (ORD 2015), https://usrtk.org/wp-content/uploads/2017/03/ORDcommentsonOPPglyphosate.pdf.

review of OPP's glyphosate cancer assessment, ORD issued a summary of comments, many of which criticized OPP's approach.[85]

First, ORD explained EPA's framework for risk assessments uses causal determinations and that OPP did not follow EPA's standard risk assessment framework.[86] In fact, the ORD epidemiologists *agreed* with IARC that there is "limited evidence" of carcinogenicity in humans, finding:

> ORD's epidemiologists agree with IARC that there is "limited evidence" of carcinogenicity in humans and understand IARC's definition of "limited evidence" as "a positive association has been observed" for which a causal association is "credible, but chance, bias, or confounding could not be ruled out with reasonable confidence [IARC Preamble, section B6]."[87]

ORD also points out that OPP evaluated data in a simplistic yes/no manner and dichotomized the epidemiological evidence to be either "causal" or "not causal."[88] In doing so, ORD noted that OPP did not adhere to the "gradations of causality" utilized in modern risk assessment approaches and the EPA Cancer Guidelines themselves.[89] ORD pointing out OPP's failure to follow its own agency

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[85] *Id*.

[86] *Id*.

[87] *Id*.

[88] *Id*.

[89] *Id*.

guidelines when evaluating the human epidemiological studies cast doubt on OPP's conclusion that glyphosate is "not likely to be carcinogenic."[90]

Second, ORD criticized OPP's use of only pairwise comparisons. IARC used trend tests, which "yielded several significant results."[91] Importantly, the EPA Cancer Guidelines allow *both* tests to be used when evaluating the incidence of tumors:

> EPA's cancer guidelines state that Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.[92]

Therefore, a positive result using just one of the tests, regardless of the results of the other, is sufficient evidence to conclude that the relationship between exposure and tumors is not by chance.[93]

Third, ORD found OPP reviewed each study individually instead of a "more inclusive, systematic approach to provide an integrated analysis of the data."[94]

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[90] *Id*.

[91] *Id*. at 2.

[92] *Id*.

[93] *Id*.

[94] *Id*.

ORD also notes that the mutagenic potential of glyphosate was not thoroughly analyzed, finding:

> A thorough evaluation of the mutagenic potential of glyphosate was not included in the 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 epidemiological study.[95]

These ORD findings on OPP's assessment are significant as they suggest that a different conclusion is more appropriate.[96] Ultimately, in pointing out the deficiencies in the studies OPP relied upon, ORD recommended that OPP to "[e]xpand the discussion of the cancer data and subsequent findings to include a detailed and thorough discussion of the rationale that caused OPP to come to a different conclusion than IARC, if not directly noting the IARC findings themselves."[97]

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[95] *Id*.

[96] *Id*

[97] *Id*. at 3.

CONCLUSION

For the foregoing reasons, the jury's verdict should be affirmed.

March 30, 2020

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(a)(7)(C), the undersigned hereby certifies that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B)(i) and Rule 29(a)(f).

1. Exclusive of the exempted portion of the brief provided in Fed. R. App. P. 32(a)(7)(B), the brief contains 6,592 words.
2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2010 in 14 point Times New Roman font. As permitted by Fed. R. App. P. 32(a)(7)(B), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

March 30, 2020

Respectfully submitted,

/s/ *Caroline Leary*
Caroline Leary

CERTIFICATE OF SERVICE

I hereby certify that on this 30th day of March 2020, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit using the appellate CM/ECF system. Counsel for all parties to the case are registered CM/ECF users and will be served by the appellate CM/ECF system.

March 30, 2020

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