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Office of Pesticide Programs
Environmental Protection Agency
Docket Center (EPA/DC), (28221T),
1200 Pennsylvania Ave. NW.,
Washington, DC 20460-0001

Re: EPA's evaluation of the carcinogenic potential of glyphosate at the Scientific Advisory Panel. Docket Number: EPA-HQ-OPP-2016-0385

Dear Sir/Madam,

We are submitting comments to the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP), which is convening to review the carcinogenic potential of glyphosate, the most widely used herbicide in the U.S. Currently, glyphosate is undergoing its registration review which began in 2009. In preparation for the SAP meeting, the U.S. Environmental Protection Agency (EPA) published its 'Glyphosate Issue Paper' which outlines the agency's proposed decision to classify glyphosate as "*Not Likely to be Carcinogenic to Humans*."[1]

This latest classification comes as the acceptability and reasonableness of glyphosate's use has been called into question with both independent scientific assessments and efficacy concerns. EPA in 1985 originally classified glyphosate as '*possibly carcinogenic to humans*' based on tumors in laboratory animals, but changed its classification to evidence of non-carcinogenicity in humans years later. This is the third cancer assessment conducted for glyphosate, with the release of this Cancer Assessment Review Committee (CARC) report in September 2015.

Over 280 million pounds of glyphosate are estimated to be used in the U.S. as of 2014 on over 100 crops and other non-agricultural use sites.[2] In 2013, EPA increased certain tolerances for residues of glyphosate on multiple food commodities –a move our organization was firmly against based on the incompleteness of EPA's toxicological database for the herbicide, including data gaps for acute and subchronic neurotoxicity and immunotoxicity, as well as an outstanding number of ecological studies which are needed for a full environmental assessment, given increasing glyphosate uses.

[1] USEPA. 2016. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs. Washington DC.
[2] Ibid.

Glyphosate uses are spurred mostly from uses on genetically engineered (GE) crops, which are engineered specifically to be tolerant of glyphosate. Since the most cultivated crops in the U.S. are corn and soybeans (over 175 million acres),[3] the majority of which rely on glyphosate, but also make up the cornerstone of the American diet, it is critical that a comprehensive human health assessment be completed without data gaps and with publicly assessable data.

In March 2015, the World Health Organization's International Agency for Research on Cancer (IARC) found that there is *sufficient evidence of carcinogenicity* in experimental organisms to classify glyphosate as "probably carcinogenic to humans" (Group 2A).[4] Based on the published, publicly available, independent scientific literature, IARC finds sufficient mechanistic evidence in animals for genotoxicity and oxidative stress. It is important here to note that IARC reviewed glyphosate AND its formulated products (Roundup), which are the most and only relevant substances for evaluating glyphosate risks to human health. This is unlike the European Food Safety Authority (EFSA) report, which reviewed glyphosate alone and finds that it is "unlikely to pose a carcinogenic hazard to humans."[5]

IARC and EFSA Cancer Classifications

IARC Group 2A. IARC has a well-defined and reputable cancer classification scheme that takes into account available human and animal data. Substances can be placed in one of several groups; Group 1 "carcinogenic to humans," Group 2A "probably carcinogenic," Group 2B "possibly carcinogenic," Group 3 "not classifiable as to its carcinogenicity," and Group 4 "probably not carcinogenic."[6]

Accordingly, Group 2A, "probably carcinogenic to humans," is used when there is *limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.* In some cases, a substance may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans*. A substance may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. A substance may also be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

For IARC, *sufficient evidence of carcinogenicity* is assigned when a *causal relationship has been established between the agent and human cancer.* That is, *a positive relationship has been*

[3] NASS. News release: U.S. Corn Growers Expect a Major Increase in 2016 Acreage https://www.nass.usda.gov/Newsroom/2016/03_31_2016.php.
[4] IARC. IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. 20 march 2015. http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf.
[5] EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. http://www.efsa.europa.eu/en/efsajournal/pub/4302.
[6] IARC. Preamble: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization (WHO) 2006. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.

observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. For experimental animal data, *a causal relationship is established between the substance and an increased incidence of malignant tumors/abnormal growth (neoplasms) or of an appropriate combination of benign and malignant neoplasms* in, (a) two or more species of animals, or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*. A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites.

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. Specifically, IARC may identify the possible mechanisms by which the substance increases the risk of cancer, which may include (i) changes in physiology, (ii) changes at the cellular level, and (iii) changes at the molecular level (including genotoxicity). IARC then assesses whether that particular mechanism is likely to be operative in humans.

With these in mind, IARC concluded, "There is sufficient evidence of carcinogenicity in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."[7] Specifically, IARC's review of glyphosate's data states,

> *"*In male CD-1 mice, *glyphosate induced a positive trend in the incidence of a rare tumor, renal tubule carcinoma. A second study reported a positive trend for haemangiosarcoma in male mice. Glyphosate increased pancreatic islet-cell adenoma in male rats in two studies. A glyphosate formulation promoted skin tumors in an initiation-promotion study in mice. Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Soil microbes degrade glyphosate to aminomethylphosphoric acid (AMPA). Blood AMPA detection after poisonings suggests intestinal microbial metabolism in humans. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells in vitro. One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations. Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and in vitro."*[8]

[7]IARC. IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. 20 march 2015. http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf.

[8] Guyton, K, Loomis Dana, Grosse, Y, et al. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. The Lancet Oncology. 16(5):490-491.

EFSA. EFSA's analysis found that neither the epidemiological data nor the evidence from animal studies demonstrated that glyphosate exposure leads to cancer in humans. Following the differing conclusions from IARC and EFSA, a group of over 90 scientists responded to EFSA's findings, highlighting several shortcomings, including that "almost no weight is given to studies from the published literature and there is an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide," redacted citations, and other transparency concerns.[9] These scientists agree that in ESFA's report, "Serious flaws in the scientific evaluation…incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate."

Unfortunately, conflicting conclusions from these two leading agencies has increased the controversy surrounding continued use of glyphosate. Earlier this year European member states were unable to come to a formal decision on the license renewal of glyphosate and the European Commission issued a limited license extension (18 months) which came with some restrictions, including obligations for member states to minimize use on playgrounds, and a ban on formulations with the ingredient polyethoxylated tallowamine, POEA. This decision, according to the Commission, will allow glyphosate-containing products to remain on the market until another agency, the European Chemicals Agency, rules on glyphosate's safety, an action due by the end of 2017.[10]

Glyphosate Formulations Most Relevant to Human Health

As mentioned earlier, the main difference between the IARC and EFSA findings (and others) is that IARC considered glyphosate-based formulations in its assessment, whereas EFSA did not. According to EFSA, a number of published studies performed with glyphosate-based formulations of unknown composition gave positive results for genotoxicity when tested *in vitro* and *in vivo*.[11] EFSA notes that the co-formulate, POEA, "has been shown to be more toxic than the active substance glyphosate on several toxicological endpoints, namely acute, short term, reproductive and developmental toxicity, further to equivocal evidence of DNA damage in vitro at high doses." However, the agency did not assess this substance or the formulations in which it occurs, concluding "the toxicity of formulations and in particular their genotoxic potential should be further considered and addressed." EFSA states that it has been mandated to conduct an assessment of POEA and suggests that "the genotoxicity, long term toxicity/carcinogenicity, reproductive/developmental toxicity and endocrine disrupting potential of this co-formulant should be clarified before setting health-based reference values and conducting the risk assessment."

[9] Portier, C, Armstrong, B, Baguley, B et al. 2015. Commentary: Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *J Epidemiol Community Health* doi:10.1136/jech-2015-207005.

[10] European Commission - Daily News. Pesticides: after EU Member States fail to take responsibility for the decision on glyphosate extension, Commission extends the approval until European Chemical Agency issues its opinion. 29 / 06 / 2016. http://europa.eu/rapid/press-release_MEX-16-2357_en.htm.

[11] EFSA. EFSA explains the carcinogenicity assessment of glyphosate. 12 November 2015. https://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf.

In addressing the toxicity of glyphosate formulations, EPA notes in its issue paper that it is collaborating with the National Toxicology Program (NTP) to evaluate glyphosate in product formulations and the differences in formulation toxicity. It is safe to assume that the findings of this collaboration will not be available until after the registration review of glyphosate is complete –meaning this important information regarding formulation toxicity, in our opinion, will continue to be a data gap for glyphosate, putting people at risk.

Since glyphosate formulations contain numerous other ingredients, EPA must investigate the totality of these formulations and their carcinogenic potential as these chemical mixtures have the most relevance to human (and environmental) health. EPA has been urged numerous times by this organization, and others, to evaluate chemical mixtures, especially those commonly formulated together, as part of the agency's risk assessment process. Glyphosate formulated products kill human cells, particularly embryonic, placental and umbilical cord cells, even at very low concentrations.[12] Studies have found that the formulated glyphosate products reduces human placental JEG3 cell viability at least two times more efficiently than glyphosate, disrupts aromatase activity and mRNA levels,[13] induce a dose-dependent formation of DNA adducts in the kidneys and liver of mice[14] (a process that can lead to carcinogenesis).[15] Similarly, a study released this year finds that glyphosate can cause changes to DNA function resulting in the onset of chronic disease. [16] In this study, the authors conclude that glyphosate acts as a glycine analogue, which incorporates into peptides during protein synthesis. This process alters a number of proteins that depend on conserved glycine for proper function, and may explain glyphosate's mechanistic link to cancer through substitution of glyphosate for glycine.

Make Publicly Available All Data

EPA, in its issue paper, indicated that it reviewed studies considered in international reviews, including IARC, studies found in open literature searches, as well as additional studies requested from the registrants that had "never been submitted to the agency." If the information in these registrant studies are the basis for conflicting carcinogenic conclusions, then EPA should publicly release these studies so that they can be independently peer-reviewed, and increase public confidence in the agency's findings.

[12] Benachour, N., & Seralini, G.-E. 2008. Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells. *Chemical Research in Toxicology*, 22(1), 97-105.
[13] Richard S, Moslemi S, Sipahutar H, Benachour N, & Seralini GE. 2005. Differential effects of glyphosate and roundup on human placental cells and aromatase. *Environ Health Perspect*, 113(6), 716-720.
[14] Marco, P., Armelle, M., Claudia, B., & Silvio, P. 1998. ^{32}P-postlabeling detection of DNA adducts in mice treated with the herbicide roundup. *Environmental and Molecular Mutagenesis*, 31(1), 55-59.
[15] Dallegrave, E., et al. 2003. The teratogenic potential of the herbicide glyphosate-Roundup® in Wistar rats. *Toxicology Letters*, 142(1-2), 45-52.; Dallegrave, E., et al. (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. *Arch Toxicol*, 81(9), 665-673.
[16] Samsel, A and Seneff, S. 2016. Glyphosate pathways to modern diseases V: Amino acid analogue of glycine in diverse proteins. *J. Biological Physics and Chemistry*. 16:9-46

The science of glyphosate is expanding and public concern is increasing. As EPA is responsive to public pressure, the convening of this SAP meeting is in part to reassure the public that the agency is being conscientious in deliberating on this important matter. However, EPA must be very transparent on how it has come to its conclusion that glyphosate is "*Not Likely to be Carcinogenic to Humans*" giving the conflicting scientific information, and eliminating concerns that the agency carbon copied industry's findings.

We urge EPA to be diligent in examining *all* the available evidence regarding the carcinogenic potential of glyphosate AND its formulations. We believe glyphosate formulations to which farmers and consumers are exposed are the most relevant for evaluating risks to human health, as an individual is not just exposed to technical-grade glyphosate. Caution must be taken not to rely on industry-sponsored data or studies that have industry sponsorship as these results have a tendency to be skewed. We encourage full transparency on this evaluation so that public confidence can be assured during this process.

Respectfully,

Nichelle Harriott
Science and Regulatory Director