



BEYOND PESTICIDES

701 E Street, SE ■ Washington DC 20003
202-543-5450 phone ■ 202-543-4791 fax
info@beyondpesticides.org ■ www.beyondpesticides.org

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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: Draft Human Health and Ecological Risk Assessments for Glyphosate. Docket Number EPA-HQ-OPP-2009-0361

Please accept these comments in response to the U.S. Environmental Protection Agency's (EPA) publication of the human health and ecological risk assessments for the herbicide glyphosate. As of 2014, more than 280 - 290 million pounds of glyphosate are estimated to be used annually in the U.S., on over 100 crops and non-agricultural use sites.¹ Glyphosate uses are spurred mostly from uses on genetically engineered (GE) crops, which are engineered specifically to be tolerant of glyphosate. There are conflicting conclusions regarding glyphosate's safety, which has increased the controversy surrounding continued use of the chemical. For instance, the World Health Organization's International Agency for Research on Cancer (IARC) finds there is *sufficient evidence of carcinogenicity* in experimental organisms to classify glyphosate as "probably carcinogenic to humans," with glyphosate's manufacturer, Monsanto, spearheading a media campaign to discredit these findings.

This latest human health assessment, including its carcinogenicity assessment, finds current glyphosate use does not exceed EPA's levels of concern (LOCs). EPA deems any and all routes of exposure to be of low concern, and concludes its aggregate assessment is protective for exposures to any lifestage (adults and children).²

We urge, based on the emerging human-relevant science surrounding glyphosate, that the agency take a precautionary approach when considering continued and expanded uses in the U.S. While EPA notes its assessment focuses only on the active ingredient, glyphosate, we assert EPA must investigate the totality of glyphosate formulations and their potential for adverse impacts, as these chemical mixtures have the most relevance to human and environmental health. Glyphosate formulations are more toxic than the active ingredient alone, a fact recognized by EPA in its ecological assessment which includes formulated glyphosate

¹ USEPA. 2017. Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs. Washington DC.

² USEPA. 2017. Glyphosate. Draft Human Health Risk Assessment in Support of Registration Review. Office of Pesticide Programs. Washington DC.

products in its review.³ In addressing the toxicity of glyphosate formulations, EPA notes it is collaborating with the National Toxicology Program (NTP) to evaluate glyphosate on product formulations and the differences in formulation toxicity.⁴ The findings of this collaboration will be important in accurately assessing real-world human health risks.

EPA must be diligent in examining all the available evidence regarding the human health potential of glyphosate and its formulations, and must update its assessment to reflect this. Further, EPA must exercise caution to not rely on industry-sponsored data or studies as these results tend to be skewed. At this time, based on conflicting cancer classifications, as well as ecological concerns outlined below, EPA should eliminate the use of glyphosate, and alternative strategies for weed management and crop desiccation be researched and employed.

Review of Cancer Findings

EPA reevaluated the human carcinogenic potential of glyphosate, including genotoxicity, epidemiological, metabolism and mechanistic studies. To assist its review, the agency convened a Scientific Advisory Panel (SAP) meeting to review the available data. EPA's review concludes that glyphosate is "not likely to be carcinogenic to humans." It is noted the SAP did not reach a consensus on the recommendations provided, including the interpretation of animal data and EPA's exclusion of certain data. Some panel members expressed the need for additional descriptors to the classification, and some even suggested the classification be "suggestive evidence of carcinogenic potential." EPA reports that for studies that show an association between glyphosate and cancer (non-Hodgkin's lymphoma (NHL)), it cannot exclude bias or chance as an explanation for the observed association, and that it cannot determine, based on the available epidemiological data reviewed, a conclusion regarding the observed associations.⁵ For other cancer types, the agency states no associations were found.

In its genotoxicity analysis, EPA concludes that although some evidence of DNA strand breaks is reported, they occurred at high doses not relevant for human health, and that the results should be interpreted with caution. It also finds that glyphosate does not induce DNA adducts in the liver or kidney. When it comes to genetic mutations, EPA finds there is no convincing evidence that glyphosate induces mutations *in vivo*. EPA finds that the potential exposures to human (occupational handlers) is significantly lower than the highest doses tested in animal carcinogenicity studies - concluding that current use patterns and doses are not relevant to adverse human health outcomes.

It is clear there is uncertainty when it comes to the carcinogenic potential of glyphosate, and there have been differing conclusions among various international agencies. While there are

³ USEPA. 2017. Registration Review – Preliminary Ecological Risk Assessment For Glyphosate and Its Salts. Office of Pesticide programs. Washington DC.

⁴ USEPA. 2016. Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs. Washington DC.

⁵ USEPA. 2017. Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. Office of Pesticide Programs. Washington DC.

some similarities between EPA's and IARC's findings concerning NHL, IARC's analysis went a step further to review formulated glyphosate products and the metabolite, AMPA, which are more relevant to human health risks than the active ingredient alone.

IARC's conclusion that "there is sufficient evidence of carcinogenicity in experimental animals," was based on findings that glyphosate caused DNA and chromosomal damage in human cells, and that glyphosate, glyphosate formulations, and AMPA induced oxidative stress in rodents and in vitro which EPA minimizes.⁶ Note, with regard to oxidative stress, EPA states there is a need for mechanistic studies to understand the mode of action of glyphosate, and that while there is some data suggesting glyphosate may cause oxidative stress or genotoxicity, EPA, unlike IARC, believes there is little mechanistic information to support these observations. Studies IARC reviewed find statistically significant association between glyphosate exposure with certain cancers and found the risk increased with increased exposure. IARC considers that glyphosate induced a positive trend in the incidence of a rare tumor, renal tubule carcinoma in male CD-1 mice, which EPA concludes is not compound-related. A positive trend for hemangiosarcoma, identified by IARC, was deemed not statistically significant by EPA. The agency also finds that incidences of (pancreatic) adenomas were not statistically significant.

It is important to highlight here that IARC's analysis is a hazard identification, not a risk assessment, as EPA's assessments are. IARC's assessment is based on a quantitative examination of the elevated risk associated with a given exposure, and includes only publicly available peer-reviewed studies and not industry data (mostly unavailable to the public) and relies on available epidemiological data that "deal with people exposed in daily life, including at work."⁷ In a statement defending its classification of glyphosate, IARC notes that its evaluation results in a classification based on "the strength of evidence that an agent causes cancer or not," i.e., how confident it is that this agent causes cancer in humans, not its potency. This includes "consideration of the level of exposure (dose) associated with the risk of developing cancer (response) and strong dose-response relationships." IARC research on cancer is still seen as a highly credible source of cancer information, and the agency stands by its findings on glyphosate.

Chemical Mixtures are More Relevant to Human Health

EPA states it is collaborating with the National Toxicology Program (NTP) to develop a research plan to evaluate the role of product formulations and the differences in formulation toxicity on human health. Preliminary information finds glyphosate formulations are not equally toxic. This is to be expected as formulations contain varying "other ingredients," as well as other co-formulated active ingredients. One ingredient – polyethoxylated tallowamine or POEA - has

⁶ 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>.

⁷ IARC response to criticisms of the Monographs and the glyphosate evaluation (January 2018) http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_response_to_criticisms_of_the_Monographs_and_the_glyphosate_evaluation.pdf.

been identified as a highly hazardous ingredient. In fact, the European Food Safety Authority (EFSA) notes the co-formulant 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,” even though the agency did not evaluate this ingredient as part of their glyphosate assessment.⁸ 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*, concluding “the toxicity of formulations and in particular their genotoxic potential should be further considered and addressed,” suggesting that “the genotoxicity, long term toxicity/carcinogenicity, reproductive/developmental toxicity and endocrine disrupting potential of this co-formulant [POEA] should be clarified before setting health-based reference values and conducting the risk assessment.”⁹

Since residential users, occupational handlers, and bystanders are exposed to the active ingredient, glyphosate, and other co-formulated ingredients, including POEA, it is disingenuous of EPA to exclude the impact of these other ingredients when conducting its cancer assessment, given the scientific evidence pointing to carcinogenicity and higher toxicity of these formulations. We urge the agency to revise its cancer findings to include an assessment of glyphosate formulations and AMPA as these are most relevant to human health, and whose impact must be clarified before conclusions are made on glyphosate’s safety.

Disparity in the Consideration of Glyphosate Formulations

As mentioned above, glyphosate is never used alone in any pesticide product, but always formulated with “other” or “inert” ingredients (co-formulants). It is notable that in EPA’s ecological assessment for glyphosate the agency spent considerable time highlighting the differences in toxicity to non-target organisms between glyphosate and its formulated products, including those containing POEA. Formulated glyphosate products have been determined by the agency as being more toxic than the active ingredient alone. EPA states, “the ecological effects of the pesticide-surfactant combination may differ from that of the single pesticide or the single surfactant,” and that, “One class of surfactants used in glyphosate formulations are the polyethoxylated tallow amines (POEA) and this class has been shown to be more toxic to aquatic animals than glyphosate alone.” In evaluating the potential risk to non-target organisms, the agency states it estimated exposure risks from (1) glyphosate only, (2) glyphosate formulations, and (3) surfactant only (POEA).

However, this same due diligence was not afforded to the human health assessment—even though formulated glyphosate products are known to be more toxic to human cells than glyphosate. EPA insists that it is only considering glyphosate *alone* as part of its human health assessment, but considers formulations for the ecological assessment. Does the agency not

⁸ EFSA. EFSA explains the carcinogenicity assessment of glyphosate. 12 November 2015. https://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf.

⁹ Ibid.

have a responsibility to assess risks from human exposures to formulated products just as it does for ecological exposures? A lack of understanding of human health risks from these formulations presents a data gap that must be filled before EPA can state that glyphosate uses do not exceed levels of concern.

Other Cancer Findings Under Scrutiny

EPA states that its cancer findings for glyphosate are in keeping with conclusions from other agencies including EFSA and the Joint Food and Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR). However, their reports have been criticized by independent scientists who have identified several shortcomings of these analyses, including undue industry influence. Following EFSA's report, a group of over 90 scientists critiqued EFSA's findings in a letter highlighting several concerns, stating, "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," along with redacted citations, and other transparency issues.¹⁰ These scientists agree that in EFSA's report, "Serious flaws in the scientific evaluation...incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate." It is also widely reported that EFSA included dozens of pages from a Monsanto study in reaching its conclusion that glyphosate is "unlikely to pose a carcinogenic hazard to humans,"¹¹ calling into question the integrity of its findings, and causing the European parliament to take action against Monsanto's influence in its decision-making process.¹²

Endocrine Disruption and Other Human Health Concerns

There is debate on glyphosate's potential to be an endocrine disruptor, and some have reported endocrine-mediated effects on endpoints relevant to toxicity.¹³ One study reports that among laboratory animals exposed to glyphosate products there were decreased concentrations of thyroid stimulating hormone, concluding that glyphosate herbicides could disrupt the hypothalamic-pituitary-thyroid (HPT) axis, which should be a parameter considered in populations exposed.¹⁴ Another finds that the co-formulants in glyphosate products "act as endocrine-disrupting chemicals at levels up to several hundred times below the level at which

¹⁰ 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.

¹¹ Neslen, Arthur (2017, September 14) EU report on weedkiller safety copied text from Monsanto study. The Guardian <https://www.theguardian.com/environment/2017/sep/15/eu-report-on-weedkiller-safety-copied-text-from-monsanto-study>.

¹² Neslen, Arthur (2017, September 28) Monsanto banned from European parliament. The Guardian <https://www.theguardian.com/environment/2017/sep/28/monsanto-banned-from-european-parliament>.

¹³ Gasnier C, Dumont C, Benachour N, et al. 2009. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. *Toxicology*. 262:184–91.

¹⁴ de Souza JS, Kizys MM, da Conceição RR, et al. 2017. Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats. *Toxicology*. ;377:25-37.

the declared active ingredient demonstrates the same activity.”¹⁵ Increases in aromatase mRNA levels and abnormal sperm morphology have also been reported.¹⁶

Glyphosate has also been linked to shorter gestational periods in pregnant women,¹⁷ and Mesnage et al. (2015) find that chronic, ultra-low dose exposure to glyphosate in drinking water results in adverse impacts on the health of liver and kidneys, including increased cellular growth that may be linked with regeneration as a result of toxic effects causing damage to tissues.¹⁸ These findings come as glyphosate is being detected in a wide range of food,^{19,20} indicating increasing human exposures at levels above those associated with organ damage (above 0.1 ppb).²¹

Impacts on Microbiota

Glyphosate works by disrupting a crucial pathway for manufacturing aromatic amino acids in plants –but not animals— and, therefore, many have assumed that it does not harm humans. However, many bacteria use the shikimate pathway, and glyphosate has been patented as an antibiotic.²² Glyphosate appears to have more negative impacts on beneficial bacteria, allowing pathogens to flourish.^{23,24} This can be seen with the destruction of soil microbiota which leads to unhealthy agricultural systems and an increasing dependence on agricultural chemicals. The destruction of bacteria in the human gut can potentially be a major contributor to a host of modern diseases including diabetes, obesity, food allergies, heart disease,

¹⁵ Defarge N, Takács E, Lozano VL, Mesnage R, et al. 2016. Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels. *Int J Environ Res Public Health*. 13(3). pii: E264.

¹⁶ Cassault-Meyer E, Gress S, Séralini GÉ, Galeraud-Denis I. 2014. An acute exposure to glyphosate-based herbicide alters aromatase levels in testis and sperm nuclear quality. *Environ Toxicol Pharmacol*. ;38(1):131-40.

¹⁷ Parvez S, Gerona RR, Proctor C, et al. 2018. Glyphosate exposure in pregnancy and shortened gestational length: a prospective Indiana birth cohort study. *Environ Health*. ;17(1):23.

¹⁸ Mesnage, R, Arno, M, Contanzo, M, et al. 2015. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environmental Health*. 14:70.

¹⁹ Damian Carrington. 2014. Over 60% of breads sold in the UK contain pesticide residues, tests show <https://www.theguardian.com/environment/2014/jul/17/pesticide-residue-breads-uk-crops>.

²⁰ Food Democracy Now! And The Detox Project. Glyphosate: Unsafe on Any Plate: Food Testing Results and Scientific Reasons for Concern.

https://s3.amazonaws.com/media.fooddemocracynow.org/images/FDN_Glyphosate_FoodTesting_Report_p2016.pdf

²¹ Ibid

²² U.S. Patent number US7771736 B2. Glyphosate formulations and their use for the inhibition of 5-enolpyruvylshikimate-3-phosphate synthase. <https://www.google.com/patents/US7771736>.

²³ Shehata AA, Schrödl W, Aldin AA, Hafez HM, Krüger M. 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. *Curr Microbiol* 66(4):350-8. Krüger, M., Shehata, A.A., Schrödl, W. and Rodloff, A., 2013. Glyphosate suppresses the antagonistic effect of *Enterococcus* spp. on *Clostridium botulinum*. *Anaerobe*, 20, pp.74-78. Schrödl, W., Krüger, S., Konstantinova-Müller, T., Shehata, A.A., Rulff, R. and Krüger, M., 2014. Possible effects of glyphosate on Mucorales abundance in the rumen of dairy cows in Germany. *Current microbiology*, 69(6), pp.817-823.

²⁴ Shehata AA, Schrödl W, Aldin AA, Hafez HM, Krüger M. 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. *Curr Microbiol* 66(4):350-8.

antibiotic-resistant infections, cancer, asthma, autism, irritable bowel syndrome, multiple sclerosis, rheumatoid arthritis, celiac disease, inflammatory bowel disease, and more.²⁵ Many are beginning to believe the rise in these same diseases is correlated with the use of glyphosate, and that glyphosate exposure can result in the inflammation that is at the root of these diseases.²⁶

Ecological Assessment

Overall, EPA finds LOCs are not exceeded for non-target organisms in its ecological assessment for glyphosate and formulated products. Survival and biomass of aquatic vegetation may be impacted, and there was some uncertainty in glyphosate's toxicity to honey bees at higher application rates, although EPA states available data suggests glyphosate has low toxicity to honey bees. However, one study reports simultaneous exposure to glyphosate and neonicotinoids have adverse effects on honey bee feeding behavior,²⁷ suggesting that a closer look is warranted. The agency finds that glyphosate formulations, especially those containing POEA, are more toxic to aquatic organisms, including amphibians, than glyphosate alone. But while the agency is seemingly unconcerned about these impacts as they note POEA is not used in products to be directly applied to waters, these formulated products can still make their way to waterways via drift and runoff.

Glyphosate's presence in surface waters is ubiquitous. U.S. Geological Survey (USGS) reports find glyphosate contamination enduring from spring through to fall when many presumed it would have already degraded.²⁸ Glyphosate and AMPA are more frequently detected in surface water rather than ground water.²⁹ In addition to surface waters, glyphosate has also been detected in significant levels in rain in agricultural areas across the Mississippi River watershed. It is also detected in more than 50 percent of soil and sediment samples, as well as in water samples from ditches and drains. AMPA was detected in more than 80 percent of wastewater treatment plant samples.³⁰

²⁵ Littman, D.R. and Pamer, E.G., 2011. Role of the commensal microbiota in normal and pathogenic host immune responses. *Cell host & microbe*, 10(4), pp.311-323.

²⁶ Swanson, N.L., Leu, A., Abrahamson, J. and Wallet, B., 2014. Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. *Journal of Organic Systems*, 9(2), pp.6-37.

²⁷ Mengoni Goñalons C, Farina WM. 2018. Impaired associative learning after chronic exposure to pesticides in young adult honey bees. *J Exp Biol*. 221(Pt 7). pii: jeb176644.

²⁸ Scribner, E. A., Bañaglin, W. A., Dietze, J. E., & Thurman, E. M. 2003. Reconnaissance Data for Glyphosate, Other Selected Herbicides, Their Degradation Products, and Anions in 51 Streams in Nine Midwestern States, 2002. U.S. Geological Survey, Open-File Report 03-217(101 p).

²⁹ Scribner, E. A., Battaglin, W. A., Gilliom, R. J., & Meyer, M. T. 2007. Concentrations of Glyphosate, Its Degradation Product, Aminomethylphosphonic Acid, and Glufosinate in Ground- and Surface-Water, Rainfall, and Soil Samples Collected in the United States, 2001-06. *US Geological Survey*, Scientific Investigations Report 2007-5122(111p).

³⁰ USGS. Common Weed Killer is Widespread in the Environment. https://toxics.usgs.gov/highlights/2014-04-23-glyphosate_2014.html

Impacts to soil and soil microorganisms were not covered in this assessment. However, studies suggest that residual persistence of glyphosate in soils after long-term, intensive use (as a result of GE cultivation), leads to impacts on soil and environmental health. According to Kremer (2017), glyphosate's presence in soil can lead to numerous adverse effects including, "altered respiration in some eukaryotic organisms due to disruption of cytochrome function; immobilization of nutrients essential for metabolic processes in microorganisms and plants; disruption of microbial diversity in plant rhizospheres; inhibition of mycorrhizal spore germination leading to poor host plant infection and establishment of the symbiosis; disruption of earthworm activity; and reduction in growth and reproduction of numerous aquatic organisms, as well as sediment inhabiting organisms."³¹ Naturally, the use of formulated products which include surfactants can increase toxicological consequences.³² Some studies have concluded that glyphosate has the potential to undermine crop health in a number of ways in cropping systems that rely on its application. These include interference with rhizosphere microbial ecology, and the reduction in the uptake and utilization of nutrient metals by crops, among others.³³

Impacts of Growing Glyphosate Resistance

Also absent from this ecological assessment was a consideration of the impacts of the widespread proliferation of glyphosate-resistant weeds. With the advent of Roundup Ready GE crops, glyphosate use has soared, producing populations of herbicide-resistant weeds that have ballooned in recent years.

The proliferation of glyphosate-resistant weeds presents an ever-growing economic concern to farmers, since a widespread distribution of hard-to-control weeds has the potential to cause significant economic losses. However, these weeds can also indirectly pose risks to the environment as farmers resort to older, more toxic herbicides to combat these weed species. Increased use of herbicides will result in higher contamination of surface waters, soil, and the public. Increased loss of natural habitat for Monarch butterflies and other pollinators, aquatic plants and animals, as well as soil organisms are all externalities that have not been taken into consideration in glyphosate's risk assessment.

Conclusion

As the most widely used herbicide in the U.S. and the world, glyphosate's use continues to increase. Glyphosate products are available and used in a variety of forms and applications, and

³¹ Kremer RJ. 2017. Soil and Environmental Health after Twenty Years of Intensive Use of Glyphosate. *Adv Plants Agric Res* 6(5): 00224. DOI: 10.15406/apar.2017.06.00224

³² Contardo-Jara V, Klingelmann E, Wiegand C. 2009. Bioaccumulation of glyphosate and its formulation Roundup Ultra in *Lumbriculus variegatus* and its effects on biotransformation and antioxidant enzymes. *Environ Pollut.* 157(1):57-63.

³³ Martinez DA, Loening UE, Graham MC. 2018. Impacts of glyphosate-based herbicides on disease resistance and health of crops: a review. *Environ Sci Eur.* 30(1):2.

the potential for their impact is far-reaching. However, EPA has taken a myopic approach to its risk assessment. As debate surrounds glyphosate's cancer classification and overall safety, the agency fails to consider actual product formulations that present exposures to the public. People are questioning whether the Roundup products they buy at the local garden store and sprayed on their food can increase their risk of cancer. EPA's human health assessment does NOT answer this question. EPA chose to ignore the wealth of evidence that show glyphosate-formulated products are more toxic than glyphosate alone. This evidence shows formulated products lead to cell death, potential endocrine disruption, liver damage, and cancer. On the contrary, EPA's ecological assessment does find it relevant to include glyphosate formulations in assessing exposures to non-target organisms, which affirms the higher toxicity of formulated products.

We urge the agency to hasten its collaboration with NTP to evaluate glyphosate formulations and their impacts on human health. Until such assessments are completed, this human health assessment should be interpreted with caution as its findings are misleading and incomplete. Given glyphosate's association with increased weed resistance, making it harder and more expensive for farmers to farm, habitat loss, and water contamination, uses of glyphosate must be restricted.

Respectfully,

Nichelle Harriott
Science and Regulatory Director
Beyond Pesticides

Megan Dunn
Healthy People and Communities Program
Director
Northwest Center for Alternatives to Pesticides
(NCAP)