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ENSSER Statement

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Glyphosate: EU pesticide approval system fails to identify full impact, to the detriment of people and the environment

EU must respect Precautionary Principle and withdraw glyphosate's authorisation

The European Network of Scientists for Social and Environmental Responsibility (ENSSER) has serious reservations about the position of "no critical areas of concern" adopted by the European Food Safety Authority (EFSA) on the herbicide active ingredient glyphosate and the European Commission's subsequent proposal to renew its market approval. We note that the European Chemicals Agency (ECHA) and subsequently EFSA have neglected to consider extensive, damning scientific evidence from laboratory studies, which demonstrate that glyphosate and its commercial formulations can give rise to toxicity and serious diseases through different mechanisms of action. This includes induction of fatty liver disease, oxidative stress, DNA damage, neurological damage and cancer. These laboratory observations are supported by investigations of human populations which show that exposure to glyphosate herbicides is strongly linked with fatty liver disease, neurological disorders, causation of oxidative stress and associated DNA damage, and non-Hodgkin lymphoma. In addition, the uncertainties identified by EFSA regarding effects of glyphosate and glyphosate-based herbicides on complex systems, including biodiversity and microbiomes, are in fact indications of potential adverse effects in these systems. Taken together, this evidence should prevent glyphosate and glyphosate herbicide market re-approval. The manner in which the Commission has dealt with this renewal is an indication that the administrative system fails to identify the full impact of glyphosate on both human health and environmental well-being, especially on a long-term basis. Most importantly, this path taken by the Commission is a flagrant abandonment of the Precautionary Principle, which the EC is legally bound to uphold.

The European Food Safety Authority (EFSA) announced its conclusion regarding the environmental and health impact assessment of the herbicide active ingredient glyphosate

as "no critical areas of concern". Although pointing out high long term ecotoxicity-related risks to mammals in over half of the proposed uses of glyphosate, as well as the lack of established guidelines to evaluate the reported effects on biodiversity and microbiomes, EFSA's assessment did not identify any critical areas of concern, thus pointing towards re-approval. In turn, and based on this conclusion, the European Commission (EC) prepared a report for the re-approval of glyphosate as an active ingredient in herbicides in the EU in accordance with Regulation (EC) No 1107/2009.

We consider EFSA's peer review (EFSA, 2023) and the corresponding EC renewal report (EC, 2023) to be overly optimistic for re-approval, not only because they do not sufficiently consider the glyphosate-induced adverse effects in the assessment, but also because they conclude that there are no critical areas of concern even though data gaps and outstanding issues have been identified. Moreover, assessment should not only focus on individual toxic effects, but also on multiple toxicity (cocktail effects) and overuse of this herbicide active ingredient leading to imbalanced use and environmental contamination.

Identified negative health effects of glyphosate

While numerous detrimental effects of formulated glyphosate-based herbicides are attributed to additives in the commercial formulations sold to farmers and the general public, or to their interaction with the active ingredient, novel mechanisms of toxicity of glyphosate itself have more recently been identified. One example is the finding that glyphosate can induce substantial genotoxicity (Mesnage et al., 2022a; Olah et al., 2022) as well as commercial glyphosate-based herbicides (Benbrook et al., 2023). Another example is the inhibitory potency of glyphosate on integrins that may lead to inhibition of physiological cell adhesion processes (Szekacs et al. 2018; Gémes et al., 2023). Glyphosate and its EU representative formulation have been demonstrated to cause changes in gut microbiome composition and metabolic function at EU regulatory approved doses. Exposure caused oxidative stress in the gut, blood and liver, which can result in cellular, organ and DNA damage, which in turn can lead to fatty liver disease and cancer (Mesnage et al., 2017, 2021, 2022a, 2022b). The carcinogenic potential of glyphosate has been amply demonstrated in many laboratory studies (Portier, 2020). Results from laboratory studies have been corroborated in human epidemiological investigations which have shown strongly linked glyphosate herbicide exposure with oxidative stress and associated DNA damage (Chang et al., 2023), fatty liver disease predisposition (Eskenazi et al., 2023) and non-Hodgkin lymphoma (Zhang et al., 2019). These effects, particularly the demonstration that glyphosate alone can cause DNA damage at regulatory acceptable doses (Mesnage et al., 2022a), should, under EU chemical hazard identification law, result in a ban of glyphosate.

The impact on biodiversity

The impact of glyphosate on biodiversity is grossly underestimated in the current assessment. Even though the EFSA statement itself emphasizes that "risks associated with the representative uses of glyphosate are complex and depend on multiple factors", it leaves

the management of these risks to mitigation measures by risk managers. We consider this unjustified and disagree that potential impacts on biodiversity can be handled with such leniency, especially regarding vulnerable ecosystems. The complexity of the impacts on these ecosystems has been demonstrated by a vast body of research investigating the terrestrial and aquatic ecotoxicity of glyphosate and its formulated products (Klátyik et al., 2023). We find it shocking that EFSA has not taken into account the fact that glyphosate herbicides can exert insecticidal action on top of their intended herbicidal activity. For example, glyphosate herbicides have been found to exert direct insecticidal effects on numerous non-target arthropod species including lacewings (*Chrysoperla carnea*, Defarge et al., 2023), spiders (e.g., *Pardosa* spp.; Evans et al., 2010; Tahir et al., 2019; Niedobova et al., 2019), mosquitos (*Aedes aegypti* larvae, Baglan et al., 2018), and pollinators such as bees (e.g., *Megachile* spp. and *Apis mellifera*; Graffigna et al., 2021; Balbuena et al., 2015; Zgurzynski and Lushington, 2019). This, considering the immense use of glyphosate-based herbicides, may be an overlooked, significant factor in the on-going insect population decline. Moreover, the assessment does not consider the combined effects of glyphosate with other pollutants (i.e. cocktail effects), although such combined effects of glyphosate are evident in the scientific literature. In addition, we express our deep concern about the fact that environmental ecotoxicity is not considered as a cut-off criterion during the environmental risk assessment process.

Consequences of the immense use of glyphosate

Glyphosate is the leading herbicide active ingredient worldwide and alone accounts for nearly one-third of the total pesticide market. This extended use of glyphosate has uninterruptedly grown since the turn of the millennium, resulting in the widespread presence of glyphosate residues in environmental and biological matrices, including human tissues (Székács and Darvas, 2018). The intensive use of glyphosate-based herbicides worldwide has resulted in the emergence of glyphosate and its major metabolite, aminomethlyphosphonic acid (AMPA), as diffuse environmental contaminants: their background levels in environmental matrices have increased. This is an indicative example of how intensive farming leads to a dependence on pesticides, with consequences due to their environmental toxicity. Due to the intensive use of glyphosate and its subsequent emergence as an environmental pollutant, a strict environmental quality standard (EQS) at the EU level (currently not existing) should be established, not only for glyphosate but for its major metabolite AMPA as well.

Abandonment of the Precautionary Principle

The available scientific information about the effects of glyphosate and glyphosate-based products on human health, the environment and biodiversity provides more than reasonable grounds for the risk manager, the EC, to suspect possible harm, even though full scientific certainty might be lacking. This is the type of situation for which the Precautionary Principle (PP) exists. The EC is committed to the PP by the Treaty on the Functioning of the EU (EU, 2012). However, its current proposal to renew the approval of glyphosate evidently completely neglects all the reported adverse effects and thus violates the PP.

References

Baglan H, Lazzari CR, Guerrieri FJ (2018) Glyphosate impairs learning in Aedes aegypti mosquito larvae at field-realistic doses. *J Exp Biol.* 221:jeb187518. doi:10.1242/jeb.187518

Balbuena MS, Tison L, Hahn M-L, Greggers U, Menzel R, Farina WM (2015) Effects of sublethal doses of glyphosate on honeybee navigation. *J Exp Biol* 218:2799–2805. doi:10.1242/jeb.117291

Benbrook, C., Mesnage, R., Sawyer, W. (2023). Genotoxicity assays published since 2016 shed new light on the oncogenic potential of glyphosate-based herbicides. *Agrochemicals* 2 (1), 47-68. https://doi.org/10.3390/agrochemicals2010005

Chang VC, Andreotti G, Ospina M, Parks CG, Liu D, Shearer JJ, Rothman N, Silverman DT, Sandler DP, Calafat AM, Beane Freeman LE, Hofmann JN (2023) Glyphosate exposure and urinary oxidative stress biomarkers in the Agricultural Health Study. *J Natl Cancer Inst.* 115: 394-404

Defarge, N., Otto, M., Hilbeck, A. (2023). A Roundup herbicide causes high mortality and impairs development of *Chrysoperla carnea* (Stephens) (Neuroptera: Chrysopidae). *Sci. Total Environ.* 865, 161158. https://doi.org/10.1016/j.scitotenv.2022.161158

Eskenazi B, Gunier RB, Rauch S, Kogut K, Perito ER, Mendez X, Limbach C, Holland N, Bradman A, Harley KG, Mills PJ, Mora AM. (2023). Association of Lifetime Exposure to Glyphosate and Aminomethylphosphonic Acid (AMPA) with Liver Inflammation and Metabolic Syndrome at Young Adulthood: Findings from the CHAMACOS Study. *Environ Health Perspect.* 2023 Mar;131(3):37001. doi: 10.1289/EHP11721

European Commission (EC) Renewal report for the active substance glyphosate. Glyphosate PLAN/2023/1497 RR - Rev 2 https://food.ec.europa.eu/system/files/2023-10/pesticides_renew_glyphosate_renewal-report_rev2.pdf

European Food Safety Authority (EFSA) (2023). Peer review of the pesticide risk assessment of the active substance glyphosate. *EFSA J.* 21 (7), 8164. https://doi.org/10.2903/j.efsa.2023.8164

European Union (2012) Treaty on the Functioning of the European Union (TFEU), Article 191. https://lexparency.org/eu/TFEU/ART_191/

Evans SC, Shaw EM, Rypstra AL (2010) Exposure to a glyphosate-based herbicide affects agrobiont predatory arthropod behaviour and long-term survival. *Ecotoxicol* 19:1249–1257. doi:10. 1007/s10646- 010- 0509-9

Gémes, B., Takács, E., Székács, I., Horvath, R., Székács, A. (2023). Comparative Assessment of the inhibitory potential of the herbicide glyphosate and its structural analogs on RGD-specific integrins using enzyme-linked immunosorbent assays. *Int. J. Mol. Sci.*23 (20), 12425. https://doi.org/10.3390/ijms232012425

Graffigna S, Marrero HJ, Torretta JP (2021) Glyphosate commercial formulation negatively affects the reproductive success of solitary wild bees in a Pampean agroecosystem. *Apidologie* 52:272–281. doi:10.1007/s13592-020- 00816-8

Klátyik, Sz., Simon, G., Oláh, M., Mesnage, R., Antoniou, M.N., Zaller, J.G., Székács, A. (2023). Terrestrial ecotoxicity of glyphosate, its formulations, and co-formulants: evidence from 2010–2023. *Environ. Sci. Eur.* 35, 51. https://doi.org/10.1186/s12302-023-00758-9

Mesnage R, Renney G, Séralini GE, Ward M, Antoniou MN. (2017). Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide. *Sci Rep.* 2017 Jan 9;7:39328. doi: 10.1038/srep39328. Erratum in: *Sci Rep.* 2018 Aug 17;8(1):12572

Mesnage R., Teixeira, M., Mandrioli, D., Falcioni, L., Ducarmon, Q.R., Zwittink, R.D., Mazzacuva, F., Caldwell, A., Halket, J., Amiel, C., Panoff, J.-M., Belpoggi, F., Antoniou, M.N. (2021). Use of shotgun metagenomics and metabolomics to evaluate the impact of glyphosate or Roundup MON 52276 on the gut microbiota and serum metabolome of Sprague-Dawley rats. *Environ. Health Perspect.* 129 (1), 17005.

Mesnage, R., Ibragim, M., Mandrioli, D., Falcioni, L., Tibaldi, E., Belpoggi, F., Brandsma, I., Bourne, E., Savage, E., Mein, C.A., Antoniou, M.N. (2022a). Comparative toxicogenomics of glyphosate and Roundup herbicides by mammalian stem cell-based genotoxicity assays and molecular profiling in Sprague-Dawley rats. *Toxicol. Sci.* 186 (1), 83-101. https://doi.org/10.1093/toxsci/kfab143

Mesnage, R., Panzacchi, S., Bourne, E., Mein, C.A., Perry, M.J., Hu, J., Chen, J., Mandrioli, D., Belpoggi, F., Antoniou, M.N. (2022b). Glyphosate and its formulations Roundup Bioflow and RangerPro alter bacterial and fungal community composition in the rat caecum microbiome. *Front. Microbiol.* **13**, 888853. https://doi.org/10.3389/fmicb.2022.888853

Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll, L., Colborn, T., Everett, L.G., Hansen, M., Landrigan, P.J., Lanphear, B.P., Mesnage, R., Vandenberg, L.N., vom Saal, F.S., Welshons, W.V., Benbrook, C.M. (2016). Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. *Environ. Health* 15, 19. https://doi.org/10.1186/s12940-016-0117-0

Niedobova J, Skalsky M, Ouředničkova J, Michalko R, Bartoškova A (2019) Synergistic effects of glyphosate formulation herbicide and tankmixing adjuvants on Pardosa spiders. *Env Poll* 249:338–344. doi:10.1016/j.envpol.2019.03.031

Olah, M., Farkas, E., Szekacs, I., Horvath, R., Szekacs, A. (2022). Cytotoxic effects of Roundup Classic and its components on NE-4C and MC3T3-E1 cell lines determined by biochemical and flow cytometric assays. *Toxicol. Rep.* 9, 914-926. https://doi.org/10.1016/j.toxrep.2022.04.014

Portier, C.J. (2020). A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. *Environ Health* 19, 18 (2020). https://doi.org/10.1186/s12940-020-00574-1

Székács, A., Darvas, B. (2018). Re-registration challenges of glyphosate in the European Union. *Front. Environ. Sci.* 6, 78. https://doi.org/10.3389/fenvs.2018.00078

Szekacs, I., Farkas, E., Gemes, B.L., Takacs, E., Szekacs, E., Horvath, R. (2018). Integrin targeting of glyphosate and its cell adhesion modulation effects on osteoblastic MC3T3-E1 cells revealed by label-free optical biosensing. *Sci. Rep.* 8, 17401 https://doi.org/10.1038/s41598-018-36081-0

Tahir HM, Basheer T, Ali S, Yaqoob R, Naseem S, Khan SY (2019) Effect of pesticides on biological control potential of Neoscona theisi (Araneae: Araneidae). *J Insect Sci.* 19:17. doi:10.1093/jisesa/iez024

Zgurzynski MI, Lushington GH (2019) Glyphosate impact on Apis mellifera navigation: a combined behavioral and cheminformatics study. *Pharmacol Toxicol* 7:806–824.

Zhang L, Rana I, Shaffer RM, Taioli E, Sheppard L. (2019). Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence. *Mutat Res Rev Mutat Res.* 2019 Jul-Sep;781:186-206. doi: 10.1016/j.mrrev.2019.02.001