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Glyphosate and neurotoxicity — a call for scientific renewal

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Glyphosate, a controversial herbicide, has been approved for use in the European Union for another 10 years despite uncertainty over whether it increases the risk of neurodegenerative disorders such as Parkinson disease. We call for new approaches to assessing the neurotoxicity of glyphosate and other pesticides and improving their regulation.

Glyphosate is a widely used herbicide, but its use is controversial owing to possible links with serious adverse health effects, including cancer and Parkinson disease (PD). On 28 November 2023, the European Commission extended marketing authorization for the use of glyphosate within the European Union (EU) for another 10 years[1]. This decision was not made without opposition; the initial vote in the Standing Committee on Plants, Animals, Food and Feed (the ScoPAFF Committee) did not reach the required majority (55% of EU countries, representing 65% of the EU population) to support the extension. The matter was then escalated to the Appeal Committee for discussion at a higher level of representation, but this committee also failed to reach the same required majority. Nine countries opposed the extension, citing concerns about the potential of glyphosate to have adverse effects on biodiversity and human health, particularly cancer. Following the tied vote of the Appeal Committee, the European Commission upheld its initial recommendation and extended the marketing authorization for glyphosate.

In addition to probable carcinogenic effects of glyphosate in humans[2], concerns have been raised about associations with neurodegeneration, particularly PD, although the evidence remains unclear. Some evidence suggests a link between glyphosate exposure and damage to the nigrostriatal system[3]. However, in a large cohort of farmers and their spouses who had been exposed to glyphosate, no effect was identified[4]. Interestingly, although the cohort for this part of the study was small, the same study did identify a suggestive association between high exposure to glyphosate and dream-enacting behaviour, which is a common prodromal sign of α-synucleinopathies[5]. A large evaluation of pesticides and their effects on dopaminergic neurons derived from induced pluripotent stem cells from people with PD did not indicate a neurotoxic effect of glyphosate[6].

The uncertainty that stems from the human studies is compounded by current regulatory procedures defined by the European Food Safety Authority (EFSA). These procedures do not provide a full assessment of the risk of PD associated with exposure to pesticides, including glyphosate[3]. This situation hinders regulatory discussions owing to the uncertainty about the potential of glyphosate to induce PD.

Despite the decision to extend authorization for the use of glyphosate, European Union citizens are not necessarily confronted with the use of glyphosate for another decade without any questions being asked. Under Article 21 of the European Committee, the European Commission can, upon request of a Member State, review the approval of an active substance at any time in light of new scientific and technical knowledge and/or monitoring data. Article 21 thus allows for the revocation of glyphosate approval if new scientific evidence emerges that indicates unacceptable health risks, including neurotoxicity for dopaminergic cells in the substantia nigra. We must, therefore, work to reduce scientific uncertainty as much as possible through studies that specifically address criticisms that were levelled at the studies in the EFSA's evaluation of glyphosate[3]. Below, we discuss some of these concerns and make recommendations for experiments and human observational studies.

The primary focus of work to reduce uncertainty over the effects of glyphosate should be to improve neurotoxicity studies. Currently, these studies typically involve exposure of experimental animals to glyphosate; we recommend that validation of reliable, in vitro alternatives is needed to minimize the use of animals. In vitro studies could enable assessment of the viability of dopaminergic neurons upon exposure to glyphosate in comparison with that of non-dopaminergic neurons. Animal studies should involve counting of dopaminergic neurons in the substantia nigra, on the basis that loss of these neurons is required for a diagnosis of definite PD in humans. New work should also examine how glyphosate affects the aggregation of pathologically misfolded α-synuclein, another pathological hallmark of PD. Importantly, studies in animals should involve proactive searching for relevant neurotoxicity to the substantia nigra even in the absence of neurological signs in exposed animals, because these signs occur only late in the process of neurodegeneration owing to the brain's large reserve capacity.

Previous investigation into the effects of glyphosate on neurons has focused on the risk of neurotoxicity mediated by mitochondrial damage. This focus is understandable, given that mitochondrial damage is the main mediator of neuronal damage caused by pesticides such as paraquat and rotenone, which are linked to PD and have been banned in many countries. However, glyphosate is also associated with other neurotoxic mechanisms, including inflammation, oxidative stress and indirect effects via changes in the gut microbiome[7,8]. Future studies should explicitly address these additional neurotoxic mechanisms.

In addition to in vitro and, if necessary, animal studies, improved epidemiological studies are needed to further examine the relationship between environmental and occupational exposure to glyphosate and other pesticides and the incidence of PD. Given that glyphosate was introduced in the early 1990s and the prodromal phase of PD can last for

more than two decades, these studies should focus on cases of PD that were diagnosed after 2010. In addition, the maximum follow-up time, to date, of 13 years is relatively short, so large-scale studies are essential and pooled analyses of existing cohort studies is necessary. The International Consortium of Agricultural Cohort Studies (AGRICOH), formed in 2010, enables studies of associations between diseases and exposures for which individual cohorts are not large enough to provide sufficient statistical power[9]. An alternative approach would be to use administrative data, such as census and electronic patient records, to link individual-level environmental glyphosate exposure with PD incidence.

Such studies would be valuable additions to previously published ecological studies conducted in Canada[10], France[11] and the USA[12], which identified geographical differences in PD frequency related to indices of pesticide exposure. Unfortunately, similar studies in Europe are challenging owing to the lack of a harmonized pesticide use reporting system. Such a system has been implemented in California, and the information generated has been used effectively to investigate the effects of pesticides on health and, specifically, the risk of developing PD[6].

Future studies must also go beyond focusing on risks associated with individual environmental toxins such as glyphosate. In reality, people are continually exposed to combinations of multiple toxins, including various pesticides, and increasing evidence suggests that co-exposure is associated with greater toxicity to the nervous system[6]. Such combination effects need to be accounted for when considering the safety of pesticides.

"The debate about glyphosate ... highlights the shortcomings of regulatory processes"

The debate about glyphosate serves as a generic wake-up call that highlights the shortcomings of regulatory processes that apply to all pesticides, with broader implications for evaluation of their safety. We strongly advocate for future studies to be conducted by scientific organizations that are independent from industry, but with unrestricted financial support from the manufacturer of the pesticide, with an appropriate intermediary organization in place to protect against conflicts of interest. We also advocate for the resulting data to be publicly deposited, with the results to be published in international, peer-reviewed journals. These criteria were not fulfilled by many of the earlier studies of glyphosate that were evaluated by the EFSA, making it difficult for external parties to critically assess previous research.

In their appraisal, the EFSA did consider the open scientific literature that examined the relationship between glyphosate and PD, but many studies were not included in the final evaluation because the work did not meet the standards required for inclusion. Therefore, before new studies are initiated, it is crucial that regulatory bodies such as the EFSA establish clear, upfront criteria for inclusion of work in regulatory processes, so that independent researchers can conduct high-quality studies that meet these criteria. Points that need to be addressed in these criteria include what experiments it should involve, which outcome measures of neurotoxicity would be deemed safe or unacceptable, and what type of scientific information would be required to support either extension or revocation of marketing approval. Pesticides that pass these improved regulatory assessments could continue to be used. However, we believe that for pesticides that have an existing marketing approval — as glyphosate now does — Article 21 should be applied to revoke that approval for any that fail newly defined assessments, either alone or upon co-exposure with other environmental toxins.

Until we have results from new studies that meet the suggested criteria, we recommend that glyphosate use is limited as much as possible, and that potential (non-chemical) alternatives to glyphosate are studied for their toxicity, efficacy and feasibility of use. Implementing these measures will increase protection for individuals who work with pesticides, their families and neighbouring communities.

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Competing interests

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