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Editorial

Why the Gut Microbiome Must Be Considered When Evaluating the Impact of Pesticides on Parkinson's Disease Risk

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Parkinson's disease (PD) is the neurodegenerative disorder most convincingly linked to pesticide exposure in epidemiological and experimental studies (e.g. [1]). The mitochondrial toxin rotenone and the oxidative stress inducer paraquat are two pesticides classically used in experimental animal studies to induce PD-like phenotypes, including non-motor and motor deficits, selective dopamine neuronal loss in the substantia nigra, and proteinopathies [2, 3]. Likewise, the gut-brain axis, particularly the influence of the microbiome, has garnered considerable attention in recent years. In an elegant and thorough review published in this issue of the *Journal of Parkinson's Disease*, Kulscarova and colleagues summarize the evidence directly relevant to the ongoing debate concerning regulations on pesticide use, from the perspective of indirect effects on the brain, through disturbances in the gut barrier function and in its microbiome initiating pathogenic event propagation from the enteric nervous system (ENS) through the central nervous system (CNS) [4].

While there are multiple routes of exposure to pesticides, by far the most common pathway for the general population is through ingestion; thus, the effects of pesticides on the gut barrier integrity and its microbiome cannot be overlooked when evaluating the safety of such chemicals. The microbiome plays a key role in the metabolism of environmental toxicants, including pesticides; thus, they can directly modulate our response to pesticide exposure via the gut-brain axis. One such pesticide highlighted in this review – glyphosate – is a widely used component of commercial pesticides (e.g. "Roundup") despite having been linked epidemiologically to parkinsonism [5]. Earlier studies have also found associations with proximity to glyphosate use in agriculture and premature death in PD patients [6]. Intriguingly, as Kulscarova and colleagues point out, the potential influence of glyphosate on dopaminergic neuronal integrity is mediated largely through dysbiosis. For example, glyphosate leads to greater production of lipopolysaccharides by gut microbiota, stimulating neuroinflammatory signaling throughout the periphery as well as the CNS. This phenomenon is important to take into account, considering that glyphosate is assumed not to act *directly* on mammalian cells (underlying the early belief that potential safety risks to humans was low), as the enzyme target is only expressed in plant cells. Despite the US regulatory authorities continuing to maintain that glyphosate poses no safety threats to humans, other governments (e.g., Mexico and Thailand) are actively taking steps

to minimize the potential risks of exposure to these and other classes of pesticides, even in the face of socio-economic and political resistance. A similar debate is currently ongoing in the European Union, where a proposal to extend the marketing authorization for the use of glyphosate by another 10 years is being met with increasingly fierce resistance, predominantly because of safety in concerns in relation to PD and other neurodegenerative disorders, as well as cancer.

Moving forward, there must be a continued push to expand the safety guidelines to include considerations of the potential effects of pesticides on the gut integrity and microbiome. This means that global coordinated efforts must be put in place to ensure that standardized biomarkers are developed, validated, and deployed to integrate key changes in the gut and its microbiome that are linked to PD pathogenesis and progression. Implementing such "gut health" screens will ultimately have very meaningful impacts on PD prevention and clinical management when it comes to altering or complementing existing PD therapeutics. It goes without saying that the regulation of pesticide use is an incredibly complex issue; the goals of minimizing risks to public health have to be aligned with global food supply/insecurity concerns.

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