Humanities & Social Sciences Communications

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https://doi.org/10.1057/s41599-024-04229-1 OPEN

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Developmental inequity and the impact of pesticide exposure on gut and brain health in developing nations – a Brazilian perspective

Jessica Gama[1], Bianca Cruz Neves[2] & Antonio Pereira Jr[1,3]✉

The Green Revolution brought substantial improvements in food production, making nutrients more accessible than at any other point in human history. However, the widespread use of agrochemicals during this period has led to significant concerns regarding environmental health and human well-being. In developing nations, where pesticide regulation is often less stringent, the use of highly hazardous chemicals poses serious health risks. This paper addresses the developmental inequities linked to pesticide exposure, particularly in Brazil, focusing on its impact on the gut microbiome and neurodevelopment. The gastrointestinal tract, home to a complex microbiome, plays an essential role in immune regulation and neurological functions. Pesticide exposure, which may begin prenatally through maternal pathways and continue postnatally, has the potential to disrupt this microbiome and affect critical neurodevelopmental processes, likely altering lifelong health outcomes. The effects of pesticides on developmental trajectory are particularly concerning during vulnerable periods of heightened cortical neuroplasticity over prenatal, infancy, and adolescent stages. This article also explores the unequal regulatory landscape for pesticides, emphasizing the disparities between more-regulated and less-regulated regions. Brazil serves as a case study to illustrate how inconsistent global pesticide standards contribute to developmental inequity, disproportionately affecting marginalized communities. The findings underscore the need for sustainable agricultural practices and stronger international regulatory coherence to ensure safe food production and to protect neurodevelopment, especially for children in low- and middle-income countries. A unified approach toward regulating pesticide use globally is crucial to safeguard public health, promote developmental equity, and advance a more sustainable relationship with the environment.

[1] Graduate Program in Neuroscience and Cell Biology, Federal University of Pará, Belém, Brazil. [2] Institute of Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [3] Institute of Technology, Federal University of Pará, Belém, Brazil. ✉email: apereira@ufpa.br

The Gut-Brain-Microbiome interface

Nutrient availability has been a critical factor in shaping animal evolution and survival throughout life's history, with significant extinctions often tied to disruptions in nutrient access (Foster et al. 2024; Martin, 2001). For instance, the extinction of the dinosaurs following a catastrophic world event led to ecological changes that favored smaller, energy-efficient organisms, eventually giving rise to mammals and ultimately humans (Alvarez et al. 1980; Meredith et al. 2011).

The gastrointestinal tract (GIT), now more popularly referred to as "the gut," emerged very early in animals' evolution, reflecting the evolutionary importance of optimizing nutrient intake and maintaining fitness. It can be conceived as a long tube with specializations along its length allowing the efficient breakdown, digestion, and absorption of key nutrients. It also has important connections with the immune, nervous, and endocrine systems. Recently, the gut has emerged as a site of intense scientific, medical, and even philosophical interest. This shift reflects a growing awareness of how deeply the gut influences not only physical health but also mental well-being, highlighting the intricate relationship between digestion, mood, and cognition.

The association between the gut and the brain emerged early in evolution, with basic neural networks regulating gut function even in primitive animals (see Fig. 1). This connection persists today in humans as the enteric nervous system (ENS), which functions largely autonomously and is known as the "second brain" (Sharkey & Mawe, 2023). The ENS maintains fundamental roles in gastrointestinal regulation and communicates with the central nervous system through pathways like the vagus nerve (Sharkey & Mawe, 2023) (see Fig. 1).

This gut-brain interaction is evident in various disorders, such as irritable bowel syndrome (IBS). IBS affects a significant portion of the global population and illustrates the complex interplay between gastrointestinal function and mental health, being associated with elevated risks of anxiety and depression (Oka et al. 2020; Barberio et al. 2021). Experimental evidence from both animal and human studies suggests a strong bidirectional relationship between brain and gut function (Takajo et al. 2019).

The human gut also hosts a diverse microbiome that plays an essential role in health, participating in digestion, immune function, and communication with both the ENS and the brain (Jandhyala et al. 2015; Kuziel, 2022; Santos et al. 2019). Disruptions to this microbiome due to exposure to environmental toxicants can lead to dysbiosis, which in turn affects immune regulation and mental health, contributing to chronic illnesses (Chiu et al. 2020; Gama et al. 2022).

The double-edged legacy of the green revolution: access to nutrients and impacts on gut and human health

Access to nutrients has never been so easy throughout human evolution as it is today, thanks to the development of large-scale agricultural practices in the last two centuries. Due to human ingenuity in this field, we finally may achieve a present without widespread famine (save wars, disease, and natural catastrophes, the three scourges of human existence). In particular, the so-called "Green Revolution" of the 1960s and 1970s dramatically increased food crop productivity, subsequently playing a leading role in reducing global poverty and food insecurity, especially in developing countries (Evenson & Gollin, 2003). This movement relied heavily on industrial advancements in plant genetics, irrigation methods, and the development of new chemical fertilizers and pesticides (Pingali, 2012). However, as with other prized achievements in human history (nuclear energy, the internet, artificial intelligence among others), we may need to be vigilant and actively work to prevent collateral damage. For instance, the commercial focus on a few high-yield crops may contribute to reduce biodiversity, impacting the resilience of food systems and the extensive use of fertilizers and pesticides led to widespread environmental degradation, affecting soil, air, and water quality, with repercussions extending to the world's oceans (John & Babu, 2021; Patel, 2013).

Emerging studies have highlighted the potential long-term impacts of modern agricultural practices on mammalian health

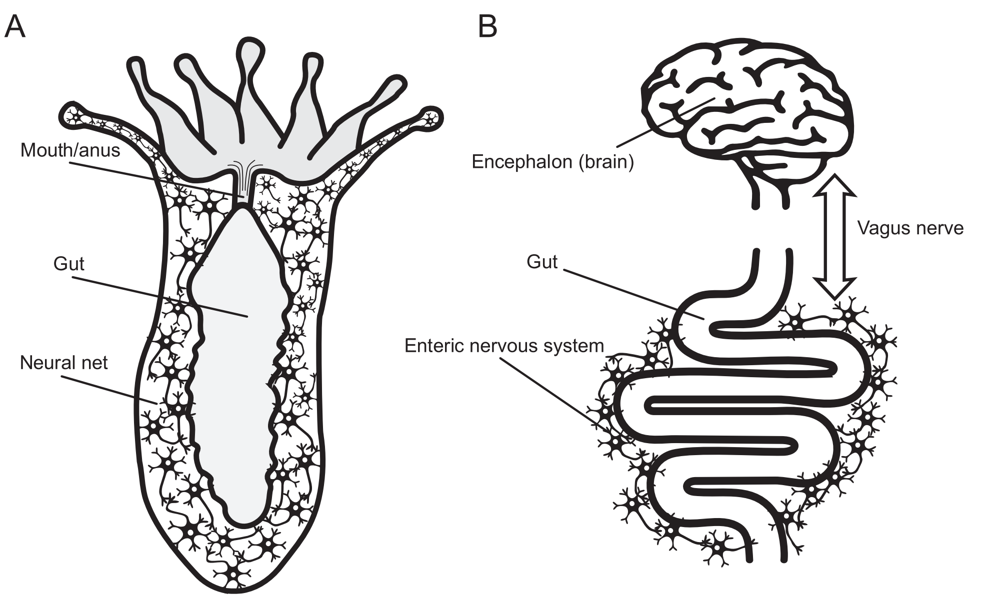

Fig. 1 Evolutionary Changes in the Nervous System Associated with the Gut. A Early evolutionary form of a cnidarian-like animal showing a simple body plan where the gut runs centrally through the organism, with a neural net encasing the gut to control basic digestive functions and motility. This represents the early "tube" structure of the gastrointestinal system, highlighting the presence of a primitive nervous system dedicated to gut regulation. **B** Modern human representation illustrating the evolution of a more complex nervous system. The gut is controlled by the enteric nervous system (ENS), often termed the "second brain," which autonomously regulates digestive functions. The brain (encephalon) interacts with the gut through the vagus nerve, establishing the foundation for the gut-brain axis, a bidirectional communication system crucial for maintaining physiological and psychological health.

(Lopes-Ferreira et al. 2022; Panis et al. 2022; Pignati et al. 2017). Pesticides used in conventional farming can accumulate in mammalian bodies, potentially disrupting gut microbiomes (Chiu et al. 2020; van Bruggen et al. 2021), endocrine functions, and fetal development. For instance, a study by Mesnage et al. (2022), involving 65 twin pairs in the UK found that the consumption of conventionally grown fruits and vegetables was associated with higher pesticide intake, such as organophosphates. The association between birth defects and the presence of agrichemicals in surface water was revealed by a landmark study (Winchester et al. 2009) showing pregnancies exposed to elevated concentrations of agrichemicals in surface water coincided with a higher risk of birth defects. In Brazil, from 1980 to 2000, a period which marked a transformative phase in the country's agricultural sector, birth defects moved from being the fifth leading cause of infant mortality to the second, though this seems to have been also greatly influenced by a decrease in mortality from other causes (Horovitz et al. 2005) and by improvements in reporting these conditions in public systems (Fernandes et al. 2023). However, a recent study conducted in the State of Mato Grosso, Brazil, a region that is heavily reliant on agribusiness and pesticide use, found a significant association between maternal exposure to pesticides and congenital malformations in children, particularly when the mother had a low education level (Ueker et al. 2016).

Importantly, a mysterious cluster of neurological patients in New Brunswick, Canada, exhibiting severe cognitive and motor impairments made the news recently, with many of them testing positive for elevated levels of Glyphosate, used as an herbicide by local industries (Sabar, 2024). While the connection of the neurological symptoms with Glyphosate exposure is not conclusive, this finding is consistent with growing evidence that chronic pesticide exposure may heighten the risk of neurological diseases (Santos et al. 2019).

Pesticides, neurodevelopment, and the gut microbiome: a complex interplay shaping early brain health

The complex bidirectional link between the gut microbiome and the human brain (Santos et al. 2019) extends through the entire spectrum of brain development, encompassing stages from fetal growth to adulthood and aging. Although current research is increasingly focused on how the gut microbiome influences the onset of various neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, the potential risks that gut dysbiosis poses during crucial early stages of brain development — both prenatal and early postnatal — remain less understood. The development of cortical brain circuits in the prenatal and early postnatal phases is significantly influenced by environmental cues (Shonkoff & Phillips, 2000). This complex process involves neural proliferation beginning around three weeks after conception, followed by cell migration from six weeks to six months. Cell differentiation starts in the second trimester of pregnancy, with synaptogenesis commencing at the end of the first trimester and continuing. Synaptic pruning then extends from late infancy into adolescence ensuring proper brain development and function (Stiles & Jernigan, 2010). Each stage of brain development is meticulously regulated by both internal and external signals, which fine-tune cortical circuits to align with the individual's early social and physical environments to optimize our eventual adaptation to them. However, this precise regulation can lead to a range of developmental outcomes, from adaptive to non-adaptive, depending on the circumstances.

Each cortical system has its critical development period characterized by peak synaptic plasticity while outside these periods plasticity significantly diminishes (Hensch, 2005). Notably, the critical periods vary in their timing and duration, with sensory and motor areas reaching maturity earlier during infancy and adolescence and frontal areas associated with cognition, emotional control, and language maturing later, around early adulthood (Kolk & Rakic, 2022). The prolonged critical period of the prefrontal cortex, which reaches the peak of maturation during adolescence, creates an extended window of vulnerability to negative environmental influences (Folha et al. 2017). The signals received during this period are pivotal in shaping the path of development of higher cognition, such as executive functions, and highlight the importance of a supportive environment for healthy brain development (Nelson & Gabard-Durnam, 2020).

Crucially, fetal brain development can be influenced even before birth by the maternal gut microbiome (Sinha et al. 2023; Vuong et al. 2020). Initial gut microbiome colonization occurs during birth, with breastfeeding playing a decisive role in its early development (Di Gesù et al. 2021). However, concerns arise as breast milk can contain pesticide residues exceeding safe intake guidelines (Dong et al. 2022; Mekonen et al. 2021). Pesticides can also cross the placenta, affecting fetal brain development by altering critical neurodevelopmental pathways, including neurotransmitter systems, neurotrophic signaling, and synaptic plasticity (López-Merino et al. 2023). The developing nervous system is particularly vulnerable to these disruptions, resulting in a range of neurodevelopmental impairments that may persist throughout life. The inadvertent consumption of pesticides, either directly or indirectly through maternal blood during pregnancy or breast milk, poses a risk to the delicate processes of neurogenesis and synaptic refinement, especially in the cerebral cortex, potentially influencing long-term health and disease risk in an individual (Gama et al. 2022; Godfrey & Barker, 2007; Kwon & Kim, 2017).

Regulations and its global disparities

While the increasing recognition of the planet's ecological limits and the overwhelming evidence of climate change and other negative impacts on human health due to industrial activity has spurred anxious debates and policy initiatives aimed at mitigating environmental harm while balancing industrial and economic needs, environmental regulations in this context often faces significant resistance from industry stakeholders and their proxies in politics, who recurrently argue that those rules impose unfair economic and operational burdens, such as increased costs, potential job losses, and impact on competitiveness. This occurs even when research increasingly shows that companies integrating environmental sustainability into their business models tend to achieve higher profitability in today's market (Eccles et al. 2014; Friede et al. 2015). This dynamic reflects a global challenge: reconciling the demands of industrial development with the urgent necessity to preserve environmental integrity and ensure public health and safety. As scientific understanding evolves, so does the framework for environmental protection, urging continuous adaptation and proactive measures in industrial practices.

Progress in this direction has been hampered by the emergence and growth of populist political movements across numerous countries during the second decade of the 21st century, which coincided with the proliferation of denialist stances on climate change and the erosion of essential environmental protections (Huber, 2020). These movements often positioned environmental regulations as hindrances to economic progress, leading to significant policy reversals. In Brazil, for instance, environmental protection measures experienced severe regression under the rule of a rightwing government (Ferrante & Fearnside, 2024). This period saw a marked reduction in the enforcement and expansion of policies aimed at safeguarding critical biomes, notably the Amazon Rainforest and the Pantanal wetlands (Ferrante & Fearnside, 2024). Both regions, essential for global biodiversity and climate stability, faced heightened threats from deforestation and large-scale agricultural expansion, which accelerated habitat loss and ecological degradation. Also, during this period, Brazil imported a record number of pesticides, some of them banned in their manufacturing countries (Ollinaho et al. 2023).

An important concern is that since we do not have a universal environmental protection code, many industries, after some countries in the global north adopt a strict posture regarding human exposure to toxicants, just relocate to other regions where these requirements are not as stringent. One classic illustrative case for this scenario is asbestos, a dangerous group of fibrous minerals that has been banned since 2005 in the European Union and other developed countries and is associated with 78% of occupational cases of cancer in the US (McCormack et al 2012). However, since 1970, because of increased public outcry against its use in Europe and in the United States, there has been a massive transfer of asbestos-processing enterprises to Mexico. By 2001, 1881 Mexican companies were importing asbestos and the export of asbestos products from Mexico tripled between 1992 and 2000 (Aguilar-Madrid et al. 2013).

The concerning disparity in how the use of harmful agrochemicals are managed globally suggests the same dynamic is playing out in this regard. While many pesticides known to be detrimental to human health and the environment are banned in developed countries, they often find a market in less developed nations with more lenient regulatory frameworks (Sarkar et al. 2021). As seen with asbestos and following domestic clamor stemming from heightened popular awareness and demand for sustainable, organic, and eco-friendly agricultural practices, developed countries began to enforce stricter environmental regulations, including rigorous assessment and monitoring procedures for pesticide approval. As a result, more harmful pesticides are increasingly being phased out in these nations. However, the manufacturers of these agrochemicals frequently turn to markets in less developed countries, where regulations may be more relaxed. This results in a scenario where substances prohibited in one part of the world continue to be sold and used in another, leading to potential health risks and environmental degradation in these regions.

Brazil: a case study

A stark example of this disparity can be seen in Brazil, which is one of the top users of pesticides, according to the United Nations Food and Agriculture Organization's (FAO) Pesticides Use Report (Shattuck et al. 2023). The country's relative permissive legislation still allows major agrochemical companies to sell products that have been banned in their home markets and, according to data from IBAMA, the Brazilian environmental agency, in 2018, over 63,000 tons of 10 out of 22 pesticides classified as highly hazardous were sold in Brazil (Grigori, 2020). In Brazil, pesticides banned in Europe, such as Atrazine, Acephate, Tiodicarb, Picoxystrobin, Aphosphate, Tebutiuron, Hexazinone, Ametrine, and Novaluron continue to be extensively utilized (Gaboardi et al. 2023). As depicted in Fig. 2, the use of highly toxic Atrazine and Glyphosate persists in Brazil, with imports of the former surging post-2019 and those of the latter notably increasing post- 2021. Glyphosate is the most widely used herbicide in the world and is a neurotoxic agent capable of deregulating signaling pathways during neurodevelopment and causing behavioral and motor disorders even in dosages lower than the limits set by regulatory agencies (Costas-Ferreira et al. 2022). While the European Union prohibited the use of Atrazine in 2003, citing concerns over its potential endocrine-disrupting effects, especially on the neuroendocrine system, it ranked as the fourth-most-used pesticide by 2018 in Brazil. Paraquat, ranked as the sixth-most-utilized pesticide in Brazil until 2021 and noted for its considerable toxicity, has faced bans in Switzerland since 1989 and in the European Union since 2017 (Albrecht et al. 2022). As exemplified by Paraquat, which cannot rapidly degrade in the environment and lingers in terrestrial and aquatic environments (Huang et al. 2019), even after these pesticides have been banned they still carry the potential to remain a serious public health concern.

Recent studies highlight the significant neurological impact of pesticide exposure in Brazil, with associations noted between pesticide use and psychiatric conditions, including anxiety, depression, and neurodegenerative diseases, such as Parkinson's disease (PD) (Szortyka et al. 2021; Vellingiri et al. 2022; Zanchi et al. 2024). For instance, a recent study on glyphosate exposure revealed increased depressive symptoms and signs of renal and hepatic dysfunction among agricultural workers exposed to the herbicide (Zanchi et al. 2024). The neurotoxic effects of pesticides are partly due to their disruption of neurotransmitter levels, particularly acetylcholine (Ach), through the inhibition of key enzymes such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). These enzymes are crucial for maintaining neuromuscular function and brain health, and their inhibition can lead to a cascade of neurotoxic effects impacting both motor and cognitive functions (Silvério et al. 2017; Zheng et al. 2024).

While the biological basis of Parkinson's disease (PD) is still unclear, despite its 'discovery' over 200 years ago, several pieces of evidence point to an association with pesticide exposure (Müller-Nedebock et al. 2023). Populations in areas with high pesticide use have shown elevated incidences of Parkinson's disease, significantly correlated with exposure to herbicides like paraquat (Brouwer et al. 2017). Paraquat and similar pesticides cause dopaminergic neuron death by generating reactive oxygen species (ROS) and activating microglia, leading to neuroinflammation. Recent research also suggests that glyphosate exposure contributes to neuroinflammation, increasing the risk of Alzheimer's disease (Zhao et al. 2024). Chronic exposure to pesticides such as glyphosate and paraquat impairs mitochondrial function and contributes to the pathogenesis of both Parkinson's and Alzheimer's diseases. Research by Wang et al. (2011) links Paraquat exposure to Parkinson's Disease and other study highlights its detrimental effects on the neuroendocrine axis (Naspolini et al. 2021). Similarly, Atrazine has been shown to have detrimental effects on monoaminergic brain pathways, increasing the expression of characteristic molecular markers of Parkinsonism (Zhao et al. 2024).

As mentioned above, neurotoxic effects of pesticides are particularly damaging during critical neurodevelopmental phases, where they may interfere with synaptogenesis and neural plasticity, increasing the risk of neurodevelopmental disorders like ADHD and ASD (Wang et al. 2011). A 2022 investigation revealed that low and repeated Paraquat aerosol exposures during pregnancy and early developmental phases could interfere with neurodevelopment (Hamdaoui et al. 2022). Additionally, studies, including a 2020 study (Ait-Bali et al. 2020), have demonstrated that exposure to Glyphosate-based herbicides during pregnancy and lactation induces various behavioral, neurochemical, and molecular abnormalities in offspring. Research by Lin et al. (2014) underscores that exposure to Atrazine during pivotal development phases like gestation and lactation might negatively impact the nervous system of both offspring and mothers. A study by Buchenauer et al. (2023) showed that maternal exposure of female mice to Glyphosate induces depression- and anxiety-like behavior in the female offspring, mediated by alterations in the microbiota

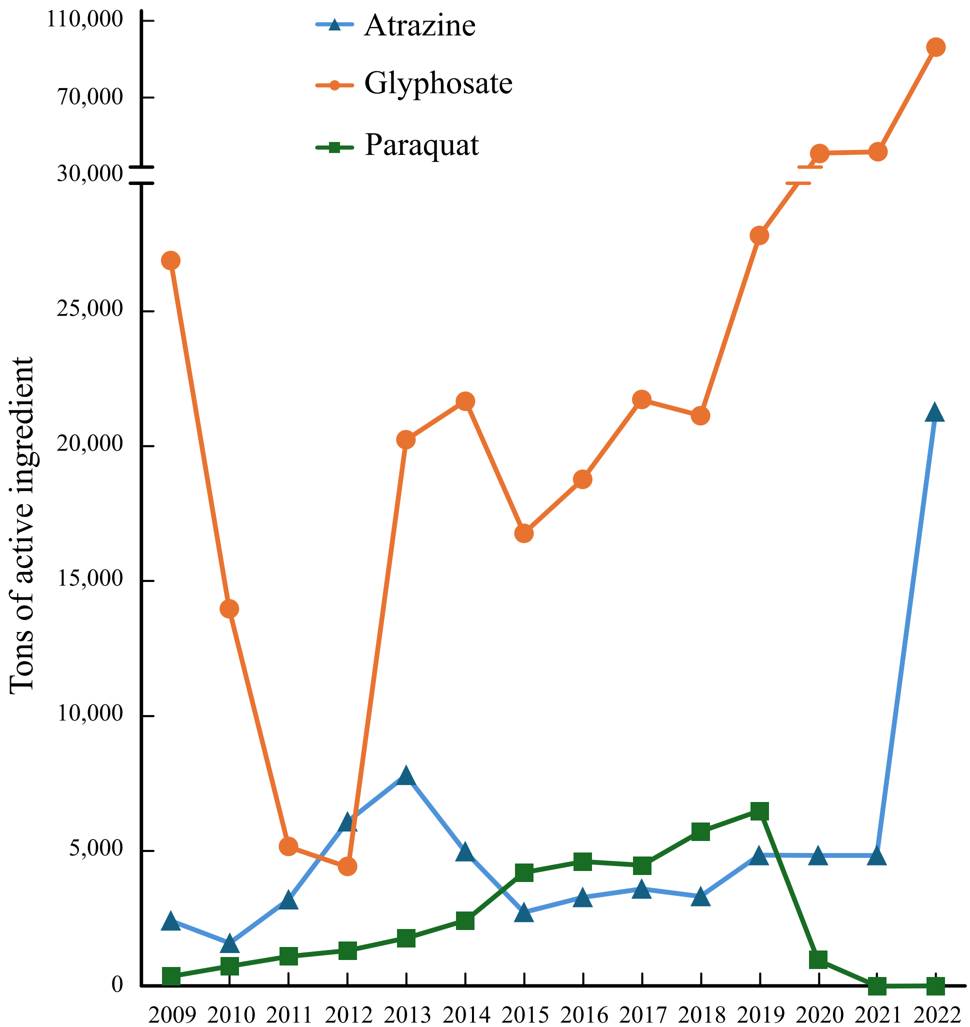

Fig. 2 Trends in pesticide imports to Brazil over the period from 2009 to 2022. The graph illustrates the annual quantities, in tons of active ingredients, of three major pesticides used in Brazil. Source: IBAMA (Brazilian Institute of the Environment and Renewable Natural Resources), 2022.

and the gut-brain axis while also causing deficits in exploratory activity and sociability (Ricci et al. 2024) in other laboratory models. Like Glyphosate, maternal exposure to Atrazine during pregnancy can negatively influence offspring health outcomes, including neurodevelopment (Chen et al. 2022).

While this study primarily focuses on Brazil, it is essential to recognize that similar patterns of pesticide use and associated health impacts are observed in other developing nations. For instance, in India, agricultural communities with high pesticide exposure report elevated rates of neurological impairments and gut health issues (Kori et al. 2018). In Pakistan, evidence suggests that pesticide exposure, among environmental pollutants, is linked to increased instances of neurodevelopmental disorders (Amen et al. 2022). Studies in Mexico also indicate that prenatal exposure to organophosphate pesticides exhibit cognitive deficits and altered behavioral patterns (Sagiv et al. 2023). Moreover, in Thailand, long-term exposure to pesticides among rural agricultural workers has been associated with an increased prevalence of neurological symptoms, including fatigue and dizziness (Pengpan et al. 2024). Unfortunately, the scarcity of reliable epidemiological data on neurodevelopmental disorders such as ADHD and ASD in low- and middle-income countries poses significant challenges in further assessing their associations with environmental risk factors (Bitta et al. 2017).

Towards a new environmental morality

The global variation in pesticide regulations and practices underscores an urgent need for a unified and transparent approach toward the use and safety standards of pesticides. Environmental degradation has worldwide implications, including the displacement of rural communities and increased migration to more developed regions fueling anti-migratory sentiments. Additionally, agricultural products grown with banned substances may eventually end up in the markets of those affluent nations. The rise of globalization and the expansion of multinational corporations have heightened public demands for these entities to be accountable, especially in their environmental and social footprints.

Such complexities demand an ethical framework that stresses the significance of ethical decision-making and moral reasoning. In the context of the present work, we would like to discuss two major philosophical paradigms associated with this approach: Extension Morality and Enactivism. A pivotal aspect in societal terms is the ability to extend innate moral sentiments to wider contexts, as seen in extension morality (McRae, 2011). This capacity reflects a transition from concrete to abstract thinking, akin to the dynamics explored in Construal-Level Theory (CLT) (Trope & Liberman, 2010), which examines how psychological distance influences thought processes and behaviors. CLT posits that distant events, such as environmental problems in other countries, are conceived in more abstract terms, whereas immediate events are perceived concretely, suggesting that abstract thinking can encourage a broader application of moral principles. Enactivism, on the other hand, is a philosophical framework rooted in the understanding that living beings dynamically interact with their environments, shaping and being shaped by them (Di Paolo, 2018), and aligns with environmental ethics by advocating for a deep understanding of the interconnectedness between human actions and the ecological system. The intrinsic value of the environment in enactivism is conferred by shared enaction, involving a vast number of organisms, including humans and their microbiome, which are fundamentally bonded in dealing with their surrounding and in maintaining their own individual integrity (autonomy) (Werner & Kiełkowicz-Werner, 2022). It suggests that ethical considerations towards the environment are inherent in understanding the mutual shaping of individuals and their surroundings (Werner & Kiełkowicz-Werner, 2022).

This broadened moral perspective, in the context of corporate responsibility, demands that multinational corporations uphold high environmental standards universally, not just where legally required. Such stance demonstrates a moral commitment that transcends basic legal requirements, acknowledging a corporation's global impact and fostering a more equitable and sustainable environmental stewardship approach. This ethical viewpoint in corporate practices could significantly contribute to a more integrated global response to environmental issues. Another level of concern regards the key role played by political actors in pesticide regulation in different countries. Agriculture in some countries is still characterized by a 'neo-extractivist' model of converting natural assets into concentrated economic wealth (Cáceres, 2015). In those countries, the state often finds itself overpowered by the strong influence of agribusiness interests and with a diminished capacity to enforce stringent pesticide regulations. The power of those groups can be felt even in the EU, where conservative pressures recently stalled a pesticide reduction plan aimed at halving their use by 2030, citing food safety concerns (Rabesandratana, 2024). These examples highlight the need for a balanced approach to agricultural practices, environmental protection, and public health, despite political and economic hurdles. Crucially, the issue with pesticides extends to their potential to adversely influence the developmental trajectory of numerous children in less developed regions. Such exposure may inequitably handicap these individuals compared to their peers in areas with less toxic exposure or those who have the means to access pesticide-free products.

In this work, we investigate how pesticide-associated toxicants, continuously released into the environment, disrupt neurodevelopmental processes in humans. These disruptions can negatively shape developmental pathways, leading to adverse outcomes that, despite being scientifically documented, are often systematically denied or dismissed (Donadelli, 2020). Protecting the gut environment from harmful pesticides is imperative, most crucially during the critical period of cortical plasticity in humans. This protection should extend to individuals both within our immediate psychological proximity and those at a greater psychological distance within the broader community. Achieving developmental equity is crucial for nurturing a sustainable and mutually beneficial relationship between humans and the Earth's environment.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Received: 27 February 2024; Accepted: 6 December 2024;
Published online: 01 February 2025

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Author contributions
The authors contributed equally to this work.

Competing interests
The authors declare no competing interests.

Ethical approval
This article does not contain any studies with human participants performed by any of the authors.

Informed consent
Informed consent was not applicable as the study did not involve collecting data from human participants.

Additional information
Correspondence and requests for materials should be addressed to Antonio Pereira Jr.

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