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The use of pesticides and its association with parkinson's disease

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ABSTRACT
Brazil is one of the countries that consumes the most pesticides, and as a consequence, both rural workers and society in general are exposed to the risks that this use poses to physical and mental health. In this sense, Parkinson's disease exemplifies such risks, as it is a neuronal disorder that presents motor and non-motor symptoms that affect quality of life. The main objective of the research was to observe the relationship between the development of Parkinson's disease and the use of pesticides, considering that it is a neurodegenerative disease that affects rural workers who handle products with such active ingredients, as well as the general population that consumes crops treated with them. Therefore, the characteristics that permeate the disease were described, and data from Brazilian regions and states were collected, with a focus on Paraná regarding the use of associated active ingredients (Paraquat, Mancozeb, and Glyphosate), the crops that use them, and also Parkinson's mortality rates by region and states from 2013 to 2020, in order to establish a parallel between use and mortality. It was observed that both mortality and pesticide use increased during the associated period. The Central-West, South, and Southeast regions were the ones that used the three analyzed active ingredients the most, while the Northeast, Southeast, and South had the highest mortality rates. Additionally, parallels between use and mortality were observed in certain states, such as Rio Grande do Sul, for example. In conclusion, Parkinson's disease is multifactorial and may be associated with pesticides containing the active ingredients Glyphosate, Mancozeb, and Paraquat. In Brazil, Parkinson's mortality is increasing, as well as the use of these products, which, with the exception of Paraquat, which has been legally banned, rank among the top 10 most widely used pesticides. This calls for continuous studies that analyze the propensity for disease development and the use of these active ingredients.

Keywords: Parkinson, Pesticides, Health.

1 INTRODUCTION

The use of pesticides is a common practice worldwide, with approximately 2.5 million tons of pesticides being used globally. In Brazil, pesticide usage is widespread, considering its economy focused on the production and export of commodities, with a usage exceeding 300,000 tons, making it one of the largest consumers. In the last forty years, the country's agricultural area has expanded by 78%, while pesticide consumption has increased by over 700% (SPADOTTO, 2021). Given that there are few Brazilian studies analyzing and discussing the chronic effects of these agricultural pesticides, it is essential to develop more research to understand the implications of pesticides on the physical and mental health of the population. In this regard, a significant portion of the population directly targeted by pesticides is rural workers, who are exposed to these chemicals daily and often handle them without the recommended and necessary protective equipment, thereby increasing the risk of exposure and the development of chronic problems. Therefore, one of the diseases that will guide the research is Parkinson's disease, a neurodegenerative disorder that presents both motor and non-motor symptoms and affects the quality of life of the affected population both physically and mentally. The study focused on determining which pesticides may be associated with Parkinson's disease. By analyzing the relationship between the increased use of active ingredients and mortality from the disease, hypotheses regarding the association between pesticide use and the onset of Parkinson's disease could be generated. The objective, therefore, is to provide a theoretical explanation of the various aspects surrounding Parkinson's disease, analyze which pesticides are associated with the disease, identify the crops that utilize them, examine the use of active ingredients, and investigate Parkinson's mortality rates by region and states, with a focus on the state of Paraná. This will enable us to understand an example of a chronic condition that affects rural communities and is associated with the physical and mental harm caused by the use of agricultural pesticides.

2 MATERIALS AND METHODS

The studies allowed for the analysis of the active ingredients Paraquat, Mancozeb, and Glyphosate, which have been scientifically proven to be associated with Parkinson's disease. Therefore, information was collected from different platforms. Data from ADAPAR were collected to determine which crops use these active ingredients; data from IBAMA were collected to observe the regions and states that use these pesticides the most; data from DATASUS were collected to visualize Parkinson's mortality by region and state. The objective was to establish a correlation between Parkinson's mortality and the use of scientifically associated pesticides.

3 LITERATURE REVIEW

3.1 PATHOPHYSIOLOGY OF PARKINSON’S DISEASE

Parkinson's disease is primarily characterized by the progressive loss of dopaminergic neurons in the midbrain, which innervate the motor portions of the basal ganglia, particularly the putamen, as well as the STN, GPi/SNr, thalamus, and cortex of the nervous system, in the substantia nigra pars compacta, along with the presence of α-synuclein-positive cytoplasmic inclusions known as Lewy bodies in the lower brainstem (CERRI et al., 2019). Genetic and environmental factors combined lead to early loss of dopaminergic neurons in the ventrolateral region of the nervous system through different cellular pathways, including protein misfolding and aggregation, endoplasmic reticulum stress, and mitochondrial dysfunction. Regarding Lewy bodies, their main composition is α-synuclein, and they initially concentrate in the olfactory bulb and brainstem but can spread to the limbic system and neocortex over time (OBESO *et al*., 2017).

Studies analyzing post-mortem human tissues, in vitro human cell lines, human brain organoids, and animal models have observed the accumulation of α-synuclein, mitochondrial dysfunction, impairment in protein production (involved in the ubiquitin-proteasome and autophagy-lysosome systems), neuroinflammation, and oxidative stress. These events are associated with disrupted vesicular transport, loss of microtubule integrity, excitotoxicity of neurons, disruption of trophic factors, dysregulation of the iron metabolic pathway, endoplasmic reticulum impairment, and enzymatic activation of poly(ADP-ribose) polymerase. Axonal mitochondria are particularly vulnerable, and these alterations contribute to impaired axonal transport, leading to initial neurodegeneration in distal axons. These mechanisms would result in apoptosis and/or necrosis (JANKOVIC, 2020).

Mitochondrial damage affects mitochondrial complex I, reducing organelle potential and promoting caspase cascade activation, leading to cell death. Certain genes associated with the disease, such as Parkin, PINK1, and DJ1, have deleterious effects that result in mitochondrial dysfunction, including impairment in mitophagy. Furthermore, organelle damage leads to the accumulation of oxidized dopamine and reduced glucocerebrosidase, with dopamine being associated with α-synuclein excess and lysosomal impairment. There is also an increase in pro-inflammatory cytokines and altered immune defense cells (JANKOVIC, 2020).

3.2 PHYSIOLOGY OF THE BASAL GANGLIA AND PARKINSON'S DISEASE

There are connections among the nuclei of the basal ganglia, and the concept is that within these connections, the flow of information remains through input processing to broad regions of the cerebral cortex, including the motor, associative, and limbic areas. The different pathways deal with different regions and functions, although they perform similar input operations. Excitatory information from the cortex and thalamus arrives at the nuclei of the basal ganglia (the striatum, composed of the caudate and putamen in humans). There, it is transformed and transmitted to smaller output nuclei (the globus pallidus internal segment, GPi, and the substantia nigra pars reticulata, SNpr) by two distinct pathways: the direct and indirect pathways. These nuclei send the segregated information to the respective cortical areas in the frontal cortex through the thalamus and also to the brainstem. The motor circuit plays a fundamental role in understanding motor signals and the symptoms of Parkinson's disease and other movement disorders (OBESO *et al*., 2017).

The output from the GPi and SNr is characterized by high-frequency inhibitory GABAergic neurons, which provide a continuous level of inhibition to the thalamus and target brainstem areas. The direct pathway has a facilitatory influence on movement by disinhibiting the thalamus, while the indirect pathway suppresses movement by increasing thalamic inhibition. In Parkinson's disease, there is a mismatch between excitation and inhibition, resulting in movement disorders. Although complex, the disease substantially interferes with the motor loop due to the deficiency of dopamine, which is characteristic of the pathology. The basal ganglia play an important role in reinforcement learning. Dopamine reinforces activity patterns by altering cortical inputs and the direct and indirect pathways (OBESO *et al.,* 2017).

Dopamine is released at a slow rate of 5 Hz, sustaining its tonic background level in the striatum. The loss of this tonic activity is the predominant factor in the manifestation of the classical symptoms of Parkinson's disease. Thus, dopamine plays a significant role in the proper functioning between the direct and indirect pathways for inhibition and also interferes with the cortex-basal ganglia-thalamus-cortex pathway. If deficient, the neurons involved in this process can oscillate together, reducing the basal ganglia's ability to change production patterns, resulting in bradykinesia (difficulty in voluntary movements and slowness of reflexes and movements), one of the symptoms of Parkinson's disease. Other disturbances in neurotransmitters, such as glutamatergic and cholinergic systems, are associated with the disease, particularly in the associative and limbic circuits, where non-motor disturbances may occur. It is worth noting that not all motor disturbances are necessarily related to the basal ganglia (OBESO *et al*., 2017).

3.3 CLINICAL PRESENTATION OF PARKINSON'S DISEASE

The primary motor symptoms of Parkinson's disease include bradykinesia, rigidity, resting tremor, and gait disturbances. Non-motor symptoms include autonomic and sleep disorders, such as a high incidence of insomnia and REM behavior, cognitive problems, and psychiatric symptoms such as depression and anxiety (CERRI *et al*., 2019). Posture becomes stooped, with axial and limb rigidity, a shuffling gait, and a lack of arm swing while walking. Hypomimia (reduced facial expression) and micrographia (reduced handwriting size) may occur as a consequence of bradykinesia. Resting tremor primarily affects the legs. Gait disturbances can lead to shorter and faster steps, which can trigger balance loss and subsequent falls. Freezing of limbs can occur after years of living with the disease, along with oral motor problems such as soft and rapid speech, swallowing difficulties, and drooling. Dystonia (constant muscle contraction accompanied by abnormal movements, such as unilateral equinovarus foot and oromandibular dystonia) and postural problems, including abnormal forward flexion (camptocormia), forward flexion of the head and neck (antecollis), and scoliosis of the spine, may also be present (SVEINBJORNSDOTTIR, 2016).

Before the onset of motor symptoms, non-motor symptoms are observed in 60-70% of patients prior to diagnosis. These symptoms involve disturbances in autonomic function, sleep, cognition, and sensations, such as apathy, excessive daytime sleepiness, sleep disturbances, constipation, anhedonia, memory problems, olfactory and gustatory dysfunction, mood fluctuations, excessive sweating, fatigue, pain, anxiety, and depression. Non-motor symptoms typically persist as the disease progresses and can be more bothersome than motor symptoms (SVEINBJORNSDOTTIR, 2016).

Neuropsychiatric symptoms are also observed in one-third to 40% of patients, such as visual hallucinations and illusions. Additionally, cognitive impairment and dementia are common and can occur at different stages, with deficits in goal-directed behavior and dysfunction in vision, speech, and memory. Progression occurs as neuropathological changes spread to cortical brain regions, varying among patients, usually starting unilaterally, with mild symptoms and a good response to treatment. As the disease progresses, motor symptoms spread contralaterally, and responses to medication become more difficult with side effects, in addition to the development of non-motor symptoms (SVEINBJORNSDOTTIR, 2016).

Biological sex, combined with age, genetic and environmental factors, and the immune system, generates clinical, pharmacological, and epidemiological differences. In women, motor symptoms emerge later, with greater postural instability, less rigidity, and more severe symptoms of fatigue, depression, pain, olfactory or gustatory impairments, restless legs, weight changes, excessive sweating, and gastrointestinal dysfunctions. In men, there is a higher risk of freezing while walking and developing camptocormia, worse clinical profiles of cognitive abilities, faster progression to advanced stages of the disease, and greater deficits in attention and memory (CERRI *et al*., 2019)

3.4 EPIDEMIOLOGY OF PARKINSON’S DISEASE

Parkinson's disease accounts for only 10% of patients with genetic mutations that could cause the disease (CERRI *et al*., 2019). The incidence of the disease varies and ranges from 5 to 35 per 100,000 new cases annually (SIMON *et al*., 2020). Between 1990 and 2015, the number of patients increased by 118% (6.2 million people). Furthermore, age-standardized rates increased by almost 22% in all regions of the world between 1990 and 2016. Projections for 2040 estimate a total of 17.5 million individuals affected (DORSEY *et al*., 2018).

The disease has a higher incidence and prevalence in the older population (RADHAKRISHNAN, 2018) and is the second most common age-related neurodegenerative disorder, affecting approximately 3% of the population aged 65 and over, and over 5% of the population aged 85 and over (CERRI *et al*., 2019). When it occurs in individuals under the age of 40, it is defined as early-onset Parkinson's disease and accounts for 3-5% of all cases of the disease (RADHAKRISHNAN, 2018). The incidence is twice as high in men compared to women, although female mortality rates are higher, and the disease progresses more rapidly in women (CERRI *et al*., 2019).

In Brazil, there are no official statistics reporting the number of patients affected by the disease. According to Hospital Albert Einstein, unofficial estimates suggest there are at least 250,000 individuals with Parkinson's disease in the country. However, a study conducted in the interior of Minas Gerais with individuals aged 64 and older revealed an incidence rate of over 3%. Considering that the Brazilian population in this age group is around 21 million people, the actual number of individuals affected by the disease would be over 600,000, excluding younger patients with the disease (VILELLA, 2019). According to IBGE, life expectancy in Brazil is projected to reach 78.6 years in 2030 and 81.2 years in 2060, indicating a progressive increase in the number of elderly individuals and a consequent rise in the number of Parkinson's cases.

3.5 ETIOLOGY OF PARKINSON'S DISEASE

The etiology of Parkinson's disease is substantially multifactorial, resulting from the interaction between environmental and genetic factors (CERRI *et al*., 2019). Several factors have been studied in association with Parkinson's disease, such as exposure to pesticides, living in rural environments, traumatic brain injury, and a history of melanoma. Limitations in research have generated conflicting etiological results (JANKOVIC, 2020).

Regarding genetic factors, the metabolite urate, an antioxidant and neuroprotective agent, can be used as a biomarker for Parkinson's disease. Elevated levels of urate have been associated with a lower risk and slower progression of the disease. Furthermore, a relationship has been observed between mutations in the GBA1 gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), and the development of the disease. Another lysosomal enzyme involved is alpha-galactosidase (GLA), encoded by a gene on the X chromosome. Reduced activity of GLA has been associated with the disease, but this correlation is significant only in women. Additionally, the rs1136666 polymorphism in the GAPDH gene is also associated with sporadic Parkinson's disease and increases the risk in older men (CERRI *et al*., 2019).

Regarding environmental risk factors, chronic stress is the most prominent. Higher levels of chronic stress are associated with an increased risk of developing Parkinson's disease, with a higher incidence observed in certain sectors such as agriculture and metallurgy. Physical activity is also an important factor, as higher levels of activity during middle age are associated with a lower risk of developing the disease, better prognosis, and lower chances of severe complications (CERRI *et al*., 2019)

3.6 PESTICIDES ASSOCIATED WITH PARKINSON'S DISEASE

Byproducts of the Industrial Revolution, such as pesticides, solvents, and heavy metals, may be associated with higher rates of Parkinson's disease. This can be observed in countries that underwent rapid industrialization, which was accompanied by increased cases of the disease, such as in China from 1990 to 2016, where the rates were high and more than doubled (DORSEY *et al*., 2018).

In the United States, a study conducted in an agricultural region found that long-term exposure to pesticides increases the risk of developing Parkinson's disease four to six times. Another study conducted in France found that the intensity of pesticide exposure is related to the development of the disease. However, in Brazil, pesticide use is widespread, as the country has a significant portion of its economy based on the production and export of commodities. Few Brazilian studies have analyzed the chronic effects of agricultural pesticides and discussed alternative models to counteract excessive pesticide use (VASCONCELLOS *et al*., 2019).

A study conducted in an agricultural region in California observed a relationship between exposure to certain pesticides and the risk of developing Parkinson's disease. The effects of ziram, paraquat, and maneb were analyzed, and when combined, they strongly increased the risk, which was higher than when administered individually or in pairs. The combinations of ziram and paraquat, and maneb and paraquat, in the work environment doubled the risk of the disease, especially for younger patients. The results suggested that these pesticides contribute to mechanisms that lead to the death of dopaminergic neurons, a characteristic of Parkinson's disease (WANG, 2011).

In Brazil, the National Health Surveillance Agency (Anvisa) banned the commercialization and use of paraquat in plantations starting from 2020, as it is not possible to determine acceptable levels for its administration considering the severity of the disease (VASCONCELLOS, 2018).

Paraquat causes generalized intracellular oxidative/nitrosative stress through a redox cycle or activation on the cell surface by NADPH oxidase. Mitochondria are directly or indirectly affected, and in neurons, the action of paraquat is believed to be mainly cytosolic. The mechanisms of paraquat toxicity have been compared to those of MPTP, which, when converted to MPP+, is sequestered via the dopamine transporter in dopaminergic neurons, substantially affecting complex I and causing oxidative stress and mitochondrial damage. However, while MPTP is an inhibitor of complex I, paraquat is inefficient in this action, although it modulates the redox cycle. Thus, it is inferred that the toxicity of MPP+ and rotenone is related to the inactivation or oxidation of mitochondrial proteins, while for paraquat, it involves oxidative modification of cytosolic proteins. Therefore, the initial targets and means of toxicity differ, although they share oxidative characteristics (BERRY *et al*., 2010).

In Brazil, the active ingredients Maneb and Ziram have already been legally banned (ANVISA, 2017). Maneb and Ziram belong to a family of fungicides called Dithiocarbamates, which are compounds derived from dithiocarbamic acid (NH_2CS_2H). Representatives of this family include sodium metam, ziram, ferbam, tiram, propineb, maneb, zineb, nabam, metiram, and mancozeb. In Brazil, five dithiocarbamates are allowed by Anvisa: mancozeb, metiram, propineb, tiram, and sodium metam (BALARDIN *et al*., 2017).

Mancozeb is associated with a higher risk of developing Parkinson's disease, as it has been found to cause neurodegeneration not only in dopaminergic neurons, which are commonly affected in the disease, but also in GABAergic neurons in *C. elegans* (NEGGA *et al*., 2012), a worm genetically similar to humans (KAMMENGA, 2019). Additionally, Mancozeb may be associated with behavioral changes, which have also been observed in the worm, indicating a potential biomarker of toxicity (PARKINSONISME VERENIGING, 2019). The effect on dopaminergic neurons may be due to the preferential transport of the fungicide into these cells through their presynaptic neurotransmitter transporters (MONTGOMERY *et al*., 2018). Montgomery et al. conducted a study using a dopamine transporter antagonist (GBR12909) in *C. elegans*, which appeared to protect dopaminergic neurons from chronic (24-hour) Mancozeb treatment.

A study using data from the AGRICAN cohort study sought to identify relationships between the incidence of Parkinson's disease and exposure to mixtures of pesticides or individual pesticides, including dithiocarbamate fungicides, rotenone, and the herbicides diquat and paraquat. While previous studies already indicated the association of maneb/mancozeb, ziram, rotenone, and paraquat with Parkinson's disease, this was the first analysis to implicate other dithiocarbamates, such as cupreb, ferbam, mancopper, metiram, thiram, and propineb, in the etiology (POUCHIEU *et al*., 2018).

Glyphosate-based herbicides are the most widely used in the world and their use is increasing. Human exposures to glyphosate are also increasing, with daily intake levels not being respected (MYERS *et al*., 2016).

Studies conducted in rats indicated that high levels of exposure would suggest neurotoxicity induced by glyphosate-based herbicides through multiple mechanisms (MYERS *et al*., 2016). Glyphosate is believed to be associated with neuroinflammation and the induction of oxidative stress in specific regions of the brain, such as the substantia nigra, cerebral cortex, and hippocampus. However, these studies used commercial formulations rather than pure glyphosate, and further research is needed to confirm the neurotoxicity (CATTANI *et al*., 2014).

Exposure to glyphosate has been suggested as a risk factor for neurodegenerative diseases such as Parkinson's and Alzheimer's, as it accelerates age-related neurodegeneration in conjunction with iron and paraquat, which can act via common mechanisms mediated by oxidative stress (PENG *et al*., 2007).

Thus, chronic and acute exposures to glyphosate can cause parkinsonism, which is a condition similar to Parkinson's disease (CATTANI *et al*., 2014). Some cases have been described in which contact with glyphosate resulted in a parkinsonism syndrome, such as the case of a 54-year-old man who accidentally sprayed the herbicide and developed clinical symptoms within a month, including slow resting tremor in the left hand and arm, as well as impaired short-term memory one year after the incident (BARBOSA *et al*., 2001).

It has been observed that glyphosate can be linked to the development of Parkinson's disease, as it induces autophagic and apoptotic cell death in differentiated PC12 neuronal cells, cytotoxicity in SH-SY5Y neuronal cells, degeneration of dopaminergic and γ-aminobutyric acid neurons in *C. elegans*. All of these indicate that glyphosate can act in different ways, but its effect on neuralcells is evident, leading to oxidative damage and subsequent cell death and neurodegeneration (CATTANI *et al*., 2014).

Therefore, exposures to glyphosate cause biological effects that are not immediately observable but are caused by early-life exposure and manifest in later stages of adulthood as chronic degenerative diseases or other health problems (CABALLERO *et al*., 2018).

4 RESULTS AND DISCUSSION

The results of the Review were subdivided into two parts. The first part will present the results related to pesticides in Paraná and Parkinson's disease, while the second part will present the results related to the sale of active ingredients and Parkinson's mortality in Brazil.

4.1 PESTICIDES IN PARANÁ AND PARKINSON'S DISEASE

The state of Paraná has a significant presence in agriculture and, as such, uses a wide variety of pesticides. The crops that have used the most pesticides from 2013 to 2021 are soybeans, corn, and wheat (SIAGRO, 2021), with herbicides, fungicides, and insecticides being the most commonly used compounds (SIAGRO, 2021).

Table 1: Volume of Pesticides Sold (in tons) in Paraná

2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
93.137,2	97.615,6	100.572,8	92.160,5	92.398,0	92.904,3	95.286,8	106.685,9	115.620,8

Source: Produced by the author based on ADAPAR data, 2022.

Paraquat, a compound associated with Parkinson's disease, had the importation, production, and commercialization of its technical and formulated products based on its active ingredient banned starting in 2017 through Resolution of the Collegiate Board of Directors - RDC nº 428, dated October 7, 2020 (OFFICIAL GAZETTE OF THE UNION, 2020). Therefore, the Paraná State Agricultural Defense Agency (Adapar) provided guidance to farmers and traders regarding the prohibition. However, the resolution allowed for the use of products in stock and acquired until the deadline for crop management in the 2020/2021 agricultural season (ADAPAR, 2020).

Table 2: Use of Paraquat in Paraná

2013	2014	2015	2016	2017	2018	2019	2020*	2021*
3,07%	1,97%	2,15%	5,08%	7,43%	5,77%	6,89%	5,85%	0,01%

*RDC 428/2020. Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient Paraquat, before its prohibition, was used in various crops such as avocado, cotton, rice, asparagus, banana, beetroot, cocoa, coffee, sugarcane, tea, citrus, coconut, kale, beans, apple, corn, olive, pastures, pear, peach, rubber tree, soybean, sorghum, wheat, and grape (ADAPAR, 2022).

In addition to Paraquat, dithiocarbamates are also associated with Parkinson's disease, and in Brazil, five of them are allowed by ANVISA: mancozeb, metiram, propineb, thiram, and metam-sodium (BALARDIN *et al*, 2017). In Paraná, the most widely used dithiocarbamate is Mancozeb, with several products containing this active ingredient, with or without usage restrictions. Metam-sodium is permitted with usage restrictions. Metiram is permitted with usage restrictions. Propineb is permitted with usage restrictions. Thiram has some products that have had their use canceled or permitted with usage restrictions (ADAPAR, 2021).

Table 3: Use of Dithiocarbamates in Paraná

Pesticide	2013	2014	2015	2016	2017	2018	2019	2020	2021
Mancozeb	0,51%	0,40%	0,67%	3,12%	2,68%	3,62%	3,54%	2,85%	2,50%
Metiram	0,18%	0,02%	0,03%	0,10%	0,08%	0,06%	0,05%	0,04%	0,03%
Propineb	0,01%	0,02%	0,03%	0,12%	0,09%	0,07%	0,06%	0,04%	0,02%
Metam-sodium	0,00%	0,00%	0,00%	0,01%	0,01%	0,01%	0,00%	0,01%	0,01%
Thiram	0,49%	0,41%	0,33%	0,19%	0,17%	0,16%	0,16%	0,15%	0,12%

Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient Mancozeb is used in crops such as avocado, chard, watercress, lettuce, cotton, garlic, endive, peanut, rice, irrigated rice, oats, banana, potato, beetroot, eggplant, broccoli, coffee, cashew, sugarcane, persimmon, starfruit, onion, carrot, barley, shallot, chicory, citrus, kale, cauliflower, carnation, chrysanthemum, pea, spinach, stevia, eucalyptus, beans, cowpea, pigeon pea, mung bean, broad bean, snap bean, fig, tobacco, gladiolus, guava, apple, papaya, mango, mangaba, passion fruit, watermelon, melon, corn, mustard, ornamentals, cucumber, pear, peach, bell pepper, cabbage, rose, arugula, soybean, sorghum, tomato, wheat, and grape (ADAPAR, 2022).

Other pesticides that may be associated with Parkinson's disease are hexachlorobenzene and glyphosate. Hexachlorobenzene has been prohibited in Brazil since 1985, but clandestine use was observed in Paraná in a study conducted in 2013, where 92.6% of the respondents claimed to be aware of the prohibition but continued to use it (VASCONCELLOS, 2018). Glyphosate, a probable carcinogen for humans (VASCONCELLOS, 2018), can act in different ways to induce neurotoxicity and oxidative stress (CATTANI *et al*, 2014). In Paraná, there is a wide variety of pesticides with glyphosate as the active ingredient, with some being approved and without usage restrictions, while others have been canceled or have usage restrictions (ADAPAR, 2022).

Table 4: Use of Glyphosate and Glyphosate-based Herbicides in Paraná

Pesticide	2013	2014	2015	2016	2017	2018	2019	2020	2021
Glyphosate	16,27 %	10,20 %	8,8%	8,07%	6,92%	6,68%	6,16%	6,40%	7,29%
Glyphosate Acid Equivalent	7,50 %	3,35 %	4,17%	13,58%	13,96%	14,71%	12,84%	11,49%	9,64%
Glyphosate Potassium	-	-	-	6,65%	6,93%	6,22%	7,65%	7,96%	8,07%
Glyphosate Potassium Salt	2,30 %	0,77 %	0,93%	2,17%	2,05%	2,61%	2,34%	2,33%	2,17%

Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient glyphosate is used in the cultivation of avocado, pineapple, açai, cotton, genetically modified cotton, plum, peanuts, anonaceous fruits, fallow areas, rice, irrigated rice, oats, black oats, ryegrass, banana, sweet potato, yacon, beetroot, cocoa, coffee, cashew, sugarcane, persimmon, taro, star fruit, Brazil nut, carrot, rye, barley, citrus fruits, coconut, cupuaçu, oil palm, duboisia, pea, eucalyptus, beans, cowpea, fig, tobacco, ginger, guava, chickpea, guarana, yam, kiwi, lentil, apple, macadamia, papaya, cassava, mango, mangaba, passion fruit, quince, millet, corn, genetically modified corn, turnip, nectarine, medlar, pecan nut, pastures, pear, peach, pine nut, pinus sp, peach palm, radish, pomegranate, rubber tree, soybean, genetically modified soybean, sorghum, wheat, triticale, and grape (ADAPAR, 2022).

4.2 SALES OF ACTIVE INGREDIENTS AND PARKINSON'S MORTALITY IN BRAZIL

Between 2016 and 2022, the best-selling active ingredients were Glyphosate and its salts, 2,4-D, and Mancozeb, ranking 1st, 2nd, and 3rd, respectively. In 2015, 2014, and 2013, Glyphosate and 2,4-D remained in the top two positions, with Mancozeb appearing in the 4th, 8th, and 9th position, respectively. Thus, Glyphosate and Mancozeb, pesticides associated with Parkinson's, are among the most sold and used active ingredients (IBAMA, 2021).

From 2013 to 2020, the states with the highest sales of the active ingredient Mancozeb were Mato Grosso, Rio Grande do Sul, Paraná, Minas Gerais, Goiás, and São Paulo. In the analysis by region, the Midwest, South, and Southeast regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Rondônia, and Pará; in the Northeast, in the states of Bahia, Maranhão, and Piauí; in the Southeast, in the states of Minas Gerais and São Paulo; in the South, in the states of Rio Grande do Sul and Paraná; and in the Midwest, in the states of Goiás, Mato Grosso, and Mato Grosso do Sul (IBAMA, 2022).

Table 5: Sales of Mancozeb by Federation Unit: 2013 to 2020, in tons. Highlighting the five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**155,76**	**141,29**	**331,09**	**665,15**	**469,8**	**1040,41**	**958,27**	**1816,09**
RO	5,65	4,59	43,60	179,76	98,93	213,04	331,38	608,56
AC	0,00	0,00	0,00	0,00	0,00	0,00	1,31	3,47
AM	2,50	2,00	2,00	1,46	4,06	1,74	7,19	1,65
RR	0,02	10,29	0,54	0,17	3,78	1,69	8,30	71,90
PA	10,33	26,12	101,52	199,47	63,14	246,54	212,21	366,18
AP	0,00	0,00	0,00	0,00	3,79	2,49	0,02	0,00
TO	137,26	98,29	183,43	284,29	296,10	545,21	397,86	764,33
NORTHEAST	**370,49**	**1007,2**	**1185,93**	**1932,84**	**1948,74**	**3257,84**	**3434,49**	**5009,22**
MA	14,54	134,59	179,75	389,81	429,75	447,87	835,24	1317,78
PI	12,06	107,49	109,54	349,31	481,35	476,69	718,99	890,54
CE	23,48	14,13	9,08	21,15	39,00	10,44	30,54	68,74
RN	5,26	6,37	4,38	6,26	8,89	26,94	17,91	33,91
PE	100,76	142,53	8,88	12,99	45,97	13,99	10,99	33,31
PB	12,85	7,15	224,22	207,30	6,01	156,68	207,76	509,89
AL	3,57	6,11	2,52	5,80	2,73	9,93	8,68	16,55
SE	26,16	7,33	4,28	20,48	16,81	32,80	51,56	62,31
BA	171,81	651,50	643,28	919,74	918,23	2082,55	1552,82	2076,19
SOUTHEAST	**3300,02**	**3028,5**	**4722,98**	**6367,52**	**5111,17**	**8240,56**	**9630,08**	**8547**
MG	1463,80	1347,07	2265,79	3192,35	2314,07	3063,19	3474,37	4422,91
ES	202,76	163,91	158,03	171,56	213,24	225,89	207,88	250,52
RJ	131,75	69,93	76,39	61,62	68,76	75,97	70,52	103,50
SP	1501,71	1447,59	2222,77	2941,99	2515,10	4875,51	5877,31	3770,07
SOUTH	**2580,26**	**3432,92**	**7968,45**	**12928,24**	**13340,12**	**15858,87**	**17658,54**	**13466,62**
PR	503,48	652,35	2861,36	4485,74	2709,51	4774,18	3819,55	3932,48
SC	796,73	725,19	1226,48	1385,89	976,31	1185,55	1385,32	1393,34
RS	1280,05	2055,38	3880,61	7056,61	9654,30	9899,14	12453,67	8140,80
CENTRAL-WEST	**1758,34**	**4256,76**	**6231,93**	**8550,42**	**8274,49**	**12206,36**	**16669,47**	**21033,68**
MS	117,23	356,80	681,01	880,43	1261,80	1599,56	1687,20	2383,50
MT	480,40	1907,35	3342,58	4472,31	5155,39	7267,89	11917,30	14780,81
GO	1139,65	1937,84	2173,27	3091,16	1797,19	3239,08	3017,19	3804,80
DF	21,06	54,77	35,07	75,83	60,11	44,39	47,78	64,57
SALES WITHOUT SPECIFICATION OF FU	254,13	337,20	1134,05	2819,46	1671,09	30,99	771,74	654,26
TOTAL SALES	8.419,01	12.273,86	21.574,4	33.232,94	30.815,09	40549,92	49162,59	50526,87

Source: Produced by the author based on data from IBAMA, 2022.

From 2013 to 2020, the states with the highest sales of the active ingredient Glyphosate were Mato Grosso, Rio Grande do Sul, Paraná, Goiás, and São Paulo. When analyzed by region, the Central-West, South, and Southeast regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Pará, and Rondônia; in the Northeast, in the states of Bahia, Maranhão, and Piauí; in the Southeast, in the states of São Paulo and Minas Gerais; in the South, in the states of Rio Grande do Sul and Paraná; and in the Central-West, in the states of Mato Grosso, Goiás, and Mato Grosso do Sul (IBAMA, 2022).

Table 6: Glyphosate Sales by State: 2013 to 2020, in metric tons. Highlighting the top five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**5387,66**	**6588,48**	**7245,08**	**6914,11**	**7655,51**	**8529,74**	**10977,18**	**12225,46**
RO	1209,10	1761,05	1666,63	1426,89	1583,98	1853,71	2574,81	2501,86
AC	23,01	70,84	64,27	104,79	102,06	109,51	126,61	184,91
AM	67,13	20,53	29,96	22,58	55,72	54,78	48,80	80,15
RR	233,56	77,21	194,63	86,99	158,11	176,75	269,51	291,58
PA	1752,00	2090,22	2035,55	2502,50	2796,32	3177,47	3853,08	4517,56
AP	50,88	89,18	48,59	78,95	84,01	85,90	85,10	95,97
TO	2051,98	2479,45	3205,45	2691,41	2869,37	3071,25	4019,27	4553,43
NORTHEAST	**16891,08**	**19136,26**	**15355,59**	**15805,61**	**17984,52**	**16438,98**	**19603,59**	**22029,34**
MA	3721,84	5252,50	3876,38	4012,97	4808,45	4292,60	5084,15	4989,37
PI	2179,91	2326,31	2539,33	2538,83	3046,86	2514,62	3005,43	2878,06
CE	75,79	87,81	60,34	95,63	102,60	180,39	209,55	236,84
RN	47,90	50,34	61,05	74,90	59,48	65,46	70,17	143,64
PE	440,83	490,10	193,75	121,64	474,17	156,16	217,44	272,85
PB	269,06	103,61	495,96	461,95	132,65	547,78	607,51	972,16
AL	317,85	410,98	292,12	358,44	224,15	476,18	433,49	477,90
SE	144,60	166,10	243,47	266,27	176,91	205,19	327,52	476,52
BA	9692,50	10248,51	7593,19	7844,98	8894,90	8100,60	9648,33	11553,29
SOUTHEATS	**34270,23**	**32339,55**	**33849,37**	**31208,87**	**29973,28**	**34374,75**	**37482,87**	**39594,6**
MG	13235,50	12991,49	13176,70	13008,51	11856,35	13951,05	15669,97	17530,22
ES	1696,31	1773,32	1328,76	1271,69	1587,66	2096,62	1610,78	2089,42
RJ	247,59	245,97	201,50	244,04	234,44	246,57	245,63	181,96
SP	19090,83	17328,79	19142,41	16,684,63	16294,83	18080,51	19956,49	19724,69
SOUTH	**54453,2**	**58527,54**	**58841,58**	**50821,26**	**56105,38**	**56211,56**	**61697,73**	**66739,24**
PR	25495,20	25837,56	27712,84	22209,81	24121,69	25059,21	24632,85	28784,61
SC	4682,94	4658,50	5191,89	4711,28	5939,06	4922,88	5664,27	6420,35
RS	24275,06	28031,48	25936,85	23900,17	26044,63	26229,47	31400,61	31534,28
CENTRAL-WEST	**67435,6**	**69994,72**	**73332,58**	**73226,87**	**60332,01**	**65201,35**	**74494,63**	**79646,53**
MS	10732,13	12400,58	15144,09	13033,06	13085,41	13813,89	15477,38	18807,73
MT	36955,87	38189,67	38836,79	41846,22	31484,08	33638,86	38685,27	37888,87
GO	19447,37	19143,68	19095,57	18041,58	15486,98	17428,17	19978,27	22521,99
DF	300,23	260,79	256,13	306,01	275,54	320,43	353,71	427,94
SALES WITHOUT SPECIFICATION OF FU	6530,72	7361,29	5324,69	7655,49	1170,30	14200,01	13336,24	25879,31
TOTAL SALES	184.967,70	193.947,87	193.945,89	185.602,22	172.150,75	195.056,02	217.592,24	246.017,44

Source: Produced by the author based on IBAMA data, 2022..

From 2013 to 2020, the states with the highest sales of the active ingredient Paraquat Dichloride were Paraná, Rio Grande do Sul, Mato Grosso, Mato Grosso do Sul, and Goiás. When analyzing the regions, the Central-West and South regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Rondônia, and Pará; in the Northeast region, in the state of Bahia; in the Southeast region, in the states of São Paulo and Minas Gerais; in the South region, in the states of Rio Grande do Sul and Paraná; and in the Central-West region, in the states of Mato Grosso do Sul, Mato Grosso, and Goiás (IBAMA, 2022).

Table 7: Sales of Paraquat Dichloride by Federative Unit: 2013 to 2020, in tons. Highlighting the five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**96,14**	**129,23**	**128,47**	**271,53**	**263,35**	**265,72**	**410,79**	**153,80**
RO	47,09	70,01	69,38	57,62	58,64	51,41	134,19	61,68
AC	0,67	0,00	0,38	0,59	2,89	0,00	1,69	-5,96
AM	0,39	0,31	0,00	0,00	0,00	0,13	0,84	0,00
RR	0,00	0,00	0,00	0,00	3,36	4,73	8,10	0,81
PA	4,71	5,34	19,55	83,61	74,76	69,57	11,22	30,70
AP	0,00	0,00	0,00	0,00	0,69	0,00	1,22	0,23
TO	43,28	53,57	39,54	129,71	123,01	140,01	253,53	60,38
NORTHEAST	**588,73**	**521,3**	**579,97**	**718,13**	**754,1**	**609,41**	**1215,08**	**574,24**
MA	61,72	40,53	69,72	89,12	117,78	74,47	211,07	44,74
PI	28,98	27,81	36,90	68,02	68,96	67,60	131,55	32,96
CE	12,84	17,30	15,75	17,41	14,90	16,65	45,36	27,19
RN	10,63	5,90	3,76	7,43	13,90	15,80	25,16	22,93
PE	32,06	32,92	15,49	11,41	30,30	4,79	22,18	8,16
PB	32,99	15,70	51,08	49,70	10,28	28,18	41,06	37,20
AL	37,49	42,18	17,70	27,15	21,47	11,51	10,55	8,17
SE	3,37	8,94	79,91	13,96	5,70	3,80	4,29	6,65
BA	368,65	330,02	289,66	433,93	470,81	386,61	723,86	386,24
SOUTHEATS	**595,61**	**705,97**	**975,26**	**1007,31**	**1263,82**	**1065,29**	**1811,92**	**821,71**
MG	193,89	219,37	334,72	347,43	363,12	472,96	700,13	231,47
ES	45,75	82,87	86,71	93,25	174,07	58,04	55,87	108,24
RJ	13,29	10,77	12,33	12,86	6,64	0,80	0,00	0,00
SP	342,68	392,96	541,50	553,77	719,99	533,49	1055,92	482,00
SOUTH	**2073,17**	**3111,18**	**3610,76**	**4601,88**	**4522,52**	**3930,51**	**5932,63**	**3780,28**
PR	1200,09	1297,23	1426,33	2041,39	1828,12	1247,56	2125,92	1201,88
SC	214,16	202,76	239,61	270,54	261,81	306,59	340,15	218,10
RS	658,92	1611,42	1944,82	2289,95	2432,59	2376,36	3466,56	2360,30
CENTRAL-WEST	**1598,99**	**1830,09**	**2474,15**	**3131,03**	**3237,88**	**3289,79**	**5147,11**	**2292,02**
MS	672,43	908,30	939,59	1197,89	1485,95	1240,16	1777,66	891,73
MT	455,94	448,00	858,70	1023,86	1014,36	1320,88	1901,38	774,37
GO	460,37	461,16	665,82	900,16	718,83	717,84	1447,76	617,93
DF	10,25	12,63	10,04	9,12	18,74	10,91	20,31	7,99
SALES WITHOUT SPECIFICATION OF FU	1840,08	2106,78	2767,61	1908,28	1714,72	4039,13	1780,86	504,11
TOTAL SALES	6.792,69	8.704,76	10.536,60	11.638,19	11.756,39	13.199,97	16.398,14	8.120,21

Source: Produced by the author based on IBAMA data, 2022.

Parkinson's disease mortality in Brazil from 1996 to 2020 has been increasing in all regions of the country. The lowest values are found in the North region, while the highest values are in the Southeast region. Among the regions, the three with the highest data are in descending order: Southeast, Northeast, and South. When analyzing each region, for the period from 2013 to 2022, it can be observed that the highest mortality rates in the North region are in the state of Pará; in the Northeast region, in the states of Bahia, Pernambuco, and Ceará; in the Southeast region, in the states of São Paulo and Minas Gerais; in the South region, in the states of Paraná and

Table 8: Parkinson's Disease Mortality: Deaths by Residence according to Region/State (ICD-10 Category: G20 Parkinson's Disease)

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**88**	**97**	**125**	**116**	**135**	**154**	**143**	**207**
RO	7	14	17	14	20	14	19	26
AC	5	2	7	3	6	11	5	2
AM	9	21	14	24	26	31	32	35
RR	2	44	4	2	2	6	1	8
PA	54	-	58	57	59	71	56	98
AP	2	2	4	1	4	4	8	14
TO	9	14	21	15	18	17	22	24
NORTHEAST	**558**	**628**	**661**	**720**	**729**	**739**	**863**	**957**
MA	42	46	50	55	45	60	57	74
PI	35	39	49	35	48	53	67	40
CE	109	122	134	154	163	155	172	184
RN	58	57	48	46	50	55	62	60
PB	48	56	50	56	65	54	65	66
PE	99	115	119	153	146	131	153	205
AL	23	19	23	45	30	31	31	34
SE	22	47	26	34	35	31	33	51
BA	122	127	162	142	147	169	223	243
SOUTHEAST	**1573**	**1786**	**1723**	**1831**	**1865**	**2091**	**2336**	**2231**
MG	352	386	397	429	428	473	582	525
ES	81	83	78	80	105	130	122	135
RJ	363	397	377	420	408	467	527	473
SP	777	920	871	902	924	1021	1105	1098
SOUTH	**618**	**645**	**609**	**723**	**771**	**925**	**892**	**959**
PR	195	218	193	242	259	298	266	286
SC	129	140	127	145	160	173	149	207
RS	294	287	289	336	352	454	477	466
CENTRAL-WEST	**197**	**198**	**231**	**216**	**259**	**289**	**341**	**336**
MS	41	49	45	39	41	61	61	48
MT	32	29	25	32	45	39	34	55
GO	84	87	104	93	104	119	169	157
DF	40	33	57	52	69	70	77	76
TOTAL	**3034**	**3354**	**3349**	**3606**	**3759**	**4198**	**4575**	**4690**

Source: Produced by the author based on DATASUS data, 2022.

It can be observed from the IBAMA and DATASUS data that the states with the highest mortality rates are among those that have used the associated pesticides the most.

Table 9: States with the highest use of active ingredients and mortality from Parkinson's disease.

REGION	FU: HIGHEST USE	FU: HIGHEST MORTALITY
North	Tocantins, Rondônia and Pará	Pará
Northeast	Bahia, Maranhão and Piauí	Bahia
Southeast	São Paulo and Minas Gerais	São Paulo and Minas Gerais
South	Paraná and Rio Grande do Sul	Paraná and Rio Grande do Sul
Central-West	Goiás, Mato Grosso and Mato Grosso do Sul	Goiás

Source: Produced by the author based on DATASUS and IBAMA data, 2022.

The collected data allowed for the development of parallels between the use of the active ingredients Paraquat, Mancozeb, and Glyphosate and mortality. When analyzing the crops, it is noted that wheat, lettuce, and corn, which are the crops that use the most pesticides in general, also use the associated agricultural chemicals. It was observed that the Southeast and South regions are among the regions that use the active ingredients the most and also have the highest Parkinson's disease mortality. When looking at the states within each region, in terms of the highest levels of use of the three active ingredients and Parkinson's disease mortality, it is found that in the North, the states of Tocantins, Rondônia, and Pará had the highest usage, with Pará having the highest mortality. In the Northeast, Bahia, Maranhão, and Piauí had the highest usage, with Bahia having higher mortality. In the Southeast, both the highest usage and mortality were concentrated in the states of São Paulo and Minas Gerais. In the South, both the highest usage and mortality were concentrated in the states of Paraná and Rio Grande do Sul. In the Central-West, there was higher usage in the states of Goiás, Mato Grosso, and Mato Grosso do Sul, and higher mortality in Goiás. Thus, in certain states such as Pará, Bahia, São Paulo, Minas Gerais, Paraná, Rio Grande do Sul, and Goiás, it was observed that there was higher usage of the active ingredients Glyphosate, Mancozeb, and Paraquat during the same period when the highest mortality from Parkinson's disease was concentrated, allowing for inferences that these compounds may be associated with the pathology and be one of its causes.

5 FINAL CONCLUSIONS

Brazil is one of the largest consumers of pesticides, which implies the need for further studies on the exposure to agricultural chemicals and the risk of developing diseases that affect both the physical and mental health of the population, especially that of rural workers, who have greater contact and risk of exposure. In this context, one of the pathologies associated with pesticide use is Parkinson's disease, whose epidemiology corresponds to the second most prevalent neurodegenerative disease in the world, being more prevalent in the elderly population. It is characterized by degeneration of dopaminergic neurons in the substantia nigra's pars compacta in the midbrain, as well as the presence of Lewy bodies, which are rich in α-synuclein. It is a disease with multifactorial causes, resulting from the combination of genetic and environmental factors, leading to dopamine deficiency, which plays a role in various processes involved in movement production. As a result, it presents typical motor symptoms such as resting tremor, bradykinesia, forward flexion, gait problems, and rigidity, but also non-motor symptoms such as sleep disturbances and cognitive and psychiatric problems. Studies have analyzed the correlation between the use of pesticides such as paraquat, ziram, maneb, glyphosate, and mancozeb, and the risk of developing the disease, with the general mechanism of action being direct or indirect involvement in the death of dopaminergic neurons or neurotoxicity. In Brazil, paraquat, ziram, and maneb are prohibited, but mancozeb and glyphosate are allowed and among the three most commonly used active ingredients. There is a growing use of agricultural pesticides and Parkinson's disease mortality in all regions of Brazil, with the Southeast, South, and Central-West regions having the highest usage, and the Northeast, Southeast, and South having the highest mortality. It was possible to establish some parallels of higher usage and mortality among states, such as Rio Grande do Sul, Paraná, São Paulo, Minas Gerais, Goiás, and Pará. Therefore, continuous study is needed to analyze the propensity for disease development and the use of these active ingredients in order to better understand the chronic effects of agricultural pesticides on the population.

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