

Examining a Link between Paraquat, Alpha-Synuclein Fibrillation and Neurodegeneration: A Review

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Introduction

Parkinson's disease is a chronic and progressive motor system disorder that is caused by the degeneration of dopaminergic neurons in the central nervous system. At the molecular level, Parkinson's disease works by decreasing the concentrations of the neurotransmitter dopamine, a chemical messenger involved in motor messaging, within the central nervous system. Low levels of dopamine in the central nervous system causes motor system dysfunction because the insufficient levels of dopamine lead to an inability for neurons to successfully transmit motor messages. At the organismal level, Parkinson's disease causes tremors, Bradykinesia, and rigidity. These symptoms ultimately lead to a diminished quality of life for individuals suffering from the disease. As a result, the etiology of Parkinson's disease must be thoroughly examined to help prevent people from acquiring and suffering from the symptoms of Parkinson's disease.

Scientists have extensively researched the etiology of Parkinson's disease to determine whether it is caused by a genetic or environmental factors. Despite numerous research studies, the absolute etiology of Parkinson's disease remains unknown. Recent studies, however, support a more prominent environmental etiology for Parkinson's disease, rather than a biological etiology for the pathogenesis of Parkinson's disease. This is because researchers have found that agricultural pesticides generally are able to work as neurotoxins, which may degenerate or impede dopamine producing nerve cells if the neurotoxins reach the central nervous system. Therefore, pesticide use in agricultural areas is of great concern because pesticide exposure may increase the risk for the pathogenesis of Parkinson's disease.

Paraquat is a type of herbicide, but it is also commonly referred to as a pesticide. Industrial farmers expose pesticides, such as paraquat, to the environment by spraying them onto their fields to eliminate weeds. This allows paraquat to accumulate in the soil at high concentrations over time.

High concentrations of paraquat in the soil are a danger for entire agricultural societies because paraquat may contaminate well water, which is often the primary source of water in agricultural societies. If the contaminated well water is ingested, the herbicide may diffuse into the bloodstream and eventually reach the central nervous system via systemic circulation. Once in the central nervous system, paraquat is able to come into direct contact with and may degenerate dopaminergic neurons. Since paraquat is a pesticide, and the fact that pesticides are known neurotoxins, paraquat is potentially linked to the pathogenesis of Parkinson's disease.

Paraquat may cause Parkinson's disease because of its role as a neurotoxin. A molecular mechanism of neurotoxins is to damage dopaminergic neurons in the central nervous system; this would directly lead to lower concentrations of dopamine in the central nervous system, thus leading to the onset of Parkinson's disease. In order to determine if people living in agricultural regions that use paraquat are at a greater risk of developing Parkinson's disease, this research reviews epidemiological studies on the correlation between pesticides and Parkinson's disease, research on the link between paraquat and the protein alpha-synuclein and research on the link between alpha-synuclein and Parkinson's disease. The goal of this study is to examine the link between paraquat usage and Parkinson's disease, and to recommend areas for future study. A potential future study is one that solely tests the effect of paraquat on alpha-synuclein fibrillation and neurodegeneration in mice to further support the positive link between paraquat and the pathogenesis of Parkinson's disease. Although researchers have concluded that pesticides may cause Parkinson's disease, there is a lack of understanding about which specific pesticides cause the disease and through which molecular pathway the pesticides cause Parkinson's disease. Based on this review that supports a definitive link between paraquat, alpha-synuclein fibrillation, and neurodegeneration, paraquat presents a biological risk because it leads to the pathogenesis of Parkinson's disease, therefore paraquat is a component of the environmental etiology of Parkinson's disease.

An Environmental Etiology of Parkinson's Disease: Pesticides

According to many epidemiological studies, researchers have found that there is a link between the use of pesticides and elevated rates of

Parkinson's disease in a population and that there is a positive correlation between pesticide exposure and Parkinson's disease. In "Parkinson's Disease Mortality and Pesticide Exposure in California 1984- 1994" by Beate Ritz and Fei Yu, Ritz and Yu explain that they found that the "mortality from PD mentioned as the underlying cause of death was 19–47% higher in counties reporting the use of restricted agricultural pesticides compared to PD mortality in counties reporting no use of restricted pesticides for agricultural purposes" (325). This illustrates that people who live in regions with pesticide exposure are at a much greater risk of dying from Parkinson's disease compared to regions that do not experience pesticide exposure. This is because the pesticides may act as neurotoxins, degenerating dopaminergic neurons, thereby causing Parkinson's disease. If the pesticides do cause Parkinson's disease, regions with high pesticide exposure, such as California, would experience a high saturation of people living with Parkinson's disease. If the percentage of people living with Parkinson's disease in a given region were high, mortality rates due to Parkinson's disease would naturally be greater. Therefore, in this study, the high rate of Parkinson's disease related deaths in California might be attributed to pesticide exposure, which supports a correlation between pesticide exposure and Parkinson's disease.

In "A Case-Control Study of Parkinson's Disease in a Horticultural Region of British Columbia," Hertzman et al. found a similar link in which they concluded that there is a risk associated with Parkinson's disease for individuals that have agricultural jobs. Hertzman et al. concluded that there is a "significant association between IP [Idiopathic Parkinson's] and having had an occupation in which exposure to pesticides was probable" (73). Occupations in which pesticide exposure is prevalent presents a risk for the workers because constant pesticide exposure could accumulate the toxin in the body at high concentrations. Consequently, high levels of neurotoxins would be present to degenerate dopaminergic neurons in the central nervous system.

A similar conclusion was made in a study held in the state of Hawaii. Petrovitch et al. in "Plantation Work and Risk of Parkinson's Disease in a Population-Based Longitudinal Study," found that "the risk of developing PD nearly doubled in those who worked on a plantation for more than 20 years compared with those who never worked on a plantation" (1789). The research conducted by Petrovitch et al. also supports the claim that

pesticides are linked to the pathogenesis of Parkinson's disease because plantations are areas of high pesticide exposure. Once in the body, the neurotoxins are able to make their way to the central nervous system and directly impair neural functioning through a molecular mechanism. If the pesticide neurotoxins work at the molecular level by damaging dopaminergic neuron signaling or causing apoptosis, Parkinson's disease would develop in the person. In addition, another epidemiological study that was conducted in the state of Washington presents a claim that connects the duration of pesticide exposure to Parkinson's disease, thereby solidifying the proposal that pesticides lead to the pathogenesis of Parkinson's disease. Engel et al. in "Parkinsonism and Occupational Exposure to Pesticides," found that "the highest tertile of years of exposure to herbicides was the only measure of duration to show a significant association with parkinsonism" (585-586). This illustrates that there is a definitive link between pesticides and Parkinson's disease, but only if the pesticide exposure is long-term, which causes pesticides to accumulate in soil at high concentrations. The above conclusions are further supported by a study done by Liou et al. in "Environmental Risk Factors and Parkinson's Disease: A Case-Control Study in Taiwan." Liou et al. concluded that "having a history of occupational herbicides/pesticides and paraquat use was associated with a significant increase in PD risk of about four- to sevenfold after other environmental factors were adjusted" (1585). This research by Liou et al. further solidifies the claim that long-term exposure to pesticides increases the chance for a person to develop Parkinson's disease because it is directly congruent to the research done by Petrovitch et al. and Engel et al.

Felix Javier Jimenez-Jimenez, Dolores Mateo and Santiago Gimenez-Roldan also conclude that there is a positive association between pesticide use and Parkinson's disease based on a pesticide's ability to contaminate well water. According to Felix Javier Jimenez-Jimenez, Dolores Mateo and Santiago Gimenez-Roldan, in "Exposure to Well Water and Pesticides in Parkinson's Disease: A Case-Control Study in the Madrid Area," they concluded that "exposure to well water might be a factor associated with the likelihood of developing PD" (149). Well water exposure is a risk factor for the development of Parkinson's disease due to the role of pesticides. As pesticides are sprayed in agricultural areas for farming purposes, the pesticides are in direct contact with surrounding soil. Over time, if the pesticide exposure is constant, the concentration of pesticides in the soil

will increase. Due to the soil contamination, the pesticides would be able to accumulate in well water because soil comes into direct contact with ground well water. When humans ingest well water that is contaminated by pesticides, pesticides are able to directly enter the human body. This means that pesticides, which act as neurotoxins, are able to diffuse in the bloodstream and thus reach the central nervous system through systemic circulation. Once the neurotoxins have reached the central nervous system, they are able to potentially diffuse across the blood brain barrier and directly come into contact with neurons, such as the dopaminergic neurons that produce dopamine. This would cause Parkinson's disease if the neurotoxins work at the molecular level by directly causing the apoptosis of dopaminergic neurons or by impeding neural functioning. This association between pesticides and Parkinson's disease is further supported by another epidemiological study that was done in Korea, which also focuses on the ability for pesticides to contaminate well water. In "Association Between Parkinsonism and Participation in Agriculture in Korea," Cho et al. found that "only rural well water was found to significantly increase the risk of PD development, with urban well water having no effect. This point supports the notion that pesticides can pollute rural well water" (26). Cho et al.'s research supports the claim that Felix Javier Jimenez-Jimenez, Dolores Mateo and Santiago Gimenez-Roldan propose about the risk associated with well water because of its role in leading to the pathogenesis of Parkinson's disease.

In contrast to the above conclusions by various epidemiological studies, Nuti et al. in "Environmental Factors and Parkinson's Disease: A Case-Control Study in the Tuscany Region of Italy," conclude a contrasting argument about the link between pesticides and paraquat. Nuti et al. conclude "the results of the present investigation did not show any significant association between the exposure to pesticides and PD" (483). According to this research, there is no relationship between pesticide exposure and Parkinson's disease. This research is unique because it is the only epidemiological study, amongst all of the studies reviewed in this research, which does not support the claim that pesticides cause Parkinson's disease. In all of these research papers, except for one paper that supports a contrasting argument, the researchers use statistically significant empirical evidence to conclude that pesticide exposure has a definitive link to the pathogenesis of Parkinson's disease. Thus, despite one research study

countering the link between pesticides and Parkinson's disease, there is strong evidence that pesticides are a biological risk factor because a majority of the research in this review supports a strong association between pesticides and Parkinson's disease. Therefore, pesticides are vital to the understanding of the environmental etiology of Parkinson's disease.

Not only has research led to the discovery of a link between pesticides and Parkinson's disease, it has also led to the finding of a positive correlation between the amount of pesticide exposure and the acquisition of Parkinson's disease. Petrovitch et al. in "Plantation Work and Risk of Parkinson's Disease in a Population-Based Longitudinal Study," found that the "age-adjusted incidence of PD tended to increase with increasing years of exposure to pesticides" (1789). This shows that there is a positive correlation between the duration of pesticide exposure and the risk of developing Parkinson's disease. This is because, in plantations, pesticides are used at a constant rate for long periods of time. Therefore, as the duration of pesticide exposure increases, the concentration of pesticides in the environment increases. Due to the elevated concentrations of pesticides, high amounts of neurotoxins are present in the environment. If these neurotoxins are able to enter the human body and find their way to the central nervous system, they could work at the molecular level, degenerating dopamine-producing neurons and thus inducing Parkinson's disease. A positive correlation between pesticide exposure and Parkinson's disease is also supported by a study conducted by Engel et al. in "Parkinsonism and Occupational Exposure to Pesticides." Engel et al. found that a "prevalence of parkinsonism increased with increasing years of exposure" (585). Both of these epidemiological studies provide strong evidence that there is a positive correlation between pesticide exposure and the development of Parkinson's disease in humans.

Ritz and Yu also support the conclusion that there is a positive correlation between pesticide exposure and Parkinson's disease with their study that was conducted in the state of California. In "Parkinson's Disease Mortality and Pesticide Exposure in California 1984- 1994" by Beate Ritz and Fei Yu, Ritz and Yu explain that they "observed an almost two-and-a-half-fold increase in risk of dying from PD (as underlying cause) during the 1989-1994 period if insecticides were reported to be applied to more than 37% of the county's area and a 50% increase when 5-37% of the county's land was treated" (326). This means that as the application of

pesticides increases, the mortality due to Parkinson's disease also increases. This occurrence is explained if there is a positive correlation between pesticide exposure and Parkinson's disease because as the pesticides exposure increases, more people in a distinct population would acquire Parkinson's disease. Due to an increased amount of people within that population having Parkinson's disease, a greater amount of people would be at risk of dying from the disease. This ultimately explains the elevated mortality rates attributed to Parkinson's disease in the state of California. Cho et al. in "Association Between Parkinsonism and Participation in Agriculture in Korea" also claim that there is a link between the duration of pesticide exposure and an increased risk of developing Parkinson's disease. Cho et al. found that "the development of PD...was weakly correlated with a longer history of farming and more frequent use of pesticides" (27). Similarly, according to Felix Javier Jimenez-Jimenez, Dolores Mateo and Santiago Gimenez-Roldan, in "Exposure to Well Water and Pesticides in Parkinson's Disease: A Case- Control Study in the Madrid Area," the authors concluded that "significantly more PD patients than controls had been exposed to well water, for 30 years or more, suggesting that prolonged exposure might be required to increase the relative risk of developing PD" (151). The research done by Felix Javier Jimenez-Jimenez, Dolores Mateo and Santiago Gimenez-Roldan support the proposal that the risk of developing Parkinson's disease increases as exposure increases. However, in contrast to the other epidemiological studies referred to in this review, the exposure they refer to is through well water, not directly through pesticides. This supports the notion that well water may play a vital role in human pesticide exposure. In accordance to the epidemiological studies stated above, in "Environmental Risk Factors and Parkinson's Disease: A Case-Control Study in Taiwan," Liou et al. found that there is an increased PD risk only after there has been long-term exposure to pesticides. Liou et al. found that "living in a rural environment for more than 20 years, farming for more than 20 years, or using herbicides/pesticides or paraquat" are risk factors for Parkinson's disease (1585). In each of these epidemiological studies, the researchers not only found a link between pesticides and Parkinson's disease, but a definitive positive correlation between the amount of pesticide exposure and the rates of Parkinson's disease in a population.

Although epidemiological research has linked pesticide exposure to Parkinson's disease, there still remains a lack of understanding about which

specific types of pesticides cause the pathogenesis of Parkinson's disease. In "Parkinsonism and Occupational Exposure to Pesticides" by Engel et al, the researchers found that "parkinsonism, as defined in this study, may be associated with long term occupational exposure to pesticides. However, we found no increased risk of parkinsonism associated with specific pesticides" (587). In addition, the studies done in Hawaii by Petrovitch et al., in California by Ritz and Yu, in Korea by Cho et al. and in Madrid by Jimenez-Jimenez, Mateo and Gimenez-Roldan also do not provide any conclusions or discussions about the relationship between a specific type of pesticide and the pathogenesis of Parkinson's disease. In "A Case-Control Study of Parkinson's Disease in a Horticultural Region of British Columbia," Hertzman et al. also do not link a specific type of pesticide to Parkinson's disease. Hertzman et al. explicitly state "no pesticide was associated with IP development" (73). Collectively, these studies provide strong evidence for the claim that pesticides lead to the development of Parkinson's disease; therefore pesticides are a factor in the environmental etiology of Parkinson's disease. However, these studies do not attribute the pathogenesis of Parkinson's disease to specific pesticides, therefore the above studies lack specificity. However, in "Environmental Risk Factors and Parkinson's Disease: A Case-Control Study in Taiwan," Liou et al. specifically studied the deleterious effects of specific pesticides. They discovered that the "use of paraquat were associated with an increased PD risk in a dose-response relationship" (1583). In a majority of the studies reviewed above, no specific relationship is found between a certain type of pesticide and the development of Parkinson's disease. However, Liou et al. propose a link between paraquat and Parkinson's disease. Therefore, the remainder of this review focuses on providing strong evidence to support the claim that paraquat causes Parkinson's disease because of paraquat's role with the molecular mechanism of Parkinson's disease.

Paraquat's Deleterious Effect in the Central Nervous System: Neurodegeneration

Paraquat has been linked to the degeneration of dopaminergic neurons because of its molecular role with the protein alpha-synuclein. Uversky, Li and Fink in "Pesticides Directly Accelerate the Rate of α -Synuclein Fibril Formation: A Possible Factor in Parkinson's Disease," concluded

that “certain pesticides induce a conformational change in α -synuclein, and these same compounds also accelerate the rate of α -synuclein fibril formation” (107). This is vital to connecting paraquat to the pathogenesis of Parkinson’s disease because alpha-synuclein fibrillation is a molecular mechanism of Parkinson’s disease. If a pesticide such as paraquat has the ability to increase the rate of alpha-synuclein fibrillation, that pesticide is a high risk factor for Parkinson’s disease because it would directly cause alpha-synuclein to fibrillate in the central nervous system at higher rates than normal. This correlates to not only an increased chance of acquiring Parkinson’s disease but also an elevated rate of Parkinson’s disease progression if a person develops the disease. Uversky, in “Neurotoxicant-Induced Animal Models of Parkinson’s Disease: Understanding the Role of Rotenone, Maneb and Paraquat in Neurodegeneration,” also supports the conclusion that pesticides cause the amplification of alpha-synuclein fibrillation. Uversky says, “paraquat markedly accelerates the invitro rate of α -synuclein fibril formation” (235). In each of these research studies, the researchers found a clear link between paraquat and its ability to amplify α -synuclein fibrillation. This provides strong support for the claim that paraquat is capable of inducing Parkinson’s disease because of its molecular role with alpha-synuclein.

Various research studies also discuss paraquat’s ability to cause neurodegeneration, especially because of paraquat’s role in inducing oxidative stress. In “The Role of Environmental Agents in Parkinson’s Disease,” Donato Di Monte found “a significant cell loss caused by systemic sub-chronic exposure to paraquat” after injecting mice with the pesticide (421). Donato Di. Monte’s mice experiment shows that paraquat is linked to the degeneration of neurons because of a certain biological mechanism that either impairs the ability for neurons to function or causes the apoptosis of neurons. This results in dopaminergic neuron damage, meaning that paraquat can directly cause Parkinson’s disease. According to Di Monte, “paraquat toxicity has been linked to a redox cycling mechanism capable of generating reactive species from the reduction of molecular oxygen... paraquat-induced oxidative stress may be significantly enhanced, accounting for the observed loss of dopaminergic neurons” (423). As a result, paraquat works at the molecular level by eliciting oxidative stress, which damages dopaminergic neurons, therefore leading to the pathogenesis of Parkinson’s disease.

Vladimir N. Uversky, in “Neurotoxicant-Induced Animal Models of Parkinson’s Disease: Understanding the Role of Roteneone, Maneb and Paraquat in Neurodegeneration,” also outlines a mode that paraquat uses to cause oxidative stress. Uversky suggests that “the influx of Ca^{2+} into cells might stimulate nitric oxide synthase, and the released nitric oxide might diffuse to dopaminergic terminals and induce mitochondrial dysfunction, causing continuous and long-lasting dopamine overflow” (235). Based on research conducted by Di Monte and Uversky, paraquat is associated with dopaminergic neurons through an oxidative stress pathway. This paraquat induced oxidative stress causes neural degeneration because paraquat, once in direct contact with dopaminergic neurons in the central nervous system, leads to mitochondrial dysfunction. The role of mitochondria is to synthesize adenosine triphosphate (ATP), a form of energy, through cellular respiration. Cells then use energy in the form of ATP for various processes; one such process is dopamine synthesis. If the mitochondria in the dopaminergic neurons become dysfunctional, the dopaminergic neurons would not be able to produce ATP. This would translate to a dopamine deficiency in the central nervous system because the dopaminergic neurons would not have enough ATP to sufficiently synthesize adequate levels of dopamine. This directly correlates to motor system dysfunction and Parkinson’s disease, as motor messages would be impaired due to insufficient amounts of dopamine in the central nervous system.

A Cause for the Molecular Mechanisms of Parkinson’s Disease: Alpha-Synuclein

Although the main role of alpha-synuclein remains unknown, the protein alpha-synuclein has been directly linked to the molecular mechanisms of Parkinson’s disease. Alpha-synuclein may cause Parkinson’s disease because of its ability to induce apoptosis due to neurotoxicity and its role in oxidative stress. Research by David Sulzer indicates that high levels of the alpha-synuclein protein may cause Parkinson’s disease. In “Clues to How Alpha-Synuclein Damages Neurons in Parkinson’s Disease,” Sulzer says, “too much wild-type α -syn protein can be toxic” (S27) and that alpha-synuclein “can form small presumably toxic oligomers known as protofibrils that interact with lipids and disrupt membranes” (S28). This means that high levels of alpha-synuclein in the central nervous system are

toxic. Therefore, alpha-synuclein may be able to degenerate dopaminergic neurons by causing the neurons to undergo apoptosis due to an induced toxicity. In “Dopamine-Dependent Neurotoxicity of α -Synuclein: A Mechanism for Selective Neurodegeneration in Parkinson Disease,” Xu et al. attribute high levels of alpha-synuclein to degeneration, thereby connecting Sulzer’s claim to a mechanism for dopaminergic neuron degeneration. Xu et al. found that “ α -synuclein overexpression resulted in the degeneration of dopaminergic neurons and motor deficits... α -synuclein overexpression resulted in age-dependent degeneration of dopaminergic axon terminals in the striatum and motor deficits” (600). This research conducted by Xu et al. provides strong evidence for the proposal that toxicity induced by high levels of alpha-synuclein fibrillation causes the degeneration of dopamine producing neurons. As a result, elevated levels of alpha-synuclein lead to the pathogenesis of Parkinson’s disease because of the toxic nature of alpha-synuclein when it accumulates at high concentrations in the central nervous system. Due to both of these research studies, there is strong support that alpha-synuclein works at the molecular level of Parkinson’s disease. This claim can be traced to the pesticide paraquat because, as supported earlier in this review, paraquat has been found to increase alpha-synuclein fibrillation. As a result, paraquat not only has a role as a pesticide but a role as a Parkinson’s disease inducer.

Another mode in which alpha-synuclein causes the degeneration of neurons is through its role in causing oxidative stress. In “Dopamine-Dependent Neurotoxicity of α -Synuclein: A Mechanism for Selective Neurodegeneration in Parkinson Disease” by Xu et al., the researchers found that

α -Synuclein-transfected DAN cells exhibited markedly increased generation of reactive oxygen species that was inhibited by the free radical spin trap phenyl-N-butyl-nitron (PBN) or the antioxidant vitamin E. Furthermore, both PBN and vitamin E inhibited apoptosis induced by wild-type or mutant α -synuclein. These results suggest that α -synuclein may potentiate dopamine-dependent generation of reactive oxygen species leading to apoptosis. (601-602)

Similarly, in “The Role of α -Synuclein in Both Neuroprotection and Neurodegeneration,” Sidhu, Wersinger, Moussa and Vernier also agree that alpha-synuclein induces oxidative stress. Sidhu, Wersinger, Moussa and Vernier say, “still another well-demonstrated entry point into the par-

kinsonian neurodegeneration is exposure to toxins triggering oxidative stress in dopamine neurons” (263). In each of these articles the researchers attribute the degeneration of dopaminergic neurons to an oxidative stress pathway that is caused by the protein alpha-synuclein. This relates to paraquat because there is strong evidence that paraquat increases the concentrations of alpha-synuclein in the central nervous system of humans. Therefore, paraquat has the potential to cause oxidative stress, which is, according to Xu et al. and Sidhu, Wersinger, Moussa and Vernier, a molecular mechanism that degenerates dopaminergic neurons. As a result, paraquat is able to cause the pathogenesis of Parkinson’s disease because of its ability to increase the levels of alpha-synuclein in the central nervous system, which causes neurotoxicity or oxidative stress, thereby leading to the apoptosis of dopaminergic neurons. Both of these mechanisms ultimately cause the levels of dopamine in the central nervous system to depreciate, thereby directly causing the development of Parkinson’s disease.

Conclusion

Epidemiological research correlates pesticide exposure to elevated rates of Parkinson’s disease in various populations around the world. Research on paraquat and pesticides associates paraquat to neurodegeneration because of its ability to increase alpha-synuclein fibrillation. In addition, research on alpha-synuclein shows that alpha-synuclein is the primary mechanism for Parkinson’s disease development at the molecular level. As a result, paraquat is a cause for the pathogenesis of Parkinson’s disease and is therefore a key component in the environmental etiology of Parkinson’s disease.

Although a conclusion has been made about the environmental etiology of Parkinson’s disease, a call for new studies is necessary to further support the claim stated in this research study. An experiment should be conducted to directly test paraquat exposure on the degeneration of dopaminergic neurons. This can be done by exposing mice to water, which would simulate contaminated well water exposure, that varies in paraquat concentrations and then measuring both alpha-synuclein fibrillation and neurodegeneration in the central nervous system of mice. The experimental groups would also be compared to a control group, which consists of mice that are not exposed to paraquat. In this experiment, quantitative

data would show paraquat's ability to cause the molecular mechanisms of Parkinson's disease and qualitative data would show the onset of external Parkinson's disease symptoms such as motor dysfunction in the mice. This type of future research would advance Parkinson's disease research to a point where paraquat is widely accepted to be a component in the environmental etiology of Parkinson's disease and thus similar substances to paraquat may come under review because of their potential to cause Parkinson's Disease.

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