

Pesticides Trigger Parkinson's Disease

Astounding body of scientific literature finds strong evidence linking Parkinson's to normal pesticide exposure and fuels movement to phase-out numerous classes of pesticides and adopt safe management approaches.

By Kagan Owens

With less than one percent of cases caused by genetics,¹ researchers have been looking for the potential risk factors for developing Parkinson's disease (PD). What they are finding is startling. The epidemiological and toxicological evidence is repeatedly identifying exposure to pesticides, as well as specific gene-pesticide interactions, as significant adverse risk factors that contribute to PD.

What Is Parkinson's Disease?

The second most common neurodegenerative disease,² Parkinson's occurs when nerve cells in the substantia nigra region of the brain are damaged or destroyed and can no longer produce dopamine, a nerve-signaling molecule that helps control muscle movement. People with PD have a variety of symptoms including loss of muscle control, trembling and lack of coordination. They may also experience anxiety, constipation, dementia, depression, urinary difficulties, and sleep disturbances. Over time, symptoms intensify.

At least one million Americans have PD and about 50,000 new cases are diagnosed each year. PD affects mostly the middle-aged and elderly. Treatments are available for the symptoms, but there is currently no cure for PD.

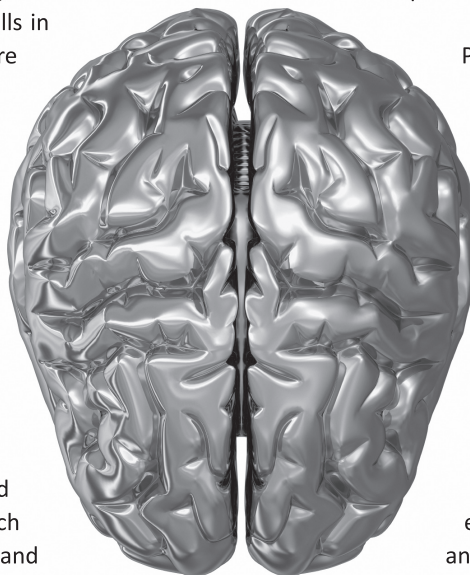
The First Link

The suspicion that pesticides might be linked to PD was theorized in the 1980's following a wave of drug induced Parkinson's-like illnesses. The drug, MPTP, which was used as a heroin substitute, is transformed in the brain after injection. The new compound, MPP+, causes the loss of dopamine producing cells and the sudden onset of a Parkinson's-like illness.³ The reason for the toxic effect is that MPP+ inhibits one of the enzymes in mitochondria, intracellular organelles that provide cells with energy.⁴ It was later discovered that MPP+ was not only the breakdown product of an obscure drug, but also the active ingredient of the herbicide

cyperquat, the closely related paraquat, and other pesticides.⁵ This discovery sparked interest in studying the link between pesticides and PD, which has uncovered links to numerous pesticides and chemical families.

Pesticide Exposure Increases Risk

While some epidemiological studies and animal data linking PD with pesticides has been inconsistent^{6,7} (likely due to study design issues such as control selections, study size, variety of diagnostic criteria used and statistical analysis), convincing evidence is continually emerging that demonstrates the pesticide exposure link to PD.^{8,9}



Published case-control studies show a statistically significant association and elevated odds-ratios (OR) for PD (that determine the elevated disease rate above the norm of 1.0) and exposure to pesticides.^{10,11} Duration of exposure¹² and level of exposure¹³ is also correlated with an increase in PD risk. In a review of 40 published epidemiological case-control studies from 1983-2005, researchers from the UK evaluated the relationship between PD and pesticide exposure, finding sufficient evidence that an association exists and is strongest for exposure to herbicides and insecticides, and after long durations of exposure. In the 31 studies that show results for pesticides in an exposure category, the ORs ranged from 0.75 to 7.0 (a ¼ to 7 times greater disease rate) -- only two of those studies reported an OR less than 1.0.¹⁴ A meta-analysis of 19 published, peer-reviewed studies done in the U.S. from 1989-1999 finds that individuals exposed to pesticides have twice the risk of developing PD than the general population.¹⁵ A 1993 case-control study finds a positive association with insecticide exposure (OR=5.75), past residency in a fumigated house (OR=5.25), and herbicide exposure (OR=3.22) to PD.¹⁶

A large Harvard School of Public Health epidemiological study of more than 140,000 adults finds that those exposed to long-term, low levels of pesticides have a 70 percent higher incidence of PD

than among people who report no exposure.¹⁷ A study of almost 3000 people in five European countries finds low level pesticide users, such as amateur gardeners, are 9% more likely to have Parkinson's, whereas high level users, like farmers, are 43% more likely.¹⁸

According to scientists, people exposed to chemicals that have a particular affinity for the substantia nigra region of the brain may be at particular risk for developing the disease.¹⁹ In 2006, the preliminary results of a Centers for Disease Control and Prevention (CDC) funded study led by the University of North Dakota's Energy & Environmental Research Center, show that the areas of the brain in laboratory-tested rats affected by pesticide exposure are the same areas linked to neurological changes associated with PD.²⁰

Rural Living, Well Water Consumption and Farming

Rural residency, well water consumption, and/or farming positively correlates with an increased incidence of developing PD.^{21,22,23,24,25} A 2001 meta-analysis of peer-reviewed studies finds that living in a rural area, drinking well water, farming and exposure to pesticides have overall PD risk estimates between 1.26 and 1.85.²⁶ Early studies in Canada find the highest prevalence of PD coincides with agricultural areas with the largest amount of pesticide use.^{27,28} One study discovered that many people living in rural areas, with no diagnosed neurological disorders, have lower levels of dopamine producing cells than urban populations.²⁹ This suggests that even in the absence of the illness, some aspect of rural life is putting people at risk for the disease. Confirming those results, another study finds that Parkinson's patients are twice as likely to be living in rural areas and drinking well water,³⁰ where farming pesticides often contaminate ground water. A California mortality study of individuals whose death certificates mention

PD as an underlying cause of death and cross-referenced with agricultural and pesticide use data finds that the counties using restricted use pesticides (RUP) for agricultural purposes have about a 40 percent increase in PD mortality when compared to those counties reporting no RUP.³¹

Occupational Exposure

Confirmed again and again, studies find that PD is associated with occupational exposure to pesticides.^{32,33,34,35,36,37,38,39,40} Studies show a two- to over a threefold increased risk of developing PD with occupational exposure, whether from working on farms,^{41,42} orchards,⁴³ or plantations.⁴⁴ A population-based case-control study in Canada finds that a history of occupational herbicide use is associated with an estimated threefold increase in PD risk and previous insecticide use results in an estimated twofold increase in risk.⁴⁵ A case-control study in northeast Italy finds a 7.7 OR for farming as an occupation.⁴⁶

Home Pesticide Use

A study published in the *Journal of the American Medical Association* raises concerns for residential pesticide exposure. Stanford University researchers find a 70 percent increased risk of developing PD for individuals that use pesticides in their home. Exposure to garden insecticides carries a 50 percent increased risk of developing the disease. Among herbicide users, the risk of developing PD increases as the number of days in contact with herbicides grows. Respondents who reported handling or applying herbicides for up to 30 days are 40 percent more likely to develop the disease, whereas respondents that reported 160 days exposure, have a 70 percent increase.⁴⁷

Age-Related Risk Factors

The United Nation's World Health Organization (WHO) recently



Occupational pesticide exposure, rural living, farming, well water consumption and residential pesticide use have all been linked to elevated rates of Parkinson's disease.



Although age may contribute to Parkinson's disease, it is not considered by scientists to be a sole cause of the disease.

released a report on children's heightened vulnerability to chemical exposures at different periods of their growth and development. The report, *Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals*, highlights the fact that the stage of a child's development when chemical exposure occurs may be just as important as the magnitude of the exposure. The report states that "neurotoxic insults during development that result in no observable phenotype at birth or during childhood could manifest later in life as earlier onset of neurodegenerative diseases such as [PD]."⁴⁸ Several studies support WHO's report showing that exposure in utero, post-natal or in childhood affect the substantia nigra causing direct damage or increasing the susceptibility to additional exposures and neurodegenerative damage in adulthood.^{49,50,51,52,53,54,55}

Aging is also found to be a risk factor for PD, yet researchers agree that aging alone is not a sufficient factor to explain PD. In one study, enhanced sensitivity of the aging nigrostriatal dopamine pathway to pesticides maneb and paraquat result in irreversible and progressive neurotoxicity, thus showing that exposure to pesticides combined with aging can increase the risk for developing PD.⁵⁶ University of Rochester scientists believe environmental contaminants such as pesticides make dopamine cells more vulnerable to damage from normal aging, infection, or subsequent exposure to pollutants.⁵⁷

Genetic Risk Factors

Researchers screening twins for genetic effects and PD show that while genetic factors play a role for early-onset PD (begins at or before the age of 50), environmental factors are most important for those with late-onset PD.^{58,59} Yet, genetics are not completely out of the picture for late-onset PD. A number of genes are linked to PD as they interact with toxic chemicals in such a way that they may not cause the disease directly, but cause subtle changes in the genes that can make individuals more or less likely to

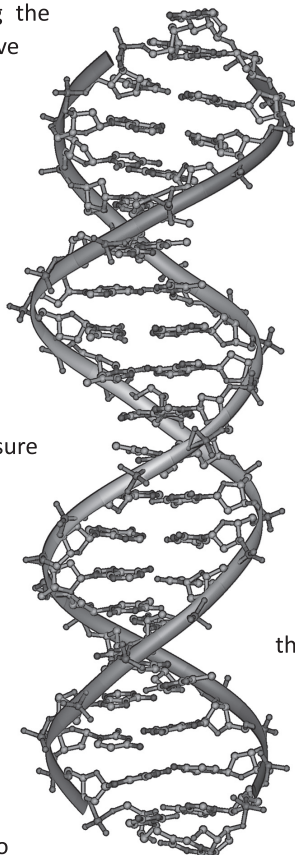
develop PD later in life.^{60,61,62} Simply put by Kenneth Olden, Ph.D., former Director of National Institute for Environmental Health Sciences (NIEHS), "Genetics load the gun. The environment pulls the trigger."⁶³

For those with a family history of the disease, exposure to certain chemicals found in pesticides may increase their risk of developing PD, according to a 2005 study. Researchers looked at specially bred fruit flies lacking both forms of the DJ-1 gene that is associated with the inherited form of PD. In the study, researchers show that flies lacking forms of the DJ-1 gene are normal under standard conditions, but when they are exposed to the herbicide paraquat and insecticide rotenone, the flies suffer from extreme oxidative or cellular stress and die. Researchers say their findings suggest that a loss of DJ-1 gene function increases sensitivity to

chemicals that cause oxidative stress, thus linking a genetic cause with environmental risk factors.⁶⁴ Other research on cultured cells and in knockout mice (mice that have had a gene removed by genetic manipulation) supports these findings, showing that DJ-1 mutations can sensitize cells to the harmful effects of oxidative stress, which occurs when unstable oxygen molecules react with certain compounds like pesticides.⁶⁵

Two other studies link family history and pesticide exposure to an increased risk of PD by looking at glutathione S-transferase

P. Glutathione S-transferases (GST) are enzymes that help rid the body of toxic chemicals that generate oxidative stress. A study published in the *Lancet* finds a significant association for PD patients exposed to pesticides and having dissimilar alleles (variant forms of the same gene causing variations of inherited characteristics) at the GSTP1 locus. The scientists believe that this helps explain the susceptibility of some individuals to the parkinsonism-inducing effects of pesticides.⁶⁶ Researchers at the St. Jude Children's Research Hospital build on those findings, reporting in the *Proceedings of the National Academy of Sciences* that the GST pi detoxification enzyme that prevents damage to the substantia nigra region of the brain acts like a sentry at the crossroads of several biochemical pathways, any one of which can lead to PD. The job of the antioxidant GST pi is to protect the cell from death caused by either toxic chemicals in the environment, such as pesticides, or a self-destruction process called apoptosis, triggered by certain stressful conditions in the cell. If GST pi levels are reduced or this enzyme is overwhelmed by toxic chemicals,



these nerves are at increased risk of death. “The majority of these cases of [PD] appear to arise because individuals who have a genetic susceptibility to the disease are exposed to environmental toxins such as pesticides and herbicides, which trigger the formation of free radicals that kill dopaminergic neurons in the substantia nigra,” states Richard Smeyne, Ph.D., associate member of the Department of Developmental Neurobiology at St. Jude. “We also know that GST pi blocks the process of cell suicide triggered by stresses that the cell can’t overcome, such as an increase in the presence of free radicals or a loss of the cell’s ability to produce energy.”⁶⁷

Enzyme deficiencies in the liver may lower resistance to pesticides, as PD patients are more likely to have a genetic deficiency in the detoxifying enzyme of the liver when compared to the normal population.⁶⁸ Scientists looking at the cytochrome P450 2D6 gene (CYP2D6) finds that this gene has a modifying effect on the risk of PD among individuals exposed to pesticides.⁶⁹ A 1998 case-control study published in *Neuroepidemiology* finds that individuals with Parkinson’s who were exposed to pesticides and had the gene known as CYP2D6 29B+ allele, are three times as likely to develop dementia along with PD than those without the gene. This allele metabolizes and detoxifies chemicals that enter the body by activating liver enzymes. Those individuals who have a mutant form of the allele may be more susceptible to pesticides because of their inability to detoxify chemicals. This study finds that individuals who have a poor metaboliser CYP2D6 genotype and have also been exposed to pesticides are more likely to develop dementia.⁷⁰

Two more genes, MnSOD and NQO1, encode enzymes that play key roles in oxidative stress and interact with pesticides to increase an individual’s PD risk. Researchers show that among subjects that were exposed to pesticides, the combined MnSOD/NQO1 variant genotype is significantly associated with a four-fold increased risk of PD.⁷¹

“All of the evidence that has been accumulating suggests that exposure to pesticides increases the risk of PD,” says Gary Miller, Ph.D., associate professor of environmental and occupational health at Emory University. “We believe that a person who is destined to get Parkinson’s because of genetics or other factors at age

80 might develop symptoms when they’re 65 or 70 if they have been exposed to pesticides.”⁷²

Pesticide Use Increases Risk in Men

While there is conclusive evidence that men are at an increased risk of being diagnosed with PD, how that factor comes in to play with pesticide exposure is not necessarily confirmed. There is some data that shows a significant association between men, exposure to pesticides, and PD.⁷³ A mouse study looking at developmental exposure to the insecticide dieldrin finds a greater effect in male offspring than in females.⁷⁴ In addition, the population-based study by Mayo Clinic researchers finds that men with PD are 2.4 times more likely to have been exposed to pesticides than those who did not have Parkinson’s. Pesticide exposure did not increase the risk of Parkinson’s in women, and no other household or industrial chemicals were significantly linked to the disease in either men or women.⁷⁵ Researchers suggest that men are at greater risk because male study respondents are more likely the ones that use pesticides in agriculture, in their occupation and/or around the home. The Mayo clinic researchers also suggest that “pesticide use combines with other risk factors in men’s environment or genetic makeup, causing them to cross over the threshold into developing the disease.”⁷⁶

Implicating Specific Pesticides and the Mechanisms by which They Induce PD

Although the evidence showing a significant association between pesticide exposure and PD is clear, implicating specific pesticides or a group of pesticides is difficult. Exposure type, duration, product and dose are difficult to ascertain in retrospective case-control studies. Due to the possibility of recall biases, the vast number of pesticides available for use, and the fact that pesticides can work synergistically, many studies analyze pesticide exposure without regard to specifics such as product or chemical names, and, therefore, do not consistently implicate,^{77,78} or estimate the PD risk associated with any particular pesticide.⁷⁹

However, there are epidemiologic and toxicologic studies that have identified specific pesticides linked to PD. (See page 18.) Studies that identify the mechanisms by which pesticides lead to PD, such as protein aggregation (a-synuclein), effects on the striatal dopaminergic



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Glossary of Common Terms

alpha-synuclein: one in a family of structurally related proteins that are prominently expressed in the central nervous system and form brain lesions that are hallmarks of some neurodegenerative diseases. Forms of hereditary PD are due to mutations and triplication in the gene for alpha-synuclein.

apoptosis: a natural process of self-destruction in certain cells that is determined by the genes and can be initiated by a stimulus or by removal of a repressor agent. Also called programmed cell death.

dopamine: a neurotransmitter formed in the brain essential to the normal functioning of the central nervous system. A reduction in its concentration within the brain is associated with Parkinson's disease.

mitochondria: spherical or rod shaped parts of the cell. Mitochondria contain genetic material (DNA and RNA) and are responsible for converting food to energy.

nigrostriatal pathway: the efferent connection between the substantia nigra and corpus striatum and one of the major dopamine pathways in the brain. Nigrostriatal pathway is particularly involved in the production of movement, as part of a system called the basal ganglia motor loop.

system and altered dopamine levels, mitochondrial dysfunction (complex I inhibition) and oxidative stress, are discussed.

Conclusion

Although studies can have methodological limitations, overall the current review shows that there is a definitive relationship between Parkinson's disease and pesticides. The new research into PD is helping scientists better understand some of the mechanisms of this serious and disabling neurodegenerative brain disorder. Knowledge of the environmental factors and genetics of this illness has allowed investigators to create models of disease that are being used to examine potential causes of neuron disease such as pesticide exposure. While many researchers are seeking to support the development of more effective treatments of this human illness, the National Institutes of Health (NIH) has said, "[W]ith better knowledge of the role of pesticides and other environmental agents in causing [PD], effective prevention will be possible by eliminating or reducing use of specific environmental agents..."⁸⁰ Researchers that have been looking at the synergistic effects of pesticides state that, "[T]he current derivation of risk assessment guidelines needs to be reevaluated."⁸¹ Advocates

oxidative stress: an imbalance of the prooxidant antioxidant ratio in which too few antioxidants are produced or ingested or too many oxidizing agents are produced; can result in cell death.

proteasomes: a protein degradation "machine" within the cell that can digest a variety of proteins into short polypeptides and amino acids. Impaired proteasomal activity has been suggested as an explanation for Parkinson's disease.

striatum: part of the basal ganglia; a large cluster of nerve cells, consisting of the caudate nucleus and the putamen, that controls movement, balance, and walking; the neurons of the striatum require dopamine to function.

substantia nigra: a small area of the brain containing a cluster of black-pigmented nerve cells that produce dopamine, which is then transmitted to the striatum. Its destruction is associated with Parkinson's disease.

ubiquitin: a 76-amino-acid protein found in all eukaryotic cells [cells of plants, animals, protozoa, fungi and most algae] that can be covalently attached to specific lysine residues in target proteins. This often forms multimeric polyubiquitin chains, which is thought to target the protein for destruction.

want to see the scientific knowledge support the banning of the chemical families associated with these effects. Because it is impossible to know your genetic disposition, all people should avoid contact with toxic pesticides.

Take Action

Let the U.S.EPA Administrator and Deputy Administrator know that they have a duty to alert the public to the scientific findings (laboratory and epidemiologic) that link pesticides with PD. In addition, urge these U.S.EPA officials to initiate an urgent and expedited review of pesticides' link to Parkinson's. Also let your elected members of Congress know how you feel.

Beyond Pesticides offers information on a plethora of non-toxic alternatives to pesticides. Learn how you can protect your family, community and the environment from the effects of pesticides in food and water, at home, on lawns, parks and gardens, in schools, hospitals and other public buildings. Resources are available at www.beyondpesticides.org. A fully cited version of this article is available at www.beyondpesticides.org/infoservices/pesticidesandyou.

Specific Pesticides Linked to Parkinson's Disease

The following are specific pesticides identified in the scientific literature to be linked to Parkinson's disease. However, the actual number is most likely much higher because implicating specific pesticides or a group of pesticides is difficult.

Benzimidazoles

Benomyl (Fungicide). University of North Dakota researchers found that benomyl affects rat brains, showing that mitochondrial enzymes are sensitive targets for inactivation by the pesticide.⁸² Exposure to benomyl at low concentrations increases the risk of developing PD by inhibiting the ubiquitin-proteasome system.⁸³

Bipyridyliums

Diquat Dibromide (Herbicide). Several days after a 72 year-old farmer was exposed to an aqueous solution of 10 percent diquat dibromide he developed severe parkinsonian syndrome.⁸⁴

Paraquat (Herbicide). Several studies show an increased risk for PD with occupational exposure to and contact with paraquat.^{85,86} A case-control study in Taiwan found that those who use paraquat are at greater risk of developing Parkinson's than those that use other pesticides.⁸⁷ A 2007 study examined a cohort of 80,000 licensed private applicators and spouses and found that farmworkers exposed to the herbicide paraquat have twice the expected risk of developing PD.⁸⁸ For those that were exposed to herbicides and could recall their exposure history, a Canadian population-based case-control study reported one individual using paraquat, between the ages of 26 and 31 years, and is the only herbicide-exposed case in the study whose onset of symptoms occurred before the age of 40.⁸⁹

Paraquat induces dopaminergic nigral apoptosis and acts through oxidative stress-mediated mechanisms.⁹⁰ In laboratory animal studies, paraquat exposure triggers processes characteristic of early stages of dopaminergic neuron degeneration by stimulating an increase in the protein α -synuclein in the brain, likely due to preferential binding of the pesticides to a partially folded α -synuclein intermediate. The protein kills the dopamine-producing brain cells which lead to PD.^{91,92,93,94,95} In 2002, researchers from the Parkinson's Institute, published that their findings "unequivocally show that selective dopaminergic degeneration, one of the pathological hallmarks of [PD], is also a characteristic of paraquat neurotoxicity."⁹⁶

For researchers testing the role of oxidative stress in paraquat exposed mice, they find that the "initial exposure acts as a 'priming' event, enhancing neuronal vulnerability to a subsequent toxic insult," suggesting that dopaminergic cell degeneration appears to be dependent on the sequence of toxic challenges and the interaction between cell vulnerability, damaging effects and protective responses. Nigrostriatal neurons are vulnerable to oxidative processes. Depending on the paraquat exposure, oxidative stress may be reversible or lead to neurodegeneration.⁹⁷

Botanicals

Rotenone (Insecticide). Rotenone, a naturally occurring pesticide, is used in laboratory studies to induce PD in rat and primate models

to study various aspects of the disease in humans.^{98,99} Laboratory studies using rats, monkeys, mice and human neuroblastoma cells find that rotenone destroys dopaminergic neurons inhibiting brain mitochondrial function, increasing excessive oxidative activity in the brain and shifting respiration to a more anaerobic state.^{100,101,102,103} Rotenone can significantly stimulate the formation of a α -synuclein fibrils.¹⁰⁴ Aging has also been found to increase the sensitivity of dopaminergic neurons to a low, systemic dose of rotenone.¹⁰⁵ Using rotenone *in vivo* and *in vitro* models, researchers find that chronic exposure to a pesticide and mitochondrial toxin brings into play three systems, DJ-1, α -synuclein, and the ubiquitin-proteasome system, and implies that mitochondrial dysfunction and oxidative stress link environmental and genetic forms of the disease.^{106,107}

Dithiocarbamates

Diethyldithiocarbamate (Herbicide). Exposure to diethyldithiocarbamate at low concentrations increases the risk of developing PD by inhibiting the ubiquitin-proteasome system.¹⁰⁸ Diethyldithiocarbamate can also significantly stimulate the formation of α -synuclein fibrils, likely due to preferential binding of the pesticides to a partially folded α -synuclein intermediate.¹⁰⁹

Mancozeb. (Fungicide). Mancozeb affects rat brain mitochondria, showing that mitochondrial enzymes, which are sensitive targets, are inactivated by the pesticide.¹¹⁰

Maneb (Fungicide). A case-report shows that after chronic exposure to maneb, a 37-year old man developed Parkinson's two years after the applications ceased.¹¹¹

University of North Dakota researchers find maneb affects rat brain mitochondria.¹¹² Low levels of maneb can injure the antioxidant system in the dopamine neurons, especially with concurrent exposures to other environmentally relevant oxidative stressors, such as paraquat.¹¹³

Ziram (Fungicide/Dog and Cat Repellent). Ziram shows inhibitory effects on proteasome activities at low concentrations. This suggests that proteasome inhibition as a potential mechanism for the epidemiological association of pesticides and PD.¹¹⁴

Organochlorines

In 1996, a German study linked PD to pesticides, finding an elevated odds ratio for organochlorine pesticides.¹¹⁵

Dieldrin (Insecticide).^{116,117,118,119,120} Low-level exposure to dieldrin, a banned but persistent pesticide ubiquitously distributed in the environment, appears to accelerate changes in the brain that can potentially lead to the onset of PD symptoms years or even decades before they might naturally develop, according to a research presentation at the 2006 American Chemical Society annual meeting. This finding "clearly shows that pesticides such as dieldrin appear to accelerate or exacerbate the already underlying disease," states Emory University's Gary Miller, Ph.D. "So it appears the more you are exposed to pesticides, the greater your risk of developing the disease earlier in life."

In studies looking at post-mortem brain tissue samples of Parkinson's patients, scientists find a significant association between dieldrin and the diagnosis of PD.^{121,122,123} Dr. Miller and his co-researchers found levels of dieldrin three times higher in the brains of 14 people who had PD than in the brains of 12 people who did not.¹²⁴

Endosulfan (Insecticide). A study testing 25 pesticides to see if exposure to them increases the risk of developing PD finds that endosulfan shows inhibitory effects on proteasome activities at low concentrations.¹²⁵

Heptachlor (Insecticide). Perinatal exposure to heptachlor, another banned pesticide that persists ubiquitously, alters the dopaminergic system and may increase the vulnerability of dopamine neurons to toxic insult.¹²⁶

Lindane (Insecticide). An autopsy case-control study finds significant levels of lindane in the brain tissues of deceased Parkinson's patients.¹²⁷

Organophosphates

Chlorfenvinphos (Insecticide). Subchronic administration of chlorfenvinphos, a pesticide that is no longer registered by the U.S. EPA, leads to a change in the brain oxidative status in rats.¹²⁸

Parathion (Insecticide). Although the researchers did not find a significant association between PD and pesticide exposure, their population-based case-control study in Washington state finds that among individual pesticides, the highest odds-ratio is seen with parathion, a highly toxic neurotoxic pesticide.¹²⁹

Chlorpyrifos (Insecticide). Researchers find that dopaminergic neurotransmission is affected by exposure to chlorpyrifos in a laboratory mice study.¹³⁰

Pyrethroids

Deltamethrin (Insecticide). One study finds that because the dopamine transporter function of the brain is affected by the vulnerability of dopamine neurons to neurotoxicants, up-regulation (increased cellular response) of deltamethrin may increase the susceptibility of dopamine neurons to toxic insult.¹³¹

Permethrin (Insecticide). Studies find that permethrin affects dopaminergic neurotransmission¹³² and up-regulation of permethrin may increase the susceptibility of dopamine neurons to toxic insult.¹³³

Virginia Tech researchers discovered that exposure to some insecticides, such as permethrin, may cause a cascade of chemical events in the brain that can lead to PD. The researchers studied the levels of dopamine, dopamine transporter protein expression, and the levels of α -synuclein in mice exposed to various doses of permethrin. The increase in dopamine uptake indicates that the mouse's system is reacting to a neurochemical insult caused by the presence of the insecticide. In some individuals, dopamine-producing neurons may be challenged by genetic factors or by previous exposure to other neurotoxins. For individuals with a genetic predisposition, exposure to permethrin may trigger chemical events in the brain that result in an increased risk for damage to the area of the brain that is selectively damaged in PD. The researchers also find that permethrin exposure results in an overproduction of the protein α -synuclein at low doses. The accumulation of the

protein is a major component of the formation of the Lewy bodies, fibrous tangles observed in the brains of patients with PD.¹³⁴

Thiocarbamate and Chlorophenoxy Herbicides

For those that were exposed to herbicides and could recall the chemicals or trade names of the products used, a Canadian population-based case-control study found that all but one PD patient had used compounds in the thiocarbamate and chlorophenoxy and chemical groups exclusively.¹³⁵

Triazines

Atrazine (Herbicide). A 2007 rat study found that atrazine decreases tissue dopamine levels by interfering with the vesicular storage and/or cellular uptake of dopamine.¹³⁶

Others

Pyridaben, Fenpyroximate, Fenazaquin (Insecticides). Research at Emory University found that commonly used pesticides are toxic to the mitochondria of cells, an effect linked to PD. PD has been associated with abnormalities of mitochondria, which are the "power plants" that provide all cells with energy. The Emory scientists exposed human neuroblastoma cells to the pesticides pyridaben, fenpyroximate and fenazaquin which inhibit complex I, a mitochondrial enzyme. Pyridaben is by far the most potent toxic compound. Pyridaben is also more potent in producing "free radicals" and oxidative damage to the cells, both of which are thought to be important in causing PD.¹³⁷

Synergistic Effects

Paraquat and Maneb. University of Rochester scientists discovered that the synergistic effects of paraquat and maneb target the nigrostriatal dopamine system and indicate progressive neurotoxicity with continuing exposure. Their findings show that while there are no or only marginal effects when these chemicals are administered individually, together they produce synergistic effects when given in combination.¹³⁸ In another study, these researchers again chronically expose mice to a low-level combination of paraquat and maneb, resulting in significant reductions in locomotor activity, levels of striatal dopamine and dopaminergic neurons in the substantia nigra, more so than when exposed individually.¹³⁹

A laboratory study found that "prenatal exposure to the pesticide maneb produces selective, permanent alterations of the nigrostriatal dopaminergic system and enhances adult susceptibility to paraquat exposure."¹⁴⁰ Additional studies show that exposure to maneb and paraquat during the post-natal and juvenile period causes Parkinson-like declines in dopaminergic neurons and makes the substantia nigra more susceptible to additional exposures in adulthood,¹⁴¹ "suggesting that developmental exposure to neurotoxicants may be involved in the induction of neurodegenerative disorders and/or alter the normal aging process."¹⁴²

Endosulfan and Zineb. Researchers at Virginia Tech examining endosulfan and zineb in human cultured neuroblastoma cells found that these pesticides, individually and together, are toxic to the impulse-conducting cells of the nervous system. Mixtures of the two pesticides had greater effects.¹⁴³ Another study found that mice exposed to endosulfan and/or zineb as juveniles and then re-exposed in their adulthood result in significantly depleted striatal dopamine levels, thus concluding that exposure to pesticides such as endosulfan and zineb during critical periods of postnatal development contributes to neurotransmitter changes in adulthood.¹⁴⁴

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