

# Pesticide Neurotoxicity featuring Parkinson's Disease

DAVID PONSONBY, M Ed

*David Ponsonby is a health educator residing in Carrollton, Texas. He developed a special interest in Parkinson's Disease (PD) after watching his late father struggle with the condition for 10 years. David felt helpless when prescription drug therapies did not reduce the tremors, or stop the progression of this degenerative disease. Fueled by the memory of his father's suffering, David has searched for answers on the cause of PD through a comprehensive review of the research. He offers a summary of one topic here. **Note:** David's contact information is provided under "More Information" should you wish to follow-up.*

[Foreword](#)

[What is Parkinson's disease \(PD\)?](#)

[The Historical Perspective of PD](#)

[The Toxin Connection](#)

[Pesticides](#)

[Genetic or acquired defects](#)

[Treatment with Glutathione and Herbs](#)

[Conclusion](#)

[More information](#)

[Glossary of Pesticides](#)

[References](#)

## Foreword

We tend to think of pesticides (herbicides and insecticides, etc.) as modern solutions to age-old problems with weeds, insects, and other scourges that can impact farmers and, indeed, entire nations. Weiss has noted that almost every major pesticide acts by inducing neurotoxicity. (Weiss, 1983) Unfortunately, the weeds and insects have not been the only victims.

Many pesticides are watered-down versions of chemicals developed for use in wartime (e.g. sarin, soman, and tabun). DDT is a classic example; first introduced in 1942, it was banned, at least in the U.S., after 1987. Often the same companies that manufacture these chemicals also provide the pharmaceutical industry; indeed they may share the same corporate identity.

An association between chemicals and neurological symptoms has been recognized for some time. Carbon disulfide, a major component of fumigant mixtures, has been associated with neurologic symptoms in the rayon industry since the 1930s. (Peters, 1988) As a specific product of neurotoxicity, I am featuring Parkinson's disease in this paper. The condition has struck a number of public figures who have imprinted its symptoms on the public consciousness: Pope John, Muhammad Ali, Janet Reno, Billy Graham, and Michael J. Fox may spring readily to mind.

This is not to say that all neurotoxins are derived from pesticides, or that all neurotoxins produce PD. It is worth noting that toxins tend to produce irreversible Parkinsonism, whereas some drug-induced forms are reversible. (Langston, 1987) Several prescription drugs induce Parkinsonism. Drug-induced Parkinsonism is still common, under-recognized and treatable, examples being aripiprazole, metoclopramide, neuroleptics, olanzapine, risperidone and ziprasidone. (Esper, 2006) Reversible Parkinsonism has also been induced by prolonged (at least 4 years) treatment for seizures with valproate. Parkinsonism is sometimes reversible in less than 3 months after substitution of valproate with carbamazepine. (Onofrj, 1998)

Parkinsonian symptoms are sometimes seen during emergence from general anesthesia. (Muravchick, 1995) Anesthesiologists, themselves, have a significantly elevated risk for PD as an underlying cause of death. (Peretz)

PD holds a particular allure since, while it has been described for two centuries, its underlying cause (or causes?) still remain a mystery. It does run in some families but hereditary aspects have been summarized by Dr. Fernandez as simply: "about 5% of the general PD population is due to hereditary causes." (Fernandez, 2006) Also, the investigations into pesticides seem to be shedding some light on what lies behind the other 95%.

## **What is Parkinson's disease (PD)?**

PD is a degenerative nervous system disorder that often starts with a barely noticeable tremor in a hand. The disorder can also cause a slowing or freezing of movement.

The two cardinal pathological features of PD are loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies in neurons in the substantia nigra and extranigral regions of the brain. So far as patients are concerned, there is a disadvantage to these features: they are only clearly evident at autopsy. The diagnosis is instead dependent upon the clinical skills of their neurologist. Yet from the perspective of a research scientist, these pathological features are wonderful because these cells can be visualized and quantified once the experimental animal models are sacrificed. The animals may also reflect changes in motor functions but parallels are limited.

Typically, Parkinson's disease (PD) is viewed as progressive, the product of many years of decline prior to becoming clinically evident.

Basically there is a threshold for the number of dopaminergic cells required for normal functioning. While some cell loss is normal, accelerated losses indicate an insult and/or dysfunction. It is said that we would all develop PD if we lived long enough. Thus, most people develop PD late in their lives, although some people are much younger: "Young Onset PD" (YOPD).

Victims may begin with fewer neurons or suffer a loss, or losses, through toxic insults, including pesticides or drugs etc.

## The Historical Perspective of PD

In the West, a classic description of the *shaking palsy* was undertaken and published by Dr. James Parkinson just after the Napoleonic Wars. This has aroused a number of questions: When did PD first develop? Was it something that emerged with the Industrial Revolution in England? Why wasn't it described before?

Dr. Parkinson lived in London which was a teeming city even at that time. Even so, he only observed a handful of cases. Presumably, cases were so rare that no one had been able to tie together the common characteristics as a distinct disorder. Part of the scarcity may have been the lack of elderly people, especially out in the community once infirmity set-in.

Even up until the Great War few people developed PD. A major epidemiological study derives from the unique data set available at Massachusetts General Hospital from 1875. Between 1875 and 1915, a period of 40 years only 17 cases of Parkinson's syndrome were diagnosed (1 case every other year). By 1960 there had been 1,366 cases (c. 30 cases p.a.). (Poskanzer)

Postencephalitic Parkinsonism was identified after World War One in connection with several serious epidemics that initially produced *encephalitis lethargica* and eventually Parkinson-like symptoms in 40% of the survivors. It was this form of Parkinson's that Oliver Sacks dealt with during his pioneering efforts with Levodopa and captured for us in his book that was also made into a movie: "*Awakenings*."

The search for a common virus has been a failure but remains an intriguing possibility. A recent Canadian survey brought to light an informal observation that school teachers (2.5 times normal) and healthcare professionals (3.2 times the risk) were disproportionately represented. They hypothesized that these occupations are exposed to viral respiratory tract infections circulating in schools and healthcare facilities. (Tsui, 1999)

### The Environmental Hypothesis

Or, to look at it another way, how do most people in any population avoid developing PD?

Many more people are exposed to environmental toxins than develop PD. Somehow, they have more resources, or greater tolerance, or perhaps the vulnerable lack something most other people have. One hypothesis surrounds the ability of the liver to detoxify. (Steventon) Only persons with an impaired ability to detoxify a particular toxin will progress to PD. (Tanner, 1991)

Sherry Rogers, MD, (who has experienced chemical sensitivities herself) notes that patients with PD may often show up to a 60% deficiency in their ability to detoxify. Impaired detoxification, together with nutrient deficiencies are common precipitating factors for Parkinson's and other diseases. (Rogers)

It has been confirmed that those with PD do have defective liver enzyme systems. (Tanner, 1991) The first enzyme (P450) was proposed by Barbeau in 1986. (Barbeau, 1986a) More than one P450 enzyme abnormality may be involved. (Ferrari) An extraordinarily high percentage of PD patients have very low activity levels of cysteine dioxygenase (Steventon) and thiolmethyltransferase (Waring), which are key hepatic enzymes in detoxifying and eliminating environmental toxins and xenobiotics. (Shen, X-M; 1996a)

Glutathione transferases (GST) metabolize xenobiotics, including pesticides. Therefore, GST polymorphisms have been examined to see if they played a role in the pathogenesis of idiopathic PD.

GSTP1-1, which is expressed in the blood-brain barrier, may influence response to neurotoxins - an inability to detoxify them - and explain the susceptibility of some people to the Parkinsonism-inducing effects of pesticides. (Menegon, 1998) This defect may also explain why some people with PD also experience colon cancer. (Chenevix-Trench 1997)

GSH depletion, leading to oxidative damage and subsequent mitochondrial dysfunction, may serve as a trigger for neuronal cell death. (Tukov, 2004)

An association has been found in the CYP2D6 gene (this gene encodes for the enzyme debrisoquine hydroxylase which metabolizes several xenobiotics including MPTP, the herbicide atrazine and organophosphate pesticides).

## The Toxic Connection

The present search is for a toxin (or toxins) that is toxic to some people, probably owing to a defect that may be inherited or acquired, which affects their ability to detoxify the substance(s).

Major exogenous toxins that affect us include: (After Stacy, 1996b)

- Alcohol withdrawal
- Amphetamines
- Bacteria: streptococcus, staphylococcus, salmonella (food poisoning)
- Carbon disulfide
- Carbon monoxide (Ringel)
- Coffee, tobacco, alcohol, sugar, food preservatives
- Cyanide
- Drinking water
- Heavy metals: mercury, aluminum, lead, cadmium
- Hydrocarbons
- Lithium
- Manganese (Mena)
- Mercury
- Heavy Metals
- Parasites
- Pesticides
- Smog and petrochemicals
- Viruses: Epstein-Barr, influenza, cytomegalovirus, herpes, HIV

A toxin model of PD has been proposed since the 1970s (Heikkila, 1971) but gained impetus from an infamous cluster of PD cases caused by intravenous injection of a compound (MPTP) by narcotics addicts. (Langston, 1983)

The neurotoxicity of MPTP was discovered in 1976 after Barry Kidston, a 23-year-old chemistry graduate student in Maryland, synthesized MPPP incorrectly and injected the result. It was contaminated with MPTP, and within three days he began exhibiting symptoms of PD. The National Institute of Mental Health found traces of MPTP in his lab and eventually discovered its effects by testing the chemical on rats.

The compound is often referred to as 1-methyl-1,2,4,6-tetrahydropyridine (MPTP). In fact, the toxic component is 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>). Researchers have identified endogenous MPP<sup>+</sup> analogs in the lumbar cerebrospinal fluid of patients with PD that mirrors MPP<sup>+</sup> in mitochondrial toxicity.

We must not overlook that conjugates of dopamine itself (e.g. cysteinyl-dopamines and a number of dihydrobenzothiazines and benzothiazines) can be toxic (i.e. endotoxins) that

contribute to substantia nigral cell death and other neuronal damage that occurs in PD. (Shen, X, 1996a)

The dopaminergic neurotoxin, 1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, N-methyl(R)salsolinol, and its oxidation product, 1,2(N)-dimethyl-6,7-dihydroxyisoquinolinium ion, accumulate in the nigro-striatal system of the human brain. (Maruyama, 1997)

A dopamine-derived neurotoxin, (R)-N-methylsalsolinol, was found to be increased significantly in the cerebrospinal fluid of untreated patients with PD. (R)-N-methylsalsolinol is selective to dopamine neurons and induces Parkinsonism in rats, (Maruyama, 1996)

### **Neurotoxic Plants**

Epidemics of neurotoxic disease in developing regions of the world are often associated with dietary dependence on plant components with inherent toxic potential or which have spoiled and become contaminated with mycotoxins. (Spencer, 1993)

The neurotoxic cycad plant is thought to have a role in the etiology of western Pacific (e.g. Guam, New Guinea, Indonesia and Japan) amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia. (Spencer, 1993) Basically, most islanders (70% by 35 years of age) would have neurodegeneration equivalent to 75 year old Americans. Neurofibrillary tangles comparable to Alzheimer's disease are classic features of Guam Parkinson-Dementia/Amyotrophic Lateral Sclerosis. (Spencer, 1991) This was eventually linked to the diet, specifically, a flour made from cycad seed, from the false sago palm (*Cycas circinalis*). (Whiting) It was also used in folk medicine. Indeed, recent reports indicate that the toxin may have built up in another food source, flying foxes, which forage on cycad seeds. (Cox, 2002)

Other diseases triggered by plant toxins include lathyrism and cassavism, types of irreversible spastic parapareses associated with staple diets of grass pea and bitter cassava root, respectively. (Spencer, 1993)

Mildewed (i.e. a fungal toxin) sugarcane poisoning produces an encephalopathy and tardive dystonia. (Spencer, 1993)

Some "weak" neurotoxins are present in less exotic foods [e.g. harman and nonharman (Kuhn, 1996c) including: bananas, beef, cheese, cocoa, eggs, and milk].

## Pesticides

Aside from toxic, or tainted, food supplies, in parts of the developing world, pesticide poisoning causes more deaths than infectious diseases. Use of pesticides is poorly regulated and often dangerous; their easy availability also makes them a popular method of self-harm. (Eddleston, 2002)

Pesticides are a broad range of substances most commonly used to control insects, weeds, and fungi (plant diseases). They are frequently classified by target organism, or mode of use, as: insecticides, herbicides, fungicides, or fumigants. (Kamel, 2004) There may also be pesticides and rodenticides; herbicides are also commonly known as “weedkillers”. Fungicides may also be referred to as “biocides.”

PD is progressive, even after occupational exposure has ceased. (Hageman, 1998)

Some mycotoxins have been developed as biological and chemical warfare agents and have probably been deployed by Iraq during the first Gulf War. Ochratoxin-A (OTA) is a common mycotoxin, similar to that of the aflatoxins. It is possible that low dose exposure to OTA will result in an earlier onset of Parkinsonism when normal age-dependent decline in striatal dopamine levels are superimposed on the mycotoxin-induced lesion. (Sava, 2006)

PD is progressive, even after occupational exposure has ceased. (Hageman, 1998)

Insecticides are often subclassified by chemical type as: organophosphates (OPs), organochlorines, carbamates, and pyrethroids. (Kamel, 2004) From a list of a couple of dozen major pesticides, 19 have been classified as neurotoxins. Atrazine, for example, affects dopamine. (Das, 2001)

Airborne chlorinated pesticides are now ubiquitous, resulting in a broad public exposure to potentially hazardous materials. By 1980, over 400 synthetic chemicals had been identified in human tissue. The main involvements were blood, breast milk, liver, and nervous tissue. (US Environmental Protection Agency [EPA], Washington, DC. Chemicals Identified in Human Biological Media, EPA 560113-80-036B, PB81-161-176, 1980.)

In the U.S., more than 18,000 products are licensed for use, and each year more than 2 billion pounds of pesticides are applied to crops, homes, schools, parks, and forests (EPA Office of Pesticide Programs 2002). Such widespread use results in pervasive human exposure. (Kamel, 2004) California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US. (Ritz, 2000) In fact, there is increased PD mortality in California counties using agricultural pesticides. (Ritz, 2000)

One elusive aspect of neurotoxicity has been catching the process in the early stages, or recognizing that neurotoxicity has occurred. There have been some promising developments.

The measurement of prolactin may provide early identification of excess exposure to neurotoxic chemicals affecting dopaminergic control of pituitary secretion. (Mutti, 1988a)

Increased serum prolactin is a common finding among subjects exposed to styrene, perchloroethylene, lead (Pb), and manganese (Mn) at levels below the current threshold limit values. (Mutti, 1988a) [Perchloroethylene - is used at dry cleaners; styrene exposure is associated with the plastics industries.] Plasma prolactin appears to be a sensitive marker of styrene-induced tubero-infundibular dopaminergic dysfunction in male subjects. (Bergamaschi, 1997)

Epidemiological risk factor analyses of typical PD cases have identified several neurotoxicants, including MPP(+) (the active metabolite of MPTP), paraquat, dieldrin, manganese and salsolinol. (Chun, 2001)

#### Carbon Disulfide

#### Chlorpyrifos and terbutaline

#### Dieldrin

#### Hydrocarbons

Solvents: Carbon disulfide; *n*-hexane; methanol (a constituent in formaldehyde and lacquer thinner); toluene (monomethylbenzene) (a constituent in lacquer thinner); xylene.

#### Lipopolysaccharide (LPS)

#### Maneb (Manganese)

Organochlorine insecticides E.g. :Aldrin; Chlordane; DDT; Heptachlor; Lindane; Methoxychlor; Mirex; Toxaphene.

Organophosphates

#### PCBs

#### Paraquat

#### Radon

#### Rotenone

### **Carbon Disulfide**

Carbon disulfide is used in agriculture as a fumigant and fungicide. A recent report cites carbon disulfide used in grain storage for the high incidence of Parkinsonism among

agricultural workers. (Peters, 1986 and 1988) However, carbon disulfide's effects aren't sufficiently narrow to even provide a useful model of PD, never mind constituting a likely candidate as an etiologic agent for PD, in general. (Langston, 1987) [return to top of list](#)

### **Chlorpyrifos and terbutaline**

Given the common use of terbutaline in the therapy of preterm labor and the nearly ubiquitous exposure of the human population to organophosphorus pesticides, the combined oxidative burden of exposure to both agents was examined in an animal model. Worsened neurodevelopmental outcomes were duly noted in the animals. (Slotkin, 2005) Once again, we see a sequence of events, including dual exposures to chemicals, working via their shared potential to elicit oxidative stress and culminating in neurotoxicity.

The text, itself, however, reveals a robust increase in oxidation from Chlorpyrifos was obtained in the forebrain and cerebellum, restricted to males. Males were also impacted differently with terbutaline. As he puts it: "There is a sex-selectivity for oxidative stress, males > females, which matches the consequent morphological, neurochemical and behavioral susceptibilities." (Slotkin, 2005)

It has been shown in an animal study that if the mother is exposed to pesticides (atrazine) while she is lactating, the male pups will develop prostatitis after they mature. (Stoker) Prostatitis involves infection and inflammation, two factors that have been postulated as contributory factors in the development of PD. [return to top of list](#)

### **Dieldrin**

One particular degenerating pesticide is called dieldrin. Dieldrin was first synthesized in 1946 and sold widely in the United States between 1950 and the mid-1970s. The popular pesticide was used for the treatment of seeds and to control soil pests like termites, grasshoppers, locusts and beetles. It is a lipid-soluble, long-lasting mitochondrial poison. (Fleming, 1994)

The EPA restricted the use of Dieldrin in 1974 because of the harmful effects but permitted its use mainly for termite control until 1987.

Although Dieldrin is no longer produced in the United States, it is still used in several developing countries around the world, leaving people open to exposure. Dieldrin was found to be the most abundant pesticide in tested river sediments during an epidemiological study recently conducted in Taiwan.

The half-life of Dieldrin in the environment is more than 50 years, Kanthasamy said: "With such continued use in some countries and its ability to accumulate, there is no telling when, if ever, the pesticide will be gone from the Earth."

- Dieldrin may be ubiquitous in the environment. (Sanchez-Ramos, 1998)
- Dieldrin can be retained for decades in lipid-rich tissue and has been measured in some postmortem PD brains. (Sanchez-Ramos, 1998)
- Dieldrin is a relatively selective dopaminergic neurotoxin in mesencephalic cultures. (Sanchez-Ramos, 1998)
- Dieldrin can initiate and promote dopaminergic neurodegeneration in susceptible individuals. (Sanchez-Ramos, 1998)

*Dieldrin ... should be investigated as a potential etiological agent of Parkinsonism.*  
(Fleming, 1994) [return to top of list](#)

## **Hydrocarbons**

Hydrocarbons are present in glue, paint, rubber and petroleum derivatives (gasoline, solvents etc.) The most important solvents with respect to Parkinsonism are: methanol, toluene, carbon disulfide and n-hexane. (Hageman, 1998) Anyone occupationally exposed to hydrocarbons might be at risk for PD. This connection has been studied in Italy. (Pezzoli, 2000)

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese (Mn) compound added to unleaded gasoline. The combustion products of MMT containing Mn, such as manganese phosphate, could cause neurological symptoms similar to PD in humans. Animal studies have confirmed that such inhalation results in manganese deposition in the following brain regions: olfactory bulb and caudate/putamen. (Normandin)

The organochlorine insecticide 1,2,3,4,5,6-hexachlorocyclohexane (lindane) but not 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) augments the nocturnal increase in pineal Nacetyltransferase activity and pineal and serum melatonin levels. (Attia)

Hydrocarbon solvent exposure proved to be a risk factor for earlier onset of PD symptoms as well as for more severe disease progression. Confirmatory and further studies are recommended. (Pezzoli, 2000)

A pre-publication report in the Dalla Area Parkinsonism Society (DAPS, October, 2007) from Dr. German at UTSW notes that people with PD (or PWPs) have ten times more organochlorine pesticide levels than controls (beta-hexachlorocyclohexane). [return to top of list](#)

## Solvents

At least three solvents have generally been implicated: carbon disulfide, *n*-hexane, and methanol, have neurotoxic properties that give rise to Parkinsonism with corticospinal signs. (Tanner, 1992b) The most important solvents have been listed: (Hageman)

- Carbon disulfide
- *n*-hexane
- methanol\*
- toluene\* (monomethylbenzene)
- xylene (neuropsychiatric symptoms but not Parkinsonism)

\* Methanol and toluene, together with ethylacetate and methylethylketone constitute lacquer thinner. Methanol is also a constituent in formaldehyde. (Hageman)

Intriguingly, “I believe that tetanus vaccine is the most neurotoxic of ALL vaccines. Tetanus toxin (tetanospasmin) is made by deactivating it with formaldehyde and ammonium sulfate. It is filtered and adsorbed onto aluminum phosphate. Tetanospasmin is one of the strongest neurotoxins known to man.” (Dr Sherri Tenpenny e-mail post, February 2008)

One case history was reported from Italy: a 55-year-old male Parkinsonian patient reported chronic exposure to *n*-hexane for 17 years. (Vanacore, 2000)

Toluene (or monomethylbenzene) is present in numerous adhesives, cleaners, gasoline, glues, inks, lacquers and paints. (Hageman) A specific toluene encephalopathy has been described. (Knox) Toluene is a very well known industrial chemical. In vivo it is oxidized to benzoic acid and was therefore regarded - back in the 50's and 60's - as far less toxic than benzene.

Specifically, after exposing rabbits to a variety of chemicals, ethylbenzene, styrene and vinyltoluene caused a marked depletion of striatal and tubero-infundibular dopamine. (Mutti, 1988a)

Styrene and toluene are common examples of aromatic hydrocarbons. Styrene exposure during the gestation-lactation period (200 mg/kg, orally) affected dopamine receptor binding, causing a significant increase in motor activity and stereotypy of rat pups. (Zaidi)

One case is on record for the development of Parkinsonism after daily exposure, for at least 9 months, to lacquer thinner. (Uitti, 1994)

A Dutch study reported 3 painters, who developed Parkinsonism after occupational exposure to various solvents for more than 20 years. (Hageman)

There are also several anecdotes on the *askthedoctor* PD forum concerning photographers who developed PD given exposure to developer, containing toluene. Specifically, in a reader's response, with regard to Polaroid's formula.

Another case report consisted of the accidental ingestion of a petroleum waste mixture. (Tetrud, 1994) [return to top of list](#)

## **Lipopolysaccharide (LPS)**

Niehaus (2003) suggests that besides pesticides, endotoxin (lipopolysaccharide, LPS) may also be an environmental neurotoxin capable of producing PD. Endotoxin is a common airborne environmental and occupational contaminant in agricultural (Olenchock, 1990) and other industries. (Thorn, 2002; Enterline, 1985)

Endotoxins are part of the outer cell wall of Gram negative bacteria. (Rietschel, 1992)

The case event of PD is supported by animal experimentation. (Castano, 2002) Several animal studies (Herrera, 2000; Liu, 2000; and Castano, 2002) have shown that LPS causes damage to the substantia nigra, resulting in PD. These animal investigations support the hypothesis that LPS may be one of the environmental factors that trigger PD.

It is suggested that LPS is one of the causes for postencephalitic Parkinsonism after encephalitis from Gram negative bacteria. Further investigation of this potential environmental factor is warranted.

Pezzoli reported reported two cases of Parkinsonism from being exposed to n-hexane. N-Hexane, similar hydrocarbons and derivatives, are by-products of lipid peroxidation and may have a nigrotoxic effect like that of MPTP. (Pezzoli, 1995) [return to top of list](#)

## **Maneb**

Fungicide / Biocide - Maneb (manganese ethylene-bis-dithiocarbamate)

Permanent Parkinsonism has been recorded in two men with chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate).

Manganese is a well-known Parkinson-igen toxin in humans. More recently, it has been shown that dithiocarbamates can also induce extrapyramidal syndromes. (Meco, 1994)

The major lesson from Maneb studies is that its combined effect with paraquat is much greater than either product, separately. A team, led by Dr. Deborah Cory-Slechta, (University of Rochester School of Medicine and Dentistry) studied the effects of a mixture of two very common agricultural chemicals, the herbicide paraquat and the fungicide maneb. Each is used by farmers on millions of acres in the United States: maneb is

applied widely on such crops as potatoes, tomatoes, lettuce, and corn, while paraquat is used on corn, soybeans, cotton, fruit, and a variety of other products. (Cory-Slechta, 2005)

In the experiment, mice exposed to either chemical had little or no brain damage but mice exposed to both mimic the very early stages of PD: though they appeared healthy, key brain cells known as dopamine neurons were dying. The mice exposed to the mixture carried nearly all of the molecular hallmarks of PD as seen in humans.

The environmental reality, Dr. Cory-Slechta points out, is that pesticides are not used in isolation from one another: “In the real world, we're exposed to mixtures of chemicals every day. There are thousands upon thousands of combinations; I think what we have found is the tip of the iceberg,” she said. “There are a dozen different fungicides related to maneb alone. I don't think we just happened to pick the right chemicals to see such an effect.”

Particularly potent may be the exposure to paraquat during the neonatal period. Combined environmental exposure to paraquat and neonatal iron, results in accelerated age-related degeneration of nigrostriatal dopaminergic neurons. (Peng, J) [return to top of list](#)

## **Organophosphates**

### *Atrazine*

Atrazine is one of the top two herbicides in the US. A member of the triazene family, it is primarily used on corn and fruits (citrus, pineapple). Atrazine is a neurotoxin and alters the production of dopamine and norepinephrine that, in turn, alters hormone levels (prolactin and luteinizing hormones). (Cox, C; 2001)

### *Diazinon*

Diazinon should have been phased out during 2003 but since it is stored in fat, those who have been exposed will experience slow-release toxicity. (Reigart)

*Dursban* (chlorpyrifos) – toxic.

*Malathion*

*Parathion* - highly toxic.

*Ronnel*

*TEPP* (tetra-ethyl-pyro-phosphate) – most toxic.

*Vapona*

Organophosphates have replaced organochlorine insecticides to become the most common ingredient. The most notorious organochlorine is DDT. Organophosphates are now the most commonly used insecticides in the world.

Organophosphates, like Diazinon and methyl parathion, are indirect acting cholinomimetics, affecting the acetyl cholinesterase enzyme (AChE). Excess AChE at skeletal muscle junctions causes muscle twitching. Effector organs become over-stimulated. (Williams, MA, 2002)

Pesticides of the organophosphate and carbamate types act to paralyze and kill insects by inhibiting their acetylcholinesterase. [*N.B. Acetylcholinesterase: Abbreviated AChE.*]

*Acetylcholinesterase* is an enzyme that breaks down the neurotransmitter acetylcholine at the synaptic cleft (the space between two nerve cells) so the next nerve impulse can be transmitted across the synaptic gap. [return to top of list](#)

## **PCBs**

Polychlorinated biphenyls (PCBs) and mercury together (as in fresh water fish) are much more potent in decreasing dopamine than if they were separate. (Seegal, 2000) There is an exception to every rule: In utero and lactational exposure to 3,4,3',4'-TCB resulted in significant elevations in concentrations of dopamine in the frontal cortex, and of dopamine and its metabolites in the substantia nigra that persisted into adulthood. (Seegal, 1997) Also, Females appear more sensitive than males to the neurochemical effects of PCB 28. (Chu et al, 1996)

Unfortunately, both increases and decreases in brain DA concentrations induce deficits in working memory. (Seegal et al, 1998)

### ***How do PCB's affect dopamine metabolism?***

PCBs inhibit two enzymes (tyrosine hydroxylase and L-aromatic amino acid decarboxylase) that are involved in dopamine synthesis. (Guarisco et al, 1999) One dose of modest PCB levels during pregnancy permanently effects dopamine regulation in the offspring. (Sauer et al, 1994)

Disappointingly, once the changes are initiated, dopamine dysfunctions persist even when PCBs are no longer found in the brain – presumably, having been detoxified, or at least, reduced to a level beyond detection. Ortho-substituted PCBs are also neuroteratogens. (Seegal, 1992)

On a cautionary note, many animal studies of PCB toxicity used virgin commercial mixtures of PCBs called by their tradename: “Aroclor”. These mixtures do not reflect the 209 kinds of individual PCB types. Also, they were usually purified of dioxin or furan contaminants. Thus, the researchers were testing a PCB mix very different from the highly toxic mixture in the real world that actually accumulates in fish. This could lead to serious underestimates of the true human health effects of PCBs, plus dioxins and furans.

PCBs were used between 1929 and 1971. The “Baby Boomers” of course, therefore were exposed throughout their critical *in utero* and childhood years. Many environmentalists are expecting a surge in PD as this group ages. The first wave has just turned 60.

[N.B. Children may be 10 times more vulnerable to chemical toxicities than adults. *Pesticides in Diets of Infants and Children*. National Research Council. Washington D.C.: National Academy Press, 1993.] [return to top of list](#)

## **Paraquat**

Paraquat is the trade name for *N,N'*-Dimethyl-4,4'-bipyridinium dichloride, a quaternary ammonium herbicide. Other members of this class include diquat, cyperquat, diethamquat, difenzoquat and morfamquat. All of these are easily reduced to the radical anion, which in turn generates superoxide radical that reacts with unsaturated membrane lipids.

Paraquat (PQ; 1, 1'-dimethyl-4, 4'-bipyridinium), a widely used herbicide that is structurally similar to the known dopaminergic neurotoxicant MPTP (1-methyl-1, 2, 3, 6-tetrahydropyridine), has been suggested as a potential etiologic factor for the development of PD (PD). Paraquat has been one of the world's most popular weed killers for decades.

Despite the apparent structural similarity to MPP<sup>+</sup>, paraquat exerts its deleterious effects on dopamine neurons differently than rotenone or MPTP. MPP<sup>+</sup> is transported into dopamine neurons through the dopamine transporter, while rotenone is not. Rotenone produces complex I inhibition and oxidative damage. (Richardson, 2005) Thus, while their effects may be similar, their pathways are different.

Paraquat was introduced in 1962. In 1994 there were 175 recorded exposures and 4 deaths. It acts to interfere with the intracellular electron transfer systems in the plant. So, ingestion of paraquat leads to the formation of free radicals (superoxide, singlet oxygen, hydroxyl and peroxide radicals) which cause lipid peroxidation damaging cell membranes leading to cell death. It is rapidly taken up by the lungs and kidneys. Antidotes are listed as: vitamin E, selenium, thiosulfate and superoxide dismutase (SOD).

Focusing on paraquat, by itself, ignores the extensive geographical overlap of its use with other agrichemicals known to adversely impact dopamine systems, including ethylenebisdithiocarbamate fungicides such as maneb. (Thiruchelvam, 2000a)

The fact that combined exposures result in potentiated effects suggests that these combinations may be important environmental risk factors for Parkinsonism. (Thiruchelvam, 2000a) The nigrostriatal dopaminergic system is a preferential target of repeated exposures to combined paraquat and maneb that tend to occur seasonally on a perennial basis. (Thiruchelvam, 2000b)

When is the exposure critical? Spreading the fertilizer as an adult; breathing in overspray as a child; or being subjected to in utero or breastfeeding exposures with a toxic mother?

Thus, paraquat (PQ) and maneb (MB) exposure during critical periods of development could permanently change the nigrostriatal dopamine (DA) system and enhance its vulnerability to subsequent neurotoxicant challenges. (Thiruchelvam, 2002) Each insult would render the subject more vulnerable to each subsequent neurotoxicant challenge and ever closer to the threshold for Parkinsonism.

Findings indicated that exposure to pesticides during the post natal period can produce permanent and progressive lesions of the nigrostriatal dopamine system, as well as enhanced adult susceptibility to these pesticides. (Thiruchelvam, 2002)

Bentonite can absorb pathogenic viruses, aflatoxin (a mold), and pesticides and herbicides including Paraquat and Roundup. The clay is eventually eliminated from the body with the toxins bound to its multiple surfaces. [Lipson, *Canadian Journal of Microbiology* (31 [1985], 50-53.)

“While there are the caveats we discussed at the end of our paper such as chronic exposure, co-exposure with other chemicals, compromised BBB, etc., we found that paraquat is unable to enter the primate brain under the conditions of our acute study in middle-aged monkeys. We recently completed a similar study in pregnant monkeys and found the same minimal uptake in the brains of both mother and fetus.” (Onofre T. DeJesus, Professor of Medical Physics; personal communication) [return to top of list](#)

## **Radon**

Interestingly, in his consideration of possible causes, Charcot suggested damp cold in a badly ventilated apartment, or ground floor dwelling. This could be interpolated to refer to carbon monoxide (Mulhearn) or even radon.

Intriguingly, in rural India and industrialized England, poorly ventilated fires can also produce carbon monoxide. (Hutton)

Radon is one item that has existed prior to industrialization. Radon is an ubiquitous noble gas in the environment and a primary source of harmful radiation exposure for humans; it decays in a cascade of *daughters* by releasing the cell damaging high energy alpha particles. (Momcilovic, 2006) According to the WHO, there is approximately 39 Bq/m<sup>3</sup> in the air we breathe.

<sup>210</sup>Po and <sup>210</sup>Bi radioactivity increased tenfold in the cortical grey and subcortical white lipid fraction in patients with PD. (Momcilovic, 1999)

Paradoxically, smoking (which usually rates as negative, or inversely correlated with PD) strongly increases radon daughter retention in the central nervous system. (Momcilovic, 2001) [return to top of list](#)

## **Rotenone**

Rotenone is frequently mentioned. It is a naturally occurring toxin and a commonly used pesticide, insecticide and piscicide (poisonous to fish). Rotenone is extracted from the dried roots, seeds and leaves of various tropical plants, including the Jewel vine, derris and hoary pea. It is highly toxic to birds and fish but conventional thought regards it as non-toxic to humans at normal doses.

Rotenone is found in 680 compounds marketed as organic garden pesticides and flea powders, said Dr. Caroline Tanner, director of clinical research at the Parkinson's Institute in California. It is often sold as a white powder that is dusted onto roses, tomatoes, pears, apples and African violets, and even on household pets.

Because rotenone is naturally occurring, it is advertised as being safer than synthetic pesticides. In addition, unlike many artificial pesticides, which linger in the environment, rotenone breaks down in five to six days of spring sunlight, or two to three days of summer sunlight.

Rotenone causes nigrostriatal degeneration similar to Parkinson disease pathology in a chronic, systemic, in vivo rodent model (Testa, 2005)

Data indicate that rotenone is not capable of causing overt dopaminergic toxicity. Rather, an increase in dopamine turnover, as indicated by a higher (DOPAC+HVA)/DA ratio, [dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] seems to be associated with rotenone-induced striatal energy impairment. (Thiffault, 2000) Rotenone is also a complex I inhibitor. (Testa, 2005)

Chronic systemic complex I inhibition caused by rotenone exposure induces features of PD (PD) in rats, including selective nigrostriatal dopaminergic degeneration and formation of ubiquitin- and alpha-synuclein-positive inclusions (Betarbet et al., 2000).

PD involves intracellular deposits of alpha-synuclein in the form of Lewy bodies and Lewy neurites. One study shows that several hydrophobic pesticides (including rotenone, dieldrin and paraquat) induce a conformational change in alpha-synuclein and significantly accelerate the rate of formation of alpha-synuclein fibrils in vitro. (Uversky, 2001)

A pharmacological model of reduced complex I activity can be created by prolonged treatment of neuroblastoma cells with low doses of rotenone, a selective inhibitor of complex I. (Sherer, 2001a)

Chronic low-grade complex I inhibition caused by in vitro rotenone exposure induced accumulation and aggregation of alpha-synuclein and ubiquitin, progressive oxidative damage and cell death, mechanisms that may be central to PD pathogenesis. (Sherer, 2002) In vitro this all took place within 4 weeks.

Folate deficiency has also been implicated in the vulnerability to rotenone and MPTP via elevated homocysteine levels. (Duan, 2002)

Exposure of rats to the pesticide and complex I inhibitor rotenone reproduces central features of PD, including: selective nigrostriatal dopaminergic degeneration and alpha-synuclein-positive cytoplasmic inclusions. (Betarbet et al., 2000; Sherer et al., 2003b)

A new protocol was recently established for chronic rotenone administration. Essentially, subcutaneous rotenone exposure caused alpha-synuclein-positive cytoplasmic aggregates in nigral neurons. (Sherer, 2003b)

Like MPTP, rotenone is highly lipophilic and thus readily gains access to all organs including the brain. However, because of its short half-life and that it does not readily leach from soil, it is not expected to be a groundwater pollutant. Consequently, the likelihood of PD being caused directly by an environmental exposure to rotenone is considered to be low, even null. (Bove, 2005)

Nevertheless, Dr. John Trojanowski, an expert on neurodegenerative diseases at the University of Pennsylvania School of Medicine, has called rotenone: “The best model we have ever had for this disease being associated with an environmental agent.”

Although these candidates have been treated under individual headings, the findings of synergy from certain combinations also raises questions about the adequacy of current risk assessment guidelines for these chemicals which are based on effect levels derived from exposures to single agents. (Thiruchelvam, 2000a) [return to top of list](#)

### **How much gets into our food?**

In a recent report, the Pesticide Residues Committee said that 1.7 percent of 3,787 food items tested in the U.K. exceeded the legal limits for pesticide content, and 30.2 percent contained traces within the legal limits. (Pesticide Residues Committee Report)

A person can consume Dieldrin while eating meat, dairy products, or (as with PCBs and mercury) consuming fish or shellfish from contaminated waters. Dieldrin also accumulates in the body, storing itself in the body's fat and leaving very slowly.

Milk intake is associated with an increased risk of Parkinson disease. It is not known whether this is due to neurotoxic contaminants in milk, and further study is warranted. (Park, 2005b)

See [this chart](#) for a database of select foods common pesticide levels from the Environmental Working Group.

### **Are legal limits also safe limits?**

This is a debatable question.

In 1985, the UN Food and Agriculture Organisation (FAO) produced a voluntary code of conduct for the pesticide industry in an attempt to limit the harmful effects of pesticides. (Eddleston, 2002)

Exposure is usually occupational, or accidental. Either you are involved in spraying such chemicals, (Dvais, 1978) even as a home gardener; or you happen to be close by when such chemicals are sprayed. Typically, chemicals may drift a short distance on the wind, especially when sprayed from the air by planes or helicopters. (Ames, 1993) Many individuals are frequently exposed to many different pesticides, or mixtures of pesticides, either simultaneously, or serially. (Kamel, 2004)

Nine blue-collar occupations in Italy accounted for 91% of exposures to hydrocarbon solvents. (Pezzoli, 2000) Clinical expression is more severe in PD patients with previous high degree solvent exposure because of the associated post-synaptic damage of the nigro-striatal pathway. (Rango, 2006) Thus a specific physiological change has been identified in this group of Italian patients.

Occupations that account for 91% of hydrocarbon exposures. (After Pezzoli, 2000)

- Chemists;
- Farmers;
- Leather workers;
- Motor mechanics;
- Petroleum, plastic, or rubber workers;
- Painters, lacquerers, furniture workers;
- Refrigeration workers;
- Textile workers, weavers;
- Typographers, lithographers;

## Genetic or acquired defects

PD patients may be unusually susceptible to exogenous, or even endogenous, toxins. Most PD patients (70%) excrete less than 5% of an acetaminophen dose as the sulfate conjugate; the corresponding figure for controls is 84%. This suggests a deficiency in detoxication pathways involving sulfur metabolism. (Steventon, 1989)

A 'significant minority' of patients express problems in sulphur biotransformation pathways. (Steventon, 2003)

- 40% of patients with Parkinson's have a defect in the S-oxidation of S-carboxymethyl-L-cysteine (4% of controls)
- 35-40% of patients with Parkinson's have a defect in the sulphation of paracetamol (4% of controls)
- 38% of patients with PD have a low capacity for the S-methylation of 2-mercaptoethanol (4% of controls)
- The relation between *GSTP1* and onset age is modified by herbicide exposure. (Wilk)
- Three single-nucleotide polymorphisms (SNPs) were associated with PD onset age in the group of men occupationally exposed to herbicides. Three additional SNPs had significant trends for the association of PD onset age across the herbicide exposure groups. (Wilk)
- genetic variation in the CYP2D6 gene (for the enzyme debrisoquine hydroxylase which metabolizes several xenobiotics including MPTP)

Thiolmethyltransferase activity is indicative of S-Methylation. In Parkinsonian patients, mean thiolmethyltransferase activity was low (300 U/mg protein) compared with that in controls (947 U/mg protein). (Waring, 1989)

A progressive impairment of mitochondrial function has been suggested to play a critical role in the pathogenesis of several neurodegenerative diseases, including PD, Alzheimer's disease and Huntington's disease. Including:

- impaired calcium buffering, (Albers)
- generation of free radicals, (Albers)
- activation of the mitochondrial permeability transition pore (Albers)
- secondary excitotoxicity (Albers)

Probable etiological factors in the disease require: (Head/Kidd)

- genetic susceptibility,
- acute toxic exposure (e.g. MPTP)
- chronic toxic exposure (e.g. pesticides like Rotenone and mercury),
- a deficiency in detoxication pathways (Steventon, 1989)
- oxidation overload
- an inadequate antioxidant defense system, and
- lack of dietary/supplemental antioxidant nutrients (e.g. glutathione, lipoic acid and NAC).

## **Rural Environment?**

Attention has re-focused on environmental toxicants in the disease etiology, particularly agrichemicals. (Barlow) Unfortunately, while numerous toxins have been proposed as a cause of PD few have been confirmed. Those that have been identified only cause a PD-like disorder in a minority of the people exposed. So there appears to be interdependence as well. Interactions between genetic susceptibilities and environmental exposures are the focus of current research regarding the cause of idiopathic PD. (Firestone)

The first observation of a correlation between early age exposure to rural environment (and drinking well water) and development of idiopathic PD dates back to 1984. These findings were subsequently confirmed elsewhere (Barbeau, 1985; 25 Tanner, 1985).

Unfortunately, while well water is probably a vehicle for the agent responsible, neither water metal concentration nor any of the herbicides and pesticides used in Saskatchewan agriculture could be confirmed. (Rajput, 1986) In a follow-up study, there was no discernible difference in the metal composition of the well water for any of 23 metals evaluated, including 7 elements implicated in the etiology of PD. (Rajput, 1987a)

Patients with early-onset Parkinson's are likely to have drunk well water and lived in a rural environment. (Rajput, 1987) In a study of kibbutzim in Israel, the incidence of PD quintupled (500%) in relation to communities using a different aquifer. (Goldsmith)

Living in a rural environment and drinking well water are risk factors for PD. (Wong, 1991)

In another Canadian study, heavy pesticide use raised the incidence of PD seven-fold (700%). (Barbeau, 1986a) Pesticide and herbicide users ranged up to 3.2 times more susceptible. [Kanthasamy, 2002]

Farming, together with herbicide and pesticide use may be the key factors. (Koller, 1990) Specifically, farmers ranged up to 5.2 times more susceptible to PD. A consistent pattern of high PD morbidity is found among occupational groups employed in agriculture and horticulture. (Tüchsen, 2000)

PD appears to be less common in countries more recently industrialized. Studies using antiparkinsonian drug sales to estimate prevalence found vegetable farming, wood pulp mills, and steel alloy industries in areas with the highest disease prevalence. (Tanner, 1996)

While diesel fuel has not been identified, specifically, compounds capable of causing Parkinsonism may exist in commonly used petroleum products. (Tetud, 1994)

There also exists a paradox between the studies in the West and those in China. Epidemiologists are turning to China, where industrialization is relatively recent and the

population is geographically stable. (Tanner, 1989d) In North America and Europe, early onset PD appears to be associated with rural residence. Factors associated with this include vegetable farming, well water drinking, wood pulp, paper and steel industries. (Tanner, 1989c)

Living in Chinese villages and exposure to wheat growing and pig raising, were associated with a decreased risk for PD. (Tanner, 1989c) Living in industrialized urban areas of China increased the risk of developing PD. (Tanner, 1989d)

Similar differences can be noted between American Black populations and in Africa. The age-adjusted prevalence rate of PD in blacks living in Copiah County, Mississippi (341 per 100,000 or 3.4 per 1,000), is slightly more than five times higher than that of blacks living in Igbo-Ora, Nigeria (67 per 100,000 or 0.67 per 1,000), suggesting a role of environment, rather than race, in the pathogenesis of PD. (Muthane)

**Comment:**

“I think it is important to remember that if pesticides have a role in Parkinson's, it may not be a predominant one. By that, I believe that many underlying genetic factors play a major role and exposure to various chemicals may accelerate the disease process. People with minimal pesticide exposure still get the disease.” (Gary W. Miller, personal correspondence q.v. Hatcher, 2008)

*Hatcher JM, Pennell KD, Miller GW: Parkinson's disease and pesticides: a toxicological perspective. Trends Pharmacol Sci. 2008 Jun; 29(6):322-9. Epub 2008 Apr 29.*

Gary W. Miller, Ph.D., Associate Professor, Center for Neurodegenerative Disease. Emory University

Ecological and case-control studies support the association of PD with: [Ascherio, 2006)

- Rural residence (Barbeau, 1987; Svenson, 1993; Rajput, 1986; Tanner, 1986; Ho, 1989; Golbe, 1990; Koller, 1990; Wong, 1991; Butterfield, 1993)
- Use of private wells (Rajput, 1986; Tanner, 1986; Koller, 1990; Wong, 1991; Goldsmith, 1990)
- Farming (Barbeau, 1987; Ho, 1989; Semchuk, 1992; Ross, 2001)
- Exposure to pesticide products (Ho, 1989; Golbe, 1990; Semchuk, 1992; Butterfield, 1993; Hubble, 1993; Hertzman, 1994; Seidler, 1996; Liou, 1997; Chan, 1998; Gorell, 1998; Menegon, 1998; Ritz, 2000)

Farming communities had more than double the proportion of Parkinsonians as control populations. (Stern, 1991; Wechsler, 1991)

Farming as an occupation and well water use had a significant positive association with PD in north-east Italy. (Zorzon, 2002)

### **Microcosm – a farming community, Fairfield MT**

In rural Fairfield, Montana, PD occurrences are much higher than the national average (1 in 10,000 people under the age of 60 or 1 in 1,000 people over the age of 60). At least 12 people living around Fairfield have developed Parkinson's (with a population of 650 i.e. 1:50 or 200 times what might normally be expected). (Pfohman, 1992) Fairfield is known as the world capital for malt barley.

### **Other rural factors?**

Farming is a risk factor for Parkinson's beyond herbicide and insecticide exposure. (Gorell, 1998)

Does the answer simply lie in the ground? An early announcement in the November, 2001 Parkinson brief newsletter from the National Parkinson Foundation of Miami, Florida poses the question of whether we can catch Parkinson's from dirt?

Microbiologist Blaine Beaman, from the University of California-Davis, is investigating a possible link between a bacterium that occurs in the soil (*Nocardia asteroides*) and PD. It is already identified as a cause of lung disease in humans but may also travel to a small part of the brain's basal ganglia to infect nerve cells that manufacture dopamine. The bacteria also deposits clumps of protein resembling the Lewy bodies that are a signature of PD.

### **What proof is required?**

- Hypotheses of a link and pathways have been delineated
- In vitro experiments -
- Laboratory animals - replication
- Acute Cases
- Retrospective studies
- PET scan confirmation
- Meta-analysis

## Treatment with Glutathione and Herbs

Glutathione is an antioxidant and free-radical scavenger, and is found in the brain. Research shows that in PD, the glutathione levels are reduced in critical dopamine neurons. David Perlmutter, MD, has led research in this area. He has indicated that glutathione allows dopamine in the brain to be more effective. Dr. Patricia Kane of the Haverford Wellness Center in Havertown, PA reports symptom improvement with the use of IV lipostabil, leucovorin, glutathione and phenylbutyrate; many other physicians now use this approach.

It is always heartening to find some good news, amidst the bad. Our primary focus has been on the neuro-toxins released in our efforts to control nature. In spite of this, Mother Nature provides some antidotes, including these relative to *n*-hexane:

The chemoprotective potential of two antioxidants, EGCG (Green Tea catechin) and Thymoquinone (from Black cumin or *Nigella sativa*) were assessed, against *n*-hexane (an important industrial solvent and ambient air pollutant) toxicity.

Treatment of cells with EGCG, at a concentration reached in plasma, reduced the reactive oxygen species formation caused by exposure to *n*-hexane and inhibited the decrease in cell proliferation. Similar effects were obtained with Thymoquinone. (McDermott)

## **Conclusion**

In conclusion, there is mounting evidence that chronic, moderate pesticide exposure is neurotoxic, including specific risks for the development of PD. (Kamel, 2004) It has proven elusive to clarify exactly what these “risks” are. One possible answer was discussed recently by Gary Miller, Ph.D., an associate professor of environmental and occupational health at Emory University. “Our current study clearly shows that pesticides such as dieldrin appear to accelerate, or exacerbate, the already underlying disease.”

Thus pesticides are a catalyst to a complex process, rather than being capable of initiating the process itself, or of making the culmination of the process into fully-fledged PD inevitable.

This leads us to the model in which environmental factors, in conjunction with genetic susceptibility, may form the underlying molecular basis for idiopathic PD. (Uversky, 2002)

**More information:**

For information on neuroprotection, and a comprehensive listing of research abstracts, contact the author: David Ponsonby [<mailto:dponsonby1@aol.com>]

## Glossary of Pesticides

Aldrin - Organochlorine insecticide.

“Aroclor” – PCB used in animal testing.

Atrazine – pesticide

Carbon Disulfide – hydrocarbon solvent

Chlordane - Organochlorine insecticide

Chlorpyrifos (Dursban)

Cyperquat - a quaternary ammonium herbicide. (Paraquat)

DDT - Organochlorine insecticide

Diazinon - phased out during 2003.

Dieldrin – (Pesticide) It is a lipid-soluble, long-lasting mitochondrial poison.

*No longer produced in the United States.*

Diethamquat - a quaternary ammonium herbicide. (Paraquat)

Difenzoquat - a quaternary ammonium herbicide. (Paraquat)

Diquat - a quaternary ammonium herbicide. (Paraquat)

Heptachlor - Organochlorine insecticide

Hydrocarbons

Solvents: Carbon disulfide; *n*-hexane; methanol (a constituent in formaldehyde and lacquer thinner); toluene (monomethylbenzene) (a constituent in lacquer thinner); xylene.

Lindane - Organochlorine insecticide

Lipopolysaccharide (LPS) – endotoxin

MMT - Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese (Mn) compound added to unleaded gasoline.

MPTP (1-methyl-1, 2, 3, 6-tetrahydropyridine)

Malathion - organophosphate

Maneb (Fungicide / Biocide - Maneb (manganese ethylene-bis-dithiocarbamate) May combine with Paraquat.

Methanol (in formaldehyde and lacquer thinner) - hydrocarbon solvent

Methoxychlor - Organochlorine insecticide

Mirex - Organochlorine insecticide

Monomethylbenzene – see under Toluene

Morfamquat - a quaternary ammonium herbicide. (Paraquat)

*n*-hexane– hydrocarbon solvent [Case history]

Organochlorine insecticides E.g. :Aldrin; Chlordane; DDT; Heptachlor; Lindane;

Methoxychlor; Mirex; Toxaphene.

Organophosphates – see separately Dursban (chlorpyrifos); Malathion; Parathion;

Ronnel; TEPP (tetra-ethyl-pyro-phosphate); Vapona. [Cholinomimetics]

PCBs - Polychlorinated biphenyls combine with mercury (Hg). There are 209 kinds.

Paraquat - *N,N'*-Dimethyl-4,4'-bipyridinium dichloride, a quaternary ammonium herbicide. one of the world's most popular weed killers for decades. (Also: cyperquat, diethamquat, difenzoquat, diquat and morfamquat)

May combine with Maneb.

Parathion - highly toxic organophosphate

Radon - is an ubiquitous noble gas in the environment.

Ronnel – organophosphate

Rotenone is a naturally occurring toxin and a commonly used pesticide, insecticide and piscicide (for killing fish). Rotenone is extracted from the dried roots, seeds and leaves of various tropical plants, including the Jewel vine, derris and hoary pea. Rotenone is found in 680 compounds marketed as organic garden pesticides and flea powders. “The best model we have ever had for this disease being associated with an environmental agent.” [Rotenone is not capable of causing overt dopaminergic toxicity.]

Styrene – aromatic hydrocarbon

TEPP (tetra-ethyl-pyro-phosphate) – most toxic organophosphate

Terbutaline – Labor drug

Toluene - (monomethylbenzene) - hydrocarbon solvent and a constituent in lacquer thinner [Case history]

Toxaphene - Organochlorine insecticide

Vapona – organophosphate

Vinyltoluene – aromatic hydrocarbon

Xylene - hydrocarbon solvent but not linked to PD.

## References:

- Abdin, M: Treatment of Organophosphate Exposure. Townsend Letter, 210 pp 110-111.
- Adam D. Pesticide use linked to Parkinson's disease. Nature. 2000 Nov 9; 408(6809):125. [No abstract available.]
- Agranoff, BW, R. Wayne Albers, Stephen K. Fisher, Michael D. Uhler: Basic Neurochemistry: Molecular, Cellular and Medical Aspects. Sixth Edition. 1998. (396 illustrations) Available @ <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?tool=bookshelf&call=bv.View..ShowSection&searchterm=parkinson&rid=bnchm.section.2391#2399>
- Alam, M. & W.J. Schmidt: Rotenone destroys dopaminergic neurons and induces parkinsonian symptoms in rats, Behav. Brain Res. 2002; 136:317-324.
- Albers, D. S. & Beal, M. F: Mitochondrial dysfunction in progressive supranuclear palsy. Neurochem Int. 2002, 40(6): 559-64.
- Ali SF, Chandra O, Hasan M. Effects of an organophosphate (dichlorvos) on open field behavior and locomotor activity: correlation with regional brain monoamine levels. Psychopharmacology (Berl). 1980; 68(1):37-42.
- Ali SF, Martin JL, Black MD, Itzhak Y. Neuroprotective role of melatonin in methamphetamine- and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity. Ann N Y Acad Sci. 1999;890:119. (No abstract available.)
- Ali, S.F. & Freyaldenhoven, T. MPTP-A model of Parkinson's Disease. In: Chemical and Neurodegenerative Disease (Ed: S.C. Bondy), Prominent Press, Scottsdale, Arizona, 1999, pp. 1-28.
- American Chemical Society meeting in San Francisco September, 2006. Press Release to PDF.
- Ames RG, Howd RA, Doherty L. Community exposure to a paraquat drift. Arch Environ Health 1993; 48:47-52.
- Andersen HR, Nielsen JB, Grandjean P. Toxicologic evidence of developmental neurotoxicity of environmental chemicals. Toxicology. 2000 Apr 3; 144(1-3):121-7. Review.
- Angus WG, Contreras ML. The effects of Aroclor 1254 on undifferentiated and NGF-stimulated differentiating PC12 cells. Neurotoxicology; VOL 15, ISS 4, 1994, P809-18.
- Angus WGR, Contreras ML. Effects of Polychlorinated Biphenyls on Dopamine Release from PC12 Cells. Toxicology Letters, 1996; 89(3):191-199, 34 references.
- Anonymous: [No authors listed] HERBICIDES and systemic fungicides. Nature. 1952 May 17; 169(4307):814-6. [No abstract available.]
- Aquilonius SM, Hartvig P: A Swedish county with unexpectedly high utilization of anti-Parkinsonian drugs. Acta Neurol Scand. 1986, 74:379-382. [Not abstracted on Medline]
- Ascherio A., Chen H., Weisskopf M. G., O'Reilly E., McCullough M. L., Calle E. E., Schwarzschild M. A. and Thun M. J: Pesticide exposure and risk for Parkinson's disease. Ann. Neurol. 2006, 60, 197-203.
- Ascherio A, Chen H, Weisskopf MG, O'Reilly E, McCullough ML, Calle EE, Schwarzschild MA, Thun MJ: Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006 Aug; 60(2):197-203. Comment in: Ann Neurol. 2008 Jan; 63(1):128.

- Aspelin AL, Grube AH: Pesticides Industry Sales and Usage: 1996 and 1997 Market Estimates. Washington, DC: Office of Pesticide Programs, United States Environmental Protection Agency; 1999. (Cited by Weiss, 2004)
- Attia AM, Mostafa MH, Soliman SA, et al., The organochlorine insecticide 1,2,3,4,5,6-hexachlorocyclohexane (lindane) but not 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) augments the nocturnal increase in pineal Nacetyltransferase activity and pineal and serum melatonin levels. *Neurochem Res* 1990; 15:673-680.
- Axelrad, JC et al., Interactions between pesticides and components of pesticide formulations in an in vitro neurotoxicity test. *Toxicology* 2002, 173, 259-268.
- Axelrad, JC et al., The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon. *Toxicology*, 2003, 185; 67-78.
- Bain LJ & LeBlanc GA: Interaction of structurally diverse pesticides with the human MDR1 gene product P-glycoprotein. *Toxicol Appl Pharmacol.* 1996, 141:288–298.
- Baldereschi M, Inzitari M, Vanni P, Di Carlo A, et al., Pesticide exposure might be a strong risk factor for Parkinson's disease. [Letter] *Ann Neurol.* 2007;
- Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol.* 2003; 157:409-414.
- Baldi I, Cantagrel A, Lebailly P, Tison F, Dubroca B, Chrysostome V, Dartigues JF, Brochard P: Association between Parkinson's disease and exposure to pesticides in southwestern France. *Neuroepidemiology.* 2003 Sep-Oct; 22(5): 305-10.
- Barbeau A et al., Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci* 1987; 14:36-41.
- Barbosa ER, Leiros da Costa MD, Bacheschi LA, Scaff M, Leite CC: Parkinsonism after glycine-derivate exposure. *Mov Disord.* 2001; 16:565-568.
- Barlow BK, Richfield EK, Cory-Slechta DA, Thiruchelvam M. A fetal risk factor for Parkinson's disease. *Dev Neurosci.* 2004 Jan-Feb; 26(1):11-23.
- Bartlett RM, Holden JE, Nickles RJ, et al., Paraquat is excluded by the blood brain barrier in rhesus macaque: An in vivo pet study. *Brain Res.* 2009 Mar 9; 1259:74-9.
- Bawaskar HS: Snake venoms and antivenoms: critical supply issues. *Journal Association Physicians India* 2004, 52:11-13. [No abstract available.]
- Behari M, Srivastava AK, Das RR, Pandey RM; Risk factors of Parkinson's disease in Indian patients. *J Neurol Sci.* 2001; 190:49-55.
- Bemis JC, Seegal RF. Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content in vitro. *Environ Health Perspect*; VOL 107, ISS 11, 1999, P879-85. Author Address: School of Public Health, University at Albany, Albany, New York.
- Benoit I. Giasson & Virginia M.-Y. Lee: A new link between pesticides and Parkinson's disease. *Nature Neuroscience* Volume 3 No 12 December 2000, 3(12):1,227–1,228.
- Bergamaschi E, Smargiassi A, Mutti A, Cavazzini S, Vettori MV, Alinovi R, Franchini I, Mergler D. Peripheral markers of catecholaminergic dysfunction and symptoms of neurotoxicity among styrene-exposed workers. *Int Arch Occup Environ Health.* 1997; 69(3):209-14.

- Berger, A: Parkinson's disease linked with pesticide (rotenone). *BMJ* 2000; 321:1175.
- Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci.* 2000 Dec; 3(12):1,301-1,306.
- Betarbet R, Sherer TB, Greenamyre JT. Animal models of Parkinson's disease. *Bioessays.* 2002 Apr; 24(4):308-18. Review.
- Betarbet R, Canet-Aviles RM, Sherer TB, Mastroberardino PG, McLendon C, Kim JH, Lund S, Na HM, Taylor G, Bence NF, Kopito R, Seo BB, Yagi T, Yagi A, Klinefelter G, Cookson MR, Greenamyre JT. Intersecting pathways to neurodegeneration in Parkinson's disease: effects of the pesticide rotenone on DJ-1, alpha-synuclein, and the ubiquitin-proteasome system. *Neurobiol Dis.* 2006 May; 22(2):404-20. Epub 2006 Jan 24.
- Bharucha NE, Stokes L, Schoenberg BS, et al: A case-control study of twin pairs discordant for Parkinson's disease: A search for environmental risk factors. *Neurology*, 1986; 36:284-288,.
- Bhatt MH, Elias MA, Mankodi AK: Acute and reversible Parkinsonism due to organophosphate pesticide intoxication: five cases. *Neurology* 1999; 52:1,467-1,471.
- Block ML et al., Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. *FASEB J.* 2004 Oct; 18(13):1618-20. Epub 2004 Aug 19.
- Bocchetta, A & Corsini, GU: Parkinson's disease and pesticides. *Lancet*, 1986, 2:1,163.
- Bove J, Prou D, Perier C, Przedborski S. Toxin-induced models of Parkinson's disease. *NeuroRx.* 2005 Jul; 2(3):484-94. Review.
- Brethead, S Lee, S & Guo, S: Sensitivity of zebrafish to environmental toxins implicated in Parkinson's disease. *Neurotox. Terat.* November-December 2004, 26(6):857-864.
- Brighina, L et al., alpha-Synuclein, pesticides, and Parkinson disease. A case-control study. *Neurology*, 2008 Online
- Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. *Brain Res.* 1999 Mar 27; 823(1-2):1-10.
- Brownell, AL et al., Mapping of brain function after MPTP-induced neurotoxicity in a primate Parkinson's disease model. *NeuroImage* 20 (2003) 1,064-1,075.
- Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG. Environmental antecedents of young-onset Parkinson's disease. *Neurology* 1993; 43:1,150-1,158.
- Caboni P, Sherer TB, Zhang N, Taylor G, Na HM, Greenamyre JT, Casida JE. Rotenone, deguelin, their metabolites, and the rat model of Parkinson's disease. *Chem Res Toxicol.* 2004 Nov; 17(11):1540-8.
- Cardoso SM, Moreira PI, Agostinho P, Pereira C, Oliveira CR. Neurodegenerative pathways in Parkinson's disease: therapeutic strategies. *Curr Drug Targets CNS Neurol Disord.* 2005 Aug; 4(4):405-19. Review.
- Carvey PM, et al., Prenatal exposure to the bacteriotoxin lipopolysaccharide leads to long-term losses of dopamine neurons in offspring: a potential, new model of Parkinson's disease. *Front Biosci*, 2003 Sep 01; 8():s826-37. [Summary]

Castano A, Herrera AJ, Cano J, et al. The degenerative effect of a single intranigral injection of LPS on the dopaminergic system is prevented by dexamethasone and not mimicked by rh-TNF-alpha, IL-1beta and IFN-gamma. *Neurochemistry*, 2002; 81:150-7.

Caudle, W.M, Richardson, J.R., Wang, M., and Miller, G.W. Perinatal heptachlor exposure disrupts dopamine neurochemistry. *Neurotoxicology*. Aug; 26(4):721-8, 2005.

Chan DKY, Woo J, Ho SC, et al. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. *J Neurol Neurosurg. Psychol*. 1998; 65:781-784.

Chassain, C, Bielicki G, Durand E, Lolignier S, et al., Metabolic changes detected by proton magnetic resonance spectroscopy in vivo and in vitro in a murin model of Parkinson's disease, the MPTP-intoxicated mouse. *J Neurochem*. 2007...

Chaturvedi S, Ostbye T, Stoessl AJ, Merskey H, Hachinski V: Environmental exposures in elderly Canadians with Parkinson's disease. *Can J Neurol Sci*. 1995 Aug; 22(3): 232-4.

Checkoway H, Savitz DA, Heyer NJ. Assessing the effects of nondifferential misclassification of exposures in occupational studies. *Applied Occupational Environmental Hygiene* 1991; 6:528-533.

Checkoway H, Nelson LM. Epidemiologic approaches to the study of Parkinson's disease etiology. *Epidemiology* 1999; 10: 327-336.

Chenevix-Trench G, Young J, Coggan M, Board PG. Glutathione S-transferase M1 and T1 polymorphisms: susceptibility to colon cancer and age of onset. *Carcinogenesis* 1997; 16:1,655-57.

Chishti MA, Fisher JP, Seegal RF. Aroclors 1254 and 1260 reduce dopamine concentrations in rat striatal slices. *Neurotoxicology (Little Rock)*; 17 (3-4). 1996. 653-660. Author Address: Sch. Public Health, Univ. Albany, Empire State Plaza, Box 509, Albany, NY 12201-0509.

Choksi NY, Kodavanti PR, Tilson HA, Booth RG. Effects of polychlorinated biphenyls (PCBs) on brain tyrosine hydroxylase activity and dopamine synthesis in rats. *Fundam Appl Toxicol*. 1997 Sep; 39(1):76-80.

Chu I, Villeneuve DC, Yagminas A, Lecavalier P, Håkansson H, Ahlborg UG, Valli VE, Kennedy SW, Bergman A, Seegal RF, et al. Toxicity of PCB 77 (3,3',4,4'-tetrachlorobiphenyl) and PCB 118 (2,3',4,4',5-pentachlorobiphenyl) in the rat following subchronic dietary exposure. *Fundam Appl Toxicol*. 1995 Jul; 26(2):282-292.]

Chu I, Villeneuve DC, Yagminas A, Lecavalier P, Poon R, Hêakansson H, Ahlborg UG, Valli VE, Kennedy SW, Bergman A, Seegal RF, Feeley M. Toxicity of 2,4,4'-trichlorobiphenyl in rats following 90-day dietary exposure. *J Toxicol Environ Health*; VOL 49, ISS 3, 1996, P301-18.

Chun HS, Gibson GE, DeGiorgio LA, Zhang H, Kidd VJ, Son JH. Dopaminergic cell death induced by MPP(+), oxidant and specific neurotoxicants shares the common molecular mechanism. *J Neurochem*. 2001 Feb; 76(4):1010-1021.

Chung, WG, Miranda CL, Maier CS: Epigallocatechin gallate (EGCG) potentiates the cytotoxicity of rotenone in neuroblastoma SH-SY5Y cells. *Brain Res*. 2007; 1176:133-42. (pdf)

Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, Gross RE. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. *Neurobiol Dis*. 2005 Nov; 20(2):360-71.

Corasaniti MT, Defilippo R, Rodino P, et al. Evidence that paraquat is able to cross the bloodbrain barrier to a different extent in rats of various age. *Funct. Neurol* 1991; 6:385-391.

- Corasaniti MT, Nistico G. Determination of paraquat in rat brain by high-performance liquid chromatography. *J Chromatogr.* 1993 Jul 23; 643(1-2):419-25.
- Corrigan FM, French M, Murray L. Organochlorine compounds in human brain. *Hum Exp Toxicol.* 1996; 15:262-264.
- Corrigan FM, Murray L, Wyatt CL, Shore RF. Diorthosubstituted polychlorinated biphenyls in caudate nucleus in Parkinson's disease. *Exp Neurol.* 1998 Apr; 150(2):339-342.
- Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D: Organochlorine insecticides in substantia nigra in Parkinson's disease. *J Toxicol. Environ Health* 2000; 59:229-234.
- Corti O, Hampe C, Darios F, Ibanez P, Ruberg M, Brice A. Parkinson's disease: from causes to mechanisms. *C R Biol.* 2005 Feb; 328(2):131-42. Review.
- Cory-Slechta DA, Thiruchelvam M, Barlow BK, Richfield EK: Developmental pesticide models of the Parkinson disease phenotype. *Environ Health Perspect.* 2005 Sep; 113(9):1263-70.
- Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B: Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemiol.* 2009 Apr 15; 169(8):919-26.
- Cox, P. A. and O. W. Sacks (2002). Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam. *Neurology* 58(6): 956-9. (e-file)
- Crinnion, WJ: Environmental Medicine, Part 4: Pesticides – Biologically Persistent and Ubiquitous Toxins. *Alt. Med. Rvw.* 2000, 5(5):432-447.
- Das PC et al., Alteration of catecholamines in pheochromocytoma (PC12) cells in vitro by the metabolites of chlorotriazine herbicide. *Toxicol Sci.* 2001 Jan;59(1):127-37
- Datz, T: Pesticides exposure associated with Parkinson's disease. *Neurology press release* 2006
- Dauer W, Kholodilov N, Vila M, et al. Resistance of  $\alpha$ -synuclein null mice to the Parkinsonian neurotoxin MPTP. *Proc Natl Acad Sci. USA* 2002; 99:14,524-29.
- Davis K, Yesavage J, Berger P: Single case study. Possible organophosphate induced Parkinsonism. *J Nerv Ment Dis.* 1978; 166:222-225.
- Dawson, T. M. & V. L. Dawson, Molecular pathways of neurodegeneration in Parkinson's disease. *Science* 2003; 302, 819-822.
- Day BJ, Patel M, Calavetta L, Chang LY, Stamler JS. A mechanism of paraquat toxicity involving nitric oxide synthase. *Proc Natl Acad Sci U S A.* 1999 Oct 26;96(22):12760-5.
- de Bie et al., Manganese-Induced Parkinsonism Associated With Methcathinone (Ephedrone) Abuse. *Arch Neurol.* 2007; 64:886-889.
- De Michele G q.v. Michele, G. A. Filla, G. Volpe, V. Marco, A. Gogliettino and G. Ambrosio et al., Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy, *Mov Disord.* 1 (1996), pp. 17-23.

De Palma G, Mozzoni P, Mutti A, Calzetti S, Negrotti A. Case-control study of interactions between genetic and environmental factors in Parkinson's disease. *Lancet*, 1998; 352: 1986–1987. [No abstract available.]

Dick, FD et al., Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup. Environ. Med.* published online 1 Mar 2007.

Di Fillipo, M, Tambasco N, Muzi G, Balucani C, et al., Parkinsonism and cognitive impairment following chronic exposure to potassium cyanide. [Letter] *Mov Disord.* 2007; 23(3):468-9.

Dick FD: Parkinson's disease and pesticide exposures. *Br Med Bull.* 2006; 79-80:219-31. Epub 2007 Jan 22.

Dillon, W: ISU researcher (Kanthasamy) helps fight Parkinson's disease.

Di Monte DA, Lavasani M, Manning-Bog AB. Environmental factors in Parkinson's disease. *Neurotoxicology.* 2002 Oct; 23(4-5):487-502.

Di Monte, DA , et al., The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol*, 2003 Sep; 2(9):531-8.

Dinis-Oliveira RJ, Remiao F, Carmo H, Duarte JA, Navarro AS, Bastos ML, Carvalho F. Paraquat exposure as an etiological factor of Parkinson's disease. *Neurotoxicology.* 2006 Jun 30; [Epub ahead of print]

Doty, RL et al., Drug-related MPTP-induced Parkinsonism: no evidence of an olfactory deficit. *Chem. Senses*, 1990, 15:567. [Abstract]

Doty, RL et al., Olfactory dysfunction in three neurodegenerative diseases. *Geriatrics*, 1991b, 46 (Suppl 1):47-51.

Drozdik, M., Bialecka, M., Myliwiec, K., et al., Polymorphism in the P-glycoprotein drug transporter MDR1 gene: a possible link between environmental and genetic factors in Parkinson's disease. *Pharmacogenetics* 2003, 13, 259–263.

Duan W et al., Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. *J Neurochem* 2002 Jan;80(1):101-10. (e-file)

Dulaney E, Stern M, Hurtig H, et al: The epidemiology of Parkinson's disease: A case-control study of young-onset versus old-onset patients. *Mov Disord.* 1990, 5(suppl 1):12.

Eddleston M (Senanayake ) et al., Pesticide poisoning in the developing world--a minimum pesticides list. *Lancet.* 2002 Oct 12; 360(9340):1163-7.

Elbaz, A et al., CYP2D6 polymorphism, pesticide exposure, and Parkinson's disease. *Annals of Neurology* Volume 55(3):430-434.

Elwan, M.A., Richardson, J.R., Guillot, T., Caudle, W.M., Miller, G.W. Pyrethroid pesticide-induced alterations in alter dopamine transporter function. *Toxicology and Applied Pharmacology*, Epub ahead of print, 2005.

Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT Jr, Scott KC, et al., Parkinsonism and occupational exposure to pesticides. *Occup Environ Med.* 2001; 58:582-589.

Enterline PE, Sykora JL, Keleti G, et al., Endotoxin, cotton dust and cancer. *Lancet*, 1985; 2:934–5.

Environmental Protection Agency. Recognition and Management of Pesticide Poisonings. 5th ed. Washington, DC: US Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances; March 1999 (EPA 735-R-98-003). Available @ [www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm](http://www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm)

Eriksson P, Talts U. Neonatal exposure to neurotoxic pesticides increases adult susceptibility: a review of current findings. *Neurotoxicology* 2000; 21:37-48.

Esper, C.D. & Factor, S.A. Drug-Induced Parkinsonism: Still Common, Under-Recognized, and Treatable. Poster 15 (PD) *Movement Disorders*, Vol. 21, No. 9, 2006.

Fall PA, Fredrikson M, Axelson O, Granerus AK: Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Mov Disord*. 1999; 14:28-37.

Ferrari, MD et al., Hepatic cytochrome P450 function and Parkinson's disease. *Lancet*, 1986, I:324. [No abstract available.]

Ferrari, MD et al., Hepatic cytochrome P450 function and Parkinson's disease. *J. Neurol. Sci.* 1990, 96:153-157.

Ferraz HB, Bertolucci PH, Pereira JS, Lima JG, Andrade LA. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. *Neurology*. 1988 Apr; 38(4):550-553.

Fidler AT, Baker EL, Letz RE. Estimation of long term exposure to mixed solvents from questionnaire data: a tool for epidemiological investigations. *Br J Ind Med* 1987; 44:133-141.

Fink, AL: Conference in Colorado Springs, August 2001. Cited by Hileman, B: The Environment and Parkinson's . *Chemical and Engineering News* v.79, n.38 17 Sep 01. Available @ [www.mindfully.org/Health/Parkinsons-And-Environment.htm](http://www.mindfully.org/Health/Parkinsons-And-Environment.htm)

Firestone JA et al., Pesticides and risk of Parkinson disease. A population-based case-control study. *Arch Neurol* 2005; 62: 91-95.

Fleming, L et al., Parkinson's disease and brain levels of organochlorine pesticides. *Ann. Neurol.* 1994, 36:100-103.

Fleming, S.M. Zhu, C. Fernagut, P.O. Mehta, A. DiCarlo, C.D. Seaman, R.L. Chesselet, M.F: Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone, *Exp. Neurol.* 187 (2004) 418-429.

Foley P & Riederer P: Influence of neurotoxins and oxidative stress on the onset and progression of Parkinson's disease. *J Neurol.* 2000 Apr;247 Suppl 2:II82-94.

Fornai, F O. M. Schluter, P. Lenzi, M. et al., Parkinson-like syndrome induced by continuous MPTP infusion: Convergent roles of the ubiquitin-proteasome system and {alpha}-synuclein. *PNAS*, March 1, 2005; 102(9):3,413-3,418.

Fredriksson A, Fredriksson M, Eriksson P. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. *Toxicol Appl Pharmacol*; VOL 122, ISS 2, 1993, P258-64. Author Address: Department of Toxicology, Uppsala University, Sweden.

Freed VH, Matin MA, Fang SC, Kar PP. Role of striatal dopamine in delayed neurotoxic effects of organophosphorus compounds. *Eur J Pharmacol.* 1976; 35:229-232.

Frigerio, R et al., Chemical exposures and Parkinson's disease: A population-based case-control study. *Movement Disorders* online June 2006.

- Fukushima T, Yamada K, Hojo N, et al. Mechanisms of cytotoxicity of paraquat: NADH oxidation and paraquat radical formation via complex I. *Exp Toxicol Pathol* 1993; 45:345-349.
- Fukushima T, Yamada K, Hojo N, Isobe A, Shiwaku K, Yamane Y. Mechanism of cytotoxicity of paraquat. III. The effects of acute paraquat exposure on the electron transport system in rat mitochondria. *Exp Toxicol Pathol*. 1994 Dec; 46(6):437-41.
- Fukushima T, Tawara T, Isobe A, Hojo N, Shiwaku K, Yamane Y. Radical formation site of cerebral complex I and Parkinson's disease. *J Neurosci Res*. 1995 Oct 15; 42(3):385-90.
- Fukushima T, Hojo N, Isobe A, et al. Effects of paraquat on mitochondrial electron transport system and catecholamine contents in rat brain. *Arch Toxicol* 1996; 70:585-589.
- Fukushima T, Gao T, Tawara T, Hojo N, Isobe A, Yamane Y. Inhibitory effect of nicotinamide to paraquat toxicity and the reaction site on complex I. *Arch Toxicol*. 1997; 71(10):633-7.
- Gainetdinov, R.R., Fumagalli, F., Wang, Y.M., Jones, S.R., Miller, G.W., and Caron, M.G. Increased MPTP neurotoxicity in vesicular monoamine transporter 2 knockout mice. *Journal of Neurochemistry*. 70: 1,973-1,978, 1998.
- Galanaud JP, Elbaz A, Clavel J, Vidal JS, et al. Cigarette smoking and Parkinson's disease: A case-control study in a population characterized by a high prevalence of pesticide exposure. *Mov Disord* 2005, Feb; 20(2):181-9.
- Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern Med*. 1993 Jun 28; 153(12):1469-75.
- Gao, H-M et al., Synergistic Dopaminergic Neurotoxicity of the Pesticide Rotenone and Inflammogen Lipopolysaccharide: Relevance to the Etiology of Parkinson's Disease *The Journal of Neuroscience*, February 15, 2003a, 23(4):1,228-1,236.
- Gao, H.M., Liu, B., Zhang, W., Hong, J.S. Critical role of microglial NADPH oxidase-derived free radicals in the in vitro MPTP model of Parkinson's disease. *Faseb J*. 2003(b); 17, 1,954-1,956.
- Gao, H.M., Liu, B., Zhang, W., Hong, J.S. Synergistic dopaminergic neurotoxicity of MPTP and inflammogen lipopolysaccharide: relevance to the etiology of Parkinson's disease. *FASEB J*. 2003(c); 17, 1,957-1,959.
- Gearhart DA, Neafsey EJ, Collins MA: Phenylethanolamine N-methyltransferase has beta-carboline 2N-methyltransferase activity: hypothetical relevance to Parkinson's disease. *Neurochem Int*. 2002 Jun; 40(7):611-20.
- Giasson B.I. & V.M.-Y. Lee, A new link between pesticides and Parkinson's disease. *Nat. Neurosci*. 2000, 3:1,227-1,228. [No abstract available.]
- Goldman SM, Tanner CM, Olanow CW, Watts RL, Field RD, Langston JW. Occupation and Parkinsonism in three movement disorders clinics. *Neurology*. 2005 Nov 8; 65(9):1430-5. Epub 2005 Sep 14.
- Goldsmith, JR et al., Clustering of Parkinson's disease points to environmental etiology. *Arch. Environ. Health*, 1990, 45:88-94. (e-file)
- Gorell, JM et al., The role of the environment in Parkinson's disease. *Environ Health Perspect* 1996; 104:652-654. [No abstract available.]

Gorell, JM et al., Occupational exposures to metals as risk factors for Parkinson's disease. *Neurology*, 1997 Mar, 48:3, 650-658. (e-file)

Gorell, JM et al., The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. *Neurology*, 1998, 50(5): P1346-1,350. (e-file)

Gorell, JM et al., Smoking and Parkinson's disease: a dose-response relationship *Neurology*, 1999, 52(1): 115-119. (e-file)

Gorell, JM et al., Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicity*, 1999b, 20(2-3):239-247.

Gorell JM, Peterson EL, Rybicki BA, Johnson CC: Multiple risk factors for Parkinson's disease. *J Neurol Sci*. 2004 Feb 15; 217(2): 169-74.

Greenamyre JT, Sherer TB, Betarbet R, Panov AV. Complex I and Parkinson's disease. *IUBMB Life*. 2001 Sep-Nov; 52(3-5):135-41. Review.

Greenamyre JT, Betarbet R, Sherer TB. The rotenone model of Parkinson's disease: genes, environment and mitochondria. *Parkinsonism Relat Disord*. 2003 Aug; 9 Suppl 2:S59-64. Review.

Greenamyre, JT & Hastings, TG: Parkinson's : Divergent Causes, Convergent Mechanisms. *Science*, 2004, 304(5674): 1,120-1,122.

Guarisco JA, Carr RI, Chambers JE. The effects of developmental exposure to polychlorinated biphenyls on D1 and D2 dopamine receptors in juvenile and adult rats. *Toxicologist* 1999 Mar; 48(1-S):288.

Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999; 341:549 –555.

Hageman, G et al., Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long term occupational solvent exposure. *J Neurology*, 1999, 246:198-206. (pdf file)

Hajicek-Dobberstein S: Soma siddhas and alchemical enlightenment: psychedelic mushrooms in Buddhist tradition. *J Ethnopharmacol*. 1995 Oct; 48(2):99-118. (e-file) [See also Wasson]

Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf War: a cross-sectional epidemiologic study. *JAMA*. 1997; 277:231-237.

Haley RW, Billecke S, La Du BN. Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. *Toxicol Appl Pharmacol*. 1999; 157:227-233.

Haley. RW et al., Effect of basal ganglia injury on central dopamine activity in Gulf War Syndrome: correlation of Proton Magnetic Resonance Spectroscopy and plasma homovanillic acid levels. *Arch Neurol*. 2000; 57:1,280-1,285.

Hancock DB, Martin ER, Mayhew GM, Stajich JM, Jewett R, Stacy MA, Scott BL, Vance JM, Scott WK: Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. *BMC Neurol*. 2008 Mar 28; 8:6.

Hardy J. Pesticide exposure and risk for Parkinson's disease. *Mov Disord*. 2006; 60(2):197-203.

Hashimoto T, Nishi K, Nagasao J, Tsuji S, Oyanagi K: Magnesium exerts both preventive and ameliorating effects in an in vitro rat Parkinson disease model involving 1-methyl-4-phenylpyridinium (MPP(+)) toxicity in dopaminergic neurons. *Brain Res*. 2008 Jan 31.

- Hatcher JM, Pennell KD, Miller GW: Parkinson's disease and pesticides: a toxicological perspective. *Trends Pharmacol Sci.* 2008 Jun; 29(6):322-9. Epub 2008 Apr 29.
- Head, K: Better Living Through Chemicals. [Editorial] *Alt. Med. Rvw.* 2000.
- Heafield MT, Fearn S, Steventon GB, Waring RH, Williams AC, Sturman SG. Plasma cysteine and sulphate levels in patients with motor neurone, Parkinson's and Alzheimer's disease. *Neurosci Lett.* 1990 Mar 2; 110(1-2):216-20.
- Heikkila R, Cohen G. Inhibition of biogenic amine uptake by hydrogen peroxide: a mechanism for toxic effects of 6-hydroxydopamine. *Science*, 1971; 172:1,257-1,258.
- Heinz GH, Hill EF, Contrera JF. Dopamine and norepinephrine depletion in ring doves fed DDE, dieldrin, and Aroclor 1254. *Toxicol Appl Pharmacol.* 1980 Mar 30; 53(1):75-82. [No Abstract available on Medline]
- Helmuth L: Neuroscience. Pesticide causes Parkinson's in rats. *Science*, 2000 Nov 10; 290(5494):1068. [No abstract available.]
- Herishanu YO, Medvedovski M, Goldsmith JR, Kordysh E: A case-control study of Parkinson's disease in urban population of southern Israel. *Can J Neurol Sci.* 2001 May; 28(2): 144-7.
- Herrera AJ, Castano A, Venero JL, et al. The single intranigral injection of LPS as a new model for studying the selective effects of inflammatory reactions on dopaminergic system. *Neurobiol Dis.* 2000; 7:429-47.
- Hertzman, C, Wiens M, Bowering D, et al. Parkinson's disease: a case-control study of occupational and environmental risk factors. *Am J Ind Med* 1990; 17:349-355.
- Hertzman, C et al., A case-control study of Parkinson's disease in a horticultural region of British Columbia. *Mov Disord* 1994; 9:69-75.
- Hesman T. Studies Link Prenatal Alcohol, Mental Illness/Drugs. Environmental toxins May Kill Brain Cells. *Brain in the News.* February 2004.
- Higgins D. S. and Greenamyre J. T. (1996) [3H] dihydrorotenone binding to NADH:ubiquinone reductase (complex I) of the electron transport chain: an autoradiographic study. *J. Neurosci.* 16, 3807-3816.
- Hileman, B: The Environment and Parkinson's . *Chemical and Engineering News* v.79, n.38 17 Sep 01. Available @ [www.mindfully.org/Health/ Parkinsons-And-Environment.htm](http://www.mindfully.org/Health/Parkinsons-And-Environment.htm)
- Hirsch EC, Hoglinger G, Rousset E, Breidert T, Parain K, Feger J, Ruberg M, Prigent A, Cohen-Salmon C, Launay JM. Animal models of Parkinson's disease in rodents induced by toxins: an update. *J Neural Transm Suppl.* 2003; (65):89-100. Review.
- Ho SC et al., Epidemiologic study of Parkinson's disease in Hong Kong. *Neurology*, 1989, 39:1,314-1,318.
- Hoogenraad T: Dithiocarbamates and Parkinson's disease [Letter]. *Lancet* 1988; 767.
- HSE. EH40/2002 Occupational Exposure Limits 2002. EH40 2002; 7-28.
- Hubble JP, Cao T, Hassanein RE, Neuberger JS, Koller WC: Risk factors for Parkinson's disease. *Neurology.* 1993 Sep; 43(9): 1,693-1,697.
- Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RE, et al., Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. *Neuroepidemiology*, 1998; 17(2):96-104.

Jamal, GA. Neurological Syndromes of Organophosphorus Compounds. *Adverse Drug Reactions. Toxicol Rev.* 1997, 16(3), 133-170.

Jamal GA, Hansen S, Julu PO: Low level exposures to organophosphorus esters may cause neurotoxicity. *Toxicology.* 2002 Dec 27; 181-182:23-33.

Jenner P, Marsden CD. MPTP-induced Parkinsonism: a model of Parkinson's disease and its relevance to the disease process. In: Marsden CD, Fahn S, eds. *Movement Disorders, Neurology 2.* London: Butterworth Scientific, 1981:55-75.

Jett DA, Navoa RV, Lyons MA. Additive inhibitory action of chlorpyrifos and polycyclic aromatic hydrocarbons on acetylcholinesterase activity in vitro. *Toxicol Lett.* 1999; 105:223-229.

Jia Z & Misra HP: Reactive oxygen species in in vitro pesticide-induced neuronal cell (SH-SY5Y) cytotoxicity: role of NFkappaB and caspase-3. *Free Radic Biol Med.* 2007 Jan 15; 42(2):288-98.

Jimenez-Jimenez FJ et al., Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. *Mov Disord* 1992c; 7:149-152.

Jowit, J: Pollutants cause huge rise in brain diseases. *The Observer*, Sunday August 15, 2004.

Kamel F, Association of pesticide exposure with neurologic dysfunction and disease. *Environ Health Perspect.* 2004 Jun; 112(9):950-8.

Kamel, F., Tanner, C., Umbach, D., et al., Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. *Am. J. Epidemiol.* 2007, 165, 364-374.

Kane, P: e-mail post.

Kanter M: Nigella sativa and derived thymoquinone prevents hippocampal neurodegeneration after chronic toluene exposure in rats. *Neurochem Res.* 2008 Mar; 33(3):579-88.

Kanter M: Protective effects of Nigella sativa on the neuronal injury in frontal cortex and brain stem after chronic toluene exposure. *Neurochem Res.* 2008 Nov; 33(11):2241-9.

Kanhasamy, A et al., A novel oxidative stress-dependent apoptotic pathway in pesticide-induced dopaminergic degeneration: relevance to environmental factors and Parkinson's disease, *J. Neurochem.* 2002; 81(suppl.); 76. [q.v. Dillon] Couldn't find abstract?

Kanhasamy AG, Kitazawa M, Kanhasamy A, Anantharam V. Dieldrin-induced neurotoxicity: relevance to Parkinson's disease pathogenesis. *Neurotoxicology.* 2005 Aug; 26(4):701-19. Review.

Karen DJ, Li W, Harp PR, Gillette JS, Bloomquist JR. Striatal dopaminergic pathways as a target for the insecticides permethrin and chlorpyrifos. *Neurotoxicology.* 2001 Dec; 2(6):811-817.

Kelada SN, Checkoway H, Kardia SL, Carlson CS, Costa-Mallen P, Eaton DL, et al. 5' and 3' region variability in the dopamine transporter gene (SLC6A3), pesticide exposure and Parkinson's disease risk: a hypothesis-generating study. *Hum Mol Genet* 2006; 15: 3055-62.

Kidd, PM: A review of nutrients and botanicals in the integrative management of cognitive dysfunction. *Altern. Med. Rev.* 1999, 4:144-161. (e-file)

Kidd, PM: Parkinson's Disease as Multifactorial Oxidative Neurodegeneration: Implications for Integrative Management. *Alternative Medicine Review*, 2000, 5(6):502-529.

Kitazawa, M., Anantharam, V. & Kanthasamy, A.G. (2003), Dieldrin induces apoptosis by promoting caspase-3-dependent proteolytic activation of Protein Kinase C $\delta$  in dopaminergic cells: Relevance to oxidative stress and dopaminergic degeneration. *Neuroscience*, 119: 945-964.

Kluwe WM & Hook JB; Metabolic activation of nephrotoxic haloalkanes. *Fed Proc.* 1980 Nov; 39(13):3129-33.

Knox, JW & Nelson, JR: Permanent encephalopathy from toluene inhalation. *NEJM.* 1966, 275:1,494-1,496. [No abstract available.]

Koller, W et al., Environmental risk factors in Parkinson's disease. *Neurology*, 1990c, 40:1,218-1,223.

Kuehn BM. Scientists probe role of genes, environment in Parkinson disease. *JAMA.* 2006; 295:1,883-5. [pdf file]

Kuhn W et al., Elevated levels of harman and norharman in cerebrospinal fluid of Parkinsonian patients. *J. Neural Transm.* 1996c, 103:1,435-1,440.

Kuopio, AM, Marttila RJ, Helenius H, Rinne UK: Environmental risk factors in Parkinson's disease. *Mov Disord.* 1999; 14:928-939.

Lai BCL, Marion SA, Teschke K, et al. Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism & Related Disorders* 2002; 8:297-309.

Langston, JW et al., Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science*, 1983a, 219:979-980.

Langston, JW: The etiology of Parkinson's disease with emphasis on the MPTP story *Neurology*, 1996, 47(6): 153-160. (FT e-file)

Langston, JW et al., Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. *Ann. Neurol.* 1999, 46:598-605.

Le Couteur D. G., McLean A. J., Taylor M. C., Woodham B. L. and Board P. G. (1999) Pesticides and Parkinson's disease. *Biomed. Pharmacother.* 53, 122-130.

Lee XP, Kumazawa T, Fujishiro M, Hasegawa C, Arinobu T, Seno H, Ishii A, Sato K. Determination of paraquat and diquat in human body fluids by high-performance liquid chromatography/tandem mass spectrometry. *J Mass Spectrom.* 2004 Oct; 39(10):1147-52.

Lewin R. Parkinson's disease: an environmental cause? *Science.* 1985 Jul 19; 229(4710):257-258. [No Abstract available on Medline]

Li AA, Mink PJ, McIntosh LJ, Teta MJ, Finley B. Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. *J Occup Environ Med.* 2005 Oct; 47(10):1059-87. Review.

Li N., Ragheb K., Lawler G., Sturgis J., Rajwa B., Melendez J. A. and Robinson J. P. (2003) Mitochondrial complex I inhibitor rotenone induces apoptosis through enhancing mitochondrial reactive oxygen species production. *J. Biol. Chem.* 278, 8516-8525.

Li X, Yin J, Cheng CM, Sun JL, Li Z, Wu YL. Paraquat induces selective dopaminergic nigrostriatal degeneration in aging C57BL/6 mice. *Chin Med J (Engl).* 2005 Aug 20; 118(16):1,357-61.

Li X, Matsumoto K, Murakami Y, Tezuka Y, Wu Y, Kadota S. Neuroprotective effects of *Polygonum multiflorum* on nigrostriatal dopaminergic degeneration induced by paraquat and maneb in mice. *Pharmacol Biochem Behav.* 2005 Oct; 82(2):345-52. Epub 2005 Oct 7.

Liberini P, Parola S, Spano PF, Antonini L. Olfaction in Parkinson's disease: methods of assessment and clinical relevance. *J Neurol.* 2000 Feb; 247(2):88-96.

Lieberman, Allan D: *Pesticide Poisoning* 2000

Ling Z, Chang QA, Tong CW, Leurgans SE, Lipton JW, Carvey PM. Rotenone potentiates dopamine neuron loss in animals exposed to lipopolysaccharide prenatally. *Exp Neurol.* 2004 Dec; 190(2):373-83.

Liou HH, Chen RC, Tsai YF, Chen WP, Chang YC, Tsai MC. Effects of paraquat on the substantia nigra of the wistar rats: neurochemical, histological, and behavioral studies. *Toxicol Appl Pharmacol.* 1996 Mar; 137(1):34-41.

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. *Neurology.* 1997 Jun; 48(6): 1583-8.

Liou HH, Chen RC, Chen TH, et al. Attenuation of paraquat-induced dopaminergic toxicity on the substantia nigra by (-)-deprenyl in vivo. *Toxicol Appl Pharmacol.* 2001 Apr 1; 172(1):37-43.

Lipson SM & Stotzky G: Specificity of virus adsorption to clay minerals. *Can J Microbiol.* 1985 Jan; 31(1):50-3.

Liu B, Jiang JW, Wilson BC, et al. Systemic infusion of naloxane reduces degeneration of rat substantia nigral dopaminergic neurons induced by intranigral injection of lipopolysaccharide. *J. Pharmacol. Exp. Ther.* 2000; 295:125-32.

Liu B, Gao HM, Hong JS. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. *Environ Health Perspect.* 2003 Jun; 111(8):1,065-73. Review.

Lockwood AH. Pesticides and Parkinsonism: is there an etiological link? *Curr Opin Neurol.* 2000; 13:687-690.

London L, Myers JE, Nell V, Taylor T, Thompson ML: An investigation into neurologic and neurobehavioral effects of long-term agrichemical use among deciduous fruit farm workers in the western cape, South Africa. *Environ Res.* 1997; 73:132-145.

London L, Myers JE: Use of a crop and job specific exposure matrix for retrospective assessment of long-term exposure in studies of chronic neurotoxic effects of agrichemicals. *Occup Environ Med* 1998; 55:194-201.

London L, Nell V, Thompson M, Myers J: Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers. *Scand J Work Environ Health* 1998; 24:18-29. [pdf file]

Lummen P. (1998) Complex I inhibitors as insecticides and acaricides. *Biochim. Biophys. Acta.* 1364, 287-296.

Maguire-Zeiss KA, Federoff HJ. Convergent pathobiologic model of Parkinson's disease. *Ann N Y Acad Sci.* 2003 Jun; 991:152-66. Review. (pdf file)

Manning-Bog AB, McCormack AL, Li J, et al. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. *J Biol Chem* 2002; 277:1,641-1,644.

Manning-Bog AB, McCormack AL, Purisai MG, Bolin LM, Di Monte DA. Alpha-synuclein overexpression protects against paraquat-induced neurodegeneration. *J Neurosci*. 2003 Apr 15; 23(8):3095-9.

Marey-Semper I, Gelman M, Lévi-Strauss M. The high sensitivity to rotenone of striatal dopamine uptake suggests the existence of a constitutive metabolic deficiency in dopaminergic neurons from the substantia nigra. *Eur J Neurosci*. 1993 Aug 1; 5(8):1029–1034.

Mariussen E, Mørch Andersen J, Fonnum F. The effect of polychlorinated biphenyls on the uptake of dopamine and other neurotransmitters into rat brain synaptic vesicles. *Toxicol Appl Pharmacol*. 1999; 161(3):274-82.

Maruyama W, Abe T, Tohgi H, Dostert P, Naoi M. A dopaminergic neurotoxin, (R)-N-methylsalsolinol, increases in Parkinsonian cerebrospinal fluid. *Ann Neurol*. 1996 Jul; 40(1):119-22.

Maruyama W, Sobue G, Matsubara K, Hashizume Y, Dostert P, Naoi M. A dopaminergic neurotoxin, 1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, N-methyl(R)salsolinol, and its oxidation product, 1,2(N)-dimethyl-6,7-dihydroxyisoquinolinium ion, accumulate in the nigro-striatal system of the human brain. *Neurosci Lett*. 1997 Feb 14; 223(1):61-4.

Maruyama W, Abe T, Tohgi H, Naoi M. An endogenous MPTP-like dopaminergic neurotoxin, N-methyl(R)salsolinol, in the cerebrospinal fluid decreases with progression of Parkinson's disease. *Neurosci Lett*. 1999 Feb 26; 262(1):13-6.

Maruyama W: [Pathogenesis of idiopathic Parkinson's disease.] [Article in Japanese] *Nippon Ronen Igakkai Zasshi*. 2001 Jul; 38(4):494-7.

Matsubara K, Kobayashi S, Kobayashi Y, Yamashita K, Koide H, Hatta M, Iwamoto K, Tanaka O, Kimura K. beta-Carbolinium cations, endogenous MPP+ analogs, in the lumbar cerebrospinal fluid of patients with Parkinson's disease. *Neurology*. 1995 Dec; 45(12):2240-5.

McCarthy S, Somayajulu M, Sikorska M, Borowy-Borowski H, Pandey S. Paraquat induces oxidative stress and neuronal cell death; neuroprotection by water-soluble Coenzyme Q10. *Toxicol Appl Pharmacol*. 2004 Nov 15; 201(1):21-31.

McConnell R, Keifer M, Rosenstock L. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. *Am. J Ind Med*. 1994; 25:325-334.

McConnell R, Delgado-Tellez E, Cuadra R, Torres E, Keifer M, Almendarez J, Miranda J, El-Fawal HA, Wolff M, Simpson D, Lundberg I. Organophosphate neuropathy due to methamidophos: biochemical and neurophysiological markers. *Arch. Toxicol*. 1999 Aug; 73(6):296-300.

McCormack AL et al., Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis*. 2002 Jul; 10(2):119-27. (e-file)

McCormack A.L. & D.A. Di Monte, Effects of l-dopa and other amino acids against paraquat-induced nigrostriatal degeneration. *J Neurochem*. 2003, 85:82–86.

McCormack AL, Atienza JG, Johnston LC, Andersen JK, Vu S, Di Monte DA. Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. *J Neurochem*. 2005 May; 93(4):1030-7.

McCormack AL, Atienza JG, Langston JW, Di Monte DA. Decreased susceptibility to oxidative stress underlies the resistance of specific dopaminergic cell populations to paraquat-induced degeneration. *Neuroscience*. 2006 Aug 25;141(2):929-37. Epub 2006 May 4.

- McDermott C, O'Donoghue MH, Heffron JJ: n-Hexane toxicity in Jurkat T-cells is mediated by reactive oxygen species. *Arch Toxicol.* 2008; 82:165–171. [[PubMed](#)]
- McDonnell L, Maginnis C, Lewis S, Pickering N, Antoniak M, Hubbard R et al. Occupational exposure to solvents and metals and Parkinson's disease. *Neurology* 2003; 61: 716-7.
- McGeer, PL et al., Rate of cell death in Parkinsonism indicates active neuropathological progress. *Ann. Neurol.* 1988, 24:574-576.
- McGeer PL, Schwab C, Parent A, Doudet D. Presence of reactive microglia in monkey substantia nigra years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration. *Ann Neurol.* 2003 Nov; 54(5):599-604.
- Meco G, Bonifati V, Vanacore N, Fabrizio E: Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). *Scand J Work Environ Health*, 1994; 20:301-305.
- Mena, MA et al., Levodopa toxicity in fetal rat midbrain neurones in culture: modulation by ascorbic acid. *Neuro. Rep.* 1993, 4:438-440.
- Mena, MA et al., Effects of retinoic acid on NB 69 human neuroblastoma cells and fetal rat mid brain neurons. *J of Neural Transm.* 1994, 8:85-97. (e-file)
- Menegon, A et al., Parkinson's disease, pesticides, and Glutathione S-transferase polymorphisms. *Lancet*, 1998, 352:1,344-1,348.
- Meseguer E, Taboada R, Sanchez V, Mena MA, Campos V, Garcia De Yebenes J. Life-threatening Parkinsonism induced by kava-kava. *Mov Disord.* 2002 Jan; 17(1):195-6.
- Michele, G. A. Filla, G. Volpe, V. Marco, A. Gogliettino and G. Ambrosio et al., Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy, *Mov Disord.* 1 (1996), pp. 17–23.
- Miller, G.W., Erickson, J., Perez, J.T., Penland, S.N., Mash, D.C., Rye, D.B, and Levey, A.I. Immunochemical analysis of vesicular monoamine transporter protein in Parkinson's disease. *Experimental Neurology.* 156: 138-148, 1999.
- Miller, G.W., Kirby, M., Levey, A.I., Bloomquist, J. Heptachlor alters expression and function of dopamine transporters. *Neurotoxicology.* 20:631-638, 1999.
- Miller, RL, Sun GY, Sun AY; Cytotoxicity of paraquat in microglial cells: Involvement of PKCdelta- and ERK1/2-dependent NADPH oxidase. *Brain Res.* 2007; 1167:129-39. Free Full Text <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2084263&blobtype=pdf>
- Mitchell, J: Nowhere to hide: the global spread of high-risk synthetic chemicals. *World Watch* 1997; 10:26-36.
- Molina-Jimenez, MF; Sanchez-Reus, MI; Benedi, J. Effect of fraxetin and myricetin on rotenone-induced cytotoxicity in SH-SY5Y cells: comparison with N-acetylcysteine. *Eur J Pharmacol.* 2003; 472:81–87.
- Molina-Jimenez, MF; Sanchez-Reus, MI; Cascales, M; Andres, D; Benedi, J. Effect of fraxetin on antioxidant defense and stress proteins in human neuroblastoma cell model of rotenone neurotoxicity. Comparative study with myricetin and N-acetylcysteine. *Toxicol Appl Pharmacol.* 2005; 209:214–225.
- Momcilovic B et al., Environmental radon daughters reveal pathognomonic changes in the brain proteins and lipids in patients with Alzheimer's disease and Parkinson's disease, and cigarette smokers. *Arh Hig Rada Toksikol.* 1999 Dec; 50(4):347-69.

Momcilovic, B. Hassan A. Alkhatib, John A. Duerre, Marvin A Cooley, William M. Long, Robert T. Harris, and Glenn I. Lykken. Environmental lead-210 and bismuth-210 accrue selectively in the brain proteins in Alzheimer disease and brain lipids in Parkinson disease. "Preference of environmental radon progeny for brain proteins in Alzheimer's Disease and brain lipids in Parkinson's Disease." *Alzheimer Disease and Associated Disorders*, No.2, April-June 2001; 15:106-115.

Momcilovic Berislav Personal e-mail correspondence, October 2005.

Momcilovic B, Lykken GI, Cooley M. Natural distribution of environmental radon daughters in the different brain areas of an Alzheimer Disease victim. *Mol Neurodegener*. 2006 Sep 11; 1(1):11 [Epub ahead of print]

Morano A et al., Risk factors for Parkinson's disease: Case-control study in the province of Caceres, Spain. *Acta Neurol Scand*. 1994, 89:164-170.

Mulhearn, RJ: The history of James Parkinson and his disease. *Aust. NZ J of Med*. 1971, 1(Suppl 1):1-6. Excerpted @ <http://www.parkinsons.ca/Week12.htm>

Muravchick S, Smith DS. Parkinsonian symptoms during emergence from general anesthesia. *Anesthesiology* 1995; 82: 305-307.

Muthane, UB et al., Melanized Nigral Neuronal Numbers in Nigerian and British Individuals. *Movement Disorders*, Vol. 21, No. 8, 2006:1,235-1,238. [pdf file]

Mutti A. Styrene exposure and serum prolactin. *J Occup Med*. 1988a Jun; 30(6):481-2. [No abstract available.]

Mutti A, Falzoi M, Romanelli A, Bocchi MC, Ferroni C, Franchini I. Brain dopamine as a target for solvent toxicity: effects of some monocyclic aromatic hydrocarbons. *Toxicology*. 1988b Apr; 49(1):77-82.

Nakano S, Noguchi T, Takekoshi H, Suzuki G, Nakano M. Maternal-fetal distribution and transfer of dioxins in pregnant women in Japan, and attempts to reduce maternal transfer with *Chlorella (Chlorella pyrenoidosa)* supplements. *Chemosphere*. 2005 Dec; 61(9):1244-55. Epub 2005 Jun 27.

Neel, LE et al., Environmental occupational risk factors and familial associations in multiple system atrophy: a preliminary investigation. *Clinical Autonomic Research* 1991, 1:9-13.

Nelson, L: Pesticides and PD. *A A Neurology*, May, 2000. (Reported by Stephenson. q.v.)

Newhouse, K; Hsuan, SL; Chang, SH; et al., Rotenone-induced apoptosis is mediated by p38 and JNK MAP kinases in human dopaminergic SH-SY5Y cells. *Toxicol Sci*. 2004; 79:137-146.

Nicklas W. J., Vyas I. and Heikkila R. E. (1985) Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *Life Sci*. 36, 2503-2508.

Niehaus, I & Lange, JH: Endotoxin: is it an environmental factor in the cause of Parkinson's disease? *Occupational and Environmental Medicine* 2003;60:378. (Letter)

Nieto M, Gil-Bea FJ, Dalfo E, et al. Increased sensitivity to MPTP in human  $\alpha$ -synuclein A30P transgenic mice. *Neurobiol. Aging* 2006; 6:848-856.

Normandin L et al., Assessment of bioaccumulation, neuropathology, and neurobehavior following subchronic (90 days) inhalation in Sprague-Dawley rats exposed to manganese phosphate. *Toxicol Appl Pharmacol* 2002 Sep 1;183(2):135-45. (e-file)

Novikova L, Garris BL, Garris DR, Lau YS. Early signs of neuronal apoptosis in the substantia nigra pars compacta of the progressive neurodegenerative mouse 1-methyl-4-phenyl-1,2,3,6-tetra-hydro-pyridine/probenecid model of Parkinson's disease. *Neuroscience*. 2006 Jun 19; 140(1):67-76.

Ohashi S, Mori A, Kurihara N, Mitsumoto Y, Nakai M. Age-related severity of dopaminergic neurodegeneration to MPTP neurotoxicity causes motor dysfunction in C57BL/6 mice. *Neurosci Lett*. 2006 Jun 19; 401(1-2):183-7.

Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury: a case-referent study. *Scand J Work Environ Health* 1981; 7:252-256.

Olenchock AS, May JJ, Pratt DS, et al., Presence of endotoxins in different agricultural environments. *Am J Ind Med*. 1990; 18:279-84.

Onofrij, M et al., Reversible Parkinsonism induced by prolonged treatment with valproate. *J of Neurology*, 1998; 245 12:794-796. (e-file)

Overstreet DH. Organophosphate pesticides, cholinergic function and cognitive performance in advanced age. *Neurotoxicology* 2000; 21:75-82.

Page WF & Tanner CM: Parkinson's disease and motor-neuron disease in former prisoners-of-war. *Lancet*. 2000 Mar 4; 355(9206):843. (Comment)

Panov A, Dikalov S, Shalbuyeva N, Taylor G, Sherer T, Greenamyre JT. Rotenone model of Parkinson disease: multiple brain mitochondria dysfunctions after short term systemic rotenone intoxication. *J Biol Chem*. 2005 Dec 23; 280(51):42026-35. Epub 2005 Oct 21.

Park, JS et al., Occupations and Parkinson's Disease: a multi-center case-control study in South Korea. *Neurotoxicology*, 2005a, 26(1):99-105.

Park M, Ross GW, Petrovitch H, White LR, Masaki KH, Nelson JS, Tanner CM, Curb JD, Blanchette PL, Abbott RD. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology*. 2005b Mar 22; 64(6):1047-51.

PCBs and Parkinson's: The Studies [#38] - Parkinson's Disease, Dopamine and PCBs.  
[http://www.foxriverwatch.com/parkinsons\\_dopamine\\_pcb\\_1.html](http://www.foxriverwatch.com/parkinsons_dopamine_pcb_1.html)

Pedarzani P et al., Tamapin: a venom peptide from the Indian red scorpion (*Mesobuthus tamulus*) which targets SK channels and AHP currents in central neurons. *J Biol Chem* 2002 Sep 17; [epub ahead of print.] (e-file)

Peng, J et al., Iron and Paraquat as Synergistic Environmental Risk Factors in Sporadic Parkinson's Disease Accelerate Age-Related Neurodegeneration. *Journal of Neuroscience*, June 27, 2007, 27(26):6,914-6,922.

Peretz C, Alexander BH, Nagahama SI, Domino KB, et al. Parkinson's disease mortality among male anesthesiologists and internists. *Mov Disord* 2005; August [Epub ahead of print].

Pesticide Residues Committee Report Available @ [http://www.pesticides.gov.uk/prc\\_home.asp](http://www.pesticides.gov.uk/prc_home.asp)

Pesticides in Diets of Infants and Children. National Research Council. Washington D.C.: National Academy Press, 1993.

Peters, HA et al., Extrapyrarnidal symptoms from carbon disulfide exposure in grain storage workers. *Neurology*, 1986, 36(Suppl. 1):342.

Peters, HA et al., Extrapyrarnidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. *Arch. Neurol.* 1988, 45:537-540.

Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, Masaki KH, Blanchette PL, Popper JS, Foley D, Launer L, White LR. Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol.* 2002 Nov; 59(11):1787-92.

Pezzoli G et al., N-hexane-induced Parkinsonism - pathogenetic hypotheses. *Movement Disorders.* 10(3):279-282, 1995 May. (e-file)

Pezzoli G et al., [Hydrocarbon exposure and Parkinson's disease.] *Neurology*, 2000, 55:667-673. (e-file) [\[Abstract/Free Full Text\]](#)

Pfohman, Robin. 1992, "Parkinson's disease, farmers, and herbicide use : New research strengthens the link", Vol. 12, No. 4 , Winter 1992, pp. 26. Available @ [http://www.eap.mcgill.ca/MagRack/JPR/JPR\\_17.htm](http://www.eap.mcgill.ca/MagRack/JPR/JPR_17.htm)

Poskanzer, DC & Schwab, RS: Cohort analysis of Parkinson's syndrome: evidence for a single etiology related to subclinical infection about 1920. *J. Chronic Dis.* 1963, 16:961-973.

Prediger RD, Batista LC, Medeiros R, Pandolfo P, Florio JC, Takahashi RN. The risk is in the air: Intranasal administration of MPTP to rats reproducing clinical features of Parkinson's disease. *Exp Neurol.* 2006 Aug 12; [pdf file]

Preux PM, Condet A, Anglade C, Druet-Cabanac M, Debrock C, Macharia W, Couratier P, Boutros-Toni F, Dumas M: Parkinson's disease and environmental factors. Matched case-control study in the Limousin region, France. *Neuroepidemiology.* 2000 Nov-Dec; 19(6): 333-337.

Priyadarshi A, Khuder SA, Schaub EA, et al. A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 2000; 21: 435-440.

Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS: Environmental risk factors and Parkinson's disease: a metaanalysis. *Environ Res.* 2001a Jun; 86(2): 122-7.

Przedborski S & Vila M: MPTP: a review of its mechanisms of neurotoxicity. *Clin Neurosci Res.* 2001b; 1:407-418. [couldn't find abstract?]

Przedborski S & Vila, M: The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine Mouse Model: A Tool to Explore the Pathogenesis of Parkinson's Disease. *Ann. NYAS* 2003; 991:189-198. [pdf file]

Przedborski S, Tieu K. Toxic animal models. In: Neurodegenerative diseases: neurobiology, pathogenesis and therapeutics (Beal MF, Lang AE, Ludolph A, eds), pp 196–221. New York: Cambridge, 2005a.

Przedborski S, Ischiropoulos H. Reactive oxygen and nitrogen species: weapons of neuronal destruction in models of Parkinson's disease. *Antioxid Redox Signaling* 7: 685–693, 2005b.

Quarelli, G: L'intossicazione professionale da CS<sub>2</sub>. *Trans. V. Int. Congress Occupational Disorders*, Budapest, 1928.

Racette BA, Tabbal SD, Jennings D, et al. Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. *Neurology* 2005; 64:230-235.

- Radad, K; Rausch, WD; Gille, G. Rotenone induces cell death in primary dopaminergic culture by increasing ROS production and inhibiting mitochondrial respiration. *Neurochem Int.* 2006; 49:379–386.
- Rajput AH, Uitti RJ, Stern W, Lavery W. Early onset Parkinson's disease in Saskatchewan: environmental considerations for etiology. *Can J Neurol Sci.* 1986; 13:312-316.
- Rajput, AH et al., Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. *Can. J. Neurol. Sci.* 1987a, 14:414-418.
- Rajput AH: Environmental causation of Parkinson's disease. *Arch Neurol.* 1993 Jun; 50(6):651-2. [No Abstract available on Medline.]
- Rango M, Canesi M, Ghione I, Farabola M, Righini A, Bresolin N, Antonini A, Pezzoli G. Parkinson's disease, chronic hydrocarbon exposure and striatal neuronal damage :a 1-H MRS study. *Neurotoxicology.* 2006 Mar; 27(2):164-8. Epub 2005 Oct 21.
- Rathke-Hartlieb S, Kahle PJ, et al. Sensitivity to MPTP is not increased in Parkinson's disease-associated mutant  $\alpha$ -synuclein transgenic mice. *J Neurochem.* 2001; 77:1,181-84.
- Rea, W et al., Pesticides & brain-function changes in a controlled environment. *Clinical Ecology*, Vol. II, No. 3, Summer 1984, pp. 145-150.
- Reigart, J & Roberti, J: Recognition and Management of Pesticide Poisonings. US EPA 735-R-98-003; 1999. Available @ [www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm](http://www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm)
- Richardson, J.R. and Miller, G.W. Acute exposure to Arochlor 1016 and 1260 differentially regulates the plasma membrane and vesicular monoamine transporters. *Toxicology Letters.* 148: 29-40, 2004.
- Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW. Paraquat neurotoxicity is distinct from that of MPTP and rotenone. *Toxicol Sci.* 2005 Nov; 88(1):193-201. Epub 2005 Sep 1.
- Richardson J. R., Caudle W. M., Guillot T. S. et al., Obligatory role for complex I inhibition in the dopaminergic neurotoxicity of 1-methyl-4-phenyl-tetrahydropyridine (MPTP). *Toxicol. Sci.* Epub 2006 Oct. 12. PMID 17038483.
- Rietschel ET, Brade H. Bacterial endotoxins. *Scientific American*, 1992; 267:54–61.
- Ringel, SP & Klawans, HL: Carbon-monoxide induced Parkinsonism. *J. Neurol. Sci.* 1972, 16:245-251.
- Ritz B & Yu F: Parkinson's disease mortality and pesticide exposure in California 1984-1994. *Int J Epidemiol.* 2000 Apr; 29(2): 323-9.
- Rocca WA et al., Time trends in the incidence of Parkinsonism in Olmsted County, Minnesota. *Neurology*, 2001 Aug 14;57(3):462-7.
- Rocha, B., Fumagalli, F., Gainetdinov, R.R., Jones, S., Miller, G.W., Caron, M.G. Cocaine self-administration in mice lacking the dopamine transporter. *Nature Neuroscience*, 1998; 1: 132-137.
- Rojo, A et al., Chronic inhalation of rotenone or paraquat does not induce Parkinson's disease symptoms in mice or rats. *Experimental Neurology*, November 2007, 208(1):120-126.
- Rommelfanger, K., Weinshenker, D. and Miller, G.W. Reduced MPTP toxicity in noradrenaline transporter knockout mice. *Journal of Neurochemistry.* 91(5):1116-24, 2004.

Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K. Chronic central nervous system effects of acute organophosphate pesticide intoxication. The Pesticide Health Effects Study Group. *Lancet*, 1991; 338:223-227.

Rosner, S, Giladi, N & Orr-Urtreger, A: Advances in the genetics of Parkinson's disease. *Acta Pharmacologica Sinica* 2008 January; 29 (1): 21-34.

Ross GW, Petrovitch H, Abbott RD, et al. Sugar cane processing is associated with Parkinson's disease in the Honolulu-Asia aging study. *Neurology*, 2001; 56:A222.

Sanchez-Ramos J, Hefti F, Weiner WI. 1987. Paraquat and Parkinson disease [Letter]. *Neurology* 37:728.

Sanchez-Ramos J, Facca A, Basit A, Song S. Toxicity of dieldrin for dopaminergic neurons in mesencephalic cultures. *Exp Neurol*. 1998 Apr; 150(2):263-271.

Sauer PJ, Huisman M, Koopman-Esseboom C, Morse DC, Smits-van Prooije AE, van de Berg KJ, Tuinstra LG, van der Paauw CG, Boersma ER, Weisglas-Kuperus N, et al. Effects of polychlorinated biphenyls (PCBs) and dioxins on growth and development. *Hum Exp Toxicol* 1994 Dec; 13(12):900-6.

Sava V, Reunova O, Velasquez A, Sanchez-Ramos J: Can low level exposure to ochratoxin-A cause Parkinsonism? *J Neurol Sci*. 2006 Jul 13; [Epub ahead of print]

Schober A. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res*. 2004 Oct; 318(1):215-24. Epub 2004 Jul 28. Review.

Schuh RA, Richardson JR, Gupta RK, et al., Effects of the organochlorine pesticide methoxychlor on dopamine metabolites and transporters in the mouse brain. *Neurotoxicology*. 2009 Mar; 30(2):274-80.

Sechi G, Agnetti V, Piredda M, Canu M, Deserra F, Omar HA, et al., Acute and persistent Parkinsonism after use of diquat. *Neurology* 1992; 42:261-263. [No abstract available on Medline.]

Seegal RF, Brosch KO, Okoniewski R, Bush B. Longterm Exposure To PCBs Alters Dopamine Concentrations In Monkey Neostriatum. 18th Annual Meeting of The Society For Neuroscience, Toronto, Ontario, Canada, November 13-18, 1988. *Soc. Neurosci. Abstr*; 1988; 14(2):885. [No Abstract Available]

Seegal RF, Bush B, Shain W. Lightly chlorinated ortho-substituted PCB congeners decrease dopamine in nonhuman primate brain and in tissue culture. *Toxicol Appl Pharmacol*. 1990 Oct; 106(1):136-144.

Seegal RF. Perinatal exposure to Aroclor 1016 elevates brain dopamine concentrations in the rat. *Toxicologist* 1992 Feb; 12(1):320.

Seegal RF, Bush B, Brosch KO. Decreases in Dopamine Concentrations in Adult, Non-human Primate Brain Persist following Removal from Polychlorinated Biphenyls. *Toxicology*, Vol. 86, Nos. 1/2, pages 71-87, 29 references, 1994a.

Seegal RF, Schantz SL. Neurochemical and Behavioral Sequelae of Exposure to Dioxins and PCBs. *Dioxins and Health*, A. Schechter, Editor; Plenum Press, New York, pages 409-447, 153 references, 1994b.

Seegal RF, Chishti MA, Fisher JP, Battaglioli G. Effects of Aroclors 1254-1260 And Individual PCB Congeners Of Dopamine And Gaba Content in Striatal Slices From Adult Rats. Source: Thirteenth International Neurotoxicology Conference on Developmental Neurotoxicity Of Endocrine Disrupters, Hot Springs, Arkansas, Usa, October 29-November 1, 1995. *Neurotoxicology (Little Rock)*; 1995, 16(4):765. [No Abstract Available]

Seegal RF, Brosch KO, Okoniewski RJ. Effects of in utero and lactational exposure of the laboratory rat to 2,4,2',4'- and 3,4,3',4'-tetrachlorobiphenyl on dopamine function. *Toxicol Appl Pharmacol* 1997 Sep; 146(1):95-103.

Seegal RF. Neurochemical effects of co-planar and non-coplanar polychlorinated biphenyls. *Neurotoxicol Teratol* 1998 May/June; 20(3):349-50.

Seegal RF. Are PCBs the major neurotoxicant in Great Lakes salmon? *Environ Res* 1999 Feb; 80(2 Pt 2):S38-S45

Seegal RF, Bemis JC. Polychlorinated biphenyls and methylmercury synergistically alter dopamine and intracellular calcium. *Neurotoxicology* 2000 Feb-Apr; 21(1-2):243.

Seegal RF.

Seidler, A. W. Hellenbrand, B.P. Robra, P. Vieregge and P. Nischan: Possible environmental, occupational and other etiologic factors for Parkinson's disease: a case-control study in Germany, *Neurology*, 46 (1996), pp. 1275–1284

Semchuk KM et al., Parkinson's disease and exposure to rural environmental factors: a population-based case-control study. *Can J Neurol Sci* 1991; 18:279-286.

Semchuk, KM et al., Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology*, 1992, 42:1,328-1,335.

Semchuk KM et al., Parkinson's disease: a test of the multifactorial etiologic hypothesis. *Neurology* 1993; 43(6):1,173-1,180.

Senanayake N, Sanmuganathan PS. Extrapyramidal manifestations complicating organophosphorus insecticide poisoning. *Hum Exp Toxicol* 1995; 14:600-04.

Shen, XM (Dryhurst) et al., Synthesis, redox properties, in vivo formation, and neurobehavioral effects of N-Acetylcysteiny conjugates of dopamine: possible metabolites of relevance to Parkinson's disease. *Chem. Res. Toxicol.* 1996a, 9:1,117-1,126.

Shen, XM & Dryhurst, G: Further insights into the influence of L-cysteine on the oxidation chemistry of dopamine: reaction pathways of potential relevance to Parkinson's disease. *Chem. Res. Toxicol.* 1996b, 9:751-763.

Sherer TB, Trimmer PA, Borland K, Parks JK, Bennett JP Jr, Tuttle JB. Chronic reduction in complex I function alters calcium signaling in SH-SY5Y neuroblastoma cells. *Brain Res.* 2001a Feb 9; 891(1-2):94-105.

Sherer TB, Betarbet R, and Greenamyre JT; Pathogenesis of Parkinson's disease, *Curr. Opin. Invest. Drugs* 2, 2001b, :657–662.

Sherer TB, Betarbet R, Stout AK, Lund S, Baptista M, Panov AV, Cookson MR, Greenamyre JT. An in vitro model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. *J Neurosci.* 2002a Aug 15; 22(16):7006-15.

Sherer, TB et al., Environment, mitochondria and Parkinson's disease. *Neuroscientist*, 2002b, 8(3):192-197.

Sherer TB, Kim JH, Betarbet R, Greenamyre JT. Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation. *Exp Neurol.* 2003a Jan; 179(1):9-16.

Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, Miller GW, Yagi T, Matsuno-Yagi A, Greenamyre JT. Mechanism of toxicity in rotenone models of Parkinson's disease. *J Neurosci*. 2003b Nov 26; 23(34):10756-64.

Sherer TB, Betarbet R, Kim JH, Greenamyre JT. Selective microglial activation in the rat rotenone model of Parkinson's disease. *Neurosci Lett*. 2003c May 1; 341(2):87-90.

Sherer TB et al., (Greenamyre JT) Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease. *J. Neurochem*. (2007) 100, 1,469–1,479.

Slechta DA, q.v. Cory-Slechta

Slotkin TA, Oliver CA, Seidler FJ. Critical periods for the role of oxidative stress in the developmental neurotoxicity of chlorpyrifos and terbutaline, alone or in combination. *Brain Res Dev Brain Res*. 2005 Jun 30; 157(2):172-80. [pdf file]

Smargiassi A, Mutti A, De Rosa A, et al. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. *Neurotoxicology* 1998; 19:709-712.

Spencer, PS et al., Long-latency neurodegenerative disease in the western Pacific. *Geriatrics*, 1991a, 46 (Supp. 1):37-42.

Spencer PS et al., Slow toxins, biologic markers, and long-latency neurodegenerative disease in the western Pacific region. *Neurology*, 1991b May; 41(5 Suppl 2):62-6; discussion 66-8.

Spencer-PS et al., Neurologic diseases associated with use of plant components with toxic potential. *Environ-Res*; VOL 62, ISS 1, 1993, P106-13.

Stacy, M: Symptom management in Parkinson's disease. *Parkinson Report*, 1996b, 18(4):1-6.

Stepens A, et al., A Parkinsonian syndrome in methcathinone users and the role of manganese. *N Engl J Med*. 2008 Mar 6; 358(10):1,009-17.

Stephenson J. Exposure to home pesticides linked to Parkinson disease. *JAMA*. 2000 Jun 21; 283(23):3055-6. [No abstract available on Medline.]

Stern M et al., The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. *Arch Neurol* 1991; 48:903-907. (e-file)

Steventon GB, Heafield MT, Waring RH, Williams AC. Xenobiotic metabolism in Parkinson's disease. *Neurology*, 1989 Jul; 39(7):883-7.

Steventon GB, An investigation into the inter-relationships of sulphur xeno-biotransformation pathways in Parkinson's and motor neurone diseases. *Drug Metabol Drug Interact*. 2003; 19(4):223-40.

Stoker TE: Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. *Toxicol Sci*. 1999 Nov; 52(1):68-79.

Stokes L, Stark A, Marshall E, Narang A. Neurotoxicity among pesticide applicators exposed to organophosphates. *Occup Environ Med*. 1995; 52:648-653.

Sun, F. V. Anantharam, C. Latchoumycandane, A. Kanthasamy, & A. G. Kanthasamy: Dieldrin Induces Ubiquitin-Proteasome Dysfunction in  $\alpha$ -Synuclein Overexpressing Dopaminergic Neuronal Cells and Enhances Susceptibility to Apoptotic Cell Death. *J. Pharmacol. Exp. Ther.*, 2005; 315(1):69-79.

- Tanner CM. Influence of environmental factors on the onset of Parkinson's disease. *Neurology* 1986; 36:215.
- Tanner, CM et al., Environmental factors in the etiology of Parkinson's disease. *Can. J. Neurol. Sci.* 1987, 14:419-423.
- Tanner CM, Chen B, Wang W, Peng M, Liu Z, Liang X, Kao LC, Gilley DW, Goetz CG, Schoenberg BS. Environmental factors and Parkinson's disease: a case-control study in China. *Neurology*. 1989 May; 39(5):660-4.
- Tanner CM, Grabler P, Goetz CG: Occupation and the risk of Parkinson's disease: A case-control study in young onset patients. *Neurology*, 1990b, 40(suppl 1):422.
- Tanner, CM & Langston, JW: Is Parkinson's disease caused by environmental toxins? *Neurology*, 1990c, 40(Suppl. 2):1-15.
- Tanner, CM & Langston, JW: Do environmental toxins cause Parkinson's disease? A critical review. *Neurology*, 1990d, 40(Suppl 3):17-30. Review. [No abstract available.]
- Tanner, CM: Liver enzyme abnormalities in Parkinson's disease. *Geriatrics*, 1991a, 46 (Supp. 1):60-63. Review
- Tanner CM. Abnormal liver enzyme-mediated metabolism in Parkinson's disease: a second look. *Neurology*. 1991b May; 41(5 Suppl 2):89-91; discussion 92. Review.
- Tanner CM. Epidemiology of Parkinson's disease. *Neurol Clin*. 1992a May; 10(2):317-29. Review.
- Tanner CM. Occupational and environmental causes of Parkinsonism. *Occup Med*. 1992b Jul-Sep; 7(3):503-13. Review.
- Tanner CM, Goldman SM. Epidemiology of movement disorders. *Curr Opin Neurol*. 1994 Aug; 7(4):340-5. Review. [No abstract available.]
- Tanner CM. Early intervention in Parkinson's disease: epidemiologic considerations. *Ann Epidemiol*. 1996a Sep; 6(5):438-41. Review.
- Tanner, CM & Goldman, SM: Epidemiology of Parkinson's disease. (Review) *Neurologic Clinics*, 1996b, 14(2):317-335.
- Tanner, CM & Ben-Shlomo, Y: Epidemiology of Parkinson's disease. *Adv Neurol*. 1999; 80:153-9. Review. [No abstract available]
- Tanner CM, Aston DA. Epidemiology of Parkinson's disease and akinetic syndromes. *Curr Opin Neurol*. 2000 Aug; 13(4):427-30. Review.
- Tanner CM, Goldman SM & Ross GW: Etiology of Parkinson's disease. In: Jankovic JJ & Tolosa E (Editors), *Parkinson's Disease and Movement Disorders*. Lippincott Williams & Wilkins, Philadelphia, PA.; 2002.
- Tanner CM: Is the cause of Parkinson's disease environmental or hereditary? Evidence from twin studies. *Adv Neurol*. 2003; 91:133-42. [No abstract available]
- Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, Myers RH: Environmental, medical, and family history risk factors for Parkinson's disease: a New England-based case control study. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 88:742-749, 1999.

Testa CM, Sherer TB, Greenamyre JT. Rotenone induces oxidative stress and dopaminergic neuron damage in organotypic substantia nigra cultures. *Brain Res Mol Brain Res*. 2005 Mar 24; 134(1):109-18. Epub 2005 Jan 6.

Tetrud, JW et al., Parkinsonism caused by petroleum waste ingestion. *Neurology*, 1994, 44:1,051-1,054.

Thiffault C, Langston JW, Di Monte DA. Increased striatal dopamine turnover following acute administration of rotenone to mice. *Brain Res*. 2000 Dec 8; 885(2):283–288.

Thiruchelvam M et al., Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? *Brain Res* 2000a Aug 11;873(2):225-34. (e-file)

Thiruchelvam M et al., The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. *J Neurosci* 2000b Dec 15; 20(24):9207-14. (e-file)

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. *Neurotoxicology*. 2002 Oct; 23(4-5):621-33.

Thiruchelvam M, McCormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, Cory-Slechta DA. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. *Eur J Neurosci*. 2003 Aug; 18(3):589-600.

Thiruchelvam M, Prokopenko O, Cory-Slechta DA, Richfield EK, Buckley B, Mirochnitchenko O. Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat + maneb-induced Parkinson disease phenotype. *J Biol Chem*. 2005 Jun 10; 280(23):22530-9. Epub 2005 Apr 11.

Thorn J, Beijer L, Jonsson T, et al., Measurement strategies for the determination of airborne bacterial endotoxin in sewage treatment plants. *Ann Occup Hyg*. 2002; 46:549–54.

Tillerson, J.L., Caudle, W.M., Reveron, M.E., and Miller, G.W. Exercise-induced recovery of behavioral and neurochemical deficits in rodent models of Parkinson's disease. *Neuroscience*, 119: 899-911, 2003.

Trojanowski JQ. Rotenone neurotoxicity: a new window on environmental causes of Parkinson's disease and related brain amyloidoses. *Exp Neurol*. 2003 Jan; 179(1):6-8. [No abstract available.]

Tsai CH, Lo SK, See LC, Chen HZ, Chen RS, Weng YH, Chang FC, Lu CS: Environmental risk factors of young onset Parkinson's disease: a case-control study. *Clin Neurol Neurosurg*. 2002 Sep; 104(4): 328-33.

Tsui, JK et al., Occupational risk factors in Parkinson's disease. *Canadian J of Pub. Health*, 1999, 90(5):334-337.

Tüchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993. *Scand J Work Environ Health*. 2000 Aug; 26(4):359–362. [[PubMed](#)]

Tukov, FF et al., Comparison of the acute neurochemical effects of repin with those of MPTP on C57BL/6N mice. *NeuroToxicology*, 2005,

Tukov FF; Rimoldi JM; Matthews JC: Characterization of the role of glutathione in repin-induced mitochondrial dysfunction, oxidative stress and dopaminergic neurotoxicity in rat pheochromocytoma (PC12) cells. *Neurotoxicology*, 2004, 25(6):989-999.

Uitti, RJ et al., Cyanide-induced Parkinsonism: a clinicopathologic report. *Neurology*, 1985, 35:921-925.

- Uitti RJ Regional metal concentrations in Parkinson's disease, other chronic neurological diseases, and control brains. *Can J Neurol Sci.* 1989a Aug;16(3):310-4.(e-file)
- Uitti, RJ et al., Parkinsonism induced by solvent abuse. *Ann. Neurol.* 1994, 35:616-619.
- US Environmental Protection Agency, Washington, DC. Chemicals Identified in Human Biological Media, EPA 560113-80-036B, PB81-161-176, 1980.]
- U.S. EPA Office of Pesticide Programs. 2002. FY 2002 Annual Report. Washington, DC:U.S. Environmental Protection Agency.
- Uversky, V.N. et al., Pesticides directly accelerate the rate of  $\alpha$ -synuclein fibril formation: a possible factor in Parkinson's disease. *FEBS Lett* (2001), 500:105–108.
- Uversky, V.N. et al., Synergistic effects of pesticide and metals on the fibrillation of  $\alpha$ -synuclein: implications for Parkinson's disease. *Neurotoxicology* 2002, 23:527–536.
- Uversky VN. Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration. *Cell Tissue Res.* 2004 Oct; 318(1):225-41. Epub 2004 Jul 16. Review.
- Vanacore, N et al., A possible association between exposure to n-hexane and Parkinsonism. *Italian Journal of Neurological Sciences* - 2000, 21(1):49-52.
- Vanacore N, Nappo A, Gentile M, Brustolin A, Palange S, Liberati A, Di Rezze S, Caldora G, Gasparini M, Benedetti F, Bonifati V, Forastiere F, Quercia A, Meco G. Evaluation of risk of Parkinson's disease in a cohort of licensed pesticide users. *Neurol Sci.* 2002 Sep; 23 Suppl 2:S119-20.
- Wang F-L et al., Reliability of environmental and occupational exposure data provided by surrogate respondents in a case-control study of Parkinson's disease. *J Clin Epidemiol* 1994; 47: 797-807.
- Waring, RH (Steventon) et al., S-Methylation in motoneuron disease and Parkinson's disease. *Lancet*, 1989, 356-357.
- Warrell DA: Clinical features of envenoming of snake bites. In Envenoming and their treatments. Edited by: Bon C, Goyffon M. Lyon, Fond. Marcel Merieux; 1996:63-76.
- Watanabe Y, Himeda T, Araki T. Mechanisms of MPTP toxicity and their implications for therapy of Parkinson's disease. *Med Sci Monit.* 2005 Jan; 11(1):RA17-23. Review.
- Wechsler-LS et al., A pilot study of occupational and environmental risk factors for Parkinson's disease. *Neurotoxicology*; VOL 12, ISS 3, 1991, P387-92. (e-file)
- Weiss, B. Behavioral toxicology and environmental health science. *Am. Psychologist*, 1983; 38:1.174-1.187. [No Abstract available on Medline]
- Weiss, B, Sherlita Amler, Robert W. Amler: Pesticides. *Pediatrics*, April 2004, 113 (4):1,030-1,036.
- Werneck A &, Alvarenga H: Genetics, drugs and environmental factors in Parkinson's disease. A case-control study. *Neuropsychiatr.* 1999 Jun; 57(2B): 347-55.
- Whiting, MG: Toxicity of cycads. *Econ. Bot.* 1963, 17:271-302.
- Widdowson PS, Farnworth MJ, Simpson MG, et al. Influence of age on the passage of paraquat through the blood-brain barrier in rats: a distribution and pathological examination. *Hum Exp Toxicol* 199a6; 15:231-236.

Widdowson PS, Farnworth MJ, Upton R, Simpson MG: No changes in behaviour, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. *Hum Exp Toxicol.* 1996b Jul; 15(7):583-91.

Wilk, JB et al., Herbicide exposure modifies GSTP1 haplotype association to Parkinson onset age. *Neurology* 2006; 67:2,206-2,210.

Williams RM: Health risks and environmental issues: Pesticide Neurotoxicity. *Townsend Letter for Doctors & Patients* July, 2002:30-32.

Wolfart J, Neuhoff H, Franz O, Roeper J. Differential expression of the small-conductance, calcium-activated potassium channel SK3 is critical for pacemaker control in dopaminergic midbrain neurons. *J Neurosci.* 2001 May 15; 21(10):3443-56.

Wong GF, Gray CS, Hassanein RS, et al: Environmental risk factors in siblings with Parkinson's disease. *Arch Neurol.* 1991, 48:287-289.

WHO - Environmental Health Criteria 140: Polychlorinated biphenyls and terphenyls (second edition). Geneva: World Health Organization, 1993.

WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002, Geneva Switzerland: World Health Organization; 2002.

Yilmazlar A, Ozyurt G. Brain involvement in organophosphate poisoning. *Environ Res.* 1997; 74:104-109.

Yumino, Kunio.; Kawakami, Ikuo.; Tamura, Mamoru.; Hayashi, Takaaki.; Nakamura, Masao. Paraquat- and diquat-induced oxygen radical generation and lipid peroxidation in rat brain microsomes. *J Biochem (Tokyo).* 2002 Apr; 131(4):565-570.

Zaidi NF et al., Effect of gestational and neonatal styrene exposure on dopamine receptors. *Neurobehav Toxicol Teratol.* 1985 Jan-Feb; 7(1):23-8. (e-file)

Zayed, J: Environmental factors in the etiology of Parkinson's disease. *Can. J. Neurol. Sci.* 1990, 17:286-291.

Zhang, Jing.; Fitsanakis, Vanessa A.; Gu, Guangyu.; Jing, Deqiang.; Ao, Mingfang.; Amarnath, Venkataraman.; Montine, Thomas J. Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. *J Neurochem.* 2003 Jan; 84(2):336-346.

Zheng W. Neurotoxicology of the brain barrier: new implications. *Clin Toxicol.* 2001; 30:711-719.

Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R: Familial and environmental risk factors in Parkinson's disease: a case-control study in north-east Italy. *Acta Neurol Scand.* 2002 Feb; 105(2): 77-82.