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9

Herbicides and the Risk of Neurodegenerative Disease

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1. Introduction

In the quest for increased agricultural productivity, longer shelf life of produce, weed-free lawns and sanitized facilities, we have developed a plethora of pesticides. Pesticides are a broad range of substances commonly used to control insects, weeds, and fungi (plant diseases). They are classified by target organism or mode of use as insecticides, herbicides, fungicides, or fumigants. Development, manufacturing and large scale application of these products have become main stream practices in industry, agriculture and domestic sectors. More than 18,000 products are registered for use in the United States, and > 1 billion pounds of pesticides are applied annually as of 2007 (EPA, 2011). Any chemical designed to kill weeds or insects certainly has potential to harm humans. Short term exposures to low dosages of these chemicals are generally non-toxic. Detoxification systems in the human body are capable of modifying and clearing these molecules from the system efficiently. However, long term exposure to these toxic chemicals combined with poor drug catabolizing cytochrome p450 activity in some individual could lead to its accumulation in the system and toxicity leading to increased risk of certain diseases. Many of the herbicides are toxic to mitochondria and cause oxidative stress. Neuronal cells, being critically dependent on mitochondrial function and sensitive to oxidative stress, often fall victim to these herbicides. Slow and progressive loss of neurons leads to neurodegenerative diseases. In this review we describe toxic effects, mechanism of action and results of animal studies of selected herbicides implicated in neurodegenerative diseases. We also discuss the need for stringent testing of these kinds of substances for neurotoxicity and recent advances in neuroprotective therapies as outlined in the overview before.

2. Specific herbicides with neurodegenerative effects

2.1 Paraquat

2.1.1 Background and history of use

Paraquat is the trade name of N,N′-dimethyl-4,4′-bipyridinium chloride, the dichloride salt of the radical 1,1′-dimethyl-4,4′-dipyridilium. It is one of the most commonly used and powerful herbicides and was synthesised in 1932 at the Rockefeller Institute by Michaelis

(Michaelis & Hill, 1933). In the early years it was called methyl viologen because it readily reduced to a stable blue or violet free radical and this property was exploited by biochemists who used the compound as an oxidation-reduction indicator. In 1955, the herbicidal properties of bipyridils were researched by Imperial Chemical Industries Ltd and the herbicidal nature of paraquat was established (Smith & Heath, 1976). In the year 1962, paraquat was introduced to the market as a herbicide by the Plant Protection Division of Imperial Chemical Industries Ltd, which is now known as Syngenta (www2.syngenta.com/en/about_syngenta/companyhistory.html). It is the third best-selling pesticide in the world (www2.syngenta.com), and is especially popular in the developing countries (Wesseling et al., 2001).

Paraquat is extensively used all over the world because it is non-selective, fast acting, and small quantities are sufficient to efficiently kill weeds, thereby reducing competition for light, water and nutrients. Through use of paraquat, fields can be quickly prepared for farming, and rain does not affect the action of the herbicide. Paraquat is used on over 100 crops in more than 120 countries across the world (Wessling et al., 2001).

2.1.2 Toxic effects and mechanism of action

Paraquat is a non-selective herbicide that requires oxygen and light energy for its action. In green plants, the light energy captured by chlorophyll is transferred as electrons through photosystem I. In the presence of the reduced form of paraquat, the electrons from the Fe-S centres of photosystem I are diverted and react with paraquat (Conning et al., 1969) to generate superoxide anion O_2^-. This in turn generates hydroxyl radicals either directly or via the intermediary hydrogen peroxide. These highly reactive radicals cause deterioration of the cell membrane leading to cellular breakdown (Matile & Moor, 1968). Browning of leaves is seen in a few hours in the presence of strong light and complete desiccation is observed in a few days. Fewer cases of resistance have been observed in comparison with resistance to herbicides with other modes of action.

Paraquat is extremely poisonous and use of the herbicide requires a licence in most countries. Use of paraquat has been banned in Finland, Austria, Sweden and Norway because of its high toxicity and frequency of poisonings (Wesseling et al., 2001). Paraquat manufactured by Syngenta, the leading producer of this herbicide, is blue in colour, has a sharp odour and contains an agent that causes vomiting, which helps prevent accidental consumption of the herbicide. Ingestion of a high dose of paraquat causes lung congestion, difficulty in breathing and an increase in heart rate. Cases of lung scarring have been reported when marijuana contaminated with paraquat was consumed. When the eyes come in contact with paraquat, it can cause corneal damage and scarring, while contact with skin leads to burns, damage to fingernails and dermatitis. Paraquat has been shown to be a mutagen to mouse, human and microorganisms; however there was no mutation observed in the sperm of male mice (Hazardous Substances Databank, 1995). There have been no adverse effects on reproduction or birth defects reported so far.

Paraquat toxicity depends on the amount, route and duration of exposure as well as the person's health at the time of exposure. Inhalation of paraquat can lead to acute respiratory distress syndrome whereas ingestion can cause direct damage to the lining of mouth or intestines. When ingested, it is distributed all over the body and toxic changes occur

primarily in the lungs, liver and kidneys (Wagner, 1981). In humans, the lethal dose for ingestion is 35 mg/Kg. Those suffering from respiratory infection are more susceptible to the toxic effects of paraquat. There is a high accumulation of paraquat in the lung tissue compared to other organs (Stevens & Sumner, 1991).

Paraquat is exceedingly toxic to aquatic species such as rainbow trout, bluegill and channel catfish. At high concentration, it is shown to inhibit photosynthesis in certain types of algae. It is not known to accumulate in tissue; however, it can bioaccumulate in weeds. Paraquat can be found in residual form bound to aquatic weeds and bottom mud (Weed Science Society of America, 1994).

The chronic effects of paraquat in humans are Parkinson's Disease (PD) and severe lung damage (Wagner, 1981). In order to understand the environmental factors that make one susceptible to PD, a study of 120 patients was carried out in Taiwan. The study included 240 controls that were selected based on age and sex. The interview comprised questions related to the history of exposure to environmental factors such as source of drinking water, probability of environmental or occupational exposure, and use of herbicides or pesticides or exposure to paraquat. The results showed that exposure to paraquat caused an increase in susceptibility to PD (Liou, 1997).

A study from California showed that consumption of well water contaminated with paraquat increased susceptibility to PD by 20-50%. Almost 91% of the study population was exposed to well water contaminated with paraquat (Gatto et al., 2009).

The predisposing factors for complex diseases such as PD are both genetic and non-genetic. Hence, it is necessary to study the joint effects of both these factors and in the case of genetic factors, the genes that are responsible for increasing the susceptibility to PD and the pathways these genes are involved in have to be identified. Out of the 1460 single nucleotide polymorphisms in the brain that have been identified in the axon guidance pathway, 183 (12.5%) have been shown to increase susceptibility to PD (Lesnick, 2007).

2.1.3 Development of animal models

In 1983, Langston reported irreversible Parkinsonism (Langston et al., 1983) in a group of young drug addicts who used synthetic heroin contaminated with 1-methyl-4 phenyl-1,2,3,6- tetrahydropyridine (MPTP). Since the contaminant caused symptoms of PD, monkey (Burns et al., 1983) and mouse (Heikkila et al., 1984) animal models of PD were developed by injecting sub lethal doses of MPTP. Animal models provide an opportunity to study the pathophysiology of PD and assist in development of successful treatment and prevention strategies. MPTP is metabolized into MPP+, which is structurally similar to paraquat. Since exposure to MPTP is minimal, but paraquat is a risk factor for PD, an animal model using paraquat is helpful for understanding the pathophysiology of PD.

Rat and mouse animal models have been developed to study the effect of exposure to paraquat, especially the neurotoxic effects. The toxic effect of paraquat on dopaminergic neurons is slow and this is reflected by the delayed and slow progression in the pathogenesis of PD. Both long and short term studies have been carried out on rats. Evans hooded rats showed loss of dopaminergic neurons in the substantia nigra region of the brain

when intraperitoneal injections of paraquat were given weekly for three weeks. The neurons of the substantia nigra pars compacta region of the brain, which are autonomic pacemakers, produce high levels of reactive oxygen species and free radicals due to the accumulation of intracellular calcium. This results in DNA damage and high levels of neurodegeneration in this region. The paraquat-induced loss of neurons was shown by comparing tyrosine hydroxylase immunohistochemistry in the substantia nigra of paraquat injected rats with the substantia nigra of saline injected control rats. Loss of approximately 70% of the neurons was observed in the paraquat injected rats. Though not many differences can be seen visually, behavioural assessment using rotorod showed measurable changes between the two groups. Biochemical assays have shown that paraquat induces oxidative stress, indicating its neurotoxic effects. The reduced form of paraquat has been shown to cause an increase in reactive oxygen species (ROS) which is selective to brain cells (Castello et al., 2007). Subtle behavioural differences were also observed in the test and control rats (Somayajulu- Nitu et al., 2009). When a similar dose was given as intraperitoneal injections to Wistar rats for 4, 6, 8, 12, and 24 weeks and immunohistochemistry studies performed, a loss of approximately 37% in the dopaminergic neurons was observed (Ossowska et al., 2005).

Dopaminergic neuron loss in the substantia nigra and intra-neuronal deposition of α-synuclein containing aggregates were also observed when C57BLJ/6 mice were injected intraperitoneally with paraquat (10mg/Kg body weight) weekly for three consecutive weeks (Manning-Bog et al., 2001). Similar studies have also been carried out with transgenic mice over-expressing α-synuclein and similar results have been obtained (Fernagut et al., 2007). The animal models help support the epidemiological link between paraquat used for agricultural purposes and PD. The C57BL/6 mouse strain has also been used for toxicology studies. When paraquat solution was applied to these mice through their nares, they showed lung pathology similar to those suffering from paraquat toxicity (Tomita et al., 2007).

2.2 Rotenone

2.2.1 Background and history of use

Rotenone is an insecticide and piscicide extracted from tropical leguminose. It was first isolated by Emmanual Geoffrey from the plant *Robinia nicou* while he was travelling in French Guiana. The details of the compound, which he called nicouline, were published posthumously in his thesis in 1895 after he died due to parasitic infection. However, rotenone has been used for many years by Africans and Asians to intoxicate fish and kill caterpillars.

Rotenone is now used in commercial gardens and is found in animal care products. It is marketed as an organic pesticide and piscicide and is available as dust, powder and spray formulations. The World Health Organisation has assigned rotenone as a moderately hazardous chemical; in Canada and USA, it is used only as a piscicide. It is also found in formulation with other pesticides such as carbaryl and lindane. It is manufactured by many companies and is available in 300 formulated products. It is effective against a large number of insect pests such as apple maggot, European corn borer, Pea aphid, Japanese beetle, Ladybird beetles, and predatory mites.

2.2.2 Toxic effects and mechanism of action

Complex I, which is present in the inner mitochondrial membrane, is the first enzyme of the electron transport chain. This enzyme is encoded by the mitochondrial genome, unlike the other enzymes which are encoded by the nuclear genome (Hatefi, 1985). Rotenone inhibits complex I of the respiratory chain, resulting in a decrease in energy production.

The toxicity of rotenone depends on the nature of the plant extract and the species from which it is extracted. It is mildly toxic to hamsters or mice, whereas it is highly toxic to rats, especially the females. For humans the toxic dose is 300-500 mg/Kg for adults and 143 mg/Kg for children. Human fatality due to rotenone has been reported very rarely because it causes immediate vomiting upon consumption. However, when the dust is inhaled it could lead to an increase in the rate of respiration followed by depression and convulsions (Uversky, 2004).

There have been no reports of endocrine disruption or teratogenic effects in humans. Studies on the carcinogenic effects of rotenone are still inconclusive. Studies on animal models of rotenone however show that it can produce symptoms of PD.

2.2.3 Development of animal models

Rotenone is involved in the pathogenesis of PD. Animal models of PD by exposure to various doses of rotenone for different durations have been developed to study the relationship between complex I and PD and also for preclinical testing of neuroprotective strategies. A number of genetic mouse models of PD are being developed; however, they fail to show the exact pathophysiology of PD. Hence, exposing the genetic mice to rotenone could help understand the link between genetic and environmental factors in the development of PD as well.

Sprague Dawley and Lewis rats were injected with varying doses of rotenone and it was shown that Lewis rats give more consistent results. A high dose of rotenone caused cardiovascular failure and non-specific brain lesions (Ferrante et al., 1997). However, a dose of 2-3 mg/Kg given for four weeks directly into the veins or subcutaneously resulted in PD-like symptoms. Rotenone was shown to act by inhibiting complex I, resulting in a decrease in the dopaminergic neurons in the substantia nigra region of the brain and also dopaminergic lesions (Hoglinger et al., 2005). The behavioural changes include unsteady movement and hunched posture. Severe rigidity was observed in some, whereas resting tremors were observed in others. Rotenone also caused loss of non- dopaminergic neurons in the basal ganglia and brainstem. The effect of rotenone was on neurons and not on oligodendrocytes, astrocytes or microglial cells. The drawback of the rotenone animal model is the variability in the effects of the same dose of rotenone, which clearly indicates the differences in the sensitivity of different strains of rat to the pesticide.

A group in Japan has shown that C57BL/6 mice, when orally fed with 30 mg/Kg of rotenone for 56 days, developed motor deficits, neurodegeneration of dopaminergic neurons and increases in the cytoplasmic accumulation of α- synuclein in the remaining dopaminergic neurons (Inden et al., 2011). Defects in complex I lead to a decrease in ATP synthesis which in turn induces mitochondrial depolarization and calcium deregulation. These factors cause an increase in the production of reactive oxygen species and hence

oxidative stress (Sohal & Weindruch, 1996). This, along with various genetic factors, results in the progression of neurodegenerative diseases. It has been shown that there is a 15-30% decrease in the activity of complex I in sporadic cases of PD (Betarbet et al., 2000). Rotenone, being lipophilic, crosses the cellular membranes and the blood brain barrier, becomes accumulated in the sub-cellular organelles such as mitochondria, inhibits complex I and impairs oxidative phosphorylation.

2.3 Maneb

2.3.1 Background and history of use

Maneb, a member of the ethylene bisdithiocarbamate (EBDC) group of fungicides, was first registered for use on both food and ornamental crops (EPA, 2005). These fungicides are used to protect crops in the field as well as to prevent them from deterioration during transportation and storage. The EBDC group includes mancozeb and metiram, and all three compounds degrade into ethylenethiourea (ETU). The EPA considers risk from ETU derived from maneb, mancozeb and metiram (EPA, 2005). In 1992 the EPA cancelled the use of EBDCs on a variety of fruits and vegetables. Despite these restrictions, approximately 2.5 million pounds of maneb are still used annually on fruit, vegetable and nut crops. There is no residential use and careful agricultural practices ensure that there is no risk of residential exposures to maneb. Lettuce, almonds, peppers and walnuts are the main crops treated with maneb, and the risks of exposure to this pesticide as of 2005 warranted its reduction or outright cancellation for use on certain crops (EPA, 2005).

2.3.2 Toxic effects and mechanism of action

Overall, maneb is considered only moderately toxic to humans (Occupational Health Services, 1991) and little is known about its mechanism of action. Maneb increased cellular glutathione in SH-SY5Y cells and produced no reactive oxygen species (Roede et al., 2011). Both maneb and its relative, mancozeb led to mitochondrial dysfunction and reduced ATP levels in rat mesencephalic cells (Domico et al., 2006). Maneb and mancozeb reduced active respiration linked to NADH (Domico et al., 2006) while manganese-EBDC (the major component of maneb) appeared to specifically inhibit mitochondrial complex III (Zhang et al., 2003). Interestingly, while maneb and mancozeb were both toxic to mesencephalic neurons, their metabolite ETU was not (Domico et al., 2006), indicating that in terms of neurotoxicity, it is the primary components of the EBDC pesticides that are most toxic to neurons, and not their product. Interestingly, the mitochondrial dysfunction caused by maneb led to a reduction in ATP, which has a subsequent impact on the functioning of the ubiquitin-proteasome system. This system is involved in the intracellular degradation of proteins, the failure of which leads to the collection of protein aggregates and is associated with PD (McNaught et al., 2001). Manganese-EBDC was neurotoxic and led to reduced proteasome activity in a dopaminergic neuronal cell line (Zhou et al., 2004), which led to cytoplasmic inclusions containing α-synuclein, a hallmark of PD. Dopaminergic cells exhibited increased oxidative stress and neurotoxicity in response to manganese-EBDC. Increasing antioxidant levels via acetylcystein increased cell viability and eliminated the manganese-EBDC-induced increase in oxidative stress (Zhou et al., 2004).

Maneb has the interesting ability to potentiate the toxicity of other chemicals. Behaviorally, maneb intensified motor deficits experienced by mice treated with MPTP (Takahashi et al., 1989; Thiruchelvam et al., 2000b). The herbicide paraquat has a chemical structure very similar to that of MPP^+, the active metabolite of MPTP. Thus, paraquat and maneb have been investigated for their combined ability to cause parkinsonian symptoms (Liou et al., 1997; Thiruchelvam et al., 2000a, 2000b). In a Taiwanese case study, PD risk was increased in those exposed to both paraquat and maneb (Liou et al., 1997). Exposure to this combination consistently led to significant changes in the nigrostriatal system (Thiruchelvam et al., 2000a, 2000b). In the presence of manganese-EBDC, striatal synaptosomes accumulated significantly more dopamine (Barlow et al., 2003). Toxicokinetic studies showed that manganese-EBDC given concurrently with paraquat led to more paraquat uptake by the brain than by other organs, indicating that the neurotoxicity of paraquat may be enhanced via maneb by directing more paraquat to be sequestered in the brain (Barlow et al., 2003).

It seems that exposure to both pesticides changes the mechanism of toxicity, at least as one study has shown. When tested independently, both paraquat and maneb triggered neuronal apoptosis via Bak, a pro-apoptotic member of the Bcl-2 gene family; however, when maneb and paraquat were tested together, Bak was inhibited and apoptosis was induced by the Bcl-2 member Bax (Fei & Ethell, 2008).

2.3.3 Development of animal models

Though there is evidence suggesting that exposure to the herbicide paraquat can contribute to PD, this model fails to take into account the overlap of areas exposed to other agrichemicals in addition to paraquat. This has led to the development of a mouse model of neurodegenerative disease using both maneb and paraquat to simulate exposure to both of these pesticides. In this model, male C57BL/6 mice (6 weeks old) were injected intraperitoneally with paraquat alone, maneb alone, or both paraquat and maneb (Thiruchelvam et al., 2000a, 2000b). The number of injections ranged from 4 (1 injection per week for 4 weeks; Thiruchelvam et al., 2000a) to 18 (2x per week for 9 weeks; Thiruchelvam et al., 2005). Essentially, the combined treatment with maneb and paraquat led to exacerbated effects on behavior, the dopaminergic system and the nigrostriatal system. Animals exhibited reduced locomotion, altered levels of dopamine and its metabolites, reduced dopamine transporter density and reduced number of dopaminergic neurons in the substantia nigra and striatum (Thiruchelvam et al., 2000a, 2000b). Unlike some other PD animal models, the maneb + paraquat model consistently induces a phenotype with impairments to both the motor system and nigrostriatal system.

The model has also been tested in a developmental context, where the mice were injected daily during post-natal days 5 – 19, and re-challenged with pesticide injection at 6.5 months of age to determine how early exposure may effect subsequent exposure (Thiruchelvam et al., 2002). Overall, the authors found that exposing mice at a young age to paraquat and maneb made them more susceptible to pesticides as adults, as only those exposed post-natally experienced toxic effects to all three treatments as adults (e.g. paraquat, maneb, and paraquat + maneb). Additionally, mice exposed to the two pesticides early in development showed more deficits than mice exposed to single pesticides (Thiruchelvam et al., 2002). It appears as though the maneb + paraquat model has no benefit over paraquat alone in rats (Cicchetti et al., 2005; Xu et al., 2011).

The combined paraquat and maneb system has been useful for investigating different neuroprotective or therapeutic agents, which may be helpful for people suffering from PD. Pre-treatment with lithium in the animal's food was able to eliminate α-synuclein protein aggregation and was neuroprotective against paraquat + maneb treatment of α-synuclein overexpressing transgenic mice (Kim et al., 2011). Similar neuroprotective effects were seen when mice exposed to maneb + paraquat were first treated with the naturally-occurring antioxidant silymarin or melatonin. Both silymarin and melatonin ameliorated the motor deficits induced by paraquat + maneb treatment such that these animals performed as well as control animals (Singhal et al., 2011). This striking effect may have been a consequence of silymarin's and melatonin's neuroprotective natures, as mice given one or the other prior to treatment with paraquat + maneb showed no significant loss of dopaminergic neurons in the substantia nigra (Singhal et al., 2011). Caffeine was also neuroprotective in the model, though the authors did not evaluate locomotor activity (Kachroo et al., 2010). Extract from the *Polygonum multiflorum* (PM) plant has also shown to be protective in this model. This herb has a long history in traditional Chinese medicine, and when given prior to and during exposure to maneb + paraquat, it was able to ameliorate the pesticide-induced motor deficits, reduction in striatal dopamine concentration and dopaminergic cell death (Li et al., 2005).

2.4 Endosulfan

2.4.1 Background and history of use

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzadioxathiepin 3-oxide) is a broad-spectrum organochlorine contact insecticide registered for use on fruits, vegetables, cereal grains, cotton and ornamental trees and shrubs. Endosulfan was first patented in 1956 and its use is an estimated 1.38 million pounds of active ingredient on average from 1987 – 1997 (EPA, 2002).

Endosulfan has established toxic effects, is persistent in the environment and has the ability to bioaccumulate (Chopra et al., 2011). Endosulfan is being phased out of use in many countries including the United States (EPA, 2010) and Canada (Health Canada, 2011). At the 5th meeting of the Conference of the Parties to the Stockholm Convention in 2011, endosulfan was banned globally. Strong opposition to this ban initially came from India, which uses and exports more endosulfan than any other country, with an estimated 113 kilotons used from 1958 – 2000 (Government of Canada, 2009). After a few concessions, India eventually agreed to the ban. The case of endosulfan use in India has a long and sordid history. Endosulfan has been applied to cashew crops via aerial spraying for over two decades. For years, residents of several villages in the Kasargod district of Kerala state had noticed increased illness and the death of animals, both wild and domestic, which seemed to coincide with the spraying (Adithya, 2009). Concerns of the villagers and doctors over the high rates of disease – including neurological disease, reproductive impairment, developmental problems and cancer – went largely unheard. Between 1998 and 2002, several groups, both national and international, conducted studies and concluded that endosulfan poisoning was responsible for the problems in Kasargod (Adithya, 2009; Quijano, 2002; Sivaraman et al., 2003). Doctors are now reporting a reduction in new cases since endosulfan was banned in Kerala in 2003 (Adithya, 2009).

2.4.2 Toxic effects and mechanism of action

Endosulfan is in the same general class of pesticides as DDT, the organochlorine pesticides. The very mechanism of action of these pesticides – which is neurotoxicity – makes them toxic to all animals, not just the insect pests that they target. They cause disruptions to the neuronal membrane which in turn lead to altered sodium and potassium kinetics (Hays & Laws, 1991). The result means that the sodium channel is not inactivated as normal, leading to a prolonged action potential (Hong et al., 1986; Soderlund & Bloomquist, 1989). This is proposed to be the mechanism leading to seizures seen in endosulfan poisoning (e.g. Pradhan et al., 1997). Additionally, endosulfan and related compounds are antagonists of the chloride channel linked to the receptor for gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, leading to over-excitation of neurons (Cole & Casida, 1986; Klaassen, 1996).

There have been several recorded cases of acute accidental and non-accidental endosulfan poisoning in humans. In these cases, nearly all victims presented with seizure or convulsions, along with nausea and vomiting (Boereboom et al., 1998; Chugh et al., 1998; Karatas et al., 2006; Pradhan et al., 1997). In the case of 23 accidental poisonings (Karatas et al., 2006), all 23 people survived the insult. In one case of non-accidental poisoning, the patient died four days following exposure, the cause of death being cerebral edema (Boereboom et al., 1998). In a second case of non-accidental ingestion, the patient survived and appeared to be back to normal at a 3 month follow up (Pradhan et al., 1997). In a retrospective study of 52 cases of endosulfan intoxication, ingestion of the pesticide in excess of 35 g was the variable most likely to predict mortality (Moon & Chun, 2009).

A variety of *in vivo* studies have demonstrated the effects of endosulfan on the central nervous system. Rats treated orally with endosulfan showed behavioral deficits such as an increased time to learn and retain a task in an operant learning paradigm (Lakshmana & Raju, 1994), which may be related to alterations in neurotransmitter levels (Ansari et al., 1987, Lakshmana & Raju, 1994). Increased serotonin levels following endosulfan were thought to lead to a motivational deficit in rats, since the animals showed problems with memory tasks but not motor tasks (Paul et al., 1994). Reduced GABA levels were detected in the offspring of female rats fed endosulfan during pregnancy (Cabaleiro et al., 2008), and neonatal exposure also led to an increase in shock-induced aggression (Zaidi et al., 1985). Male mice injected with endosulfan as juveniles and subsequently challenged as adults showed reduced concentrations of dopamine and its metabolite DOPAC in brain samples (Jia & Misra, 2007).

There is a wealth of literature investigating the effects of endosulfan on the GABAergic system, and the ability of endosulfan to cause increased excitation in neurons is indicative of its neurotoxic nature. Fewer studies have directly investigated the toxic effects on neurons, either in culture or *in vivo*. The EPA's Federal Insecticide, Fungicide and Rodenticide Act guideline neurotoxicity studies failed to find overt signs of neuropathy associated with endosulfan treatment of rats (Silva & Gammon, 2009). In rats, endosulfan led to engorged blood vessels in the meninges and cerebral hemorrhages (Singh et al., 2007). Endosulfan-treated rats were shown to have increased lipid peroxidation in cerebral tissue, a sign of damaging oxidative stress (Hincal et al., 1995). *In vitro* studies have shown that endosulfan inhibited proliferation and differentiation of neural stem cells while also inhibiting neurite formation (Kang et al., 2001). Additionally, PC 12 cells

incubated with endosulfan were reduced in number, had unusual morphology and exhibited increased apoptosis (Yang et al., 2004). Although studies directly showing the ability of endosulfan to kill neurons are lacking, what is clearly known is that endosulfan interferes with the GABAergic system, causing over-excitation due to lack of GABA receptor-mediated inhibition. It is known that indirect excitotoxicity of this type leads to cell death in some pathologies, such as brain damage associated with chronic alcoholism (Dodd, 2002).

2.4.3 Development of animal models

In the case of endosulfan, animal models have been restricted to establishing the typical toxicological endpoints such as LD_{50} levels. It is clear that endosulfan has a toxic effect on the brain, but there is no clearly established animal model developed in order to evaluate its role specifically in neurodegenerative disease. In fact, there are relatively few *in vitro* studies showing that endosulfan is capable of killing neurons. Given the global ban on endosulfan, the establishment of an animal model for continued neurotoxicity testing seems somewhat unnecessary, except for studying the long-term effects of endosulfan exposure, as exposed populations still exist. Given the number and variety of pesticides that human populations are exposed to regularly, it seems unlikely that a banned substance will continue to be researched in the way that endosulfan has in the past.

2.5 Atrazine

2.5.1 Background and history of use

Atrazine (6-chloro-N^2-eyhyl-N^4-isopropyl-1,3,5-triazine-2,4-diamine) is one of the most heavily used herbicides in the United States, with an estimated use of 76.5 million pounds per year (EPA, 2003). Atrazine was first registered for use as an herbicide by JR Geigy SA (currently known as Syngenta) in 1958, and is widely employed in the control of broadleaf plants (EPA, 2003; Gammon et al., 2005). Measures were taken in the 1990s to reduce the amount of atrazine contamination in surface and groundwater, including the establishment of a Maximum Contaminant Level of 3 parts per billion for atrazine (EPA, 2003). Despite established usage limits, data show that the overall use of atrazine has changed very little since the late 1980s (Kiely et al., 2004). Approximately 80 million pounds of atrazine are applied annually (Kiely et al., 2004), with particularly heavy usage on corn, sorghum and sugarcane. In fact, atrazine is the main pesticide used on these three crops, and treatment with atrazine amounts to 75% of all American corn, 58.5% of all sorghum and 76% of all sugarcane (EPA, 2003). In addition to its pervasive use in agriculture, atrazine is also used in residential settings and on golf courses, adding to the potential for human exposure, though data on these routes of exposure are lacking. Oral exposure through food consumption of atrazine is very low (Ribaudo & Bouzaher, 1994), but the chemical properties of atrazine mean that it enters surface and groundwater through leaching and runoff (Ribaudo & Bouzaher, 1994). Exposure through drinking water is the most likely route of exposure for the majority of the American population, except for occupational exposure experienced by atrazine applicators and farmers and their families, who are at an increased risk of exposure (Curwin et al., 2007). A complete European ban on atrazine came into effect between 2005 - 2007 (Ackerman, 2007). Given the estimated economic impacts of banning atrazine in the United States, it is unlikely that total or even partial bans on its use are forthcoming

(Ribaudo & Bouzaher, 1994). Whether or not these estimated impacts are realistic is another question (Ackerman, 2007), and the use of atrazine in the United States remains a contentious issue.

2.5.2 Toxic effects and mechanism of action

Atrazine functions as an herbicide by inhibiting photosynthesis in the target plant. Specifically, atrazine prevents electron transfer at complex II in the chloroplast (Gysin & Knuesli, 1960). Thus, the mechanism of toxicity is similar to the mechanism whereby dopaminergic neurons are killed in the paraquat model of PD (Franco et al., 2010).

The possible neurotoxic effects of atrazine are much less researched than the endocrine effects, which have received much attention. Despite the lower number of studies, there is evidence that atrazine is neurotoxic. Atrazine administered orally is capable of crossing the blood-brain barrier and could be measured in brain tissue, along with didealkyl atrazine, its major metabolite (Ross et al., 2009). A small body of literature has examined the neurotoxic effects of atrazine in both *in vitro* and *in vivo* studies. Many of these studies show damage which is similar to that seen in neurodegenerative diseases such as PD. *In vivo*, both chronic and acute exposures to atrazine affect brain monoamine systems with associated changes to behavior. Behavioral effects vary, however, such that dietary atrazine treatment led to hyperactivity after 6 months of treatment (Rodríguez et al., 2005), or hypoactivity after 8 months of treatment (Bardullas et al., 2011). Different strains used (Long-Evans versus Sprague-Dawley) might account for these results, or the fact that testing continued throughout the year, which might have affected activity levels overall (Bardullas et al., 2011). Atrazine treatment also impaired performance in learning tasks (Bardullas et al., 2011).

The *in vivo* chronic treatment of rats with atrazine also leads to alterations in brain neurotransmitter levels. After 6 or 12 months of atrazine, dopamine levels were reduced in the striatum (Bardullas et al., 2011; Rodriguez et al., 2005), and norepinephrine levels were reduced in the prefrontal cortex (Rodriguez et al., 2005). In fact, dopamine and its metabolites were reduced in the murine striatum after as few as 14 days of atrazine exposure (Coban & Filipov, 2007). After 6 months, serotonin was reduced in the hypothalamus (Rodriguez et al., 2005), and in the striatum after 14 days (Coban & Filipov, 2007), while reduced serotonin was not seen after 12 months in a separate experiment (Bardullas et al., 2011). Atrazine treatment reduced numbers of tyrosine hydroxylase immunoreactive neurons in the substantia nigra pars compacta and the ventral tegmental area (Coban & Filipov, 2007; Rodriguez et al., 2005), indicating that it is neurotoxic to dopaminergic neurons. Atrazine also caused general neurodegeneration in the hippocampus of the female mouse (Giusi et al., 2006). *In vivo* microdialysis experiments further showed that dopamine release in the striatum is reduced as a consequence of an acute exposure to atrazine (Rodríguez et al., 2005).

In vitro studies show that exposure to atrazine disrupts the dopaminergic system. Studies using striatal slices showed that atrazine treatment lowered the level of dopamine released in the striatum, but it did not affect the level of the rate-limiting enzyme tyrosine hydroxylase. There is an indication that the reduction in dopamine could be associated with a decrease in dopamine-producing neurons in the substantia nigra (Filipov et al., 2007).

Additionally, the uptake and sequestration of dopamine into vesicles appeared impaired and perhaps as a consequence of this, the ratio of dopamine metabolites/dopamine increased (Filipov et al., 2007; Hossain & Filipov, 2008). PC12 cells are neuronal cells derived from a tumour of the rat adrenal medulla that produce catecholamines including dopamine. Intracellular dopamine concentration was reduced in undifferentiated PC12 cells treated with atrazine, and the relationship was dose-dependent, while tyrosine hydroxylase levels, though slightly reduced, were not significantly effected (Das et al., 2000; Das et al., 2003). Intracellular norepinephrine was decreased and the cells exhibited reduced norepinephrine release and reduced dopamine β-hydroxylase, the enzyme which converts dopamine to norepinephrine (Das et al., 2000; Das et al., 2003). Moreover, atrazine metabolites produced unique and varying effects on dopamine and norepinephrine release in PC12 cells, with certain metabolites increasing levels of dopamine and/or norepinephrine, and other decreasing catecholamine levels (Das et al., 2001).

2.5.3 Development of animal models

Unlike other herbicides, a standard model for testing the neurodegenerative effects of atrazine has not been established. The chemical has been tested on rats and mice *in vivo*, but the protocols vary in terms of route of administration, dose, time, animal strain and endpoint. Before atrazine can be firmly established as a confirmed neurotoxicant, these parameters need to be standardized. A lack of standardization across studies may help to account for differences seen in results, and though these studies point to atrazine as being a toxic agent, the link remains tenuous. Behavioral endpoints need to be established to help further demonstrate the detrimental effects of atrazine. It has been demonstrated in cell culture and brain slice preparations that atrazine negatively impacts the catecholaminergic system, but the long-term ramifications of this toxicity are not clear, and need to be known in order to say with more confidence that atrazine is linked to neurodegenerative disease.

2.6 Aldrin/dieldrin

2.6.1 Background and history of use

Aldrin is an organochlorine insecticide which breaks down into dieldrin. It is a PBT chemical, meaning that it is persistent, bioaccumulative and toxic. Aldrin was widely used in the United States to control insect infestations on corn, cotton and citrus until it was completely banned for agricultural use in 1985 amid health concerns (EPA Persistent Bioaccumulative and Toxic (PBT) Chemical Program, 2011). However, given its persistent nature, aldrin is still found in the environment where humans and animals may still be at risk of exposure. Since the majority of the literature concerns specifically dieldrin, it is dieldrin that will primarily be covered here.

2.6.2 Toxic effects and mechanism of action

As an organochlorine insecticide, dieldrin is similar in action to endosulfan. It kills insects via the same mechanism as endosulfan, by inhibiting GABA receptors and causing neuronal over-excitation (e.g. Ikeda et al., 1998). Dieldrin is neurotoxic, particularly to dopaminergic cells (reviewed by Kanthasamy et al., 2005). Dieldrin produced time- and dose-dependent

increases in neurotoxicity in both GABAergic and dopaminergic cells in mesencephalic cell culture, but the effect was more pronounced in the dopaminergic neurons (Sanchez-Ramos et al., 1998). Moreover, dieldrin was toxic to dopaminergic PC12 cells at lower doses than it was to both pancreatic endocrine cells and human cortical neurons (Kitazawa et al., 2001). Dieldrin may be toxic to dopaminergic neurons by producing reactive oxygen species (ROS). Treatment of dopaminergic SN4741 cells with dieldrin lead to a slow increase in ROS production, particularly H_2O_2, which eventually led to apoptosis (Chun et al., 2001). ROS combines with nitric oxide, producing reactive nitrogen species which affect the respiratory chain of the mitochondria resulting in a decrease in ATP synthesis and increase in lipid peroxidation (Ebadi & Sharma, 2003). These changes in the membrane properties affect cellular homeostasis leading to dysfunction of the mitochondria and neurotoxicity.

In addition to killing dopaminergic neurons, dieldrin may also cause dopamine dysfunction. While Thiffault and colleagues (2001) found that treating mice with a single injection of dieldrin was insufficient to cause any reduction in dopamine or its metabolites in the striatum, long term exposures have the potential to severely alter normal brain chemistry. Mice exposed for 30 days showed decreases in dopamine metabolite levels, as well as decreases is dopamine transporter expression in the striatum (Hatcher et al., 2007). Developmental exposure to dieldrin appears to be detrimental as well, as female mice exposed to low diedrin levels had offspring that were predisposed to increased toxicity from other agents (Richardson et al., 2006). Additionally, at 12 weeks of age, mice exposed *in utero* showed dose-dependent increases in dopamine transporter and vesicular monoamine transporter 2 mRNA levels, indicative of dopamine dysfunction, and opposite to what was seen with post-natal exposures.

Dieldrin produces contrary effects on dopamine efflux in PC12 cells. Extracellular dopamine was increased while intracellular levels were decreased when dopamine content was measured via HPLC (Kitazawa et al., 2001). When measured in PC12 cells loaded with radionuclide-labeled dopamine, dopamine efflux was found to be inhibited in the presence of dieldrin (Alyea & Watson, 2009). Time course and other methodological differences could account for these contradictory results.

2.6.3 Development of animal models

As is the case with several of the pesticides mentioned above, there has been little progress in terms of the formal development of an animal model for investigating the neurotoxic effects of dieldrin. Although dieldrin has often been administered directly to mice (Hatcher et al., 2007; Richardson et al., 2006; Thiffault et al., 2001) these studies have used varying treatment parameters, meaning that often conflicting results must be evaluated carefully. The ban on dieldrin also means that there is less interest in fully establishing its status as a factor in neurodegeneration, and it is unlikely to see further development as a model of PD. However, dieldrin still persists in the environment, making low-dose chronic exposure studies all the more important. Organochlorines appear to be particularly high risk factors for the development of neurodegenerative disease (Seidler et al., 1996) and the toxicity of dieldrin, endosulfan and DDT are not in dispute. The development of a standardized animal model for testing dieldrin will not only help to further identify its particular neurotoxicity, but may also help contribute to our overall understanding of how the organochlorines may contribute to PD development.

3. Evidence for a correlation of herbicide exposure and neurodegenerative disease

Animal models of pesticide contribution to neurodegenerative disease are largely focussed on the development of Parkinson's disease. These have been discussed in the above section. For the purpose of reviewing additional evidence for correlation of pesticide exposure and the development of neurodegenerative disease, this section will discuss the human epidemiological evidence. This section will further be divided into reviews of the neurodegenerative diseases most often associated with pesticide exposure: Parkinson's disease, Alzheimer's disease and Amyotrophic lateral sclerosis.

3.1 Parkinson's disease (PD)

Interest in the association of PD and pesticide exposure by sparked with the observation nearly 30 years ago that exposure to the chemical MPTP caused PD symptoms (Langston et al., 1983). MPP+, the toxic metabolite of MPTP which is structurally similar to paraquat, is selectively uptaken by dopaminergic neurons. Recently, the epidemiology of PD has been extensively reviewed, including thorough reviews of the association between PD and pesticides (Brown et al., 2006; Wirdefeldt et al., 2011). The epidemiological data for pesticide exposure and PD are extensive, and the following review is not meant to be exhaustive.

In examining the case-controlled literature, Wirdefeldt and colleagues found that there were 38 published case-control studies looking at pesticide exposure and incidence of PD. Of these, exactly half found a positive association, and half found no association (Wirdefeldt et al., 2011). When 31 of the studies were presented in a forest plot, it was clear that although half of the 38 case-controlled studies found no significant association, most of the studies still report increased risk for the case group (Brown et al., 2006). When these studies were further broken down into those which attempted to examine the effects of different types of pesticides (herbicides, fungicides, insecticides and organochlorines), herbicide exposure was positively associated with PD, as was insecticide exposure (Brown et al., 2006). In one study, after controlling for additional pesticide exposure, herbicide exposure was still a significant independent risk factor for PD (Semchuk et al., 1992). Paraquat exposure specifically presented a significant risk (Hertzman et al., 1990; Liou et al., 1997), and risk was increased, though non-significantly, in other studies (Firestone et al., 2005; Hertzman et al., 1994). Overall, this indicated that there is a link between Paraquat exposure and the incidence of PD. In a meta-analysis of 19 studies, the authors calculated a combined odds ratio for PD risk of 1.94, indicating a positive association (Priyadarshi et al., 2000).

There appear to be several factors influencing the possibly that an individual will develop PD as a consequence of exposure to agrichemicals. Studies indicate that there may be a critical period of exposure, as greater risk was associated with exposure at specific age periods (Semchuk et al., 1992). Perhaps exposure duration is a more important factor, as several studies indicate that risk increases with an increasing duration of exposure, particularly in excess of 10 or 20 years (Gorell et al., 1998; Liou et al., 1997; Seidler et al., 1996). As with some other toxins, the danger may be in the dose, as there was a greater association seen with high doses compared to low doses (Nelson et al., 2000, as cited in Brown et al., 2006) although trying to determine dose in case-controlled studies is often

tricky and imprecise, and in other cases, the relationship between dose and risk may even be reversed (Kuopio et al., 1999). Most likely, it is a combination of long duration and high dose that has a greater effect on risk (Nelson et al., 2000, as cited in Brown et al., 2006; Seidler et al., 1996).

PD risk is also associated with different – but related – environmental factors such as rural living, farming and drinking well water. Studies have shown higher occurrence of PD in rural versus urban areas in Canada (Barbeau et al., 1987), the United States (Lee et al., 2002), and Denmark (Tuchsen et al., 2000). Drinking well water is a risk factor for PD (Tsai et al., 2002); however, this tends to be dependent on rural living, so the two factors are interrelated (Koller et al., 1990). If farming is a legitimate risk factor for PD, it is difficult to detect in case-control studies. Wirdefeldt and colleagues (2011) report that of 34 case-control studies that considered farming and PD prevalence, there was significantly increased risk in only 7 studies. A meta-analysis published by Priyadarshi and colleagues (2001) found an association with farming in the United States (including exposure to farm animals or living on a farm). The meta-analysis is of interest because the authors calculated odds ratios based on all the existing published data, rather than just grouping the studies together based on whether or not the original authors found a significant association.

Several confounding factors need to be addressed in these studies. For example, smoking is negatively correlated with PD incidence, but very few case-control studies have corrected for smoking. Defining pesticide exposure is challenging, and considering this, it is not surprising that few studies manage to find a significant association. Exposure assessment largely relies on the ability of the patient to recall their exposure based on general questions, and often these questions aren't given in the published study. Exposure is often defined in a dichotomous way. Where exposures are residential or non-occupational, patient recall may be unreliable. Clearly there needs to be a more reliable and objective way of establishing pesticide exposure. Specific biomarkers could be used, or tissue samples could be analyzed for pesticide concentrations. For example, higher levels of dieldrin (Corrigan et al., 1998) and lindane (Corrigan et al., 2000) were detected in brain samples taken from PD patients post-mortem. Increasing plasma dieldrin levels were also associated with PD in never smokers (Weisskopf et al., 2010). For a persistent organic pollutant such as dieldrin, this is simple enough, but it may be troublesome for pesticides which break down more rapidly, or do not accumulate.

All of us are exposed to pesticides and environmental toxins on a regular basis and the incidence of PD does not seem to reflect this fact. Humans have evolved biological mechanisms for the detoxification and metabolism of xenobiotics, and it is feasible that perturbations in these mechanisms could help determine whether or not an individual develops a neurodegenerative disease in response to pesticides. Individuals with mutations in the CYP2D6 gene – which is responsible for metabolizing environmental toxicants – may lack sufficient means to remove toxins before they contribute to neurodegeneration. These individuals have been termed "poor metabolizers" and show undetectable CYP2D6 activity (reviewed by Elbaz et al., 2007). There appears to be a strong association between CYP2D6 dysfunction and PD occurrence.

Overall, the evidence suggests an association between pesticide exposure and PD risk. Brown and colleagues (2006) demonstrated that this may be particularly true for herbicide

exposure. Future epidemiological studies need to include certain methodological considerations, chiefly exposure assessment in non-occupational situations. Additionally, studies need to accurately assess additional factors such as smoking and control for these factors in statistical analyses.

3.2 Alzheimer's disease (AD)

There is little evidence for the role of pesticide exposure in the development of AD, the most common type of dementia. As with PD, rural living is associated with higher incidence rates of AD in countries including Italy (Rocca et al., 1990) and Finland (Sulkava et al., 1988). A recent study conducted in the Andalusia region of Spain found that there was a greater risk of developing AD in districts with high pesticide use (Parrón et al., 2011).

There are two case studies in the literature which describe individuals aged 55 (Cannas et al., 1992) and 59 (Lake et al., 2004) diagnosed with AD who experienced long-term occupational pesticide exposure. These case studies offer little evidence that chronic pesticide exposure can lead to AD, but occupational exposure is a legitimate risk factor. A study investigating neurodegenerative disease incidence in different occupations found increased AD (and PD) in non-horticultural farmers below the age of 65 (Park et al., 2005). In a cohort study of the elderly in France, occupational exposure to pesticides decreased cognitive performance and increased risk of developing both AD and PD in men (Baldi et al., 2003). A study of the residents of an agricultural community in Utah found increased risk of AD and dementia among those exposed to pesticides, with organophosphate pesticides being identified as particularly dangerous (Hayden et al., 2010), while a case-control study conducted in Quebec, Canada found no significant risk of AD with exposure (Gauthier et al., 2001). However, an analysis of the Canadian Study of Health and Aging looking at 258 cases of clinically diagnosed AD found a positive association with pesticides (Canadian Study on Heath and Aging Working Group, 1994). Compared to PD, there is more consensus that pesticide exposure increases risk of AD. Although there have been very few studies, most have found a significant association.

3.3 Amyotrophic lateral sclerosis (ALS)

ALS is a motor neuron disease caused by the degeneration of neurons in the brain and spinal cord. As with AD, there is little scientific literature on the correlation between pesticides and development of ALS, although from what little data are available, there does appear to be a relationship. Of 6 identified epidemiological studies that included pesticide risk of ALS, 5 of these found a significant association. Most recently, in a case-control study of ALS in northern Italy, Bonvicini and colleagues (2010) found that compared to age- and sex-matched controls, more ALS cases had experienced occupational pesticide exposure in excess of 6 months. There was an increased risk of ALS among employees of the Dow Chemical Company who were exposed to the herbicide 2,4-dichlorophenoxyacetic acid versus other Dow employees (Burns et al., 2001). Similar studies have found positive associations for populations exposed to pesticides (McGuire et al., 1997; Qureshi et al., 2006), and the relationship was found to be dependent on dose (Morahan & Pamphlett, 2006). Overall, the relationship tends to be stronger for males than females (McGuire et al., 1997; Morahan & Pamphlett, 2006). In one study using participants in the American Cancer

Society's Cancer Prevention Study II, no association between pesticide exposure and ALS was detected (Weisskopf et al., 2009).

Although epidemiological studies are lacking, there are other hypotheses regarding how pesticide exposures may contribute to ALS. Evidence suggests that certain individuals are genetically susceptible to ALS due to mutations in specific genes which are involved in the handling and detoxification of xenobiotics. The paraoxonase enzymes are responsible for detoxifying organophosphates and are coded for by the genes PON1-3. These genes have been implicated in the development of ALS through pesticide exposure. When investigating PON polymorphisms in a control population versus a population exposed to organophosphates, Sirivarasai and colleagues (2007) found that the exposed group exhibited three polymorphisms in PON1 that were not observed in the control group. The exposed group also had reduced enzyme levels (Sirivarasai et al., 2007). A number of studies have found polymorphisms in the PON locus to be positively associated with ALS (Cronin et al., 2007; Landers et al., 2008; Saeed et al., 2006; Slowik et al., 2006; Valdmanis et al., 2008). However, the data are far from conclusive, and a recent meta-analysis failed to find a significant association between ALS and PON (Wills et al., 2009).

In conclusion, given the evidence presented above, occupational exposure to pesticides appears to present a significant risk for developing various neurodegenerative diseases. Certain allelic mutations may pre-dispose individual to increased toxicity from pesticides if they lack sufficient detoxification mechanisms. Case-control studies have proven useful for establishing links between exposure and disease development, but certain methodological considerations must be addressed. Studies must control for certain confounding factors such a smoking, and pesticide exposure assessment should be standardized and refined.

4. Recent advances in the development of neuroprotective agents

Neurons are post-mitotic, that is they do not undergo cell division. Hence, populations of neurons that have been killed cannot be easily replaced by surviving cells. These cells are also more susceptable to oxidative stress in comparison to other cell types. Morevoer, there is an increase in oxidative stress and hence oxidative damage with age. In PD, the patient remains asymptomatic until 50% of the neurons in the substantia nigra are lost. No drug designed so far can prevent neurodegeneration and halt the progression of the disease. The primary treatment available for PD is administration of dopamine agonists which inhibit dopamine degradation and provide temporary symptomatic relief (Obeso et al., 2000). The use of antioxidants such as Vitamin E has failed for PD, though it has shown more positive results for diseases such as AD and ALS (Sano et al., 1997; The Parkinson's Study Group, 1993).

Levodopa – L-3, 4-dehydroxyphenylalanine is a standard, highly effective drug used for the treatment of PD and other therapies that are being studied are usually compared to it (Fahn, 1999). Upon crossing the blood brain barrier , levodopa is converted to dopamine by the enzyme L- aminodecarboxylase. When levodopa is converted to dopamine, dopamine receptors are activated which in turn lessens the symptoms of PD. Levodopa is more effective in higher doses in comparison with lower doses; however, the high dose might result in adverse effects such as dyskinesia (Fahn et al., 2004).

Levodopa does not cure PD and the dose might have to be standardised for each patient.

The substantia nigra region of the brain is prone to high oxidative stress even under normal conditions because of the high levels of reactive metabolites produced by dopamine. Using neuroprotective agents that reduce oxidative stress and protect the mitochondria, thereby decreasing neurodegeneration, would be the ideal therapy for PD. Coenzyme Q10 (CoQ10), a naturally occurring compound that participates in the electron transport chain, is an effective antioxidant. Both fat and water soluble CoQ10 have been used for animal and preclinical studies. The clinical trial for fat soluble CoQ10 formulation in the treatment of PD has been halted as it was not effective. The water soluble formulation (www.zymes.com/) of CoQ10 (consisting of CoQ10, polyethylene glycol, and α- tocopherol) however, has been shown to be an effective prophylactic agent that prevents progression to PD. A dose of 50 μg/ml has shown to be effective in preventing the degeneration of dopaminergic neurons in Long Evans Hooded rats injected with paraquat (Somayajulu-Nitu et al., 2009). These rats did not show PD - like symptoms and there was no motor impairment or decrease in the number of dopaminergic neurons. Water soluble CoQ10 may also be useful as a therapeutic treatment for PD (Facecchia et al., unpublished data)

Pre-treatment of C56BL/6 mice with caffeine before injecting them with a combination of maneb and paraquat helps reduce the loss of dopaminergic neurons. A chronic dose of 20 mg/Kg increased the expression of tyrosine hydroxylase in the substantia nigra region (Kachroo et al., 2010).

Other neuroprotective agents that have been studied and have shown positive results are silymarin and melatonin (Singhal et al., 2010). Lithium feeding for a period of three months prevented accumulation of α- synuclein in nine - month old α- synuclein transgenic mice that were injected with paraquat and maneb. It also protected α-synuclein enhanced green fluorescent protein overexpressing dopaminergic N27 cells that were treated with hydrogen peroxide (Kim et al., 2011).

Polygonum multiflorium is a Chinese herb and its extract contains an ethanol soluble fraction and an ethanol insoluble fraction. The ethanol soluble fraction has been shown to prevent a decrease in the number of dopaminergic neurons in the substantia nigra region of C57BL/6 mice injected with paraquat and maneb twice a week for six weeks (Li et al., 2005).

Autophagy is an inducible process that is activated by factors such as stress, pathogenic invasion, or nutrient or growth factor deprivation. Mutation of genes such as *a- synuclein* and *tau* could result in the expression of misfolded and aggregated proteins that can be removed by autophagy enhancement thereby preventing neurodegeneration (Pan et al., 2009). Feeding mice with 1% trehalose for 2.5 months has been shown to decrease PD - like symptoms in transgenic mice with mutation in the *tau* gene (Rodriguez- Navarro et al., 2010).

5. Conclusions and recommendations

In conclusion, we have provided evidence that environmental exposures to pesticides can contribute to the development of neurodegenerative diseases. Typical toxicological testing does not normally account for the neurotoxic effects of pesticides, rather, these tests focus on establishing LC50 values and evaluating toxicity to organs such as kidney, liver and lungs.

Neurotoxicity testing seldom evaluates the effects of long-term, low-dose exposure to pesticides, which is a much more likely human exposure scenario. We suggest that long-term low-dose *in vivo* and *in vitro* testing of pesticides for neurotoxicity should become standard procedure before introducing new products into the environment. Neurons are particularly susceptible to long-term exposure to toxic chemicals given their post-mitotic and non-regenerating nature. Neurotoxicology studies should examine biochemical, behavioral and histological effects of pesticide exposure in order to establish a more complete picture of the potential toxicity of chemicals. Moreover, behavioral testing should examine not only motor effects, but also deficits in learning, memory or cognition (Walsh & Chrobak, 1987), which may not be as overt but are still highly detrimental. Although mammalian models have long been the standard for toxicity testing, non-mammalian systems are becoming more common, and present new alternatives for long-term neurotoxicity testing (Peterson et al., 2008). Histological examination of the brain for signs of toxicity is obviously an important consideration. Assessing neurodegeneration in the dopaminergic system, particularly the substantia nigra, may be considered as a parameter for neurotoxicity testing, given the apparent susceptibility of the dopaminergic system to a variety of compounds, some pesticides included (Storch et al., 2004). Hopefully, future toxicity studies will consider the potential of a pesticide to induce cell death specifically in the brain, and probable neurotoxicants will be kept out of the environment.

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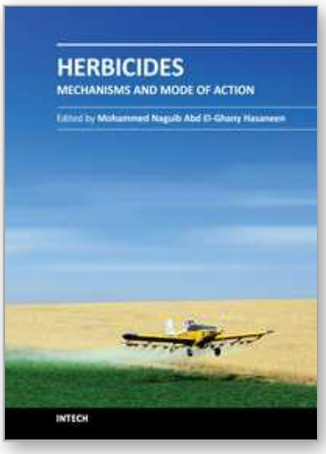

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This volume contains two sections: Mechanisms of herbicidal action (chapters 1-4) and Mode of action of selected herbicides on controlling diseased, weed growth and productivity and/or growth and development of field crops (chapters 5-10). Topics by chapters are: molecular mechanism of action, immunosensors , laboratory studies, molecular modeling, weed resistance, community response, use of herbicides in biotech culture, gene flow, herbicides and risk, herbicides persistence. These recurring themes reinforce my view, held over a very long time, that experience with one crop or problem can sometimes be relevant, often to an unexpected extent, to an apparently dissimilar situation in a different crop. I hope that readers interested in herbicides and pesticides will be satisfied with all the chapters in the book as its content might be of interest and value to them in the future.

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