SUPPLEMENTARY MATERIAL

Pesticides And Parkinson's Disease – Is There A Link?

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Abbreviations:

2,4-D	2,4-Dichlorophenoxyacetic acid
GABA	γ-Aminobutyric acid
H_2O_2	Hydrogen peroxide
NMDA	*N*-Methyl-D-aspartate
NO	Nitric oxide
PD	Parkinson's disease
ROS	Reactive oxygen species

Epidemiological evidence

Case reports and case series

Twelve cases have been reported of acute exposure to pesticides giving rise to symptoms similar to those experienced in Parkinson's disease (PD), after attempted suicide, occupational pesticide exposure in farming and house fumigation (Arima et al. 2003; Bhatt et al. 1999; Bocchetta and Corsini 1986; Lazzarino De Lorenzo 2000; Müller-Vahl et al. 1999; Sechi et al. 1992; Shahar and Andraws 2001; Stefano et al. 1989). Nine of the cases involved organophosphate pesticides, eight of which recovered with treatment (three with an anti-parkinsonism drug) and/or removal from the apparent exposure. The remaining three cases involved exposure to other pesticides over longer time periods, one of which recovered following removal from the exposure source. Two studies also describe three young cases (about 30 years of age) showing parkinsonism who had chronic exposure to the fungicide maneb, two of whom responded to treatment (Ferraz et al. 1988; Meco et al. 1994).

One case series study was identified that examined the life histories of a group of 21 young onset PD patients (Rajput et al. 1986; Rajput et al. 1987). The study found no association with young onset PD and the use of paraquat or other herbicides in agriculture, although this is consistent with current thinking that young onset PD is a primarily genetic disease (Tanner 2003).

Incidence, prevalence and mortality studies

Parkinson's disease was found to be significantly associated with the geographical distribution of pesticide usage in agriculture in one of the three prevalence studies (Barbeau et al. 1987) and in all the three mortality studies (Ritz and Yu 2000; Strickland et al. 1996; Vanacore et al. 1991). In a second prevalence study an increased risk of parkinsonism was

observed with the general use of pesticides, but not for specific pesticides (Engel et al. 2001a). In the other prevalence study and the only incidence study looking at pesticide exposure no association was found with hexachlorobenzene exposure and the chronology of major herbicide and pesticide usage, respectively (Bennett et al. 1988; Sala et al. 1999). However, other risk factors have also been associated with PD including farming as an occupation (Goldsmith et al. 1990; Goldsmith et al. 1997; Granieri et al. 1991; La Bella et al. 1990; Lee et al. 2002; Rybicki et al. 1993; Schulte et al. 1996; Wang et al. 1994a), and rural living (Ben-Shlomo et al. 1993; Bennett et al. 1988; Errea et al. 1999; Imaizumi 1995; Svenson et al. 1993; Tandberg et al. 1995), although there are some conflicting findings regarding the association with rural living (Ferraz et al. 1996; Kuopio et al. 1999b; Rybicki et al. 1993; Sethi et al. 1989; Taba and Asser 2002).

Cohort studies

Four of the five cohort studies reviewed identified farming or agriculture as an occupation (which was considered a proxy for pesticide exposure) as a significant risk factor for PD (Baldi et al. 2003; Petrovitch et al. 2002; Tüchsen and Jensen 2000; Vanacore et al. 2002). Standardised hospitalisation rates (Tüchsen et al. 2000), incidence and relative risk rates (Baldi et al. 2003; Petrovitch et al. 2002) for PD were all increased for agricultural workers. The relative risk was shown to increase with number of years of plantation work and of self-reported pesticide use (Petrovitch et al. 2002) and also with the cumulative occupational exposure to pesticides (Baldi et al. 2003). One study identified a significantly lower prevalence of PD amongst farmers compared with non-farm workers (Yesalis III et al. 1985). However, these studies should be treated with caution as other occupational groups were also identified at an increased risk of PD (Tüchsen et al. 2000), and none were designed to investigate PD risk specifically. Indeed, only one study (Vanacore et al. 2002) assembled

their cohort from a population of licensed pesticide applicators and none of the studies had an independent measure of pesticide exposure (rather, all the studies used occupation as an exposure variable). Apart from one Danish study (Tüchsen et al. 2000), the numbers of PD cases identified in each study were small (up to 116), limiting their power to detect an association. In addition the criteria used to define cases were not given, and in two studies (Baldi et al. 2003; Yesalis III et al. 1985) health status was self-reported and not clinically confirmed.

Potential cellular mechanisms in the development of Parkinson's disease

A number of potential mechanisms involved in the death of dopaminergic neurons in the substantia nigra have been proposed, an understanding of which is important when evaluating the potential role of pesticides in PD development. Discussed in more detail below are the potential mechanisms outlined in Figure 3.

Inhibition of Complex I of the mitochondrial electron transport chain has been strongly implicated in the pathogenesis of PD. The potential involvement of Complex I inhibition was first identified when it was found that 1-methyl-4-phenylpyridine, the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, accumulates in the mitochondria of dopaminergic neurons and exerts its toxicity by inhibition of Complex I of the mitochondrial electron transport chain (Foley and Riederer 2000; Greenamyre et al. 1999; Greenamyre et al. 2001; Nicklas et al. 1992; Sherer et al. 2002). Additionally, a decrease of about 30% in Complex I activity in the substantia nigra, striatum, skeletal muscle and platelets has been noted in idiopathic PD patients without detectable structural or mitochondrial DNA changes (Foley and Riederer 2000), further suggesting a role for Complex I in PD pathogenesis.

The mechanisms by which Complex I inhibition may lead to the neurodegeneration seen in PD are yet to be fully determined. However, there is evidence that oxidative stress may have a role in PD pathogenesis, for example, brains from PD patients have been found to have elevated markers of oxidative damage (Sherer et al. 2002). The source of this oxidative stress is believed to result from the inhibition of Complex I, which leads to an increased production of reactive oxygen species (ROS). This could then result in a feed-forward cycle whereby the ROS further damage Complex I, further increasing ROS production and hence Complex I damage (Sherer et al. 2002). Reactive oxygen species (in the form of H_2O_2) are also produced

during the auto-oxidation of dopamine and during the synthesis and metabolism of dopamine by tyrosine hydroxylase and monoamine oxidase, respectively (Foley and Riederer 2000). Normally, H_2O_2 is removed by glutathione, but glutathione is present at levels lower than elsewhere in the brain and has found to be further reduced amongst PD patients. As a result, this leads to higher than normal levels of H_2O_2 in the neurons, which decompose to hydroxyl radicals via the iron mediated Fenton reaction (Bharath et al. 2002; Foley and Riederer 2000). This would require iron in the free ferrous form, which is present at high levels in the substantia nigra and has been found to be higher in PD patients compared with age matched controls (Bharath et al. 2002). Overall, this suggests an important role for oxidative stress in the development of PD.

Complex I dysfunction may also result in neurons being vulnerable to excitotoxic insults by altering adenosine triphosphate levels, by impaired calcium homeostasis or both (Sherer et al. 2002). Glutamate is the predominant excitatory neurotransmitter in the brain. It does, however, have excitotoxic properties under some conditions (Greenamyre et al. 1999). The impaired mitochondrial Complex I activity associated with PD may predispose neurons to excitotoxic cell death by removal of the Mg^{2+} blockade of the *N*-methyl-D-aspartate (NMDA) glutamate receptor. This blockade normally acts to prevent the excitotoxic stimulation of glutamate caused by an abnormal cellular influx of calcium. Without the blockade even normal cellular levels of glutamate may cause excitotoxic activation of the NMDA receptors and lead to a potentially fatal increase in intracellular calcium concentration (Sherer et al. 2002). The sequestration of calcium in the mitochondria, which may normally mitigate this effect, is decreased when electron transport is impaired (Greenamyre et al. 1999).

Nitric oxide (NO) has also been suggested as contributing to nigrostriatal injury. Inducible NO synthase is known to be increased in the substantia nigra in PD and increased NO could

also elevate local oxidative stress. Although NO is an effective free radical scavenger, it can react with the superoxide radical to form the peroxynitrite anion, a potent oxidative radical. NO also directly inhibits mitochondrial respiration (mainly at the level of Complex IV, but also at Complex I; Foley and Riederer 2000), thus adding to the oxidative stress.

Finally, three different components of Lewy bodies, wild-type human α-synuclein, parkin and ubiquitin carboxyterminal hydrolase, have been associated with genetic mutations in familial PD, which points to the possibility that altered protein conformation and/or degradation could be a key and common factor in sporadic PD. Transgenic mouse models in which α-synuclein is overexpressed show features of PD, including loss of dopaminergic nigrostriatal neurons and motor impairment (Betarbet et al. 2002a; Di Monte et al. 2002). Mice containing a doubly mutated human α-synuclein gene also showed an age-related decline in motor coordination and adverse effects on the integrity of dopamine terminals (Richfield et al. 2002).

Other pesticides

While there is evidence for neurotoxic effects of some other pesticides, all the mechanistic systems seen in PD are not consistently effected. A review of these other pesticides is presented below.

While the main neurotoxic effect of lindane is the inhibition of $GABA_A$ receptors (Rivera et al. 1998), other neurotransmitter levels were increased including dopaminergic neurons in the substantia nigra (Artigas et al. 1988). It is not clear whether the observed changes in other neurotransmitter pathways are due to the release of the inhibitory action of GABA.

When administered to mice the organophosphate **c**hlorpyrifos resulted in a small decrease in striatal dopamine uptake, a decrease in mitochondrial function, an increase in dopamine

turnover and a decrease in open field behaviour (Karen et al. 2001). Although the organophosphate dichlorvos is a directly acting inhibitor of acetylcholinesterase, marked changes to the dopaminergic neurotransmitter system, including decreased dopamine binding and increased activity of tyrosine hydroxylase and dopamine-β-hydroxylase, are also seen (Choudhary et al. 2002). The authors suggested that alterations in the dopamine system may be a causative mechanism behind the behavioural and functional changes associated with delayed organophosphate neurotoxicity.

At high doses carbaryl has been shown to induce tremor, which can be reduced by prior treatment with L-dopa (Rigon et al. 1994). Carbaryl potentiated the catalepsy induced by the striatal dopaminergic receptor blocker, haloperidol. This led the authors to suggest that the effects of carbaryl involved a disturbance of the balance between cholinergic and dopaminergic systems.

Injection of 2,4-dichlorophenoxyacetic acid (2,4-D) into one striatum of a rat produced a marked depression in locomotor activity and circling behaviour and an increase in dopamine metabolism (Bortolozzi et al. 2001) indicated neurotoxicity in the basal ganglia. In pregnant rats treated with a 1:1 mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid there was delayed ontogeny of brain dopamine (but not noradrenaline), together with a delay in the development of certain neurobehaviour in pups (Mohammad and St Omer 1985).

A heightened locomotor and stereotype response was observed in rats receiving the antifungal agent, triadimefon, at very high doses (Hill et al. 2000), primarily through the potentiation of dopamine activity. There was an increase in dopamine uptake and release in the striatum and nucleus accumbens.

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Table S1 Summary of case-control studies investigating the risk of Parkinson's disease and pesticide exposure

Reference	Cases				Controls			
	Source	Definition	Number	Age (years)	Source	Definition	Number	Matching
Ho et al. (1989), Hong Kong	Geriatric day hospital and old peoples home	Cardinal signs[a], exclusion criteria applied	35	Range: 65–87	As cases	No disease specified	105	Age, sex and source of case
Tanner et al. (1989), China	Neurology clinic	≥ 2 Cardinal signs, exclusion criteria applied	100	Mean: 57.2 Range: 31–77	As cases	Non-PD diagnosis	200	Age and sex
Golbe et al. (1990), USA	Movement disorder clinic	Not reported, but exclusion criteria were applied	106	Not reported	Cases	Spouse	106	None
Hertzman et al. (1990), Canada	Physician lists	Generally accepted criteria	57	Range: 50–79	Regional electoral roll	None	122	Age and sex
Koller et al. (1990), USA	Movement disorder clinic	≥ 2 Cardinal signs, exclusion criteria applied	150	Mean: 66	Neurology and medical clinics	Excluded if signs of parkinsonism, exposure to neuroleptics, or severe dementia	150	Age and sex
Zayed et al. (1990), Canada	GPs and neurology consultants	≥ 3 Cardinal signs, exclusion criteria	42	Mean: 57.8 SD: 11.1	Telephone directory	PD excluded	84	Age and sex

		applied						
Stern et al. (1991), USA	Neurology clinic	Not reported, but exclusion criteria were applied	149	YOPD <40 OOPD >60	Case nominations or hospital patient/volunteer	Non-parkinsonism	149	Age, sex and race
Wechsler et al. (1991), USA	Neurology clinic and PD support groups	Not reported	34	Mean: 68.4	Neurology clinic	Non-parkinsonism	25	Yes – no details given
Wong et al. (1991), USA	Hospital PD centre	≥ 2 Cardinal signs, exclusion criteria applied	38	Mean: 68.4	Neurology and general medicine clinics	Non-PD diagnosis	38	Yes – no details given
Falope et al. (1992), Nigeria & USA	Neurology clinic	≥ 3 Cardinal signs	50	Mean: 65.9	Medical clinics	Non-PD diagnosis	50	Age and sex
Jiménez-Jiménez et al. (1992), Spain	Movement disorder clinic	Not reported	128	Mean: 66.8 SD: 9.1	Hospital emergency room	Non-neurological ailments	256	Age and sex
Semchuk et al. (1992), Canada	Hospital case register	≥ 2 Cardinal signs	130	Mean: 68.5 SD: 11.5	Community	Non-parkinsonism and no dementia	260	Age and sex
Butterfield et al. (1993), USA	YOPD support groups	≥ 2 Cardinal signs, exclusion criteria applied	63	All <50	Catchment area of cases	Diagnosed with rheumatoid arthritis	68	Frequency matched for age sex, year of birth and diagnosis
Hubble et al. (1993), USA	Rural: PD outreach clinic	≥ 2 Cardinal signs, exclusion criteria	31	Mean: 69 SD: 10.2	Rural: news media and senior citizens'	Signs of PD or other neurodegenerative	45	Not reported

		applied			lunch program	disease excluded		
	Urban: PD clinic and PD support groups		32		Urban: neurology and case contacts		31	
Hertzman et al. (1994), Canada	GPs and hospital records	≥ 2 Cardinal signs, exclusion criteria applied	127	Mean: 70.5	Electoral rolls and hospital records	Healthy subjects and community cardiac disease patients	245	No
Morano et al. (1994), Spain	Neurology clinic	Hoehn and Yahr staging criteria	74	Mean: 65.4 SD: 1.1	Accident and Emergency, and Neurology outpatients	Non-neurological and functional CNS pathology	148	Not reported
Chaturvedi et al. (1995), Canada	Cohort of Canadians ≥ 65 years	Not reported	87	≥ 65	As cases	Not reported	2070	Not reported
Seidler et al. (1996), Germany	Neurology clinics	UK PD Brain Bank criteria	380	Mean: 52.5 SD: 6.6	Random addresses	Non PD	755	Age and sex
Liou et al. (1997), Taiwan	Movement disorder clinic	≥ 2 Cardinal signs	120	Mean: 58.3	Outpatient clinics	Non-PD diagnoses, previous brain disease excluded	240	Yes
Chan et al. (1998), Hong Kong	Neurology outpatients clinic	≥2 Cardinal signs, plus others and family history	215	<60–80+	Hospital	No disease reported	313	Yes
Gorell et al. (1998), USA	Health care provider	Not reported, but exclusion criteria	144	>50	As cases	No disease	464	Frequency matched for

		were applied						age and sex
McCann et al. (1998), Australia	Hospital, residential care home and community groups	≥ 2 Cardinal signs	224	Mean: 70.3 SD: 0.6	As cases	No disease	310	Yes
Menegon et al. (1998), Australia	Community groups, hospital wards and outpatient clinics	Cardinal signs, exclusion criteria applied	95	Mean: 72 SD: 9	As cases	Healthy	95	Not reported
Smargiassi et al. (1998), Italy	Hospital outpatients	UK PD Brain Bank criteria	86	Mean: 66.4 SD: 9.7	As cases	Cardiology, nephrology, ophthalmology, and dermatology patients	86	Not reported
Fall et al. (1999), Sweden	GP lists and prescription records	≥ 1 Cardinal sign and progression, exclusion criteria applied	113	Mean: 62.9 SD: 8.9	Regional population register	No disease	263	Not reported
Kuopio et al. (1999a), Finland	Community	UK PD Brain Bank criteria and no dementia	123	Mean: 68.7 SD: 8.9	Population register	Healthy	246	Age, sex and municipality
Taylor et al. (1999), USA	Movement disorder clinic	≥ 2 Cardinal signs, L-dopa responsive, and other signs	140	Range: 31–88	In-laws and friends nominated by cases	Healthy	147	Yes
Werneck and Alvarenga	Neurology clinic	UK PD Brain Bank	92	Mean: 70.6	Neurology clinic	Non-parkinsonism	110	Age and sex

(1999), Brazil		criteria						
Nelson et al. (2000), USA[b]	Medical care program	Not reported	496	Not reported	As cases	Healthy	541	Frequency matched for age and sex
Preux et al. (2000), France	Inpatient and outpatients	UK PD Society criteria	140	Mean: 71.1 SD: 7.5	As cases	Ophthalmology, ENT, endocrinology and rheumatology patients	280	Age and sex
Behari et al. (2001), India	Movement disorder clinic	≥ 2 Cardinal signs, progression, and responsive to L-dopa	377	Mean: 56.8 SD: 11.1	Neurology clinic	Non-parkinsonism	377	Age and sex
Herishanu et al. (2001), Israel	Neurology clinic	≥ 2 Cardinal signs, progression, and responsive to L-dopa	93	Not reported	Hospital neurology dermatology, internal medicine, and outpatient clinics	Non-PD diagnosis, those with extrapyramidal signs or neurodegenerative disease excluded	93	Age and sex
Kamel et al. (2001), USA[b]	Cohort of licensed pesticide applicators	Self-reported PD	55	Not reported	As cases	Non-PD	22 286	Not reported
Kirkey et al. (2001), USA	Health care provider	Not reported	144	>50	As cases	Disease free	464	Frequency matched for age and sex
Vidal et al. (2002), France[b]	Insurance service	Neurologist	227	Not reported	As cases	PD free	562	Age, sex and

		confirmed						place of residence
Zorzon et al. (2002), Italy	PD Centre and movement disorder clinic	≥ 2 Cardinal signs, asymmetry and clinical progression, exclusion criteria applied	136	Mean: 70 SD: 9.2	Neurology clinic	Non-parkinsonism	272	Age and sex
Duzcan et al. (2003), Turkey	Village	≥ 2 Cardinal signs or advice of relatives of deceased	36	>50	As cases	Non-neurological	108	Age and sex
Firestone et al. (2005), USA	Health care provider	≥2 Cardinal signs, one of which had to be bradykinesia or resting tremor	250	Range 37–88	As cases	Non-neurological	388	Age, sex and source of case

Abbreviations: CNS, central nervous system; ENT, ear, nose and throat; GP, General Practioner; OOPD, old onset Parkinson's disease; PD, Parkinson's disease; SD, Standard deviation; YOPD, young onset Parkinson's disease

[a]Cardinal signs: tremor, rigidity, bradykinesia, postural instability. [b]Reported as conference abstracts.