Published Online January 22, 2007

Parkinson's disease and pesticide exposures

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Introduction: Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder in which loss of dopaminergic neurons in the basal ganglia leads to tremor, bradykinesia, rigidity and postural instability.

Methods: Literature search using Medline with keywords 'Parkinson's disease' and 'pesticides', limited to English, was undertaken, supplemented by articles from the author's files.

Results: Many studies have found an association between pesticides and PD, but no one agent has been consistently identified. Those implicated include organochlorine insecticides, maneb and paraquat. One meta-analysis of pesticide exposure and PD found an almost doubling of risk in those exposed. Associations with specific agents may be confounded by exposure to other pesticides, making it difficult to identify the causative agent.

Conclusions: The available evidence indicates that pesticides are associated with PD, but further research is needed to identify long-term biomarkers of exposure, improve methods for estimating pesticide-exposure and undertake prospective cohort studies of pesticide-exposed workers.

Keywords: Parkinson's disease/parkinsonism/pesticides

Introduction

Accepted: December 4, 2006

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Parkinson's disease (PD) is a movement disorder, which develops as a consequence of degeneration of the dopaminergic neurons within the basal ganglia. The disease becomes clinically apparent once $\sim 70\%$ of the dopaminergic neurons of the substantia nigra are lost. Neuropathologically, Lewy bodies are typical of PD, although these intra-cytoplasmic neuronal inclusions, which contain α-synuclein, may be found in other conditions such as dementia with Lewy bodies. PD is principally a disease of ageing, with a peak age of onset of 65 years, although both young onset PD, generally defined as disease onset <40 years, and a rare juvenile form occur.

PD presents with resting tremor, slow movements (bradykinesia) and rigidity and, later, postural instability occurs. Almost half of PD

DOI: 10.1093/bmb/ldl018

sufferers show asymmetry with signs and symptoms being more marked on one side of the body. The condition was first described by Parkinson,[1] an English surgeon, in 1817 in his classic monograph 'an essay on the shaking palsy'. He described the main features of what is now known as PD and gave case histories of six sufferers, one of whom was a gardener (case I).

The reported incidence of PD varies across the world,[2] although whether this reflects genuine differences in disease incidence or better case ascertainment in North American and Western European populations is less clear. There is some evidence to suggest that PD is commoner in Caucasians than Chinese, although this may reflect differing environmental exposures rather than greater genetic susceptibility to the disease.

The diagnosis of PD is essentially a clinical one, but diagnosis can be difficult and other causes of parkinsonism should be considered. Vascular parkinsonism, due to cerebral infarcts, may be confused with PD, but the stepwise progression typical of vascular parkinsonism together with a failure to respond to L-dopa should alert the treating clinician to the correct diagnosis. Patients treated with major tranquilizers or anti-emetics may develop drug-induced parkinsonism but this should be distinguished from PD. Post-mortem studies in the early 1990s found that 24% of patients clinically thought to have had PD actually had another condition (e.g. progressive supra-nuclear palsy or multi-system atrophy). More recently, the diagnostic accuracy of PD, at least among movement disorder specialists, has improved to 90%.[3] Diagnostic imprecision has implications for research into the causes of PD, especially when considering studies carried out before the early 1990s, as studies that included a significant proportion of people with parkinsonism rather than PD would have had reduced statistical power to detect associations.

A number of different clinical diagnostic criteria for PD have been published, including the Ward and Gibb criteria, the Gelb criteria and the UK Parkinson's Disease Society (PDS) Brain Bank clinical diagnostic criteria.[4] Of these, the most widely used have been the three-step UK PDS Brain Bank criteria: step 1 requires the presence of bradykinesia and at least one of muscular rigidity, 4–6 Hz rest tremor and postural instability; step 2 lists 16 exclusion criteria including a history of definite encephalitis and step 3 lists eight supportive criteria, at least three of which are required for a diagnosis of definite PD.

Genetic research has identified a number of rare familial forms of PD because of single gene mutations.[5] These breakthroughs have given researchers valuable new insights into some of the mechanisms that may underlie PD, but nonetheless most cases of PD remain unexplained. Two large twin studies[6,7] failed to find evidence of a significant genetic

contribution to the burden of typical PD, although in one study,[6] genetic factors did seem to make a contribution in younger onset PD (defined in that study as onset <50 years of age).

The generally held view is that PD is due to both environmental and genetic factors and that it is not one disease but rather a number of phenotypically similar conditions.

Studies of environmental risk factors for PD received a fillip following reports of parkinsonism in a small number of drug abusers who had consumed a synthetic opiate, 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[8] MPTP is metabolized to the neurotoxin 1-methyl-4-phenylpyridinium (MPP^+), which was originally developed as the herbicide, cyperquat. The chemical structure of MPP^+ is similar to the widely used bipyridinium herbicide paraquat. This finding prompted a number of epidemiological studies of the association between pesticide exposure and PD.

Pesticide types

A pesticide may be defined as any agent used to kill undesired organisms such as insects (insecticide), snails and slugs (molluscicide), rodents (rodenticide), plants (herbicide) or fungi (fungicide). Pesticides can be categorized in a number of ways, including their acute toxicity to humans, their chemical group or their mode of action. Laboratory studies have identified a number of mechanisms by which pesticides might lead to PD including mitochondrial dysfunction (e.g. complex I inhibition), oxidative stress, protein aggregation and altered dopamine levels. Several pesticides act by inhibition of mitochondrial enzymes, thus disrupting cellular respiration. MPTP is a mitochondrial complex 1 inhibitor as is rotenone (derris root). It had been thought on the basis of their chemical structural similarity that paraquat acted on the brain in a way similar to MPTP. However, *in vitro* research suggests that paraquat exerts its toxicity on dopaminergic neurons in a different way to MPTP.[9] The toxicological and epidemiological evidence that pesticides might lead to PD has recently been extensively reviewed by Brown *et al.*[10]

Case reports

There have been a number of case reports of parkinsonism[11,12] and PD[13] in individuals exposed to pesticides. The utility of such reports is that they suggest hypotheses to be tested in case–control or cohort studies: they are not, of themselves, terribly persuasive and provide only weak evidence of an association.

Ecological studies

Few ecological studies have explored the association between pesticide usage and PD prevalence.[14,15] These studies tend to show an increased prevalence of PD in the highest pesticide usage areas. A Canadian study[14] examined PD prevalence, as measured using health insurance data, Levodopa sales information and death certification. Rather than directly measure pesticide exposure, they employed water supply information. The most heavily farmed hydrological areas were found to have the highest prevalence of PD and the highest use of pesticides.

Mortality studies

A handful of studies have examined PD mortality and pesticide usage indices. For example, a Californian study found that the proportional mortality ratio for PD was higher in counties using pesticides than counties without such use and a dose–response effect was seen when examining counties by increasing insecticide use.[15] This is an interesting observation, but some caution must be exercised as death certificates are imprecise measures of disease incidence.

Case–control studies

Case–control studies of risk factors for PD have implicated the use of well water, rural residency and agricultural work as risk factors.[16] These associations have been inconsistent and the findings for rural residency, in particular, are difficult to assess because of varying definitions of rurality. It may be that these factors are simply surrogate measures of pesticide exposure.

A number of case–control studies of the association between pesticide exposure and PD have been carried out, principally in North America, but also in Asia and Europe. In general, these studies have found an association between pesticide exposure and an increased risk of having PD,[17] although several studies have not. Although some studies have implicated specific pesticide groups such as herbicides, very few have found associations with individual agents such as paraquat.[18,19] Several methodological issues might have influenced these inconsistent results, including varying case definitions of PD, selection bias, overmatching of cases and controls, low quality exposure estimates and recall bias.[10] A range of case definitions of PD have been used in epidemiological studies including the Unified Parkinson's

Disease Rating Scale (UPDRS),[10] the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria,[20] the Hoehn and Yahr scale[10] and the finding of two or more of the cardinal signs of PD (resting tremor, bradykinesia, cogwheel rigidity and postural instability).[19] The use of different case definitions may make it harder to compare and interpret studies. Selection bias may arise when some individuals (cases or controls) are more likely to be recruited than others, e.g. sourcing study participants from hospitals, especially major teaching hospitals, may mean that they are more likely to have severe or unusual disease. Overmatching occurs where cases and controls are too closely matched such that they are likely to share risk factors for the disease of interest, thus obscuring any association that does exist. Overmatching may be a problem in studies where controls are recruited from the spouses, relatives or friends of cases or drawn from the same locality as the cases. One example is a study[21] that recruited two control groups, one of which comprised neighbourhood controls who may have shared both occupational and environmental exposures with cases. Recall bias may occur where cases make greater efforts to recall exposures of interest than do controls, thus leading to the identification of false associations.

A meta-analysis of 19 studies of pesticide exposure and PD[17] found an almost doubling of risk in pesticide-exposed groups. The association between pesticides and PD was of similar size when comparing North American (OR 2.15, 95% CI 1.14–4.05) and all studies (OR 1.94, 95% CI 1.49–2.53).

Both herbicide usage and insecticide usage have been associated with PD in case–control studies. There is less epidemiological evidence to implicate fungicides, although indirect evidence of an association comes from a study set in south-western France, in which the main agents used in the vineyards are fungicides.[20] That case–control study found a significantly increased risk of PD among pesticide-exposed subjects (OR 2.2, 95% CI 1.1–4.3), although poor recall of agents used precluded more detailed analysis.

Cohort studies

Cohort studies usually provide stronger evidence of an association between an exposure and a disease than case–control studies as the ascertainment of exposure pre-dates disease onset. Undertaking large-scale cohort studies is expensive and time-consuming: as a result, few cohort studies have examined pesticide exposure and PD. However, two cohort studies have explored agricultural employment as a risk factor for PD and both have found a significant association.

A cohort study of over 2 million men and women of working age, identified from the Danish population register as resident of Denmark in 1981 and followed up for 13 years, found a significantly increased risk of first hospital admission with PD in agricultural and horticultural workers.[22] A prospective cohort study set in Hawaii found that work in pineapple and sugar cane plantations for >10 years was associated with an increased relative risk of PD.[23] An analysis using pesticide exposure showed a non-significantly increased risk of PD in this cohort.

A cohort study of pesticide-exposed workers in Washington, USA, using detailed estimates of pesticide exposure, found a marginally non-significant increased prevalence ratio of parkinsonism among those workers with the longest pesticide exposures.[24] Subjects completed a self-administered questionnaire regarding the duration of pesticide-exposed employment, together with factors likely to influence exposure, such as work activity, method of application and use of personal protective equipment. A prospective cohort study in south-western France (the PAQUID study) of some 1500 elderly people found an increased relative risk of PD among men with occupational pesticide exposure based on a job exposure matrix for pesticides produced from occupational histories.[25]

The largest cohort study yet carried out is that of Ascherio *et al.*,[26] who undertook a study of pesticide exposure and PD in over 140 000 people drawn from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort. That study, which was based on self-reported current or frequent past exposure to pesticides and self-reported PD diagnosis (validated in the majority of cases by a neurologist's diagnosis of 'definite' or 'probable' PD), found that the relative risk for PD among individuals exposed to pesticides was 1.7 (95% CI 1.2–2.3).

Although most studies have found an association between pesticides and PD, no single agent has clearly been linked to this association.

Specific agents

A number of pesticides have been implicated in PD on the basis of the findings from case reports and case–control studies. However, it is striking how rarely any of these putative associations have been confirmed in subsequent studies. As farming, horticulture and forestry employ a wide range of pesticides, identifying the causative agent is challenging and any identified associations may simply be markers for pesticide exposure more generally. Li *et al.*[2] recently published a sceptical review of the reported association between pesticide exposure and PD. Although it is tempting to conclude that these associations are due

to selection and recall biases or confounding, an alternative explanation is that exposure to a number of different pesticides, perhaps in combination, leads to PD. Thiruchelvam *et al.*[27] have proposed a multiple hit hypothesis for PD, suggesting that, although exposures to individual agents such as paraquat may not lead to PD, exposure to a combination of agents affecting dopaminergic systems at multiple points might lead to neuropathological changes. Studies on mice indicate that a combination of paraquat and maneb can cause nigrostriatal neurotoxicity beyond that caused by these agents individually.[27]

Diphenyl

One recent Swedish case series reported five cases of PD among a group of 255 diphenyl-exposed paper mill workers. All five men had worked in the paper-coating area, with the highest exposure to diphenyl. Their mean age at disease onset was 51 years, considerably younger than the mean age at onset of idiopathic PD. Diphenyl is used as a fungicide in preserving citrus fruits and the diphenyl-impregnated papers manufactured in this mill were used to wrap these fruits.[13]

Dithiocarbamates

Exposure to maneb, a manganese-containing carbamate fungicide (manganese ethylene-bis-dithiocarbamate), has been associated with parkinsonism.[12] Laboratory studies suggest that dithiocarbamates can cause dopamine depletion and induce degeneration of dopaminergic neurons.[10] An agricultural engineer, heavily exposed to maneb during the development of a new seed dressing machine, developed parkinsonism at the age of 37.[12] Although heavy exposure to manganese is known to cause parkinsonism, it is the globus pallidus that is affected in manganese-induced parkinsonism rather than the substantia nigra.

Bipyridinium herbicides

Paraquat, a widely used herbicide, has been linked to PD in epidemiological surveys[18,19] and laboratory work has shown that it causes selective degeneration of dopaminergic neurons.[28] Some studies have found evidence of dopamine depletion, α-synuclein protein aggregation and increased oxidative stress in paraquat-treated rodents.[10] Parkinsonism has been reported in a farmer acutely exposed to the herbicide diquat dibromide.[11]

Organochlorines

One large German case–control study (380 cases, 379 neighbourhood controls and 376 regional controls) found an association between organochlorine use and PD, although only 14 subjects, including seven cases, reported any use of organochlorines.[21] Little weight should be given to this finding, given the small number of subjects reporting such exposure. However, it demonstrates the difficulty in identifying suspect agents when barely 1% of subjects report any use of a class of chemicals that were once so widely used. A small study of Greenland Inuit found a significantly elevated level of dichlorodiphenyldichloroethylene—a contaminant and breakdown product of DDT—in PD sufferers when compared with controls.[29] Circumpolar populations have a diet, rich in marine animals, known to be contaminated with organochlorines. This observation merits further investigation: the Inuits are exposed to pesticides via their diet and may offer an opportunity to study the proposed association between PD and organochlorine insecticides, independent of other pesticide exposures.

Post-mortem studies have found that the brains of those who died of PD were more likely to have detectable levels of dieldrin than those who died of other illnesses.[30] Elevated levels of lindane and dieldrin (organochlorine insecticides) have since been found in the substantia nigra in PD brains.[31] The neurotoxicity of dieldrin has been extensively reviewed by Kanthasamy *et al.*,[32] who concluded that the banned pesticide, dieldrin, shows many of the properties of established dopaminergic neurotoxins, including dopamine depletion, selective toxicity to dopaminergic neurons, oxidative stress, mitochondrial dysfunction, α-synuclein aggregation and apoptosis. However, before concluding that the association is causal, it should be noted that organochlorine insecticides are the only pesticides for which long-term biomarkers of exposure are available. The association between brain organochlorines and PD may simply be a marker for pesticide exposure more generally rather than, as might be assumed, implicating organochlorine insecticides in the development of PD.

Organophosphates

In India, Bhatt *et al.*[33] described five cases of acute, reversible parkinsonism after poisoning with organophosphate pesticides. Three members of the same family developed parkinsonism after living in a flat repeatedly fumigated with an organophosphate spray. Other relatives, living in the same flat, were asymptomatic, suggesting a genetic susceptibility to these compounds among affected family members.

These are intriguing observations, but their relevance to a possible association between organophosphates and PD is unclear.

Seidler *et al.*[21] found an association between exposure to organophosphate pesticides and PD, as well as to organochlorines. A recent North American study[34] did not find a significant association between PD and pesticide exposure, but found that the odds ratios for organophosphates were highest for parathion that carries the highest ranking (1a, extremely hazardous) on the WHO hazard classification.

Pyrethroids

Laboratory studies have shown that pyrethroids, such as permethrin, up-regulate dopamine transporter activity, which may, in turn, increase the susceptibility of dopaminergic neurons to neurotoxins.[35]

Nicotine

One pesticide that may actually reduce the risk of developing PD is nicotine: cigarette smoking is associated with a halving of the risk of developing PD with exposure–response relationships reported for both dose (pack years) and duration since stopping smoking. This association has been repeatedly observed and does not seem to be due to confounding by differential mortality among smokers. Cigarette smoke contains many different chemicals, but nicotine is a strong candidate as the agent responsible for tobacco's protective effect against PD. Thus, research into nicotine may offer new treatments for PD.[36]

Animal models

Two of the three widely used animal models of PD employ pesticides: rotenone and MPTP. One criticism of such laboratory animal models is that neither the dose nor the route of administration of pesticides is representative of likely human exposures.[2] Thus, for example, chronic subcutaneous infusion of rotenone has been used to induce parkinsonism in rats. Such an approach is not representative either of the dermal and inhalational exposures likely to occur in the work setting or in terms of ingestion of pesticides from contaminated well water or foods.

Early life exposures to pesticides

Animal studies have found evidence that male mice exposed to maneb *in utero* are at increased risk of developing neurodegeneration if subsequently exposed, as adults, to paraquat.[37] These laboratory findings have led to the speculation that pesticide-exposed children may be at increased risk of PD in later life, although evidence for this association is lacking. Equally, it can be hypothesized that in old age, a pesticide exposure might 'tip the balance' in an individual with pre-existing dopaminergic cell depletion, thus leading to PD. At present, too little is known about the timing of pesticide exposures and the role this may play in the development of PD. A large prospective cohort study of children and their exposure to environmental pesticides is required to study the role of early life pesticide exposures.

Exposure estimation

Pesticides may be absorbed by inhalation, ingestion or, in some cases, such as the organophosphates, through the skin, i.e. dermal absorption. Indeed, for some pesticides, such as the organophosphorous insecticides, dermal absorption is the most important route of uptake. The pesticide formulation (powder, granules, candles, liquid concentrate, pre-mixed solution and gas), packaging, method of application (e.g. knapsack spraying, fogging, dipping and aircraft crop-dusting), worker training, the use of personal protective equipment (gloves, goggles, impermeable clothing and respiratory protective equipment) and prevailing weather can all influence exposure. Ideally, exposure estimates would take account of all possible routes of exposures and the main factors influencing exposure. One major challenge that researchers face in this area is that many sufferers cannot recollect which agents they have used, making it difficult to establish an association between a specific agent and PD. In addition, some pesticide users apply a range of different agents, sometimes as mixtures, making it even more difficult to implicate specific agents.

Pesticide exposures may arise not only through work but also in the home, e.g. insecticides for human parasites, flea treatments on family pets, exposure to timber treatment agents, use of garden pesticides and the ingestion of pesticide-contaminated water or food. The last exposure is difficult to quantify. Most developed nations regularly test foodstuffs for pesticide contamination, whereas less developed countries may not: generally, few food samples tested in developed countries exceed published permissible pesticide levels. This issue is a

source of considerable public concern. At present, there is no evidence in man that such low-level dietary intake is a risk factor for PD, but further research is needed.

Direct measurements of pesticide exposure or absorption are the exception, rather than the rule in studies of the health effects of pesticide exposure.[38] Cross-sectional or cohort studies can measure pesticide exposures in a subset of participating subjects and then use these figures to validate exposure estimates for the cohort as a whole. However, such measurements are rarely available for retrospective studies and instead researchers must rely on estimates of pesticide exposure of varying precision.[10] Some studies have employed simple metrics such as ever/never exposed to pesticides, whereas others have relied on exposure duration.[2] Employing a simple dichotomous measure such as any exposure versus no exposure can lead to exposure misclassification, thus reducing a study's statistical power to detect an association where one exists. Although self-reported exposure has been shown to be reliable in respect of broad categories of pesticides, recall is poorer for specific agents[39] and one study found a poor correlation between self-reported exposure and urinary pesticide metabolites.[38] A more detailed approach to pesticide exposure estimation uses a job-exposure matrix modified by subjective exposure estimation techniques.[40]

In the absence of long-term biomarkers of exposure to most pesticides, organochlorines being a notable exception, there is a need for more detailed estimates of pesticide exposure, addressing all routes of exposures and integrating both occupational and environmental exposures to produce better validated exposure indices. To date, exposure estimation of pesticides has received insufficient attention in PD research and further work is required to better characterize these exposures.

Summary

There is evidence of a modest increase in the risk of PD in association with pesticide exposure,[10,17,26] but no single agent has been implicated consistently.[17] A meta-analysis of case–control studies[17] and the largest cohort study[26] yet undertaken both indicate an approximate doubling of the risk of PD with pesticide exposure, although there is little evidence, as yet, of an exposure–response relationship. Whether this is a class effect or is attributable to a small number of agents remains unclear. Any reported associations with specific agents may be confounded by exposure to other pesticides, thus making it difficult to identify the causative agent. Indeed,

some have argued that the observed association is due to bias or confounding, but neither explanation is wholly persuasive. Currently, the available evidence indicates that pesticides are risk factors for PD, although exposure to such agents cannot explain all cases of the disease. Further laboratory and epidemiological research into the role of pesticides in PD is needed. Areas for further research include the identification of long-term biomarkers of exposure, improved methods for estimating pesticide exposure and prospective cohort studies of pesticide-exposed workers.

References

1 Parkinson J (1817) An Essay on the Shaking Palsy. London, Sherwood, Neely and Jones.
2 Li AA, Mink PJ, McIntosh LJ, Teta MJ, Finley B (2005) Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. *J Occup Environ Med*, **47**, 1059–1087.
3 Hughes AJ, Daniel SE, Lees AJ (2001) Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. *Neurology*, **57**, 1497–1499.
4 Litvan I, Bhatia KP, Burn DJ *et al.* (2003) SIC Task force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord*, **18**, 467–486.
5 Gasser T (2005) Genetics of Parkinson's disease. *Curr Opin Neurol*, **18**, 363–369.
6 Tanner CM, Ottman R, Goldman SM *et al.* (1999) Parkinson disease in twins. *JAMA*, **281**, 341–346.
7 Wirdefeldt K, Gatz M, Schalling M, Pedersen NL (2004) No evidence for heritability of Parkinson disease in Swedish twins. *Neurology*, **63**, 305–311.
8 Langston JW, Ballard P, Tetrud JW, Irwin I (1983) Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science*, **219**, 979–980.
9 Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW (2005) Paraquat neurotoxicity is distinct from that of MPTP and rotenone. *Toxicol Sci*, **88**, 193–201.
10 Brown TP, Rumsby PC, Capelton AC, Rushton L, Levy LS (2006) Pesticides and Parkinson's disease—is there a link? *Environ Health Perspect*, **114**, 156–164.
11 Sechi GP, Agnetti V, Piredda M *et al.* (1992) Acute and persistent parkinsonism after use of diquat. *Neurology*, **42**, 261–263.
12 Meco G, Bonifati V, Vanacore N, Fabrizio E (1994) Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). *Scand J Work Environ Health*, **20**, 301–305.
13 Wastensson G, Hagberg S, Andersson E, Johnels B, Barregard L (2006) Parkinson's disease in diphenyl-exposed workers—a causal association? *Parkinsonism Relat Disord*, **12**, 29–34.
14 Barbeau A, Roy M, Bernier G, Campanella G, Paris S (1987) Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci*, **14**, 36–41.
15 Ritz B, Yu F (2000) Parkinson's disease mortality and pesticide exposure in California 1984–1994. *Int J Epidemiol*, **29**, 323–329.
16 Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS (2001) Environmental risk factors and Parkinson's disease: a meta-analysis. *Environ Res*, **86**, 122–127.
17 Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S (2000) A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology*, **21**, 435–440.
18 Hertzman C, Wiens M, Bowering D, Snow B, Calne D (1990) Parkinson's disease: a case–control study of occupational and environmental risk factors. *Am J Ind Med*, **17**, 349–355.
19 Liou HH, Tsai MC, Chen CJ *et al.* (1997) Environmental risk factors and Parkinson's disease: a case–control study in Taiwan. *Neurology*, **48**, 1583–1588.
20 Baldi I, Cantagrel A, Lebailly P *et al.* (2003) Association between Parkinson's disease and exposure to pesticides in Southwestern France. *Neuroepidemiology*, **22**, 305–310.

21 Seidler A, Hellenbrand W, Robra B-P *et al*. (1996) Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case–control study in Germany. *Neurology*, **46**, 1275–84.
22 Tüchsen F, Jensen AA (2000) Agricultural work and the risk of Parkinson's disease in Denmark, 1981–1993. *Scand J Work Environ Health*, **26**, 359–362.
23 Petrovitch H, Ross GW, Abbott RD *et al*. (2002) Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol*, **59**, 1787–1792.
24 Engel LS, Checkoway H, Keifer MC *et al*. (2001) Parkinsonism and occupational exposure to pesticides. *Occup Environ Med*, **58**, 582–589.
25 Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues J-F, Brochard P (2003) Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol*, **157**, 409–414.
26 Ascherio A, Chen H, Weisskopf MC *et al*. (2006) Pesticide exposure and risk for Parkinson's disease. *Ann Neurol*, **60**, 197–203.
27 Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA (2000) Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? *Brain Res*, **873**, 225–234.
28 McCormack AL, Thiruchelvam M, Manning-Bog AB *et al*. (2002) Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis*, **10**, 119–127.
29 Koldkjaer OG, Wermuth L, Bjerregaard P (2004) Parkinson's disease among Inuit in Greenland: organochlorines as risk factors. *Int J Circumpolar Health*, **63** (Suppl 2), 366–368.
30 Fleming L, Mann JB, Bean J, Briggle T, Sanchez-Ramos JR (1994) Parkinson's disease and brain levels of organochlorine pesticides. *Ann Neurol*, **36**, 100–103.
31 Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D (2000) Organochlorine insecticides in substantia nigra in Parkinson's disease. *J Toxicol Environ Health A*, **59**, 229–234.
32 Kanthasamy AG, Kitazawa M, Kanthasamy A, Anantharam V (2005) Dieldrin-induced neurotoxicity: relevance to Parkinson's disease pathogenesis. *Neurotoxicology*, **26**, 701–719.
33 Bhatt MH, Elias MA, Mankodi AK (1999) Acute and reversible parkinsonism due to organophosphate pesticide intoxication: five cases. *Neurology*, **52**, 1467–1471.
34 Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT Jr, Checkoway H (2005) Pesticides and risk of Parkinson disease: a population-based case–control study. *Arch Neurol*, **62**, 91–95.
35 Elwan MA, Richardson JR, Guillot TS, Caudle WM, Miller GW (2006) Pyrethroid pesticide-induced alterations in dopamine transporter function. *Toxicol Appl Pharmacol*, **211**, 188–197.
36 Quik M (2004) Smoking, nicotine and Parkinson's disease. *Trends Neurosci*, **27**, 561–568.
37 Barlow BK, Richfield EK, Cory-Slechta DA, Thiruchelvam M (2004) A fetal risk factor for Parkinson's disease. *Dev Neurosci*, **26**, 11–23.
38 Perry MJ, Marbella A, Layde PM (2006) Nonpersistent pesticide exposure self-report versus biomonitoring in farm pesticide applicators. *Ann Epidemiol*, **16**, 701–707.
39 Engel LS, Seixas NS, Keifer MC, Longstreth WT Jr, Checkoway H (2001) Validity study of self-reported pesticide exposure among orchardists. *J Expo Anal Environ Epidemiol*, **11**, 359–368.
40 Semple SE, Dick F, Cherrie JW (2004) Exposure assessment for a population-based case–control study combining a job-exposure matrix with interview data. *Scand J Work Environ Health*, **30**, 241–248.