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Pesticides and Parkinson's Disease

Drouin-Ouellet Janelle and Cicchetti Francesca
Centre de Recherche du CHUL (CHUQ), Université Laval
Canada

1. Introduction

Neurodegenerative diseases form a subset of pathologies that are characterized by a progressive and specific loss of neurons paralleled by the emergence of misfolded proteins in various cell types, the significance of which is still highly debated (Harris et al. 2009). These pathological traits result in mixed impairments of motor, cognitive and psychological functions (Harris et al. 2009). Parkinson's disease (PD), which is characterized by a prominent loss of dopaminergic neurons and the formation of Lewy bodies - nuclear inclusions largely composed of α-synuclein - is the second neurodegenerative disorder in importance after Alzheimer's disease.

The prevalence of PD increases exponentially between 65 and 90 years of age. Approximately 0.3% of PD cases are found in the general population as opposed to 3% in individuals over 65 (Moghal et al. 1994). While a very small fraction of PD is related to monogenic mutations, over 90% of cases are likely linked to environmental causes (referred to as idiopathic PD), suspected to be in part related to well-water consumption, exposure to heavy metals and pesticides (De Michele et al. 1996; Schapira 1996; Tanner et al. 1999) (**Table 1**). Recent work conducted in animal models has suggested that the onset of the

Environmental factors		References
	Rural living	(Morano, 1994)
	Well-water drinking	(Gatto, 2009)
Exposure to:	Heavy metals	(Seidler, 1996)
	Pesticides	(Pryadarshi, 2000)
	Magnetic fields	(Noonan, 2002)
	Herbicides	(Costello, 2009)
Professions related to:	Wood/pulp plants	(Tanner, 1989)
	Orchards	(Hertzman, 1990)
	Planer mills	(Hertzman, 1990)
	Steel/alloy industry	(Rybicki, 1993)
	Railroad and car shop mechanic	(Seidler, 1996)
	Carpentry	(Fall, 1999)
	Cleaning	(Fall, 1999)
	Logging	(Tsui, 1999)
	Mining	(Tsui, 1999)
	Oil and gas	(Tsui, 1999)
	Farming	(Gorell, 2004)
	Forestry	(Park, 2005)

Table 1. Potential environmental risk factors for Parkinson's disease

disease later in life may derive from various non-exclusive scenarios, namely chronic exposure to low levels of neurotoxicants, time-limited exposure early in life with later manifestation due to the decline of certain brain cell populations with advanced aging, and/or increased sensitivity to exposure with advanced age (see (Di Monte et al. 2002)). These hypotheses are particularly relevant to the interpretation of the epidemiological data gathered over the years and which will be reviewed in this chapter.

1.1 Clinical and pathological features of Parkinson's disease

One of the challenging aspects of PD is the heterogeneous nature and variability of the symptomatology and pathology (Lewis and Barker 2009). Two main subtypes of the disease have emerged from clinical observations based on the age of onset and the evolution/progression of the disease. While the disease in younger patients is rather typified by symptoms of resting tremors, older patients are more likely to suffer from "postural imbalance and gait disorders" (Selikhova et al. 2009). These disparate clinical manifestations may reflect various etiologies derived from interactions between genetic and environmental factors. While this disorder has for long been viewed for its predominant motor deficits, a much more complex scheme of the pathophysiology is being unveiled, and includes several non-motor features such as cognitive impairments, depression, anxiety and sleep-related disturbances (see **Figure 1**). The nature and diversity of the handicaps caused

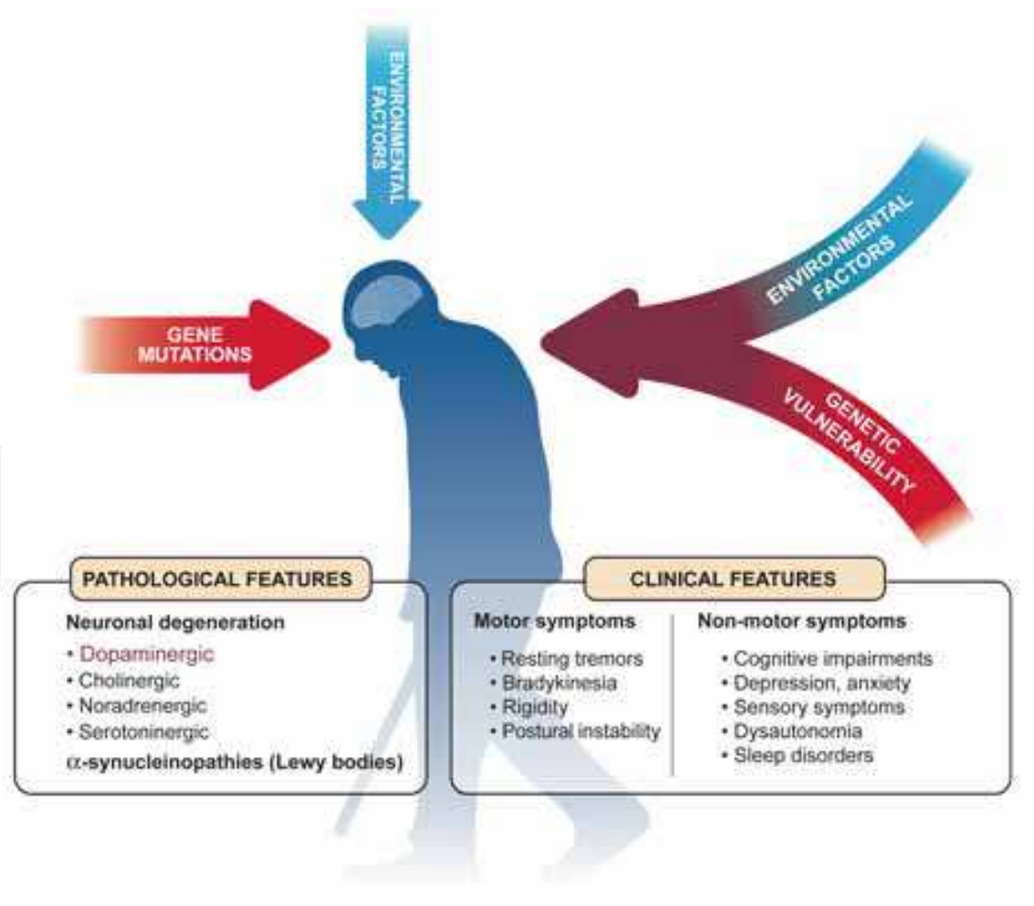

Fig. 1. Current views of the etiology and pathology of Parkinson's disease

by PD make it a very debilitating condition. The long-standing history and research devoted to the motor impairments of the disease have revealed that they result, in large part, from a loss of a specific subpopulation of dopaminergic neurons within the basal ganglia, a subset of brain structures involved in the control of psychomotor behaviors. Conversely, the non-motor alterations observed in PD have been related, for example, to the loss of non-dopaminergic cells, such as the noradrenergic (Zarow et al. 2003), serotoninergic (Braak et al. 2004) and cholinergic neurons of various other brain nuclei (**Figure 1**). PD is also characterized by a synucleinopathy, another pathological hallmark which consists in the entanglement of the mutated form of α-synuclein, which leads to Lewy body formation further postulated to cause cell damage by impairing neuronal functions (Waxman and Giasson 2009).

2. Is pesticide exposure a risk factor for Parkinson's disease?

2.1. Evidence from epidemiological studies

The historical observations, in the late 70's, of the sudden appearance of parkinsonism in seven young individuals exposed to 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al. 1983) gave birth to the notion of a potential link between environmental factors and the development of PD. MPTP itself does not pose a likely exposure risk for the general population. However, MPTP bears striking similarities to other naturally occurring as well as manmade substances, namely the heavily used pesticides rotenone and paraquat. The specific relationship between exposure to pesticides and the development of PD has received increasing attention since the early 80's, when Barbeau discussed the association between manganese or MPTP intoxication and the pathogenesis of this disorder. He proposed that individuals being frequently exposed to environmental compounds bearing chemical conformations similar to MPTP could develop comparable parkinsonism syndromes (Barbeau, 1984). A few years later, he reported his observations of an association between living in an agricultural environment and the risk of developing PD in the province of Quebec, Canada, where pesticide use was strikingly high at the time (Barbeau et al. 1987). While the epidemiological studies published in the last three decades have raised awareness of the potential health issues related to pesticide-promoted agriculture, they have not indisputably demonstrated a specific relationship between these toxins and the development of PD. In the following sections, we will attempt to shed light on the investigations published since 1989, discussing both the positive evidence and the lack of association between pesticide exposure and neurodegeneration.

2.1.1 Pesticides and Parkinson's disease: Positive associations from retrospective studies

Evidence tying pesticide use and PD has surfaced from all over the world, although the identification of specific compounds under this general heading has been more complex. Considering this important limitation, dithiocarbamates and pesticides of the organochlorine family of insecticides have been the targets of the vast majority of retrospective case-control studies conducted to date. Despite small sample sizes, a large number of these inquiries have revealed a positive correlation between pesticide contact and PD. Such observations were made in nursing homes for elderly in two Hong Kong districts, where 3.4% of these residents (> 60 years) suffered from PD (odds ratio (OR) = 3.6; 95%

confidence interval (CI) 1.0-12.9)[1] (Ho et al. 1989). The results of another study involving 106 patients diagnosed with PD (their spouses serving as controls), showed that patients had significantly greater rural experience and were more likely to have routinely sprayed pesticides in comparison to their partners (OR = 7.0, $p < 0.05$) (Golbe et al. 1990). In a population-based case-control study comprising 130 PD subjects living in Calgary and 260 randomly selected age- and sex-matched community controls, herbicide (OR = 3.06; 95% CI 1.34-7.00, $p = 0.006$) and insecticide use (OR = 2.05; 95% CI 1.03-4.07, $p = 0.042$) (but not fungicide) were found to be significant predictors of PD, after controlling for confounding factors or interactions between the exposure variables (Semchuk et al. 1992). A link between herbicide exposure and PD (OR = 3.22, $p = 0.033$) was also found in young onset PD patients (i.e. diagnosed before the age 50) as compared to controls diagnosed with rheumatoid arthritis (Butterfield et al. 1993) (see **Table 2** for details).

In the late 90's, three additional studies reported a connection between the risk of developing PD and exposure to pesticides. In a Hong Kong hospital-based, case-control study regrouping 215 PD cases and 313 controls, the duration of exposure to farm pesticides correlated with increased PD risk (multivariate analysis). Pesticide exposure in women conducting farming activities (OR = 6.84; 95% CI 1.90-24.7; $p = 0.003$) was also found, although this was not the case for men. It should be noted that sample sizes were very small (6 men and 13 women with PD; 13 control men and 3 women) (Chan et al. 1998). In a population-based case-control study referring to a cohort of men and women over 50 pooled from medical centers of metropolitan Detroit (144 PD cases and 464 controls), a significant association between occupational exposure to herbicides (OR = 4.10; 95% CI 1.37-12.24) or insecticides (OR = 3.55; 95% CI 1.75-7.18) was reported. However, no relation was found again with regard to fungicide exposure (Gorell et al. 1998). In 1999, a case-control study conducted in southeastern Sweden and involving the participation of 113 idiopathic PD cases and 263 control subjects reported an increased risk of idiopathic PD in men (10 men with PD and 10 men in controls had a history of handling pesticides), which was associated with agricultural labor and pesticide contact (OR = 2.8; 95% CI 0.89–8.7) (Fall et al. 1999).

[1] A relative risk (RR) is a comparative measure of the observed risk of developing PD in individuals who are exposed to pesticides vs. the observed risk of developing PD in a group of "equivalent" subjects who were not exposed. A RR of 1.0 indicates that there is no increased risk. Using 1.0 as the benchmark, a reported RR of, for example, 1.34 may indicate that the PD risk from pesticide exposure is 0.34 or 34% higher. However, for the result to be taken into consideration, the RR has to achieve statistical significance, using confidence interval (CI) levels. The generally agreed upon confidence level is 95%, where there is a 5% chance that the significant result is due to the random luck of draw. The CI implies that there is a 95% probability that the "real" RR lies anywhere in the range between the numbers of the interval. The CI is affected by sample size and by variability among subjects. This signifies that the findings are statistically significant only when the lower number of the interval exceeds 1.0. Additionally, the narrower is the interval, the more statistical power there is to the result. When the higher number of the interval is below 1.0, pesticide exposition is either not associated to PD, or is protective against PD. Any RR rating of less than 2 is very weak, difficult to interpret and very likely to be due to either bias, confounding factors or chance. Case-control studies often prevent you from evaluating a RR, but the odd ratio (OR) can always be calculated and interpreted. A case-control design usually involves the selection of research subjects on the basis of having PD rather than on the basis of having been exposed to pesticide. The probability of developing PD in pesticide-exposed subjects can be estimated, but not the probability of being exposed to pesticides when you have PD. The OR offers a reasonable interpretation, as long as the outcome event is rare and its interpretation rely strongly on how the controls were recruited, and is usually higher than the RR.

An additional number of retrospective studies reporting a relationship between pesticide exposure and PD were conducted after 2000. Using a cohort of 310 men, mostly orchardists who had previously participated in a cohort study of men occupationally exposed to pesticides in Washington State, Engel *et al.* (2001a) found a significant association for older subjects exposed to pesticides (Prevalence ratio (PR) = 2.0; 95% CI 1.0-4.2). Similar results were obtained for the middle tertile but did not reach statistical significance (PR = 1.9; 95% CI 0.9-4.0). However, no specific pesticide, or classes of pesticides, were associated with an increased risk of having PD (Engel et al. 2001a). In another study in Israel, the second strongest predictor of PD risk in 93 PD patients living in cities and 93 age- and sex- matched controls was exposure to pesticides (OR = 6.34; 95% CI 0.75-53.8, $p = 0.06$) (Herishanu et al. 2001). A subsequent case-control study performed in northeastern Italy and composed of 136 PD cases and 272 controls affected by other neurological diseases reported a positive association between pesticide exposure and PD (crude OR = 2.0; 95% CI 1.1-3.5, $p = 0.0237$). The mean length of exposure to pesticides was also significantly different in these cases, as compared to control subjects (4.1 years, standard deviation (SD) = 10.9 and 2 years, SD = 6.4, respectively; $p < 0.05$) (Zorzon et al. 2002). Gender differences were also outlined in a study involving 113 prevalent cases of PD. Multivariate analyses were independently performed for men and women, and ownership of licenses for pesticide use was positively associated with PD, but only in men (OR = 3.68; 95% CI 1.57–8.64) (Baldereschi et al. 2003). A population-based study in a genetically isolated community in a rural area of Turkey pointed to an increase in the prevalence of parkinsonism (4.1%) in individuals ≥ 65 years of age (36 cases of parkinsonism and 108 age- and sex-matched community controls). In this cohort, pesticide exposure was significantly associated with parkinsonism (OR = 2.96; 95% CI 1.31-6.69, $p = 0.015$) (Duzcan et al. 2003). An increased prevalence in men was also demonstrated (OR = 2.4; 95% CI, 1.1-5.4; $p = 0.04$) in a cohort that included every PD patients in Olmsted County (MN), from 1976 through 1995. Cases were matched to general population controls for age and gender (Frigerio et al. 2006) (see **Table 2** for details and **Figure 2** for geographical mapping of studies conducted).

In counterpart to the positive association of the use of pesticide *per se* and the occurrence of PD, the authors of another case-control study conducted in British Columbia (Canada), and involving 127 PD cases and 245 controls (121 with cardiac disease and 124 randomly selected from electoral registers) established a significant association between idiopathic PD in men practicing a profession in which exposure to pesticides was highly probable (OR = 2.32; 95% CI 1.10-4.88). However, they considered occupational exposure to several chemicals, including organochlorines, organophosphates, carbamates and dithiocarbamates, but none of these chemicals alone were connected with idiopathic PD (Hertzman et al. 1994). The authors concluded that the pathogenesis of PD is more likely to be multifactorial, thus excluding the possibility of a single-agent hit.

2.1.2 Pesticides and Parkinson's disease: Lack of association from retrospective studies

A comparable number of retrospective epidemiological studies have failed to identify a relationship between pesticide exposure and the risk of developing PD. In a case-control study using 150 PD cases from a Kansas movement disorder clinic and 150 age- and sex-matched controls attending other neurological and medical centers, no significant difference in the incidence of PD was detected for exposure to herbicides or pesticides with respect to the number of years of exposure, type of herbicide or pesticide, circumstances of exposure,

surface of land or type of crops on which herbicides/pesticides were employed, except for a marginal significance for exposure to herbicides/pesticides sprayed on corn (Koller et al. 1990). In another case-control study in which 42 PD subjects were matched to 84 controls of the Community Health Department of Valleyfield (Quebec, Canada), pesticide handling did not relate to PD. Oddly, other factors frequently identified as risk factors for PD, such as living in rural (OR = 0.31; 95% CI 0.11-0.91, $p < 0.05$) or industrial areas or working in mines (OR = 0.15; 95% CI 0.04-0.55, $p < 0.05$), were associated with a decreased risk for being struck with the disease (Zayed et al. 1990). Another case-control study using a cohort of 80 patients with late-onset PD (> 60 years old) and 69 early-onset patients (< 40 years old) recruited from various American hospitals, and 149 age- and sex-matched control subjects selected by the case subjects (relatives and spouses were not eligible) or from hospital files failed to implicate exposure to herbicides or pesticides in the incidence of PD (Stern et al. 1991). Moreover, in a case-control study involving 19 families harboring two or more PD cases, and 38 controls, herbicide and pesticide exposure was not a significant risk factor, although statistically significant differences were found with the following factors: rural residence, well-water consumption and farming (Wong et al. 1991). Additionally, in a study realized in a selected urban area of Madrid, among 128 unselected PD patients and 256 age- and sex-matched controls, past exposure to pesticides (for at least one year) and duration of exposure was apparently not associated with an increased risk of developing PD (Jimenez-Jimenez et al. 1992) (see **Table 2** for details and **Figure 2** for geographical mapping of studies conducted).

In South East Queensland and Central West New South Wales in Australia, a case-control study involving 224 PD cases and 310 control subjects reported no significant difference between patients and controls for exposure to herbicides and pesticides, but rural residence emerged as a significant risk factor for PD (McCann et al. 1998). Furthermore, exposure to pesticides and herbicides was similar between 86 PD cases and 86 matched controls, which were all outpatients from the same hospital (Smargiassi et al. 1998), and between 140 PD cases who were recruited from the Boston University Medical Center, where 147 friends and in-laws served as control subjects (Taylor et al. 1999). One other study undertaken in 1999 failed to detect an association between herbicide and pesticide exposure and PD, which consisted in a community-based case-control study in rural municipalities of the southwestern part of Finland using 123 PD cases and 246 matched control subjects (Kuopio et al. 1999). Additionally, no risk association was found with pesticide and/or herbicide contact in a case-control study in the Limousin region of France, using a cohort composed of 140 PD patients and 280 age-matched control subjects. The duration of exposure to pesticides or herbicides, however, was not determined (Preux et al. 2000).

More recently, a population-based case-control study using a cohort of 250 idiopathic PD cases and 388 healthy control subjects derived from a health care system database in western Washington State and the University of Washington, observed no significant association between occupational exposure and PD, but suggested a gradient of risk for occupational titles that paralleled the predicted level of pesticide exposure (e.g. pesticide worker > crop farmer > combined animal and crop farmer > dairy farmer) *(*OR = 2.07; 95% CI 0.67-6.38). ORs were also elevated for herbicides (OR = 1.41; 95% CI 0.51-3.88) and particularly paraquat (OR = 1.67; 95% CI 0.22-12.76), but there was no evidence of risk for exposure to pesticides used on a home basis (Firestone et al. 2005). The same group reported that the risk of PD was not significantly associated with exposure to pesticides in general. When

exploring specific pesticides, the only increased risk trend was for men exposed to parathion, the most potent organophosphate known, although this was not statistically significant. The cohort was composed of 404 idiopathic PD cases and 526 controls (Firestone et al. 2010). In New Delhi, India, a case-control study involving 377 PD patients attending a movement disorder clinic and an equal number of outpatients with other neurological diseases, did not report any significant correlation between the occurrence of PD and exposure to insecticides, herbicides and rodenticides. Nevertheless, exposure to herbicides was increased among control subjects (Behari et al. 2001). This is, to our knowledge, the only report of a trend towards a negative correlation between pesticide use and PD, although it did not reach statistical significance.

Taken together, the results of the retrospective epidemiological analyses are inconsistent, which reflects the great variability in the methodologies employed and the increased bias inherent to self-report studies. In addition, most of the studies described above used a relatively small number of subjects, with an even smaller number of subjects presenting a past history of pesticide exposure. This drawback considerably decreases statistical power and therefore limits the relevant analyses. Overall, despite the large number of retrospective studies conducted in the past 20 years, the association between pesticide/herbicide exposure and the increased risk of PD remains inconclusive, although the available evidence tends to suggest that pesticide exposure plays a role in some idiopathic forms of the disease.

2.1.3 From the angle of prospective studies and meta-analysis

In an attempt to eliminate recall bias, some epidemiological studies have used a prospective approach. The first study conducted in such a manner analyzed the relationship between exposure to pesticides and an increased risk of developing PD 30 years following the determined moment of initial pesticide exposure. Among the 7 986 participants in a cohort of Hawaiian plantation workers, 116 men were diagnosed with PD during the 30-year follow-up, with a significantly increased incidence among men who worked for more than 10 years on a plantation. Despite the fact that age-adjusted incidence of PD was higher in men exposed to pesticides, in comparison with those spared from pesticide exposure, this analysis did not reach statistical significance (Petrovitch et al. 2002). Another prospective cohort study - of 1 507 French elderly - used a job exposure matrix to assess occupational exposure and revealed that subjects who had been occupationally exposed to pesticides exhibited lower cognitive performance. The authors of this study further reported that exposure to pesticides increased the relative risk of developing PD in men (OR = 5.63; 95% CI 1.47-21.58), but not in women, after confounding factors (smoking and education level) were taken into account (Baldi et al. 2003b). In a subsequent study focusing specifically on PD and using 84 PD cases and 252 population-based controls belonging to the same French elderly cohort, a positive association was observed with occupational pesticide exposure (OR = 2.2; 95% CI 1.1-4.3). However, no clear dose-response relationship was found (Baldi et al. 2003a). Using participants enrolled in the Cancer Prevention Study II Nutrition Cohort, Ascherio *et al.* (2006) reexamined whether individuals exposed to pesticides expressed a higher risk for PD. In 1982, participants completed a survey concerning occupation and exposure to selected chemicals or dusts, including pesticides. After follow-up surveys in 1997, 1999, and 2001, 7 864 participants reported exposure to pesticides, of which 1 956 were farmers, ranchers, or fishermen, thereby revealing a 70% higher incidence of PD in individuals exposed to pesticides (adjusted relative risk (RR), 1.7; 95% CI 1.2-2.3; $p = 0.002$).

The RR for pesticide exposure was similar in farmers and non-farmers. No relation was found between risk for PD and any of the other occupational exposures surveyed (e.g. asbestos, chemicals/acid solvents, coal and stone dust, dyes, gasoline exhaust) (Ascherio et al. 2006) (see **Table 2** for details and **Figure 2** for geographical mapping of studies conducted).

In 2000, Priyadarshi and colleagues conducted a meta-analysis encompassing 19 studies published between 1989 and 1999. When all studies were combined, the OR for PD risk in association with pesticide exposure was 1.94 and 2.15 for studies performed in the United States alone, corresponding to a 2-fold risk increase. The risk of PD increased with duration of exposure, but no significant dose-response relationship was established and no specific type of pesticides was identified (Priyadarshi et al. 2000). The consistency of the results obtained in the studies selected for this meta-analysis allowed the authors to conclude that exposure to pesticides may be a risk factor for PD, independently of the place where the study was conducted.

2.1.4 Additional types of analyses

Other methodologies have been employed to assess the possible link between pesticide exposure and PD. For example, one study used a proportional odds model for survival data comparing all PD cases that were recorded as underlying or associated causes of death occurring in California, with all deaths from ischemic heart disease during the same period. They further classified Californian counties into several pesticide use categories based on data from pesticide use reports. Results showed that mortality from PD as the underlying cause of death was higher in counties in the category of agricultural pesticide use. Moreover, a dose-response relationship was reported for insecticide use per area of county land treated, but not for the amounts of restricted pesticides used or length of residency in a county prior to death (Ritz and Yu 2000).

2.1.5 Analyses of quantitative measures of pesticides

Finally, a few studies have assessed the link between pesticide exposure and PD by quantifying pesticide levels in PD patients. This has been tackled by measuring pesticides in both the serum and brain of deceased patients. A case-control study at the University of Texas Southwestern Medical Center collected serum samples from 50 PD patients and 43 controls to quantify the levels of 16 organochlorine pesticides. Hexachlorocyclohexane was detectable in 76% of PD patients and 40% of controls. The higher frequency of detection in PD cases was significant ($p < 0.05$), as was the OR for the presence of this pesticide in serum predicting the diagnosis of PD (OR = 4.39; 95% CI 1.67-11.6). None of the other 15 organochlorine pesticides showed detectable differences between controls and PD patients (Richardson et al. 2009). In addition, a study used organochlorine pesticide exposure data collected several years prior to the onset of PD as a potential biomarker for PD. Forty thousand two hundred and twenty-one serum samples of individuals aged ≥ 15 years were collected between 1968 and 1972 as part of a nested case-control study within the Finnish Mobile Clinic Health Examination Survey, and were analyzed in 2005–2007 for organochlorine pesticides. A total of 196 incident PD cases were identified during the follow-up in 1994 and were matched to 349 controls. Overall, 5 organochlorine pesticides were found at high levels, but only weak association emerged with this analysis. Only

increased dieldrin concentrations were associated with increased odds of PD (OR per interquartile range 1.95; 95% CI 1.26–3.02, p = 0.003) after adjustment for confounding factors (Weisskopf et al. 2010). Although this study presents an interesting design, with data collected *prior* to the development of PD, several limitations have to be taken into account. Serum samples were collected only once and reflect past pesticide exposure, but not exposure during the following decades. Importantly, exposure to pesticides with shorter half-lives that could have contributed to the pathology cannot be ruled out.

The presence of organochlorines was also verified in *post-mortem* brain samples of 20 PD patients and 14 non-neurological control subjects. Of all the organochlorines measured, dieldrin and dichlorodiphenyltrichloroethane (DDT) were the only pesticides detected. Dieldrin was found in 6 out of 20 PD brains and in none of 14 control samples. The association between dieldrin and the diagnosis of PD was significant (p = 0.031) (Fleming et al. 1994). Others have analyzed organochlorine concentrations in brain areas more specifically affected by the pathology (e.g. caudate nucleus). There were indeed significantly higher concentrations of dieldrin in PD tissues as compared to controls (Corrigan et al. 1998). The same group reported significantly higher levels of dieldrin and lindane in the substantia nigra (another structure largely affected by neuronal degeneration in PD) of PD patients as compared to nonparkinsonian controls (Corrigan et al. 2000).

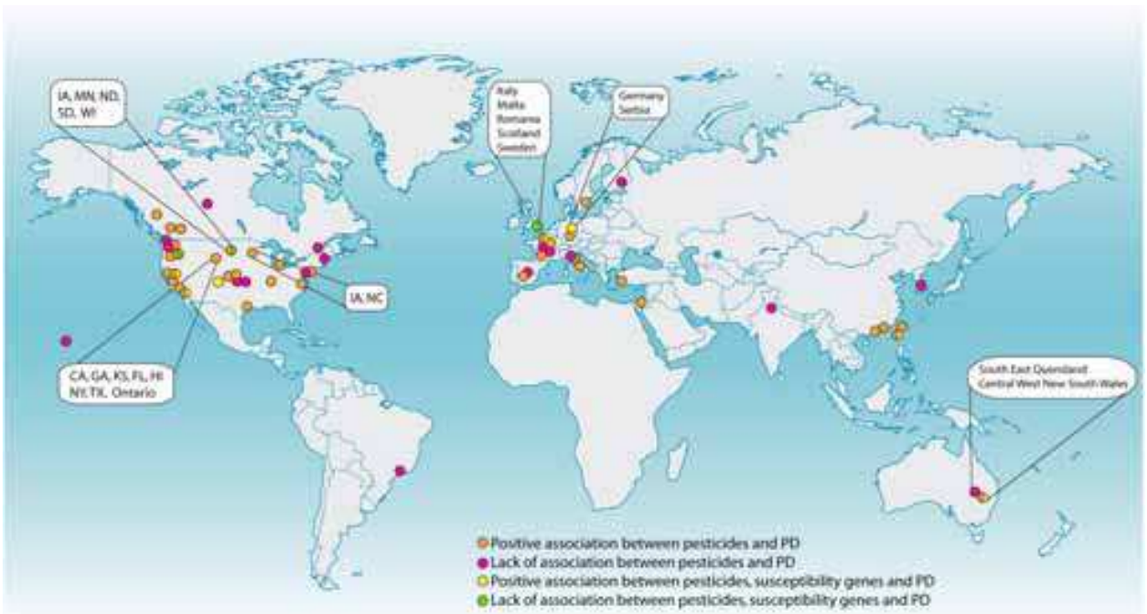

Fig. 2. Mapping of epidemiological studies assessing the relationship between pesticide exposure and the risk of developing Parkinson's disease. *Orange* circles represent studies reporting a positive association between pesticide exposure and PD, whereas *pink* circles illustrate studies reporting a lack of association. Studies assessing the vulnerability of specific gene polymorphisms are represented by a *yellow* circle for a positive association, and a *green* circle for a lack of association. Double-colored circles depict positive or lack of associations in studies assessing both the risk of PD from pesticide exposure alone, or including genetic vulnerability.

2.2 Epidemiological studies targeting specific pesticides

2.2.1 Organochlorines

Organochlorines are cholinesterase inhibiting pesticides that were introduced on a large scale on the world market during the 60's and 70's. These compounds are classified as moderately (e.g. DDT, endosulfan, toxaphene), highly (e.g. aldrin, dieldrin, endrin) or extremely toxic (e.g. hexachlorobenzene) by the International Program of Chemical Safety of the World Health Organization. A case-control study of 380 PD patients recruited from nine German clinics, 379 neighborhood and 376 regional control subjects found a significantly elevated risk of PD for general pesticide use and for organochlorines (OR = 5.8; 95% CI 1.1-30.4) and alkylated phosphates (OR = 2.5; 95% CI 1.3-4.6) in particular (Seidler et al. 1996). More recently, another group reported that organochlorine and organophosphorus pesticides were significantly associated with PD in a family-based case-control study involving 319 cases and 296 relatives and other controls, matched on genetic and demographic factors. Other controls were ascertained as spouses, unrelated controls or as related controls in families where no environmental risk factor data were available. PD patients reported significantly greater direct pesticide application/contact than their unaffected relatives (OR = 1.61; 95% CI 1.13–2.29). Furthermore, PD was associated with the highest frequency of exposure in both genders (OR = 2.15; 95% CI 1.06-4.35 for men and OR = 2.43; 95% CI 1.18-5.01 for women). A dose-response trend (OR = 2.47; 95% CI 1.12-5.44) and an association of PD with the lowest duration (p = 0.0058) were also reported, but only in women. Nevertheless, an association with PD was significant for the highest duration (OR = 2.70; 95% CI 1.35-5.40) and cumulative exposure (OR = 2.34; 95% CI 1.14-4.79), and significant dose-response trends were detected (p = 0.021 for duration and p = 0.036 for cumulative exposure). The latter associations were restricted to individuals without a family history of PD (Hancock et al. 2008). Moreover, a recent community-based case-control study examined the relationship between PD and pesticides in a population characterized by a high prevalence of exposure. Dose-effect analyses were performed using a cohort of 224 PD cases and 557 controls from the French Health Insurance (*Mutualité Sociale Agricole)* database for agricultural workers and related occupations. Twenty-nine pesticide families, based on a chemical classification, were analyzed in men exclusively. PD and overall professional pesticide use were positively associated (OR = 1.8; 95% CI 1.1-3.1), and a dose-effect relationship was found for the number of years of usage ($p < 0.01$). Insecticides were associated with PD (OR = 2.2; 95% CI 1.1-4.3), and more particularly insecticides belonging to the organochlorine family (OR = 2.4; 95% CI 1.2-5.0). In men with late-onset PD, these associations were more prominent ($p < 0.01$) and were characterized by a dose-effect relationship (Elbaz et al. 2009) (see **Table 2** for details and **Figure 2** for geographical mapping of studies conducted).

An association between PD risk and exposure to several specific pesticides was reported in a study that enrolled individuals applying for certification for using restricted pesticides in Iowa and North Carolina. Data were obtained from licensed private pesticide applicators and spouses participating in the Agricultural Health Study Cohort. In this particular study, PD cases were selected based on self-report, thus the diagnosis was not confirmed by a neurologist. PD cases were compared with cohort members who did not report PD. The incidence of the disease was associated with cumulative days of pesticide use, applying pesticides themselves more than half of the time (OR 1/4 = 1.9; 95% CI 0.7-4.7). However, prevalence of PD was not associated with overall pesticide use. The investigators further

observed elevated ORs for the prevalence of PD for the herbicides pendimethalin, paraquat, and cyanazine, and for the fumigants CS_2/CCl_4 and ethylene dibromide. ORs for incident PD were also elevated for the herbicides dicamba, trifuralin, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and butylate, the insecticides lindane and phorate, the fungicides chlorothalonil and benomyl, and the fumigant CH_3Br (Kamel et al. 2007). A more recent study employed a geographic information system that integrated data from California pesticide use reports and land-use maps (instead of surveys) to assess the degree and nature of pesticide exposure in PD patients to estimate potential well-water contamination with agricultural pesticides among 368 PD cases and 341 population controls who participated in the Parkinson's Environment and Genes Study. The study investigated six different pesticides (diazinon, chlorpyrifos, propargite, paraquat, dimethoate and methomyl). Elevated levels of possible well-water contamination with methomyl (OR = 1.67; 95% CI 1.00–2.78), chlorpyrifos (OR = 1.87; 95% CI 1.05–3.31), and propargite (OR = 1.92; 95% CI 1.15–3.20) were associated with a 70 to 90% increase in RR of PD. They further showed that exposure to a higher number of water-soluble and organophosphate pesticides also increased the RR of PD in that cohort (Gatto et al. 2009). Another recent study employed a multicenter case-control study design involving 8 movement disorder centers in North America to evaluate the relationships between occupations, specific job tasks, or exposure and the risk of parkinsonism. Five-hundred nineteen PD patients and 511 controls that were primarily non-blood relatives, or acquaintances, participated in the study. Pesticide use was associated with an elevated risk of parkinsonism (OR = 1.90; 95% CI 1.12-3.21, $p = 0.02$). In addition, the use of any of the 8 pesticides selected *a priori* as presenting a particular interest to the development of animal models of PD (2,4-dichlorophenoxyacetic acid (2,4-D), paraquat, permethrin, dieldrin, diquat, maneb, mancozeb and rotenone; cf. section 2.3) also increased the risk of parkinsonism (OR = 2.20; 95% CI 1.02-4.75. $p = 0.04$). 2,4-D was the only pesticide significantly associated *per se* with an increased risk for PD (2.59; 95% CI 1.03-6.48 p = 0.04) (Tanner et al. 2009).

2.2.2 Paraquat, maneb and rotenone

Some epidemiological studies have gone further with their analyses, isolating specific classes of pesticides or individual pesticides to determine their possible influence on the probability of developing PD. One of these pesticides is paraquat, a contact herbicide belonging to the heterocyclic quaternary ammonium family and a very potent, self-regenerating oxidizing agent and photosynthesis inhibitor which is widely used in agriculture, based in part on the fact that it acts quickly and is characterized by a short bioavailability. A first report was based on 57 PD cases and 122 age-matched, randomly selected controls from regional electoral rolls, all < 80 years of age, where four PD patients and no controls reported paraquat contact. Although an OR could not be calculated (no exposed controls), a Fisher's exact test gave a significant probability estimate of 0.01 for the association between paraquat contact and development of PD (Hertzman et al. 1990). Over 120 PD cases recruited from the Movement Disorder Clinic of the National Taiwan University Hospital in Taipei and 240 hospital controls recruited from the neurological or medical outpatient clinics at the same hospital, 28 PD cases and 18 control subjects reported having been previously exposed to paraquat. In the univariate analysis, the use of herbicides and pesticides (OR = 2.89; 95% CI 2.28-3.66, $p < 0.01$), and the use of paraquat (OR = 3.22; 95% CI 2.41-4.31, $p < 0.01$) were associated with an increased PD risk that also followed a

dose-response relationship. The biological gradient between PD and the previous use of herbicides and pesticides, and paraquat specifically, remained significant even after adjusting for multiple risk factors. Of note, there was a greater risk of developing PD for subjects who had used paraquat and other herbicides/pesticides than for those who had used herbicides/pesticides but not paraquat (Liou et al. 1997).

Considering that the geographical distribution of paraquat and maneb overlaps in several areas of the USA, their potentially synergistic neurotoxic effects have been more closely examined. Both compounds are similarly applied, but paraquat has a much longer half-life than maneb. Costello and coll. have reported that exposure to paraquat and maneb within 500 m of the residence increased PD risk by 75% (OR 1/4 = 1.75; 95% CI 1.13-2.73), using the geographic information system that integrated data from the California pesticide use reports and land-use maps reported by Gatto et al. (2009). This study incorporated 368 idiopathic PD cases and 341 population controls from the Central Valley of California. The authors also evaluated PD risk for two separate periods of pesticide exposure (between the years 1974–1989 and 1990–1999). The risk of developing PD was higher in younger subjects or when exposed at a younger age to either maneb or paraquat alone (OR 1/4 = 2.27; 95% CI 0.91-5.70) or to both pesticides in combination (OR 1/4 = 4.17; 95% CI 1.15-15.16) (Costello et al. 2009) (see **Table 2** for details and **Figure 2** for geographical mapping of studies conducted).

More recently, a case-control study in eastern Texas recruited 100 PD cases and 84 controls, and observed a strong association between the risk for PD and the use of organic pesticides such as rotenone within the past year of gardening (OR = 10.9; 95% CI 2.5-48.0, $p < 0.001$) and any rotenone use in the past (OR = 10.0; 95% CI 2.9-34.3, $p < 0.001$). Exposure to several other pesticides was also evaluated, and an elevated risk was associated with domestic use of chlorpyrifos products (OR = 2.0; 95% CI 1.02-3.8, $p = 0.043$). A possible association of increased PD risk with the domestic use of paraquat was also observed, but did not reach statistical significance (Dhillon et al. 2008).

2.3 Evidence from animal studies

2.3.1 Paraquat- and maneb-induced animal models of Parkinson's disease

If epidemiological studies have left a rather confusing picture of the contribution of pesticides to PD, basic research has also addressed the question by attempting to duplicate the clinical and pathological signs of PD in both petri dishes and small laboratory animals. The following section is devoted to some *in vitro*, but particularly *in vivo* work performed in rodents in the hope of shedding light on the role of environmental toxins, such as pesticides, to the development of a syndrome resembling human parkinsonism.

It has been suggested that dopaminergic cell degeneration observed in PD is consequential to the toxic accumulation and aggregation of proteins, mitochondrial dysfunction and oxidative stress. The neurotoxicity of paraquat resides within its strong redox cycling properties that leads to its transformation to the reduced paraquat radical which is then readily reoxidized by O_2, thereby generating reactive oxygen species, including superoxide anions (O_2^-) (Autor 1977; Bus et al. 1974; Jones and Vale 2000). The oxidative stress thus generated is believed to cause lipid peroxidation, inhibition of complex I in the mitochondrial respiratory chain, as well as cell death. Several animal studies have reported that paraquat can cause dopaminergic neuronal degeneration, the vast majority of which used a systemic paraquat administration approach [e.g.: (Brooks et al. 1999; Fredriksson et al. 1993; Kang et al. 2009; Kuter et al. 2007; Li et al. 2005; Peng et al. 2004; Shimizu et al. 2003; Somayajulu-Nitu et al. 2009; Tawara et al.

1996)]. Systemic administration of paraquat can also produce motor deficits such as decreased locomotor activity, reduced spontaneity in gait performance, and impaired pole test performance (Brooks et al. 1999; Li et al. 2005; Somayajulu-Nitu et al. 2009), and can induce the upregulation and aggregation of α-synuclein in the substantia nigra of wild-type mice (Manning-Bog et al. 2002). Although this model – as any animal model of human diseases – does not entirely mimic the human pathology, studies of paraquat-induced parkinsonism in animal models have provided valuable information with regards to the potential mechanisms involved in neurodegenerative processes associated with environmental toxicity. Pathological observations made in animal models thus imply that paraquat is unlikely a single contributor to the etiology of PD.

One of the most compelling findings of animal studies has derived from using combination of paraquat and maneb. Indeed, combined administration of both compounds to rodents has been useful to demonstrate the potential synergistic effects of environmental compounds in reproducing some features of PD in animals. In addition to causing nigrostriatal dopaminergic depletion [e.g. (Cicchetti et al. 2005; Drouin-Ouellet et al. 2007; Saint-Pierre et al. 2006; Thiruchelvam et al. 2000a; Thiruchelvam et al. 2003a; Thiruchelvam et al. 2000b)], the paraquat and maneb combination has also been shown to potentiate α-synuclein-induced toxicity (Norris et al. 2007; Thiruchelvam et al. 2004). Moreover, systemic administration of paraquat and maneb induces motor impairments reminiscent of PD.

Two studies have further explored the effect of a developmental exposure to paraquat and maneb followed by a re-challenge latter in adult life. Early postnatal exposure to the combination of compounds generated a decrease in activity, striatal dopamine depletion and dopaminergic cell loss in the substantia nigra. An adult re-challenge of the paraquat/maneb combination showed an even more striking decrease in locomotor activity, striatal dopamine levels, and dopaminergic cell loss. While postnatal exposure to paraquat or maneb alone produced minimal changes in adulthood, a re-challenge at that time unveiled a quiescent toxicity due to these pesticides (Thiruchelvam et al. 2002). Another study assessed whether *in utero* exposure to paraquat and maneb would interfere with the development of the nigrostriatal dopaminergic pathway and enhance its vulnerability to dopaminergic neurotoxicant exposures in adulthood. Only males exposed to maneb prenatally and to paraquat in adulthood displayed significant decrease in locomotor activity, changes in striatal dopamine and selective dopaminergic neuronal loss in the substantia nigra (Barlow et al. 2004). The results obtained with the paraquat- and maneb-induced animal model have provided support for a multi-hit hypothesis in PD pathogenesis and recapitulate most epidemiological studies assessing this particular hypothesis, although the routes of delivery employed (mainly intraperitoneal (i.p.) and subcutaneous (s.c)) remain unrepresentative of human exposure. Taken together, research shows 1) an age-related propensity to incur degeneration of the nigrostriatal pathway in response to toxin (herbicide, pesticide, fungicide) exposure (Thiruchelvam et al. 2003b; Thiruchelvam et al. 2002), and 2) an exacerbation of nigrostriatal pathology by double-exposure whereby early (prenatal, postnatal) contact with these toxins predispose older animals to the effects of re-exposure to the toxins (Carvey et al. 2003; Ling et al. 2002; Thiruchelvam et al. 2002). The mechanism for the increased sensitivity to toxins in adults and/or re-exposed animals is to date unknown.

2.3.2 Rotenone-induced animal models of Parkinson's disease

Unlike quaternary amines like paraquat or diquat, rotenone crosses the blood-brain barrier due to its lipophilic attributes. This insecticide has been targeted as a potentially active agent

in PD pathogenesis based on its ability to inhibit complex I of the mitochondrial respiratory chain, which triggers the production of reactive oxygen species and the activation of mitochondria-dependent apoptotic molecular pathways. This subsequently leads to oxidative damage targeting proteins, lipids and DNA, ultimately leading to dopaminergic cell death (Dauer and Przedborski 2003; Vila and Przedborski 2003). Mutations in specific genes linked to mitochondrial proteins have also been associated with some familial forms of PD (Bueler, 2009). However, the specific mechanism involved in the enhanced vulnerability of nigral dopaminergic neurons to rotenone is still undeciphered. In opposition, an *in vitro* study has suggested that complex I inhibition might not be necessary for dopaminergic neuronal death (Choi et al. 2008). Nevertheless, rotenone has been suggested to act as a proteosome inhibitor (Chou et al. 2010; Wang et al. 2006b).

The most studied rotenone-induced animal model of PD involved a chronic mode of intravenous (i.v.) delivery via osmotic minipumps, although other delivery methods have also been explored, including i.p., and s.c. osmotic minipumps as well as intranasal and oral routes. In the vast majority of these studies, the substantia nigra dopaminergic neurons were affected, in addition to other types of neurons within the striatum. Several studies have reported that rotenone administration generated motor deficits reminiscent of several clinical features of PD such as hypokinesia, rigidity, hunched posture, unsteady movements, prolonged descent latency as well as resting tremors [e.g. (Alam et al. 2009; Alam et al. 2004; Alam and Schmidt 2004; Betarbet et al. 2000; Hoglinger et al. 2005; Luo et al. 2007; Pasha et al. 2005; Richter et al. 2007; Sherer et al. 2003; Tapias et al. 2009)]. Moreover, ubiquitin and α-synuclein aggregates were detected in striatal and nigral neurons in animals challenged with rotenone [e.g. (Betarbet et al. 2006; Cannon et al. 2009; Hoglinger et al. 2005; Inden et al. 2007; Luo et al. 2007; Monti et al. 2009; Takeuchi et al. 2009)]. As for paraquat and maneb-induced animal models of PD, rotenone induces peripheral toxicity leading to a high mortality rate, a phenomenon that does not resemble the human form of the disease (see review Cicchetti et al. 2009; Lapointe et al. 2004).

The mode of administration of rotenone employed in most animal studies does not mimic the route of exposure experienced in humans, as it is more likely that rotenone gains access to the brain via direct exposure of neurons in the gut and/or olfactory regions, i.e. the only nervous system structures directly exposed to environmental compounds (Lerner and Bagic 2008). One study administered rotenone intranasally daily for one month at a dose range similar to that used in i.p., i.v., and s.c. delivery studies, but reported no change in the nigrostriatal dopaminergic system and no behavioral alterations. A few studies have also explored the oral route of administration of rotenone and have observed degeneration of dopaminergic cells and their terminals. All of these studies also reported an upregulation or aggregation of α–synuclein accompanied with motor impairments (Inden et al. 2007; Inden et al. 2009; Pan-Montojo et al. 2010; Takeuchi et al. 2009). One of these studies administered rotenone intragastrically and observed α–synuclein accumulation and aggregation first at the periphery, and then in structures of the central nervous system affected in PD (Pan-Montojo et al. 2010). This reflects, to some extent, the course of the PD pathogenesis, where the synucleinopathy is restricted to the peripheral organs at the presymptomatic stages, whereas at latter stages, the substantia nigra and other nuclei of the midbrain and forebrain display similar pathological changes (Braak et al. 2003). The effect of chronic oral administration of rotenone to transgenic mice overexpressing human α–synuclein was also investigated. Despite increased cytoplasmic expression of α–synuclein and PINK1, along with decreased spontaneous locomotor movements induced by rotenone, no change in brain

dopamine levels or nigrostriatal cell loss was observed. The authors concluded that this model could mimic presymptomatic PD features and compensatory changes in early PD stages (George et al. 2010).

2.3.3 Animal model of Parkinson's disease induced by other pesticides

Most of the studies pertaining to the effects of various pesticides, especially organochlorines, have demonstrated some dopaminergic alterations within the nigrostriatal system (Miller et al. 1999; Pittman et al. 2003; Schuh et al. 2009), while others have failed to report such changes (Hatcher et al. 2008; Thiffault et al. 2001). However, results do suggest that developmental or adult exposure to dieldrin increases the vulnerability of nigrostriatal dopaminergic neurons by persistently altering the development of the dopaminergic system, or by inducing oxidative stress (Hatcher et al. 2007; Richardson et al. 2006). When probing other pesticides such as heptachlor, endosulfan and zineb, studies have shown their detrimental effect on the development of the dopaminergic system, subsequently leading to an increased vulnerability in adulthood (Caudle et al. 2005; Jia and Misra 2007; Richardson et al. 2008). Taken together, these studies suggest that developmental pesticide exposure causes long-term alterations of the dopaminergic system thereby rendering it more susceptible to dopaminergic damage in adulthood. Longitudinal epidemiological studies assessing the effect of pesticide exposure during the developmental stages would be of high relevance to evaluate the impact of such exposure on neurological disorder development in adulthood.

3. Genes and pesticide exposure

Although 90-95% of PD cases are of unknown etiology, 5-10% of patients are known to have monogenic forms of the disease. To date, 13 loci and 9 genes are associated with both autosomal dominant (e.g. α-synuclein, ubiquitin C-terminal hydrolase L1 (UCHL1), LRRK2, GIGYF2, Omi/Htra2) and autosomal recessive (e.g. parkin, PINK1, DJ-1, ATP13A2) PD, but additional genes have also been associated with the disease. Genes may also play a role in the sporadic form of PD, given the role of the encoded proteins in various important cellular functions such as in mitochondrial (e.g. α-synuclein, parkin, PINK1, Omi/HtrA2, DJ-1, POLG1) and lysosomal (e.g. α-synuclein, ATP13A2, GBA) functions, protein degradation (e.g. parkin, UCHL1, α-synuclein), developmental regulation (e.g. α-synuclein, parkin, UCHL1, LRRK2, Omi/HtrA2, Nurr1, PITX3, various microRNAs, etc.), and their localization at the synapse (e.g. α-synuclein, parkin, LRRK2, UCHL1, synphilin, etc.) (for a review, see Biskup 2008) (see **Table 3** for details and **Figure 2** for geographical mapping of studies conducted). Alterations in these proteins contribute to the pathological features encountered in the different forms of PD.

3.1 Susceptibility genes involved in the metabolism of pesticides

In recent years, a subset of epidemiological studies has thus focused on investigating a potential association between candidate genes for susceptibility to PD and exposure to pesticides. The first gene polymorphisms that have been studied code for glutathione-*S*-transferases (GSTs), which are a ubiquitous group of detoxification enzymes involved in the metabolism of several toxins, including pesticides, and that can protect cells against oxidative stress (Di Ilio et al. 1995). Using a cohort of 95 PD and an equal number of control

subjects, four *GST* classes were genotyped (*GSTM1*, *GSTT1*, *GSTP1*, and *GSTZ1*). In subjects who had been exposed to pesticides, there was a significant difference in *GSTP1* genotype between PD patients and controls (p = 0.009), but other *GST* polymorphisms did not show any association with PD (Menegon et al. 1998). A second study assessed the relationship between *GST* polymorphisms, PD and pesticide exposure in a multicenter study of paired relatives diagnosed with PD, designed for genetic linkage analyses. Seven single-nucleotide polymorphisms (SNPs) were genotyped in the *GSTP1* class, of which 3 were connected to the age of onset in the group of men occupationally exposed to herbicides. Significant trends were observed in the herbicide exposure group for the association of age of PD onset for three additional SNPs. The authors also reported that herbicide exposure modified the association between *GSTP1* and the age of onset. Furthermore, one haplotype was associated with earlier onset of PD (7.93 years) in the occupationally exposed group (p = 0.008) and a later PD onset (2.82 years) in the non-exposed group (p = 0.048) (Wilk et al. 2006). GSTP1 is expressed at the level of the blood-brain barrier and could influence the response to neurotoxins such as pesticides, by offering protection against the oxidative damage that is hypothesized to play a role in PD pathogenesis. However, another study failed to corroborate these results and reported that seven *GST* polymorphisms were in fact not associated with PD, nor was pesticide use (238 Japanese PD cases and 370 controls). In this particular study, controls were not matched to cases, which led to a significant difference between the age of subjects (controls being younger than cases) and the number of pesticide users was small, which gave negligible power to the analysis (Kiyohara et al. 2010).

Similar analyses were conducted to probe the potential association between PD and the organophosphates diazinon, chlorpyrifos, and parathion, and the influence of a functional polymorphism at position 55 in the coding region of the *PON1* gene (*PON1-55*). This gene codes for paraoxonase, an enzyme which hydrolyzes organophosphates and predicts the susceptibility of an individual to these compounds, more particularly the insecticides diazinon and chlorpyrifos (Costa et al. 2003). Exposure to chlorpyrifos was associated with an increased risk of PD, both at low and high frequency levels of exposure, and more prominently among people over 60 (OR = 2.65; 95% CI 1.19-5.90). An association between PD and high, but not low levels of diazinon exposure, was also reported, but not with parathion. Within subjects exposed to organochlorines, carriers of the variant *MM PON1-55* genotype displayed an increased risk of PD compared with subjects carrying the wild-type or heterozygous genotype and without a history of exposure (diazinon, OR = 2.2; 95% CI 1.1-4.5; chlorpyrifos, OR = 2.6; 95% CI 1.3-5.4). Additionally, the effect estimate for chlorpyrifos was greater in earlier-onset cases and controls (≤ 60 years of age; OR = 5.3; 95% CI 1.7-16), but no increase in PD risk was noted for parathion (Manthripragada et al. 2010).

In a larger case-control study, Dick and colleagues (2007) investigated the interactions between several polymorphic genes that metabolize foreign chemicals, metabolize or transport dopamine and that occur relatively frequently in the European population (*CYP2D6*, *PON1*, *GSTM1*, *GSTT1*, *GSTM3*, *GSTP1*, *NQO1*, *CYP1B1*, *MAO-A*, *MAO-B*, *SOD2*, *EPHX*, *DAT1*, *DRD2* and *NAT2*), exposure to solvents, pesticides and metals, and risk of PD. Nine hundred and fifty-nine prevalent cases of parkinsonism (767 with PD) and 1 989 control subjects were recruited from five European centers. Parkinsonism was modestly, but significantly associated with *MAO-A* polymorphism in males (G vs. T, OR = 1.30; 95% CI

1.02-1.66, adjusted for confounding factors). Although a possible interaction between a *GSTM1* null genotype and solvent exposure was shown, other gene-environment interactions failed to show any significant association (Dick et al. 2007).

3.2 Susceptibility genes involved in pesticide transport to the brain

The *multidrug resistance protein 1* (*MDR1* or *ABCB1*) gene encodes an integral membrane glycoprotein expressed in various tissues, including the blood-brain barrier, and which regulates brain penetration of a wide range of endogenous molecules and xenobiotics, including several pesticides such as organochlorines (Bain and LeBlanc 1996). In a case-control study, Zschiedrich and coll. (2009) evaluated the potential relationship between *ABCB1* variants and PD in relation to pesticide exposure in 599 PD patients and control subjects. Despite the fact that *ABCB1* was not associated with PD in this particular study, a different genotype distribution was observed between patients exposed to pesticides compared to non-exposed patients (OR = 4.74; 95% CI 1.009-22.306, p = 0.047), suggesting that common *ABCB1* variants may interact with pesticide exposure to influence PD risk (Zschiedrich et al. 2009). A second study evaluated the association between two polymorphisms in *ABCB1*, PD and organochlorine insecticide exposure among 207 cases and 482 matched control subjects enrolled in the French health system for agricultural workers described previously (Elbaz et al. 2009). As for the study of Zschiedrich and coll. (2009), *ABCB1* polymorphisms were not associated with PD. However, the OR for organochlorines was 3.5 (95% CI 0.9-14.5) times higher among homozygous carriers of variant *G2677* (A,T) alleles than noncarriers. The case-only analysis uncovered an association between carrying two variant *G2677* (A,T) alleles and organochlorines (OR = 5.4; 95% CI 1.1-27.5), as well as with the number of cumulative lifetime number of hours of exposure (overall, p = 0.005; analyses restricted to subjects exposed to organochlorines, p = 0.03) (Dutheil et al. 2010).

3.3 Susceptibility genes involved in elimination of toxic compounds derived from pesticides

A case-control study evaluated the role of manganese-containing superoxide dismutase (MnSOD) and NAD(P)H: quinone oxidoreductase 1 (NQO1) genes with PD risk in a southwestern Taiwanese population with a high prevalence of pesticide exposure. MnSOD is an enzyme that converts superoxide anions (O_2^-) into hydrogen peroxide (H_2O_2) and dioxygen (O_2). Suppressing free radicals within mitochondria protects against the detrimental effects of oxidative stress on cell integrity. In Japanese patients with familial PD, the *MnSOD* C allele is significantly related to the disease (Shimoda-Matsubayashi et al. 1997). NQO1 is also an enzyme that reduces several neurotoxic quinonoid compounds, which leads to protection of the cells against reactive oxygen species damage during redox cyclic processes (Chen et al. 2000). The genotypes of *MnSOD (−9 TNC)* and *NQO1 (609 CNT)* genes were determined among the 153 patients with idiopathic PD and 155 matched healthy controls. After adjustment for confounding factors, a significant association was found between pesticide exposure and PD risk (OR = 1.68; 95% CI 1.03-2.76, p = 0.023). In this population, *MnSOD* and *NQO1* polymorphisms were not associated with increased PD risk, but there was a significant difference in genotype distribution among subjects exposed to pesticide for the *MnSOD* C allele (OR = 2.49; 95% CI 1.18-5.26, p = 0.0072) and for the *NQO1*

T allele (OR = 2.42; 95% CI 1.16-4.76, p = 0.0089). Furthermore, a significant association was reported between the combined *MnSOD*/*NQO1* variant genotype among subjects exposed to pesticides and increased PD risk (OR = 4.09; 95% CI 1.34-10.64, p = 0.0052) (Fong et al. 2007).

3.5 Susceptibility genes targeted in Parkinson's disease

Two studies have examined the possible interaction between the dopamine transporter (DAT) gene (*SLC6A3*), of which eight haplotypes have been identified (grouped into two evolutionary clades (A and B)), and PD risk after pesticide exposure. In a case-control study of 293 cases and 395 controls that were classified by the number of risk alleles, a significant interaction between occupational pesticide exposure in men and the number of risk alleles was reported, the OR for having two or more risk alleles reaching 5.66 (95% CI 1.73–18.53) among subjects exposed to pesticides (Kelada et al. 2006). A subsequent study independently investigated the genetic variability in the DAT locus in 324 incident PD cases and 334 controls from the rural California case-control study using the previously described geographic information system for pesticide exposure evaluation (Costello et al. 2009; Gatto et al. 2009). Two SNPs were genotyped for the *DAT* 5′ A clades and the 3′ variable number of tandem repeats (VNTR), the susceptibility alleles being defined as the 5′ A clade and the 3′ VNTR 9-repeat. Carriers of one susceptibility allele who were highly exposed to paraquat and maneb had an increased PD risk (OR = 2.99; 95% CI 0.88-10.2), and this was more prominent in those with two or more alleles (OR = 4.53; 95% CI, 1.70-12.1). Similar results were also obtained for occupational pesticide analysis (Ritz et al. 2009).

Furthermore, it has been suggested that SNPs might lead to slight alterations in the *PINK1* gene and might play an important role in the development of sporadic late-onset PD (Wang et al. 2006a). In a study with 48 PD cases and 61 controls from Brazil carrying *PINK1* SNPs, 31.3% and 39.4% presented the *PINK1* SNP *IVS1−7* A→G polymorphism, respectively. Exposure to various environmental risk factors (living in rural areas, well-water drinking, and exposure to pesticides, herbicides or organic solvents) in collaboration with *PINK1* SNP *IVS1−7* A→G polymorphism had a significant effect in lowering the age of PD onset, whereas when singling out exposures to the various environmental factors, no association was found between such exposures, *PINK1* SNP *IVS1−7* A→G polymorphism and PD (Godeiro et al. 2010).

A case-control study with 833 case-control pairs further examined the possible interaction between *SNCA* REP1 genotypes (coding for α-synuclein), which have been shown to confer susceptibility to sporadic PD, and pesticide exposure on the risk of PD in human. This epidemiological study did not find any interaction between the *SNCA* REP1 genotype and herbicides, although both *SNCA* REP1 score (OR = 1.18; 95% CI 1.02-1.37; p = 0.03) and pesticide exposure were significantly associated with PD in younger subjects (≤ 59.8 years of age; OR = 1.80; 95% CI 1.12-2.87; p = 0.01 for all pesticides; OR = 2.46; 95% CI 1.34–4.52; p = 0.004 for herbicides) (Brighina et al. 2008).

Taken together, the results of the gene-environment epidemiological studies converge toward an influence of certain gene polymorphisms on the effect of exposure to at least some pesticides on PD and its onset. They further suggest that individual genetic susceptibility may affect the outcome of epidemiological studies. This is a very likely explanation for the inconsistent results reported thus far and needs to be taken into account when reviewing past studies on the effect of pesticide exposure and PD risk.

4. Conclusion

Numerous challenges must be faced in interpreting epidemiological studies, as illustrated in this chapter. Data gathered thus far originate from various approaches, which include case reports, mortality studies (geographical analysis of death certification), ecological studies (e.g. analyzing pesticide exposure from levels detected in the environment), case-control and cohort studies. The discrepancies in the results obtained with epidemiological studies are largely due to issues related to the methodological approaches utilized, case ascertainment, selection of controls and diagnostic criteria, all factors likely to introduce bias. Most methodologies employed are based on self-surveys and recall of chemical usage, which can be particularly precarious when collected from patients suffering from neurodegenerative disorders. Furthermore, questionnaires used to determine the type and length of pesticide exposure may vary significantly among studies - with the accuracy for self-reported pesticide exposure being high for broad categories and commonly employed pesticides, but not for specific pesticides (Engel et al. 2001b). Unbiased selection of controls is also of utmost importance but may be challenging. Controls and cases may be recruited from the general population or be hospital-based, which can result in selection bias for both cases and controls if participation is influenced by factors such as disease severity, personal income, cultural differences and geographic location. Control subjects are very often relatives or friends of the subjects, allowing for the possibility of similar exposure history and thus invalidating the risk estimate due to bias.

Misdiagnosis remains frequent in PD, especially in the early stages of the disease, and can thus have a significant impact on the outcomes of clinical and epidemiological studies (Litvan et al. 2003). A single causative factor might also be difficult to identify, because such a factor may differ among patients with different clinical manifestations. Stratifications of clinical subsets (e.g. age of onset, progression, motor symptoms, etc.) may help identify environmental causes of PD. Several elements, such as age, family history of PD, earlier head trauma due to accidents, smoking habits, caffeine consumption and infectious diseases, as well as environmental factors including well-water drinking and farming, have all been suggested to play a role in the incidence of PD, and can be sources of confounding factors. All of these potential biases may pose a significant hurdle in evaluating the actual contribution of pesticide exposure to PD. Despite accumulating evidence supporting the hypothesis that pesticide exposure may be responsible for the etiology of PD, at least in a subset of cases, the overall picture remains inconclusive but at least convincing enough to justify the debate to be pursued and the issue to be clarified.

Future research should focus on understanding how combining compounds that target different cellular functions might work cooperatively to also cause neuronal damage. As challenging as this task might be, pesticide properties, such as biological availability, persistence in the environment as well as application methods that can lead to widespread exposure, should be taken into account when evaluating the potential of a pesticide to participate to PD pathogenesis. In addition, genetic vulnerability is likely a key player in the outcome of pesticide exposure. In that regard, more studies are clearly needed to target specific polymorphisms. Finally, epidemiological studies have thus far provided rather disparate and somehow incoherent results, and segregation of different PD subtypes, as well as better methodologies with regard to the evaluation of pesticide exposure, might help in pinpointing the involvement of specific compounds in PD incidence and provide us with tools to design and develop drug targets to prevent PD pathogenesis.

	Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
Pesticides	(Ho, 1989)	China	7/34	7/105	3.6 (1.0-12.9)		Pesticide and herbicide use combined
	(Golbe, 1990)	USA	14/106	2/106	7.0	$p < 0.05$	
	(Hertzman, 1990)	Canada	31/57	57/121	1.34	$p = 0.184$	Analysis includes glyphosate, picloram, formaldehyde, malathion, 2,4-D, tebuthiuron, paraquat, diazinon, atrazine, pyrethrum, diquat and bromacil
	(Koller, 1990)	USA	NA/150	NA/150	1.1	$p = 0.82$	Pesticide and herbicide use combined
	(Zayed, 1990)	Canada	23/42	43/84	1.23 (0.46-3.29)	$p = 0.35$	Pesticide use
			6/42	16/84	0.81 (0.24-2.68)		1-10 years of pesticide use
			4/42	8/84	1.08 (0.24-4.66)		11-20 years of pesticide use
			5/42	10/84	1.23 (0.24-4.12)		21-30 years of pesticide use
			8/42	9/84	1.23 (0.56-6.57)		>30 years of pesticide use
	(Wong, 1991)	USA	NA/38	NA/38	1.0 (0.33-3.06)	$p = 1.00$	Pesticide and herbicide use combined
	(Jimenez-Jimenez, 1992)	Spain	43/128	70/256		NS	
	(Semchuck, 1992)	Canada	NA/130	NA/260	2.25 (1.27-3.99)	$p = 0.005$	Pesticide use
					1.41 (0.73-2.73)	NS	16-25 years of pesticide use
					2.27 (1.08-4.76)	$p = 0.03$	26-35 years of pesticide use
					2.21 (0.99-4.94)	NS	36-45 years of pesticide use
					2.25 (0.91-4.72)	NS	46-55 years of pesticide use
	(Hubble, 1993)	USA	NA/63	NA/76	3.42 (1.27-7.32)	$p = 0.004$	
	(Hertzman, 1994)*	Canada	33/71	22 /80	2.03 (1.00-4.12)		♂/Vs. controls with cardiac disease
				16/60	2.32 (1.10-4.88)		♂/Vs. controls randomly selected
			9/56	5/41	1.11 (0.32-3.80)		♀/Vs. controls with cardiac disease
				8/64	1.36 (0.48-3.85)		♀/Vs. controls randomly selected
	(Morano, 1994)	Spain	40/74	60/148		$p = 0.056$	Chi Square = 3.64
	(Chaturvedi, 1995)	Canada	22/87	323/2070	1.81 (0.92-3.36)	NS	Occupational exposure to pesticides and fertilizers combined
			12/87	178/2070	1.67 (0.67-3.63)	NS	Exposure to pesticides and herbicides combined as a hobby
	(Liou, 1997)	Taiwan	46/120	41/240	2.89 (2.28-3.66)	$p < 0.01$	Pesticide and herbicide exposure combined
			14/120	21/240	1.41 (0.52-3.85)	NS	1-19 years of combined pesticide and herbicide exposure
			32/120	20/240	6.72 (2.62-17.21)	$p < 0.01$	≥20 years of combined pesticide and herbicide exposure
	(Chan, 1998)	China	19/215	16/313	0.75 (0.26-2.22)	$p = 0.608$	Pesticide exposure in farming
					1.05 (0.992-1.11)	$p = 0.090$	Number of years exposed to pesticides
	(McCann, 1998)	Australia	NA/224	NA/310	1.2 (0.8-1.5)	$p = 0.5$	Pesticide and herbicide exposure combined
	(Menegon, 1998)	Australia	39/95	26/95	2.3 (1.2-4.4)	$p = 0.02$	

Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
(Smargiassi, 1998)	Italy	25/86	20/86	1.15 (0.56-2.36)	NS	Pesticide and herbicide exposure combined
(Fall, 1999)	Sweden	10/NA	10/NA	2.8 (0.89-8.7)	$p = 0.081$	♂/Handling pesticides within any occupation
		6/NA	8/NA	1.9 (0.46-7.3)	$p = 0.45$	♂/Handling pesticides within agriculture
(Kuopio, 1999)	Finland	16/123	42/246	0.65 (0.33-1.29)	$p = 0.221$	Regular use of pesticides
		32/123	54/246	1.23 (0.74-2.04)	$p = 0.431$	Occasional use of pesticides
		48/123	96/246	1.02 (0.63-1.65)	$p = 0.935$	Regular and occasional use of pesticides
(Taylor, 1999)	USA	NA/140	NA/147	1.02 (0.90-1.17)	$p = 0.73$	
(Werneck, 1999)	Brazil	6/92	3/110	2.49 (0.53-13.14)		Pesticide, herbicide and insecticide use combined
(Preux, 2000)	France	42/140	68/280		$p = 0.21$	Pesticide and herbicide exposure combined
(Engel, 2001)*	USA	48/65				PR = 0.8 (0.5-1.2)
(Herishanu, 2001)	Israel	6/93	1/93	6.81 (0.75-64.89)	$p < 0.1$	
(Zorzon, 2002)	Italy	25/136	28/272	1.6 (1.0-2.4)	$p = 0.035$	
(Baldereschi, 2003)	Italy	7/113	82/4383	3.68 (1.57-8.64)		Pesticide-use licence
		7/58	51/2247	4.41 (1.84-10.56)		♂/Pesticide-use licence
(Baldi, 2003a)	France	8/24			$p = 0.07$	♂/RR = 5.63 (1.47-21.58)
					NS	♀/RR = 1.02 (1.47-21.58)
(Baldi, 2003b)*	France	19/84	38/252	2.20 (1.11-4.34)	$p = 0.02$	
(Duzcan, 2003)	Turkey	15/36	21/108	2.96 (1.31-6.69)	$p = 0.015$	
(Firestone, 2005)	USA	19/156	28/241	1.01 (0.53-1.92)	NS	♂/Occupational exposure
		178/250	280/388	0.95 (0.66-1.37)	NS	Home-based exposure
(Ascherio, 2006)*	USA	43/413	NA		$p = 0.0003$	Pesticide and herbicide use combined, RR 1.8 (1.3-2.5)
(Frigerio, 2006)*	USA	24/90	10/78	2.4 (1.1-5.4)	$p = 0.04$	♂/Pesticides (including herbicides, insecticides and others)
		6/59	8/51	0.6 (0.2-1.9)	$p = 0.4$	♀/Pesticides (including herbicides, insecticides and others)
(Kedala, 2006)	USA	47/178	55/239	1.30 (0.81-2.06)	NS	
(Fong, 2007)	Taiwan	85/153	66/155	1.68 (1.03-2.76)	$p = 0.023$	
(Kamel, 2007)*	USA	67/82	65116/78938	0.5 (0.2-1.1)		Prevalent PD
		68/75	45325/54744	1.3 (0.5-3.3)		Incident PD
(Brighina, 2008)*	USA	303/833	278/833	1.11 (0.89-1.38)	$p = 0.37$	
(Cho, 2008)	Korea	44/230	8/75	1.105 (0.999-1.221)	$p = 0.091$	
(Dhillon, 2008)*	USA	70/100	59/84	1.0 (0.5-1.9)	$p = 0.972$	
(Hancock, 2008)*	USA	200/319	147/296	1.61 (1.13-2.29)		
		143/228	102/215	1.80 (1.20-2.70)		Negative family history
		57/91	45/81	1.20 (0.58-2.50)		Positive family history
(Costello, 2009)*	USA	110/368	75/341	1.52 (1.08-2.14)		
(Elbaz, 2009)*	France	48/224	121/557	1.4 (0.9-2.3)	$p = 0.18$	Gardening exposure
		107/224	225/557	1.8 (1.1-3.1)	$p = 0.02$	Professional exposure

	Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
	(Ritz, 2009)	USA	93/324	74/334	1.44 (1.01-2.06)		
	(Tanner, 2009)	Canada/USA	44/519	27/511	1.90 (1.12-3.21)	$p = 0.02$	Pesticides
			21/519	11/511	2.20 (1.02-4.75)	$p = 0.04$	Any of 8 specific pesticides
	(Dutheil, 2010)	France	41/207	97/482	1.4 (0.8-2.4)	$p = 0.22$	Gardening exposure
			96/207	207/482	1.8 (1.1-3.3)	$p = 0.03$	Professional exposure
	(Firestone, 2010)	USA	12/252	24/326	0.6 (0.30-1.29)	NS	♂
			3/152	1/200	3.9 (0.39-39.4)	NS	♀
Fungicides	(Semchuck, 1992)	Canada	NA/130	NA/260	1.63 (0.81-3.29)	NS	
	(Hertzman, 1994)*	Canada	20/71	20 /80	1.04 (0.49-2.24)		♂/Vs. controls with cardiac disease
				26/60	0.52 (0.25-1.08)		♂/Vs. controls randomly selected
			5/56	6/41	0.53 (0.13-2.18)		♀/Vs. controls with cardiac disease
				12/64	0.44 (0.14-1.33)		♀/Vs. controls randomly selected
	(Gorell, 1998)*	USA	NA/144	9/464	1.50 (0.43-5.26)	$p = 0.526$	
	(Engel, 2001)*	USA	35/65				PR = 0.8 (0.6-1.3)
	(Firestone, 2005)	USA	2/156	6/241	0.38 (0.07-2.05)	NS	♂/Occupational exposure
			14/250	39/388	0.55 (0.29-1.05)	NS	Home-based exposure
	(Brighina, 2008)*	USA	NA/833	NA/833	0.83 (0.44-1.59)	$p = 0.58$	
	(Dhillon, 2008)*	USA	4/100	6/84	0.5 (0.2-2.0)	$p = 0.349$	
	(Elbaz, 2009)*	France	NA/118	NA/291	1.5 (0.8-3.0)	$p = 0.22$	♂
			NA/106	NA/266	3.5 (1.2-10.3)	$p = 0.02$	♀
	(Tanner, 2009)	Canada/USA	1/519	1/511	1.01 (0.06-16.28)	$p > 0.99$	Mancozeb
Herbicides	(Stern, 1991)	USA	81/149	77/149	0.9 (0.6-1.5)	$p = 0.73$	
			NA/149	NA/149	0.9 (0.5-1.7)	NS	Early onset
					1.3 (0.7-2.4)	NS	Late onset
	(Semchuck, 1992)	Canada	NA/130	NA/260	3.06 (1.34-7.00)	$p = 0.006$	Herbicide use
					1.40 (0.46-4.30)	NS	16-25 years of herbicide use
					4.82 (1.51-15.35)	$p = 0.004$	26-35 years of herbicide use
					3.84 (1.16-12.70)	$p = 0.021$	36-45 years of herbicide use
					4.88 (1.28-18.60)	$p = 0.013$	46-55 years of herbicide use
	(Butterfield, 1993)	USA	18/63	6/68	3.22	$p = 0.033$	
	(Hertzman, 1994)*	Canada	47/71	55 /80	1.02 (0.50-2.07)		♂/Vs. controls with cardiac disease
				38/60	1.19 (0.57-2.45)		♂/Vs. controls randomly selected
			12/56	13/41	0.55 (0.21-1.48)		♀/Vs. controls with cardiac disease
				19/64	0.67 (0.29-1.56)		♀/Vs. controls randomly selected
			6/127	5 /121	1.11 (0.32-3.87)		♂/Vs. controls with cardiac disease/Paraquat
				4/124	1.25 (0.34-4.63)		♂/Vs. controls randomly selected/Paraquat

Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
(Seidler, 1996)	Germany	61/380	46/379	1.7 (1.0-2.7)		Dose-years=1-40/Vs. Neighboring controls
		59/380	44/376	1.7 (1.0-2.6)		Dose-years=1-40/Vs. Regional controls
		34/380	27/379	1.4 (0.8-2.5)		Dose-years=41-80/Vs. Neighboring controls
		34/380	15/376	3.0 (1.5-6.0)		Dose-years=41-80/Vs. Regional controls
		20/380	11/379	2.2 (0.9-5.2)		Dose-years>80/Vs. Neighboring controls
		20/380	10/376	2.4 (1.0-6.0)		Dose-years>80/Vs. Regional controls
(Liou, 1997)	Taiwan	31/120	21/240	3.22 (2.41-4.31)	$p < 0.01$	Paraquat
		7/120	13/240	0.96 (0.24-3.83)	NS	1-19 years of paraquat exposure
		24/120	9/240	6.44 (2.41-17.2)	$p < 0.01$	≥20 years of paraquat exposure
(Gorell, 1998)	USA	NA/144	7/464	3.36 (1.09-10.33)	$p = 0.034$	
(Kuopio, 1999)	Finland	16/123	37/246	0.79 (0.38-1.66)	$p = 0.539$	Regular use of herbicides
		25/123	34/246	1.71 (0.90-3.23)	$p = 0.101$	Occasional use of herbicides
		41/123	71/246	1.40 (0.79-2.48)	$p = 0.245$	Regular and occasional use of herbicides
(Taylor, 1999)	USA	NA/140	NA/147	1.06 (0.68-1.65)	$p = 0.81$	
(Behari, 2001)	India	20/377	40/377		$p = 0.01$ NS	Chi square = 6.67
(Engel, 2001)*	USA	39/65				PR = 0.9 (0.6-1.3)
(Firestone, 2005)	USA	9/156	8/241	1.41 (0.51-3.88)	NS	♂/Occupational exposure
		116/250	175/388	1.09 (0.77-1.53)	NS	Home-based exposure
		2/156	2/241	1.67 (0.22-12.76)	NS	♂/Paraquat
(Frigerio., 2006)*	USA	7/90	5/78	1.2 (0.4-3.9)	$p = 0.8$	♂
(Brighina, 2008)*	USA	NA/833	NA/833	1.25 (0.94-1.66)	$p = 0.12$	
(Dhillon, 2008)*	USA	23/100	22/84	0.8 (0.4-1.7)	$p = 0.616$	
(Hancock, 2008)*	USA	15/319	8/296	2.07 (0.69-6.23)		Chlorophenoxy acid/ester
		57/319	40/296	1.53 (0.92-2.53)		Phosphonoglycine
		5/319	7/296	1.08 (0.32-3.59)		Triazine
(Costello, 2009)*	USA	149/368	152/341	1.01 (0.71-1.43)		Exposure 1974-1999/Paraquat
		3/368	1/341	3.04 (0.30-30.86)		Exposure 1974-1999/Maneb
		88/368	49/341	1.75 (1.13-2.73)		Exposure 1974-1999/Paraquat+Maneb
(Elbaz, 2009)*	France	NA/118	NA/291	1.4 (0.7-2.6)	$p = 0.35$	♂
		NA/106	NA/266	1.2 (0.4-3.8)	$p = 0.72$	♀
(Gatto, 2009)*	USA	79/368	60/341	1.10 (0.75-1.63)		Paraquat
(Ritz, 2009)	USA	38/324	15/324	2.80 (1.52-5.25)		Paraquat+Maneb
(Tanner, 2009)	Canada/USA	16/519	7/511	2.59 (1.03-6.48)	$p = 0.04$	2,4-D
		9/519	4/511	2.80 (0.81-9.72)	$p = 0.10$	Paraquat
		1/519	1/511	1.02 (0.06-16.60)	$p = 0.99$	Diquat

	Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
Insecticides	(Stern, 1991)	USA	130/149	136/149	0.5 (0.2-1.1)	*p* = 0.10	
			NA/149	NA/149	0.6 (0.2-1.7)	NS	Early onset
			NA/149	NA/149	0.8 (0.3-2.1)	NS	Late onset
	(Semchuck, 1992)	Canada	NA/130	NA/260	2.05 (1.03-4.07)	*p* = 0.042	Insecticide use
					1.49 (0.58-3.81)	NS	16-25 years of insecticide use
					2.33 (0.78-6.94)	NS	26-35 years of insecticide use
					1.75 (0.63-4.83)	NS	36-45 years of insecticide use
					3.50 (1.03-11.96)	*p* = 0.040	46-55 years of insecticide use
	(Butterfield, 1993)	USA	24/63	8/68	5.75	*p* < 0.001	
	(Hertzman, 1994)*	Canada	53/71	65/80	0.62 (0.28-1.38)		♂/Vs. controls with cardiac disease
				54/60	0.33 (0.12-0.90)		♂/Vs. controls randomly selected
			29/56	24/41	0.65 (0.27-1.57)		♀/Vs. controls with cardiac disease
				47/64	0.41 (0.19-0.88)		♀/Vs. controls randomly selected
	(Seidler, 1996)	Germany	46/380	38/379	1.4 (0.9-2.1)		Dose-years=1-40/Vs. Neighboring controls
			70/380	55/376	1.8 (1.1-2.7)		Dose-years=1-40/Vs. Regional controls
			21/380	16/379	1.5 (0.9-2.5)		Dose-years=41-80/Vs. Neighboring controls
			46/380	25/376	2.5 (1.4-4.5)		Dose-years=41-80/Vs. Regional controls
			26/380	24/379	1.6 (0.07-3.4)		Dose-years>80/Vs. Neighboring controls
			21/380	14/376	2.1 (0.9-4.8)		Dose-years>80/Vs. Regional controls
	(Gorell, 1998)	USA	NA/144	19/464	3.15 (1.54-6.49)	*p* = 0.002	
	(Fall, 1999)	Sweden	5/NA	7/NA	2.2 (0.48-9.0)	*p* = 0.40	♂/Handling pesticides within agriculture
	(Behari, 2001)	India	NA/377	NA/377		*p* = 0.169	Chi square = 1.89
	(Engel, 2001)*	USA	51/65				PR = 0.9 (0.6-1.5)
	(Firestone, 2005)	USA	15/156	25/241	0.88 (0.44-1.76)	NS	♂/Occupational exposure
			141/250	236/388	0.82 (0.58-1.14)	NS	Home-based exposure
			5/156	1/241	8.08 (0.92-70.85)	NS	♂/Parathion
			6/156	9/241	1.04 (0.35-3.06)	NS	♂/Malathion
			8/156	10/241	1.67 (0.22-12.76)	NS	♂/Diazinon
	(Frigerio, 2006)*	USA	8/90	3/78	2.5 (0.6-9.8)	*p* = 0.2	♂
	(Brighina, 2008)*	USA	NA/833	NA/833	0.95 (0.74-1.22)	*p* = 0.69	
	(Dhillon, 2008)*	USA	27/100	3/84	10.0 (2.9-34.3)	*p* < 0.001	Rotenone
	(Hancock, 2008)*	USA	7/319	1/296	5.93 (0.63-56.10)		Botanical insecticides
			38/319	32/296	1.31 (0.75-2.28)		*N*-Methyl carbamate
			53/319	21/296	1.89 (1.11-3.25)		Organophosphorus
	(Elbaz, 2009)*	France	NA/118	NA/291	2.2 (1.1-4.3)	*p* = 0.03	♂
			NA/106	NA/266	1.4 (0.5-3.8)	*p* = 0.49	♀

	Study	Country	Exposed/ Total cases	Exposed/ Total controls	OR (95% CI)	*p* value	Specifications
	(Gatto, 2009)*	USA	73/368	41/341	1.58 (1.03-2.43)		Diazinon
			78/368	51/341	1.41 (0.94-2.11)		Dimethoate
			78/368	53/341	1.28 (0.85-1.91)		Methomyl
			67/368	41/341	1.45 (0.94-2.24)		Chlorpyrifos
			77/368	53/341	1.31 (0.88-1.96)		Propargite
	(Tanner, 2009)	Canada/USA	7/519	2/511	3.21 (0.65-15.80)	$p = 0.15$	Permethrin
			3/519	2/511	1.30 (0.21-7.94)	$p = 0.77$	Dieldrin
			1/519	1/511	0.82 (0.05-13.34)	$p = 0.89$	Rotenone
	(Firestone, 2010)	USA	5/252	1/326	5.8 (0.66-50.79)	NS	♂/Parathion
			10/252	12/326	1.0 (0.39-2.30)	NS	♂/Malathion
			7/252	11/326	0.8 (0.30-2.15)	NS	♂/Diazinon
	(Manthripragada, 2010)*	USA	125/351	89/363	1.55 (1.05-2.30)		Diazinon
			88/351	74/363	1.56 (1.02-2.40)		Chloropyrifos
			90/351	83/363	0.98 (0.65-1.48)		Parathion
Organochlorines	(Hertzman, 1994)*	Canada	29/71	33/80	0.89 (0.45-1.76)		♂/Vs. controls with cardiac disease
				28/60	0.80 (0.40-1.63)		♂/Vs. controls randomly selected
			16/56	12/41	0.75 (0.34-1.64)		♀/Vs. controls with cardiac disease
				23/64	0.75 (0.29-1.96)		♀/Vs. controls randomly selected
	(Seidler, 1996)	Germany	7/380	5/379	1.6 (0.4-6.2)		Vs. Neighboring controls
				2/376	5.8 (1.1-30.4)		Vs. Regional controls
	(Kuopio, 1999)	Finland	54/123	53/246	1.04 (0.68-1.60)	$p = 0.855$	DDT
	(Engel, 2001)*	USA	45/65				PR = 0.8 (0.5-1.3)
	(Hancock, 2008)*	USA	42/319	21/296	1.99 (1.09-3.64)		
	(Elbaz, 2009)*	France	NA/118	NA/291	1.9 (1.1-3.5)	$p < 0.05$	♂
			NA/118	NA/291	3.0 (1.2-7.9)	$p < 0.05$	♂/> 65 years at onset
	(Dutheil, 2010)	France	42/101	71/234	2.2 (1.1-4.5)	$p = 0.02$	♂
	(Firestone, 2010)	USA	14/252	22/326	0.8 (0.40-1.64)	NS	♂/DDT

* Summary of selected data only

Abbreviations: 2,4-D: 2,4-Dichlorophenoxyacetic acid
DDT: dichlorodiphenyltrichloroethane
NA: Not available
NS: Not significant
PD: Parkinson's disease
OR: Odds ratio
PR: Prevalence ratio
RR: Relative risk

Table 2. Summary of case-control studies investigating pesticide exposure and the risk of developing Parkinson's disease

Study	Country	Carriers/ Exposed cases	Carriers/ Exposed controls	OR (95% CI)	*p* value	Specifications
(Menegon, 1998)	Australia	32/39	12/26		$p = 0.009$	*GSTP1* (*AB*, *BB*, *AC*)
(Kedala, 2006)	USA	14/47	23/55	1.63 (0.52-5.15)		*DAT*, 1 risk allele
		26/47	15/55	5.66 (1.73-18.53)	S	*DAT*, 2 or more risk alleles
(Wilk, 2006)*	USA	104/278			$p = 0.04$	*GSTP1* SNP *rs749174*
					$p = 0.04$	*GSTP1* SNP *rs1871042*
					$p = 0.009$	*GSTP1* SNP *rs947895*
(Dick, 2007)*	Scotland, Italy, Sweden, Romania and Malta				NS	*CYP2D6, PON1, GSTM1,GSTT1, GSTM3, GSTP1, NQO1, CYP1B1, NAT2* analyzed
(Fong, 2007)*	Taiwan	31/153	18/155	2.49 (1.18-5.26)	$p = 0.0072$	*MnSOD C* allele
		55/153	41/155	2.42 (1.16-4.76)	$p = 0.0089$	*NQO1 T* allele
		20/153	11/155	4.09 (1.34-10.64)	$p = 0.0052$	combined *MnSOD* (*T/C* and *C/C*)/*NQO1* (*C/T* and *T/T*)
(Brighina, 2008)*	USA	NA	NA	1.18 (1.02-1.37)	$p = 0.03$	Rep1 score (α-synuclein gene (*SNCA*))
				1.28 (0.95-1.72)	$p = 0.10$	Herbicides
				0.91 (0.69-1.19)	$p = 0.49$	Insecticides
				0.92 (0.46-1.84)	$p = 0.81$	Fungicides
						No significant pairwise interaction (multivariate analysis)
(Ritz, 2009)	USA	10/38	4/15	2.99 (0.88-10.21)	p for trends =	*DAT*, 1 risk allele, Paraquat+Maneb
		24/38	6/15	4.53 (1.70-12.09)	0.006	*DAT*, 2 or more risk alleles, Paraquat+Maneb
		28/77	18/53	2.00 (0.71-5.67)	p for trends =	*DAT*, 1 risk allele, pesticides
		36/77	17/53	2.83 (1.01-7.92)	0.05	*DAT*, 2 or more risk alleles, pesticides
(Zschiedrich, 2009)	Serbia, Germany	17/19		4.74 (1.01-22.31)	$p = 0.047$	*c.3435C/T* SNP of the *ABCB1* gene
(Dutheil, 2010)	France			5.4 (1.1-27.5)	$p = 0.04$	Carriers of 2 variant G2677 (A,T) alleles (ABCB1 gene) and organochlorines
				4.1 (1.0-17.0)	$p = 0.05$	Carriers of 2 variant *C3435T* alleles (*ABCB1* gene) and organochlorines
(Kiyohara, 2010)*	Japan	187/NA	194/NA	0.77 (0.39-1.52)	$p = 0.449$	*GSTO1 rs4925 Ala/Ala* genotype (*GST* gene)
		151/NA	75/NA	1.96 (0.51-7.46)	$p = 0.323$	*GSTO1 rs4925 Ala/Asp+Asp/Asp* genotype (*GST* gene)
(Manthripragada, 2010)*	USA	48/32	35/15	2.24 (1.12-4.48)		*PON1-55 MM*/Diazinon
		48/27	35/13	2.61 (1.25-5.44)		*PON1-55 MM*/Chloropyrifos
		48/20	35/14	1.21 (0.57-2.60)		*PON1-55 MM*/Parathion

* Summary of selected data only

Abbreviations: DAT: Dopamine transporter; GST: glutathione-S transferase; NA: Not available; NS: Not significant; S: significant; SNP: single-nucleotide polymorphisms

Table 3. Summary of studies investigating genetic vulnerability, pesticide exposure and the risk of developing Parkinson's disease

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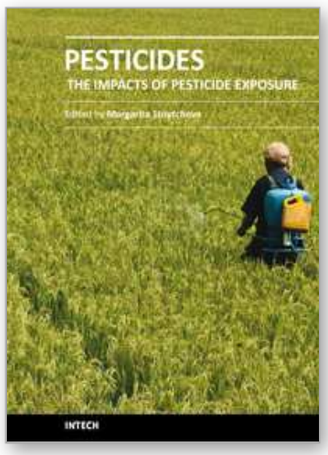

Pesticides - The Impacts of Pesticides Exposure
Edited by Prof. Margarita Stoytcheva

ISBN 978-953-307-531-0
Hard cover, 446 pages
Publisher InTech
Published online 21, January, 2011
Published in print edition January, 2011

Pesticides are supposed to complete their intended function without â€œany unreasonable risk to man or the environmentâ€. Pesticides approval and registration are performed â€œtaking into account the economic, social and environmental costs and benefits of the use of any pesticideâ€. The present book documents the various adverse impacts of pesticides usage: pollution, dietary intake and health effects such as birth defects, neurological disorders, cancer and hormone disruption. Risk assessment methods and the involvement of molecular modeling to the knowledge of pesticides are highlighted, too. The volume summarizes the expertise of leading specialists from all over the world.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Drouin-Ouellet Janelle and Cicchetti Francesca (2011). Pesticides and Parkinson's Disease, Pesticides - The Impacts of Pesticides Exposure, Prof. Margarita Stoytcheva (Ed.), ISBN: 978-953-307-531-0, InTech, Available from: http://www.intechopen.com/books/pesticides-the-impacts-of-pesticides-exposure/pesticides-and-parkinson-s-disease

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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