House Memorial 42: Parkinson’s Disease and Pesticide Exposure

A Review of the Association between Pesticide Exposure and Parkinson’s Disease

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Executive Summary
The NMDOH developed conclusions and recommendations about the potential association of pesticide exposure and Parkinson’s disease (PD) based on the literature assessed. Two main categories were analyzed: studies without genetic interactions and studies with genetic interactions. Within these two categories, the following categories of pesticides were identified: 1) general, 2) organochlorine, 3) organophosphorus, 3) botanical, 4) quaternary ammonium, and 5) carbamate or dithiocarbamate.

There were many ways in which the reviewed studies described exposure to pesticides, including spraying pesticides, handling or direct contact, using or applying pesticides, performing jobs likely involving pesticide use, or unspecified exposure such as proximity to agricultural spraying.

To assess the existing epidemiological evidence for the association between exposure to pesticides and PD that could pertain to specific potentially exposed populations, the reviewed studies were grouped into two broad exposure/use categories: 1) exposure with pesticide use specified, including general use (occupational or residential use could not be distinguished), agricultural use (including farming), other occupational use, and residential use (including gardening), and 2) exposure with pesticide use not specified, including in an agricultural setting, in another occupational setting, in proximity to a pesticide use area, and in a residential setting.

Because there are no available data about the specific pesticides historically utilized, the amount, and where these pesticides were used, assessing the risk of pertinent populations in New Mexico is not currently possible. However, the following conclusions and recommendations apply to anyone in New Mexico who uses pesticides.

1. Pesticide Exposure without Genetic Interactions
Of the selected studies which addressed exposure to pesticides and the risk of PD, the majority of the evidence suggested an association between PD and pesticide exposure, including: herbicides and insecticides as well as chemical groups of pesticides such as organochlorine (lindane), organophosphorus (chlorpyrifos), quaternary ammonium (paraquat), botanicals (rotenone), and a mixture of dithiocarbamate (maneb) with paraquat. Furthermore, there appears to be good epidemiologic evidence for the association between the general pesticide use category and PD development. The association between PD and more specific pesticide use settings appears to be inconclusive for 1) agricultural use of pesticides, which included farming, 2) other occupational use, and 3) residential use of pesticides, which included gardening. The majority of the studies falling into the exposure with pesticide use not specified category provided inconsistent and inconclusive evidence for
the association with PD development. This included pesticide exposure with use not specified in agricultural, other occupational and residential settings as well as proximity to a pesticide use area. However, there were other factors which were stronger predictors for PD including family history of PD, head trauma, and lack of smoking. **Recommendations:** 1) Individuals who decide to use pesticides should first protect themselves and others from exposure by following the directions for application that are appropriate for the given pesticide. Gardeners who want to reduce the amount of pesticides they use may wish to learn more about Integrated Pest Management (IPM) principles: [http://aces.nmsu.edu/pubs/_circulars/cr-655/welcome.html](http://aces.nmsu.edu/pubs/_circulars/cr-655/welcome.html). 2) Under the federal Worker Protection Standard, agricultural workers and pesticide handlers must be trained and informed about pesticides used on the establishment. Violations should be reported to NMDA.

2. **Pesticide Exposure with Genetic Interactions**

Among selected studies which addressed the effect of exposure to pesticides on genetically susceptible individuals/populations for the development of PD, the majority of the evidence on the genes studied suggested that genes modulated the risk between pesticide exposure and the risk of PD. These studies suggested that genotypes may interact with pesticide exposure to increase the risk for PD. Specific pesticides involved in gene-environment interactions with the development of PD included organophosphorus insecticides (specifically, chlorpyrifos and diazinon), the quarternary ammonium herbicide paraquat, and a mixture of maneb (dithiocarbamate) with paraquat. Specific genotypes implicated in these interactions included CYP2D6, *MDR1*, *MnSOD*, *NQO1*, *NOS1* SNPs, *GSTT*, *PON1*, *DAT*, and *GSTT1*. Other factors that play a role in PD include family history of PD, head trauma, and smoking status. Some individuals may be more susceptible to PD with pesticide exposure than others based on specific genes. **Recommendation:** 1) Individuals who decide to use pesticides should first protect themselves and others from exposure by following the directions for application that are appropriate for the given pesticide. Gardeners who want to reduce the amount of pesticides they use may wish to learn more about Integrated Pest Management (IPM) principles: [http://aces.nmsu.edu/pubs/_circulars/cr-655/welcome.html](http://aces.nmsu.edu/pubs/_circulars/cr-655/welcome.html). 2) Under the federal Worker Protection Standard, agricultural workers and pesticide handlers must be trained and informed about pesticides used on the establishment. Violations should be reported to NMDA.
Background

2013 Legislative Session
During the 2013 legislative session, House Memorial 42 (HM 42) passed, which identified public concerns about pesticide exposure and the development of Parkinson’s disease (PD). This memorial requested a review of the historical agricultural use of pesticides by the New Mexico Department of Agriculture (NMDA) and a review of the pertinent scientific literature on the relationship of pesticide use and the development of PD by the New Mexico Department of Health (NMDOH). Using this information, the NMDOH was directed to prepare a report assessing the risk of pertinent populations of New Mexicans with recommendations, as appropriate. This document incorporates information provided by NMDA and provides the methods utilized to conduct a systematic review of the literature as well as the resulting findings and recommendations.

Federal Regulation of Pesticides
The United States federal government passed the first laws regulating pesticides in 1910. The Insecticide Act, as it was known, was intended to protect consumers from impure or fraudulently labeled insecticides and fungicides. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) replaced it in 1947, requiring for the first time that all pesticides be registered and labeled according to minimum standards. It wasn't until 1970 that Congress created the US Environmental Protection Agency (EPA) and transferred administration of FIFRA to it from USDA.

Since then there have been many changes to the laws governing the registration, labeling, and use of pesticides. Before 1974, there were no standards for worker reentry into pesticide treated fields, and thus the agricultural worker protection standard was passed in 1992. Many pesticides have disappeared and new, safer chemicals – for pesticide workers, the public, and the environment – have been developed. In general, modern pesticides are effective at lower rates, are safer to apply, and have fewer side effects or unintended consequences in the environment.

Under FIFRA, EPA registers pesticides and prescribes label directions to prevent unreasonable adverse effects on human health or the environment. Under the Federal Food, Drug and Cosmetic Act (FFDCA), EPA establishes tolerances (maximum legally permissible levels) for pesticide residues in food. Tolerances are enforced by the Food and Drug Administration's Health and Human Services Department and the US Department of Agriculture’s Food Safety and Inspection Service. In 1996, Congress passed the Food Quality Protection Act (FQPA). This law sets a "reasonable certainty of no harm" standard when setting tolerances for pesticides in food. It requires EPA to periodically re-evaluate existing registrations and tolerances to make sure they meet the requirements of current standards. By 2006
EPA reviewed nearly 10,000 tolerances, recommending the revocation or modification of 4,600 tolerances and confirming the safety of 5,200 tolerances.

Agricultural workers and pesticide handlers are protected under the federal Worker Protection Standard, which requires employers to train and inform their people about the pesticides used on the establishment. Appendix I, provided by the NMDA, lists the pesticides of most interest to the public group Pesticides and Parkinson’s Committee (PPC), the class of the pesticide, and historical use. Therefore, the list is not meant to be comprehensive of all pesticides ever used. Additionally, the NMDA does not have information which would allow an historical assessment of how much of each pesticide was used and where. Appendix III, also provided by the NMDA, is a report published by the United States Geological Survey (USGS). The document describes a method which could be used to calculate annual county-level pesticide use for selected herbicides, insecticides, and fungicides applied to agricultural crops grown in the conterminous United States from 1992 through 2009.

**Pesticide Regulation in New Mexico**

In New Mexico, pesticides and pesticide applicators are regulated by the Pesticide Control Act, administered by the NMDA. Rules promulgated under this law govern pesticide registration, the licensing of pesticide applicators, recordkeeping requirements, standards for use, storage and disposal of pesticides, penalties for noncompliance, inspection of application equipment, and applicator safety. Pesticides comprise a wide range of substances designated to deter or kill insects (insecticides), rodents (rodenticides), plants (herbicides), fungi (fungicides), etc. Pesticides also have subclasses based on their chemical components (e.g., organophosphate) or their application method (e.g., fumigant).

**Registration**

All pesticides must be registered with NMDA before they can be distributed or used in the state. Any product that claims to control, mitigate, or repel a pest is a pesticide, including insecticides, herbicides, fungicides, rodenticides, disinfectants, sanitizers, insect repellents, microbial pesticides, desiccants, and more. This includes consumer products like insect repellent, weed killers, sanitizers, wasp sprays, etc., purchased at big box stores, grocery stores, and drug stores, in addition to pesticides purchased and used by agricultural producers and professional pest control applicators. There are approximately 11,000-12,000 pesticides registered annually with NMDA. These products are formulated from an estimated 1,100 active ingredients.

Registered pesticides may be restricted – available for purchase and use only by certified applicators – by either federal or state law. Products restricted by federal law are automatically
restricted in the state. Certain 2,4-D herbicides that are not federally restricted are restricted in New Mexico by state law. About eight percent of federally registered pesticides are restricted.

Licensing

Any person who wants to purchase or use a restricted pesticide must be certified and licensed through NMDA. In addition, anyone who applies any pesticide for hire must hold a commercial applicator or operator/technician license. Currently there are about 5,000 individuals licensed in New Mexico. Nearly 1,600 of those individuals are licensed with commercial businesses that perform pest control for hire.

Federal and state laws require applicators to 1) use only registered pesticides and to follow all label directions, 2) keep records of pesticide applications, 3) only apply pesticides in categories they are certified in; and more.

Inspection/Enforcement

Federal and state laws require that dealers sell restricted pesticides to licensed applicators only. Applicators must follow all label directions; keep records of their pesticide applications; only apply pesticides in categories they are certified in; not be careless or negligent in their use of pesticides; and more.

NMDA inspects those businesses that sell pesticides. In addition to pesticide dealers who sell restricted pesticides, markets like feed stores, hardware stores, box stores, discount stores, garden centers, and others are inspected to make sure the pesticides for sale are registered and are displayed, stored and sold safely and in accordance with federal and state laws.

NMDA inspects pesticide applicators. Inspectors verify they are applying pesticides in accordance with the product labels and with state and federal law. Agricultural establishments are also inspected to assure compliance with the Worker Protection Standard. Although some inspections are conducted during a pesticide application, most compliance monitoring is based on the records kept by the applicators.

NMDA investigates an average of about 35 complaints a year alleging pesticide misuse, drift, or other violations. When violations can be documented NMDA takes enforcement action against the applicator. Complaints may involve damage to non-target plants, personal exposure, ineffective pest control, or licensing issues.
Methods

**Literature Search**
The NMDOH conducted a systematic search for relevant information in the scientific literature via the search engine PubMed ([http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed](http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed)). In order to reduce the chance that information supporting a particular conclusion would be preferentially identified while other information was missed, the literature search was designed to be as comprehensive as possible. The search was conducted in July 2013 to identify all peer-reviewed articles published before that date. Key and free-text words included “Parkinson’s disease,” “pesticide,” “insecticide,” “fungicide,” and “rodenticide.” In addition to the articles identified through PubMed, the public group PPC also submitted articles for potential inclusion. In order to allow enough time to review articles, the deadline for the public to submit articles was August 2, 2013.

**Inclusion and Exclusion Criteria**
Because the focus of HM 42 is on the association between pesticide exposure and PD development, the NMDOH included studies (whether through PubMed or submitted by the public) if they addressed health outcomes among people. To be included, the studies had to address not only PD but also pesticide exposure. For this review, articles were included if they focused on PD. The signature signs and symptoms of PD include bradykinesia,\(^1\) resting tremor,\(^2\) cogwheel rigidity,\(^3\) and postural reflex\(^4\) impairment. Only peer-reviewed journal articles, government agency reports, and reports from nationally or internationally recognized organizations and authorities in public health such as the World Health Organization (WHO) were included for review. The scientific peer-review process ensures the quality and relevance of research activities, and helps maintain scientific objectivity and credibility. Government agencies have internal procedures and processes which guide reviews.

Articles were excluded if they met any of the following criteria: 1) animal model (anything but human), 2) cell lines or cell cultures, 3) treatment/protective factors, 4) no measures of association (odds ratio, relative risk), 5) miscellaneous (no pesticide exposure or PD not addressed; mechanism of action study; biomarkers of exposure; case report (report of a single case of PD); predictive toxicity (extrapolation of animal toxicity data to predict human effects or extrapolation of toxicity based on chemical structure); letter to the editor; summary of conference), or 6) article written in language other than English. Additionally, we excluded review articles that summarized original articles that we have

\(^1\) Slowness of movement  
\(^2\) Tremor that occurs when muscle is relaxed  
\(^3\) Increase in muscle tone causing resistance to externally imposed joint movements  
\(^4\) Automatic movements that control equilibration when the body is upright and moving
already included, except for those reviews that attempted to evaluate the level of evidence for the association between exposure to pesticides and PD development.

Data Extraction Form
Eight epidemiologists from NMDOH extracted data from the studies selected for review and recorded the information on a standardized form (see end of report). Extracted data included information about study participants such as race/ethnicity, age, and sex, measure of association (odds ratio), statistically significant findings, and any recommendations the study made.

Data Synthesis
Two of the epidemiologists working on the data extractions also conducted the data synthesis and analysis. Data from the extraction form were summarized into two main categories of PD articles: 1) pesticide exposure without genetic interactions and 2) pesticide exposure with genetic interactions.

Results
Selection of Studies
Through the PubMed search, a total of 1547 potentially relevant publications were identified (Appendix II). In addition, 94 article titles were submitted by the PPC for review. Of these, 13 articles had been duplicated within the PPC document, 29 were excluded based on our criteria, and 52 were possible inclusions. Of the 52, 51 were already included in the PubMed search results. Thus one article was added to bring the total of articles to review to 1548. Of these, 1444 were excluded based on the previously identified inclusion/exclusion criteria. The final list of articles that were included for this review can be found in the References section of the report.

1. Pesticide Exposure without Genetic Interactions
Of the selected studies which addressed the association between pesticide exposure and Parkinson’s disease without investigating genetic interactions, there were four categories: 1) pesticides (general): specific pesticide not identified (includes general categories such as insecticide, fungicide, herbicide), 2) organochlorine, 3) organophosphorus, 4) botanical, 5) quaternary ammonium, and 6) carbamate or dithiocarbamate.

There were many ways in which authors of the reviewed studies described exposure to pesticides, including spraying pesticides, handling or direct contact, using or applying pesticides, performing jobs likely involving pesticide use, or unspecified exposure/use such as a proximity to agricultural spraying.
To assess the existing epidemiological evidence for the association between exposure to pesticides and PD that could pertain to specific potentially exposed populations, we grouped reported pesticide uses (note that some studies reported multiple uses of pesticides and multiple chemical classes of pesticides) into two broad exposure/use categories: 1) exposure with pesticide use specified, including general use (setting not specified, e.g., residential, agricultural, or occupational or could not be distinguished), agricultural use (including farming), other occupational use, and residential use (including gardening), and 2) exposure with pesticide use not specified, including in an agricultural setting, in another occupational setting, in proximity to a pesticide use area, and in a residential setting.

The studies are summarized here by the type of pesticides evaluated for potential association with PD. The studies presenting positive associations between pesticide exposure and risk of PD are summarized first.

**Pesticides (General)**

Of the 61 studies analyzing an association between general exposure to pesticides and PD development, 35 provided statistically significant evidence to support this association and 26 studies did not have statistically significant evidence. Herbicides and insecticides as functional categories of pesticides each had the same number of studies associated with increased risk of PD (n=7). Out of the seven studies reporting increased risk of PD due to herbicide use, statistically significant ORs ranged from 1.33 to 4.1, with the highest OR involving occupational, long-term exposure greater than 20 years compared with no exposure. Among seven studies reporting increased risk of PD due to insecticide use, statistically significant ORs ranged from 1.53 to 5.81, with the highest OR involving exposure lasting 10 years or longer, as compared to those with less than 10 years’ exposure. Fungicides had the least number of studies (n=2), with ORs of 2.2 and 5.6. The remainder of the studies with a positive association fell under the general pesticides category. Out of these studies, there were statistically significant ORs ranging from 1.21 to 17.12. However, the study finding the OR of 17.12 did not adjust for family history of PD, which had an OR of 21.4. The next highest OR was 5.63.

There appears to be good epidemiologic evidence for the association between the general pesticide use category and PD development; of the 26 pesticides use results falling into this exposure/use category, 17 results demonstrated a positive association with the risk for PD and 9 results did not demonstrate statistically significant association. The association between PD and pesticide use appears to be inconclusive for 1) agricultural use of pesticides, which included farming (of the 14 results, 6 results demonstrated evidence for the association and 8 did not), 2) other occupational use (of the 16 results, 9 results demonstrated positive evidence and 7 did not), and 3) residential use of pesticides,
which included gardening (of the 6 results falling into this pesticide use category, 3 results demonstrated a positive association with PD and 3 did not).

The majority of the pesticide use results falling into the pesticide use not specified category provided no evidence for an association with PD. This included pesticide use not specified in agricultural, other occupational and residential settings as well as proximity to a pesticide use area.

For all of the reviewed studies, factors that tended to increase the risk of PD due to pesticide exposure included increased duration and frequency of exposure, family history of PD, and head trauma. Smoking appeared to act as a protective factor, decreasing the risk of PD. Studies with occupational exposure tended to have a longer duration/frequency of pesticide use compared to residential exposure such as gardening. Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure.

The limitation of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration through statistical analyses. For example, with respect to recall bias, many studies mentioned that PD patients were more likely to recall pesticide exposure compared to controls. For competing risk factors, at least one paper demonstrated that farming as an occupation was an independent risk factor for PD, regardless of pesticide exposure status.

Positive association
The studies which, for the most part, found a positive and statistically significant association between general pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. A positive association means the authors found an increased risk [odds ratio (OR) or relative risk (RR) over one (1)] of PD among those exposed to pesticides compared to unexposed individuals. Confidence intervals (CI) that include one (1) indicate that the association is not statistically significant.

Golbe and co-authors (1990), conducted a case-control study, which mainly focused on nutritional/dietary risk factors for PD, however, they also investigated the association between PD and rural living or pesticide use. This study involved 106 PD patients with spouses as controls (71 males and 35 females). Pesticide exposure (assessed by a telephone-administered questionnaire) was positive if respondents answered yes to the question “sprayed pesticides or insect spray at least once a year for five years?” PD development was associated with pesticide exposure (OR=7.0, p<0.05).

Butterfield et al. (1993) conducted a case-control study of PD but instead focused on young-onset Parkinson’s disease (YOPD). The authors chose this population in order to minimize recall bias
shorter life history to remember) and on the premise that early PD may be associated with higher exposures. YOPD patients diagnosed before the age of 50 (n=63) were frequency-matched on sex, year or birth, and year of diagnosis with rheumatoid arthritis patients (RA) in the Oregon-Washington region of the US. There was a higher proportion of YOPD cases with a family history of PD and more non-whites among RA controls than the YOPD group. A questionnaire was used to assess exposure and employment history. YOPD subjects with a history of farm employment or residency, had a mean of 10.6 years of exposure compared with a mean of 6.4 years for controls (t-test p=0.101). Logistic regression models were used to estimate the YOPD risk associated with exposure to pesticides at a frequency of more than 10 times a year in any one year (insecticides, herbicides, and fumigants). The ORs were adjusted for age, age at diagnosis, race, sex, educational level and family history of PD. The risk for YOPD was statistically significantly associated with exposure to three pesticide classes: herbicides (OR=3.46, p=0.011; adjusted odds ratio (aOR)=3.22, p=0.033), past residency in a fumigated house (OR=3.29, p=0.068; aOR=5.25, p=0.045) and exposure to insecticides (OR=4.04, p=0.002; aOR=5.75, p=0.001). There was no statistically significant association between YOPD development and exposure to fungicides (crude OR=1.50, p=0.742), rodenticides (OR=2.42, p=0.618), and “ever lived within ¼ mile of agricultural spraying?” (OR=1.99, p=0.106). Logistic regression analysis comparing the relative strength of association between insecticides and herbicides exposure found adjusted ORs of 4.84 for insecticides (p=0.008) and 1.53 for herbicides (p=0.510), when both variables were modeled simultaneously.

Semchuk et al. (1993) conducted a population-based, case-control study to test the hypothesis of multi-factorial etiology of PD development, using occupational and chemical exposure data, medical, and smoking history data, and family history of PD and essential tremors in Calgary, Canada. There were 130 cases (75 males and 55 females) with neurologist-confirmed idiopathic PD and two community controls of 260 subjects (150 males and 110 females) matched by sex and age (± 2.5 years). Exposure and family history information was obtained by personal interview. Occupational and chemical exposures included exposure to pesticides (herbicides, insecticides, and fungicides), work-related exposure to aluminum, carbon monoxide, cyanide, manganese, mercury, mineral oils, and ionizing radiation. Information on family history of PD and essential tremor, smoking, and history of various viral and other medical conditions was collected together with a detailed lifetime occupational history, including exposure dates and descriptive information on all work-related contact with pesticides and other chemicals. Occupational and chemical exposures were coded for the period between the subject’s 16th and 55th birthdays and for each 10-year age interval between the subject’s 16th and 55th
birthdays. Both univariate and multivariate conditional logistic regression analyses methods were used to estimate the risk for PD (crude and adjusted ORs, respectively) associated with the following variables: family history of PD, previous head trauma, exposure to herbicides, family history of essential tremor, and smoking status. The crude OR for herbicide exposure was 3.06 (CI=1.34-7.00, p<0.01). When adjusted for different combinations of the variables previously cited, the adjusted ORs ranged from aOR=2.83 (CI=1.13-7.06, p<0.05) to aOR=3.09 (CI=1.27-7.56, p<0.05). When all five variables were included in the model, family history of PD was the strongest predictor of PD risk followed by history of head trauma. The results of this analysis demonstrate that the ORs for PD remained at approximately three, even after controlling for the effects of the other variables, such as family history of PD and previous head trauma. The authors concluded that their results support the hypothesis of a multifactorial etiology of PD, which likely involves genetic, environmental, head trauma and possible other factors.

Hubble and co-authors (1993) conducted a small case-control study in Kansas involving two sites: one rural (Hays) and one urban (Kansas City) to investigate the effect of rural residency on the development of PD. In the urban population, there were 32 cases and 31 controls. In the rural population, there were 31 cases and 44 controls. All subjects were examined by a neurologist and the PD diagnosis was based on the presence of two or more of the cardinal signs of PD (i.e., tremor, rigidity, and bradykinesia) and responsiveness to the PD drug, levodopa. Patients with historical signs or symptoms of neurological disorders were excluded. Information on exposure factors was collected by self-administered questionnaire and included ever living or working on a farm, pesticide use for more than 20 days for any one year, pesticide use for more than 20 days for 5 years, living or working on a farm with livestock, smoking more than 100 cigarettes during a lifetime, head trauma, having received professional help for depression, and others. Lifetime occupational histories were obtained. Rural living was defined as residency in a town of less than 2500 population. Logistic regression modeling was conducted on the pooled data from urban plus rural sites. However, rural living was so common among subjects in the control (urban) site (51% had lived in a rural setting for more than 20 years) that it did not serve to distinguish controls from patients. On the other hand, pesticide exposure emerged as a variable distinct from rural living and served as a strong predictor of PD among these subjects. Three significant predictors of PD emerged in order of the strength of their association with PD: pesticide factor (used pesticides for more than 20 days in any given year and having done so for more than 5 years), reported family history of neurologic disorders, and history of depression. When all three predictors were positive, the probability for PD in the subject was 92.3% (OR=12.0). Pesticide use had
an OR of 3.42 (CI=1.27-7.32, p=0.0041) in the stepwise logistic regression. Several variables were not predictive of PD: head trauma, ethnicity, history of central nervous system (CNS) infection, and fresh produce consumption, but the sample size was also small. Recommendations included investigation into the identity of specific chemical agents that may be responsible for the development of PD and exploration of the nature of familial influence.

A case-control study conducted in a geographically defined horticultural region in Okanagan Valley, British Columbia aimed to identify possible risk factors for idiopathic PD (Hertzman et al., 1994). There were 127 PD cases (71 males and 56 females) and 245 controls (140 males and 105 females), categorized into two groups: 121 subjects (80 males and 41 females) with chronic cardiac disease (CD) and 124 randomly selected voters (60 males and 64 females). There was approximately the same number of males and females within the different age groups. There were similar years of residence in the Okanagan Valley for all groups. The occupational exposure questionnaire included questions on 79 different agricultural chemicals used in the tree fruit industry, including: 1) any pesticide; 2) specific pesticides: paraquat, azinphos-methyl, ferbam, phosalone; and 3) pesticides grouped into: chlorophenoxy compounds (chlorophenoxyxs), organochlorines, organophosphates, carbamates, borates, copper salts, dithiocarbamates, insecticides, herbicides, fungicides, and acaricides. Exposure was defined as handling the chemical or working in an area that had been recently sprayed with the chemical. Full occupational history information was collected. Separate analyses were conducted for PD vs. CD and PD vs. voters groups using logistic regression and adjusting for sex and age. The study found a statistically significant association between PD in men and having an occupation in which there was probable exposure to pesticides through handling or direct contact. However, no specific pesticide exposure was associated with PD development for either gender. For men’s exposure to pesticides, the aOR was 2.03 (CI=1.00-4.12) a compared with CD controls; aOR=2.32 (CI=1.10-4.88), compared with voters. For women’s exposure to pesticides, aOR=1.11 (CI=0.32-3.80) for comparison with CD controls and OR=1.36 (CI=0.48-3.85) as compared with voters group. There were no statistically significant findings when exposure was grouped by specific pesticides or occupation. The authors concluded that although occupational exposure to agricultural chemicals may predispose individuals to the development of PD, the pathogenesis is multi-factorial rather than related to any specific chemical. The authors were concerned with recall bias and therefore they used two control groups, assuming that patients with chronic diseases may be more introspective and therefore, more likely to identify past exposures. They also noted that educational attainment may correlate positively with the ability to
recall the name of the pesticide and negatively with the level of exposure to the pesticide. Thus, they recommended that future studies should control for these factors.

Semchuk and Love (1995) examined the effects of exposure misclassification in proxy-derived data on agricultural work, pesticide use, rural living, well water drinking, head trauma, smoking status, and family history of PD or essential tremor on Parkinson's disease risk estimates. The data were collected in 1989 as part of a population-based case-control study of PD in Calgary, Canada. For each neurologist-confirmed PD case, two matched (by sex and age) community controls were randomly selected. Forty cases and 77 controls were randomly selected as index respondents. The cases, controls, and one proxy respondent (spouse or offspring) for each index respondent were interviewed using a structured questionnaire. The data were analyzed using conditional logistic regression. Odds ratios estimated the risk of PD associated with environmental variables (rural living, farm living and well water drinking), agricultural variables (agricultural work, crop farming, grain farming, herbicide use, insecticide use, and fungicide use), and other variables (family history of PD, head trauma, family history of essential tremor, and smoking status). Incorporation of proxy-derived data for 30% of the cases and controls, or both, resulted in misclassification of exposure for some variables, in some cases leading to considerable attenuation of the ORs. The adjusted PD risk estimates were calculated for the three probable risk factors (herbicide use, family history of PD, and head trauma) when only self-responder data were used and when the analysis was replicated using proxy-derived data for about 30% of the cases and controls. Specifically, the study results show that the adjusted odds ratio for PD development and herbicide use was 3.09 (CI=1.27-7.56) when only self-responder data were used for the analysis and the adjusted ORs remained reduced for the mixed self- and proxy-responder data use situation. In summary, the study results indicate that pooling dichotomously classified data derived in part from self- and proxy respondents may result in biased estimates of PD risk associated with agricultural exposure (including pesticide use), family history of PD, and head trauma.

A case-control study conducted in Germany investigated a number of potential etiologic factors for PD development, including exposure to pesticides (use of herbicides, insecticides, organochlorines, alkylated phosphates and carbamates), farming activity, well-water drinking, exposure to wood preservatives, head trauma, the number of previous episodes of general anesthesia, and other factors such as the number of amalgam fillings (Seidler et al., 1996). PD cases (n=380) from 9 neurological clinics across Germany were recruited for the study and 379 neighborhood controls and 376 regional controls were enrolled. The cases were determined by using the UKPDS Brain Bank clinical diagnostic criteria. A detailed residential history was taken from each participant. To assess pesticide exposure, participants
were asked about years of pesticide application and frequency of use. Then, a toxicological expert categorized all pesticides named by subjects with regular pesticide use, which fell into five groups: organochlorines, alkylated phosphates and carbamates, inhibitors of cellular metabolism (cellular respiration, enzyme activity, membrane excitation), and “other” category. Occupational exposure was assessed by "ever" versus "never" exposure to a list of neurotoxic substances. In addition, a job exposure matrix was constructed for job titles and industries named by participants. Smoking and educational status were included as covariates in the multivariate analyses to adjust for potential confounding; both variables were strongly inversely associated with PD. Therefore, ORs were adjusted for smoking and educational status, for patients vs. neighborhood control subjects, and for patients vs. regional control subjects. The study showed a significantly increased OR for pesticide usage and the risk of PD, but none for rural factors. Duration of herbicide and insecticide use prior to PD diagnosis showed a positive trend across the number of exposure years; however, the ORs and p-values for trend were statistically significant only in the comparison with regional controls. The study found that PD patients were more likely than control subject to have used herbicides (aOR significant only for comparison with regional control subjects for exposure duration of 41-80 years (aOR=3.0, CI=1.5-6.0), insecticide (aOR significant only for comparison with regional control subjects for exposure duration of 1-40 years (aOR=1.8, CI=1.1-2.7) and 41-80 years (aOR=2.5, CI=1.4-4.5). The authors also analyzed the risk of PD for organochlorine and organophosphate exposures. These results are provided in subsequent sections. A dose-response gradient was seen with increasing number of exposure years to wood preservatives (ever vs. never), but that trend was not statistically significant. The gradient was more pronounced when exposure was considered only for 15 years prior to PD diagnosis. The authors concluded that environmental factors may play a role in the etiology of PD, possibly acting through a genetic predisposition. They recommended conducting more precise exposure assessments, possibly involving biological monitoring for newly diagnosed PD cases as well as setting up a population-based PD registry to capture the disease incident rates, which would likely approximate a prospective assessment of PD risk factors.

A case-control study by Gorrel et al. (1998) investigated exposure to pesticides (herbicides, insecticides, and fungicides), farming, well water use, and rural living as the risk factors for PD. Cases and controls were drawn from residents of the tri-county metropolitan Detroit area who were receiving primary medical care form the Henry Ford Health System (HFHS). Cases (n=144) diagnosed by staff neurologists were selected from the HFHS databases. Controls (n=464) were frequency matched on sex, race, and age. Controls who reported any of eight symptoms of potentially undiagnosed PD were
excluded. Participants were administered a risk factor questionnaire by trained interviewers face to face. The questionnaire focused on occupational history but also included questions on pesticide use and farming. Logistic regression was used for the analysis. Exposure to herbicides and insecticides at work was significantly greater for PD patients than for controls (i.e., for occupational herbicide exposure, aOR=4.10, CI=1.57-12.24, p=0.012; for insecticide exposure aOR=3.55, CI=1.75-7.18, p<0.01); but there was no association between PD and exposure to fungicides (aOR=1.60, CI=0.47-5.45, p=0.453). The association with PD was greater in those with ≥ 10 years of occupational exposure to insecticides (aOR=5.81, CI=1.99-16.97) compared to those with < 10 years of exposure (aOR=2.39, CI=0.89-6.40). Farming was also significantly associated with PD (OR=2.79; CI=1.03-7.55). Farming as a variable was found to be independent from the pesticides exposure variable: the OR for farming was relatively unchanged after adjusting for any of the three pesticide classes. Furthermore, the association between occupational exposure to herbicides and the risk for PD increased dramatically for those with 10 or more years of well water exposure (increase from OR=4.10 to OR=13.98, CI=1.46-133.53). There was, however, no statistically significant association between the risk for PD and exposure to residential spraying of insecticides (OR=1.02, CI=0.62-1.65, p=0.951; aOR=1.03, CI=0.63-1.70, p=0.92) nor while gardening as a hobby (for exposure to herbicides, insecticides, or fungicide aOR=1.39, CI=0.84-2.28, p=0.200; aOR=0.90, CI=0.58-1.38, p=0.619; and aOR=0.96, CI=0.55-1.66, p=0.879, respectively), or as a resident or worker on a farm (for exposure to herbicides, insecticides, and fungicides aOR=1.64, CI=0.70-3.82, p=0.253; aOR=1.28, CI=0.69-2.40, p=0.435; aOR=0.96, CI=0.29-3.12, p=0.944; respectively).

In summary, the results of this study show a significant association of occupational exposure to herbicides and insecticides with PD and no association between the risk for PD and residential spraying of insecticides or gardening or being a resident or worker on a farm.

Priyadarshi et al. (2000) searched a medical abstract database for articles about exposure to or use of pesticide or both (i.e., pesticide use and exposure) and PD as of August 1999 to conduct a meta-analysis. Articles were excluded for the following reasons: 1) language was other than English, 2) pesticide not included as a risk factor, 3) duplication of the studies with same cohort, 4) insufficient data for determining an estimate of relative risk or a confidence interval, 5) disease studied was not specifically designated as PD. A total of 19 case-control studies from various countries were examined. The OR for the studies reporting positive association between PD and exposure to pesticides ranged from 1.1 to 7 and included a total of 2110 PD cases; eight of these studies reported estimated ORs that were statistically significant. Significant heterogeneity was detected among the studies (p<0.01).
random-effect model including all studies yielded a combined OR of 1.94 (CI=1.49 – 2.53). For those studies conducted only in the US, the OR was 2.15 (CI =1.14-4.05).

Ritz et al. (2000) conducted an ecological study using death certificate data in California. There were 7516 deaths with an underlying cause of PD for the study time period (1984–1994) and 15,222 deaths with PD mentioned as a contributing cause of death for the same time period (except for 1994, when contributing cause data were not available). Exposure to pesticides was categorized by county based on pesticide use reports, and then agricultural census data were employed to create measures of land per county treated with pesticides. Prevalence odds ratios (PORs) were used to estimate the risk of pesticide exposure for PD mortality compared to death from (underlying) ischemic heart disease (n=498,461). Logistic regression models were used to control for the effect of age, sex, race, birthplace, year of death, and education. The POR for residents in low, moderate or high restricted pesticide-use counties compared to long term-residents of no agricultural pesticide-use counties were 1.52 (CI=1.35 – 1.72), 1.49 ( CI=1.31–1.69) and 1.49 (CI=1.30–1.71), respectively. While an elevated risk was observed, a dose-response was not.

Priyadarshi et al. (2001) conducted a meta-analysis of case-control studies examining the associations of rural living, well water drinking, farming, and exposure to pesticides with PD. For the pesticide studies the number of cases ranged from 38 to 224 and the number of controls ranged from 38 to 464. The number of females and males were similar in both cases and controls in most studies. Of the 14 studies that examined the association of exposure to pesticides with PD, one study show a negative association, two studies showed no association and the remaining 11 studies reported a positive association. The random-effect model including all studies yielded a combined OR of 1.85 (CI=1.31 – 2.60). For studies conducted in the United States, the combined OR was 2.16 (CI=1.95 –2.39). The overall conclusion from this study was the risk of PD increased with longer exposure duration to pesticides.

Zoron et al. (2002) carried out a case-control study to investigate the association of familial and environmental risk factors with PD. Neurologist-confirmed cases of PD (n=136) were age- and sex-matched, with 272 controls affected by neurological diseases unrelated with PD. The risk of developing idiopathic PD was associated with the following factors: positive family history of PD, positive family history of essential tremor (ET), age of mother at subject's birth, rural birth, rural living, well water use, farming as an occupation, exposure to pesticides, head trauma, exposure to general anesthesia and to ionizing radiations, food restriction, concentration camp imprisonment and smoking status. Of 136 cases, 74 were women. In the conditional multiple logistic regression analysis, the following factors
increased the risk for PD: positive family history of PD (OR= 41.7, CI=12.2 -142.5, p<0.0001), positive family history of ET (OR=10.8, CI=2.6-43.7), age of mother at subject's birth (OR=2.6, CI=1.4-3.7, p<0.0013), farming as an occupation (OR= 7.7, CI=1.4-44.1, p=0.0212) and well water use (OR=2.0, CI=1.1-3.6, p=0.0308. Smoking showed an inverse relationship with PD (OR= 0.7, CI=0.4-1.1, p<0.06).

After adjusting for smoking, exposure to pesticides (aOR=1.6, CI=1.0-2.4, p=0.035) and rural living (aOR =1.5, CI=1.0-2.4, p=0.044) were no longer significant. The mean length of exposures to pesticides was significantly different in cases and control subjects (4.1 years, SD 10.9 and 2 years, SD6.4, respectively; p<0.05). The mean length of well water use was significantly longer in cases (5.7 years, SD 13.2) when compared to control subjects (2 years, SD6; p<0.01).

Baldi et al. (2003b) conducted a prospective cohort study of elderly French residents (1122 men and 1670 women were enrolled in this study). Occupational and environmental exposure to pesticides and PD or Alzheimer’s diagnosis was assessed by questionnaire. A job exposure matrix was created and nineteen job titles for 320 subjects were assessed to involve non-null pesticide exposure. A cumulative exposure index was calculated for 228 subjects (71.3%); 173 subjects reported having a primary job in agriculture. In men, the risk of PD was associated with past occupational exposure to pesticides (aRR=5.63, CI=1.47-21.58) following adjustment for smoking and education; no association was found for women (aRR=1.02, CI=0.22-4.82). Results were not statistically significant for other exposures to pesticide, i.e., main job in agriculture (aRR=1.62, CI=0.31-8.63 for men and aRR=0.81, CI=0.10-6.40 for women), rural residency (aRR=1.45, CI=0.38-5.49 for men and aRR=1.32, CI=0.40-4.30 for women), and residency in a district planted with vineyards (aRR=0.46, CI=0.09-2.29 for men and aRR=0.87, CI=0.24-3.19 for women).

Baldi et al. (2003a) conducted a case-control study of residents in two regions in Southwestern France. Cases were 70 years old, over and lived in the study regions at the time of interview, and were recruited through area hospitals. Cases were matched 1:3 with controls for age and sex. Controls were enrolled in the PAQUID study – a study on pathological cerebral aging and loss of independence in the elderly. PD status was excluded for controls based on a symptom questionnaire. The agricultural study region largely included vineyards, where fungicides were used heavily, as compared to insecticides or herbicides. Occupational exposure was assessed through the gathering of occupational histories and having engineers to construct a job exposure matrix, rather than relying on subjects’ recall. For occupational exposure, there was an increased risk for PD, when taking into account age, sex, educational level and smoking (aOR=2.2, CI=1.1-4.3). Demonstration of a dose-response relationship failed when exposure was calculated by quartiles. With exposure assessed from lowest to highest, the
first two exposure quartiles were not significant while the 3rd was statistically significant (aOR=6.6, CI=1.7-25.0); however, the highest exposure quartile had aOR=0.7 (CI= 0.1 – 3.1) and was not significant.

Baldereschi et al. (2003) investigated the association of major lifestyle-related risk factors with the prevalent cases of PD identified by the Italian Longitudinal Study on Aging. 5632 individuals were randomly selected from the population of eight centers and screened for parkinsonism using both a questionnaire and a neurological examination; 113 prevalent PD cases were identified. PD was defined among those affected by parkinsonism by exclusion of all other possible causes. Age, male sex, and having a pesticide-use license were significantly related to PD. Heavy smoking was inversely related with PD. Age (OR=1.1, CI= 1.06-1.15) and having a pesticide-use license (aOR=3.68, CI= 1.57-8.64) retained their significant correlation with PD in the multivariate analysis after adjustment for all the variables under investigation (i.e., age, sex, years of schooling, smoking status (never, 0.01–19.99 pack years, >=20 pack years), and having a pesticide-use license). In multivariate analyses for men and women separately, having a pesticide use license was positively associated with PD only in men (aOR=4.41, CI=1.84-10.56 for men). In this study, farming for at least 10 years was not associated with the risk for PD (aOR=1.2, CI=0.72-1.97).

Gorell et al. (2003) sought to determine the relative contribution of potential PD risk factors to the development of PD. Subjects from a health system in tri-county Detroit metropolitan area were recruited. Lifetime cumulative exposure was calculated for each pesticide group. Variables included occupational exposure to selected metals, family history of PD, occupational exposure to pesticides, occupational exposure to farming, and smoking. Cases (n=144) and 464 controls, selected between 1988 to 1992, were matched on sex, race, and age. An interviewer-administered risk factor questionnaire provided a history of all jobs held for 6 months or longer. An industrial hygienist reviewed each job history and assessed the possibility of exposure to different metals. Long-term (>20 years) exposure to manganese had the highest adjusted odds ratio (aOR=10.6, CI=1.1-106.0, p=0.044), while occupational exposure to herbicides aOR=4.1 (CI=1.37-12.23) and occupational exposure to insecticides aOR=3.55 (CI= 1.75-7.18, p=0.001) were also associated with PD. For farming in general as an occupation aOR=2.79, (CI=1.03-7.54, p=0.043).The final multivariate model after stepwise logistic regression had a population attributable risk (PAR) of 54.1% and included the following variables: smoking less than or equal to 30 pack years, PD in first- and second-degree relatives, occupational insecticide exposures, occupational lead and copper exposure ( both >20 years). These results suggest that PD is a multi-factorial condition, with various environmental and genetic risk factors playing a role in its development.
Yesavage et al. (2004) assessed whether pharmacy database information from the US Department of Veterans Affair (VA) medical centers could be used to screen for areas of higher PD prevalence among patients exposed to pesticides. Pharmacy datasets (1997-2001) were used to compare the use of anti-parkinsonian medications and two VA medical centers in California (in Palo Alto near the ocean and in Fresno downwind from extensively farmed parts of the Central Valley). These areas were seen as a proxy for pesticide exposure (low=Palo Alto, higher=Fresno). Patients at Fresno exhibited higher ORs for the use of PD medications (carbidopa/levodopa prescriptions) than patients at Palo Alto; OR (Fresno/Palo Alto) from 1.5 (CI=1.1-1.9) in 1997 to 1.8 (CI=1.5-2.2) in 2000.

Park et al. (2005) utilized death certificate data from 22 states from 1982 to 1998 through the National Occupational Mortality Surveillance System to develop a case-control study. Cases were defined as having one of several neurodegenerative diseases, including PD. Controls were all decedents with no mention of neurologic disease, degenerative or otherwise and excluding certain exposures (e.g. solvents). Priority occupations associated with neurodegenerative disease (n=87) were identified from a previous study with statistically significant elevated proportionate mortality ratios (PMRs). Of 2,614,346 deaths identified from 1992 to 1998 among participating states, 33,678 were due to PD. The following occupational groups had a significant association with PD: biological scientists [mortality odds ratio (MOR)=2.04, CI=1.39-2.92]; post-secondary teachers (MOR=1.61, CI=1.39-1.85); teachers (primary/secondary) (MOR=1.30, CI=1.18-1.43; clergy (MOR=1.79, CI=1.58-2.02); other religious workers (MOR= 1.70, CI= 1.27-2.21. PD risk was significantly elevated across all three farming specifications in all age groups, but the strongest association was for non-horticultural farmers (MOR=1.16, CI=1.11-1.22), with much higher risk below age 65 (MOR=2.23, CI=1.47-3.26). Of all of the occupations, there was the strongest significant relationship with PD among farmers under age 65. This was either due to early onset of PD attributable to farming exposures or the excess cases that might not be discernible above the greatly increased background cases at older ages. MORs were adjusted for age, race, sex, region, and SES. In other occupations where pesticide usage might be expected (e.g., farm workers, horticultural specialty workers), significant elevations were not observed although horticultural specialty workers did show a non-significant excess of PD (MOR=1.65, CI=0.92–2.71). This analysis based on death certificate data was limited by lack of work history and potential misclassification of cause of death. Thus, in many respects, morbidity data are preferred to analyze the association between PD and many exposures.

Galanaud et al. (2006) conducted a case-control study where 292 cases were chosen from those enrolled in a French insurance system for agricultural workers who submitted an application for PD
health care coverage among ages 18-75. Controls were chosen from the same insurance group, but without signs of PD and matched with cases by age and geography. Exposure was assessed by interview with a questionnaire. Data were gathered on smoking status, pesticide exposure, and alcohol consumption. There was a decreased risk of PD with smoking, (OR=0.6, CI=0.4—0.9). PD risk among those who had never smoked but did have professional pesticide use was 2.0 (CI=1.1—3.6); the risk was not statistically significant for those who ever smoked (OR= 0.9, CI=0.5--1.8).

Wastensson et al. (2006) analyzed cases of PD in a group of paper mill workers in Sweden exposed to the fungicide diphenyl. Subjects were identified from company files and trade union cards where job titles and time of employment were noted. Initially, 506 exposed workers who had worked in production of diphenyl-impregnated paper anytime from 1954 to 1970 were identified. However, only 284 were still living in Sweden in August 2002. The resulting cohort of workers still alive and under the age of 80 years (255 workers) included only those with job titles or other designations indicating that they had worked in the large hall where the production of diphenyl-impregnated paper took place. Given that the number of expected prevalent cases in the exposed group was estimated to be 0.9 (versus the five cases found), this resulted in a relative risk of 5.6 (CI=1.8-13, p=0.002). The authors also looked at PD risk among the deceased workers (n=222). Nine cases of PD were found in the exposed group compared to the 4.3 cases of PD expected from data on the lifetime risk of developing PD in the general population (RR=2.1, CI=0.96-4.0).

Frigerio et al. (2006) recruited 149 PD cases (90 men) and 129 controls from the Rochester Epidemiology Project from 1975 through 1996. Each case was individually matched by age (±1 year) and sex to a general population control who resided in Olmsted County, MN, and who was free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). All subjects who farmed for five or more years were asked additional detailed questions about the main type of crops, the use of pesticides (including herbicides, insecticides, and other pesticides), and the names of the specific products used. In this study, the use of pesticides by male farmers was more common in cases than in controls; however, because of limited power, the difference was not statistically significant. Exposure to pesticides related or unrelated to farming was associated with PD in men (OR=2.4, CI=1.1-5-4; p=0.04). This association remained statistically significant after adjustment for education divided in four quartiles (aOR=2.8, CI=1.2-6.5, p=0.02) or smoking ever vs. never (aOR=2.5, CI=1.1-5.7, p=0.03).

Ascherio et al. (2006) prospectively examined whether individuals exposed to pesticides are at higher risk for PD than those not exposed. The study population was comprised of participants from the
Cancer Prevention Study II (CPS II) Nutrition Cohort, a longitudinal investigation of US men and women initiated in 1992 by the American Cancer Society. In 1982, as part of the original CPS II mortality study, participants completed a four-page survey that included questions on occupation and exposure to broad chemical categories, including pesticides/herbicides. If exposed, participants were asked to report the duration of exposure in years. Follow-up surveys were conducted in 1997, 1999, and 2001. The 143,325 individuals who returned the 2001 survey and did not have a diagnosis or symptoms of PD at baseline (1992) were included in the analyses. Individuals exposed to pesticides had a 70% higher incidence of PD than those not exposed (aRR=1.7, CI=1.2-2.3; p=0.002). The relative risk for pesticide exposure was similar in farmers and non-farmers.

Kamel et al. (2006) used data obtained from licensed private pesticide applicators and spouses participating in the Agricultural Health Study to evaluate the relation of self-reported PD to pesticide exposure. Individuals applying for certification to use restricted-use pesticides in Iowa or North Carolina were enrolled in this cohort study. Cohort members, who were enrolled in 1993-1997, provided detailed information on lifetime pesticide use. At follow-up in 1999-2003, 68% of the cohort was interviewed. Cases were defined as participants who reported physician-diagnosed PD at enrollment (prevalent cases, n=83) or follow-up (incident cases, n=78). Cases were compared with cohort members who did not report PD (n=79,557 at enrollment and n=55,931 at follow-up). Incident PD was associated with cumulative days of pesticide use at enrollment (highest quartile vs. lowest, OR=2.3, CI=1.2-4.5; p-trend = 0.009). Although positive, there was not a statistically significant association with personally applying pesticides more than half the time (OR=1.9, CI=0.7-4.7). Associations between the risk for PD and exposure to specific pesticides are discussed in other relevant sections. Prevalent PD was not associated with overall pesticide use.

Dick et al. (2007a) conducted a case-control study of 959 prevalent cases of parkinsonism (767 with PD) and 1989 controls in Scotland, Italy, Sweden, Romania and Malta. Cases with drug-induced or vascular parkinsonism or dementia were excluded. Subjects completed an interviewer-administered questionnaire about lifetime occupational and hobby exposure to solvents, pesticides, iron, copper and manganese. Lifetime and average annual exposures were estimated blind to disease status using a job-exposure matrix modified by subjective exposure modeling. Multiple logistic regression analysis was conducted with adjustments for age, sex, country, tobacco use, ever knocked unconscious and family history of PD. Analyses showed a positive but non-significant association between PD and any exposure to pesticides (aOR=1.25, CI=0.97 to 1.61) and low pesticide exposure vs. no exposure (aOR=1.09,
However, there was a statistically significant positive association between PD and high pesticide exposure vs. no exposure (aOR=1.39, CI=1.02-1.89).

Hancock et al. (2008) observed that the frequency of pesticide exposure (>10 days per year), exposure duration (>25 years), and cumulative days of exposure (>215 days) were statistically significantly associated with a 2-fold increased risk for PD in a dose-response manner (p<0.013). The authors conducted a case-control study using 319 cases and 296 controls who were relatives of the cases. Subjects were recruited from the Morris K. Udall PD Research Center of Excellence at Duke University Medical Center. Cases were confirmed by an in-person examination. Pesticide exposure was assessed using a telephone questionnaire. Questions included: "Have you ever applied pesticides to kill weeds, insects, or fungus at work, in your home, in your garden, or on your lawn?" Individuals provided only a "yes/no" answer for this question, so separation of residential applications from occupational applications for analysis was not possible. If the answer was "yes," individuals were asked to list the name of any pesticides they remembered using. For each pesticide, individuals were asked the number of days it was used per year, whether it was currently being used, the years application started and stopped (if applicable), and whether protective gear, such as a mask, rubber gloves, or rubber boots, was used during application. The study examined the associations of pesticide application, well-water consumption, and farming residences/occupations with PD while controlling for age at examination, sex, cigarette smoking and caffeine consumption. By recruiting controls that were relatives of the cases, the authors argue that there is less likelihood for spurious association due to unmeasured genetic and environmental factors compared to a population-based sample. Cases were significantly more likely to report pesticide application than their unaffected relatives (OR=1.61, CI=1.13-2.29). Frequency, duration, and cumulative exposure were also significantly associated with PD in a dose-response pattern (p<0.013). The association was modified by family history of PD, as only individuals with no family history of PD had an increased risk of PD associated with pesticide exposure (OR=1.8, CI=1.2-2.7). When examining associations of herbicide application with PD, there was no statistically significant positive association with PD for individuals who reported ever applying herbicides (OR=1.59, CI=1.00-2.54), as compared to individuals who never applied pesticides. However, there was significant positive association with PD for individuals who reported ever applying pesticides other than herbicides (OR=1.61, CI=1.09-2.38), as compared to individuals who never applied pesticides. When examining associations between insecticide application and PD, only individuals who reported ever applying insecticides were significantly more likely to develop PD (OR=1.83, CI=1.20-2.81). There was no statistically significant increased risk of PD among individuals who reported ever applying pesticides
other than insecticides. In addition, specific insecticide classes (organochlorines and organophosphates) were found to be associated with PD and these are cited in the corresponding sections, below. Well-water consumption and living on a farm were not associated with PD. Because the association between pesticide exposure and PD only existed for those with a no family history of the disease, the authors recommended that pesticides should be considered as an effect modifier in future candidate gene studies.

Elbaz et al. (2009) conducted a case-control study of 224 cases on 557 controls. Cases were those with PD selected from the Mutualité Sociale Agricole (health insurance company for farmers whether retired or active). Controls were from the same health insurance company but without PD. Pesticide exposure was evaluated in two phases including an expert evaluation. Analyses were performed by broad category (insecticide, herbicide, fungicide) and 29 pesticide families (this part of the analysis was restricted to men). The authors found an association between professional exposure to pesticides overall and PD (OR=1.8, CI=1.1-3.1) as well as a dose-response relationship between the length of exposure (p-trend=0.01 for ≤38 and >38 years of exposure vs. no exposure) and PD. Associations between pesticides and PD were generally stronger in men with older onset PD than younger onset PD. Thus, genetics seemed to play a larger role in younger cases, whereas environmental exposures played a larger role in older cases. Professional pesticide use was associated with PD in a population characterized by a high prevalence of exposure. For gardening with non-professional pesticide use, there was a positive but not statistically significant risk of PD (OR= 1.4, CI= 0.9-2.3 and p=0.18).

Hristina et al. (2010) conducted a case control study in Belgrade from 2001-2005 to examine the association between residential and occupational exposure to pesticides and PD development. There were a total of 110 PD cases with 220 hospital controls which were matched by age, sex, and geography. PD cases, significantly more frequently than controls, spent some time during their life in rural settings (p < 0.001). The authors examined a number of variables for potential association with PD including occupation, type of agricultural work, and type of nonagricultural work, exposure to any pesticides, insecticides, fungicides, well water drinking, and spring water drinking, and occupational exposure to chemicals and metals. The final logistic regression analysis, in which an adjustment was made for smoking, included gardening (ever), exposure to insecticides (residential plus occupational), occupational exposure to dyes, occupational exposure to naphtha and its derivatives, well water drinking (ever), spring water drinking (ever) and service sector worker. All of these variables had a positive and statistically significant association with PD, with the exception of service worker. For
exposure to insecticides through occupation and residence the aOR=3.22 (CI=1.32–7.87). The most frequently used insecticide was imidakloprid, followed by malathion, cipermetrin, and dimetatox. However, the relationship to individual insecticides was not examined nor was the quantity of exposure. For gardening at any time during life the OR was 5.51 (CI=3.04–10.01). Of note is that PD was not associated with agricultural occupation (p=0.424) and thus was not included in the final model. It was postulated that well water could serve as a vehicle for various chemicals’ exposure, which can initiate the development of PD.

Sanyal et al. (2010) investigated the possible impact of environmental risk factors on idiopathic PD development in a case-control study performed in Eastern India between January 1st, 2006 and December 10th, 2009. PD patients (140 men, 35 women) and 350 non-PD age-sex matched controls were included in the study. Subjects were given a structured neurological examination and administered a questionnaire, which elicited detailed information on demographic data, pesticides, herbicides, family history, occupation, dietary and smoking habits. The multivariate analysis revealed that pesticide exposure was positively associated with PD development (OR=17.12, CI=4.97-58.84). Other factors associated positively with the risk of PD were family history of PD in first and second degree relatives (OR=21.4, CI=6.36-70.12), exposure to chemicals other than pesticides and herbicides (OR=7.54, CI=2.72-20.89), rural living (OR=4.05, CI=2.53-6.49), and previous history of depression (OR=1.98, CI=1.18-3.29), whereas, smoking appeared to be a protective factor (OR=0.45, CI=0.26-0.79). Well water drinking for at least five years, though a significant risk factor on univariate analysis (OR=4.5, CI=2.1-9.9), could not be proved significant in multivariate analysis. Head trauma, vegetarian dietary habit, occupation involving physical exertion and exposure to domestic pets were not as significant risk factors for PD.

Moisan et al. (2011) conducted a cross-sectional study to examine the relationship between PD prevalence and farming type as a proxy for pesticide exposure. Examples of farming type included cattle ranching, general field cropping, and mixed cropping, with pesticide exposure varying greatly by farming type. Cases were identified using data from a French organization that reimburses current farmers and retired farmers for health insurance. PD prevalence was then estimated in five French districts. The authors split the exposures (farming type) into 5 quintiles, by density. For example, an area with the lowest density of cattle farms would be placed in the 1st quintile for that exposure category, whereas an area with the highest density of cattle farms would be placed in the 5th quintile. After adjustment for age, sex, district, and income, the risk of PD increased with the density of farms specialized in fruits and permanent crops (FSFPC) (OR5th vs. 1st quintile=1.21, CI =1.02-1.43, p-trend=0.008). The association between
PD prevalence and FSFPC was similar across all districts. The authors noted that 1) there was a high use of insecticides and herbicides in FSFPC and thus FSFPC pesticide applicators were potentially more exposed to pesticides than persons applying pesticides to other crops and 2) while cases were not confirmed by a neurologist, it was unlikely that diagnostic misclassification depended on farming type. Additionally, through a validation study, the authors noted that the sensitivity/specificity of the case definition did not depend on FSFPC density (p= 0.980).

Van der Mark et al. (2012) conducted a meta-analysis of 46 studies on PD and pesticide exposure, including 39 case-control, 4 cohort, and 3 cross-sectional studies. Exposure to pesticides was classified as ever vs. never exposed and by exposure assignment based on job title. The authors reported a statistically significant association between pesticide exposure and PD risk (summary risk ratio or sRR=1.62, CI=1.40-1.88) and between PD and job title–based exposure assignment (sRR=2.5, CI= 1.5-4.1). Self-reported pesticide exposure was also associated with PD development (sRR=1.5, CI=1.3- 1.8). The authors indicate that conclusions are limited by subjective exposure assessment and recommended that future studies focus on more objective methods of pesticide exposure assessment.

Van Maele-Fabry et al. (2012) conducted a meta-analysis of 12 cohort studies of workers occupationally exposed to pesticides with an outcome that included parkinsonian disorders or associated diseases (Parkinson’s disease, parkinsonism). Only those results for PD are reported here. The method of exposure assessment varied among the 12 studies and five of the studies only included men. The small number of studies prevented conclusions about specific chemical class of pesticides likely to be related to PD. Studies restricted to banana, sugarcane and pineapple plantations showed an increased mRR of 2.05 (CI=1.23–3.42) for PD, as did studies where the PD diagnosis was confirmed by a neurologist mRR 2.56 (CI=1.46–4.48). This meta-analysis provided some support for the hypothesis that pesticide exposure increases the risk of PD.

Noyce et al. (2012) reported a statistically significant positive association between exposure to pesticides (or herbicides or insecticides) and PD using a systematic review and meta-analysis of the risk factors for PD. For 36 case-control studies combined, there was a positive association between pesticide exposure and the later diagnosis of PD (OR=1.77, CI=1.48–2.12); for two combined cohort studies, the relative risk (RR) was 1.78 (CI=1.30-2.42), and for all studies combined, the RR was 1.78 (CI=1.50-2.10). After the authors conducted the Egger test, which suggested evidence of publication bias (p<0.001), the trim and fill method was used to account for this bias. This resulted in diminished summary estimates for pesticide exposure (RR declined from 1.78 to 1.53; CI= 1.29-1.80).
Savica and co-authors (2013) investigated specifically how PD risk factors, including pesticide use, affected the development of PD in men and women separately. This study of 196 case-control pairs (392 individuals) revealed that in men but not in women, lack of coffee consumption (never vs. ever), history of head trauma, and pesticide use were independent but relatively rare risk factors for PD and subjects who had at least one of these three risk factors (composite exposure variable) had over five-times greater risk of PD development (OR=5.28, CI=2.67-10.43). However, the magnitude of the effect due to exposure to pesticides alone or specific type of pesticides used were not provided.

Pezzoli and Cereda (2013), who investigated the risk of PD associated with exposure to pesticides and solvents using meta-analyses of data from cohort and case-control studies, found a marginal and non-statistically significant association (RR=1.26, p=0.075) between exposure to pesticides and PD development, for five pooled cohort studies. For three cohort studies investigating the role of employment in agricultural jobs, the pooled estimate for risk of PD was RR=1.33 (p<0.001). In primary analyses including all case-control studies, the authors also found that PD was associated with exposure to any type of pesticides, herbicides, and insecticides. For pesticides, the OR was 1.76 (CI=1.56—2.04); for herbicides, the OR was 1.33 (CI=1.08-1.65); for insecticides, the OR was 1.53 (CI=1.12-2.08). However, no association was observed with fungicides, rodenticides, organochlorines, and organophosphates. The authors concluded that the literature supports the hypothesis that exposure to pesticides is a risk factor for PD.

One review article (Kieburtz and Wunderle, 2013) evaluated the level of evidence for the association between pesticide exposure and the development of PD among 4 studies by choosing one of two categories: 1) sufficient evidence of an association 2) limited suggestive evidence. For the sufficient evidence category, the articles needed to demonstrate a consistent positive relationship and that bias or chance can be ruled out with reasonable confidence. For the limited suggestive evidence category, the studies suggested a positive relationship, but bias or chance could not be ruled out with confidence. The authors concluded that for these 4 studies, there is limited suggestive evidence of an association between pesticide exposure and PD.

**Lack of association**

The studies which could find no association between general pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations.

Ho et al. (1989) surveyed eight old age homes in two areas of Hong Kong to find PD cases and controls. The Initial pool was comprised of 561 subjects. Of these, 35 cases were identified through
examination by trained doctor and independently checked by 2 other examiners. Controls (n=105) matched by age and sex were those that were free of PD and dementia. A person-to-person interview with a structured questionnaire was used to collect information on social characteristics, medical history, health practices, and environmental factors such as rural living, farming practices, exposure to pesticides and consumption of raw vegetables. Informants were used for those PD patients with dementia. Other variables identified included smoking, drinking alcohol, and tea drinking. Risk of PD among those living in rural areas over 40 years was 4.9 (CI=1.4-18.2). The risk was not statistically significant for 21-40 years of residency (OR=2.1). Risk of PD among those farming over 20 years was OR=5.2 (CI=1.6-17.7). There was a positive but not statistically significant association between previous use of pesticides and herbicides and PD development (OR= 3.6, CI=1.0-12.9). Consumption of raw vegetables increased the risk for PD (OR=10.8, CI=2.4-40.0). There was a protective effect of drinking black or other tea, but this effect was not statistically significant. Smoking was also protective effect of (OR=0.6, CI=0.2-1.3), but it was not statistically significant. Patients with PD showed a much higher frequency of eating raw vegetables. A case control study carried out by Koller et al. (1990) included 150 PD cases, which were randomly selected from the Movement Disorder Clinic at the University of Kansas Medical Center. PD was confirmed by the presence of two or more cardinal signs of the disease and responsiveness to levodopa therapy. Controls (n=150) matched by age and sex were randomly recruited from the same clinic as the cases. All control subjects were examined and those with any parkinsonian signs were excluded. Exposure information was collected through a questionnaire administered by a trained interviewer. Exposure data collected included rural versus urban living, number of years spent farming, number of years drinking well water, and exposure to herbicides or pesticides. There was a statistically significant difference in the number of years that PD patients spent living in a rural environments compared to controls (OR=1.9, p=0.01).There was also an association between well water use and PD (OR=1.7, p=0.03), though that was dependent on rural living. There was no association between PD and pesticide use (OR=1.1, p=0.8).

A pilot case-control study by Wechler et al. (1991) involved subjects (cases and controls) recruited from a neurology clinic in Seattle, (some cases were recruited from area Parkinson’s support groups). The study included 34 cases of PD (no discussion of how PD was classified or verified) and 25 controls (average age 68.4 and 58.9 years, respectively). Exposure to various environmental factors and occupations was assessed through a self-administered questionnaire mailed to participants. The return rate of the questionnaires was 49% (59 of 121 distributed). A non-significant but elevated odds ratio was reported for males working in farming occupations (OR =3.1, CI=0.3-35.2). Analysis of occupational
exposure to pesticides was limited to males, because too few females worked in the occupations of interest. However, analysis of pesticide exposure at home included both males and females. More home-use of 3 pesticides (Kleenup grass & weed killer, Orthotrix, and Pestkill) was observed among PD cases than controls, but the trend was not significant for any of those pesticides. No measures of association were reported for pesticide use. Although no clear trends were observed for pesticide exposure, the authors recommended that future studies should examine the association between PD and exposure to specific pesticides.

Another case-control study was carried out with 161 cases and 149 matched controls (Stern et al., 1991). There were 2 groups of cases: young onset (<40 year olds; 46%) and old onset (>60 year olds; 53.7%). There were 60.4% males and 39.6% females; 98.0% Whites and 4.0% Blacks). The risk factors evaluated for their association with PD development included well water drinking, rural living, insecticide and herbicide exposure, head injury, smoking, education. Exposure was assessed by using a structured questionnaire. There was no statistically significant association between PD and exposure to insecticides (OR=0.5, CI=0.2-1.1) and herbicides (OR=0.9, CI=0.6-1.5). There was a non-statistically significant difference in the risk for PD between young/old onset groups given insecticide or herbicide exposure. Self-reporting of exposures in structured questionnaires may have introduced recall bias.

A case-control study of 19 families having two or more siblings with PD was conducted in Kansas to investigate possible risk factors for PD (Wong et al., 1991). Nineteen sibling pairs examined by a neurologist for PD were analyzed. PD was defined as the presence of at least two of the cardinal signs of parkinsonism (i.e., tremor, bradykinesia, rigidity, and postural instability). Patients with atypical features and dementia were excluded. Two control groups were selected for comparison; 38 individuals who were age- and sex-matched to the PD patients were randomly selected from the general neurology and medicine clinics. Demographic data included lifetime histories of places of residence; sources of drinking water; occupations, such as farming; and exposure to herbicides and pesticides. A comparison of parkinsonian siblings with siblings with essential tremor revealed no differences in any risk factors for the years of shared environment. Rural living and drinking well water (p=0.07), but not farming and herbicide/pesticide exposure (for herbicide/pesticide use OR=1.0, p=1.00), were significantly increased in 38 parkinsonians compared with 38 normal control subjects.

Smargiassi et al. (1998) carried out a questionnaire-based case-control study to investigate the possible association between exposure to environmental factors, including occupational exposure to pesticides and herbicides and PD development. Cases included 86 patients with neurologist-confirmed idiopathic PD and 86 controls similar in sex and age in Northern Italy, recruited in outpatient specialist
centers of the same University Hospital (glaucoma, psoriasis vulgaris, essential arterial hypertension and renal diseases). Exposure was defined as occupational or residential contact with a given factor for at least 10 consecutive years prior to the onset of PD. Subjects who never smoked were excluded. In this study, occupational exposure to pesticides and herbicides was not associated with the development of PD (OR=1.15, CI=0.56-2.36). However, the following risk factors were identified for PD: well water use (OR= 2.78, CI= 1.46-5.28) and occupational exposure to industrial chemicals (OR= 2.13, CI= 1.16-3.91), which included pesticides and herbicides. Among industrial chemicals, only organic solvents were identified as significant risk factors for PD (OR= 2.78, CI= 1.23-6.26). Smoking habit was negatively associated with PD (OR= 0.41, CI= 0.22-0.75), confirming the "protective" role of tobacco smoking suggested by many studies.

Werneck and Alvarenga (1999) conducted a case-control study in the city of Rio de Janeiro, Brazil to investigate the relationship between exposure to potential risk factors (herbicides and pesticides [unspecified], occupational exposure to chemicals, ingestion of drugs with secondary PD effects, rural life, water well source, family history, cranial trauma, and cigarette smoking) and development of PD. 92 subjects (41 men & 51 women, average age 70.55 yrs) diagnosed with PD between Jan 30, 1996-Feb 1, 1997 were randomly selected at the Neurology Dept of IASERJ Central Hospital; 110 controls (47 men & 63 women, average age 68.38 yrs) selected in the same hospital and matched with by sex and age (+/- 2 yrs); all controls underwent examination to exclude those showing any signs of parkinsonism or dementia; a questionnaire was used to investigate potential risk factors. Contact with herbicides and insecticides (“Have you regularly inhaled or handled herbicides and insecticides? For how long?”) for a minimum period of 15 years was required for enrollment in the study. No significant association was found between PD and general herbicide/pesticide exposure (OR=2.49, CI=0.53-13.14). Six cases (6.36%) and 3 controls (2.72%) had contact with herbicides and pesticides; four individuals used them during rural residency (all had PD) and two PD cases were positively associated with family history (OR=14.5, CI=2.98-91.38), the use of drugs with secondary PD action (OR=11.01, CI=3.41-39.41), and with exposure to chemical agents (OR=5.87, CI=1.48-27.23). PD was inversely associated with cigarette smoking (OR=0.39, CI=0.16-0.95). Univariate analysis showed cigarette smoking to be a protective factor for PD development.

Kuopio et al. (1999) studied the environmental risk factors of PD in Finland, particularly the factors related to rural environment, in a study in 1992. The population of 196,864 people, including urban and rural areas comprised this community-based case-control study. The case subjects (n= 123; 63 males and 60 females; 96 urban and 27 rural) were matched with control subjects (n=246; 126 males
and 120 females; 192 urban and 54 rural). Analyses were carried out by conditional logistic regression model. The use of DDT had been the same in both groups (OR=1.04, CI=0.68-1.60, p=0.855). The use of pesticides (regular use OR=0.65, CI=0.33-1.29, p=0.221; occasional use OR=1.23, CI=0.74-2.04, p=0.431; for both OR=1.02, CI=0.63-1.65, p=0.935), herbicides (regular use OR=0.79, CI=0.38-1.66, p=0.539; occasional use OR=1.71, CI=0.90-3.23, p=0.101; and for both OR=1.40, CI=0.79-2.48, p=0.245), or mercury-containing pickling solutions (regular use OR=1.37, CI=0.53-3.53, p=0.58; occasional use OR=1.47, CI=0.58-3.70, p=0.420; for both OR=1.58, CI=0.79-3.42, p=0.240), considering regular and occasional use separately and both regular and occasional use together, was not associated with increased risk of PD. Only three case subjects and five control subjects recalled the use of paraquat-containing products.

Tuschen et al. (2000) conducted a prospective, hospital-based cohort study to examine the possible association between agricultural and horticultural work and the subsequent morbidity from PD. Fixed cohorts of 2,273,872 men and women aged 20-59 years on 1 January 1981 and identified in the Central Population Register of Denmark were followed. All first-time hospitalizations with PD as the principal diagnosis during the 13 years until 31 December 1993 were recorded. Standardized hospitalization ratios (SHR) were calculated using all gainfully employed persons as the standard and by multiplying the ratio by 100. Statistically significantly high risks for PD were found for farmers (79 cases, SHR=130, CI=103-163) and for all men in agriculture and horticulture (109 cases, SHR=134, CI=109-162). A consistent, but non-significant pattern of high risks for PD was found among other occupational groups known to be potentially exposed to pesticides (e.g., agriculture or horticulture workers); however, no data on exposure to pesticides per se were collected nor evaluated.

PD cases (n=93) and age-and sex-matched controls (n=93) recruited in medical facilities in S. Israel were administered a validated exposure questionnaire (Herishanu et al., 2001). A multivariate logistic regression was applied for data analysis. Ninety-three consecutive unselected urban patients diagnosed between 1989-1995 as suffering from PD and treated at the outpatient PD clinic of Soroka University Medical Center in Beer-Sheva (the only general hospital in the entire region serving approximately 600,000 inhabitants) were compared to 93 age- (± two years) and sex-matched controls. The latter were recruited from the outpatient dermatology, neurology and internal medicine clinics of this hospital. Inclusion criteria for PD were progressive disorder and presence of at least two of the cardinal signs of tremor, rigidity, bradykinesia, postural instability, and good response to L-dopa. Additional criteria were absence of significant cognitive impairment and lack of an alternative etiology known to cause secondary parkinsonism. Controls presenting extrapyramidal signs, or evidence of other
neurodegenerative diseases, such as Alzheimer’s disease or essential tremor, were excluded from this study. All subjects (patients and controls) resided in Beer-Sheva or in other towns of the Negev. The risk of PD due to pesticide exposure was increased but not statistically significant (OR=6.81, CI=0.75-6.44, p <0.1). Multivariate logistic regression analysis showed history of work in construction was the strongest predictor of PD risk, followed by exposure to pesticides. Smoking was found to be a strong protective factor for PD development.

Petrovich et al. (2002) conducted a prospective cohort study with 30 years of follow-up on the island of Oahu, HI. Male subjects of Japanese ancestry (n=8006) were enrolled in the Honolulu Heart program which began in 1965. Diagnosis of PD was identified through hospitalization records, death certificates, and review of medical records for all patients with PD from a local neurologist’s office. After 1991, the diagnosis of PD was based on a complete reexamination of the entire cohort. Exposure was assessed by occupational exposure histories including questions on type of plantation work and length of time working on plantations. Information on confounding variables including age, smoking pack years, and coffee consumption was also collected. Workers who had over 20 years of work on a plantation were 1.9 times (CI=1.0-3.5) more likely to have PD compared to men with no plantation work. However, self-reported pesticide exposure was not significantly associated with PD. Study data implicate occupational pesticide exposure as a likely factor in PD in those study subjects who had worked on plantations for more than a decade.

Abbott et al. (2003) examined data from a 1965 cohort of 8,006 Japanese-American men who were interviewed about environmental, life-style, and physical attributes at selected examinations to study the relationship between these factors and the incidence of PD. All subjects were PD-free at the start of follow-up for clinical PD. Independent effects of each factor on the risk of PD were examined through the use of proportional hazards regression models. Results were not statistically significant (p=0.101) for exposure to pesticides and risk of PD (no ORs were reported). Among non-drinkers of coffee, risk of PD was 3-times higher in men who were exposed to pesticides for more than 3 years (63.4/10,000 person-years) as compared to men with no exposure to pesticides (21.4/10,000 person-years, p=0.044). Risk of PD in nonsmokers also seemed to increase susceptibility to pesticides for exposures beyond 3 years versus men who were not exposed (27.4 versus 11.8/10,000 person-years, p=0.053). The authors reported that their results indicated cigarette smoking and coffee drinking reduced the susceptibility to PD associated with exposure to pesticides.

Exposure to pesticides was not associated with increased risk for PD in a retrospective case-control study conducted by Nuti and co-authors (2004) in Tuscany, Italy. Other environmental factors
studied for their potential association with PD development were residency in rural areas and well-water drinking. PD patients (n=190; 106 males and 84 females) were identified as cases for the study. A population of 190 controls (106 males and 84 females) was recruited. There was no significant difference in mean age and sex between cases and controls. However, controls were more likely to be cigarette smokers. The results of this study did not show any statistically significant difference between PD patients and controls for time spent in rural or industrial residence, in well water drinking or in the exposure to herbicides and pesticides. The ORs for exposure to pesticides and the risk for PD were as follows: OR=0.82 for 1-10 years of exposure duration, OR=1.00 for 11-20 years of exposure duration, OR=0.90 for 21-30 years of exposure, and OR= 1.2 for ≥30 years of exposure. Although the findings of this study did not show any statistically significant association between the risk for PD development and residency in rural area, well-water drinking, and exposure to pesticides these findings indicated a protective effect of cigarette smoking on PD development.

Confirmed PD cases (n=250) and 388 age-, sex-, clinic location-, and enrollment period-matched controls were administered a structured interview to assessed exposure to pesticides (Firestone et al., 2005). PD case patients were identified between 1992 and 2002 at the Group Health Cooperative (GHC) in western Washington State or the University of Washington. To ensure complete ascertainment, subjects were identified using a combination of provider referrals and computerized databases containing diagnostic coding and pharmacy information. Pesticides were grouped into organophosphates, any pesticide, and not exposed and exposure was categorized into low/med/high for analyses. Only lifelong well-water consumption had a statistically significant association with the risk of PD (OR=1.81, CI=1.02-3.21). Odds ratios for occupational exposure were not significant but suggested a gradient that paralleled an expected increase in pesticide exposure by occupation (pesticide worker: OR=2.07, CI=0.67-6.38; crop farmer: OR=1.65, CI=0.84-3.27; animal and crop farmer: OR=1.10; CI=0.60-2.00; and dairy farmer: OR=0.88, CI=0.46-1.70). The authors found no evidence of risk from home-based pesticide exposure. For example, any pesticide exposure resulted in an OR of 0.95 (CI=0.66-1.37). Risk for herbicides was elevated but not statistically significant (OR=1.09, CI= 0.77-1.53).

Brown and co-authors (2006) conducted a literature review of epidemiological studies with pesticide exposure as one of the risk factors for PD development. Of the 38 case-control studies reviewed, all but 10 were already reviewed as original articles in this report. The 9 studies not included, reporting either positive or no association between risk of PD and exposure to pesticides, are summarized here. Fungicide exposure was not found to be a significant risk factor for PD, nor was exposure to rodenticides (Behari et al. 2001). Falope et al., (1992) reported an OR of 1.0 (CI=0.33-3.06).
for the risk of PD and exposure to pesticides. Chaturvedi et al. (1995) examined pesticide exposure and fertilizer exposure and reported an OR of 1.81 (CI=0.92-3.36). Taylor et al. (1999) found that pesticide exposure was not a significant risk factor for PD after adjustment for confounding variables (OR=1.02, CI=0.9-1.2). The relationship between exposure duration and PD risk was investigated by Nelson et al., 2000 and a positive association was observed with high doses of pesticides compared with low doses. There was also a positive correlation with duration of exposure to, and high doses of, herbicides and insecticides. Preux et al. (2000) found an OR of 1.34 (CI=0.85-2.1) and exposure to pesticides assessed through question “Have you ever been exposed to pesticides?” Vidal et al., 2002 had an OR of 1.7 (CI=1.1-2.8). Duzcan et al. (2003) asked “Have you been exposed to pesticides for more than 20 days during a year for at least 10 years?” and the OR was 1.96 (CI=1.31-6.69) indicating a statistically significant association with PD. Kamel et al. (2001) did not find a significant association with paraquat exposure, although risk was elevated: OR= 1.5 (CI=0.7-3.0); for maneb, OR=1.6 (CI=0.7-4.1).

A case-control study examining the association between exposure to pesticides, well water use, and rural exposures and the risk for PD was carried out by Wright and Keller-Byrne (2005). Residents of eastern Missouri and southwestern Illinois were enrolled in the study in 1995. Cases (n=102) were recruited from PD support groups and matched with 133 controls. A self-administered questionnaire was used to assess exposure history. Occupational pesticide use was not associated with PD (aOR=1.2, CI=0.3-4.8) after adjustment for smoking, rural living, familial PD, and other variables. However, exposure to 30 or more years of well water was associated with an increased risk of PD (aOR=8.7, CI=1.5-52). An elevated risk of PD was detected for any well water exposure during the first 40 years compared to no well water exposure (OR=7.3; CI=2.3-22.6) and for any exposure during childhood (first 20 years of life) compared to less than 20 years of exposure during childhood (aOR=8.3; CI=2.5-27.6). Among primary well water users in the first 20 years, the risk of PD was 11 times greater compared to subjects with no childhood exposure to well water (aOR=11.1, CI=2.1-51.8). There was also an exposure-response relationship for well water use; for each five-year increase of exposure before the age of 20, the risk of disease increased by 90% (OR=1.9, CI=1.3-2.8). Multivariate regression analyses adjusted for marital status, smoking, rural living, farm living, familial PD, familial essential tremor, head trauma, orchard employment, residential and occupational pesticide use.

Hofmann et al. (2006) investigated mortality among a cohort of workers from a Costa Rican banana plantation. The cohort included 40,959 individuals who worked on the plantation between 1972 and 1979. Their employment records were linked with the Costa Rican Mortality Registry to determine PD diagnosis as the cause of death through 1999. Although exposure to the nematocide, 1,2-dibromo-3-
chloropropane (DBCP) was the primary interest for this study, the study could not distinguish between exposure to DBCP and exposure to other agricultural chemicals, including pesticides such as organophosphates, paraquat, and other pesticides. There were a total of 6 reported PD deaths during the follow-up period. Compared to the local population, male banana plantation had an elevated, but non-significant increased risk of mortality from PD (SMR= 2.39, CI=0.88-5.20) that was based on small numbers (n=6). Relative to national mortality, the SMR for PD was lower for the banana plantation workers, but above the null value (SMR=1.11, CI=0.41-2.41). No deaths from PD were reported for female workers. The lack of precise exposure information and the likely misclassification of cause of death in the Mortality Registry were the major limitations of this retrospective mortality study.

Cho et al. (2008) conducted a case-control study with participants recruited from Seoul National University Hospital which was comprised of 235 PD patients, 133 multiple system atrophy (MSA) patients, and 77 normal control subjects, according to the criteria of the United Kingdom Parkinson’s Disease Society (UKPDS) brain bank, but without the criterion of a positive family history. Environmental factor data were collected by face-to-face interviews using a structured questionnaire and included detailed information on duration of participation in farming, farming type, tap-water and well-water drinking, number and severity of pesticide intoxications, number and severity of carbon monoxide (CO) intoxications, and smoking history. Data on exposure to pesticides included the annual frequency of pesticide spraying and the duration of farming. The pesticides poisoning data included the annual frequency of acute poisoning episodes. The combined variable of (farming years)*(annual frequency of pesticide spraying) resulted in an OR of 1.1 (CI= 1.0–1.2, p<0.086) for results greater than 30. The final logistic regression model demonstrated that smoking more than 10 pack-years was protective (OR=0.31). After adjusting for age, binary logistic regression analysis showed that drinking rural well water for more than 10 years significantly increased the risk of developing PD (by 2.4 for each 10-year period). The development of PD was not correlated with a history of direct pesticide exposure, but it was weakly correlated with a longer history of farming and more frequent use of pesticides. Farming greater than five years had an OR of 1.2 (CI=1.0-1.3, p=0.041). The spraying of pesticides more frequently than once per year had an OR of 1.1 (CI=1.0-1.2).

Petersen et al. (2008) investigated the association of dietary exposure to PCBs and methylmercury with PD in the Faroe Islands, where, the prevalence of PD is twice as high as would be expected, according to the authors. The OR for occupational exposure to pesticides (OR=6.00, CI=0.62-57.7) suggested an increased, but non-significant risk for PD, where pesticide exposure was classified as ever/never. However, only 2% of the population was exposed to pesticides. Hexachlorocyclohexane (8-
HCH), which is an organochlorine pesticide, was also examined. This is addressed in the following section. Whale meat consumption in adulthood was also associated with PD. For those who ate whale meat at least twice per month, there was an increased risk compared to those who ate whale meat less than twice per month (OR=6.5, CI=3.02–14.1). Blubber consumption in adulthood (same frequency) also increased risk (OR=5.61, CI=2.5–12.8).

Firestone et al. (2010) conducted a case-control study of self-reported exposure histories among 404 PD cases and 526 controls, matched for age and sex. Newly diagnosed, idiopathic PD cases were identified between 1992 and 2006 at the Group Health Cooperative (GHC) and the University of Washington. A panel of neurologists confirmed PD diagnoses by medical chart review, requiring at least two of the four cardinal signs of PD (bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment), one of which had to be bradykinesia or resting tremor. In women, the risk estimate was increased but not statistically significant for the general category of pesticides (aOR=3.9; CI=0.39–39.4), with adjustment for age, ethnicity, and smoking, though the number of exposed subjects was quite small. The risk estimate was also increased for women exposed to category of solvents (aOR=1.7, CI=0.98–3.04) and again it was not statistically significant. In men, none of the risk estimates were increased. For farming and related occupations, although none of the estimates was statistically significant, the trend paralleled an expected increase in pesticide exposure by occupation (i.e., a pesticide worker has a higher expected exposure than a crop farmer, who has a higher expected exposure than an animal farmer), and risk estimates were generally higher for women than men. The study also replicated the commonly observed inverse association between smoking and PD. The authors concluded that the risk of PD was not significantly affected by farming work, metal work, or exposure to pesticides, metals, or solvents. The authors also examined specific pesticides (malathion, parathion, diazinon, DDT, 2,4-D, and paraquat) which are addressed in subsequent sections.

Skeie et al. (2010) conducted a case-control study of 212 incident PD patients and 172 age- and gender-matched controls residing in four counties in Norway with a population of one million residents. Health outcomes studied were based on the Unified Parkinson Disease Rating Scale (UPDRS) and classified into tremor dominant (TD), postural instability and gait difficulties (PIGD), and intermediate (IND), based on symptoms. Several environmental risk factors were studied including occupation, smoking, alcohol, coffee consumption, and pesticide exposure. Pesticide exposure was self-reported and not quantified. Self-reported pesticide exposure, whether occupational or private use, was similar in patients and controls (18.0% vs. 17.1%, p=0.46). Agricultural work was associated with a higher risk of PD (OR=1.75, CI=1.03-3.0, p=0.009). There were no differences identified with other occupations. In the
regression model which included intake of alcohol, coffee, and smoking, only coffee (p=0.007) and alcohol intake (p=0.021) remained significant whereas smoking was no longer significant. Thus, from this paper it seems as though only coffee intake reduces the risk of PD in general while associations to alcohol and smoking differ between PIGD and TD-PD patients.

Rugbjerg et al. (2011) conducted a case-control study focusing on recall bias in assessing pesticide exposure. A total of 403 cases were identified through a prescription plan database; patients were included as cases if they had at least one prescription for an anti-parkinsonian drug during the period of 1995-2002. All potential cases were confirmed by an initial screening phone interview about chronic diseases, anti-parkinsonian drugs taken, and the reason for their use. Those taking the drugs for known or suspected PD had an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist with a specialty in movement disorders. Controls (n=405), which were identified through stratified random sampling of the British Columbia (BC) Ministry of Health Services client registry (representing 97.5% of the population), were matched to cases by birth year, gender, and geographic region. Subjects were interviewed about job history, medical/personal habits history, and beliefs about the disease risk factors. Each participant’s job history was reviewed by an occupational (also called industrial) hygienist who was blind to case status to determine whether potential exposures of interest commonly associated with an occupation were reported. This occupational hygiene interview was conducted with those reporting pesticide exposures above background. The risk estimates for subcategories of pesticides tended to follow the same pattern: the highest risk estimates were for self-reports; the hygiene review resulted in reductions in risk estimates; and there were slightly higher risk estimates for exposures through pesticide spraying. For example, self-reported exposure to pesticides was associated with an OR of 1.76 (CI=1.15—2.70) among 40-69 year-old participants. When exposures were based on the hygiene interview, the risk decreased to a non-statistically significant OR of 1.51 (CI=0.85—2.69). None of the ORs for pesticide subcategories were statistically significant, except self-reported insecticide exposure (OR=1.80, CI=1.03-3.15). In a second model looking at the relationship between agricultural work and PD (36 cases and 17 controls), those reporting agricultural jobs had a statistically increased risk of PD (OR=2.47, CI=1.18–5.15) when adjusted for gender, birth year, and smoking. However, when hygiene-reviewed exposures were added, the elevated and statistically significant OR for agricultural work remained (OR=2.47, CI=1.18–5.15), but the risk due to pesticide exposure was no longer elevated (OR=0.83, CI=0.43–1.61). This study provides little support for pesticide exposure as a cause of PD. The relationship to agricultural jobs suggests that
farming exposures other than those to pesticides, e.g., solvents, fuels, exhaust, dust, microorganisms, traumatic injuries, or endotoxins, should be considered as risk factors for PD.

Parron et al. (2011) conducted an ecological study using averaged prevalence rates of PD in selected Andalusian (South Spain) health districts categorized into areas of high and low environmental pesticide exposure. The pesticide exposure categories were based on the number of hectares devoted to intensive agriculture and pesticide sales per capita. A total of 17,429 cases were collected from computerized hospital records (minimum dataset) between 1998 and 2005. In a bivariate analysis, a statistically significantly increased risk (prevalence rate ratio) was found for PD development (OR= 1.30, CI=1.22-1.39, p<0.001) when comparing prevalence rates of high pesticide exposure areas relative to low exposure areas. Males living in high pesticide use areas had a small but significantly increased risk for PD (OR=1.21, CI=1.11-1.32, p<0.001) as compared to males living in areas of low pesticide use. Similar to males, females showed statistically increased risk (OR=1.40, CI=1.28-1.52, p<0.001). A stepwise multiple logistic regression analysis of the PD development adjusted for exposure to pesticides, gender and age, showed no age differences between the populations residing in high relative to low exposure to pesticides (OR=1.06, CI=1.05-1.06, p<0.001); however, males had an increased risk for PD development (OR=1.18, CI=1.10-1.28, p<0.001) but the OR for exposure to pesticides was 0.94 (CI=0.87-1.010, p=0.096). Therefore, although living in areas with high pesticide use was a statistically significant risk factor for PD in bivariate analysis, this association could not be confirmed significant in multivariate analysis. The authors postulated that these contradictory results may in part be explained by 1) districts of low environmental exposure to pesticides having a greater use of herbicides but located in inland areas, where residents were more likely to drink well water from groundwater aquifer and 2) methodological differences among the studies.

Feldman at al. (2011) found no association between occupational pesticide exposure and PD development in a prospective cohort study of males from the Swedish Twin Study, which followed 14,169 Swedish men for up to 43 years. The authors assessed exposure to 14 chemical and biological compounds, including pesticides, through a job exposure matrix (JEM) based on occupation. The JEM assessed the probability of occupational exposure to chemical and biological compounds in four classes. Class 0 represented a very low probability of exposure (less than 1/10 of persons within the occupational family expose) while class 3 represented a high probability of exposure (more than 2/3 exposed). Hazard ratios (HR) with 95% confidence intervals adjusted for age, smoking and education were used to estimate the relative risk of disease associated with exposure. For the risk of PD, the reported hazard ratios were 0.8 (CI=0.3-2.2) for class 1 probability of pesticide exposure vs. unexposed
and 0.9 (CI=0.5-1.4) for the higher or class 2 probability of pesticide exposure. The authors concluded that there was no association between Parkinson’s disease or Parkinsonian disorders and occupational exposure to pesticides and other chemicals examined. There was, however, a significant association with inorganic dust exposure.

A positive but non-statistically significant association was found between the risk for PD and exposure to pesticides among gardeners in a cohort study in Denmark (Kenborg et al., 2012). 3124 male members of the Danish Union of Gardeners who were said to have been regularly exposed to a mixture of pesticides during their active working life were recruited for the study. Standardized hospitalization rate ratios (SHR) for PD were calculated as the ratio of two numbers: the numerator (“observed”), which was the actual number of hospital admissions over a specified time period, and the denominator (“expected”), which was the number of hospital admissions that would be expected if patients under the care of that facility experienced hospital admissions at the national rate for patients with similar characteristics. Twenty-eight gardeners were hospitalized with a primary diagnosis of PD, while 24.5 were expected for the general population. The subjects were followed from 1977-2008 for a primary diagnosis of PD and were compared to the general Danish population (using the national insurance database) and matched by age, gender, and calendar period specific rates. The estimated SHR was 1.14 (CI=0.76-1.65). Despite the non-statistically significant findings, the authors concluded that their study indicated a weak but dose-related association between exposure to pesticides and risk for PD and recommended the need for larger studies.

Steenland and co-authors (2013) recruited elderly patients (ages 65 and over) in facilities where free medical exams were provided. Patients were screened with a three-tier tool and evaluated for PD and Alzheimer’s disease. Linear and logistic regression analyses were applied. The authors reported an adjusted OR (aOR) of 2.57 (CI=0.91-7.26, p=0.07) for occupational exposure to pesticides with adjustments for age, sex and education.

Organochlorine
Organochlorine (OC) pesticides include DDT, aldrin, dieldrin, heptachlor, chlordane, and lindane, among others. Lindane is also known as gamma-hexachlorocyclohexane (HCH). Technical-grade HCH was used as an insecticide in the United States and typically contained 10-15% gamma-HCH as well as the alpha (α), beta (β), delta (δ), and epsilon (ε) forms of HCH.5 β-HCH is a by-product of the manufacturing

process of the insecticide \( \gamma \)-HCH (lindane) and may be present in lindane; however, pure \( \beta \)-HCH is not used as a pesticide.

Of the 12 studies analyzing an association between OC pesticide exposure and PD development, 7 provided statistically significant evidence to support this association and 5 studies did not have statistically significant evidence. Out of the 7 studies reporting increased risk of PD due to OC pesticide use, statistically significant ORs ranged from 1.4 to 5.8. Most of the statistically significant exposures studied were related to lindane, but one study also included dieldrin.

In one study, the consumption of traditional foods such as whale blubber increased the exposure to \( \beta \)-HCH, which is persistent in the marine environment. The half-life of this chemical is approximately 8 years. Risk factors for PD previously mentioned still apply (e.g. smoking reducing the risk of PD). Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration.

**Positive association**
The studies which, for the most part, found a positive and statistically significant association between OC pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations.

The previously described case-control study by Seidler and co-authors (1996) found that PD patients were more likely than control subject to have used OC pesticides; however, the adjusted OR was statistically significant only in comparison to the regional control (aOR=5.8, CI= 1.1-30.4) but not for the neighborhood control (aOR=1.6, CI=0.4-6.2). Hancock *et al.* (2008), which was previously described, also examined the risk of exposure to two classes of insecticides: OC and organophosphates. There was an increased risk of PD associated with OC pesticide exposure (OR=1.99, CI= 1.09-3.64). Elbaz *et al.* (2009) found in this previously described study that in men, insecticides were associated with PD (OR=2.2, CI=1.1-4.3) and OC pesticides (mainly lindane) in particular (OR=2.4, CI=1.2-5.0).

The Faroe Island study (Peterson *et al.*, 2008), also previously described, looked specifically at \( \beta \)-HCH, which is persistent in the marine environment and was found at increased levels among the Faroese due to consumption of traditional foods such as whale blubber. Current \( \beta \)-HCH levels among the Faroese were associated with an increased risk of PD (OR=1.4, CI=1.1–2.0). Richardson *et al.* (2009) conducted a case-control study in which 50 PD patients, 43 controls, and 20 patients with Alzheimer’s disease (AD) who had been seen at the University of Texas Southwestern Medical Center on June 10,
2002 and Dec. 31, 2007 had serum levels of 19 OC pesticides measured. The researchers identified ß-HCH, which was the main OC compound present, age, and sex (being male) as predictor variables for PD status. ß-HCH was detectible in the largest number of PD patients (76%, detectible range 0.12/1.80 ng/mL) of any of the pesticides tested. The OR for PD among those with ß-HCH levels was over four times higher compared to controls (OR=4.39, CI= 1.67 – 11.6). There was no statistical difference observed with any of the other pesticides. The authors noted that ß-HCH levels remained constant over time: there was no difference in ß-HCH levels in samples taken at the two time points (6/10/2002 and 12/31/2007). This is largely because the half-life of ß-HCH is approximately 8 years, which means there could be a decreased clearance of ß-HCH in the PD patients. Future studies with DNA samples and demographic data on environmental factors such as smoking would provide a way to determine whether ß-HCH levels were the result of genetic polymorphisms in one or more enzymes involved in the metabolism of ß-HCH or environmental factors.

Weisskopf et al. (2010) used Finnish Mobile Clinic (FMC) Health Examination Survey data to form a nested case-control study within this survey population. Serum samples were collected during 1968 to 1972 and analyzed in 2005-2007 for OC pesticides. Incident PD cases were identified through the Social Insurance Registry and confirmed by review of medical records. There were 101 cases and 349 controls matched for age, sex, municipality, and vital status. Locations of cases were rural, semi-rural and industrial communities. Nine persistent OC pesticides were investigated. Only five OC pesticides were found at levels higher in the FMC than the United States National Health and Nutrition Examination Survey (NHANES) population, so these were the pesticides of focus chosen by the authors. These included ß-hexachlorocyclohexane (ß-HCH), p,p’dichloro-diphenyl-dichlorethylne (p,p’DDE), hexachlorobenzene (HCB), and dieldrin. Cases and controls were 20-79 years old at baseline. Because of strong confounding by cigarette smoking among smokers, analyses were restricted to never smokers (n=68 cases, n= 183 controls). Only dieldrin had a significant association with PD among never smokers (aOR=1.95, CI=1.26-3.02, p=0.003), when adjusted for age, sex, region, smoking, triglycerides, cholesterol and other pesticides. Increasing dieldrin concentrations were associated with increased but non-statistically significant ORs (OR per inter quartile range =1.28, CI=0.97-1.69, p=0.08). Drawbacks to the study include that there was a one-time-only measurement of pesticides in serum and this measurement happened decades before the development of PD. Thus, variations in exposure to the pesticides after FMC blood collection are not captured and could introduce measurement error since past exposures do not necessarily predict future exposures. Five pesticides were at higher concentrations in FMC than NHANES because FMC blood was collected before bans on these pesticides.
in Finland. Based on chemical properties, toxicokinetics, and use patterns, the authors determined that cyclodienes, including dieldrin, are among the more likely candidates to contribute to the development of PD. Dieldrin use was banned in Finland in 1969.

Richardson et al. (2011) conducted a case-control study (n=283) to investigate the association between β-HCH levels in blood serum and PD development. Four cohorts representing two discrete time periods (2001-2003 vs. 2006-2008) at two sites were matched by age and by gender; however, the study did not control for smoking. The reported adjusted odds ratio (OR) was from 1.02 to 1.12 for risk of PD per 1 ng/mg increase in β-HCH serum levels across the four cohorts and OR=1.03 (CI=1.00–1.07, p = 0.031) in the pooled analysis. The OR in subjects with β-HCH levels above the inter-quartile range of 39.08 ng/mg cholesterol was 2.85 (CI= 1.8-4.48; p value < 0.001). The authors concluded that elevated levels of serum β-HCH were associated with increased risk for PD development.

**Lack of association**

The studies which, for the most part, could find no association between OC pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. All of the studies which follow were already described in the general pesticides section, but analyses on OCs specifically are highlighted here.

Hertzman et al. (1994) did not find a statistically significant association between PD development and exposure to OC as a group of pesticides in a case-control study carried out in a horticultural region of British Columbia. The authors estimated exposure through an occupational exposure questionnaire.

The review article by Brown et al. (2006) included one paper related to OC exposure that was not included in our review. Kamel et al. (2001) found an elevated increase for OC pesticide exposure, but it was not a statistically significant (OR=1.8 , CI=0.9- 3.2).

A later paper by Kamel and colleagues (2006) evaluated the risk of PD due to exposure to the OC pesticides aldrin, dieldrin, chlordane, DDT, heptachlor, lindane, and toxaphene. Exposure was estimated through a self-administered questionnaire. However, there were no statistically significant odds ratios for either prevalent or incident PD and any of these pesticides (e.g., aOR=1.4 for incident PD and lindane, CI=0.8-2.5). The OR was adjusted for age, state, and type of participant (applicator or spouse).

Rugbjerg et al. (2011) did not find a statistically significant association with self-reported OC pesticide exposure after adjustments for gender, birth year (5-year age groups), and smoking (cumulative pack-years) (aOR=1.23, CI=0.53, 2.85).
Pezzoli and Cereda (2013) investigated the risk of PD associated with exposure to pesticides and solvents using meta-analyses of data from cohort and case-control studies. The authors included prospective cohort and case-control studies providing risk and precision estimates. No association was observed with exposure to OC pesticides.

Organophosphorus
Commonly used organophosphorus (OP) pesticides (also called organophosphates) have included parathion, malathion, methyl parathion, chlorpyrifos, and diazinon, among others. Of the 8 studies analyzing an association between OP pesticide exposure and PD development, 3 studies provided statistically significant evidence to support this association and 5 studies did not have statistically significant evidence. Out of the 3 studies reporting increased risk of PD due to OP pesticide use, statistically significant ORs ranged from 1.89 to 2.5. There was only one study which found a statistically significant association between a specific OP pesticide (chlorpyrifos) and PD. The other two studies examined OP pesticides in general. Although other studies examined malathion, parathion, and diazinon, these were no statistically significant associations with PD. Risk factors for PD previously mentioned still apply (e.g. smoking reducing the risk of PD). Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration.

Positive association
The studies which, for the most part, found a positive and statistically significant association between OP pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. With the exception of Amanpreet et al. (2008), all of the studies have already been described in the general pesticides section.

The case-control study conducted in Germany by Seidler et al. (1996;) found that PD patients were more likely than control subject to have used alkylated phosphates/carbamates; however, the adjusted OR was statistically significant only for comparison with regional control subjects (aOR=2.5, CI=1.3-4.6). There was no relationship in comparison to neighborhood controls (aOR=1.8, CI=0.9-3.3). Hancock et al. (2008) examined the risk of exposure to two classes of insecticides: organochlorines and organophosphates. Exposure to organophosphorus pesticides was associated with an increased risk of PD (OR=1.89, CI=1.11-3.25).

Amanpreet et al. (2008) conducted a case-control study in Texas in order to identify the risk of PD associated with specific pesticide and chemical products. The authors identified cases (n=100) and
controls (n=84) from a cohort of PD patients from a neurology practice. Inclusion criteria (age >=50, location of residence in East Texas, diagnosed with PD by standard clinical/lab diagnostic criteria by a neurologist specializing in movement disorders etc.) were identical for cases and controls; the only difference between the two was that controls had no history of PD. A questionnaire gathered information on demographics, lifestyle activities, family medical history, occupational history, spraying herbicides/pesticides, and use of specific pesticides. There was an increased risk of PD associated with the use of chlorpyrifos products (OR=2.0, CI=1.02-3.8). The authors note that chlorpyrifos are widely used as pesticides in agriculture, as well as in residential settings for termite treatments and lawn care. Although the risk of malathion and parathion exposures were also examined, malathion had an elevated risk that was not statistically significant (OR=1.3, CI=0.7-2.4) and parathion did not have an elevated risk (OR=0.7, CI=0.2–2.5). The small sample size of this case-control study likely limited the ability to find statistically significant results.

**Lack of association**

The studies which, for the most part, could find no association between OP pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. All of the studies which follow were already described in the general pesticides section, but analyses on OPs specifically are highlighted here.

Firestone *et al.* (2005) demonstrated that the odds ratio for OP were elevated but not statistically significant (OR=1.07, CI=0.46-2.49). The authors reported that the odds ratios for OP paralleled the World Health Organization hazard classifications, with parathion (OR=8.08, CI=0.92-70.85) much higher than diazinon (OR=1.04, CI=0.35-3.06) or malathion (OR=1.01, CI=0.37-2.72), but none of which were statistically significant. Kamel *et al.* (2006) examined the association of several OP pesticides and prevalent and incident PD. While there was an elevated risk for prevalent PD from exposure to chlorpyrifos, it was not statistically significant (OR=1.2, CI=0.7-2.1). There was also an elevated risk for incident PD associated with malathion exposure but this was not statistically significant either (OR=1.2, CI=0.6-2.1).

Firestone *et al.* (2010) examined occupational exposures to specific pesticides; the only increased risk estimate was for men exposed to parathion (OR=5.8, CI=0.66-50.8), the most potent of the OP reported. However, this was not statistically significant. There were no statistically significant associations for parathion, malathion, or diazinon, either.

Rugbjerg *et al.* (2011) did not find a statistically significant association between OP pesticide exposures that had been reviewed by an industrial hygienist and PD (OR=0.74, CI=0.20-2.78). The
authors note that since the self-reported risk estimates were uniformly higher, this could suggest that recall bias is at play.

Pezzoli and Cereda (2013) investigated the risk of PD associated with exposure to pesticides and solvents using meta-analyses of data from cohort and case-control studies. The authors included prospective cohort and case-control studies providing risk and precision estimates. No association was observed with exposure to OP.

**Botanical**
Botanical pesticides include rotenone, pyrethrins, and neem, among others. Of the 3 studies analyzing an association between botanical pesticide and PD development, all provided statistically significant evidence to support this association. Rotenone was the only botanical pesticide for which ORs were reported. These ORs ranged from 1.7 to 10.9. The highest OR was associated with exposure from gardening in the past year. In the same study, any rotenone use had only a slightly lower risk (OR=10.0). Risk factors for PD previously mentioned still apply (e.g. smoking reducing the risk of PD). Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration.

**Positive association**
The studies which, for the most part, found a positive and statistically significant association between OP pesticide exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations.

A study by Amanpreet et al. (2008), which was previously described, also examined rotenone exposure and PD risk. The risk of PD for use of organic pesticides such as rotenone in the past year in gardening was 10.9 (CI=2.5-48.0). For any rotenone use, the risk was slightly lower (OR=10.0, CI=2.9-34.3).

Tanner et al. (2011) conducted a case control study nested in the Agricultural Health Study (AHS), which assessed lifetime use of pesticides that either inhibit mitochondrial complex I or cause oxidative stress and the relationship with PD. The AHS cohort members included private pesticide applicators and their spouses. The controls were matched to cases by age, sex, and state (Iowa or North Carolina) at a ratio of approximately 3 controls per case. Diagnosis of PD was determined by agreement of two neurologists after independent review. Pesticide use was assessed by computer-assisted telephone interviews. Based on 110 PD cases and 358 controls, PD was associated with the use of a
group of pesticides that inhibit mitochondrial complex I (OR= 1.7, CI=1.0–2.8), which includes rotenone (OR=2.5, CI=1.3–4.7).

Kamel et al. (2006) did report an OR for rotenone and prevalent PD (OR=1.7), but no CI was reported. This OR was based on anywhere from 4-10 cases (specific number not cited for rotenone). It is likely that an association was not detected due to the small sample size, but without a CI, the direction of the association cannot be determined.

**Quaternary Ammonium**
The primary pesticide in this category includes paraquat. Of the 8 studies analyzing an association between quaternary ammonium pesticide exposure and PD development, 3 studies provided statistically significant evidence to support this association and 5 studies did not have statistically significant evidence. Out of the 3 studies reporting increased risk of PD due to quaternary ammonium pesticide use, statistically significant ORs ranged from 1.36 to 3.01. The highest OR was associated with paraquat exposure among traumatic brain injury patients. The risk of PD for paraquat exposure alone ranged from 1.36 to 2.5. Paraquat was the only quaternary pesticide evaluated in these studies. Risk factors for PD previously mentioned still apply (e.g. smoking reducing the risk of PD). Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration.

**Positive association**
The studies which, for the most part, found a positive and statistically significant association between quaternary ammonium exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. All of the studies which follow, with the exception of Costello et al. (2009) and Lee et al. (2012) were already described in the general pesticide section, but analyses on paraquat specifically are highlighted here.

Costello et al. (2009) conducted a study of 368 PD cases and 341 controls to examine the association between pesticide exposure during 1974-1999 and PD. Logistic regression was used to control for age, sex, and race. GIS modeling of the pesticide use registry (PUR) provided estimates of actual pesticide exposure, which is an improvement over memory responses from surveys. The combined residential ambient exposure to maneb (dithiocarbamate) and paraquat within 500 m of the home, during 1974-1999 resulted in an increased risk of PD after adjustment for age, sex, non-white race, education, and smoking status, as reported in Table 3 of the paper (aOR=1.75, CI=1.13-2.73). The risk of PD was not increased among those exposed to paraquat alone during 1974-1999 (aOR=1.01,
CI=0.71-1.43) nor for those exposed to paraquat or maneb only during 1990-1999 (aOR=0.96, CI=0.64-1.43). Also, exposure to both maneb and paraquat during 1974-1989 resulted in increased risk for PD (aOR=2.14, CI=1.24-3.68). The risk of PD increased among persons aged ≤60 years at the time of diagnosis exposed to both maneb and paraquat during 1974-1989 (aOR=4.17, CI=1.15-15.16) as well as persons aged >60 years exposed to both maneb and paraquat in 1974-1989 (aOR=2.15, CI=1.15-4.02) compared to those not exposed and as reported in Table 3 of the paper. The risk of PD for persons aged ≤60 years at the time of diagnosis exposed to maneb or paraquat alone was not statistically significant (aOR=1.77, CI= 0.84-3.75 for 1974-1999; aOR=2.27, CI=0.91-5.07 for 1974-1989; and aOR=2.00, CI=0.84-4.74 for 1990-1999). The authors concluded that exposure to a combination of maneb and paraquat increases risk for PD, especially in younger persons and/or when exposure occurs at younger ages.

Tanner et al. (2011) examined the use of a group of pesticides that cause oxidative stress and found an increased risk (OR=2.0; CI=1.2−3.6). Paraquat, which falls into this group, was also associated with an increased risk (OR=2.5; CI=1.4−4.7).

Lee, et al. (2012) conducted a case-control study involving 357 incident idiopathic PD cases and 754 population controls in Central California (Fresno, Kern and Tulare counties) investigated PD risk due to both traumatic brain injury (TBI) and exposure to pesticides (specifically paraquat). The authors reported a two-fold increase of PD risk for PD patients reporting a TBI (aOR=2.00, 95% CI 1.28-3.14) and a moderate (but weaker) PD risk for exposure to paraquat alone (aOR = 1.36, 95% CI 1.02 – 1.81). However, the risk for developing PD increased three-fold (aOR= 3.01, 95% CI 1.51-6.01) in TBI patients exposed to paraquat compared to those exposed to neither risk factor. The authors concluded that exposure to these two risk factors may act together to increase PD risk in a more than additive manner.

Lack of association
The studies which, for the most part, could find no association between paraquat exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations.

Hertzman et al. (1994), as previously reported, did not find a statistically significant association between PD development and exposure to paraquat among men in a case-control study carried out in a horticultural region of British Columbia (OR=1.25, CI=0.34-4.63).

Kamel et al. (2006) reported an elevated OR for paraquat and prevalent PD but it was not statistically significant (OR=1.8, CI=1.0-3.4). There was not an association with incident PD and paraquat.
Elbaz et al. (2009) previously described, also looked at paraquat exposure; however, no statistically significant association was found (for men over age of 65, OR=1.4 (CI=0.6–3.1). The authors indicate that there may be several reasons an association was not found: 1) paraquat is mainly used as a nonselective herbicide to kill weeds around fields, thus resulting in lower exposure levels compared to other herbicides 2) if gene-environment interactions are involved, paraquat may be associated with PD only among susceptible individuals and 3) toxicological studies have suggested that maneb (dithiocarbamate fungicide) and paraquat act synergistically.

Wang and co-authors (2011) conducted a case-control study (362 incident PD case and 341 controls) among residents of Central Valley, California to investigate association between residential and occupational exposure to ziram, maneb, and paraquat and the risk for PD. GIS-based models were used to estimate both residential and occupational exposure to ziram, maneb, and paraquat from 1974 – 1999. Pesticide Regulation Pesticide Use Report (PUR) data were combined with land use maps and geocoded address information to estimate exposure within a 500-m radius around occupational/residential addresses. The PD risk was estimated for ambient exposures to each pesticide separately and in combinations for both occupational and residential exposures. The combined exposure to maneb, ziram, and paraquat showed a stronger association with PD development than exposure to these individual pesticides alone; those results are described in the carbamate section, below. There was no association between exposure to paraquat and PD for residential exposure alone (OR=0.77, CI=0.50–1.17); there was also no statistically significant association for workplace exposure only (OR=1.07, CI=0.59–1.96), but there was a weak statistically significant association for both residential and occupational exposure combined (OR=1.50, CI=1.03–2.18).

A retrospective cohort study conducted in UK reported no evidence of increased mortality from PD (as the underlying or contributing cause of death) among paraquat workers Tomenson and Campbell (2011). The study population was a cohort of workers in Widnes, UK who manufactured paraquat in any of four plants between 1961 and 1995. The cohort group was comprised of 926 males and 42 females as of 6/30/2009. However, females were excluded from the final analysis because of their small numbers. Paraquat exposure was assessed qualitatively for 729 male workers based on their highest exposure to 11 substances including paraquat. Approximately 300 of the 729 workers had high or medium exposure to paraquat. Workers with high exposures were engineering maintenance workers in two plants, and process operators and plant supervisors from all plants. By 06/30/2009, there had been one death from PD as the underlying cause of death, but zero deaths which mentioned PD as a contributing cause among 307 workers. Standardized mortality ratios (SMRs) were calculated using local and national
mortality rates. The SMR using local mortality rates was 31 (CI=1-171) and the SMR for local mortality rates was 32 (CI=1–176) for local mortality. The authors concluded that there was no evidence of increased mortality (underlying and mentioned cause) from PD. The following were some limitations of this study: 1) PD could only be ascertained if underlying or contributing cause of death was recorded on the death certificate and 2) a full quantitative paraquat exposure assessment was not conducted. However, the authors argued that the latter was not a limitation because the one worker who died of PD was assessed as having a medium exposure to paraquat and that the level of exposure had declined drastically between 1979 and 1993.

*Carbamate or Dithiocarbamate*

This type includes the carbamate pesticide methomyl and dithiocarbamate pesticides maneb, zineb, ziram, and mancozeb. Of the 4 studies analyzing an association between carbamate or dithiocarbamate pesticide exposure and PD development, 2 studies provided statistically significant evidence to support this association and 2 studies did not have statistically significant evidence. Out of the 2 studies reporting increased risk of PD due to dithiocarbamate pesticide use, statistically significant ORs ranged from 1.74 to 8.09. The study with the OR of 1.74 examined the residential exposure to a mixture of maneb, a dithiocarbamate, and paraquat, described in the previous section. This OR was adjusted for occupational exposure. The risk of PD was higher among younger individuals (under age 60) exposed to maneb and paraquat compared to those diagnosed at age 60 and over. The highest OR was among those individuals exposed to a combination of maneb and paraquat residentially and occupationally. In this case, the workplace exposures estimates were higher than residential. This study also indicated that exposures were especially high for those workers diagnosed with PD before the age of 60. Risk factors for PD previously mentioned still apply (e.g. smoking reducing the risk of PD). Collectively, the studies support a multifactorial etiology of PD, influenced by family history of PD, head trauma, and pesticide exposure. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration.

*Positive association*

The studies which, for the most part, found a positive and statistically significant association between carbamate exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. All of the studies which follow were already described in the general pesticides section, but analyses on carbamates specifically are highlighted here.

Costello *et al.* (2009) enrolled 368 incident PD cases and 341 population controls from the Central Valley of California in a case-control study between 1998-2007. The authors developed and
validated an exposure assessment tool based on geographic information systems that integrated information from California Pesticide Use Reports (PUR) and land-use maps to estimate historical exposure to agricultural pesticides in the residential environment. They generated estimates for maneb and paraquat exposures incurred between 1974 and 1999. Combined exposure to both pesticides within 500 m of the home increased PD risk by 75% (aOR=1.75, CI=1.13-2.73), compared to no exposure to these pesticides and after adjustment for age, sex, non-white race, education, and smoking status. The risk of PD was not increased among those exposed to maneb alone during 1974-1999 (aOR=3.04 CI=0.30-30.860) as well as for those exposed to paraquat or maneb only during 1990-1999 (aOR=0.96, CI=0.64-1.43). Cases under the age of 60 years at the time of diagnosis were at much higher risk when exposed to both maneb and paraquat in combination aOR=5.07, CI=1.75-14.71 for exposure during 1974-1999 and aOR=4.17, CI=1.15-15.16 for exposure during 1974-1989) as compared to no exposure.

A case-control study by Wang and co-authors (2011), reported that the combined exposure to maneb, ziram, and paraquat at both workplace and residential settings resulted in a substantially greater increase of the risk for PD than exposure to these individual pesticides alone. The study showed that combined exposure to ziram, maneb and paraquat at workplaces increased risk of PD three-fold (OR=3.09, CI=1.69 – 5.64), while combined exposure to ziram and paraquat (without maneb) resulted in an 80% increased risk (OR=1.82, CI =1.03 – 3.21). Workplace exposure estimates were higher than residential and those were especially high for those workers diagnosed with PD at a younger age (before age 60) and exposed to the combination of maneb and paraquat both occupationally and residually (OR=8.09, CI=2.31 – 33.19). The risk of PD for combined exposure to ziram and paraquat was 5.98 (CI=1.95 – 18.32). The authors suggested that the different mechanisms by which the individual chemicals contribute to dopaminergic neuron death may act together to dramatically increase the risk of PD. This was the first epidemiologic study reporting 1) effects of ziram and PD risk 2) ambient exposure to pesticides at work being associated with a greater risk of PD than residential exposure alone; and 3) workers who were also exposed at home had the greatest risk of developing PD.

Lack of association
The studies which, for the most part, could find no association between carbamate exposure and risk of PD are summarized here. In some cases, however, the studies were mixed with both positive and no associations. Both studies have already been described previously.

Hertzman et al. (1994) did not find a statistically significant association between PD development and exposure to dithiocarbamates (including ferbam) among men in a case-control study carried out in a horticultural region of British Columbia (OR=1.06, CI=0.48, 2.37). Kamel et al. (2006)
found an elevated but non-statistically significant OR for carbamate and incident PD (OR=1.7, CI=0.7, 3.7). There was no association between prevalent PD and carbamate.

2. Pesticide Exposure with Genetic Interactions
Recent research of PD pathogenesis has revealed that certain environmental-genetic interactions may contribute more to the PD development than environmental or genetic factors alone. Multiple epidemiological studies investigated the effect of pesticide exposure on genetically susceptible individuals/populations or gene-environment relationship for the development of PD. This means that specific genotypes may either enhance or diminish the impact of pesticide exposure on the development of PD. The studies are summarized here by the type of pesticides evaluated for potential interaction with the genetic makeup of exposed individuals. The studies presenting positive associations between pesticide exposure and risk of PD are summarized first.

Pesticides (General)
Of the 11 studies analyzing an association between general pesticide exposure and PD development with possible genetic interactions, 6 provided statistically significant evidence to support an interaction effect between pesticide exposure and genes in modulating the risk of PD and 5 studies did not have statistically significant evidence that there was an interaction between genes and pesticide exposure in PD risk. Out of the 6 studies reporting an increased risk of PD due to general pesticide exposure interacting with genes, statistically significant ORs ranged from 3.17 to 4.9. Genotypes which were implicated include CYP2D6, MDR1, MnSOD, NQ01, and N0S1 SNPs. These genotypes have been associated with metabolism of pesticides or other chemicals. Of the 5 studies that did not have evidence of an interaction between genes, pesticide exposure and PD, the genotypes included SNCA, GST, MAO-A, and MDR1. For 2 studies, the association between PD and pesticide exposure alone could not be determined. Collectively, the studies indicate that genotypes may interact with pesticide exposure to increase the risk of PD. The limitations of the studies included exposure misclassification, recall bias, small sample size, and competing risk factors that may not have been taken into consideration in statistical analyses.

Positive association with interaction
The studies which, for the most part, found a positive and statistically significant association between general pesticide exposure and PD development with genetic interactions are summarized here. In some cases, however, the studies were mixed with both positive and no associations.
Hubble et al. (1998) conducted a study among PD patients with dementia (PD+D) and the controls were those without dementia (PD-D). The authors sought to examine the interaction between non-genetic variables and three candidate gene markers: poor debrisoquine metabolizer allele (CYP 2D6 29B+), monoamine oxidase B allele 1, and apolipoprotein Eɛ4 allele. Subjects with PD were recruited from the outpatient clinic of the Parkinson’s Disease Center at the University of Kansas Medical Center. PD was defined by the presence of 2 of 3 cardinal features reported by the authors including tremor, rigidity and bradykinesia and sustained responsiveness to levodopa therapy. Patients with a history or clinical features suggestive of atypical parkinsonism and patients who developed clinically obvious cognitive deficits prior to the motor deficits of PD were excluded. The determination of dementia was based on the Mattis Dementia Rating Scale (DRS). Controls were subjects with total DRS scores above 136, no single DRS subtest score more than 2 standard deviations below the mean and no clinical suspicion of mild dementia. Pesticide exposure was reported by the patient through questionnaire. Exposure was defined as pesticide use for more than 20 days within any calendar year. The initial model looked at genetic and non-genetic variables in a stepwise fashion. There was not a relationship between CYP 2D6 29B+ and PD + D (p=0.659). When pesticide exposure was combined with different variables to assess interactions, the results were mixed. The only significant relationship was with the poor metabolizer gene (CYP 2D6 29B+). There was an approximately three-fold increased risk of PD+D given pesticide exposure and presence of the poor metabolizer gene (OR=3.17, CI=1.11–9.05). The authors suggested that pesticide exposure and CYP 2D6 29B+ interact to increase the risk of PD+D. There was no relationship with pesticide exposure combined with the monoamine oxidase B allele 1 or the apolipoprotein Eɛ4 allele.

Drozdzik et al. (2003) recruited 107 PD cases and 103 matched controls of Polish origin from Western Pomerania, Poland. A total of 107 unrelated patients with idiopathic PD (56 males, 51 females) aged 24–82 years were enrolled in the study as cases. All patients were examined by consultant neurologists. PD was diagnosed if at least two of the four main signs of the disease reported by the authors (i.e. tremor at rest, rigidity, hypokinesis, and postural reflex impairment) were observed. There is a hypothesis about association between the 3435TT genotype of the MDR1 gene and early onset PD). The risk of PD development in patients exposed to pesticides versus non-exposed subjects was significantly increased in heterozygous (3435CT) patients (OR=2.9, CI=1.2–7.1, p<0.01), non-statistically significant in homozygous (3435TT) patients (OR=1.3, CI=0.4–4.4) and approximately five times higher for both groups together (3435CT + 3435TT) (OR=4.9, CI=1.7–14.6). In summary, this study revealed an association between the MDR1 gene polymorphism and PD in subjects exposed to pesticides.
Consequently, the authors indicate that prevention or treatment methods could be implemented in those individuals with the 3435T allele who are exposed to pesticides. These methods could include elimination of exposure to pesticides or, if this is not possible, provide antioxidants to reduce the effects on brain cells.

Elbaz et al. (2004) performed a case–control study of PD in a population characterized by a high prevalence of pesticide exposure and studied the joint effect of pesticide exposure and cytochrome P450 D6 (CYP2D6*4) gene activity with PD. Subjects (190 cases and 419 controls) were selected among those enrolled in a French health insurance for agricultural workers. As part of the study protocol, they were examined by a neurologist with experience in movement disorders. Whenever it was impossible to directly examine the patient, the patient’s treating neurologist was contacted to obtain clinical information. PD was defined as the presence of parkinsonism (presence of at least two cardinal signs: rest tremor, bradykinesia, rigidity, impaired postural reflexes) after exclusion of other causes of parkinsonism. Controls were recruited among all Mutualité Sociale Agricole affiliates who made requests to be reimbursed for health care expenses. A maximum of three controls were matched to each case for age, sex, and region of residency. Cases between ages 18-75 had submitted coverage for PD. Pesticide exposure was assessed by occupational health physicians using an individual “expert evaluation procedure.” Occupational pesticide exposure combined with low CYP2D6*4 (two alleles) activity resulted in increased risk for PD (OR=4.74, CI=1.29—17.45, p=0.02). When occupational exposure and gardening exposure were combined, the risk was slightly lower for the poor metabolizers (two alleles of CYP2D6*4) (OR=3.28, CI=1.16–9.27). Thus poor metabolizers may have an increased risk of PD with pesticide exposure. Without pesticide exposure, there is no increased risk.

In another case-control study of a Taiwanese population Fong et al. (2007), the association between exposure to pesticides and the PD risk was examined in conjunction with genotypes implicated in pesticide metabolism: manganese-containing superoxide dismutase (MnSOD, allele-9 T>C) and NAD(P)H:quinone oxidoreductase 1 (NQO1, allele 609 C>T). PD patients (n=153) and controls (n=155) were matched for age, sex, and origin. PD risk was statistically significantly associated with exposure to pesticides (OR=1.69, CI=1.07-2.65, p=0.023) and this association remained significant after adjustment for age, sex, and cigarette smoking (aOR=1.68, CI=1.03–2.76, p=0.023). Considering genetic factors, there were no significant differences in frequencies of both genotypes of MnSOD and NQO1 polymorphisms between PD patients and the control subjects (p>0.05). However, the difference in genotype distribution was significant among subjects who had been exposed to pesticides, with aOR of 2.49 (CI=1.18–5.26, p=0.0072) for MnSOD C allele and aOR of 2.42 (CI=1.16–4.76, p=0.0089) for NQO1 T
allele, respectively. Furthermore the combined MnSOD/NQO1 variant genotype was significantly associated with a 4.09-fold increased risk of PD (CI=1.34–10.64, p=0.0052), among subjects exposed to pesticide. This study provided evidence that susceptible variants of MnSOD and NQO1 genes may interact with occupational pesticide exposure to increase PD risk in southwestern Taiwanese.

Hancock et al. (2008) examined the joint effect of exposure to pesticides and nitric oxide synthase genes, which may create nitric oxide that contributes to neurodegeneration in PD. For the pesticide exposure portion of the study, families with PD were selected. Individuals enrolled through the Udall Center were administered a structured telephone questionnaire to collect detailed environmental risk factor data on demographics, health and habits, and pesticide and other chemical exposures. The pesticide exposure section assessed whether participants applied pesticides at work or in their home, garden, or lawn. Only first-hand exposures were considered. Participants who reported applying pesticides were asked to list the name of any pesticide they remembered using, the number of days it was used, and the years application started and stopped (if applicable). The reported pesticides were classified into specific chemical classes, but sample size was not sufficient to examine gene-environment interactions. Instead, the reported pesticide chemicals were classified more broadly into functional groups (e.g., insecticides or herbicides). Those cases who reported applying these prior to the age at disease onset were considered ever exposed. Gene-environment interaction analyses focused on 163 cases and 178 relatives and other controls from 168 sporadic PD families with environmental risk factor data available. Interactions were found between pesticides (insecticides, herbicides) and the NOS1 SNPs (single nucleotide polymorphisms) rs12829185 (OR=3.12, CI=1.71–5.71), rs1047735 (no OR given), and rs2682826 (OR=3.52, CI=1.78–6.95). The authors indicate that findings support NOS1 and NOS2A as genetic risk factors for PD and show that these genes might modify the effects of established environmental factors for PD.

Zschieidrich et al. (2009) conducted a large case-control study to investigate the potential relationship between MDR1 variants and PD. MDR1 variants were determined in 599 Europeans (415 PD patients and 184 healthy controls recruited between 1999 and 2006). The population was further stratified by ethnicity, age at PD onset (≤45 years vs. >45) and exposure to pesticides. For 86 German patients and 54 German controls from the population-based study, data on private use of pesticides were obtained through a structured interview (answer options “never,” “very rarely,” “occasionally,” and “regularly.”) Occupational exposure to pesticides in these individuals was estimated by using a job exposure matrix (JEM). Patients were classified as “exposed” when either answering “occasionally” or “regularly” in the interview or when obtaining a JEM score of >10. Genomic DNA was extracted from
venous blood samples. To test for the potential interaction between the c.3435C/T variant and pesticide exposure with respect to PD risk, a case-only analysis was performed. The case-only analysis revealed a statistically different genotype distribution at the c.3435C/T between PD patients exposed to pesticides compared to those non-exposed (OR=4.74; CI=1.01-22.3; p=0.047). The study demonstrated evidence that genetic variants of the MDR1 might act as a modulator of PD risk in patients exposed to pesticides. Thus variants in MDR1 could be another example of a susceptibility factor increasing the risk for PD in conjunction with an environmental factor, such as pesticide exposure. However no ORs were provided for the relationship between pesticide exposure and PD without variants of MDR1. The authors indicate that the results suggest another link between genetic variants of detoxifying enzymes, pesticide exposure, and PD.

Positive association without interaction

The studies which could find no evidence to support a gene-environment interaction affecting the association between general pesticide exposure and the risk of PD are summarized here.

Fong et al. (2005) conducted a case-control study to investigate the association between paraoxonase I (PNO1) polymorphism, pesticide exposure and risk of PD in Taiwanese population. Patients with idiopathic PD (n=125; 69 women and 56 men) were recruited for the study from a general hospital between July 2002 and June 2004. Unrelated controls (n=162; 90 women and 72 men) matched with the patients on age and sex were recruited from the outpatient clinic with diagnoses of back pain or cervical spondylosis. History of exposure to environmental factors and data on other factors were collected using a questionnaire filled out during a face-to-face interview. These included data on years of farming, drinking water sources, occupational exposure to pesticides, duration of pesticide exposure, and age at the initial pesticide exposure. A positive exposure was defined as an occupational or residential contact with a given factor for at least 12 months prior to the onset of PD. Buccal mucosa cells were collected from each PD and control subjects to determine PNO1 polymorphism status. There was a statistically significant association between the risk of PD and exposure to pesticides (OR=1.72, CI=1.07-2.75, p=0.025) and the risk of PD did not increase for those who had ever used well water. The relative risk of PD was 2.14 with ≥36 years of exposure to pesticides (OR=2.14, CI=1.23-3.71, p=0.005). There was no difference between the patients and the controls in the genotype of PNO1 (p=0.504). This study revealed the strong relationship between long-term (≥36 years) exposure to pesticides and the development of PD. No significant differences were observed in the distribution of PNO1 genotypes between PD patients and controls.
Brighina et al. (2008) conducted a case-control study in order to investigate the possible joint effects of SNCA REP1 genotypes and pesticide exposure and the risk of PD. The study involved 833 case-control pairs (472 case-unaffected sibling pairs and 361 case-unrelated control pairs). Cases (patients with PD) who resided in MN or in one of the surrounding four states (WI, IO, SD, or ND) were recruited prospectively from the Dept. of Neurology at the Mayo Clinic (Rochester, MN) after June 1, 1996. Controls included unaffected siblings of cases or unrelated population control subjects, who screened negative for PD or were confirmed not to have PD by clinical assessment. Cases included more men than the control group (63.6% vs. 57.0%); the median age at PD onset was 61.9 years; case and controls were primarily white and of European descent. Genomic DNA was extracted from leukocytes (venous blood samples were obtained from all cases and controls). Pesticide exposure data were obtained by telephone interview using a structured risk factors questionnaire. Exposure to pesticide was classified as “overall” (occupational, including farming; residential, including gardening; or both) and was categorized by indication for use (herbicides, insecticides, or fungicides) and by chemical group of the active ingredients. Analyses were 1) adjusted for age and sex and 2) performed for subjects overall and stratified by family history of PD, age at study, and sex. The authors observed a statistically significantly increased risk of PD with increasing SNCA REP1 bp length (OR=1.18 for each score unit; CI=1.02-1.37; p=0.03). Pesticide use (ever/never) was not associated with an increased risk of PD in the sample overall (OR=1.11, CI= 0.89-1.38, p=0.37); however, pesticide use was associated with PD in younger subjects only (≤59.8 years, OR=1.80, CI=1.12-2.87, p=0.01). For the functional pesticides subgroups (herbicides, insecticides, or fungicides), only herbicides use was associated with PD and only in younger subjects (OR=2.46, CI=1.34-4.52, p=0.004). This may be related to the fact that in this study population, the frequency of pesticide exposures considered separately were significantly greater in younger than in older subjects. Patients with PD were more likely than controls to use pesticides belonging to the chlorophenoxy acid or esters chemical class, which are used as herbicides (OR=1.52, CI=1.04-2.22, p=0.004). Furthermore, 2,4-D was the most commonly reported chlorophenoxy herbicide by the study subjects. No other subclass was significantly associated with PD, though there were 44 different chemical subclasses of pesticides identified. Also, the number of chemical subclasses reported was greater in younger than older subjects. In multivariate analysis, both SNCA REP1 score and pesticide exposures were statistically significantly associated with PD in younger subjects, but there were no pairwise interactions; the latter finding suggests other genetic loci confer susceptibility to PD in families. After restricting the susceptibility analysis to the youngest quartile of subjects, the best-fitted model included SNCA REP1 genotype score and herbicides; both SNCA REP1 genotype score (OR=1.65, CI=1.16-
2.35) and herbicides (OR=2.39, CI=1.29-4.41) were significant. The study findings suggest that SNCA REP1 genotype and exposure to herbicides have independent effects on risk of PD, primarily in younger individuals.

Kiyohara et al. (2010) examined the relationship of the seven GST polymorphisms (GSTM1 deletion, GSTT1 deletion, GSTP1 rs1695, GSTO1 rs4925, GSTO1 rs11191972, GSTO2 rs156697 and GSTO2 rs2297235) and risk of PD, with special reference to the interaction with self-reported use of pesticides (home pesticide use, occupational pesticide use, and either home or occupational pesticide use) or cigarette smoking. This case-control study involved 238 PD patients as cases and 370 controls recruited from a Japanese population. PD patients were recruited at hospitals in Fukuoka Prefecture, Kyushu Island (southern Japan), Osaka, Kyoto, and Wakayama Prefecture. Eligible cases were those within 6 years of PD onset and presented at one of the 11 collaborating hospitals between April 1, 2006 and March 31, 2008. Hospital controls were recruited from among patients without a previous diagnosis of a neurodegenerative/malignant disease. Controls were not matched to cases. Genomic DNA was extracted from buccal samples. An unconditional logistic regression model was developed for each polymorphism (presence or absence of a null allele or a number of less active alleles) and was used to predict PD status. There were three measures for biologic interactions (additive scale): 1) the relative risk, 2) attributable proportion, and 3) synergy index. No statistically significant ORs, adjusted for age, sex, smoking status, pesticide exposure, and region of residence, were found for the GST polymorphisms, indicating that none of the GST polymorphisms was associated with PD. Cigarette smoking was statistically significantly associated with decreased risk for PD, however, no interaction was observed with any of the GSTs studied. Self-reported pesticide use was not associated with increased risk of PD (home pesticide use: p=0.19; occupational pesticide use: p=0.74; either home or occupational pesticide use: p=0.16). There was no evidence of interaction between self-reported pesticide use and either GST polymorphism. The study assessed interactions between the GSTO1 rs4925 and GSTO2 re156697 SNPs and pesticide use, specifically. The results suggest that the tested GST polymorphisms did not have an important role in PD susceptibility in the studied Japanese population. The power of the study to detect an interactive effect between GSTP polymorphisms and pesticide use was low due to a small number of pesticide users.

**Unknown association without interaction**

The studies which found no evidence to support a genetic interaction with the risk of PD, but did not specifically address the contribution of pesticide exposure to PD risk alone are summarized here.
A case-control study of 959 prevalent cases of parkinsonism (767 with PD) and 1989 controls was carried out across five European centers by Dick and co-authors (2007b). Occupational hygienists estimated the average annual intensity of exposure to solvents, pesticides and metals, (iron, copper, manganese) and were blind to disease status. There was a modest but significant association between the MAO-A polymorphism in males and the risk of PD (G vs. T; aOR=1.30, CI =1.02-1.66). Also, the gene-environment interactions analysis for all cases (parkinsonism and PD) yielded little evidence of interaction effects between environmental and genetic factors; none of the analyses conducted being significant at the 5% level. However, the authors noted that a number of interactions may be worthy of further study. There were possible interaction effects between GSTM1 null genotype and solvent exposure (which were stronger when limited to PD cases only). For polymorphism PON55 in combination with pesticide exposure, there was an aOR of 4.4 (CI=0.88 to 22.3, p=0.07) adjusted for age, sex, country, ever used tobacco containing product, ever knocked unconscious and first degree family history of PD.

Kiyohara et al. (2013) recruited 606 subjects (238 PD cases and 368 controls) from various hospitals in Japan. Prevalent cases were within 6 years of the onset of PD and presented at one of the hospitals included in the study. The study aimed to determine the impact of the MDR1 C3435T polymorphism on PD risk alone or in combination with environmental factors (smoking status, alcohol use, pesticide use). Subjects with the TT genotype of the MDR1 C3435T polymorphism showed a non-significantly increased risk of PD (OR=1.49, CI=0.85-2.25) compared with those with the CC genotype. A gene-environment interaction was suggested only for alcohol consumption, with a combination of at least one T allele and ever drinking alcohol conferring significantly higher risk of PD (OR=1.83, CI=1.07-3.15, p=0.029), compared with the CC genotype and never drinking alcohol.

**Organochlorine**

Organochlorine (OC) pesticides include DDT, aldrin, dieldrin, heptachlor, chlordane, and lindane, among others. Lindane is also known as gamma-hexachlorocyclohexane (HCH). Technical-grade HCH was used as an insecticide in the United States and typically contained 10-15% gamma-HCH as well as the alpha (α), beta (β), delta (δ), and epsilon (ε) forms of HCH (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=138). Only one OC study examined the gene-OC pesticide exposure interaction. While there was a positive association between OC exposure and the risk of PD, the gene ABCB1 did not modify this risk.

**Positive association without interaction**
The studies which could find no evidence to support a gene-environment interaction affecting the association between general pesticide exposure and the risk of PD are summarized here.

Dutheil et al. (2010) conducted a case-control study to examine the association between PD and two polymorphisms in the gene ABCB1, as well as the interaction between ABCB1 polymorphism and OC insecticides. Patients enrolled in the French health system for agricultural workers (Mutualité Sociale Agricole) with PD (n=207) were examined by a neurologist and were matched to controls (n=482). Participants were classified as never users of pesticides, users of pesticides for gardening, and professional users of pesticides. Detailed information on lifelong pesticides use was obtained for professional users by occupational health physicians. Pesticides were coded using a pesticide dictionary and were grouped into various categories of pesticides. However, the authors focused on OC pesticides because in previous studies they were found to display the most robust association with PD and a dose-effect trend. Males with OC insecticide exposure (confirmed non-gardening exposure) were found to have an increased risk of PD (OR=2.2, CI=1.1-4.5), which was statistically significant. The occurrence of two ABCB1 polymorphisms (C3435T, G2677) did not differ between cases and controls (p=0.43 and p=0.97, respectively). Although statistically not significant, the risk of PD among those men who had OC exposure and were homozygous carriers of variant G2677 (A,T) was 3.5 (CI=0.9-14.5).

**Organophosphorus**

Commonly used organophosphorus (OP) pesticides (also called organophosphates) have included parathion, malathion, methyl parathion, chlorpyrifos, and diazinon, among others. Of the 2 studies analyzing an association between OP pesticide exposure and PD development with possible genetic interactions, both provided statistically significant evidence to support an interaction effect between OP pesticide exposure and genes in modulating the risk of PD. Both studies examined the PON1-55 MM genotype and one study examined the PON1-192QQ. There was an interaction effect with chlorpyrifos (OR=2.61) for the MM genotype compared to unexposed heterozygous carriers in one study and in another the OR was 2.45. There was also increased risk for chlorpyrifos exposure for individuals with the PON1-192QQ genotype (OR=1.95). The highest risk for PD was when there was chlorpyrifos and both genotypes (OR=3.28). Diazinon exposure in combination with the MM genotype also increased risk (OR=5.30). The PON1 gene appears to play a mediating role in the etiology of PD among individuals exposed to chlorpyrifos, diazinon, and potentially other pesticides which are detoxified by PON1 enzymes.

**Positive association with or without interaction**
The studies which, for the most part, found a positive and statistically significant association between general pesticide exposure and PD development with and without genetic interactions are summarized here.

Manthripragada et al. (2010) examined the association between PD and exposure to diazinon, chlorpyrifos, parathion as well as the influence of the PON1-55 MM variant genotype on PD risk. From 2001 to 2008, 351 cases and 363 controls were recruited from three rural California counties. Pesticide exposure was assessed by self-reporting and a geographic information system (GIS). The authors found an increased risk of PD among carriers of PON1-55 MM exposed to OP pesticides (for diazinon, OR=2.2, CI=1.1-4.5) compared to the heterozygous genotype and those not exposed. Carrying the MM genotype and having been exposed to chlorpyrifos increased the risk of PD nearly three times compared to unexposed wildtype/heterozygous PON1-55 carriers (OR=2.61, CI=1.25-5.44). Those who were exposed to chlorpyrifos but did not carry the homozygous variant genotype experienced a moderate increase in PD risk (OR=1.48, CI=1.04-2.12). For chlorpyrifos exposure among those individuals with an onset of PD at age 60 or younger and MM genotype carriers, there was also an increased risk (OR=5.3, CI=1.7-16). For diazinon exposure among individuals with carriers of the MM genotype, there was a doubling of risk compared with individuals with the wildtype or heterozygous genotype and no diazinon exposure (OR=2.24, CI=1.12-4.48). Those who were exposed to any diazinon but did not carry the homozygous variant genotype exhibited little to no increased risk of PD (OR=1.18, CI=0.83-1.68). For those highly exposed to diazinon, the authors found an even larger increase in risk for MM carriers (zero/low versus high: OR=5.30, CI=1.71-16.4), and strong interaction on the multiplicative scale (ORinteraction=4.59, CI = 1.37-15.4). The authors did not find any increase in PD risk with parathion exposure, even among those who were PON1-55 MM genotype carriers.

Lee et al. (2013) found increased risk of PD among PON1-55 MM carriers with exposure to chlorpyrifos (aOR=2.45, CI=1.24-4.83); no statistically significant interaction was observed between exposure to diazinon and parathion (for diazinon, aOR=1.84, CI=0.97-3.47; for parathion, aRO=1.78, CI=0.89-3.60). The risk of PD among PON1-192QQ carriers with exposure to chlorpyrifos was also increased (aOR=1.95, CI=1.13-3.37) and again, it was not statistically significant for exposure to diazinon (aOR=1.53, CI=0.90-2.61) and parathion (aOR=1.65, CI=0.95-2.89). The highest risk of PD was found among those with PON1-55 MM-192QQ and exposure to chlorpyrifos (OR=3.28, CI=1.02-10.58).

**Quarternary Ammonium**
The primary pesticide in this category includes paraquat. Of the 3 studies analyzing an association between quaternary ammonium pesticides and PD development with possible genetic interactions, 2
provided statistically significant evidence to support an interaction effect between quaternary ammonium exposure and genes in modulating the risk of PD. These studies looked at DAT and GSTT1 genotypes. There was an interaction effect with maneb and paraquat exposure and PD (OR=4.53) with individuals who had two or more DAT susceptibility genes compared to those with zero susceptibility genes. There was also increased risk of PD among those highly exposed to paraquat with a GSTT1 homozygous deletion (OR=11.1). One study did not find an interaction with SNCA and it was unknown if there was an association between PD and paraquat exposure without SNCA.

Positive association with interaction

The studies which found evidence to support a gene-environment interaction affecting the association between quaternary ammonium pesticide exposure and risk of PD are summarized here.

Ritz et al. (2009) conducted a population-based case-control study of 324 incident PD patients and 334 population controls. Subjects were recruited in three California counties. Cases were recruited by referral and confirmed by UCLA movement disorder specialists. Exposure to pesticides was assessed using telephone interview and GIS modeling. Participants also provided blood or buccal samples for genetic analyses. The study looked at the association between exposure to paraquat and maneb and PD alone, as well as the gene-environment hypothesis that dopamine transporter (DAT) genetic variants interact with pesticide exposure to increase the risk of PD. High residential exposures to both paraquat and maneb between 1974 and 1999 increased the risk of PD more than two-fold (aOR=2.32, CI=1.23–4.40), and occupational exposure increased the risk of PD by approximately 50% in males (aOR=1.56, CI=0.95–2.56), but the latter association was statistically non-significant. The authors found that high exposure to maneb and paraquat increased PD risk almost 3-fold but not significantly, in subjects who carried one DAT susceptibility allele (OR=2.99, CI=0.88-10.21); in carriers of two or more susceptibility alleles, the risk of PD was increased as much as a 4.5-fold (OR=4.53, CI=1.70–12.1) and was statistically significant. In subjects with little or no residential exposure to these pesticides, there was no increase in risk with susceptibility allele carrier status or increasing number of susceptibility alleles.

Goldman and Samuel (2012) recruited participants from the Agricultural Health Study (prospective study of licensed pesticide applicators, mostly farmers) and their spouses for the Farming and Movement Evaluation case-control study. PD risk was the outcome measured. Subjects from Iowa and North Carolina with PD (n=87) and 343 matched controls were recruited. Paraquat use was determined by interview. PD diagnosis was confirmed by in-person examination. Subjects were genotyped for homozygous deletion of GSTM1 and GSTT1. These are glutathione transferase genes, which detoxify a wide range of xenobiotic compounds. The hypothesis was that a deficient enzyme
might enhance the neurotoxicity of paraquat. Analyses were restricted to men because no women used paraquat. The general risk of PD (without reference to genotype) for those who ever used paraquat was statistically significantly increased (aOR=2.6, CI=1.3-5.0) with adjustment for age, sex, state (Iowa or North Carolina), and smoking status. Men with functional GSTT1 and paraquat use had a statistically insignificant PD risk (aOR=1.5, CI=0.6-3.6); homozygous deletion of GSTT1 (GSTT1*0) and paraquat exposure had an OR of 11.1 (CI=3.0-44.6, p=0.027). PD risk with GSTT1*0 and no paraquat exposure was not significant: aOR=1.1 (CI=0.4-2.4). Greater total years of paraquat use was strongly associated with increased risk of PD in those with GSTT1*0 (p trend= 0.001).

(Unknown association without interaction)

The studies which found evidence to support a genetic interaction with the risk of PD, but did not specifically address the contribution of pesticide exposure to PD risk alone are summarized here.

Gatto *et al.* (2010) used a population-based case-control study to examine if the risk of PD depended on the combined presence of α-synuclein (*SNCA*) gene variations and pesticide exposures. Abnormal aggregation of the α-synuclein protein, a major component of Lewy bodies and a hallmark of PD, is believed to be important in the molecular pathogenesis of the disease. Several single nucleotide polymorphisms (SNPs) and haplotypes in the *SNCA* promoter have also been shown to be associated with the risk of sporadic PD, and increasing REP1 length is associated with an increased risk of PD, as well as possibly with a decrease in age of PD onset. PD cases (n=333) were recruited from three rural California counties and matched to 336 population controls from the same area. Cases were confirmed by University of California, Los Angeles (UCLA) movement disorder specialists. This study was unique in that it estimated long-term pesticide exposure from agricultural applications in rural counties of California’s Central Valley using a geographic information system approach that integrates unique state-mandated pesticide use reports (PUR) and land use data. The authors summed intensity of pesticide applications (pounds per acre applied within a 500-meter buffer zone) at residences across a 26-year period (1974 to 1979) to calculate the cumulative total intensity of ambient paraquat exposure for each subject. Exposure to paraquat at or above the median value in the control population was considered high and below the median (including no exposure) was considered low/no exposure. There were no statistically significant findings regarding the interaction between pesticide exposure and *SNCA* variations on the risk of PD. However, there were some positive, non-significant associations. For example, among those who were homozygous or heterozygous for the *REP1 263* genotype and high paraquat exposure, the aOR=1.45 (CI=0.59–3.59) compared to those without low or no paraquat exposure.
exposure, as adjusted age, sex, education, race, smoking status, and family history of PD (positive/negative in a first-degree relative).

**Carbamate or Dithiocarbamate**

This type includes the carbamate pesticide Methomyl and dithiocarbamate pesticides maneb, zineb, ziram, mancozeb. There was one study which examined the exposure of maneb and paraquat among individuals with the DAT susceptibility gene. The risk for PD increased with exposure to these two pesticides among individuals with two or more DAT susceptibility genes (OR=4.53).

**Positive association and/or interaction**

There was one study that found an evidence to support a gene-environment interaction affecting the association between dithiocarbamates pesticide exposure and risk of PD and it is summarized here.

Ritz et al. (2009) study, which was described in the previous section, addressed the combination of maneb and paraquat exposure, with a resulting increased OR among those carrying DAT susceptibility alleles. High exposure to maneb and paraquat in carriers of one susceptibility allele increased PD risk three-fold (OR=2.99, CI=0.88-10.2), but this was not statistically significant. In carriers of two or more alleles, the PD risk increased four-fold (OR=4.53, CI=1.70-12.1). Similar results were obtained for occupational exposure to maneb and paraquat.
References


Brown TP, Rumsby PC, Capleton AC et al. 2006. Pesticides and Parkinson's disease—is there a link? Environmental Health Perspectives 114(2):156-64.


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Report Details
Brief description, including the study population (race/ethnicity, age, sex) and outcome measures: (i.e. cancer)
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Measure of Association (i.e. odds ratios, rate ratio)
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Statistically Significant Finding? (cite p-value or confidence intervals for controls versus exposed, i.e.).
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Study Recommendations (if any)?