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The Association Between Ambient Exposure to Organophosphates and Parkinson's Disease Risk

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Abstract

Objectives—There is a general consensus that pesticides are involved in the etiology of Parkinson's disease (PD), although associations between specific pesticides and the risk of developing Parkinson's disease have not been well studied. This study examines the risk of developing PD associated with specific organophosphate pesticides and their mechanisms of toxicity.

Methods—This case-control study uses a geographic information system (GIS)-based exposure assessment tool to estimate ambient exposure to 36 commonly used organophosphates (OPs) from 1974-1999. All selected OPs were analyzed individually and also in groups formed according to their presumed mechanisms of toxicity.

Results—The study included 357 incident PD cases and 752 population controls living in the Central Valley of California. Ambient exposure to each OP evaluated separately increased the risk of developing PD. However, most participants were exposed to combinations of OPs rather than a single pesticide. Risk estimates for OPs grouped according to different presumed functionalities and toxicities were similar and did not allow us to distinguish between them. However, we observed exposure-response patterns with exposure to an increasing number of OPs.

Conclusions—This study adds strong evidence that OPs are implicated in the etiology of idiopathic PD. However, studies of OPs at low doses reflective of real-world ambient exposure are needed to determine the mechanisms of neurotoxicity.

INTRODUCTION

Parkinson's disease is an idiopathic neurodegenerative disease associated with aging, environmental and genetic factors, and gender.(1, 2) Although many studies have found associations between pesticides and Parkinson's disease (PD), much heterogeneity of

findings remain to be explained.(3) While a number of methodological limitations may contribute to conflicting reports in the literature, including difficulties in correctly ascertaining PD case status, inappropriate control selection, and lack of statistical power, the major limitations of most studies are due to inadequate lifetime exposure assessment for pesticides. Previous studies generally assigned pesticide exposure based on self-report, which is likely affected by recall bias. In addition, many studies define occupational pesticide exposure as exposure to any type of pesticide or pesticides belonging to broad pesticide classes (i.e., insecticides, fungicides, herbicides), further contributing to conflicting findings if some but not all pesticides in each class contribute to PD etiology.(3)

Organophosphate (OP) pesticides represent the largest group of insecticides and are commonly used in farming in the US despite being responsible for millions of poisonings and thousands of deaths worldwide.(4-6) Some humans who experienced acute OP poisonings also developed signs of parkinsonism, suggesting that OPs may have an effect on the striatal dopaminergic system.(7, 8) While the main mechanism of OP toxicity is oxidative stress likely mediated by cholinesterase inhibition, there has recently been some suggestion that OPs may disrupt mitochondrial functions.(5)

This study aims to assess if specific organophosphates affect PD risk and whether organophosphates with presumed functional and/or neurotoxic mechanisms, such as teratogenicity or oxidative stress generation, contribute to PD risk. Since mitochondrial inhibition has been proposed as a prominent pathological pathway for PD etiology, we assess the group of OPs presumably having this action in our human population.

MATERIALS AND METHODS

All of the research procedures described in this study were approved by the UCLA Internal Review Board for human subjects. Written informed consent was obtained from all participants.

Participant recruitment

Incident idiopathic PD patients were enrolled between January 1, 2001, and January 1, 2007, and population-based controls from the mostly rural agricultural tri-county area (Kern, Tulare, Fresno) in central California between January 1, 2002, and early 2011. Subject recruitment methods(9, 10) and case definition criteria(11, 12) have been described in detail elsewhere.

Briefly, cases were defined as individuals who: 1) had been diagnosed with PD for the first time by a physician within the past 3 years; 2) were residents of Fresno, Kern, or Tulare Counties and had lived in California for at least 5 years; 3) had been seen by UCLA movement disorder specialists and confirmed as having clinically "probable" or "possible" PD; 4) did not have any other diagnosed neurological condition or serious psychiatric condition; 5) were not in the last stages of a terminal illness; 6) had agreed to participate in the study.

Of the 1,167 PD patients initially identified through neurologists, large medical groups, and public service announcements, 604 did not meet eligibility criteria (397 with an initial PD diagnosis more than 3 years prior to recruitment, 134 lived outside the tri-county area, 51 without idiopathic PD, and 22 were too ill to participate). Of 563 eligible cases, 90 could not be examined by the study movement disorder specialists (56 declined to participate or moved away, 18 had become too ill, and 16 died prior to their appointment). Of 473 patients examined, 107 did not meet eligibility critera (94 did not meet published criteria for idiopathic PD(13, 14) when examined initially, an additional 13 were reclassified as non-PD during further follow-up),(15) Additionally, 6 subjects withdrew before the exposure interview and 3 were excluded due to a PD diagnosis outside our study period, leaving a total of 357 idiopathic PD cases for this study.

Population-based controls were recruited initially from Medicare lists (2001) and, after the implementation of the Health Insurance Portability and Accountability Act (HIPAA), from residential tax assessor records for the tri-county area. Two sampling strategies, described in detail elsewhere,(9) were implemented to increase enrollment success and achieve representativeness of the control population: 1) random selection of residential parcels and enrollment via mail and phone and 2) clustered random selection of five households and enrollment via in-person visits to homes.

Of the 1,212 potential controls contacted through the first recruitment strategy, 457 were ineligible: 409 were <35 years of age, 44 were too ill to participate, and 4 primarily resided outside the study area. Of the 755 eligible population controls, 409 declined enrollment in the study, became too ill to participate, or moved out of the area after screening and prior to enrollment. A total of 346 population controls enrolled based on the first strategy. Of the 346 controls, 341 provided all information needed in this analysis. Of the 4,756 individuals screened for eligibility through the second strategy, 3,515 were ineligible (88% due to age criteria). From 1,241 eligible population controls, 634 declined participation and 607 enrolled. We excluded 196 of the 607 enrolled controls from the analysis because 183 only completed an abbreviated questionnaire, 2 did not provide ethnicity information, and 11 provided incomplete residential or occupational histories. There were 24 participants recruited at their homes that did not provide information on family history of PD and were assumed to not have a family history of PD. Additionally, more than one control was recruited from some neighborhood clusters of five homes, which potentially may introduce biases due to correlated exposures if these controls had been neighbors between 1974-1999. However, after selecting one control at random and excluding all others from multiple control clusters (n=23) our results were comparable and thus we will report on all controls recruited under the second strategy. In total, 752 controls provided all information necessary for the following analyses.

For all study participants, we conducted telephone interviews to obtain demographic information, other risk factor data, as well as residential and workplace addresses.

GIS-based Environmental Pesticide Exposure Assessment

Using our Geographic Information System (GIS)-based system, we combined pesticide use reports (PUR) data, land use maps, and geocoded address information(16, 17) to produce

estimates of pesticide exposure within a 500-meter radius circular buffer around participants' workplace and residential addresses as suggested in previous literature.(18-20) Using a 500-meter buffer also represents an intermediate distance for pesticide applications as some studies suggested a 200-meter buffer while others found a 1250-meter buffer to work best depending on the pesticide examined.(21, 22) Residential and workplace addresses were automatically geocoded to TigerLine files (Navteq, 2006), and then manually resolved in a multi-step process similar to that described by McElroy.(19) A specific address was considered precisely geocoded if it was resolved at the level of an actual address, a parcel/lot centroid, street centroid, or street intersection. Less precisely geocoded addresses were resolved at the zip code, city, county, state centroids, or did not have enough information to be geocoded. A technical discussion(16) and a detailed description(10) of our approach has been provided elsewhere.

Briefly, since 1974 the California Department of Pesticide Regulations has collected PURs for agricultural pesticide application. Each PUR record included the name of the pesticide's active ingredient, the poundage applied, the crop and acreage of the field, the application method, and location and date of application. Our GIS-based computer model combines data from PURs with California Department of Water Resources (CDWR) land use maps and historical workplace and residential addresses from study participants to estimate ambient pesticide exposure. Annual exposure estimates were calculated by adding the poundage of pesticide applied in each 500 meter buffer surrounding the workplace or residential address and weighting the total poundage by the proportion of acreage treated within the buffer. For each of the pesticides examined in this study, we summed the annual pounds applied per acre to obtain 26 annual exposure values for each pesticide separately for workplace and residential addresses. These annual exposure estimates were then averaged across the 26-year study period from 1974 to 1999. We chose to include a pesticide from the organophosphate (OP) class if five or more cases or controls were exposed to any amount of that pesticide and included a total of 36 OPs in this study (Appendix).

For the present analysis, we considered a participant exposed to a specific OP pesticide if their 26-year average ambient exposure was equal to or greater than the medians observed in the controls at either residence or workplace addresses, respectively. Thus, ambient exposures to individual pesticides were calculated and determined separately at workplace and residential addresses. We were also able to determine if participants were exposed only at residential addresses, workplace addresses, or at both residential and workplace addresses. It is important to emphasize that ambient exposures at workplace addresses are not necessarily associated with occupational exposures as a result of job tasks. Participants who work within 500 meters of a field where a pesticide was applied would be considered ambiently exposed to that pesticide even if that participant's occupation was unrelated to agriculture and pesticide application. Study participants were considered unexposed to pesticides if 1) they did not work or live within 500 meters of pesticide applications in the tri-county area between 1974 and 1999 and thus could not be assigned an exposure estimate or 2) were never exposed to at least the median value of the control group for any pesticide.

Statistical Analysis

All selected OPs were analyzed individually and also in groups according to their presumed mechanisms of toxicity, such as being a carcinogen (carcinogenic: known or possible carcinogen; non-carcinogenic: not likely or not listed as carcinogen), teratogen, or endocrine disruptor, and their acute toxicity due to acetylcholinesterase inhibition (toxic: extreme or high toxicity; non-toxic: moderate or slight toxicity) based on the Pesticide Action Network Pesticide Database (see Appendix).(23) We also grouped OPs according to some presumed mitochondrial disrupting potential based on some recent literature (see Appendix). However, these classifications by presumed mechanism were not mutually exclusive (i.e., a pesticide may have been assigned to multiple groups).

For the analysis of the individual OPs (Table 2) as well as for the groups of OPs with different mechanisms of toxicity (Table 3), we created a variable for each OP or group of OPs with the same mechanism of toxicity individually, which were analyzed in separate models. We took a different approach when we assessed the association between mitochondria disrupting OPs and PD risk (Table 4). We created and analyzed a single variable that categorized all the participants into mutually exclusive groups: 1) participants with no exposure to pesticides, 2) those exposed to non-mitochondria disrupting OPs, and 3) those exposed to 1-7 and 8-14 mitochondria disrupting OPs.

Logistic regression analyses were conducted to assess associations between PD and the GIS-based estimates of individual and grouped ambient OP exposures at workplace and residential addresses. Trend tests were conducted using an ordinal count variable. We adjusted for age at diagnosis (cases) or age at interview (controls) as a dichotomous variable ($\leq$ 60 or > 60 years), gender, race (White vs. non-White), education (< 12 years, 12 years, > 12 years), having a 1st degree family member with PD (yes, no), smoking (current, former, never), and included an indicator variable for participants exposed to other pesticides including organochlorines, dithiocarbamates, and paraquat but not OPs.

We used SAS 9.2 (SAS Institute Inc., Cary, NC, USA) to perform unconditional logistic regression analyses.

RESULTS

Study participants were predominantly White, over the age of 60, and a minority reported a family history of Parkinson's disease (Table 1). Cases were slightly older than controls, more often male, and had completed fewer years of formal education. They were also more likely to have never smoked cigarettes or to have stopped smoking.

Effect estimates for each individual OP separately are shown in Table 2. All OPs investigated were associated with 100% or greater risk of developing PD. Generally, exposures at workplace addresses or at both residential and workplace addresses conferred a greater risk than exposures at residences only. Acephate, ethephon, phorate, naled, malathion, merphos, chlorpyrifos, disulfoton, dimethoate, and monocrotophos were the only OPs that were strongly associated with increased risks of developing PD at residential

addresses only, workplaces addresses only, as well as at residential and workplace addresses together.

All groups of OPs classified by presumed mechanism/toxicity appeared to be associated with similarly increased odds of developing PD – i.e., none of the groupings seemed more important than the others (Table 3). Again, exposures at workplace addresses only or at both residential and workplace addresses were associated with a greater increase in risk of PD than exposures at residential addresses only. This pattern also held for OPs with presumed mitochondrial disrupting function – i.e., we could not distinguish risk between those exposed to OPs with and without such presumed function (Table 4). Moreover, our data suggested a trend where exposure to an increasing number of potential mitochondria disrupting OPs at workplaces (p-trend = 0.0014), or at both residences and workplaces (p-trend < 0.0001), was associated with an increasing risk of PD.

DISCUSSION

This population-based case-control study conducted in the Central Valley of California found exposure to all OPs included in this study to be associated with an increased odds of developing PD. Thus those classified as teratogens, endocrine disruptors, and carcinogens exhibited similar effects as those assigned mitochondrial disrupting function suggesting that the true mechanisms of neurotoxic action might not be known or that many OPs contributing to these groups have multiple mechanisms of toxicity. Also, we may not be able to distinguish between mechanisms due to OPs exhibiting multiple mechanisms – e.g., seven of the twelve OP endocrine disruptors were also presumed mitochondrial disruptors. Generally, ambient exposure at residential addresses resulted in weaker associations with PD than at workplace addresses or exposure in both locations, suggesting that workplace related ambient exposures and exposure at multiple locations might be higher than exposure at residential addresses only. This may be due to the fact that most people do not work at their residence and thus are not present when the OPs are applied agriculturally during daytime work hours. The hydrolytic properties of OPs can cause the active ingredients to break down quickly outdoors and being present during or shortly after applications of OPs may contribute to the risk of developing PD.(24, 25)

A strength of this study is the unique GIS-based pesticide exposure assessment method that was utilized to assess ambient pesticide exposure at residential and workplace addresses from drift and/or contact with dust and soils contaminated with pesticides in this heavily agricultural region.(26) The specific type, amount, and location of an applied pesticide active ingredient can be identified using historical PUR records, which is a vast improvement over the majority of previous studies that relied on less accurate exposure assessment, such as self-reported exposures. A recent meta-analysis of 46 studies showed a moderate association between general pesticide exposure and PD (summary RR: 1.62; 95% CI: 1.40, 1.88).(3) However, it also found substantial heterogeneity of results between studies included in the analysis. The authors attributed this heterogeneity to unreliable self-reported exposure, which may have introduced non-differential misclassification that typically biases results towards the null thereby preventing the detection of existing associations between pesticides and PD risk. Another issue with most of the studies included

in the meta-analysis is that the majority of the studies defined pesticide exposure as ever/ never exposure to any pesticide or to broad subgroups such as herbicides, insecticides, and fungicides. This approach assumes that all pesticides or pesticides belonging to broad pesticide subgroups similarly affect the risk of developing PD, which is unlikely and may introduce bias due to exposure misclassification. Thus, estimates of the risk of developing PD after exposure to specific pesticides are probably needed to understand, at least in part, this heterogeneity.

A limitation of our exposure assessment method is that the precise resolution of the GIS-based pesticide exposure estimation relies on how accurately participants reported their workplace and residential addresses. Workplace addresses tend to be recalled with less accuracy than residential addresses leading to less precise geocoding. Indeed, workplace addresses were geocoded less precisely than residential addresses in this study. However, the geocoding quality of addresses for cases and controls was similar. We found that when assessing geocoded data in our study, 24.6% of cases and 21.2% of controls spent 50% or more of the years between 1974-1999 at precisely geocoded workplace addresses while 37.5% of cases and 48.4% of controls spent 50% or more of these years at precisely geocoded residential addresses. This suggests that geocoding precision is not likely to account for difference in the estimated effects.

A limitation of all pesticide research is the issue of correlated exposures. It is difficult to distinguish the effect that individual pesticides have on PD risk since people who are exposed to pesticides are often concurrently exposed to multiple pesticides. Thus, it is not possible to separate individual pesticide effects by simply adjusting for other pesticides. The ambient pesticide exposure estimates we derived contain an inherent amount of uncertainty as we were not able to measure historical pesticide serum levels in participants. Therefore, we decided to take a conservative approach and only consider participants exposed to a particular pesticide if they were assigned ambient exposure to that pesticide equal to or above the controls' median exposure value. This increases the specificity of our exposure assessment and participants who are less likely to be exposed will also be less likely to be misclassified as exposed.

Despite these limitations, our GIS model provides a valid and high quality indicator of passive pesticide exposure from applications and drift in close proximity to workplaces and residences. It is unlikely that the GIS-based results are affected by selection bias because our participants did not self-report pesticide exposures and were most likely not aware of their historical exposures to specific pesticides applied within 500 meters of their residences and/or workplaces. There is also no reason to suspect that cases and controls would choose to differentially participate in this study based on whether or not they lived and/or worked near agricultural plots during the 26-year exposure period we investigated.

The primary mechanism ascribed to OP toxicity is the inhibition of acetylcholinesterase (AChE) leading to an accumulation of acetylcholine at cholinergic synapses and over-stimulation of muscarinic and nicotinic receptors.(6) Although inhibition of AChE results in cholinergic system overstimulation and consequently cell death(27, 28), it is unlikely to be the primary mechanism for PD development.(5) OPs also may exhibit a number of non-

cholinergic mechanisms of toxicity such as the inhibition of mitochondrial processes.(5) Concerning the presumed mitochondrial disrupting properties of OPs, this mechanism has not been studied extensively yet and the majority of the existing studies used large experimental doses of OPs that may have caused non-specific general toxicity and are not reflective of real-world ambient exposures and potential mechanisms. Thus, the current literature is insufficient to establish whether individual OPs are mitochondrial disruptors at ambient exposure levels and our results do not support such a specific mechanism for the pesticides we evaluated.

Oxidative stress occurs when the body's antioxidant defenses are not able to neutralize an excess of reactive oxygen species (ROS).(29) The brain utilizes a large amount of oxygen that may lead to an increased production of ROS and is also particularly susceptible to oxidative damage as it is composed largely of polyunsaturated fatty acids.(28) When AChE is inhibited an excessive amount of ROS may be generated when cells are not able to maintain energy levels due to high energy consumption and inhibition of oxidative phosphorylation.(30) Oxidative stress may also originate from the mitochondria when their function is disrupted.(31, 32) Dopaminergic neurons, unlike other neurons, are autonomously active pacemakers and have a greater reliance on oxidative phosphorylation. (33) However, grouping OP pesticides according to some presumed function/toxicity did not allow us to distinguish OPs from each other according to whether or not they increased PD risk differently in our human population.

Besides governing aerobic respiration, mitochondria also are involved in the apoptotic neurodegenerative processes.(5) Apoptosis may be caused by increased production of ROS and the translocation and inhibition of proteins involved in respiration such as cytochrome C.(34) Mevinphos has been shown to disrupt oxidative phosphorylation by causing the dysfunction of Complexes I through IV, which leads to cell death due to ATP depletion.(35) Monocrotophos have also been shown to induce apoptosis in neurons and inhibit metabolism.(34) Chlorpyrifos and chlorpyrifos-oxon exposure resulted in increased mitochondrial length, decreased number of mitochondria, and decreased mitochondria movement in axon at concentrations that did not inhibit AChE.(36) Taken together, the evidence that OPs cause cell death specifically mediated through the disruption of mitochondrial functioning is not adequate and our results suggest that while a large number of OPs increased PD risk the mechanisms of action remain to be explored.

In conclusion, this study adds strong evidence that OPs are implicated in the etiology of idiopathic PD. Additionally, ambient exposure to OPs at workplaces and combined ambient exposure at residences and workplaces seem to be especially important. This is the first study to show in a human population that exposure to increasing numbers of OPs is associated with elevated risks of PD. Future studies should further examine possible neurotoxic mechanisms of OPs at low doses that are reflective of real-world ambient exposure.

Acknowledgments

Appendix

Appendix

List of organophosphate pesticides included in this study

Pesticide	Chem Code	Acute Toxicity	Carcinogen	Cholinesterase inhibitor	Teratogen	Endocrine disruptor	Mitochondria disruptor
Profenofos	2042	0	0	1	0	0	0
Fenamiphos	1857	1	1	1	0	0	0
Dialifor	1799	0	0	1	0	0	0
Methamidophos	1697	1	0	1	0	0	0
Methidathion	1689	1	1	1	0	0	0
Acephate	1685	0	1	1	0	1	0
Leptophos	1676	0	0	1	0	0	0
Ethephon	1626	0	0	1	0	0	0
Tetraethyl pyrophosphate (TEPP)	577	1	0	1	0	0	0
Demeton	566	1	0	1	0	0	0
Sulfotep	558	1	0	1	0	0	0
Phosphamidon	482	1	1	1	0	1	1
Mevinphos	480	1	0	1	0	1	1
Phosalone	479	0	0	1	0	0	0
Phorate	478	1	0	1	0	0	0
Parathion	459	1	1	1	0	1	1
Naled	418	0	0	1	1	0	0
Parathion-methyl	394	1	0	1	0	1	1
Oxydemeton-methyl	382	1	0	1	1	1	0
Malathion	367	0	1	1	0	1	1
Phosmet	335	0	1	1	0	0	0
Azinphos-methyl	314	1	0	1	0	0	0
Merphos	293	0	0	1	0	0	0
Ethion	268	1	0	1	0	0	0
Chlorpyrifos	253	0	0	1	0	1	1
Disulfoton	230	1	0	1	0	0	0
Dimethoate	216	1	1	1	1	1	1

Pesticide	Chem Code	Acute Toxicity	Carcinogen	Cholinesterase inhibitor	Teratogen	Endocrine disruptor	Mitochondria disruptor
Diazinon	198	0	0	1	1	1	0
Dioxathion	192	1	0	1	0	0	0
Tribufos	190	0	1	1	0	0	0
Dichlorvos	187	1	1	1	0	1	1
Carbophenothion	110	1	0	1	0	0	0
Trichlorfon	88	0	1	1	0	1	0
Dicrotophos	72	1	1	1	0	0	0
Bensulide	70	0	0	1	0	0	0
Monocrotophos	52	1	0	1	0	0	1

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What this paper adds

- Commonly used pesticide exposure estimation techniques are not sophisticated enough to assess concurrent exposure to specific pesticides, which is vital to understanding the etiology of Parkinson's disease

- This study uses a geographic information system-based approach that utilizes historical pesticide use and study participant address records to assess historical exposures to specific organophosphate pesticides

- This study found that all of the specific organophosphate pesticides included in the study increased the risk of Parkinson's disease, but the mechanism(s) behind this risk increase is unclear

- In order for epidemiological studies to better assess specific pesticide mechanisms in human populations, more animal and cell model research must be conducted to examine neurotoxic mechanisms of pesticides at low doses that are reflective of real-world ambient exposure

Table 1

Demographic Characteristics of the Study Population

	Case (n=357)		Control (n=752)	
	n	%	n	%
Age (Mean and Range) [*]	68.3 (34-88)		66.9 (35-99)	
60	75	21.0	221	29.4
> 60	282	79.0	531	70.6
Gender				
Female	152	42.6	401	53.3
Male	205	57.4	351	46.7
1st Deg. Relative with PD				
No	305	85.4	689	91.6
Yes	52	14.6	63	8.4
Race				
White	287	80.4	526	70.0
Non-White	70	19.6	226	30.0
Education				
<12 years	66	18.5	111	14.8
12 years	96	26.9	156	20.7
>12 years	195	54.6	485	64.5
Smoker Status				
Never smoker	187	52.4	362	48.1
Former smoker	150	42.0	304	40.4
Current smoker	20	5.6	86	11.5

[*]
Age represents age at PD onset for cases and age at interview for controls

Table 2

Effect estimates (ORs and 95% CIs) for ambient exposures to organophosphates at residences and workplaces during 1974–1999

Pesticide and CA Chem Codes	Residences only				Workplaces only				Residences and Workplaces			
	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI
Not exposed to pesticides	65	220	1.00	reference	65	220	1.00	reference	65	220	1.00	reference
Not exposed to OPs, but exposed to other pesticides	3	12	Not reported	Not reported	6	13	Not reported	Not reported	4	3	Not reported	Not reported
Profenofos 2042	17	27	2.24	(1.12, 4.47)	22	16	4.26	(2.05, 8.84)	7	11	1.73	(0.61, 4.89)
Fenamiphos 1857	15	29	1.88	(0.91, 3.86)	19	19	3.22	(1.56, 6.62)	9	10	2.71	(1.04, 7.09)
Methamidophos 1697	18	42	1.52	(0.80 ,2.87)	18	28	2.45	(1.23, 4.89)	20	12	4.72	(2.09, 10.62)
Methidathion 1689	29	60	1.62	(0.94, 2.78)	32	48	2.46	(1.42, 4.27)	41	66	2.11	(1.28, 3.49)
Acephate 1685	45	64	2.5	(1.52, 4.10)	43	45	3.22	(1.91, 5.44)	26	38	2.44	(1.34, 4.43)
Ethephon 1626	43	68	2.09	(1.28, 3.42)	31	38	3	(1.68, 5.38)	26	33	2.32	(1.27, 4.26)
Demeton 566	8	31	0.87	(0.37, 2.04)	23	15	4.74	(2.27, 9.92)	9	4	5.93	(1.69, 20.87)
Mevinphos 480	23	52	1.34	(0.74, 2.43)	37	32	3.92	(2.21, 6.95)	16	15	3.21	(1.47, 6.98)
Phosalone 479	12	23	1.99	(0.91, 4.39)	10	9	3.47	(1.31, 9.23)	10	8	3.65	(1.34, 9.91)
Phorate 478	31	53	2.04	(1.18, 3.53)	24	31	2.45	(1.31, 4.57)	28	28	3.19	(1.72, 5.94)
Parathion 459	34	84	1.43	(0.86, 2.37)	35	52	2.29	(1.34, 3.91)	50	69	2.43	(1.51, 3.91)
Naled 418	36	66	2.16	(1.29, 3.61)	47	53	2.99	(1.80, 4.95)	35	51	2.16	(1.27, 3.70)
Parathion-methyl 394	20	36	1.81	(0.96, 3.42)	20	17	4.47	(2.12, 9.41)	10	16	1.68	(0.71, 4.00)
Oxydemeton-methyl 382	27	56	1.7	(0.97, 2.98)	29	47	2.21	(1.26, 3.88)	22	12	5.86	(2.68, 12.82)
Malathion 367	52	81	2.16	(1.36, 3.43)	44	43	3.16	(1.88, 5.32)	25	31	2.69	(1.45, 5.01)
Phosmet 335	26	88	1.41	(0.86, 2.31)	43	55	2.9	(1.74, 4.81)	34	52	1.93	(1.13, 3.30)
Azinphos-methyl 314	30	76	1.46	(0.86, 2.45)	22	36	2.12	(1.14, 3.95)	37	40	2.88	(1.66, 4.98)
Merphos 293	27	31	3.13	(1.67, 5.79)	16	17	2.72	(1.27, 5.83)	8	7	3.73	(1.22, 11.42)
Ethion 268	13	25	1.93	(0.90, 4.11)	25	25	3.83	(1.98, 7.40)	9	9	3.44	(1.26, 9.42)
Chlorpyrifos 253	46	88	1.69	(1.06, 2.69)	31	57	1.94	(1.12, 3.34)	39	64	1.92	(1.15, 3.18)
Disulfoton 230	24	45	1.82	(1.01, 3.28)	24	26	2.97	(1.55, 5.67)	16	15	2.88	(1.32, 6.33)
Dimethoate 216	47	100	1.71	(1.08, 2.72)	54	62	3.04	(1.89, 4.90)	66	85	2.59	(1.66, 4.05)
Diazinon 198	47	109	1.47	(0.93, 2.32)	37	64	1.93	(1.16, 3.21)	58	71	2.61	(1.64, 4.16)

Pesticide and CA Chem Codes	Residences only				Workplaces only				Residences and Workplaces			
	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI
Tribufos 190	23	57	1.36	(0.77, 2.42)	27	40	2.28	(1.26, 4.10)	24	23	3.15	(1.62, 6.12)
Trichlorfon 88	15	32	1.55	(0.77, 3.12)	19	17	4.24	(2.01, 8.95)	6	5	3.35	(0.95, 11.78)
Monocrotophos 52	32	51	2.03	(1.18, 3.51)	21	25	2.66	(1.36, 5.21)	24	15	5.53	(2.62, 11.65)

*
Adjusted for sex, education, smoking, age, family history of PD, race, and other pesticides.

Note: The following OPs were not included in this analysis due to too few exposed participants at either residences only, workplaces only, or at residences and workplaces: leptophos, sulfotep, phosphamidon, carbophenothion, dicrotophos, TEPP, dioxathion, dialifor, dichlorvos, and bensulide

Table 3

Effect estimates for ambient exposures to subsets of organophosphates based on mechanism of toxicity at residences and workplaces during 1974-1999

Mechanism of toxicity**	Residences only				Workplaces only				Residences and workplaces			
	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI	Case	Control	Adjusted OR*	95% CI
Not exposed to pesticides	65	220	1.00	reference	65	220	1.00	reference	65	220	1.00	reference
Not exposed to OPs, but exposed to other pesticides	3	12	Not reported	Not reported	6	13	Not reported	Not reported	4	3	Not reported	Not reported
Exp to cholinesterase inhibiting OPs	75	175	1.45	(0.97, 2.16)	39	75	1.79	(1.09, 2.94)	165	254	2.24	(1.58, 3.19)
Exp to highly acutely toxic OPs	69	154	1.53	(1.01, 2.30)	45	78	1.88	(1.17, 3.03)	133	196	2.4	(1.65, 3.47)
Exp to teratogen OPs	64	146	1.54	(1.01, 2.34)	53	82	2.11	(1.33, 3.34)	99	144	2.41	(1.62, 3.58)
Exp to endocrine disruptor OPs	74	166	1.53	(1.03, 2.30)	39	83	1.57	(0.96, 2.55)	143	206	2.41	(1.67, 3.48)
Exp to carcinogen OPs	36	78	1.56	(0.95, 2.56)	36	46	2.73	(1.59, 4.71)	29	29	3.21	(1.75, 5.91)
Exp to mitochondria disruptor OPs	69	138	1.7	(1.13, 2.58)	53	84	2.22	(1.41, 3.51)	110	168	2.23	(1.52, 3.27)

*
Adjusted for sex, education, smoking, age, family history of PD, race, and other pesticides.

**
Please refer to the Appendix for the classification of pesticides under each mechanism of toxicity. Note: Since participants are not mutually exclusively exposed to OP groups, the numbers of participants in this table do not add up to the total participants included in the study population. Furthermore, odds ratios and 95% confidence intervals were not reported for participants who were not exposed to OPs but were exposed to other pesticides as these pesticides were not of interest in this analysis.

Table 4

Effect estimates for ambient exposures to presumed mitochondrial disrupting organophosphates at residences and workplaces during 1974–1999

	Residences only				Workplaces only				Workplaces and Residences			
	Cases	Controls	Adjusted OR*	95% CI	Cases	Controls	Adjusted OR*	95% CI	Cases	Controls	Adjusted OR*	95% CI
Not exposed to pesticides	65	220	1.00	reference	65	220	1.00	reference	65	220	1.00	reference
Not exposed to OPs, but exposed to other pesticides	3	12	Not reported	Not reported	6	13	Not reported	Not reported	4	3	Not reported	Not reported
Exposed only to OPs that do not disrupt mitochondria**	18	59	1.09	(0.59, 2.01)	15	25	2.06	(0.99, 4.29)	9	15	2.07	(0.84, 5.06)
Exposed to presumed mitochondria disrupting OPs**												
1-7 OPs	74	153	1.63	(1.09, 2.44)	46	75	2.16	(1.34, 3.48)	80	143	1.98	(1.32, 2.97)
8-14 OPs***	-	-			-	-			37	34	3.37	(1.90, 5.95)

*
Adjusted for sex, education, smoking, age, family history of PD, race, and other pesticides.

**
Please refer to the Appendix for the classification of pesticides under each mechanism of toxicity.

***
A total of seven different presumed mitochondria inhibiting OPs were included. Participants who were exposed to the same OP pesticide at workplaces and residences were considered exposed to two pesticides.

Note: Odds ratios and 95% confidence intervals were not reported for participants who were not exposed to OPs but were exposed to other pesticides as these pesticides were not of interest in this analysis.