Published in final edited form as:
Eur J Epidemiol. 2011 July ; 26(7): 547–555. doi:10.1007/s10654-011-9574-5.

Parkinson's disease risk from ambient exposure to pesticides

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Abstract

Due to the heavy and expanding agricultural use of neurotoxic pesticides suspected to affect dopaminergic neurons, it is imperative to closely examine the role of pesticides in the development of Parkinson's disease (PD). We focus our investigation on pesticide use in California's heavily agricultural central valley by utilizing a unique pesticide use reporting system. From 2001 to 2007, we enrolled 362 incident PD cases and 341 controls living in the Central Valley of California. Employing our geographic information system model, we estimated ambient exposures to the pesticides ziram, maneb, and paraquat at work places and residences from 1974 to 1999. At workplaces, combined exposure to ziram, maneb, and paraquat increased risk of PD three-fold (OR: 3.09; 95% CI: 1.69, 5.64) and combined exposure to ziram and paraquat, excluding maneb exposure, was associated with a 80% increase in risk (OR:1.82; 95% CI: 1.03, 3.21). Risk estimates for ambient workplace exposure were greater than for exposures at residences and were especially high for younger onset PD patients and when exposed in both locations. Our study is the first to implicate ziram in PD etiology. Combined ambient exposure to ziram and paraquat as well as combined ambient exposure to maneb and paraquat at both workplaces and residences increased PD risk substantially. Those exposed to ziram, maneb, and paraquat together experienced the greatest increase in PD risk. Our results suggest that pesticides affecting different mechanisms that contribute to dopaminergic neuron death may act together to increase the risk of PD considerably.

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Keywords

Case–control study; Geographic information systems (GIS); Paraquat; Parkinson's disease; Pesticide; Ziram

Introduction

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons of the substantia nigra. PD has an estimated annual incidence of approximately 17 per 100,000 and an increasing prevalence worldwide due to the growth of aging populations [1]. Recently, a number of animal studies have suggested biologic mechanisms for specific pesticides that may increase PD risk. Paraquat has been shown to damage dopaminergic neurons by promoting oxidative stress and cell death [2–5]. Exposure to manganese ethylene-bisdithiocarbamate, the major active ingredient in the dithiocarbamate fungicide maneb, selectively produces dopaminergic neurodegeneration in mice by disrupting mitochondrial function, increasing oxidative stress, and inhibiting proteasomal function [6, 7]. Ziram, another dithiocarbamate, has been shown to cause dopaminergic neuron damage in cell culture by inhibiting the E1 ligase of the ubiquitin proteasome system (UPS) [8]. Recent animal studies reported that the dopaminergic toxicity of paraquat is enhanced when co-administered with maneb [9–11]. These studies suggest that different toxins may potentially act together and contribute to PD pathology via different pathways linked to dopaminergic neurodegeneration.

The impact of pesticide exposures on humans in agricultural communities is of special concern. Not only are pesticide applicators disproportionately exposed to pesticides due to infrequent use of personal protective equipment and improper pesticide mixing and application, but those living and working near farms are also exposed due to drifting pesticide spray [12–14]. Even though the association between PD, farm work, and pesticide exposures is supported by the literature [15–17], very few studies to date have reported findings for specific chemical agents [18–24]. Many studies in human populations employed a case–control design that lends itself to recall bias when pesticides are assessed retrospectively via self-report [23, 25]. Occupational cohort studies of PD to date have been limited by a paucity of PD cases handling specific pesticides or relying on participant recall to obtain data on specific pesticides [19].

We accessed data from the Pesticide Use Report (PUR) system maintained by California's Department of Pesticide Regulation (CA DPR) and used a geographic information system (GIS) to assess ambient exposures to specific pesticide [26]. For the first time, we assess ambient exposures to ziram, maneb, and paraquat derived from occupational in addition to residential addresses. We focus on ziram because it is structurally related to maneb and is a more potent inhibitor of the UPS [8].

Materials and methods

All procedures described have been approved by the UCLA-IRB for human participants and informed consent was obtained from all participants.

Participant recruitment

We recruited persons with PD and population controls from Fresno, Tulare, and Kern counties ("tri-county" area), largely agricultural areas in Central California, details are provided elsewhere [27]. Briefly, PD cases newly diagnosed between January 1998 and January 2007, residing in the tri-county area and living in California for at least 5 years prior

to diagnosis were recruited into our study within 3 years of diagnosis. We collaborated with practicing neurologists, Kaiser Permanente, Kern and Visalia Medical Centers and the Veteran's Administration, Parkinson's disease support groups, local newspapers, and radio stations that broadcast public service announcements to recruit participants in the tri-county area.

Of the 1,167 PD cases we invited and who responded to participate in the study, 604 were not eligible: 397 had been diagnosed more than 3 years prior to contact, 51 denied a PD diagnosis, 134 lived outside the tri-county area, and 22 were too ill to participate. Of the 563 cases found eligible, 473 were examined by a UCLA movement disorder specialist at least once and confirmed as having clinically "probable" or "possible" PD; the remaining 90 potential cases could not be examined or interviewed (54% withdrew, 32% were too ill or died, and 14% moved away). Among those examined, we excluded 83 for whom we were unable to confirm a diagnosis of idiopathic PD, leaving us with 390 cases. We were able to re-examined 71% of the cases and excluded another 21 participants misdiagnosed with PD. Of the remaining 369 cases, 362 provided all information needed for analyses.

Initially controls older than 65 years of age were identified from Medicare enrollee lists in 2001 and were invited to participate in our study, but due to Medicare prohibiting the continued use of enrollees after HIPAA implementation, we changed our recruitment plan and recruited the remaining 70% of our controls from randomly selected residential units (parcels) from tri-county tax assessor records. We mailed letters of invitation to a random selection of parcels and also attempted to identify head-of-household names and telephone numbers for these parcels using marketing companies' services and Internet searches. We contacted 1,212 potential controls by mail and/or phone for eligibility screening to recruit one person per household. Eligibility criteria were: (1) not having PD, (2) being at least 35 years of age, (3) currently residing primarily in one of the three counties, and (4) having lived in California for at least 5 years prior to the screening. Of the 457 ineligible controls, 409 were too young, 44 were terminally ill and 4 primarily resided outside the study area. Of the 755 eligible population controls, 409 declined participation, were too ill or moved out of the area before honoring an appointment and 346 were enrolled, and 341 provided all information needed for analyses.

For all study participants, we conducted telephone interviews to obtain demographic and exposure information.

GIS-based ambient pesticide exposures assessment

Employing our GIS-based system, we combined PUR data, land use maps, and geocoded address information [26, 28] to produce estimates of pesticide exposure within a 500-m radius buffer around participants' occupational and residential addresses as suggested in previous literature [29–31]. A technical discussion of our GIS-based approach is provided elsewhere, here we briefly summarize the data sources and exposure modeling process [26]. In a previous validation study, our GIS-derived measure for organochlorine exposures identified those with high serum dichlorodiphenyldichloroethylene levels with high specificity (87%) [32].

Pesticides use reporting

Since 1974, the CA DPR has recorded agricultural application of restricted-use pesticides (defined as "agents with harmful environmental or toxicological effects"), and for all agriculturally applied pesticides from 1990 onwards. The location of each PUR record is referenced to the Public Land Survey System (PLSS), a nationwide grid that parcels land into sections at varying resolutions. Each PUR record includes the name of the pesticide's

active ingredient, the poundage applied, the crop and acreage of the field, the application method, and the date of application.

Land use maps

Because the PUR records only link an agricultural pesticide application to a whole PLSS grid section, we added information from land use maps to more precisely locate the pesticide application as described in detail elsewhere [28]. Briefly, the California Department of Water Resources periodically (every 7–10 years) performs countywide surveys of location and extent of land use and crop cover. We constructed historical electronic maps of land use and crop type from digital maps from recent surveys [33] (1996–1999) and manually digitized earliest available paper maps (1977–1995). Using the PLSS grid section and crop type reported on the PUR, we further refined pesticide applications using the more detailed land use geography.

Geocoding

We obtained historical occupational and residential addresses from all study participants. Addresses reported for the period of 1974–1999 in the tri-county area were automatically geocoded to TigerLine files (Navteq 2006), and then manually resolved in a multi-step process similar to that described by McElroy [30]. We considered geocoded addresses as having high accuracy if we were able to geocode to the actual address, a parcel/lot centroid, street centroid, or street intersection. Inaccurately geocoded addresses were considered to be those geocoded at the zipcode, city, county, state centroids, or did not have enough information to be geocoded.

Pesticide exposure estimates at occupational and residential addresses

First we combined the PUR data, land use maps, and geocoded address information and created 500 meter buffers around addresses in our GIS for each year in the 26-year period from 1974 to 1999. Then we calculated annual ambient exposures to the individual pesticides, maneb, ziram, and paraquat, for each participant by summing the pounds of pesticides applied in each buffer and weighting the total poundage by the proportion of the acreage treated. For each of the three pesticides examined in this study, we summed the annual pounds applied per acre to obtain 26 annual exposure values for each pesticide separately for occupational and residential addresses.

Average pesticide exposures were then calculated for the following exposure time windows: (1) 1974–1999, (2) 1974–1989, (3) 1990–1999 to address a possible extended induction period for PD and assess the influence of age at exposure. A participant was considered exposed to a particular pesticide when the pounds per acre measured was greater than zero during the time window. We created exposure measures for single and combined pesticides by creating categories of co-exposures to different pesticides. Participants who did not work or live in the tri-county area between 1974 and 1999 could not be assigned an exposure estimate and were considered unexposed.

In the same manner, we also created exposure estimates for organophosphates and organochlorines, two pesticide classes that also contribute to neurodegeneration [34, 35]. Participants were considered exposed if they had any exposure to at least one organophosphate or organochlorine pesticide.

Statistical analysis

We conducted analyses of occupational and residential exposures to maneb, ziram, and paraquat individually and in different combinations. We also conducted analyses stratified by exposure time window and by age. We adjusted for age at diagnosis (cases) or age at

interview (controls), sex, ethnicity (White vs. non-White), education (<12 years, 12 years, >12 years), having a 1st degree family member with PD (yes, no), and smoking (current, former, never). We also adjusted for organophosphate and organochlorine exposure in some analyses.

We used SAS 9.1 (SAS Institute Inc., Cary, NC, USA) to perform unconditional logistic regression analyses.

Results

Study participants were predominantly White, over the age of 60, and the 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 education. They were also more likely to have never smoked cigarettes.

When assessing combinations of exposure to all three pesticides, combined exposure to all three pesticides at both workplaces (OR: 3.09; 95% CI: 1.69, 5.64) and residences (OR: 1.86; 95% CI: 1.09, 3.18) was most strongly associated with PD risk, followed by combined exposure to ziram and paraquat only at workplaces (OR: 1.82; 95% CI: 1.03, 3.21) (Table 2). Adjustment for exposure to organophosphate and organochlorine pesticides, shifted risk estimates slightly towards the null value and increased confidence interval sizes (results not shown), but combined exposure to maneb, ziram, and paraquat at workplaces remained strongly associated with PD risk (organophosphate and organochlorine adjusted OR: 2.61; 95% CI: 1.24, 5.48). The rarity of exposure to maneb alone and exposure to ziram and maneb without paraquat precludes estimation of effects for these combinations of pesticides. Exposure to paraquat alone was not associated with PD risk at residences but was associated with an increased risk at workplaces.

When considering the main effects of exposure to ziram, maneb, and paraquat, participants exposed to these three pesticides at both residences and work places experienced a greater increase in risk of PD than those exposed at residences or workplaces only (Table 3). Participants exposed to maneb experienced a similar increase in PD risk when exposed at either workplaces or residences only. However, those exposed to ziram at workplaces only experienced higher PD risk than those exposed at residences only. PD risk did not increase for participants exposed to paraquat at workplaces or residences only.

Combined exposure to ziram and paraquat at workplaces was associated with a two-fold increase in PD risk in the overall 1974–1999 time window (Table 4). Furthermore, this combination exposure contributed to PD risk at workplaces in both early and late time windows, while only the early time window contributed to PD risk at residences. These patterns were also observed for combined exposure to maneb and paraquat.

Estimated PD risk increase was generally much larger for those diagnosed with PD at a younger age (age ≤60) (Table 5). Younger onset patients that were exposed to a combination of ziram and paraquat at workplaces (OR: 5.98; 95% CI: 1.95, 18.32) experienced a greater risk of PD than when exposed at residences (OR: 2.78; 95% CI: 1.10, 7.07). Similarly, for younger onset patients, exposure to maneb and paraquat alone and in combination was associated with a much larger risk at workplaces than at residences.

Discussion

The population-based case–control study of PD we conducted in a heavily agricultural region of California shows that combined exposure to ziram and paraquat, apart from maneb exposure, conferred an increased risk for developing PD. Our results suggest that exposure

to paraquat, maneb and ziram may act together to increase the risk of PD more strongly than exposure to each individual pesticide alone or exposure to any combination of two pesticides. Only the early time window was important for ambient residential exposures to either ziram and paraquat or maneb and paraquat. In contrast, ambient workplace exposure during the early or late time window to either ziram and paraquat or maneb and paraquat increased PD risk, suggesting that although there may be a long induction period for these combinations of pesticides, potentially more intense occupational exposures later in life may also contribute to risk of developing PD. Finally, younger participants consistently experienced the greatest risks when exposed to a combination of either maneb and paraquat or ziram and paraquat. We not only confirm our previous results for residential exposures to paraquat and maneb with our new occupational address based exposure measures [18], but also observe that risk estimates at workplaces were generally larger than at residences and that exposures at both work places and residences together further increase risks.

The vast majority of previous epidemiological studies relied on self-reported pesticide exposures and thus may suffer from biased exposure assessment as study participants may misreport their historical pesticide use [36–40]. The issue of recall bias is especially problematic when attempting to estimate exposures to specific pesticides via self-report. The Agricultural Health Study cohort [19] attempted to estimate effects for several specific pesticides but found no pesticide or functional group to be more than weakly associated with incident PD, possibly due to the small number of cases who reported exposure to specific pesticides. Furthermore, self-reported pesticide exposure cannot account for risk in those not actively applying pesticides who nevertheless are potentially chronically exposed to pesticides from drift and contact with contaminated dust in heavily agricultural areas [14].

A strength of our study is that our GIS-based pesticide exposure assessment allow us to derive pesticide exposure information for participants who work or live near agricultural pesticide applications and may be unknowingly exposed due to pesticide drift. Additionally, our GIS-based methods employing the PUR data is an improvement over pesticide exposure assessment methods based on recall only, since it identifies the exact type, amount, and location of a pesticide active ingredient applied historically, and eliminates differential recall of exposure according to case status. Another strength is that we were able to obtain exposure data at occupational in addition to residential addresses. Since agricultural pesticides are applied during working hours, exposure estimates at workplaces may more accurately reflect true pesticide exposure and risk estimates are expected to be of greater magnitude if participants are present when pesticides are applied to fields. Finally, our population-based study is the only study to date in which movement disorder specialists examined patients multiple times to confirm diagnoses, thus reducing disease misclassification.

Our GIS-based method, which uses a 26-year average pesticide estimate at participants' occupational and residential addresses, cannot be considered a quantitative measure of exposure because the derived poundage of active ingredient per acre applied does not translate easily into a measure of human neurotoxicity across pesticides or pesticide classes. In addition, pesticides vary in toxicity so that fewer pounds of a highly toxic pesticide may have the same effect as a greater poundage of a less toxic pesticide. Thus, we considered participants exposed if they experienced any exposure and created mutually exclusive pesticide exposure categories to assess multiple pesticides.

Another limitation is that the accuracy of our GIS-based pesticide exposure estimation relies on the quality of self-reported addresses. Occupational addresses were generally geocoded less accurately than residential addresses and addresses with lower geocoding accuracy tended to be assigned less exposure than accurately geocoded addresses (results not shown).

Exposure estimates could only be obtained for participants with an occupational address located in the tri-county area between 1974 and 1999. Of the 703 participants, 26% of cases and 26% of controls were missing occupational address information, while only 4% of cases and 4% of controls were missing residential address information. Different from our previously published work [18], we classified participants with missing data as unexposed to maintain statistical power when assessing the risk of pesticide exposures at occupational addresses. This approach would bias effect estimates towards the null as long as the resulting exposure misclassification is non-differential by case status, as suggested by the comparable percentages of cases and controls with missing address information.

Despite these limitations, we believe that our GIS model provides us with an accurate qualitative indicator of ambient pesticide exposure from applications and drift in close proximity to workplaces and residences. It is unlikely that our GIS-based results are affected by selection bias because participants were likely unaware of their historical ambient workplace or residential exposure to specific pesticides associated with PD risk, thus their enrollment would not be associated with pesticide exposure.

Our study confirms observations from cell culture studies conducted by our research group that implicate ziram in the pathology of PD [8] and is the first epidemiologic study that provides strong evidence in a human population that (1) the combination of maneb, ziram, and paraquat confers a greater risk of PD than exposure to these individual chemicals alone, suggesting the pesticides that affect different mechanisms leading to dopaminergic cell death may act together to increase the risk of PD; (2) exposure to ziram and paraquat increases the risk of PD independent of combined exposures to maneb and paraquat; and (3) ambient exposure derived from workplaces is associated with a greater risk for developing PD than ambient exposure at residences and those exposed at both workplaces and residences experience the greatest PD risk.

Acknowledgments

This work was supported by National Institute of Environmental Health Science [grant numbers ES10544, U54ES12078, 5P30 ES07048], National Institute of Neurological Disorders and Stroke [grant number NS 038367], and Department of Defense Prostate Cancer Research Program [grant number 051037]; in addition, initial pilot funding was provided by the American Parkinson's Disease Association.

Abbreviations

CA DPR	California department of pesticide regulation
CI	Confidence interval
GIS	Geographic information system
HIPAA	Health insurance portability and accountability act
OR	Odds ratio
PD	Parkinson's disease
PLSS	Public land survey system
PUR	Pesticide use report
UCLA	University of California Los Angeles
UPS	Ubiquitin proteasome system

References

1. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003; 18(1):19–31. [PubMed: 12518297]
2. Shimizu K, Matsubara K, Ohtaki K, Fujimaru S, Saito O, Shiono H. Paraquat induces long-lasting dopamine overflow through the excitotoxic pathway in the striatum of freely moving rats. Brain Res. 2003; 976(2):243–52. [PubMed: 12763259]
3. Purisai MG, McCormack AL, Cumine S, Li J, Isla MZ, Di Monte DA. Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration. Neurobiol Dis. 2007; 25(2):392–400. [PubMed: 17166727]
4. McCormack AL, Thiruchelvam M, Manning-Bog AB, et al. Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 2002; 10(2):119–27. [PubMed: 12127150]
5. Ossowska K, Smialowska M, Kuter K, et al. Degeneration of dopaminergic mesocortical neurons and activation of compensatory processes induced by a long-term paraquat administration in rats: implications for Parkinson's disease. Neuroscience. 2006; 141(4):2155–65. [PubMed: 16797138]
6. Zhou Y, Shie FS, Piccardo P, Montine TJ, Zhang J. Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: relevance to Parkinson's disease. Neuroscience. 2004; 128(2):281–91. [PubMed: 15350641]
7. Zhang J, Fitsanakis VA, Gu G, et al. Manganese ethylene-bisdithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. J Neurochem. 2003; 84(2):336–46. [PubMed: 12558996]
8. Chou AP, Maidment N, Klintenberg R, et al. Ziram causes dopaminergic cell damage by inhibiting E1 ligase of the proteasome. J Biol Chem. 2008; 283(50):34696–703. [PubMed: 18818210]
9. Cory-Slechta DA, Thiruchelvam M, Barlow BK, Richfield EK. Developmental pesticide models of the Parkinson disease phenotype. Environ Health Perspect. 2005; 113(9):1263–70. [PubMed: 16140639]
10. Barlow BK, Thiruchelvam MJ, Bennice L, Cory-Slechta DA, Ballatori N, Richfield EK. Increased synaptosomal dopamine content and brain concentration of paraquat produced by selective dithiocarbamates. J Neurochem. 2003; 85(4):1075–86. [PubMed: 12716439]
11. Thiruchelvam M, Prokopenko O, Cory-Slechta DA, Buckley B, Mirochnitchenko O. Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat + maneb-induced Parkinson disease phenotype. J Biol Chem. 2005; 280(23):22530–9. [PubMed: 15824117]
12. WHO. Public health impact of pesticide used in agriculture. World Health Organization; Geneva: 1990.
13. Ecobichon DJ. Pesticide use in developing countries. Toxicology. 2001; 1–3(160):27–33.
14. Ward MH, Lubin J, Giglierano J, et al. Proximity to crops and residential exposure to agricultural herbicides in iowa. Environ Health Perspect. 2006; 114(6):893–7. [PubMed: 16759991]
15. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental risk factors and Parkinson's disease: a metaanalysis. Environ Res. 2001; 86(2):122–7. [PubMed: 11437458]
16. Petrovitch H, Ross GW, Abbott RD, et al. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol. 2002; 59(11):1787–92. [PubMed: 12433267]
17. Ascherio A, Chen H, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006; 60(2):197–203. [PubMed: 16802290]
18. Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. Am J Epidemiol. 2009; 169(8):919–26. [PubMed: 19270050]
19. Kamel F, Tanner C, Umbach D, et al. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 2007; 165(4):364–74. [PubMed: 17116648]
20. Elbaz A, Clavel J, Rathouz PJ, Moisan F, Galanaud JP, Delemotte B, Alperovitch A, Tzourio C. Professional exposure to pesticides and Parkinson's disease. Ann Neurol. 2009; 66(4):494–504. [PubMed: 19847896]

21. Liou HH, Tsai MC, Chen CJ, et al. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology. 1997; 48(6):1583–8. [PubMed: 9191770]
22. Dhillon AS, Tarbutton GL, Levin JL, et al. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromed. 2008; 13(1):37–48.
23. Seidler A, Hellenbrand W, Robra BP, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology. 1996; 46(5):1275–84. [PubMed: 8628466]
24. Hancock DB, Martin ER, Mayhew GM, et al. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol. 2008; 8:6. [PubMed: 18373838]
25. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurol Clin. 1996; 14(2):317–35. [PubMed: 8827174]
26. Goldberg, DW.; Zhang, X.; Marusek, JC.; Wilson, JP.; Ritz, B.; Cockburn, MG. Development of an automated pesticide exposure analyst for California's central valley. Proceedings of the urban and regional information systems association GIS in public health conference; 2007. p. 136-56.http://www.dwgold.com/conferences/Proceedings/urisaHealth2007.pdf
27. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 2005; 20(9):1133–42. [PubMed: 15954133]
28. Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. Environ Health Perspect. 2003; 111(12):1582–9. [PubMed: 14527836]
29. Chester G, Ward RJ. Occupational exposure and drift hazard during aerial application of paraquat to cotton. Arch Environ Contam Toxicol. 1984; 13(5):551–63. [PubMed: 6486883]
30. McElroy JA, Remington PL, Trentham-Dietz A, Robert SA, Newcomb PA. Geocoding addresses from a large population-based study: lessons learned. Epidemiology. 2003; 14(4):399–407. [PubMed: 12843762]
31. MacCollom GB. Drift comparisons between aerial and ground orchard application. J Econ Entomol. 1986; 79:459–64.
32. Ritz B, Costello S. Geographic model and biomarker-derived measures of pesticide exposure and Parkinson's disease. Ann N Y Acad Sci. 2006; 1076:378–87. [PubMed: 17119217]
33. CDWR. [Cited 5 May 2010] Land use survey. 2010. Available from: http:// www.water.ca.gov/landwateruse/lusrvymain.cfm
34. Chan JY, Chan SH, Dai KY, Cheng HL, Chou JL, Chang AY. Cholinergic-receptor-independent dysfunction of mitochondrial respiratory chain enzymes, reduced mitochondrial transmembrane potential and ATP depletion underlie necrotic cell death induced by the organophosphate poison mevinphos. Neuropharmacology. 2006; 51(7–8):1109–19. [PubMed: 16984802]
35. Hatcher JM, Richardson JR, Guillot TS, et al. Dieldrin exposure induces oxidative damage in the mouse nigrostriatal dopamine system. Exp Neurol. 2007; 204(2):619–30. [PubMed: 17291500]
36. Baldi I, Cantagrel A, Lebailly P, et al. Association between Parkinson's disease and exposure to pesticides in southwestern France. Neuroepidemiology. 2003; 22(5):305–10. [PubMed: 12902626]
37. Dick FD, De Palma G, Ahmadi A, et al. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup Environ Med. 2007; 64(10):666–72. [PubMed: 17332139]
38. Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT Jr, Checkoway H. Pesticides and risk of Parkinson disease: a population-based case-control study. Arch Neurol. 2005; 62(1):91–5. [PubMed: 15642854]
39. Frigerio R, Sanft KR, Grossardt BR, et al. Chemical exposures and Parkinson's disease: a population-based case-control study. Mov Disord. 2006; 21(10):1688–92. [PubMed: 16773614]
40. Nuti A, Ceravolo R, Dell'Agnello G, et al. Environmental factors and Parkinson's disease: a case-control study in the Tuscany region of Italy. Parkinsonism Relat Disord. 2004; 10(8):481–5. [PubMed: 15542008]

Table 1

Demographic characteristics of the study population

	Case		Control		OR	95% CI
	(N = 362)	%	(N = 341)	%		
Age (mean and range)	68.2 (34–88)		67.6 (34–92)			
≤60	77	21	87	26	1.00	Reference
>60	285	79	254	74	1.27	(0.89, 1.80)
Sex						
Female	156	43	165	48	1.00	Reference
Male	206	57	176	52	1.24	(0.92, 1.67)
1st deg. relative with PD						
No	307	85	303	89	1.00	Reference
Yes	55	15	37	11	1.47	(0.95, 2.30)
Race						
White	291	80	279	82	1.00	Reference
Non-white	71	20	62	18	1.10	(0.75, 1.60)
Education						
<12 years	68	19	38	11	1.19	(0.72,1.98)
<12 years	96	27	64	19	1.00	Reference
>12 years	198	55	239	70	0.55	(0.38, 0.80)
Smoker status						
Never smoker	191	53	146	43	1.00	Reference
Ex smoker	151	42	161	47	0.72	(0.53, 0.98)
Current smoker	20	6	34	10	0.45	(0.25, 0.81)

Table 2

Effect estimates (ORs and 95% CIs) for ambient pesticide exposures to paraquat, maneb, and ziram in the Central California Valley study population for the 1974–1999 time window of exposure

	Occupational[b]				Residential[c]			
	Case (N = 362)	Control (N = 341)	Adjusted OR[a]	95% CI	Case (N = 362)	Control (N = 341)	Adjusted OR[a]	95% CI
Not exposed to paraquat, maneb, or ziram	164	191	1.00	Reference	122	136	1.00	Reference
Exposed to paraquat, not maneb or ziram	81	78	1.26	(0.86, 1.86)	109	125	0.91	(0.63, 1.31)
Exposed to maneb, not ziram or paraquat	1	3	_ *d*	_ *d*	2	1	_ *d*	_ *d*
Exposed to ziram, not maneb or paraquat	6	6	1.37	(0.42, 4.49)	4	3	1.48	(0.32, 6.85)
Exposed to ziram and maneb, not paraquat	1	0	_ *d*	_ *d*	1	0	_ *d*	_ *d*
Exposed to maneb and paraquat, not ziram	26	21	1.41	(0.75, 2.68)	34	21	1.59	(0.86, 2.95)
Exposed to ziram and paraquat, not maneb	37	24	1.82	(1.03, 3.21)	37	27	1.37	(0.78, 2.42)
Exposed to maneb, ziram, and paraquat	46	18	3.09	(1.69, 5.64)	53	28	1.86	(1.09, 3.18)

[a] Adjusted for age, sex, education, smoking, family history of PD, and race

[b] Pesticide exposure derived from self-reported occupational addresses

[c] Pesticide exposure derived from self-reported residential addresses

[d] Not calculated due to insufficient cell counts

Table 3

Effect estimates (ORs and 95% CIs) for ambient exposures to ziram, maneb, and paraquat at residences and workplaces for the 1974–1999 time window of exposure

	Case (N = 341)	Controls (N = 341)	Adjusted OR[a]	95% CI
Ziram				
Not exposed to ziram	229	253	1.00	Reference
Exposed at residences only	43	40	1.13	(0.70, 1.82)
Exposed at workplaces only	38	30	1.52	(0.90, 2.58)
Exposed at both residences and workplaces	52	18	3.01	(1.69, 5.38)
Maneb				
Not exposed to maneb	236	266	1.00	Reference
Exposed at residences only	52	33	1.71	(1.06, 2.77)
Exposed at workplaces only	36	25	1.77	(1.02, 3.09)
Exposed at both residences and workplaces	38	17	2.26	(1.22, 4.20)
Paraquat				
Not exposed to paraquat	101	110	1.00	Reference
Exposed at residences only	71	90	0.77	(0.50, 1.17)
Exposed at workplaces only	28	30	1.07	(0.59, 1.96)
Exposed at both residences and workplaces	162	111	1.50	(1.03, 2.18)

[a]Adjusted for age, sex, education, smoking, family history of PD, and race

Table 4

Effect estimates (ORs and 95% CIs) for ambient exposures to maneb, ziram, and paraquat by time window of exposure

Time window of exposure	Occupational[b]				Residential[c]			
	Case (N = 362)	Control (N = 341)	OR[a]	95% CI	Case (N = 362)	Control (N = 341)	OR[a]	95% CI
Maneb and paraquat exposure								
1974–1999 overall time window								
Not exposed to maneb or paraquat	170	197	1.00	Reference	126	139	1.00	Reference
Exposed to parauqat, not maneb	118	102	1.37	(0.97, 1.94)	146	152	0.98	(0.70, 1.38)
Exposed to maneb, not paraquat	2	3	0.96	(0.16, 5.99)	3	1	3.21	(0.32, 32.68)
Exposed to maneb and paraquat	72	39	2.15	(1.36, 3.41)	87	49	1.73	(1.11, 2.68)
1974–1989 time window								
Not exposed to maneb or paraquat	180	212	1.00	Reference	144	165	1.00	Reference
Exposed to maneb or paraquat	124	96	1.43	(0.99, 2.07)	145	137	1.15	(0.81, 1.63)
Exposed to maneb and paraquat	58	33	1.82	(1.08, 3.07)	73	39	2.05	(1.23, 3.40)
1990–1999 time window								
Not exposed to maneb or paraquat	269	279	1.00	Reference	227	228	1.00	Reference
Exposed to maneb or paraquat	71	52	1.15	(0.74, 1.81)	110	95	0.88	(0.61, 1.28)
Exposed to maneb and paraquat	22	10	1.69	(0.74, 3.84)	25	18	0.91	(0.46, 1.82)
Ziram and paraquat exposure								
1974–1999 overall time window								
Not exposed to ziram or paraquat	165	194	1.00	Reference	124	137	1.00	Reference
Exposed to parauqat, not ziram	107	99	1.30	(0.91, 1.86)	143	146	0.99	(0.70, 1.41)
Exposed to ziram, not paraquat	7	6	1.65	(0.52, 5.17)	5	3	1.75	(0.40, 7.62)
Exposed to ziram and paraquat	83	42	2.37	(1.52, 3.68)	90	55	1.60	(1.05, 2.46)
1974–1989 time window								
Not exposed to ziram or paraquat	175	211	1.00	Reference	144	165	1.00	Reference
Exposed to ziram or paraquat	121	90	1.55	(1.06, 2.26)	154	139	1.13	(0.80, 1.61)
Exposed to ziram and paraquat	66	40	1.71	(1.05, 2.78)	64	37	1.79	(1.05, 3.05)
1990–1999 time window								
Not exposed to ziram or paraquat	267	277	1.00	Reference	218	227	1.00	Reference
Exposed to ziram or paraquat	62	53	1.04	(0.66, 1.64)	93	81	1.03	(0.70, 1.51)
Exposed to ziram and paraquat	33	11	2.16	(1.01, 4.63)	51	33	1.06	(0.61, 1.84)

[a] Adjusted for age, sex, education, smoking, family history of PD, and race; exposure time windows are mutually adjusted for each other

[b] Pesticide exposure derived from self-reported occupational addresses

[c] Pesticide exposure derived from self-reported residential addresses

Table 5

Effect estimates (ORs and 95% CIs) for ambient exposures to maneb, ziram, and paraquat by age at PD diagnosis for the 1974–1999 time window of exposure

	Occupational[b]				Residential[c]			
	Case (N = 362)	Control (N = 341)	OR[a]	95% CI	Case (N = 362)	Control (N = 341)	OR[a]	95% CI
Maneb and paraquat exposure								
60 years old or younger								
Not exposed to maneb or paraquat	30	56	1.00	Reference	20	38	1.00	Reference
Exposed to maneb or paraquat	29	28	1.78	(0.87, 3.64)	36	42	1.53	(0.73, 3.19)
Exposed to maneb and paraquat	18	3	8.75	(2.31, 33.19)	21	7	4.82	(1.69, 13.76)
Over 60 years old								
Not exposed to maneb or paraquat	140	141	1.00	Reference	106	101	1.00	Reference
Exposed to maneb or paraquat	91	77	1.22	(0.82, 1.83)	113	111	0.89	(0.60, 1.32)
Exposed to maneb and paraquat	54	36	1.48	(0.88, 2.50)	66	42	1.28	(0.78, 2.09)
Ziram and paraquat exposure								
60 years old or younger								
Not exposed to ziram or paraquat	28	53	1.00	Reference	21	38	1.00	Reference
Exposed to ziram or paraquat	30	29	1.90	(0.91, 3.93)	35	37	1.65	(0.79, 3.45)
Exposed to ziram and paraquat	19	5	5.98	(1.95, 18.32)	21	12	2.78	(1.10, 7.07)
Over 60 years old								
Not exposed to ziram or paraquat	137	141	1.00	Reference	103	99	1.00	Reference
Exposed to ziram or paraquat	84	76	1.17	(0.76, 1.72)	113	112	0.88	(0.59, 1.30)
Exposed to ziram and paraquat	64	37	1.93	(1.10, 3.03)	69	43	1.38	(0.85, 2.26)

[a] Age stratified models adjusted for age, sex, education, smoking, family history of PD, and race

[b] Pesticide exposure derived from self-reported occupational addresses

[c] Pesticide exposure derived from self-reported residential addresses