Original Contribution

Parkinson’s Disease and Residential Exposure to Maneb and Paraquat From Agricultural Applications in the Central Valley of California

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Evidence from animal and cell models suggests that pesticides cause a neurodegenerative process leading to Parkinson’s disease (PD). Human data are insufficient to support this claim for any specific pesticide, largely because of challenges in exposure assessment. The authors developed and validated an exposure assessment tool based on geographic information systems that integrated information from California Pesticide Use Reports and land-use maps to estimate historical exposure to agricultural pesticides in the residential environment. In 1998–2007, the authors enrolled 368 incident PD cases and 341 population controls from the Central Valley of California in a case-control study. They generated estimates for maneb and paraquat exposures incurred between 1974 and 1999. Exposure to both pesticides within 500 m of the home increased PD risk by 75% (95% confidence interval (CI): 1.13, 2.73). Persons aged ≤60 years at the time of diagnosis were at much higher risk when exposed to either maneb or paraquat alone (odds ratio = 2.27, 95% CI: 0.91, 5.70) or to both pesticides in combination (odds ratio = 4.17, 95% CI: 1.15, 15.16) in 1974–1989. This study provides evidence that exposure to a combination of maneb and paraquat increases PD risk, particularly in younger subjects and/or when exposure occurs at younger ages.

case-control studies; fungicides, industrial; geographic information systems; herbicides; maneb; paraquat; Parkinson disease; pesticides

Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; GIS, geographic information system; MPP+, toxic metabolite of 1-methyl-4-phenylpyridinium; OR, odds ratio; PD, Parkinson’s disease; PLSS, Public Land Survey System; PUR, Pesticide Use Reporting.

Parkinson’s disease (PD) has been reported to occur at high rates among farmers and in rural populations, contributing to the hypothesis that agricultural pesticides might be causal agents (1–4). Animal studies have linked certain pesticides to Parkinsonism and dopaminergic cell death. The pesticide rotenone can produce the behavioral and neuropathologic features of PD in some rodent models through chronic systemic inhibition of mitochondrial complex I (5, 6). Exposure to a combination of the fungicide maneb and the herbicide paraquat in mice leads to increased substantia nigra neuronal pathology (7), age-dependent motor degeneration, progressive reductions in dopamine metabolites and turnover (8), and reduced tyrosine hydroxylase and dopamine transporter immunoreactivity (9, 10).

Human evidence is insufficient to identify any particular pesticide compound, including those implicated by animal studies, as being responsible for causing PD (11). Methodological limitations have clouded the interpretation of most epidemiologic studies exploring pesticide exposures and PD in humans. Past studies have generally relied on self-reports and recall of chemical usage, making them vulnerable to information bias and differential recall bias (12).

Because pesticides applied from the air or ground may drift from their intended treatment sites, with measurable concentrations subsequently detected in the air, in plants, and in animals up to several hundred meters from application sites (13–15), accurate methods of estimating environmental exposures in rural communities are sorely needed.
Geographic information system (GIS)-based methods for assessing exposure to pesticides have become popular in recent years and may prove an effective solution when pesticide data exist. We developed and employed a validated GIS-based exposure assessment tool to estimate pesticide exposure from applications to agricultural crops, relying on California Pesticide Use Reporting (PUR) data, land-use maps, and geocoded residential historical locations (16). We investigated whether exposure to the pesticides maneb and paraquat, alone and in combination, increased risk of incident PD among residents of the Central Valley of California, an area well-known for its intensive agriculture and potential for pesticide exposure.

MATERIALS AND METHODS

All procedures described have been approved by the University of California, Los Angeles, institutional review board for human subjects, and informed consent was obtained from all participants.

Subject recruitment

We used a population-based approach for recruiting cases and controls from a largely agricultural population in California. Details are provided elsewhere (17). Briefly, persons with PD newly diagnosed between January 1998 and January 2007 who resided in 1 of 3 central California counties (Fresno, Tulare, or Kern county) and had lived in California for at least 5 years prior to diagnosis were recruited into our study within 3 years of diagnosis. Altogether, 28 (90%) of the 31 practicing local neurologists who provided care for PD patients assisted in recruiting cases for this study. We solicited collaboration from Kaiser Permanente Medical Center (Fresno, California), Kern Medical Center (Bakersfield, California), and Visalia Medical Clinic (Visalia, California) and from the Veterans Administration, PD support groups, local newspapers, and local radio stations that broadcast public service announcements.

Of the 1,167 PD cases who were initially invited, 604 were not eligible: For 397, the case’s diagnosis date fell outside the 3-year range prior to contact; 51 denied having received a PD diagnosis, 134 lived outside the tricounty area, and 22 were too ill to participate. Of the 563 eligible cases, 473 (84%) were examined by a University of California, Los Angeles, movement disorder specialist at least once and were confirmed to have 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 out of the area prior to the examination or did not honor a scheduled appointment). We examined but excluded another 96 patients because they had other causes of Parkinsonism. This left us with 377 cases; of these, 368 provided all information needed for analyses.

Controls aged 65 years or older were identified from Medicare lists in 2001, but because of implementation of the Health Insurance Portability and Accountability Act, which prohibits the use of Medicare enrollees, 70% of our controls were recruited from randomly selected tax assessor residential units (parcels) in each of the 3 counties. We mailed letters of invitation to a random selection of residential living units and also attempted to identify head-of-household names and telephone numbers for these parcels, using the services of marketing companies and Internet searches.

We contacted 1,212 potential population controls by mail and/or telephone for eligibility screening. Eligibility criteria were: 1) not having PD, 2) being at least 35 years of age, 3) currently residing primarily in 1 of the 3 designated counties, and 4) having lived in California for at least 5 years prior to the screening. Only 1 person per household was allowed to enroll. Of the potential controls contacted, 457 were ineligible: 409 were too young, 44 were terminally ill, and 4 resided primarily outside of the study area. Of the 755 eligible controls, 409 (54%) declined participation, were too ill to honor an appointment, or moved out of the area prior to interview; 346 (46%) were enrolled, and 341 provided all information needed for analyses.

Assessment of environmental pesticide exposure

We conducted telephone interviews to obtain demographic and exposure information. Detailed residential history forms were mailed to subjects in advance of their interview and were reviewed in person or over the phone. We estimated pesticide exposures in the residential environment from applications to agricultural crops employing a validated GIS-based system, which combined PUR data and land-use maps (16, 18), to produce estimates of residential ambient pesticide applications within a set distance of subjects’ homes. We recorded and geocoded lifetime residential histories and estimated ambient exposures for all historical addresses at which participants had resided between 1974 and 1999, the period covered by the PUR data. A technical discussion of our GIS-based approach is provided elsewhere (16); here we briefly summarize the data sources and the exposure modeling process.

Residential addresses. Addresses were automatically geocoded to TigerLine files (NAVTeq (Chicago, Illinois), unpublished data, 2006), and discrepancies were then manually resolved in a multistep process similar to that described by McElroy et al. (19). Resulting locations were recorded, along with the relevant year range of residence, so they could be matched to the appropriate year-specific PUR and land-use data (below). For our GIS model, we relied on addresses in Fresno, Kern, and Tulare counties (the tricounty area) at which participants had resided between 1974 and 1999. Out of 9,568 total residential years contributed by cases (26 years × 368 cases), 7,593 years (79%) were spent at addresses within the tricounty area as compared with 6,757 (76%) of 8,866 years contributed by controls (26 years × 341 controls). We geocoded these tricounty residential addresses for the period 1974–1999 with similar precision for cases and controls; that is, both had spent 88% of their respective residential years at addresses we considered to have been mapped with high precision (i.e., at the level of a residential parcel, street address, or street intersection rather than a zip code or city centroid).
**Pesticide use reporting.** PUR data are recorded by the California Department of Pesticide Regulation for any commercial application of restricted-use pesticides (defined as agents with harmful environmental or toxicologic effects (20)) and, since 1990, for all commercial uses of pesticides regardless of toxicologic profile. 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 link an agricultural pesticide application only 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 (18). The California Department of Water Resources periodically (every 7–10 years) performs countywide large-scale surveys of land use and crop cover, which allowed us to identify the locations of specific crops within each PLSS grid section. Digital maps from more recent (1996–1999) surveys are available (21), and paper maps were manually digitized for earlier periods (1977–1995). The 1977 land-use survey was conducted closest in time to 1974, when PUR data became available. We constructed historical electronic maps of land use and crop type, and using the PLSS grid section and the crop type reported in the PUR record, we allocated pesticide applications to an agricultural site to which we assigned a GIS-based location.

**Deriving estimates of residential pesticide exposure.** The time-specific total exposure at each location, by pesticide, was derived through summation of exposures over a fixed 500-m radius (suggested in previous literature (13, 15, 19)) around the home for the relevant years of residence. The numbers of pounds of pesticide applied annually per acre were summed for each residential buffer and weighted by the proportion of treated acreage in each buffer, resulting in pesticide application rates that could be averaged over specific calendar periods of each subject’s lifetime.

**Statistical analysis**

We estimated residential exposures to maneb and paraquat, alone and in combination, for the following time windows: 1) 1974–1999, 2) 1974–1989, and 3) 1990–1999, to assess the possibility of an extensive induction period prior to PD onset and the influence of age at exposure. We stratified models by sex and age (≤60 years, >60 years) and, in additional sensitivity analyses, controlled for exposure to some groups of pesticides suspected to increase PD risk.

We controlled for occupational exposure to pesticides among subjects who had held jobs in the agricultural sector, assigning them to categories of “likely exposed to pesticides” when they reported pesticide handling and applications or fieldwork and “possibly exposed to pesticides” when they reported managerial, produce processing, and other nonfield farm work; all other subjects were considered “not occupationally exposed to pesticides” (22). In some models, we also adjusted for residential exposures to groups of other pesticides that some studies have found to be linked to dopaminergic cell damage or possibly PD (organochlorines, organophosphates, and dithiocarbamates (23) and proteasome inhibitors (24)).

We considered the following demographic variables as potential confounders in all analyses: age (age at diagnosis for cases and age at interview for controls), sex, race (white, nonwhite), education (<12 years, 12 years, >12 years), and cigarette smoking (current, former, never). We used SAS 9.1 (SAS Institute Inc., Cary, North Carolina) to perform unconditional logistic regression analyses.

**RESULTS**

Study participants were predominantly Caucasian, over the age of 60, and without a family history of PD (Table 1). Cases were slightly older than controls, were more often male, and had completed fewer years of education. They were also more likely to have been occupationally exposed to pesticides and to be never or former smokers.

We did not find increased risks of PD among subjects exposed to paraquat alone during the years 1974–1999 (Table 2). While the rarity of sole maneb exposure (4 subjects) precluded any meaningful interpretation of the maneb-only results, combined exposure to both maneb and paraquat increased the risk of PD by 75% (odds ratio (OR) = 1.75, 95% confidence interval (CI): 1.13, 2.73), an effect estimate which was essentially unchanged after adjustment for occupational pesticide exposure (OR = 1.74, 95% CI: 1.11, 2.72).

When we examined 2 separate exposure time windows, the years 1974–1989 and 1990–1999, the risk increase observed for the whole period was found to be mainly attributable to exposures incurred during the earlier window (OR = 2.14, 95% CI: 1.24, 3.68), while being exposed during the later window did not seem to increase PD risk (Table 2). Furthermore, for younger (<60 years) subjects, exposure to both maneb and paraquat in both windows increased PD risk as much as 4- to 6-fold (Table 3). Exposure to either maneb or paraquat alone during 1974–1989 also increased risk of PD in younger subjects (OR = 2.27, 95% CI: 0.91, 5.70). When we examined exposure windows among our older subjects (≥60 years), combined exposure to both pesticides in the earlier window only (1974–1989) was also associated with a 2-fold increase in PD risk (OR = 2.15, 95% CI: 1.15, 4.02), but no increase was found for either the later window (1990–1999) or the combined exposure periods (Table 3). Stratification by sex suggested no differences in estimates between males and females.

**DISCUSSION**

In this population-based case-control study, agricultural application of both maneb and paraquat within 500 m of a residence during the period 1974–1999 greatly increased the risk of developing PD, especially when exposure occurred between 1974 and 1989 or when PD was diagnosed at a younger age (≤60 years). Exposure to both pesticides during the earlier time window (1974–1989) also doubled the risk for older cases. Associations were particularly
strong for younger-onset patients (≤60 years), who would have been children, teenagers, and young adults during the exposure period: Among those exposed in the earlier time window, risk was increased more than 4-fold with exposure to both pesticides and more than 2-fold with exposure to just 1 of the pesticides. Consistent with some theories regarding the progression of PD pathology (25), these data suggest that the critical window of exposure to toxicants may be years before the onset of motor symptoms which lead to diagnosis.

Pesticide and herbicide exposures have previously been implicated in idiopathic PD. Paraquat is structurally similar to the toxic metabolite (MPP+) of the 1-methyl-4-phenylpyridinium ion (a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), an agent known to induce Parkinsonian symptoms in humans that has been widely used to study

<table>
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<th>Variable</th>
<th>Cases (n = 368)</th>
<th>Controls (n = 341)</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
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<td>&gt;19</td>
<td>77</td>
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a The odds ratio was calculated for all nonwhites versus whites.
Parkinsonism in animal models (26). MPP+ is believed to cause cell death by interfering with mitochondrial respiration (27), because it concentrates in mitochondria and inhibits complex I of the electron transport chain (28). Many lines of evidence point to possible mitochondrial dysfunction in PD. Several genes have been identified in familial forms of PD that are linked to mitochondrial function (PINK1 and DJ1), and in sporadic cases of PD, pathologic free radical reactions that damage mitochondria and decrease electron transport activity have been described (29). Impaired electron transport hampers adenosine triphosphate production and leads to the diversion of electrons from their normal electron transport recipients and, thus, further formation of damaging free radicals (29).

Although paraquat is also used to induce Parkinsonism in some animal models, the mechanism by which it produces symptoms is not yet understood (30). Recent mammalian and yeast-cell experiments suggest that mitochondria take up paraquat actively across their membranes, where complex I reduces it to the paraquat radical cation that subsequently produces mitochondria-damaging superoxide (31). It has also been suggested that maneb may inhibit the ubiquitin proteasome system, thereby damaging the dopaminergic neuron (24, 32). Additionally, maneb has been linked to Parkinsonism in mice also exposed to paraquat. In 3 recent studies, investigators reported that only when mice were exposed to a combination of the fungicide maneb and the
herbicide paraquat (paraquat + maneb), not to either pesticide alone, did they exhibit increased neuronal pathology (7), age-dependent motor degeneration and progressive reductions in dopamine metabolites and dopamine transporter immunoreactivity (9).

The fungicide maneb and the herbicide paraquat are both used in the Central Valley of California and are often used on the same crops, including potatoes, dry beans, and tomatoes. The average amount of maneb applied near the homes of these study subjects was relatively stable throughout both time windows; however, annual paraquat exposure increased during the later (1990–1999) time window. Persons living near fields sprayed with maneb and paraquat may also be exposed to a host of other agricultural chemicals. When we controlled for the influence of other groups of pesticides suspected a priori to be risk factors for PD in our study, the odds ratios for combined maneb and paraquat exposure and PD in the younger subjects were still in the 3–10-fold range and statistically significant; however, our precision decreased, probably because of correlated exposures. Correlation between pesticides is an inherent problem when assessing the effects of human exposure. However, since adjustment for other pesticides did not remove the association for maneb and paraquat, our data provide compelling evidence that these 2 pesticides may in fact affect PD risk in humans, as has been suggested by animal experiments.

Paraquat and maneb are applied by ground, aerial, and backpack methods; however, paraquat has a much longer field half-life of 1,000 days (33), as compared with only 12–36 days for maneb (34). Both chemicals bind strongly to soil, though, and are not thought to be a threat to groundwater (35, 36). Such strong binding could result in contaminated soil getting blown or tracked into homes by wind, pets, and shoes, thereby increasing exposure for persons who live closer to agricultural application sites (3, 37, 38).

In a previous validation study, our prediction model for a serum measure of dichlorodiphenyldichloroethylene (DDE) explained 47% of the biomarker’s variance (39). Additionally, our GIS-derived measure of organochlorine exposure identified persons with high serum DDE levels reasonably well (specificity of 87%) (39).

Although our GIS model allowed us to calculate the number of pounds of each active ingredient applied per acre within a 500-m buffer, these quantities are not comparable across pesticides. That is, a pound of active ingredient does not represent the same human neurotoxicity across pesticides, and no information currently exists that would allow us to standardize these measures. Thus, while we believe that our model provided us with an accurate indicator of any pesticide exposure from applications close to a residence, our exposure measure cannot be considered quantitative beyond a crude rank ordering of low/medium likelihood of exposure and high likelihood of exposure. Since we hypothesized that coexposure to 2 pesticides, maneb and paraquat, would increase the risk of PD, we also lacked the statistical power to perform extensive categorical analyses (note that only 3 cases and 1 control were exposed solely to maneb). We conducted additional analyses after dichotomizing pounds per acre at their median and mean levels and found that exposure to both pesticides at the highest level was associated with PD, especially in persons aged ≤60 years; however, wide confidence intervals surrounding our point estimates rendered these results generally uninformative (results not shown).

In only 1 previous analysis, conducted within the Agricultural Health Study cohort (40), did researchers assess the effects of maneb and paraquat exposures. Statistical power was limited by the small number (n = 78) of incident cases identified during follow-up and the very small number (n = 4–10) of cases exposed to maneb/mancozeb (OR = 2.1) and paraquat (OR = 1.4). In a small Taiwanese study, the only case-control study to date with sufficient statistical power to examine exposure to the herbicide paraquat, Liou et al. (41) reported a 4- to 6-fold increase in PD risk among long-term applicators. In a case-control study from the Mayo Clinic (Rochester, Minnesota), Brighina et al. (42) presented associations between self-reported pesticide exposure and PD in subjects younger than 60 years only (for all pesticides, OR = 1.80, 95% CI: 1.12, 2.87; for herbicides, OR = 2.46, 95% CI: 1.34, 4.52).

Our exposure estimates did not depend on the subject’s recall of pesticide exposure and are therefore unlikely to have been biased by differential exposure misclassification. Since all of our PD diagnoses were clinically confirmed, we expect disease misclassification to have been minimal. Non-differential exposure misclassification is a possibility in our study and may have attenuated our effect estimates.

Our results may be biased if cases and controls selected themselves into our study according to their potential for pesticide exposure, but our subjects were not asked to self-report environmental exposures and probably were unaware of their true historical exposures. There is no reason to suspect that cases and controls would have chosen to participate on the basis of their historical residence near certain agricultural plots. We saw no difference in estimated effects when we restricted analyses to only those subjects with more (≥12 years) or less (<12 years) education. Similarly, we saw no difference in our results when we restricted the sample to persons whose addresses had been mapped with high precision in the tricounty area during the period 1974–1999 (363 cases, 336 controls).

Our analysis has confirmed 2 previous observations from animal studies: 1) exposure to multiple chemicals may potentiate the effect of each chemical (of interest, since humans are often exposed to more than 1 pesticide in the environment) and 2) the timing of exposure is important. To our knowledge, this is the first epidemiologic study to provide strong evidence that 2 specific pesticides, suggested by animal research as potentially acting synergistically to become neurotoxic, strongly increase the risk of PD in humans, especially given combined exposure and when encountered earlier in life.

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REFERENCES


