ENVIRONMENTAL
HEALTH
PERSPECTIVES

ehponline.org

Well Water Consumption and Parkinson's Disease in Rural California

Nicole M. Gatto, Myles Cockburn, Jeff Bronstein, Angelika D. Manthripragada, and Beate Ritz

doi: 10.1289/ehp.0900852 (available at http://dx.doi.org/)

NIEHS
National Institute of
Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

Well Water Consumption and Parkinson's Disease in Rural California

Nicole M. Gatto[1], Myles Cockburn[2], Jeff Bronstein[3], Angelika D. Manthripragada[1], Beate Ritz[1,3,4]

[1]Department of Epidemiology, University of California Los Angeles

[2]Department of Preventive Medicine, University of Southern California

[3]Department of Neurology, University of California Los Angeles

[4]Department of Environmental Health Sciences, University of California Los Angeles

Address for Correspondence:
Beate Ritz, M.D., Ph.D.
Vice Chair, Department of Epidemiology
Professor of Epidemiology, Environmental Health Sciences, and Neurology
UCLA, Schools of Public Health and Medicine
BOX 951772
650 Charles E. Young Drive
Los Angeles, CA 90095-1772
Phone:310 206 7458
Fax: 310 206 6039
Email: britz@ucla.edu

Running Title: Well Water, Pesticides and Parkinson’s

Keywords: agriculture, contamination, Parkinson’s, pesticide, well water

Acknowledgements: This work was supported by National Institute of Environmental Health Science [ES10544, U54ES12078,5P30 ES07048, **T32ES01545**], National Institute of Neurological Disorders and Stroke [NS 038367], and Department of Defense Prostate Cancer Research Program [051037]; in addition, initial pilot funding was provided by the American Parkinson’s Disease Association.

Disclosures: None of the authors have any disclosures of financial interest. The UCLA Human Subjects Committee approved all study protocol and informed consent was obtained from all subjects. No conflicts of interest to declare.

Article Descriptor: Parkinson’s disease

Abbreviations:

CA DPR	California Department of Pesticide Regulation
CDWR	California Department of Water Resources
GIS	Geographic Information System
HIPAA	Health Insurance Portability and Accountability Act
JEM	Job Exposure Matrix
PD	Parkinson’s disease
PLSS	Public Land Survey System
PUR	Pesticide Use Report

Manuscript Outline:

ABSTRACT

Introduction: Consumption of pesticide contaminated well water has been hypothesized to play a role in Parkinson's disease (PD), and several previous epidemiologic studies support this hypothesis. **Objectives:** We investigated whether consumption of water from private wells located in areas with documented historical pesticide use was associated with an increased risk of PD. **Methods:** We employed a GIS-based model to estimate potential well water contamination from agricultural pesticides, among 368 cases and 341 population controls enrolled in the Parkinson's Environment and Genes study. We separately examined six pesticides (diazinon, chlorpyrifos, propargite, paraquat, dimethoate, and methomyl) from among 26 chemicals selected for their potential to pollute groundwater or because they are of interest for PD, and to which at least 10% of our population were exposed. **Results:** Cases were more likely to have consumed private well water, and had consumed it on average 4.3 years longer than controls (p=0.02). High levels of possible well water contamination with methomyl (OR = 1.67, 95%CI = 1.00, 2.78), chlorpyrifos (OR = 1.87, 95% CI = 1.05, 3.31) and propargite (OR = 1.92, 95% CI = 1.15, 3.20) resulted in ~70% - 90% increases in risk of PD. Adjusting for ambient pesticide exposures only slightly attenuated these increases. Exposure to a higher number of water soluble pesticides and organophosphate pesticides also increased the risk of PD. **Conclusion:** Our study, the first to use agricultural pesticide application records, adds evidence that consumption well water presumably contaminated with pesticides may play a role in the etiology of PD.

INTRODUCTION

Multiple lines of evidence link pesticides as possible contributors to the pathogenesis of Parkinson's disease (PD). Many epidemiological studies previously reported associations between pesticide exposure, rural living, and farming and the development of PD (Ben-Shlomo et al. 1993; Burguera et al. 1992; Morano et al. 1994; Svenson et al. 1993). A number of animal studies have also supported a potential etiological role of pesticides in PD (Betarbet et al. 2000; Norris et al. 2007; Sherer et al. 2001; Thiruchelvam et al. 2003; Thiruchelvam et al. 2000; Thiruchelvam et al. 2002). Ingestion of contaminated drinking water is a potentially important vehicle for pesticide exposure in human populations. Epidemiologic studies previously examined links between well water consumption and PD, and a majority provided support for positive associations (Firestone et al. 2005; Hancock et al. 2007; Nuti et al. 2004; Priyadarshi et al. 2001; Wright and Keller-Byrne 2005). All existing studies have relied on self-reports of well water consumption and used broad ever/never exposure categories; thus, such studies might have suffered from recall bias and exposure misclassification. Most importantly, no study to date has attempted to specify pesticide exposure levels by assessing or estimating the contamination of well water with specific pesticides.

While the Safe Drinking Water Act was passed in 1974(Safe Drinking Water Act of 1974)to regulate the public drinking water supply, private wells in the United States are not subject to the same regulations, and thus are not similarly monitored or held to the same water quality standards as public systems. Furthermore, many private wells are dug or driven at shallow depths (i.e., less than 15-20 yards) which place them at risk of being contaminated by land activities such as pesticide applications in the vicinity of a well(US EPA). Pesticides may move from their initial intended area of application; measurable concentrations of pesticides have been detected in air, water, plants, and animals up to several hundred meters from application sites (Chester and Ward 1984; Currier et al. 1982; MacCollom et al. 1986) emphasizing the need for methods of assessing environmental exposures due to drift and contamination of soil, air and water in agricultural communities. Geographic Information System (GIS)-based methods of assessing exposures to pesticides may prove an effective solution when comprehensive pesticide application data exist. We developed and employed a GIS-based exposure assessment tool to estimate pesticide exposures from applications to agricultural crops utilizing data from California Pesticide Use Reports (PUR), land-use maps, and geocoded residential historical addresses (Goldberg et al. 2007). We combined this information with data on well water consumption collected in interviews with study participants to estimate exposure to potentially pesticide-contaminated well water. Here we investigated whether consumption of water from private wells located in areas with documented historical agricultural pesticide use was associated with an increased risk of PD among residents of the Central Valley of California well-known for its intensive agricultural activities.

METHODS

Study population

We used a population-based approach for recruiting cases and controls from a largely agricultural population in California. Details are provided elsewhere(Kang et al. 2005). Briefly, study subjects were recruited between January 2001 and January 2007, resided in Fresno, Tulare, and Kern Counties, and had to have lived in California for at least 5 years prior to diagnosis or interview. Cases were recruited within 3 years of diagnosis, were not in the last stages of a terminal illness, agreed to participate, and were confirmed as having clinically probable or possible PD by a UCLA movement disorder specialist. A diagnosis of clinically probable or possible PD was confirmed if patients met the following criteria: 1) manifestation of at least two of the following: resting tremor, bradykinesia, or cogwheel rigidity; 2) no suggestion of a parkinsonian syndrome due to trauma, brain tumor, infection, cerebrovascular disease, other known neurologic disease, or treatment with dopamine-blocking or dopamine-depleting agents; 3) no atypical features such as prominent oculomotor palsy, cerebellar signs, vocal cord paresis, severe orthostatic hypotension, pyramidal signs, amyotrophy, or limb apraxia; 4) asymmetric onset; and 5) if treatment with levodopa had been initiated, symptomatic improvement after treatment. Probable cases met criteria 1 through 4 plus/minus criterion 5. Possible cases had at least one sign from criterion 1 and fulfilled criteria 2 and 3. Although sometimes included in criterion 1, postural reflex impairment was excluded since it usually occurs late in PD and may typically occur early in other parkinsonian disorders, such as multiple system atrophy and vascular parkinsonism. 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, Kern and Visalia Medical Centers and the Veteran's Administration, Parkinson's disease 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: 397 because their diagnosis date fell outside the three year range prior to contact, 51 denied having received a PD diagnosis, 134 lived outside the tri-county area, and 22 were too ill to participate. Of the 563 eligible cases, 473 (84%) 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 out of the area prior to the exam or did not honor a scheduled appointment). We examined but excluded another 93 patients due to other causes of Parkinsonism and one case's diagnosis was still not confirmed at the time of this analysis, leaving us with 379 cases; of these, 368 provided all information needed for analyses.

Controls older than 65 years of age were identified from Medicare lists in 2001, but due to the implementation of the Health Insurance Portability and Accountability Act (HIPAA), which provides federal protections for personal health information held by covered entities and prohibited us from the use of Medicare enrollees as controls, more than 70% of our controls were recruited from randomly selected tax assessor residential units (parcels) in each of the three 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 controls by mail and/or phone for eligibility screening. 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. Only one person per household was allowed to enroll. 457 controls were ineligible, 409 were too young, 44 were terminally ill, and 4 primarily resided outside of the study area. Of the 755 eligible population 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.

Data Collection

Trained interviewers who were blind to case/control status conducted structured telephone interviews to obtain demographic and exposure data from study participants. Detailed questionnaires that queried subjects for their lifetime residential addresses were mailed to subjects in advance of their interview and reviewed in person or over the phone; we asked about the type of water supply at each address (public supply, private well, filtered water, bottled water, other). All subjects provided informed consent, and the study was approved by the UCLA Institutional Review Board.

Pesticide exposure assessment

We geocoded lifetime residential addresses and estimated ambient pesticide application rates from agricultural uses (in pounds per acre per year) within 500m of subjects' homes employing a validated GIS-based system, which combined California PUR data and land use maps(Goldberg et al. 2007; Rull and Ritz 2003). We estimated ambient exposure for all historical residential addresses inhabited between 1974 and 1999, the period covered by the PUR data. A technical discussion of our GIS-based approach is provided elsewhere (Goldberg et al. 2007), here we briefly summarize the data sources and exposure modeling process.

Geocoding Residential Addresses

Addresses were automatically geocoded to TigerLine files (Navteq 2006), and then manually resolved in a multi-step process similar to that described by McElroy (McElroy et al. 2003). Resulting locations were recorded along with the relevant year range of residence and 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 (tri-county area) between 1974 and 1999, inclusive. Of 9,568 total residential years contributed by cases (26 years times 368 cases), 7,266 (76%) years were spent at addresses within the tri-county area compared to 6514 (73%) of 8,866 years contributed by controls (26 years times 341 controls). We geocoded these tri-county residential addresses during the period with similar precision for cases and controls i.e. both spent 88% of their respective residential years at addresses we considered to be 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.

Pesticides Use Reporting and Land Use Maps

PURs are collected by the State of California Department of Pesticide Regulation (CA DPR) for any commercial application of restricted-use pesticides (defined as “agents with harmful environmental or toxicological effects”) and, since 1990, all commercial uses of pesticides regardless of toxicological 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 (approximately one square mile). 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. Because the PUR records only link 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 (Rull and Ritz 2003). The California Department of Water Resources (CDWR) periodically (i.e., every 7 to 10 years) performs countywide large-scale surveys of land use and crop cover, which allowed us to identify the location of specific crops within each PLSS grid section. Digital maps from more recent (1996 to 1999) surveys are available and paper maps were manually digitized for earlier periods (1977 to 1995). The 1977 land use survey was conducted closest in time to 1974 when PUR became available. We constructed historical electronic maps of land use and crop type, and using the PLSS grid section and crop type reported on the PUR, we allocated pesticide applications to an agricultural site to which we assigned a GIS-based location.

Ambient Pesticide Exposure Estimates

Pesticide application rates for individual chemicals (in pounds of active ingredient per acre) were summed across PLSS sections by year, then these annual rates were divided by the actual area within a 500m radius around the home (Chester and Ward 1984; MacCollom GB. Currier WW. Baumann GL 1986; McElroy et al. 2003) (i.e., “residential buffer”) to represent the portion of a chemical application rate that a person might have been exposed to for the relevant years of residence. Total annual application rates were then weighted by the proportion of treated acreage in the residential buffer using land use information, again to more accurately predict exposure. This resulted in ambient pesticide exposure estimates for each subject for each year. We additionally summed pesticide application rates across the 1974 – 1999 period to calculate a 26-year cumulative total ambient pesticide exposure estimate for each subject.

Selection of Pesticides Relevant for Well Water Contamination

We selected pesticides from the CA DPR Groundwater Protection List (Title 3. Division 6. Chapter 4. Subchapter 1. Article 1. 6800) that includes chemicals previously detected in California groundwater (n=7), or designated as having the potential to pollute groundwater and expected to be detected in groundwater in California (n=62) (California Department of Pesticide Regulation) based on their solubility, adsorption and/or half-life. Two pesticides in the first category (simazine, diuron) and 17 pesticides from the latter category had been applied in our study areas during the period of interest. We selected four additional pesticides that were not named on the CA DPR Groundwater Protection List but were identified by other states as being a concern to groundwater due to their high runoff or leaching potential also based on their solubility, adsorption and/or half-life (chlorpyrifos, trichlorfon, propargite, dicofol)(Cook et al. 2008). We also selected three chemicals of special interest for PD (paraquat, maneb, permethrin), but whose chemistry did not necessarily qualify them as potential groundwater contaminants (Ascherio et al. 2006; Brown et al. 2006; Miller et al. 1998). In total, 26 pesticides were selected for analyses (Table 1).

Pesticide exposures from private well water

Our well water pesticide exposure estimates were based on a combination of pesticide use/application data and self-reports of private wells as drinking water sources at a residential address. We assumed that private wells were likely to be located within 500m residential buffers, and thus agricultural pesticides applied within this area were considered a source of potential contamination for water drawn from the private well. We used our GIS-modeled pesticide application data to determine which agent could have potentially contaminated a subject’s well water. Each year at a residential address that fell into the 1974-1999 period and for which a private well was reported as the source of drinking water, we considered as a potentially exposed residential year, and calculated the annual level of exposure for each chemical with our GIS-PUR model. Then, we calculated a cumulative well water exposure measure for each chemical for the entire 1974-1999 period by summing over the years a subject was presumed to have been exposed i.e., years the subject had been drinking potentially contaminated well water. Thus, for the 1974-1999 period, subjects who lived at residences supplied with water from a private well were classified as possibly exposed to pesticides in well water at a level equivalent to the cumulative application rate predicted from our model for all years exposed (i.e., cumulative ambient pesticide application rate greater than 0). Subjects were considered unexposed if they: 1) did not report private well water as their source of water for a given address during the 1974-1999 period (including 5.25% of addresses for which data on water supply was missing), 2) reported private well water as their source of water for a given address before 1974 or after 1999 or, 3) reported private well water use during the 1974-1999 period but pesticides had not been applied in the buffer of the reported address according to our GIS model (i.e., cumulative ambient pesticide application rate equal to 0).

We also considered a second exposure classification that combined information about pesticide exposures from ambient sources and ingestion of well water, and compared subjects who were unexposed (no well water use and no ambient exposure) to subjects who were 1) ambiently exposed only [no well water use during 1974-1999, but pesticides were applied near the residence(s)], and 2) ambiently exposed and well water was their drinking water source for all or a portion of the 1974-1999 time period.

We individually examined only those pesticides from the list of 26 selected chemicals for which at least 10% of our population were ambiently exposed, i.e., six pesticides (diazinon, chlorpyrifos, propargite, paraquat, dimethoate, and methomyl). For subjects suspected to have been well water-pesticide exposed, we created categories of any exposure versus no exposure, and high and low exposures versus no exposure (high exposure categories were based on the median values of possible pesticide exposure in the well water of controls). We also examined combined exposure measures according to the number of pesticides applied from within two chemical classes in our list of 26, i.e., organophosphate (n=10 total; grouped as 5-10, 1-4 vs. 0) and n-methylcarbamate pesticides (4 total; grouped as 3-4, 1-2 vs. 0) (Table 1). Similarly, we examined possible exposure to water soluble pesticides as a group [19 total; grouped as 10-17, 1-9 vs. 0; (no one was exposed to all 19)] and all pesticides as a group [26 total; grouped as 12-24, 1-11 vs. 0; (no one was exposed to all 26)]. For the combined measures (pesticide chemical classes, water soluble pesticides, all pesticides) we followed our well water-pesticide exposure definition described above and counted subjects as exposed to an individual pesticide if the application rate was greater than 0 and unexposed if application rate was equal to 0.

Statistical analyses

We used multivariable unconditional logistic regression methods to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to assess associations between possible exposure to pesticides from well water consumption and PD risk adjusting for age (continuous), sex, education (<12 years, 12 years, >12 years), race/ethnicity (white, non-white), family history of PD (yes, no in first degree relative) and smoking (never, former, current). In additional models, we adjusted for ambient exposure to the pesticide in order to examine the risk associated with consumption of potentially contaminated well water after controlling for the contribution of ambient exposure to the pesticide. As adjustment for occupational exposure [using a job-exposure-matrix (JEM) to estimate occupational pesticide exposure] did not appreciably change our results, (odds ratios adjusted for occupational exposure to pesticides as estimated with the JEM were not more than 5% different than odds ratios not adjusted for occupational exposure), we thus opted for a more parsimonious model and did not to adjust for occupational pesticide exposure in our final model. We analyzed each of the six individual pesticides listed above separately and also examined the total number of water-soluble, organophosphate and n-methylcarbamate pesticides and all pesticides together. We conducted tests and report p-values for trend using ordinal variables for pesticide use. All analyses used SAS version 9.1 (SAS Institute Inc., Cary, NC, USA.).

RESULTS

Study participants were predominantly Caucasian, over the age of 65, and without a family history of PD (Table 2). Cases were slightly older than controls, more likely to be male, and had completed fewer years of education. They were also more likely to have never smoked cigarettes.

In our population, 16.9% of all subjects reported private well water as their drinking water source some time during the 1974-1999 period. Cases were more likely to have consumed water from private wells than controls during this period (Table 2), and reported drinking well water on average 4.3 (of the 26) years longer than controls (p=0.02).

Consumption of well water presumably contaminated at any level by one of the six pesticides that we examined separately was associated with elevated PD risk, but only for diazinon did the 95% CI exclude the null (Table 3). However, high levels of possible contamination resulted in 31% - 90% increases in risk compared to no well water contamination, with stronger associations seen for methomyl (OR = 1.67, 95% CI = 1.00, 2.78), chlorpyrifos (OR = 1.87, 95% CI = 1.05, 3.31) and propargite (OR = 1.92, 95% CI = 1.15, 3.20). Only for diazinon in well water was the dose-response reversed, i.e., lower rather than higher levels of possible contamination with diazinon resulted in greater increases in risk of PD (Table 3). Adjusting for ambient pesticide exposures only slightly attenuated all well water pesticide effect estimates, with the largest change seen for propargite.

For all six pesticides examined individually, PD risk associated with possible contamination of well water and ambient exposures (19-75% increase) was greater than the risk associated with ambient exposures alone (15-57% risk increase) (Table 4); also indicating that ambient exposure only to most of these agents still increased the risk.

Finally, our combined estimates suggested that a higher number of water soluble pesticides presumably contaminating well water increased the risk of PD (Table 5). Specifically, subjects exposed to ≥12 of the 26 pesticides included in the study, or ≥10 water soluble pesticides experienced a 66-68% greater risk. Also, subjects potentially exposed to the greatest number of organophosphate pesticides in presumably contaminated well water experienced risk increases of similar magnitude (71%), and there was a trend with an increasing numbers of organophosphates (p-trend = 0.04). However, possible contamination with multiple chemicals in the n-methyl carbamate class only slightly increased the risk of PD if at all (the 95% CIs included the null), and no trend was observed with increasing numbers.

DISCUSSION

Our study population resides in a largely agricultural region of Central California with documented historical pesticide use since 1974. We found that potential exposure to pesticides from consumption of drinking water from private wells suspected to be contaminated with diazinon, methomyl, chlorpyrifos, propargite or dimethoate in the 1974-1999 period was associated with an elevated risk of PD. High levels of possible well water contamination with methomyl, chlorpyrifos and propargite resulted in ~70% - 90% increases in risk of PD compared to residents without such exposures from well water. For paraquat, the well water and ambient risk estimates were generally small and uninformative, which might be explained by our previous observation that exposure to paraquat may require coinciding maneb exposure to increase PD risk(Costello et al. 2009). Paraquat was examined in this study because of its interest to PD, and we recognized that its physical properties including low water solubility and high adsorption make it less likely to contaminate groundwater. Thus, we expected lower well water risk estimates for this pesticide compared to others examined in this study. We also found that adjustment for ambient sources of pesticide exposure (i.e., inhalational, ingestional, or skin absorption routes of exposure) slightly attenuated but did not eliminate the observed associations for possible well water contamination. The PD risk associated with a combined exposure to pesticides in the environment and in presumably contaminated well water was greater than the risk associated with ambient exposure alone. These results suggest that while exposure to the selected pesticides in the environment alone increases the risk of PD (20-50%), exposures from consumption of potentially contaminated well water may confer some additional, independent risk above ambient exposure. Furthermore, consumption of well water presumably contaminated by a greater number of pesticides, specifically of water soluble pesticides or chemicals belonging to the organophosphate class, further increased the risk of PD. Because greater estimated effect sizes were noted for diazinon and chlorpyrifos when these pesticides were examined individually, we were concerned that the observed increases in PD risk for water soluble and organophosphate classes of pesticides could have been mainly due to these two pesticides. We thus examined the water soluble class after removing diazinon, and the OP class removing both chlorpyrifos and diazinon, and found that the associations persisted. For the OPs, the OR for possible exposure in well water to 1-3 pesticides in this class was 1.07 (95% CI = 0.66, 1.76) and for ≥4 the OR was 1.90 (1.07, 3.03), p-trend = 0.04. For the water soluble pesticides, the OR for possible well water exposure to 1-8 pesticides in this class was 1.06 (95% CI = 0.65, 1.72) and for ≥8, the OR was 1.63 (95% CI = 0.98, 2.70), p-trend = 0.08. These results suggest that the association between PD risk and the water soluble or OP classes of pesticides investigated in this study is not dominated by one or two specific chemicals, but rather that exposure to a number of these types of pesticides in water may increase PD risk.

Besides inhibiting acetylcholinesterase (Milatovic et al. 2006; Singh and Agarwal 1983), carbamate (Zhou et al. 2004) and OP (Sharma et al. 2005) pesticides are suspected to be involved in the etiological pathway leading to PD, for example, by disturbing redox processes that inhibit antioxidant enzymes thus enhancing lipid peroxidation and oxidative stress (Lukaszewicz-Hussain 2008) or inhibiting the proteasome or mitochondrial function in neurons. Studies spanning two decades have examined the association between well water exposure and PD risk. Many of these studies were small, i.e., included fewer than 100 cases (Marder et al. 1998; Morano et al. 1994; Smargiassi et al. 1998; Wang et al. 1993; Wechsler et al. 1991; Wong et al. 1991); all relied on self-reported well water consumption to define ever/never exposure groups, and none attempted to assess levels of general or specific pesticide contamination in well water. The majority of these studies reported small relative increases in PD risk from ever being exposed to well water (ORs ranging from 1.02 – 2.8), and several found no associations (Chan et al. 1998; Golbe et al. 1990; Gorell et al. 1998; Hertzman et al. 1994; Marder et al. 1998; Tanner et al. 1999), or even reported protective associations (McCann et al. 1998; Wang et al. 1993), perhaps due to the absence of a toxic agent in the well water consumed in these study populations. Several studies included both rural and urban populations, and some of the wells may not have been located in areas where agricultural chemicals could have contaminated them. In fact, several authors noted that the introduction of chemicals to agricultural practices was a recent phenomenon in their study areas (De Michele et al. 1996; Liou et al. 1997; Tanner et al. 1989), and doubted that the period when pesticides may have contaminated well water would have been relevant to initiation of disease among the subjects they studied.

It is possible that one or more of the associations we are reporting here do not reflect an etiologic contribution of the particular pesticide to PD risk, per se, rather that the pesticide we suspected to have contaminated the well water consumed by our population acted as a surrogate measure for another unidentified pesticide, i.e., other pesticides in use that are strongly correlated with the pesticide we examined. Exposure to mixtures of chemicals is a problem inherent in the assessment of exposure in humans. Among the 26 pesticides purposefully selected for our study, several were generally co-applied. For the six pesticides we individually examined, for example, among subjects who were ambiently exposed to chlorpyrifos at their residences, 80% were also exposed to diazinon and 91% to paraquat; of subjects ambiently exposed to paraquat 73% were also exposed to diazinon, 82% to methomyl and 80% to propargite. Thus, it was also impossible to estimate the effects for all the six pesticides together in the same model, i.e., to estimate the effect for one chemical while adjusting for all others. To avoid issues of multiple testing as much as possible while still evaluating the most relevant water contaminants, we restricted the pesticides selected for analyses to those with a high probability of being found in groundwater based on their physical properties/chemistry and using the CA DPR list of pesticides previously detected in groundwater or recognized as potential groundwater contaminants as a guide. Nevertheless, we cannot rule out that some of our findings might be due to chance.

It is also possible that well water in rural locations may be contaminated with multiple agricultural and industrial agents and metals, in addition to pesticides. DeMichele (De Michele et al. 1996) noted that farming practices and exposure to chemicals vary from area to area as a possible explanation for diverging results in the literature. To our knowledge, no previous study of PD has estimated pesticide residue contamination historically in drinking water; we are the first to implement a semi-quantitative approach to estimating pesticide exposure. Our well water pesticide exposure estimates do not exclusively reflect exposure from water ingestion alone because the suspected contamination was derived from data on applications in proximity of wells supplying water to residences, and these same chemicals were likely also air and soil contaminants. However, we did adjust and possibly may have even overadjusted for ambient pesticide exposure in our models, and found minimal attenuations in our well water risk estimates, i.e., the associations for most chemicals remained after adjustment. An additional limitation is that our models for water contamination did not take into account some geological factors such as soil quality, groundwater depth and direction of groundwater flow that could influence the likelihood that a pesticide reaches the water drawn from private wells. Thus, our pesticide well water exposure estimates may not completely reflect actual levels of exposure to pesticides from consuming well water.

Our study is unique among those that have examined PD risk from well water consumption in that we utilized existing historical California PUR data, which we combined with land use maps to derive pesticide application rates for the study area over an extended period. Thus, our well water pesticide exposure measure is an estimate derived from our GIS models; we did not sample well water to directly measure actual current or historical pesticide levels. Rajput et al. (Rajput et al. 1987) found no differences in concentrations of several metals in samples taken from wells that provided drinking water to PD cases and controls in Canada. However, given that well water sampling in that study was performed at the time of PD diagnosis, measured levels may not have accurately reflected contamination during the critical exposure window for PD years or decades before diagnosis.

In an attempt to validate our model for well water pesticide contamination, we obtained domestic well water sample data from the CA DPR; the agency analyzed these samples for multiple chemicals on a non-routine basis for nearly 3 decades (1980-present). The current database contains over 95,000 records from approximately 9,300 domestic wells located in about 4,100 township range sections throughout California, and lists as detected about 200 possible pesticide active ingredients and breakdown products. Sampling, however, did not follow any standardized schedule and were not conducted randomly for all private wells. When we crossreferenced the DPR data with addresses for our study subjects, data on testing for and detecting pesticides were available for wells located in the same township range section as a residence for no more than 20 cases and 17 controls and for a total of nine pesticides. For two of the more common pesticides identified (simazine and diuron), our GIS models had identified ~7.5% of the PEG population as being ambiently exposed. We cross-tabulated DPR detections (yes, no/non-detect) with our ambient exposure measures (yes, no) and found moderate concordances. For simazine, our model-predicted exposures corresponded with the DPR detections 63.5% of the time; for diuron, it was 65%. However, it is not possible to know whether the wells sampled by CA DPR were the same wells from which study subjects had drawn their drinking water.

Our study represents a significant improvement over other previous studies (Ascherio et al. 2003; Marder et al. 1998; Morano et al. 1994; Smargiassi et al. 1998; Wang et al. 1993; Wechsler et al. 1991; Wong et al. 1991) in that we did not have to rely on study subjects' recall of their own pesticide use to derive exposure estimates, a procedure criticized for its potential to introduce differential exposure misclassification bias if cases and controls recall differently. An additional strength of our current study is that all of our PD diagnoses were clinically confirmed by a study movement disorder specialist, and thus we expect our results to be affected by disease misclassification only minimally.

In conclusion, our study, the first of its kind to apply a semi-quantitative approach to estimating pesticide exposure in well water, contributes evidence that consumption of well water potentially contaminated with pesticides may play a role in the etiology of PD.

REFERENCES

Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. 2003. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology 60(5): 790-795.

Ascherio A, Chen H, Weisskopf MG, O'Reilly E, McCullough ML, Calle EE, et al. 2006. Pesticide exposure and risk for Parkinson's disease. Ann Neurol 60(2): 197-203.

Ben-Shlomo Y, Finnan F, Allwright S, Davey Smith G. 1993. The epidemiology of Parkinson's disease in the Republic of Ireland: observations from routine data sources. Ir Med J 86(6): 190-191, 194.

Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. 2000. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3(12): 1301-1306.

Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. 2006. Pesticides and Parkinson's disease--is there a link? Environ Health Perspect 114(2): 156-164.

Burguera JA, Catala J, Taberner P, Munoz R. 1992. [Mortality from Parkinson's disease in Spain (1980-1985). Distribution by age, sex and geographic areas]. Neurologia 7(3): 89-93.

California Department of Pesticide Regulation. California Code of Regulations (Title 3. Food and Agriculture) Division 6. Pesticides and Pest Control Operations. 6800. Groundwater Protection List. .

Chan DK, Woo J, Ho SC, Pang CP, Law LK, Ng PW, et al. 1998. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry 65(5): 781-784.

Chester G, Ward RJ. 1984. Occupational exposure and drift hazard during aerial application of paraquat to cotton. Arch Environ Contam Toxicol 13(5): 551-563.

Cook JL, Baumann M, Jackman JA, Stevenson D. 2008. Pesticide Characteristics that Affect Water Quality. Texas Agricultural Extension Service, Texas A & M University, College Station, Texas. Available: http://insects.tamu.edu/extension/bulletins/water/water_01.html [accessed December 2008]

Costello S, Wahner A, Bronstein J, Cockburn M., Zhang X, Ritz B. 2009. Paraquat and Maneb exposure and Parkinson’s disease in the California Central Valley. Am Journal of Epidemiology (In Press).

Currier WW, MacCollom GB, Baumann GL. 1982. Drift residues of air-applied carbaryl in an orchard environment. J Econ Entomol 75(6): 1062-1068.

De Michele G, Filla A, Volpe G, De Marco V, Gogliettino A, Ambrosio G, et al. 1996. Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord 11(1): 17-23.

Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Jr., Checkoway H. 2005. Pesticides and risk of Parkinson disease: a population-based case-control study. Arch Neurol 62(1): 91-95.

Golbe LI, Farrell TM, Davis PH. 1990. Follow-up study of early-life protective and risk factors in Parkinson's disease. Mov Disord 5(1): 66-70.

Goldberg D.W. Zhang X. Marusek J.C. Wilson J.P. Ritz B. Cockburn M.G. (editors). 2007. Development of an Automated Pesticide Exposure Analyst for the California's Central Valley. In: Proceedings of the Urban and Regional Information Systems Association GIS in Public Health Conference. New Orleans, LA.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. 1998. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50(5): 1346-1350.

Hancock DB, Martin ER, Stajich JM, Jewett R, Stacy MA, Scott BL, et al. 2007. Smoking, caffeine, and nonsteroidal anti-inflammatory drugs in families with Parkinson disease. Arch Neurol 64(4): 576-580.

Hertzman C, Wiens M, Snow B, Kelly S, Calne D. 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord 9(1): 69-75.

Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. 2005. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord 20(9): 1133-1142.

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, et al. 1997. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 48(6): 1583-1588.

Lukaszewicz-Hussain A. 2008. Subchronic intoxication with chlorfenvinphos, an organophosphate insecticide, affects rat brain antioxidative enzymes and glutathione level. Food Chem Toxicol 46(1): 82-86.

MacCollom GB. Currier WW. Baumann GL. 1986. Drift comparisons between aerial and ground orchard application. J Econ Entomol 79: 459-464.

Marder K, Logroscino G, Alfaro B, Mejia H, Halim A, Louis E, et al. 1998. Environmental risk factors for Parkinson's disease in an urban multiethnic community. Neurology 50(1): 279-281.

McCann SJ, LeCouteur DG, Green AC, Brayne C, Johnson AG, Chan D, et al. 1998. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology 17(6): 310-317.

McElroy JA, Remington PL, Trentham-Dietz A, Robert SA, Newcomb PA. 2003. Geocoding addresses from a large population-based study: lessons learned. Epidemiology 14(4): 399-407.

Milatovic D, Gupta RC, Aschner M. 2006. Anticholinesterase toxicity and oxidative stress. ScientificWorldJournal 6: 295-310.

Miller DB, Ali SF, O'Callaghan JP, Laws SC. 1998. The impact of gender and estrogen on striatal dopaminergic neurotoxicity. Ann N Y Acad Sci 844: 153-165.

Morano A, Jimenez-Jimenez FJ, Molina JA, Antolin MA. 1994. Risk-factors for Parkinson's disease: case-control study in the province of Caceres, Spain. Acta Neurol Scand 89(3): 164-170.

Norris EH, Uryu K, Leight S, Giasson BI, Trojanowski JQ, Lee VM. 2007. Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model. Am J Pathol 170(2): 658-666.

Nuti A, Ceravolo R, Dell'Agnello G, Gambaccini G, Bellini G, Kiferle L, et al. 2004. Environmental factors and Parkinson's disease: a case-control study in the Tuscany region of Italy. Parkinsonism Relat Disord 10(8): 481-485.

Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. 2001. Environmental risk factors and Parkinson's disease: a metaanalysis. Environ Res 86(2): 122-127.

Rajput AH, Uitti RJ, Stern W, Laverty W, O'Donnell K, O'Donnell D, et al. 1987. Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. Can J Neurol Sci 14(3 Suppl): 414-418.

Rull RP, Ritz B. 2003. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. Environ Health Perspect 111(13): 1582-1589.

Safe Drinking Water Act of 1974. Public Law 93-523.

Sharma Y, Bashir S, Irshad M, Nag TC, Dogra TD. 2005. Dimethoate-induced effects on antioxidant status of liver and brain of rats following subchronic exposure. Toxicology 215(3): 173-181.

Sherer TB, Betarbet R, Greenamyre JT. 2001. Pesticides and Parkinson's disease. ScientificWorldJournal 1: 207-208.

Singh DK, Agarwal RA. 1983. Inhibition kinetics of certain organophosphorus and carbamate pesticides on acetylcholinesterase from the snail Lymnaea acuminata. Toxicol Lett 19(3): 313-319.

Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. 1998. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. Neurotoxicology 19(4-5): 709-712.

Svenson LW, Platt GH, Woodhead SE. 1993. Geographic variations in the prevalence rates of Parkinson's disease in Alberta. Can J Neurol Sci 20(4): 307-311.

Tanner CM, Chen B, Wang W, Peng M, Liu Z, Liang X, et al. 1989. Environmental factors and Parkinson's disease: a case-control study in China. Neurology 39(5): 660-664.

Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. 1999. Parkinson disease in twins: an etiologic study. Jama 281(4): 341-346.

Thiruchelvam M, McCormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, et al. 2003. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. Eur J Neurosci 18(3): 589-600.

Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. 2000. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. J Neurosci 20(24): 9207-9214.

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology 23(4-5): 621-633.

US EPA. Private Drinking Water Wells. Available: <http://www.epa.gov/safewater/privatewells/basicinformation.html> [accessed January 2009.

Wang WZ, Fang XH, Cheng XM, Jiang DH, Lin ZJ. 1993. A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. Neuroepidemiology 12(4): 209-218.

Wechsler LS, Checkoway H, Franklin GM, Costa LG. 1991. A pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology 12(3): 387-392.

Wong GF, Gray CS, Hassanein RS, Koller WC. 1991. Environmental risk factors in siblings with Parkinson's disease. Arch Neurol 48(3): 287-289.

Wright JM, Keller-Byrne J. 2005. Environmental determinants of Parkinson's disease. Arch Environ Occup Health 60(1): 32-38.

Zhou Y, Shie FS, Piccardo P, Montine TJ, Zhang J. 2004. Proteasomal inhibition induced by manganese ethylene-bis-dithiocarbamate: relevance to Parkinson's disease. Neuroscience 128(2): 281-291.

Table 1. Pesticides selected for study; cumulative application rates during the period 1974-1999[a] in a 500 m buffer around residences with a private well reported as water supply, water solubility, and reason for selection

Pesticide	Median (range) pesticide application rate (lbs per acre)[b]	Chemical Family/Usage	Reason included[c]	Water Soluble
Triflumizole	6.51 (0.56 – 31.9)	Azole/Fungicide	3	yes
Vinclozolin	1.92 (<0.01 – 8.1)	Dicarboximide/Fungicide	3	yes
Maneb	11.24 (1.52-169.1)	Dithiocarbamate/Fungicide	1	no
Aldicarb	11.18 (0.19 – 221.0)	N-methyl carbamate/Insecticide	3	yes
Methomyl	8.26 (<0.01 – 302.8)	N-methyl carbamate/Insecticide	3	yes
Carbofuran	3.88 (<0.01 – 52.2)	N-methyl carbamate/Insecticide, Nematicide	3	yes
Carbaryl	44.25 (0.01 – 756.0)	N-methyl carbamate/Insecticide, Nematicide, Plant growth regulator	3	yes
Dicofol	14.38 (<0.01 – 239.2)	Organochlorine/Acaricide	4	no
Acephate	4.97 (0.06 – 34.9)	Organophosphate/Insecticide	3	yes
Azinphos-methyl	34.76 (0.36 – 671.7)	Organophosphate/Insecticide	3	yes
Chlorpyrifos	28.97 (<0.01 – 884.3)	Organophosphate/Insecticide	4	no
Diazinon	44.31 (0.07 – 2493.0)	Organophosphate/Insecticide	3	yes
Dimethoate	14.42 (<0.01 – 437.1)	Organophosphate/Insecticide	3	yes
Oxydemeton-methyl	1.37 (0.06 – 70.9)	Organophosphate/Insecticide	3	yes
Parathion	57.45 (0.01 – 1412.3)	Organophosphate/Insecticide	3	yes
Trichlorfon	7.14 (0.07 – 42.7)	Organophosphate/Insecticide	4	yes
Disulfoton	8.33 (<0.01 – 174.5)	Organophosphate/Insecticide, Nematicide	3	yes
Phorate	11.43 (0.12 – 207.8)	Organophosphate/Insecticide, Nematicide	3	yes
Permethrin	0.69 (<0.01 – 292.3)	Pyrethroid/Insecticide	1	no
Paraquat	19.38 (0.01 – 1683.5)	Quaternary ammonium/Herbicide	1	yes
Chlorothalonil	18.86 (0.02 – 1265.4)	Substituted benzene/Fungicide	3	no
Diuron	53.59 (0.69 – 788.4)	Substituted urea/Herbicide	2	yes
Propargite	34.84 (<0.01 – 2116.8)	Sulfite ester/Acaricide	4	no
Simazine	29.83 (1.15 – 632.8)	Triazine/Herbicide	2	yes
Linuron	3.93 (0.09 – 55.9)	Urea/Herbicide	3	yes
Chloropicrin	6.83 (<0.01 – 370.9)	Unclassified/Fumigant, Nematicide	3	no

[a] using data on cumulative pesticide application rates for years during this period when pesticides were applied

[b] based on the distribution in controls

[c] 1: of interest to PD, 2: detected by DPR in groundwater, 3: identified by DPR or other agencies as potential groundwater contaminant, 4: high relative runoff or leaching potential

Table 2. Characteristics of PEG Study Population

Characteristic	Cases (n=368)	Controls (n=341)	Odds Ratio	95% CI
Age (years)	69.6 ± 10.3	67.6 ± 11.4	1.02	1.00, 1.03
Female sex	161 (43.8%)	165 (48.4%)	0.83	0.62, 1.12
Race				
White	314 (85.3%)	292 (85.6%)	ref	
Non-White	54 (14.7%)	49 (14.4%)	1.03	0.68, 1.56
Black	2 (0.5%)	11 (3.2%)		
Latino	46 (12.5%)	29 (8.5%)		
Asian	4 (1.1%)	8 (2.4%)		
Native American	2 (0.5%)	1 (0.3%)		
Education				
<12 years	68 (18.5%)	38 (11.1%)	2.14	1.38, 3.32
12 years	100 (27.2%)	64 (18.8%)	1.87	1.30, 2.69
>12 years	200 (54.4%)	239 (70.1%)	ref	
Smoking Status				
Current	22 (5.9%)	34 (10.0%)	0.48	0.27, 0.86
Former	151 (41.0%)	161 (47.2%)	0.70	0.52, 0.96
Never	195 (53.0%)	146 (42.8%)	ref	
1st degree relative with PD	55 (15.0%)	38 (11.1%)	1.40	0.90, 2.18
Ever had private well	67 (18.2%)	53 (15.5%)	1.21	0.82, 1.80
Total years used well water	18.3 ± 9.3	14.0 ± 10.0		

Table 3. Risk of Parkinson’s Disease from Potential Exposure to Individual Pesticides in Well Water

<u>Pesticide</u> Exposure level	Cases/ Controls	OR[a]	95% CI	Exposure level[b]	Cases/ Controls	OR[a]	95% CI	OR[c]	95% CI
Diazinon									
None	295/300	1.0 (ref)		None	295/300	1.0 (ref)		1.0 (ref)	
Any	73/41	1.58	1.03, 2.43	Low	45/21	2.00	1.14, 3.50	2.00	1.14, 3.50
				High	28/20	1.16	0.62, 2.14	1.14	0.53, 2.43
Dimethoate									
None	290/290	1.0 (ref)		None	290/290	1.0 (ref)		1.0 (ref)	
Any	78/51	1.41	0.94, 2.11	Low	33/26	1.28	0.74, 2.24	1.29	0.74, 2.24
				High	45/25	1.53	0.90, 2.62	1.47	0.83, 2.58
Methomyl									
None	290/288	1.0 (ref)		None	290/288	1.0 (ref)		1.0 (ref)	
Any	78/53	1.28	0.85, 1.91	Low	26/26	0.86	0.48, 1.56	0.87	0.48, 1.58
				High	52/27	1.67	1.00, 2.78	1.40	0.80, 2.43
Chlorpyrifos									
None	301/300	1.0 (ref)		None	301/300	1.0 (ref)		1.0 (ref)	
Any	67/41	1.45	0.94, 2.24	Low	25/21	1.05	0.56, 1.96	1.05	0.56, 1.96
				High	42/20	1.87	1.05, 3.31	1.81	1.00, 3.30
Propargite									
None	291/288	1.0 (ref)		None	291/288	1.0 (ref)		1.0 (ref)	
Any	77/53	1.31	0.88, 1.96	Low	22/27	0.73	0.40, 1.34	0.73	0.40, 1.34
				High	55/26	1.92	1.15, 3.20	1.94	1.07, 3.52
Paraquat									
None	289/281	1.0 (ref)		None	289/281	1.0 (ref)		1.0 (ref)	
Any	79/60	1.10	0.75, 1.63	Low	32/30	0.89	0.52, 1.54	0.89	0.51, 1.54
				High	47/30	1.31	0.79, 2.17	1.26	0.72, 2.20

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

[b] based on median value in controls to distinguish between low and high exposure levels

[c] Adjusted for above covariates and ambient pesticide exposure

Table 4. Risk of Parkinson's Disease from Potential Inhalation and/or Ingestion of Pesticides

Pesticide	Cases/Controls	OR[a]	95% CI
Diazinon			
Unexposed	165/188	1.0 (ref)	
Ambient Pesticide Only	130/112	1.29	0.92, 1.81
Ambient and Well Water	73/41	1.75	1.12, 2.76
Dimethoate			
Unexposed	150/180	1.0 (ref)	
Ambient Pesticide Only	140/110	1.57	1.12, 2.22
Ambient and Well Water	78/51	1.72	1.12, 2.65
Methomyl			
Unexposed	147/165	1.0 (ref)	
Ambient Pesticide Only	143/123	1.23	0.87, 1.72
Ambient and Well Water	78/53	1.41	0.91, 2.18
Chlorpyrifos			
Unexposed	186/210	1.0 (ref)	
Ambient Pesticide Only	115/90	1.42	1.00, 2.01
Ambient and Well Water	67/41	1.63	1.04, 2.57
Propargite			
Unexposed	152/164	1.0 (ref)	
Ambient Pesticide Only	139/124	1.24	0.88, 1.75
Ambient and Well Water	77/53	1.45	0.94, 2.23
Paraquat			
Unexposed	131/140	1.0 (ref)	
Ambient Pesticide Only	158/141	1.15	0.82, 1.62
Ambient and Well Water	79/60	1.19	0.77, 1.83

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

Table 5. Risk of Parkinson's Disease from Potential Exposure[a] to Pesticides in Well Water by Chemical Family or Water Solubility of Pesticide

Pesticide Family or Water Solubility, number to which exposed	Cases/Controls	OR[b]	95% CI	p-trend
Water soluble (n= 19 total)				
0	273/275	1.0 (ref)		
1-9	43/39	1.03	0.63, 1.67	
≥10	52/27	1.68	1.01, 2.81	0.07
Organophosphates (n=10 total)				
0	272/277	1.0 (ref)		
1-4	36/33	1.03	0.61, 1.74	
≥5	60/31	1.71	1.06, 2.76	0.04
N-methyl carbamate (n=4 total)				
0	281/282	1.0 (ref)		
1-2	44/30	1.35	0.81, 2.26	
≥3	43/29	1.24	0.73, 2.08	0.26
All pesticides (n=26 total)				
0	270/273	1.0 (ref)		
1-11	36/35	0.95	0.57, 1.60	
≥12	62/33	1.66	1.04, 2.66	0.06

[a] based on exposed/unexposed classification

[b] Adjusted for age, race, sex, education, family history of PD