CONFIDENTIAL: Attorney-Client Work Product

Exponent®

Sensitivity Analyses of the Tanner et al. Case-Control Study of Parkinson's Disease in the Agricultural Health Study

Prepared by:

Edmund Lau, MS
Heather Watson, PhD
Jack Mandel, MPH, PhD

September 10, 2013

Case ID: 220300429

SYNG-PQ-36932783

Introduction

The Agricultural Health Study (AHS) is a cohort study of pesticide applicators and their spouses recruited between 1993 and 1997 from Iowa and North Carolina (see, for example, Alavanja et al. 1996; Kamel et al. 2007). The AHS is sponsored and conducted by the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA). It is one of the largest prospective studies conducted on agricultural exposures and health, with the advantages of including family members of pesticide applicators and assessing exposures largely prior to the diagnosis of disease. The study aims to accomplish the following: 1) to identify and quantify cancer risks among men and women exposed to pesticides and other agricultural agents, 2) to evaluate risks of non-cancer health endpoints, 3) to evaluate disease risk from farm exposures among family members (spouses and children) of pesticide applicators, 4) to evaluate the relationships among agricultural exposures, biomarkers of exposure, biologic effects, and genetic susceptibility factors related to carcinogenesis, and 5) to evaluate the influence of lifestyle factors such as cooking practices, diet, tobacco, alcohol, and physical activity on risk of cancer and other diseases.

Between 1993 and 1997, potential participants were solicited from private and commercial applicator lists from the two states. The initial enrollment questionnaire, which was self-administered, requested data on basic demographic variables, medical conditions, use of 50 pesticides, crops grown and livestock raised, use of protective clothing and equipment, fruit and vegetable intake, tobacco and alcohol use, and family members. Some participants were re-interviewed using an abbreviated questionnaire to assess reliability of the information provided in the enrollment questionnaire. Additional take-home questionnaires requested more detailed data on similar topics as the enrollment questionnaire. To improve exposure classification by combining questionnaire data with sample monitoring data, an exposure monitoring component was originally designed to include information on pesticide exposure from all routes – air, skin, food, and water – and from both environmental and occupational sources. However, because of cost and practical considerations it was not possible to monitor for all factors that could influence exposure.

Following enrollment into the AHS, pesticide applicators and their spouses were asked to complete a self-administered questionnaire collecting their basic demographic information, pesticide use history (for applicators only), and health status, including whether they had ever been diagnosed with Parkinson's disease (PD). Approximately one month after the baseline questionnaire, applicators were asked to complete a supplemental questionnaire collecting additional detailed information on their history of pesticide use.

Due to the low response rate to the supplemental questionnaire (about 50%), the investigators sought to address non-responders through telephone interviews and "structured refusal conversion procedures," but cost precluded such efforts. Instead, the investigators conducted a series of smaller studies to identify factors affecting the response rate. These analyses revealed many statistically significant differences between responders and non-responders (Tarone et al. 1997). Unfortunately, there were no data to compare characteristics between eligible individuals who did (77%) and did not (23%) complete the initial enrollment questionnaire. Nevertheless, the authors concluded that any selection bias would be minimal.

Five years after enrollment, in 1999-2003, follow-up telephone interviews were conducted with 57,251 (67.5%) cohort members. For those who were not interviewed, 13% percent of the cohort could not be contacted, 12% declined the interview, 2.5% were deceased, <1% were excluded due to illness. The remaining 4% were excluded for various other reasons. Those who were successfully interviewed were again asked to self-report if they had ever been diagnosed with PD.

Parkinson's Disease and Paraquat

The study by Kamel et al. (2007) found no association between paraquat and PD incidence in the AHS (relative risk=1.0). However, a subsequent nested case-control study by Tanner et al. (2011), known as the Farming and Movement Evaluation (FAME) study, reported a significant positive association between paraquat and PD risk. To better understand the discrepancy in findings and further explore the AHS data, the data from the FAME study were requested by Syngenta from NIEHS/NIH.

The FAME study focused on the association between PD and exposure to pesticides with potential properties of mitochondrial dysfunction and oxidative stress. As reported by Tanner et al. (2011), this study examined life-long use of 31 selected potential oxidative stressor pesticides, such as paraquat, and potential mitochondrial inhibitor pesticides, such as rotenone, in association with the development of PD. PD cases were identified from the AHS enrollees who self-reported having been diagnosed with PD or whose mortality records indicated such a condition. Potential controls were randomly selected from all other AHS participants, excluding those who were subsequently diagnosed with PD or Parkinsonism and those who were seriously ill, dead, or cognitively impaired. Controls were matched to cases on age, sex, and state in a three-to-one ratio.

One distinct feature of the FAME study is the use of home visits with in-person examinations to confirm PD among cohort members. The "Cognitive Abilities Screening Instrument," a standardized, video-taped assessment of Parkinsonism, was used along with standardized medical and neurological histories, a handwriting sample, medication use evaluation, and a smell identification test. Two neurologists independently reviewed all available diagnostic information of all self-reported PD cases and those suspected of having PD among the potential controls. Agreement between the two independent neurological reviews constituted a positive confirmed diagnosis of PD. According to Tanner et al. (2011), 156 (92%) out of 170 suspected PD cases and 542 (84%) out of 644 potential controls were screened by telephone for study eligibility. Of these, 137 (88%; 124 with home visits and 13 with proxy interviews and medical records) of the 156 eligible suspected cases (including four potential controls who self-reported PD at screening) and 383 (71%) of the 542 eligible screened controls were evaluated for PD. Based on the available diagnostic information, 115 suspected cases (74%; 110 with pesticide data; 101 living, 9 dead) were confirmed as PD. None of the 383 controls (358 with pesticide data) were confirmed as PD.

Data

A Freedom of Information Act (FOIA) request was submitted to the NIH in September 2011 (NIH FOI Case No. 39251), requesting the questionnaire, study data, and other documentation from the AHS. The FOIA request specifically referenced the data underlying the AHS study

results published by Kamel et al. (2007) and the FAME study results published by Tanner et al. (2011).

The NIH provided a dataset relevant to the Kamel et al. (2007) study in November 2011. We used this dataset to successfully replicate the results reported by Kamel et al. (2007). The NIH rejected the FOIA request for the FAME study data, citing ownership by the Parkinson Institute, a non-government entity not covered by the FOIA. An appeal to the NIH FOIA office was made and an agreement was reached, resulting in the release of a de-identified dataset for the FAME study in April 2012. This dataset had 468 records and 61 variables, matching the number of cases and controls reported by Tanner et al. (2011). Although results from the FAME study could be replicated using this dataset, very little additional information was provided for a sensitivity analysis to assess the results and conclusions. In particular, we were interested in examining various exposure classifications and outcome assessments to determine the reliability and validity of the reported associations. An appeal was made to NIH for additional information, and a supplemental dataset with 24 additional variables was provided in July 2012, but this dataset could not be merged with the initial dataset. NIH subsequently provided a combined dataset with 160 variables in September 2012, including new information on pesticide use from the AHS baseline and supplemental questionnaires. A complete listing of the 160 variables in this combined dataset is provided at the end of this report (Appendix 1). Even with this expanded dataset, a number of critical variables, such as age at diagnosis, were not provided due in part to privacy concerns.

Methods and Results

We performed a number of analyses to assess the reliability and validity of the FAME study results. Specifically, we conducted a detailed examination of the exposure data to determine if the exposure responses were consistent across questionnaires. We tested alternative logistic regression models by including or excluding certain covariates and testing the robustness of the odds ratio (OR) estimates. We also tested alternative exposure classifications by applying reasonable but different classification rules to the pesticide use responses from questionnaires. In addition, to test the robustness of the OR to random exposure misclassification, which may have occurred due to the use of self-reported and proxy-reported data on pesticide use, we randomly reassigned some subjects from exposed to unexposed and vice versa.

Reliability of Exposure

Proper exposure classification is critical to the estimation of valid associations between pesticide exposure and PD risk. With multiple responses to pesticide use available from different questionnaires (the AHS enrollment questionnaire in 1993-1997, the AHS follow-up in questionnaire 1999-2003, and the FAME questionnaire in 2002-2005), the FAME dataset offered an opportunity to evaluate the reliability of the exposure classification by examining the consistency of reported use of paraquat and other pesticides across questionnaires. Table 1 summarizes the consistency of exposure reporting among the AHS and FAME questionnaires for eleven different pesticides. If responses from at least two of the questionnaires were in agreement, then the exposure was considered consistent. Exposure was classified as "new exposure" if none was reported in the AHS or in the follow-up questionnaire, but exposure was reported in the FAME questionnaire. Responses among the three questionnaires that were contradictory or inconsistent (e.g., reporting having used a certain pesticide in the AHS enrollment questionnaire, but later reporting never having used it in the FAME questionnaire) were classified as "inconsistent."

The consistency of reported pesticide exposure across questionnaires varied substantially by type of pesticide (Table 1). Of the 11 pesticides examined in the FAME study, seven (paraquat, aldrin, DDT, dieldrin, 2 4-D, trifluralin, permethrin) had a modest percentage (7-13%) of missing responses and a corresponding percentage of consistent responses ranging from to 66% to 78%. The percentage of new exposure among this group of pesticides ranged from 5%-15%, and inconsistent responses was in the 5%-12% range. For paraquat use in particular, 78% of the respondents had consistent responses across at least two questionnaires, 6% of the respondents had new exposure (i.e., began using paraquat after AHS enrollment), 9% had inconsistent responses, and 7% had missing responses in one or more questionnaires. By comparison, the other four pesticides (rotenone, acifluorfen, copper, ferbam) had a considerably higher proportion of missing and incomplete responses (as much as 50%) and substantially less consistency in the responses regarding their use.

Cumulative Lifetime Use Distribution

The FAME study examined associations between PD and lifetime days of pesticide use for 11 pesticides, including paraquat, by calculating ORs that compared unexposed subjects (i.e., those who had never used the pesticide) with two groups of exposed subjects: those with non-zero lifetime days of pesticide use at or below the median among controls (e.g., 8 days for paraquat use), and those with lifetime days of pesticide use above the median among controls, using pesticide data from the FAME questionnaire. Tanner et al. (2011) reported a statistically significantly increased OR for PD among those at or below the median for lifetime days of paraquat use (OR=2.4, 95% CI=1.0-5.5, $p<0.05$), compared with never users, and an even stronger OR among those above the median (OR=3.6, 95% CI=1.6-8.1, $p<0.005$).

We examined the sensitivity of the results to the use of the median lifetime days of pesticide use among control subjects as the dividing criterion. To this end, we evaluated alternative cutoffs, including the 25th, 33rd, 66th, and 75th percentiles among controls based on the FAME questionnaire data, to dichotomize the lifetime days of use for the OR calculations. We also dichotomized exposure based on percentiles of lifetime days of pesticide use among the cases instead of the controls.

Varying the cutoff point for cumulative lifetime years of paraquat use by using various percentiles of the case or control distribution moderately affected the estimated association (Table 2). The OR for greater use (i.e., lifetime years of use above the cutoff) did not follow a clear pattern with respect to the percentile cutoff, but tended to be lower if the case distribution was used instead of the control distribution (the latter of which is more commonly used to define cutoffs in case-control studies). The OR for lesser use of paraquat (i.e., lifetime years of use at or below the cutoff) also did not follow a clear pattern with respect to the percentile cutoff, and was higher for three of the five estimated ORs if the case distribution was used instead of the control distribution.

Misclassification Testing

To better understand the sensitivity of the ORs for PD to the classification of paraquat exposure based on the FAME questionnaire data, we performed several data simulations to test the following three misclassification schemes:

1. Exposure reclassification of a randomly fixed number of subjects (two, four, or six)
2. Exposure reclassification of a randomly selected fixed proportion of subjects (10% or 20%)
3. Exposure reclassification of a randomly selected proportion of subjects based on the fraction of proxy respondents in each exposure category, since information on pesticide use is likely less reliable when provided by a proxy informant such as a spouse.

In the FAME study, 23 cases (among 110) and 49 controls (among 358) reportedly used paraquat, with a resulting OR of 2.5 (95% CI: 1.4-1.7, p=0.004) for ever vs. never use. We randomly reassigned the exposure status of these subjects according to each of the three described schemes, and performed one thousand iterations for each scenario. Separate analyses were performed for all PD cases and for only incident PD cases (i.e., PD diagnosed after the initial AHS enrollment). Table 3 summarizes the distribution of ORs from the first two sets of sensitivity analyses, where exposure status was reclassified for a fixed number (2, 4, or 6) or proportion (10% or 20%) of subjects. Results were fairly consistent with those of Tanner et al. (2011) (Table 3). The OR from the simulations ranged from as low as 1.5 up to 3.5, with a median of 2.2, if six subjects were misclassified. If 20% of the subjects were misclassified, the OR ranged from 1.0 up to 3.4, with a median of 1.7. In the analysis based on incident cases only, the OR ranged from 1.3 to 3.7 (median=2.3) if six subjects were misclassified, and from 0.8 to 3.9 (median=1.7) if 20% of subjects were misclassified. In general, lesser deviations from the OR of 2.5 reported by Tanner et al. (2011) were observed when a smaller number or proportion of subjects was misclassified.

Table 4 summarizes the simulation testing results from random reassignment of exposure status based on the proportion of proxy responses to questions about pesticide use in the FAME questionnaire. We also tested the impact of increasing the proportion of proxy responses by

adding 5% (total=11%) or 10% (total=16%) to the original 6% of subjects in the FAME study whose pesticide use was reported by a spouse or other family member. The median OR was 1.9 if the degree of misclassification was based on the actual proportion of the proxy responses (Table 4) and the median OR declined in concert with an increasing simulated proportion of proxy respondents.

Stratified and Other Alternative Analyses

To further evaluate the sensitivity of the ORs for the associations between paraquat exposure and PD risk in the FAME study, we tested a series of alternative models by using different subsets of the data or using alternative covariates as follows:

1. Separate analyses for incident and prevalent PD cases
2. Analyses stratified by state of residence at AHS entry (Iowa or North Carolina)
3. Analyses with additional covariates (e.g., family history of PD and education) in the logistic regression model (in addition to reference age [in tertiles], sex, state, cigarette smoking [ever/never], and pesticide use [ever/never], as modeled by Tanner et al. [2011])
4. Analyses of combinations of pesticide use. We investigated ever vs. never use of either paraquat or maneb, either paraquat or ziram, or any of the three pesticides (paraquat, maneb, or ziram). These analyses were undertaken to investigate potential synergistic effects of multiple pesticides because growers with multiple crops may use paraquat on certain crops and other pesticides on other crops.
5. Analyses with or without exposure reported by proxy respondents
6. Analyses with PD cases reclassified as to disease incidence or prevalence status. We determined disease incidence or prevalence status based on the AHS enrollment year and the duration of PD at the time of the FAME study. For example, if a subject was enrolled in the FAME study in 2002 and had reportedly had PD for 12 years at that time, then PD would have been initially diagnosed in 1990, before AHS enrollment. Therefore, we would classify this PD case as a prevalent PD case. Similarly, if another subject had reportedly had PD for 3 years at the time of FAME study enrollment in 2002, then we would have classified this case as an incident PD case, since the diagnosis would have occurred after the AHS enrollment period. Applying this logic, we determined that four PD cases labeled in the FAME dataset as prevalent should instead have been classified as

incident, whereas six PD cases originally identified as incident should instead have been classified as prevalent.

7. Analyses using an alternative exposure classification based on the additional pesticide use data from the AHS questionnaires to revise or impute FAME questionnaire data. For this alternative exposure classification, if a subject had reported using a pesticide in either of the earlier AHS questionnaires but had missing data for that pesticide in the FAME questionnaire data, then this subject would have been reclassified as ever exposed to that pesticide. In addition, if a subject had reported using a pesticide in either of the earlier AHS questionnaires but reported never having used that pesticide in the FAME questionnaire, then this subject would have been reclassified as ever exposed. Unfortunately the year of use of a pesticide was not included in the available dataset, so we could not evaluate the temporality of pesticide exposure, AHS enrollment, and PD diagnosis.

All of these analyses were conducted based on the assumption that any past exposure to paraquat occurred before PD diagnosis. Table 5 summarizes the results using various combinations of these seven approaches.

In the extended sensitivity analysis, using an alternative exposure classification that incorporated AHS data, but otherwise leaving the analysis unchanged, resulted in an OR of 2.0 as compared with the OR of 2.5 reported by Tanner et al. (2011) for ever vs. never paraquat exposure (Table 5). The OR for the alternative exposure classification remained in the range of 1.9-2.2 if proxy respondents were excluded, if family history and education were included as additional covariates in the logistic regression model, or if only incident cases were included.

Inclusion/exclusion of proxy respondents tended to have a minimal impact on the OR if all else remained constant. For example, if proxy respondents were excluded but the analysis was otherwise left unchanged from that of Tanner et al. (2011), the OR for ever vs. never paraquat exposure was 2.6. The majority of cases were incident, such that the results of the sensitivity analysis of only incident cases were similar those for both incident and prevalent cases. Due at least in part to the smaller number of cases, the results based on only prevalent cases were more variable, with the OR ranging from 2.2 to 3.3.

Table 6 summarizes the results of the same analyses restricted to Iowa pesticide applicators and their spouses, and Table 7 summarizes the results restricted to North Carolina pesticide applicators and their spouses. The ORs tended to be higher than 2.5 among Iowa residents if the original FAME exposure classification was used, but were somewhat lower than 2.5 if the alternative exposure classification was applied (Table 6). By contrast, among North Carolina residents, all ORs were less than 2.5, although the ORs tended to be slightly higher when using the alternative exposure classification compared with the original FAME exposure classification.

Across all sensitivity analyses, the ORs were generally lower for paraquat or maneb exposure, with the median OR ranging from 1.6 to 2.3 (Table 8). For paraquat or ziram exposure, the median OR ranged from 1.5 to 2.8 (Table 9); and for paraquat, maneb, or ziram exposure, the median OR ranged from 1.8 to 2.3 (Table 10). The OR tended to be lower when including the proxy responses for paraquat or ziram exposure than when excluding proxy data (Table 9).

Discussion

The FAME study clearly included a number of records with inconsistent exposure classification when compared with responses from the AHS questionnaires. Our analysis showed that 9% of responses for paraquat exposure were not consistent across questionnaires and 7% were missing (Table 1). We attempted to remedy both of these deficiencies by using paraquat exposure reported in earlier questionnaires. A number of PD cases were also misclassified as incident or prevalent. Despite these inaccuracies, the estimated association between ever vs. never use of paraquat and PD risk exhibited a degree of robustness, as demonstrated by the relative insensitivity of the OR to a number of alternative exposure cutoffs, classifications, and definitions, outcome classifications, and multivariate models tested in the reanalyses. When subjected to some artificially introduced exposure classification errors (Table 3), the resulting OR decreased only slightly from 2.5 to around 2.2 - 2.4, and did not drop below 2.0 until 10% of the records were reclassified. Even with 20% of the records randomly reclassified, the median OR from 1,000 iterations was 1.7.

The interpretation of associations with prevalent PD is problematic because reported exposure may have occurred after disease onset, because estimated associations may be influenced by the impact of exposure on disease survival instead of incidence, and because prevalent cases may not

be representative of all cases if patients with more severe disease were not enrolled in the AHS or FAME. Nevertheless, our separate analyses restricted to incident PD cases did not reveal dramatic differences in the magnitude of the estimated association with paraquat use (Table 5). However, we were limited to the data provided to us through the FOIA request as opposed to having access to the entire cohort database. Thus, we could not evaluate other potential control samples to assess the robustness of the findings.

The marked difference in the paraquat-PD association between Iowa and North Carolina participants in the FAME study received little attention in the Tanner et al. (2011) report. As shown in Tables 6 and 7, analyses stratified by state revealed a substantially weaker association among North Carolina participants than Iowa participants. It is known that the questionnaires presented challenges to a number of North Carolina participants due to their illiteracy.

Estimates of associations between PD risk and exposure to paraquat along with maneb and/or ziram did not reveal evidence of synergistic effects (Table 8, 9, and 10). On the contrary, the ORs for these combined pesticides tended to be lower than the corresponding ORs for paraquat exposure alone, and some were not statistically significant.

In summary, the extensive set of alternative analyses presented here shows that there is some degree of robustness in the estimated association between paraquat exposure and risk of PD in the FAME study, despite some inaccuracies and imprecision in the data. However, the precise magnitude of the OR was uncertain and the lower bound of many confidence intervals approached or included the null value of 1.0. Of note, the measure of paraquat exposure in the FAME study and in our reanalysis was crude, with exposure dichotomized as ever or never, with no accounting for either intensity or duration of use. As a result, firm conclusions cannot be drawn about the association between paraquat exposure and PD risk. Furthermore, given that many participants were occupationally exposed to multiple pesticides, it is difficult to isolate the effect of one particular chemical. And finally, the absence of the entire AHS dataset precluded any additional analyses which might clarify some of the results.

Table 1: Consistency in pesticide exposure reporting among the AHS enrollment questionnaire (1993-1997), the AHS follow-up questionnaire (1999-2003), and the FAME enrollment questionnaire (2002-2005).

Consistency of Reporting	Paraquat	Rotenone	Aldrin	DDT	Dieldrin	2,4-D	Trifluralin	Acifluorfen	Copper	Ferbam	Permethrin
Consistent	364 (77.8%)	191 (40.8%)	339 (72.4%)	309 (66.0%)	335 (71.6%)	380 (81.2%)	344 (73.5%)	175 (37.4%)	192 (41%)	187 (40%)	347 (74.1%)
New Exposure	28 (6.0%)	16 (3.4%)	29 (6.2%)	70 (15.0%)	24 (5.1%)	40 (8.5%)	36 (7.7%)	17 (3.6%)	17 (3.6%)	22 (4.7%)	35 (7.5%)
Inconsistent	43 (9.2%)	8 (1.7%)	57 (12.2%)	58 (12.4%)	47 (10.0%)	25 (5.3%)	38 (8.1%)	22 (4.7%)	4 (0.9%)	2 (0.4%)	33 (7.1%)
Missing	33 (7.1%)	253 (54.1%)	43 (9.2%)	31 (6.6%)	62 (13.3%)	23 (4.9%)	50 (10.7%)	254 (54.3%)	255 (54.5%)	257 (54.9%)	53 (11.3%)
Total	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)	468 (100.0%)

Table 2: Association of cumulative lifetime days of paraquat use with PD in men by varying cutoffs defined by percentiles among controls or cases.

		Unexposed		Below Cutoff			At or Above Cutoff			
Basis for Cutoff		**Cases**	**Controls**	**Cases**	**Controls**	**Odds Ratio vs. None (95% CI)**	**Cases**	**Controls**	**Odds Ratio vs. None (95% CI)**	**P-Value for Trend**
Controls	50th	47	207	10	23	2.4 (1.0-5.5)	13	23	3.6 (1.6-8.1)	<0.01
Controls	25th	47	207	7	16	2.1 (0.9-4.7)	16	33	3.5 (1.6-8.0)	0.01
Controls	33rd	47	207	7	17	2.4 (0.9-6.4)	16	32	2.8 (1.4-5.9)	0.01
Controls	66th	47	207	14	33	2.3 (0.9-6.0)	9	16	2.9 (1.4-6.0)	0.01
Controls	75th	47	207	19	38	2.3 (1.1-4.7)	4	11	3.8 (1.5-9.8)	0.01
Cases	25th	47	207	5	11	2.3 (0.7-7.2)	18	38	2.8 (1.4-5.6)	0.01
Cases	33rd	47	207	7	16	2.4 (0.9-6.4)	16	33	2.8 (1.4-5.9)	0.01
Cases	50th	47	207	9	21	2.3 (1.0-5.5)	14	28	3.0 (1.4-6.6)	0.01
Cases	66th	47	207	18	37	2.7 (1.3-5.2)	5	12	2.8 (0.9-9.1)	0.01
Cases	75th	47	207	19	37	2.8 (1.4-5.5)	4	12	2.2 (0.6-7.7)	0.01

Table 3: Random reassignment of exposure status of subjects per 1,000 replications for paraquat exposure and PD

Exposure		OR		**Range of OR from Simulated Exposure**					
Incident and Prevalent PD Cases									
Yes	No	Tanner et al. (2011) OR	Number or Percent Misclassified	Min	25th %	50th %	Mean	75th %	Max
72	372	**2.5**	2	2.0	2.2	**2.4**	2.4	2.5	3.1
72	372	**2.5**	4	1.6	2.2	**2.3**	2.3	2.5	3.3
72	372	**2.5**	6	1.5	2.0	**2.2**	2.3	2.4	3.5
72	372	**2.5**	10%	1.2	1.8	**2.0**	2.0	2.2	3.3
72	372	**2.5**	20%	1.0	1.5	**1.7**	1.7	1.9	3.4
Incident PD Cases Only									
62	336	**2.6**	2	1.8	2.2	**2.6**	2.5	2.6	3.6
62	336	**2.6**	4	1.3	2.2	**2.5**	2.4	2.6	4.1
62	336	**2.6**	6	1.3	2.1	**2.3**	2.3	2.6	3.7
62	336	**2.6**	10%	1.1	1.8	**2.1**	2.1	2.3	4.2
62	336	**2.6**	20%	0.8	1.5	**1.7**	1.8	2	3.9

Table 4: Proportional reassignment of exposure status of subjects per 1,000 replications for paraquat exposure and PD. Original proportion and 5% and 10% increases on the original proportion.

Exposure		**OR**	**Proxy % Misclassified**	**OR from Simulated Exposure**					
Yes	No	Tanner et al. (2011)	Increase	Min	25th %	50th %	Mean	75th %	Max
72	372	**2.5**	Original	1.3	1.7	**1.9**	2.0	2.1	3.4
72	372	**2.5**	+5%	1.0	1.5	**1.7**	1.7	1.9	3.3
72	372	**2.5**	+10%	0.8	1.3	**1.5**	1.5	1.7	3.2

Table 5: Sensitivity testing of ever vs. never paraquat exposure in association with PD in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Prevalent/Incident PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Excluded	No	Original	No	49 (14.3)	19 (25.3)	2.6 (1.3-5.0)	0.01
Both	Excluded	Yes	Original	No	49 (14.3)	19 (25.3)	2.7 (1.4-5.4)	<0.01
Both	Included	No	Original	No	49 (14.1)	23 (23.7)	2.5 (1.4-4.7)	<0.01
Both	Included	No	Historical	No	82 (23.4)	33 (33.0)	2.0 (1.1-3.4)	0.02
Both	Included	Yes	Original	No	49 (14.1)	23 (23.7)	2.7 (1.4-5.0)	<0.01
Both	Included	Yes	Historical	No	82 (23.4)	33 (33.0)	2.1 (1.2-3.7)	0.01
Both	Excluded	No	Historical	No	79 (22.9)	27 (35.1)	2.1 (1.2-3.9)	0.01
Both	Excluded	Yes	Historical	No	79 (22.9)	27 (35.1)	2.2 (1.2-4.1)	0.01
Incident	Excluded	No	Original	No	49 (14.5)	12 (25.0)	2.6 (1.2-5.8)	0.02
Incident	Excluded	Yes	Original	No	49 (14.5)	12 (25.0)	2.7 (1.2-6.1)	0.02
Incident	Included	No	Original	No	49 (14.3)	13 (23.2)	2.6 (1.2-5.6)	0.02
Incident	Included	No	Original	Yes	49 (14.1)	13 (24.5)	2.6 (1.2-5.7)	0.02
Incident	Included	Yes	Original	No	49 (14.3)	13 (23.2)	2.7 (1.2-5.9)	0.02
Incident	Included	Yes	Original	Yes	49 (14.1)	13 (24.5)	2.7 (1.2-6.0)	0.01

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Prevalent/Incident PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Included	No	Historical	No	82 (23.7)	18 (31.0)	1.9 (0.9-3.7)	0.08
Incident	Included	Yes	Historical	No	82 (23.7)	18 (31.0)	1.9 (0.9-3.9)	0.08
Incident	Excluded	No	Historical	No	79 (23.2)	16 (32.7)	2.0 (0.9-4.1)	0.07
Incident	Excluded	Yes	Historical	No	79 (23.2)	16 (32.7)	2.0 (0.9-4.2)	0.07
Prevalent	Excluded	No	Original	No	47 (16.5)	7 (25.9)	2.7 (0.9-7.6)	0.07
Prevalent	Excluded	Yes	Original	No	47 (16.5)	7 (25.9)	3.3 (1.1-10.)	0.03
Prevalent	Included	No	Original	No	49 (14.5)	10 (24.4)	2.5 (1.0-6.0)	0.04
Prevalent	Included	No	Original	Yes	49 (14.5)	10 (22.7)	2.4 (1.0-5.7)	0.05
Prevalent	Included	Yes	Original	No	49 (14.5)	10 (24.4)	2.8 (1.1-6.9)	0.03
Prevalent	Included	Yes	Original	Yes	49 (14.5)	10 (22.7)	2.7 (1.1-6.4)	0.03
Prevalent	Included	No	Historical	No	82 (23.9)	15 (35.7)	2.2 (1.0-4.8)	0.05
Prevalent	Included	Yes	Historical	No	82 (23.9)	15 (35.7)	2.3 (1.0-5.1)	0.04
Prevalent	Excluded	No	Historical	No	75 (26.2)	11 (39.3)	2.5 (0.9-6.3)	0.05
Prevalent	Excluded	Yes	Historical	No	75 (26.2)	11 (39.3)	2.7 (1.0-7.0)	0.04

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Table 6: Sensitivity testing of ever vs. never paraquat exposure in association with PD in Iowa residents in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Exclude	No	Original	No	24 (9.6)	14 (24.1)	3.6 (1.6-8.0)	<0.01
Both	Exclude	No	Historical	No	45 (17.8)	18 (31.0)	2.3 (1.1-4.7)	0.02
Both	Exclude	Yes	Original	No	24 (9.6)	14 (24.1)	4.1 (1.7-9.2)	<0.01
Both	Exclude	Yes	Historical	No	45 (17.8)	18 (31.0)	2.5 (1.2-5.0)	0.01
Both	Include	No	Original	No	24 (9.5)	16 (21.6)	3.3 (1.5-6.9)	<0.01
Both	Include	No	Historical	No	46 (18.0)	21 (28.4)	2.1 (1.1-4.0)	0.02
Both	Include	Yes	Original	No	24 (9.5)	16 (21.6)	3.7 (1.7-8.1)	<0.01
Both	Include	Yes	Historical	No	46 (18.0)	21 (28.4)	2.2 (1.1-4.3)	0.02
Incident	Exclude	No	Original	No	24 (9.6)	8 (22.9)	3.7 (1.3-9.7)	0.01
Incident	Exclude	No	Historical	No	45 (17.8)	10 (28.6)	2.3 (0.9-5.4)	0.06
Incident	Exclude	Yes	Original	No	24 (9.6)	8 (22.9)	3.8 (1.3-10.)	0.01
Incident	Exclude	Yes	Historical	No	45 (17.8)	10 (28.6)	2.2 (0.8-5.4)	0.09
Incident	Include	No	Original	No	24 (9.5)	9 (22.0)	3.6 (1.4-9.0)	0.01
Incident	Include	No	Original	Yes	24 (9.5)	8 (20.5)	3.3 (1.2-8.4)	0.02
Incident	Include	No	Historical	No	46 (18.0)	11 (26.8)	2.1 (0.9-4.7)	0.08
Incident	Include	Yes	Original	No	24 (9.5)	9 (22.0)	3.7 (1.3-9.6)	0.01

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Include	Yes	Original	Yes	24 (9.5)	8 (20.5)	3.3 (1.2-8.8)	0.02
Incident	Include	Yes	Historical	No	46 (18.0)	11 (26.8)	2.0 (0.8-4.7)	0.12
Prevalent	Exclude	No	Original	No	24 (10.8)	6 (26.1)	3.8 (1.2-1.9)	0.02
Prevalent	Exclude	No	Historical	No	45 (20.1)	8 (34.8)	2.7 (0.9-7.3)	0.05
Prevalent	Exclude	Yes	Original	No	24 (10.8)	6 (26.1)	6.0 (.73-1.1)	<0.01
Prevalent	Exclude	Yes	Historical	No	45 (20.1)	8 (34.8)	3.3 (1.1-9.2)	0.03
Prevalent	Include	No	Original	No	24 (9.5)	7 (21.2)	3.2 (1.1-8.9)	0.03
Prevalent	Include	No	Original	Yes	24 (9.5)	8 (22.9)	3.4 (1.2-9.1)	0.02
Prevalent	Include	No	Historical	No	46 (18.0)	10 (30.3)	2.4 (0.9-5.9)	0.06
Prevalent	Include	Yes	Original	No	24 (9.5)	7 (21.2)	4.1 (1.3-12.)	0.01
Prevalent	Include	Yes	Original	Yes	24 (9.5)	8 (22.9)	4.3 (1.5-12.)	0.01
Prevalent	Include	Yes	Historical	No	46 (18.0)	10 (30.3)	2.7 (1.0-6.6)	0.04

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Table 7: Sensitivity testing of ever vs. never paraquat exposure in association with PD in North Carolina residents in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Exclude	No	Original	No	25 (27.2)	5 (29.4)	1.3 (0.3-4.6)	0.67
Both	Exclude	No	Historical	No	34 (37.0)	9 (47.4)	1.9 (0.5-6.1)	0.32
Both	Exclude	Yes	Original	No	25 (27.2)	5 (29.4)	1.3 (0.3-4.7)	0.67
Both	Exclude	Yes	Historical	No	34 (37.0)	9 (47.4)	1.9 (0.5-6.2)	0.32
Both	Include	No	Original	No	25 (26.6)	7 (30.4)	1.6 (0.5-5.1)	0.40
Both	Include	No	Historical	No	36 (37.9)	12 (46.2)	2.0 (0.6-5.9)	0.22
Both	Include	Yes	Original	No	25 (26.6)	7 (30.4)	1.6 (0.5-5.1)	0.40
Both	Include	Yes	Historical	No	36 (37.9)	12 (46.2)	2.0 (0.6-6.0)	0.22
Incident	Exclude	No	Original	No	25 (28.7)	4 (30.8)	1.5 (0.3-6.5)	0.55
Incident	Exclude	No	Historical	No	34 (39.1)	6 (42.9)	1.8 (0.4-6.9)	0.42
Incident	Exclude	Yes	Original	No	25 (28.7)	4 (30.8)	1.6 (0.3-6.8)	0.52
Incident	Exclude	Yes	Historical	No	34 (39.1)	6 (42.9)	1.8 (0.4-7.1)	0.42
Incident	Include	No	Original	No	25 (28.1)	4 (26.7)	1.6 (0.3-6.5)	0.54
Incident	Include	No	Original	Yes	25 (26.6)	5 (35.7)	2.0 (0.5-8.0)	0.30
Incident	Include	No	Historical	No	36 (40.0)	7 (41.2)	1.9 (0.5-7.2)	0.35
Incident	Include	Yes	Original	No	25 (28.1)	4 (26.7)	1.6 (0.3-6.8)	0.52

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Include	Yes	Original	Yes	25 (26.6)	5 (35.7)	2.1 (0.5-8.4)	0.29
Incident	Include	Yes	Historical	No	36 (40.0)	7 (41.2)	1.9 (0.5-7.4)	0.34
Prevalent	Exclude	No	Original	No	23 (37.1)	1 (25.0)	0.6 (0.0-7.9)	0.71
Prevalent	Excluded	No	Historical	No	30 (48.4)	3 (60.0)	2.0 (0.1-22.)	0.58
Prevalent	Excluded	Yes	Original	No	23 (37.1)	1 (25.0)	0.6 (0.0-7.9)	0.71
Prevalent	Excluded	Yes	Historical	No	30 (48.4)	3 (60.0)	1.9 (0.1-23.)	0.60
Prevalent	Included	No	Original	No	25 (29.1)	3 (37.5)	1.8 (0.3-10.)	0.49
Prevalent	Included	No	Original	Yes	25 (29.1)	2 (22.2)	1.2 (0.1-8.1)	0.82
Prevalent	Included	No	Historical	No	36 (41.4)	5 (55.6)	2.2 (0.3-12.)	0.38
Prevalent	Included	Yes	Original	No	25 (29.1)	3 (37.5)	1.8 (0.3-10.)	0.49
Prevalent	Included	Yes	Original	Yes	25 (29.1)	2 (22.2)	1.2 (0.1-8.3)	0.82
Prevalent	Included	Yes	Historical	No	36 (41.4)	5 (55.6)	2.2 (0.3-12.)	0.38

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Table 8: Sensitivity testing of ever vs. never paraquat or maneb exposure in association with PD in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Excluded	No	Original	No	51 (14.5)	19 (23.2)	2.0 (1.0-3.8)	0.03
Both	Excluded	No	Historical	No	51 (14.5)	19 (23.2)	2.0 (1.0-3.8)	0.03
Both	Excluded	Yes	Original	No	51 (14.5)	19 (23.2)	2.2 (1.1-4.2)	0.02
Both	Excluded	Yes	Historical	No	51 (14.5)	19 (23.2)	2.2 (1.1-4.2)	0.02
Both	Included	No	Original	No	52 (14.5)	23 (20.9)	1.8 (0.9-3.2)	0.06
Both	Included	No	Historical	No	52 (14.5)	23 (20.9)	1.8 (0.9-3.2)	0.06
Both	Included	Yes	Original	No	52 (14.5)	23 (20.9)	1.9 (1.0-3.5)	0.03
Both	Included	Yes	Historical	No	52 (14.5)	23 (20.9)	1.9 (1.0-3.5)	0.03
Incident	Excluded	No	Original	No	51 (14.7)	12 (23.5)	2.2 (0.9-4.7)	0.06
Incident	Excluded	No	Historical	No	51 (14.7)	12 (23.5)	2.2 (0.9-4.7)	0.06
Incident	Excluded	Yes	Original	No	51 (14.7)	12 (23.5)	2.3 (1.0-5.0)	0.05
Incident	Excluded	Yes	Historical	No	51 (14.7)	12 (23.5)	2.3 (1.0-5.0)	0.05
Incident	Included	No	Original	No	52 (14.7)	13 (21.7)	2.0 (0.9-4.2)	0.07
Incident	Included	No	Original	Yes	52 (14.5)	13 (22.4)	2.0 (0.9-4.2)	0.07
Incident	Included	No	Historical	No	52 (14.7)	13 (21.7)	2.0 (0.9-4.2)	0.07
Incident	Included	Yes	Original	No	52 (14.7)	13 (21.7)	2.1 (0.9-4.5)	0.06

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Included	Yes	Original	Yes	52 (14.5)	13 (22.4)	2.1 (0.9-4.4)	0.06
Incident	Included	Yes	Historical	No	52 (14.7)	13 (21.7)	2.1 (0.9-4.5)	0.06
Prevalent	Excluded	No	Original	No	47 (16.2)	7 (22.6)	1.9 (0.7-5.1)	0.21
Prevalent	Excluded	No	Historical	No	47 (16.2)	7 (22.6)	1.9 (0.7-5.1)	0.21
Prevalent	Excluded	Yes	Original	No	47 (16.2)	7 (22.6)	2.3 (0.8-6.4)	0.12
Prevalent	Excluded	Yes	Historical	No	47 (16.2)	7 (22.6)	2.3 (0.8-6.4)	0.12
Prevalent	Included	No	Original	No	51 (14.6)	10 (20.0)	1.6 (0.6-3.6)	0.27
Prevalent	Included	No	Original	Yes	51 (14.6)	10 (19.2)	1.6 (0.7-3.5)	0.27
Prevalent	Included	No	Historical	No	51 (14.6)	10 (20.0)	1.6 (0.6-3.6)	0.27
Prevalent	Included	Yes	Original	No	51 (14.6)	10 (20.0)	1.8 (0.7-4.2)	0.17
Prevalent	Included	Yes	Original	Yes	51 (14.6)	10 (19.2)	1.8 (0.7-4.2)	0.16
Prevalent	Included	Yes	Historical	No	51 (14.6)	10 (20.0)	1.8 (0.7-4.2)	0.17

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Table 9: Sensitivity testing of ever vs. never paraquat or ziram exposure in association with PD in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Excluded	No	Original	No	46 (13.1)	19 (23.2)	2.3 (1.1-4.3)	0.01
Both	Excluded	No	Historical	No	46 (13.1)	19 (23.2)	2.3 (1.1-4.3)	0.01
Both	Excluded	Yes	Original	No	46 (13.1)	19 (23.2)	2.5 (1.2-4.9)	0.01
Both	Excluded	Yes	Historical	No	46 (13.1)	19 (23.2)	2.5 (1.2-4.9)	0.01
Both	Included	No	Original	No	46 (12.8)	21 (19.1)	1.8 (0.9-3.3)	0.05
Both	Included	No	Historical	No	46 (12.8)	21 (19.1)	1.8 (0.9-3.3)	0.05
Both	Included	Yes	Original	No	46 (12.8)	21 (19.1)	2.1 (1.1-3.9)	0.02
Both	Included	Yes	Historical	No	46 (12.8)	21 (19.1)	2.1 (1.1-3.9)	0.02
Incident	Excluded	No	Original	No	46 (13.3)	12 (23.5)	2.5 (1.1-5.5)	0.02
Incident	Excluded	No	Historical	No	46 (13.3)	12 (23.5)	2.5 (1.1-5.5)	0.02
Incident	Excluded	Yes	Original	No	46 (13.3)	12 (23.5)	2.8 (1.2-6.2)	0.02
Incident	Excluded	Yes	Historical	No	46 (13.3)	12 (23.5)	2.8 (1.2-6.2)	0.02
Incident	Included	No	Original	No	46 (13.0)	12 (20.0)	2.2 (1.0-4.8)	0.04
Incident	Included	No	Original	Yes	46 (12.8)	12 (20.7)	2.2 (1.0-4.8)	0.05
Incident	Included	No	Historical	No	46 (13.0)	12 (20.0)	2.2 (1.0-4.8)	0.04
Incident	Included	Yes	Original	No	46 (13.0)	12 (20.0)	2.4 (1.0-5.3)	0.03

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Included	Yes	Original	Yes	46 (12.8)	12 (20.7)	2.4 (1.0-5.2)	0.04
Incident	Included	Yes	Historical	No	46 (13.0)	12 (20.0)	2.4 (1.0-5.3)	0.03
Prevalent	Excluded	No	Original	No	45 (15.5)	7 (22.6)	2.0 (0.7-5.5)	0.16
Prevalent	Excluded	No	Historical	No	45 (15.5)	7 (22.6)	2.0 (0.7-5.5)	0.16
Prevalent	Excluded	Yes	Original	No	45 (15.5)	7 (22.6)	2.4 (0.8-6.9)	0.09
Prevalent	Excluded	Yes	Historical	No	45 (15.5)	7 (22.6)	2.4 (0.8-6.9)	0.09
Prevalent	Included	No	Original	No	46 (13.1)	9 (18.0)	1.5 (0.6-3.6)	0.33
Prevalent	Included	No	Original	Yes	46 (13.1)	9 (17.3)	1.5 (0.6-3.5)	0.33
Prevalent	Included	No	Historical	No	46 (13.1)	9 (18.0)	1.5 (0.6-3.6)	0.33
Prevalent	Included	Yes	Original	No	46 (13.1)	9 (18.0)	1.8 (0.7-4.3)	0.18
Prevalent	Included	Yes	Original	Yes	46 (13.1)	9 (17.3)	1.8 (0.7-4.3)	0.17
Prevalent	Included	Yes	Historical	No	46 (13.1)	9 (18.0)	1.8 (0.7-4.3)	0.18

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Table 10: Sensitivity testing of ever vs. never paraquat, maneb, or ziram exposure in association with PD in the FAME study

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Both	Excluded	No	Original	No	51 (14.5)	19 (23.2)	2.0 (1.0-3.8)	0.03
Both	Excluded	No	Historical	No	51 (14.5)	19 (23.2)	2.0 (1.0-3.8)	0.03
Both	Excluded	Yes	Original	No	51 (14.5)	19 (23.2)	2.2 (1.1-4.2)	0.02
Both	Excluded	Yes	Historical	No	51 (14.5)	19 (23.2)	2.2 (1.1-4.2)	0.02
Both	Included	No	Original	No	52 (14.5)	23 (20.9)	1.8 (0.9-3.2)	0.06
Both	Included	No	Historical	No	52 (14.5)	23 (20.9)	1.8 (0.9-3.2)	0.06
Both	Included	Yes	Original	No	52 (14.5)	23 (20.9)	1.9 (1.0-3.5)	0.03
Both	Included	Yes	Historical	No	52 (14.5)	23 (20.9)	1.9 (1.0-3.5)	0.03
Incident	Excluded	No	Original	No	51 (14.7)	12 (23.5)	2.2 (0.9-4.7)	0.06
Incident	Excluded	No	Historical	No	51 (14.7)	12 (23.5)	2.2 (0.9-4.7)	0.06
Incident	Excluded	Yes	Original	No	51 (14.7)	12 (23.5)	2.3 (1.0-5.0)	0.05
Incident	Excluded	Yes	Historical	No	51 (14.7)	12 (23.5)	2.3 (1.0-5.0)	0.05
Incident	Included	No	Original	No	52 (14.7)	13 (21.7)	2.0 (0.9-4.2)	0.07
Incident	Included	No	Original	Yes	52 (14.5)	13 (22.4)	2.0 (0.9-4.2)	0.07
Incident	Included	No	Historical	No	52 (14.7)	13 (21.7)	2.0 (0.9-4.2)	0.07
Incident	Included	Yes	Original	No	52 (14.7)	13 (21.7)	2.1 (0.9-4.5)	0.06

Prevalent or Incident PD	Proxy Respondent	Additional Covariates*	Exposure Classification**	Alternative Incident/Prevalent PD***	Controls (%)	Cases (%)	OR (95% CI)	P-value
Incident	Included	Yes	Original	Yes	52 (14.5)	13 (22.4)	2.1 (0.9-4.4)	0.06
Incident	Included	Yes	Historical	No	52 (14.7)	13 (21.7)	2.1 (0.9-4.5)	0.06
Prevalent	Excluded	No	Original	No	47 (16.2)	7 (22.6)	1.9 (0.7-5.1)	0.21
Prevalent	Excluded	No	Historical	No	47 (16.2)	7 (22.6)	1.9 (0.7-5.1)	0.21
Prevalent	Excluded	Yes	Original	No	47 (16.2)	7 (22.6)	2.3 (0.8-6.4)	0.12
Prevalent	Excluded	Yes	Historical	No	47 (16.2)	7 (22.6)	2.3 (0.8-6.4)	0.12
Prevalent	Included	No	Original	No	51 (14.6)	10 (20.0)	1.6 (0.6-3.6)	0.27
Prevalent	Included	No	Original	Yes	51 (14.6)	10 (19.2)	1.6 (0.7-3.5)	0.27
Prevalent	Included	No	Historical	No	51 (14.6)	10 (20.0)	1.6 (0.6-3.6)	0.27
Prevalent	Included	Yes	Original	No	51 (14.6)	10 (20.0)	1.8 (0.7-4.2)	0.17
Prevalent	Included	Yes	Original	Yes	51 (14.6)	10 (19.2)	1.8 (0.7-4.2)	0.16
Prevalent	Included	Yes	Historical	No	51 (14.6)	10 (20.0)	1.8 (0.7-4.2)	0.17

*Additional covariates were family history of PD and education.
**"Historical" is the alternative exposure classification based on the questionnaire history.
***"Alternative prevalent/incident PD" is based on using the calculated relative diagnosis year to determine prevalent versus incident PD cases.

Appendix 1. Contents of the September 2012 NIH dataset for the FAME study

	Name	Type	Len	Format	Label
1	NIEHSID	Char	10		FAME Pseudo ID Number
2	fameCC	Num	8	CC.	Case status
3	pd_phaseI	Num	8	PDPIF.	Phase I PD status among FAME cases
4	refageT	Num	8	AGET_F.	Reference age
5	IsMale	Num	8	ISMALE.	Is male
6	stateIsIA	Num	8	STATEISIA.	State
7	vital_status	Num	8	YES_NO.	Died < FAME enrollment
8	AHSEnrollYear	Num	8		Year enrolled in AHS
9	FAMEnrollYear	Num	8		Year enrolled in FAME
10	yrs_dxToFAME_cat	Num	8	DXF_F.	Yrs from PD dx to FAME enrollmt or death
11	hasFHPD	Num	8	YN_F.	family history of PD in 1st degree relative
12	ever100cig	Num	8	YN_F.	Ever smoked 100+ cigs (< FAME ref yr, else < AHS E/S qx)
13	CASI_S1	Num	8		CASI total Score raw
14	olfscore	Num	8		BSIT total score
15	yrs_dxToFAME	Num	8		Yrs from PD dx to FAME enrollmt or death
16	educgtHS	Num	8	ED_C.	Highest education > HS (L2-L3c, then E5/S5)
17	resttrem	Num	8		Resting tremor (0-no sign, 0.5-questionable, 1-sign)
18	bradyk	Num	8		Bradykinesia (0-no sign, 0.5-questionable, 1-sign)
19	rigid	Num	8		Rigidity (0-no sign, 0.5-questionable, 1-sign)
20	posrefl	Num	8		Postural reflex impairmt (0-no sign, 0.5-questionable, 1-sign)
21	asymm	Num	8		Asymmetric onset (0-no sign, 0.5-questionable, 1-sign)
22	respLdopa	Num	8		Response to L-dopa (0-no sign, 0.5-questionable, 1-sign)
23	IfProxy_pest	Num	8	YN_F.	Proxy informant used
24	everOxidStress	Num	8	YN_F.	Ever used a FAME oxidative stressor < ref yr
25	everComplexIinhib	Num	8	YN_F.	Ever used a FAME Complex I inhibitor < ref yr
26	everFm9a1	Num	8	YN_F.	Ever used 2,4-D < ref yr
27	everFm9a2	Num	8	YN_F.	Ever used Aldrin < ref yr

28	everFm9a3	Num	8	YN_F.	Ever used Benomyl, etc. < ref yr
29	everFm9a4	Num	8	YN_F.	Ever used Acifluorfen, etc. < ref yr
30	everFm9a5	Num	8	YN_F.	Ever used Carbendazim, etc. < ref yr
31	everFm9a6	Num	8	YN_F.	Ever used Carbon disulfide < ref yr
32	everFm9a7	Num	8	YN_F.	Ever used Chloranil < ref yr
33	everFm9a8	Num	8	YN_F.	Ever used Copper compounds < ref yr
34	everFm9a9	Num	8	YN_F.	Ever used Cyanides < ref yr
35	everFm9a10	Num	8	YN_F.	Ever used Cyhalothrin, etc. < ref yr
36	everFm9a11	Num	8	YN_F.	Ever used DDT < ref yr
37	everFm9a12	Num	8	YN_F.	Ever used Dichlone < ref yr
38	everFm9a13	Num	8	YN_F.	Ever used Dieldrin < ref yr
39	everFm9a14	Num	8	YN_F.	Ever used Diquat < ref yr
40	everFm9a15	Num	8	YN_F.	Ever used Ferbam, carbamate < ref yr
41	everFm9a16	Num	8	YN_F.	Ever used Mancozeb, etc. < ref yr
42	everFm9a17	Num	8	YN_F.	Ever used Maneb, Manex < ref yr
43	everFm9a18	Num	8	YN_F.	Ever used Mercury compounds < ref yr
44	everFm9a19	Num	8	YN_F.	Ever used Metam-sodium, etc. < ref yr
45	everFm9a20	Num	8	YN_F.	Ever used Paraquat < ref yr
46	everFm9a21	Num	8	YN_F.	Ever used Parathion methyl < ref yr
47	everFm9a22	Num	8	YN_F.	Ever used Permethrin, etc. < ref yr
48	everFm9a23	Num	8	YN_F.	Ever used Pybuthrin, etc. < ref yr
49	everFm9a24	Num	8	YN_F.	Ever used Pyridaben, etc. < ref yr
50	everFm9a25	Num	8	YN_F.	Ever used Rotenone, etc. < ref yr
51	everFm9a26	Num	8	YN_F.	Ever used Thiabendazole, etc. < ref yr
52	everFm9a27	Num	8	YN_F.	Ever used Thiram < ref yr
53	everFm9a28	Num	8	YN_F.	Ever used Trifluralin, etc. < ref yr
54	everFm9a29	Num	8	YN_F.	Ever used Vegadex, etc. < ref yr
55	everFm9a30	Num	8	YN_F.	Ever used Zineb, etc. < ref yr
56	everFm9a31	Num	8	YN_F.	Ever used Ziram, etc. < ref yr
57	fm9sumDays1	Num	8		Days used 2,4-D < ref yr
58	fm9sumDays4	Num	8		Days used Acifluorfen, etc. < ref yr

59	fm9sumDays2	Num	8		Days used Aldrin < ref yr
60	fm9sumDays8	Num	8		Days used Copper compounds < ref yr
61	fm9sumDays11	Num	8		Days used DDT < ref yr
62	fm9sumDays13	Num	8		Days used Dieldrin < ref yr
63	fm9sumDays15	Num	8		Days used Ferbam, carbamate < ref yr
64	fm9sumDays20	Num	8		Days used Paraquat < ref yr
65	fm9sumDays22	Num	8		Days used Permethrin, etc. < ref yr
66	fm9sumDays25	Num	8		Days used Rotenone, etc. < ref yr
67	fm9sumDays28	Num	8		Days used Trifluralin, etc. < ref yr
68	Fm9SumDaysR1_G3	Num	8	G3_F.	2,4-D: days exposed (none, <=, > median)
69	Fm9SumDaysR4_G3	Num	8	G3_F.	Acifluorfen, etc.: days exposed (none, <=, > median)
70	Fm9SumDaysR2_G3	Num	8	G3_F.	Aldrin: days exposed ((none, <=, > median)
71	Fm9SumDaysR8_G3	Num	8	G3_F.	Copper compounds: days exposed (none, <=, > median)
72	Fm9SumDaysR11_G3	Num	8	G3_F.	DDT: days exposed (none, <=, > median)
73	Fm9SumDaysR13_G3	Num	8	G3_F.	Dieldrin: days exposed (none, <=, > median)
74	Fm9SumDaysR15_G3	Num	8	G3_F.	Ferbam: days exposed (none, <=, > median)
75	Fm9SumDaysR20_G3	Num	8	G3_F.	Paraquat: days exposed (none, <=, > median)
76	Fm9SumDaysR22_G3	Num	8	G3_F.	Permethrin: days exposed (none, <=, > median)
77	Fm9SumDaysR25_G3	Num	8	G3_F.	Rotenone: days exposed (none, <=, > median)
78	Fm9SumDaysR28_G3	Num	8	G3_F.	Trifluralin, etc.: days exposed (none, <=, > median)
79	fm9sumDays1m	Num	8		males only:Days used 2,4-D < ref yr
80	fm9sumDays4m	Num	8		males only:Days used Acifluorfen, etc. < ref yr
81	fm9sumDays2m	Num	8		males only:Days used Aldrin < ref yr
82	fm9sumDays8m	Num	8		males only:Days used Copper compounds < ref yr
83	fm9sumDays11m	Num	8		males only:Days used DDT < ref yr
84	fm9sumDays13m	Num	8		males only:Days used Dieldrin < ref yr
85	fm9sumDays15m	Num	8		males only:Days used Ferbam, carbamate < ref yr
86	fm9sumDays20m	Num	8		males only:Days used Paraquat < ref yr
87	fm9sumDays22m	Num	8		males only:Days used Permethrin, etc. < ref yr
88	fm9sumDays25m	Num	8		males only:Days used Rotenone, etc. < ref yr
89	fm9sumDays28m	Num	8		males only:Days used Trifluralin, etc. < ref yr

90	fm9sumYrsMed1	Num	8		Est yrs used 2,4-D (median)
91	fm9sumYrsMed2	Num	8		Est yrs used Aldrin (median)
92	fm9sumYrsMed4	Num	8		Est yrs used Blazer, etc. (median)
93	fm9sumYrsMed8	Num	8		Est yrs used Copper compounds (median)
94	fm9sumYrsMed11	Num	8		Est yrs used DDT (median)
95	fm9sumYrsMed13	Num	8		Est yrs used Dieldrin (median)
96	fm9sumYrsMed15	Num	8		Est yrs used Ferbam, carbamate (median)
97	fm9sumYrsMed20	Num	8		Est yrs used Paraquat (median)
98	fm9sumYrsMed22	Num	8		Est yrs used Permethrin, etc. (median)
99	fm9sumYrsMed25	Num	8		Est yrs used Rotenone, etc. (median)
100	fm9sumYrsMed28	Num	8		Est yrs used Trifluralin, etc. (median)
101	fm9sumYrsMed1_G3	Num	8	G3_F.	fm9sumYrsMed1: 2,4-D exposure (none, <=, > median)
102	fm9sumYrsMed2_G3	Num	8	G3_F.	fm9sumYrsMed2: Aldrin exposure (none, <=, > median)
103	fm9sumYrsMed4_G3	Num	8	G3_F.	fm9sumYrsMed4: Blazer, etc.exposure (none, <=, > median)
104	fm9sumYrsMed8_G3	Num	8	G3_F.	fm9sumYrsMed8: Copper compounds exposure (none, <=, > median)
105	fm9sumYrsMed11_G3	Num	8	G3_F.	fm9sumYrsMed11: DDT exposure (none, <=, > median)
106	fm9sumYrsMed13_G3	Num	8	G3_F.	fm9sumYrsMed13: Dieldrin exposure (none, <=, > median)
107	fm9sumYrsMed15_G3	Num	8	G3_F.	fm9sumYrsMed15: Ferbam, carbamate exposure (none, <=, > median)
108	fm9sumYrsMed20_G3	Num	8	G3_F.	fm9sumYrsMed20: Paraquat exposure (none, <=, > median)
109	fm9sumYrsMed22_G3	Num	8	G3_F.	fm9sumYrsMed22: Permethrin, etc. exposure (none, <=, > median)
110	fm9sumYrsMed25_G3	Num	8	G3_F.	fm9sumYrsMed25: Rotenone, etc. exposure (none, <=, > median)
111	fm9sumYrsMed28_G3	Num	8	G3_F.	fm9sumYrsMed28: Trifluralin, etc. exposure (none, <=, > median)
112	eEver2_4D	Num	3	_NOYES.	2,4-D ever (Ap,Sp)
113	eYears2_4D	Num	8	_HRBYRE.	2,4-D yrs (Ap)
114	eDays2_4D	Num	8	_HRBDAY.	2,4-D dpy (Ap)
115	eLifeTimeDays2_4D	Num	8		2,4-D lifetime days (Ap)
116	eLTDCat2_4D	Num	8	PEST4XA.	2,4-D lifetime days (Ap)
117	fEverAcifluorfen	Num	3	_NOYES.	acifluorfen ever (Ap)
118	eEverAldrin	Num	3	_NOYES.	aldrin ever (Ap,Sp)
119	fEverAldrin	Num	3	_NOYES.	aldrin ever TH (Ap)
120	fYearsAldrin	Num	8	_HRBYRF.	aldrin yrs (Ap)

121	fDaysAldrin	Num	8	_HRBDAY.	aldrin dpy (Ap)
122	fLifeTimeDaysAldrin	Num	8		aldrin lifetime days (Ap)
123	fLTDCatAldrin	Num	8	PEST4XA.	aldrin lifetime days (Ap)
124	fEverCopper	Num	8	_NOYES.	copper ever (Ap)
125	eEverDDT	Num	3	_NOYES.	DDT ever (Ap,Sp)
126	fEverDDT	Num	3	_NOYES.	DDT ever TH (Ap)
127	fYearsDDT	Num	8	_HRBYRF.	DDT yrs (Ap)
128	fDaysDDT	Num	8	_HRBDAY.	DDT dpy (Ap)
129	fLifeTimeDaysDDT	Num	8		DDT lifetime days (Ap)
130	fLTDCatDDT	Num	8	PEST4XA.	DDT lifetime days (Ap)
131	eEverDieldrin	Num	3	_NOYES.	dieldrin ever (Ap,Sp)
132	fEverDieldrin	Num	3	_NOYES.	dieldrin ever TH (Ap)
133	fYearsDieldrin	Num	8	_HRBYRF.	dieldrin yrs (Ap)
134	fDaysDieldrin	Num	8	_HRBDAY.	dieldrin dpy (Ap)
135	fLifeTimeDaysDieldrin	Num	8		dieldrin lifetime days (Ap)
136	fLTDCatDieldrin	Num	8	PEST3XA.	dieldrin lifetime days (Ap)
137	fEverFerbam	Num	3	_NOYES.	ferbam ever (Ap)
138	eEverParaquat	Num	3	_NOYES.	Paraquat ever (Ap,Sp)
139	fEverParaquat	Num	3	_NOYES.	Paraquat ever TH (Ap)
140	fYearsParaquat	Num	8	_HRBYRF.	Paraquat yrs (Ap)
141	fDaysParaquat	Num	8	_HRBDAY.	Paraquat dpy (Ap)
142	fLifeTimeDaysParaquat	Num	8		Paraquat lifetime days (Ap)
143	fLTDCatParaquat	Num	8	PEST4XA.	Paraquat lifetime days (Ap)
144	eEverPermethrin	Num	8	_NOYES.	permethrin ever (Ap,Sp)
145	e1EverPermethrin	Num	3	_NOYES.	permethrin crops ever (Ap,Sp)
146	e1YearsPermethrin	Num	8	_HRBYRE.	permethrin crops yrs (Ap)
147	e1DaysPermethrin	Num	8	_HRBDAY.	permethrn crops dpy (Ap)
148	e1LifeTimeDaysPermethrin	Num	8		permethrin crops lifetime days (Ap)
149	e1LTDCatPermethrin	Num	8	PEST4XA.	permethrin crops lifetime days (Ap)
150	e2EverPermethrin	Num	3	_NOYES.	permethrin animals ever (Ap,Sp)
151	e2YearsPermethrin	Num	8	_HRBYRE.	permethrin animals yrs (Ap)

152	e2DaysPermethrin	Num	8	_HRBDAY.	permethrin animals dpy (Ap)
153	e2LifeTimeDaysPermethrin	Num	8		permethrin animals lifetime days (Ap)
154	e2LTDCatPermethrin	Num	8	PEST4XA.	permethrin animals lifetime days (Ap)
155	fEverRotenone	Num	8	_NOYES.	rotenone ever (Ap)
156	eEverTrifluralin	Num	3	_NOYES.	trifluralin ever (Ap,Sp)
157	eYearsTrifluralin	Num	8	_HRBYRE.	trifluralin yrs (Ap)
158	eDaysTrifluralin	Num	8	_HRBDAY.	triflualin dpy (Ap)
159	eLifeTimeDaysTrifluralin	Num	8		trifluralin lifetime days (Ap)
160	eLTDCatTrifluralin	Num	8	PEST4XA.	trifluralin lifetime days (Ap)