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Phorate Exposure and Incidence of Cancer in the Agricultural Health Study

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Abbreviations

2,4,5 TP: 2,4,5 trichlorophenoxy propionic acid

AHS: Agricultural Health Study

CI: 95% Confidence Interval

NHL: non-Hodgkin's lymphoma

OR: Odds Ratio

PPE: Personal Protective Equipment

Ref: Reference

RR: Rate Ratio

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Abstract

Background: We recently reported a link between use of the organophosphate pesticide, phorate, and risk of prostate cancer among applicators with a family history of prostate cancer in the Agricultural Health Study (AHS). *Objective:* This finding, together with findings of associations between other organophosphate pesticides and cancer more broadly, prompted us to examine phorate exposure and overall cancer incidence in the AHS. Adding 3 years of follow-up and using more detailed exposure information allowed us to see if the prostate cancer finding held. *Methods:* The AHS is a prospective study of licensed restricted use pesticide applicators from North Carolina and Iowa. To our knowledge, this is the largest examination of workers occupationally exposed to phorate. Pesticide exposure and other information was collected using two self-administered questionnaires completed from 1993 to 1997. Poisson regression was used to calculate rate ratios (RR) and 95% confidence intervals (CI), adjusting for potential confounders. *Results:* Phorate use was not related to the incidence of all cancers combined or to any individual cancer, although we had insufficient numbers to study non-Hodgkin's lymphoma or leukemia, which have been linked to organophosphates in other studies. While prostate cancer risk was not significantly related to phorate use overall or among those without a family history, the risk tended to increase among applicators with a family history of prostate cancer. The interaction RR was 1.53 (CI = 0.99-2.37). *Conclusion:* The observed statistical interaction suggests a gene-environment interaction between family history and phorate exposure in the incidence of prostate cancer but other explanations are also possible.

Introduction

Phorate (O,O-diethyl S[(ethylthio)methyl]phosphorothioate, trade-name: thimet) is an organophosphate compound used agriculturally, primarily in the production of corn, cotton, and potatoes to control sap feeding insects including various beetles, mites, grubs, and worms. There are no registered residential uses. Phorate was first registered for use in the U.S. in 1959 (U.S.EPA 2001). In the U.S., almost 2.5 million acres are treated annually with 2-3 million pounds of phorate, making it the sixth most common organophosphate used (Donaldson D et al. 2002).

The currently limited body of literature does not provide evidence to suggest that phorate is mutagenic, genotoxic or carcinogenic (Bingham E et al. 2001; CDPR 1996; Lin et al. 1987; Pandita 1986). However, several epidemiologic studies have found associations between exposure to organophosphate pesticides and non-Hodgkin's lymphoma (NHL) (Cantor et al. 1992; Zahm et al. 1993) as well as leukemia (Brown et al. 1990; Clavel et al. 1996), and the International Agency for Research on Cancer considers insecticide application to be an exposure that is probably carcinogenic in humans (Group 2A) (IARC 1991). Recent findings from the Agricultural Health Study linking lung cancer with exposure to diazinon and chlorpyrifos (Alavanja et al. 2004) and prostate cancer with exposure to chlorpyrifos, coumaphos, fonofos, and phorate among applicators with a family history of prostate cancer (Alavanja et al. 2003) prompted us to examine risk for all cancers among phorate users in the same cohort over a longer follow-up period. The aforementioned insecticides belong to the organothiophosphate subgroup, are similar to phorate in chemical structure, and must be converted in the body to their bioactive, neurotoxic oxon forms which irreversibly inhibit acetylcholine esterase by phosphorylating a serine hydroxyl group in the active site of the enzyme (Pope 1999; Sultatos 1994). Little is

known of the carcinogenicity of the oxon species. To our knowledge, this is the largest epidemiological examination of an occupational group exposed to phorate.

Methods

Cohort Enrollment and Follow-Up

The Agricultural Health Study (AHS) has been described elsewhere (Alavanja et al. 1996). It is a prospective cohort including 52,395 private applicators (farmers) from Iowa and North Carolina and 4,916 commercial applicators (employees of pest control companies or persons who apply pesticides as employees of businesses whose primary function is not pesticide application) from Iowa licensed to apply restricted use pesticides (82.4% of eligible applicators). Incident tumors diagnosed between enrollment (December 31, 1993 to December 31, 1997) and December 31, 2002 were identified using population-based tumor registries of both states. Subjects were censored in the year they moved out of the state, as determined by an extensive search of address records, or the year they died, as determined using the National Death Index and state death registry records. Less than 2% of the cohort was lost to follow-up. The average follow-up time of 7.5 years represents an increase of 3.2 years over the previously published prostate cancer paper. All participants provided informed consent and the protocol was approved by all appropriate Institutional Review Boards.

Exposure Assessment

Applicators were given two self-administered questionnaires upon enrollment. The enrollment questionnaire collected information on days of use per year, years of use, and decade of first use for 22 pesticides, as well as information on: ever/never use of 28 additional pesticides (including phorate); application methods; use of personal protective equipment (PPE); smoking; alcohol consumption; farm activities; cancer history in first degree relatives; and basic demographic data. A supplemental take-home questionnaire collected information on days of use per year, years of use, and decade of first use for the 28 pesticides for which only ever/never

use information was collected in the enrollment questionnaire. The take-home questionnaire, which was completed by 25,291 (44%) of the participants, also collected additional information on work practices, physical activity, medical conditions, and occupational exposures from non-farming jobs. Both questionnaires are available at <http://www.aghealth.org/questionnaires.html>. Applicators who did not return a questionnaire were generally similar to those who did with respect to many characteristics including use of crop insecticides; however, small differences were observed with respect to education, age, family size, and vegetable consumption (Tarone et al. 1997). Due to changing pesticide exposure patterns over time, pesticide exposure information, pesticide handling practices, and other information was updated by computer aided telephone interview from 1999-2003. However, due to the proximity of this interview period to the end of cancer incidence follow-up, it is unlikely that this exposure information was etiologically relevant, and we have not used the interview information here.

We estimated phorate exposure using phorate lifetime exposure-days, calculated by multiplying the frequency of phorate use in an average year and the number of years of use, using the midpoints of the questionnaire categories, and intensity-weighted exposure-days, calculated by multiplying lifetime exposure-days by an intensity score calculated using the following algorithm: intensity score = (mixing status + application status + equipment repair) * PPE (Dosemeci et al. 2002). This algorithm takes into account the effect of exposure modifying factors by assigning different weights to various activities based on the inverse of their potential contribution to total exposure. For example, since dermal absorption is often the most important exposure route for pesticide applicators (Maroni et al. 2000), the use of chemically resistant gloves was weighted to confer a greater reduction in intensity score than any other single item of PPE, and use of disposable outer clothing reduced the intensity score to a lesser degree.

Statistical Analysis

In contrast to the previously published tumor specific analysis of prostate cancer, which examined prostate cancer risk with respect to the ever/never use of pesticides among all male pesticide applicators without a prior prostate cancer diagnosis, this analysis was limited to the subset of applicators who completed the take-home questionnaire. Prevalent cancer cases (n = 620) and applicators who did not provide information on phorate exposure or other variables (n = 3,655) were excluded from this analysis, leaving 5,903 exposed and 15,113 non-exposed applicators. Participants with missing information tended to be older and live in North Carolina. They were also likely to have missing information for more than one of the variables listed above.

Cancer sites were selected for analysis if there were 15 or more incident diagnoses among phorate-exposed subjects. Specifically, these sites were: all cancers combined; cancers of the colon, lung, and prostate; and the grouping of lymphohematopoietic cancers, which contains both Hodgkin's and non-Hodgkin's lymphoma, leukemia, and multiple myeloma. All statistical analyses were conducted in AHS data release 0412.01 using Stata version 8 (StataCorp 2003). Poisson regression was used to calculate incidence rate ratios (RR) and 95% confidence intervals (CI). Both lifetime exposure-days and intensity-weighted exposure-days for exposed applicators were categorized into tertiles based on the distribution of the exposure metric among cancer cases. In order to improve resolution at high exposure levels, lifetime exposure-days were further categorized by splitting the top tertile at the median when the split left at least four exposed cases in each new category. When using intensity-weighted exposure-days as the exposure measurement, the highest tertile was not split due to a small number of cases. Finally, since measures of lifetime cumulative exposure do not distinguish between infrequent exposure

over a long period of time and more frequent exposure over a short period of time, which could make a difference with respect to cancer, we examined cancer incidence in relation to average days of use per year categorized as none, low, and high (low and high categorized at the median) and stratified by low and high years of use (categorized at median).

Both the lifetime and intensity-weighted exposure-days analyses used the non-exposed and lowest exposed categories as the reference group. Cancer specific analyses were adjusted for age as a continuous variable, applicator type (private/commercial), state of residence (Iowa/North Carolina), education (\leq high school graduate, $>$ high school graduate), pack-years of smoking categorized at the median (never, ≤ 12 , >12), history of the specific tumor in first degree relatives (yes/no), and use of the five most correlated pesticides (aldicarb, ethylene dibromide, aldrin, 2,4,5 trichlorophenoxy propionic acid [2,4,5 TP], and butylate). Pearson correlation coefficients ranged between 0.39 (aldicarb) and 0.36 (butylate). Use of each correlated pesticide was categorized as never, low, and high usage, using the median lifetime exposure-days of use to distinguish between low and high usage. Though the results of these more fully adjusted analyses and the analyses adjusted for age and smoking only were consistent, we chose to present the more fully adjusted results to address the fact that farmers are exposed to many agents. To assess trends in dose-response patterns, we performed linear trend tests by assigning each exposure category the median value in that category and treating the variable as a continuous variable.

To further examine the risk of prostate cancer, a parsimonious model was obtained by removing variables that did not alter point estimates by more than 5%, leaving variables for age and state of residence in the model. We used an interaction term obtained by taking the product

of family history of prostate cancer and category of lifetime exposure-days to evaluate effect modification between phosphate exposure and family history of prostate cancer.

Results

Table 1 displays selected characteristics of applicators by their level of exposure, with “lowest exposed” referring to those in the lowest exposed tertile of lifetime exposure-days, and “other exposed” referring to those in the remaining tertiles. Overall, those in the non-exposed category tended to be less likely to report producing corn, slightly less likely to report family history of any cancer, and younger than those in either of the exposed categories. Additionally, compared to the exposed applicators, the non-exposed were also exposed to significantly fewer of the pesticides that were assessed in the questionnaires. Finally, residents of North Carolina were more likely than residents of Iowa to be non-exposed. These differences between the non-exposed group and either of the two exposed groups suggest that the lowest exposed group may be the more appropriate reference group.

Table 2 displays adjusted associations between selected cancer sites and phorate lifetime exposure-days. Phorate use did not appear to be associated with the incidence of all cancers combined. For prostate and colon cancer, the results differed depending on the reference group. The risk estimates for both cancers increased monotonically with increasing exposure category relative to the lowest exposed, but the point estimates and linear trend tests were not significant. However, the point estimates were not elevated compared to the non-exposed. Phorate use was not related to any other examined cancer.

Because phorate use was uncommon in North Carolina, we repeated our analysis of all cancers combined restricting the data to applicators from Iowa. The results were similar to those presented above (not shown). Nor were they meaningfully different when we adjusted for lifetime exposure-days to all pesticides rather than the five most correlated pesticides (not shown). Finally, the results were also consistent when we examined days of use per year by

years of use (not shown). Namely, we observed slightly elevated but insignificant point estimates for prostate and colon cancer, and no discernible pattern with any other examined cancer.

Because of the large number of applicators excluded due to missing information on covariates, we repeated the analysis in Table 2 on all applicators without missing phorate exposure information by assigning the missing covariates an unspecified category (not shown). The results of this analysis of 17,051 non-exposed and 6,488 exposed applicators did not substantially differ from the results presented above.

Using the intensity-weighted exposure-days metric, though the number of cases was slightly reduced due to individuals with missing data on intensity metric covariates, with the exception of prostate cancer, the results were not meaningfully different from those presented above (not shown). Phorate use was not associated with all cancers combined. Colon cancer risk estimates were not elevated using the non-exposed reference group, but compared to the lowest exposed they increased monotonically with exposure category (RR in highest exposed = 1.81; CI = 0.58-5.60). Rate ratios for prostate cancer were uninfluenced by exposure category regardless of reference group. Phorate use was not associated with any other examined cancers.

Though too few exposed melanoma cases ($n = 14$) prevented inclusion of results in tables, there were some interesting, yet statistically insignificant observations. In particular, melanoma risk estimates tended to increase with lifetime and intensity-weighted exposure-days category regardless of reference group. Relative to the unexposed, risk estimates were also elevated among low and high days of use per year, but only in applicators with high years of use.

When prostate cancer risk was stratified by family history of prostate cancer, risk estimates did not increase across categories of lifetime exposure-days in the stratum of applicators reporting no family history (Table 3). However, in applicators with a family history, the risk estimates tended to increase. The RR in the highest compared to the lowest exposed was 1.91 (CI = 0.86-4.24). The interaction RR indicated that the risk increase associated with an increase associated with an increase in phorate exposure category was 1.53 (CI = 0.99-2.37) times higher in those with, compared to those without a family history of prostate cancer. To account for latency of exposure, we repeated the analysis among applicators whose first use of phorate was prior to 1980 (not shown). Too few exposed applicators with a family history of prostate cancer prevented us from conducting the same analysis among those whose first exposure was after 1980. The results were consistent with those presented above.

For comparison with the previously published prostate cancer analysis, we repeated the analysis using methodology comparable to that used in the previously published prostate cancer study. That is, we used logistic regression to calculate odds ratios (OR) among all enrolled male applicators without prior history of prostate cancer, categorizing phorate exposure as ever/never. We used the cross product of ever/never phorated exposure and family history of prostate cancer to assess effect modification (not shown). We found that the age adjusted prostate cancer risk was significantly elevated in those with (OR = 1.53; CI = 1.09-2.14, 249 exposed cases), but not in those without (OR = 1.11; CI = 0.95-1.31, 73 exposed cases) a family history of prostate cancer. The interaction OR was 1.40 (CI = 0.96-2.04), adjusted for age and family history of prostate cancer. The corresponding interaction OR from the previous paper was 1.64 (CI = 1.02-2.63).

Discussion

Phorate use was not related to the occurrence of all cancers combined in this study. While previous studies have observed suggestive increases in the risk of NHL and leukemia associated with the use of organophosphate pesticides (Brown et al. 1990; Cantor et al. 1992; Clavel et al. 1996; Zahm et al. 1993), the risk of lymphohematopoietic cancers overall was not associated with phorate use in this cohort. Too few exposed cases of NHL, leukemia, Hodgkin's lymphoma, and multiple myeloma prevented evaluations of these cancers individually. Since the lymphohematopoietic grouping may not be etiologically homogeneous, it would be prudent for follow-up studies to examine each cancer separately as more cancer cases develop in the cohort.

Prostate cancer risk was not significantly associated with phorate use. However, among applicators reporting a family history of prostate cancer, the risk associated with phorate exposure was elevated, while there was no corresponding increase among those without a family history. An elevated interaction term of similar magnitude was observed in an examination of prostate cancer in a paper by Alavanja et al. (Alavanja et al. 2003). The study conducted here is a chemical specific analysis carried out on 135 phorate-exposed prostate cancer cases using information on lifetime exposure-days and intensity-weighted lifetime-exposure days to examine dose-response relationships. In contrast, the previously published prostate cancer study was a tumor specific analysis and in quantifying phorate use as ever/never use could not examine dose-response trends. Also, this study was carried out over a longer average follow-up period of 7.5 years compared to 4.3 years. Despite the analytic differences, the results are generally consistent with the previous paper.

Family history of prostate cancer is strongly and consistently linked to prostate cancer in the scientific literature (Bostwick et al. 2004). For example, monozygotic twins have higher

prostate cancer concordance than dizygotic twins (Gronberg et al. 1994), risk is elevated several fold in individuals with an affected father or brother (Glover, Jr. et al. 1998; Spitz et al. 1991; Steinberg et al. 1990; Whittemore et al. 1995) and may increase if a greater number of first degree relatives are affected (Steinberg et al. 1990). Finally, cancers in individuals with affected family members occur at younger ages compared to individuals without affected family members (Bratt et al. 1999; Gronberg et al. 1999). Farming occupation has also been modestly but significantly associated with prostate cancer (Blair et al. 1985; Checkoway et al. 1987; Sharma-Wagner et al. 2000; van der Gulden and Vogelzang 1996; Van Maele-Fabry and Willems 2004). In particular, the results of several studies suggest that this association may be due exposure to pesticides (Potti et al. 2003). Significant associations were found specifically among those individuals who were ever employed in the mixing and application of pesticides (Fleming et al. 1999; Settimi et al. 2001) and cancer risk increased with both the number of days of pesticides applied per year (van der Gulden et al. 1995) and the number of acres sprayed with herbicides in one year (Morrison et al. 1993).

While a number of exposures shared in common between study subjects and their first degree relatives could lead to a statistical interaction between phorate use and family history of prostate cancer, the presence of family history of prostate cancer may serve as a surrogate for an inherited genetic trait, such as a polymorphism in a metabolism enzyme. The active form of most organophosphates, including phorate and chlorpyrifos, is the corresponding oxon (Pope 1999; Sultatos 1994), and both of these insecticides are metabolized using many of the same enzymes (Tang et al. 2001; Usmani et al. 2004). It is known that polymorphic variants of several cytochrome P450 isoforms vary considerably in their ratio of bioactivation to detoxification of chlorpyrifos (Dai et al. 2001; Tang et al. 2001). Thus it is possible that the observation of an

interaction of family history and phorate exposure reflects the presence of an inherited polymorphism that alters the balance between bioactivation and detoxification in the body.

There are some limitations of this study. At the current time, investigation of certain cancers is hindered by small numbers of exposed cases, making it difficult to do analyses of some cancers. However, as the cohort ages, more cancer cases will accrue and allow for more statistically powerful investigations. Additionally, some exposure misclassification is likely, though there is no reason to believe that it occurred differentially between cancer cases and cancer-free subjects since exposure information was gathered prior to disease.

Another general limitation of studies of pesticide applicators is that few applicators are exposed to one agent. To attempt to control for potential confounding from other pesticides, the risk estimates were adjusted for use of the five pesticides most correlated with phorate. However, the use of other pesticides did not likely confound the observed relationships since the correlations coefficients, which ranged between 0.36 for butylate and 0.39 for aldicarb, were not very high. Moreover, risk estimates were similar when they were adjusted for cumulative lifetime exposure-days to all pesticides. An examination of pesticide usage and specific farming activities found that these activities likely resulted in minimal confounding (Coble et al. 2002).

The exposure measures in this study are an improvement over previous studies of pesticide exposures because they attempt to quantify cumulative lifetime exposure by incorporating measures of frequency, duration, and intensity of exposure to specific pesticides as opposed to using qualitative measures of exposure. The measure of intensity used information such as application methods and PPE use was used to calculate a more precise measure of actual exposure. Furthermore, recruitment and follow-up of participants was very complete, as 82% of eligible participants enrolled, and fewer than 2% were lost to follow-up. Although the response

to the take-home questionnaire was not complete, the measured differences between respondents and non-respondents were not likely to be influential here (Tarone et al. 1997). Thus, the applicators returning the take-home questionnaire were likely representative of the overall cohort in terms of cancer risk.

In summary, at this time, no clear association between phorate and any cancer was observed. However, the study findings are not inconsistent with the hypothesis that there is an interaction between phorate exposure and family history of prostate cancer in the incidence of this cancer, suggesting that there may be an inherited genetic variability that alters susceptibility to prostate cancer. Future analyses of the AHS in order to further investigate the relationship between phorate exposure and the risk of prostate cancer are warranted.

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Table 1. Characteristics of applicators by phorate exposure in the Agricultural Health Study (1993-1997).

Characteristic	Non-exposed N = 15,113		Lowest exposed N = 2,407		Other exposed N = 3,496	
	Number	%	Number	%	Number	%
Age						
<40	1,981	13.1	167	6.9	218	6.2
40-49	4,161	27.5	581	24.1	797	22.8
50-59	3,630	24.0	666	27.7	992	28.4
60+	5,341	35.3	993	41.3	1,489	42.6
Gender						
Male	14,589	96.5	2,387	99.2	3,475	99.4
Female	524	3.5	20	0.8	21	0.6
State of residence						
Iowa	9,783	64.7	2,261	93.9	2,945	84.2
North Carolina	5,330	35.3	146	6.1	551	15.8
Applicator type						
Commercial	1,779	11.8	101	4.2	219	6.3
Private	13,334	88.2	2,306	95.8	3,277	93.7
Smoking History						
Never	8,262	54.7	1,429	59.4	1,977	56.6
Light (≤ 12 pack-years)	3,437	22.7	542	22.5	793	22.7
High (12+ pack-years)	3,414	22.6	436	18.1	726	20.8
Education						
High School or Less	8,183	54.2	1,273	52.9	2,050	58.6
More than High School	6,930	45.9	1,134	47.1	1,446	41.4
Family history of cancer^a						
No	8,257	58.7	1,225	53.0	1,763	53.0
Yes	5,809	41.3	1,084	47.0	1,561	47.0
Alcohol^{a,b}						
No	5,149	34.8	593	24.9	944	27.4
Yes	9,641	65.2	1,789	75.1	2,506	72.6
Corn farming						
No	4,897	32.4	149	6.2	366	10.5
Yes	10,216	67.6	2,258	93.8	3,130	89.5
Use of correlated pesticides						
Aldicarb	932	6.2	111	4.6	444	12.7
Ethylene Dibromide	687	4.6	42	1.8	102	2.9
Aldrin	1,466	9.7	674	28.0	1,028	29.4
2,4,5-TP	590	3.9	122	5.1	257	7.4
Butylate	3,038	20.1	940	39.1	1,437	41.1
Number of pesticides used ^c	10.7 \pm 5.9		16.0 \pm 5.9		17.0 \pm 6.5	

^aColumn numbers do not add up to total N due to missing information. ^bBased on reported alcohol consumption in the past 12 months. ^cMean \pm Standard Deviation.

Table 2. Rate ratios for selected cancers by phorate lifetime exposure-days among Agricultural Health Study (1993-1997) applicators, using non-exposed and lowest exposed applicators as the reference group.

Lifetime Exposure-Days ^a	Cases (n)	Non-exposed Reference RR ^b	Non-exposed Reference CI ^b	Lowest Exposed Reference RR	Lowest Exposed Reference CI
All Cancer					
0	689	1.00	Ref ^b		
>0-8.75	111	0.84	0.68-1.04	1.00	Ref
>8.75-38.75	84	0.94	0.74-1.19	1.14	0.85-1.53
>38.75-108.5	62	0.89	0.68-1.17	1.08	0.78-1.49
>108.5	38	0.94	0.67-1.33	1.19	0.79-1.78
<i>p</i> -trend ^c		0.71		0.53	
Lymphohematopoietic Cancer					
0	72	1.00	Ref		
>0-8.75	9	0.59	0.20-1.12	1.00	Ref
>8.75-38.75	9	0.88	0.40-2.03	1.24	0.48-3.22
>38.75	8	0.64	0.52-2.17	0.84	0.30-2.33
<i>p</i> -trend		0.30		0.57	
Colon Cancer					
0	53	1.00	Ref		
>0-8.75	6	0.47	0.20-1.13	1.00	Ref
>8.75-38.75	7	0.90	0.40-2.03	2.22	0.72-6.83
>38.75	10	1.07	0.49-2.52	2.48	0.84-7.36
<i>p</i> -trend		0.74		0.18	
Lung Cancer					
0	69	1.00	Ref		
>0-8.75	6	0.81	0.34-1.96	1.00	Ref
>8.75-38.75	5	1.00	0.39-2.61	1.14	0.34-3.84
>38.75-108.5	4	0.82	0.29-2.37	0.85	0.22-3.23
>108.5	4	0.95	0.31-2.94	0.63	0.14-2.86
<i>p</i> -trend		0.91		0.47	
Prostate Cancer					
0	286	1.00	Ref		
>0-8.75	53	0.89	0.65-1.21	1.00	Ref
>8.75-38.75	38	0.91	0.64-1.29	1.08	0.71-1.66
>38.75-108.5	28	0.92	0.62-1.38	1.16	0.73-1.86
>108.5	16	0.93	0.55-1.57	1.31	0.72-2.37
<i>p</i> -trend		0.78		0.40	

^aLifetime exposure-days = years of use x days of use per year. ^bRR, rate ratio; CI, 95% confidence interval; Ref, reference group. Incidence rate ratios adjusted for age, state of residence, applicator type, education, family history of site specific cancer, smoking, and use of aldicarb, ethylene dibromide, aldrin, 2,4,5-TP, and butylate. ^c*p*-value for trend test.

Table 3. Incidence rate ratios for prostate cancer by phorate lifetime exposure-days after stratification by family history of prostate cancer among male Agricultural Health Study (1993-1997) applicators.

Lifetime Exposure-Days ^a	Cases (n)	Non-exposed Reference RR ^b	Reference CI ^b	Lowest Exposed Reference RR	Reference CI
No Family History					
0	270	1.00	Ref ^b		
>0-8.75	49	1.01	0.74-1.39	1.00	Ref
>8.75-24.5	35	1.05	0.73-1.51	1.03	0.67-1.60
>24.5	35	0.91	0.64-1.30	0.92	0.59-1.43
<i>p</i> -trend ^c			0.66		0.69
Family History					
0	56	1.00	Ref		
>0-8.75	10	0.69	0.35-1.39	1.00	Ref
>8.75-24.5	11	1.27	0.65-2.49	1.90	0.80-4.50
>24.5	17	1.48	0.85-2.58	1.91	0.86-4.24
<i>p</i> -trend			0.11		0.16
Interaction ^d		1.18	0.96-1.44	1.53	0.99-2.37

^aLifetime exposure-days = years of use x days of use per year. ^bRR, rate ratio; CI, 95% confidence interval; Ref, reference group. Rate ratios adjusted for age and state of residence. ^c*p*-value for trend test. ^d Rate ratio and 95% confidence interval for the cross product of family history of prostate cancer and lifetime exposure-days category, adjusted for age, state of residence, and family history of prostate cancer.