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Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort

Michael C. R. Alavanja[1], Claudine Samanic[1], Mustafa Dosemeci[1], Jay Lubin[1], Robert Tarone[1], Charles F. Lynch[2], Charles Knott[3], Kent Thomas[4], Jane A. Hoppin[5], Joseph Barker[6], Joseph Coble[1], Dale P. Sandler[5], and Aaron Blair[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.
[2] Department of Epidemiology, University of Iowa, Iowa City, IA.
[3] Battelle/Centers for Public Health Research and Evaluation, Durham, NC.
[4] US Environmental Protection Agency, Research Triangle Park, NC.
[5] National Institute for Environmental Health Sciences, Research Triangle Park, NC.
[6] IMS, Inc., Silver Spring, MD.

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The authors examined the relation between 45 common agricultural pesticides and prostate cancer incidence in a prospective cohort study of 55,332 male pesticide applicators from Iowa and North Carolina with no prior history of prostate cancer. Data were collected by means of self-administered questionnaires completed at enrollment (1993–1997). Cancer incidence was determined through population-based cancer registries from enrollment through December 31, 1999. A prostate cancer standardized incidence ratio was computed for the cohort. Odds ratios were computed for individual pesticides and for pesticide use patterns identified by means of factor analysis. A prostate cancer standardized incidence ratio of 1.14 (95% confidence interval: 1.05, 1.24) was observed for the Agricultural Health Study cohort. Use of chlorinated pesticides among applicators over 50 years of age and methyl bromide use were significantly associated with prostate cancer risk. Several other pesticides showed a significantly increased risk of prostate cancer among study subjects with a family history of prostate cancer but not among those with no family history. Important family history-pesticide interactions were observed.

agrochemicals; fungicides, industrial; herbicides; insecticides; pesticides; prostatic neoplasms; risk

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; EPTC, *S*-ethyl dipropylthiocarbamate; OR, odds ratio; SIR, standardized incidence ratio; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid.

Prostate cancer is the most common malignancy among men in the United States and in most Western countries (other than nonmelanoma skin cancer), and in the United States, it is the second leading cause of cancer death (1, 2). Despite the common occurrence of this tumor, its etiology remains largely unknown.

Age, family history, African-American ethnicity, hormonal factors, and possibly a high consumption of animal fat and red meat are the most consistent risk factors reported (3–10). An inverse association with vegetable and fruit consumption has been suggested (9, 11, 12), while smoking may be related to the occurrence of fatal prostate cancer (13).

Farming has been the most consistent occupational risk factor for prostate cancer (14, 15). Farm-related potential risk factors include exposures to insecticides, fertilizers, herbicides, and other chemicals (16–23). However, the role of specific agricultural chemicals has not been firmly established because of the lack of precise exposure data (20, 21). We examined the exposure-response relation between 45 important agricultural pesticides and prostate cancer incidence in the Agricultural Health Study cohort

Reprint requests to Dr. Michael C. R. Alavanja, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS, Room 8000, Rockville, MD 20892 (e-mail: alavanjm@mail.nih.gov).

while controlling for known and suspected risk factors for prostate cancer.

MATERIALS AND METHODS

Cohort enrollment

The Agricultural Health Study is a prospective cohort study of 89,658 people, including 52,395 private applicators and 4,916 commercial applicators licensed to apply restricted use pesticides and 32,347 spouses of farmer applicators from Iowa and North Carolina (24). Private applicators were farmers or nursery workers, and "commercial" applicators were persons employed by pest control companies or businesses that use pesticides (e.g., warehouse operators, grain mills). Pesticide applicators were enrolled when they completed an enrollment questionnaire. In Iowa, both commercial and farmer applicators attend the same pesticide certification testing sessions, and both were invited to participate in the study. In North Carolina, because private and commercial applicators attend separate training, only private applicators were enrolled. Private and commercial applicators were also asked to complete "take-home" questionnaires that sought more extensive information on occupational activities. Recruitment of applicators and their spouses began in December 1993 and continued until December 1997. Male spouses are too few for meaningful analysis at this time.

Questionnaires

The enrollment questionnaire sought information on the use of 50 pesticides (ever/never), crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, smoking, alcohol consumption, fruit and vegetable intake, multiple vitamin use, medical conditions, medical conditions in first-degree relatives including a history of prostate cancer, and basic demographic data (all questionnaires are at http://www.aghealth.org). For 22 of the 50 pesticides in the enrollment questionnaire, we also obtained information on the duration of use (years) and frequency of use (days per year). Information on application methods and protective equipment was used to compute an exposure "intensity index I" (25). For the remaining 28 pesticides listed in the enrollment questionnaire, exposure information was limited to ever versus never used. The enrollment questionnaire also included two activities (painting and engine repair) that frequently result in exposure to solvents. The take-home questionnaires included the following: detailed use information on the 28 pesticides reported as ever/never use in the enrollment questionnaire, more detailed information on personal protective equipment use, dietary and cooking practices, supplemental vitamin use, height and weight (used for body mass index), occupational exposures to welding and solvents, nonfarm jobs, and hours spent in strenuous physical activity.

Cohort follow-up

Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and to the National Death Index to ascertain vital status; prostate cancer cases diagnosed prior to enrollment were excluded from the analyses. Incident cases were identified from enrollment (i.e., 1993–1997) through December 31, 1999. Study subjects alive but no longer residing in Iowa or North Carolina were identified through personal contacts with the study subject, motor vehicle records, pesticide registration records, and the Internal Revenue Service address database (which has current address information on all Americans filing a tax return). This includes over 98 percent of the Agricultural Health Study cohort. Fewer than 0.4 percent of the cohort were lost to mortality or cancer incidence follow-up (n = 319).

Analysis

A standardized incidence ratio for prostate cancer was computed to compare prostate cancer incidence among male cohort members with incidence in the male populations of Iowa and North Carolina. Expected numbers for the standardized incidence ratio were developed from 5-year age and calendar-time (i.e., 1994–1998), race-specific cancer incidence rates from the population-based cancer registries in Iowa and North Carolina. The statistical significance of the standardized incidence ratios and 95 percent confidence intervals was based on standard methods (26, 27).

Because the follow-up period for case ascertainment was less than 5 years (i.e., an average of 4.3 years) and the prostate cancer incidence rate did not vary appreciably, multivariate logistic regression (28) was used to compare prostate cancer cases with noncases on a number of factors possibly associated with prostate cancer risk. In this analysis, we examined 50 pesticides, crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, regular recreational physical activity, smoking, alcohol consumption, red meat consumption, fruit and vegetable intakes, multiple vitamin use, medical conditions, medical conditions in first-degree relatives including a history of prostate cancer, "high pesticide exposure events" (29), age, race, state of residence, license type, education, and basic demographic data. All analyses excluded both female applicators and 414 prevalent prostate cancer cases.

Factor analysis was used to examine the interrelations among ever/never use of 50 pesticides, state (Iowa, North Carolina), and age (≤50 and >50 years) (30). Only variables that shared at least 15 percent of the variance with the factor, corresponding to a factor-loading score of 0.40 or higher, were considered when interpreting the factors. Factor scores were computed for each subject and then divided into tertiles based on the factor scores for cases. The upper tertile was divided in half, and the upper half was then divided in half again to examine more extreme exposure scores (resulting in categories at ≤33.3 percent, 33.4–66.7 percent, 66.8–83.3 percent, 83.4–91.6 percent, >91.6 percent). Logistic regres-

TABLE 1. Characteristics of licensed pesticide applicators in the Agricultural Health Study, 1993–1997

Characteristics*	Prostate cancer		Cohort member		Adjusted odds ratio†	95% confidence interval	*p* value
	Cases	%	Noncases	%			
Total (all)	566		54,766				
Age (years)							
<55	67	11.8	38,860	70.9	1.0‡		<0.0001§
55–59	78	13.8	5,374	9.8	5.2	3.1, 8.7	
60–64	139	24.6	4,581	8.4	12.8	8.1, 20.2	
65–69	159	28.1	3,165	5.8	22.4	14.2, 35.3	
70–74	77	13.6	1,804	3.3	19.6	11.4, 33.6	
≥75	46	8.1	980	1.8	25.6	13.5, 48.6	
Race							
White	546	96.5	53,425	97.6	1‡		0.50
Black and other races	20	3.5	1,341	2.4	1.55	0.5, 4.4	
Residence							
Iowa	326	57.6	35,560	64.9	1‡		0.29
North Carolina	240	42.4	19,206	35.1	0.82	0.6, 1.1	
Education (years)							
<12	97	18.6	4,669	9.1	1‡		0.36§
12	279	53.4	24,631	48.1	1.41	0.9, 2.2	
>12	147	28.1	21,958	42.8	1.35	0.8, 2.2	
License type							
Private	541	95.6	50,090	91.5	1‡		0.41
Commercial	25	4.4	4,676	8.5	1.10	0.6, 2.0	
Smoker							
Never	195	39.8	25,159	51.1	1‡		0.06§
Former	243	49.6	15,423	31.4	1.30	0.9, 1.7	
Current	52	10.6	8,629	17.5	1.42	0.9, 2.2	
Family history of prostate cancer							
No	391	81.1	45,342	91.4	1‡		0.0001
Yes	91	18.9	4,271	8.6	1.90	1.4, 2.7	

Table continues

sion analysis was performed to evaluate the association between factor scores and the risk of prostate cancer, controlling for the same potentially confounding variables as above.

Unconditional logistic regression analysis was also used to evaluate risks associated with a reported history of mixing or applying specific pesticides. We used the "never used the specific pesticide" category as the reference group and the five percentile categories described above as the exposed groups. Exposure variables for the 22 pesticides included in the enrollment questionnaire, evaluated on the entire Agricultural Health Study male cohort, included the following: 1) application days per year; 2) total years of exposure; 3) an exposure "intensity index I," which includes information about the application method, a score for whether the applicator repaired his own pesticide application equipment, and a score for the use of protective equipment (25); and 4) a cumulative pesticide exposure score: (application days per year) × (total years of exposure) × (exposure intensity index I). We omitted pesticides from this analysis if a total of five or fewer applicators were exposed to the chemical.

For the subset of male applicators (n = 24,034) who also completed the take-home questionnaires, exposure variables (for 28 additional pesticides) included the following: 1) application days per year; 2) total years of exposure; 3) an exposure "intensity index II," which included information about mixing methods, an application methods score, whether an enclosed tractor was used in applying pesticides, whether the applicator repaired his own pesticide application equipment, whether the applicator washed his pesticide equipment, a score for the use of protective equipment, personal hygiene information, whether the applicator changed clothes after a chemical spill, and the frequency of replacing gloves (25); and 4) a cumulative pesticide expo-

TABLE 1. Continued

Characteristics	Prostate cancer		Cohort member		Adjusted odds ratio†	95% confidence interval	*p* value
	Cases	%	Noncases	%			
Vegetable							
<5 times/week	156	32.0	17,001	34.0	1‡		0.76§
5–7 times/week	169	34.6	18,250	36.5	0.75	0.5, 1.0	
>1/day	163	33.4	14,808	29.5	0.93	0.7, 1.3	
Red meat							
0–<2 times/week	115	35.2	7,150	30.2	1‡		0.70§
2 times/week	84	25.7	6,612	27.9	0.96	0.7, 1.4	
≥3/week	128	39.1	9,942	41.9	0.94	0.7, 1.3	
Supplemental vitamin use							
No	218	69.0	15,771	67.6	1‡		0.40§
Not regularly	38	12.0	3,556	15.2	0.92	0.6, 1.4	
Regularly	60	19.0	4,004	17.2	0.87	0.6, 1.2	
Hours of exercise/week (leisure time)							
None	120	37.5	5,678	24.2	1‡		0.23§
<1	53	16.6	4,148	17.7	0.68	0.5, 1.0	
1–1.5	46	14.4	3,978	17.0	0.80	0.5, 1.2	
1.6–4	46	14.4	4,557	19.4	0.64	0.4, 1.0	
4.1–8	32	10.0	2,792	11.9	0.86	0.5, 1.4	
>8	23	7.2	2,312	9.9	0.57	0.3, 1.0	
Body mass index							
Quartile 1 (lowest)	69	23.8	5,838	25.2	1.0‡		0.44§
Quartile 2	83	26.2	5,742	24.8	1.34	0.9, 2.0	
Quartile 3	86	27.1	5,798	25.1	1.23	0.8, 1.8	
Quartile 4 (highest)	79	24.9	5,761	24.9	1.31	0.9, 2.0	
High pesticide exposure event							
No	276	87.6	19,825	85.0	1‡		0.48
Yes	39	12.4	3,510	15.0	1.11	0.8, 1.6	

* Information on age, race, state of residence, education, license type, smoking history, family history of prostate cancer, and vegetable intake was taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 new prostate cancer cohort members; 414 cohort members had prostate cancer before enrollment into the study and were not included in this analysis. Information on high pesticide exposure events, supplemental vitamin use, hours of leisure exercise per week, body mass index, and red meat intake was taken from the farmer applicator and commercial applicator questionnaire completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members. Data reflect cohort characteristics as of December 31,1999. Missing data for some questions are responsible for differences in total cell counts.

† Odds ratios of prostate cancer adjusted for age, race, state of residence, education, license type, smoking history, family history of prostate cancer, vegetable intake, supplemental vitamin use, body mass index, high pesticide exposure events, exercise per week, and red meat intake.

‡ Reference group.

§ *p* value for trend test.

sure score: (application days per year) × (total years of exposure) × (exposure intensity index II). For both algorithms, exposure-response was assessed by a linear trend test, treating the cumulative score as a continuous variable, and also by selecting the median cumulative score of each exposure category and treating the cumulative score as a categorical variable. Analyses of prostate cancer risk were conducted by state and by license type in Iowa (i.e., private vs. commercial) to evaluate the consistency of findings within the cohort. All odds ratios were adjusted for age as a categorical variable (<55, 55–59, 60–64, 65–69, 70–74, and ≥75 years). Institutional review boards approved the study

TABLE 2. Risk from occupational exposures to licensed pesticide applicators off the farm and from painting and welding on the farm, Agricultural Health Study, 1993–1997

Exposure	Prostate cancer		Cohort member		Adjusted odds ratio*	95% confidence interval*	*p* value*
	Cases	%	Noncases	%			
			Off-the-farm jobs†				
Pesticides‡							
No	278	95.2	20,103	90.8	1		0.27
Yes	14	4.8	2,028	9.2	0.74	0.4, 1.3	
Solvents‡							
No	267	91.4	18,138	82.0	1		0.02
Yes	25	8.6	3,993	18.0	0.60	0.4, 0.9	
Gasoline‡							
No	268	91.8	18,128	81.9	1		0.003
Yes	24	8.2	4,003	18.1	0.53	0.3, 0.8	
Asbestos‡							
No	278	95.2	20,833	94.1	1		0.50
Yes	14	4.8	1,298	5.9	0.8	0.5, 1.4	
Grain dust‡							
No	276	94.5	19,768	89.3	1		0.36
Yes	16	5.5	2,363	10.7	0.79	0.5, 1.3	
Wood dust‡							
No	275	94.2	19,725	89.1	1		0.12
Yes	17	5.8	2,406	10.9	0.68	0.4, 1.1	
Silica/sand dust‡							
No	281	96.2	21,090	95.3	1		0.76
Yes	11	3.8	1,041	4.7	1.10	0.6, 2.0	
Engine exhaust‡							
No	257	88.0	17,048	77.0	1		0.58
Yes	35	12.0	5,083	23.0	0.88	0.6, 1.4	

Table continues

proposal and the manner in which informed consent was obtained from study participants.

RESULTS

This analysis was restricted to the 55,332 male private and commercial applicators with no history of prostate cancer at enrollment. A total of 1,197 deaths occurred among male applicators during the mean follow-up period of 4.3 years. A total of 566 incident prostate cancers were observed between enrollment and December 31, 1999. Based on age-adjusted state incidence rates, 494.5 prostate cancer cases were expected, yielding a standardized incidence ratio of 1.14 (95 percent confidence interval (CI): 1.05, 1.24). For the same period, cancer incidence from all sites was significantly less than expected, with an overall standardized incidence ratio of 0.80 (95 percent CI: 0.76, 0.83). The prostate cancer standardized incidence ratio (SIR) appeared higher among commercial applicators (SIR = 1.41, 95 percent CI: 0.89, 2.11) than among private applicators (SIR = 1.13, 95 percent CI: 1.04, 1.24) and higher among Iowa Whites (SIR = 1.27, 95 percent CI: 1.13, 1.27) than among North Carolina Whites (SIR = 1.10, 95 percent CI: 0.99, 1.21). There were too few prostate cancer cases among non-Whites in North Carolina (n = 19) and Iowa (n = 0) for meaningful calculation of standardized incidence ratios at this time. For the subset of the male applicator cohort (n = 24,034) who completed the take-home questionnaire, the prostate cancer standardized incidence ratio of 1.22 (95 percent CI: 1.09, 1.36) and the overall cancer standardized incidence ratio of 0.81 (95 percent CI: 0.75, 0.87) were similar to those for the entire cohort.

Odds ratios for prostate cancer increased sharply with age, and cases were more likely to have a family history of prostate cancer (table 1). Nineteen percent of prostate cancer cases reported a family history of prostate cancer among first-degree relatives, compared with 8.6 percent of noncases. No other characteristic in table 1 was statistically significant after adjustment for the other characteristics shown. A nearly significant positive association was observed for cigarette smoking.

TABLE 2. Continued

Exposure	Prostate cancer		Cohort member		Adjusted odds ratio	95% confidence interval	*p* value
	Cases	%	Noncases	%			
Lead solder‡							
No	281	96.2	21,172	95.7	1		0.57
Yes	11	3.8	959	4.3	0.84	0.5, 1.5	
Welding fumes‡							
No	260	89.0	18,147	82.0	1		0.25
Yes	32	11.0	3,984	18.0	0.80	0.6, 1.2	
Other metals‡							
No	281	96.2	21,340	96.4	1		0.34
Yes	11	3.8	791	3.6	1.36	0.7, 2.5	
Pneumatic drill‡							
No	284	97.3	20,550	92.9	1		0.10
Yes	8	2.7	1,581	7.1	0.55	0.3, 1.1	
No exposure off the farm reported‡							
No	232	79.5	18,541	83.8	1		0.10
Yes	60	20.5	3,590	16.2	1.27	0.9, 1.7	
			On farm				
Painting on farm§							
No	254	44.8	19,485	35.6	1		0.22
Yes	312	55.2	35,281	64.4	1.13	0.9, 1.4	
Welding on farm§							
No	1	51.4	19,209	35.1	1		0.33
Yes	275	48.6	35,559	64.9	0.91	0.8, 1.1	

* Odds ratios, 95% confidence intervals, and *p* values adjusted for age and family history of prostate cancer; the "no" exposure was always used as the reference category.

† Eight occupational exposures occurring off the farm including x-rays, cotton dust, mineral dust, electroplating fumes, lead, mercury, cadmium, and mixing herbicides in the military were omitted from the table because fewer than five exposed cases were observed.

‡ Information on all off-the-farm jobs/activities completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members.

§ Information on age and on family history of prostate cancer, painting (on-farm activity), and welding (on-farm activity) taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 prostate cancer cohort members; 414 cohort members had prostate cancer before enrollment into the study and were not included in this analysis. Missing data for some questions are responsible for the differences in total cell counts.

Table 2 lists odds ratios for prostate cancer by selected occupational exposures on and off the farm. No characteristic in table 2 was significantly associated with prostate cancer after adjustment for age and family history of prostate cancer.

Table 3 lists the 50 herbicides, insecticides, fungicides, and fumigants for which information concerning the frequency, duration, intensity, and cumulative exposure score was available in this study.

Results of the factor analysis showed a tendency for the use of certain pesticides to group together (table 4). Three factors explained almost 90 percent of the variance in pesticide usage in the observed data (appendix table 1). Factor 1 showed significant loading scores (i.e., correlations) with the herbicides atrazine, dicamba, cyanazine, metolachlor, *S*-ethyl dipropylthiocarbamate (EPTC), alachlor, imazethapyr, 2,4-dichlorophenoxyacetic acid (2,4-D), trifluralin, chlorimuron ethyl, metribuzin, petroleum oil, pendimethalin, and butylate and with the insecticide terbufos. These are pesticides used primarily on corn, soybeans, and other grain crops, which are especially important in Iowa. Factor 2 showed significant loading scores for North Carolina residence (i.e., −70 for Iowa). Pesticides descriptive of this factor include one herbicide (paraquat), three insecticides (parathion, carbaryl, aldicarb), one fumigant (methyl bromide), and four fungicides (benomyl, chlorothalonil, maneb/mancozeb, and metylaxyl). These pesticides are used on cotton, tobacco, vegetables, and fruit crops raised mostly in North Carolina that require intensive treatment for insects, nematodes, and fungi. Factor 3 loaded heavily on study

TABLE 3. Pesticides evaluated in this study for an association with prostate cancer by frequency of use,* duration of use,† intensity of use,‡ and cumulative use,§ Agricultural Health Study, 1993–1997

Herbicides	Insecticides	Fungicides	Fumigants
Alachlor	Aldicarb	Benomyl	Aluminum phosphide
Atrazine	Aldrin	Captan	Ethylene dibromide
Butylate	Carbofuran	Chlorothanil	Carbon tetrachloride/carbon disulfide
Chlorimuron-ethyl	Carbaryl	Maneb/macozeb	Methyl bromide
Cyanazine	Chlordane	Metalaxyl	
Dicamba	Chlorpyrifos	Ziram	
2,4-D¶	Coumaphos		
EPTC¶	Dichlorvos¶		
Glyphosate	Diazinon		
Imazethypyr	Dieldrin		
Metolachlor	DDT¶		
Metribuzin	Fonofos		
Paraquat	Heptachlor		
Pendimethalin	Lindane		
Petroleum oil as herbicide	Malathion		
2,4,5-T¶	Parathion		
2,4,5-TP¶	Permethrin (for crops)		
Trifluralin	Permethrin (for animals)		
	Phorate		
	Terbufos		
	Toxaphine		
	Trichlorofon		

* Frequency as application days/year.
† Duration as years of application.
‡ Intensity as the algorithm score.
§ Cumulative exposure as the product of frequency × duration × intensity.
¶ 2,4-D, 2,4-dichlorophenoxyacetic acid; EPTC, *S*-ethyl dipropylthiocarbamate; dichlorvos, 2,2-dichloroethenyl dimethylphosphate; DDT, dichlorodiphenyltrichloroethane; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid.

subjects over 50 years of age; on chlorinated insecticides no longer registered for use in the United States, including aldrin, chlordane, dieldrin, dichlorodiphenyltrichloroethane (DDT), heptachlor, and toxaphene; and on two chlorinated phenoxy herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP).

Table 4 shows odds ratios for categories of factor scores and tests of linear trends adjusted for age and family history of prostate cancer. Factor 3 was significantly associated with an excess risk of prostate cancer, while factor 1 and factor 2 were not.

Table 5 displays odds ratios for the 10 pesticides for which ever versus never use data and cumulative exposure scores were available from the enrollment questionnaires. For 35 additional pesticides for which similar cumulative exposure data were available (listed in table 3), no exposure-response association with prostate cancer was observed, and they were omitted from table 5 to save space (five pesticides were excluded from the analysis because five or fewer cases were exposed (i.e., trichlorofon, ziram, aluminum phosphide, ethylene dibromide, and carbon tetrachloride/carbon disulfide)). No meaningful differences were found in the exposure-response when analyzed as either a continuous or a categorical variable, so only the categorical analysis results are presented. We computed odds ratios adjusted for age and family history (reduced model) and for all the variables listed in table 1 (full model). Because the full model did not substantially change the odds ratio estimates for any pesticide, we provide the results from the reduced model in table 5. Among the pesticides listed in the enrollment questionnaire, only methyl bromide, a fumigant used by approximately 12 percent of the cohort, showed a significant linear trend ($p = 0.008$) with prostate cancer risk. This trend is almost entirely due to the elevated risk in the two highest exposure categories. Odds ratios were 1 (reference, no exposure), 1.01 (95 percent CI: 0.66, 1.56), 0.76 (95 percent CI: 0.47, 1.25), 0.70 (95 percent CI: 0.38, 1.28), 2.73 (95 percent CI: 1.18, 6.33), and 3.47 (95 percent CI: 1.37, 8.76). The trend in prostate cancer risk with methyl bromide did not differ by tumor grade; that is,

TABLE 4. Odds ratios, confidence intervals, and number of prostate cancer cases for factor scores, based on factor analysis of 50 pesticides, family history of prostate cancer, and age,* Agricultural Health Study, 1993–1997

Factor	Level†					*p* value, linear trend
	I (lowest exposure)	II	III	IV	V (highest exposure)	
Factor 1 (herbicides)						
Odds ratio	1.0	0.99	1.18	1.10	1.25	0.53
95% confidence interval		0.78, 1.26	0.89, 1.56	0.78, 1.55	0.88, 1.76	
No. of cases	188	189	94	48	47	
Factor 2 (fumigants/fungicides, North Carolina)						
Odds ratio	1.0	1.04	0.97	0.94	0.84	0.82
95% confidence interval		0.83, 1.30	0.74, 1.28	0.66, 1.34	0.59, 1.18	
No. of cases	188	189	95	46	48	
Factor 3 (older age, chlorinated pesticides)						
Odds ratio	1.0	1.29	1.51	1.37	1.39	0.005
95% confidence interval		1.02, 1.63	1.15, 2.00	0.96, 1.97	0.99, 1.97	
No. of cases	188	189	95	47	47	

* Adjusted for age and family history of prostate cancer.

† Levels = tertiles, with the upper tertile divided in half, and the resulting half divided in half again (levels IV and V) (i.e., level I, 0–33.3; level II, 33.4–66.6; level III, 66.7–83.3; level IV, 83.4–91.6; and level V, 91.7–100.0).

both well-differentiated tumors and poorly differentiated tumors were observed to have a significant linear trend with methyl bromide exposure ($p = 0.03$ and $p = 0.04$, respectively) (data not shown). Methyl bromide was also associated with a significantly increased risk of prostate cancer among private applicators in both states, with a linear trend p of 0.05 in North Carolina (odds ratios (ORs) for previously defined categories = 1 (reference), 0.9, 0.8, 0.7, 2.8, and 3.8) and a linear trend p of 0.04 in Iowa (ORs for previously defined exposure categories = 1 (reference), 1.7, 1.2, and 4.4; no cases in higher exposure categories), and among commercial applicators in Iowa, with a linear trend p of 0.01 (ORs for previously defined exposure categories = 1 (reference), 1.1, 3.1, 8.9, and 14.0; no cases in the highest exposure category). Similarly, significantly elevated exposure-response trends were observed for frequency of use, with $p = 0.02$ (ORs = 1 (reference), 0.93, 0.76, 1.31, 1.44, and 4.39), and lifetime application days, with $p = 0.02$ (ORs = 0.87, 0.78, 0.97, 2.09, and 2.63). The odds ratio for ever versus never use of methyl bromide data was elevated but not significantly (OR = 1.10, 95 percent CI: 0.85, 1.36).

Few differences were found between the cohort members who completed the take-home questionnaire (i.e., 40 percent applicators) and those that did not (31). These take-home questionnaires sought more detailed information on 28 pesticides (including 18 currently used pesticides and 10 pesticides no longer currently registered for use in the United States). Applicators who ever used any one of five insecticides, including three chlorinated insecticides associated with factor 3 (i.e., aldrin, DDT, and heptachlor), were at a significantly elevated risk of prostate cancer: carbofuran (OR = 1.25, 95 percent CI: 1.03, 1.52), permethrin for animal use (OR = 1.38, 95 percent CI: 1.01, 1.89), aldrin (OR = 1.32, 95 percent CI: 1.09, 1.60), DDT (OR = 1.37, 95 percent CI: 1.12, 1.67), and heptachlor (OR = 1.20, 95 percent CI: 1.00, 1.47). Little evidence was found, however, to support an exposure-response trend for prostate cancer with the use of any pesticide other than methyl bromide (table 5), and this significant association was unchanged when other pesticides were added to the logistic model (data not shown).

To assess the possible influence of a family history of prostate cancer on pesticide-associated risks (table 6), we assessed effect modification by including a cross-product term in the logistic model, that is, age + family history + pesticide exposure + (family history × pesticide exposure). Significant interaction odds ratios occurred among persons who used butylate (OR = 1.93, 95 percent CI: 1.19, 3.11), a widely used thiocarbamate herbicide; four commonly used organophosphorothioate insecticides including coumaphos (OR = 2.58, 95 percent CI: 1.29, 5.18), fonofos (OR = 2.04, 95 percent CI: 1.21, 3.44), chlorpyrifos (OR = 1.65, 95 percent CI: 1.02, 2.66), and phorate (OR = 1.64, 95 percent CI: 1.02, 2.63); and a pyrethroid, permethrin (for animal use) (OR = 2.31, 95 percent CI: 1.17, 4.56). Similar results were found in North Carolina and Iowa (results not shown). These associations did not change when other pesticides were added to the logistic model. Several other pesticides had nonsignificant but elevated interaction odds ratios ($p < 0.10$), including EPTC (OR = 1.68, 95 percent CI: 0.96, 2.94) (thiocarbamate herbicide), terbufos (OR = 1.52, 95 percent CI: 0.94, 2.45) (organophosphorothioate), dicamba (OR = 1.51, 95 percent CI: 0.95, 2.43) (benzoic herbicide), 2,2-dichloroethenyl dimethylphosphate (dichlorvos) (OR = 1.92, 95 percent CI: 0.98, 3.75) (organophosphate), aldicarb (OR = 2.01, 95 percent CI:

TABLE 5. Odds ratios,* confidence intervals, and number of exposed cases of prostate cancer by ever/never exposed and cumulative exposure score for methyl bromide and selected pesticides with no observed exposure-response association with prostate cancer,† Agricultural Health Study, 1993–1997

Pesticide	Ever/never use‡	Cumulative exposure score categories§ from enrollment questionnaire¶ and the farmer applicator and commercial applicator questionnaire#						*p* value, linear trend
		0 (no exposure, reference category)	I (lowest exposure)	II	III	IV	V (highest exposure)	
			Herbicides					
Alachlor¶								
Odds ratio	1.00	1	0.91	1.11	1.35	0.70	0.77	0.52
95% confidence interval	0.83, 1.20		0.70, 1.18	0.85, 1.45	0.95, 1.92	0.44, 1.12	0.48, 1.26	
No. of cases	263/303	303	81	82	40	20	20	
Atrazine¶								
Odds ratio	0.94	1	1.02	0.91	0.89	0.82	0.97	0.34
95% confidence interval	0.78, 1.14		0.79, 1.31	0.71, 1.18	0.65, 1.23	0.54, 1.25	0.63, 1.48	
No. of cases	364/202	202	113	114	57	27	28	
			Insecticides					
Carbofuran¶								
Odds ratio	1.25	1	1.29	1.93	1.00	0.68	1.01	0.23
95% confidence interval	1.03, 1.52		0.95, 1.74	1.42, 2.62	0.66, 1.51	0.38, 1.23	0.58, 1.77	
No. of cases	166/400	400	54	50	26	12	13	
Chlorpyrifos¶								
Odds ratio	0.90	1	0.95	1.04	0.89	0.64	0.73	0.23
95% confidence interval	0.74, 1.09		0.70, 1.30	0.75, 1.42	0.58, 1.36	0.35, 1.18	0.41, 1.31	
No. of cases	174/392	392	49	48	24	12	12	
Permethrin¶ (animal, animal confinement area application)								
Odds ratio	1.38	1	1.30	2.31	1.11	1.73	0.74	0.63
95% confidence interval	1.01, 1.89		0.76, 2.24	1.38, 3.87	0.54, 2.25	0.63, 4.75	0.24, 2.33	
No. of cases	48/518	518	16	16	8	4	4	
Aldrin#								
Odds ratio	1.32	1	1.44	1.12	1.56	0.87	1.38	0.70
95% confidence interval	1.09, 1.60		0.98, 2.11	0.76, 1.66	0.92, 2.64	0.38, 1.99	0.60, 3.19	
No. of cases	207/359	226	33	34	17	7	8	
DDT#,**								
Odds ratio	1.37	1	1.18	1.17	0.76	1.38	1.14	0.89
95% confidence interval	1.12, 1.67		0.84, 1.66	0.81, 1.69	0.46, 1.27	0.71, 2.68	0.59, 2.21	
No. of cases	323/243	178	50	45	23	11	11	

Table continues

0.95, 4.23) (carbamate insecticide), and carbofuran (OR = 1.58, 95 percent CI: 0.98, 2.55) (carbamate insecticide). No fungicide or fumigant, no chlorinated or inorganic insecticides, and no herbicides of the following chemical classes—acetamides, triazines, pyrimidines, phosphinic acids, imidazolines, bipyridyls, chlorinated phenoxies, dinitroanilines, or aliphatic hydrocarbons—had elevated ($p < 0.10$) interaction odds ratios.

To examine the specificity of these pesticide associations with family history, we examined the risk of prostate cancer from exposure to the same 45 pesticides, stratified by those with and without a family history of any cancer other than prostate cancer in a first-degree relative (data not shown). Only butylate (OR = 1.52, 95 percent CI: 1.13, 2.02) had a significantly elevated risk of prostate cancer in the group with a family history of cancer (other than prostate cancer), and only butylate showed significant effect modification, although a number of other nonsignificant interactions were observed. Permethrin for animal use (OR = 1.59, 95 percent CI: 1.07, 2.36) and phorate (OR = 1.31,

TABLE 5. Continued

Pesticide	Ever/never use	Cumulative exposure score categories from enrollment questionnaire and the farmer applicator and commercial applicator questionnaire						*p* value, linear trend
		0 (no exposure, reference category)	I (lowest exposure)	II	III	IV	V (highest exposure)	
Heptachlor#								
Odds ratio	1.20	1	1.08	0.86	1.00	0.64	0.66	0.41
95% confidence interval	0.99, 1.47		0.67, 1.74	0.53, 1.41	0.51, 1.98	0.20, 2.03	0.21, 2.09	
No. of cases	165/401	273	20	19	10	6	3	
			Fumigants					
Methyl bromide¶								
Odds ratio	1.10	1	1.01	0.76	0.70	2.73	3.47	0.004
95% confidence interval	0.77, 1.36		0.66, 1.56	0.47, 1.25	0.38, 1.28	1.18, 6.33	1.37, 8.76	
No. of cases	84/482	482	23	22	11	6	5	
			Fungicides					
Captan¶								
Odds ratio	1.05	1	1.07	1.09	1.89	0.95	2.79	0.11
95% confidence interval	0.78, 1.43		0.50, 2.30	0.48, 2.48	0.58, 6.12	0.23, 3.93	0.35, 22.1	
No. of cases	48/518	518	7	6	3	2	1	

* Odds ratios adjusted for age and family history of prostate cancer.

† Five pesticides (i.e., trichlorofon, ziram, aluminum phosphide, ethylene dibromide, carbon tetrachloride/carbon disulfide) were not included in this table because we observed five or fewer exposed cases. Thirty-five other pesticides (i.e., cyanazine, dicamba, 2,4-dichlorophenoxyacetic acid, thiocarbamate, glyphosate, imazethapyr, metachlor, trifluralin, coumaphos, 2,2-dichloroethenyl dimethylphosphate, fonofos, permethrin for crop use, turbufos, chlorothalonil, butylate, chlorimuron-ethyl, metribuzin, paraquat, pendimehalin, petroleum oil used as herbicide, 2,4,5-trichlorophenoxyacetic acid, 2,4,5-trichlorophenoxypropionic acid, aldicarb, carbaryl, chlordane, diazinon, dieldrin, lindane, malathion, parathion, phorate, toxaphene, benomyl, maneb/macozeb, methylaxyl) were not included in this table because they did not demonstrate a significant exposure-response association with prostate cancer.

‡ Study subjects in the ever/never analysis equal or exceed the number in the exposure-response analysis because of occasional missing data for the exposure algorithm.

§ Categories: 0 (no use), I (0.1–33.3 percentile of use), II (33.4–66.7 percentile of use), III (66.8–83.3 percentile of use), IV (83.4–91.6 percentile of use), and V (>91.6 percentile of use).

¶ Information on age, family history of prostate, ever/never use of 50 pesticides, and cumulative use of 22 pesticides taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 prostate cancer cohort members.

Information on cumulative pesticide use of 28 pesticides from farmer applicator and commercial applicator questionnaire completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members.

** DDT, dichlorodiphenyltrichloroethane.

95 percent CI: 1.03, 1.67) were the only chemicals observed to have a significant excess risk among those with no family history of cancer, but no significant effect modification was observed (data not shown). We also examined the risk of any cancer other than prostate cancer (n = 816 other cancers) among those exposed to each of the 45 pesticides, stratified by a family history of any cancer (other than prostate cancer), and found little evidence of effect modification (data not shown).

DISCUSSION

The literature suggests that prostate cancer may be elevated among farmers (14, 16, 18–22, 32, 33). Consistent with these earlier reports, we found that farmers in the Agricultural Health Study cohort experienced a small but statistically significant excess of prostate cancer compared with the general population in Iowa and North Carolina (SIR = 1.14). It is challenging to relate cancer risks to specific lifestyle or agricultural exposures. We used four approaches in this paper. First, we evaluated a broad range of factors including demographic characteristics, lifestyle factors, agricultural factors, and nonfarm occupational factors to identify associations with prostate cancer. Second, factor analysis was used to identify groupings of pesticide exposures that might be related to prostate cancer. Third, analyses of individual pesticides were conducted. Finally, effect modification was assessed between individual pesticide use and a family history of prostate cancer.

In the factor analysis, three temporally and geographically distinct factors of pesticide use were identified. Only one of these factors (factor 3) was significantly related to prostate cancer. This factor included ever use of the chlorinated pesticides aldrin, chlordane, dieldrin, DDT, heptachlor, and

TABLE 6. Odds ratios, confidence intervals, and number of prostate cancer cases by exposure status to 15 of 45* evaluated pesticides with and without a first-degree family history of prostate cancer, Agricultural Health Study, 1993–1997

Pesticide (chemical class)	Prostate cancer risk for those with exposure to pesticide but no family history of prostate cancer†			Prostate cancer risk for those with exposure to pesticide and a family history of prostate cancer‡			Statistical interaction between family history of prostate cancer and exposure to pesticide§		
	Odds ratio	95% confidence interval	No. of prostate cancer cases	Odds ratio	95% confidence interval	No. of prostate cancer cases	Interaction odds ratio	95% confidence interval	*p* value
Herbicides									
Alachlor (acetamide)	0.93	0.76, 1.14	190	1.36	0.88, 2.10	56	1.50	0.93, 2.41	0.10
Atrazine (triazine)	0.88	0.72, 1.09	253	1.28	0.77, 2.12	70	1.52	0.88, 2.62	0.13
Butylate (thiocarbamate)	0.96	0.77, 1.20	110	1.78	1.16, 2.73	44	1.93	1.19, 3.11	0.007
Dicamba (benzoic)	0.95	0.77, 1.17	163	1.35	0.88, 2.08	50	1.51	0.95, 2.43	0.09
EPTC¶	0.90	0.67, 1.20	55	1.44	0.89, 2.34	24	1.68	0.96, 2.94	0.07
Insecticides									
Aldicarb (carbamate)	0.81	0.57, 1.16	35	1.60	0.83, 3.09	11	2.01	0.95, 4.23	0.07
Carbofuran (carbamate)	1.14	0.92, 1.42	118	1.81	1.18, 2.77	43	1.58	0.98, 2.55	0.06
Chlorpyrifos (organophosphorothioate)	0.82	0.66, 1.02	121	1.29	0.84, 1.98	40	1.65	1.02, 2.66	0.04
Coumaphos (organophosphorothioate)	0.86	0.57, 1.28	26	2.17	1.24, 3.82	16	2.58	1.29, 5.18	0.008
2,2-Dichloroethenyl dimethylphosphate (organophosphate)	0.95	0.66, 1.37	32	1.75	1.00, 3.06	16	1.92	0.98, 3.75	0.06
Fonofos (organophosphonodithioate)	0.92	0.71, 1.19	71	1.80	1.14, 2.84	30	2.04	1.21, 3.44	0.008
Permethrin, animal use (pyrethriod)	1.13	0.77, 1.66	30	2.38	1.34, 4.25	16	2.31	1.17, 4.56	0.02
Phorate (organophosphorodithioate)	1.05	0.85, 1.30	140	1.67	1.09, 2.56	48	1.64	1.02, 2.63	0.04
Terbufos (organophosphorodithioate)	0.99	0.80, 1.23	126	1.45	0.95, 2.23	40	1.52	0.94, 2.45	0.09
Fumigants									
Methyl bromide (halogenated hydrocarbon)	0.93	0.70, 1.23	58	1.31	0.75, 2.29	16	1.36	0.73, 2.54	0.34

* Five pesticides (i.e., trichlorofon, ziram, aluminum phosphide, ethylene dibromide, carbon tetrachloride/carbon disulfide) were not included in this table because we observed five or fewer exposed cases. Thirty other pesticides (i.e., chlorimuron-ethyl, cyanazine, 2,4-dichlorophenoxyacetic acid, glyphosate, imazethapyr, metachlor, trifluralin, permethrin for crop use, chlorothalonil, metribuzin, paraquat, pendimethalin, petroleum oil used as herbicide, 2,4,5-trichlorophenoxyacetic acid, 2,4,5-trichlorophenoxypropionic acid, aldrin, carbaryl, chlordane, diazinon, dieldrin, dichlorodiphenyltrichloroethane, heptachlor, lindane, malathion, parathion, toxaphene, benomyl, captan, maneb/macozeb, methylaxyl) were not included in this table because they did not demonstrate a significant exposure-response association with prostate cancer.

† Reference group, no family history of prostate cancer and no pesticide exposure.

‡ Reference group, family history of prostate cancer and no pesticide exposure.

§ Adjusted for age and family history of prostate cancer.

¶ EPTC, *S*-ethyl dipropylthiocarbamate.

toxaphene; ever use of two chlorinated phenoxy herbicides (2,4,5-T and 2,4,5-TP); and farmers over the age of 50 years. Three of the chlorinated insecticides in this factor, that is, aldrin, DDT, and heptachlor, were associated with a significant excess risk of prostate cancer in ever/never analyses, although no exposure-response pattern was observed for these chemicals. Because the factors in this analysis are based on ever versus never use (pesticide) data, they would be more apt to show statistical significance if several chemicals in the factor had the same association with prostate cancer. Lacking an exposure-response pattern with individual pesticides suggests that the relation with chlorinated pesticides could be due to other exposures not identified in this analysis.

Among the 45 specific pesticides evaluated, the only statistically significant exposure-response trend observed occurred with methyl bromide. This could be a chance observation because we evaluated a large number of pesticides. However, methyl bromide was significantly associated with prostate cancer risk among both North Carolina and Iowa pesticide applicators and among both private and commercial applicators. The association was also found

when we used other measures of exposure, including frequency of use (days per year) and total days of use in a lifetime. Moreover, the pattern of risk was not substantially changed when other pesticides were added to the logisitic model with methyl bromide. Methyl bromide is an alkylating agent (34), and the National Institute for Occupational Safety and Health considers it to be a potential occupational carcinogen (35). Additionally, evidence of genotoxicity was observed in a small cross-sectional study of nonsmoking methyl bromide fumigation workers, with excesses of micronuclei and gene mutations (i.e., *HPRT* mutations) observed in the lymphocytes and oropharyngeal cells of exposed workers (36). Field testing by the National Institute for Occupational Safety and Health demonstrates that concentrations of methyl bromide in the breathing zones of agricultural workers conducting soil fumigation under tarpaulins (a common soil fumigation procedure used by many farmers in North Carolina but not in Iowa) frequently exceeded the recommended occupational limits set by the Institute (37). Approximately 27,000 tons of methyl bromide were used in 1997 in the United States for soil fumigation (87 percent), commodity and quarantine treatment (8 percent), and structural fumigation (5 percent) (38). Our data would suggest that, if methyl bromide is responsible for an elevated prostate cancer risk, it may be among only those with relatively frequent use. Because we had no specific a priori hypothesis linking methyl bromide to prostate cancer, we cannot rule out the possibility that our observation occurred by chance alone; however, the consistency of the findings argues against this.

A family history of prostate cancer among first-degree relatives conferred a twofold excess risk of prostate cancer on these subjects, consistent with other reports (8). Furthermore, significant associations between specific pesticides and prostate cancer risk were observed largely among those with a family history of prostate cancer. Although a family history of cancer other than prostate cancer seemed to have a similar pattern of prostate cancer risk with some pesticides, only butylate had a statistically significant positive association. No pattern of effect modification was seen when we evaluated all cancers, other than prostate, and a history of cancer other than prostate cancer. These findings tend to mitigate the possibility of a family history-driven case-recall bias in these data. The specificity for family history of prostate cancer suggests the possibilities of familial genes that enhance susceptibility or of shared environmental risk factors for prostate cancer among family members. The significant effect modification in selected chemical classes (e.g., thiocarbamates, organophosphorothioates, and pyrethoid) lends further support to this hypothesis.

This study does have limitations. First, the exposure weightings used in our algorithm are based on a literature review and not on direct measurements of exposure made within the study cohort. An exposure-monitoring effort within the study cohort is under way and will help to refine our estimates of exposure in the future. Second, some subjects in this study were asked to recall pesticide use from years ago. For the oldest members of the cohort, this was decades earlier. Although recall can be faulty after many years, previous evaluation of this issue has shown that recall of pesticide use by the Agricultural Health Study cohort is comparable with the recall of other variables, such as diet and alcohol consumption, which have been used by epidemiologists in other studies as a standard procedure (39). Third, follow-up of this cohort is relatively short, and it is not possible to evaluate time-dependent exposures and risk.

The Agricultural Health Study has five principal strengths. First, the data collection prior to the diagnosis of cancer precludes the possibility of case-ascertainment bias. Second, detailed information on exposure for each pesticide included days of use per year, years of use, application methods, and protective equipment use, adding specificity to the analysis. Third, ascertainment of and statistical adjustment for other occupational, demographic, and lifestyle factors previously suggested as prostate cancer risk factors mitigate the possibility of uncontrolled confounding. Fourth, the large size of the study gives sufficient statistical power to examine the risk of exposure to a number of specific chemical exposures. Fifth, the outcome is cancer incidence obtained from population-based tumor registries, which eliminates survival problems.

In conclusion, farmers and commercial pesticide applicators have a small but significantly higher rate of prostate cancer than the general population of Iowa and North Carolina. Occupational use of a widely used halogenated fumigant, methyl bromide, was shown to be significantly associated with a risk of prostate cancer in the Agricultural Health Study cohort among those with the highest exposure. A pattern of chlorinated pesticide use may also be related to prostate cancer risk. A family history of prostate cancer appeared to significantly modify the prostate cancer risks among those using several widely used insecticides, including chlorpyrifos, coumaphos, fonofos, phorate, and permethrin for animal use, and a herbicide, butylate. The methyl bromide and family history findings are novel and unexpected and need to be confirmed in later follow-up periods in this cohort and in other studies of prostate cancer in farmers.

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(*Appendix follows*)

APPENDIX

APPENDIX TABLE 1. Results of factor analysis for pesticide use, age, and state (n = 42,948), Agricultural Health Study, 1993–1997*

Variable	Factor I	Factor II	Factor III
Herbicides			
Atrazine	58†	0	1
Dicamba	54†	−23	3
Cyanazine	55†	−12	4
Metolachlor	59†	8	−11
EPTC‡	48†	−8	−2
Alachlor	49†	10	3
Imazethapyr	60†	−22	−11
Glyphosate	31	27	−5
Trifluralin	60†	−2	−2
2,4-D‡	47†	0	8
Chlorimuron ethyl	54†	17	−13
Metribuzin	65†	−1	3
Paraquat	19	51†	4
Petrolium oil	44†	12	12
Pendimethalin	50†	30	−15
Butylate	52†	9	8
2,4,5-TP‡	6	10	44†
2,4,5-T‡	6	0	56†
Insecticides			
Permethrin (crop)	32	30	−8
Terbufos	40†	−1	4
Fonofos	30	−9	12
Trichlorfon	2	10	2
Carbofuran	30	16	16
Chlorpyrifos	31	22	0
Coumaphos	9	1	16
Permethrin (animal)		23	−58†
Dichlorvos‡	18	−5	21
Lindane	14	6	36
Malathion	34	16	16
Parathion	6	40†	25
Carbaryl	11	44†	17
Diazinon	7	39	25
Aldicarb	5	61†	−5
Phorate	36	−2	19
Aldrin	9	−7	65†
Chlordane	0	18	53†
Dieldrin	−1	0	59†
DDT‡	−11	11	62†
Heptachlor	10	−13	65†
Toxaphene	6	27	43†

Table continues

APPENDIX TABLE 1. Continued

Variable	Factor I	Factor II	Factor III
Fumigants			
Methyl bromide	−11	59†	−3
Aluminum phosphide	14	16	15
80/20 mix	2	11	38
Ethylene dibromide	−2	31	25
Fungicides			
Chlorothalonil	2	53†	−11
Captan	14	16	9
Ziram	−5	23	22
Benomyl	−3	61†	6
Mancozeb	−8	58†	10
Metylaxyl	−1	62†	−3
State of Iowa	36	−70†	10
Age of ≥50 years	−21	−11	52†
% of variance explained	0.44	0.30	0.15
% of cumulative variance	0.44	0.74	0.89

* Factor loadings are multiplied by 100 and rounded to the nearest integer.

† Indicates a factor loading score of greater than or equal to ±0.40.

‡ EPTC, *S*-ethyl dipropylthiocarbamate; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; dichlorvos, 2,2-dichloroethenyl dimethyl-phosphate; DDT, dichlorodiphenyltrichloroethane.