Retinal Degeneration in Licensed Pesticide Applicators

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Background *Retinal degeneration is the leading cause of visual impairment in older adults, but little is known about its relationship to neurotoxic exposures.*
Methods *The Agricultural Health Study is a cohort study of licensed pesticide applicators from Iowa and North Carolina. We used cross-sectional data from self-administered questionnaires given at enrollment in 1994–1996 to compare pesticide use in 154 applicators who reported retinal degeneration and 17,804 controls.*
Results *Retinal degeneration was associated with fungicide use (odds ratio = 1.8, 95% confidence interval = 1.3–2.6). This relationship was seen in subgroups defined by state, demographic characteristics, or medical history, as well as in the entire group. Risk increased with cumulative days of fungicide use (P for trend = 0.011) and was greater when application methods involving greater personal exposure were used. Retinal degeneration was also related to use of organochlorine or carbamate insecticides, but these associations were less consistent. Since nearly all applicators used organophosphate insecticides and herbicides, these exposures could not be effectively evaluated.*
Conclusions *These results suggest that exposure to some fungicides and insecticides may increase risk of retinal degeneration.* Am. J. Ind. Med. 37:618–628, 2000.
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KEY WORDS: retinal degeneration; fungicides; insecticides; organochlorines; carbamates; organophosphates; application methods

INTRODUCTION

Retinal degeneration is the leading cause of visual impairment in older adults, but its etiology is not well understood. The epidemiology of macular degeneration, the most common form of retinal degeneration, has been described [Vingerling et al., 1995; Pauleikhoff and Koch, 1995]. Prevalence increases with age, from less than 1% for individuals in their fifties to 3% for those in their eighties. Prevalence is higher in women and lower in African-Americans. Other proposed risk factors include light eye color, hypertension, history of cardiovascular disease, diabetes, sun exposure, and low antioxidant levels, but studies of these risk factors have produced inconsistent results. Studies demonstrating familial aggregation suggest that genetic susceptibility may play a role in macular degeneration [Vingerling et al., 1995; Pauleikhoff and Koch, 1995].

Little is known concerning the possible relationship of retinal degeneration to occupational or environmental exposure to neurotoxicants. Available evidence mainly concerns exposure to pesticides, primarily organophosphate insecticides. Clinical studies in Japan have suggested that a wide range of ocular disturbances, including retinal degeneration, may be associated with organophosphate exposure [Ishikawa, 1973; Dementi, 1994]. A cross-sectional study of fenthion sprayers in India found macular

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degeneration in 19% of the workers, compared to 3% of controls [Misra et al., 1985]. Studies of rats and dogs found that several organophosphates produced ocular toxicity, including abnormal electroretinograms and histological evidence of retinal degeneration, and suggested that the retina may be more sensitive to organophosphates than other neural structures [Dementi, 1994]. Animal data submitted to the US Environmental Protection Agency by pesticide registrants has also provided evidence that organophosphate exposure is associated with retinal degeneration [Dementi, 1994; Boyes et al., 1994]. Few studies have examined the effects of pesticides other than organophosphates. Case reports suggest that ocular toxicity may also result from exposure to carbamate [Morse et al., 1979] or organochlorine insecticides [Kilburn, 1997; Taylor et al., 1978]. Two animal studies indicate that fungicides may also produce ocular toxicity: one found histological evidence of retinal degeneration after treatment of beagle dogs with thiram [Maita et al., 1991], and a second showed that radiolabeled benomyl was concentrated in mouse retina after systemic administration [Hellman and Laryea, 1990].

To investigate the relationship of retinal degeneration to pesticide exposure, we used data from the Agricultural Health Study, a prospective cohort study of licensed pesticide applicators in Iowa (IA) and North Carolina (NC). Cross-sectional data collected at the time of enrollment included applicators' self-reports of a physician diagnosis of retinal degeneration as well as information on pesticide exposure.

MATERIALS AND METHODS

Population and Questionnaires

The Agricultural Health Study is a collaborative effort of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the US Environmental Protection Agency. The methods of this study have previously been described in detail [Alavanja et al., 1996]. Briefly, applicators who use restricted pesticides must obtain state certification or training every one to three years. All individuals applying for certification in IA or NC in 1994 through 1996 were invited to enroll in the study. Approximately 52,400 private applicators were enrolled in the study, 82% of those eligible.

Data collected with two questionnaires were used for the present cross-sectional analysis. At the time of enrollment, the participants completed a self-administered questionnaire that collected information on demographic characteristics, lifestyle, medical history, crops and livestock raised, and pesticide use. A supplemental questionnaire, completed at home by 43% of the enrolled private applicators, sought additional information in all these categories. Enrollees who did or did not complete the supplemental questionnaire were very similar in most respects, including lifestyle, crops raised, and pesticide use [Tarone et al., 1997]; nevertheless, potential for selection bias remains. This issue is being addressed in another study within the Agricultural Health Study.

This analysis is based on the 17,958 private applicators who completed both questionnaires and provided information on retinal degeneration and the major covariates: age, sex, state, and education. Most were farmers (99%) and most were white men (97%). Cases of retinal degeneration were the 154 applicators who answered "Yes" to the question, "Has a doctor ever told you that you had retinal or macular degeneration?" The remaining 17,804 applicators, who answered in the negative, served as controls. Because of missing data, the number of applicators included in each analysis is somewhat less; exact numbers are given in the tables.

Analysis

We analyzed the data by logistic regression by using SAS™ (Cary, NC). Since age, sex, and education were associated with retinal degeneration (Table I), we included these variables in all models; age was used as a continuous variable and education as a three-level ordinal variable. We also included state of residence (IA or NC) in the models, since farming practices and pesticide use differed by state. Some analyses were stratified by state. We also repeated certain analyses after excluding applicators less than 50 years old; analyses restricted to older applicators were also adjusted for age.

In order to evaluate potential confounders, we examined the relationship of retinal degeneration to several factors associated with this condition in previous studies, including demographic, host, and lifestyle characteristics and aspects of medical history. To assess the internal consistency of self-reported diagnoses, we investigated the association of retinal degeneration with visual dysfunction and other eye diseases. We examined the relationship of retinal degeneration to several factors representing potential pesticide exposure, including current farm size, crops under cultivation, and lifetime use of pesticides classified by function and chemical type. Data were available on ever use of 35 specific fungicides, 29 organophosphate insecticides, eight carbamate insecticides, 10 organochlorine insecticides, four pyrethroid insecticides, 13 fumigants, and 52 herbicides. Data on cumulative days of use of specific pesticides were available for a subset of each class. Since initial analyses indicated that retinal degeneration was related to the use of fungicides and insecticides but not to the use of herbicides or fumigants, we focused further analyses on aspects of fungicide and insecticide exposure, including use of specific chemicals, application methods, and use of personal protective equipment. Finally, we examined the relationship of retinal degenera-

TABLE I. Relationship of Retinal Degeneration to Characteristics of Pesticide Applicators in Iowa and North Carolina*

Characteristic	Percent with characteristic		Adjusted OR[a] (95% CI)
	Cases	Controls	
Demographic characteristics			
Age			
18–30	3	8	0.7 (0.3–1.8)
31–40	4	22	0.3 (0.1–0.7)
41–50	16	26	1.0 (referent)
51–60	21	23	1.7 (1.0–2.9)
61–70	36	17	4.5 (2.8–7.4)
71–94	21	5	9.1 (5.3–15.8)
Trend test $P < 0.001$			
Sex			
Men	92	97	1.0 (referent)
Women	8	3	3.5 (1.9–6.4)
State			
Iowa	59	64	1.0 (referent)
North Carolina	41	36	1.2 (0.8–1.6)
Education			
< High school	7	9	0.5 (0.3–1.0)
High school	44	48	1.0 (referent)
> High school	49	44	1.6 (1.2–2.3)
Trend test $P = 0.00004$			
Host characteristics			
Eye color			
Brown	32	27	1.0 (referent)
Blue	45	47	0.8 (0.6–1.2)
Green, grey, or hazel	24	27	0.7 (0.5–1.2)
Skin reaction to first sun exposure each year			
No sunburn	19	22	1.0 (referent)
Mild sunburn	58	56	1.3 (0.8–1.9)
Severe sunburn	23	22	1.1 (0.7–1.9)
Trend test $P = 0.696$			
Lifestyle characteristics			
Ever smoke cigarettes			
No	46	54	1.0 (referent)
Yes	54	46	1.2 (0.9–1.7)
Pack-years smoked			
0	48	56	1.0 (referent)
1–5	14	11	1.7 (1.0–2.8)
6–15	12	14	0.9 (0.5–1.6)
16–30	12	10	1.1 (0.6–1.9)
31+	14	9	1.4 (0.8–2.3)
Trend test $P = 0.434$			

(*Continued*)

TABLE I. (*Continued*)

Characteristic	Percent with characteristic Cases	Controls	Adjusted OR[a] (95% CI)
Drinks per month in last year			
0	62	53	1.0 (referent)
1–5	14	12	1.1 (0.7–1.8)
6–10	4	10	0.5 (0.2–1.2)
11–30	11	13	1.0 (0.6–1.7)
31+	9	11	1.0 (0.6–1.8)
Trend test $P = 0.724$			
Vegetable servings per week			
0–4	20	31	1.0 (referent)
5–10	42	45	1.3 (0.8–2.1)
11+	38	24	1.7 (1.0–2.8)
Trend test $P = 0.028$			
Fruit servings per week			
0–4	44	57	1.0 (referent)
5–10	38	34	1.0 (0.7–1.5)
11+	18	9	1.3 (0.8–2.2)
Trend test $P = 0.380$			
Use vitamins			
No	53	68	1.0 (referent)
Yes, irregularly	18	15	1.6 (1.0–2.5)
Yes, at least once a week	30	17	1.6 (1.1–2.3)
Trend test $P = 0.011$			

*Total number of cases = 133–154; total number of controls = 17,010–17,804.
[a]All models include age (as a continuous variable), sex, state, and education (as a ordinal variable), except the model with categorical age variables, which did not include the continuous age variable, and the model with categorical education variables, which did not include the ordinal education variable.

tion to occupational exposure to neurotoxicants other than pesticides.

The proportion of applicators with missing data for a given variable ranged up to 16% for cases and 6% for controls; in general, cases were more likely to have missing data. Applicators who were older, female, from North Carolina, or less educated were also more likely to have missing data. We examined the effect of missing data by using the analyses shown in Tables III and V, two examples with a high proportion of missing data. Missing responses were recoded as ‘‘no’’ for variables positively associated with retinal degeneration and as ‘‘yes’’ for variables inversely associated with retinal degeneration. In all cases, results were substantially unchanged although point estimates were slightly closer to one and less precise.

The Institutional Review Boards of the National Cancer Institute and the National Institute of Environmental Health Sciences, National Institutes of Health, approved the Agricultural Health Study. The study was explained to potential participants, and consent was signified by return of questionnaires.

RESULTS

Demographic, Host, and Lifestyle Characteristics, and Sun Exposure (Table I)

We examined characteristics that some previous studies had suggested were related to retinal degeneration; selected results are presented in Table I. The mean (SD) age of the cases was 60.6 (12.9) and of the controls 48.8 (13.1); the odds ratio (OR) for each 10-year increment in age was 2.2 [95% confidence interval (CI) = 1.9–2.5]. Cases and controls also differed in gender, education, and consumption of vegetables. Since many lifestyle factors are related to age, we repeated these analyses restricting the data to applicators at least 50 years old; results were virtually identical (data not shown). There was no difference between groups in the daily hours of sun exposure either at the time of interview or ten years previously, nor in the use of hats with brims to protect eyes from sun exposure (data not shown).

Visual Dysfunction, Other Eye Diseases, and Other Medical Conditions (Table II)

The extent of visual dysfunction in cases was consistent with the self-reported diagnosis. Applicators reporting retinal degeneration were also more likely to have other eye diseases and several physician-diagnosed medical conditions and poisonings potentially related to retinal degeneration. Essentially the same relationships were observed when the analyses were limited to applicators at least 50 years old (data not shown).

Current Farm Size and Crops (Table III)

Despite large differences between IA and NC in farming practices, cases from both states had smaller farms than controls and were less likely to raise livestock or grain but more likely to raise orchard fruit (apples or peaches); ORs for farm size or for raising livestock, grain, or orchard fruit were similar in the two states. Since these results reflected farming practices at the time the questionnaires were completed, and might therefore be heavily influenced by age, we repeated the analyses in a subset restricted to applicators at least 50 years old. Similar results were observed, although the risk estimates were less precise (data not shown).

Pesticide Use (Table IV)

Initial analyses of ever use of pesticides classified by function and chemical type were stratified by state, since patterns of pesticide use may vary by state. The main finding was that fungicide use was associated with retinal degeneration in both states; use of other pesticides was sometimes related to retinal degeneration, but the results were less consistent. Interactions of pesticide use by state

TABLE II. Relationship of Retinal Degeneration to Visual Dysfunction and Other Eye Diseases and Medical Conditions in Pesticide Applicators in Iowa and North Carolina*

	Percent with condition		
Condition	**Cases**	**Controls**	**Adjusted OR[a] (95% CI)**
Visual dysfunction and eye diseases			
Wear glasses to correct nearsightedness	67	40	2.4 (1.7–3.4)
Wear glasses to correct farsightedness	68	47	1.0 (0.7–1.4)
Legally blind in either eye	17	1	11.6 (7.3–18.5)
Problem with blurred or double vision once a month or more often in last year	24	5	4.8 (3.2–7.1)
Problem with night vision once a month or more often in last year	32	9	4.6 (3.2–6.6)
Cataracts[b]	31	4	5.3 (3.6–7.9)
Glaucoma[b]	4	1	1.8 (0.8–4.3)
Detached retina[b]	13	1	14.0 (8.1–24.0)
Other medical conditions			
Diabetes[b]	13	4	2.3 (1.4–3.8)
Myocardial infarction[b]	10	3	1.7 (1.0–3.0)
Arrhythmia[b]	18	6	1.9 (1.2–2.9)
Angina[b]	11	5	1.3 (0.8–2.2)
Hypertension requiring medication[b]	40	16	2.1 (1.5–2.9)
Stroke[b]	5	1	3.2 (1.5–6.9)
Head injury requiring medical attention[b]	17	12	1.6 (1.0–2.4)
Lead poisoning[b]	1	0.2	5.0 (1.1–22.0)
Pesticide poisoning[b]	3	2	1.5 (0.6–3.6)

*In each case, data are shown for participants with the condition, and the comparison group is participants without the condition. Total number of cases = 148–154; total number of controls = 17,395–17,804.
[a]All models include age (as a continuous variable), sex, state, and education (as a ordinal variable).
[b]Self-report of physician diagnosis of condition.

TABLE III. Relationship of Retinal Degeneration to Current Farm Size and Crops in Pesticide Applicators in Iowa and North Carolina*

	North Carolina			Iowa		
	Percent raising crop			Percent raising crop		
Crop	Cases (n = 44)[a]	Controls (n = 5,614)[a]	Adjusted OR[b] (95% CI)	Cases (n = 85)[a]	Controls (n = 11,333)[a]	Adjusted OR[b] (95% CI)
Planted > 50 acres[c]	24	54	0.4 (0.2–0.9)	92	97	0.5 (0.2–1.0)
Livestock or poultry	25	43	0.5 (0.2–1.0)	52	73	0.6 (0.4–0.9)
Grain	45	70	0.5 (0.2–0.8)	92	98	0.3 (0.1–0.6)
Orchard fruit	20	6	2.6 (1.2–5.6)	7	2	2.7 (1.1–6.4)
Other fruit	23	12	1.5 (0.7–3.1)	5	3	1.1 (0.4–3.1)
Vegetables	20	21	0.8 (0.4–1.7)	5	5	0.7 (0.3–2.0)
Cotton	11	13	1.5 (0.6–3.8)	0	0	—
Christmas trees	16	8	2.3 (1.0–5.2)	0	0.4	—
Peanuts	18	13	2.2 (1.0–4.7)	1	0	—
Tobacco	29	43	0.7 (0.4–1.4)	0	0	—

*In each case, data are shown for participants who raised the crop, and the comparison group is participants who did not raise the crop.
[a] Total number of cases or controls.
[b] All models include age (as a continuous variable), sex, and education (as a ordinal variable).
[c] Excludes applicators who did not own or work on a farm.

TABLE IV. Relationship of Retinal Degeneration to Ever Use of Pesticides, Classified by Function and Chemical Type, in Pesticide Applicators in Iowa and North Carolina*

	North Carolina			Iowa		
	Percent ever using any pesticide in class			Percent ever using any pesticide in class		
Pesticide class	Cases (n = 63)[a]	Controls (n = 6,428)[a]	Adjusted OR[b] (95% CI)	Cases (n = 91)[a]	Controls (n = 11,376)[a]	Adjusted OR[b] (95% CI)
Fungicides	75	67	2.0 (1.1–3.6)	27	16	1.7 (1.1–2.8)
Organochlorine insecticides	73	54	1.6 (0.9–2.9)	68	43	1.5 (0.9–2.4)
Organophosphate insecticides	90	85	2.1 (0.9–5.0)	92	91	1.3 (0.6–2.8)
Carbamate insecticides	83	81	1.1 (0.6–2.2)	67	45	1.9 (1.2–3.0)
Pyrethroid insecticides	21	21	1.4 (0.7–2.6)	24	31	0.9 (0.6–1.5)
Fumigants	44	45	1.2 (0.7–2.0)	18	8	1.7 (1.0–2.9)
Herbicides	90	95	0.8 (0.3–2.1)	97	99	0.5 (0.1–1.6)

*In each case, data are shown for participants who used the pesticide, and the comparison group is participants who did not use the pesticide.
[a] Total number of cases or controls.
[b] All models include age (as a continuous variable), sex, and education (as a ordinal variable).

were not significant ($P > 0.15$). When we combined data from NC and IA, we found that retinal degeneration was associated with use of fungicides (OR = 1.8, 95% CI = 1.3–2.6), organochlorines (OR = 1.5, 95% CI = 1.1–2.2), organophosphates (OR = 1.6, 95% CI = 0.9–2.9), and carbamates (OR = 1.6, 95% CI = 1.1–2.4). Use of pyrethroids, fumigants, or herbicides was not related to retinal degeneration (data not shown). Therefore, subsequent analyses were focused on use of fungicides, organochlorines, organophosphates, and carbamates.

Effects in Subgroups

After combining data from the two states to provide larger numbers, restricting the analysis to applicators ≥ 50 years old or to white men did not change the results, nor did stratifying on level of education ($\leq$ high school or > high school). ORs for fungicide use in these subgroups ranged from 1.6 to 2.1. Elevated ORs were also observed for organochlorines (1.4–1.9), organophosphates (1.4–1.9), and carbamates (1.3–1.9) in these subgroups. We also examined the consequence of excluding one at a time applicators with other medical conditions which were potential confounders (cataracts, lead poisoning) or which might have been mistaken for retinal degeneration by the applicators (diabetic retinopathy, detached retina). ORs for use of fungicides (1.8–2.2), organochlorines (1.5–1.8), organophosphates (1.2–1.6), and carbamates (1.5–1.8) were not substantially changed by these exclusions.

Lifetime Pesticide Use

The risk of retinal degeneration increased with increasing total lifetime days of fungicide use (P for trend = 0.011). Compared to applicators who did not use fungicides, the OR for 1–50 days of use was 1.4 (95% CI = 0.9–2.3), and the OR for ≥ 51 days was 2.0 (95% CI = 1.2–3.2). A similar dose–response relationship was observed for organochlorine use (P for trend = 0.006). Compared to applicators who did not use organochlorines, the OR for 1–50 days was 1.3 (0.9–2.0) and for ≥ 51 days 1.8 (1.2–2.7). In contrast, there was no dose–response relationship for use of organophosphates (P for trend = 0.516) or carbamates (P for trend = 0.322).

Specific Pesticides

We investigated the relationship of retinal degeneration to ever use of specific pesticides which were used by at least 1% of the control applicators. Retinal degeneration was associated with ever use of 9 of 12 specific fungicides (benomyl, captan, chlorothanonil, copper ammonia carbonate, ferbam, maneb, metalaxyl, PCNB, and sulfur; ORs = 1.5–2.9); ever use of 3 of 10 specific organochlorines (DDT, dicofol, and endosulfan; ORs = 1.7–3.7); ever use of 7 of 21 specific organophosphates (dichlorvos, cygon, guthion, imidan, malathion, orthene, and prolate; ORs = 1.6–3.5); and ever use of 2 of 5 carbamates (carbaryl, oxanyl; ORs = 1.8–2.5). One organophosphate had an inverse association with retinal degeneration (terbufos; OR = 0.5).

Data on cumulative days of use of specific pesticides were available for a subset of each class. Table V shows that dose–response relationships were observed for five of the six fungicides evaluated and Table VI shows that dose–response relationships were found for four of the seven organochlorines evaluated. In contrast, dose–response relationships (P for trend < 0.05) were observed for only two of nine organophosphates evaluated, dichlorvos and diazinon, and only one of three carbamates evaluated, carbaryl (data not shown).

TABLE V. Relationship of Retinal Degeneration to Lifetime Days of Use of Specific Fungicides in Pesticide Applicators in Iowa and North Carolina*

	Percent using fungicide		
Days used fungicide	Cases	Controls	Adjusted OR[a] (95% CI)
Benomyl			
0	85	93	1.0 (referent)
1–50	6	4	1.5 (0.7–3.1)
51+	8	3	2.6 (1.4–5.0)
Trend test $P = 0.006$			
Captan			
0	88	96	1.0 (referent)
1–50	3	2	1.3 (0.4–4.1)
51+	8	2	4.0 (2.0–8.1)
Trend test $P = 0.001$			
Chlorothalonil			
0	88	93	1.0 (referent)
1–50	6	3	2.0 (0.9–4.4)
51+	6	4	2.4 (1.1–5.2)
Trend test $P = 0.022$			
Maneb			
0	86	92	1.0 (referent)
1–50	4	4	1.0 (0.4–2.2)
51+	10	4	2.3 (1.3–4.3)
Trend test $P = 0.023$			
Metalaxyl			
0	80	82	1.0 (referent)
1–50	13	13	1.3 (0.7–2.2)
51+	8	6	2.3 (1.1–4.5)
Trend test $P = 0.034$			
Ziram			
0	98.7	99.6	1.0 (referent)
1–50	0.7	0.2	2.8 (0.4–20.9)
51+	0.7	0.2	3.2 (0.4–25.1)
Trend test $P = 0.219$			

*Total number of cases = 118–149; total number of controls = 15,959–17,413.
[a]All models include age (as a continuous variable), sex, state, and education (as a ordinal variable).

Potential Confounding by Multiple Exposures

The use of different classes of pesticides was highly correlated and numbers of applicators with unique exposures were too small for traditional analyses of interaction or effect modification. Therefore, we examined the potential for confounding by restricting the analysis to groups with specific patterns of exposure. Among applicators who did not use fungicides, retinal degeneration was associated with both carbamate use (OR = 1.5, 95% CI = 1.0–2.4) and organochlorine use (OR = 1.4, 95% CI = 0.9–2.3), but not with organophosphate use (OR = 1.2, 95% CI = 0.6–2.4).

TABLE VI. Relationship of Retinal Degeneration to Lifetime Days of Use of Specific Organochlorines in Pesticide Applicators in Iowa and North Carolina*

Days used organochlorine	Percent using organochlorine		Adjusted OR[a] (95% CI)
	Cases	Controls	
Aldrin			
0	74	84	1.0 (referent)
1–50	20	12	1.2 (0.7–1.8)
51+	6	4	1.1 (0.6–2.3)
Trend test $P = 0.558$			
Chlordane			
0	70	81	1.0 (referent)
1–50	22	16	1.1 (0.7–1.6)
51+	8	2	2.2 (1.2–4.1)
Trend test $P = 0.086$			
DDT			
0	52	78	1.0 (referent)
1–50	32	15	1.6 (1.1–2.5)
51+	15	7	1.8 (1.1–2.9)
Trend test $P = 0.011$			
Dieldrin			
0	91	97	1.0 (referent)
1–50	5	3	1.0 (0.5–2.1)
51+	3	0.5	4.4 (1.7–11.1)
Trend test $P = 0.057$			
Heptachlor			
0	84	89	1.0 (referent)
1–50	11	9	0.9 (0.5–1.5)
51+	5	2	1.5 (0.7–3.2)
Trend test $P = 0.649$			
Lindane			
0	82	87	1.0 (referent)
1–50	11	9	1.0 (0.6–1.8)
51+	7	4	1.9 (1.0–3.7)
Trend test $P = 0.135$			
Toxaphene			
0	89	89	1.0 (referent)
1–50	8	8	0.7 (0.4–1.3)
51+	3	3	0.7 (0.3–1.8)
Trend test $P = 0.247$			

*Total number of cases = 141–148; total number of controls = 17,224–17,357.
[a]All models include age (as a continuous variable), sex, state, and education (as a ordinal variable).

Conversely, fungicide use was associated with retinal degeneration both in applicators who did not use carbamates (OR = 1.5, 95% CI = 0.7–3.3) and in those who did not use organochlorines (OR = 1.9, 95% CI = 0.9–3.8). There were too few applicators in the group who did not use organophosphates to evaluate the effect of fungicides.

We also evaluated the effect of raising orchard fruit on risks related to pesticide use, and vice versa. After excluding applicators who raised orchard fruit, associations of retinal degeneration with use of fungicides (OR = 1.6, 95% CI = 1.1–2.4), organochlorines (OR = 1.5, 95% CI = 1.0–2.1), organophosphates (OR = 1.5, 0.8–2.7), and carbamates (OR = 1.5, 95% CI = 1.0–2.3) were maintained. In contrast, after excluding applicators who used fungicides from the analysis, we found that retinal degeneration was no longer associated with raising orchard fruit (OR = 1.2, 95% CI = 0.3–4.9). A similar result was found after excluding applicators who used carbamates (OR = 0.9, 95% CI = 0.1–7.1). After excluding applicators who used organochlorines, the OR for orchard fruit remained elevated, but the estimate was imprecise (OR = 1.9, 95% CI = 0.4–8.1). There were too few applicators in the group who did not use organophosphates to evaluate the effect of raising orchard fruit.

Application Methods and Personal Protective Equipment

We found that the risk associated with fungicide use was restricted to applicators who used hand spray guns, backpack sprayers, or mist blowers/foggers (Table VII). In contrast, the risk associated with insecticide use did not depend on application method: retinal degeneration was not associated with any particular method of applying either crop insecticides or animal insecticides (data not shown).

Since fungicide application methods associated with retinal degeneration may involve greater personal exposure, we also explored the possibility that wearing personal protective equipment would reduce the risk associated with fungicide use. In our questionnaire, questions concerning use of personal protective equipment were not posed

TABLE VII. Relationship of Retinal Degeneration to Methods of Fungicide Application in Pesticide Applicators in Iowa and North Carolina*

Method used to apply fungicide	Percent using method		Adjusted OR[a] (95% CI)
	Cases	Controls	
Hand spray gun	22	11	1.8 (1.1–3.0)
Backpack sprayer	20	7	3.1 (1.8–5.5)
Mist blower/fogger	7	2	4.3 (1.9–9.8)
Boom on tractor, truck, or trailer	12	16	1.0 (0.5–1.9)
Pre-applied to seed	11	9	1.3 (0.7–2.5)
Airblast	2	2	1.3 (0.3–5.6)
Aerial application	1	1	2.0 (0.3–15.0)

*Each application method was evaluated individually regardless of whether other methods were used. In each case, data are shown for participants who used the particular method to apply fungicides, and the comparison group is participants who used fungicides but did not use the application method. Participants who did not apply fungicides were treated as missing. Total number of cases = 90–114, total number of controls = 12,509–14,708.
[a]All models include age (as a continuous variable), sex, state, and education (as a ordinal variable).

specifically in relation to fungicide use, but referred to equipment usually employed while working with any pesticide. Using this information, we found that fungicide users who wore personal protective equipment and those who did not were both at increased risk compared to applicators who did not use fungicides. For example, compared to applicators who did not use fungicides, fungicide users who wore cartridge respirators were at risk (OR = 3.0, 95% CI 1.7–5.3) as were those who did not wear respirators (OR=1.7, 95% CI 1.1-2.4). Similar results were obtained for those who did or did not use chemically resistant gloves, chemically resistant boots, or disposable clothing (data not shown). Since use of personal protective equipment was strongly related to cumulative days of fungicide use (trend test $P < 0.001$ for all four types of equipment), we examined the association of retinal degeneration with use of personal protective equipment after stratification by cumulative days of fungicide use. Compared to applicators who did not use a cartridge respirator, risk for those who did use a respirator was elevated among those who had used fungicides for 1–50 days (OR = 2.3, 95% CI = 0.9–6.2) and among those who had used fungicides for 51+ days (OR = 1.6, 95% CI = 0.7–3.7), but not among those who did not use fungicides (OR = 0.6, 95% CI = 0.2–1.6). Only a small number of cases were available for these analyses (n = 22–27). Similar results were obtained for use of chemically resistant gloves, chemically resistant boots, or disposable clothing (data not shown).

Occupational Exposures to Agents Other Than Pesticides

We investigated the relationship of retinal degeneration to other potentially neurotoxic exposures sustained both on and off the farm. The only farming-related activity which was positively associated with retinal degeneration was repairing equipment used for pesticide application (OR = 1.4, 95% CI = 1.0–2.1). Welding was associated with a decreased risk (OR = 0.7, 95% CI = 0.4–1.0), which was not altered by adjusting for farm size. Repairing engines and painting were not significantly related to retinal degeneration (data not shown). Similar proportions of applicators with and without retinal degeneration had ever had a job off the farm (OR = 1.0, 95% CI = 0.7–1.4). Exposure to pesticides in a nonfarm job was significantly associated with retinal degeneration (OR = 2.0, 95% CI = 1.2–3.3), but exposure to solvents or metals was not (data not shown).

DISCUSSION

In this study, we found a consistent association of retinal degeneration with fungicide use. The relationship was seen in subgroups defined by state, demographic characteristics, or medical history, as well as in the entire group of applicators. There was a dose–response relationship for cumulative days of use of any fungicide as well as for five of six specific fungicides evaluated.

There was also some evidence that retinal degeneration was related to use of organochlorine and carbamate insecticides, but these associations were less consistent than with fungicides. We found a dose–response relationship for organochlorines but not for carbamates. Retinal degeneration was related to use of fewer than half the specific organochlorines or carbamates evaluated. However, stratified analyses suggested that risks associated with using carbamates or organochlorines were independent of risks associated with fungicide use.

In contrast, organophosphate use was significantly associated with retinal degeneration only in NC but not in IA or both states together, nor in most subgroups, and no dose–response relationship was observed. However, the relationship of organophosphate use to retinal degeneration was difficult to evaluate because most applicators used organophosphates. It would, therefore, be premature to conclude that organophosphate use presents no risk.

Retinal degeneration was also positively associated with raising orchard fruit and inversely associated with having a large farm or raising livestock or grain. However, the risk associated with raising orchard fruit was not found after excluding applicators who used fungicides or carbamates, suggesting that it is in fact related to pesticide use. Increased risk of retinal degeneration was also associated with raising Christmas trees or peanuts. Although small numbers precluded our examining these associations further, they may also reflect pesticide use, since 78% of peanut growers use the fungicide chlorothanonil and 35% of Christmas tree growers use the organophosphate chlorpyrifos [Alavanja et al., 1999].

Applicators who used certain methods to apply fungicides were at greater risk of retinal degeneration than those who used other methods. The methods associated with greater risk—hand spray gun, backpack sprayer, and mist blower—all potentially involve greater contact with the fungicide than the methods not associated with greater risk, such as tractor boom [Rutz and Krieger, 1992; Brouwer et al., 1994]. This suggests that use of personal protective equipment might help reduce risk. However, we found that, among applicators who used fungicides, risk was higher in those who reported using personal protective equipment than in those who did not. Several features of our data may explain this apparently anomalous result. Applicators who had used fungicides longer were more likely to use protective equipment, suggesting that use of personal protective equipment may be a marker for greater exposure. Although we stratified on days of fungicide use, our data are evidently not extensive enough to account for differences in fungicide use when evaluating the effect of personal protective equipment. Alternatively, although an applicator might report usually using personal protective equipment, we do not know whether he used it when applying fungicides. Moreover, applicators who currently use personal protective equipment may formerly have sustained high exposures without using such equipment. Thus, misclassification may provide a partial explanation for our finding, especially if the misclassification is differential.

Age, sex, and education were all strongly related to retinal degeneration. Associations of retinal degeneration with age and sex have previously been reported [Vingerling et al., 1995; Pauleikhoff and Koch, 1995]. The relationship to education might be due to better access to medical care or to better reporting of the condition by more educated applicators. However, the association of retinal degeneration with fungicide or insecticide use were not explained by confounding by applicator characteristics, since they persisted after adjusting for age, sex, and education and also after stratification by these and other possible confounders including several medical conditions. Occupational exposures to other neurotoxicants were not related to retinal degeneration, and the association of retinal degeneration with fungicide or insecticide use persisted after excluding applicators with a history of lead poisoning, so it is unlikely that confounding by these exposures would explain the effects observed here. Moreover, the fact that retinal degeneration was not associated with use of pyrethroid insecticides, herbicides, or fumigants suggests that our findings are not due to recall bias.

Macular degeneration is the most prevalent form of retinal degeneration and so may account for a large portion of our case group. When we considered risk factors previously associated with macular degeneration [Vingerling et al., 1995; Pauleikhoff and Koch, 1995], we found associations with age, gender, diabetes, and cardiovascular disease, but not with eye color, race, cigarette smoking, dietary antioxidants, or sun exposure. Differences between published studies and our results may be due to the fact that our population was relatively homogeneous for some characteristics, like race and sun exposure. Other characteristics, such as cigarette smoking, may be differently distributed in our population than in the underlying populations of other studies. On the other hand, with the exception of age and gender, no risk factor has been consistently associated with macular degeneration in all studies [Vingerling et al., 1995; Pauleikhoff and Koch, 1995].

The mechanisms through which fungicide exposure might cause retinal degeneration are unclear. In general, fungicides are not known to be potent neurotoxicants [Edwards et al., 1991]. However, retinal degeneration was observed in dogs after treatment with thiram [Maita et al., 1991], and retinal lesions have also been observed in rabbits and dogs after treatment with other thiocarbamates (see review in Maita et al. [1991]). A potential mechanism for the toxicity of thiocarbamates involves metabolic formation of carbon disulfide [Edwards et al., 1991], a known neurotoxicant that has been shown to damage the retina in humans [Vanhoorne et al., 1996] and animals [Merigan et al., 1988; Eskin et al., 1988]. Concentration of radiolabled benomyl in the mouse retina [Hellman and Laryea, 1990] suggests that this agent may also be toxic to the retina. Retinal degeneration was related to ever use of nine of twelve specific fungicides and to cumulative days of use of five of six specific fungicides, suggesting that the relationship may not be restricted to a particular chemical class. These results could however be an artifact resulting from overlap in use of different fungicides.

The major strengths of this study are the large sample size, the use of an internal control group for comparison, and the availability of relatively detailed information on pesticide use. The study is limited by its cross-sectional design and by the fact that all information was acquired by using self-administered questionnaires, including both the diagnosis of retinal degeneration and the history of pesticide exposure. The increase in visual dysfunction among applicators reporting retinal degeneration is, however, congruent with the diagnosis. Moreover, the consistency of the association of retinal degeneration with fungicide use lends weight to our findings.

In summary, we found a consistent association of retinal degeneration with fungicide use. The association was present in multiple subgroups, a dose–response relationship was observed, and the result was not explained by confounding or recall bias. The risk associated with fungicide use was greater when application methods potentially involving greater exposure were used. We also found a less consistent relationship of retinal degeneration to use of organochlorines and carbamates. Small numbers and highly correlated exposures limited our ability to examine confounding of one exposure by another. Nevertheless, stratified analyses suggested that risks associated with fungicide or insecticide use were independent. Because previous studies of retinal degeneration have focused primarily on organophosphate exposure [Dementi, 1994; Boyes et al., 1994; Misra et al., 1985], and since our study is limited by exclusive use of questionnaire information to establish the diagnosis and evaluate exposure, these findings must be considered exploratory.

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