Pesticide Use and Chronic Bronchitis Among Farmers in the Agricultural Health Study

Jane A. Hoppin, ScD,[1]* Martin Valcin, MPH,[1,2] Paul K. Henneberger, ScD,[2] Greg J. Kullman, PhD,[2] David M. Umbach, PhD,[3] Stephanie J. London, MD, DrPH,[1] Michael C.R. Alavanja, DrPH,[4] and Dale P. Sandler, PhD[1]

Background *Farmers have increased risk for chronic bronchitis. Few investigators have considered pesticides.*
Methods *We evaluated pesticides as risk factors for chronic bronchitis using the Agricultural Health Study enrollment data on lifetime pesticide use and history of doctor-diagnosed chronic bronchitis from 20,908 private pesticide applicators, primarily farmers.*
Results *A total of 654 farmers (3%) reported chronic bronchitis diagnosed after age 19. After adjustment for correlated pesticides as well as confounders, 11 pesticides were significantly associated with chronic bronchitis. Heptachlor use had the highest odds ratio (OR = 1.50, 95% Confidence Interval (CI) = 1.19, 1.89). Increased prevalence for chronic bronchitis was also seen for individuals who had a history of a high pesticide exposure event (OR = 1.85, 95% CI = 1.51, 2.25) and for those who also applied pesticides in off-farm jobs (OR = 1.40, 95% CI = 1.04, 1.88). Co-morbid asthma and current farm activities did not explain these results.*
Conclusions *These results provide preliminary evidence that pesticide use may increase chronic bronchitis prevalence.* Am. J. Ind. Med. 50:969–979, 2007. *© 2007 Wiley-Liss, Inc.*

KEY WORDS: respiratory disease; agricultural exposures; pesticides; occupational exposure

INTRODUCTION

Many agricultural exposures are risk factors for chronic bronchitis and other respiratory diseases [Melbostad et al., 1997; Becklake, 1998; Kimbell-Dunn, 2001; Zock et al., 2001; Omland, 2002]. Farmers perform a variety of activities that potentially put them at risk for chronic bronchitis, including confinement farming [Donham et al., 1984; Von Essen and Romberger, 2003; Monso et al., 2004], grain handling [Dosman et al., 1980; Husman et al., 1987; Chen et al., 1991; Kimbell-Dunn, 2001], and livestock production [Vohlonen et al., 1987; Melbostad et al., 1997].

Pesticides are potential risk factors for respiratory disease among farmers, with most research suggesting associations with asthma and related symptoms. Several specific pesticides were associated with wheeze among farmers and commercial pesticide applicators in the Agricultural Health Study (AHS) [Hoppin et al., 2002a; Hoppin et al., 2006]. Carbamate insecticides were associated with asthma among male farmers in Saskatchewan [Senthilselvan et al., 1992].

Abbreviations: AHS, Agricultural Health Study; BMI, body mass index; CI, confidence interval; HPEE, high pesticide exposure event; OR, odds ratio.

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, North Carolina
[2]Field Studies Branch, National Institute for Occupational Safety and Health, Morgantown, West Virginia
[3]Biostatistics Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, North Carolina
[4]Occupational Epidemiology Branch, National Cancer Institute, NIH, DHHS, Rockville, Maryland

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH). Mention of any company or product does not constitute endorsement by NIOSH.

Contract grant sponsor: Intramural Research Program of the National Institutes of Health (National Institute of Environmental Health Sciences (NIEHS) and National Cancer Institute).

*Correspondence to: Jane A. Hoppin, NIEHS, Epidemiology Branch, MD A3-05, P.O. Box 12233, Research Triangle Park, NC 27709-2233. E-mail: hoppin1@niehs.nih.gov

Accepted 15 August 2007
DOI 10.1002/ajim.20523. Published online in Wiley InterScience (www.interscience.wiley.com)

In a small study, low-level exposure to organophosphates among 25 farmers in Sri Lanka was associated with restrictive lung function [Peiris-John et al., 2005].

Pesticides may also be associated with chronic bronchitis. Pesticides have been associated with cough and phlegm among participants in the Singapore Chinese Health Study [LeVan et al., 2005]. Recently, specific pesticides have been associated with chronic bronchitis among non-smoking farm women in the AHS [Valcin et al., 2007]. To further explore the association of pesticides with chronic bronchitis, we analyzed data for the farmer pesticide applicators in the AHS.

METHODS

The AHS is a large, prospective study of Iowa and North Carolina pesticide applicators and their spouses [Alavanja et al., 1996]. The study enrolled over 52,000 licensed private pesticide applicators, mostly farmers, from 1993 to 1997, representing more that 82% of applicators in both states. After completing the enrollment questionnaire, 22,756 (44%) applicators returned a second mailed questionnaire; applicators who did or did not return this second questionnaire were similar regarding demographics, farming practices, and medical history [Tarone et al., 1997]. Our analysis was limited to private applicators who returned both questionnaires because information on chronic bronchitis was obtained from the second questionnaire. A case was defined as a self-reported doctor's diagnosis of chronic bronchitis after age 19. We excluded diagnoses before age 20 to reduce misclassification of disease. All cases represent prevalent disease; we lacked useful data on duration of disease. We could not base our definition of chronic bronchitis on the presence of cough and phlegm because information on these symptoms was not collected.

We analyzed data from 20,400 male applicators and 508 female applicators to evaluate associations between chronic bronchitis and lifetime pesticide exposure and off-farm exposures on the longest-held job. Farmers provided general information on pesticide use history, as well as detailed information regarding the ever use of 50 specific pesticides, the total years and days per year of use for each pesticide, and whether or not they had ever experienced a high pesticide exposure event (HPEE). HPEE was defined as "an incident or experience while using any type of pesticide which caused an unusually high personal exposure." Individuals who reported having a job off the farm were asked about ever-exposure to 19 potential occupational hazards including organic dusts, inorganic dusts, and pesticides for the off-farm job that they had held the longest.

We assessed each pesticide individually in a logistic base model that controlled for state, age (10-year categories), gender, and pack years of smoking (0, 1–19, 20–39, 40–135 pack-years). Using goodness-of-fit tests, we selected this base model after determining that modeling smoking categorized as pack-years fit the data better than other measures of smoking including ever smoking, smoking status as a three level variable (current, past, never) or years smoked or pack-years as continuous variables. Race and education were not associated with chronic bronchitis, and body mass index (BMI) did not confound our results; thus we did not include these variables in the base model. We limited our analysis to exposures reported by at least five cases.

We determined odds ratios (ORs) for ever use of each pesticide and assessed the dose–response of each pesticide using categories of lifetime days. We created the lifetime days variable by multiplying years of use by days of application and then categorizing the results. In addition to a category for unexposed (0 lifetime days), the number of categories depended on the population prevalence of ever-use for each pesticide. For highly used chemicals (prevalence >50%), we used five categories; for prevalence between 30% and 50%, we used four categories; and for prevalence less than 30%, we used three categories. Categories were collapsed if they contained fewer than five exposed cases. Chi-square tests for trend were performed using these ordinal categories. We addressed potential confounding of one pesticide's effect by other correlated pesticides as follows. Limiting ourselves to pesticides for which the ever/never dichotomy showed a statistically significant association with chronic bronchitis, we calculated Spearman correlation coefficients for each pesticide with all others. Any pesticide which had a correlation with a given pesticide of 0.20 or greater was included as a potential confounder in the logistic regression model for that pesticide. At most three potentially confounding pesticides appeared in any model.

For off-farm job exposures, we limited our analysis to those participants who reported having a job off the farm (65%). We assessed potential off-farm risk factors individually in the base model and after adjusting these variables for other similar exposure in the following groups: (1) organic dusts—cotton, wood, and grain; (2) inorganic dusts—mineral, sand, and asbestos; (3) chemicals—solvents, gasoline, and pesticides; and (4) fumes—welding, engine exhaust, and lead solder.

We conducted analyses to explore potential effect modification and confounding by additional factors: smoking and asthma. Smoking is an established risk factor for chronic bronchitis and other investigators have identified interactions between smoking and occupational exposures and chronic bronchitis [Schenker, 2000]. To assess potential effect modification by smoking, we used models with interaction terms involving smoking and the significant agricultural exposures. Chronic bronchitis and asthma are frequently co-morbid conditions [Bobadilla et al., 2002]. To evaluate whether our results were driven by the asthmatics in the case group, we excluded all asthmatics from the sample and then reran the models to assess if the estimates changed meaningfully.

We used the dataset release P1REL0310 from the AHS. All statistical analyses were done using SAS v9.1 (Cary, NC).

RESULTS

A total of 654 (3%) farmers reported a history of doctor-diagnosed chronic bronchitis after age 19 (Table I). Prevalence of chronic bronchitis diagnosis increased with increasing age, BMI, and years on the farm. Current and former smokers were more likely to report chronic bronchitis than never smokers. Those who reported chronic bronchitis were more likely than controls to report a history of other respiratory outcomes, including asthma, emphysema, and wheeze.

Pesticide use and pesticide exposure were associated with prevalent chronic bronchitis among AHS farmers (Table II). Farmers who reported having a HPEE in their lifetime were more likely to report chronic bronchitis (OR = 1.83, 95% CI = 1.50, 2.24). HPEEs were independently associated with chronic bronchitis and did not modify the odds ratios for the individual pesticides. After adjustment for base-model covariates (age, state, gender, and pack years), 14 insecticides and 4 herbicides were significantly associated with prevalent chronic bronchitis. Heptachlor, an organochlorine insecticide, had the highest odds ratio (OR = 1.71, 95% CI = 1.37, 2.13); four other organochlorine insecticides also had elevated odds ratios (chlordane, DDT, lindane, toxaphene). Specific organophosphates (coumaphos, diazinon, dichlorvos, malathion, parathion), carbamates (carbaryl and carbofuran), and permethrin were associated with chronic bronchitis. Two chlorophenoxy herbicides (2,4,5-T and 2,4,5-TP) and two other herbicides (chlorimuron-ethyl and petroleum oil) were associated with chronic bronchitis as well. We found no association between chronic bronchitis and any fungicides or fumigants.

Use of specific pesticides can be correlated with use of other pesticides. Of the 18 pesticides that were significant in the base model, 11 remained statistically significant after adjusting for the correlated pesticides (Table III). Four pesticides remained unadjusted by other pesticides under our criteria (carbofuran, chlorimuron-ethyl, permethrin on crops and petroleum oil); thus, these odds ratios are identical to those in Table II. Heptachlor again had the highest odds ratio (OR = 1.50, 95% CI = 1.19,1.89). Only DDT remained significant among the other organochlorine pesticides (OR = 1.27, 95% CI = 1.04,1.56). Three commonly used insecticides (diazinon, malathion, carbaryl) remained significant; although each appeared to attenuate the estimate for the others. The odds ratios for two chemicals commonly used on animals (coumaphos and permethrin) remained elevated (i.e., >1.25) but were no longer statistically significant. The chlorphenoxy herbicides (2,4,5-T and 2,4,5-TP) remained elevated after mutual adjustment.

TABLE I. General Characteristics of 20,908 Farmers in the Agricultural Health Study by Chronic Bronchitis Status (1993–7)

	Chronic Bronchitis[a]			
	Cases (N = 654)		Controls (N = 20,254)	
Characteristic	N	%[b]	N	%[b]
Age (years)				
20–39	96	15	5392	27
40–49	138	21	5300	26
50–59	176	27	4706	23
60–69	164	25	3643	18
70+	80	12	1213	6
State of residence				
Iowa	383	59	13715	68
North Carolina	271	41	6539	32
Race				
White	639	98	19879	98
Other	12	2	316	2
Gender				
Female	38	6	470	2
Male	616	94	19784	98
Education				
High school grad and below	410	64	11303	57
Beyond high school	228	36	8531	43
Smoking status				
Never smoker	263	40	11279	56
Former smoker	282	43	6333	31
Current smoker	106	16	2591	13
Pack years				
none	263	40	11279	56
1–19	202	31	5921	29
20–39	111	17	1874	9
40+	78	12	1180	6
BMI (kg/m^2)				
<23	48	8	2049	12
23–27.9	258	45	8807	50
28–30.9	128	22	3751	21
31–33.9	78	14	1938	11
34+	67	12	1106	6
Respiratory conditions				
Asthma	155	24	853	4
Emphysema	58	9	148	1
Wheeze in past year	363	57	3474	17
Farm life and job history				
Raised on farm[c]	602	92	18526	92
Lived on farm 30+ years	537	82	15194	75
Job off farm (ever)	460	71	13078	65

[a]Self-report of a doctor's diagnosis of chronic bronchitis over the age 19.
[b]Percentages are based on the number of individuals who responded to the question; missing individuals are not included.
[c]Lived at least half of life on a farm before 18.

TABLE II. Lifetime Pesticide Exposure and the Association With Chronic Bronchitis Among Farmers in the Agricultural Health Study (1993–7)

Pesticide exposure	Cases (n = 654) %	Controls (n = 20,254) %	Odds ratio[a]	95% Confidence interval	
High pesticide exposure event	21	14	1.83	1.50	2.24
Insecticides					
Carbamates					
Aldicarb	8	8	1.01	0.74	1.38
Carbaryl	56	43	1.43	1.20	1.70
Carbofuran	36	29	1.41	1.19	1.67
Organochlorines					
Aldrin	22	17	1.19	0.97	1.47
Chlordane	28	19	1.37	1.14	1.65
Dieldrin	6	4	1.25	0.88	1.78
DDT	37	23	1.43	1.19	1.73
Heptachlor	20	12	1.71	1.37	2.13
Lindane	18	13	1.40	1.13	1.73
Toxaphene	17	11	1.40	1.13	1.75
Organophosphates					
Chlorpyrifos	41	42	1.13	0.96	1.32
Coumaphos	13	9	1.42	1.11	1.83
Diazinon	30	21	1.47	1.22	1.76
Dichlorvos	13	11	1.36	1.06	1.73
Fonofos	22	23	1.10	0.90	1.36
Malathion	75	64	1.66	1.38	1.99
Parathion	12	8	1.33	1.03	1.73
Phorate	32	30	1.15	0.96	1.38
Terbufos	37	40	1.04	0.88	1.25
Pyrethroids					
Permethrin (animals)	13	13	1.37	1.07	1.75
Permethrin (crop)	15	13	1.26	1.00	1.59
Herbicides					
2,4-D	78	78	1.10	0.90	1.35
2,4,5-T	28	19	1.51	1.25	1.81
2,4,5-TP	9	5	1.69	1.26	2.25
Alachlor	55	56	1.06	0.89	1.25
Atrazine	68	72	0.97	0.81	1.17
Butylate	25	27	0.99	0.82	1.20
Chlorimuron-ethyl	33	32	1.21	1.02	1.44
Cyanazine	41	43	1.06	0.88	1.27
Dicamba	48	53	1.00	0.83	1.21
EPTC	20	20	1.12	0.91	1.39
Glyphosate	77	77	0.99	0.82	1.19
Imazethapyr	36	44	0.87	0.72	1.06
Metolachlor	43	47	0.99	0.84	1.18
Metribuzin	36	38	1.09	0.91	1.30
Paraquat	19	16	1.17	0.94	1.46
Pendimethalin	34	37	0.95	0.80	1.12
Petroleum oil	24	21	1.25	1.04	1.52
Trifluralin	50	54	0.98	0.82	1.16
Fumigants					
80/20 mix	7	4	1.29	0.93	1.78
Aluminum phosphide	3	3	1.03	0.65	1.62

TABLE II. (*Continued*)

Pesticide exposure	Cases (n = 654) %	Controls (n = 20,254) %	Odds ratio[a]	95% Confidence interval	
Fumigants					
Ethylene dibromide	5	4	1.02	0.70	1.46
Methyl bromide	17	15	0.91	0.72	1.17
Fungicides					
Benomyl	10	8	0.98	0.74	1.31
Captan	12	11	1.09	0.84	1.40
Chlorothalonil	8	7	0.87	0.64	1.19
Maneb/mancozeb	12	8	1.19	0.91	1.56
Metalaxyl	21	19	1.00	0.81	1.24
Ziram	1	1	1.48	0.59	3.69

[a]Odds ratios adjusted for age, state, gender, and pack years.

TABLE III. Pesticides Associated With Chronic Bronchitis Among Farmers in the Agricultural Health Study (1993–7) Adjusted for up to Three Correlated Pesticides With Correlations ≥0.20

	Base model results			Adjusted for correlated pesticides				
Pesticides[a]	Odds ratio[b]	95% Confidence interval		Odds ratio[c]	95% Confidence interval		Three most correlated variables[d]	Spearman correlation coefficients
Insecticides								
Carbamates								
Carbaryl	1.43	1.20	1.70	1.22	1.01	1.48	Diazinon, chlordane, malathion	0.37, 0.30, 0.26
Carbofuran	1.41	1.19	1.67	1.40	1.18	1.66	N/A	N/A
Organochlorines								
Chlordane	1.37	1.14	1.65	1.08	0.87	1.34	DDT, diazinon, carbaryl	0.36, 0.30, 0.30
DDT	1.43	1.19	1.73	1.27	1.04	1.56	Chlordane, 2,4,5-T, toxaphene	0.36, 0.29, 0.28
Heptachlor	1.71	1.37	2.13	1.50	1.19	1.89	DDT; 2,4,5-T, lindane	0.25, 0.23, 0.21
Lindane	1.40	1.13	1.73	1.15	0.91	1.47	Diazinon, dichlorvos, chlordane	0.24, 0.23, 0.22
Toxaphene	1.40	1.13	1.75	1.17	0.92	1.50	Parathion, DDT, chlordane	0.31, 0.28, 0.29
Organophosphates								
Coumaphos	1.42	1.11	1.83	1.29	0.98	1.68	Dichlorvos, permethrin	0.20, 0.20, N/A
Diazinon	1.47	1.22	1.76	1.25	1.02	1.53	Carbaryl, chlordane, lindane	0.37, 0.30, 0.24
Dichlorvos	1.36	1.06	1.73	1.15	0.87	1.51	Permethrin, lindane, coumaphos	0.31, 0.23, 0.20
Malathion	1.66	1.38	1.99	1.44	1.19	1.76	Carbaryl, chlordane, diazinon	0.26, 0.24, 0.21
Parathion	1.33	1.03	1.73	1.07	0.81	1.42	Toxaphene, carbaryl, DDT	0.31, 22, 0.21
Pyrethroids								
Permethrin (animals)	1.37	1.07	1.75	1.26	0.96	1.66	Dichlorvos, coumaphos	0.31, 0.20, N/A
Permethrin (crops)	1.26	1.00	1.59	1.26	1.00	1.59	NA	NA
Herbicides								
2,4,5-T	1.51	1.25	1.81	1.31	1.06	1.62	2,4,5-TP; DDT, chlordane	0.37, 0.29, 0.26
2,4,5-TP	1.69	1.26	2.25	1.41	1.15	1.73	2,4,5-T	0.37, N/A
Chlorimuron-ethyl	1.21	1.02	1.44	1.20	1.00	1.42	N/A	N/A
Petroleum oil	1.25	1.04	1.52	1.25	1.03	1.52	N/A	N/A

N/A = not applicable (no correlated variables were significant and had correlation coefficients of 0.20 or greater).
[a]These pesticides were significant after adjustment for age, state, gender, and pack-years.
[b]Adjusted for age, state, gender, and pack years. Odds ratios from Table II.
[c]Adjusted for base-model covariates and up to three correlated pesticides.
[d]Not more than three correlated items were both significant in ever/never models and had correlation coefficients of at least 0.20.

Table IV presents the dose–response models for the pesticides that remained significant after adjustment for correlated pesticides and the two other pesticides with significant dose–response trends (dichlorvos and permethrin on crops). Despite significant tests of trend, we found little evidence for monotonic increases over all dose levels. Carbaryl, DDT, dichlorvos, malathion, and permethrin on crops all had their highest ORs in their highest lifetime days category. DDT showed a significant dose–response trend with risk increasing with increasing number of days of lifetime use. Individuals who used malathion more than 235 days in their lifetime had a 70% increased risk of chronic bronchitis. We saw little evidence that increasing use of herbicides was associated with increased risk of chronic bronchitis, with the potential exception of 2,4,5-TP.

We also evaluated pesticide application activities as risk factors. Using solvents as pesticide additives was associated with chronic bronchitis (OR = 1.39, 95% CI = 1.07, 1.79). Farmers who applied pesticides to animals were more likely to report chronic bronchitis than those who did not (OR = 1.39, 95% CI = 1.18, 1.64). Current farm activities, including crop production, animal handling and production, were not associated with chronic bronchitis, except for handling stored hay (OR = 1.34, 95% CI = 1.14, 1.58) and butchering animals (OR = 1.34, 95% CI = 1.07, 1.68). We saw no evidence of confounding of the pesticide results by these current farm activities.

A total of 65% of farmers (n = 13,538) reported holding a job off the farm. Individuals who reported a diagnosis of chronic bronchitis were also more likely than controls to report having had a job off the farm (OR = 1.20, 95% CI = 1.01, 1.43). Odds ratios for off-farm exposures and chronic bronchitis are presented in Table V. Pesticide use off the farm (OR = 1.40, 95% CI = 1.04, 1.88) and solvent use (OR = 1.34, 95% CI = 1.08, 1.66) were significantly associated with chronic bronchitis among farmers.

We saw no evidence of differential effects of these agricultural and occupational exposures among smokers and non-smokers. In models containing a three-level variable for smoking (current, past, and never), we observed no interaction between smoking and pesticide or occupational exposures (data not shown). We had 263 cases of chronic bronchitis among non-smokers (40% of all cases); stratified models suggested similar risk factors for smokers and non-smokers (data not shown).

In models limited to non-asthmatics (499 cases and 19,401 controls), we observed no major differences from the pesticide results for the whole sample. We saw some attenuation of the correlated-pesticide-adjusted results in Table III for heptachlor (from OR = 1.50 to OR = 1.31, 95% CI = 0.99, 1.73), diazinon (from OR = 1.25 to OR = 1.17, 95% CI = 0.92, 1.48), permethrin on crops (from OR = 1.26 to OR = 1.13, 95% CI = 0.86,1.49), permethrin on animals (from OR = 1.26 to OR = 1.16, 95% CI = 0.84,1.59), and 2,4,5-T (from OR = 1.31 to OR = 1.19, 95% CI = 0.92, 1.53). The odds ratios for carbaryl and malathion increased when asthmatics were removed from the sample. We also saw few differences from the dose–response models presented in Table IV. The odds ratio for pesticide use off the farm was attenuated from 1.40 to 1.32 (95% CI = 0.93,1.87).

DISCUSSION

Pesticide use, both on and off the farm, was associated with prevalent self-reported chronic bronchitis. Both general and specific pesticide activities were associated with chronic bronchitis among farmers after controlling for smoking and other risk factors. Other investigators have reported that non-specific pesticide use, particularly insecticide use, was associated with the respiratory symptoms cough and phlegm [Wilkins et al., 1999; Sprince et al., 2000; LeVan et al., 2005]. Our work here complements our previous report among non-smoking farm women in the AHS [Valcin et al., 2007] which suggested that specific pesticides may contribute to chronic bronchitis risk. While limited by the cross-sectional nature of the analysis and the lack of detailed information on historic farm activities, these results suggest that pesticides in addition to the traditional agricultural risk factors may contribute to chronic bronchitis risk.

Previous investigators have reported increased cough and/or phlegm among Ohio grain farmers applying pesticides [Wilkins et al., 1999], Iowa farmers applying pesticides to animals [Sprince et al., 2000], individuals working with insecticides in rural Beijing [Zhang et al., 2002], Singapore residents using pesticides and other chemicals in the workplace [LeVan et al., 2005], and chronic bronchitis cases in Lebanon [Salameh et al., 2006]. Ohio grain farmers working with pesticides were approximately 50–80% more likely to report chronic cough or phlegm than other farmers after adjustment for other farming risk factors [Wilkins et al., 1999]. In Iowa Farm Family Health and Hazard Surveillance project, farmers applying pesticides to livestock were almost twice as likely to report chronic phlegm, even after controlling for animal exposures themselves [Sprince et al., 2000]. Among residents in rural Beijing, China, chronic cough, and phlegm were twice as common among individuals working with insecticides; though no information was reported regarding animal exposures [Zhang et al., 2002]. In a case-control study in Lebanon, use of pesticides was associated with chronic bronchitis after adjustment for smoking; the odds ratio for occupational exposure was 8.85 (95% CI = 1.15, 66.7) [Salameh et al., 2006]. We too saw evidence of increased prevalence of chronic bronchitis with a number of non-specific metrics of pesticide exposure. Individuals who reported applying pesticides in off-farm jobs had a higher prevalence of chronic bronchitis. Application of insecticides to animals was associated with an increased prevalence of chronic bronchitis, but there was no association

TABLE IV. Selected Pesticide*-Specific Dose–Response Models for Chronic Bronchitis Among Farmers in the Agricultural Health Study (1993–7)

Lifetime days[a]	Cases (n = 654) %	Controls (n = 20254) %	Odds ratio*	95% Confidence interval		P-trend[b]
Insecticides						
Carbaryl						0.266
none	46	59	1.00	—		
1–14	19	17	1.21	0.96	1.52	
15–55	14	10	1.23	0.93	1.62	
56–170	11	9	1.09	0.80	1.50	
171–235	5	3	1.16	0.76	1.79	
236+	6	3	1.26	0.83	1.91	
Carbofuran						0.004
none	65	72	1.00	—		
1–14	15	11	1.48	1.17	1.88	
15–55	13	10	1.42	1.11	1.83	
56–170	6	5	1.20	0.83	1.71	
>170	2	2	1.40	0.81	2.43	
DDT						0.019
none	65	79	1.00	—		
1–14	15	10	1.22	0.94	1.59	
15–55	10	6	1.31	0.96	1.78	
56+	11	6	1.38	1.02	1.86	
Heptachlor						0.013
none	81	88	1.00	—		
1–14	11	6	1.65	1.24	2.20	
15–55	6	4	1.39	0.96	2.02	
56+	3	2	1.31	0.80	2.16	
Diazinon						0.182
none	71	80	1.00	—		
1–14	14	10	1.31	1.02	1.70	
15–55	8	6	1.10	0.79	1.53	
56+	7	5	1.21	0.86	1.70	
Dichlorvos						0.065
none	87	89	1.00	—		
1–14	3	4	0.88	0.53	1.46	
15–55	3	3	1.09	0.64	1.83	
56+	7	5	1.45	1.02	2.05	
Malathion						0.008
none	26	37	1.00	—		
1–14	28	26	1.47	1.17	1.85	
15–55	24	20	1.46	1.15	1.86	
56–170	13	11	1.35	1.01	1.80	
171–235	4	3	1.48	0.96	2.29	
236+	5	3	1.70	1.11	2.59	
Permethrin (animals)						0.105
none	87	88	1.00	—		
1–14	6	5	1.35	0.92	1.97	
15–55	4	4	1.20	0.76	1.89	
56+	4	4	1.33	0.85	2.08	

(*Continued*)

TABLE IV. (*Continued*)

Lifetime days[a]	Cases (n = 654) %	Controls (n = 20254) %	Odds ratio*	95% Confidence interval		P-trend[b]
Permethrin (crops)						0.059
none	86	87	1.00			
1–14	7	7	1.17	0.84	1.64	
15–55	5	3	1.75	1.19	2.57	
56–170	1	2	0.61	0.27	1.38	
>170	2	1	1.64	0.88	3.06	
Herbicides						
2,4,5–T						0.387
none	74	74	1.00	—		
1–14	16	16	1.40	1.09	1.80	
15–55	6	6	1.25	0.87	1.79	
56+	4	4	0.96	0.63	1.47	
2,4,5-TP						0.071
none	92	96	1.00	—		
1–14	3	2	1.12	0.69	1.80	
15–55	3	1	1.62	0.95	2.78	
56+	2	1	1.38	0.77	2.48	
Chlorimuron-ethyl						0.239
none	68	69	1.00	—		
1–14	21	20	1.27	1.04	1.56	
15–28	7	7	1.27	0.92	1.75	
29+	5	5	0.94	0.63	1.38	
Petroleum oil						0.119
none	77	80	1.00	—		
1–14	8	7	1.30	0.97	1.76	
15–55	7	6	1.41	1.03	1.94	
56+	8	8	1.07	0.80	1.45	

*These pesticides were significant in ever/never models adjusted or significant *P*-trend.
[a]Adjusted for age, state, gender, pack-years, and the correlated variables (see Table III).
[b]Chi-square test for trend.

TABLE V. Off-Farm Exposures and Chronic Bronchitis Among Farmers in the Agricultural Health Study (1993–7)

Longest-held off farm job exposure[a]	Cases (n = 460) %	Controls (n = 13078) %	Odds ratio	95% Confidence interval	
Organic dusts					
Cotton dust	2	2	1.00	0.58	1.71
Grain dust	9	8	1.31	0.99	1.73
Wood dust	11	10	1.12	0.87	1.45
Inorganic dusts					
Asbestos	7	6	1.16	0.85	1.58
Mineral/mining	2	2	1.28	0.76	2.18
Silica/sand dust	6	5	1.29	0.91	1.83
Chemicals					
Gasoline	14	15	0.74	0.58	0.96
Pesticides	8	7	1.40	1.04	1.88
Solvents	19	17	1.34	1.08	1.66
Fumes					
Engine exhaust	22	21	1.10	0.89	1.36
Lead solder	5	4	0.88	0.59	1.32
Welding fumes	17	16	1.16	0.91	1.48

Models adjusted for age, state, gender, pack-years, and other within group exposures (e.g., organic dusts).
[a]Analysis limited to those (65%) reporting having had a job off the farm.

with current animal exposures. Having a HPEE was associated with an 80% increased prevalence in chronic bronchitis. On the other hand, inclusion of the HPEE variable in the pesticide-specific models did not confound the associations nor did we see evidence of an interaction between a history of HPEE and individual pesticides.

Previous evidence suggests that insecticides are the functional group of pesticides most associated with chronic bronchitis and the current analysis implicated four specific chemical classes of insecticides: organochlorines, organophosphates, carbamates, and pyrethroids. These chemicals came on the market in different eras and may potentially reflect the change from one pesticide to another over time; however, by controlling for correlated pesticides this is unlikely to explain our results. While insecticides might be a marker of animal activities in the past, due to their use in livestock settings, not all of the pesticides associated with prevalent chronic bronchitis have been used in animal operations (e.g., carbofuran). Seven of the eleven pesticides associated with chronic bronchitis were insecticides. Five of these (carbaryl, DDT, diazinon, malathion, and permethrin use on animals) were also significantly associated with chronic bronchitis among non-smoking farm women [Valcin et al., 2007]. All these chemicals are commonly used products [Kirrane et al., 2004] and thus more likely to have sufficient power to observe significant results among farm women who were not licensed pesticide applicators. These insecticides also showed some evidence of dose–response trends in the current analysis with the highest odds ratio in the highest category of use for carbaryl, DDT, and malathion. While it is possible that the intensity of other farm exposures increased at the same rate as use of these chemicals, the presence of a dose–response suggests that the associations may not be due to other farm-related factors, such as animals.

Herbicides, as a group, have not been previously associated with chronic bronchitis among farming populations. We observed increased prevalence for chronic bronchitis with four herbicides (2,4,5-T; 2,4,5-TP; chlorimuron-ethyl; and petroleum oil); however none showed strong evidence of dose–response trends. The phenoxy-herbicides, 2,4,5-T and 2,4,5-TP, are broad-spectrum herbicides which were banned in the late 1970s [EXTOXNET, 1998]. While there is little evidence of adverse respiratory effects associated with these chemicals, a clinical epidemiology study of 2,4,5-T exposed manufacturing workers showed decreased pulmonary function among exposed workers who also smoked [Suskind and Hertzberg, 1984]. We saw no evidence of interaction with smoking with individual pesticides in our data. Chlorimuron-ethyl, a sulfonylurea post-emergent herbicide used for peanuts and soybeans [Meister, 2005], was associated with wheeze among commercial pesticide applicators in the AHS [Hoppin et al., 2006]. It is only available as a dry formulation, which may make it more likely to result in exposure via the respiratory route. Petroleum oil herbicide and use of solvents either as pesticide additives or in off the farm occupations were associated with an increased prevalence of chronic bronchitis which is consistent with the growing literature on solvent exposure and respiratory effects [Blanc et al., 2005; LeVan et al., 2005].

Confinement farming and exposure to animals such as poultry livestock and pigs have been well documented as risk factors for chronic bronchitis [Donham et al., 1984; Melbostad et al., 1997; Omland, 2002; Von Essen and Romberger, 2003; Monso et al., 2004]. A limitation of our analysis is the lack of information on historic exposure to farm animals; we are restricted to questionnaire information on current farm activities. While currently raising poultry and livestock was not associated with prevalent chronic bronchitis, butchering animals was. None of the current animal exposures confounded the pesticide results. Some of the observed associations with pesticides may be attributable to underlying associations with historic animal production, but it is not likely to account in full for the observed associations. For example, permethrin use on animals was associated with chronic bronchitis, but permethrin use on crops was also associated with chronic bronchitis. These two uses were not correlated. While other authors also had minimal control for animal exposures [Wilkins et al., 1999; Zhang et al., 2002], only prospective data will allow the determination of whether pesticides are independently associated with chronic bronchitis.

The complexity of farming operations certainly allows the possibility that multiple exposures may confound our results. We believe, however, that we minimized potential confounding by adjusting for the three highest correlated pesticides. The highest correlation was 0.37 between diazinon and carbaryl, suggesting that even among these commonly used pesticides the correlation is not extreme. For the off-farm exposures, we controlled for related types of exposures in the same model (e.g., all organic dusts). Smoking is the major risk factor for chronic bronchitis, a conclusion supported by our data as well. Other authors have suggested interactions between smoking and occupational exposures [Mannino, 2005; Jaen et al., 2006] but we saw no evidence of this in our data.

The cross-sectional nature of this analysis of prevalent chronic bronchitis limits full evaluation of farming hazards, because much of the data was based on current farm activities. Current farming activities are often used as surrogates for past activities, but evidence suggests that chronic bronchitis may result in a change in farming habits. Tupi et al. [1987] showed that farmers with chronic bronchitis planned to reduce, finish, or change the line of farm production more than twice as often as healthy farmers and that 37% considered health reasons to be the main determinant of a change in future activities. In a meta-analysis of longitudinal occupational studies of lung function, individuals with chronic bronchitis at enrollment were more likely to leave their occupational cohort than were other members [Radon et al., 2002]. Thus, our results may underestimate the impact of farming exposures, if individuals changed their farm exposures as a result of diagnosis before enrollment. This potential underestimation may be evident in the lack of association we found between disease and current animal exposures. The study benefited, however, by having information on lifetime pesticide use and exposures related to longest held non-farm occupation. Furthermore, farmers in the AHS have been demonstrated to provide plausible [Hoppin et al., 2002b] and reliable [Blair et al., 2002] information regarding their pesticide use.

We relied on self-reported doctor diagnosis of chronic bronchitis; this may have resulted in misclassification of disease status. Chronic bronchitis is defined as the presence of productive cough and phlegm for at least 3 months in each of 2 successive years [Ferris, 1978]. In the AHS enrollment questionnaire, we did not have data on these respiratory symptoms, and thus, had to rely on the self-reported diagnosis information. Self-reported physician diagnosis of chronic bronchitis agreed well with physician records (86%) in a respiratory cohort study conducted in Tucson, Arizona [Bobadilla et al., 2002]. The prevalence of self-reported chronic bronchitis in the AHS is similar to that reported in NHANES (3%, [NCHS, 2006]), as well as that among California farmers as defined based on symptom criteria (3.8%) [Koivunen et al., 2005]. These data suggest that our chronic bronchitis outcome is a reasonable surrogate for doctor-diagnosed chronic bronchitis. Investigations relying on a self-reported history of doctor-diagnosed chronic bronchitis have reported associations consistent with studies that used symptom criteria [Forastiere et al., 1998; Blanchet et al., 2004]. People with chronic bronchitis frequently have a history of asthma and the risk factors for these outcomes may be similar. When we excluded individuals who reported a history of asthma, we saw attenuation of some associations, but the overall findings remained the same. This observation suggests that the majority of our findings are not driven by the asthmatics in the sample. Chronic bronchitis may also be confused with farmer's lung; however in our earlier work, we did not observe the same patterns of association with farmer's lung and pesticides [Hoppin et al., 2007] that we observed for chronic bronchitis. Only DDT use was associated with both chronic bronchitis and farmer's lung in the AHS [Hoppin et al., 2007]. Additionally, for farmer's lung we observed associations with current farm activities, such as handling silage, that we did not observe for chronic bronchitis. While it is possible that some of the reported chronic bronchitis cases, may be farmer's lung, it is unlikely that these cases are responsible for the observed associations.

Respiratory diseases including chronic bronchitis are an important cause of morbidity among farmers and their families [Schenker et al., 1998]. Our analysis of over 20,000 farmers in North Carolina and Iowa is one of the largest of farming and chronic bronchitis to date and the only one with data for specific pesticides. Albeit limited by the cross-sectional nature of the data and the lack of information on historic farming exposures, our results suggest that lifetime pesticide use, particularly insecticides, may contribute to chronic bronchitis.

ACKNOWLEDGMENTS

The authors thank Stuart Long for programming assistance and the participants of the Agricultural Health Study. We also thank the field stations for collecting the data. M. Valcin was supported by a research fellowship provided by the Association of Teachers of Preventive Medicine in affiliation with NIOSH and NIEHS.

REFERENCES

Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, Blair A. 1996. The Agricultural Health Study. Environ Health Perspect 104:362–369.

Becklake M. 1998. Occupational exposures as a cause of chronic airways disease. Philadelphia: Lippincott-Raven Publishers.

Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, Steen WC, Samanic C, Dosemeci M, Alavanja MC. 2002. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13:94–99.

Blanc PD, Eisner MD, Balmes JR, Trupin L, Yelin EH, Katz PP. 2005. Exposure to vapors, gas, dust, or fumes: Assessment by a single survey item compared to a detailed exposure battery and a job exposure matrix. Am J Ind Med 48:110–117.

Blanchet MR, Israel-Assayag E, Cormier Y. 2004. Inhibitory effect of nicotine on experimental hypersensitivity pneumonitis in vivo and in vitro. Am J Respir Crit Care Med 169:903–909.

Bobadilla A, Guerra S, Sherrill D, Barbee R. 2002. How accurate is the self-reported diagnosis of chronic bronchitis? Chest 122:1234–1239.

Chen Y, Horne SL, McDuffie HH, Dosman JA. 1991. Combined effect of grain farming and smoking on lung function and the prevalence of chronic bronchitis. Int J Epidemiol 20:416–423.

Donham KJ, Zavala DC, Merchant JA. 1984. Respiratory symptoms and lung function among workers in swine confinement buildings: A cross-sectional epidemiological study. Arch Environ Health 39:96–101.

Dosman JA, Cotton DJ, Graham BL, Li KY, Froh F, Barnett GD. 1980. Chronic bronchitis and decreased forced expiratory flow rates in lifetime nonsmoking grain workers. Am Rev Respir Dis 121:11–16.

EXTOXNET. 1998. Pesticide Information Profiles.

Ferris BG. 1978. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 118:1–120.

Forastiere F, Balmes J, Scarinci M, Tager IB. 1998. Occupation, asthma, and chronic respiratory symptoms in a community sample of older women. Am J Respir Crit Care Med 157:1864–1870.

Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP. 2002a. Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am J Respir Crit Care Med 165: 683–689.

Hoppin JA, Yucel F, Dosemeci M, Sandler DP. 2002b. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 12:313–318.

Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MCR, Sandler DP. 2006. Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. Am J Epidemiol 163:1129–1137.

Hoppin JA, Umbach DM, Kullman GJ, Henneberger PK, London SJ, Alavanja MCR, Sandler DP. 2007. Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study. Occup Environ Med 64:334–342.

Husman K, Koskenvuo M, Kaprio J, Terho EO, Vohlonen I. 1987. Role of environment in the development of chronic bronchitis. Eur J Respir Dis Suppl 152:57–63.

Jaen A, Zock JP, Kogevinas M, Ferrer A, Marin A. 2006. Occupation, smoking, and chronic obstructive respiratory disorders: A cross sectional study in an industrial area of Catalonia, Spain. Environ Health 5:2.

Kimbell-Dunn MR. 2001. Work-related respiratory symptoms in New Zealand farmers. Am J Ind Med 39:292–300.

Kirrane EF, Hoppin JA, Umbach DM, Samanic C, Sandler DP. 2004. Patterns of pesticide use and their determinants among wives of farmer pesticide applicators in the Agricultural Health Study. J Occup Environ Med 46:856–865.

Koivunen ME, Gee SJ, Park EK, Lee K, Schenker MB, Hammock BD. 2005. Application of an enzyme-linked immunosorbent assay for the analysis of paraquat in human-exposure samples. Arch Environ Contam Toxicol 48:184–190.

LeVan TD, Von Essen S, Romberger DJ, Lambert GP, Martinez FD, Vasquez MM, Merchant JA. 2005. Polymorphisms in the CD14 gene associated with pulmonary function in farmers. Am J Respir Crit Care Med 171:773–779.

Mannino DM. 2005. Epidemiology and global impact of chronic obstructive pulmonary disease. Semin Respir Crit Care Med 26:204–210.

Meister RT. 2005. Crop Protection Handbook 2005 Willoughby. Ohio: Meister Media Worldwide.

Melbostad E, Eduard W, Magnus P. 1997. Chronic bronchitis in farmers. Scand J Work Environ Health 23:271–280.

Monso E, Riu E, Radon K, Magarolas R, Danuser B, Iversen M, Morera J, Nowak D. 2004. Chronic obstructive pulmonary disease in never-smoking animal farmers working inside confinement buildings. Am J Ind Med 46:357–362.

National Center for Health Statistics (NCHS). 2006. National Health and Nutritional Evaluation Survey 1999–2000 Questionnaire Files: National Center for Health Statistics, Centers for Disease Control.

Omland O. 2002. Exposure and respiratory health in farming in temperate zones—A review of the literature. Ann Agric Environ Med 9:119–136.

Peiris-John RJ, Ruberu DK, Wickremasinghe AR, van-der-Hoek W. 2005. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. Respir Med 99:1319–1324.

Radon K, Goldberg M, Becklake M. 2002. Healthy worker effect in cohort studies on chronic bronchitis. Scand J Work Environ Health 28:328–332.

Salameh PR, Waked M, Baldi I, Brochard P, Saleh BA. 2006. Chronic bronchitis and pesticide exposure: A case-control study in Lebanon. Eur J Epidemiol 21:681–688.

Schenker M. 2000. Exposures and health effects from inorganic agricultural dusts. Environ Health Perspect 108 (Suppl 4):661–664.

Schenker MB, Christiani D, Cormier Y, Dimich-Ward H, Doekes G, Dosman J, Douwes J, Dowling K, Enarson D, Green F, Heederik D, Husman K, Kennedy S, Kullman G, Lacasse Y, Lawson B, Malmberg P, May J, McCurdy S, Merchant J, Myers J, Nieuwenhuijsen M, Olenchock S, Saiki C, Schwartz D, Seiber J, Thorne P, Wagner G, White N, Xu XP, Chan-Yeung M. 1998. Respiratory health hazards in agriculture. Am J Respir Crit Care Med 158:S1–S76.

Senthilselvan A, McDuffie HH, Dosman JA. 1992. Association of asthma with use of pesticides—Results of a cross-sectional survey of farmers. Am Rev Respir Dis 146:884–887.

Sprince NL, Lewis MQ, Whitten PS, Reynolds SJ, Zwerling C. 2000. Respiratory symptoms: Associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project. Am J Ind Med 38:455–462.

Suskind RR, Hertzberg VS. 1984. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372–2380.

Tarone RE, Alavanja MC, Zahm SH, Lubin JH, Sandler DP, McMaster SB, Rothman N, Blair A. 1997. The Agricultural Health Study: Factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. Am J Ind Med 31:233–242.

Tupi K, Vohlonen I, Terho EO, Husman K. 1987. Effects of respiratory morbidity on occupational activity among farmers. Eur J Respir Dis Suppl 152:206–211.

Valcin M, Henneberger PK, Kullman GJ, Umbach DM, London SJ, Alavanja MCR, Sandler DP, Hoppin JA. 2007. Chronic bronchitis among non-smoking farm women in the Agricultural Health Study. J Occup Environ Med 49:574–583.

Vohlonen I, Tupi K, Terho EO, Husman K. 1987. Prevalence and incidence of chronic bronchitis and farmer's lung with respect to the geographical location of the farm and to the work of farmers. Eur J Respir Dis Suppl 152:37–46.

Von Essen S, Romberger D. 2003. The respiratory inflammatory response to the swine confinement building environment: The adaptation to respiratory exposures in the chronically exposed worker. J Agric Saf Health 9:185–196.

Wilkins JR, III, Engelhardt HL, Rublaitus SM, Crawford JM, Fisher JL, Bean TL. 1999. Prevalence of chronic respiratory symptoms among Ohio cash grain farmers. Am J Ind Med 35:150–163.

Zhang LX, Enarson DA, He GX, Li B, Chan-Yeung M. 2002. Occupational and environmental risk factors for respiratory symptoms in rural Beijing, China. Eur Respir J 20:1525–1531.

Zock JP, Sunyer J, Kogevinas M, Kromhout H, Burney P, Anto JM. 2001. Occupation, chronic bronchitis, and lung function in young adults. An international study. Am J Respir Crit Care Med 163:1572–1577.