ORIGINAL ARTICLE

Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study

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Background: Farmer's lung, or hypersensitivity pneumonitis, is an important contributor to respiratory morbidity among farmers.

Methods: Using the 1993–7 enrolment data from the Agricultural Health Study, we conducted a cross-sectional study of occupational risk factors for farmer's lung among ~50 000 farmers and farm spouses in Iowa and North Carolina using hierarchical logistic regression controlling for age, state, and smoking status. Participants provided information on agricultural exposures, demographic characteristics, and medical history via self-administered questionnaires. Approximately 2% of farmers (n = 481) and 0.2% of spouses (n = 51) reported doctor-diagnosed farmer's lung during their lifetime. We assessed farmers and spouses separately due to different information on occupational exposure history. Only pesticide exposures represented lifetime exposure history, all other farm exposures represented current activities at enrolment.

Results: Among farmers, handling silage (OR = 1.41, 95% CI 1.10 to 1.82), high pesticide exposure events (OR = 1.75, 95% CI 1.39 to 2.21), and ever use of organochlorine (OR = 1.34, 95% CI 1.04 to 1.74) and carbamate pesticides (OR = 1.32, 95% CI 1.03 to 1.68) were associated with farmer's lung in mutually-adjusted models. The insecticides DDT, lindane, and aldicarb were positively associated with farmer's lung among farmers. Current animal exposures, while not statistically significant, were positively associated with farmer's lung, particularly for poultry houses (OR = 1.55, 95% CI 0.93 to 2.58) and dairy cattle (OR = 1.28, 95% CI 0.86 to 1.89). The occupational data were more limited for spouses; however, we saw similar associations for dairy cattle (OR = 1.50, 95% CI 0.72 to 3.14) and organochlorine pesticides (OR = 1.29, 95% CI 0.64 to 2.59).

Conclusion: While historic farm exposures may contribute to the observed associations with pesticides, these results suggest that organochlorine and carbamate pesticides should be further evaluated as potential risk factors for farmer's lung.

Farmer's lung, the most common type of hypersensitivity pneumonitis, is an important source of respiratory morbidity among farmers. Estimates of the prevalence of farmer's lung in farming populations range from 0.5% to 4.4%, owing to differences in diagnostic practices, and differences in farming practices and climate.[1 2] Farmer's lung is more common in the Northern latitudes and among dairy farmers.[1 3] The Canadian Centre for Occupational Health and Safety estimates that as many as 2–10% of Canadian farm workers have farmer's lung.[4] Although thermoactinomycetes and other bacteria in mouldy hay are well-established causes of farmer's lung,[3 5 6] other factors are also hypothesised to influence the development of hypersensitivity pneumonitis.[3 7] For example, low molecular weight chemicals, such as isocyanates, may bind to circulating proteins, and lead to sensitisation and hypersensitivity pneumonitis.[7] Pesticides are an unexplored risk factor for farmer's lung. Laboratory data suggest that specific pesticides may alter immunological function in a manner consistent with farmer's lung disease.[8–14]

Most studies on farmer's lung to date have been clinically based within a specific farming region.[3] These studies have provided insight into exposures associated with farmer's lung, as well as ways to reduce exposure and allow individuals to return to their farming activities. These studies generally represent a narrow range of exposures and farm experiences, however, and few have included farm women. To explore the potential risk factors for farmer's lung in a large, heterogeneous farming population, we conducted a cross-sectional analysis of the enrolment data from the Agricultural Health Study (AHS), a prospective cohort study of farmers and their spouses in Iowa and North Carolina, USA.[15]

MATERIALS AND METHODS

We analysed the cross-sectional enrolment data from the AHS to assess occupational predictors of farmer's lung among farmers and their spouses. The AHS enrolled pesticide applicators at pesticide licensing sites from 1993 to 1997. At enrolment, applicators completed an initial questionnaire and were asked to complete a more detailed questionnaire at home for return by mail (the ''take-home questionnaire''). Married applicators were given questionnaires for their spouses to complete. Over 52 000 licensed private pesticide applicators, primarily farmers, in North Carolina and Iowa were enrolled, representing more than 84% of the licensed private pesticide applicators in these states. Over 32 000 spouses were enrolled, representing approximately 75% of married applicators. The response rate for the applicator take-home questionnaire was low (~40%); however, individuals who returned the take-home questionnaire were similar to those who did not

Abbreviations: AHS, Agricultural Health Study; DDT, dichlorodiphenyl trichloroethane

on occupational, farming, pesticide use, medical and smoking characteristics.[16] For applicators, farmer's lung information is limited to those who returned the take-home questionnaire. Although the AHS includes commercial pesticide applicators, we did not include them in this analysis, because of limited information on farming history and the few farmer's lung cases (n = 18) among the 2313 commercial applicators who provided information on farmer's lung.

All exposure and outcome information came from the self-administered questionnaires completed by applicators and spouses at enrolment. The questionnaires provided information on basic demographic factors, smoking and medical history, and detailed information on farming practices including pesticide use. The applicators provided detailed information on their lifetime use of pesticide and on their current farming practices; spouses provided less detail on their lifetime use of pesticide, but provided similar information on current farm activities. Information on pesticide use included (1) three global questions on personal pesticide use (ever mix or apply any pesticide, duration of pesticide use in years and frequency of pesticide application in days/year), (2) ever use any of 50 pesticides and (3) duration of use and frequency of application for each of the 50 pesticides for applicators. Total lifetime days of pesticide use were calculated using the responses to years of use and days of application. Copies of the enrolment questionnaires are available at http://aghealth.org/questionnaires.html. Cases were defined as all individuals reporting a doctor's diagnosis of farmer's lung. Controls were individuals who reported not having a farmer's lung diagnosis; individuals with other respiratory diseases were included in the control group.

We evaluated exposures from four broad groups of agricultural and occupational exposures for their association with farmer's lung: hay and grain, animals, pesticides and other occupational exposures. Selection of pesticides and other occupational exposures was based on previous analyses of respiratory symptoms in this cohort[17 18] and other literature. For both applicators and spouses we had information on current hay- and grain-handling activities, current animal production activities, lifetime pesticide exposures and current occupational exposures on the farm. The hay and grain exposures included handling hay, handling grain, grinding feed, working with silage and growing grain; for spouses, this exposure group was limited to growing grain and grinding feed. The animal exposures for applicators were raising dairy cattle, beef cattle, hogs, working in poultry houses, working in swine confinement areas and performing veterinary procedures. For spouses, animal exposures were personal contact with dairy cattle, beef cattle, hogs, poultry and performing veterinary procedures. The pesticide group contained variables associated with lifetime use of permethrin insecticides, organochlorine insecticides, organophosphate insecticides, carbamate pesticides, phenoxy herbicides and triazine herbicides, as well as a history of a high pesticide exposure event for applicators. Other exposures for both applicators and spouses included cleaning with solvents, driving diesel tractors, grinding metal and driving combines; welding was included in models for applicators only (too few exposed cases ($n<5$) among spouses).

To simultaneously examine the many farming-related exposures and to control for possible confounding among the exposure variables, we used two-stage hierarchical logistic regression models with the four main groups as second-level variables (hay and grain, animals, pesticides and other exposures) and their individual components as first-level variables. Separate models were constructed for applicators and spouses owing to the different exposure information available. Models were adjusted for age, state and smoking status (current, past and never), and, for applicators, cigarettes smoked per day. There were so few smokers among spouses that additional adjustment for amount smoked had no effect. For applicators, we constructed expanded models using individual pesticides from the organochlorine (aldrin, chlordane, dichlorodiphenyl trichloroethane (DDT), dieldrin, heptachlor, lindane and toxaphene) and carbamate (aldicarb, benomyl, carbaryl, carbofuran) groups; these expanded models had six second-level variables (first four variables plus organochlorines and carbamates) and 11 additional first-order variables to represent each of the individual pesticides. We also constructed dose–response models for lifetime use of pesticide, and evaluated the trend using χ^2 tests. We fitted hierarchical logistic regression models with SAS Proc GLIMMIX, adapted for hierarchical modelling of multiple exposures using a penalised likelihood function[19]; this analysis used the P1REL0310 release of the AHS Phase I dataset. The AHS was reviewed and approved by institutional review boards at the National Institutes of Health, University of Iowa (Iowa City, Iowa, USA), and Battelle Public Health Research Institute (Durham, North Carolina, USA).

RESULTS

Farmer's lung information was available for 21 393 private pesticide applicators (farmers) and 30 242 spouses. A total of 481 (2.2%) farmers and 51 (0.2%) spouses reported a doctor's diagnosis of farmer's lung in their lifetime. Subjects ranged in age from 14–92 years, with a mean (SD) age of 49 (13) years for farmers and of 47 (17) years for spouses. Farmer's lung cases were less likely to report current smoking than controls (table 1). Compared with controls, individuals with farmer's lung were heavier at enrolment and were more likely to also report a history of adult asthma, chronic bronchitis and emphysema; however, they were equally likely to report childhood asthma diagnoses. These prevalent farmer's lung cases were more likely to report current respiratory and allergic symptoms than the controls. Current wheeze and shortness of breath were common among cases (40% and 47%, respectively). Allergic symptoms (runny nose, sinus problems, watery eyes, colds and flu) were more common among cases. Among individuals with these symptoms, cases were more likely to report that their symptoms were worse after working with grains and hay (data not shown). Individuals with farmer's lung ranged in age from 16 to 88 years and some were diagnosed many years prior to enrolment. Age at diagnosis was collected in 20-year intervals; thus, it is difficult to ascertain recent cases.

Residents of Iowa and those who lived on farms as children were more likely to report a history of farmer's lung. Most individuals with farmer's lung had lived or worked on farms $\geqslant$30 years, and individuals with farmer's lung were more likely to live on larger farms. Spouses who reported farmer's lung were more likely to report current farm work and more likely to work $\geqslant$30 days in the field; comparable information was not collected from farmers. Cases of farmer's lung were less likely to report using respirators for pesticide application, but more likely to report using dust masks than controls. No information is available on the use of respiratory protection for grain and hay handling.

A total of 427 (88%) of the 484 farmers who reported farmer's lung had complete data on all model covariates and were included in the hierarchical models. Table 2 presents the odds ratio (OR) estimates for the individual variables in each of the exposure groups for farmers. Handling silage, fermented agricultural byproducts used for animal feed, was associated with farmer's lung (OR 1.41, 95% CI 1.10 to 1.82). Other hay and grain variables were not associated with farmer's lung

Table 1 Demographic, medical and smoking characteristics of private applicators and spouses at enrolment (1993–7) in the Agricultural Health Study, by farmer's lung status

	Farmers		Spouses	
	Farmer's lung (n = 481) n (%)	Controls (n = 20 912) n (%)	Farmer's lung (n = 51) n (%)	Controls (n = 30 191) n (%)
Characteristic				
Sex				
Female	4 (1)	511 (2)	50 (98)	29 981 (99)
Male	477 (99)	20 401 (98)	1 (2)	210 (1)
Age				
<40 years	72 (15)	5620 (27)	8 (16)	9361 (31)
40–49 years	135 (28)	5403 (26)	11 (22)	8617 (29)
50–59 years	124 (26)	4844 (23)	18 (35)	7211 (24)
⩾60 years	150 (31)	5045 (24)	14 (28)	5002 (17)
Education				
<High school	46 (10)	1856 (9)	3 (7)	1472 (6)
High school	228 (49)	9853 (48)	20 (46)	10 879 (40)
>High school	196 (42)	8756 (43)	21 (48)	14 658 (54)
State				
Iowa	449 (93)	13 882 (66)	45 (88)	20 771 (69)
North Carolina	32 (7)	7030 (34)	6 (12)	9420 (31)
Smoking status				
Never smoked	275 (57)	11 475 (54)	39 (77)	21 784 (72)
Past smoker	171 (36)	6671 (32)	9 (18)	5270 (18)
Current smoker	35 (7)	2766 (13)	3 (6)	3137 (10)
BMI (kg/m^2)				
<23	38 (9)	2130 (12)	8 (19)	6638 (31)
23–25	113 (26)	5396 (30)	13 (31)	5941 (28)
26–27	87 (20)	3685 (20)	4 (10)	2608 (12)
⩾28	193 (45)	7042 (39)	17 (40)	6060 (29)
Age at diagnosis (years)				
<20	21 (4)		7 (15)	
20–39	224 (48)		17 (37)	
40–59	187 (40)		18 (39)	
⩾60	37 (8)		4 (9)	
Other respiratory diseases				
Childhood asthma	12 (2)	559 (3)	3 (6)	608 (2)
Adult asthma*	58 (12)	420 (2)	8 (16)	825 (3)
Chronic bronchitis	92 (19)	781 (4)	14 (28)	1273 (4)
Emphysema	30 (6)	188 (1)	2 (4)	97 (0)
Respiratory and allergic symptoms in the past year (farmers only)				
Wheeze	192 (40)	3789 (18)	–†	
Shortness of breath	218 (47)	5159 (25)	–†	
Runny nose	353 (74)	13 566 (67)		
Sinus problems	194 (42)	6990 (35)		
Watery eyes	209 (45)	7117 (36)		
Cold	414 (88)	16 418 (80)		
Flu	179 (38)	6082 (30)		
Farming history				
Lived on farm as a child	459 (96)	19 095 (92)	39 (78)	18 137 (60)
Years lived on farm				
<5	1 (0)	297 (1)	0 (0)	1941 (7)
5–10	4 (1)	416 (2)	1 (2)	2331 (8)
11–20	13 (3)	1457 (7)	0 (0)	4969 (17)
21–30	42 (9)	2827 (14)	11 (22)	5337 (18)
⩾31	414 (87)	15 582 (76)	39 (76)	15 263 (51)
Farm size (acres)				
0	5 (1)	1329 (7)	1 (2)	1576 (6)
<5 acres	9 (2)	770 (4)	0 (0)	877 (3)
5–49	17 (4)	1984 (10)	4 (8)	2281 (8)
50–199	69 (15)	3613 (18)	11 (22)	4791 (17)
200–499	158 (34)	5646 (28)	15 (31)	8303 (29)
500–999	132 (28)	4284 (21)	12 (24)	6553 (23)
⩾1000	79 (17)	2577 (13)	6 (12)	3988 (14)
Days worked in field‡				
None	–†		11 (22)	14 529 (49)
<10			8 (16)	5858 (20)
10–30			11 (22)	5254 (18)
31–100			12 (24)	3367 (11)
⩾100			7 (14)	846 (3)
Respiratory protection when applying pesticides				
Cartridge respirator	36 (7)	1974 (9)	–†	
Dust mask	122 (25)	4300 (21)	–†	

*Diagnosed after age 20 years.
†Not asked.
‡In the past year; asked of spouses only.

Table 2 Farming exposure prevalences and mutually adjusted ORs for farmer's lung among farmers in the Agricultural Health Study, 1993–7

Exposure	Farmer's lung (n = 427) n (%)	Controls (n = 17 952) n (%)	OR* (95% CI)
Hay and grain group†			
Grind feed	265 (62)	8465 (47)	1.15 (0.88 to 1.51)
Grow grain	411 (96)	15 541 (87)	1.04 (0.61 to 1.79)
Handle grain	379 (89)	13 028 (73)	1.13 (0.80 to 1.60)
Handle hay	295 (69)	10 506 (59)	1.09 (0.83 to 1.42)
Handle silage	148 (35)	3768 (21)	1.41 (1.10 to 1.82)
Animal group†			
Beef cattle	208 (49)	6988 (39)	1.02 (0.79 to 1.31)
Dairy cattle	38 (9)	1018 (6)	1.28 (0.86 to 1.89)
Hogs	171 (40)	6285 (35)	0.85 (0.64 to 1.14)
Poultry houses	16 (4)	606 (3)	1.55 (0.93 to 2.58)
Swine areas	148 (35)	5281 (29)	0.93 (0.69 to 1.24)
Veterinary procedures	207 (49)	7245 (40)	0.95 (0.75 to 1.20)
Other exposures†			
Diesel tractors	416 (97)	16 653 (93)	1.17 (0.65 to 2.11)
Drive combines	391 (92)	14 450 (81)	1.06 (0.73 to 1.55)
Grind metal	335 (79)	12 435 (69)	0.99 (0.75 to 1.31)
Solvents to clean	248 (58)	9063 (51)	1.08 (0.88 to 1.34)
Welding	330 (77)	11 679 (65)	1.19 (0.91 to 1.56)
Pesticide group‡			
High pesticide exposure event	114 (27)	2617 (15)	1.75 (1.39 to 2.21)
Carbamate pesticides	320 (75)	12 656 (71)	1.32 (1.03 to 1.68)
Organochlorine insecticides	313 (73)	10 623 (59)	1.34 (1.04 to 1.74)
Organophosphate insecticides	411 (96)	16 566 (92)	1.03 (0.62 to 1.70)
Permethrin insecticides	126 (30)	4216 (24)	1.12 (0.89 to 1.41)
Phenoxy herbicides	392 (92)	14 502 (81)	1.18 (0.81 to 1.70)
Triazine herbicides	395 (93)	14 396 (80)	1.19 (0.81 to 1.74)

*ORs adjusted for age, state, smoking status and cigarettes per day and all other exposures.
†Grain, animal and other farm exposures are based on current activities.
‡Pesticide group variables are based on lifetime exposure.

among farmers. Working in poultry houses (OR 1.55, 95% CI 0.93 to 2.58) and raising dairy cattle (OR 1.28, 95% CI 0.86 to 1.89) both exhibited elevated ORs for farmer's lung, but both had 95% CIs that included unity. No other occupational exposures were associated with farmer's lung among farmers. Three variables from the lifetime pesticide exposure group were associated with farmer's lung: history of a high pesticide exposure event (OR 1.75, 95% CI 1.39 to 2.21), use ever of organochlorine pesticides (OR 1.34, 95% CI 1.04 to 1.74) and use ever of carbamate pesticides (OR 1.32, 95% CI 1.03 to 1.68). No association was observed for other chemical classes of pesticides, organophosphate insecticides, permethrin insecticides, phenoxy herbicides and triazine herbicides.

Spouses had far fewer cases of farmer's lung (n = 51) than farmers, and even fewer had complete information on all model covariates (n = 38, 75%). The pattern of missing covariate

Table 3 Farming exposure prevalences and mutually adjusted ORs for farmer's lung among farm spouses in the Agricultural Health Study, 1993–7

Exposure	Farmer's lung (n = 38) n (%)	Controls (n = 26 011) n (%)	OR* (95% CI)
Hay and grain group†			
Grind feed	11 (29)	1321 (5)	2.21 (0.95 to 5.13)
Grow grain	35 (92)	22 104 (85)	1.32 (0.42 to 4.16)
Animal group†			
Beef cattle	17 (45)	7841 (30)	0.99 (0.54 to 1.82)
Dairy cattle	7 (18)	1985 (8)	1.50 (0.72 to 3.14)
Hogs	18 (47)	7134 (27)	1.29 (0.69 to 2.41)
Poultry	5 (13)	2603 (10)	1.04 (0.49 to 2.19)
Veterinary services	14 (37)	2968 (11)	1.39 (0.68 to 2.82)
Other exposures†			
Diesel tractors	22 (58)	8118 (31)	1.19 (0.61 to 2.34)
Drive combines	8 (21)	2724 (11)	0.84 (0.41 to 1.72)
Grind metal	5 (13)	330 (1)	1.82 (0.75 to 4.41)
Solvents to clean	17 (45)	4653 (18)	1.68 (0.91 to 3.12)
Pesticide group‡			
Carbamate pesticides	21 (55)	7718 (30)	1.41 (0.75 to 2.66)
Organochlorine insecticides	10 (26)	1776 (7)	1.29 (0.64 to 2.59)
Organophosphate insecticides	21 (55)	6216 (24)	1.30 (0.65 to 2.59)
Permethrin insecticides	8 (21)	1213 (5)	1.40 (0.67 to 2.90)
Phenoxy herbicides	16 (42)	3601 (14)	1.35 (0.68 to 2.65)
Triazine herbicides	11 (29)	1399 (5)	1.58 (0.75 to 3.31)

*ORs adjusted for age, state, smoking status and all other exposures.
†Grain, animal and other farm exposures are based on current activities.
‡Pesticide group variables are based on lifetime exposures.

information was similar between case and control spouses (data not shown). Table 3 presents the OR estimates for farmer's lung associated with current farming exposures and lifetime use of pesticide. In general, spouses with farmer's lung were more likely to report current agricultural activities than those without farmer's lung. Grinding feed, working with dairy cattle, cleaning with solvents and lifetime use of triazine herbicides all had OR ⩾1.5; however, none achieved statistical significance. When we ran reduced models limited to the hay and grain and animal groups, we observed increased ORs for grinding feed (OR 2.96, 95% CI 1.42 to 6.18) and working with dairy cattle (OR 1.71, 95% CI 0.87 to 3.35); this model included 45 farmer's lung cases.

The organochlorine and carbamate variables were composite variables based on use ever of a number of pesticides. To further evaluate which individual pesticides explained the associations with farmer's lung, we expanded our hierarchical framework for farmers to include two more groups (organochlorines and carbamates), which allowed us to estimate ORs for each organochlorine and carbamate pesticide individually (table 4). In these models, the OR estimates for the exposures in the hay and grain, animal and other exposure groups are essentially unchanged, with the exception of driving diesel tractors where the OR increased from 1.17 to 1.45 (95% CI 0.74 to 2.82). Two organochlorine pesticides associated with farmer's lung were lindane (OR 1.25, 95% CI 0.98 to 1.60) and DDT (OR 1.25, 95% CI 0.95 to 1.65). Two carbamate pesticides were associated with farmer's lung, but in opposite directions. Aldicarb, an insecticide, had a positive association (OR 1.65, 95% CI 1.04 to 2.61), whereas benomyl, a fungicide, had an inverse association (OR 0.60, 95% CI 0.33 to 1.07). All pesticide results were adjusted for all model covariates including current farm activities. We observed no interaction between specific pesticides and current farm exposures (data not shown). Because farming activities and use of pesticide practices change over time, we constructed stratified model to assess whether risks for older farmers (60 years or older) differed from those for younger farmers. Among older farmers the risk for organochlorines was greater (OR 1.86, 95% CI 0.97 to 3.57) than younger farmers (OR 1.27, 95% CI 0.96 to 1.66), but the CIs for these estimates overlapped. Although we had limited numbers to assess differences for individual chemicals by farmer's age, DDT and heptachlor appeared more associated with farmer's lung among older farmers, whereas lindane seemed more associated with farmer's lung among younger farmers. We saw no other differences between older and younger farmers.

To assess whether duration of pesticide use influenced farmer's lung risk, we used variables related to lifetime use of

Table 4 Mutually adjusted ORs for farmer's lung among farmers in the Agricultural Health Study, 1993–7; results from expanded models including individual pesticides

Exposure	Farmer's lung: Cases (n = 395) n (%)	Farmer's lung: Controls (n = 16 563) n (%)	OR* (95% CI)
Grain group†			
Grind feed	249 (63)	7934 (48)	1.13 (0.86 to 1.50)
Grow grain	379 (96)	14 455 (87)	0.80 (0.46 to 1.37)
Handle grain	356 (90)	12 234 (74)	1.13 (0.78 to 1.64)
Handle hay	282 (71)	9796 (59)	1.16 (0.88 to 1.53)
Handle silage	143 (36)	3534 (21)	1.44 (1.12 to 1.87)
Animal group†			
Beef cattle			1.04 (0.80 to 1.35)
Dairy cattle	33 (8)	956 (6)	1.15 (0.76 to 1.72)
Hogs	163 (41)	5910 (36)	0.89 (0.66 to 1.20)
Poultry houses	14 (4)	563 (3)	1.42 (0.83 to 2.42)
Swine areas	141 (36)	4968 (30)	0.90 (0.67 to 1.22)
Veterinary procedures	272 (69)	9187 (56)	0.93 (0.73 to 1.19)
Other exposures†			
Diesel tractors	388 (98)	15 414 (93)	1.45 (0.74 to 2.82)
Drive combines	369 (93)	13 479 (81)	1.26 (0.83 to 1.93)
Grind metal	316 (80)	11 596 (70)	0.98 (0.73 to 1.32)
Solvents to clean	237 (60)	8418 (51)	1.16 (0.93 to 1.44)
Welding	315 (80)	10 911 (66)	1.32 (0.99 to 1.76)
Pesticide group‡			
High pesticide exposure event	104 (26)	2439 (15)	1.71 (1.35 to 2.17)
Organophosphate insecticides	383 (97)	15 283 (92)	1.26 (0.72 to 2.18)
Permethrin insecticides	120 (30)	3857 (23)	1.16 (0.91 to 1.48)
Phenoxy herbicides	363 (92)	13 431 (81)	1.12 (0.77 to 1.64)
Triazine herbicides	367 (93)	13 357 (81)	1.14 (0.76 to 1.70)
Organochlorines‡			
Aldrin	148 (38)	3511 (21)	1.05 (0.79 to 1.39)
Chlordane	133 (34)	4516 (27)	0.96 (0.74 to 1.25)
DDT	153 (39)	4469 (27)	1.25 (0.95 to 1.65)
Dieldrin	55 (14)	1303 (8)	0.86 (0.61 to 1.21)
Heptachlor	141 (36)	3012 (18)	1.15 (0.87 to 1.52)
Lindane	128 (32)	3334 (20)	1.25 (0.98 to 1.60)
Toxaphene	68 (17)	2436 (15)	0.86 (0.63 to 1.18)
Carbamates‡			
Aldicarb	25 (6)	1655 (10)	1.65 (1.04 to 2.61)
Benomyl	10 (3)	1610 (10)	0.60 (0.33 to 1.07)
Carbaryl	232 (59)	9494 (57)	1.19 (0.94 to 1.49)
Carbofuran	153 (39)	4672 (28)	1.12 (0.89 to 1.40)

*ORs adjusted for age, state, smoking status and cigarettes per day and all other exposures.
†Grain, animal and other farm exposures are based on current activities.
‡Pesticide group variables are based on lifetime exposure.

Table 5 Dose–response models for pesticide use variables and farmer's lung in the Agricultural Health Study; models adjusted for base model covariates alone and for all model covariates

	Farmer's lung		Adjusted for age, state and smoking		Adjusted for all model covariates*	
Exposure variable	**Cases n (%)**	**Controls n (%)**	**OR (95% CI)**	**p Trend†**	**OR (95% CI)**	**p Trend†**
Farmer models						
Mixed/applied pesticides (years)						
1–10	64 (15)	4541 (26)	1.00	<0.0001	1.00	0.0056
11–20	105 (25)	6534 (33)	1.08 (0.80 to 1.46)		0.92 (0.66 to 1.27)	
21–30	148 (35)	4980 (25)	1.72 (1.27 to 2.33)		1.30 (0.93 to 1.81)	
⩾30	109 (26)	3094 (16)	2.10 (1.50 to 2.94)		1.50 (1.03 to 2.20)	
Applied Pesticides (days/year)						
1–4	69 (15)	3709 (19)	1.00	0.0005	1.00	0.26
5–9	126 (27)	4974 (25)	1.16 (0.86 to 1.57)		1.02 (0.74 to 1.41)	
10–19	153 (32)	6104 (31)	1.24 (0.93 to 1.66)		1.00 (0.72 to 1.36)	
20–39	92 (20)	3551 (18)	1.57 (1.14 to 2.17)		1.23 (0.87 to 1.75)	
⩾40	33 (7)	1492 (8)	1.87 (1.22 to 2.87)		1.16 (0.72 to 1.90)	
Lifetime days of pesticide application						
1–75	78 (17)	5170 (26)	1.00	<0.0001	1.00	0.088
76–200	93 (20)	4227 (21)	1.20 (0.88 to 1.62)		1.09 (0.78 to 1.51)	
201–400	155 (33)	5083 (26)	1.65 (1.25 to 2.18)		1.38 (1.01 to 1.88)	
⩾401	147 (31)	5304 (27)	1.71 (1.29 to 2.27)		1.26 (0.92 to 1.73)	
Spouse models‡						
Mixed/applied pesticides (years)						
None	12 (27)	13 186 (51)	1.00	0.0012		
<11	11 (25)	7128 (28)	1.67 (0.73 to 3.81)			
⩾11	21 (48)	5649 (22)	3.29 (1.59 to 6.80)			
Applied pesticides (days/year)						
None	12 (27)	13 186 (51)	1.00	0.0022		
<5	12 (27)	6317 (24)	1.83 (0.82 to 4.11)			
⩾5	20 (46)	6468 (25)	3.06 (1.49 to 6.30)			
Lifetime days of pesticide application						
None	12 (27)	13 186 (53)	1.00	0.0004		
1–20	6 (14)	3359 (14)	1.92 (0.71 to 5.15)			
21–110	10 (23)	4520 (18)	2.12 (0.91 to 4.95)			
⩾111	16 (36)	3694 (15)	4.03 (1.88 to 8.61)			

*Model covariates including all farming exposures in table 2.
†p trend calculated using χ^2 test for trend.
‡Fully adjusted models for spouses were not run due to the limited number of cases.

all pesticides to construct dose–response models for both farmers and spouses; for farmers we also constructed dose–response models for the pesticides individually associated with farmer's lung. Table 5 presents the results from two modeling strategies for total pesticide use: adjusting for the base model covariates alone (age, state and smoking) and using the hierarchical model to adjust for all model covariates. The models for spouses were limited to base model adjustments owing to the small sample size. We observed significant dose–response trends for years of pesticide application irrespective of model adjustments for applicators, although the ORs were attenuated with the inclusion of all covariates. The OR for the highest quartile (⩾30 years) was 2.10 (95% CI 1.50 to 2.94) for base model adjustment only and 1.50 (95% CI 1.02 to 2.21) for the fully adjusted models. For spouses, we also observed increased prevalence of farmer's lung with more years of pesticide use, but lack the sample size to run fully adjusted models. Adjustment for all model covariates including animals, and hay and grains diminished, but did not eliminate the association between years of pesticide use and farmer's lung. For spouses, the OR for more than 11 years of pesticide application adjusted for base model, and animal and grain covariates was 2.05 (95% CI 0.91 to 4.63). For farmers, we also constructed dose–response models with three levels for lindane and DDT using lifetime days of pesticide application (0, 1–20, ⩾21 days); there were too few benomyl and aldicarb cases to allow dose–response modelling. We saw no evidence of a monotonic increase with increasing lifetime exposure, and the results were similar to the use ever analysis. The OR for the highest category of DDT use was 1.41 (95% CI 1.01 to 1.98), slightly higher than the OR of 1.25 reported for use ever.

DISCUSSION

Farmer's lung is associated with handling mouldy hay and grain, and has increased prevalence in northern latitudes.[3] Iowa farm residents, both farmers and their wives, had greater prevalence of farmer's lung than farmers in North Carolina. This observation is consistent both with farm production patterns associated with generation of mouldy hay and northern regions. Dairy farmers represent a population at high risk for farmer's lung[6 20] and our results for silage, animal feed and raising dairy cattle suggest these to be important factors among the AHS cohort. Among farmers, working with silage was associated with farmer's lung; for spouses, grinding feed and working with dairy cattle were associated with farmer's lung. Among both the farmers and the spouses, hay and grain handling activities had stronger effect estimates than animal contact activities. Because all farm exposure information was based on activities during the year of enrolment, our results suggest that individuals with farmer's lung continue farm work including tasks which may have contributed to their disease. This inference is consistent with clinical practice, which advises work practice changes to reduce the actual exposures that resulted in disease.[21]

Pesticide use and handling is the one exposure category for which we had lifetime exposure information. With the exception of two case reports suggesting a role of pesticides and hypersensitivity pneumonitis,[22–24] no previous population-based study has associated pesticides with farmer's lung. Our large sample size and heterogeneous population allowed us to assess this relationship while adjusting for traditional risk factors. For farmers, a history of a high pesticide exposure event was strongly associated with a diagnosis of farmer's lung. High

pesticide exposure events were based on response to the question ''have you ever had an incident or experience while using *any* type of *PESTICIDE* which caused you *unusually high* personal exposure?'' These events are relatively common and are associated with risk-taking attitudes and behaviours.[25 26] We reviewed information regarding the type of pesticide, body part exposed and decade of exposure for farmer's lung cases, and saw no clear pattern of a specific chemical or a specific body part being affected. Thus, a history of a high pesticide exposure event may be a marker of more risky behaviour—for example, less likely to use respiratory protection when working with mouldy grain, rather than a marker of an individual chemical exposure. We have no information to assess respiratory protection for grain handling.

Both organochlorine and carbamate pesticides were associated with farmer's lung after controlling for current farming activities. When we evaluated specific chemicals, only two of nine organochlorines (DDT and lindane) and one of four carbamates (aldicarb) were associated with increased risk for farmer's lung. DDT and lindane were widely used insecticides; DDT was removed from the market in the 1970s although lindane remains in use. These pesticides may have been used by dairy farmers historically and their association with farmer's lung is as a surrogate for past exposure to dairy animals, rather than risk from pesticides per se. Aldicarb, on the other hand, is a highly toxic crop insecticide and is unlikely to be a surrogate for past animal-related activities. Given the lack of prior hypotheses, these observations may be due to chance or confounding by historic farm activities. Limited toxicology data do suggest, however, that some of these pesticides may contribute to immune responses similar to those observed in farmer's lung.[8–14]

The pathogenesis of farmer's lung involves an acute insult from a triggering antigen, generally bacteria related to mouldy hay, followed by cough, fever, chills and malaise.[27 28] The immune response triggers alveolar macrophages, which increase in number and secrete large amounts of cytokines such as tumour necrosis factor α and interleukin (IL)1.[27 28] Most exposed individuals make antibodies to the antigens, but only a small subset (1–15%) progress to clinical disease.[28] The three pesticides positively associated with farmer's lung in this analysis, lindane, DDT and aldicarb, have been associated with immunological effects in a limited number of studies. In a study of 20 lindane-poisoned patients and 20 controls, Seth *et al*[14] reported elevated tumour necrosis factor α, IL2 and IL4, and decreased interferon γ levels in blood among poisoned individuals. Lindane has also been shown to stimulate macrophage activating factor without addition of mitogens in peripheral blood lymphocytes of rainbow trout.[11] DDT has been shown to inhibit murine macrophage response to mycobacterium.[13] o, p′-DDT stimulated the production of nitric oxide and proinflammatory cytokines, and upregulated the expression of NFκB transactivation in mouse macrophages.[12] Using human blood samples, Daniel *et al*[9] showed that individuals with higher plasma levels of dichlorodiphenyl dichloroethene (DDE, the primary DDT metabolite) had increased TH2 immunity as indicated by plasma IL4. Some carbamates inhibit IL2-dependent proliferation of CTLL2 cells, a mouse T cell line; however, of all the carbamates tested, aldicarb had the weakest effect on IL2.[8] Aldicarb affected macrophage function in C3H mice, reducing IL1 production.[10] Taken together, these models suggest that these pesticides may stimulate immune function in a manner that may enhance the effect of farmer's lung agents; however, given the paucity of whole animal models and human data, future work is needed to evaluate whether these pesticides influence the risk of farmer's lung.

Farmers are exposed to multiple respiratory toxicants during their daily activities, and many of these exposures are correlated to some degree. We used hierarchical logistic regression models to adjust for multiple exposures. The Spearman correlations among exposure variables were generally low (<0.3). The highest observed correlation for applicators was for working in swine areas and working with hogs ($r = 0.72$); there were six other correlations among model variables that exceeded 0.5, with the maximum being 0.56 for aldrin and heptachlor. For spouses, only the correlation between organophosphates and carbamates exceeded 0.5 ($r = 0.53$). Given these statistical methods and the observed correlations, it is unlikely that current farm activities confounded the results for pesticide exposures. Even with this analytical strategy, some individual exposures may appear important by chance. Although we have no data to evaluate whether historic farming activities may be associated with the observed results, we think that the specific pesticides identified are unlikely to be surrogates for historic farming activities related to farmer's lung. We relied on self-reported information on pesticide use and farming activities. Farmers, in general, and AHS participants, in particular, have been demonstrated to provide reproducible and accurate recall of their personal pesticide use.[29–31] Although individuals with farmer's lung may have over-reported their history of pesticide use, it seems unlikely, given the number of different medical conditions contained on the questionnaire, the lack of association with most pesticides, and the absence of previous reports of associations between pesticides and farmer's lung. Farmer's lung may predispose individuals to both asthma and emphysema; asthma within a year or two of diagnosis[32 33] and emphysema as a long-term sequela.[34–36] Our data are consistent with increased asthma and emphysema among those with farmer's lung, because individuals with farmer's lung were also more likely to report asthma and emphysema than those without farmer's lung. However, our data are also indicative of the challenge of reporting farmer's lung, both in the lay public and among clinicians, because we observed increased rates of all respiratory diseases except childhood asthma. Because disease status was self-reported, some of our cases probably did not meet strict clinical criteria for farmer's lung. Owing to the clinical difficulties in assessing farmer's lung, incorrect ascertainment of farmer's lung is as likely owing to inconsistent diagnostic practice as faulty recall by participants.[7] Although we have no medical records to confirm or refute these self-reports, the prevalence of farmer's lung in our sample is similar to, but slightly lower than, those reported in other farming populations with clinical confirmation of disease.[3] We observed the expected inverse relationship between current cigarette smoking and farmer's lung,[3 37] thus supporting the likelihood that our cases are farmer's lung cases rather than chronic bronchitis and emphysema, which are positively associated with cigarette smoking. Farmer's lung has clinical similarities to organic dust toxic syndrome and some similar risk factors.[5] With our questionnaire, we have limited ability to discriminate between these two conditions. However, the expected low prevalence and the expected inverse association with smoking, as well as the similar prevalence of colds and flu among cases and controls, gives us some confidence that our cases represent farmer's lung and not organic dust toxic syndrome.

Notwithstanding the potential for disease misclassification, this large cross-sectional questionnaire-based study allowed us to explore a broad range of occupational exposures in a heterogeneous farming population and to suggest factors previously not considered; however, we have no information on historic farm activities that may have contributed to the development of farmer's lung. The cross-sectional nature of the analysis may underestimate the impact of some exposures because more severely affected individuals may have changed

Main messages

- Pesticides may be overlooked risk factors for farmer's lung. Dichlorodiphenyl trichloroethane, lindane and aldicarb were independently associated with farmer's lung after controlling for other common risk factors. However, confounding by historic farm activities cannot be ruled out.
- A history of high pesticide exposure events may contribute to farmer's lung risk.
- Individuals with farmer's lung continue to farm decades after diagnosis.

Policy implications

Prospective studies of farmers are necessary to ascertain the role of pesticides in the development of farmer's lung.

their exposures as a result of disease diagnosis.[38–40] Additionally, in relying on cross-sectional data, we cannot assess whether exposure occurred prior to farmer's lung diagnosis. All farming exposures, except pesticides, were based on current farm practices at the time of enrolment. Hence, if an individual had farmer's lung early in life and had changed farming practices as a result, we would underestimate the impact of that exposure. This may explain our low-risk estimates for dairy farming, a known risk for farmer's lung.[3] Additionally, individuals may leave farming as a result of severity of disease. However, it is unlikely that our cases left farming as a result of severity of disease. Bouchard *et al*[21] showed that cognitive and behavioural motives rather than severity of disease were predictive of leaving farming; however, 55% of farmer's lung cases left farming after the diagnosis.

This analysis of farmer's lung is one of the largest to date, with over 500 cases reported in a population of almost 52 000 farm residents. Additionally, this sample represents one of the most heterogeneous samples with regard to farming practices ever studied, providing the opportunity to explore factors previously associated with farmer's lung and to identify potential factors that may influence farmer's lung risk. Even with self-reported disease history, we observed similar results for smoking, occupational activities and regional variation, as reported in other studies. Use of pesticides and high pesticide exposure events were independently associated with farmer's lung after adjusting for current farm activities, suggesting new areas to consider with regard to farmer's lung risk.

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