Suicide and Pesticide Use among Pesticide Applicators and Their Spouses in the Agricultural Health Study

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Background: An association may exist between pesticide exposure and suicide.

Objective: We sought to evaluate the existence of an association between pesticide use and suicide using data from the Agricultural Health Study (AHS), a prospective cohort study of licensed pesticide applicators and their spouses in Iowa and North Carolina.

Methods: Via linkage to state mortality files and the National Death Index, we identified 110 suicides occurring between enrollment in the AHS (from 1993 to 1997) and 31 May 2009, among 81,998 cohort members contributing 1,092,943 person-years of follow-up. The average length of follow-up was 13.3 years. AHS participants provided data on pesticide use and potential confounders via self-administered questionnaires at enrollment. We evaluated several measures of pesticide use: use of any pesticide, ever use of 50 specific pesticides, cumulative lifetime days of use and intensity-adjusted cumulative lifetime days of use of 22 specific pesticides, and ever use of 10 functional and chemical classes of pesticides. We used Cox proportional hazards regression models to estimate adjusted hazard ratios and 95% confidence intervals.

Results: After adjusting for age at enrollment, sex, number of children in family, frequency of alcohol consumption during the past 12 months, and smoking status, we found no association between prior pesticide use and suicide in applicators and their spouses. Results were the same for applicators and spouses together or for applicators alone and were consistent across several measures of pesticide use.

Conclusions: Our findings do not support an association between moderate pesticide use and suicide.

Key words: farmers, pesticide applicators, pesticides, spouses, suicide. *Environ Health Perspect* 119:1610–1615 (2011). http://dx.doi.org/10.1289/ehp.1103413 [Online 13 July 2011]

Several studies have reported higher suicide rates among farmers than the general population (Blair et al. 1993; Browning et al. 2008; Gunderson et al. 1993; Lee et al. 2002; Meltzer et al. 2008; Miller and Burns 2008; Page and Fragar 2002; Stallones 1990), although two studies found lower rates among Canadian farmers (Pickett et al. 1993, 1999). A review noted higher suicide rates among farmers than any other occupational group in the United Kingdom (Gregoire 2002).

Other studies suggested associations between chronic exposure to pesticides and suicide among farmers and other agricultural populations. In Australia, pesticide applicators had higher suicide rates than the general population (MacFarlane et al. 2009, 2010), whereas applicators in Italy had a lower rate of accidents and suicide (Torchio et al. 1994). Parrón et al. (1996) found higher suicide rates in an intensive agricultural area of southeastern Spain than in other areas with similar demographic and socioeconomic compositions; they tentatively attributed the increased rates to pesticide exposure. Colorado farmers potentially exposed to pesticides had higher suicide rates than the general population (Stallones 2006), and ecological and case studies suggested an association between organophosphate pesticide (OP) use and suicide (London et al. 2005).

The Agricultural Health Study (AHS) is a large, prospective cohort study of private pesticide applicators (mostly farmers), commercial applicators, and spouses of private applicators in Iowa and North Carolina. It was designed to study associations between cancer and other chronic diseases and farm-related exposures (Alavanja et al. 1996). Previously, AHS participants in the highest category of use of chlorpyrifos, an OP, were reported to be twice as likely to commit suicide as those who never used chlorpyrifos (Lee et al. 2007). Because that study was based on few cases and evaluated only one pesticide, we wanted to evaluate more fully the possible associations between the use of pesticides, particularly OPs, and suicide among applicators and their spouses in the AHS.

Methods

Population and case definition. The AHS cohort, enrolled from 1993 to 1997, provided data on demographic and lifestyle factors, pesticide use, and other agricultural exposures at enrollment (Alavanja et al. 1996). Most private and commercial applicators were men (97% and 96%, respectively), whereas most spouses were women (99%). Mortality data including date and cause of death were obtained by linking the cohort to state mortality files and the National Death Index. We used the *International Classification of Diseases, 9th Revision* (ICD-9) [World Health Organization (WHO) 1977] codes to identify suicides from 1993 to 1998 and *10th Revision* (ICD-10) (WHO 1992) codes for those from 1999 to 2009. ICD-9 codes beginning with E95 or 95 or ICD-10 codes X60–X84 identified suicides listed as underlying or contributing causes of death. We excluded 129 individuals < 18 years of age at enrollment, 1 individual from a couple in which the private applicator and spouse had both committed suicide (the excluded individual was randomly chosen from the couple to avoid correlated death times), and an additional 7,528 cohort members missing covariate information. The analysis included a total of 81,988 cohort members: 48,098 private applicators [contributing 647,006 person-years (PY)], 4,781 commercial applicators (68,240 PY), and 29,119 spouses of private applicators (377,697 PY). The average length of follow-up was 13.3 years. We identified 110 suicides that occurred between enrollment and 31 May 2009.

The institutional review boards (IRBs) of the National Institutes of Health, Battelle Centers for Public Health Research and Evaluation (North Carolina field station), the University of Iowa (Iowa field station), and Westat (study coordinating center) approved this study, and the IRB of Brigham Young University exempted it. The study was explained to all potential participants, who indicated consent by returning the enrollment questionnaire.

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Exposure assessment. Applicators and spouses provided information on pesticide use and other factors via questionnaires completed at enrollment (AHS 2011). This information included years of use (duration) and average days per year of use (frequency) for any pesticide in addition to ever use for 50 specific pesticides. For applicators, information was also collected on duration and frequency of use for 22 of the 50 pesticides. We evaluated suicide risk in relation to 10 pesticide categories (four functional: fumigants, fungicides, herbicides, and insecticides; and six chemical: phenoxy herbicides, triazine herbicides, carbamates, organochlorine insecticides, organophosphate insecticides, and pyrethroid insecticides) as well as individual pesticides and overall pesticide use.

For both applicators and spouses, we evaluated cumulative lifetime days of use of any pesticide. For applicators only, we also evaluated cumulative lifetime days of use and intensity-adjusted cumulative lifetime days of use for 22 individual pesticides, although we present results for only the 17 pesticides for which there were at least five exposed cases. Duration and frequency of use data were collected in seven and eight categories, respectively. Using values set to the midpoint of each category, or 50% greater than the lower bound in the highest category, we determined an applicator's cumulative lifetime days of use for any pesticide and for each specific pesticide as the product of the duration and frequency values. We categorized cumulative lifetime days of use of any pesticide into quartiles based on the distribution of use for all applicators and spouses. We categorized specific pesticides into three levels based on the distribution of use for all applicators: *a*) none, *b*) used for less than or equal to the median lifetime days of use, and *c*) used for more than the median lifetime days. We also evaluated intensity-adjusted cumulative lifetime days of use, calculated as previously described (Dosemeci et al. 2002) and again categorized in three levels: none, ≤ median, > median.

Statistical analysis. We employed Cox proportional hazards regression models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for the association of suicide with each measure of pesticide use. Survival times were defined as the time (in days) between enrollment in the AHS and death for those who died from suicide (n = 110) or some other cause (n = 5,980) or the time between enrollment and 31 May 2009, for study participants still alive (n = 75,908). We ran models for applicators only and for applicators and spouses combined. There were too few suicides among spouses (n = 9) to analyze data on spouses alone. Possible confounding variables identified from prior reports (categorized as in Table 1) included age, sex, state of residence, race/ethnicity, education level, marital status, number of children in family (as a measure of social connection), size of farm worked last year, frequency of alcohol consumption during the past 12 months, smoking status, and ever diagnosed with heart disease or diabetes (as measures of chronic disease). We did not consider depression as a potential confounder, as it may be an intervening variable. Although spouses were not asked about number of children in family, farm size, or ever being diagnosed with heart disease, we inferred spouses' answers for the first two items from applicators' responses and based the last item on spouses' responses to questions on myocardial infarction, angina, and arrhythmia.

We evaluated all covariates significantly associated with suicide in both unadjusted and age- and sex-adjusted models as potential confounders (α = 0.05). We then performed manual backward selection using α = 0.05 to select a base model from the covariates identified in the first step. As an alternative model selection method, we performed manual forward selection using α = 0.05 and selected the same model as with the backward selection method. We evaluated whether additional covariates should be included in the base model with likelihood ratio tests (α = 0.05) and evaluated model fit using the Akaike information criterion and the Schwarz Bayesian criterion.

Table 1. Characteristics of suicide cases and all pesticide applicators and spouses.

Characteristic	Cases[a] *n*	Cases[a] PY	Total[a] *n*	Total[a] PY	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Age at enrollment (years)						
18–35	27	164	17,741	245,354	1.14 (0.68, 1.91)	1.09 (0.65, 1.82)
36–45	32	243	24,406	331,257	Reference	Reference
46–65	36	217	33,448	442,276	0.84 (0.52, 1.35)	0.87 (0.54, 1.40)
> 65	15	79	6,403	74,056	2.07 (1.12, 3.82)	1.97 (1.07, 3.65)
Sex						
Male	100	648	51,679	698,643	Reference	Reference
Female	10	54	30,319	394,300	0.17 (0.09, 0.33)	0.18 (0.09, 0.34)
State of residence						
Iowa	61	406	55,734	743,676	Reference	Reference
North Carolina	49	296	26,264	349,267	1.72 (1.18, 2.50)	1.65(1.13, 2.41)
Applicator type or spouse						
Private applicator	89	569	48,098	647,006	Reference	Reference
Commercial applicator	12	81	4,781	68,240	1.30 (0.71, 2.37)	1.35 (0.73, 2.49)
Spouse (of private applicator)	9	51	29,119	377,697	0.17 (0.09, 0.34)	0.41 (0.07, 2.55)
Race/ethnicity						
White, non-Hispanic	102	669	79,567	1,060,879	Reference	Reference
Other	7	24	2,328	30,698	2.37 (1.10, 5.10)	2.15 (1.00, 4.63)
Education level						
≤ Some high school	10	53	5,737	73,003	1.39 (0.71, 2.76)	1.08 (0.54, 2.18)
High school graduate	48	324	36,854	489,551	Reference	Reference
GED, 1–3 years of vocational education beyond high school, or some college	37	224	22,292	299,743	1.26 (0.82, 1.94)	1.35 (0.87, 2.08)
≥ College graduate	13	87	15,725	212,110	0.63 (0.34, 1.16)	0.68 (0.37, 1.27)
Marital status						
Married or living as married	87	572	73,042	970,990	Reference	Reference
Divorced or separated	11	61	2,457	33,299	3.72 (1.99, 6.97)	2.70 (1.43, 5.09)
Widowed, never married, or other	12	69	6,420	87,645	1.54 (0.84, 2.82)	1.03 (0.54, 1.94)
Number of children in family						
≤ 1	44	265	19,642	266,403	Reference	Reference
> 1	66	437	62,356	826,540	0.48 (0.33, 0.70)	0.52 (0.34, 0.79)
Size of farm worked last year						
Did not work on a farm or < 5 acres	8	41	6,048	80,244	Reference	Reference
≥ 5 acres	81	553	69,263	922,473	0.88 (0.43, 1.82)	0.96 (0.46, 2.00)
Frequency of alcohol consumption during past 12 months						
Never	38	232	29,979	393,657	0.99 (0.67, 1.48)	1.11 (0.73, 1.68)
< Every day	67	435	51,239	689,157	Reference	Reference
Every day	5	35	780	10,129	5.04 (2.03, 12.51)	4.20 (1.69, 10.43)
Smoking status						
Never	39	275	49,202	658,739	Reference	Reference
Past	32	194	20,959	277,039	1.95 (1.22, 3.12)	1.57 (0.97, 2.54)
Current	39	234	11,837	157,164	4.20 (2.69, 6.55)	3.66 (2.34, 5.73)
Ever diagnosed with heart disease						
No	100	657	75,880	1,016,855	Reference	Reference
Yes	5	14	4,843	59,577	0.85 (0.34, 2.08)	0.87 (0.34, 2.19)
Ever diagnosed with diabetes (other than while pregnant)						
No	101	653	78,411	1,048,599	Reference	Reference
Yes	7	43	2,625	31,850	2.26 (1.05, 4.87)	2.25 (1.03, 4.91)
Ever diagnosed with depression						
No	85	586	76,603	1,022,481	Reference	Reference
Yes	18	85	4,059	53,221	4.06 (2.44, 6.75)	5.43 (3.25, 9.10)

[a]Information for specific covariates was missing for 0–8% of participants. [b]Adjusted for age at enrollment and sex.

The applicator-only base model included age at enrollment (18–35, 36–45, 46–65, > 65 years), number of children in family (≤ 1, > 1), frequency of alcohol consumption during the past 12 months (never, < every day, every day), and smoking status (never, past, current). The base model for applicators and spouses together also included sex.

Table 2. Suicide and pesticide use among applicators and spouses.

Variable	Cases[a] n	Cases[a] PY	Total[a] n	Total[a] PY	Adjusted HR[b] (95% CI)
Years personally mixed or applied pesticides					
None	7	54	13,904	180,992	Reference
≤ 5	29	152	13,009	175,839	1.53 (0.60, 3.87)
> 5	73	493	50,952	681,370	0.83 (0.33, 2.08)
					p_{trend} = 0.03
Days per year personally mixed or applied pesticides					
None	8	59	14,124	183,728	Reference
< 20	71	466	46,745	622,313	0.98 (0.42, 2.28)
≥ 20	30	175	16,997	232,178	0.89 (0.36, 2.20)
					p_{trend} = 0.67
Cumulative lifetime days personally mixed or applied pesticides[c]					
≤ 9	22	129	20,736	271,553	Reference
> 9–109	33	220	21,524	287,320	0.65 (0.37, 1.16)
> 109–370	26	182	19,747	265,712	0.51 (0.27, 0.94)
> 370	28	169	15,777	212,577	0.61 (0.33, 1.13)
					p_{trend} = 0.52
Medical visits related to pesticide use[d]					
No	91	592	49,022	663,393	Reference
Yes	9	57	3,492	47,305	1.32 (0.66, 2.62)
Functional pesticide classes[e] ever personally mixed or applied					
Fumigants					
No	85	542	69,238	920,494	Reference
Yes	25	160	12,178	164,901	0.98 (0.62, 1.54)
Fungicides					
No	74	470	61,607	818,170	Reference
Yes	36	232	19,761	266,561	0.89 (0.59, 1.34)
Herbicides					
No	14	83	20,326	265,005	Reference
Yes	96	619	61,406	824,414	0.69 (0.35, 1.36)
Insecticides					
No	18	112	22,312	291,593	Reference
Yes	92	590	59,560	799,710	0.85 (0.49, 1.49)
Chemical pesticide classes[f] ever personally mixed or applied					
Phenoxy herbicides					
No	37	219	25,338	336,166	Reference
Yes	67	455	40,178	542,779	0.70 (0.45, 1.06)
Triazine herbicides					
No	38	225	25,769	342,148	Reference
Yes	66	449	39,747	536,796	0.71 (0.47, 1.09)
Carbamates					
No	48	309	39,193	518,688	Reference
Yes	62	393	42,656	572,294	0.80 (0.54, 1.17)
Organochlorine insecticides					
No	66	445	54,499	726,683	Reference
Yes	44	257	26,745	356,697	0.88 (0.58, 1.35)
Organophosphate insecticides					
No	26	170	28,870	377,315	Reference
Yes	84	532	52,979	713,702	0.82 (0.50, 1.33)
Pyrethroid insecticides					
No	87	538	68,400	907,912	Reference
Yes	23	164	13,326	181,574	1.09 (0.68, 1.74)

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; DDVP, 2,2-dichlorovinyl dimethyl phosphate; EPTC, *S*-ethyl dipropyl(thiocarbamate).
[a]Information for specific pesticide covariates was missing for 0–20% of participants. [b]Adjusted for age at enrollment, sex, number of children in family, frequency of alcohol consumption during the past 12 months, and smoking status. [c]Category boundaries set at the quartiles of the distribution of cumulative lifetime days of pesticide use for all applicators and spouses. [d]Not asked on the spouse questionnaire. Only results for applicators are shown. [e]Fumigants included aluminum phosphide, methyl bromide, carbon tetrachloride/carbon disulfide (80/20 mix), and ethylene dibromide. Fungicides included benomyl, captan, chlorothalonil, maneb/mancozeb, metalaxyl, and ziram. Herbicides included 2,4-D; 2,4,5-T; 2,4,5-TP; alachlor; atrazine; butylate; chlorimuron ethyl; cyanazine; dicamba; EPTC; glyphosate; imazethapyr; metolachlor; metribuzin; paraquat; pendimethalin; petroleum oil; and trifluralin. Insecticides included aldicarb, aldrin, carbaryl, carbofuran, chlordane, chlorpyrifos, coumaphos, DDT, DDVP, diazinon, dieldrin, fonofos, heptachlor, lindane, malathion, parathion, permethrin (for animals), permethrin (for crops), phorate, terbufos, toxaphene, and trichlorfon. [f]Phenoxy herbicides included 2,4-D; 2,4,5-T; and 2,4,5-TP. Triazine herbicides included atrazine, cyanazine, and metribuzin. Carbamates included aldicarb, benomyl, carbaryl, and carbofuran. Organochlorine insecticides included aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, and toxaphene. Organophosphate insecticides included chlorpyrifos, coumaphos, DDVP, diazinon, fonofos, malathion, parathion, phorate, terbufos, and trichlorfon. Pyrethroid insecticides included permethrin (for animals) and permethrin (for crops).

Additional analyses included stratifying models by state of residence, number of children in family, and use of chemical-resistant gloves (applicators only). We formally compared HRs from the two strata using a 95% CI constructed from the standard error of the difference between HRs. To additional models, we added state, marital status, race/ethnicity, ever being diagnosed with diabetes, or cumulative lifetime days of use of any pesticide. We evaluated all four functional classes of pesticides together in a single model. Additionally, we evaluated carbamates, herbicides, organochlorine insecticides, OPs, and pyrethroid insecticides together in another model. Some analyses were repeated, restricting the sample to male applicators, applicators who personally used pesticides, individuals who did not report a physician diagnosis of depression, or cohort members ≤ 50 years of age at enrollment (because pesticide use among younger applicators is probably less likely to change during follow-up than use among older applicators). We separately evaluated suicides committed within 5 years of enrollment or more than 5 years past enrollment. We evaluated pesticide use during the year prior to enrollment. Finally, we used within-category medians to assess dose–response trends in cumulative lifetime days of use and intensity-adjusted cumulative lifetime days of use.

We used the P1REL090600 release of the Phase I data set, the REL090500.00 release of the demographic data set, and the REL201004.00 release of the mortality data set for this study and performed all analyses with SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

In models adjusted for age at enrollment and sex, risk for suicide was significantly greater if participants *a*) were > 65 years of age compared with 36–45 years of age, *b*) were living in North Carolina, *c*) were of a race/ethnicity other than white/non-Hispanic, *d*) were divorced or separated compared with married or living as married, *e*) drank alcohol every day during the 12 months prior to enrollment compared with drank alcohol < every day, *f*) were current smokers compared with never smokers, or *g*) had ever been diagnosed with diabetes or depression (Table 1). Suicide risk was significantly lower for women than men and for participants with > 1 child compared with ≤ 1 child (Table 1).

We found little evidence that suicide was associated with overall pesticide use among applicators and spouses combined (Table 2). We saw no significant dose–response relationships between pesticide use (measured by duration, frequency, or cumulative lifetime days of use of any pesticide) and suicide. Only 37% of suicide cases (*n* = 41), all applicators, provided information on experiencing a high pesticide exposure event, and only seven cases experienced one (HR = 1.13; 95% CI: 0.50, 2.57). No cases reported being diagnosed with pesticide poisoning, but medical visits related to pesticide use were not significantly associated with suicide among applicators (Table 2).

For no specific functional or chemical class of pesticides, including OPs, was ever use significantly associated with suicide (Table 2). Only use of pyrethroid insecticides had an HR of > 1.0 (HR = 1.09; 95% CI: 0.68, 1.74), but that was not significant.

Among applicators and spouses together, ever use of individual pesticides was typically inversely associated with suicide, although estimates were often based on small numbers of exposed cases (Table 3). Five herbicides (atrazine, dicamba, imazethapyr, metolachlor, and pendimethalin) showed significant inverse associations; no positive association was statistically significant. The HR for (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), however, was elevated (HR = 1.55; 95% CI: 0.95, 2.53).

Among applicators alone, none of the 22 individual pesticides showed a significant dose–response relationship between cumulative lifetime days of use and suicide (Table 4). Repeating those analyses with intensity-adjusted cumulative lifetime days of use, we found HRs that were generally < 1.0 but not significant (data not shown). We found significant inverse dose–response relationships between three intensity-adjusted pesticides and suicide: (2,4-dichlorophenoxy)acetic acid (2,4-D) (≤ 381 days vs. none: HR = 0.85; 95% CI: 0.53, 1.37; > 381 days vs. none: HR = 0.56; 95% CI: 0.33, 0.96; p_{trend} = 0.04), metolachlor (≤ 221 days vs. none: HR = 0.49; 95% CI: 0.26, 0.91; > 221 days vs. none: HR = 0.47; 95% CI: 0.25, 0.87; p_{trend} = 0.03), and terbufos (≤ 189 days vs. none: HR = 0.71; 95% CI: 0.38, 1.31; > 189 days vs. none: HR = 0.45; 95% CI: 0.22, 0.95; p_{trend} = 0.04).

When we stratified by state of residence or number of children in family separately and used the ever-use herbicide variables for applicators and spouses, we observed the same results in each stratum: generally inverse associations between herbicides and suicide with a few being significant (data not shown). Formal comparison of the stratum-specific HRs showed no significant differences. Data on use of chemical-resistant gloves were available only for applicators. Stratification by this variable yielded similar results in both strata for general use and herbicide variables (data not shown).

Results remained unchanged when state, marital status, race/ethnicity, ever being diagnosed with diabetes, or cumulative lifetime days of use of any pesticide were added to the models one at a time (data not shown). Evaluating all four functional pesticide classes together in a single model or evaluating carbamates, herbicides, organochlorine insecticides, OPs, and pyrethroid insecticides together in another model did not change results (data not shown). Excluding cohort members who had been diagnosed with depression changed results slightly: a few more pesticides were inversely associated with suicide and a few more inverse associations were significant (data not shown). Restricting analyses to male applicators, to applicators who personally used pesticides, or to cohort members ≤ 50 years of age at enrollment did not change results (data not shown). Likewise, evaluating pesticide use during the year prior to the enrollment of cohort members in the AHS did not change results (data not shown).

Evaluating suicides committed more than 5 years after enrollment in the AHS showed no significant associations between suicide and general pesticide use or the functional and chemical class pesticide variables, although most HRs were slightly more negative (data not shown). Similarly we found no significant associations between pesticide use and suicide committed within 5 years of enrollment (data not shown).

Table 3. Suicide and ever use of specific pesticides among applicators and spouses.

	Cases[a]		Total[a]		Adjusted HR[b,c]
Ever personally mixed or applied[d]	n	PY	n	PY	(95% CI)
Fumigants					
Carbon tetrachloride/carbon disulfide (80/20 mix)	5	39	2,906	38,622	1.01 (0.41, 2.51)
Ethylene dibromide	5	30	1,851	25,051	1.32 (0.54, 3.27)
Methyl bromide	15	89	8,095	109,723	0.80 (0.46, 1.41)
Fungicides					
Benomyl	10	72	5,650	76,856	0.86 (0.45, 1.67)
Captan	8	44	5,805	76,640	0.87 (0.42, 1.81)
Chlorothalonil	13	83	4,698	63,921	1.32 (0.74, 2.37)
Maneb/mancozeb	7	48	5,330	72,448	0.64 (0.30, 1.40)
Metalaxyl	26	172	12,087	164,844	1.08 (0.68, 1.73)
Herbicides					
2,4-D	68	443	43,444	585,213	0.79 (0.52, 1.21)
2,4,5-T	24	194	10,539	140,942	1.55 (0.95, 2.53)
2,4,5-TP	10	90	4,703	63,527	1.25 (0.64, 2.44)
Alachlor	38	252	27,687	374,305	0.68 (0.44, 1.03)
Atrazine	56	402	37,529	506,172	0.64 (0.43, 0.96)
Butylate	26	231	16,164	220,059	0.91 (0.58, 1.45)
Chlorimuron ethyl	26	194	19,380	264,693	0.66 (0.42, 1.05)
Cyanazine	28	188	21,655	292,910	0.70 (0.45, 1.10)
Dicamba	33	271	26,363	356,274	0.63 (0.41, 0.98)
EPTC	17	148	10,678	145,053	0.97 (0.57, 1.66)
Glyphosate	77	509	49,703	667,712	0.94 (0.61, 1.45)
Imazethapyr	22	161	22,309	301,466	0.49 (0.30, 0.80)
Metolachlor	28	169	24,339	330,230	0.54 (0.35, 0.84)
Metribuzin	33	233	22,846	310,544	0.77 (0.50, 1.19)
Paraquat	19	152	12,658	172,340	0.70 (0.42, 1.16)
Pendimethalin	30	196	23,582	320,020	0.56 (0.36, 0.87)
Petroleum oil	32	211	24,022	324,356	0.65 (0.42, 1.00)
Trifluralin	41	290	27,759	375,427	0.79 (0.52, 1.19)
Insecticides					
Aldicarb	10	64	6,094	83,166	0.73 (0.37, 1.41)
Aldrin	11	57	9,298	123,387	0.71 (0.37, 1.38)
Carbaryl	55	357	37,073	497,220	0.99 (0.66, 1.48)
Carbofuran	23	181	13,691	184,258	0.99 (0.61, 1.59)
Chlordane	25	147	13,522	181,216	1.18 (0.73, 1.90)
Chlorpyrifos	40	263	22,784	308,881	0.99 (0.66, 1.48)
DDT	26	137	13,145	172,271	1.43 (0.85, 2.41)
DDVP	8	58	5,571	75,408	1.05 (0.51, 2.18)
Diazinon	34	208	18,850	254,163	1.16 (0.76, 1.76)
Fonofos	15	120	10,957	147,693	0.85 (0.49, 1.49)
Heptachlor	9	57	7,613	101,052	0.80 (0.39, 1.64)
Lindane	14	99	9,394	125,975	0.92 (0.52, 1.63)
Malathion	62	388	40,702	548,502	0.93 (0.61, 1.42)
Parathion	14	86	7,815	105,287	0.94 (0.53, 1.67)
Permethrin (for animals)	7	41	7,062	96,228	0.72 (0.33, 1.57)
Permethrin (for crops)	18	138	7,820	106,468	1.38 (0.82, 2.31)
Phorate	22	153	16,424	221,404	0.80 (0.49, 1.30)
Terbufos	24	176	19,527	263,680	0.67 (0.42, 1.07)
Toxaphene	9	64	7,092	94,595	0.72 (0.36, 1.45)

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; DDVP, 2,2-dichlorovinyl dimethyl phosphate; EPTC, *S*-ethyl dipropyl(thiocarbamate).
[a]Information for specific pesticides was missing for 1–6% of participants. [b]Adjusted for age at enrollment, sex, number of children in family, frequency of alcohol consumption during the past 12 months, and smoking status. [c]For each pesticide, the applicators and spouses who did not use the pesticide served as the reference group. [d]Fewer than five cases used aluminum phosphide, coumaphos, dieldrin, trichlorfon, or ziram.

Discussion

We found no association between pesticide use up to enrollment in the AHS and subsequent incidence of suicide in pesticide applicators and their spouses. This finding was consistent for use of any pesticide or individual pesticides, for functional or chemical classes, and for cumulative lifetime days of pesticide use. Results were the same for applicators and spouses together or for applicators only.

Although many studies have reported higher suicide rates among farmers and pesticide applicators than the general population (Blair et al. 1993; Browning et al. 2008; Gunderson et al. 1993; Lee et al. 2002; MacFarlane et al. 2009, 2010; Meltzer et al. 2008; Miller and Burns 2008; Page and Fragar 2002; Stallones 1990), others have found lower rates (Pickett et al. 1993, 1999; Torchio et al. 1994). A recent mortality analysis showed lower suicide rates among AHS participants than among the general populations of Iowa and North Carolina at least 15 years of age, although deaths due to unintentional injuries were elevated (Waggoner et al. 2011). The lower suicide rate in the AHS could reflect misclassification of suicides as unintentional injuries (e.g., collision with objects).

Another possible explanation for the lower suicide rate in the AHS is that individuals at risk of suicide may be less likely to enroll initially. This self-selection, if nondifferential by exposure, should not bias estimated HRs, although it might reduce precision. To reduce the influence of the healthy worker effect on their standardized mortality ratios (SMRs), Waggoner et al. (2011) calculated relative SMRs (rSMRs), a ratio of a cause-specific SMR and the SMR for all other causes except the cause of interest. The rSMR for suicide among applicators was 1.06 (95% CI: 0.87, 1.28) (Waggoner JK, personal communication), suggesting that the deficit in suicides observed in the AHS may be due to the healthy worker effect.

Previous studies that reported higher suicide rates among farmers and pesticide applicators had less-detailed pesticide exposure information than that available in the AHS (London et al.

Table 4. Suicide and dose response for specific pesticides among applicators.

Cumulative lifetime days of use of[c]	Cases[a] n	Cases[a] PY	Total[a] n	Total[a] PY	Adjusted HR[b] (95% CI)
Fumigants					
Methyl bromide					
None	84	546	44,681	604,613	Reference
≤ 26[d]	9	59	3,919	53,240	0.98 (0.49, 1.98)
> 26	5	24	3,467	47,046	0.62 (0.25, 1.53)
					p_{trend} = 0.30
Fungicides					
Chlorothalonil					
None	89	577	47,968	648,713	Reference
≤ 28	6	29	2,041	27,769	1.32 (0.58, 3.03)
> 28	6	45	2,035	27,983	1.31 (0.57, 3.01)
					p_{trend} = 0.51
Herbicides					
2,4-D					
None	34	211	13,153	178,829	Reference
≤ 64	36	245	20,023	270,683	0.79 (0.49, 1.27)
> 64	25	165	18,453	249,665	0.61 (0.36, 1.04)
					p_{trend} = 0.11
Alachlor					
None	54	353	24,026	325,520	Reference
≤ 51	17	106	13,169	177,726	0.62 (0.36, 1.08)
> 51	18	118	12,351	168,066	0.69 (0.40, 1.18)
					p_{trend} = 0.24
Atrazine					
None	45	259	16,342	222,136	Reference
≤ 56	25	152	18,518	250,121	0.56 (0.34, 0.93)
> 56	27	219	17,104	231,261	0.68 (0.41, 1.10)
					p_{trend} = 0.37
Cyanazine					
None	64	402	29,498	399,275	Reference
≤ 39	15	84	10,993	147,671	0.74 (0.42, 1.30)
> 39	12	94	9,376	128,369	0.67 (0.36, 1.25)
					p_{trend} = 0.25
Dicamba					
None	61	343	24,905	337,385	Reference
≤ 39	14	133	13,824	186,574	0.49 (0.27, 0.88)
> 39	15	108	10,737	146,204	0.67 (0.37, 1.19)
					p_{trend} = 0.24
EPTC					
None	73	446	39,292	531,770	Reference
≤ 25	7	66	6,184	83,741	0.69 (0.32, 1.51)
> 25	9	75	3,797	52,139	1.36 (0.68, 2.74)
					p_{trend} = 0.36
Glyphosate					
None	24	136	12,692	171,041	Reference
≤ 39	42	276	21,334	288,296	1.04 (0.63, 1.72)
> 39	30	209	17,954	244,520	0.88 (0.51, 1.50)
					p_{trend} = 0.49
Imazethapyr					
None	68	415	28,483	385,978	Reference
≤ 25	10	87	14,731	199,218	0.34 (0.17, 0.66)
> 25	12	74	6,219	84,531	0.87 (0.46, 1.62)
					p_{trend} = 0.75
Metolachlor					
None	65	437	26,995	364,519	Reference
≤ 51	10	29	12,185	164,929	0.37 (0.19, 0.73)
> 51	15	112	10,599	144,974	0.63 (0.36, 1.12)
					p_{trend} = 0.17
Trifluralin					
None	53	318	23,874	322,942	Reference
≤ 56	18	122	14,077	190,441	0.65 (0.38, 1.11)
> 56	22	163	11,453	155,823	0.98 (0.59, 1.63)
					p_{trend} = 0.80
Insecticides					
Carbofuran					
None	69	408	36,836	499,756	Reference
≤ 25	12	90	8,025	107,940	0.89 (0.48, 1.65)
> 25	10	84	4,665	63,161	1.19 (0.61, 2.32)
					p_{trend} = 0.59
Chlorpyrifos					
None	61	394	30,791	415,705	Reference
≤ 25	17	120	11,766	159,792	0.77 (0.45, 1.33)
> 25	20	124	9,443	128,517	1.12 (0.67, 1.86)
					p_{trend} = 0.54
Fonofos					
None	76	471	39,562	536,183	Reference
≤ 25	6	40	5,625	75,713	0.65 (0.28, 1.51)
> 25	8	71	4,498	61,030	1.05 (0.50, 2.18)
					p_{trend} = 0.88
Permethrin (for crops)					
None	75	469	42,318	572,345	Reference
≤ 25	9	71	4,441	60,458	1.17 (0.58, 2.34)
> 25	5	40	2,538	34,973	0.99 (0.40, 2.45)
					p_{trend} = 0.99
Terbufos					
None	67	423	31,348	424,772	Reference
≤ 39	12	76	9,353	125,951	0.68 (0.36, 1.26)
> 39	9	73	8,841	120,368	0.53 (0.26, 1.06)
					p_{trend} = 0.07

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; EPTC, *S*-ethyl dipropyl(thiocarbamate).
[a]Information for specific pesticides was missing for 0–4% of applicators. [b]Adjusted for age at enrollment, number of children in family, frequency of alcohol consumption during the past 12 months, and smoking status. [c]Fewer than five cases used captan, coumaphos, 2,2-dichlorovinyl dimethyl phosphate (DDVP), permethrin (for animals), and trichlorfon. [d]Category boundaries set at the median cumulative lifetime days of use of each pesticide among applicators who used them (i.e., both cases and controls).

2005; Parrón et al. 1996; Pickett et al. 1998; Stallones 2006). For example, one study inferred exposure from the fact that the study area had the highest density of greenhouses in the world (Parrón et al. 1996), and another inferred exposure from the occupation listed on death certificates (Stallones 2006). Pickett et al. (1998) found no association between suicide among Canadian farmers and three exposure measures: *a*) acres sprayed with herbicides, *b*) acres sprayed with insecticides, and *c*) the costs of purchased agricultural chemicals. We did not replicate a previous finding from the AHS that suggested an association of chlorpyrifos with suicide (Lee et al. 2007). We had 65% more suicide cases among applicators using chlorpyrifos (n = 38) than in the previous study (n = 23), suggesting that the present results may be more reliable.

Other rural lifestyle factors besides pesticide use may explain the higher suicide rates among farmers observed in other studies. Farmers have ready access to lethal means such as guns, pesticides, and other chemicals (Booth et al. 2000; Goldney 2002; Gregoire 2002; Hawton and van Heeringen 2009; Nock et al. 2008). The social change that occurs when small farms are incorporated into larger ones could also contribute to higher suicide rates via higher unemployment rates and a breakdown in family relationships (Goldney 2002; Stallones 1990).

Factors previously reported to increase suicide risk, such as old age, male sex, unmarried status, social isolation, frequent alcohol consumption, frequent smoking, and being diagnosed with depression, did so in our study also, suggesting that there is nothing unusual about suicide cases in the AHS. Further, AHS farmers are generally similar to other U.S. farmers (Lynch et al. 2005), so our results should be generalizable.

The tendency for herbicide use to be inversely associated with suicide, even if only a few associations were statistically significant, is perplexing. These inverse associations did not change meaningfully in a variety of analyses. Individuals who later committed suicide may have experienced mental problems, financial stress, stress in general, or other problems that might have caused them to farm less or use herbicides less than they otherwise would, leading to apparent inverse associations between herbicide use and suicide. However, the prospective design of our study helps alleviate this concern, particularly because results were similar for suicides committed within 5 years of enrollment and those committed later.

Our results may be surprising, given the association between pesticide use and physician-diagnosed depression found previously in the AHS (Beseler et al. 2006, 2008). Suicide, however, is not equivalent to depression. Only 17% (n = 18) of suicide cases in our study had been diagnosed with depression (Table 1). Other risk factors such as alcohol/substance use, mood disorders, and personality traits/disorders (e.g., impulsivity, aggressiveness, hopelessness, high emotional reactivity) are also important risk factors for suicide (Goldney 2002; Hawton and van Heeringen 2009; Nock et al. 2008) that cannot be ignored. Although depression may be underreported in the AHS, underreporting is not likely to account for our results, and our results did not change meaningfully when we excluded cohort members who had been diagnosed with depression.

Our study has several strengths. Selection bias was likely to be minimal, as 84% of eligible applicators and 75% of eligible spouses were enrolled in the AHS. The AHS collected detailed information on pesticide use before suicides occurred, including data on the use of individual pesticides and duration, frequency, and intensity of use. We were able to control for potential confounding factors. Finally, suicide from death certificates is a relatively valid outcome (Moyer et al. 1989).

Limitations include the small number of suicides (n = 110), which meant low power for estimating HRs for some individual pesticides. Further, participants were farmer owners/operators and their spouses or they were commercial applicators, that is, not farm workers. Therefore, results may not be generalizable to farm workers who may be more highly exposed than AHS farmers. Some information potentially useful for a suicide analysis was unavailable from AHS questionnaires. For example, information on financial situation or pertinent life events such as divorce or death of a family member was unavailable, as was information on personality or access to mental health care. Measures of acute high-intensity pesticide exposure were unavailable for most of the cohort, particularly suicide cases, and dose–response information was available for only 22 of 50 pesticides. Using data on past pesticide use instead of ongoing use could also misclassify pesticide use if ongoing use, and not past use, is what increases suicide risk.

In conclusion, we found little evidence that pesticide use increases suicide risk in pesticide applicators and their spouses. This finding, although based on relatively few suicides, was consistent across multiple measures of pesticide use and was robust to varying analytic strategies. Although this null finding needs confirmation in different populations, it could be reassuring to farming populations.

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