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ORIGINAL ARTICLE

Pesticide use and fatal injury among farmers in the Agricultural Health Study

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Abstract

Purpose To assess whether pesticide use practices were associated with injury mortality among 51,035 male farmers from NC and IA enrolled in the Agricultural Health Study.

Methods We used Cox proportional hazards models adjusted for age and state to estimate fatal injury risk associated with self-reported use of 49 specific pesticides, personal protective equipment, specific types of farm machinery, and other farm factors collected 1–15 years preceding death. Cause-specific mortality was obtained through linkage to mortality registries.

Results We observed 338 injury fatalities over 727,543 person-years of follow-up (1993–2008). Fatal injuries increased with days/year of pesticide application, with the highest risk among those with 60+ days of pesticide application annually [hazard ratio (HR) = 1.87; 95% confidence interval (CI) = 1.10, 3.18]. Chemical-resistant glove use was associated with decreased risk (HR = 0.73; 95% CI = 0.58, 0.93), but adjusting for glove use did not substantially change estimates for individual pesticides or pesticide use overall. Herbicides were associated with fatal injury, even after adjusting for operating farm equipment, which was independently associated with fatal injury. Ever use of five of 18 herbicides (2,4,5-T, paraquat, alachlor, metribuzin, and butylate) were associated with elevated risk. In addition, 2,4-D and cyanazine were associated with fatal injury in exposure–response analyses. There was no evidence of confounding of these results by other herbicides.

Conclusion The association between application of pesticides, particularly certain herbicides, and fatal injuries among farmers should be interpreted cautiously but deserves further evaluation, with particular focus on understanding timing of pesticide use and fatal injury.

Keywords Pesticides · Mortality · Wounds and injuries

Abbreviations

AHS	Agricultural Health Study
CI	Confidence interval
HR	Hazard ratio

Introduction

According to the Census for Fatal Occupational Injuries, farming remained one of the most hazardous occupations in the United States in 2008, with an estimated annual fatality rate of 40.3/100,000 workers (Bureau of Labor Statistics 2010). The complex farming environment may contribute

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to this increased risk. While exposure to animals (Solomon 2002) and machinery (Myers and Hendricks 2009) have been examined in regard to fatal injury, pesticide exposure has not. Pesticide use, particularly insecticide use, may contribute to fatal and non-fatal injury via neurotoxic mechanisms (London et al. 2012). Personal characteristics also play a role, with older farmers (Myers et al. 2009) and men (Myers and Hard 1995) at greater risk of fatal injury, and disabled farmers at increased risk of non-fatal injury (Sprince et al. 2002). Also, failure to use personal protective equipment when handling chemicals has been associated with increased risk of non-fatal injury (Day et al. 2009).

A recent all-cause mortality analysis of farmers enrolled in the Agricultural Health Study (AHS), a prospective cohort study of licensed pesticide applicators in IA and NC showed an increased risk of fatal injury against a backdrop of low all-cause mortality (Waggoner et al. 2011). While machinery is often the proximal mechanism of fatality, other intrinsic factors preceding the injury, including pesticide exposure, may contribute to increased risk. Medical examiner/death certificate-based studies have limited ability to identify these preceding factors; however, with its prospective data, the AHS cohort is uniquely suited to do so. Our objective was to identify whether pesticide use characteristics and other farm factors were associated with unintentional fatal injury.

Methods

Study population

The AHS is a large prospective cohort that includes 52,394 private pesticide applicators, mostly farmers, in NC and IA. Among eligible applicators, 82% enrolled in the study from 1993 to 1997 by completing a self-administered questionnaire at the time of pesticide licensing; 44% of the cohort completed a second take-home questionnaire within 4 months of enrollment. Institutional Review Boards of the National Institutes of Health and its contractors approved the study; return of the questionnaire implied consent. The present study is restricted to male private applicators ($N = 51{,}035$).

Outcome classification

Deaths were identified through annual linkage with death registries in NC and IA and the National Death Index. Injury deaths from enrollment through the end of follow-up (December 31, 2008) were defined by International Classification of Diseases (ICD) codes indicating a fatal injury ICD-9: E800–E999; ICD-10: V01-Y98. Both traffic and non-traffic motor vehicle accidents were included. Non-occupational fatal injuries were excluded, including homicide, suicide, forces of nature, medical complications, and railway, water, and air transportation accidents. No participants were lost to mortality follow-up. The comparison population consisted of farmers who did not experience a fatal injury during the study period, regardless of vital status. Individuals contributed person-years from enrollment through the end of follow-up or the date of death, whichever was earlier.

Exposure assessment

For all applicators, we had information from the enrollment questionnaire on factors that may be related to fatal injury, including occupational, behavioral, and demographic variables. The enrollment questionnaire obtained information on the use of 50 pesticides, with detailed information for 22 of these (including lifetime frequency and duration of use), general pesticide application information, use of personal protective equipment, farm characteristics, animal exposures, smoking and drinking history, medical history, and demographic factors. For personal protective equipment, we focused on the use of chemical-resistant gloves because these were shown in measurement studies of AHS applicators to be the single factor most associated with the greatest reduction in exposure among application methods studied (Hines et al. 2011; Thomas et al. 2010). The take-home questionnaire provided additional information for 28 pesticides not covered in detail on the enrollment questionnaire, as well as information on farm machinery use and additional medical characteristics. The take-home questionnaire also provided information about high pesticide exposure events, defined as "an incident or experience while using any type of pesticide which caused you unusually high personal exposure." Differences between applicators who completed only the enrollment questionnaire and those who completed both questionnaires were small, with the most important being the slightly increased age of those completing both (Tarone et al. 1997). All AHS questionnaires are available on line at http://aghealth.nci.nih.gov/questionnaires.html.

Pesticides

Information was collected on average frequency of application of specific pesticides. To assess exposure–response for the frequency of pesticide application (days/year), we created 3- or 4-level variables depending on the number of users. Exposure–response was not evaluated for pesticides used by <1% of the cohort. For chemicals used by <5% of injured farmers, we split the distribution among users at the median (≤median or >median), with non-users as the referent group. For more frequently used pesticides, we split the distribution of users into tertiles, with non-users as the referent group. Using these criteria, 36 chemicals had sufficient data to assess exposure–response: 26 based on tertiles of use and ten chemicals were analyzed based on a median split. Due to low usage, we did not assess exposure–response models for fungicides and fumigants.

Farm practices

For those who completed the take-home questionnaire, we also assessed whether regular use patterns for large farm machinery, including driving combines, tractors, and trucks were associated with fatal injury. For tractors and trucks, frequency of use categories were daily, weekly, monthly, or less than monthly; for combine driving, a harvest-only activity, the categories were never, 1–10, 11–30, and ≥31 days/growing season. For tractors and trucks, we combined the lowest two groups to create the referent group. For combines, never users served as the referent group.

Other farm exposures evaluated included butchering animals (yes, no) and farm acreage, presented in the original categories of <5 acres (referent), 5–49, 50–199, 200–499, 500–999, and ≥1,000. We also examined collapsed categories of poultry and livestock production volumes: none (referent), <50, 50–499, and >500 animals.

Statistical analysis

We used Cox proportional hazards models to calculate hazard ratios for risk of fatal injury, using age as the timescale and adjusting for state as a covariate in all models. We considered other covariates (smoking, drinking, and acreage), but did not include them except as noted because they did not confound results, as determined by a 10% or greater change of the point estimate. Statistical significance was set at $p = 0.05$. Results are presented for exposures with 5 or more deaths. To examine exposure–response relationships, we created a "dose" variable by assigning consecutive integers to the response categories (starting with 0 for the referent group with no exposure and dividing the remaining exposed population into tertiles) and treated it as a continuous variable in model fitting.

Because farmers use multiple pesticides, we assessed potential confounding by examining pairwise correlations between chemicals that were significantly associated with fatal injury in single agent models. For chemicals with Spearman's correlations ≥0.3, we constructed models including both chemicals, with one in dose categories and the other as ever used, running analysis with each chemical in each role. Using this process, we found no evidence of any inter-chemical confounding. These analyses, completed using SAS 9.2 (Cary, NC, USA), utilized AHS data release AHSREL0905.00.

Results

Among the 51,035 male farmers, 338 injury deaths occurred over the average follow-up period of 13.3 years, which provided 730,234 person-years, for a rate of 46.3 injury deaths/100,000 person-years. Farmers having a fatal injury were primarily white and 61% were from Iowa, representative of the cohort's demographics (Table 1). Injury mortality increased with age, although decade-specific hazard ratios were not significantly increased. Decedents were similar to the entire cohort (at enrollment) with regard to body mass index. Individuals who were divorced or separated at enrollment were more likely to experience a fatal injury, as were decedents who reported experiencing difficulty with balance monthly or more frequently. Increased age, smoking, tremor, and depression were non-significantly associated with increased risk of fatal injury. Greater than high school education was associated with significantly decreased injury risk.

Days/year of pesticide application but not years or cumulative days was significantly associated with fatal injury (60+ days/year application: hazard ratio (HR) = 1.87; 95% Confidence Interval (CI) = 1.10, 3.18; p trend = 0.02; Table 2). Adjusting for ever drinking slightly attenuated this estimate (HR = 1.67, 95% CI = 0.95, 2.94). Use of chemical-resistant gloves was associated with a significant reduction in risk (HR = 0.73; 95% CI = 0.58, 0.93), but adding glove use to models did not change risk estimates for the frequency of pesticide use (60+ days/year HR = 1.92, 95% CI = 1.13, 3.27; p trend = 0.04).

After adjustment for age and state, ever use of seven of 49 pesticides was associated with significantly increased risk of fatal injury; none was associated with decreased risk (Table 3). Significant HRs were seen for ever use of five of 18 herbicides: 2,4,5-T, alachlor, butylate, metribuzin, and paraquat. No insecticide was significantly associated with risk, although there was a suggestive association with ever use of coumaphos (HR = 1.39, 95% CI = 0.97, 1.99). Of four fumigants evaluated, risk was significantly increased for users of carbon tetrachloride/carbon disulfide. Ziram was the only fungicide of 6 evaluated that was significantly associated with fatal injury. Adjusting the model for use of chemical-resistant gloves did not change the findings with the exception of increased HRs for paraquat ($HR_{paraquat|gloves}$ = 1.56; 95% CI = 1.18, 2.05) and parathion ($HR_{parathion|gloves}$ = 1.36; 95% CI = 1.00, 1.84).

In evaluating exposure–response for individual chemicals, we used frequency of use because this metric was associated with injury for the use of any pesticide (Table 2). For 17 of 18 herbicides, we evaluated exposure–response; 14 were based on four categories of frequency of use (Table 4), three by median split only. Significant trends

Table 1 Enrollment demographics and medical conditions for all male farmers and for male fatal injuries in the AHS, 1993–2008

Variable	Entire cohort (n = 51,035)		Fatal injuries (n = 338)		Age and state adj.	
	N	%	*N*	%	HR[a]	95% CI[a]
State						
NC	19,602	38	133	39	1.00	(Ref)
IA	31,433	62	205	61	1.15[b]	(0.92, 1.45)[b]
Race						
White	48,277	95	314	93	1.00	(Ref)
Other	2,758	5	24	7	1.38	(0.89, 2.12)
Age at enrollment						
<40	16,158	32	71	21	1.00	(Ref)
40–49	13,668	27	67	20	1.02	(0.63, 1.64)
50–59	10,773	21	69	20	1.45	(0.71, 2.94)
60–69	7,494	15	76	22	1.67	(0.71, 3.92)
70+	2,604	5	55	16	2.63	(0.98, 7.00)
BMI category (kg/m^2)						
<25	36,834	72	246	73	1.00	(Ref)
25–30	10,829	21	66	20	0.80	(0.61, 1.06)
>30	3,372	7	26	8	1.15	(0.76, 1.72)
Marital status						
Married	42,647	84	277	82	1.00	(Ref)
Divorced or separated	2,216	4	19	6	1.67	(1.05, 2.68)
Widowed	508	1	9	3	1.64	(0.83, 3.23)
Never	5,413	11	31	9	1.15	(0.75, 1.75)
Smoker status at enrollment						
Never	26,090	53	149	47	1.00	(Ref)
Ever	23,111	47	167	53	1.22	(0.97, 1.53)
Alcohol consumption at enrollment						
Never	16,176	34	118	38	1.00	(Ref)
Ever	31,095	66	191	62	1.11	(0.86, 1.43)
Education						
High school or less	30,893	61	239	71	1.00	(Ref)
Greater than high school	20,027	39	99	29	0.73	(0.57, 0.93)
Ever farm machinery injury[c]						
No	16,487	75	109	72	1.00	(Ref)
Yes	5,580	25	43	28	1.16	(0.81, 1.67)
Difficulty with balance[c]						
Yearly or less	20,347	94	134	89	1.00	(Ref)
Monthly or more	1,242	6	16	11	1.69	(1.00, 2.86)
Shaking or trembling of your hands[c]						
Yearly or less	20,088	93	132	90	1.00	(Ref)
Monthly or more	1,416	7	15	10	1.53	(0.90, 2.62)
Depression						
Never	44,930	96	285	94	1.00	(Ref)
Ever	1,703	4	19	6	1.55	(0.96, 2.51)
Previous injury[c]						
No	16,378	75	109	72	1.00	(Ref)
Yes	5,537	25	43	28	1.16	(0.81, 1.67)
High pesticide exposure event[c]						
No	18,555	86	126	88	1.00	(Ref)
Yes	3,110	14	18	13	0.95	(0.58, 1.57)

[a] *HR* hazard ratio, *CI* confidence interval

[b] Hazards by state are adjusted for age only

[c] Take-home questionnaire variable; data available for approximately 40% of the cohort

Table 2 General pesticide use characteristics and fatal injury among male farmers in the AHS, 1993–2008

Variable/risk factor	Entire cohort ($n = 51{,}035$)		Fatal injuries ($n = 338$)		Age and state adj.		p trend
	N	%	N	%	HR[a]	95% CI[a]	
Days/year mixed or applied pesticides							
<5 or 5–9	19,473	42	124	40	1.00	(Ref)	0.02
10–19	14,080	30	92	30	1.16	(0.88, 1.53)	
20–39	9,087	19	58	19	1.24	(0.90, 1.71)	
40–59	2,384	5	17	6	1.54	(0.92, 2.59)	
60 or greater	1,877	4	16	5	1.87	(1.10, 3.18)	
Years applied pesticides							
<1	4,803	9	36	11	1.00	(Ref)	0.79
2–5	5,262	10	27	8	0.82	(0.49, 1.37)	
6–10	7,226	14	41	12	0.90	(0.57, 1.42)	
11–20	15,722	31	89	26	0.84	(0.56, 1.25)	
21–30	11,578	23	81	24	0.91	(0.60, 1.37)	
>30	6,444	13	64	19	0.97	(0.63, 1.48)	
Cumulative days personally mixed/applied pesticides							
0–56	15,198	30	96	28	1.00	(Ref)	0.09
57–200	10,931	21	67	20	0.87	(0.63, 1.21)	
201–396	11,910	23	69	20	0.92	(0.67, 1.27)	
≥397	12,996	25	106	31	1.27	(0.96, 1.69)	
Ever wear protective equipment when handling pesticides							
No	8,043	16	69	20	1.00	(Ref)	
Yes	42,985	84	269	80	0.78	(0.59, 1.03)	
Chemically resistant gloves used when handling pesticides							
No	16,464	32	136	40	1.00	(Ref)	
Yes	34,564	68	202	60	0.73	(0.58, 0.93)	

[a] *HR* hazard ratio, *CI* confidence interval

were observed for 2,4-D, butylate, and cyanazine. For 2,4-D, alachlor, and cyanazine, the HR was significant in the highest tertile of use. For the three herbicides analyzed by median split, only chlorimuron-ethyl showed increased risk ($HR_{>5\ days/year} = 1.59$; 95% CI = 0.98, 2.60; p trend = 0.06). No insecticides showed an exposure–response relationship between days/year of application and fatal injury (data not shown). When we analyzed cumulative days of use for individual chemicals, only the trends for 2,4-D [$HR_{high(>116\ days)} = 1.37$; 95% CI = 1.01, 1.88; p trend = 0.04] and cyanazine persisted [$HR_{high(>56\ days)} = 1.48$; 95% CI = 1.05, 2.01; p trend = 0.05]; carbofuran was the sole insecticide that showed an exposure–response [$HR_{high(>50.75\ days)} = 1.74$; 95% CI = 1.22, 2.50; p trend = 0.01].

Driving combines was associated with fatal injury, with an HR of 1.87 (95% CI = 1.07, 3.27) for 31 or more days per, p trend = 0.03 (Table 5). Adjusting for smoking and alcohol use did not substantially change results. Daily tractor driving was associated with increased risk, though not significantly so (HR = 1.41; 95% CI = 0.79, 2.52). While livestock production was not associated with fatal injury, butchering animals was (HR = 1.36; 95% CI = 1.01, 1.84). Poultry production showed a significant association with fatal injury, approximately doubling the risk of fatal injury regardless of flock size (HRs ranged from 1.78 to 2.26). These factors were unrelated to days/year of pesticide application and adjusting for driving combines, butchering animals, or poultry production did not alter pesticide findings (data not shown).

Discussion

The rate of fatal injury within this cohort (46.3 injury deaths/100,000 person-years) was similar to that reported for farmers and ranchers nationally in 2008 (40.3 injury deaths/100,000 person-years) (Bureau of Labor Statistics 2010). Based on comparisons within the AHS cohort, we observed increased risk for 60+ days of pesticide application/year as well as increased risk associated with specific herbicides, in both ever use and exposure–response models. Conversely, we saw a decrease in risk with use of chemical-resistant gloves. We cannot assess whether this latter reduction is a result of an attenuation of pesticide exposures

Table 3 Ever/never pesticide use and fatal injury among male farmers in the AHS, 1993–2008

Pesticide	Entire cohort (*n* = 51,035)		Fatal injuries (*n* = 338)		Age and state adj.	
	N	%	*N*	%	HR[a]	95% CI[a]
Herbicides						
2,4-D	37,218	76	259	80	1.24	(0.94, 1.64)
2,4,5-T	9,782	22	99	35	1.41	(1.09, 1.83)
2,4,5-TP	4,181	9	41	15	1.35	(0.96, 1.91)
Alachlor	24,767	54	184	60	1.30	(1.03, 1.64)
Atrazine	35,185	71	243	74	1.25	(0.97, 1.61)
Butylate	14,472	32	107	37	1.29	(1.01, 1.65)
Chlorimuron-ethyl	17,196	38	111	39	1.19	(0.93, 1.52)
Cyanazine	19,129	42	138	45	1.19	(0.95, 1.50)
Dicamba	22,952	50	148	49	1.02	(0.81, 1.28)
EPTC	8,836	20	60	20	1.14	(0.85, 1.52)
Glyphosate	37,555	76	238	73	0.91	(0.71, 1.16)
Imazethapyr	19,705	43	125	41	1.12	(0.89, 1.42)
Metolachlor	21,522	47	134	44	0.98	(0.78, 1.23)
Metribuzin	20,566	46	144	50	1.29	(1.02, 1.64)
Paraquat	11,161	25	91	32	1.35	(1.05, 1.74)
Pendimethalin	20,937	46	131	46	1.07	(0.85, 1.36)
Petroleum oil	21,311	48	144	50	1.14	(0.90, 1.44)
Trifluralin	24,530	53	154	52	0.99	(0.79,1.25)
Insecticides						
Aldicarb	5,785	13	30	10	0.79	(0.53, 1.16)
Aldrin	8,740	19	72	25	0.98	(0.73, 1.30)
Carbaryl	25,949	56	170	57	0.88	(0.69, 1.11)
Carbofuran	12,569	28	99	33	1.19	(0.93, 1.52)
Chlordane	11,607	26	84	29	0.87	(0.66, 1.13)
Chlorpyrifos	20,762	42	132	41	1.05	(0.84, 1.32)
Coumaphos	3,822	9	35	12	1.39	(0.97, 1.99)
DDT	11,835	26	106	37	1.00	(0.76, 1.33)
Dichlorvos	4,527	10	29	10	1.02	(0.69, 1.50)
Diazinon	14,326	32	91	32	0.94	(0.73, 1.21)
Dieldrin	3,081	7	31	11	1.10	(0.75, 1.63)
Fonofos	9,984	22	67	22	1.05	(0.79, 1.38)
Heptachlor	7,018	16	68	24	1.17	(0.88, 1.57)
Lindane	8,447	19	52	18	0.93	(0.69, 1.26)
Malathion	32,513	70	210	71	0.96	(0.75, 1.24)
Parathion	7,232	16	60	21	1.24	(0.93, 1.66)
Permethrin on livestock	5,803	13	31	10	0.95	(0.65, 1.38)
Permethrin on crops	6,242	14	28	9	0.69	(0.46, 1.03)
Phorate	15,078	34	102	35	1.03	(0.81, 1.32)
Terbufos	18,182	40	104	34	0.83	(0.65, 1.06)
Toxaphene	6,695	15	50	18	0.94	(0.68, 1.29)
Trichlorfon	316	1	2	1		
Fumigants						
Aluminum phosphide	2,178	5	19	7	1.48	(0.91, 2.38)
Carbon tetrachloride/carbon disulfide	2,482	6	31	11	1.54	(1.04, 2.28)
Ethylene dibromide	1,708	4	11	4	0.96	(0.53, 1.76)
Methyl bromide	8,048	16	54	17	0.92	(0.68, 1.25)

Table 3 continued

Pesticide	Entire cohort (n = 51,035)		Fatal injuries (n = 338)		Age and state adj.	
	N	%	N	%	HR[a]	95% CI[a]
Fungicides						
Benomyl	4,840	11	36	12	1.04	(0.73, 1.48)
Captan	4,940	11	30	10	0.96	(0.65, 1.40)
Chlorothalonil	4,192	9	21	6	0.67	(0.42, 1.07)
Maneb/mancozeb	4,531	10	34	12	1.07	(0.74, 1.53)
Metalaxyl	11,174	24	76	26	1.08	(0.83, 1.40)
Ziram	760	2	9	3	1.97	(1.01, 3.83)

[a] *HR* hazard ratio, *CI* confidence interval

or differences in risk taking behavior. As expected, operation of machinery was associated with increased risk as shown by the association with combine use.

Risk for fatal injury increased with the number of days/year of any pesticide application. While herbicides were most strongly associated, the risk estimate for the highest category of applying any pesticide was higher than that of the highest category for any individual chemical. Typically, insecticides rather than herbicides are associated with neurotoxicity as shown previously (Gomes et al. 1998; Kamel et al. 2005; London et al. 1998; Pilkington et al. 2001), and neurotoxicity might predispose to higher rates of fatal injury. The increased risk of fatal injury associated with herbicides was unexpected—we know of no other reports of such associations. Rather than direct toxicity, this finding may instead suggest that some activity related to herbicide use is associated with fatal injury. Although this may be a chance finding, it was specific in that we found associations with several different herbicides, and the increased risk was not due to correlated use of other pesticides. Furthermore, not all herbicides, including some that are commonly used, were associated with fatal injury.

Observed associations with days/year rather than years or cumulative days of use, as well as the fact that for some chemicals risks were only seen in the highest exposure category, suggest that acute rather than chronic pathways may be operating. However, frequency of use may instead be a risk indicator: individuals in the highest category may also have more days of overall farm activities/year (e.g., tractor driving) or more overall complex work environments (e.g., use of multiple types of farm equipment) leading to more opportunities for injury; we did observe increased risk among people who drove combines routinely. While we recognize the complexity in assessing multiple simultaneous exposures, our pesticide results did not appear to be confounded by frequency of other farm activities.

Although they did not explain any of the pesticide associations, activities involving farm machinery and working with animals were also independently associated with fatal injury. Machinery is often responsible for fatal injury (Richardson et al. 1997; Solomon 2002; Voaklander et al. 1999). While tractors are often the primary cause for injury, we did not observe a significant association with reported patterns of tractor driving, perhaps due to limited variability in tractor usage within our cohort or lack of details about the specific injury (e.g., presence of a roll over protective structure). Also, several types of machinery used on farms were not enumerated at enrollment [e.g., ATVs (Thomas et al. 2010)], and it is not clear whether and to what extent these might be associated with fatal injury and pesticide use. We did, however, observe elevations in risk for use of combines and butchering animals. Neither association has, to our knowledge, been reported previously.

Use of chemical-resistant gloves was associated with decreased risk of fatal injury. This association was also seen in a study of non-fatal farm injuries conducted among 252 cases and 504 controls in Australia, where use of personal protective equipment was associated with a 21% decreased risk of non-fatal injury (Day et al. 2009). While this decreased risk may be the result of lower pesticide exposure, it could also identify individuals who are generally more cautious.

Fatal injuries may be unreported suicides (Kraus et al. 2005; Rockett et al. 2010). Although the rate of suicide in this cohort is lower than the general population, the rate of injuries is higher (Waggoner et al. 2011). Beard and colleagues saw no evidence of an association of pesticides with suicide in the AHS. Moreover, individual herbicides were generally inversely associated with suicide in the AHS, with a few significantly so (Beard et al. 2011).

Strengths of this study include its size and prospective nature; we followed more than 51,000 farmers over 13 years. This large study provides information complementary to other studies that are generally small and rely on medical examiner reports (Bernhardt and Langley 1999; Richardson et al. 1997). While we used death certificates for our outcome and thus did not have information about what participants were doing when the fatality occurred, this prospective cohort allowed identification of potential risk factors predating the injury that cannot be identified based on

Table 4 Exposure–response associations for selected herbicides and fatal injury among male farmers in the AHS, 1993–2008

Herbicide (days/year)	Entire cohort (*n* = 51,035)		Fatal injuries (*n* = 338)		Age and state adj.		*p* trend
	N	%	*N*	%	HR[a]	95% CI[a]	
2,4-D							
0	12,025	25	65	21	1.00	(Ref)	0.01
<5	15,015	31	92	29	1.02	(0.73, 1.41)	
5–9	11,114	23	71	22	1.08	(0.76, 1.53)	
≥10	10,490	22	89	28	1.54	(1.11, 2.15)	
Alachlor							
0	21,264	47	123	42	1.00	(Ref)	0.07
<5	8,759	19	65	22	1.24	(0.91, 1.68)	
5–9	8,064	18	53	18	1.08	(0.77, 1.51)	
≥10	7,075	16	53	18	1.41	(1.02, 1.96)	
Atrazine							
0	14,255	29	84	26	1.00	(Ref)	0.18
<5	13,581	28	91	28	1.14	(0.84, 1.56)	
5–9	11,284	23	82	26	1.24	(0.90, 1.72)	
≥10	9,803	20	64	20	1.23	(0.88, 1.73)	
Butylate[b]							
0	15,873	74	96	66	1.00	(Ref)	0.02
<5	2,209	10	21	14	1.69	(1.05, 2.74)	
5–9	2,275	11	18	12	1.53	(0.92, 2.57)	
≥10	1,102	5	10	7	1.66	(0.83, 3.32)	
Cyanazine							
0	26,761	59	170	56	1.00	(Ref)	0.05
<5	8,211	18	56	18	1.11	(0.80, 1.53)	
5–9	6,183	14	43	14	1.09	(0.76, 1.57)	
≥10	4,343	10	36	12	1.54	(1.06, 2.24)	
Dicamba							
0	22,673	50	157	52	1.00	(Ref)	0.27
≤2.5	11,566	26	67	22	0.85	(0.62, 1.16)	
>2.5–7	7,009	16	45	15	0.95	(0.66, 1.36)	
>7	3,819	8	33	11	1.42	(0.95, 2.12)	
EPTC							
0	36,261	81	239	80	1.00	(Ref)	0.63
<5	4,199	9	31	10	1.20	(0.82, 1.76)	
5–9	2,664	6	16	5	0.95	(0.56, 1.61)	
≥10	1,733	4	11	4	1.16	(0.63, 2.14)	
Glyphosate							
0	11,923	24	88	28	1.00	(Ref)	0.79
<5	16,711	34	106	33	0.88	(0.66, 1.18)	
5–9	10,433	21	67	21	0.98	(0.71, 1.36)	
≥10	9,868	20	57	18	0.92	(0.65, 1.30)	
Imazethapyr							
0	25,706	57	177	59	1.00	(Ref)	0.35
<5	8,985	20	57	19	1.03	(0.74, 1.44)	
5–9	6,853	15	43	14	1.10	(0.77, 1.59)	
≥10	3,467	8	22	7	1.25	(0.78, 1.99)	

Table 4 continued

Herbicide (days/year)	Entire cohort ($n = 51{,}035$)		Fatal injuries ($n = 338$)		Age and state adj.		p trend
	N	%	N	%	HR[a]	95% CI[a]	
Metolachlor							
0	24,381	54	170	57	1.00	(Ref)	0.89
<5	7,566	17	49	16	0.95	(0.69, 1.32)	
5–9	7,251	16	43	14	0.91	(0.64, 1.28)	
≥10	6,183	14	38	13	1.03	(0.72, 1.48)	
Metribuzin[b]							
0	13,574	63	92	63	1.00	(Ref)	0.41
≤2.5	4,574	21	31	21	1.09	(0.71, 1.67)	
>2.5–7	2,490	12	15	10	1.04	(0.59, 1.83)	
>7	824	4	8	5	1.56	(0.71, 3.39)	
Pendimethalin[b]							
0	13,585	63	89	61	1.00	(Ref)	0.46
<5	3,961	18	32	22	1.35	(0.90, 2.03)	
5–9	2,603	12	15	10	1.06	(0.61, 1.84)	
≥10	1,378	6	9	6	1.17	(0.56, 2.44)	
Petroleum oil[b]							
0	16,991	79	112	77	1.00	(Ref)	0.14
<5	2,073	10	13	9	0.96	(0.54, 1.70)	
5–9	1,219	6	8	6	1.16	(0.56, 2.39)	
≥10	1,090	5	12	8	1.72	(0.92, 3.20)	
Trifluralin							
0	21,467	47	145	49	1.00	(Ref)	0.49
<5	8,601	19	49	17	0.82	(0.59, 1.15)	
5–9	8,890	20	52	18	0.89	(0.64, 1.24)	
≥10	6,420	14	48	16	1.23	(0.88, 1.73)	

[a] *HR* hazard ratio, *CI* confidence interval

[b] Take-home questionnaire variable; data available for approximately 40% of the cohort

medical examiner reports. In contrast, studies based on medical examiner reports (which we did not have) tend to include more detailed data regarding the immediate circumstances of the fatality (for example, lack of a roll over protective structure on a tractor or blood alcohol concentration of the decedent). Lastly, given the number of analyses performed, there is a possibility of some chance findings.

We relied on self-reported pesticide use information provided by participants at the time of enrollment. Farmers (Blair and Zahm 1993), including those in the AHS (Blair et al. 2002; Hoppin et al. 2002), have been shown to provide accurate information regarding their pesticide use. Except for three applicators that died within a year following enrollment, we do not know which chemicals were used in the year immediately preceding death. We also relied on death certificates to determine our outcome, which are valid for broad categories of injury reporting (Moyer et al. 1989). We studied risk factors for all injuries grouped together. While it is possible that risk factors for subtypes of injury differ, we felt the intrinsic factors that put someone at a higher risk for injury would not be specific to one type over another and thus studied a general grouping. Similar groupings are seen in other injury mortality studies (Crandall et al. 1997; Cubbin et al. 2000; Richardson et al. 1997).

Risk factors for non-fatal injury have previously been studied in this cohort. Hearing problems were associated with significantly increased risk of non-fatal injuries from animals (Sprince et al. 2003a), machinery (Sprince et al. 2002), and falls (Sprince et al. 2003b). While we could not examine hearing problems in our present study, we did see increased risk associated with other age-related conditions, such as difficulty with balance and tremor.

In this large cohort of male farmers, pesticide use, in addition to farm machinery use, was associated with fatal injury. Given our lack of information about whether a pesticide was used 1 year or many years before fatal injury and the unexpected associations with herbicides, these findings should be considered cautiously.

Table 5 Farm exposures and fatal injuries among male farmers in the AHS, 1993–2008

Variable/risk factor	Entire cohort (n = 51,035)		Fatal injuries (n = 338)		Age and state adj.		p trend
	N	%	*N*	%	HR[a]	95% CI[a]	
Drive combines (per growing season)[b]							
Never	4,368	20	28	19	1.00	(Ref)	0.03
1–10 days	4,395	20	29	20	1.36	(0.79, 2.34)	
11–30 days	8,899	41	61	41	1.56	(0.93, 2.59)	
31 or more days	3,963	18	30	20	1.87	(1.07, 3.27)	
Drive tractors[b]							
Never/once/month	2,317	11	18	12	1.00	(Ref)	0.19
Weekly	9,857	45	67	44	1.09	(0.63, 1.89)	
Daily	9,792	45	68	44	1.41	(0.79, 2.52)	
Drive trucks[b]							
Never/once/month	10,575	49	64	42	1.00	(Ref)	0.30
Weekly	5,855	27	51	34	1.40	(0.97, 2.03)	
Daily	5,277	24	37	24	1.18	(0.77, 1.82)	
Butcher animals							
No	43,932	86	284	84	1.00	(Ref)	
Yes	7,103	14	54	16	1.36	(1.01, 1.84)	
Acres planted last year							
None/did not work on a farm	3,510	8	24	8	1.00	(Ref)	0.30
5–49	4,340	9	37	12	1.25	(0.74, 2.11)	
50–199	8,166	18	60	20	1.11	(0.67, 1.84)	
200–499	12,913	28	85	28	0.99	(0.59, 1.66)	
500–999	10,205	22	63	21	1.00	(0.59, 1.72)	
≥1,000	6,742	15	32	11	0.84	(0.47, 1.51)	
Poultry production							
None/did not work on a farm	40,246	90	242	85	1.00	(Ref)	0.0003
<50	2,046	5	20	7	1.78	(1.13, 2.82)	
50–499	1,033	2	13	5	2.26	(1.29, 3.96)	
≥500	1,169	3	11	4	1.97	(1.06, 3.66)	
Livestock production							
None/did not work on a farm	21,193	47	145	50	1.00	(Ref)	0.76
<50	3,750	8	26	9	1.00	(0.66, 1.53)	
50–499	13,874	31	86	29	0.97	(0.72, 1.31)	
≥500	6,287	14	35	12	0.94	(0.63, 1.40)	

[a] *HR* hazard ratio, *CI* confidence interval

[b] Take-home questionnaire variable; data available for approximately 40% of the cohort

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Conflict of interest The authors declare that they have no conflict of interest.

References

Beard JD et al (2011) Suicide and pesticide use among pesticide applicators and their spouses in the Agricultural Health Study. Environ Health Perspect 119(1):1–30

Bernhardt JH, Langley RL (1999) Analysis of tractor-related deaths in North Carolina from 1979 to 1988. J Rural Health Off J Am Rural Health Assoc Natil Rural Health Care Assoc 15(3):285–295

Blair A, Zahm SH (1993) Patterns of pesticide use among farmers: implications for epidemiologic research. Epidemiology (Camb, MA) 4(1):55–62

Blair A et al (2002) Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology (Camb, MA) 13(1):94–99

Bureau of Labor Statistics (2010) Selected occupations with high fatal injury rates, 2008, p 19. In: Census of fatal occupational injuries. http://www.bls.gov/iif/oshwc/cfoi/cfch0007.pdf. Accessed 21 Mar 2011

Crandall CS, Fullerton L, Olson L, Sklar DP, Zumwalt R (1997) Farm-related injury mortality in New Mexico, 1980–91. Accid Anal Prev 29(2):257–261

Cubbin C, LeClere FB, Smith GS (2000) Socioeconomic status and the occurrence of fatal and nonfatal injury in the United States. Am J Public Health 90(1):70–77

Day L et al (2009) Risk factors for work related injury among male farmers. Occup Environ Med 66(5):312–318. doi:10.1136/oem.2008.040808

Gomes J, Lloyd O, Revitt MD, Basha M (1998) Morbidity among farm workers in a desert country in relation to long-term exposure to pesticides. Scand J Work Environ Health 24(3):213–219

Hines CJ, Deddens JA, Coble J, Kamel F, Alavanja MC (2011) Determinants of captan air and dermal exposures among orchard pesticide applicators in the Agricultural Health Study. Ann Occup Hyg 55(6):620–633. doi:10.1093/annhyg/mer008

Hoppin JA, Yucel F, Dosemeci M, Sandler DP (2002) Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 12(5):313–318. doi:10.1038/sj.jea.7500232

Kamel F et al (2005) Neurologic symptoms in licensed private pesticide applicators in the Agricultural Health Study. Environ Health Perspect 113(7):877–882

Kraus JF, Schaffer K, Chu L, Rice T (2005) Suicides at work: misclassification and prevention implications. Int J Occup Environ Health 11(3):246–253

London L, Nell V, Thompson ML, Myers JE (1998) Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers. Scand J Work Environ Health 24(1):18–29

London L et al (2012) Neurobehavioral and neurodevelopmental effects of pesticide exposures. Neurotoxicology 43(13):451–462. doi:10.1016/j.neuro.2012.01.004

Moyer LA, Boyle CA, Pollock DA (1989) Validity of death certificates for injury-related causes of death. Am J Epidemiol 130(5):1024–1032

Myers JR, Hard DL (1995) Work-related fatalities in the agricultural production and services sectors, 1980–1989. Am J Ind Med 27(1):51–63

Myers JR, Hendricks KJ (2009) Agricultural tractor overturn deaths: assessment of trends and risk. Am J Ind Med. doi:10.1002/ajim.20775

Myers JR, Layne LA, Marsh SM (2009) Injuries and fatalities to US farmers and farm workers 55 years and older. Am J Ind Med 52(3):185–194. doi:10.1002/ajim.20661

Pilkington A et al (2001) An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. Occup Environ Med 58(11):702–710

Richardson D, Loomis D, Wolf SH, Gregory E (1997) Fatal agricultural injuries in North Carolina by race and occupation, 1977–1991. Am J Ind Med 31(4):452–458

Rockett IR et al (2010) Suicide and unintentional poisoning mortality trends in the United States, 1987–2006: two unrelated phenomena? BMC Public Health 10:705. doi:10.1186/1471-2458-10-705

Solomon C (2002) Accidental injuries in agriculture in the UK. Occup Med (Oxf, England) 52(8):461–466

Sprince NL et al (2002) Risk factors for machinery-related injury among Iowa farmers: a case–control study nested in the Agricultural Health Study. Int J Occup Environ Health 8(4):332–338

Sprince NL et al (2003a) Risk factors for animal-related injury among Iowa large-livestock farmers: a case–control study nested in the Agricultural Health Study. J Rural Health 19(2):165–173

Sprince NL et al (2003b) Risk factors for falls among Iowa farmers: a case–control study nested in the Agricultural Health Study. Am J Ind Med 44(3):265–272. doi:10.1002/ajim.10267

Tarone RE et al (1997) The Agricultural Health Study: factors affecting completion and return of. Am J Ind Med 31(2):233–242

Thomas KW et al (2010) Urinary biomarker, dermal, and air measurement results for 2,4-D and chlorpyrifos farm applicators in the Agricultural Health Study. J Eposure Sci Environ Epidemiol 20(2):119–134. doi:10.1038/jes.2009.6

Voaklander DC, Hartling L, Pickett W, Dimich-Ward H, Brison RJ (1999) Work-related mortality among older farmers in Canada. Can Fam Physician 45:2903–2910

Waggoner JK et al (2011) Mortality in the Agricultural Health Study, 1993–2007. Am J Epidemiol 173(1):71–83. doi:10.1093/aje/kwq323