

Death by Agriculture 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 North Carolina and Iowa 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 per 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, injuries

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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 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 Iowa and North Carolina 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.

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METHODS

Study population

The AHS is a large prospective cohort that includes 52,394 private pesticide applicators, mostly farmers, in North Carolina and Iowa. Among eligible applicators, 82% enrolled in the study from 1993–1997 by completing a self-administered questionnaire at the time of pesticide licensing; 42% 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 North Carolina and Iowa, and the National Death Index. Injury deaths from enrollment through the end of follow-up (December 31, 2008) were defined by ICD codes indicating a fatal injury (International Classification of Diseases (ICD)-9: E800–E999; ICD-10: V01–Y98). Both traffic and nontraffic 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 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 herbicides. To assess exposure-response for 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 (\leq 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 days, 11–30 days, and ≥ 31 days per 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 $\geq 1,000$. 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 percent 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 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), utilized AHS data release AHSREL0905.00.

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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 nonsignificantly associated with increased risk of fatal injury. Greater than high school education was associated with significantly decreased injury risk.

Table 1

Enrollment demographics and medical conditions for all male farmers and for male fatal injuries in the Agricultural Health Study, 1993–2008.

Variable	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
State						
NC	19,602	38	133	39	1.00	(ref)
IA	31,433	62	205	61	1.15 b	(0.92 ^b 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)

Variable	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
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						

Variable	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
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)

^aHR = Hazard Ratio; CI = Confidence Interval

^bHazards by state are adjusted for age only.

^cTake-home questionnaire variable; data available for approximately 40% of the cohort.

Days per year of pesticide application but not years or cumulative days was significantly associated with fatal injury (60+ days per year application: Hazard Ratio (HR)=1.87; 95% Confidence Interval (CI)=1.10, 3.18; $p_{\text{trend}}=0.02$; [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 frequency of pesticide use (60+ days per year HR=1.92, 95%CI=1.13, 3.27; $p_{\text{trend}}=0.04$).

Table 2

General pesticide use characteristics and fatal injury among male farmers in the Agricultural Health Study, 1993–2008.

Variable/Risk factor	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR*	95% CI ^a	
Days per year mixed or applied pesticides							

Variable/Risk factor	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR *	95% CI ^a	
<5 or 5 to 9	19,473	42	124	40	1.00	(ref)	0.02
10 to 19	14,080	30	92	30	1.16	(0.88 1.53)	
20 to 39	9,087	19	58	19	1.24	(0.90 1.71)	Open in a separate window
40 to 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 to 5	5,262	10	27	8	0.82	(0.49 1.37)	
6 to 10	7,226	14	41	12	0.90	(0.57 1.42)	
11 to 20	15,722	31	89	26	0.84	(0.56 1.25)	
21 to 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 to 56	15,198	30	96	28	1.00	(ref)	0.09
57 to 200	10,931	21	67	20	0.87	(0.63 1.21)	
201 to 396	11,910	23	69	20	0.92	(0.67 1.27)	
>=397	12,996	25	106	31	1.27	(0.96 1.69)	

Variable/Risk factor	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR *	95% CI ^a	
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)	

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^aHR = Hazard Ratio; CI = Confidence Interval

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 4 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_{paration | gloves}=1.36; 95%CI=1.00, 1.84).

Table 3

Ever/never pesticide use and fatal injury among male farmers in the Agricultural Health Study, 1993–2008.

Pesticide	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR *	95% CI ^a
Herbicides						
2,4-D	37,218	76	259	80	1.24	(0.94

Pesticide	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
						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)
Chlorimuronethyl	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

Pesticide	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
Insecticides						1.25)
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)
DDVP	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)

Pesticide	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.	
	N	%	N	%	HR*	95% CI ^a
Permethrin on livestock	5,803	13	31	10	0.95	(0.65 1.38)
Permethrin or pyrethriod 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)
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)

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^aHR = Hazard Ratio; CI = Confidence Interval

In evaluating exposure-response for individual chemicals, we used frequency of use because this metric was associated with injury for 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 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^b=1.59; 95%CI=0.98, 2.60; p_{trend}=0.06). No insecticides showed an exposure-response relationship between days per 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).

Table 4

Exposure-response associations for selected herbicides and fatal injury among male farmers in the Agricultural Health Study, 1993–2008.

Herbicide days/year	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR*	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 to 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 to 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 to 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

Herbicide days/year	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR*	95% CI ^a	
< 5	2,209	10	21	14	1.69	(1.05 2.74)	
5 to 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 to 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)	
>2.5to7	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 to 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 to 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 to 9	6,853	15	43	14	1.10	(0.77 1.59)	
≥ 10	3,467	8	22	7	1.25	(0.78 1.99)	
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 to 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)	
>2.5to7	2,490	12	15	10	1.04	(0.59 1.83)	

Herbicide days/year	Entire Cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR*	95% CI ^a	
> 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 to 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 to 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 to 9	8,890	20	52	18	0.89	(0.64 1.24)	
≥ 10	6,420	14	48	16	1.23	(0.88 1.73)	

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^aHR = Hazard Ratio; CI = Confidence Interval

^bTake-home questionnaire variable; data available for approximately 40% of the cohort.

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 per year of pesticide application and adjusting for driving combines, butchering animals, or poultry production did not alter pesticide findings (data not shown).

Table 5

Farm exposures and fatal injuries among male farmers in the Agricultural Health Study, 1993–2008.

Variable/Risk factor	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR *	95% CI ^a	
Drive combines (per growing season) ^b							
Never	4,368	20	28	19	1.00	(ref)	0.03
1 to 10 days	4,395	20	29	20	1.36	(0.79 2.34)	
11 to 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 per 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 per 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/didn't work on a farm	3,510	8	24	8	1.00	(ref)	0.30
5 to 49	4,340	9	37	12	1.25	(0.74 2.11)	
50 to 199	8,166	18	60	20	1.11	(0.67 1.84)	
200 to 499	12,913	28	85	28	0.99	(0.59)	

Variable/Risk factor	Entire cohort (n = 51,035)		Fatal Injuries (n = 338)		Age & state adj.		p-trend
	N	%	N	%	HR *	95% CI ^a	
						1.66)	
500 to 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/didn't 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 to 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/didn't 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 to 499	13,874	31	86	29	0.97	(0.72 1.31)	
>500	6,287	14	35	12	0.94	(0.63 1.40)	

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^aHR = Hazard Ratio; CI = Confidence Interval

^bTake-home questionnaire variable; data available for approximately 40% of the cohort.

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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 per 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 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 per 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 for 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 per 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 per 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 JD 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 which 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 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 one year or many years before fatal injury and the unexpected associations with herbicides, these findings should be considered cautiously.

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Abbreviations

AH Agricultural Health

S Study

CI Confidence interval

HR Hazard ratio

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Footnotes

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The authors declare that they have no conflict of interest.