

## Mortality in the Agricultural Health Study: 1993-2007

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### Abbreviations:

AHS	Agricultural Health Study
CI	confidence interval
LTAS.net	Life Table Analysis System.net
SMR	standardized mortality ratio
rSMR	relative standardized mortality ratio

## ABSTRACT

Comparing agricultural cohorts to the general population is challenging because the general healthiness of farmers may mask potential adverse health effects of farming. Using the Agricultural Health Study (AHS), a cohort of 89,656 pesticide applicators and spouses in North Carolina and Iowa, the authors computed standardized mortality ratios (SMRs) comparing deaths from enrollment (1993-1997) through 2007 to state-specific rates. To compensate for the cohort's overall healthiness, relative SMRs (rSMRs) were estimated by calculating the SMR for each cause relative to the SMR for all other causes. In 1,198,129 person-years of follow-up, 6,419 deaths were observed. All-cause mortality was less than expected ( $SMR_{\text{applicators}}=0.54$ ; 95% Confidence Interval (CI):0.52,0.55;  $SMR_{\text{spouses}}=0.52$ ; 95%CI:0.50,0.55). Mortality from all cancers, heart disease, and diabetes were significantly below 1.0. In contrast, applicators experienced elevated machine-related deaths ( $SMR=4.15$ ; 95%CI:3.18,5.31), motor vehicle non-traffic accidents ( $SMR=2.80$ ; 95%CI:1.81,4.14), and collisions with objects ( $SMR=2.12$ ; 95%CI:1.25,3.34). In the rSMR analysis for applicators, relative mortality was elevated for lymphohematopoietic cancers, melanoma, and digestive system, prostate, kidney, and brain cancers. Among spouses rSMRs exceeded 1.0 for lymphohematopoietic cancers and malignancies of the digestive system, brain, breast, and ovary. Unintentional fatal injuries remain an important risk for farmers; mortality from several cancers was elevated relative to other causes.

**Keywords:** agriculture, healthy worker effect, mortality, neoplasms, pesticides, wounds and injuries

Compared to the general population, farmers have lower mortality from all-causes combined, heart disease, all cancers combined, and lung cancer (1-6). This may be attributed to lower tobacco and alcohol use and the higher physical demands of farm work (3), but other factors may be involved. Contrary to these deficits, farmers experience excess mortality from unintentional fatal injuries (7-9). Machine-related fatality has been identified as a leading cause of death in agriculture (10). Additionally, farmers experience higher mortality from certain types of cancer, including lymphohematopoietic malignancies and cancers of the prostate, lip, and eye when compared to the general population (2-5).

While the number of farms and farmers has decreased during the twentieth century, nearly three million people in the United States were still involved in agriculture in the year 2000 (11). Farming is a complex and changing business requiring extensive use of large machinery, pesticides, and commercial fertilizers. Hazards posed by these practices warrant further study of mortality in agricultural populations. The AHS, a large prospective cohort of pesticide applicators and their spouses in North Carolina and Iowa, was established to examine occupational and environmental factors affecting morbidity and mortality of farmers and pesticide applicators (12). While other agricultural cohorts exist, the large size of the AHS enhances its ability to examine death from less common causes. The AHS includes individuals with a wide range of pesticide use history, from spouses with little use to farmers who use pesticides on their own farms to commercial pesticide applicators who apply pesticides for a living. A wide variety of other agricultural exposures are also captured by this cohort.

A previous mortality study in the AHS based on follow-up from enrollment (1993-1997) through December 31, 2000 found deficits when compared to the general populations of Iowa and North Carolina. Overall mortality and mortality from cardiovascular disease, diabetes,

chronic obstructive pulmonary disease, all cancers, and lung, esophageal, and stomach cancer were all reduced (1). Some of these deficits were likely due to the healthy worker effect, observed when occupational cohorts, typically in good health, are compared to the general population (13, 14), which can mask risks associated with occupational exposures. With an additional 750,976 person-years of follow-up, we enhanced our prior analysis by examining mortality in the cohort from additional rare causes of death. We also made a formal adjustment to account for the healthy worker effect.

## MATERIALS AND METHODS

### Study population

The AHS includes 52,394 private pesticide applicators (mainly farmers) in North Carolina and Iowa, 4,916 commercial applicators in Iowa, and 32,346 spouses of farmers. Applicators enrolled in the study from 1993-1997 at pesticide licensing facilities by completing a self-administered questionnaire. A spouse questionnaire was sent home with the applicator for the spouse to complete and return by mail. Institutional review boards of the National Institutes of Health and its contractors approved the study; consent was implied by return of the questionnaire. At enrollment, farmers represented 82% of those eligible, commercial applicators represented 47% of those licensed in Iowa, and 75% of spouses of farmers participated. In general, commercial applicators tend to be younger than farmers and apply pesticides more days per year. Except for all-cause and all-cancer deaths, we combined farmers and commercial applicators as “applicators” because too few deaths occurred among commercial applicators for stand alone analysis.

## Outcome classification

Person-year accumulation extended from enrollment through the end of follow-up (December 31, 2007) or the date of death. Deaths were identified through annual linkage with death registries in North Carolina and Iowa, and the National Death Index. We coded underlying cause of death according to the International Classification of Diseases version in effect at the time of death (9 or 10) (15, 16).

## Statistical analysis

We calculated standardized mortality ratios using AHS data release AHSREL0905.00, distinguishing results by applicator status (applicator or spouse). We used the National Institute for Occupational Safety and Health Life Table Analysis System.NET (LTAS.net) version 2.0.16 (Cincinnati, OH) (17, 18), which groups deaths into 28 major and 119 minor categories, to calculate SMRs for any category with 5 or more deaths. The program groups some cancers together. For the general population comparison, state-specific rates were stratified by race, gender, and 5-year age and calendar time period. Rates for 2005 were assumed to apply through 2007. We calculated summary SMRs from the state-specific observed and expected counts and used a formula based on Byar's approximation to the exact Poisson test (19) to calculate 95% two-sided confidence intervals.

Several statistical approaches have been suggested regarding reduction of the healthy worker effect in occupational studies. For instance, instead of comparing the cohort to the general population, compare it to a different occupational cohort (20). A comparable occupational population in North Carolina and Iowa would be our preferred reference group;

however, none are readily available. An alternative would be to compare the observed and expected counts for each specific cause of interest with an independent referent set of values consisting of the all-cause observed and expected values minus the observed and expected values from the outcome of interest. Thus, we define the relative standardized mortality ratio as the ratio of the cause-specific SMR to the SMR for all-other causes, omitting the cause of interest [i.e.,  $rSMR_x = SMR_x / SMR_{not\ x}$ ]. This approach allows us to calculate confidence limits for rSMRs using standard procedures (19).

Because SMRs represent weighted sums of stratum-specific SMRs, a comparison of two SMRs is informative if either of the following two conditions is met: (1) all stratum-specific SMRs are the same within each disease subgroup [ $cause_x$  and  $cause_{not\ x}$ ] (no heterogeneity across state, race, gender, age, or calendar period); or (2) within each stratum, the stratum-specific weight for  $cause_x$  equals the stratum-specific weight for  $cause_{not\ x}$  (a stratum-specific weight for a given cause is the expected number of deaths in that stratum divided by the total expected number of deaths across all strata) (19). To examine these conditions, we computed stratum-specific SMRs and weights for selected common and rare causes of death. We did not observe heterogeneity and thus have found no evidence to contradict the validity of the rSMRs.

To calculate rSMRs, we used Poisson regression in SAS version 9.2 (Cary, NC), because for each  $cause_x$  the observed deaths for  $cause_x$  and  $cause_{not\ x}$  are independent Poisson variables. This approach is related to comparing standardized mortality ratios for exposed and unexposed groups as described in Breslow and Day (19). We calculated rSMRs for chronic diseases only, not for injuries, which we do not believe would be influenced by the healthy worker effect.

## RESULTS

Applicators were mainly male and spouses were mainly female in this predominantly white cohort (Table 1). Among 89,656 applicators and spouses, there were 6,419 deaths: 4,675 farmers, 205 commercial applicators, and 1,539 spouses. The mean follow-up period was 13.4 years, providing 1,198,129 person-years (farmers, 696,419; commercial applicators, 67,484; spouses, 434,277). While most applicators were from Iowa (64%), more deaths occurred among applicators in North Carolina (57%) consistent with the older age of the North Carolina sample. At enrollment, decedents were older and had more years of applying pesticides than the overall cohort.

Compared to the general populations of North Carolina and Iowa, applicators in the cohort were less likely to die from all-causes (SMR=0.54; 95%CI: 0.52, 0.55). The all-cause mortality for farmers (SMR=0.54; 95%CI: 0.52, 0.55) was similar to that of commercial applicators (SMR=0.59; 95%CI: 0.52, 0.68). Spouses also experienced reduced mortality (all-cause SMR=0.52, 95%CI: 0.50, 0.55).

### Injury

Applicators experienced significantly increased mortality from certain unintentional fatal injuries compared to the general population (Table 2). Machinery-related deaths (SMR=4.15; 95%CI: 3.18, 5.31) were most elevated, followed by motor vehicle non-traffic accidents (SMR=2.80; 95%CI: 1.81, 4.14) and collisions with objects (SMR=2.12; 95%CI: 1.25, 3.34). Mortality among applicators was less than in the general population for motor vehicle accidents involving pedestrians, falls, accidental poisoning, and violence.

Among spouses, injury mortality was not significantly elevated compared to the general population. Transportation-related deaths were reduced; specifically, deaths from motor vehicle accidents involving the driver (SMR=0.56; 95%CI: 0.31, 0.92). Fatal falls and violence were also less than expected.

#### Non-cancer internal causes of death

Mortality from nearly all non-cancer internal causes of death was significantly lower among applicators than in the general population (Table 3). Deaths from heart disease were half those expected (SMR=0.54; 95%CI: 0.51, 0.56), as were deaths from other diseases of the circulatory system (cerebrovascular and arterial diseases; SMR=0.51; 95%CI: 0.46, 0.57). We also observed reduced mortality from diabetes. Deaths from chronic lung and liver diseases commonly associated with tobacco and alcohol use were significantly lower [e.g. chronic obstructive pulmonary disease (SMR=0.31; 95%CI: 0.26, 0.36) and cirrhosis (SMR=0.24; 95%CI: 0.16, 0.34)]. No non-cancer internal causes were significantly greater than 1.0.

Compared to the general population, spouses also experienced lower mortality from most non-cancer internal causes (Table 3). Deaths from heart disease and other circulatory diseases were both near half the expected (SMR=0.47; 95%CI: 0.42, 0.53; SMR=0.55; 95%CI: 0.46, 0.64, respectively). Mortality was also significantly reduced for diseases of the respiratory, digestive, and genito-urinary systems, and for diabetes. Like applicators, spouses experienced fewer tobacco and alcohol-related deaths; for example, both chronic obstructive pulmonary disease (SMR=0.27; 95%CI: 0.20, 0.35) and cirrhosis (SMR=0.40; 95%CI: 0.22, 0.67) showed significant deficits.



## Cancer

Among applicators, deaths from all cancers combined were significantly lower than expected (SMR=0.61; 95%CI: 0.58, 0.64). For commercial applicators, the all-cancer SMR was significantly reduced (72 deaths; SMR=0.75; 95%CI: 0.59, 0.93); likewise for farmers (1,372 deaths; SMR=0.60; 95%CI: 0.57, 0.64). Mortality for several individual cancer sites (Table 4) was also lower than expected, including the digestive system, lung, prostate, bladder, and brain. Cancers of the eye, ovary, and thyroid were non-significantly elevated among applicators.

Spouses also experienced a significantly deficit for all cancers combined compared to the general population (all-cancer SMR=0.65; 95%CI: 0.60, 0.70). Fewer than expected deaths were observed for cancers of the digestive system and of female genital organs (Table 4). Deaths from lung, breast, and ovarian cancer were also significantly less than expected. Leukemia and non-Hodgkin's lymphoma were elevated but not significantly so.

## Relative standardized mortality ratios – cancer deaths

The rSMR analysis for cancer mortality identified some aspects that were potentially masked in the SMR analysis (Table 5). For applicators, the rSMR analysis showed deaths from all cancers were greater than expected relative to other causes within the cohort (rSMR=1.20; 95%CI: 1.13, 1.27). This finding was true both for commercial applicators (rSMR=1.39; 95%CI: 1.11, 1.75) and farmers (rSMR=1.18; 95%CI: 1.11, 1.26). Among all applicators, rSMRs were significantly elevated for prostate cancer, multiple myeloma, leukemia, non-Hodgkin's lymphoma, melanoma, brain cancer, kidney cancer, and digestive cancers (specifically intestine and pancreas). Relative mortality rates from cancers of the eye (rSMR=3.69; 95%CI: 1.54, 8.87), ovary (rSMR=3.00; 95%CI: 1.25, 7.21), and thyroid (rSMR=2.85; 95%CI: 1.43, 5.71) were also

significantly elevated, but numbers were small. Only lung cancer (rSMR=0.78; 95%CI: 0.71, 0.86) and other respiratory cancers (rSMR=0.27; 95%CI: 0.11, 0.65) had significantly reduced relative mortality.

Like applicators, deaths from all cancers among spouses were elevated relative to other causes in the cohort (all cancer rSMR=1.43; 95%CI: 1.30, 1.58; Table 5). Leukemia (rSMR=2.10; 95%CI: 1.49, 2.97) and non-Hodgkin's lymphoma (rSMR=2.15; 95%CI: 1.58, 2.93) had the highest rSMRs. For spouses, cancers of the breast, ovary, brain, and digestive system (specifically, intestine and pancreas) showed rSMRs that were significantly greater than 1.0. Neoplasms of benign and unspecified nature were also significantly elevated relative to all other causes of death. Only lung cancer had a significantly decreased rSMR.

#### Relative SMRs – non-cancer internal causes

For non-cancer internal causes, only one elevated rSMR was observed among applicators and spouses (Table 6). Among applicators, relative to all other causes, deaths from cardiomyopathy were elevated (rSMR=1.29; 95%CI: 1.03, 1.62). Relative to all other causes, findings were similar to those expected for heart disease (rSMR=0.99; 95%CI: 0.93, 1.06) and other circulatory diseases (rSMR=0.95; 95%CI: 0.86, 1.06). The rSMRs for cirrhosis, chronic obstructive pulmonary disease, pneumonia, diabetes, and mental and psychological disorders were significantly less than 1.0.

For spouses, the rSMR analysis showed mortality from heart disease was lower than expected (rSMR=0.88; 95%CI: 0.77, 1.00); specifically, ischemic heart disease remained lower than expected (rSMR=0.84, 95%CI: 0.73, 0.97). However, rSMRs for other circulatory diseases

did not differ significantly from 1, nor did that for diabetes. The rSMRs for mental and psychological disorders and respiratory diseases were significantly lower than expected.

## DISCUSSION

Consistent with previous mortality findings from this cohort (1), participants in the Agricultural Health Study had lower overall mortality rates than the general populations of North Carolina and Iowa. The AHS is larger than most agricultural cohorts, and this analysis not only provides new information on rare causes of death but is also more recent than most of the previous published studies. Similar to other studies (2, 4, 5, 21), applicators and spouses showed a mortality experience reflective of a healthy lifestyle. Despite this, applicators had increased mortality due to unintentional fatal injuries compared to the general population. Additionally, after adjusting for the lower overall mortality of the cohort, applicators experienced excess mortality from lymphohematopoietic cancers, melanoma, and malignancies of the digestive system, prostate, kidney, brain, thyroid, eye, and ovary, and from cardiomyopathy. Spouses experienced excess death from lymphohematopoietic cancers and malignancies of the digestive system, breast, ovary, and brain after adjustment for the lower overall mortality.

The increased risk of unintentional fatal injuries among applicators is consistent with other studies (7-9), but was not observed previously in this cohort (1), possibly due to fewer deaths. Farmers face significant occupational hazards from machines as highlighted by the observed SMRs exceeding 2 for machine injury, motor vehicle non-traffic accidents, and collisions with objects. Deaths from machine accidents and motor vehicle non-traffic accidents may be related, as tractor deaths can be classified as either, depending on where they occur (on

or off the roadway) (15, 16). Combining deaths from these two categories, we observe an annual rate of 6.9 machine-related deaths/100,000 person-years (which includes deaths from tractor rollovers), about 25% higher than the 2007 United States annual average of 5.5 tractor overturn deaths/100,000 person-years in the agricultural population, as calculated from a report by the National Institute for Occupational Safety and Health (22). Animals are a known risk factor for fatal and non-fatal farm injury (23, 24); however, we did not see increased animal-related fatality. Although Iowa is ranked 7<sup>th</sup> in the United States for cattle and calf production, poultry and hogs are the most common livestock raised in Iowa and North Carolina (25). Therefore, our failure to observe elevated animal-related fatality may be due to a lower level of large animal production than in other agricultural regions.

Consistent with our previous mortality analysis (1), we continued to observe deficits for several major causes of death, including cardiovascular disease, all cancers, lung cancer, and diabetes. All-cause mortality was approximately half that expected, similar to the previous mortality study and other studies of farmers (1-5). Higher physical activity inherent to farming likely plays a significant protective role in these deficits. The deficit in smoking-related deaths (e.g., chronic obstructive pulmonary disease and lung cancer) is reflective of a higher prevalence of never smokers [53% of applicators and 72% of spouses, versus 46% of U.S. adults age 45 and older in 1995(26)]. While these deficits may reflect a healthy lifestyle, they are also consistent with the healthy worker effect that is typically observed in working populations.

To account for the lower overall mortality in the cohort, we used an rSMR analysis that compares the SMR for each cause to the SMR for all other causes. These rSMRs are meant to be exploratory and to be interpreted in relation to the mortality experience of all other causes of death in the cohort. In doing so, we identified unusually high relative mortality from

lymphohematopoietic cancers, digestive cancers and from cancers of the prostate, breast, brain, and ovary, which were not apparent in the SMR analysis. We did not observe any increased rSMRs for non-cancer internal causes, with the exception of cardiomyopathy among applicators.

We observed increased rSMRs for lymphohematopoietic cancers for applicators and spouses, consistent with meta-analyses among farmers (27-29). Svec and colleagues noted an increased risk of lymphohematopoietic cancers was associated with occupational exposure to animals, which occurred primarily in agricultural settings, though this effect could have been confounded by pesticides (30). Previous findings from the AHS have implicated several individual pesticides as being associated with these cancers (31).

Farmers are at higher risk of prostate cancer (32), possibly associated with specific pesticides (33, 34). Chlorinated pesticides and methyl bromide were significantly associated with increased risk among applicators over 50 years of age (35). Increased prostate cancer mortality has been seen in other farming populations (5, 36), but not all (7, 21). We observed elevated mortality for prostate cancer only in the rSMR analysis.

An analysis of cancer incidence in the Agricultural Health Study through 2002 identified an increased incidence of ovarian cancer among the 1,563 female applicators, but not among the 32,127 female spouses (37). We observed increased ovarian cancer mortality among applicators and spouses relative to all other causes. The larger rSMR for applicators compared to spouses is likely a chance occurrence reflecting the small number of female applicators in the cohort. We also observed increased breast cancer relative mortality among spouses in the cohort. Although risk was not significantly increased among applicators, rSMRs were similar (spouses, 1.58; applicators, 1.76) and few applicators are female.

We conducted our analyses separately for applicators and spouses, as applicators are expected to have greater occupational exposures to pesticides and other farm exposures than their spouses. Applicators are licensed to apply restricted use pesticides; however, 58% of spouses in Iowa and 45% in North Carolina reported having applied at least one pesticide at enrollment (38). Both men and women are represented among the applicators, with 1,563 female applicators contributing 20,886 person-years, thus providing a unique occupationally exposed group to examine female-related cancers.

The cohort includes both private and commercial pesticide applicators; private applicators (mainly farmers) dominate the cohort, but both groups use similar pesticides. Commercial applicators contributed only 205 of the 4,880 deaths observed for applicators; thus their inclusion in the study population had little influence on the overall findings. Additionally, when analyzed separately, the mortality experience for both groups was similar: we observed that both farmers and commercial applicators experienced significantly fewer deaths than expected overall and had elevated cancer risk in the rSMR analyses. While an Australian study (39) focusing on cancer mortality and incidence among pest control operators found rates similar to the general population, Fleming et al. (5) noted SMRs less than 1.0 for most causes of death among commercial applicators in Florida.

SMR analyses are useful to assess the disease experience of a population relative to a general population; however, this strategy has some inherent limitations. While gaining statistical stability by comparing to state and national rates, the ability to control for confounding is limited to factors reported on the death certificates. Those factors do not address the healthy worker effect. We used the rSMR analysis which allowed us to adjust for the overall disease experience in our study population. Both the SMR and rSMR analyses have limited ability to

evaluate exposures which may contribute to elevated or lowered mortality. We relied on death certificates for our outcome measure. The overall validity of death certificates tends to be fairly high and is expected to be comparable across underlying causes for deaths occurring within a state (40, 41). By comparing the rates within states, we have comparable reporting for the cohort and population rates. We used the LTAS.net program to calculate SMRs; this program groups deaths to reflect occupational hazards, as illustrated by the fine strata for falls and the peculiar combinations of cancers (e.g., colon and small intestine grouped as “intestine”). All SMR analyses face limitations with rare diseases. Our study benefitted from its large sample size and person-years of follow-up, which have more than doubled since the previous analysis (1).

In summary, our analysis of 6,419 deaths occurring from 1993–2007 among 89,656 pesticide applicators and spouses showed that applicators were at an elevated risk of death from machine injury. The cohort experienced a lower mortality rate overall when compared to the general population. After adjusting for the lower mortality of the cohort, we observed relatively higher mortality among applicators from lymphohematopoietic cancers, melanoma, and malignancies of the digestive system, prostate, kidney, brain, thyroid, eye, and ovary. Among spouses, we observed higher adjusted mortality for lymphohematopoietic cancers and malignancies of the digestive system, breast, ovary, and brain. Extended follow-up of this cohort will provide valuable information through the accumulation of deaths from rare diseases as the cohort ages.

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#### Disclaimers:

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

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The authors declare no conflict of interest.



## Tables

Table 1	Characteristics of the Agricultural Health Study Cohort at enrollment (1993-1997) and decedents through 2007.
Table 2	Standardized Mortality Ratios (SMRs) for Deaths from Injuries in the Agricultural Health Study through 2007.
Table 3	SMRs for Non-Cancer Internal Causes of Death in the Agricultural Health Study through 2007.
Table 4	Standardized Mortality Ratios (SMRs) for Deaths from Cancers and Benign Nature Neoplasms in the Agricultural Health Study through 2007.
Table 5	Relative Standardized Mortality Ratios (rSMRs) for Deaths from Cancers and Benign Nature Neoplasms in the Agricultural Health Study through 2007.
Table 6	Relative Standardized Mortality Ratios (rSMRs) for Non-Cancer Internal Causes of Death in the Agricultural Health Study cohort through 2007.

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Table 1. Characteristics of the Agricultural Health Study cohort and Decedents at Study Enrollment (1993-1997).

		Applicators		Spouses	
		Cohort (n = 57,310)	Deceased (n = 4,880)	Cohort (n = 32,346)	Deceased (n = 1,539)
		%	%	%	%
Age at enrollment (years)					
	< 40	34	6	31	4
	40-59	47	32	52	36
	60-79	18	59	17	57
	80 +	0	3	0	3
Current age (in 2006) or age at death (years)					
	< 40	8	2	5	1
	40-59	50	19	53	21
	60-79	37	58	39	60
	80 +	5	21	4	17
State					
	Iowa	64	43	67	53
	North Carolina	36	57	33	47
Race					
	Asian/Pacific Islander	0	0	0	0
	Black	2	5	1	2
	Native American	0	1	0	1
	White	97	94	98	97
	Other	0	0	0	0
Gender					
	Male	97	98	1	2
	Female	3	2	99	98
Education status					
	<= High school	57	73	46	62
	> High school	43	27	54	38
Smoking history					
	Never	53	36	72	64
	Past	30	42	17	21
	Current	17	22	10	15
Drinks per month					
	None	33	53	46	67
	< 1	13	11	25	16
	1 to 5	14	10	15	8
	6 to 10	11	6	7	4
	> 10	29	19	8	7
Body Mass Index (kg/m2)					
	< 25	26	29	49	44
	25-30	51	48	32	34
	> 30	23	23	19	23
Years applied pesticides					
	Never	2	1	51	61
	<= 1 year	3	2	5	4
	2-5 years	13	9	13	7
	6-10 years	16	13	9	6
	11-20 years	32	23	11	9
	21-30 years	23	25	6	5
	> 30 years	12	26	4	9

Table 2. Standardized Mortality Ratios (SMRs) for Deaths from Injuries in the Agricultural Health Study cohort through 2007.

Major cause of death Minor cause of death	Applicators (n = 496)				Spouses (n = 66)					
	Obs.	Exp.	SMR	95% CI**		Obs.	Exp.	SMR	95% CI	
Transportation injuries	167	196	0.85*	0.73,	0.99	29	50	0.58*	0.39,	0.83
Railway, water & air transportation	8	12	0.67	0.29,	1.32	0		--		
Motor vehicle - driver	99	117	0.85	0.69,	1.03	15	27	0.56*	0.31,	0.92
Motor vehicle - passenger	9	15	0.59	0.27,	1.12	10	12	0.81	0.39,	1.49
Motor vehicle - pedestrian	5	14	0.36*	0.12,	0.85	1		--		
Motor vehicle - other & unspecified	18	23	0.78	0.46,	1.24	2		--		
Motor vehicle - nontraffic	25	9	2.80*	1.81,	4.14	0		--		
Other transportation injuries	3	6	--			1		--		
Falls	43	68	0.63*	0.46,	0.85	6	18	0.34*	0.12,	0.73
Falls into hole	12	15	0.78	0.40,	1.37	3		--		
Falls, building or structure	7	4	1.76	0.65,	3.84	0		--		
Other falls	24	49	0.49*	0.32,	0.73	3		--		
Other injury (major)	164	169	0.97	0.83,	1.13	17	41	0.42*	0.24,	0.67
Collision with objects	18	9	2.12*	1.25,	3.34	1		--		
Machine	62	15	4.15*	3.18,	5.31	3		--		
Suffocation	15	22	0.69	0.39,	1.14	3		--		
Fire	8	15	0.53	0.23,	1.04	0		--		
Accidental poisoning	15	39	0.39*	0.22,	0.64	4		--		
Medical complications	7	10	0.67	0.27,	1.38	3		--		
Forces of nature	5	6	0.83	0.34,	2.41	0		--		
Other injuries	34	53	0.64*	0.44,	0.90	3		--		
Violence	122	219	0.56*	0.46,	0.67	14	36	0.39*	0.21,	0.65
Intentional self harm	106	187	0.57*	0.46,	0.69	9	28	0.32*	0.15,	0.61
Assault & homicide	16	32	0.50*	0.28,	0.81	5	8	0.61	0.20,	1.43

\*Significant at P = 0.05 based on confidence interval excluding 1.0.

CI = confidence interval; Exp = expected; Obs = observed

\*\*calculated using Byar's approximation to the Poisson exact test.

All estimates are adjusted for age, calendar year, gender, race, and state.

SMRs not estimated for < 5 observed deaths.

Table 3. Standardized Mortality Ratios (SMRs) for Non-Cancer Internal Causes of Death in the Agricultural Health Study cohort through 2007.

Major cause of death Minor cause of death	Applicators (n = 2,743)				Spouses (n = 797)			
	Obs.	Exp.	SMR	95% CI**	Obs.	Exp.	SMR	95% CI
Blood & blood-forming organs diseases	27	40	0.68*	0.45, 0.98	12	13	0.89	0.46, 1.56
Coagulation & hemorrhagic conditions	7	9	0.76	0.31, 1.57	4		--	
Other diseases of blood-forming organs	20	31	0.65	0.40, 1.00	8	10	0.82	0.35, 1.62
Diabetes mellitus	98	242	0.48*	0.33, 0.49	42	95	0.44*	0.32, 0.60
Mental & psychological disorders	33	139	0.24*	0.16, 0.33	9	45	0.20*	0.09, 0.38
Alcoholism	10	46	0.22*	0.10, 0.40	0		--	
Other mental disorders	23	93	0.25*	0.16, 0.37	9	40	0.23*	0.10, 0.43
Nervous system disorders	126	272	0.46*	0.39, 0.55	64	114	0.56*	0.43, 0.72
Multiple sclerosis	0		--		3		--	
Other nervous system diseases	126	260	0.48*	0.40, 0.58	61	104	0.59*	0.45, 0.76
Heart diseases	1376	2569	0.54*	0.51, 0.56	292	620	0.47*	0.42, 0.53
Rheumatic heart disease	8	12	0.69	0.30, 1.36	7	10	0.72	0.29, 1.49
Hypertension with heart disease	40	78	0.52*	0.37, 0.70	7	24	0.29*	0.12, 0.59
Ischemic heart disease	1099	2105	0.52*	0.49, 0.55	211	467	0.45*	0.39, 0.52
Chronic diseases of the endocardium	32	50	0.64*	0.44, 0.90	14	20	0.70	0.38, 1.17
Cardiomyopathy	75	109	0.69*	0.54, 0.87	13	27	0.48*	0.26, 0.83
Conductive disorder	61	104	0.59*	0.45, 0.75	22	34	0.64*	0.40, 0.97
Other heart diseases	61	112	0.54*	0.42, 0.70	18	38	0.47*	0.28, 0.75
Other circulatory system diseases	376	731	0.51*	0.46, 0.57	147	270	0.55*	0.46, 0.64
Cerebrovascular disease	236	457	0.52*	0.45, 0.59	105	176	0.60*	0.49, 0.72
Hypertension without heart disease	15	42	0.35*	0.20, 0.58	6	18	0.34*	0.13, 0.74
Diseases of arteries/veins/lymphatic vessels	125	231	0.54*	0.45, 0.64	36	76	0.47*	0.33, 0.65
Respiratory system diseases	346	903	0.38*	0.34, 0.43	92	303	0.30*	0.24, 0.37
Pneumonia	76	192	0.40*	0.31, 0.50	17	58	0.29*	0.17, 0.47
Chronic obstructive pulmonary disease	165	539	0.31*	0.26, 0.36	50	187	0.27*	0.20, 0.35
Asthma	8	10	0.79	0.34, 1.56	4		--	
Other respiratory diseases	97	162	0.60*	0.49, 0.73	21	50	0.42*	0.26, 0.64

Digestive system diseases	125	324	0.39*	0.32,	0.46	50	109	0.46*	0.34,	0.61
Stomach & duodenum diseases	12	21	0.58	0.30,	1.02	5	7	0.72	0.23,	1.68
Hernia & intestinal obstruction	11	19	0.58	0.29,	1.04	2		--		
Cirrhosis & other liver diseases	33	138	0.24*	0.16,	0.34	14	35	0.40*	0.22,	0.67
Other digestive system diseases	69	146	0.47*	0.37,	0.60	29	58	0.50*	0.33,	0.72
Skin & subcutaneous tissue diseases	5	9	0.53	0.17,	1.23	1		--		
Musculoskeletal & connective system diseases	15	30	0.50*	0.28,	0.83	14	24	0.58*	0.32,	0.97
Arthritis & spondylitis	6	12	0.50	0.18,	1.08	6	8	0.73	0.27,	1.59
Other musculoskeletal system diseases	9	18	0.51*	0.23,	0.96	8	16	0.50*	0.21,	0.98
Genito-urinary system diseases	69	141	0.49*	0.38,	0.62	28	52	0.53*	0.35,	0.77
Acute glomerulonephritis, renal failure	7	17	0.42*	0.17,	0.86	2				
Chronic & unspecified nephritis, renal failure	43	79	0.54*	0.39,	0.73	15	26	0.58*	0.32,	0.96
Other genito-urinary diseases	19	46	0.42*	0.25,	0.65	11	21	0.52*	0.26,	0.94
Tuberculosis and HIV	3		--			0		--		
Symptomatic & ill-defined conditions	15	40	0.37*	0.21,	0.62	1		--		
Other & unspecified causes	129	252	0.51*	0.43,	0.61	45	98	0.46*	0.33,	0.61

\*Significant at P = 0.05 based on confidence interval excluding 1.0.

CI = confidence interval; Exp = expected; Obs = observed

\*\*calculated using Byar's approximation to the Poisson exact test.

All estimates are adjusted for age, calendar year, gender, race, and state.

SMRs not estimated for < 5 observed deaths.



Table 4. Standardized Mortality Ratios (SMRs) for Deaths from Cancers and Benign Nature Neoplasms in the Agricultural Health Study cohort through 2007.

Major cause of death Minor cause of death	Applicators (n = 1,641)				Spouses (n = 676)			
	Obs.	Exp.	SMR	95% CI**	Obs.	Exp.	SMR	95% CI
All Cancers	1624	2662	0.61*	0.58, 0.64	665	1,022	0.65*	0.60, 0.70
Buccal & pharynx	16	47	0.34*	0.19, 0.55	3		--	
Digestive & peritoneum	422	619	0.68*	0.62, 0.75	141	197	0.72*	0.60, 0.84
Esophagus	48	94	0.51*	0.38, 0.68	3		--	
Stomach	26	50	0.52*	0.34, 0.76	5	12	0.42*	0.14, 0.99
Intestine	158	211	0.75*	0.64, 0.88	68	80	0.85	0.66, 1.07
Rectum	32	46	0.69*	0.47, 0.97	4		--	
Biliary, liver & gallbladder	50	71	0.70*	0.52, 0.93	18	22	0.81	0.48, 1.28
Pancreas	103	138	0.75*	0.61, 0.91	38	52	0.72*	0.51, 0.99
Peritoneum, other & unspecified site	5	8	0.63	0.21, 1.48	5	6	0.91	0.29, 2.12
Respiratory	422	1005	0.42*	0.38, 0.46	110	293	0.38*	0.31, 0.45
Trachea, bronchus & lung	417	971	0.43*	0.39, 0.47	108	287	0.38*	0.31, 0.45
Other respiratory	5	34	0.15*	0.05, 0.34	2		--	
Breast	11	12	0.94	0.47, 1.69	136	170	0.80*	0.67, 0.94
Female genital organs	8	5	1.46	0.63, 2.88	71	114	0.62*	0.49, 0.79
Cervix	1		--		4		--	
Uterus, other & unspecified site	1		--		19	27	0.70	0.42, 1.09
Ovary	5	3	1.61	0.52, 3.76	45	64	0.70*	0.51, 0.94
Other female genital organs	1		--		3		--	
Prostate	171	210	0.81*	0.70, 0.95	1		--	
Urinary	106	146	0.73*	0.60, 0.88	21	30	0.69	0.43, 1.06
Kidney	71	82	0.87	0.68, 1.09	12	20	0.61	0.32, 1.07
Bladder & other urinary site	35	64	0.55*	0.38, 0.76	9	11	0.83	0.38, 1.58
Other & unspecified site	230	345	0.67*	0.58, 0.76	96	118	0.81*	0.66, 0.99
Bone	3		--		2		--	
Melanoma	38	50	0.76	0.54, 1.05	10	13	0.75	0.36, 1.38
Other skin	4		--		1		--	

Mesothelioma	8	11	0.71	0.29, 1.46	2	--			
Connective tissue	9	14	0.65	0.30, 1.23	6	6	1.00	0.37, 2.18	
Brain & other nervous	59	78	0.76*	0.58, 0.98	25	30	0.83	0.54, 1.23	
Eye	5	3	1.98	0.64, 4.62	3	--			
Thyroid	8	5	1.53	0.66, 3.02	1	--			
Other & unspecified site	96	163	0.59*	0.48, 0.72	46	61	0.76	0.56, 1.01	
Lymphatic & hematopoietic	238	271	0.88*	0.77, 1.00	86	88	0.97	0.78, 1.20	
Hodgkin's disease	5	5	1.03	0.34, 2.41	1	--			
Non-Hodgkin's lymphoma	90	108	0.84	0.67, 1.03	42	38	1.11	0.80, 1.50	
Multiple myeloma	52	51	1.01	0.76, 1.33	10	18	0.56	0.27, 1.04	
Leukemia	91	107	0.85	0.68, 1.04	33	30	1.09	0.75, 1.53	
Benign & unspecified nature neoplasms	17	26	0.66	0.38, 1.06	11	11	1.05	0.52, 1.87	

\*Significant at P = 0.05 based on confidence interval excluding 1.0.

CI = confidence interval; Exp = expected; Obs = observed

\*\*Calculated using Byar's approximation to the Poisson exact test.

All estimates are adjusted for age, calendar year, gender, race, and state.

SMRs not estimated for < 5 observed deaths.

Table 5. Relative Standardized Mortality Ratios (rSMRs) for Deaths from Cancers and Benign Nature Neoplasms in the Agricultural Health Study cohort through 2007.

Major cause of death Minor cause of death	Applicators (n = 1,641)			Spouses (n = 676)		
	rSMR	95% CI**		rSMR	95% CI	
All Cancers	1.20*	1.13,	1.27	1.43*	1.30,	1.58
Buccal & pharynx	0.63	0.38,	1.03	--		
Digestive & peritoneum	1.29*	1.17,	1.43	1.41*	1.18,	1.67
Esophagus	0.95	0.71,	1.26	--		
Stomach	0.96	0.66,	1.42	0.81	0.34,	1.95
Intestine	1.41*	1.20,	1.65	1.65*	1.29,	2.10
Rectum	1.28	0.91,	1.82	--		
Biliary, liver & gallbladder	1.31	0.99,	1.73	1.56	0.98,	2.48
Pancreas	1.40*	1.15,	1.70	1.40*	1.01,	1.93
Peritoneum, other & unspecified site	1.18	0.49,	2.83	1.74	0.72,	4.18
Respiratory	0.76*	0.69,	0.84	0.70*	0.57,	0.85
Trachea, bronchus & lung	0.78*	0.71,	0.86	0.70*	0.57,	0.85
Other respiratory	0.27*	0.11,	0.65	--		
Breast	1.76	0.97,	3.17	1.58*	1.32,	1.88
Female genital organs	2.72*	1.36,	5.45	1.20	0.95,	1.53
Cervix	--			--		
Uterus, other & unspecified site	--			1.34	0.85,	2.11
Ovary	3.00*	1.25,	7.21	1.35*	1.00,	1.82
Other female genital organs	--			--		
Prostate	1.53*	1.31,	1.78	--		
Urinary	1.36*	1.12,	1.65	1.33	0.86,	2.04
Kidney	1.62*	1.28,	2.05	1.18	0.67,	2.07
Bladder & other urinary site	1.02	0.73,	1.42	1.59	0.83,	3.06
Other & unspecified site	1.25*	1.10,	1.43	1.59*	1.29,	1.95
Bone	--			--		
Melanoma	1.42*	1.03,	1.96	1.44	0.77,	2.69
Other skin	--			--		

Mesothelioma	1.32	0.66,	2.64	--		
Connective tissue	1.21	0.63,	2.32	1.92	0.86,	4.28
Brain & other nervous	1.42*	1.10,	1.83	1.60*	1.08,	2.37
Eye	3.69*	1.54,	8.87	--		
Thyroid	2.85*	1.43,	5.71	--		
Other & unspecified site	1.10	0.90,	1.34	1.47*	1.09,	1.97
Lymphatic & hematopoietic	1.67*	1.46,	1.90	1.92*	1.54,	2.38
Hodgkin's disease	1.93	0.80,	4.63	--		
Non-Hodgkin's lymphoma	1.57*	1.27,	1.93	2.15*	1.58,	2.93
Multiple myeloma	1.89*	1.44,	2.48	1.08	0.58,	2.01
Leukemia	1.59*	1.29,	1.96	2.10*	1.49,	2.97
Benign & unspecified nature neoplasms	1.23	0.76,	1.98	2.01*	1.11,	3.63

\*Significant at P = 0.05 based on confidence interval excluding 1.0.

\*\*Calculated using Byar's approximation to the Poisson exact test.

All estimates are adjusted for age, calendar year, gender, race, and state.

SMRs not estimated for < 5 observed deaths.

Table 6. Relative Standardized Mortality Ratios (rSMRs) for Non-Cancer Internal Causes of Death in the Agricultural Health Study cohort through 2007.

Major cause of death Minor cause of death	Applicators (n = 2,743)			Spouses (n = 797)		
	rSMR	95% CI**		rSMR	95% CI	
Blood & blood-forming organs diseases	1.26	0.86,	1.84	1.72	0.97,	3.03
Coagulation & hemorrhagic conditions	1.42	0.67,	2.97	--		
Other diseases of blood-forming organs	1.58	0.99,	2.50	1.57	0.78,	3.15
Diabetes mellitus	0.75*	0.61,	0.91	0.84	0.62,	1.14
Mental & psychological disorders	0.44*	0.31,	0.62	0.38*	0.20,	0.72
Alcoholism	0.40*	0.21,	0.74	--		
Other mental disorders	0.46*	0.30,	0.69	0.43*	0.22,	0.83
Nervous system disorders	0.86	0.72,	1.03	1.08	0.84,	1.38
Multiple sclerosis	--			--		
Other nervous system diseases	0.90	0.75,	1.07	1.13	0.88,	1.46
Heart diseases	0.99	0.93,	1.06	0.88	0.77,	1.00
Rheumatic heart disease	1.28	0.64,	2.57	1.39	0.66,	2.91
Hypertension with heart disease	0.96	0.70,	1.31	0.55	0.26,	1.15
Ischemic heart disease	0.96	0.90,	1.03	0.84*	0.73,	0.97
Chronic diseases of the endocardium	1.18	0.84,	1.68	1.33	0.79,	2.26
Cardiomyopathy	1.29*	1.03,	1.62	0.92	0.54,	1.60
Conductive disorder	1.09	0.85,	1.40	1.24	0.81,	1.88
Other heart diseases	1.01	0.79,	1.30	0.91	0.57,	1.44
Other circulatory system diseases	0.95	0.86,	1.06	1.05	0.88,	1.24
Cerebrovascular disease	0.96	0.84,	1.09	1.15	0.95,	1.41
Hypertension without heart disease	0.66	0.40,	1.09	0.65	0.29,	1.45
Diseases of arteries/veins/lymphatic vessels	1.00	0.84,	1.20	0.90	0.65,	1.25
Respiratory system diseases	0.69*	0.62,	0.77	0.55*	0.45,	0.68
Pneumonia	0.73*	0.58,	0.92	0.56*	0.34,	0.90
Chronic obstructive pulmonary disease	0.55*	0.47,	0.65	0.49*	0.37,	0.66
Asthma	1.47	0.74,	2.95	--		
Other respiratory diseases	1.11	0.91,	1.36	0.80	0.52,	1.24

Digestive system diseases	0.71*	0.59,	0.85	0.87	0.66,	1.16
Stomach & duodenum diseases	1.08	0.61,	1.91	1.38	0.57,	3.31
Hernia & intestinal obstruction	1.08	0.60,	1.95	--		
Cirrhosis & other liver diseases	0.44*	0.31,	0.62	0.76	0.45,	1.29
Other digestive system diseases	0.87	0.69,	1.11	0.96	0.66,	1.38
Skin & subcutaneous tissue diseases	0.98	0.41,	2.36	--		
Musculoskeletal & connective system diseases	0.93	0.56,	1.55	1.11	0.65,	1.87
Arthritis & spondylitis	0.92	0.41,	2.05	1.40	0.63,	3.13
Other musculoskeletal system diseases	0.94	0.49,	1.81	0.95	0.48,	1.91
Genito-urinary system diseases	0.91	0.71,	1.15	1.02	0.70,	1.49
Acute glomerulonephritis, renal failure	0.78	0.37,	1.63	--		
Chronic & unspecified nephritis, renal failure	1.01	0.75,	1.37	1.11	0.67,	1.85
Other genito-urinary diseases	0.77	0.49,	1.21	1.00	0.55,	1.81
Tuberculosis & HIV	--			--		
Symptomatic & ill-defined conditions	0.69	0.42,	1.15	--		
Other & unspecified causes	0.95	0.80,	1.13	0.87	0.65,	1.18

\*Significant at P = 0.05.

\*\*Calculated using Byar's approximation to the Poisson exact test.

All estimates are adjusted for age, calendar year, gender, race, and state.

SMRs not estimated for < 5 observed deaths.