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Pesticide Use and Myocardial Infarction Incidence Among Farm Women in the Agricultural Health Study

Shile B. Dayton, MPH[1], **Dale P. Sandler, PhD**[2], **Aaron Blair, PhD**[3], **Michael Alavanja, DrPH**[3], **Laura E. Beane Freeman, PhD**[3], and **Jane A. Hoppin, ScD**[2]

[1] School of Public Health, University of Nevada Reno, Reno, NV

[2] Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, US Department of Health and Human Services, Research Triangle Park, NC

[3] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD

Abstract

Objective—Evaluate the relationship between pesticide use and myocardial infarction (MI) among farm women.

Background—Little is known about the potential association between pesticide use and cardiovascular outcomes.

Methods—We used logistic regression to evaluate pesticide use and self-reported incident non-fatal MI among women in the Agricultural Health Study.

Results—Of those MI-free at enrollment (n=22,425), 168 reported an MI after enrollment. We saw no association with pesticide use overall. Six of 27 individual pesticides evaluated were significantly associated with non-fatal MI, including chlorpyrifos, coumaphos, carbofuran, metalaxyl, pendimethalin and trifluralin, which all had odds ratios greater than 1.7. These chemicals were used by <10% of the cases and their use was correlated, making it difficult to attribute the risk elevation to a specific pesticide.

Conclusion—Pesticides may contribute to MI risk among farm women.

Keywords

pesticides; farm women; agricultural exposures; myocardial infarction

Introduction

Pesticide poisonings sometimes involve cardiac complications. For example, organophosphate poisoning has been associated with arrythmias and cardiac anomalies (1,2). However, little is known about the cardiac risks associated with low-level chronic exposure to pesticides. Studies of mortality among US crop and livestock farmers (3) and licensed pesticide applicators (4) have suggested increased risk of myocardial infarction (MI) mortality, while other studies of other farming populations have shown deficits in MI mortality (5,6) or no evidence of an association (7). These studies, although focusing on

Corresponding Author: Jane A. Hoppin, ScD., NIEHS, Epidemiology Branch, MD A3-05, PO Box 12233, Research Triangle Park, NC 27709-2233, (919) 541–7622, (919) 541–2511 (fax), hoppin1@niehs.nih.gov.

agricultural populations, have generally not evaluated potential MI risk from specific pesticides. In an ecological analyses using crop patterns as a surrogate for pesticide exposure, Schrienemachers reported greater risk for acute fatal MIs in US counties with high-wheat production (8). An analysis of both fatal and non-fatal MIs among male pesticide applicators in the Agricultural Health Study (AHS) provided no evidence of an association of MI with pesticides (9). Little information is available regarding MI risk among farm women. In general, farm women have been historically underrepresented in health research (10). To better assess MI risk associated with pesticides among women, we used data from the AHS to investigate potential agricultural risk factors for MI among farm women.

Methods

Study Population

The AHS is a prospective study of 52,395 licensed private pesticide applicators, mainly farmers, and 32,346 spouses of farmers from Iowa and North Carolina enrolled from 1993 to 1997 (11). Spouses enrolled via a self-administered questionnaire brought home by the enrolled applicator (81% returned the questionnaire by mail; 19% completed the interview by phone). In 1999–2003, 69% of applicators and 76% of spouses completed a followup phone interview.

Sample Population

Our study population consisted of all female participants in the AHS, including both female spouses of applicators (N=23,703) and female applicators (N=912), who completed both the enrollment questionnaire and the follow-up phone interview. Information on occurrence of MI was obtained at the follow-up phone interview. Women who had an MI prior to enrollment were excluded (n=193). Also excluded were women missing information on smoking status (n=1,234), body mass index (n=719), and age (n=1). The final analytical sample included 22,425 farm women.

Outcome

For our primary analysis, MI was defined as having a positive response to the question, “Has a doctor ever told you that you had (been diagnosed with) a myocardial infarction (heart attack)?” Women who reported having had a diagnosis of MI were also asked, “at what age?” Responses to the latter question were used to classify reported MIs as incident or prevalent based on woman’s age at diagnosis and age at enrollment. Incident MI were defined as those occurring at an age greater than or equal to age at enrollment.

Exposure Assessment

Information on demographic characteristics, medical history, and agricultural exposure history including personal pesticide use and current farm activities was obtained from the enrollment questionnaire. We focused on lifetime pesticide use history and current farm activities at enrollment. Women provided information on ever use of 50 individual pesticides as well as overall lifetime use of pesticides. Because we included both spouses and applicators, the exposure assessment for pesticides was limited to the detail provided on the spouse questionnaire. Farm activities evaluated included contact with animals, operation of farm equipment, farm maintenance activities, and solvent use on the farm. Questionnaires are available at www.aghealth.org/questionnaires.html.

Statistical Assessment

To assess the association between farming exposures and MI, we used logistic regression controlling for age, BMI, smoking status, and state of residence. Logistic regression was suitable for this analysis because of the short duration from enrollment to MI (generally less than five years). Goodness-of-fit tests were used to identify covariates to be included in the model. Our model showed little change in fit when smoking status was modeled as a three-level variable (current, past, never) compared to when we combined past and current smokers; therefore, the two-level variable (ever, never) was used in the analysis. Other parameterizations of smoking (e.g., pack years) were evaluated, but none fit the model better than the two-level variable; probably due to the low frequency of smoking in our sample. We also considered alcohol consumption, education, and physical activity, but did not include them in the final model because they did not affect the point estimates.

Using the individual pesticide variables, we created summary variables for pesticide functional categories (fumigants, fungicides, herbicides and insecticides) and subclassifications of insecticide classes (carbamates, organochlorines, and organophosphates). We evaluated each group and pesticide individually. We limited our analysis to individual pesticides that had at least five reported cases of MI among those exposed.

Pesticide use can be correlated. To address potential confounding by correlated variables, we looked at the correlations between pesticides that were significant in the single pesticide models. For pairs of pesticides with a Spearman correlation of 0.3 or higher, we included both pesticides in the model to evaluate the impact on the odds ratios.

To assess possible misclassification of self-reported MI, we repeated our analyses, excluding women with self-reported angina or arrhythmia. Additionally, to assess the overall risk of incident MI, we conducted an analysis including both fatal and non-fatal MIs. Fatal MIs were identified using ICD-10 codes (I21–I22) from death certificates for all women in the AHS who had died since time of enrollment until December 31, 2005. The number of MI deaths was too small (N=48) to evaluate MI mortality alone.

SAS version 9.0 was used for all statistical analyses. The AHS data sets used were P1REL0506 and P1REL0612.01 releases.

Results

A total of 168 incident non-fatal doctor-diagnosed MIs were reported among the 22,425 farm women who completed the follow-up interview (Table 1). Cases were older and had lived on farms longer. Women with incident MI were more likely to have reported a history of hypertension, diabetes, angina, and arrythmia at enrollment. Alcohol consumption was more common among controls than cases (66% vs. 38%). Women who were licensed pesticide applicators were more likely to report MI (9% vs. 4%).

MI risk was not associated with ever use of any pesticide (OR=0.9, 95% CI=0.7,1.2) nor was it associated with either number of days or number of years applied pesticides (Table 2). Incident MI was associated with ever use of a few specific pesticides, but not with use of specific chemical classes. Six of 27 specific pesticides were statistically significantly associated with increased MI: the insecticides chlorpyrifos (Odds Ratio (OR) = 2.1, 95% Confidence Interval (CI) =1.2, 3.7), coumaphos (OR = 3.2, 95% CI = 1.5, 7.0), and carbofuran (OR = 2.5, 95% CI = 1.3, 5.0); the herbicides pendimethalin (OR = 2.5, 95% CI =1.2, 4.9) and trifluralin (OR = 1.8, 95% CI = 1.0, 3.1); and the fungicide metalaxyl (OR=2.4, 95% CI =1.1, 5.3). There was no association between non-fatal MI and farming activities reported at enrollment (Table 3) and these activities did not confound the pesticide associations.

The six chemicals significantly associated with MI were correlated with each other, particularly among cases (r=0.3–0.7). To evaluate whether this correlation influenced our results, we built models which included two pesticides at a time. In doing this, the odds ratios for MI remained elevated but no longer statistically significant. Chlorpyrifos was correlated with all of the five other pesticides. When chlorpyrifos was included in a model with coumaphos, the estimates were both attenuated ($OR_{chlorpyrifos}$ = 1.4, 95% CI=0.7,2.8 and $OR_{coumaphos}$ = 3.1, 95% CI=1.3, 7.1), but the number of exposed cases decreased as well due to missing exposure information for one of the pesticides in the model. The other pairwise models of pesticides suggested some evidence of potential confounding or interaction of the pesticides, but given the small number of exposed cases (n=5 to 14), we lacked statistical power to explore this further. Women who used at least one of the six pesticides had an elevated risk of MI (OR=1.6, 95% CI=1.1,2.4).

Female pesticide applicators may have greater pesticide exposure and may have used more toxic chemicals. To assess whether our results were driven by the 3.7% of the women who were private pesticide applicators, we reran our main analyses excluding female applicators. With these women excluded (n=15 cases), eight pesticides were significantly associated with MI, the six previously observed and petroleum oil (OR=1.9, 95% CI=1.0,3.8) and terbufos (OR=2.1, 95%CI=1.0,4.4). The point estimates of all eight pesticides were very similar to those observed in the full sample with the exception of chlorpyrifos; the odds ratio for chlorpyrifos reduced from 3.2 to 2.2 (95%CI=1.2, 4.2).

Exclusion of women with self-reported angina (n = 29) or arrhythmia (n = 26) did not substantially change our results With these women excluded, we observed significant risk for incident MI for coumaphos (OR=3.7, 95% CI=1.6,8.6) and chlorpyrifos (OR=2.3, 95%CI=1.2, 4.3) and non-significant, but elevated risks, for carbofuran (OR=2.2, 95% CI=1.0, 5.1), pendimethalin (OR=2.1, 95% CI=0.9, 4.8) and trifluralin (OR=1.3, 95%CI=0.6,2.6). There were too few metalaxyl exposed cases (n=3) to estimate MI risk. When we included the 48 women with fatal MIs since enrollment, there were only 2 more cases who had ever applied pesticides and none who reported using the pesticides associated with non-fatal MIs, so the results were essentially unchanged from the analysis including the non-fatal MIs only (data not shown).

Discussion

We investigated the relationship between agricultural pesticide use and the incidence of myocardial infarction among women in the Agricultural Health Study. Little is known about the effect of chronic low-dose pesticide exposure on cardiovascular outcomes as the majority of human data is from poisoning episodes. Six pesticides were positively associated with non-fatal MI among the farm women. The insecticide coumaphos had the highest odds ratio. We saw no associations between MI and total lifetime days of pesticide use or for various farm activities, such as operating farm equipment or solvent use. While we observed associations with use of specific chemicals for women in the AHS, no associations were seen for MI among the men in the cohort (9).

Pesticide exposure information was collected at least one year prior to an MI event. These data were limited to ever use of specific pesticides and total days of use of all pesticides, thus we lacked the opportunity to assess exposure-response relationships for these specific pesticides. However, these data represent a unique resource regarding use of specific pesticides among farm women. While the reliability and validity of this information from farm women has not been characterized, the quality of self-reported pesticide use from the pesticide applicators in the AHS has been demonstrated to be reliable and accurate (12,13). The concordance of pesticide use reports between applicators and spouses also supports the reliability of pesticide use information provided by farm women (14).

Our findings of an increased risk of MI associated with ever use of specific pesticides are intriguing, but the sample size is small and the exposure detail limited. The pesticides associated with MI were all registered with the EPA for at least 15 years prior to our collection of the exposure data. Coumaphos, registered in 1958, was in use the longest (13). The six pesticides associated with MI have no common use patterns, although among case women the use of these pesticides was correlated. Of the six, three were insecticides, two herbicides, and one was a fungicide. Chlorpyrifos and coumaphos are both organophosphate insecticides; chlorpyrifos is used on both crops and livestock, but coumaphos is used exclusively on animals. Carbofuran, a carbamate insecticide is used on crops. Pendimethalin and trifluralin are herbicides used on annual grasses and broadleaf weeds among crops and metalaxyl is a fungicide used on crops and in soil treatment for disease control. The acute toxicities of these pesticides vary from slightly toxic (pendimethalin) to highly toxic (coumaphos and carbofuran) (15). Chlorpyrifos, coumaphos, and carbofuran all inhibit acetylcholinesterase to varying degrees (15). Thus, it is unlikely that our observations for these six chemicals could result from some common use pattern or toxicity. While our findings for these unrelated pesticides make it difficult to speculate on a potential mechanism, our results do suggest that pesticide exposures that do not result in poisonings may be a risk factor for MI in women.

Even in this large cohort of 22,425 farm women, use of most individual pesticides is rare. Only 26 of 50 pesticides queried at enrollment had a sufficient number of exposed cases to be evaluated. The pesticides associated with MI were among the less commonly used pesticides among farm women. The prevalence of chlorpyrifos use at enrollment was 5% among females, while coumaphos use was used by fewer than 1%. On the other hand, approximately 60% of these women reported applying some pesticide in their lifetime. The most commonly used chemicals were the herbicide glyphosate (37%) and the insecticide carbaryl (33%). Given this low exposure prevalence and the lack of information on duration and frequency of use, we were limited in our ability to assess potential confounding by related exposures and were unable to assess dose-response. However, when we controlled for correlated pesticides and when we excluded people with angina and arrythmia, the associations remained elevated though no longer statistically significant.

We relied on self-reported MI as our primary outcome. Accuracy of self-reported MIs among middle-aged and elderly Americans generally ranges from 53 to 72 percent, validity decreases with age (16,17). The inaccuracy of reporting of an MI is most commonly associated with diagnoses of other cardiac outcomes, such as unstable angina, especially among women with an age greater than 64 years when self-report was compared to hospital records (16,17). Other investigators have used self-reported MI as an outcome (18,19). When we repeated the analysis after removing women who reported arrhythmia and angina, our results were similar. Because we relied on self-reported data, we may have underestimated MI risk because women who had medical interventions that may have prevented MIs or undetected MIs were included in our comparison group. Inclusion of MI deaths, on the other hand, may include some over-reporting of outcome resulting from inaccurate reporting of MIs as cause of death for women of advanced age (20). However our estimates were similar when we included fatal cases.

Farm women appear to be at low risk for MI death compared to other women (5,21). Our estimate of 1.5 non-fatal MIs/1000 woman-years is lower than other US populations (22,23).

In previous AHS analyses, cardiovascular disease mortality for farm women was 60% that of the general population in IA and NC (5). Even in this low risk population, we saw increased risk of incident MI among women who used specific pesticides. Among male applicators in the AHS cohort, we saw no association with pesticides and MI risk (9). In that analysis, we had a more highly exposed population with detailed pesticide use information with a larger number of cases. Thus it is somewhat surprising that we would see associations between pesticide use and MI among farm women in our cohort but not among men, particularly given the large magnitude of the effect estimates. With our small numbers, chance may explain our findings, however, our results could suggest a different role for pesticides in MI risk for women than men. While we lacked use information to evaluate exposure-response relationships, the prospective nature of the analysis adds strength to these findings. While we cannot rule out chance, these results suggest the need for future investigation of pesticides and MI risk among farm women.

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Abbreviations

AHS	Agricultural Heath Study
BMI	Body Mass Index
CI	Confidence Interval
MI	Myocardial Infarction
OR	Odds Ratio

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Table 1

Demographics of 22,425 farm women enrolled in the Agricultural Health Study completing both enrollment (1993–1997) and follow-up questionnaires (1999–2003)

	Cases N=168		Controls N=22257	
Age at Enrollment (years)	**N**	**%**	**N**	**%**
17 – 39	8	5	6642	30
40 – 49	21	13	6529	29
50 – 59	51	30	5529	25
60 – 88	88	52	3557	16
State				
Iowa	95	57	16003	72
North Carolina	73	43	6254	28
Licensed Pesticide Applicator				
Yes	15	9	815	4
No	153	91	21442	96
Body Mass Index (kg/m^2)				
15.0 – 25.0	60	36	10705	48
25.1 – 30.0	58	35	7306	33
over 30	50	30	4246	19
Smoking Status				
Never	112	67	16356	73
Ever	56	33	5901	27
Alcohol Consumption at Enrollment (drinks/month)				
Never	105	64	9662	44
1–10	53	32	10621	48
11+	6	4	1715	8
Years Lived on a Farm (years)				
0–15	31	18	5240	24
15–30	30	18	5849	26
30–45	33	20	5897	26
45+	74	44	5271	24
Days per year mixing pesticides				
none	109	65	12802	58
1–5	22	13	4712	21
5–9	15	9	2179	10
10–19	11	7	1612	7
20+	11	7	952	4
Year(s) spent mixing pesticides				
none	109	65	12815	58
1 – 5	9	5	3406	15
6 – 10	13	8	1824	8
11 – 20	15	9	2214	10

	Cases N=168		Controls N=22257	
Age at Enrollment (years)	**N**	**%**	**N**	**%**
21+	22	13	1998	9
Education				
High School or Less	101	65	8762	44
More then High School	55	35	11162	56
Strenuous Exercise During Leisure Time (hr/week)*				
None	45	35	3452	21
<1	18	14	2969	17
1–2	25	20	3289	19
3–5	26	20	4452	26
> 6	13	10	2858	17
Medical History at Enrollment				
Family History of a Heart Attack	25	16	2359	11
Angina**	29	19	423	2
Arrhythmia**	26	17	1278	6
Diabetes**	35	23	630	3
Hypertension**	73	47	3106	14

*The highest level reported during summer or winter

**Self-reported doctor diagnosis

Table 2

Odds Ratios for incident non-fatal MI and pesticide use among 22,425 farm women in the Agricultural Health Study

	Cases (N=168)		Controls (N=22257)		Odds Ratio*	95% Confidence Interval	
	N	%	N	%			
Ever Applied Pesticides	92	55	13357	60	0.9	0.7	1.2
FUMIGANTS	7	4	522	2	1.5	0.7	3.2
METHYL BROMIDE	5	3	347	2	1.7	0.7	4.3
FUNGICIDES	16	10	1365	6	1.3	0.8	2.3
CAPTAN	5	3	601	3	1.1	0.4	2.6
MANEB	6	4	376	2	1.7	0.7	3.9
METALAXYL	7	5	385	2	2.4	1.1	5.3
HERBICIDES	54	33	8980	41	0.8	0.6	1.2
2,4–D	27	17	3652	17	1.1	0.7	1.7
ALACHLOR	9	6	1085	5	1.2	0.6	2.4
ATRAZINE	13	8	1192	6	1.5	0.8	2.7
BUTYLATE	5	3	343	2	2.1	0.8	5.2
CHLORIMURON-ETHYL	5	3	424	2	1.8	0.7	4.5
CYANAZINE	6	4	739	3	1.2	0.5	2.9
DICAMBA	5	3	1019	5	0.8	0.3	1.9
GLYPHOSATE	46	29	8096	37	0.8	0.6	1.2
METOLACHLOR	5	3	863	4	0.9	0.4	2.2
METRIBUZIN	5	3	452	2	1.5	0.6	3.7
PETROLEUM OIL	10	7	852	4	1.8	0.9	3.4
PENDIMETHALIN	9	6	592	3	2.5	1.2	4.9
TRIFLURALIN	15	10	1360	6	1.8	1.0	3.1
INSECTICIDES	77	47	9497	43	1.1	0.8	1.6
CARBAMATES	63	38	7576	34	1.1	0.8	1.5
CARBARYL	55	36	7087	33	1.0	0.7	1.4
CARBOFURAN	9	6	478	2	2.5	1.3	5.0
ORGANOCHLORINES	21	14	1951	9	1.1	0.7	1.7
CHLORDANE	14	10	998	5	1.7	0.9	2.9

	Cases (N=168)		Controls (N=22257)		Odds Ratio*	95% Confidence Interval	
	N	%	N	%			
DDT	11	8	856	4	1.0	0.6	1.9
ORGANOPHOSPHATES	49	30	6411	29	1.1	0.8	1.5
CHLORPYRIFOS	14	9	1056	5	2.1	1.2	3.7
COUMAPHOS	7	4	314	1	3.2	1.5	7.0
DIAZINON	13	9	2388	11	0.8	0.4	1.4
FONOFOS	5	3	448	2	1.7	0.7	4.3
MALATHION	31	21	4639	22	0.9	0.6	1.3
TERBUFOS	9	6	735	3	1.9	1.0	3.8

* Odds Ratios adjusted for age, BMI, smoking status, and state.

Table 3

Farm Exposures and Risk of MI among 22,425 farm women enrolled in the Agricultural Health Study

	Cases (N=168)		Controls (N=22,257)				
Exposure	**N**	**%**	**N**	**%**	**Odds Ratio***	**95% Confidence Interval**	
Animal Activities							
Grind Feed	11	8	1513	7	1.2	0.7	2.3
Contact with Farm Animals	19	13	2974	14	1.4	0.9	2.3
Milk Cows	7	5	1051	5	1.1	0.5	2.3
Farm Equipment Operation							
Drive Trucks	54	37	8205	39	1.2	0.8	1.6
Diesel Tractors	46	32	7301	35	1.3	0.9	1.8
Gasoline Tractors	44	31	5804	28	1.4	1.0	2.0
Maintenance Activities							
Welding	6	4	567	3	1.3	0.6	2.9
Repair Engines	5	4	640	3	1.0	0.4	2.5
Grind Metal	7	5	615	3	1.4	0.7	3.1
Solvent Exposures							
Clean with Solvents	33	23	4595	22	1.2	0.8	1.8
Paint	40	28	7124	34	0.9	0.6	1.3

*Odds Ratios adjusted for age, BMI, smoking status, and state.