Human & Experimental Toxicology (2007) **26:** 243–250
http://het.sagepub.com

Neurologic symptoms in licensed pesticide applicators in the Agricultural Health Study

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Exposure to high levels of many pesticides has both acute and long-term neurologic consequences, but little is known about the neurotoxicity of chronic exposure to moderate pesticide levels. We analysed cross-sectional data from 18 782 Caucasian, male, licensed pesticide applicators, enrolled in the Agricultural Health Study from 1993 to 1997. Applicators provided information on lifetime pesticide use, and 23 neurologic symptoms typically associated with pesticide intoxication. Increased risk of experiencing ≥10 symptoms during the year before enrollment was associated with cumulative pesticide use, personally mixing or applying pesticides, pesticide-related medical care, diagnosed pesticide poisoning, and events involving high personal pesticide exposure. Greatest risk was associated with use of organophosphate and organochlorine insecticides. Results were similar after stratification by pesticide use during the year before enrollment, or exclusion of applicators with a history of pesticide poisoning, or high-exposure events. Use of pesticide application methods likely to involve high personal exposure was associated with greater risk. Groups of symptoms reflecting several neurologic domains, including affect, cognition, autonomic and motor function, and vision, were also associated with pesticide exposure. These results suggest that neurologic symptoms are associated with cumulative exposure to moderate levels of organophosphate and organochlorine insecticides, regardless of recent exposure or history of poisoning. *Human & Experimental Toxicology* (2007) **26,** *243–250*

Key words: insecticides; neurologic symptoms; organochlorine insecticides; organophosphate insecticides; pesticides; pesticide applicators

Introduction

Pesticides are used extensively throughout the world. In the US, more than 18 000 products are licensed for use, and each year more than two billion pounds of pesticide products are used.[1] High-level exposure to some types of pesticides is neurotoxic; both acute and chronic effects have been reported in humans from exposure to organophosphate, carbamate, organochlorine, and pyrethroid insecticides, herbicides, fungicides, and fumigants.[2,3]

Organophosphates have been studied most extensively. Organophosphate poisoning produces an acute response, which includes symptoms of cognitive, motor, and sensory dysfunction.[2,3] The effects of such poisoning may persist long after the immediate episode has resolved; sequelae include increased neurologic symptoms, deficits in neurobehavioral performance, decreased vibration sensitivity, and impaired nerve conduction.[4] These consequences can be detected up to ten years after poisoning,[5] suggesting permanent residual damage. Even less severe poisoning can have long-term effects.[6]

Questions remain concerning the neurologic effects of moderate pesticide exposure. Most studies show effects on cognitive and psychomotor function in chronically exposed individuals without a history of poisoning, although clinical measures of peripheral nerve function, such as vibration sensitivity and nerve conduction, are not generally affected.[4] Many studies of moderate exposure have also found increases in neurologic symptoms representing a range of neurologic domains, including affect, cognition, and motor, sensory, and autonomic function.[4] These symptoms may represent early

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Received 31 October 2005; revised 23 May 2006; accepted 26 July 2006

 10.1177/0960327107070582

evidence of neurologic dysfunction, before objective clinical signs can be found, using non-invasive techniques. A recent review of the experimental literature indicated that chronic exposure to moderate levels of pesticides also impairs neurologic function in animals,[7] supporting the findings in humans. Unresolved issues in human studies include the importance of a history of pesticide poisoning compared to chronic moderate exposure; the role of acute exposure, which often confounds chronic exposure; and the effects of pesticides other than organophosphates.

The Agricultural Health Study (AHS) is a large cohort study of licensed pesticide applicators and their spouses.[8,9] Questionnaires completed by applicators at enrollment provided information on neurologic symptoms during the prior year, as well as detailed information on lifetime pesticide use and exposure. We used this information for a cross-sectional analysis of the relationship of symptoms to several measures of pesticide exposure. Some of these results have been reported previously.[10]

Methods

The AHS cohort was recruited from 1993 to 1997, in two states in the US, Iowa and North Carolina.[8,9] In both states, licenses to use restricted use pesticides must be renewed every 3 years. All individuals applying for new or renewed licenses were invited to enroll in the study. Approximately 52 400 private applicators participated, 82% of those eligible. At enrollment, applicators completed a self-administered questionnaire. All enrolled applicators were requested to complete a supplemental self-administered questionnaire at home, and 44% complied. Applicators completed the two questionnaires a median of 1 month apart. Those who returned the supplemental questionnaire were similar to those who did not, in most respects, including pesticide exposure.[11] Together, the two questionnaires collected information on demographic characteristics, lifestyle, medical history, neurologic symptoms, and pesticide use, using questions with fixed responses. Questionnaires are available at http://www.aghealth.org. The present analysis was restricted to applicators with complete information on neurologic symptoms, 89% of those who returned the supplemental questionnaire. To reduce heterogeneity, the analysis was further restricted to Caucasian males, aged 18–75 (mean: 45), who comprised 92% of otherwise eligible cohort members.

The applicators provided information on 23 symptoms (Table 1). The list of symptoms was based on an established questionnaire, Q16, previously used to evaluate the occupational effects of neurotoxicants.[12] Applicators reported the frequency of experiencing each symptom, ranging from never to more than once per week. For our primary analysis, we compared applicators who had experienced 10 or more of the 23 symptoms at least once in the year before enrollment (cases), with those who had experienced fewer than 10 symptoms (controls). Approximately 20% of the applicators were in the case group; the remaining 80% were controls. We also evaluated symptoms categorized *a priori* in groups representing several functional domains. We used the affect, cognitive, autonomic, and motor groups listed in Table 1, plus a group consisting of the two vision symptoms; we did not analyse the group of 'other' symptoms, because this was too heterogeneous to provide interpretable results. Group symptom variables were created by summing, for each applicator, the number of times per year any symptom in the group was experienced and then dichotomizing the distribution of the sums so that the positive category included approximately 10% of the participants.

Table 1 Neurologic symptoms experienced by licensed applicators enrolled in the Agricultural Health Study from 1993 to 1997 ($n = 18\ 782$)

Domain	*Symptom*	%[a]
Affect	Anxiety	52
	Irritability	37
	Depression	27
Cognition	Memory	24
	Concentration	20
Sensory	Numbness or paresthesia	27
	Poor night vision	12
	Blurred or double vision	10
	Changes in smell or taste	6
Motor	Twitches	17
	Weakness	15
	Poor balance	12
	Tremor	11
	Difficulty speaking	4
Autonomic	Nausea	27
	Loss of appetite	18
	Excessive sweating	17
	Fast heart rate	15
Other	Headache	68
	Fatigue	58
	Insomnia	43
	Dizziness	28
	Loss of consciousness	2

[a]Percent of applicators experiencing symptom at least once in the year before enrollment.

We constructed several measures of pesticide exposure using questionnaire data. Applicators reported duration (years) and frequency (days/year) of use for any pesticide in categories. A variable for cumulative days of use was created by multiplying duration times frequency using midpoints of the reported categories, and then categorizing the product in quartiles. Separate questions elicited information on the proportion of time the applicator had personally mixed or applied pesticides (never, <50% of the time, ≥50% of the time); whether the applicator had ever sought pesticide-related medical care (never, doctor visit, hospitalized) or been given a diagnosis of pesticide poisoning (never, ever); and whether the applicator had ever experienced an incident involving high personal pesticide exposure (never, yes involving only dermal exposure, yes involving inhalation or ingestion). Variables for cumulative lifetime days of use of pesticides in functional groups (insecticides, herbicides, fungicides and fumigants) or chemical subgroups of insecticides (organophosphates, organochlorines, carbamates and pyrethroids) were created by multiplying duration by frequency of use for each pesticide in the functional or chemical group, summing across pesticides in the group, and then categorizing the sum into never use and two or three categories of use, depending on the distribution. Applicators reported methods used to apply pesticides separately for herbicides, crop insecticides, and fungicides. We classified application methods as likely to involve low personal exposure (aerial application, tractor boom, preapplied to seed) or high personal exposure (airblast, mist blower, backpack sprayer, hand spray gun), and then categorized applicators as using low exposure methods only, or using both low and high exposure methods.

We estimated associations of symptom outcomes with pesticide exposure using logistic regression, with adjustment for age (18–30, 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, 66–75 years), state (Iowa, NC), education (≤high school, >high school), cigarette smoking (0, >0–30, >30 pack-years), and alcohol use (any consumption in past year). Results were similar after adjustment for a multilevel education variable or for marital status. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

The Institutional Review Boards of the National Institutes of Health, the University of Iowa (Iowa Field Station), and Battelle (North Carolina Field Station) approved the AHS. The AHS was explained to potential participants who indicated consent by returning questionnaires.

Results

Of the applicators included in this analysis, 95% were farmers, 70% were from Iowa, 44% had more than a high school education, 43% had ever smoked cigarettes, and 66% had consumed alcoholic beverages in the year before enrollment. These results have previously been reported in more detail.[10]

Cumulative lifetime days of pesticide use was associated with experiencing ≥10 symptoms in the year before enrollment; applicators in the highest quartile of use had a 1.2-fold increase in risk (Table 2). Applicators who personally applied pesticides at least 50% of the time had a 1.3-fold increase in risk, and those who personally mixed pesticides at least 50% of the time had a 1.4-fold increase in risk (Table 2). Applicators who had ever seen a doctor or been hospitalized for pesticide-related illness had a 2.0- to 2.3-fold increase in risk, while those who had been diagnosed by a physician with pesticide poisoning had a 2.5-fold increase (Table 2). Seeking medical care for pesticide-related illness increased risk, even when individuals with doctor-diagnosed pesticide poisoning were excluded from the analysis (OR for doctor visit: 2.1). Applicators who had ever experienced a high-exposure event, involving mainly dermal exposure, had a 1.8-fold increase in risk, while those experiencing an event that also included inhalation of fumes or ingestion of pesticide, had a 3.0-fold increase in risk (Table 2). Risk estimates for high exposure events were similar when individuals with doctor-diagnosed pesticide poisoning were excluded from the analysis (OR for dermal exposure: 1.8, OR for inhalation or ingestion: 3.0).

When pesticides were considered in functional groups, the proportion of applicators who had ever used any pesticide in the group was greater among cases than controls for insecticides, fungicides, and fumigants, but not for herbicides (Table 3). Results were similar in the two states, except that insecticide use was associated with greater risk in North Carolina (OR: 2.6) than in Iowa (OR: 1.6). Increasing lifetime days of use of insecticides was associated with increasing risk of experiencing ≥10 symptoms (Figure 1); applicators in the highest category of use had a 2.5-fold increase in risk. Risk was at least as great among applicators who had not used insecticides during the past year, as among applicators who had used insecticides during the past year (Figure 1). Increases associated with insecticide use persisted after excluding from the analysis applicators who had experienced doctor-diagnosed pesticide poisoning, high exposure events, or both (OR: 2.2–2.4 for the highest category of use). There was a small increase in risk associated with increased use of fumigants or herbicides, but fungicide use had little effect (Figure 1). When all functional groups were analysed in the same model, the elevated risks associated with insecticides and fumigants persisted, but there was no increased risk associated

Table 2 Association of neurologic symptoms with pesticide exposure among licensed pesticide applicators enrolled in the AHS from 1993 to 1997 ($n=18\ 782$)

Exposure	*Cases*		*Controls*		*Adj OR*[a]	*95% CI*[a]
	n	%	*n*	%		
Lifetime days of use of any pesticide						
0–64	815	23	3722	26	1.0	Referent
65–200	765	22	3091	21	1.2	1.0–1.3
201–396	936	27	3795	26	1.1	1.0–1.3
397–7000	965	28	3870	27	1.2	1.1–1.3
Personally apply pesticides						
No	53	2	274	2	1.0	Referent
<50% of the time	647	19	2776	19	1.3	0.9–1.7
≥50% of the time	2777	80	11421	79	1.3	1.0–1.8
Personally mix pesticides						
No	100	3	571	4	1.0	Referent
<50% of the time	726	21	3281	23	1.3	1.0–1.6
≥50% of the time	2659	76	10626	73	1.4	1.1–1.7
Ever sought medical care for pesticide-related illness						
No	3141	89	14014	95	1.0	Referent
Doctor visit	328	9	645	4	2.3	2.0–2.6
Hospitalized	54	2	128	1	2.0	1.4–2.7
Ever diagnosed with pesticide poisoning						
No	3454	96	14726	98	1.0	Referent
Yes	127	4	236	2	2.5	2.0–3.1
Ever had event involving high personal exposure						
No	2688	76	13022	88	1.0	Referent
Yes, mainly dermal exposure[b]	478	13	1184	8	1.8	1.6–2.0
Yes, inhalation or ingestion[b]	381	11	604	4	3.0	2.7–3.5
Crop insecticide application methods						
Don't apply	681	19	3023	20	1.0	Referent
Low exposure methods only	2094	58	8974	60	1.0	0.9–1.1
Low and high exposure methods	817	23	2984	20	1.4	1.2–1.6
Herbicide application methods						
Don't apply	154	4	889	6	1.0	Referent
Low exposure methods only	765	21	4634	31	0.9	0.7–1.1
Low and high exposure methods	2683	74	9502	63	1.5	1.2–1.8
Fungicide application methods						
Don't apply	2506	70	10949	73	1.0	Referent
Low exposure methods only	563	16	2086	14	1.3	1.2–1.4
Low and high exposure methods	503	14	1864	13	1.4	1.3–1.6

[a]OR and 95% CI for relative risk of experiencing ≥10 symptoms in the year before enrollment, calculated by logistic regression with adjustment for age, state, education, cigarette smoking, and alcohol use.
[b]Mainly dermal exposure: applicators reported exposure to head or face, arms, hands, torso, groin, legs or feet; inhalation or ingestion: applicators also reported exposure from breathing fumes or swallowing pesticide.

with herbicides or fungicides (ORs for the highest category of use for insecticides, herbicides, fungicides, and fumigants were 2.4, 0.9, 1.0, and 1.2, respectively).

For each of the insecticide chemical groups (organophosphates, organochlorines, carbamates and pyrethroids), ever use was greater among cases than controls (Table 3); results were similar in Iowa and North Carolina. Increased risk of ≥10 symptoms was associated with increased use of organophosphate and organochlorine insecticides; applicators in the highest category of use had 2.2-fold increase in risk for both chemical classes (Figure 2). Again, the increase was similar in applicators who had or had not used the chemicals during the past year (Figure 2). We found increased risk associated with use of organophosphate insecticides among applicators who had never experienced doctor-diagnosed pesticide poisoning or high exposure events (OR: 1.6–1.7 for highest category of use). There was a small increase in risk associated with use of carbamates, but little effect of pyrethroids (Figure 2). Effects of organophosphate and organochlorine insecticides were reduced, but still important, when all groups were analysed together (ORs for the highest category of use of organophosphates, organochlorines, carbamates, and pyrethroids were 1.6, 1.7, 1.2, and 1.0, respectively).

We categorized applicators as using only pesticide application methods likely to involve low personal exposure, or also using methods likely to involve

Table 3 Use of pesticides in functional groups or insecticides in chemical groups by licensed applicators enrolled in the Agricultural Health Study from 1993 to 1997 (n = 18 782)

Group	*No. of chemicals in group*	*Cases*[a]		*Controls*[a]		*Adj OR*[b]	*95% CI*[b]
		n	*%*	*N*	*%*		
Functional pesticide groups							
Insecticides	21	3459	95	13983	92	1.8	1.6–22
Herbicides	18	3558	98	1485	98	1.0	0.8–1.3
Fungicides	6	1265	35	4753	31	1.3	1.2–1.4
Fumigants	4	832	23	3014	20	1.4	1.3–1.6
Insecticide chemical groups							
Organophosphates	10	3306	91	13184	87	1.5	1.3–1.7
Organochlorines	7	1794	50	6776	45	1.7	1.6–1.9
Carbamates	3	2196	61	9466	56	1.4	1.3–1.6
Pyrethroids	1	992	28	3204	22	1.3	1.2–1.4

[a]Table entries show number (n) and percent (%) of cases or controls who ever used any chemical in the indicated group.
[b]OR and 95% CI for relative risk of experiencing $\geq$10 symptoms in the year before enrollment, calculated by logistic regression with adjustment for age, state, education, cigarette smoking, and alcohol use; comparison is to applicators who never used any chemical in group.

high personal exposure. Use of high exposure methods to apply crop insecticides, herbicides, or fungicides was associated with increased risk of experiencing $\geq$10 symptoms (Table 2).

Results for symptom groups defined *a priori* to reflect several domains of neurologic function were consistent with results for all symptoms considered together. Use of any pesticide was associated with a small increase in risk of experiencing symptoms related to affect, cognition, autonomic or motor function, or vision (Figure 3). There was a substantial increase in risk associated with use of any insecticide, or organophosphate or organochlorine insecticides, and a small increase for fumigants (Figure 3). Results were similar for all five symptom groups.

Discussion

In this study, we found that increased risk of experiencing $\geq$10 symptoms in the previous year was associated with cumulative lifetime use of insecticides, with a weaker relationship to fumigants. Among insecticides, the strongest associations were for organophosphates and organochlorines. Increased risk was found even among applicators who had no history of doctor-diagnosed pesticide poisoning or high exposure events, and

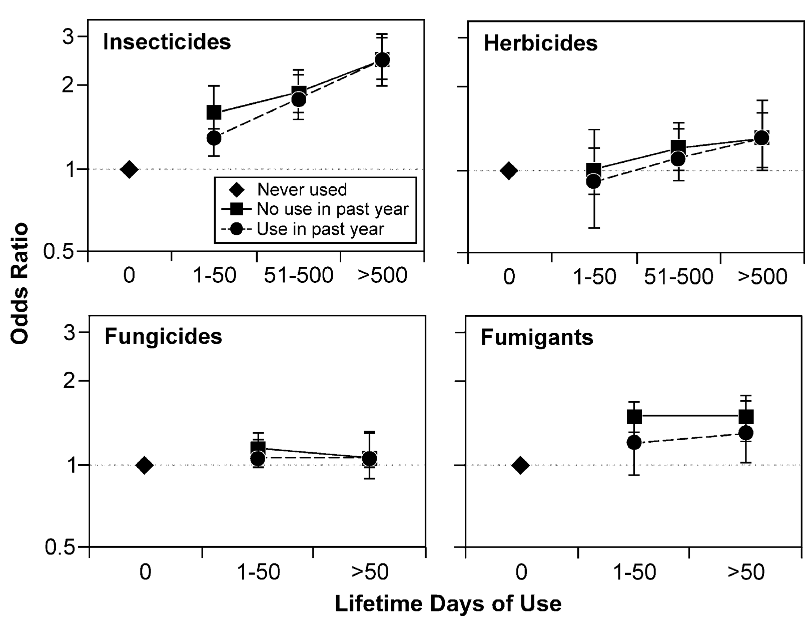

Figure 1 Association of neurologic symptoms with cumulative use of pesticides in functional groups among licensed pesticide applicators enrolled in the AHS from 1993 to 1997 (n = 18 782). ORs and 95% CIs for relative risk of experiencing $\geq$10 symptoms were calculated by logistic regression with adjustment for age, state, education, cigarette smoking, and alcohol use; ORs are shown on a log scale.

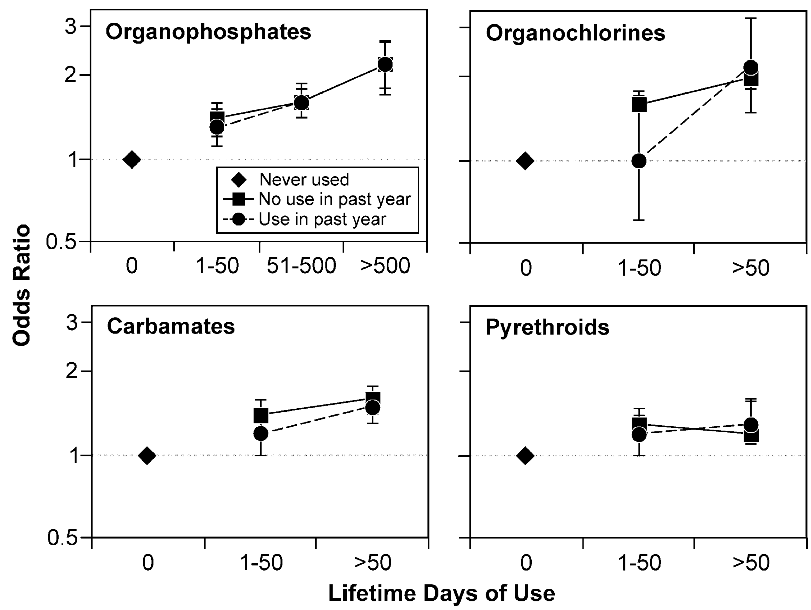

Figure 2 Association of neurologic symptoms with cumulative use of insecticides classified by chemical type among licensed pesticide applicators enrolled in the AHS from 1993 to 1997 ($n = 18\ 782$). ORs and 95% CIs for relative risk of experiencing ≥ 10 symptoms were calculated by logistic regression with adjustment for age, state, education, cigarette smoking, and alcohol use; ORs are shown on a log scale.

accounting for recent exposure did not reduce the association with cumulative use. Effects were found for symptom groups reflecting specific neurologic domains as well as for all symptoms together.

Most previous studies of pesticides and neurologic symptoms have focused on organophosphate insecticides. Farmers, farmworkers, greenhouse workers, commercial termiticide applicators, and sheep dippers had higher symptom prevalence than less exposed comparison groups.[13–20] Some,[14,17,21] although not all,[22,23] studies found increased symptom prevalence associated with inhibition of erythrocyte acetylcholinesterase activity, a biomarker of recent organophosphate exposure. Increased symptom prevalence has also been reported among workers exposed to moderate levels of DDT,[24] or fumigants.[25] We found that symptoms were associated primarily with organophosphate

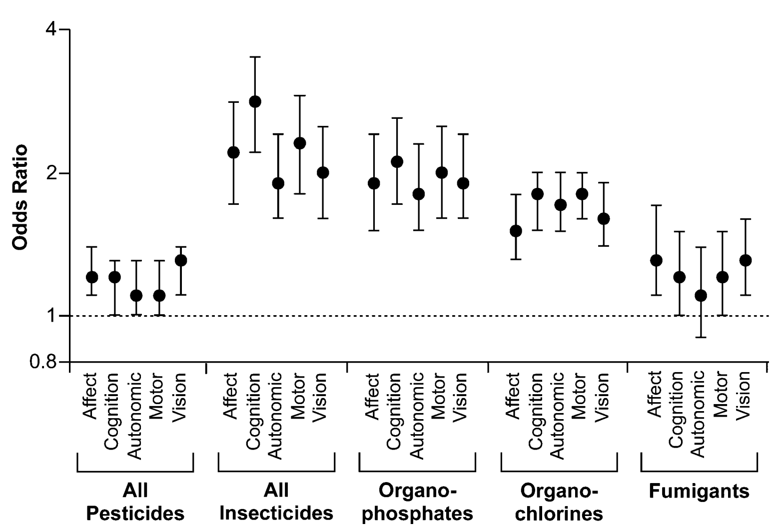

Figure 3 Association of symptoms in several neurologic domains with cumulative use of pesticides among licensed pesticide applicators enrolled in the AHS from 1993 to 1997 ($n = 18\ 782$). Symptoms included in groups were affect: anxiety, irritability, depression; cognition: memory, concentration; motor: twitches, weakness, balance, tremor, difficulty speaking; autonomic: nausea, loss of appetite, excessive sweating, fast heart rate; vision: poor night vision, blurred/double vision. ORs and 95% CIs for relative risk of experiencing more symptoms in group were calculated by logistic regression with adjustment for age, state, education, cigarette smoking, and alcohol use. Results are presented for the highest category of use for each type of pesticide; ORs are shown on a log scale.

and organochlorine insecticides, but there were also weak relationships with carbamates and fumigants. The relative neurotoxicity of specific chemicals may differ for acute high-level and chronic moderate exposure. For example, the strong associations that we observed for organochlorine insecticides, if causal, may be related to their long half-lives.[2]

Two previous studies found that increased symptom prevalence was associated with acute but not chronic exposure.[13,17] In contrast, our results suggest that, at moderate levels, cumulative exposure is at least as important as recent exposure. We confirmed previous reports that doctor-diagnosed pesticide poisoning is associated with increased symptom prevalence,[4] and showed that high personal exposure events conferred equally great risk, even in the absence of diagnosed poisoning. Two previous studies that excluded poisoned individuals found no relationship of moderate organophosphate exposure to symptom prevalence,[26,27] although a similar study of DDT did find an association.[24] We found that increased risk of experiencing ≥ 10 symptoms had a dose-related association to cumulative exposure to all insecticides and to organophosphate and organochlorine insecticides, whether or not we excluded individuals with a history of pesticide poisoning or those who had experienced high exposure events, indicating that moderate exposure itself is associated with increased risk.

Our finding that pesticide use was associated with symptoms reflecting several neurologic domains is consistent with previous reports.[4] These results were not due to confounding by head injury, depression, or neurologic disease, since associations were similar when individuals reporting these conditions were excluded from the analysis.[10] The earliest manifestation of neurotoxicity following moderate pesticide exposure may, in fact, be an increase in one or more among many symptoms, not restricted to particular aspects of neurologic function. This may be a characteristic of the response to chronic toxicant exposure at moderate levels, since a similar increase in a wide range of symptoms is associated with solvent exposure in mild cases of chronic solvent-related toxic encephalopathy.[28] Furthermore, experimental studies suggest that chronic exposure of rodents to acetylcholinesterase-inhibiting insecticides affects a range of neurologic functions, including neuromotor and sensory function, vestibular function, affect, and tremor; conditioned behaviors including memory, avoidance conditioning, and spatial learning and memory were also affected.[7] Other types of pesticides, including some organochlorine and pyrethroid insecticides, fungicides, and fumigants also had effects.[7]

Limitations of our study include its cross-sectional design and the fact that all data were self-reported, raising concern about recall bias. However, symptom reports and details of pesticide exposure were collected in separate portions of the questionnaires, completed at different times. We observed associations primarily with insecticides, and not with herbicides or fungicides, and accounting for recent exposure did not affect associations with cumulative exposure. Thus, it is unlikely that recall bias accounts for our findings. The study was also limited by lack of detail on some potentially confounding variables, such as alcohol use, although adjustment using available data did not change the results.

An important strength of our study is its large size. Further, since farming practices differ in Iowa and North Carolina, the AHS cohort represents a diverse farming population. Associations of symptoms with pesticides were similar in the two states, suggesting that our results may be generally pertinent to farmer applicators. The primary strength of the study is the availability of detailed exposure information. Farmers, in general, and AHS cohort members, in particular, report pesticide use reliably,[29,30] suggesting that our exposure measures are reasonably accurate. We made internal comparisons of more with less exposed applicators, and adjusted for multiple potential confounders, mitigating concerns about confounding.

In conclusion, we found that experience of neurologic symptoms was related to cumulative lifetime exposure to pesticides, particularly organophosphate and organochlorine insecticides. These associations were present in individuals with no history of pesticide poisoning or high exposure events and were independent of recent exposure. More attention to the risks associated with chronic pesticide exposure at moderate levels may be required.

Acknowledgements

This work was supported by intramural research funds from NIEHS (Epidemiology Branch) and NCI (Division of Cancer Epidemiology and Genetics). We thank Dr Marie Richards and Marsha Shepherd for data analysis, and the Iowa Field Station (Dr Charles Lynch, Nyla Logsden-Sackett, Patricia Gillette, Ellen Heywood), the North Carolina Field Station (Charles Knott, Dr Margaret Pennybacker, Joy Herrington) and the Westat Co-ordinating Center (Jack Cahill, Stanley Legum, Marsha Dunn, Paul Schroeder, Kate Torres), for conducting the AHS.

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