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Hearing Loss among Licensed Pesticide Applicators in the Agricultural Health Study Running title: Hearing Loss among Licensed Pesticide Applicators

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Abstract

Objective—We evaluated self-reported hearing loss and pesticide exposure in licensed private pesticide applicators enrolled in the Agricultural Health Study in 1993–1997 in Iowa and North Carolina.

Methods—Among 14,229 white male applicators in 1999–2003, 4,926 reported hearing loss (35%). Logistic regression was performed with adjustment for state, age, and noise, solvents, and metals. We classified pesticides by lifetime days of use.

Results—Compared to no exposure, the odds ratio (95% confidence interval) for the highest quartile of exposure was 1.19 (1.04–1.35) for insecticides and 1.17 (1.03–1.31) for organophosphate insecticides. Odds of hearing loss were elevated for high pesticide exposure events (1.38, 1.25–1.54), pesticide-related doctor visits (1.38, 1.17–1.62) or hospitalization (1.81, 1.25–2.62), and diagnosed pesticide poisoning (1.75, 1.36–2.26).

Conclusions—Although control for exposure to noise or other neurotoxicants was limited, this study extends previous reports suggesting that organophosphate exposure increases risk of hearing loss.

INTRODUCTION

Hearing loss imposes many burdens on workers, including communication difficulties, possible job loss, and stigma. Hearing loss may also increase risk of occupational injury because of inability to hear warning signals or shouts.[1–3] Hearing loss is commonly associated with aging, noise exposure, and head trauma, but a growing body of evidence also links hearing loss to chemical exposure, most notably solvents and heavy metals.[4–7] Hearing loss has also been a noted side-effect of certain antibiotics and antineoplastics (e.g., the aminoglycosides and cisplatin).[7]

Several pesticides are neurotoxic and could potentially affect hearing. A few case studies have pointed to acute poisoning with organophosphate insecticides (OPs) as one potential cause of permanent, bilateral hearing loss.[8,9] Several recent articles have suggested that non-poisoned pesticide applicators exposed to OPs or pyrethroids may also sustain hearing loss.[10–12]

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However, these studies were small and had little information on details of pesticide exposure or effects of specific chemicals. Pesticide classes other than OPs and pyrethroids have not previously been considered.

The Agricultural Health Study (AHS) is a prospective study of a cohort of licensed pesticide applicators and their families.[13] The purpose of the research reported here was to investigate the association between pesticide exposures and self-reported hearing loss among private pesticide applicators in the AHS. In particular, we wished to determine whether exposures to *pesticides* in general, to *classes of pesticides*, and to *individual pesticides* were associated with hearing loss among cohort members.

MATERIALS AND METHODS

Population and questionnaires

Between 1993 and 1997, applicants for certification to use restricted-use pesticides in Iowa or North Carolina were recruited to participate in the Agricultural Health Study (AHS). Details of the AHS are described elsewhere.[13] Briefly, 52,393 private applicators (82% of those eligible) completed a self-administered Enrollment Questionnaire. Enrolled applicators were asked to complete a supplemental, self-administered Applicator Questionnaire, and 22,915 of them (44%) complied. Those who completed both questionnaires were similar in most respects, including pesticide exposure, to those who completed only the Enrollment Questionnaire.[14] The Enrollment and Applicator Questionnaires elicited information on pesticide exposure, demographic characteristics, lifestyle, and medical history. AHS Questionnaires are available on the website (www.aghealth.org/questionnaires).

Five years after enrollment, follow-up telephone interviews were conducted with AHS cohort members. Among private applicators (primarily farmers) who completed the Applicator Questionnaire at enrollment, 16,246 (73%) also completed the follow-up interview. Those of the original applicators who did not complete the interview included 12% who could not be contacted, 10% who declined the interview, 1% who were excluded for various reasons, and 4% who were deceased; the remainder were not interviewed because of illness (<1%), language difficulties (<1%), or other reasons (1%). Individuals with hearing loss were a subset of the latter three categories. Private applicatorswho were interviewed, comp ared to those who were not, were slightly younger (22% vs. 27% > 60 years old) and were more likely to be from Iowa (67% vs. 61%), to have more than a high school education (44% vs. 37%), and never to have smoked (55% vs. 51%). Information from the follow-up interviews used for the present analysis was self-report of hearing loss, head injury requiring medical treatment, and hypertension.

AHS protocols were approved by the Institutional Review Boards (IRBs) of the National Institutes of Health, Westat (Coordinating Center), the University of Iowa (Iowa Field Station), and Battelle Memorial Institute (North Carolina Field Station). Participants implied consent by completing questionnaires and interviews. The statistical analysis described here was granted exemption from Ohio State University IRB oversight.

Case definition

In the five-year follow-up interview, cohort members were asked, “Do you have trouble with your hearing in one or both ears (this is without a hearing aid)?” To define the study population, we first excluded individuals who reported never using pesticides; these were most likely individuals who held a license in order to purchase pesticides but did not personally use them. We also excluded potential cases whose hearing losses were attributable to a congenital condition (n=319; 2%) or infection/injury (n=859; 5.3%) (determined by responses to survey questions). There were too few non-white or female applicators for analysis (about 1.5% of

eligibles); thus these individuals were also excluded. Limiting the data set to applicators who completed both questionnaires at enrollment and the follow-up interview, there were 16,246 subjects. Of these, 428 did not personally mix or apply pesticides; 111 did not answer the hearing loss question; 36 failed to answer whether hearing loss was since birth; 22 failed to report if their hearing loss was due to an infection/injury; and 242 were non-white or female. Thus, there were 14,229 applicators available for analysis. Among these, 4,926 subjects met the case inclusion criterion by answering the hearing question in the affirmative and 9,303 met the criterion to serve as controls by answering "no" to the question.

Pesticide exposure

We used pesticide exposure information collected at enrollment on frequency and duration of use of any pesticide, as well as 49 specific, commonly-used pesticides (Table 1). We evaluated pesticides classified by function, chemical type, or specific pesticide. Functional groups were herbicides (18 chemicals), insecticides (21 chemicals), fungicides (6 chemicals) and fumigants (4 chemicals). Insecticides were further categorized as organophosphates (10 chemicals), organochlorines (7 chemicals), or carbamates (3 chemicals); permethrin (crops or animals) was not further categorized.

A variable for cumulative days of use for each pesticide class was created by multiplying years of use (duration) by days of use per year (frequency) for each pesticide in the class, summing over all pesticides in the class, and then categorizing as follows. For classes where at least 40% of the study population was exposed (insecticides, herbicides, organophosphates, and organochlorines), we categorized exposed subjects in tertiles with those reporting zero exposure serving as the reference category, resulting in four exposure categories. When less than 40% of subjects were exposed (carbamates and pyrethroids), these were dichotomized at the median and referenced to those reporting no exposure (three categories). When less than 10% of subjects were exposed (fungicides and fumigants), those reporting any exposure were compared to those reporting none (two categories). The same procedure was followed for individual pesticides using intensity-weighted days of use, created as described by Dosemeci et al. using their general algorithm.[15]

Self-reported information on pesticide-related medical attention came from the question, "As a result of using pesticides, how often have you seen a doctor or been hospitalized?" Information on pesticide poisoning events came from the question, "Has a doctor ever told you that you had been diagnosed with pesticide poisoning?" High pesticide exposure events were ascertained by the question, "Have you ever had an incident or experience while using *any* type of *PESTICIDE* which caused you *unusually high* personal exposure?" These responses were dichotomized as ever/never. Data were also available on the time interval between a high pesticide exposure event and washing (less than an hour versus an hour or more), as well as whether the event involved inhalation or ingestion.

Variables for noise, solvent, and metal exposure were created as follows. The noise variable was created by summing the positive responses to questions pertaining to grinding animal feed (yes/no), working in swine areas (yes/no), driving gasoline tractors in summer and winter (<once/month, monthly, weekly, daily), and grinding metal in summer and winter (<once/month, monthly, weekly, daily), and the sum was then dichotomized at the median (median=9.0; range=4–18). The solvent variable was created by summing the positive responses to questions pertaining to using gasoline to clean in summer and winter (<once/month, monthly, weekly, daily), painting in the summer (<once/month, monthly, weekly, daily), being diagnosed with solvent poisoning (yes/no), and being exposed to solvents on a non-farm job (yes/no); the sum was dichotomized at the median (median=4.0; range=3–11). The metals variable was created by summing the positive responses to questions pertaining to non-farm job exposures to lead solder, lead, mercury, cadmium, and other metals (all yes/no);

the sum was dichotomized with a score above zero being "exposed" (91% of subjects had a score of 0; median=0.0; range=0–5). These activities were chosen in creating the noise, solvent, and metals variables because they were associated with hearing loss in this study; other activities were considered for inclusion, but did not add anything to the explanatory ability of the variables.

Age at enrollment was categorized into quartiles, using all subjects: ≤39, 40–48, 49–58, and ≥59, with age ≤39 serving as the reference category; similar results were obtained using a more finely stratified age variable. Among smokers, pack-years of cigarette smoking were categorized into quartiles of 1 to 5, 6 to 15, 16 to 30, and greater than 30; non-smokers were the referent. Drinks of alcohol per month in the year preceding enrollment were categorized into tertiles of 1 to 10, 11 to 30, and greater than 30; nondrinkers and individuals drinking less than one drink per month were the referent. Subjects were asked, "Did you mix or apply herbicides during military operations?" This variable was coded to a "yes/no" response for military application of herbicides and also to an "ever/never" response for military service.

Data on use of five types of personal protective equipment (PPE) were obtained: chemical resistant gloves, face shield or goggles, cartridge respirator or gas mask, disposable outer clothing, and other (boots, apron, waterproof pants). A PPE score was constructed by assigning points for use of each combination of equipment based on theoretical ability to reduce exposure (15Dosemeci et al., 2002). Scores ranged from 0.1 to 1.0; a lower score indicated greater protection (lower exposure). Scores were utilized as independent variables after categorization into tertiles.

Data analysis

Enrollment data were extracted from AHS Phase I data release P1REL0506.01 and follow-up data were from release AHS Phase II data release P2REL0506.03. Analyses were performed using versions 14 and 15 of SPSS (SPSS Inc., Chicago, Illinois) and version 8.2 of SAS (SAS Institute, Inc., Cary, North Carolina). Logistic regression models were constructed using hearing loss (defined above) as the dependent variable. All models included age at enrollment and state (Iowa or North Carolina); models with pesticide variables were additionally adjusted for solvent, noise, and non-farm metal exposures. Education, PPE use, diagnosis of high blood pressure, smoking, head trauma, and alcohol use did not confound the relationship of hearing loss with cumulative pesticide exposure, OP exposure or insecticide exposure (≤2% change in OR estimate), so these factors were not included in final models. State-stratified results did not differ appreciably from those reported here and are therefore not shown. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. P-values (two-sided) for trend for cumulative days of pesticide use were calculated, where applicable, using a continuous variable defined by the midpoints of the levels of the categorical variable.

We used two-stage hierarchical logistic regression to increase precision when evaluating multiple individual pesticides.[16] The first-stage model contained covariates and indicators for specific pesticides. The second-stage model included variables for functional pesticide groups (insecticides, herbicides, fungicides, fumigants) and several chemical groups (organophosphates, organochlorines, carbamates, phenoxyacetates (e.g., 2,4-D), and triazines/triazones (e.g., atrazine)); all groups included at least three pesticides.

We investigated interactions between OP exposure and age, smoking, metal, noise, or solvent exposures, as well as between a diagnosis of pesticide poisoning and metal, noise, or solvent exposures. Interactions were investigated first by stratified analyses followed by creation of interaction variables and subsequent formal testing of the interaction coefficients in logistic models ($p<0.15$ for significance).

RESULTS

Demographic and lifestyle characteristics

The median age among cases was 54 and among controls 45. Overall prevalence of self-reported hearing loss was about 35%, and prevalence increased monotonically with age (Table 2). Controlling for age, applicators from Iowa had ~50% increased odds of hearing loss compared to North Carolina operators (Table 2). Those with less than a college education had approximately 30% increased odds of hearing loss (Table 2). Former or current smokers also had approximately 30% increased odds, although there was a slight trend with increasing numbers of pack-years of smoking (Table 2). The relationship between hearing loss and years of smoking was similar to that for pack-years of smoking (not shown). Alcohol drinkers had modestly elevated odds compared to non-drinkers, but no trend was evident with increasing numbers of drinks per month in the year preceding enrollment (Table 2). Individuals with higher exposures to metals, noise, or solvents had 14–35% increased odds of hearing loss, and those reporting head injuries requiring medical treatment or a medical diagnosis of hypertension had, respectively, 33% and 23% increased odds (Table 2).

General exposure to pesticides

Lifetime days of use of any pesticide were modestly associated with hearing loss (Table 3). Controlling for age, state, and exposures to solvents, metals, and noise, the OR for hearing loss associated with cumulative lifetime days of use of any pesticide was 1.14 in the highest compared to the lowest quartile of exposure (p-value for trend <0.05). Being hospitalized for pesticide-related medical care was more strongly associated with hearing loss (OR=1.81) than simply visiting a physician (OR=1.38), and those who reported ever having had a physician-diagnosed pesticide poisoning had an increased odds of hearing loss (OR = 1.75) compared to those who did not. Experiencing an event involving unusually high pesticide exposure was modestly associated with hearing loss (OR=1.38). Odds of hearing loss did not increase with the time interval between high pesticide exposure event and washing the exposed body part, nor were there differences between events that involved ingestion or inhalation and those that did not (Table 3). Use of personal protective equipment was minimally associated with hearing loss (Table 3), and only weakly correlated with cumulative pesticide exposure (Pearson r=0.002). Stratification by level of protection from PPE did not appreciably alter the association of hearing loss with pesticide, insecticide, or OP exposures.

This study was restricted to white applicators because of the small numbers of minorities available for study (~1.5% of total). Analyses of 234 non-whites (69 cases and 165 controls) showed a negative association between cumulative lifetime days of pesticide exposure (median split; adjusted OR=0.50; 95% CI=0.27–0.93).

Exposure to pesticide classes and specific chemicals

Exposure to insecticides was associated with a modest increase in odds of hearing loss, but there was no evidence of a trend with cumulative exposure. Exposure to herbicides, fungicides, or fumigants was not associated with hearing loss (Table 3). OPs were modestly associated with hearing loss with a 17% increase in odds in the highest quartile of exposure (Table 3). Similar results were obtained when cumulative days of OP use was considered in 10 categories. Carbamates, organochlorines and pyrethroids were not associated with hearing loss (Table 3).

In our hierarchical models with 49 pesticides, ORs were minimally elevated for the herbicides metribuzin (OR=1.10; 95% CI=0.98–1.24), atrazine (OR=1.22; 95% CI=1.07–1.38), and 2,4,5-T (OR=1.10; 95% CI=0.98–1.25); the fungicide ziram (OR=1.24; 95% CI=0.83–1.86); the inorganic fumigant aluminum phosphide (OR=1.20; 95% CI=0.97–1.48); the organochlorine insecticides heptachlor (OR=1.19; 95% CI=1.04–1.36) and DDT (OR=1.10;

95% CI=0.97–1.25); and the organophosphate fonofos (OR=1.11; 95% CI=0.99–1.24). Results were similar when the second stage model included only variables for pesticide functional groups.

Because OPs as a class showed the strongest associations with hearing loss of any insecticide type, we also considered individual OPs in analyses using traditional logistic regression. Table 4 presents results for all intensity-weighted OPs except for trichlorfon, which had only 59 exposed subjects. The associations with hearing loss were elevated (ORs > 1.2 for at least one category of use) for malathion, fonofos, diazinon, phorate, and parathion. Significant trends ($p<0.05$) were noted for diazinon, fonofos, phorate, and terbufos. Analyses of cumulative days of unweighted OP exposure gave similar results. Similar although slightly attenuated and less precise results were obtained from a model including all OPs.

Confounding and effect modification

Several factors associated with hearing loss could potentially have confounded associations with pesticide exposure: cigarette smoking, alcohol use, history of high blood pressure, history of head trauma, and military service. We ran models with either insecticides or OPs controlling for each of these variables separately, as well as for age, state, and solvent, noise, and metal exposures, and found that results pertaining to pesticide exposures changed no more than 2% (not shown). Military service might affect hearing in two ways: through repeated exposures to loud noise or to high intensity noise; or by participation in large-scale herbicide spraying activities among some service personnel, particularly those deployed to Vietnam. Only 79 subjects reported using herbicides in the military, of whom 35 were hearing loss cases; the association of hearing loss with this exposure was modest (adjusted OR=1.18; 95% CI=0.73–1.91). The association with military service per se (yes/no) was weaker (adjusted OR=1.07; 95% CI=0.98–1.18). About 66% of respondents served in the military; when primary analyses of insecticides and OPs were restricted to the 34% with no military experience, results were not qualitatively changed.

We explored interactions of exposure to OPs as a class with smoking, metal, noise, and solvent exposures, as well as interaction of pesticide poisoning with smoking, metal, noise, and solvent exposures. No interaction terms were significant ($p>0.15$). However, stratified analyses showed stronger effects of OPs among smokers who reported more pack-years of smoking compared to nonsmokers (adjusted OR=1.09, 95% CI=0.97–1.23 for ever OP exposure among those with 15 or fewer pack-years of smoking; adjusted OR=1.22, 95% CI=0.89–1.69 among those with 16 to 30 pack-years; and adjusted OR=1.33, 95% CI=0.93–1.92 among those with more than 30 pack-years). Effect modification by age was also explored; no evidence was found for interaction with OP exposure in stratified analyses and no interaction coefficients were statistically significant ($p>0.15$) (not shown).

DISCUSSION

We found a positive association between self-reported hearing loss and several general measures of pesticide exposure, including high pesticide exposure events, pesticide poisoning, and medical treatment for pesticide exposure. Increasing cumulative days of pesticide use were weakly related to increasing odds of hearing loss, with a 14% increase in odds in the highest exposure category. Increased odds of hearing loss was also weakly associated with insecticides and, more specifically, with OPs, with a 17% increase in odds in the highest exposure category for the latter.

Literature on pesticide exposures and hearing loss, in either animals or humans, is sparse. Case reports provide some evidence in humans. Petty[9] reported two OP poisoning cases wherein permanent nerve damage, to the vestibular and cochlear components of the eighth cranial nerve,

was sustained, and Harell et al.[8] reported a case of extreme malathion poisoning after which the patient sustained profound hearing loss lasting approximately six years. Two cross-sectional studies are also available. Ernest et al.[17] studied 34 insecticide manufacturing workers chronically exposed to OPs and found hearing loss in both exposed workers and a control group of 34 workers from areas of the plant unexposed to OPs, but found no association of hearing loss with OP exposure. Teixeira et al.[10] reported relative risks of 7 to 9 among OP- and pyrethroid-exposed insecticide applicators compared to unexposed workers. These are stronger associations than those reported in the present study, but Teixeira et al.[10] assessed hearing loss by audiometry and measuring central nervous system auditory functions, a more sensitive and less error-prone assessment than used in the present study. The authors found no strong evidence of potentiation of pesticide effects with noise.

Major risk factors for hearing loss are age, sex, and noise exposure.[18–20] In particular, hearing loss increases with age among farmers.[21,22] This trend is also evident in our study, with prevalence increasing from 22% to 40% to 52% at ages <45, 45 to 64, and 65 or older. However, we found that the association of pesticide exposure with hearing loss was not modified or confounded by age.

Wilkins et al.[23] found an approximate 50% increase in odds of elevated hearing thresholds with high lifetime years of tractor use, and Hwang et al.[21] reported a monotonic increase in risk with increasing lifetime exposure to noisy farm equipment. We had limited information on lifetime use of noisy farm equipment, including tractors, grinders, animal feeding equipment, power tools, chain saws, etc. We created a noise variable from questions about current use of grinders, tractors, and other farm and non-farm sources of noise. The resulting measure was associated with a 14% increase in hearing loss. Using an indirect measure of noise exposure, which likely results in misclassification, may account for the weakness of this association. The association of hearing loss with pesticide exposure was independent of noise. Some may argue that tractor use is correlated with pesticide application, and that a noise variable based on tractor use is not independent of pesticide exposure. There was, however, little evidence for correlation of cumulative lifetime days of pesticide exposure with the noise exposure score in our study (Pearson r=0.02).

We had no data on firearm use, a major source of noise exposure which likely also contributes to hearing loss. Firearm use has been found in previous studies of farmers to be a significant predictor of elevated hearing thresholds and self-reported hearing loss.[21,24] Although firearm use is fairly common among rural populations,[23] there is little reason to suspect that it is correlated with pesticide exposure. Firearm use may also have contributed to hearing loss among those who had been in the military. Restriction of analyses of insecticides and OPs to the 34% of subjects with no military experience did not qualitatively change results.

Previous studies have suggested that chemical exposures other than pesticides, particularly organic solvents, may increase risk of hearing loss,[4,6,7,25] and others have examined the combined effects of ototoxins and noise.[12,25–28] Chang et al.[28] found a 10-fold increase in risk among toluene-and-noise-exposed workers compared to workers exposed only to noise. Sass-Kortsak et al.[29] found age and noise to be important risk factors for hearing loss, but no effect of styrene. We also found associations of hearing loss with solvent and metal exposures. Since many pesticide formulations include solvents, metals, and other so-called inert ingredients, it is possible that these exposures play a role in the associations between hearing loss and pesticide exposure observed in this study. However, the associations we observed were specific to insecticides, and particularly to OPs. Moreover, the association of hearing loss with pesticide exposure was present after adjustment for solvent and metal exposure, suggesting that the latter do not fully account for the former.

Stratified analyses showed a monotonic increase in odds of hearing loss associated with OP exposures across levels of smoking, suggesting possible interaction. This relationship has not been previously reported and warrants further investigation. Previous studies have documented a relationship between smoking and risk of hearing loss, and suggested an additive effect with occupational noise exposure.[30,31] Animal studies have identified nicotinic receptors in hair cells, suggesting potential for direct ototoxic effects of smoking.[32,33]

In this study, odds of hearing loss was greater among applicators from Iowa than from North Carolina, even after adjustment for age and exposure to noise, solvents, metals, and pesticides. This association persisted after adjustment for behavioral (cigarette and alcohol use) and socio-demographic (education and marital status) factors. It is possible that agricultural practices differ between the states to such an extent that there is a fundamental difference in exposure between the two populations. For example, there may be more intensive use of both pesticides and heavy agricultural equipment in Iowa that was not captured with the survey instruments used in this study.

The limited analysis of non-white applicators found an inverse association of hearing loss with pesticide exposure, in contrast to results for white applicators. This finding provides some justification for maintaining the homogeneity of the present study population by restricting it to white applicators, but deserves further attention. As with differences across states, there may be fundamental differences in agricultural practices across races.

A concern in this study is reliance on self-report to assess hearing loss. Given the stigma associated with hearing loss and the consequent reluctance to admit to it, it is plausible that there is under-reporting of the outcome variable of this study. Gomez et al.[34] evaluated agreement between assessment of hearing loss by questionnaire and audiometry, and found overall agreement ranged from 70% to 80% with sensitivity from 61% to 79% and specificity from 69% to 87%, depending on sound frequency and ear tested. The low sensitivity suggests that under-reporting of hearing loss in our study could be a problem. Nonetheless, it is likely that misclassification of disease status is independent of pesticide exposure, and any resulting bias would likely be toward the null. The fact that known or suspected risk factors for hearing loss were associated with the self-reported outcome provides some reassurance.

Another concern is that cases were prevalent, not recruited into the study upon diagnosis or self-perception of a hearing deficit, and cases who participated in the follow-up interview may be different from those who did not. However, development of a condition like hearing loss is not a discrete event; a deficit may exist for years before definitive diagnosis. Less than two percent of applicators originally enrolled in the study explicitly declined the follow-up interview because of hearing loss. It seems unlikely that individuals with hearing loss and low pesticide exposure were more likely to drop out of the cohort than those with hearing loss and high exposure, creating a spurious association.

Reverse causality is one possible explanation for some of these findings; that is, hearing loss may contribute to an incident that results in excessive exposure to pesticides. Previous studies have shown that hearing deficit can contribute to occupational injury, although most of these studies evaluated traumatic injury.[1–3] In the present study, some of the largest relative odds were associated with high pesticide exposure events and poisoning requiring medical treatment. Nonetheless, hearing loss was also associated with cumulative days of use, that is, with chronic low-dose exposure, which is unlikely to result from hearing loss. Further, the association was specific to OP insecticides, and was not found with other types of pesticides, also suggesting that reverse causality does not account for our findings.

There are a number of strengths to the present study: a large population, the largest extant study of hearing loss among an agricultural population; an internal control group which mitigates

potential confounding; detailed information on pesticide exposure; and information on additional potential causes of hearing loss (e.g., congenital hearing loss, injury/infection). Farmers in the AHS have been shown to provide reliable[35] and plausible[36] data on their use of pesticides. The study benefited, further, by collecting data on reported exposures related to longest held non-farm occupation and lifetime pesticide use. Follow-up of this cohort has been on-going and continues to generate timely, useful data.

In conclusion, we found that self-reported hearing loss among licensed pesticide applicators in Iowa and North Carolina was related to some indicators of pesticide exposure and that these associations could not be explained by more established risk factors. Together with previous studies, these results suggest that exposure to insecticides and, in particular, organophosphates, may contribute to hearing loss. Farmers and other agricultural workers face a multitude of risks from physical and chemical agents; hearing loss may, after the conduct of studies employing more sensitive measurements of both hearing loss and pesticide exposures, be added to the known risks from chemical exposures.

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TABLE 1

Pesticides listed by general class of agent identified in the Agricultural Health Study

Classification	Chemical
herbicides	
chloroacetanilide	alachlor; metolachlor
benzoic acid	dicamba
dinotroaniline	pendimethalin; trifuralin
imidazolinone	imazethapyr
mixture	petroleum oil
organophosphorus	glyphosate
phenoxyacetate	2,4 D; 2,4,5 T; 2,4,5 TP
quaternary ammonium	paraquat
triazinone	metribuzin
thiocarbamate	EPTC; butylate
sulfonyl urea	chlorimuron-ethyl
triazine	atrazine; cyanazine
insecticides	
carbamate	aldicarb; carbaryl; carbofuran
organochlorine	aldrin; chlordane; dieldrin; DDT; heptachlor; lindane; toxaphene
organophosphate	chlorpyrifos; coumaphos; diazinon; DDVP; fonofos; malathion; parathion; phorate; terbufos; trichlorfon
pyrethroid	permethrin
fungicides	
anilide	metalaxyl
aromatic	chlorothalonil
carbamate	benomyl
dithiocarbamate	maneb
phthalimide	captan; ziram
fumigants	
inorganic	aluminum phosphide
inorganic	80/20 mix
inorganic	ethylene dibromide
inorganic	Brom-o-gas

TABLE 2

Demographic and lifestyle, and environmental characteristics of self-reported hearing loss cases and controls among white, male private pesticide applicators enrolled in the Agricultural Health Study, 1993–1997

	Case		Control			
Characteristic	**n**	**%**	**n**	**%**	**OR[1]**	**95% CI**
Age at enrollment						
≤39	668	14	2988	32	1.0	referent
40–48	1082	22	2408	26	2.03	1.82–2.27
49–58	1363	28	2036	22	3.09	2.77–3.44
≥59	1813	36	1871	20	4.61	4.14–5.13
Trend					p<0.0001	
State						
North Carolina	1296	26	3000	32	1.0	referent
Iowa	3630	74	6303	68	1.53	1.41–1.66
Education[1]						
college grad	758	16	2002	22	1.0	referent
some college	1170	24	2266	25	1.36	1.21–1.52
high school grad	2451	51	4253	46	1.28	1.16–1.42
<high school grad	463	9	606	7	1.37	1.18–1.61
missing	84		176			
Smoking status at enrollment[1]						
never	2400	49	5458	59	1.0	referent
former	1950	40	2702	29	1.33	1.23–1.44
current	545	11	1089	12	1.25	1.11–1.40
missing	31		54			
Smoking pack-years at enrollment[1]						
nonsmoker	2400	50	5458	59.9	1.0	referent
0.1–5	712	15	1223	13.4	1.23	1.10–1.37
6–15	704	15	1025	11.3	1.40	1.25–1.56
16–30	492	10	749	8.2	1.27	1.12–1.45
>30	477	10	654	7.2	1.32	1.15–1.51
Trend					p=0.001	
missing	141		194			
Ever use alcohol in year preceding enrollment[1]						
nondrinker	1652	34	3181	35	1.0	
drinker	3143	66	5873	65	1.16	1.07–1.26
missing	131		249			
Alcohol drinks per month in year preceding enrollment[1]						
nondrinker	1652	35	3181	35	1.0	referent
1–10	1986	41	3670	41	1.15	1.05–1.25
11–30	631	13	1250	14	1.14	1.01–1.29
31+	526	11	953	10	1.26	1.11–1.44
missing	131		249			
Trend					p=0.01	
Noise exposure score[2]						
≤8	2195	46	4433	50	1.00	referent
9–14	2531	54	4501	50	1.14	1.05–1.23
Missing	200		369			
Non-farm job metal exposure score[2]						
None	4276	90	8273	92	1.00	referent
1–5	463	10	685	8	1.35	1.18–1.54
Missing	187		345			
Solvent exposure score[2]						
≤4	2578	55	5367	60	1.00	referent

	Case		Control			
Characteristic	**n**	**%**	**n**	**%**	**OR[1]**	**95% CI**
5–11	2130	45	3543	40	1.25	1.16–1.35
Missing	218		393			
Head injury requiring[2] medical attention						
No	3812	78	7504	81	1.00	referent
Yes	1107	22	1797	19	1.33	1.21–1.46
Missing	7		2			
Ever diagnosed with high[2] blood pressure						
No	3357	68	7170	77	1.00	referent
Yes	1568	32	2131	23	1.23	1.13–1.34
Missing	1		2			

[1] All models included age and state

[2] Models additionally included exposure to noise, metals, and solvents where appropriate

TABLE 3

Pesticide exposures and self-reported hearing loss cases and controls identified in the Agricultural Health Study

	Case		Control			
Exposure	**n**	**%**	**n**	**%**	**OR[1]**	**95% CI**
Cumulative lifetime days of pesticide use						
1–64	1048	22	2318	26	1.0	referent
65–200	1038	22	1940	22	1.04	0.93–1.17
201–400	1289	27	2359	26	1.09	0.97–1.22
401–7000	1361	29	2335	26	1.14	1.02–1.28
Missing	190		351			
Trend					p = 0.03	
Pesticide-related medical care						
No	4393	92	8592	94	1.0	referent
Doctor visit	331	7	445	5	1.38	1.17–1.62
Hospitalized	64	1	73	1	1.81	1.25–2.62
Missing	138		193			
Use of personal protective equipment						
Low protection	921	19	1827	20	1.0	referent
Moderate protection	3033	64	5683	63	1.05	0.95–1.17
High protection	799	17	1508	17	1.07	0.94–1.22
Missing	173		285			
High pesticide exposure event						
No	3913	82	7803	86	1.0	referent
Yes	859	18	1278	14	1.38	1.24–1.53
Missing	154		222			
Interval between high exposure event and washing						
No event	3913	83	7803	86	1.0	referent
<60 minutes	468	10	760	8	1.38	1.21–1.58
≥60 minutes	357	7	469	5	1.39	1.19–1.62
Missing	188		271			
High exposure event involving inhalation or ingestion						
No event	3913	82	7803	86	1.0	referent
No inhalation or ingestion	500	11	795	9	1.34	1.17–1.52
Inhalation or ingestion	347	7	456	5	1.47	1.26–1.72
Missing	166		249			
Ever diagnosed with pesticide poisoning						
No	4711	97	9034	98	1.0	referent
Yes	149	3	144	2	1.75	1.36–2.26
Missing	66		125			
Exposure to Insecticides[2]						
None	566	12	1210	13	1.00	referent
2.5 – 51.5	1472	30	2652	29	1.20	1.06–1.37
52 – 175	1423	29	2711	29	1.14	1.004–1.30
> 175	1430	29	2694	29	1.19	1.04–1.35
Trend					p=0.35	
Missing	35		36			
Exposure to Herbicides[2]						
≤50	492	10	908	10	1.00	referent
50.01 – 260.75	1461	30	2795	30	0.98	0.85–1.12
261 – 650.75	1474	30	2774	30	1.03	0.89–1.18
≥651	1466	30	2792	30	1.04	0.91–1.20
Trend					p=0.34	
Missing	33		34			
Exposure to Fungicides[2]						
None	4399	90	8314	90	1.00	referent

	Case		Control			
Exposure	**n**	**%**	**n**	**%**	**OR[1]**	**95% CI**
≥1	483	10	940	10	1.00	0.88–1.13
Missing	44		49			
Exposure to Fumigants[2]						
None	4603	94	8736	94	1.0	referent
≥1	272	6	515	6	1.04	0.88–1.22
Missing	51		52			
Exposure to Organophosphates[2]						
None	734	15	1522	16	1.0	referent
2.5 – 38.75	1392	29	2575	28	1.12	1.00–1.26
39 – 129.5	1371	28	2602	28	1.09	0.97–1.23
> 129.5	1393	28	2568	28	1.17	1.03–1.31
Trend					p=0.08	
Missing	36		36			
Exposure to Carbamates[2]						
None	2972	63	5711	64	1.0	referent
2.5 – 20	929	20	1678	19	1.07	0.97–1.18
> 20	846	17	1587	17	1.06	0.96–1.18
Trend					p=0.38	
Missing	179		327			
Exposure to Organochlorines[2]						
None	1511	54	2905	55	1.0	referent
2.5 – 17.5	440	16	790	15	1.06	0.91–1.22
18.75 – 57.75	404	15	787	15	1.01	0.87–1.16
> 57.75	425	15	778	15	1.08	0.93–1.25
Trend					p=0.37	
Missing	2146		4043			
Exposure to Pyrethroids[2]						
None	3508	74	6689	75	1.0	referent
2.5 – 17.5	595	13	1085	12	1.06	0.94–1.19
> 17.5	611	13	1155	13	1.03	0.92–1.16
Trend					p=0.69	
Missing	212		374			

[1] ORs adjusted for state, age, solvent exposure, noise exposure, and metal exposures

[2] Variable based on reported non-intensity-adjusted cumulative lifetime days of use

TABLE 4

Ever use of specific organophosphates[1] by self-reported hearing loss cases and controls identified in the Agricultural Health Study

	Case		Control			
Exposure	**n**	**%**	**n**	**%**	**OR[2]**	**95% CI**
Cumulative lifetime days of chlorpyrifos use						
None	2533	55	4927	57	1.0	referent
1–63	677	15	1270	15	1.08	0.96–1.21
64–235	679	15	1230	14	1.13	1.01–1.27
>235	672	15	1243	14	1.15	1.02–1.29
Trend					p=0.07	
Missing	365		633			
Cumulative lifetime days of coumaphos use						
None	4035	90	7743	91	1.0	referent
Any	466	10	805	9	1.07	0.94–1.22
Missing	425		755			
Cumulative lifetime days of DDVP use						
None	3933	86	7646	88	1.0	referent
1–202	319	7	507	6	1.08	0.91–1.25
>202	333	7	493	6	1.16	1.00–1.36
Trend					p=0.06	
Missing	341		657			
Cumulative lifetime days of diazinon use						
None	3646	77	7186	80	1.0	referent
0.5–54.6	372	8	619	7	1.23	1.06–1.42
55–161.8	344	7	574	6	1.13	0.97–1.32
>161.8	364	8	590	7	1.25	1.07–1.46
Trend					p=0.01	
Missing	200		334			
Cumulative lifetime days of fonofos use						
None	3370	73	6831	78	1.0	referent
1–68.25	375	8	658	8	1.02	0.88–1.18
68.26–242.83	431	9	601	7	1.30	1.13–1.50
>242.83	423	9	612	7	1.19	1.03–1.37
Trend					p=0.04	
Missing	327		601			
Cumulative lifetime days of malathion use						
None	1423	30	3258	37	1.00	referent
0.88–57.75	1027	22	1992	22	1.09	0.98–1.21
58–212	1116	24	1825	20	1.32	1.18–1.46
>212	1128	24	1851	21	1.20	1.08–1.34
Trend					p=0.09	
Missing	232		377			
Cumulative lifetime days of parathion use						
None	4306	91	8328	93	1.00	referent
Any	417	9	636	7	1.21	1.04–1.40
Missing	203		339			
Cumulative lifetime days of phorate use						
None	2998	63	6444	72	1.00	referent
1.5–54.6	609	13	847	9	1.21	1.06–1.37
54.83–176.4	539	11	874	10	1.10	0.96–1.24
>176.4	593	13	834	9	1.25	1.10–1.41
Trend					p=0.004	
Missing	187		304			
Cumulative lifetime days of terbufos use						
None	2647	58	5255	61	1.00	referent

	Case		Control			
Exposure	**n**	**%**	**n**	**%**	**OR[2]**	**95% CI**
1.25–91	626	14	1168	13	0.96	0.86–1.09
91.2–348.1	630	14	1155	13	1.00	0.89–1.13
>348.1	674	14	1115	13	1.17	1.04–1.31
Trend					p=0.01	
Missing	349		610			

[1] Based on intensity-weighted cumulative days of use

[2] ORs adjusted for state, age, solvent exposure, noise exposure, and metal exposures