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Occupational pesticide use and self-reported olfactory impairment in United States farmers

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Abstract

Objectives: Pesticide exposure may impair human olfaction, but empirical evidence is limited. We examined associations between occupational use of 50 specific pesticides and olfactory impairment, both self-reported, among 20,409 participants in the Agricultural Health Study, a prospective cohort of pesticide applicators (mostly farmers, 97% male).

Methods: We used logistic regression models to estimate odds ratio (OR) and 95% confidence intervals (CI) for associations between pesticide use at enrollment (1993-1997) and olfactory impairment reported two decades later (2013-2016), adjusting for baseline covariates.

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CONTRIBUTORS

SS, HC and DPS conceptualized this analysis. SS led the data analysis and prepared the first draft of the manuscript which was overseen by HC and DPS. DMU provided statistical help. LEBF and DPS were involved in data acquisition and study management. All the authors were involved in data interpretation, reviewing and editing the manuscript, and providing final manuscript approval. All contributors meet the criteria for authorship. HC and DPS contributed equally to this manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare they have no actual or potential competing financial interests.

DATA SHARING STATEMENT

Requests for data, including the data used in this manuscript, are welcome as described on the Study Website (https://www.aghealth.nih.gov/collaboration/process.html). Data requests may be made directly at www.aghealthstars.com; registration is required. The Agricultural Health Study is an ongoing prospective study. The data sharing policy was developed to protect the privacy of study participants and is consistent with study informed consent documents as approved by the NIH Institutional Review Board. Dr. Dale Sandler is the NIEHS Principal Investigator of the Agricultural Health Study and is responsible for ensuring participant safety and privacy.

Results: About 10% of participants reported olfactory impairment. The overall cumulative days of any pesticide use at enrollment was associated with a higher odds of reporting olfactory impairment [OR (highest vs. lowest quartile): 1.17 (95% CI: 1.02-1.34), p-trend=0.003]. In the analyses of 50 specific pesticides, ever-use of 20 pesticides showed modest associations with olfactory impairment, with ORs ranging from 1.11 to 1.33. Of these, higher lifetime days of use of 12 pesticides were associated with higher odds of olfactory impairment as compared to never use (p-trend ≤0.05), including two organochlorine insecticides (DDT and lindane), two organophosphate insecticides (diazinon and malathion), permethrin, the fungicide captan, and six herbicides (glyphosate, petroleum distillates, 2,4-D, 2,4,5-T, and metribuzin), although many of these did not exhibit clear, monotonic exposure-response patterns.

Conclusions: Overall, we found relatively broad associations between pesticides and olfactory impairment, involving many individual pesticides and covering several chemical classes, suggesting that pesticides could affect olfaction through multiple pathways. Future epidemiological studies with objective measurement of olfaction are required to confirm these findings.

Keywords

Pesticides; Olfaction; Farmers; Agricultural Health Study

INTRODUCTION

Olfactory impairment is common among older adults, affecting about 25% of those 50 years or older and over 60% of those older than 80 years.[1,2] Olfactory deficit may negatively impact human functioning such as safety, diet and nutrition, and overall quality of life,[3] and has been associated with increased mortality in older adults.[4,5] Olfactory impairment is likely an early manifestation of neurodegenerative conditions including Parkinson's and Alzheimer's diseases[6,7] and thus may be critical to understanding the process of early neurodegeneration. Although research on modifiable risk factors for olfactory impairment among older adults could have major public health significance, empirical data are limited.

Exposure to pesticides can occur through occupational or residential use, or indirectly from air drifts, food, and water or soil contamination. Although poorly studied, pesticide exposures may jeopardize human sense of smell through several mechanisms.[8] Direct contact with inhaled pesticides may damage peripheral olfactory epithelium through acute or chronic inflammation. Further, inhaled or ingested pesticides may exert neurotoxic effects on the central nervous system including central olfactory pathways through several mechanisms, leading to olfactory deficit.[8-10] Prior evidence linking certain pesticides or their functional classes (for example, organochlorine insecticides dichlorodiphenyltrichloroethane (DDT) and dieldrin, organophosphate insecticides, and herbicide paraquat) with neurocognitive dysfunction and Parkinson's and Alzheimer's diseases provides indirect support for the pesticide-olfactory impairment hypothesis.[11-14] Several toxicological studies have also shown olfactory impairment in animals exposed to certain pesticides (including organophosphate insecticide malathion and herbicide paraquat).[15-17] An investigation in the Agricultural Health Study (AHS) reported the first evidence that unusually high pesticide exposure events are associated with higher odds of reporting a

poor sense of smell.[18] Here we evaluated possible associations between chronic occupational exposures to specific pesticides and self-reported olfactory impairment in the same population.

METHODS

Study population

In 1993-1997, 52,394 private pesticide applicators (97.4% male, mainly farmers) enrolled in the AHS by completing an enrollment questionnaire at local pesticide licensing locations [19]. Participants were also asked to complete an additional take-home questionnaire, which was returned by 44% (n=22,916) of the enrollees. Those who returned the take-home questionnaire were largely similar,[20] but more likely to be older, from Iowa, and former or never smokers than those who did not (Supplementary Table 1). Participants were also asked to report pesticide application practices, other farm exposures, socio-demographics, lifestyle, and medical history. Follow-up interviews were conducted in 1999-2003, 2005-2010, and 2013-2016 to update information on farm exposures and medical history. Participants were asked about olfactory impairment at the third follow-up in 2013-2016, which was completed by 24,145 applicators. All study questionnaires can be found at https://aghealth.nih.gov/collaboration/questionnaires.html. All applicable institutional review boards approved the study.

Self-reported pesticide use

Pesticide exposure at enrollment—The enrollment questionnaire asked about general pesticide use including days and years participants personally mixed or applied pesticides. The questionnaire also sought information on ever-use of 50 specific pesticides and duration and frequency of use for 22 of them. The take-home questionnaire further asked participants to provide duration and frequency of use for the remaining 28 pesticides. These questionnaires also asked for detailed information on pesticide use practices including application methods, mixing processes, personal protective equipment use, and other workplace hygiene factors.

Our primary analyses focused on pesticides reported at enrollment, and we used two exposure metrics: ever-use and exposure-intensity weighted life-time days of use (IWLD) as measures of cumulative exposure to pesticides. The IWLD was estimated as the product of years of use and days used per year weighted by exposure intensity and then grouped into four categories: never use (referent category) and tertiles of days use among users. Exposure intensity was derived using an algorithm that incorporated information on mixing practices, application methods, repair of pesticide application equipment, and personal protective equipment use. Details on its development are described elsewhere.[21]

Pesticide exposure at the first follow up—We also considered cumulative pesticide use (i.e., IWLD) through the first follow-up in our secondary analyses. At the first follow-up, applicators were asked to provide the names and number of days of use for each pesticide that they used in the year before the interview or, for pesticides that they no longer used, in the most recent year of use. Participants also provided information on pesticide

application practices. To estimate cumulative exposure through the first follow-up, we assumed that pesticide usage reported in the most recent year represented pesticide use during the period since enrollment.

Self-reported olfactory impairment

In the third follow-up (2013-2016), participants were asked “do you suffer from a loss of sense of smell or significantly decreased sense of smell?” Positive response to the question was considered ‘olfactory impairment’. Participants were also asked “when did you start losing your sense of smell?” with four response choices: ≤ 1, 1-5, 5-10, and > 10 years prior to the third follow-up.

Statistical analysis

Of the 24,145 who completed the third follow up questionnaire, we excluded 2,549 participants with proxy-provided responses, 402 missing information on olfaction, and 785 with missing data on baseline covariates that were selected for confounding adjustment. For ever-use analyses and for the IWLD analyses for the 22 pesticides for which frequency and duration of use were asked in the enrollment questionnaire, our overall analytical sample included 20,409 applicators. In the IWLD analyses for the 28 pesticides for which frequency and duration of use were asked only in the take-home questionnaire, our overall analytic sample size was 11,847. Sample sizes for individual pesticide analyses differed due to missing data on specific pesticides.

We used logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between pesticide use at enrollment and olfactory impairment reported about 19 years later (on average, range: 16 to 22 years) in the third follow-up, adjusting for baseline age (continuous linear function), sex, state of residence, education, smoking status, and other farming tasks (including repairing engines, replacing asbestos brake linings, handling stored grain, working in swine confinement areas, welding, and painting). These common farming activities may result in exposures to airborne irritants (e.g., dusts, fumes, solvents, and metals) which may in turn damage olfaction.[8] For age at enrollment, we further explored other functional forms including quadratic terms, restricted quadratic splines, and age categories and got similar results. We therefore adjusted age as a continuous linear variable throughout the analyses. We also adjusted for ever-use of specific pesticides that were correlated with the pesticide of interest (with Spearman correlation coefficient ≥ 0.40). In the IWLD analyses, we estimated P for trend using the median value for each exposure category as a continuous variable in regression models. For all the analyses, exposures were modeled as a fixed variable (not time varying) in relation to the outcome.

To examine the robustness of our results, we conducted six sensitivity analyses. First, we conducted analyses using two other exposure metrics – lifetime days of use (not weighted by exposure intensity) and average days per year of use. Second, we performed analysis excluding individuals who reported a history of head injury or were missing data on head injury among those who returned the take-home questionnaire (n=10,162). Third, we excluded participants who self-reported Parkinson’s disease in any AHS surveys because

olfactory impairment is one of the most common prodromal symptoms of Parkinson's disease (n=20,184) [6,22]. Fourth, we restricted to participants who reported olfactory impairment with onset reported ≤ 10 years before the third follow-up to reduce the possibility of reverse causality (n=19,563). Fifth, we examined associations between IWLD of pesticides through the first follow-up and olfactory impairment with onset reported ≤ 10 years before the third follow-up to account for more proximal exposures (n=19,563); for this analysis as well, IWLD was modelled as a fixed variable (not time varying). Because some participants did not participate in the first follow-up survey, in this analysis, we used multiple imputation to estimate cumulative exposure for those who did not complete the first follow-up (16%). Details on imputation are described elsewhere.[23] Lastly, as only about 40% of the enrollees completed the third follow-up survey, we applied inverse probability of censoring weights to see if selective attrition of the cohort over time biased our results.[24] We performed statistical analyses using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Statistical significance was determined using two-sided tests with α of 0.05.

RESULTS

The average age at enrollment was 46 years (standard deviation: 11 years; range: 15-87); 97% were male and 98% white. About 10% reported olfactory impairment (n=2,069) about two decades later at the third follow-up. Of these, 1,223 reported the loss ≤ 10 years before the third follow-up, 617 reported loss > 10 years before, and 229 did not respond to the question on time of onset. Older participants, those from Iowa, current smokers, and those involved in activities including repairing engines, replacing asbestos brake linings, and welding more likely to report olfactory impairment (Table 1). Further, participants with head injury at baseline and those who reported having Parkinson's disease in any AHS survey were more likely to report olfactory impairment.

In the analysis of lifetime days of use of any pesticides, compared with the lowest usage quartile, the OR for the highest quartile was 1.17 (95% CI: 1.02, 1.34, P for trend=0.003, Table 2). In the ever-use analyses, 20 of the 50 specific pesticides examined were significantly associated with olfactory impairment, including four organochlorines (dieldrin, DDT, toxaphene, and lindane), two carbamates (carbaryl and carbofuran), four organophosphates (chlorpyrifos, dichlorvos, malathion, and parathion), permethrin (both on animal and crop use), the fumigant carbon tetrachloride/carbon disulfide 80/20 mix, two fungicides (captan and metalaxyl), and six herbicides (dicamba, glyphosate, paraquat, petroleum distillates, 2,4-dichlorophenoxyacetic acid (2,4-D), and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)); ORs were mostly modest, ranging from 1.11 to 1.33 (Table 2). Although not statistically significant, several other pesticides had ORs of similar or higher magnitude (for example, coumaphos and chlorothalonil, Table 2). The results were generally similar when we excluded those with head injury among those who returned take-home questionnaire (Supplementary Table 2) or excluded self-reported Parkinson's disease (Supplementary Table 3). When we restricted analyses to participants who reported olfactory impairment with onset ≤ 10 years before the third follow-up, results were generally similar, although associations for a few pesticides were no longer significant (for example, toxaphene and lindane); results for other pesticides became stronger (for example, DDT and fumigant carbon tetrachloride/carbon disulfide 80/20 mix) (Table 2).

In the IWLD analyses (Table 3), we found statistically significant trends (P for trend ≤ 0.05) for two organochlorine insecticides (DDT and lindane), two organophosphate insecticides (diazinon and malathion), permethrin use on crops, the fungicide captan, and six herbicides (glyphosate, metolachlor, petroleum distillates, 2,4-D, 2,4,5-T, and metribuzin). Although ORs were generally elevated for higher exposure categories as compared to never use, for some of these, OR estimates did not show a clear, monotonic exposure-response pattern. For metolachlor, the trend was inverse. Results were generally similar when we excluded self-reported Parkinson's disease cases from the analysis (Supplementary Table 4).

The results were similar when we used unweighted lifetime days of pesticide use (Supplementary Table 5). However, in the analysis that examined average days per year of use, we noted that associations were much stronger for those who reported more frequent days per year and that dose-response was more apparent than for other lifetime measures for organochlorine insecticides toxaphene [OR: 2.31 (95% CI: 1.26, 4.25)] and lindane [OR: 3.07 (95% CI: 1.76, 5.35)], fungicide metalaxyl [OR: 1.74 (95% CI: 1.11, 2.73)], and herbicides paraquat [OR: 2.06 (95%CI: 1.13, 3.75)] (Supplementary Table 6).

When we restricted analyses to participants who reported olfactory impairment with onset reported ≤ 10 years before the third follow-up (Table 3), overall results were similar but the P for trend for a few pesticides were no longer statistically significant; these results were similar to those examining IWLD of pesticides through the first follow-up in relation to olfactory impairment with onset reported ≤ 10 years before the third follow-up (Supplementary Table 7). In the analysis that examined ever-use of pesticides in relation to olfactory impairment using inverse probability of censoring weights, the results were generally similar (Supplementary Table 8).

DISCUSSION

In this large epidemiologic study of United States farmers, we found that occupational use of pesticides was associated with higher odds of reporting olfactory impairment. The association seems to be relatively broad, not limited to just a few pesticides and involving several chemical classes. The results were consistent across several sensitivity analyses. Overall, our data offer novel empirical evidence supporting the notion that occupational exposures to pesticides may harm human sense of smell.

Few epidemiological studies have explored the association between pesticides and poor olfaction in humans. There have been case reports of anosmia in individuals reporting exposure to unusually high levels of pesticides.[25,26] Other studies have examined farming in relation to olfaction, but findings are inconsistent.[27-29] For example, a study of olfaction among pesticide-exposed Latino farmworkers compared with non-farm workers (primarily construction or production workers) from North Carolina found no difference in performance in odor identification between the two groups, but found that farmworkers performed poorly as compared with non-farmers in an olfactory threshold test.[29] This difference in olfactory threshold between the groups persisted over a 2-year follow-up period.[28] In contrast, another study conducted among attendants of an agricultural trade show in Nebraska found no association between farming and olfactory function.[27]

In a prior analysis of AHS farmers, a history of unusually high pesticide exposure events was associated with elevated olfactory impairment, and the association was stronger if there was a longer delay in cleaning with soap and water.[18] These associations were statistically significant for the organochlorine insecticides DDT and lindane and the herbicides alachlor, metolachlor, 2,4-D, and pendimethalin. Notably, our current investigation also found similar associations for occupational use of organochlorine insecticides DDT and lindane for both ever-use and IWLD analyses, and for the herbicide 2,4-D among the highest users compared to never users. To our knowledge, no epidemiologic studies have found specific pesticides to be associated with olfactory impairment. However, Bello and Dumancas[30] reported an association for urinary levels of 2,4-dichlorophenol (a precursor and environmental degradate of 2,4-D and other chlorophenols) and olfactory impairment among participants aged ≥ 40 years in a cross-sectional analysis of the 2013-2014 National Health and Nutrition Examination Survey data.

Our study is the first epidemiological study to comprehensively examine occupational use of pesticides and olfactory impairment among farmers. We found modest associations with several pesticides. These observations are biologically plausible as pesticides may cause olfactory impairment via both peripheral and central nervous systems.[8,10] Inhaled pesticides may damage the olfactory epithelium and olfactory receptor neurons by inducing oxidative stress, acute or chronic inflammation, and pathophysiological changes (for example, hyperplasia and metaplasia). Pesticides that find their way to the brain via olfactory structures, by bypassing the blood brain barrier, or via ingestion may affect olfaction-associated central nervous system processes and neurotransmitter systems resulting in diminished olfactory abilities. Further, pesticides that enter through the olfactory structures or the digestive tract may initiate synucleinopathy in the olfactory bulb and the gut, which may later spread to brain, as posited by the Braak hypothesis.[9] Over time, these peripheral and central mechanisms may individually or synergistically contribute to age-related olfactory impairment and neurodegeneration.

Pesticides have also been shown to alter olfactory function in animals including honeybees, fish, and rodents.[15-17] For example, intraperitoneal administration of paraquat in rats has been shown to impair olfactory discrimination ability.[15] Similarly, exposures to the organophosphate insecticides diazinon[31] and malathion[32] and herbicide glyphosate[16] have been shown to alter olfactory responses in salmonids. The pesticides diazinon, malathion, and glyphosate, either ever-use or IWLD, were also linked with olfactory deficits in our current analysis. Some of these pesticides associated with olfactory impairment were also associated with Parkinson’s and Alzheimer’s diseases and poor cognitive function in prior studies.[11,12,14] For example, the organophosphate insecticides diazinon, malathion, and parathion,[33] the fungicide captan,[34] the herbicides paraquat,[12] 2,4-D,[35] and 2,4,5-T[36] have been associated with PD. Likewise, higher serum levels of DDT were associated with increased risk for Alzheimer’s disease.[14] While our study limits us from making causal inferences about pesticides’ roles in the development of olfactory impairment and their relevance to prodromal neurodegeneration, current findings may provide clues for future investigations.

The 10% prevalence of self-reported olfactory impairment in the current study is similar to the prevalence observed in other studies.[1,2,37] However, self-reported olfactory impairment is subject to error. Self-reported olfactory impairment has low sensitivity (ranging from < 20% to > 60%) but good specificity (ranging 80% to > 90%) compared to objective smell identification tests that are often the choice for use in epidemiologic studies.[1,2,37] Self-reported olfactory impairment relies on one's ability to notice potential impairment and cannot differentiate various modalities of the impairment (for example, identification vs. threshold or discrimination). Further, we asked about olfactory impairment once about twenty years after study enrollment, and we used predefined categories to capture age at onset. Future epidemiological studies need to confirm our findings with objectively evaluated olfactory impairment and to assess whether pesticide exposures impact various domains of olfaction.

We considered a range of covariates and co-exposures as potential confounders in our analysis; still, some of the observed associations could be explained by inadequate control of confounding. For example, the AHS did not collect information on conditions such as chronic sinonasal disease that may affect both olfaction and pesticide use, and information on head injury and a history of high pesticide exposure events was available only for the subset that returned the take-home questionnaire. Additionally, we did not consider other environmental exposures in our analysis that may have confounded our results.

Information on specific pesticides was also based on self-reports. However, self-reports can capture lifetime exposures better than biomarkers that only represent a snapshot of pesticide use given the short half-lives of *most* pesticides. AHS pesticide applicators have been shown to provide reliable and plausible information on specific pesticide uses. For example, in a subsample of 4088 AHS participants in Iowa who completed the same questionnaire 1 year after their enrollment, the agreement for ever/never use of specific pesticides and application practices ranged from 70% to > 90%; although somewhat lower agreement, ranging from 50 to 71%, was found for duration, frequency, and decade first applied for the specific pesticides.[38] Further, in a comparison of AHS participant's responses on the decade of first use and duration of use for specific pesticides to the year the pesticides were first registered for use in the US, <7% reported first use before pesticide registration date and < 5% participants overestimated their duration of use.[39]

We restricted our analysis to those who completed the third follow up when we first asked about olfactory deficit. Selective attrition that may have resulted from pesticide exposure or factors associated with olfactory dysfunction may have biased our results. We did not observe any influence on effect estimates when we corrected for potential selection bias using inverse probability of censoring weights, and a prior AHS study also suggested no evidence of bias when exposure and outcome are not strongly associated with participation (as likely in our current investigation).[40] However, we cannot rule out potential selection bias. In addition, we made multiple comparisons and some findings could be due to chance.

Further, our results may not be generalizable to populations with relatively lower levels of pesticide exposure or to seasonal or other farmworkers who are more racially and socioeconomically diverse than our study participants. Lastly, the current study focused on

pesticides that were commonly used at the time of enrollment or in the past and did not account for pesticide exposure changes since the first follow up. Future studies on pesticides and olfaction should focus on newer pesticides as well as changes in pesticide exposures resulting from the regulatory and usage pattern changes.

Despite the limitations, ours is the first study that has comprehensively evaluated exposures to overall and specific pesticides in relation to olfactory function among older adults. Notably, we asked about sense of smell nineteen years after exposure assessment, and thus the results could not be readily explained by reverse causation. Further, we analyzed both overall and specific pesticide use in relation to olfactory impairment among farmers who have been shown to provide reliable and valid information on pesticide exposures.[38,39] Future studies need to confirm our findings with objectively assessed sense of smell.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGES

What is already known about this subject?

- Pesticide exposure may impair olfaction, but empirical evidence is very limited.
- We know of only one epidemiologic investigation linking specific pesticides with olfactory impairment. That study, conducted within the Agricultural Health Study (AHS), found that unusually high pesticide exposure events are associated with higher odds of reporting a poor sense of smell, but it did not focus on long-term use of pesticides.
- Olfactory impairment increases with age, is common in patients with neurodegenerative diseases, and could be an early sign of future neurodegenerative disease.

What are the new findings?

- We report the first evidence of associations between chronic occupational exposure to many individual pesticides (covering several chemical classes) and olfactory impairment reported many years after exposure.

How might this impact on policy or clinical practice in the foreseeable future?

- Because they represent the earliest evidence for associations between occupational uses of specific pesticides and self-reported olfactory impairment, these findings warrant confirmation in studies with objectively assessed sense of smell.

Table 1.

Characteristics of participants at enrollment in the Agricultural Health Study (n=20,409), Iowa and North Carolina

Characteristics	No OI, n (%) (n=18340)	OI, n (%) (n=2069)
Age (years)[a]		
≤45	9220 (50.3)	812 (39.2)
>45-55	5098 (27.8)	584 (28.2)
>55-65	3332 (18.2)	520 (25.1)
>65	690 (3.8)	153 (7.4)
Sex		
Female	528 (2.9)	48 (2.3)
Male	17812 (97.1)	2021 (97.7)
Race[b]		
Other	291 (1.6)	25 (1.2)
White	18033 (98.4)	2042 (98.8)
State[a]		
Iowa	12765 (69.6)	1500 (72.5)
North Carolina	5575 (30.4)	569 (27.5)
Marital status[a,c]		
Never married	1636 (8.9)	129 (6.2)
Married/Living as married	15911 (86.9)	1845 (89.3)
Divorced/Widowed	773 (4.2)	93 (4.5)
Education		
≤ High school	9591 (52.3)	1057 (51.1)
1-3 year beyond high school	4820 (26.3)	584 (28.2)
≥ College graduate	3929 (21.4)	428 (20.7)
Smoking status[a]		
Never	10496 (57.2)	1037 (50.1)
Former	5666 (30.9)	726 (35.1)
Current	2178 (11.9)	306 (14.8)
Chewing tobacco use		
No	15825 (86.3)	1790 (86.5)
Yes	2515 (13.7)	279 (13.5)
Snuff use		
No	17534 (95.6)	1977 (95.6)
Yes	806 (4.4)	92 (4.4)
Alcohol intake (past 12 months)[d]		
No	5720 (32.1)	619 (30.9)
Yes	12081 (67.9)	1386 (69.1)

Characteristics	No OI, n (%) (n=18340)	OI, n (%) (n=2069)
Ever diagnosed with head injury[a,e,f]		
No	9114 (87.3)	1048 (83.6)
Yes	1325 (12.7)	205 (16.4)
Repair engines[a]		
No	10264 (56)	1103 (53.3)
Yes	8076 (44)	966 (46.7)
Replace asbestos brake linings[a]		
No	15402 (84)	1676 (81)
Yes	2938 (16)	393 (19)
Handle stored grain		
No	4823 (26.3)	524 (25.3)
Yes	13517 (73.7)	1545 (74.7)
Work in swine confinement areas		
No	12736 (69.4)	1431 (69.2)
Yes	5604 (30.6)	638 (30.8)
Weld		
No	5144 (28)	539 (26.1)
Yes	13196 (72)	1530 (73.9)
Paint		
No	5144 (28)	569 (27.5)
Yes	13196 (72)	1500 (72.5)
Parkinson's disease[a,g,h]		
No	18237 (99.6)	1947 (94.8)
Yes	70 (0.4)	106 (5.2)

Abbreviations: OI, Olfactory impairment

[a] p-value from Chi-square tests ≤ 0.05

[b] Race missing: n=18

[c] Marital status missing n=22

[d] Alcohol intake missing: n=603

[e] Head injury missing: n=8717

[f] Information on these variables was asked only in the take-home survey (completed by 44% of the enrollees)

[g] Parkinson's disease missing n=49

[h] All characteristics except for Parkinson's disease were asked at enrollment; self-reported Parkinson's disease at enrollment or at any follow-up to the third.

Table 2.

General pesticide use and ever-use of pesticide at enrollment in relation to self-reported olfactory impairment reported in the third follow-up in the Agricultural Health Study (n=20,409), Iowa and North Carolina

	Any OI[a] (n=20,409)			Time-Restricted OI[b] (n=19,563)	
Pesticides	**No OI n (%) (n=18340)**	**OI n (%) (n=2069)**	**OR (95% CI)**	**OI n (%) (n=1223)**	**OR (95% CI)**
Overall pesticide					
lifetime days					
0-64	4867 (26.5)	499 (24.1)	Ref	302 (24.7)	Ref
>64-225	6042 (32.9)	607 (29.4)	0.93 (0.82, 1.06)	353 (28.9)	0.92 (0.79, 1.09)
>225-458	3959 (21.6)	461 (22.3)	1.04 (0.91, 1.19)	253 (20.7)	0.96 (0.80, 1.14)
>458	3469 (18.9)	501 (24.2)	1.17 (1.02, 1.34)	314 (25.7)	1.18 (1.00, 1.40)
Insecticide	17260 (94.1)	1989 (96.2)	1.37 (1.08, 1.74)	1172 (95.9)	1.31 (0.97, 1.76)
Organochlorine	9720 (54.5)	1330 (65.7)	1.26 (1.13, 1.41)	788 (66.2)	1.20 (1.05, 1.38)
Aldrin	3251 (19.4)	517 (27.6)	1.04 (0.90, 1.20)	314 (28.6)	1.06 (0.88, 1.27)
Chlordane	4492 (26.4)	657 (34.1)	1.10 (0.98, 1.24)	398 (35.0)	1.07 (0.93, 1.24)
Dieldrin	1161 (6.9)	217 (11.5)	1.19 (1.00, 1.43)	123 (11.2)	1.06 (0.85, 1.34)
DDT	3951 (23.4)	666 (34.8)	1.27 (1.11, 1.44)	425 (37.7)	1.33 (1.13, 1.56)
Heptachlor	2817 (16.8)	454 (24.1)	1.09 (0.94, 1.26)	278 (25.2)	1.16 (0.96, 1.40)
Toxaphene	2412 (14.2)	367 (19.2)	1.20 (1.06, 1.37)	213 (18.9)	1.12 (0.95, 1.32)
Lindane	3663 (21.5)	521 (26.9)	1.19 (1.06, 1.33)	289 (25.3)	1.10 (0.95, 1.27)
Carbamate	12244 (68.0)	1537 (75.4)	1.38 (1.23, 1.54)	923 (76.7)	1.41 (1.22, 1.63)
Aldicarb	1694 (10.1)	171 (9.0)	0.93 (0.77, 1.12)	115 (10.3)	1.05 (0.83, 1.32)
Carbaryl	9611 (56.5)	1204 (62.5)	1.21 (1.09, 1.36)	717 (63.6)	1.21 (1.05, 1.40)
Carbofuran	4976 (29.1)	672 (34.5)	1.16 (1.04, 1.28)	397 (34.5)	1.13 (1.00, 1.29)
Organophosphate	16507 (90.0)	1934 (93.6)	1.45 (1.20, 1.75)	1135 (93.0)	1.37 (1.08, 1.73)
Chlorpyrifos	7884 (43.3)	963 (46.8)	1.15 (1.04, 1.26)	568 (46.7)	1.15 (1.02, 1.30)
Coumaphos	1634 (9.7)	222 (11.6)	1.15 (0.99, 1.34)	125 (11.0)	1.09 (0.89, 1.32)
Diazinon	5648 (33.2)	720 (37.4)	1.07 (0.96, 1.19)	428 (37.9)	1.05 (0.92, 1.21)
Dichlorvos	2123 (12.4)	309 (15.9)	1.22 (1.07, 1.40)	175 (15.2)	1.20 (1.01, 1.42)
Fonofos	4057 (23.6)	497 (25.4)	0.99 (0.89, 1.11)	286 (24.7)	0.99 (0.86, 1.15)
Malathion	12742 (72.8)	1579 (79.1)	1.29 (1.15, 1.45)	928 (78.7)	1.26 (1.09, 1.47)
Parathion	2554 (15.1)	363 (18.9)	1.21 (1.07, 1.38)	221 (19.6)	1.19 (1.01, 1.40)
Phorate	6001 (35.2)	741 (38.4)	1.01 (0.91, 1.12)	433 (38.1)	1.01 (0.89, 1.16)
Terbufos	7105 (41.2)	864 (44.0)	1.07 (0.97, 1.18)	503 (43.5)	1.09 (0.96, 1.23)
Trichlorfon	104 (0.6)	16 (0.8)	1.31 (0.77, 2.24)	8 (0.7)	1.03 (0.50, 2.13)
Permethrin (crops)	2327 (13.7)	303 (15.7)	1.23 (1.07, 1.40)	177 (15.5)	1.23 (1.04, 1.45)
Permethrin (animals)	2638 (15.3)	342 (17.5)	1.21 (1.06, 1.38)	202 (17.5)	1.30 (1.10, 1.53)
Fumigant	4197 (22.9)	531 (25.7)	1.15 (1.02, 1.29)	336 (27.5)	1.18 (1.03, 1.37)
CCl_4/CS_2	955 (5.6)	171 (8.9)	1.28 (1.07, 1.53)	111 (9.8)	1.40 (1.13, 1.73)
Aluminum phosphide	913 (5.4)	112 (5.8)	1.06 (0.86, 1.30)	71 (6.3)	1.16 (0.90, 1.49)
Ethylene dibromide	619 (3.6)	66 (3.4)	0.86 (0.66, 1.12)	43 (3.8)	0.91 (0.66, 1.26)

Pesticides	Any OI[a] (n=20,409)			Time-Restricted OI[b] (n=19,563)	
	No OI n (%) (n=18340)	OI n (%) (n=2069)	OR (95% CI)	OI n (%) (n=1223)	OR (95% CI)
Methyl bromide	2395 (14.0)	258 (13.4)	0.98 (0.82, 1.17)	162 (14.3)	0.94 (0.75, 1.17)
Fungicide	6529 (35.6)	767 (37.1)	1.14 (1.03, 1.27)	469 (38.4)	1.15 (1.00, 1.31)
Benomyl	1513 (9.1)	176 (9.4)	1.00 (0.80, 1.24)	107 (9.7)	0.93 (0.71, 1.22)
Captan	2087 (12.3)	288 (14.9)	1.21 (1.06, 1.39)	170 (14.8)	1.22 (1.03, 1.45)
Chlorothalonil	1153 (6.8)	142 (7.4)	1.23 (0.99, 1.52)	91 (8.0)	1.27 (0.98, 1.66)
Maneb	1523 (8.9)	187 (9.7)	1.12 (0.91, 1.37)	117 (10.3)	1.12 (0.87, 1.43)
Metalaxyl	3749 (21.9)	434 (22.5)	1.15 (1.00, 1.31)	268 (23.7)	1.16 (0.98, 1.38)
Ziram	253 (1.5)	28 (1.5)	0.98 (0.66, 1.46)	20 (1.8)	1.18 (0.74, 1.87)
Herbicide	17913 (97.7)	2035 (98.4)	1.23 (0.85, 1.78)	1199 (98.1)	1.09 (0.70, 1.68)
Alachlor	9641 (55.8)	1161 (59.4)	1.06 (0.96, 1.17)	680 (58.7)	1.04 (0.92, 1.18)
Butylate	5776 (34.1)	720 (37.6)	1.03 (0.92, 1.15)	416 (36.9)	1.00 (0.87, 1.16)
Chlorimuron ethyl	6482 (37.9)	734 (38.1)	1.00 (0.91, 1.11)	436 (38.4)	1.04 (0.92, 1.18)
Dicamba	9506 (55.2)	1158 (59.3)	1.11 (1.00, 1.24)	658 (57.1)	1.08 (0.94, 1.25)
EPTC	3658 (21.5)	448 (23.1)	1.04 (0.93, 1.17)	257 (22.4)	1.04 (0.89, 1.21)
Glyphosate	14086 (77.2)	1678 (81.5)	1.33 (1.18, 1.50)	991 (81.4)	1.31 (1.13, 1.53)
Imazethapyr	7892 (46.9)	903 (47.4)	0.94 (0.84, 1.05)	511 (45.5)	0.93 (0.81, 1.08)
Metolachlor	8338 (48.3)	978 (49.7)	1.02 (0.93, 1.13)	577 (49.6)	1.06 (0.93, 1.20)
Paraquat	3905 (22.8)	480 (24.9)	1.15 (1.02, 1.29)	294 (25.8)	1.13 (0.97, 1.32)
Pendimethalin	7663 (44.6)	885 (45.7)	1.04 (0.94, 1.14)	534 (46.8)	1.09 (0.96, 1.23)
Petroleum distillates	8490 (49.9)	1070 (55.5)	1.16 (1.05, 1.28)	631 (55.6)	1.19 (1.05, 1.35)
Trifluralin	9091 (55.5)	1111 (60.0)	1.07 (0.95, 1.21)	637 (58.4)	1.03 (0.89, 1.19)
2,4-D	14175 (78.0)	1692 (82.3)	1.14 (1.00, 1.29)	992 (81.5)	1.11 (0.95, 1.31)
2,4,5-T	3738 (22.1)	563 (29.4)	1.22 (1.08, 1.39)	343 (30.5)	1.24 (1.06, 1.45)
2,4,5-TP	1666 (9.9)	221 (11.5)	0.88 (0.74, 1.04)	138 (12.3)	0.91 (0.73, 1.12)
Atrazine	13400 (73.4)	1579 (76.9)	1.09 (0.97, 1.22)	929 (76.5)	1.10 (0.94, 1.27)
Cyanazine	7748 (44.9)	949 (48.5)	1.06 (0.95, 1.17)	562 (48.6)	1.13 (0.98, 1.29)
Metribuzin	8089 (49.0)	1012 (54.1)	1.08 (0.96, 1.21)	590 (53.6)	1.13 (0.97, 1.31)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; CCl_4/CS_2, Carbon tetrachloride/Carbon disulfide 80/20 mix; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; OI, Olfactory Impairment; OR, Odds Ratio

[a] All olfactory impairment cases

[b] Olfactory impairment with onset reported ≤ 10 years before the third follow-up

[c] Odds ratios are adjusted for age, sex, state of residence, education, smoking status, ever performed following tasks at least once each year (repair engines, replace asbestos brake linings, handle stored grain, work in swine confinement areas, weld and paint), and correlated pesticides (correlated ever-use of pesticides with Spearman correlation ≥ 0.40); correlated pesticides are not adjusted for overall lifetime days.

Table 3.

Intensity weighted lifetime days of use of pesticides at enrollment in relation to self-reported olfactory impairment reported in the third follow-up in the Agricultural Health Study (n=20,409), Iowa and North Carolina

			Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
Pesticides	**Exposure[a]**	**No OI (n (%))**	**OI (n (%))**	**OR (95% CI)**	**P-trend**	**OI (n (%))**	**OR (95% CI)**	**P-trend**
Insecticide								
Organochlorine								
Aldrin[d]	Never	8080 (83.9)	849 (75.7)	Ref	0.25	477 (74.2)	Ref	0.30
	>0–315	565 (5.9)	96 (8.6)	1.10 (0.86, 1.41)		59 (9.2)	1.16 (0.85, 1.58)	
	>315–952	489 (5.1)	77 (6.9)	1.00 (0.76, 1.31)		47 (7.3)	1.05 (0.74, 1.48)	
	>952	501 (5.2)	99 (8.8)	1.18 (0.91, 1.53)		60 (9.3)	1.21 (0.88, 1.68)	
Chlordane[d]	Never	8080 (82.0)	857 (73.2)	Ref	0.08	500 (74.2)	Ref	0.35
	>0–231	580 (5.9)	108 (9.2)	1.46 (1.17, 1.83)		58 (8.6)	1.29 (0.96, 1.73)	
	>231–637	607 (6.2)	104 (8.9)	1.29 (1.03, 1.63)		55 (8.2)	1.12 (0.83, 1.52)	
	>637	586 (5.9)	102 (8.7)	1.24 (0.98, 1.56)		61 (9.1)	1.16 (0.87, 1.56)	
Dieldrin[d]	Never	9363 (96.7)	1074 (94.5)	Ref	0.63	615 (94.9)	Ref	0.17
	>0–210	114 (1.2)	22 (1.9)	1.06 (0.66, 1.70)		14 (2.2)	1.12 (0.63, 2.00)	
	>210–653	94 (1.0)	23 (2.0)	1.31 (0.82, 2.11)		12 (1.9)	1.15 (0.61, 2.14)	
	>653	111 (1.1)	17 (1.5)	0.82 (0.49, 1.40)		7 (1.1)	0.55 (0.25, 1.21)	
DDT[d]	Never	7873 (81.3)	794 (69.5)	Ref	0.02	440 (66.7)	Ref	0.01
	>0–328	601 (6.2)	115 (10.1)	1.33 (1.06, 1.68)		71 (10.8)	1.40 (1.05, 1.86)	
	>328–1583	622 (6.4)	113 (9.9)	1.26 (1.00, 1.59)		67 (10.2)	1.23 (0.91, 1.65)	
	>1583	592 (6.1)	121 (10.6)	1.38 (1.10, 1.74)		82 (12.4)	1.54 (1.17, 2.03)	
Heptachlor[d]	Never	8535 (88.1)	938 (82.4)	Ref	0.32	545 (83.6)	Ref	0.88
	>0–289	396 (4.1)	60 (5.3)	0.99 (0.73, 1.33)		37 (5.7)	0.99 (0.68, 1.43)	
	>289–893	384 (4.0)	71 (6.2)	1.18 (0.89, 1.56)		30 (4.6)	0.81 (0.54, 1.20)	
	>893	374 (3.9)	69 (6.1)	1.13 (0.85, 1.51)		40 (6.1)	1.05 (0.73, 1.50)	
Toxaphene[d]	Never	9303 (90.1)	1050 (85.7)	Ref	0.27	613 (86.5)	Ref	0.66
	>0–298	344 (3.3)	57 (4.7)	1.26 (0.94, 1.69)		33 (4.7)	1.25 (0.86, 1.81)	

Pesticides	Exposure[a]	No OI (n (%))	Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
			OI (n (%))	OR (95% CI)	P-trend	OI (n (%))	OR (95% CI)	P-trend
	>298–1050	335 (3.2)	67 (5.5)	1.49 (1.13, 1.96)		33 (4.7)	1.24 (0.85, 1.80)	
	>1050	344 (3.3)	51 (4.2)	1.12 (0.82, 1.53)		30 (4.2)	1.06 (0.72, 1.57)	
Lindane[d]	Never	8777 (85.5)	957 (78.4)	Ref	<.0001	552 (78.3)	Ref	0.0006
	>0–315	513 (5.0)	83 (6.8)	1.31 (1.03, 1.68)		45 (6.4)	1.27 (0.92, 1.75)	
	>315–1176	498 (4.9)	85 (7.0)	1.42 (1.11, 1.82)		54 (7.7)	1.62 (1.20, 2.18)	
	>1176	474 (4.6)	95 (7.8)	1.64 (1.29, 2.07)		54 (7.7)	1.60 (1.18, 2.17)	
Carbamate								
Aldicarb[d]	Never	9177 (93.3)	1099 (94.3)	Ref	0.09	629 (93.6)	Ref	0.33
	>0–613	213 (2.2)	25 (2.1)	1.05 (0.68, 1.62)		15 (2.2)	1.07 (0.61, 1.85)	
	>613–2408	223 (2.3)	26 (2.2)	1.05 (0.68, 1.62)		17 (2.5)	1.16 (0.68, 1.98)	
	>2408	227 (2.3)	16 (1.4)	0.63 (0.37, 1.07)		11 (1.6)	0.72 (0.38, 1.37)	
Carbaryl[d]	Never	5720 (58.8)	605 (52.5)	Ref	0.90	341 (51.7)	Ref	0.96
	>0–341	1347 (13.9)	184 (16.0)	1.16 (0.97, 1.39)		106 (16.1)	1.19 (0.94, 1.50)	
	>341–2015	1351 (13.9)	204 (17.7)	1.33 (1.11, 1.60)		116 (17.6)	1.30 (1.03, 1.65)	
	>2015	1302 (13.4)	159 (13.8)	1.11 (0.88, 1.39)		96 (14.6)	1.10 (0.83, 1.46)	
Carbofuran	Never	12129 (71.4)	1277 (66.0)	Ref	0.51	753 (65.8)	Ref	0.99
	>0–350	1600 (9.4)	239 (12.3)	1.27 (1.09, 1.47)		134 (11.7)	1.20 (0.99, 1.46)	
	>350–1260	1631 (9.6)	221 (11.4)	1.16 (1.00, 1.36)		142 (12.4)	1.25 (1.03, 1.50)	
	>1260	1616 (9.5)	199 (10.3)	1.06 (0.90, 1.25)		115 (10.1)	0.99 (0.81, 1.22)	
Organophosphate								
Chlorpyrifos	Never	9449 (54.9)	1023 (51.9)	Ref	0.64	607 (52.2)	Ref	0.99
	>0–435	2532 (14.7)	344 (17.5)	1.26 (1.10, 1.44)		199 (17.1)	1.25 (1.05, 1.48)	
	>435–1715	2658 (15.4)	305 (15.5)	1.06 (0.93, 1.22)		185 (15.9)	1.09 (0.92, 1.30)	
	>1715	2573 (14.9)	299 (15.2)	1.07 (0.94, 1.23)		172 (14.8)	1.04 (0.87, 1.24)	
Coumaphos	Never	15223 (90.6)	1693 (88.9)	Ref	0.99	1007 (89.6)	Ref	0.34
	>0–394	539 (3.2)	77 (4.0)	1.19 (0.93, 1.53)		42 (3.7)	1.09 (0.79, 1.51)	
	>394–1369	513 (3.1)	76 (4.0)	1.26 (0.98, 1.61)		46 (4.1)	1.29 (0.94, 1.76)	
	>1369	531 (3.2)	59 (3.1)	0.95 (0.72, 1.26)		29 (2.6)	0.78 (0.53, 1.15)	
Diazinon[d]	Never	7891 (79.4)	866 (72.9)	Ref	0.01	500 (73.2)	Ref	0.18

			Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
Pesticides	**Exposure[a]**	**No OI (n (%))**	**OI (n (%))**	**OR (95% CI)**	**P-trend**	**OI (n (%))**	**OR (95% CI)**	**P-trend**
	>0–515	698 (7.0)	118 (9.9)	1.45 (1.17, 1.79)		70 (10.2)	1.47 (1.12, 1.92)	
	>515–3923	679 (6.8)	99 (8.3)	1.22 (0.97, 1.54)		55 (8.1)	1.15 (0.85, 1.55)	
	>3923	668 (6.7)	105 (8.8)	1.40 (1.11, 1.76)		58 (8.5)	1.26 (0.93, 1.70)	
Dichlorvos	Never	14949 (87.8)	1630 (84.3)	Ref	0.08	974 (85.0)	Ref	0.06
	>0–315	691 (4.1)	93 (4.8)	1.15 (0.92, 1.44)		47 (4.1)	1.00 (0.74, 1.37)	
	>315–1143	697 (4.1)	111 (5.7)	1.33 (1.08, 1.64)		64 (5.6)	1.33 (1.02, 1.75)	
	>1143	684 (4.0)	99 (5.1)	1.22 (0.98, 1.52)		61 (5.3)	1.29 (0.98, 1.70)	
Fonofos	Never	13149 (76.8)	1461 (75.0)	Ref	0.39	869 (75.4)	Ref	0.47
	>0–429	1289 (7.5)	183 (9.4)	1.19 (1.01, 1.41)		105 (9.1)	1.19 (0.96, 1.48)	
	>429–1550	1371 (8)	147 (7.5)	0.87 (0.72, 1.04)		87 (7.6)	0.90 (0.71, 1.13)	
	>1550	1310 (7.7)	158 (8.1)	0.95 (0.80, 1.14)		91 (7.9)	0.94 (0.75, 1.19)	
Malathion[d]	Never	3562 (34.8)	345 (28.3)	Ref	0.01	182 (26.0)	Ref	0.01
	>0–360	2215 (21.6)	281 (23.1)	1.24 (1.05, 1.47)		165 (23.5)	1.44 (1.15, 1.80)	
	>360–1344	2290 (22.4)	280 (23.0)	1.17 (0.98, 1.38)		169 (24.1)	1.39 (1.11, 1.74)	
	>1344	2172 (21.2)	311 (25.6)	1.33 (1.13, 1.58)		185 (26.4)	1.50 (1.21, 1.87)	
Parathion[d]	Never	9549 (93.1)	1099 (90.5)	Ref	0.23	638 (91.3)	Ref	0.54
	>0–315	232 (2.3)	41 (3.4)	1.41 (1.00, 1.99)		23 (3.3)	1.32 (0.85, 2.06)	
	>315–1700	239 (2.3)	40 (3.3)	1.39 (0.98, 1.98)		18 (2.6)	1.01 (0.62, 1.66)	
	>1700	237 (2.3)	34 (2.8)	1.22 (0.84, 1.77)		20 (2.9)	1.17 (0.73, 1.88)	
Phorate[d]	Never	6682 (67.8)	741 (63.6)	Ref	0.64	438 (65.1)	Ref	0.15
	>0–315	1082 (11)	148 (12.7)	1.09 (0.90, 1.32)		82 (12.2)	1.05 (0.81, 1.35)	
	>315–1117	1036 (10.5)	147 (12.6)	1.16 (0.96, 1.41)		90 (13.4)	1.26 (0.99, 1.61)	
	>1117	1057 (10.7)	130 (11.1)	0.95 (0.78, 1.17)		63 (9.4)	0.80 (0.61, 1.05)	
Terbufos	Never	10133 (59.3)	1099 (56.4)	Ref	0.07	652 (56.9)	Ref	0.06
	>0–621	2300 (13.5)	278 (14.3)	1.08 (0.94, 1.25)		163 (14.2)	1.13 (0.94, 1.35)	
	>621–2279	2387 (14.0)	272 (14.0)	1.00 (0.87, 1.16)		149 (13.0)	0.96 (0.79, 1.16)	
	>2279	2274 (13.3)	299 (15.3)	1.15 (1.00, 1.33)		182 (15.9)	1.21 (1.01, 1.44)	
Permethrin								
Permethrin (crops)	Never	14678 (86.7)	1625 (84.9)	Ref	0.001	962 (85)	Ref	0.001

			Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
Pesticides	**Exposure[a]**	**No OI (n (%))**	**OI (n (%))**	**OR (95% CI)**	**P-trend**	**OI (n (%))**	**OR (95% CI)**	**P-trend**
	>0–245	744 (4.4)	94 (4.9)	1.15 (0.92, 1.44)		54 (4.8)	1.16 (0.87, 1.55)	
	>245–963	779 (4.6)	89 (4.6)	1.09 (0.87, 1.37)		46 (4.1)	0.99 (0.73, 1.34)	
	>963	726 (4.3)	106 (5.5)	1.42 (1.15, 1.76)		70 (6.2)	1.55 (1.19,2.01)	
Permethrin (animals)	Never	14557 (84.9)	1610 (82.7)	Ref	0.38	950 (82.6)	Ref	0.28
	>0–350	845 (4.9)	125 (6.4)	1.39 (1.14, 1.70)		73 (6.3)	1.48 (1.15, 1.92)	
	>350–1382	886 (5.2)	110 (5.6)	1.16 (0.94, 1.43)		68 (5.9)	1.31 (1.01, 1.70)	
	>1382	866 (5.0)	102 (5.2)	1.10 (0.89, 1.37)		59 (5.1)	1.15 (0.87, 1.52)	
Fumigant								
CCl_4/CS_2[d]	Never	9947 (96.2)	1146 (93.5)	Ref	0.11	651 (91.9)	Ref	0.01
	>0–63	129 (1.2)	27 (2.2)	1.44 (0.94,2.20)		19 (2.7)	1.83 (1.12, 3.01)	
	>63–331	136 (1.3)	26 (2.1)	1.22 (0.79, 1.87)		18 (2.5)	1.48 (0.89, 2.46)	
	>331	125 (1.2)	27 (2.2)	1.40 (0.91, 2.14)		20 (2.8)	1.80 (1.10, 2.95)	
Aluminum phosphide[d]	Never	9963 (96.3)	1181 (95.8)	Ref	0.67	681 (95.6)	Ref	0.90
	>0–56	124 (1.2)	21 (1.7)	1.37 (0.85,2.20)		14 (2.0)	1.68 (0.95,2.95)	
	>56–248	128 (1.2)	18 (1.5)	1.16 (0.70, 1.92)		9 (1.3)	1.05 (0.53, 2.09)	
	>248	130 (1.3)	13 (1.1)	0.84 (0.47, 1.51)		8 (1.1)	0.93 (0.45, 1.92)	
Ethylene dibromide[d]	Never	9937 (96)	1182 (95.6)	Ref	0.56	679 (95.4)	Ref	0.18
	>0–196	138 (1.3)	18 (1.5)	1.15 (0.69, 1.90)		7 (1.0)	0.77 (0.36, 1.67)	
	>196–919	137 (1.3)	19 (1.5)	1.24 (0.75, 2.04)		12 (1.7)	1.31 (0.71, 2.42)	
	>919	135 (1.3)	18 (1.5)	1.14 (0.68, 1.90)		14 (2.0)	1.45 (0.81, 2.58)	
Methyl bromide	Never	14751 (86.6)	1673 (86.9)	Ref	0.55	971 (85.9)	Ref	0.27
	>0–294	740 (4.3)	81 (4.2)	1.01 (0.79, 1.31)		50 (4.4)	1.00 (0.73, 1.37)	
	>294–1260	782 (4.6)	90 (4.7)	1.05 (0.81, 1.36)		61 (5.4)	1.09 (0.80, 1.48)	
	>1260	765 (4.5)	81 (4.2)	0.93 (0.71, 1.21)		49 (4.3)	0.83 (0.59, 1.17)	
Fungicide								
Benomyl[d]	Never	8915 (93.5)	1040 (92.3)	Ref	0.15	593 (91.7)	Ref	0.07
	>0–343	199 (2.1)	36 (3.2)	1.66 (1.13, 2.43)		21 (3.2)	1.73 (1.07, 2.81)	
	>343–1773	220 (2.3)	20 (1.8)	0.87 (0.53, 1.45)		12 (1.9)	0.95 (0.50, 1.79)	
	>1773	197 (2.1)	31 (2.8)	1.47 (0.94, 2.28)		21 (3.2)	1.73 (1.02, 2.95)	

Pesticides	Exposure[a]	No OI (n (%))	Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
			OI (n (%))	OR (95% CI)	P-trend	OI (n (%))	OR (95% CI)	P-trend
Captan	Never	14920 (89.3)	1647 (86.9)	Ref	0.05	977 (86.5)	Ref	0.10
	>0–9	667 (4.0)	90 (4.7)	1.21 (0.96, 1.53)		51 (4.5)	1.22 (0.91, 1.64)	
	>9–161	528 (3.2)	74 (3.9)	1.24 (0.96, 1.59)		48 (4.3)	1.39 (1.02, 1.89)	
	>161	584 (3.5)	85 (4.5)	1.29 (1.02, 1.64)		53 (4.7)	1.30 (0.97, 1.75)	
Chlorothalonil	Never	15917 (93.7)	1788 (93.4)	Ref	0.94	1048 (92.6)	Ref	0.41
	>0–539	345 (2.0)	47 (2.5)	1.29 (0.93, 1.78)		29 (2.6)	1.31 (0.88, 1.95)	
	>539–3080	362 (2.1)	44 (2.3)	1.20 (0.85, 1.69)		28 (2.5)	1.22 (0.80, 1.87)	
	>3080	372 (2.2)	36 (1.9)	1.00 (0.69, 1.46)		27 (2.4)	1.22 (0.79, 1.89)	
Maneb/Mancozeb[d]	Never	9130 (93.1)	1086 (93.1)	Ref	0.82	618 (92.1)	Ref	0.58
	>0–425	232 (2.4)	22 (1.9)	0.81 (0.51, 1.28)		14 (2.1)	0.89 (0.50, 1.56)	
	>425–2688	232 (2.4)	30 (2.6)	1.05 (0.69, 1.60)		20 (3.0)	1.20 (0.72, 1.99)	
	>2688	216 (2.2)	28 (2.4)	1.03 (0.67, 1.58)		19 (2.8)	1.14 (0.68, 1.91)	
Metalaxyl[d]	Never	8425 (82.8)	995 (82.2)	Ref	0.14	573 (82.2)	Ref	0.64
	>0–239	578 (5.7)	73 (6.0)	1.07 (0.83, 1.38)		41 (5.9)	1.03 (0.74, 1.44)	
	>239–1323	599 (5.9)	69 (5.7)	1.13 (0.85, 1.51)		41 (5.9)	1.06 (0.73, 1.53)	
	>1323	577 (5.7)	73 (6.0)	1.28 (0.94, 1.74)		42 (6.0)	1.11 (0.75, 1.64)	
Herbicide								
Alachlor	Never	7629 (44.9)	794 (41.0)	Ref	0.08	478 (41.7)	Ref	0.19
	>0–788	3131 (18.4)	358 (18.5)	1.01 (0.88, 1.16)		206 (18.0)	0.99 (0.84, 1.18)	
	>788–2958	3153 (18.6)	391 (20.2)	1.10 (0.97, 1.26)		228 (19.9)	1.09 (0.92, 1.29)	
	>2958	3070 (18.1)	393 (20.3)	1.13 (0.99, 1.29)		235 (20.5)	1.11 (0.94, 1.32)	
Butylate[d]	Never	6975 (71.1)	790 (67.8)	Ref	0.17	462 (68.8)	Ref	0.31
	>0–455	949 (9.7)	126 (10.8)	1.08 (0.87, 1.32)		73 (10.9)	1.08 (0.83, 1.41)	
	>455–1512	974 (9.9)	117 (10.0)	0.96 (0.78, 1.19)		60 (8.9)	0.86 (0.65, 1.15)	
	>1512	916 (9.3)	133 (11.4)	1.17 (0.95, 1.44)		77 (11.5)	1.18 (0.90, 1.53)	
Chlorimuron ethyl[d]	Never	7021 (68.1)	828 (67.3)	Ref	0.58	485 (68.3)	Ref	0.62
	>0–236	1130 (11.0)	141 (11.5)	1.09 (0.90, 1.32)		80 (11.3)	1.11 (0.86, 1.42)	
	>236–662	1076 (10.4)	131 (10.7)	1.04 (0.85, 1.26)		69 (9.7)	0.96 (0.74, 1.26)	
	>662	1089 (10.6)	130 (10.6)	1.06 (0.87, 1.30)		76 (10.7)	1.08 (0.84, 1.40)	

			Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
Pesticides	**Exposure[a]**	**No OI (n (%))**	**OI (n (%))**	**OR (95% CI)**	**P-trend**	**OI (n (%))**	**OR (95% CI)**	**P-trend**
Dicamba	Never	7694 (45.3)	793 (41.0)	Ref	0.68	493 (43.2)	Ref	0.95
	>0–551	3080 (18.1)	379 (19.6)	1.15 (1.00, 1.33)		214 (18.8)	1.12 (0.93, 1.35)	
	>551–2170	3166 (18.6)	396 (20.5)	1.14 (0.99, 1.32)		229 (20.1)	1.13 (0.94, 1.36)	
	>2170	3063 (18.0)	366 (18.9)	1.09 (0.94, 1.26)		205 (18.0)	1.04 (0.87, 1.26)	
EPTC	Never	13352 (78.9)	1487 (77.3)	Ref	0.38	889 (77.9)	Ref	0.55
	>0–315	1212 (7.2)	132 (6.9)	0.93 (0.77, 1.12)		77 (6.7)	0.95 (0.75, 1.22)	
	>315–1176	1217 (7.2)	160 (8.3)	1.12 (0.94, 1.34)		93 (8.2)	1.13 (0.90, 1.42)	
	>1176	1147 (6.8)	144 (7.5)	1.07 (0.89, 1.28)		82 (7.2)	1.06 (0.83, 1.34)	
Glyphosate	Never	4163 (23.0)	381 (18.6)	Ref	0.00	226 (18.7)	Ref	0.02
	>0–672	4590 (25.4)	573 (28)	1.38 (1.21, 1.59)		340 (28.1)	1.39 (1.16, 1.65)	
	>672–2610	4748 (26.3)	523 (25.6)	1.22 (1.06, 1.41)		302 (25.0)	1.17 (0.98, 1.41)	
	>2610	4572 (25.3)	567 (27.7)	1.41 (1.22, 1.62)		342 (28.3)	1.40 (1.17, 1.68)	
Imazethapyr	Never	8934 (53.6)	1000 (52.9)	Ref	0.65	611 (54.8)	Ref	0.86
	>0–338	2545 (15.3)	310 (16.4)	1.00 (0.86, 1.16)		172 (15.4)	0.97 (0.80, 1.18)	
	>338–992	2677 (16.1)	287 (15.2)	0.88 (0.76, 1.03)		163 (14.6)	0.88 (0.72, 1.07)	
	>992	2519 (15.1)	294 (15.5)	0.97 (0.83, 1.13)		168 (15.1)	0.98 (0.80, 1.19)	
Metolachlor	Never	8916 (52.2)	988 (50.6)	Ref	0.05	586 (50.5)	Ref	0.21
	>0–720	2704 (15.8)	367 (18.8)	1.20 (1.05, 1.36)		217 (18.7)	1.25 (1.05, 1.47)	
	>720–2604	2756 (16.1)	315 (16.1)	0.99 (0.86, 1.14)		191 (16.5)	1.06 (0.89, 1.26)	
	>2604	2693 (15.8)	282 (14.4)	0.91 (0.79, 1.05)		166 (14.3)	0.94 (0.78, 1.13)	
Paraquat[d]	Never	8817 (85.4)	1022 (83.2)	Ref	0.11	589 (83.1)	Ref	0.09
	>0–275	501 (4.9)	68 (5.5)	1.17 (0.90, 1.53)		38 (5.4)	1.14 (0.80, 1.61)	
	>275–1080	507 (4.9)	72 (5.9)	1.29 (0.98, 1.68)		40 (5.6)	1.24 (0.88, 1.76)	
	>1080	498 (4.8)	66 (5.4)	1.27 (0.95, 1.70)		42 (5.9)	1.38 (0.96, 1.97)	
Pendimethalin[d]	Never	6521 (63.2)	755 (61.3)	Ref	0.55	440 (62.1)	Ref	0.73
	>0–315	1282 (12.4)	154 (12.5)	1.01 (0.84, 1.21)		92 (13.0)	1.06 (0.83, 1.34)	
	>315–1176	1250 (12.1)	180 (14.6)	1.28 (1.07, 1.53)		94 (13.3)	1.18 (0.93, 1.49)	
	>1176	1264 (12.3)	143 (11.6)	1.03 (0.85, 1.25)		82 (11.6)	1.03 (0.80, 1.33)	
Petroleum distillates[d]	Never	8058 (78.7)	911 (74.1)	Ref	0.03	530 (74.6)	Ref	0.05

Pesticides	Exposure[a]	No OI (n (%))	Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
			OI (n (%))	OR (95% CI)	P-trend	OI (n (%))	OR (95% CI)	P-trend
	>0–502	733 (7.2)	100 (8.1)	1.18 (0.94, 1.47)		55 (7.7)	1.15 (0.86, 1.54)	
	>502–2438	734 (7.2)	112 (9.1)	1.34 (1.09, 1.67)		63 (8.9)	1.35 (1.02, 1.78)	
	>2438	717 (7.0)	106 (8.6)	1.27 (1.02, 1.58)		62 (8.7)	1.31 (0.99, 1.74)	
Trifluralin	Never	7297 (45.1)	742 (40.5)	Ref	0.11	453 (42.2)	Ref	0.16
	>0–1020	2960 (18.3)	331 (18.1)	1.02 (0.88, 1.19)		180 (16.8)	0.95 (0.78, 1.15)	
	>1020–3875	3030 (18.7)	377 (20.6)	1.11 (0.95, 1.28)		216 (20.1)	1.07 (0.89, 1.29)	
	>3875	2897 (17.9)	382 (20.9)	1.13 (0.98, 1.32)		225 (20.9)	1.12 (0.92, 1.35)	
2,4-D	Never	4001 (22.3)	364 (17.9)	Ref	0.05	225 (18.8)	Ref	0.26
	>0–1302	4646 (25.9)	516 (25.4)	1.14 (0.98, 1.31)		312 (26.0)	1.16 (0.96, 1.39)	
	>1302–5208	4858 (27.0)	548 (27.0)	1.08 (0.93, 1.26)		309 (25.8)	1.03 (0.85, 1.24)	
	>5208	4459 (24.8)	600 (29.6)	1.20 (1.03, 1.39)		354 (29.5)	1.16 (0.96, 1.40)	
2,4,5-T[d]	Never	7999 (82.2)	828 (71.6)	Ref	0.05	472 (70.9)	Ref	0.23
	>0–280	568 (5.8)	116 (10.0)	1.64 (1.32, 2.05)		74 (11.1)	1.82 (1.38, 2.38)	
	>280–971	586 (6.0)	117 (10.1)	1.65 (1.32, 2.07)		65 (9.8)	1.56 (1.17, 2.08)	
	>971	579 (5.9)	95 (8.2)	1.33 (1.05, 1.70)		55 (8.3)	1.29 (0.95, 1.75)	
2,4,5-TP[d]	Never	9291 (95.3)	1071 (92.5)	Ref	0.25	621 (93.1)	Ref	0.72
	>0–315	159 (1.6)	26 (2.2)	1.16 (0.75, 1.79)		15 (2.2)	1.12 (0.64, 1.94)	
	>315–1250	148 (1.5)	35 (3.0)	1.66 (1.13, 2.44)		20 (3.0)	1.62 (0.99, 2.64)	
	>1250	148 (1.5)	26 (2.2)	1.20 (0.78, 1.85)		11 (1.6)	0.82 (0.44, 1.54)	
Atrazine	Never	4859 (26.9)	473 (23.2)	Ref	0.50	286 (23.7)	Ref	0.55
	>0–1054	4386 (24.2)	509 (25.0)	1.12 (0.98, 1.29)		300 (24.9)	1.15 (0.96, 1.37)	
	>1054–4340	4530 (25.0)	523 (25.7)	1.07 (0.93, 1.23)		302 (25.0)	1.06 (0.89, 1.27)	
	>4340	4318 (23.9)	531 (26.1)	1.10 (0.96, 1.27)		318 (26.4)	1.12 (0.94, 1.34)	
Cyanazine	Never	9485 (55.6)	1007 (51.7)	Ref	0.33	594 (51.6)	Ref	0.56
	>0–539	2503 (14.7)	321 (16.5)	1.12 (0.97, 1.29)		189 (16.4)	1.20 (1.00, 1.43)	
	>539–2200	2592 (15.2)	301 (15.5)	1.00 (0.86, 1.15)		190 (16.5)	1.13 (0.95, 1.36)	
	>2200	2490 (14.6)	318 (16.3)	1.10 (0.95, 1.27)		178 (15.5)	1.11 (0.92, 1.33)	

			Any OI[b] (n=20,409)			Time-restricted OI[c] (n=19,563)		
Pesticides	**Exposure[a]**	**No OI (n (%))**	**OI (n (%))**	**OR (95% CI)**	**P-trend**	**OI (n (%))**	**OR (95% CI)**	**P-trend**
Metribuzin[d]	Never	5550 (58.3)	605 (53.6)	Ref	0.02	359 (55.1)	Ref	0.37
	>0–315	1323 (13.9)	156 (13.8)	0.99 (0.81, 1.21)		100 (15.4)	1.14 (0.88, 1.46)	
	>315–1000	1361 (14.3)	176 (15.6)	1.10 (0.91, 1.34)		93 (14.3)	1.04 (0.81, 1.35)	
	>1000	1286 (13.5)	191 (16.9)	1.24 (1.02, 1.50)		99 (15.2)	1.15 (0.89, 1.48)	

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; CCl_4/CS_2, Carbon tetrachloride/Carbon disulfide 80/20 mix; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; OI, Olfactory Impairment; OR, Odds Ratio

[a]Exposure categories: Never use and categorized into tertiles among users

[b]All olfactory impairment cases

[c]Olfactory impairment with onset reported ≤ 10 years before the third follow-up

[d]Odds ratios are adjusted for age, sex, state of residence, education, smoking status, ever performed following tasks at least once each year (repair engines, replace asbestos brake linings, handle stored grain, work in swine confinement areas, weld and paint), and correlated pesticides (correlated ever-use of pesticides with Spearman correlation ≥ 0.40)

[e]Frequency and duration of pesticide was asked only in the take-home questionnaire