HHS Public Access

Author manuscript

Sleep Health. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Sleep Health. 2018 February ; 4(1): 20–26. doi:10.1016/j.sleh.2017.08.006.

Sleep Apnea and Pesticide Exposure in a Study of US Farmers

Brittney O. Baumert[1], **Megan Ulmer Carnes**[1], **Jane A. Hoppin**[2], **Chandra L. Jackson**[1], **Dale P. Sandler**[1], **Laura Beane Freeman**[3], **Paul K. Henneberger**[4], **David M. Umbach**[5], **Srishti Shrestha**[1], **Stuart Long**[6], and **Stephanie J. London**[1]

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

[2]Department of Biological Sciences, Center for Human Health and the Environment, North Carolina State University, NC, USA

[3]Occupational and Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD, USA

[4]Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA

[5]Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA

[6]Westat, Durham, NC, USA

Abstract

Introduction—Carbamate and organophosphate pesticides inhibit acetylcholinesterase and poisoning leads to respiratory depression. Thus, involvement in sleep apnea is plausible, but no data exist at lower levels of exposure. Other pesticides could impact sleep apnea by different mechanisms but have not been studied. Our study examines the associations between pesticide exposure and sleep apnea among pesticide applicators from a US farming population.

Participants and Methods—We analyzed data from 1,569 male pesticide applicators, mostly farmers, from an asthma case-control study nested within the prospective Agricultural Health Study. On questionnaires, participants reported use of specific pesticides and physician diagnosis plus prescribed treatments for sleep apnea. We used multivariable logistic regression to estimate associations between ever use of 63 pesticides and sleep apnea (234 cases, 1,335 non-cases).

Corresponding Author: Stephanie J. London, M.D., Dr.P.H., National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Rall Bldg, A306, Research Triangle Park, NC 27709, Ph: (919) 541-5772, london2@niehs.nih.gov.

Competing Financial Interests: None

Declaration of Interest: The authors declare no conflicts.

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

Results—The most notable association was for carbofuran, a carbamate, (100 exposed cases, Odds Ratio (OR): 1.83, 95% Confidence Interval (CI) 1.34–2.51, P= 0.0002). Carbofuran use began before reported onset of sleep apnea in all cases.

Discussion—This study adds to the known adverse health outcomes of exposure to carbofuran, a pesticide cancelled in the US in 2009 for most agricultural purposes but persists in the environment and remains in use in some other countries.

Conclusions—We conducted the first epidemiological study investigating the association of pesticide exposure and sleep apnea. Our results in a male agricultural population suggests that exposure to carbofuran is positively associated with sleep apnea.

Keywords

Pesticides; Sleep Apnea; Carbofuran; Carbamates; Sleep Disorder Breathing; Agriculture

Introduction

Sleep-disordered breathing is characterized by instantaneous cessations in the rhythm of breathing (apneas) or momentary or prolonged reduction in the amplitude of breathing (hypopneas) (1). Sleep apneas and hypopneas can be caused by obstruction of the upper airway (obstructive), by reduced respiratory motor neuron function (central) or reflect mixed obstructive and central etiologies (1). Most sleep apnea-hypopnea events result from anatomical anomalies combined with a disturbance in the neurochemical control of the upper airway musculature (1–3). The neurotransmitter acetylcholine influences the function of upper airway motor neurons that control breathing during wakefulness and sleep (4).

Sleep apnea is a major contributor to morbidity, mortality, and reduced quality of life (1). In men, obstructive sleep apnea prevalence has been estimated at 3.3% with highest rates at ages 45–64 (5). Risk factors include increasing age, male gender, central obesity, craniofacial and upper airway abnormalities, cardiovascular disease, and diabetes. Central sleep apnea accounts for under five percent of patients presenting for sleep apnea evaluation (5, 6). Obstructive and central sleep apnea can co-occur, but there are distinct risk factors for central apnea including heart failure, stroke, high altitude, and opioid medication use (6). Data on environmental contributors to sleep apnea are few. Associations with air pollutants were identified in two recent population based studies (7, 8) an increased risk was reported in World Trade Center-exposed rescue or recovery workers (9). Two smaller studies have reported associations with solvent exposure (10, 11).

Both organophosphate and carbamate pesticides act by inhibiting acetylcholinesterase, an enzyme that hydrolyzes acetylcholine. Therefore, these agents can interfere with neuronal function, including control of respiration (4). In pesticide poisoning, respiratory depression occurs and may be fatal (12, 13). In animal studies, exposure to these pesticides elicits a spectrum of neurochemical, neurophysiological, and neurobehavioral deficits including respiratory depression and interference with sleep-wake cycles (14). Thus, exposure to pesticides that inhibit acetylcholinesterase is potentially relevant to sleep apnea in humans. Pesticides in other chemical classes are also neurotoxic and could theoretically be relevant to

sleep apnea (15). Recent data suggest that carbamates can interact with the melatonin receptor (16) and that melatonin may play a role in sleep apnea (16–18) providing an alternative, or complementary mechanism for carbamates to impact this disorder.

No epidemiological studies exist of sleep apnea in relation to pesticide exposure. We aimed to address this gap by investigating associations between sleep apnea and pesticide exposure among male pesticide applicators in the Agricultural Lung Health Study (ALHS).

Participants and Methods

Study population

The Agricultural Lung Health Study (ALHS) is a case-control study of current asthma nested within the prospective Agricultural Health Study (AHS). The AHS enrolled pesticide applicators applying for, or renewing, pesticide-use licenses in North Carolina and Iowa (19) along with their spouses in 1993–1997. The ALHS identified potential asthma cases and non-cases among respondents to an AHS follow-up telephone interview conducted 2005–2010 (24,171 pesticide applicators, 19,959 spouses). The Institutional Review Board of the National Institute of Environmental Health Sciences approved the study. All participants provided informed consent.

Details of ALHS enrollment have been published (20, 21). Briefly, we enrolled 3,301 ALHS participants between 2009 and 2013 (1,223 asthma cases; response rate=51.7%, and 2,078 non-cases; response rate=50.0%). We included three categories of asthma cases: doctor diagnosed current asthma (n=876), potential undiagnosed asthma based on current asthma symptoms and medication use in non-smokers (n=309), and overlapping diagnoses of current asthma and either chronic obstructive pulmonary disease (COPD) or emphysema in non-smokers (n=38). Non-cases were randomly selected from those without the above conditions. We analyzed only the 1,596 male pesticide applicators; 97% of pesticide applicators were men.

Sleep apnea assessment

Information on physician-diagnosed sleep apnea came from the ALHS computer-assisted telephone interview. We classified participants who reported ‘yes’ to “Have you ever been told by a doctor that you have sleep apnea?” and ‘yes’ to one of four possible sleep apnea treatments (“CPAP”, “surgery”, “bi-level”, or “other oral device”) as sleep apnea cases (n=236). Requiring treatment in the definition increases reliability of this self-reported outcome (22). Participants reporting ‘yes’ to physician-diagnosed sleep apnea but not reporting a treatment for sleep apnea were excluded from analysis (n=49). Otherwise individuals were classified as non-cases (n=1360).

Assessment of Pesticide Exposure

On earlier AHS questionnaires (www.aghealth.nih.gov) individuals provided names of chemicals used ever in their lifetimes (Phase One, 1993–1997), in the most recent farming season (Phase Two, 1999–2003), and since last study contact (Phase Three, 2005–2010). Reported names were linked to pesticide active ingredient names using the Environmental

Protection Agency (EPA) Pesticide Classification Code (23). We analyzed the 63 pesticides reported by >1% of applicators at Phase Three that were also reported by at least 5 (of 236) sleep apnea cases. The 63 pesticides included 40 herbicides and plant growth regulators, 19 insecticides, 3 fungicides, and 1 rodenticide.

For 22 of the 63 pesticides, we had data on lifetime days of exposure, from the AHS Phase One enrollment questionnaire, to assess dose-response to individual pesticides (23). We divided lifetime days of use into approximate tertiles for comparison with never users.

Statistical analyses

Using logistic regression, we estimated odds ratios and 95% confidence intervals for both ever-never pesticide exposure and lifetime days of pesticide exposure in relation to sleep apnea. Consistent with previous AHS analyses, we included continuous age and state (North Carolina or Iowa) in all models. We additionally included asthma status, the design variable for selection of ALHS participants.

We evaluated as potential covariates additional variables implicated in sleep apnea etiology from the literature including body mass index (BMI, continuous), history of diabetes, cardiovascular disease, hypertension, alcohol use (24-hour recall), caffeine intake (24-hour recall), and smoking (never, past, current and pack-years). We calculated BMI from height and weight measured at the ALHS home visit. Individuals were classified as having cardiovascular disease if they answered ‘yes’ to either ever experienced heart failure (asked in ALHS) or ever experienced a stroke (asked at AHS Phase Three). Final models included all the aforementioned covariates except alcohol use, caffeine intake, or smoking because they did not separately change regression coefficients by at least 10%.

Analyses included the 1,569 individuals (98.3% of 1,596) with complete covariate data (234 cases of sleep apnea and 1,335 non-cases). A secondary analysis evaluated waist circumference, measured at the ALHS home visit, as an alternative adiposity adjustment variable to BMI (sleep apnea cases=227, non-cases=1,307).

In additional analyses, we compared the year of first pesticide exposure to onset of sleep apnea. We also examined effect modification, and interaction, separately by asthma status and personal protective equipment use. In addition to the uncorrected P values presented in the tables, we calculated False Discovery Rate adjusted P values (P_{FDR}) for the primary analysis, accounting for 63 tests using the Benjamini-Hochberg method (24). Adjustment variables were the same as in the main analyses. We used SAS (SAS Institute Inc., Cary, NC, Version 9.3, except for tetrachoric correlations calculated using Version 9.4). Analyses used the following releases of the AHS data: P3REL201209.00, PIREL201209.00 and AHSREL201304.00.

Results

Nearly all participants were white (98.4%); few (<5%) were current smokers. Sleep apnea cases were slightly older than non-cases (Table 1). As expected, BMI was higher among cases (Table 1); the adjusted odds ratio (OR) per unit increase in BMI was 1.16 (95%

Confidence Interval (CI) 1.13–1.19). Sleep apnea was more common among asthmatics (Table 1); adjusted OR:2.47, 95% CI 1.87–3.27. The 234 sleep apnea cases reported the following use of each of the queried treatments: CPAP (n=215, 91.9%), “surgery” (n=16, 6.8%), “bi-level” (n=23, 9.8%), “other oral device” (n=22, 9.4%); more than one treatment could be listed.

We evaluated ever/never use of 63 pesticides in relation to sleep apnea. The 63 pesticides included 40 herbicides and plant growth regulators, 19 insecticides, 3 fungicides, and 1 rodenticide. Four pesticides were associated with sleep apnea at nominal P<0.05 (Table 2). Carbofuran, a carbamate pesticide, was the most statistically significant finding (P=0.0002) with the largest number (n=100) of exposed cases (OR:1.83, 95% CI 1.34–2.51) (Table 2). Among the three carbamate pesticides, only carbofuran gave P<0.05 but odds ratios for both aldicarb (OR:1.52, 95% CI 0.80–2.88) and carbaryl (OR:1.11, 95% CI 0.81–1.54) (Table 2) were also above one. Bifenthrin, a pyrethroid, was also positively associated with sleep apnea at P<0.05 but with wide confidence intervals reflecting only 5 exposed cases (OR: 4.39, 95% CI 1.33–14.46, P=0.015). Two pesticides showed inverse associations at nominal P<0.05: picloram, an acetic acid herbicide (25 exposed cases, OR:0.61, 95% CI 0.38–1.00, P=0.048), and metalaxyl, a fungicide (34 exposed cases, OR: 0.59, 95%CI 0.38–0.92, P=0.020) (Table 2). When we control the false discovery rate among all 63 pesticides, only the association with carbofuran (P_{FDR}=0.01) meets the P_{FDR}<0.05 threshold. The P_{FDR} values are very high for the associations with other three pesticides with uncorrected P<0.05 (P_{FDR}:0.510 for picloram, 0.42 for both bifenthrin and metalaxyl).

Although we hypothesized that organophosphate insecticides might be related to sleep apnea because, like carbamates, they inhibit acetylcholinesterase, none among eight were associated at nominal P <0.05 (Table 2). Among the three with ORs>1.00 (disulfoton, tebupirimfos and terbufos), terbufos was the most strongly associated with sleep apnea (124 exposed cases, OR:1.34, 95% CI 0.97–1.85, P=0.072, P_{FDR}=0.51).

Participants were queried on prior AHS questionnaires about “unusually high personal exposure” incidents. There were 334 incidents reported by 298 participants. Deleting the 7 participants reporting a carbofuran incident (1 case and 6 non-cases) changed the OR only from 1.83 to 1.84 (95% CI 1.34–2.52).

For carbofuran, all 96 (of 100) sleep apnea cases with available timing data reported first exposure before onset of sleep apnea; use began a median of 26.5 years before (interquartile range=19.5–32.5). We had data on lifetime days of use for carbofuran (Table 3). The positive association with carbofuran did not attenuate at higher exposures (P_{trend}=0.003).

Smoking was not significantly associated with sleep apnea (crude OR:0.59, 95% CI 0.27–1.31) in our population with few current smokers, nor was current alcohol intake (crude OR: 1.18, 95% CI 0.85–1.64). Therefore, neither were included in our primary models. However, adjustment did not materially alter results. The OR for carbofuran was 1.84 (95 % CI 1.34–2.53) after smoking adjustment and remained 1.83 (95% CI:1.33–2.51) after alcohol adjustment.

We adjusted for BMI because of its established relationship with sleep apnea. Waist circumference, a more specific index of central obesity, was too highly correlated with BMI (Pearson correlation=0.88) to include both in models. Results were very similar when waist circumference replaced BMI in models for any of the four pesticides associated with sleep apnea at P<0.05; OR for carbofuran was 1.81 (95% CI 1.31–2.49) versus 1.83 with BMI adjustment. We saw no consistent effect measure modification by use of personal protective equipment, defined by use of respirator or dust mask. Likewise, results did not differ materially by asthma status (data not shown).

Discussion

In a cohort of male pesticide applicators, primarily farmers, we examined 63 pesticides in relation to sleep apnea. The most statistically significant association was for the carbamate pesticide carbofuran (OR:1.83, 95% CI 1.34–2.51, P=0.0002). We confirmed that exposure to carbofuran began before the reported age of onset of sleep apnea for all cases with information on timing of first exposure.

The primary mode of action of carbofuran, like other carbamates and organophosphates, is via inhibition of the enzyme acetylcholinesterase. Organophosphates are regarded as irreversible inhibitors of acetylcholinesterase, whereas carbamates, including carbofuran, are slowly reversible inhibitors. With either, acetylcholine accumulates at nerve junctions, leading to overstimulation of acetylcholine receptors with later toxicity and potential perturbation of the sympathetic, parasympathetic, and peripheral nervous systems (4, 25). Acetylcholinesterase acts on cholinergic neurons involved in control of breathing in the sleep-wake cycle (1). Poisoning by any pesticides with this mechanism of action could result in respiratory depression (4, 26). Thus, carbamates could play a role in the onset and/or progression of central sleep apnea. Carbofuran can influence neurologic function via mechanisms other than acetylcholinesterase inhibition. In fish, carbofuran impacts levels of other neurotransmitters including dopamine, norepinephrine and serotonin. The degree and direction of these changes varies by brain region (27). Behavioral changes observed in fish after carbofuran exposure may be more sensitive indicators of neurotoxicity than altered brain catecholamine levels (28). Carbofuran increased various oxidative stress parameters in the rat brain and produced motor and cognitive deficits; administration of the antioxidant N-acetylcysteine reduced these effects (29). Of note, recently a computational approach has shown that carbofuran mimics melatonin, a critical hormone in the sleep-wake cycle, and can bind to its receptor (16). The increasing data implicating melatonin, a hormone crucial in the regulation of the sleep-wake cycle, in the sleep apnea or its severity (17, 18, 30) together with the ability of carbofuran to mimic melatonin (16) provides an alternative or complementary mechanism for an impact of carbofuran exposure on sleep apnea.

Because obstructive sleep apnea is much more common than central, most of the sleep apnea in our study likely has a strong obstructive component. The etiology of obstructive and central sleep apnea is often mixed, and a putative cause of central sleep apnea could be synergistic with causes of the obstructive disorder. The overlap between central sleep apnea and obstructive sleep apnea suggests that some common mechanisms are likely involved (1).

Ideally, we would have classified sleep apnea based on objective measures such as polysomnography. Instead, we identified sleep apnea from self-report of doctor diagnosis plus treatment. Requiring treatment in the definition increases reliability of this self-reported outcome (22). Because bias in estimating relative measures of association increases with a case definition that is less specific but more sensitive (31), requiring treatment in the definition increases specificity of the outcome reducing potential bias. Sleep apnea prevalence as defined in our study of older men (mean age 63.4 years) was relatively high at 14.8%; reported prevalence of obstructive sleep apnea in US men aged 45–64 is 4.7% (5). Our higher prevalence of sleep apnea reflects, in part, oversampling of asthmatics; increased rates of sleep apnea reported in asthmatics were confirmed in our analysis (32). We also had a relatively high prevalence of sleep apnea reported by non-cases (10.8%). However, based on polysomnography, much sleep apnea in the general population is undiagnosed making the true prevalence uncertain (22). Because we used self-reported sleep apnea rather than polysomnography our non-case group likely includes some individuals with undiagnosed sleep apnea; this misclassification will tend to attenuate associations with pesticide exposure rather than result in a spurious positive association. Alternatively, if likelihood of diagnosis with and treatment for sleep apnea is related to pesticide use, bias away from the null could result. Sleep apnea risk factors such as higher BMI and cardiovascular disease increase likelihood of referral for evaluation and thus physician diagnosis (22, 33). If these factors are related to prior pesticide use, confounding could occur; however, we adjusted for both.

The use of self-reported pesticide exposure creates the possibility of exposure misclassification. Nonetheless, data from the parent AHS supports the validity of self-reporting in our study population. Few AHS pesticide applicators self-reported a decade of first use inconsistent with the year a pesticide was first registered for use in the US (34). Overestimation of use duration was very low for carbofuran (<1%), our primary finding (34). Among orchardists, repeatability of reports of ever use approximately 20 years after initial report was found to be sufficiently accurate for epidemiological analyses, especially for more commonly used pesticides (35).

Our study has other limitations. With 234 cases, few were exposed to some individual pesticides. Lifetime days of use information, available for some pesticides, was likely underestimated because it was collected on the first AHS questionnaire. However, that questionnaire was completed prior to the reported year of sleep apnea onset for nearly all cases (92%) providing prospective data for this analysis. Because the response rate for entry into the ALHS was about 50%, selection bias is possible if non-response was jointly related to sleep apnea diagnosis and pesticide use. Earlier questionnaires did not query sleep apnea so we cannot estimate the response rate with respect to this outcome. However, sleep apnea is more common in asthmatics and the response rate was very similar by asthma status (20). Using asthma as a surrogate outcome to assess selection bias, it is reassuring that the association between asthma and carbofuran is very similar among all 23,498 male applicator respondents to the AHS Phase Three questionnaire from whom ALHS participants were sampled, (OR:1.09, 95% CI 0.97–1.23) and in ALHS participants (OR:1.18, 95% CI 0.95–1.47).

Lifetime days of use of carbofuran varied relatively little and odds ratios for sleep apnea were elevated at the lowest tertile of exposure (<14.5 lifetime days). Even if we underestimated lifetime exposure, we do not know if exposure at this level if sufficient to induce chronic effects on control of breathing in sleep apnea.

Our study has several strengths. We could assess temporality of sleep apnea onset in relation to first exposure to specific pesticides. For carbofuran, first use preceded diagnosis for all cases with temporal information. Use of specific pesticides was much higher in our farming population than in the general population, thereby increasing power. We had some data to evaluate dose-response with cumulative lifetime days of pesticide exposure and data on pesticide poisoning events. We also could adjust for various potential confounders including BMI and waist circumference based on objective measurements.

In 2009, the US EPA cancelled the use of carbofuran on crops for human or animal consumption based on evidence of toxicity (36). Canada and the European Union have also cancelled its use, but it is still employed in some other countries. US EPA classifies carbofuran as a Toxicity Category One pesticide, the most toxic category. Because of the steep exposure-response curve, small differences in exposure may lead to adverse effects and concern has been raised, especially for children, due to residual carbofuran in the food supply (36).

We found little evidence of association between sleep apnea and organophosphates; however, since the 1990s, when our cohort was enrolled, carbamates have been the most commonly used pesticides, largely replacing organophosphates. Before cancellation, carbofuran was the most commonly used carbamate in US agriculture.

Our motivating hypothesis was based on acetylcholinesterase inhibition by organophosphates and carbamates. However, because other mechanisms may be involved in neurotoxicity of these pesticide classes and others, we examined all 63 individual pesticides (15, 29, 37). We note that about 3 of 63 tests would be expected to result in $P<0.05$ by chance alone and we identified four, including the carbamate, carbofuran ($P=0.0002$). We saw modest correlation of ever use among the 63 pesticides: 18% of all tetrachoric correlations were >0.4; Bonferroni correction for multiple testing would be conservative, especially with positively correlated tests, increasing the chance of false negatives. Carbofuran would pass a Bonferroni-adjusted critical P value of $0.05/63=0.0008$. However, similar conclusions are obtained when we control the false discovery rate across all 63 pesticides using the Benjamini-Hochberg procedure, which is less conservative than a Bonferroni correction; only the association with carbofuran ($P_{FDR}=0.01$) meets a 0.05 P_{FDR} threshold whereas the other three pesticides with uncorrected $P<0.05$ for association with sleep apnea have high P_{FDR} values (0.42–0.51).

Conclusions

We conducted the first epidemiological study investigating the association of pesticide exposure and sleep apnea. Our results in a US male farming population suggests that exposure to carbofuran is positively associated with sleep apnea.

Acknowledgments

This work was supported by the intramural research program of the NIH, National Institute of Environmental Health Sciences (NIEHS) (Z01-ES049030 and ZO1-ES102385) and National Cancer Institute (Z01-CP010119). This work was also supported in part by American Recovery and Reinvestment Act (ARRA) funds through NIEHS contract number NO1-ES-55546. We thank the numerous study staff at Social & Scientific Systems, Inc. who played a role in the data collection and Dr. Marie Richards of Westat for computational assistance. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health (NIOSH). Mention of any company or product does not constitute endorsement by NIOSH.

References

1. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010; 90:47–112. [PubMed: 20086074]
2. King ED, O'Donnell CP, Smith PL, Schwartz AR. A model of obstructive sleep apnea in normal humans. Role of the upper airway. Am J Respir Crit Care Med. 2000; 161:1979–1984. [PubMed: 10852777]
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165:1217–1239. [PubMed: 11991871]
4. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Curr Neuropharmacol. 2013; 11:315–335. [PubMed: 24179466]
5. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998; 157:144–148. [PubMed: 9445292]
6. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007; 131:595–607. [PubMed: 17296668]
7. Weinreich G, Wessendorf TE, Pundt N, Weinmayr G, Hennig F, Moebus S, Mohlenkamp S, Erbel R, Jockel KH, Teschler H, Hoffmann B. Heinz Nixdorf Recall study g. Association of short-term ozone and temperature with sleep disordered breathing. Eur Respir J. 2015; 46:1361–1369. [PubMed: 26160864]
8. Zanobetti A, Redline S, Schwartz J, Rosen D, Patel S, O'Connor GT, Lebowitz M, Coull BA, Gold DR. Associations of PM10 with sleep and sleep-disordered breathing in adults from seven U.S. urban areas. Am J Respir Crit Care Med. 2010; 182:819–825. [PubMed: 20508218]
9. Glaser MS, Shah N, Webber MP, Zeig-Owens R, Jaber N, Appel DW, Hall CB, Weakley J, Cohen HW, Shulman L, Kelly K, Prezant D. Obstructive sleep apnea and World Trade Center exposure. J Occup Environ Med. 2014; 56(Suppl 10):S30–34. [PubMed: 25285973]
10. Godderis L, Dours G, Laire G, Viaene MK. Sleep apnoeas and neurobehavioral effects in solvent exposed workers. Int J Hyg Environ Health. 2011; 214:66–70. [PubMed: 20843741]
11. Ulfberg J, Carter N, Talback M, Edling C. Occupational exposure to organic solvents and sleep-disordered breathing. Neuroepidemiology. 1997; 16:317–326. [PubMed: 9430132]
12. Rauh VA, Garcia WE, Whyatt RM, Horton MK, Barr DB, Louis ED. Prenatal exposure to the organophosphate pesticide chlorpyrifos and childhood tremor. Neurotoxicology. 2015; 51:80–86. [PubMed: 26385760]
13. Stallones L, Beseler C. Pesticide illness, farm practices, and neurological symptoms among farm residents in Colorado. Environ Res. 2002; 90:89–97. [PubMed: 12483798]
14. Gaspari RJ, Paydarfar D. Dichlorvos-induced central apnea: effects of selective brainstem exposure in the rat. Neurotoxicology. 2011; 32:206–214. [PubMed: 21241738]
15. Costa LG, Giordano G, Guizzetti M, Vitalone A. Neurotoxicity of pesticides: a brief review. Front Biosci. 2008; 13:1240–1249. [PubMed: 17981626]
16. Popovska-Gorevski M, Dubocovich ML, Rajnarayanan RV. Carbamate Insecticides Target Human Melatonin Receptors. Chem Res Toxicol. 2017
17. Butler MP, Smales C, Wu H, Hussain MV, Mohamed YA, Morimoto M, Shea SA. The Circadian System Contributes to Apnea Lengthening across the Night in Obstructive Sleep Apnea. Sleep. 2015; 38:1793–1801. [PubMed: 26039970]

18. Reutrakul S, Siwasaranond N, Nimitphong H, Saetung S, Chirakalwasan N, Chailurkit LO, Srijaruskul K, Ongphiphadhanakul B, Thakkinstian A. Associations between nocturnal urinary 6-sulfatoxymelatonin, obstructive sleep apnea severity and glycemic control in type 2 diabetes. Chronobiol Int. 2017; 34:382–392. [PubMed: 28128991]
19. Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, Blair A. The Agricultural Health Study. Environ Health Perspect. 1996; 104:362–369. [PubMed: 8732939]
20. House JS, Wyss AB, Hoppin JA, Richards M, Long S, Umbach DM, Henneberger PK, Beane Freeman LE, Sandler DP, Long O'Connell E, Barker-Cummings C, London SJ. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. J Allergy Clin Immunol. 2016
21. Carnes MU, Hoppin JA, Metwali N, Wyss AB, Hankinson JL, O'Connell EL, Richards M, Long S, Beane Freeman LE, Sandler DP, Henneberger PK, Barker-Cummings C, Umbach DM, Thorne PS, London SJ. House Dust Endotoxin Levels Are Associated with Adult Asthma in a U.S. Farming Population. Ann Am Thorac Soc. 2016
22. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997; 20:705–706. [PubMed: 9406321]
23. Hoppin JA, Long S, Umbach DM, Lubin JH, Starks SE, Gerr F, Thomas K, Hines CJ, Weichenthal S, Kamel F, Koutros S, Alavanja M, Beane Freeman LE, Sandler DP. Lifetime organophosphorous insecticide use among private pesticide applicators in the Agricultural Health Study. J Expo Sci Environ Epidemiol. 2012; 22:584–592. [PubMed: 22854518]
24. Reiner A, Yekutieli D, Benjamini Y. Identifying differentially expressed genes using false discovery rate controlling procedures. Bioinformatics. 2003; 19:368–375. [PubMed: 12584122]
25. Kubin L, Fenik V. Pontine cholinergic mechanisms and their impact on respiratory regulation. Respir Physiol Neurobiol. 2004; 143:235–249. [PubMed: 15519558]
26. Gammon DW, Liu Z, Becker JM. Carbofuran occupational dermal toxicity, exposure and risk assessment. Pest Manag Sci. 2012; 68:362–370. [PubMed: 21834090]
27. Gopal K, Ram M. Alteration in the neurotransmitter levels in the brain of the freshwater snakehead fish (Channa punctatus) exposed to carbofuran. Ecotoxicology. 1995; 4:1–4. [PubMed: 24197545]
28. Bretaud S, Saglio P, Saligaut C, Auperin B. Biochemical and behavioral effects of carbofuran in goldfish (Carassius auratus). Environ Toxicol Chem. 2002; 21:175–181. [PubMed: 11804052]
29. Kamboj A, Kiran R, Sandhir R. Carbofuran-induced neurochemical and neurobehavioral alterations in rats: attenuation by N-acetylcysteine. Exp Brain Res. 2006; 170:567–575. [PubMed: 16307259]
30. Zirlik S, Hildner KM, Targosz A, Neurath MF, Fuchs FS, Brzozowski T, Konturek PC. Melatonin and omentin: influence factors in the obstructive sleep apnoea syndrome? J Physiol Pharmacol. 2013; 64:353–360. [PubMed: 23959732]
31. Brenner H. Correcting for exposure misclassification using an alloyed gold standard. Epidemiology. 1996; 7:406–410. [PubMed: 8793367]
32. Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Peppard PE. Association between asthma and risk of developing obstructive sleep apnea. JAMA. 2015; 313:156–164. [PubMed: 25585327]
33. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015; 7:1311–1322. [PubMed: 26380759]
34. Hoppin JA, Yucel F, Dosemeci M, Sandler DP. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol. 2002; 12:313–318. [PubMed: 12198579]
35. Engel W, Vogt A, Batsford SR. Validity of prior absorption of serum samples with Reiter's spirochetes in serological diagnosis of Borrelia burgdorferi infections. Eur J Clin Microbiol Infect Dis. 2000; 19:960–963. [PubMed: 11205637]
36. Agency EP. Carbofuran; Product Cancellation Order. 2009. [cited 2016 October 18]. Available from: https://www.federalregister.gov/documents/2009/03/18/E9-5833/carbofuran-product-cancellation-order

37. Gupta A, Agarwal R, Shukla GS. Functional impairment of blood-brain barrier following pesticide exposure during early development in rats. Hum Exp Toxicol. 1999; 18:174–179. [PubMed: 10215108]

Table 1

Characteristics of sleep apnea cases and controls in the ALHS

	Sleep Apnea cases (n=234)	Non-cases (n=1335)
Characteristic	**n (%)/mean (SD)**	**n (%)/mean (SD)**
Asthma		
No	113 (48.3)	934 (70.0)
Yes	121 (51.7)	401 (30.0)
State of residence		
Iowa	176 (75.2)	924 (69.2)
North Carolina	58 (24.8)	411 (30.8)
Cardiovascular Disease		
No	205 (87.6)	1292 (96.8)
Yes	29 (12.4)	43 (3.2)
Hypertension		
No	113 (48.3)	855 (64.0)
Yes	121 (51.7)	480 (36.0)
Diabetes		
No	186 (79.5)	1212 (90.8)
Yes	48 (20.5)	123 (9.2)
Age at home visit (years)	64.7 (10.6)	63.2 (11.6)
Body Mass Index (BMI)	34.5 (6.1)	29.8 (5.6)

Definition of Abbreviation: ALHS = Agricultural Lung Health Study

Table 2

Sleep apnea and pesticide use among male applicators in the ALHS*

	Sleep Apnea (N=1569)					
	Cases (n=234)	Non-cases (n=1335)				
Pesticide	**Exposed, n (%)**	**Exposed, n (%)**	**OR**	**95% CI†**		**P-value‡**
Herbicide						
Acetic acid						
Clopyralid	23 (9.8)	109 (8.2)	1.09	0.63	1.87	0.765
Flumetsulam	21 (9.0)	111 (8.3)	0.98	0.57	1.68	0.929
Dicamba	137 (58.5)	736 (55.1)	1.08	0.76	1.53	0.681
Picloram	25 (10.7)	204 (15.3)	0.61	0.38	1.00	0.048
Amide						
Dimethenamid	13 (5.6)	87 (6.5)	0.90	0.47	1.73	0.759
Fomesafen	11 (4.7)	94 (7.0)	0.56	0.28	1.15	0.114
Anilide						
Sulfentrazone	8 (3.4)	44 (3.3)	1.34	0.58	3.13	0.495
Mesotrione	18 (7.7)	151 (11.3)	0.76	0.43	1.32	0.323
Chloroacetanilide						
Acetochlor	33 (14.1)	215 (16.1)	0.69	0.44	1.08	0.101
Alachlor	134 (57.3)	796 (59.6)	0.82	0.60	1.12	0.219
Metolachlor	136 (58.1)	719 (53.9)	1.19	0.86	1.65	0.285
Cyclohexene oxime						
Clethodim	9 (3.8)	45 (3.4)	1.59	0.72	3.53	0.252
Sethoxydim	46 (19.7)	318 (23.8)	0.82	0.57	1.20	0.311
Dinitroaniline						
Pendimethalin	102 (43.6)	594 (44.5)	0.99	0.73	1.35	0.970
Trifluralin	116 (49.6)	716 (53.6)	0.83	0.60	1.14	0.251
Imidazolinone						
Imazaquin	40 (17.0)	199 (14.9)	1.11	0.74	1.67	0.614
Imazethapyr	96 (41.0)	552 (41.3)	0.96	0.68	1.36	0.816
Nitrile						

	Sleep Apnea (N=1569)					
	Cases (n=234)	Non-cases (n=1335)				
Pesticide	**Exposed, n (%)**	**Exposed, n (%)**	**OR**	**95% CI†**		**P-value‡**
Bromoxynil	53 (22.6)	307 (23.0)	0.95	0.65	1.38	0.778
Nitrophenyl ether						
Acifluorfen	24 (10.3)	194 (14.5)	0.77	0.47	1.25	0.284
Lactofen	7 (3.0)	36 (2.7)	0.94	0.39	2.29	0.894
Organophosphorus						
Glufosinate Ammonium	19 (8.1)	111 (8.3)	0.95	0.55	1.67	0.869
Glyphosate	210 (89.7)	1224 (91.7)	1.05	0.62	1.77	0.860
Oxazole						
Isoxaflutole	14 (6.0)	84 (6.3)	1.00	0.53	1.91	0.996
Protroleum products						
Petroleum Distillates	75 (32.0)	450 (33.7)	0.96	0.69	1.34	0.822
Phenoxy						
2,4-D	208 (88.9)	1138 (85.2)	1.58	0.96	2.60	0.073
Fluazifop-butyl	34 (14.5)	191 (14.3)	1.23	0.80	1.91	0.349
Fenoxaprop-p-ethyl	9 (3.8)	65 (4.9)	0.87	0.40	1.89	0.719
Pyridine						
Triclopyr	18 (7.7)	118 (8.8)	1.00	0.57	1.74	0.999
Quaternary ammonium						
Paraquat	48 (20.5)	295 (22.1)	1.15	0.78	1.69	0.492
Sulfonanilide						
Cloransulam-methyl	13 (5.6)	55 (4.1)	1.44	0.72	2.87	0.297
Triazine						
Atrazine	202 (86.3)	1087 (81.4)	1.54	0.97	2.43	0.065
Simazine	18 (7.7)	95 (7.1)	1.16	0.65	2.06	0.622
Triazinone						
Metribuzin	100 (42.7)	602 (45.1)	0.82	0.60	1.14	0.242
Urea Substitute						
Chlorimuron Ethyl	82 (35.0)	491 (36.8)	0.96	0.69	1.32	0.782
Nicosulfuron	38 (16.2)	172 (12.9)	1.50	0.97	2.32	0.068

	Sleep Apnea (N=1569)					
	Cases (n=234)	Non-cases (n=1335)				
Pesticide	**Exposed, n (%)**	**Exposed, n (%)**	**OR**	**95% CI[†]**		**P-value[‡]**
Rimsulfuron	16 (6.8)	72 (5.4)	1.49	0.81	2.74	0.198
Thifensulfuron-methyl	10 (4.3)	92 (6.9)	0.67	0.32	1.39	0.281
Other						
Bentazon	60 (25.6)	356 (26.7)	0.95	0.67	1.36	0.790
Clomazone	22 (9.4)	187 (14.0)	0.60	0.36	1.01	0.053
Plant Growth Regulator						
Maleic Hydrazide	8 (3.4)	61 (4.6)	0.87	0.36	2.09	0.747
Insecticide						
Biological						
Bacillus Thuringiensis	14 (6.0)	81 (6.1)	1.25	0.64	2.43	0.508
Carbamate						
Aldicarb	17 (7.3)	102 (7.6)	1.52	0.80	2.88	0.205
Carbaryl	128 (54.7)	729 (54.6)	1.11	0.81	1.54	0.511
Carbofuran	100 (42.7)	392 (29.4)	1.83	1.34	2.51	0.0002
Organochlorine						
Lindane	51 (21.8)	261 (19.5)	1.05	0.73	1.53	0.787
Organophosphate[§]						
Acephate	15 (6.4)	138 (10.3)	0.67	0.34	1.32	0.246
Chlorpyrifos	111 (47.4)	672 (50.3)	0.90	0.66	1.23	0.513
Diazinon	62 (26.5)	400 (30.0)	0.85	0.60	1.20	0.343
Dimethoate	10 (4.3)	66 (4.9)	0.93	0.45	1.93	0.853
Disulfoton	11 (4.7)	80 (6.0)	1.11	0.53	2.33	0.776
Malathion	162 (69.2)	979 (73.3)	0.94	0.67	1.32	0.735
Tebupirimfos	19 (8.1)	94 (7.0)	1.06	0.59	1.89	0.846
Terbufos	124 (53.0)	579 (43.4)	1.34	0.97	1.85	0.072
Pyrethroid						
Bifenthrin	5 (2.1)	11 (0.82)	4.39	1.33	14.5	0.015

	Sleep Apnea (N=1569)					
	Cases (n=234)	Non-cases (n=1335)				
Pesticide	**Exposed, n (%)**	**Exposed, n (%)**	**OR**	**95% CI†**		**P-value‡**
Cyfluthrin	28 (12.0)	137 (10.3)	1.24	0.77	2.02	0.377
Lambda Cyhalothrin	18 (7.7)	87 (6.5)	1.38	0.75	2.53	0.298
Permethrin	31 (13.2)	140 (10.5)	1.49	0.93	2.38	0.098
Tefluthrin	19 (8.1)	76 (5.7)	1.36	0.75	2.48	0.314
Other						
Fly Spray	7 (3.0)	22 (1.6)	1.89	0.72	4.97	0.197
Fungicide						
Captan	34 (14.5)	174 (13.0)	1.07	0.69	1.67	0.758
Chlorothalonil	15 (6.4)	99 (7.4)	0.99	0.52	1.89	0.975
Metalaxyl	34 (14.5)	310 (23.2)	0.59	0.38	0.92	0.020
Rodenticide						
Warfarin	5 (2.1)	46 (3.4)	0.41	0.14	1.17	0.094

Definition of Abbreviation: ALHS = Agricultural Lung Health Study

*Adjusted for age, state, BMI, diabetes, hypertension, asthma, and cardiovascular disease.

†OR: Odds Ratio, 95 % CI: 95% Confidence Interval

‡P values are uncorrected. With either Bonferroni correction for 63 tests or control of the false discovery rate at 5%, only the association with carbofuran would be considered statistically significant.

§Organophosphorus Insecticide is a different chemical class than Organophosphorus Herbicide.

Table 3

Sleep apnea in relation to lifetime days of use of carbofuran among male applicators in the ALHS [*]

	Sleep Apnea (N=1569)						
	Cases (n=234)	Non-cases (n=1335)					
Lifetime days of use	**Exposed, n (%)**	**Exposed, n (%)**	**OR[†]**	**95% CI[‡]**		**p-value[§]**	**Trend p-value[§]**
Never use	126 (57.8)	859 (69.5)	ref	ref	ref	ref	
< 14.5	33 (15.1)	144 (11.7)	1.69	1.06	2.67	0.03	
≥14.5 to <38.75	26 (11.9)	115 (9.3)	1.71	1.03	2.83	0.04	
≥38.75	33 (15.1)	117 (9.5)	1.75	1.08	2.82	0.02	0.003
Missing	16	100					

Definition of Abbreviation: ALHS = Agricultural Lung Health Study

[*]Adjusted for age, state, BMI, asthma, cardiovascular disease, hypertension, diabetes

[†]OR: odds Ratio

[‡]95% CI: 95% confidence interval

[§]P-value, uncorrected