2016

Neurotoxic Effects of Occupational Exposures in Agricultural Workers

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Neurotoxic effects of occupational exposures in agricultural workers

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ABSTRACT

Background: Pesticides and organic solvents are two classes of neurotoxic substances regularly used in agriculture. Pesticides have been studied in relation to a range of nervous system effects, and have been repeatedly shown to relate to depression in agricultural workers. Likewise, occupational solvent exposure is recognized as a risk factor for central nervous system effects, including mood disturbances and cognitive impairment, across various industries. Many gaps in knowledge regarding the effects of chronic exposure to these substances on mental/neurological health in agricultural workers still exist. The specific aims of the current analysis were to 1.) Estimate associations between metrics of a.) pesticide exposure and b.) organic solvent exposure and results from the Center for Epidemiologic Studies Depression Scale of depressed mood; and 2.) Estimate associations between questionnaire-based organic solvent exposure metrics and measures of central nervous system function assessed from a battery of nine neurobehavioral tests.

Methods: This was a cross-sectional analysis of a subsample of 701 licensed pesticide applicators (i.e., the Neurobehavioral Testing Study add-on) that participated in the Agricultural Health Study (AHS) in Iowa and North Carolina and were evaluated for neurobehavioral (NB) performance between 2006 and 2008. Participants eligible for the NB Study were male farmers that completed all phases of AHS questionnaires. Further exclusion criteria excluded AHS participants with a diagnosis of various medical conditions, as well as those who reported drinking >42 alcoholic beverages/week, reported pesticide poisoning at AHS Phase 3, or lived >150 miles away from testing facilities. Stratified random sampling was conducted among eligible participants to provide adequate representation of individuals with higher lifetime use of selected organophosphate pesticides. A total of 1,807 AHS participants were subsequently eligible for the NB Study, of which 39% participated. Ever-use and cumulative use of pesticide information was compiled from all phases of the AHS for 16 specific organophosphates, 4 specific carbamates, all-organophosphate pesticide use, all-pesticide use, and high pesticide exposure events (HPEEs). At the time of neurobehavioral evaluation, solvent exposure was assessed in a questionnaire. An ever-use and categorical years of use variable based on the median years of exposure for each measure were derived for gasoline, paint/lacquer thinner, petroleum distillates, and use of any solvent (sample sizes for benzene, toluene, and turpentine were not large enough to evaluate). Three solvent-based activity variables ascertained at enrollment were also evaluated (ever-use of solvent additives in mixing pesticides, ever-use of gasoline to clean hands or equipment, and ever-use of other solvents for cleaning). Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D). Various neurobehavioral functions, including attention, visual scanning/processing, motor speed, motor coordination, learning, memory, and motor speed/scanning were evaluated using a battery of nine tests administered by trained professionals. Multivariable linear regression was employed to estimate the association between each measure of pesticide exposure and solvent exposure and CES-D score; as well as each measure of solvent exposure and performance on each neurobehavioral test.

Results: Direction of associations between pesticide exposure measures and CES-D score were inconsistently positive and negative. However, few specific pesticide measures were found to be significantly associated with CES-D score ($p<0.05$). Disulfoton and ethoprop were consistently

associated with greater depressive symptoms when examined as ever-use and cumulative lifetime days of use. HPEE was also associated with greater depressive symptoms. Dichlorvos appeared to consistently relate to less depressive symptoms when assessed as ever-use and cumulative lifetime days of use; ever-use of malathion showed a similar effect, but not when characterized as cumulative use. More statistically significant ($p<0.05$) effects of pesticide exposure were seen when evaluating CES-D as a continuous versus binary outcome. Forty-one percent of participants reported any solvent exposure. Solvent exposure measures consistently appeared to be risk factors for greater depressive symptoms. Several variables involving any solvent use, gasoline use, and petroleum distillate use showed statistically significant positive associations with CES-D score. More effects of solvent exposure were seen when evaluating CES-D as a continuous rather than binary outcome. No clear pattern of association existed between solvent exposure and general neurobehavioral function. Several negative associations were found between gasoline and painter thinner exposure and tests assessing motor speed. Petroleum distillate measures appeared to relate to better performance on a test evaluating motor coordination. Performance on tests of attention, memory, learning, and visual scanning/information processing did not appear to be substantially affected by solvent exposure.

Conclusions: Results from the current study may suggest relationships between neurotoxic chemicals, such as some pesticides and organic solvents, and mental/neurobehavioral health outcomes that exist on a linear scale. This study serves as a justification for further research as well as early behavioral interventions in agricultural workers. That is, because subtle changes in central nervous system function can occur with exposures that may exist on a sub-clinical level, efforts should be taken to minimize exposure and prevent further progression that could eventually lead to clinical disorders.

INTRODUCTION

Problem Statement

The National Institute for Occupational Safety and Health (NIOSH) has considered neurotoxic disorders one of the ten leading causes of work-related disease and injury since 1983 based on four reasons: the large number of chemicals characterized by neurotoxic properties; the vulnerability of the nervous system to damage; the large number of workers exposed to neurotoxic substances; and the importance of a healthy nervous system for daily functioning and subsequent potential severity of neurotoxic disorder. It has been estimated that approximately eight million workers may be exposed full-time to neurotoxic agents.[1] Neurotoxic effects occur from a large range of chemicals, especially those lipid-soluble in nature, and a large variation of central nervous system (CNS) disturbances may result. The extent of exposure to neurotoxic substances within U.S. workers in unknown, and existing systems for health and safety surveillance do not adequately measure the range of effects produced by such substances. CNS changes can lead to workplace accidents and greatly influence quality of life.[1] The agricultural industry provides workers with opportunity for exposure to various neurotoxic substances, including pesticides and organic solvents.[2,3] There is a deficit of research that focuses on neurological symptoms in farmers exposed to these substances.

Several national and international agencies recommend a battery of screening tests for the evaluation of neurotoxicity of substances in humans.[1,4] NIOSH and the National Academy of Sciences have supported that neurotoxicity test data is inadequate.[1] Additionally, NIOSH calls for research on the magnitude of neurotoxic effects that have been identified.[1] Much of the past research on occupational exposures in farmers, particularly on pesticides, has relied on report of a diagnosis of neurological disorders.[3,5-7] However, small changes in mental or behavioral

functioning induced by chemicals are often undiagnosed or unrecognized.[3,8] Neurologic symptoms may indicate early signs of dysfunction before clinically measurable signs appear.[9] The proposed study uses a battery of neurobehavioral tests as well as a valid, reliable, and internally consistent diagnostic scale for depressive mood[10] to not only accurately record symptoms and function, but also measure the magnitude of neurological effects on continuous scales.

Research regarding risk factors for central nervous system dysfunction in agricultural workers will contribute to policy and practice to better protect an industry of workers that are shown to experience high rates of mental health problems.[9,11,12] It will inform occupational health and safety standards, worker practice, education and training programs, as well as exposure and medical monitoring/surveillance. Specifically, quantifying the severity of depressive symptoms to which agricultural workers may be vulnerable due to various aspects of pesticide and organic solvent exposures would support knowledge of how depression develops in agricultural workers. Additionally, evaluating risk for solvent-induced neurobehavioral dysfunction in agricultural workers could identify an area for increased awareness, caution, training, and protection in agricultural practice.

Literature Review

Neurotoxic disorders are one of the ten leading causes of work-related disease and injury due to the widespread use of neurotoxic substances and the potential adverse effects that have implications on work and life.[1] Two classes of neurotoxic substances regularly used in agriculture include pesticides and organic solvents.[1,3,9] For example, pesticides have been studied in relation to a range of nervous system effects, and have been repeatedly shown to relate to

depression in agricultural workers.[5,6,9,10,13-16] Likewise, occupational solvent exposure has been consistently shown to induce many variations of chronic central nervous system disorders in various industries.[3,17-20] However, many gaps in knowledge regarding the neurotoxicity of agricultural exposures still exist. A majority of studies on depression in relation to pesticide exposure have relied on self-report of physician-diagnosed depression,[5,6] and a few have used criteria from diagnostic screening tests, but in a dichotomized fashion (i.e., depressed vs. non-depressed).[10,13] However, diagnostic scales have been underutilized in determining the magnitude of depressive symptoms on a continuous incremental scale experienced by agricultural workers; and how depressive symptoms may relate to acute high-level or chronic low- to moderate-level pesticide exposure. Additionally, there is an even larger gap regarding neurobehavioral outcomes attributed to solvent use specifically in agricultural workers; although tasks that require solvents are regularly performed by farmers, and farmers often hold secondary jobs involving solvent exposure.[2,21-23]

Neurotoxic manifestations of pesticide exposure

Farmers are shown to suffer from high rates of depression, anxiety, and reduced mental health-related quality of life.[11,12,24-26] Estimates of depression prevalence in farmers have ranged between about 8% and 20%, compared to a national prevalence of approximately 8%.[6,27] Many risk factors for depression exist in this population that are often out of the farmer's control, including financial strain, social isolation, long and physically demanding work requirements, working conditions and processes that rely on variable weather, and health comorbidities.[10-12,28] Exposure to neurotoxic substances, however, can be limited with appropriate engineering controls, worker practices, and use of personal protective equipment.

Farmers are vulnerable to substantial pesticide exposure; approximately 70% of insecticides used in the U.S. are used in agriculture.[29] These substances, such as organophosphate pesticides, can induce neurotoxicity due to an inhibition of acetylcholinesterase, leading to overabundant amounts of acetylcholine remaining in neurotransmitter synapses, which can cause damage over time; as well as a possible disruption of serotonin, leading to mood or behavioral changes.[10,30,31] Signs of toxicity can be observed when at least 20% of the acetylcholinesterase activity is inhibited; and rat models have supported that chronic inhalation exposure to the organophosphate dichlorvos over two years can deplete more than 90% of the enzyme's activity. But evidence supports that the most important predictor of toxicity is how rapidly the acetylcholinesterase inhibition occurs, which has a direct impact on the adaptation abilities of the nervous system.[32] Organophosphates, carbamates, organochlorines, pyrethroid insecticides, herbicides, fungicides, and fumigants have been supported to induce a range of neurologic effects and complaints, from mood disorders to central and peripheral nervous system disruptions.[9,15,16,33,34]

Cumulative exposure to various specific pesticides, pesticide poisoning, high pesticide exposure events, and pesticide classes including organophosphates, insecticides, organochlorines, and fumigants have been found to relate to self-reported physician-diagnosed depression.[5-7,35,36] For example, self-reported physician-diagnosed depression was found to be associated with ever-use of fumigants, herbicides, organochlorines, organophosphates, and some specific carbamates in a longitudinal analysis of Agricultural Health Study (AHS) participants.[5] Additionally, the ever-use of some specific organophosphates, including diazinon, malathion, and parathion were consistent risk factors for depression.[5] Similarly, a cross-sectional study of AHS participants demonstrated pesticide poisoning and high pesticide exposure events to be risk

factors for a diagnosis of depression (odds ratios=2.57, 1.65, respectively); cumulative exposure to all pesticides was not found to be associated with depression until poisoning cases were excluded.[6] A study of agricultural workers in France found an association between herbicide use and self-reported treatment/hospitalization for depression, but not for insecticides or fungicides.[36] Two studies that focused on wives participating in the AHS supported pesticide poisoning and husbands' ever-use of carbamates to be associated with a diagnosis of depression, but not wives' ever-use or cumulative use of pesticides or husbands' use of other pesticides.[7,35] Relying on self-report of diagnosed depression may result in misclassification due to misreporting or an under-diagnosis of the condition.

On the other hand, several studies have evaluated depression by using self-report or clinical measures of symptomology as opposed to report of diagnosis. For example, an AHS study evaluated complaints of neurologic symptoms reported by pesticide applicators and found associations between report of high- versus low-frequency of depressive symptoms and high cumulative use of any pesticide, all insecticides, organophosphates, organochlorines, and fumigants.[9] Depressive symptoms relied on self-report as opposed to clinical ascertainment, and symptoms were not evaluated on a continuous scale. Cross-sectional and longitudinal analyses of Colorado farm residents have found pesticide poisoned participants to be between two and nearly five times more likely to score high vs. low on the clinical Center for Epidemiologic Studies Depression Scale of depressed mood (using a threshold score of 16).[10,13] A study of sheep farmers in the UK chronically exposed to low levels of organophosphates were more likely to exhibit clinical depression as assessed by the Hospital Anxiety and Depression Scale when compared to rural police officer controls.[33] Another study on sheep farmers found an association between clinical depression, as determined by the PHQ-9 Depression scale, and pesticide

poisoning, but not for ever-use of pesticides.[37] While an analysis of depressive symptoms obtained from the clinical Brief Symptom Inventory (BSI) showed that the median scores of depression in both organophosphate and carbamate poisoned banana farmers were higher than in the referent group, a multivariable model employed a threshold BSI cutoff to demonstrate that reporting multiple pesticide poisonings was associated with an elevated depression score.[38] Therefore, a majority studies evaluating pesticide exposure and clinically-screened depression have typically relied upon dichotomous outcomes.

The magnitude of incremental changes in depressive symptoms in relation to chronic low- or moderate-level pesticide exposure in a diverse sample of farmers is not well-established. Using a valid, reliable, and internally consistent diagnostic scale for depressive mood, such as the Center for Epidemiologic Studies Depression Scale (CES-D),[39] would allow for an evaluation of the severity of symptoms that may exist on a sub-clinical or undiagnosed level. This is particularly important because farmers have been found to be reluctant to seek treatment for mental health conditions despite displaying depressive symptoms.[6,40] Furthermore, employing a continuous scale for depressive symptoms may allow the examination of subtle changes that may not otherwise be detectable with a binary classification for depression. Quantifying the extent to which chronic low- to moderate-levels of exposure may relate to depressive symptom severity could inform monitoring and evaluation programs to better protect the mental health of agricultural workers and provide opportunities for intervention of modifiable risk factors.

Neurotoxic manifestations of organic solvent exposure

Organic solvents constitute a wide variety of organic chemicals that differ variably in structure, such as carbon disulfide, n-hexane, methyl n-butyl ketone, toluene, benzene, xylene, and trichloro-ethylene.[1,2,20,41] Due to their lipid-solubility, solvents are readily absorbed, can cross the blood-brain barrier, and subsequently undergo biotransformation. Resulting metabolites, which can often have greater toxicity than their parent compounds, accumulate in lipid-rich tissues such as those found in the nervous system.[17,42] However, the specific mechanism that leads to neurotoxic effects is not well understood.[43] For example, one animal study on rats exposed to unleaded gasoline found reductions in neurotransmitters norepinephrine, dopamine, and serotonin (which is linked to mood disorders), and, as seen in organophosphate exposure, a reduction in acetylcholinesterase activity.[44]

Solvents that can produce CNS disorders are present in a variety of occupational sources, including paints, varnishes, lacquers, stains, glues, adhesives, gasoline, and cleaning/degreasing agents.[1,17] Chronic exposure to solvents can lead to chronic solvent-induced encephalopathy, which is defined by mild to severe cognitive impairment.[3,41,43,45] Additionally, there are several categories of recognized solvent-induced CNS disorders according to severity as defined by the International Solvent Workshop.[17,18,46] Type 1 is characterized by fatigue, memory impairment, irritability, difficulty in concentrating, and mild mood disturbances. Type 2A includes sustained personality or mood changes, such as emotional instability and diminished impulse control and motivation. Type 2B involves impairment in intellectual function manifested by diminished concentration, memory, and learning capacity. Type 3 categorizes severe and pronounced neurologic effects that are not typical of occupational exposures.[17] Workers that come into regular contact with such substances have been shown to be at a higher risk for Type 1, Type 2A, and Type 2B neurobehavioral dysfunction than unexposed workers in studies on a variety of

different industries.[17] While these classifications may constitute overt clinical outcomes, research has also identified the importance of chronic low solvent exposures in inducing subtle neurobehavioral effects.[8] Furthermore, a global reduction in solvent exposures attributed to better occupational hygiene practices has led to milder or less obvious chronic solvent-induced encephalopathy symptoms, which contributes to an underdiagnoses of the condition.[18,20,47,48] Therefore, subtle neurotoxic effects induced by solvent exposure should be studied using validated neurobehavioral tests.

Studies of neurotoxic effects of chronic chemical exposures in farmers have mainly focused on pesticide exposure.[14-16,31,49] However, maintenance and repair of farm machinery and equipment are primary regular tasks performed by farmers, and often require use of solvent-based materials (e.g., paints, adhesives, gasoline, degreasers, lubricants, etc.).[2,50,51] While studies on solvent exposures in agricultural workers have evaluated correlations with some health outcomes,[21,52] those focusing on neurotoxic effects of solvent exposures are scarce. A study on a rural population of both farming and non-farming individuals in Ecuador found years of exposure to solvents to be associated with several neurobehavioral outcomes in mixed directions.[53] Solvent use was associated with improved visual perception/memory (Benton Visual Retention test), negatively associated with psychomotor performance (Trails B test), and positively associated with manual dexterity (Santa Anna test). Among the non-significant associations, no relationship was found between solvent use and performance on the Profile of Mood States (POMS), which includes a depression component. However, the evaluation of solvent exposure in this study was not specific to the farming group alone, and only used one general metric of exposure.

While there is a deficit of research pertaining to agricultural workers, the neurotoxic manifestations of solvents have been extensively researched in a wide variety of other occupations.[47] Many of these studies employ validated clinical scales to evaluate these associations. For example, in relation to mental health, one study found that rotogravure printers exposed to toluene displayed higher depression scores on the Symptom Checklist (SCL-35) than controls 20 years after exposure.[54] A study on solvent-exposed munitions workers and mental health outcomes consistently found significantly higher mood/emotional impairment across a variety of clinical tests in the solvent-exposed group versus unexposed controls, and exposure-response associations with years of exposure.[55] Likewise, presence of exposure and duration of exposure were both positively associated with tension-anxiety, hostility, depression, and confusion domains presented on the POMS scale in a study of Venezuelan adhesive factory workers exposed to organic solvent mixtures.[56]

On the other hand, some occupational studies have found null results regarding solvents and mental health-related outcomes. An assessment of gun factory workers found no difference in Hospital Anxiety and Depression scores between those with long-term low-level exposure to solvents and those with no exposure.[57] Similarly, acetone-exposed acetate fiber workers demonstrated similar scores on the Manifest Anxiety Scale and Self-Rating Depression Scale as unexposed controls.[58] The effects of occupational solvent exposure on mental health and depression warrants further research.

In addition to mental health, other CNS outcomes have been studied in relation to solvent exposure using a large variety of clinical scales. Since the range of neurobehavioral domains that may be affected by neurotoxic exposures is extremely wide, researchers typically administer batteries of tests. The Neurobehavioral Evaluation System (NES) is a computerized battery that

includes over a dozen neurobehavioral tests of psychomotor speed and control, perpetual speed, learning, attention, and affect.[59] Many occupational studies have employed the NES battery or similar adaptations to evaluate the range of CNS effects in solvent-exposed workers.[56,58,60-67] For example, a study on shipyard painters in Korea found visual scanning/processing speed (Symbol Digit Substitution test) to be worse in those with more than 20 years of work duration compared to the group with less than 10 years of work duration after controlling for age and education; no associations were found for measures of psychomotor speed.[60] A study of paint factory workers in Taiwan used environmental sampling to compare no-, low-, and high-exposure groups and found associations with increasing exposure and poorer performance on measures of sustained attention (Continuous Performance test), processing speed (Pattern Comparison test), and visual memory (Pattern Memory test).[61] There were no associations for eight other administered neurobehavioral tests. Likewise, a study of union painters in Michigan found that increasing solvent exposure ascertained by questionnaire was related to poorer visual scanning/processing speed (Symbol Digit Substitution test) and memory (Pattern Memory test, Digit Span test), but not psychomotor speed (Simple Reaction Time).[62] Deficits in visual scanning/processing (Symbol Digit Substitution), psychomotor speed (Simple Reaction time), and manual dexterity (Santa Anna test) have also been found in Venezuelan adhesive factory workers when compared to controls, and poorer performance correlated with years of exposure. Null associations were found for tests of memory (Digit Span, Benton tests) and motor control/speed (Pursuit Aiming test).[56]

In light of the potential neurotoxic effects of solvent exposure, a lack of routine use of adequate personal protective equipment (PPE) during farm activities by agricultural workers is concerning.[2,68] Both inhalation and dermal exposure are potential routes of exposure. A pilot

study in Kentucky supported that farm tasks involving solvents are often performed indoors and/or without PPE. Dermal patches detected very high levels of xylene and toluene, although n-hexane and benzene were also detected.[2] Additionally, at least 22-28% of agricultural workers surveyed from North Carolina and Iowa reported cleaning equipment with solvents at least once a month; 8% reported mixing solvents with pesticides, and 16% reported using solvents in off-farm jobs.[23] Therefore, agricultural workers are at risk for neurotoxic effects induced by solvents. Research on the extent to which this occupational population may experience solvent-induced CNS effects would contribute to an understanding of worker practices involving solvents and potential implications for strategies to reduce exposure and prevent adverse effects.

Specific Aims

The current study was a cross-sectional analysis of the central nervous system effects related to chemical exposures for which agricultural workers are at risk. As mentioned, neurotoxic disorders are a leading cause of workplace-related illness and injury in the U.S. because of the widespread use of neurotoxic substances and the potential for work and life impairment due to central nervous system dysfunction. Examples of central nervous system effects include mood disorders, such as depression, and impaired neurobehavioral functions, such as learning, memory, attention, and motor coordination. Pesticides and organic solvents are supported to be neurotoxic, and the abovementioned literature shows that both are regularly used by agricultural workers. Research has supported that pesticides are associated with depression, both physician-diagnosed and diagnostic scale-confirmed, in agricultural workers. The quantified magnitude of symptoms related to pesticide exposure is less supported. Additionally, solvents have consistently been reported to induce a range of mood disruptions and neurobehavioral

deficits; however, the relationship between solvent exposure and CNS effects in agricultural workers has scarcely been an area of focus in the literature. Therefore, the specific aims of the current analysis were as follows:

Aim 1: A.) Estimate associations between metrics of pesticide exposure and results from the Center for Epidemiologic Studies Depression Scale (CES-D) of depressed mood. B.) Estimate associations between questionnaire-based organic solvent exposure metrics and results from the CES-D scale of depressed mood. Based on the supporting evidence discussed above, it was hypothesized that those with neurotoxic exposures would show more depressive symptoms than those without exposures; furthermore, there would be a positive relationship between cumulative lifetime exposures and depressive symptoms.

Aim 2: Estimate associations between questionnaire-based organic solvent exposure metrics and measures of central nervous system function assessed from a battery of nine neurobehavioral tests. As demonstrated in other occupational groups, it was hypothesized that solvent exposure would be associated with reduced neurobehavioral function.

AIM 1 ANALYSIS: Occupational exposures and depressive symptoms in agricultural workers

Background

Pesticides and organic solvents are two classes of neurotoxic substances regularly used in agriculture.[1,3,9] Pesticides have been studied in relation to a range of nervous system effects, and have been repeatedly shown to relate to depression in agricultural workers.[5,6,9,10,13-16] Likewise, occupational solvent exposure is recognized as a risk factor for central nervous system effects, including mood disturbances and changes, across various industries.[3,17-20] Many gaps in knowledge regarding the effects of chronic exposure to these substances on depressed mood, especially as a continuous measure, in agricultural workers still exist. The specific aims of the current analysis were to estimate associations between metrics of a.) pesticide exposure and b.) organic solvent exposure and results from the CES-D scale of depressed mood.

Methods

Data Source

The current study was a cross-sectional analysis of the neurological outcomes of a subsample of 701 licensed pesticide applicators (i.e., the Neurobehavioral Testing Study add-on) that participated in the Agricultural Health Study (AHS) in Iowa and North Carolina, a collaborative project from the National Cancer Institute, the National Institute of Environmental Health Sciences, and the Environmental Protection Agency.[14-16,22] Information regarding exposure to pesticides, demographics, and co-exposures was collected in three phases between 1993 and 2007 for all AHS participants. Phase 1 of exposure data collection was a self-administered enrollment questionnaire completed at the time of pesticide licensing/recertification and an additional take-home questionnaire completed by 44% of private pesticide applicators

(i.e., farmers) between 1993 and 1997. Subsequently, Phase 2 was a 5-year follow-up phone interview and Phase 3 was a 10-year follow-up phone interview.[22,69] Participants eligible for the Neurobehavioral Testing Study were male (i.e., 99% of AHS sample), AHS participants that were farmers at enrollment, and completed all three phases of questionnaires. Further exclusion criteria excluded AHS participants with a diagnosis of amyotrophic lateral sclerosis, diabetes, multiple sclerosis, Parkinson's disease, retinal or macular degeneration, hypothyroidism, or stroke, as well as those who reported drinking at least 42 alcoholic beverages per week, reported being diagnosed with pesticide poisoning during the Phase 3 interview, or lived greater than 150 miles away from the testing facilities. Random sampling was conducted among eligible participants using a stratified design that allowed oversampling of individuals with higher lifetime use of 10 organophosphate pesticides ascertained in Phase 1 (equal sampling from below and above 75% of exposures in Iowa and 66% of exposures in North Carolina) to assure representation of high-end exposure. A total of 1,807 AHS participants were subsequently eligible for the Neurobehavioral (NB) Testing Study, of which 39% participated (N = 701). Assessment of neurobehavioral function was conducted between 2006 and 2008, occurring no more than one year after the Phase 3 interview. Participants provided informed written consent and were compensated for time and travel. Appropriate Institutional Review Boards approved the study protocol.[14-16]

Pesticide Exposure Assessment

Pesticide exposure was obtained by the AHS and NB Study questionnaire through self-report of frequency and duration of use of specific pesticides, high pesticide exposure events, and pesticide poisoning.[9,15,22] Pesticide exposure information was ascertained in slightly different

ways for each phase/questionnaire: Phase 1 involved reporting ever-use, frequency of use, and years of use for 50 specific pesticides at enrollment and a checklist regarding ever-use of specific chemicals in the take-home questionnaire; Phases 2 and 3 involved open-ended responses in regards to pesticide use since last interview; and the NB Study questionnaire ascertained pesticide ever-use and days of use information for the past 12 months. All pesticide exposure occurred prior to NB testing.[15,16]

The current analysis evaluated 16 organophosphate (OP) pesticides (acephate, chlorpyrifos, coumaphos, diazinon, dichlorvos, dimethoate, disulfoton, ethoprop, fonofos, malathion, parathion, phorate, phosmet, tebupirimfos, terbufos, and tetrachlorvinphos) and four carbamate pesticides (aldicarb, benomyl, carbaryl, and carbofuran) that were sufficiently represented among participants in the NB Study (ever-use $N \geq 50$). All OP pesticides were introduced at either enrollment or the take-home questionnaire in Phase 1, with the exception of tebupirimfos, which was reported initially at Phase 2 after being introduced in 1995. For each individual pesticide, a dichotomous (i.e., ever- vs. never-use at any interview) and a continuous (i.e., cumulative lifetime days of use across all interviews) variable were evaluated. Cumulative days of use for Phase 1 was determined by multiplying the number of days used per year by the number of years used (with the pesticides first reported in the take-home portion assumed to have days used per year and years used equal to the median number of days used per year and years used for all insecticides reported at enrollment for each individual); and determined individually for Phases 2 and 3 and the NB Study questionnaire by multiplying the number of days used per year by years since last interview. Subsequently, these cumulative values were summed for a cumulative lifetime days of use estimate for each pesticide. In addition to the ever-use variable and cumulative lifetime days of use variable for each of the 20 identified pesticides

(16 OPs and 4 carbamates), a summary variable reflecting cumulative lifetime days of use for all OP pesticides, a summary variable reflecting cumulative lifetime days of use for all pesticides (i.e., any of the 50 pesticides included in Phase 1), and a dichotomous variable indicating whether or not a participant had ever experienced a high pesticide exposure event (HPEE) (reported in Phase 1, 2, or 3) were also evaluated. Because cumulative exposure variables tend to be heavily skewed right, $\log_{10}$-transformed cumulative lifetime days of exposure variables were employed in the regression analyses to normalize residuals.[15,16] Therefore, in total, there were 43 measures of pesticide exposure.

Organic Solvent Exposure Assessment

Organic solvent exposure was assessed in the NB Study questionnaire by ascertaining ever-use and years of use for six individual measures of exposure: gasoline, paint/lacquer thinner, turpentine, benzene, toluene, and petroleum distillates. Specifically, the question was phrased: "Have you ever worked with or been exposed to any of the following chemicals for 8 hours a week or more in a past job, your present job, or at home (i.e. hobbies)." Two summary variables were also evaluated: ever-use and cumulative years of use of any solvents. The number of years used for each continuous measure was categorized based on the median number of years of exposure for those reporting ever-use for each respective measure; resulting in a categorical variable for each measure including never-use (referent), years of use at or below the median (i.e., low duration), and years of use above the median (i.e., high duration). The number of respondents for benzene, toluene, and turpentine were not large enough to include in the analysis (N=18, 11, and 5, respectively). Three dichotomous variables ascertained at AHS enrollment (i.e., Phase 1) were also assessed: ever-use of solvent additives when personally mixing

pesticides; ever-use of gasoline to clean hands or equipment; and ever-use of other solvents for cleaning. Therefore, in total, seven ever-use variables and four categorical years of use variables were examined.

Outcome Measure

Depressive symptoms were measured at the time of the NB Study using the Center for Epidemiologic Studies Depression Scale (CES-D), a widely-used self-report scale designed to evaluate current level of depressive symptomology related to depressed affect, positive affect, somatic and retarded activity, and interpersonal relations. The scale has consistently demonstrated validity, reliability, and internally consistency.[39] Participants were asked to "please indicate how often you've felt this way during the past week" in regards to 20 items representing personal feeling or behaviors listed on a questionnaire. Individual items are self-reported on a Likert scale with 0 representing rarely or none of the time and 3 representing most or all of the time (5-7 days). Total scores range from 0 to 60; higher scores reflect greater levels of depressive symptoms. Because of the tendency for CES-D score distributions to be heavily skewed right, $\log_{10}$-transformed CES-D score values were used in any linear regression models to normalize residuals. A CES-D score of 16 or higher may be indicative of a high risk for clinical depression or need for treatment,[13,39] therefore a dichotomous depression variable was created based on this threshold (i.e., a score of below 16 indicated low-risk for depression and a score of 16 or above indicated high-risk for depression) for use in an alternative logistic regression analyses for comparison with results from the linear analysis.

Statistical Analysis

Covariates assessed for inclusion in multivariable analyses as potential confounders were obtained from self-report on the questionnaires. In particular, covariates considered in the pesticide exposure analysis included state (i.e., Iowa or North Carolina), age in years, education, marital status, smoking status, alcohol use, personal protective equipment (PPE) use, co-exposures (i.e., ever-use of organic solvents, welding, or soldering), off-farm job presence, and head injury.

Covariates considered for the solvent exposure analysis included state, age in years, education, marital status, smoking status, alcohol use, PPE use, co-exposures (i.e., cumulative organophosphate exposure or cumulative all-pesticide exposure, ever exposure to welding, and ever exposure to soldering), head injury, and HPEE. Off-farm job exposure was not considered due to the non-specificity of source of exposure in the phrasing of the solvent exposure questionnaire (see *Organic Solvent Exposure Assessment*) and the main focus of the analysis being neurotoxicity of solvent exposure in this specific population (i.e., not source of exposure).

Univariate analyses were used to explore the distribution of CES-D scores (characterized as continuous and high- vs. low-risk dichotomous), pesticide and solvent exposure metrics, and covariates across the entire sample with frequencies and percentages or means and standard deviations (or geometric means and geometric standard deviations for skewed distributions) reported.

Covariates that were individually associated with the $\log_{10}$-transformed CES-D score outcome at a p-value of less than 0.20 through simple linear regression were included in a base model selection that sequentially excluded each covariate with a p-value of 0.20 or greater using a multiple linear regression backward elimination approach; this was conducted using the specific covariates identified for the pesticide exposure analysis and solvent exposure analysis

separately. Therefore, two base linear models were generated: one to be employed in the model of an association between pesticide exposure measures and CES-D score, and one for solvent exposure measures and CES-D score.

Subsequent multivariable analyses employed linear regression models, one for each pesticide exposure variable and each organic solvent exposure variable, controlling for qualified covariates in the base models. The few participants with missing values for variables were excluded from the appropriate multivariable models. Crude and multivariable (i.e., adjusted) beta coefficients with standard errors and p-values were calculated for the relationships between each pesticide variable and CES-D score, as well as each solvent variable and CES-D score.

Similarly, exploratory alternative analyses employed logistic regression using the dichotomous depression outcome (i.e., high-risk vs. low-risk) to compare continuous vs. binary classification of depressive symptoms. The same processes of base model selection were repeated for the logistic regression analyses as were used in the linear regression procedures. Crude and multivariable odds ratios (ORs) with 95% confidence intervals (CIs) were produced for the relationships between each pesticide variable and high- vs. low-risk for depression, as well as each solvent exposure variable and high- vs. low-risk for depression.

All statistical analyses were conducted using SAS software (versions 9.3 and 9.4; SAS Institute Inc., Cary, NC).

Results

Descriptive Characteristics

Table 1 displays the demographic characteristics of the 701 agricultural workers that participated in the study. Approximately half of participants were from Iowa (51%) and half

from North Carolina (49%). The mean age was about 61 years (SD=11.7) and roughly half of the sample had at least a high school education (49%). A large majority of participants were married or living as married (89%). Most of the participants were never smokers (57%), followed by past smokers (36%), and current smokers (7%). A majority of the sample reported drinking 0 alcoholic drinks per week (57%), followed by 1-7 drinks per week (33%), and more than 7 drinks per week (10%). Eighty-six percent of participants reported using PPE. In regards to co-exposures, 41% of the sample reported solvent exposure, 20% reported welding exposure, and 5% reporting soldering. A majority of the participants did not work an off-farm job (61%). Over a third of the sample had not experienced a head injury (76%), followed by 13% experiencing a head injury with loss of consciousness, and 10% reporting a head injury with no loss of consciousness. More than a third of participants reported no HPEEs (77%).

CES-D Scores

Table 2 exhibits the distribution of CES-D scores across the sample. The mean score was 6.5 (SD=6.4; median=5; range=0 – 44). When applying the threshold of a score of less than 16 vs. 16 or greater, about 92% of the sample had a low-risk for depression and approximately 8% were high-risk for depression.

Pesticide Analysis

Characteristics of pesticide exposure across the sample are displayed in Table 3, with geometric means representing the analog of mean $\log_{10}$ values. All but one participant reported exposure to any pesticides, and 97% reported use of OP pesticides. The most common OP pesticide reported was malathion (N=541), while the least common was dimethoate (N=66). The

most commonly reported carbamate exposure was carbaryl (N=440), followed by carbofuran (N=290), aldicarb (N=131), and benomyl (N=116). Univariate distributions of cumulative lifetime days of use are shown for those reporting ever-use (Table 3). As mentioned above, a majority of the sample had not experienced any HPEEs (77%).

Backward elimination linear regression model selection for covariates associated with CES-D score in relation to pesticide exposure confounding resulted in a base model adjusting for marital status and solvent exposure; additionally, though not supported by the model selection procedure, age was included in the final base model due to its well-supported association with mental health.[70,71] See Appendix A for estimates for all covariates. Therefore, the final linear model used in the multivariable (i.e., adjusted) analysis assessing the relationship between pesticide exposure and CES-D score was:

$$\text{Log}_{10}(\text{CES-D score}) = \beta_0 + \beta_1[(\text{ever-use of pesticide}) \text{ or } (\log_{10}(\text{cumulative pesticide exposure}))] + \beta_2(\text{age}) + \beta_3(\text{marital status}) + \beta_4(\text{solvent exposure}) + \varepsilon_i$$

Results for the effects of ever-use of specific pesticides and HPEE on CES-D score are shown in Table 4. Crude and adjusted estimates were similar. There was no consistent pattern of directionality of associations. In the adjusted analysis controlling for age, marital status, and solvent exposure, ever-use of disulfoton and ethoprop were significantly ($p<0.05$) associated with greater depressive symptoms (i.e., higher CES-D score); while ever-use of dichlorvos and malathion were significantly associated with less depressive symptoms. Reporting a HPEE was associated with greater depressive symptoms. No other ever-use associations reached statistical significance.

Crude and adjusted results for the effects of cumulative lifetime days of exposure on CES-D score were similar (Table 5). No consistent directionality of associations was observed. Cumulative exposure to both disulfoton and ethoprop were associated with greater depressive symptoms; while higher exposure to dichlorvos was associated with less depressive symptoms. No other relationships reached statistical significance.

Several hypothetical examples predicting CES-D score are given in Appendix I. For example, an individual that is 60 years old, single, reported solvent exposure, and was exposed to disulfoton for 20 cumulative lifetime days was predicted to have a CES-D score of 7.74; whereas the same person instead exposed to 56 cumulative lifetime days of disulfoton was predicted to have a CES-D score of 8.25 (Appendix I.2). One must note that actual CES-D scores are whole integers, however; the magnitude of difference between scores is the estimate to be interpreted.

Although crude associations existed for dichlorvos, ethoprop, and all OP exposure, results from the multivariable logistic regression analysis revealed no effects of pesticide exposures on high- vs. low-risk for depression (adjusted for age, smoking, alcohol use, solvent exposure, and off-farm job). See Appendix B.

Organic Solvent Analysis

Characteristics of solvent exposure are shown in Tables 6.A and 6.B. Forty-one percent of the sample reported some solvent exposure, with gasoline exposure most common (32%), followed by petroleum distillates (25%), and paint thinner (11%). Exposures to benzene, toluene, and turpentine were all reported by less than 3% of the sample, and were therefore not evaluated in further analyses. Mean years of use of any solvent, gasoline, paint thinner, and petroleum distillates were approximately 33, 26, 22, and 29 years, respectively. Furthermore, at enrollment,

10% of participants reported using solvent additives when mixing pesticides, 41% using gasoline to clean hands or equipment, and 28% using other solvents to clean. Cumulative exposure to specific solvent measures was categorized based on medians of exposure distributions, which are exhibited in Table 6.B. Sample sizes for any solvent use and gasoline use were large enough to further categorize duration of exposure into smaller levels for exploration in multivariable analyses (Appendix C).

Backward elimination linear regression model selection for covariates associated with CES-D score examined in relation to confounding with solvent exposure resulted in a base model adjusting for state, marital status, and HPEE; additionally, age was again forced into the multivariable model. See Appendix D for base model estimates.

Results of the crude and adjusted analyses of the effects of solvent exposure metrics on CES-D score were comparable (Table 7). All estimates revealed a positive estimate for the relationship between ever-use and duration of exposure and greater depressive symptoms (i.e., higher CES-D score). After adjusting for age, state, marital status, and HPEE, the statistically significant ($p<0.05$) risk factors for greater CES-D score included ever-use of any solvents, high duration of any solvent exposure, ever-use of gasoline, ever-use of petroleum distillates, and low duration of petroleum distillate exposure. Further categorization of duration of any solvent exposure and cumulative gasoline exposure variables into quartiles failed to show any different/additional trends in increasing CES-D score with increasing exposure (Appendix E). Associations between the three solvent-related activity measures collected at enrollment (i.e., using solvent additives when mixing pesticides, using gasoline to clean hands or equipment, and using other solvents to clean) and CES-D score were not statistically significant (Table 7).

Hypothetical examples predicting CES-D score with solvent exposure can be found in Appendix I. For example, a 45 year old participant that is married, from Iowa, has not experienced an HPEE, and has never been exposed to any solvent for 8 hours per week or more may have a CES-D score of about 4.37; and the same individual with a high duration of any solvent exposure may have a CES-D score of 5.38 (Appendix I.4). Again, however, CES-D scores in reality are whole integers; therefore the magnitude of difference between groups should be interpreted.

Results from the logistic regression analysis indicated that, while all estimates were positive, many less statistically significant associations existed for the binary CES-D outcome than were examined in the linear regression analysis. After controlling for age, marital status, smoking, alcohol use, lifetime organophosphate pesticide use, and HPEE, ever-use of any solvent was associated with an 80% higher odds of being high-risk for depression relative to never-use (95% CI: 1.02-3.13) (Appendix F.1). Further categorization of selected solvent variables also indicated that highest duration of gasoline exposure (i.e., over 45 years) was associated with a 2.56 times greater likelihood of being high-risk for depression relative to never use of gasoline (95% CI: 1.05-6.24) (Appendix F.2).

Summary of Findings

Direction of associations between pesticide exposure measures and CES-D score were inconsistently positive and negative. However, few specific pesticide measures were found to be significantly associated with CES-D score. Disulfoton and ethoprop were consistently associated with greater depressive symptoms when examined as ever-use and cumulative lifetime days of use. HPEE was also associated with greater depressive symptoms. Dichlorvos appeared to

consistently relate to less depressive symptoms when assessed as ever-use and cumulative lifetime days of use; ever-use of malathion showed a similar effect, but not when characterized as cumulative use. Any effects of pesticide exposure were seen when evaluating CES-D as a continuous rather than a binary outcome.

Unlike the pesticide measures, solvent exposure measures consistently appeared to be risk factors for greater depressive symptoms. Several variables involving any solvent use, gasoline use, and petroleum distillate use were positively associated with CES-D score. Again, more effects of solvent exposure were seen when evaluating CES-D as a continuous rather than binary outcome.

Interpretation/implications of findings and strengths and limitations of the current study are discussed in the *Discussion* chapter.

AIM 2 ANALYSIS: Organic solvent exposure and neurobehavioral function in agricultural workers

Background

Sources of organic solvent exposure include paints, varnishes, lacquers, stains, glues, adhesives, gasoline, and cleaning/degreasing agents. A variety of solvent-induced central nervous system disorders are recognized by public health agencies, including symptoms of fatigue; irritability; mild or sustained mood disturbances; personality changes such as emotional instability, diminished impulse control, and effects on motivation; and impairment in intellectual function manifested by diminished concentration, memory, and learning capacity.[17,18,45] Very little research evaluating neurotoxicity of solvents in agricultural workers exists, although maintenance and repair of farm machinery and equipment requiring solvent-based materials are regular tasks performed by farmers.[2,23] Farm tasks involving solvents may often be performed indoors and without PPE; both inhalation and dermal exposure are of concern.[2,72] Therefore, agricultural workers could be at risk for neurotoxic effects induced by solvents. The current analysis aimed to estimate associations between questionnaire-based organic solvent exposure and measures of neurobehavioral (NB) function.

Methods

Data Source

A subsample of 701 licensed pesticide applicators (i.e., the Neurobehavioral Testing Study add-on) that participated in the Agricultural Health Study (AHS) in Iowa and North Carolina were evaluated for neurobehavioral performance. Participants eligible for the Neurobehavioral Testing Study (NB Study) were male farmers that completed all three phases of

AHS questionnaires. Further exclusion criteria excluded AHS participants with a diagnosis of amyotrophic lateral sclerosis, diabetes, multiple sclerosis, Parkinson's disease, retinal or macular degeneration, hypothyroidism, or stroke, as well as those who reported drinking at least 42 alcoholic beverages per week, reported being diagnosed with pesticide poisoning during the AHS Phase 3 interview, or lived greater than 150 miles away from the testing facilities. Stratified random sampling was conducted among eligible participants to provide adequate representation of individuals with higher lifetime use of selected organophosphate pesticides. A total of 1,807 AHS participants were subsequently eligible for the NB Study, of which 39% participated (N=701). Assessment of neurobehavioral function was conducted between 2006 and 2008. Participants provided informed written consent and were compensated for time and travel. Appropriate Institutional Review Boards approved the study protocol.[14-16]

Exposure Assessment

Organic solvent exposure was assessed in the NB Study questionnaire by determining ever-use and years of use for six individual measures of exposure: gasoline, paint/lacquer thinner, turpentine, benzene, toluene, and petroleum distillates. Two summary variables were compiled: ever-use and cumulative years of use of any solvents. The number of years used for each continuous measure was categorized based on the median number of years of use for those reporting ever-use for each respective measure, resulting in a categorical variable for each measure including never-use (referent), low duration of use, and high duration of use. The number of respondents for benzene, toluene, and turpentine were not large enough to include in the analysis (N=18, 11, and 5, respectively). Three dichotomous solvent-related activity variables collected at AHS enrollment were also evaluated: ever-use of solvent additives when personally

mixing pesticides; ever-use of gasoline to clean hands or equipment; and ever-use of other solvents for cleaning. In summary, seven binary variables and four categorical years of use variables were examined.

Outcome Measures

Nine outcomes represented various tests of neurobehavioral (NB) function, assessed on a continuous scale, which were administered to participants in private rooms by trained personnel blinded to participants' exposure status during the NB Study. These tests are commonly used in studies on the effects of neurotoxic substances in humans and represent a wide variety of NB function.[14,15] Eight tests were administered in English from the computerized Neurobehavioral Evaluation System, Version 3 (NES3).[73-76] Additionally, the manual Grooved Pegboard (Lafayette Instruments, Lafayette, IN)[77] test was given. Only dominant hand performance results are presented for the Finger Tapping and Grooved Pegboard tests because of the similarity in performance between both hands. Participants unable to complete individual tests in the allotted time or after two attempts were excluded from the appropriate NB test data and contribute to varying sample sizes across tests.[14,15] Further detail for each test is summarized below.[14]

A. **The Continuous Performance Test** evaluated sustained attention. Participants were asked to press the space bar on a computer keyboard as fast as possible every time the letter "S" appeared, but no action was to be taken for other letters that appeared. One new letter appeared on screen every second for 300 seconds. Performance was calculated in milliseconds as mean reaction time for responding to the letter "S."

B. **The Digit-Symbol Test** assessed visual scanning and information-processing speed. Nine digit-symbol pairs were displayed across the top of a touchscreen while nine symbols were displayed across the bottom. Random integers 1-9 individually appeared in the middle of the screen 36 times and participants were to touch the symbol at the bottom of the screen that was paired with the integer from the options at the top of the screen as quickly as possible. Performance was measured as time in seconds taken to complete all 36 items.

C. **The Finger Tapping** test measured motor speed and dexterity. Participants pressed the space bar on a computer keyboard as many times as possible using the index finger of their dominant hand, until instructed to stop. Following a practice trial, four 10-second trials were administered. Performance was defined as average number of taps across all four trials.

D. **The Grooved Pegboard** test evaluated dexterity and fine motor coordination.[77] The manual test was comprised of a metal board with 25 notched pegs and 25 holes with randomly-positioned slots at their perimeters. Participants inserted the pegs into the slots as quickly as possible in sequence until all pegs were placed or after three minutes had passed. Performance was calculated as number of seconds required to place all pegs.

E. **Auditory Verbal Learning Test (AVLT) Total Recall** assessed verbal learning and memory. After listening to a recorded list of 12 words, participants were asked to repeat as many of the words as they could remember aloud. Three trials were conducted using identical words lists. Performance was measured as total number of correct responses for all three trials, ranging from 0 to 36.

F. **The AVLT Delayed Recall** test measured memory and was conducted approximately 20 minutes after completion of the AVLT Total Recall test. Participants were asked to recall as many words as possible from the original 12-item list aloud. Performance was defined as the number of correct words identified, ranging from 0 to 12.

G. **The AVLT Recognition** test followed the AVLT Delayed Recall and also evaluated memory. A recorded list of 24 words comprised of the 12 words previously presented and 12 new words were presented in random order. Participants were to identify only words from the original list. Performance was calculated as the number of true positives minus the number of false positives, ranging from -12 to 12.

H. **The Sequences A** test assessed motor speed and tracking and involved a touchscreen with circles containing the letters "A" through "U" displayed in random order. Participants were asked to touch the circles in alphabetical order as quickly as possible. Performance was measured as time in second taken to complete the sequence correctly.

I. **The Sequences B** test also measured motor speed and tracking and followed the Sequences A test. Circles containing numbers "1" through "11" and letters "A" through "J" were displayed on the touchscreen in random order. Participants were instructed to touch the circles in sequence but alternate between number and letter in numerical and alphabetical order as quickly as possible. Performance was defined as time in seconds taken to complete the sequence correctly.

Statistical Analysis

Covariates considered for confounding were obtained from self-report on the questionnaires as well as performance on several measures during the NB Study. In particular,

covariates considered included state, age in years, education, marital status, smoking status, alcohol use, PPE use, co-exposures (i.e., cumulative organophosphate exposure or cumulative all-pesticide exposure, ever exposure to welding, and ever exposure to soldering), caffeine consumption, head injury, height in centimeters, anti-depressant use, visual acuity measured using the Optec 1000 (Stereo Optical Co, Chicago, IL) during the NB Study examination, and performance on several measures from the NES3 including Adult Reading Test (ART) ability (scored 0-60) and positive and negative affect (scored 1-5) from the Positive and Negative Affect Schedule.[14,15,73-75,78]

Univariate analyses were used to explore the distributions of performance on neurobehavioral tests, solvent exposure metrics, and covariates across the entire sample with frequencies and percentages or means and standard deviations reported. Participants previously determined to have studentized residual values that exceeded the absolute value of 4.0 for each NB tests were excluded.[14,15,79] Two outlier participants were excluded from the Digit-Symbol test, one participant from the Sequences A test; and one participant from the Sequences B test.[14,15]

A base linear model was created for the multivariable analyses for each individual neurobehavioral outcome. Specifically, covariates that were individually associated with an outcome at a p-value of less than 0.20 were included in a base model selection that sequentially excluded each covariate with a p-value of at least 0.20 using a multiple linear regression backward elimination approach. Nine separate base models were generated: one for each outcome.

Subsequent multivariable analyses employed linear regression models assessing the relationship between each separate solvent measure and each separate neurobehavioral outcome

controlling for qualified covariates in the base models. Participants with missing values for variables were excluded from the appropriate multivariable models. Crude and multivariable (i.e., adjusted) beta coefficients with standard errors and p-values were calculated. Beta coefficients of the timed NB tests (Continuous Performance Test, Digit-Symbol, Grooved-pegboard, Sequences A and Sequences B) were multiplied by -1 for consistency in interpreting the direction of associations across all outcomes (i.e., negative beta coefficients indicate poorer NB performance with ever/increasing exposure).

All statistical analyses were conducted using SAS software (versions 9.3 and 9.4; SAS Institute Inc., Cary, NC).

Results

Characteristics of the Sample

In addition to demographic characteristics explained in the previous analysis, 75% of the sample reported regular caffeine consumption, and 93% were not taking anti-depressant medications. The average height was 179 centimeters (SD=6.5), the average ART reading score was 29.9 (SD=10.2), and average positive and negative affect scores were 3.5 (SD=0.7) and 1.4 (SD=0.4), respectively. A majority of the sample (84%) had good vision (20/20-20/40). See Table 1.

Distributions of solvent exposure across the sample are shown in Tables 6.A and 6.B; 41% of the sample reported exposure to any solvents and sample sizes for each specific solvent or solvent-related activity varied. Performance scores for the nine NB tests are summarized in Table 8. Sample sizes varied due to incomplete tests from some participants. Performance was

similar to previous general-population studies, as discussed in a previous study of this population.[15]

Linear Regression Results

After selecting base models, each NB outcome was associated with a specific set of covariates, which are listed in Table 9. Base model association estimates for each covariate and each outcome are exhibited in Appendix G.

Crude associations between solvent exposure and NB performance are displayed in Table 10. Negative beta estimates indicated poorer performance on NB tests, while positive estimates indicated better performance. Many significant ($p<0.05$) crude associations existed between measures of ever-use of solvents and duration of solvent exposure and all NB performance outcomes (N = 39), particularly in regards to any solvent exposure and gasoline exposure. Furthermore, a majority of the crude associations were negative (N=35), reflecting poorer performance with increasing exposure. Five crude associations existed between solvent-related activities ascertained at enrollment and NB performance; directionality was inconsistent.

When adjusting for each set of outcome-specific covariates, a majority of the associations were no longer statistically significant ($p>0.05$) (Table 11). In regards to specific measures of ever-use and duration of exposure, there were no significant associations for the Continuous Performance Test, Digit-Symbol Test, AVLT Total Recall test, AVLT Delayed Recall test, AVLT Recognition test, or Sequences B tests. Directionality of all associations for the Finger Tapping test was consistently negative, but only three associations reached statistical significance. Ever-use of gasoline, high duration of gasoline exposure, and low duration of paint thinner exposure groups demonstrated significantly less finger taps than the respective never-use

groups. All but one of the associations were positive for the Grooved Pegboard test, but only two reached statistical significance. Ever-use of petroleum distillates and low duration of petroleum distillate exposure were related to quicker performance relative to never-use of petroleum distillates. There was inconsistent directionality in associations for the Sequences A test, and the only significant association involved longer latency in performance for high duration of gasoline exposure relative to never-use of gasoline. Several additional associations for NB tests were revealed by further categorizing duration of exposure to any solvent and duration of exposure to gasoline into smaller levels, such as an additional positive association for the Grooved Pegboard test involving duration of any solvent exposure, and two associations found for select AVLT tests (Appendix H).

Among the solvent-related activity measures ascertained at enrollment, three significant associations existed after controlling for covariates (Table 11). Using gasoline to clean hands or equipment, using other solvents to clean, and using solvents when mixing pesticides were related to poorer performance on the Digit-Symbol test, AVLT Recognition test, and Sequences A test, respectively.

A hypothetical example of the results of the linear regression model involves a 60 year old male farmer, from Iowa, with a 29 ART score, 3.6 positive affect score, and never exposed to gasoline predicted to achieve 53.47 finger taps on the Finger Tapping test; the same person having ever used gasoline would have 51.84 predicted finger taps. Similarly, the same person with a low duration of gasoline exposure (i.e., $\leq$21 years) would have 52.34 finger taps; and the same person with a high duration of gasoline exposure (i.e., >21 years) would have 51.26 finger taps (Appendix I.5).

Summary of Findings

No clear pattern of association existed between solvent exposure and general neurobehavioral function. Several negative associations were found between gasoline and paint thinner exposure and tests assessing motor speed. Petroleum distillate measures appeared to relate to better performance on a test evaluating motor coordination. Performance on tests of attention, memory, learning, and visual scanning/information processing did not appear to be substantially affected by solvent exposure. Interpretation/implications of findings and strengths and limitations are discussed in the *Discussion* chapter below.

DISCUSSION

Weight of the evidence

Aim 1.A. Pesticide Exposure and Depressive Symptoms

One aim of the current study was to assess the relationship between pesticide exposure measures and depressive symptoms assessed on the Center for Epidemiologic Studies Depression Scale (CES-D). In general, direction of associations between pesticide exposure measures and CES-D score were inconsistently positive and negative. However, some specific pesticide measures were found to be significantly associated with CES-D score. Disulfoton and ethoprop were consistently associated with greater depressive symptoms when examined as both ever-use and cumulative lifetime days of use. High pesticide exposure event was a risk factor for greater depressive symptoms. Dichlorvos appeared to relate to less depressive symptoms when assessed as both ever-use and cumulative lifetime days of use; ever-use of malathion showed a similar effect, but not cumulative use of malathion. The only associations between pesticide exposure and CES-D score were demonstrated when evaluating CES-D as a continuous rather than a binary outcome.

An evaluation of physician-diagnosed depression among pesticides applicators from the Agricultural Health Study (AHS) found several positive associations with specific carbamates and specific organophosphates.[5] The current study, however, found no associations between carbamates and depressive symptoms, and some positive and some negative associations among several specific organophosphates. Discrepancies could relate to differences in outcome assessment. Another AHS study found pesticide poisoning to be a risk factor for diagnosed depression, but not cumulative pesticide exposure.[6] Analyses of AHS wives also found pesticide poisoning to relate to diagnosed depression, but not cumulative pesticide use.[7,35] Similarly, the

results of this analysis found high pesticide exposure events (HPEEs) to be a risk factor for depressive symptoms, and a majority of cumulative measures to show null effects. A study in France also found no association between insecticide use and self-reported treatment/hospitalization for depression.[36] Studies that have employed measures of depressive symptoms as opposed to diagnosed depression have supported relationships between chronic organophosphate exposure and greater symptoms.[9,33] Although the findings of the current analysis were inconsistent with these studies, they are supported by the findings of one study on sheep farmers, which demonstrated only an effect for pesticide poisoning, but not ever-use of pesticides in general.[37]

When concluding a real exposure-response relationship, directional consistency, dose-response, and consistency with the literature are three factors that should be met. Overall, no directional consistency was observed for ever-use and cumulative measures of pesticide exposure, and few significant associations existed. Although inconsistencies also exist in the literature for the association between various measures of chronic pesticide use and various measures of depression, the associations found for few specific organophosphate pesticides in this study may be due to chance and not reflect a real association. On the other hand, pesticide poisoning has consistently been shown to relate to depression in the literature.[6,7,10,13,35,38] Similarly, the current study found high pesticide exposure events to be a significant risk factor for depressive symptoms, likely supporting evidence for a real exposure-response relationship for this specific pesticide measure.

While some measures demonstrated statistical significance, the clinical significance of the magnitude of effects may be called into question. That is, the changes in CES-D associated with specific pesticide exposure measures are so subtle that they may not be of importance to

practice. On the other hand, so many of the socio-environmental risk factors for depression cannot easily be altered by the farmers; therefore, limiting modifiable risk factors for depression where possible should be considered, such as reducing occupational exposures through safe workers practices.[10-12,28] Furthermore, demonstrating subtle changes in mental health associated with exposures that are not detected on a threshold-based classification of depression provides justification for early intervention to prevent further progression toward clinical disorder.

Aim 1.B. Organic Solvent Exposure and Depressive Symptoms

Organic solvent exposure measures appeared to be more consistent risk factors for greater depressive symptoms than pesticide exposure measures. Several variables involving any solvent use, gasoline use, and petroleum distillate use were positively associated with CES-D score. More effects of solvent exposure were seen when evaluating CES-D as a continuous rather than binary outcome.

Although mental health outcomes associated with solvent exposure have not been studied in an agricultural population, one study on a rural Ecuadorian population in which approximately 67% of the sample were farm members found no association between general solvent use and mental health performance on the Profile of Mood States scale.[53] The current study, however, found several associations between more specific solvent use measures and higher depressive symptoms among an all-farming population. Although some studies in other industries have found null effects,[57,58] there is a large evidence base for research supporting a real association between presence and duration of solvent exposure and mental health dysfunction as measured by a variety of scales.[54-56] The need for consistency in methods of outcome assessment is imperative.

In the evaluation for a real exposure-response relationship, three factors are supported by the results of this analysis. First, all estimates exhibited a positive direction. Second, some dose-response was observed; greater depressive symptoms were exhibited by those with exposure or higher duration of some exposures than those never exposed across several measures. Third, as explored above, there is an evidence-base in the literature to support this finding.

The results of this analysis can again be disputed for clinical significance in terms of the small magnitude of effects found. But, as previously discussed, it may be worthwhile to consider these associations in light of the many unmodifiable risk factors for depression and an opportunity for early intervention.

Aim 2. Organic Solvent Exposure and Neurobehavioral Function

No clear pattern of association existed between solvent exposure and general neurobehavioral function. Several negative associations were found between gasoline and painter thinner exposure and tests assessing motor speed. Petroleum distillate measures appeared to relate to better performance on a test evaluating motor coordination. Performance on tests of attention, memory, learning, and visual scanning/information processing did not appear to be substantially affected by solvent exposure.

As mentioned, this is a new topic of research in that neurobehavioral function has scarcely been studied in an agricultural population. A sample of rural Ecuadorians, in which 67% of participants were farm members, was found to exhibit mixed results of neurobehavioral function associated with general solvent use.[53] Specifically, solvent use was related to improved visual perception/memory, poorer psychomotor performance, and improved manual dexterity. Several null associations were found for other functions. Similarly, the current analysis found

mixed effects of solvent use on functions of motor ability; but no effects on other performance measures. Studies of workers of various other industries have demonstrated negative associations between solvent exposure and neurobehavioral function evaluated on Neurobehavioral Evaluation System tests, including poorer visual scanning/processing speed,[56,60-62] poorer sustained attention,[61] worse visual memory,[61,62] reduced psychomotor speed,[56] and poorer manual dexterity.[56] However, many of these studies have also found null effects on other neurobehavioral functions. The inconsistencies demonstrated across the literature are also demonstrated from results of the current study.

This was the first study to the author's knowledge to evaluate neurotoxic effects of organic solvent exposure in a population of all agricultural workers. No definitive conclusions from the current results can be drawn in relation to general associations between solvent exposure and neurobehavioral function. While some significant associations were observed between exposure and psychomotor function, some were risk effects and some were protective. Literature supports risk or null effects in other industries, but little supports protective effects. Therefore, further research focused on this population is needed.

Strengths and limitations

There were several strengths to the current study. First, the large sample size for an occupational study evaluating neurobehavioral function through clinical tests is an improvement over many other studies that often use much smaller sample sizes. Additionally, farming practices and commodities vary considerably in North Carolina and Iowa; therefore, this analysis evaluated neurotoxicity of agricultural exposures across a diverse occupational sample.[9] Second, this study emphasized subtle effects of neurotoxic substances as opposed to associations with

clinically-diagnosed or binary conditions, which is important for understanding the risk and progression of neurotoxic effects, as well as providing an opportunity for primary prevention/early intervention.[8] Third, widely-used, valid, reliable, and consistent clinical scales were employed to assess outcomes.[39,74,76] Fourth, exposure assessment using questionnaires can better characterize long-term cumulative or low-level exposures than can environmental sampling or biomarker data capturing exposure information for a given point in time. Task-based exposure measures allow for consideration of all routes of exposure, including inhalation of pesticides or solvent fumes as well as dermal exposure to pesticides or solvents.[2]

There are various limitations to the current study. For example, the analysis used a cross-sectional design. Although pesticide exposure was collected longitudinally throughout the AHS, baseline mental health and neurobehavioral information was unavailable and assessed at the same time as a majority of the solvent exposure measures. Therefore, no assumption can be made in regards to the temporality/sequence of exposure-response relationships.

This analysis was unable to use a true never-exposure group. Ninety-nine percent and 97% of participants reported using any pesticide or organophosphate pesticides, respectively. Furthermore, the definition of solvent exposure consisted of at least eight hours of use in a week. Those that may have used solvents for shorter durations were subsequently considered never exposed, although they may still have had some measure of exposure. Therefore, the analysis was strictly based on a gradient of exposure and no true never-exposure reference group.

Because exposure information was self-reported, there is a possibility for exposure misclassification due to recall bias. Little effects of the solvent-based activities ascertained at enrollment were found, but these results may have nonetheless been unreliable with responses having been collected at least 10 years prior to NB evaluation. Task-based activities would have

likely changed for workers over that period of time. Although pesticide exposure was self-reported, it was assessed repeatedly over three phases of questionnaires, making the cumulative estimates more reliable than produced from any one questionnaire alone. Additionally, multiple studies have supported that recall of pesticide use many years later as well as consistencies with expert judgment provided reliable self-reported exposure information.[80-83]

There is minimal risk for outcome misclassification because diagnostic tests were administered by trained personnel blinded to exposure status, which is an improvement over previous studies that have analyzed self-reported conditions. However, the CES-D scale only reflects depressive symptoms experienced over a seven-day period (i.e., current mood state); and depressed mood is not static over time.[10,39,54] The current analysis only has CES-D scores from one test period available. On the other hand, previous research has found associations between depression diagnosed from the CES-D scale and pesticide poisoning experienced up to three years before.[10] Solvent-induced neurobehavioral outcomes are often irreversible, or exist for long periods of time after exposure ceases, therefore neurobehavioral function may be less static than depressive symptoms.[17,19]

There may be selection bias presented in the current design. While participation from Iowa and North Carolina does present a broad range of farm and personal characteristics, only those persons pursuing restricted-use pesticide certification were enrolled and only those residing within 150 miles of neurobehavioral testing facilities were eligible. Therefore, farmers that do not use pesticides, live in more rural/remote areas, or are financially disadvantaged and have no reliable means of transportation may not have been included in the sample. Exposure may be limited in this population relative to other occupational groups because of the training/testing in safe handling of pesticides required to obtain a license to use restricted-use pesticides, at which

point AHS participants were recruited.[22] The stratified sampling procedure in which participants with high-end exposure to organophosphates were oversampled has further implications for the generalizability of both pesticide and solvent-exposed samples.

Additionally, a healthy worker effect must be considered in interpreting results, as those with moderate-to-severe depression or adverse neurological symptoms may not be working or may not have completed all phases of the AHS (i.e., remained enrolled for at least 10 years), and subsequently would have been ineligible for participation in Neurobehavioral Testing (NB) Study; participants are older (i.e., survival effect) or healthier than their peers if they were able to participate in all questionnaires. In fact, nearly 70% of the sample reported still farming.[15] A general-population study of CES-D performance found that 21% of participants scored 16 or higher on the scale,[39] while the current study found that approximately 8% of participants scored 16 or higher. On the other hand, an AHS study previously found that participants reporting depression at enrollment were equally likely to drop out by the first follow-up as non-depressed participants.[84] Lastly, though response rate was relatively low for the NB study (39%), a previous study has supported that participants of this sample were comparable to non-participants across many demographic characteristics.[14]

Employing a large number of statistical tests causes the results to be subject to the pitfalls of multiple comparisons. That is, the more tests done in an analysis, the higher the probability that any significant effects were found due to chance. Statistical adjustments were not made in analyzing the results as to not increase the risk for type II error, although protection against type I error was reduced.[85] Furthermore, the number of tests for which to control becomes arbitrary with so many different exposures and outcomes evaluated.[86,87] However, multiple comparisons should still at least be taken into consideration when interpreting the results of the current study,

with awareness that the estimates could have been produced due to chance. But as discussed previously, when significant associations are supported by directional consistency, significant dose-response, and literature support, it is more likely that the results found are not due to chance. These factors are demonstrated by some of the current results (e.g., solvent exposure and depressive symptoms; solvent exposure and Finger Tapping performance), but not others.

There is some information unavailable in the data that was subsequently not considered in the analysis. For example, though information regarding baseline depression or NB function (i.e., prior to any exposure) was not ascertained, indicators for cognitive reserve, a psychological concept representing an inherent ability to cope with and adapt to mental challenges, exist.[88,89] One of which indicators includes education, which was evaluated in the analysis. Performance on the Adult Reading Test measure also represents intellectual functioning, and thereby potentially reflects inherent NB function pre-exposure.[15] Furthermore, it cannot be assumed that depression would have been differentially distributed among exposure groups prior to exposure, thereby its baseline levels are not of substantial concern. Depressive symptoms measured by the CES-D scale can be influenced by life events (e.g., vacation, illness/injury, relationship occurrences, financial events, etc.),[39,90,91] however, data was not available to assess or control for these covariates. On the other hand, evaluation of the scale has still found test-retest reliability to be moderate one year apart even with various life events occurring.[39] Data was also not available on income, but because participants of the AHS are a homogenous group (i.e., male farmers in specified regions; at least 97% white[22]), income may not vary substantially; and education serves as a measure of socioeconomic status in the current analysis.

Future sensitivity analyses could employ exclusions for characteristics that were not substantial enough to assess for confounding. For example, very small groups of participants

reported conditions such as pesticide poisoning, solvent poisoning, and use of various medications or drugs. Previous studies have employed sensitivity analyses to exclude these groups, finding mixed effects on results.[6,14,15]

The issue of age and duration of exposure and their effects on health outcomes is often of concern due to collinearity or interaction. However, individual effects of exposures were still seen when controlling for age, a conservative method in light of potential collinearity between duration and age. Additionally, select correlation analyses supported that associations between age and duration of exposure were only low-to-moderate (results not shown). Additionally, there was enough variation of age in categorical solvent groups as to not suspect a lack of controlling for age appropriately with a continuous variable (results not shown). Furthermore, it is possible for the effects of age to interact with cumulative exposure to lead to health effects not exhibited by either variable alone. However, an exploration of interaction terms within the statistical models revealed no such significant interaction (results not shown).

Despite the limitations, this study provided a novel and innovative strategy to evaluate variable central nervous system effects of neurotoxic substances encountered regularly by agricultural workers.

PUBLIC HEALTH IMPLICATIONS AND CONCLUSIONS

The current study opens a door to an important area of research for which much future attention is needed. An AHS study on the prevalence of exposure to various occupational exposures in agricultural workers found that farmers reporting more frequent use of pesticides were 27% more likely to use solvents compared to farmers using pesticides less frequently.[23] Because pesticides and solvents both have neurotoxic characteristics, it would be relevant to understand any potential interaction effects of co-exposure, particularly in occupational groups that regularly use both substances. Although this topic has not yet been explored in an agricultural population (or in occupational health studies in general), a cumulative risk assessment model has supported that environmental exposure to pesticides and solvents together can affect Disability Adjusted Life Years.[92]

NIOSH, the Occupational Safety and Health Administration (OSHA), and the American Conference of Governmental Industrial Hygienists (ACGIH) have characterized at least 19 organophosphate pesticides as occupational hazards, for which occupational exposure limits have been assigned (ranging from 0.05 to 10 mg/m^3).[93] In published recommendations, these substances are noted to have central nervous system effects. Not only does NIOSH recommend sampling techniques to capture inhalation as a source of organophosphate pesticide exposure, but ACGIH also provides skin notations indicating dermal absorption risk as well.[93] Additionally, NIOSH had published recommendations for dozens of organic solvents, which are also recognized as hazardous through both inhalation and dermal routes.[2] For example, a pilot study in Kentucky found dermal patches detecting up to 36,000 µg/patch for toluene and up to 5,700 µg/patch for xylene in a sample of agricultural workers performing maintenance/repair of machinery.[2] Furthermore, neurotoxicity studies have demonstrated gasoline constituents to have

neurologic effects at or below their ACGIH Threshold Limits Values.[8] Therefore, research should attempt to quantify the extent to which agricultural workers from various commodities are exposed to neurotoxic substances in order to influence recommendations for exposure limits, engineering controls, and worker practices pertinent to this group. Specific recommendations for agricultural workers should be developed particularly because small farms (with 10 or fewer employees) are exempt from OSHA enforcement activities.[94]

The current study found that approximately 14% of participants did not use personal protective equipment (PPE), but other surveys have found much larger proportions of agricultural workers reporting a lack of PPE.[2,72] Worker practice interventions should train agricultural workers in safe practices to reduce exposure to both pesticides and solvents. For example, interventions involving education of adverse health outcomes, simulation of exposures, farmer feedback, and provision of cognitive behavioral strategies have shown to be successful in increasing PPE use post-intervention and relative to comparison groups.[95,96]

In addition to interventions focused on exposure, interventions targeting mental/neurological health in agricultural workers are also recommended. Depressive symptoms in agricultural workers and their family members are influenced by factors such as financial strain, social isolation, long and physically demanding work requirements, working conditions and processes that rely on variable weather, and health comorbidities.[10-12,28] Therefore, behavioral practices, such as stress management activities, can help reduce risk for depression and anxiety. Because farmers have been found to be reluctant to seek treatment for mental health conditions despite displaying depressive symptoms,[6,40] agricultural workers should be trained in recognizing mental health or neurobehavioral dysfunction, provided with healthcare resources, and encouraged to pursue screening and/or treatment.

Results from the current study may suggest relationships between neurotoxic chemicals, such as some pesticides and organic solvents, and mental/neurobehavioral health outcomes that exist on a linear scale. This research serves as a justification for early behavioral interventions in agricultural workers. That is, because subtle changes in central nervous system function can occur with exposures that may exist on a sub-clinical level, efforts should be taken to minimize exposure and prevent further progression that could eventually lead to clinical disorders.

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Table 1: Demographic characteristics (N=701)

Age (Mean, SD)	61.3 (11.7)
State (North Carolina/Iowa) (n,%)	
Iowa	356 (50.8)
North Carolina	345 (49.2)
Education (n,%)	
<High School	355 (50.6)
High School+	346 (49.4)
Marital status* (n,%)	
Married	620 (88.8)
Single/Divorced/Widowed	78 (11.2)
Smoking (n,%)	
Never	403 (57.5)
Current	47 (6.7)
Past	251 (35.8)
Alcohol use (n,%)	
0 drinks/week	401 (57.2)
1-7 drinks/week	231 (33.0)
>7 drinks/week	69 (9.8)
Personal protective equipment use (n,%)	
No	97 (13.8)
Yes	604 (86.2)
Off-farm job* (n,%)	
No	423 (60.7)
Yes	274 (39.3)
Head injury (n,%)	
No	536 (76.5)
Yes- No loss of consciousness	71 (10.1)
Yes- Loss of consciousness	94 (13.4)
Solvent exposure (n,%)	
No	413 (58.9)
Yes	288 (41.1)
Welding exposure (n,%)	
No	561 (80.0)
Yes	140 (20.0)
Soldering exposure (n,%)	
No	665 (94.9)
Yes	36 (5.1)
High pesticide exposure event (n, %)	
No	538 (76.8)
Yes	163 (23.3)
Caffiene consumption (n, %)	
No	176 (25.1)
Yes	525 (74.9)
Anti-depressant use (n, %)	
No	650 (92.7)
Yes	51 (7.3)
Visual acuity (n, %)	
20/20 - 20/40	592 (84.5)
20/50 - 20/200	109 (15.6)
Height: cm (Mean, SD)	179.0 (6.5)
Reading ability: 0-60* (Mean, SD)	29.9 (10.2)
Positive affect: 1-5 (Mean, SD)	3.5 (0.7)
Negative affect: 1-5 (Mean, SD)	1.4 (0.4)

SD: Standard deviation; OP: Organophosphate

*Missing values of n<5

Table 2: Center for Epidemiologic Studies Depression (CES-D) Scale scores across entire sample

	Total Sample (N = 692)*		
	n (%)	**Mean (SD)**	**Median (Range)**
CES-D Score (0-60)	--	6.5 (6.4)	5.0 (0.0 - 44.0)
Risk for depression			
Low (score < 16)	634 (91.6)	--	--
High (score 16+)	58 (8.4)	--	--

SD: Standard deviation

*Missing N=9

Table 3: Distribution of cumulative lifetime days of pesticide use for those reporting ever-use

	Total Sample (N=701)			
	n (%)	GM (GSD)	Min.	Max.
Organophosphates				
Acephate	166 (23.7)	51.8 (2.8)	2.5	500.5
Chlorpyrifos	418 (59.6)	35.4 (3.7)	2.0	767.3
Coumaphos	94 (13.4)	15.7 (4.8)	1.0	1682.5
Diazinon	302 (43.1)	21.8 (3.9)	1.0	846.0
Dichlorvos	128 (18.3)	80.1 (7.1)	1.0	8680.0
Dimethoate	66 (9.4)	23.3 (3.2)	2.0	457.3
Disulfoton	110 (15.7)	29.2 (2.5)	2.0	236.0
Ethoprop	121 (17.3)	29.0 (2.6)	2.5	316.0
Fonofos	201 (28.7)	32.9 (3.4)	2.0	457.3
Malathion	541 (77.2)	35.4 (4.2)	2.0	2625.0
Parathion	147 (21.0)	23.8 (4.8)	1.0	1667.5
Phorate	230 (32.8)	30.9 (3.8)	1.0	1627.5
Phosmet	101 (14.4)	33.0 (3.0)	2.5	600.0
Tebupirimfos	69 (9.8)	35.4 (2.5)	4.0	250.0
Terbufos	356 (50.8)	50.6 (3.7)	2.0	752.3
Tetrachlorvinphos	69 (9.8)	33.0 (3.0)	3.0	581.6
Carbamates				
Aldicarb	131 (18.7)	36.5 (4.1)	2.0	742.3
Benomyl	116 (16.5)	16.0 (6.3)	0.3	767.3
Carbaryl	440 (62.8)	37.9 (4.9)	1.0	1387.5
Carbofuran	290 (41.4)	23.7 (3.7)	1.0	752.3
All Organophosphate Pesticides	682 (97.3)	193.2 (4.0)	2.0	8763.3
All Pesticides	700 (99.9)	984.5 (3.0)	10.0	11676.8
High Pesticide Exposure Event				
No	538 (76.8)	--	--	--
Yes	163 (23.3)	--	--	--

SD: Standard deviation; GM: Geometric mean; GSD: Geometric standard deviation

Table 4: Relationship between **ever-use** pesticide exposures and log10-transformed CESD score (linear regression)

	Crude		Adjusted*	
EVER VS. NEVER EXPOSED	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**
Organophosphates				
Acephate	**0.070 (0.035)**	**0.046**	0.058 (0.036)	0.109
Chlorpyrifos	0.005 (0.031)	0.869	0.013 (0.031)	0.674
Coumaphos	-0.079 (0.044)	0.070	-0.080 (0.044)	0.069
Diazinon	-0.033 (0.030)	0.274	-0.044 (0.030)	0.153
Dichlorvos	**-0.105 (0.038)**	**0.006**	**-0.085 (0.039)**	**0.030**
Dimethoate	-0.072 (0.051)	0.159	-0.074 (0.051)	0.149
Disulfoton	**0.098 (0.041)**	**0.018**	**0.090 (0.042)**	**0.031**
Ethoprop	**0.139 (0.039)**	**<0.001**	**0.128 (0.040)**	**0.001**
Fonofos	-0.016 (0.033)	0.639	0.009 (0.034)	0.785
Malathion	-0.064 (0.036)	0.072	**-0.070 (0.035)**	**0.049**
Parathion	0.027 (0.037)	0.468	0.022 (0.037)	0.551
Phorate	-0.047 (0.032)	0.144	-0.029 (0.032)	0.370
Phosmet	0.033 (0.042)	0.440	0.056 (0.043)	0.195
Tebupirimfos	-0.069 (0.050)	0.165	-0.049 (0.050)	0.328
Terbufos	-0.011 (0.030)	0.723	-0.003 (0.030)	0.910
Tetrachlorvinphos	-0.068 (0.050)	0.175	-0.052 (0.050)	0.302
Carbamates				
Aldicarb	0.054 (0.039)	0.162	0.046 (0.039)	0.238
Benomyl	0.021 (0.040)	0.608	0.003 (0.041)	0.944
Carbaryl	0.014 (0.031)	0.660	-0.011 (0.032)	0.739
Carbofuran	-0.043 (0.030)	0.159	-0.036 (0.031)	0.240
High Pesticide Exposure Event	0.069 (0.036)	0.051	**0.077 (0.036)**	**0.031**

SE: Standard error

*Adjusted for age, marital status, and solvent use

Bolded if p < 0.05

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Table 5: Relationship between pesticide exposures (**log10-transformed lifetime days of exposure**) and log10-transformed CESD score (linear regression)

	Crude		Adjusted*	
LIFETIME DAYS OF EXPOSURE	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**
Organophosphates				
Acephate	0.036 (0.020)	0.066	0.029 (0.020)	0.142
Chlorpyrifos	0.006 (0.017)	0.717	0.010 (0.017)	0.552
Coumaphos	-0.007 (0.031)	0.809	-0.006 (0.031)	0.845
Diazinon	-0.010 (0.019)	0.617	-0.018 (0.020)	0.357
Dichlorvos	**-0.043 (0.018)**	**0.018**	**-0.037 (0.018)**	**0.046**
Dimethoate	-0.050 (0.034)	0.149	-0.050 (0.034)	0.143
Disulfoton	**0.067 (0.027)**	**0.014**	**0.061 (0.027)**	**0.024**
Ethoprop	**0.082 (0.025)**	**0.001**	**0.075 (0.026)**	**0.004**
Fonofos	-0.008 (0.020)	0.687	0.005 (0.020)	0.822
Malathion	-0.009 (0.018)	0.618	-0.013 (0.018)	0.479
Parathion	0.001 (0.023)	0.965	-0.002 (0.023)	0.927
Phorate	-0.028 (0.019)	0.142	-0.018 (0.019)	0.344
Phosmet	0.029 (0.026)	0.269	0.043 (0.027)	0.109
Tebupirimfos	-0.040 (0.031)	0.197	-0.027 (0.031)	0.384
Terbufos	-0.011 (0.016)	0.493	-0.008 (0.016)	0.603
Tetrachlorvinphos	-0.032 (0.031)	0.295	-0.021 (0.031)	0.495
Carbamates				
Aldicarb	0.029 (0.023)	0.191	0.026 (0.023)	0.252
Benomyl	-0.014 (0.027)	0.608	-0.020 (0.027)	0.449
Carbaryl	0.011 (0.016)	0.480	-0.003 (0.017)	0.853
Carbofuran	-0.025 (0.019)	0.198	-0.024 (0.020)	0.218
All Organophosphate Pesticides	-0.014 (0.022)	0.505	-0.010 (0.022)	0.641
All Pesticides	-0.024 (0.031)	0.441	-0.017 (0.031)	0.586

SE: Standard error

*Adjusted for age, marital status, and solvent use

Bolded if p < 0.05

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Table 6.A: Lifetime years of use for all organic solvent exposure variables

	Total Participants (N=701)		
	n (%)	Mean (SD)	Median (Range)
Any Solvents	288 (41.1)	33.1 (19.1)	36.0 (1.0 - 82.0)
Gasoline	223 (31.8)	25.6 (20.0)	21.0 (1.0 - 82.0)
Paint Thinner	77 (11.0)	21.5 (19.2)	17.0 (1.0 - 65.0)
Petroleum Distillates	178 (25.4)	28.6 (14.8)	30.5 (1.0 - 70.0)
Benzene	18 (2.6)	27.1 (23.9)	21.0 (1.0 - 70.0)
Toluene	11 (1.6)	12.7 (12.3)	10.0 (1.0 - 30.0)
Turpentine	5 (0.7)	38.8 (15.0)	49.0 (20.0 - 51.0)
Solvents in mixing pesticides	72 (10.3)	--	--
Gasoline to clean*	282 (41.2)	--	--
Solvents to clean*	193 (28.1)	--	--

SD: Standard deviation

*Missing values n<18

Table 6.B: Solvent exposure duration categories (category year cutoffs fall at medians of ever-used values) (N=701)

	n (%)	Mean (SD)
Any solvents		
Never use	413 (58.9)	--
Low duration (1-36 years)	146 (20.8)	17.2 (12.2)
High duration (>36 years)	142 (20.3)	49.4 (7.8)
Gasoline		
Never use	478 (68.2)	--
Low duration (1-21 years)	115 (16.4)	8.6 (6.6)
High duration (>21 years)	108 (15.4)	43.7 (11.9)
Paint thinner		
Never use	624 (89.0)	--
Low duration (1-17 years)	40 (5.7)	5.9 (5.3)
High duration (>17 years)	37 (5.3)	38.5 (13.5)
Petroleum distillates		
Never use	523 (74.6)	--
Low duration (1-30.5 yrs)	89 (12.7)	16.3 (8.9)
High duration (>30.5 yrs)	89 (12.7)	40.9 (7.4)

SD: Standard deviation

Table 7: Relationship between solvent exposures and log10-CESD score (linear regression)

	Crude		Adjusted*	
	Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Any solvents				
Ever vs. never	**0.078 (0.030)**	**0.011**	**0.068 (0.034)**	**0.044**
Never use	Ref.		Ref.	
Low duration (1-36 years)	0.060 (0.038)	0.117	0.048 (0.041)	0.242
High duration (>36 years)	**0.097 (0.039)**	**0.013**	**0.090 (0.042)**	**0.033**
Gasoline				
Ever vs. never	**0.082 (0.032)**	**0.011**	**0.074 (0.036)**	**0.039**
Never use	Ref.		Ref.	
Low duration (1-21 years)	0.077 (0.041)	0.063	0.067 (0.045)	0.137
High duration (>21 years)	**0.088 (0.042)**	**0.037**	0.081 (0.045)	0.070
Paint thinner				
Ever vs. never	0.070 (0.048)	0.146	0.064 (0.048)	0.184
Never use	Ref.		Ref.	
Low duration (1-17 years)	0.052 (0.065)	0.424	0.049 (0.065)	0.454
High duration (>17 years)	0.088 (0.067)	0.186	0.079 (0.066)	0.234
Petroleum distillates				
Ever vs. never	**0.092 (0.035)**	**0.008**	**0.082 (0.037)**	**0.027**
Never use	Ref.		Ref.	
Low duration (1-30.5 years)	**0.107 (0.046)**	**0.021**	**0.097 (0.048)**	**0.043**
High duration (>30.5 years)	0.077 (0.045)	0.088	0.067 (0.047)	0.158
Solvents in mixing pesticides (yes vs.	0.000 (0.049)	0.997	0.027 (0.050)	0.592
Gasoline to clean (yes vs. no)	0.028 (0.031)	0.360	0.028 (0.031)	0.370
Solvents to clean (yes vs. no)	0.016 (0.034)	0.633	0.004 (0.034)	0.894

SE: Standard error

*Adjusted for state, age, marital status, and HPEE

Bolded if p < 0.05

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Table 8: Distrubutions of NB test scores

	N	Mean (SD)	Median (Range)
Continuous Performance Test (CPT): ms	693	427.9 (44.9)	421.2 (318.6 - 612.3)
Digit-symbol: s (with 2 exclusions)	692	117.6 (23.1)	112.1 (73.6 - 213.6)
Finger Tapping, dominant hand: # taps	695	53.6 (9.6)	55.0 (9.0 - 86.0)
Grooved Pegboard, dominant hand: s	700	92.0 (24.1)	86.0 (51.0 - 180.0)
Auditory Verbal Learning (AVLT) Total Recall: # correct	696	19.9 (5.1)	20.0 (5.0 - 34.0)
AVLT Delayed Recall: # correct	695	6.6 (2.8)	7.0 (0.0 - 12.0)
AVLT Recognition: true positives minus false positives	694	8.3 (2.6)	9.0 (-3.0 - 12.0)
Sequences A latency: s (with 1 exclusion)	680	42.9 (14.6)	40.3 (14.8 - 93.8)
Sequences B latency: s (with 1 exclusion)	672	64.6 (21.2)	59.9 (22.8 - 144.4)

SD: Standard deviation

Table 9: Outcome-specific base models

NB Outcome	Base Model	R^2
Continuous Performance Test	Adjusted for age, caffiene use, reading ability, positive affect, and visual acuity	0.234
Digit-symbol	Adjusted for state, age, education, smoking, reading ability, positive affect, and visual acuity	0.490
Finger Tapping, dominant hand	Adjusted for state, age, reading ability, and positive affect	0.160
Grooved Pegboard, dominant hand	Adjusted for state, age, education, PPE, welding exposure, caffiene use, reading ability, and visual acuity	0.360
Auditory Verbal Learning (AVLT) Total Recall	Adjusted for age, education, smoking, reading ability, positive affect, and negative affect	0.290
AVLT Delayed Recall	Adjusted for state, age, education, all pesticide use, head injury, antidepressant use, reading ability, positive affect, negative affect, and visual acuity	0.279
AVLT Recognition	Adjusted for state, age, education, reading ability, positive affect, and negative affect	0.210
Sequences A latency	Adjusted for state, age, reading ability, and positive affect	0.418
Sequences B latency	Adjusted for state, age, reading ability, and positive affect	0.427

Table 10: Crude relationships between solvent exposure duration and NB test performance using linear regression

	Continuous Performance Test: ms	Digit-symbol: s	Finger Tapping, dominant hand: # taps	Grooved Pegboard, dominant hand: s	AVLT Total Recall: # correct	AVLT Delayed Recall: # correct	AVLT Recognition: (TP-FP)	Sequences A latency: s	Sequences B latency: s
	Beta* (SE)	**Beta* (SE)**	**Beta (SE)**	**Beta* (SE)**	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**	**Beta* (SE)**	**Beta* (SE)**
Any solvents									
Ever vs. never	-4.642 (3.467)	**-4.224 (1.783)**	**-2.797 (0.736)**	-0.608 (1.850)	-0.274 (0.390)	-0.318 (0.217)	**-0.576 (0.197)**	**-3.793 (1.130)**	**-4.361 (1.656)**
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-36 years	3.957 (4.323)	2.106 (2.206)	-1.068 (0.916)	**4.586 (2.299)**	0.728 (0.484)	0.195 (0.271)	-0.207 (0.246)	0.704 (1.397)	0.318 (2.049)
> 36 years	**-13.488 (4.369)**	**-10.738 (2.229)**	**-4.588 (0.928)**	**-5.947 (2.322)**	**-1.311 (0.491)**	**-0.849 (0.274)**	**-0.958 (0.250)**	**-8.324 (1.401)**	**-9.285 (2.088)**
Gasoline									
Ever vs. never	-5.281 (3.668)	**-6.785 (1.878)**	**-3.400 (0.776)**	-3.791 (1.949)	**-0.824 (0.411)**	**-0.638 (0.229)**	**-0.665 (0.209)**	**-5.369 (1.188)**	**-6.980 (1.741)**
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-21 years	0.459 (4.717)	-1.836 (2.415)	**-2.281 (0.990)**	0.332 (2.485)	0.236 (0.522)	-0.421 (0.293)	-0.178 (0.265)	-2.081 (1.525)	-3.675 (2.235)
> 21 years	**-11.236 (4.788)**	**-11.827 (2.433)**	**-4.603 (1.020)**	**-8.180 (2.549)**	**-1.964 (0.538)**	**-0.870 (0.302)**	**-1.188 (0.273)**	**-8.718 (1.536)**	**-10.412 (2.269)**
Paint thinner									
Ever vs. never	3.206 (5.457)	2.869 (2.807)	-1.296 (1.164)	**7.179 (2.897)**	1.117 (0.609)	0.551 (0.341)	0.148 (0.311)	1.862 (1.776)	2.754 (2.583)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-17 years	3.321 (7.417)	4.875 (3.814)	-1.674 (1.573)	**9.665 (3.912)**	1.210 (0.823)	**0.946 (0.460)**	0.331 (0.420)	4.491 (2.408)	4.130 (3.506)
> 17 years	3.086 (7.603)	0.755 (3.910)	-0.888 (1.631)	4.492 (4.059)	1.017 (0.854)	0.123 (0.477)	-0.049 (0.436)	-0.909 (2.468)	1.304 (3.594)
Petroleum distillates									
Ever vs. never	-2.140 (3.940)	-2.210 (2.031)	**-2.224 (0.838)**	2.599 (2.089)	-0.115 (0.442)	-0.222 (0.247)	**-0.441 (0.224)**	-2.131 (1.291)	-2.257 (1.889)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-30.5 years	-3.413 (5.255)	-1.235 (2.703)	-1.536 (1.106)	4.908 (2.758)	0.085 (0.583)	-0.230 (0.326)	**-0.742 (0.296)**	-1.149 (1.734)	-1.983 (2.553)
> 30.5 years	-0.910 (5.178)	-3.163 (2.676)	**-2.920 (1.111)**	0.290 (2.758)	-0.318 (0.586)	-0.213 (0.327)	-0.137 (0.297)	-3.046 (1.683)	-2.505 (2.451)
Solvents in mixing pesticides (yes vs. no)	5.104 (5.586)	3.334 (2.874)	0.961 (1.200)	**7.648 (2.983)**	1.051 (0.628)	0.665 (0.351)	0.509 (0.320)	-0.833 (1.820)	4.827 (2.673)
Gasoline to clean (yes vs. no)	-2.035 (3.493)	-2.269 (1.800)	0.141 (0.754)	0.709 (1.874)	0.195 (0.391)	0.170 (0.218)	-0.086 (0.201)	-0.734 (1.145)	0.857 (1.676)
Solvents to clean (yes vs. no)	1.279 (3.819)	-0.216 (1.966)	0.299 (0.822)	1.751 (2.043)	-0.358 (0.426)	-0.178 (0.238)	**-0.430 (0.218)**	0.606 (1.250)	3.141 (1.830)

SE: Standard error; AVLT: Auditory Verbal Learning; TP: True positives; FP: False positives

*For the timed NB tests, beta estimates were multiplied by -1 so that negative scores always indicate poorer test performance.

Bolded if p < 0.05

Risk (negative) correlation (higher exposure -> worse NB performance)

Protective (positive) correlation (higher exposure -> better NB performance)

Table 11: Relationship between solvent exposure duration and NB test performance using multiple linear regression **controlling for NB test-specific base model covariates (Table 9)**

	Continuous Performance Test: ms	Digit-symbol: s	Finger Tapping, dominant hand: # taps	Grooved Pegboard, dominant hand: s	AVLT Total Recall: # correct	AVLT Delayed Recall: # correct	AVLT Recognition: (TP-FP)	Sequences A latency: s	Sequences B latency: s
	Beta* (SE)	**Beta* (SE)**	**Beta (SE)**	**Beta* (SE)**	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**	**Beta* (SE)**	**Beta* (SE)**
Any solvents									
Ever vs. never	-0.956 (3.077)	0.378 (1.428)	-1.376 (0.758)	2.966 (1.746)	0.177 (0.334)	0.088 (0.208)	-0.087 (0.197)	-0.826 (0.973)	0.775 (1.419)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-36 years	-0.071 (3.850)	0.387 (1.728)	-1.077 (0.913)	3.156 (2.055)	0.125 (0.418)	0.056 (0.251)	-0.143 (0.237)	-0.282 (1.175)	0.189 (1.697)
> 36 years	-1.940 (4.012)	0.367 (1.796)	-1.715 (0.952)	2.738 (2.177)	0.233 (0.433)	0.125 (0.262)	-0.023 (0.248)	-1.435 (1.222)	1.457 (1.785)
Gasoline									
Ever vs. never	0.328 (3.273)	-0.888 (1.522)	**-1.632 (0.807)**	0.417 (1.833)	-0.159 (0.356)	-0.183 (0.222)	-0.074 (0.210)	-1.620 (1.035)	-0.810 (1.509)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-21 years	1.522 (4.181)	0.829 (1.913)	-1.101 (1.004)	1.716 (2.229)	0.382 (0.451)	-0.203 (0.276)	0.277 (0.260)	-0.073 (1.293)	0.077 (1.881)
> 21 years	-0.955 (4.305)	-2.556 (1.893)	**-2.175 (1.011)**	-0.994 (2.293)	-0.753 (0.468)	-0.162 (0.279)	-0.434 (0.263)	**-3.135 (1.283)**	-1.691 (1.877)
Paint thinner									
Ever vs. never	-3.043 (4.813)	-0.614 (2.039)	-2.052 (1.074)	2.539 (2.486)	0.596 (0.521)	0.361 (0.296)	0.057 (0.280)	0.004 (1.368)	0.343 (1.974)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-17 years	-5.916 (6.562)	-1.036 (2.774)	**-2.915 (1.454)**	2.250 (3.275)	0.392 (0.705)	0.560 (0.398)	0.113 (0.379)	1.490 (1.863)	-0.061 (2.689)
> 17 years	-0.046 (6.695)	-0.173 (2.834)	-1.130 (1.500)	2.853 (3.402)	0.815 (0.729)	0.146 (0.413)	-0.004 (0.392)	-1.543 (1.898)	0.763 (2.740)
Petroleum distillates									
Ever vs. never	-0.737 (3.508)	0.847 (1.586)	-1.018 (0.839)	**4.189 (1.866)**	0.157 (0.382)	0.032 (0.230)	-0.001 (0.218)	0.479 (1.075)	1.684 (1.563)
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-30.5 years	-4.380 (4.649)	-0.010 (2.044)	-0.744 (1.075)	**4.800 (2.373)**	0.148 (0.501)	-0.111 (0.294)	-0.396 (0.278)	0.051 (1.395)	-0.634 (2.031)
> 30.5 years	2.807 (4.594)	1.685 (2.026)	-1.293 (1.077)	3.585 (2.362)	0.166 (0.505)	0.176 (0.295)	0.396 (0.279)	0.881 (1.362)	3.816 (1.966)
Solvents in mixing pesticides (yes vs. no)	0.555 (4.957)	-0.408 (2.105)	-0.153 (1.121)	3.399 (2.452)	0.854 (0.539)	0.379 (0.309)	0.342 (0.291)	**-2.771 (1.412)**	1.151 (2.073)
Gasoline to clean (yes vs. no)	-2.142 (3.086)	**-2.642 (1.309)**	-0.088 (0.696)	0.386 (1.524)	0.197 (0.331)	0.064 (0.189)	-0.148 (0.181)	-0.993 (0.885)	0.341 (1.287)
Solvents to clean (yes vs. no)	-0.002 (3.372)	-0.970 (1.424)	0.098 (0.756)	0.900 (1.673)	-0.501 (0.360)	-0.260 (0.204)	**-0.486 (0.195)**	0.073 (0.961)	2.255 (1.398)

SE: Standard error; AVLT: Auditory Verbal Learning; TP: True positives; FP: False positives

*For the timed NB tests, beta estimates were multiplied by -1 so that negative scores always indicate poorer test performance.

Bolded if p < 0.05

Risk (negative) correlation (higher exposure -> worse NB performance)

Protective (positive) correlation (higher exposure -> better NB performance)

Appendix A: Pesticide analysis base model selection

A.1: Backwards elimination of covariates associated with continuous log10-CES-D score (linear regression)

	Crude p-value	Base model p-value	Beta - age forced	p-value - age forced
State	0.107	--	--	--
Age	0.530	Forced	0.001	0.565
Education	0.532	--	--	--
Marital status	0.105	0.135	0.073	0.125
Smoking	0.252	--	--	--
Alcohol use	0.187	--	--	--
PPE use	0.564	--	--	--
Solvent use	0.011	0.014	0.074	0.016
Welding	0.893	--	--	--
Soldering	0.149	--	--	--
Off-farm job	0.631	--	--	--
Head injury	0.767	--	--	--

R-sq (with age): 0.013

Final base model: Adjusted for age, marital status, and solvent use

A.2: Backwards elimination of covariates associated with high- vs. low- risk for depression (logistic regression)

	Crude p-value	Base model p-value	p-value - age forced
State	0.070	--	--
Age	0.387	Forced	0.783
Education	0.819	--	--
Marital status	0.130	--	--
Smoking	0.059	0.094	0.109
Alcohol use	0.067	0.113	0.111
PPE use	0.244	--	--
Solvent use	0.020	0.065	0.063
Welding	0.669	--	--
Soldering	0.062	--	--
Off-farm job	0.052	0.098	0.135
Head injury	0.852	--	--

ORs and 95% CIs not shown

AIC (with age): 399.875

Final base model: Adjusted for age, smoking, alcohol use, solvent exposure, and off-farm job

Appendix B: Pesticide exposure and high- vs. low-risk for depression using logistic regression

B.1: Relationship between pesticide exposures (**ever vs. never exposed**) and high-risk for depression (logistic regression)

	Crude	Adjusted*
EVER VS. NEVER EXPOSED	**OR (95% CI)**	**OR (95% CI)**
Organophosphates		
Acephate	1.146 (0.619 - 2.121)	0.846 (0.438 - 1.633)
Chlorpyrifos	1.031 (0.595 - 1.785)	1.055 (0.598 - 1.860)
Coumaphos	0.578 (0.225 - 1.485)	0.674 (0.258 - 1.761)
Diazinon	0.869 (0.502 - 1.505)	0.805 (0.457 - 1.420)
Dichlorvos	**0.392 (0.153 - 1.001)**	0.466 (0.179 - 1.216)
Dimethoate	0.683 (0.239 - 1.951)	0.733 (0.252 - 2.132)
Disulfoton	0.865 (0.398 - 1.880)	0.738 (0.331 - 1.645)
Ethoprop	**1.941 (1.052 - 3.584)**	1.576 (0.825 - 3.011)
Fonofos	0.778 (0.416 - 1.454)	0.975 (0.504 - 1.884)
Malathion	0.764 (0.417 - 1.400)	0.812 (0.436 - 1.512)
Parathion	0.591 (0.274 - 1.278)	0.579 (0.263 - 1.278)
Phorate	0.620 (0.332 - 1.157)	0.784 (0.409 - 1.506)
Phosmet	0.529 (0.206 - 1.357)	0.571 (0.217 - 1.502)
Tebupirimfos	0.302 (0.072 - 1.267)	0.400 (0.094 - 1.709)
Terbufos	0.904 (0.528 - 1.549)	0.993 (0.569 - 1.734)
Tetrachlorvinphos	0.302 (0.072 - 1.267)	0.364 (0.086 - 1.550)
Carbamates		
Aldicarb	1.467 (0.778 - 2.768)	1.299 (0.675 - 2.499)
Benomyl	1.699 (0.898 - 3.217)	1.534 (0.796 - 2.956)
Carbaryl	0.908 (0.524 - 1.575)	0.715 (0.398 - 1.286)
Carbofuran	0.738 (0.420 - 1.297)	0.797 (0.447 - 1.421)
High Pesticide Exposure Event*	1.573 (0.875 - 2.830)	1.577 (0.861 - 2.891)

B.2: Relationship between pesticide exposures (**log10-transformed lifetime days of exposure**) and high-risk for depression (logistic regression)

	Crude	Adjusted*
LIFETIME DAYS OF EXPOSURE (log10)	**OR (95% CI)**	**OR (95% CI)**
Organophosphates		
Acephate	1.014 (0.715 - 1.438)	0.852 (0.584 - 1.244)
Chlorpyrifos	0.981 (0.722 - 1.333)	1.000 (0.726 - 1.378)
Coumaphos	0.787 (0.412 - 1.503)	0.882 (0.461 - 1.685)
Diazinon	0.888 (0.619 - 1.274)	0.831 (0.575 - 1.202)
Dichlorvos	0.697 (0.446 - 1.088)	0.758 (0.483 - 1.191)
Dimethoate	0.688 (0.314 - 1.505)	0.720 (0.327 - 1.587)
Disulfoton	0.896 (0.537 - 1.496)	0.807 (0.474 - 1.372)
Ethoprop	1.422 (0.958 - 2.111)	1.226 (0.807 - 1.863)
Fonofos	0.874 (0.596 - 1.280)	0.991 (0.666 - 1.474)
Malathion	1.046 (0.761 - 1.437)	1.079 (0.780 - 1.493)
Parathion	0.610 (0.344 - 1.085)	0.600 (0.331 - 1.088)
Phorate	0.730 (0.491 - 1.086)	0.838 (0.557 - 1.261)
Phosmet	0.660 (0.358 - 1.216)	0.693 (0.373 - 1.288)
Tebupirimfos	0.437 (0.165 - 1.159)	0.524 (0.196 - 1.400)
Terbufos	0.933 (0.699 - 1.245)	0.972 (0.723 - 1.307)
Tetrachlorvinphos	0.418 (0.150 - 1.168)	0.475 (0.168 - 1.343)
Carbamates		
Aldicarb	1.264 (0.885 - 1.805)	1.189 (0.818 - 1.726)
Benomyl	0.875 (0.516 - 1.485)	0.821 (0.476 - 1.414)
Carbaryl	0.982 (0.736 - 1.310)	0.838 (0.612 - 1.148)
Carbofuran	0.861 (0.596 - 1.243)	0.872 (0.604 - 1.259)
All Organophosphate Pesticides	**0.697 (0.491 - 0.990)**	0.742 (0.516 - 1.068)
All Pesticides	0.790 (0.462 - 1.353)	0.872 (0.508 - 1.497)

OR: Odds ratio; CI: Confidence interval

*Adjusted for age, smoking, alcohol use, solvent exposure, and off-farm job

Bolded if $p \leq 0.05$

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Appendix C: Further categorization of duration of most common solvent exposures

Quartiles	n	%
Any solvents		
Never use	413	58.92
1-18 years	76	10.84
19-36 years	70	9.99
37-49 years	72	10.27
> 49 years	70	9.99
Gasoline		
Never use	478	68.19
1-6 years	58	8.27
7-21 years	57	8.13
22-45 years	54	7.70
> 45 years	54	7.70

Appendix D: Solvent analysis base model selection

D.1: Backwards elimination of covariates associated with log10-transformed CES-D score (linear regression)

	Crude p-value	Base model p-value	Beta - age forced	p-value - age forced
State	0.107	0.105	0.045	0.136
Age	0.530	forced	0.001	0.393
Education	0.532	--	--	--
Marital status	0.105	0.113	0.079	0.099
Smoking	0.252	--	--	--
Alcohol use	0.187	--	--	--
PPE use	0.564	--	--	--
Welding	0.893	--	--	--
Soldering	0.149	--	--	--
Head injury	0.767	--	--	--
HPEE	0.051	0.040	0.077	0.031

R-sq (with age): 0.014

Final base model: Adjusted for state, age, marital status, and HPEE

D.2: Backwards elimination of covariates associated with high- vs. low-risk of depression (logistic regression)

	Crude p-value	Base model p-value	p-value - age forced
State	0.070	--	--
Age	0.387	forced	0.690
Education	0.819	--	--
Marital status	0.130	0.192	0.207
Smoking	0.059	0.083	0.096
Alcohol use	0.067	0.121	0.116
PPE use	0.244	--	--
Welding	0.669	--	--
Soldering	0.062	--	--
Head injury	0.852	--	--
Lifetime OP exp.	0.044	0.031	0.031
HPEE	0.130	0.060	0.073

ORs and 95% CIs not shown

AIC (with age): 397.119

Final base model: Adjusted for age, marital status, smoking, alcohol use, lifetime OP pesticide exposure, and HPEE

Appendix E: Relationship between solvent exposures and log10-CESD score (linear regression) using smaller categories of duration

	Crude		Adjusted*	
	Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Any solvents				
Never use	Ref.		Ref.	
1-18 years (N=76)	0.060 (0.049)	0.220	0.053 (0.051)	0.292
19-36 years (N=70)	0.059 (0.051)	0.249	0.042 (0.054)	0.437
37-49 years (N=72)	**0.160 (0.050)**	**0.002**	**0.146 (0.052)**	**0.005**
> 49 years (N=70)	0.029 (0.052)	0.568	0.023 (0.056)	0.680
Gasoline				
Never use	Ref.		Ref.	
1-6 years (N=58)	0.059 (0.056)	0.296	0.050 (0.058)	0.382
7-21 years (N=57)	0.095 (0.056)	0.087	0.083 (0.059)	0.160
22-45 years (N=54)	0.069 (0.057)	0.227	0.056 (0.059)	0.344
> 45 years (N=54)	0.107 (0.057)	0.060	0.109 (0.060)	0.068

SE: Standard error

*Adjusted for state, age, marital status, and HPEE

Bolded if p ≤ 0.05

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Appendix F: Solvent exposure and high- vs. low-risk for depression using logistic regression

F.1: Relationship between solvent exposures and high-risk for depression (logistic regression)

	Crude		Adjusted*	
	OR (95% CI)		OR (95% CI)	
Any solvents				
Ever vs. never	**1.903**	**(1.107 - 3.270)**	**1.791**	**(1.024 - 3.130)**
Never use	Ref.		Ref.	
1-36 years	1.866	(0.970 - 3.589)	1.700	(0.864 - 3.342)
> 36 years	**1.942**	**(1.009 - 3.739)**	1.898	(0.949 - 3.795)
Gasoline				
Ever vs. never	1.613	(0.931 - 2.793)	1.522	(0.858 - 2.700)
Never use	Ref.		Ref.	
1-21 years	1.427	(0.699 - 2.913)	1.278	(0.611 - 2.674)
> 21 years	1.813	(0.921 - 3.569)	1.816	(0.893 - 3.690)
Paint thinner				
Ever vs. never	1.554	(0.731 - 3.306)	1.474	(0.677 - 3.208)
Never use	Ref.		Ref.	
1-17 years	0.964	(0.287 - 3.245)	0.939	(0.271 - 3.256)
> 17 years	2.240	(0.891 - 5.629)	2.060	(0.794 - 5.345)
Petroleum distillates				
Ever vs. never	1.532	(0.859 - 2.729)	1.335	(0.729 - 2.445)
Never use	Ref.		Ref.	
1-30.5 years	**2.056**	**(1.028 - 4.110)**	1.902	(0.924 - 3.916)
> 30.5 years	1.066	(0.461 - 2.465)	0.870	(0.364 - 2.079)
Solvents in mixing pesticides (yes vs. no)	1.665	(0.781 - 3.549)	2.216	(0.993 - 4.941)
Gasoline to clean (yes vs. no)	1.358	(0.770 - 2.394)	1.484	(0.825 - 2.671)
Solvents to clean (yes vs. no)	1.275	(0.696 - 2.335)	1.190	(0.637 - 2.222)

F.2: Relationship between solvent exposures and high-risk for depression (logistic regression) using smaller categories of solvent exposure

	Crude		Adjusted*	
	OR (95% CI)		OR (95% CI)	
Any solvents				
Never use	Ref.		Ref.	
1-18 years (N=76)	2.019	(0.906 - 4.502)	2.080	(0.914 - 4.737)
19-36 years (N=70)	1.699	(0.707 - 4.085)	1.359	(0.544 - 3.393)
37-49 years (N=72)	**2.428**	**(1.115 - 5.284)**	2.130	(0.950 - 4.779)
> 49 years (N=70)	1.456	(0.576 - 3.684)	1.587	(0.594 - 4.244)
Gasoline				
Never use	Ref.		Ref.	
1-6 years (N=58)	0.748	(0.222 - 2.522)	0.705	(0.205 - 2.421)
7-21 years (N=57)	2.162	(0.947 - 4.937)	1.862	(0.789 - 4.393)
22-45 years (N=54)	1.351	(0.505 - 3.618)	1.265	(0.461 - 3.473)
> 45 years (N=54)	**2.306**	**(1.007 - 5.283)**	**2.558**	**(1.049 - 6.238)**

OR: Odds ratio; CI: Confidence interval

*Adjusted for age, marital status, smoking, alcohol use, lifetime OP pesticide exposure, and HPEE

Bolded if p ≤ 0.05

Risk (positive) correlation (higher exposure -> more depressions symptoms)

Protective (negative) correlation (higher exposure -> less depressions symptoms)

Appendix G: NB BASE MODELS

*Timed test betas multiplied by -1

**If both pesticide vars are significant, continue with all-pesticide variable only

G.1: Backwards elimination of co-variates associated with Continuous Performance Test

	Initial crude p-value	Final Beta*	Final p-value
State	0.066	--	--
Age	<0.001	-1.527	<0.001
Education	0.001	--	--
Marital status	0.963	--	--
Smoking	0.574	--	--
Alcohol use	0.005	--	--
PPE use	0.263	--	--
ALL pesticides (log cont.)	0.347	--	--
OP pesticides (log cont.)	0.997	--	--
Welding	0.820	--	--
Soldering	0.795	--	--
Caffeine	0.011	8.090	0.020
Head injury	0.512	--	--
Height	0.130	--	--
Anti-depressant	0.973	--	--
Reading ability	<0.001	0.622	<0.001
Positive affect	<0.001	4.449	0.055
Negative affect	0.314	--	--
Visual acuity	<0.001	-7.584	0.080

G.2: Backwards elimination of co-variates associated with Digit-Symbol Test

With exclusions	Initial crude p-value	Final Beta*	Final p-value
State	<0.001	-4.622	0.001
Age	<0.001	-1.103	<0.001
Education	<0.001	3.155	0.023
Marital status	0.985	--	--
Smoking (cur vs. nev)	0.103	-0.677	0.796
Smoking (past vs. nev)		2.394	0.083
Alcohol use	<0.001	--	--
PPE use	0.045	--	--
ALL pesticides (log cont.)	0.985	--	--
OP pesticides (log cont.)	0.977	--	--
Welding	0.696	--	--
Soldering	0.728	--	--
Caffeine	0.304	--	--

Head injury	0.750	--	--
Height	0.055	--	--
Anti-depressant	0.869	--	--
Reading ability	<0.001	0.427	<0.001
Positive affect	<0.001	4.779	<0.001
Negative affect	0.401	--	--
Visual acuity	<0.001	-5.212	0.005

G.3: Backwards elimination of co-variates associated with Finger Tapping

	Initial crude p-value	Final Beta	Final p-value
State	<0.001	-2.297	0.001
Age	<0.001	-0.246	<0.001
Education	0.145	--	--
Marital status	0.900	--	--
Smoking	0.390	--	--
Alcohol use	0.006	--	--
PPE use	0.397	--	--
ALL pesticides (log cont.)	0.257	--	--
OP pesticides (log cont.)	0.556	--	--
Welding	0.497	--	--
Soldering	0.986	--	--
Caffeine	0.851	--	--
Head injury	0.224	--	--
Height	0.032	--	--
Anti-depressant	0.844	--	--
Reading ability	<0.001	0.137	<0.001
Positive affect	0.001	0.961	0.066
Negative affect	0.566	--	--
Visual acuity	<0.001	--	--

G.4: Backwards elimination of co-variates associated with Grooved Pegboard

	Initial crude p-value	Final Beta*	Final p-value
State	<0.001	-3.207	0.042
Age	<0.001	-1.059	<0.001
Education	0.005	2.263	0.158
Marital status	0.528	--	--
Smoking	0.299	--	--
Alcohol use	0.004	--	--
PPE use	0.010	3.483	0.117
ALL pesticides (log cont.)	0.801	--	--
OP pesticides (log cont.)	0.936	--	--

Welding	0.002	3.879	0.036
Soldering	0.707	--	--
Caffeine	0.019	3.456	0.042
Head injury	0.341	--	--
Height	0.271	--	--
Anti-depressant	0.856	--	--
Reading ability	<0.001	0.128	0.102
Positive affect	0.001	-6.365	0.003
Negative affect	0.497	--	--
Visual acuity	<0.001	--	--

G.5: Backwards elimination of co-variates associated with Auditory Verbal Learning (AVLT) Total Recall

	Initial crude p-value	Final Beta	Final p-value
State	0.042	--	--
Age	<0.001	-0.174	<0.001
Education	<0.001	0.859	0.014
Marital status	0.786	--	--
Smoking (cur vs. nev)	0.001	0.916	0.170
Smoking (past vs. nev)		-0.387	0.272
Alcohol use	0.061	--	--
PPE use	0.113	--	--
ALL pesticides (log cont.)	0.186	--	--
OP pesticides (log cont.)	0.499	--	--
Welding	0.368	--	--
Soldering	0.362	--	--
Caffeine	0.112	--	--
Head injury	0.376	--	--
Height	0.064	--	--
Anti-depressant	0.453	--	--
Reading ability	<0.001	0.099	<0.001
Positive affect	<0.001	0.625	0.019
Negative affect	0.012	-1.156	0.005
Visual acuity	<0.001	--	--

G.6: Backwards elimination of co-variates associated with AVLT Delayed Recall

	Initial crude p-value	Final Beta	Final p-value
State	0.003	-0.315	0.126
Age	<0.001	-0.090	<0.001
Education	<0.001	0.632	0.002
Marital status	0.241	--	--
Smoking	0.001	--	--

Alcohol use	0.205	--	--
PPE use	0.134	--	--
ALL pesticides (log cont.)**	0.005	0.562	0.004
OP pesticides (log cont.)	0.123	--	--
Welding	0.342	--	--
Soldering	0.719	--	--
Caffeine	0.337	--	--
Head injury: no loss of consc. vs. none	0.122	-0.374	0.250
Head injury: loss of consc. vs. none		0.364	0.200
Height	0.013	--	--
Anti-depressant	0.069	0.874	0.017
Reading ability	<0.001	0.041	<0.001
Positive affect	<0.001	0.350	0.020
Negative affect	0.020	-0.685	0.003
Visual acuity	<0.001	-0.369	0.165

G.7: Backwards elimination of co-variates associated with AVLT Recognition

	Initial crude p-value	Final Beta	Final p-value
State	<0.001	-0.795	<0.001
Age	<0.001	-0.061	<0.001
Education	<0.001	0.703	<0.001
Marital status	0.796	--	--
Smoking	0.424	--	--
Alcohol use	0.296	--	--
PPE use	0.032	--	--
ALL pesticides (log cont.)	0.194	--	--
OP pesticides (log cont.)	0.570	--	--
Welding	0.633	--	--
Soldering	0.686	--	--
Caffeine	0.665	--	--
Head injury	0.260	--	--
Height	0.010	--	--
Anti-depressant	0.506	--	--
Reading ability	<0.001	0.043	<0.001
Positive affect	<0.001	0.207	0.148
Negative affect	0.050	-0.459	0.036
Visual acuity	0.004	--	--

G.8: Backwards elimination of co-variates associated with Sequences A

With exclusion	Initial crude p-value	Final Beta*	Final p-value
State	<0.001	-2.819	0.001
Age	<0.001	-0.639	<0.001
Education	<0.001	--	--
Marital status	0.835	--	--
Smoking	0.044	--	--
Alcohol use	0.001	--	--
PPE use	0.371	--	--
ALL pesticides (log cont.)	0.759	--	--
OP pesticides (log cont.)	0.762	--	--
Welding	0.585	--	--
Soldering	0.502	--	--
Caffeine	0.381	--	--
Head injury	0.464	--	--
Height	0.138	--	--
Anti-depressant	0.644	--	--
Reading ability	<0.001	0.400	<0.001
Positive affect	<0.001	2.211	0.001
Negative affect	0.548	--	--
Visual acuity	<0.001	--	--

G.9: Backwards elimination of co-variates associated with Sequences A

With exclusion	Initial crude p-value	Final Beta*	Final p-value
State	<0.001	-4.936	<0.001
Age	<0.001	-0.954	<0.001
Education	<0.001	--	--
Marital status	0.659	--	--
Smoking	0.088	--	--
Alcohol use	0.010	--	--
PPE use	0.085	--	--
ALL pesticides (log cont.)	0.668	--	--
OP pesticides (log cont.)	0.161	--	--
Welding	0.476	--	--
Soldering	0.238	--	--
Caffeine	0.891	--	--
Head injury	0.275	--	--
Height	0.003	--	--
Anti-depressant	0.770	--	--
Reading ability	<0.001	0.530	<0.001
Positive affect	<0.001	4.177	<0.001
Negative affect	0.897	--	--

Visual acuity	<0.001	--	--

Appendix H: Exploring linear regression (controlling for covariates) with two largest exposure variables as quartiles

	Continuous Performance Test (CPT): ms	Digit-symbol: s (with exclusions)	Finger Tapping, dominant hand: # taps	Grooved Pegboard, dominant hand: s	AVLT Total Recall: # correct	AVLT Delayed Recall: # correct	AVLT Recognition: (TP - FP)	Sequences A latency: s (with exclusion)	Sequences B latency: s (with exclusion)
	Beta* (SE)	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**	**Beta* (SE)**
Any solvents									
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-18 years (N=76)	2.195 (4.968)	1.261 (2.152)	-1.315 (1.138)	2.728 (2.536)	**1.212 (0.534)**	0.425 (0.313)	0.015 (0.295)	0.904 (1.464)	2.198 (2.105)
19-36 years (N=70)	-2.629 (5.209)	-0.654 (2.309)	-0.794 (1.216)	3.632 (2.694)	-1.077 (0.559)	-0.375 (0.333)	-0.330 (0.315)	-1.686 (1.565)	-2.197 (2.247)
37-49 years (N=72)	-2.774 (5.147)	1.567 (2.236)	-1.456 (1.192)	**5.219 (2.661)**	0.420 (0.555)	0.137 (0.326)	-0.432 (0.309)	-1.335 (1.511)	2.996 (2.234)
> 49 years (N=70)	-0.947 (5.388)	-1.059 (2.375)	-1.995 (1.250)	-0.118 (2.808)	0.063 (0.575)	0.097 (0.342)	0.431 (0.324)	-1.600 (1.609)	-0.333 (2.322)
Gasoline									
Never use	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-6 years (N=58)	-3.263 (5.628)	-0.804 (2.447)	-0.617 (1.274)	1.081 (2.834)	1.105 (0.600)	0.012 (0.351)	0.482 (0.331)	0.497 (1.667)	1.914 (2.399)
7-21 years (N=57)	6.326 (5.602)	2.594 (2.551)	-1.625 (1.334)	2.395 (2.943)	-0.362 (0.608)	-0.446 (0.367)	0.042 (0.346)	-0.684 (1.701)	-1.915 (2.482)
22-45 years (N=54)	-5.611 (5.718)	-4.502 (2.480)	-1.026 (1.321)	-0.391 (2.917)	-1.052 (0.620)	-0.401 (0.363)	**-0.826 (0.342)**	**-4.132 (1.671)**	-4.080 (2.477)
> 45 years (N=54)	3.928 (5.839)	-0.476 (2.507)	**-3.408 (1.347)**	-1.626 (3.049)	-0.432 (0.636)	0.074 (0.370)	-0.037 (0.349)	-2.128 (1.708)	0.539 (2.463)

SE: Standard error; AVLT: Auditory Verbal Learning; TP: True positives; FP: False positives

*For the timed NB tests, beta estimates were multiplied by -1 so that negative scores always indicate poorer test performance.

Bolded if p ≤ 0.05

Risk (negative) correlation (higher exposure -> worse NB performance)

Protective (positive) correlation (higher exposure -> better NB performance)

Appendix I: Multivariate regression hypothetical examples

I.1: Analysis 1- Dichlorvos vs. CES-D score

		CES-D score	Intercept	cumulative days of exposure	age	marital status (0=married; 1=single)	solvent use (0=no; 1=yes)
Example 1	**Hypothetical value**	**5.14**	--	20	60	0	1
(Q1)	Beta	--	0.651	-0.037	0.001	0.069	0.064
	Model value	0.71	0.651	-0.048	0.045	0.000	0.064
Example 2	**Hypothetical value**	**4.94**	--	57.5	60	0	1
(Median)	Beta	--	0.651	-0.037	0.001	0.069	0.064
	Model value	0.69	0.651	-0.065	0.045	0.000	0.064
Example 3	**Hypothetical value**	**4.59**	--	421.75	60	0	1
(Q3)	Beta	--	0.651	-0.037	0.001	0.069	0.064
	Model value	0.66	0.651	-0.097	0.045	0.000	0.064

I.2: Analysis 1- Disulfoton vs. CES-D score

		CES-D score	Intercept	cumulative days of exposure	age	marital status (0=married; 1=single)	solvent use (0=no; 1=yes)
Example 1	**Hypothetical value**	**7.74**	--	20	60	1	1
(Q1)	Beta	--	0.637	0.061	0.000	0.076	0.068
	Model value	0.89	0.637	0.079	0.029	0.076	0.068
Example 2	**Hypothetical value**	**7.84**	--	24.5	60	1	1
(Median)	Beta	--	0.637	0.061	0.000	0.076	0.068
	Model value	0.89	0.637	0.085	0.029	0.076	0.068
Example 3	**Hypothetical value**	**8.25**	--	56	60	1	1
(Q3)	Beta	--	0.637	0.061	0.000	0.076	0.068
	Model value	0.92	0.637	0.107	0.029	0.076	0.068

I.3: Analysis 1- Ethoprop vs. CES-D score

		CES-D score	Intercept	cumulative days of exposure	age	marital status (0=married; 1=single)	solvent use (0=no; 1=yes)
Example 1	**Hypothetical value**	**5.62**	--	20	45	0	0
(Q1)	Beta	--	0.619	0.075	0.001	0.074	0.062
	Model value	0.75	0.619	0.097	0.033	0.000	0.000
Example 2	**Hypothetical value**	**5.70**	--	24.5	45	0	0
(Median)	Beta	--	0.619	0.075	0.001	0.074	0.062
	Model value	0.76	0.619	0.104	0.033	0.000	0.000
Example 3	**Hypothetical value**	**6.07**	--	56	45	0	0
(Q3)	Beta	--	0.619	0.075	0.001	0.074	0.062

	Model value	0.78	0.619	0.131	0.033	0.000	0.000

I.4: Analysis 1- Any solvent vs. CES-D score

		CES-D score	Intercept	cumulative solvent exposure (0=never; 1=high duration)	age	state (0=IA; 1=NC)	marital status (0=married; 1=single)	HPEE (0=no; 1=yes)
Example 1	**Hypothetical value**	**4.37**	--	0	45	0	0	0
(never)	Beta	--	0.604	0.090	0.001	0.016	0.079	0.078
	Model value	0.64	0.604	0.000	0.037	0.000	0.000	0.000
Example 2	**Hypothetical value**	**5.38**	--	1	45	0	0	0
(>36 years)	Beta	--	0.604	0.090	0.001	0.016	0.079	0.078
	Model value	0.73	0.604	0.090	0.037	0.000	0.000	0.000

I.5: Analysis 2- Gasoline vs. Finger Taps

		# of finger taps	Intercept	gasoline exposure (0=never)	age	state (0=IA; 1=NC)	reading score	positive affect
Referent	**Hypothetical value**	**53.47**	--	0	60	1	29	3.6
(Never)	Beta	--	62.475	-1.632	-0.243	-1.638	0.134	0.928
	Model value	53.47	62.475	0.000	-14.589	-1.638	3.883	3.342
Example 1	**Hypothetical value**	**51.84**	--	1	60	1	29	3.6
(Ever)	Beta	--	62.475	-1.632	-0.243	-1.638	0.134	0.928
	Model value	51.84	62.475	-1.632	-14.589	-1.638	3.883	3.342
Example 2	**Hypothetical value**	**52.34**	--	1	60	1	29	3.6
(low)	Beta	--	62.263	-1.101	-0.240	-1.688	0.134	0.935
	Model value	52.34	62.263	-1.101	-14.374	-1.688	3.872	3.365
Example 3	**Hypothetical value**	**51.26**	--	1	60	1	29	3.6
(high)	Beta	--	62.263	-2.175	-0.240	-1.688	0.134	0.935
	Model value	51.26	62.263	-2.175	-14.374	-1.688	3.872	3.365