

**ORGANIC SOLVENT EXPOSURE AND NEUROPSYCHOLOGICAL
FUNCTION AMONG FISHERS IN NORTH CAROLINA**

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ABSTRACT
Organic Solvent Exposure and Neuropsychological Function among
Fishers in North Carolina
(Under the direction of Dana Loomis)

Commercial fishers work with a variety of organic solvents that are toxic to the central nervous system including fuel and styrene. The goal of my research was to characterize fishers' occupational exposure to these solvents and determine the effect of exposure on neuropsychological function. The study population consisted of 238 fishers and other workers from North Carolina who were recruited to participate in an ongoing longitudinal cohort study. Participants were followed for approximately 2.5 years.

Three studies were conducted. First, a self-monitoring approach was used to obtain repeat measurements of personal exposure to benzene in fuel emissions among a subgroup of fishers (n=50). Predicted exposure levels were determined for categories of engine type using mixed-effect linear regression models. Second, weekly or biweekly telephone interviews (n=13,028) containing self-reported descriptions of maintenance work, as well as self-reports of symptoms were analyzed to estimate crude and adjusted rate ratios using Poisson regression methods. Finally, the effect of cumulative and recent maintenance work on neuropsychological test performance was estimated using Generalized Estimating Equations (GEEs). The data for these analyses included 723 neuropsychological examinations among 219 fishers.

Personal exposure to fishers on boats equipped with 2-stroke, 4-stroke, and diesel engines were estimated to be 50.1, 32.6 and 27.9 $\mu\text{g}/\text{m}^3$, respectively. Fishers reported higher rates of symptoms indicative of cognitive effects in weeks they did maintenance work involving solvents compared to weeks they did not. However, no strong or consistent relationship between self-reported exposure to solvents during maintenance work and objective neuropsychological performance was observed.

Exposure to neurotoxic organic solvents was documented in this population. The conflicting results regarding the effect of maintenance work on neuropsychological symptoms versus neuropsychological test outcomes may be explained by variety of factors. Neuropsychological testing may not be adequately sensitive to measure the subtle effects of solvents. Alternatively, the exposure levels may not have been high enough to affect the central nervous system. If this is the case, the associations between maintenance work and self-reported symptoms may have been biased. However, it is also possible that exposure misclassification resulted in attenuation of the associations between maintenance work and neuropsychological test performance.

for Thierry

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LIST OF ABBREVIATIONS

$\mu\text{g}/\text{m}^3$	micrograms per cubic meter
95% CI	95% Confidence Interval
ACGIH	American Conference of Governmental Industrial Hygienists
ADT	Automatic Thermal Desorption
AML	Acute Myeloid Leukemia
BDI	Beck Depression Inventory
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CGWA	Controlled Oral Word Association
CTE	Chronic Toxic Encephalopathy
GC/PID	Gas Chromatograph/Photo-Ionization Detector
GEE	Generalized Estimating Equations
HIV	Human Immunodeficiency Virus
ILO	International Labor Organization
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NIOSH	National Institute for Occupational Safety and Health
IRB	Institutional Review Board
kg/m^3	kilograms per cubic meter
L-N Sequencing	Letter-Number Sequencing
LOQ	Limit of Quantitation
MSDS	Material Safety Data Sheet
NC DHHS	North Carolina Division of Health and Human Services
NC SEARCH	North Carolina Study of Estuaries and River Cohort Health
NIOSH	National Institute for Occupational Safety and Health
OR	Odds Ratio
PEAS	Possible Estuary Associated Syndrome
PPM	Parts per million

REML	Restricted Maximum Likelihood Estimates
Rey AVL T	Rey Auditory Verbal Learning Test
Rey O Copy	Rey-Osterreith Copy
RR	Risk Ratio or Rate Ratio
SDMT	Symbol Digit Modalities Test
STAI	State Trait Anxiety Inventory
TLV	Threshold Limit Value
TMT	Trail Making Test
WHO	World Health Organizations
WRAT-3	Wide Range Achievement Test
US EPA	United States Environmental Protection Agency

CHAPTER I

Background on Organic Solvent Exposure to Commercial Fishers and Neurotoxic Effects of Organic Solvents

A. Use of Organic Solvents in the Commercial Fishing Trade

Commercial fishing is known to be a dangerous occupation. In fact, the commercial fishing industry has one of the highest mortality rates of any industry group in the United States (CDC 2001) and a similar trend has been observed worldwide. (Conway 2002; ILO 1999) Studies of injuries and their causes have been conducted among Alaskan fishers, who have a fatality rate that is 28 times the rate of for all workers. (Lincoln and Conway 2999; Thomas and others 2001) Similar work on injury trends and prevention is underway in North Carolina. (Loomis 2001) However, little research has been done on the risks of occupational disease in this population. A recent review of the international literature on the health of fishers, highlights the gaps in our knowledge and describes risk factors such as high rates of alcoholism, smoking, poor diet and potentially hazardous exposures that are likely to greatly increase their risk of ill-health. (Matheson and others 2001)

After the discovery of *Pfiesteria piscicida* (Burkholder 1999), a dinoflagellate believed to produce a toxin that could harm the human nervous system, in the estuarine waters of North Carolina, a study of the health of commercial fishers was begun. (Moe and others 2001) The focus of my doctoral research was the effect of exposure to organic solvents on the neuropsychological function of commercial fishers enrolled in this cohort. Commercial fishers are exposed to a variety of organic solvents that are known to be toxic to the nervous system including gasoline, diesel fuel and styrene.

1. Maintenance Work Exposures

Commercial fishers do much of their own boat and equipment maintenance. Analysis of 13,551 person interviews among commercial fishers in North Carolina (Moe and others 2001) revealed that the most frequently reported maintenance activities involving exposure to organic solvents were work on boat motors or other mechanical equipment (n=2,263 reports) and use glues, epoxies or resin to repair a fiberglass boat (n=530 reports). Work on boat motors and other mechanical equipment involves exposure to fuel through both inhalation and skin contact when gasoline is used to clean hands and equipment. (Egeghy and others 2002) The most common types of resins used by fishers for fiberglass boat repair contain styrene and acetone to dissolve the resin. Rarely reported activities

(<0.1%) included coating pots or nets with tar (n=144 reports) and use of fungicidal paints (copper oxide paint) (n=136 reports).

Table I.1 shows the number of reports per year of follow-up for these solvent-related maintenance activities. Although, the absolute number of reports is different in each year, maintenance work reports per total fishing person time did not vary substantially over the follow-up period. However, rates for fiberglass boat repair approximately double during April and May (from 0.006 to 0.012 reports per person-day of exposure.) Rates for motor or mechanical work do not fluctuate greatly by month.

2. Glues Epoxies and Resins used for Fiberglass Boat Repair

Commercial fishers are also exposed to styrene when they rebuild or repair their fiberglass boats. Fiberglass boats are damaged by sunlight. Gelcoat, which is the smooth external surface of the boat, fades and osmotic blistering occurs when water gets into the gel coat laminate. As a boat ages it becomes brittle and the “spider web” cracks that form need to be repaired. Fishers routinely purchase polyester and vinyl ester resins and gelcoats that contain styrene, from marine supply stores to restore their boats.

Although styrene was the exposure of interest for this research, the exposure data available described the number of hours fiberglass boat repair work was done using glues, epoxies and resins. In order to confirm that styrene-based resins were commonly used for fiberglass boat repair project, 119 commercial fisher participants from ongoing studies (Kirrane 2001; Loomis 2001) were invited to participate in a supplemental telephone interview. Follow-back regarding chemical exposure had been designed into the research protocols for these studies and had been approved by the Institutional Review Board (IRB).

Fishers were asked to describe their fiberglass boat repair projects and were questioned about the types of chemicals they used, the methods used to work with or apply the products (e.g. brush, rag, spray process etc.) and how often they used the products. In addition, they were asked to provide product trade names so that the manufacturer could be contacted and the Material Safety Data Sheet (MSDS) could be obtained. If a participant did

not know the product name or manufacturer, they were asked where they bought the product. The marine supply retailers identified by participants were then contacted to determine what types of resins they sold.

An incentive of \$5.00 was offered to compensate the subject for the time required to answer the questions. Of the 119 commercial fishers invited to participate, 6 (5%) refused and 16 (13%) could not be reached by telephone after multiple attempts. A total of 97 (82%) completed the questionnaire.

Approximately 72% (n=70) of the participating fishers reported “ever” doing fiberglass repair work. All of these fishers used either marine resin or gel coat during the fiberglass repair work described in the interview, indicating that questions about fiberglass repair projects captured potential chemical exposure. In addition, most of the resins and gelcoats used contained styrene. The manufacturer and styrene content of the products are shown in Table I.2. The weight percentage of styrene in the polyester and vinylester resins ranged from 15%-60%. More than 40% of the fishers bought their resin in bulk from a 55-gallon drum at a local marine supply store or from a friend and did not know the name of the product. The most popular brand of resin sold in bulk at the 12 marine supply companies reached by telephone was Clearcoat. Bondo and AOC brands were also sold in bulk. The three most popular brands of gel coat contained 35-60% styrene by weight. Again, more than half of those queried could not remember the trade name of gel coat they used.

The number of times resin use was reported in the year preceding the interview ranged from zero to more than 50 times. Approximately 63% of the participants reported this activity between 1 and 5 times. Resins were most often applied with fiberglass mat cloth using a brush or roller. Less frequently a rag, squeegee or putty knife was used to apply the material. Most projects (78%) involving resins were repairs to cracks or holes in boats. Approximately 6% of people reported rebuilding their entire boat and approximately 11% reported adding new features such as a bulkhead or killbox. Analyses of the weekly or biweekly telephone surveys conducted as part of the parent cohort study showed that the median number of hours spent per interview period on fiberglass repair projects was 5 hours

and most (91%) of the fiberglass jobs were done outside where ventilation is presumed to reduce the airborne concentration of styrene.

The frequency of resin and gel coat use is summarized in table I.3. Twenty-nine (29) people reported using gel coats during the previous year. The number of times gel coats were reported ranged from 0 to 35 with about 80% of the participants using this material two or fewer times. The gel coating was applied typically with brushes or rollers, but there were three reports of spray application processes. Spray application is likely to result in higher exposure because the gel coat is aerosolized during this process.

Approximately 95% of those who did fiberglass repair projects reported using acetone as a cleaner. Other cleaners used were gasoline and turpentine. Over half of the participants cleaned the resin from their hands using acetone during and after fiberglass repair projects. Acetone was also used to clean brushes, rollers and tools. Other materials used to repair fiberglass boats included fillers (silica or sawdust), putty, glue and paints.

3. Fuel Emissions from Boat Motors

In addition to the intermittent exposure to fuel commercial fishers receive during maintenance activities, they are exposed to fuel emissions from their boat engines while they are fishing. Boat engines are powered by either gasoline or diesel fuel, which are both complex organic solvent mixtures.

Personal exposure to fuel was anticipated to depend on a variety of factors including the type of engine used. Many commercial fishers use carbureted 2-stroke engines to power their boats. The United States Environmental Protection Agency (US EPA) is working with manufacturers to phase out these engines because they produce approximately 70% more fuel emissions than 4-stroke or fuel injected 2-stroke engines. Fuel emissions from 2-stroke engines are relatively high because oil is mixed with the fuel to lubricate the pistons and the fuel intake and exhaust port are open simultaneously during a portion of the combustion-compression cycle. No studies evaluating personal exposure to fuel while using 2-stroke engines were identified through a literature review. However, the hydrocarbon emissions per

kilogram of fuel consumed are known to be 60-100 times greater for snowmobiles equipped with 2-stroke engines compared to gasoline powered cars and diesel buses. (Bishop and others 2001)

B. Organic Solvent Neurotoxicity

The term “organic solvent” refers to a diverse group of volatile chemical compounds that are soluble in lipids and used for extracting, dissolving or suspending materials that are insoluble in water such as oils and resins. (NIOSH, 1987) Approximately 49 million tons of organic solvents are produced in the United States annually and about 9.8 million workers are potentially exposed (NIOSH, 1987).

1. Metabolism and Neurotoxic Mechanism

Organic solvents enter the blood stream primarily through inhalation or skin absorption within minutes of exposure. Uptake via inhalation depends on the blood-air partition coefficient of the particular solvent, ventilation rate, blood perfusion in the lungs and duration of exposure. (NIOSH 1987) Absorption through the skin occurs if the solvent is soluble in lipids and water and is influenced by the presence of cuts or abrasions on the skin, duration of exposure, skin thickness and perfusion. (NIOSH 1987)

Styrene and approximately 25-30% of the constituents in gasoline are classified as aromatic hydrocarbons. Aromatics are highly volatile posing an inhalation hazard. The longer chained hydrocarbons in gasoline and diesel fuel are less volatile. However, evidence from studies of animals suggests that these compounds may have a relatively high anesthetic potential despite lower uptake because their blood/lipid partition coefficient is higher compared to aromatic compounds. (Ritchie and others 2001)

Once in the blood stream, organic solvents accumulate in the fatty tissues or are metabolized in the liver through oxidative reactions catalyzed by cytochrome P-450 followed by conjugation with glucuronic acid, sulfuric acid, glutathione or glycine. Metabolic products are usually water-soluble compounds that can be excreted in the urine but may include reactive intermediates that are more toxic than the parent compound. (NIOSH 1987)

Much of the organic solvent is eliminated through exhalation, however. It is noteworthy that alcohol and possibly co-exposure to multiple solvents can result in increased blood levels of solvents due to competition for enzymes needed for metabolism while chronic alcohol consumption may result in lower blood levels by inducing solvent metabolizing enzymes. (Baker and others 1986)

The extent and type of nervous system damage caused by organic solvents depends on the chemical as well as the duration and intensity of exposure. In general, the central and peripheral nervous systems are important targets of organic solvents because they have a high content of fatty tissue as well as a high blood supply. Cellular damage to myelin sheaths covering axons of the peripheral nervous system may occur and this damage may interfere with neurotransmission. Many solvents (i.e. alcohol) are capable of crossing the blood brain barrier causing damage to or destroying brain cells. Cells in the central nervous system may not regenerate in the same manner as the cells that make up other systems. Since nerve cell loss occurs progressively in the second half of life (Hartman 1995), nerve cell damage from solvent exposure may interact synergistically with the aging process.

In addition to directly targeting the lipid rich tissue of the central nervous system, organic solvents also interact with the neurochemical mechanisms including those that control pituitary actions and hormone production. (Hartman 1995) Damage to the nervous system that manifests in subclinical neuropsychological changes may be secondary to damage to the pulmonary or renal system. (Tarter and others 1988)

2. Epidemiology

a) Organic Solvent Mixtures

Acute exposure to solvent mixtures, such as fuel or paint, can cause central nervous system depression and symptoms ranging in severity from dizziness to unconsciousness and death from respiratory arrest at high levels. (Hartman 1995; NIOSH 1987) The less severe effects are usually transient (Kulig 1990), but cases of residual cognitive impairment lasting years after an accidental solvent intoxication episode have been reported. (Hartman 1995; Stollery 1996) Impairments in neuropsychological measures of memory, reaction time,

perceptual and sensory motor speed, manual coordination and mood after acute exposure have been documented in experimental settings. (NIOSH 1987)

The effects of chronic exposure to relatively low levels of organic solvents are more difficult to study and consequently, not as well understood as the effects of acute exposure. Frequent findings of cross sectional studies of currently employed painters, carpet layers, printers, jet fuel workers, electronics workers and nail technicians include decrements on neuropsychological measures of memory, psychomotor function, attention and mood, and some have observed a dose response effect. (Baker 1994; Baker and Fine 1986; Broadwell and others 1995; Escalona and others 1995; Jang and others 1999; LoSasso and others 2002; Ohnishi and others 1995; Tsai and others 1997)

Since the occupational groups studied in the cross sectional studies above were currently employed and neurobehavioral test outcomes were often measured during or after the work shift, acute and chronic effects of solvents cannot be distinguished. It is also unclear whether the dose-response relationships observed in some of the studies can be attributed to the cumulative effects of solvent exposure rather than age, which is correlated with cumulative exposure and is an independent predictor of neuropsychological functioning. (Baker 1994) On the other hand, cross sectional studies may underestimate risk of chronic solvent exposure because they fail to capture workers who have left work due to neurological or psychiatric disorders. More recent studies have employed designs and analytical methods better suited to distinguish the acute and chronic effects of solvent exposure. These recent studies are summarized in Table I.4.

Morrow and colleagues compared currently employed painters with and without a history of chronic exposure and observed an interaction between acute and chronic exposure with the poorest performance on neurobehavioral tests in active workers with a history of chronic exposure. (Morrow and others 1997) However, a study with a similar objective observed no differences in neuropsychological function on tests administered to currently exposed carpet layers and age-matched controls before the beginning of the workday when the effects of acute exposure were assumed to have diminished. (Muijser and others 1996)

Nasterlack and colleagues compared currently employed painters and construction workers with at least 10 years in the industry with regard to their recent exposure and their cumulative exposure to solvents and found small differences in mood and behavior assessed by questionnaire but no significant differences in neuropsychological test scores. (Nasterlack and others 1999) On the other hand, Eller and colleagues observed that long-term exposure to high levels of toluene was associated with decrements in neuropsychological function among workers in a printing plant. (Eller and others 1999)

The studies described above controlled for age by adjusting multivariate models techniques or by matching on age. These analytical techniques do not address the complex interaction between age and solvent exposure. Older workers may be more susceptible to the effects of solvents because of biological changes that occur during the aging process. Age while exposed, as well as the cumulative number of years exposed may both be important factors in determining the effect on the nervous system. (Kieswetter and others 2000) The studies that employed stratified analyses to evaluate the interaction between age and exposure include the last three studies listed in Table I.4. Daniell and colleagues designed their study to test the interaction between age, solvent exposure and alcohol consumption. (Daniell and others 1999) Neuropsychological tests were administered to retired painters who had high solvent exposure, aerospace workers with varying exposure and carpenters with minimal solvent exposure. They found an increased number of abnormal test scores among solvent exposed workers that they attributed to residual CNS damage. (Daniell and others 1999) No adverse delayed effects of due to previous toluene exposure in older age groups were observed among printing plant workers over the age of 54 years. (Kieswetter and others 2000) In fact, the investigators reported a paradoxical result that the older, more highly exposed printers, performed better on neuropsychological tests and reported fewer symptoms. The study of the interaction between solvent exposure among floor layers and age found larger decrements in visual memory, perceptual speed and motor speed in the highest exposure group. (Nordling Nilson and others 2002)

Despite the conflicting findings of the epidemiologic studies of chronic solvent exposure, there is clinical evidence to suggest that chronic exposure to organic solvents can

result in mild or severe chronic toxic encephalopathy (CTE) that may not be reversible. (Baker and White 1985; Hartman 1995) Diagnostic criteria for CTE are recognized. (Baker and Seppalainen 1986; WHO 1985) The least severe form of CTE is characterized by subjective complaints of fatigue, irritability, depression and episodes of anxiety. The “mild or moderate” form of the disease includes emotional and cognitive components that can be measured by neuropsychological tests of mood, memory, learning and psychomotor function. At its most severe, CTE is characterized by a global emotional, intellectual and neuropsychological decline or dementia. CNS damage is believed to be more widespread with increasing duration and intensity of solvent exposure. (Hanninen 1990) Individual susceptibility and concomitant depression have also been observed to be important factors in recovery. (Dryson and Ogden 2000)

b) Gasoline and Diesel Fuel

Both diesel fuel and gasoline contain a host of known and possible neurotoxic substances, but liquid gasoline poses a greater inhalation risk because it is highly volatile and typically contains between 25% and 30% aromatic hydrocarbons, many of which are known neurotoxic agents. (Ritchie and others 2001) By contrast, diesel fuel is distilled to exclude the aromatics and therefore has a negligible vapor pressure at normal ambient temperatures. Most of the hydrocarbons in diesel exhaust tend to have low vapor pressures, and adsorb onto the particles present in the exhaust emissions. (Muzyka and others 1998) Therefore, the health hazards typically associated with exposure to the particulate matter in diesel exhaust are lung cancer and respiratory disease. (NIOSH 1988) However, there is increasing concern that the longer chained hydrocarbons may have a relatively high anesthetic potential based on the pharmacokinetic and animal evidence recently reviewed by Ritchie and colleagues. (Ritchie and others 2001) Finally, the simultaneous exposure to the many toxic hydrocarbons present in fuel may pose unique hazards that remain largely unrecognized.

c) Styrene

Styrene is a highly volatile monomer that is polymerized to form hard, durable plastic products. Fiberglass boats are made from styrene-based polyester resins that are reinforced with fiberglass cloth and typically used in conjunction with a methyl ethyl ketone peroxide

(MEKP) liquid hardener. The smooth exterior surface of the boat is achieved by applying a gel coat, which is also a polyester resin. Vinyl ester or epoxy resin can also be used with fiberglass or other fibrous material to make boats but the resulting product is termed composite rather than fiberglass. Vinyl ester resins also contain styrene while epoxy resins do not (they are formed by reacting bisphenol A and epichlorohydrin).

Based on evidence animal and human chamber studies, a consensus has emerged that styrene can affect the central nervous system at exposure levels higher than 50 ppm. (ACGIH 2001; Hartman 1995) There is also evidence from epidemiological studies of working populations of decrements on neuropsychological or neurobehavioral measures (predominantly reaction time) among workers exposed to mean levels of less than 50 ppm. (Cherry and Gautrin 1990; Edling and others 1993; Letz and others 1990; Tsai and Chen 1996; Yokayama and others 1992) The American Conference of Governmental Industrial Hygienists (ACGIH) has set the Threshold Limit Value (TLV) to 20 ppm in order to protect against CNS effects as well as irritation of the mucous membranes and respiratory system. (ACGIH 2001) Acetone, the chemical typically used to dissolve styrene-based resins, is considered one of the least toxic solvents. (Hartman 1995) Methyl ethyl ketone peroxide (MEKP), the hardener used with polyester resins, targets the eyes, skin, respiratory system, and liver and kidney damage has been documented in animals. (NIOSH 1990)

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Table I.1. Number of maintenance work reports and rates per year of follow-up, commercial fishers (n=238), North Carolina, 1999-2001

Maintenance Activity Reported	Number of Reports		
	1999 (April- December)	2000 (January- December)	2001 (January- October)
Any maintenance activity	435	2011	1308
Coating crab pots with tar	7	70	67
Using copper oxide paint	9	78	49
Work on motors or other mechanical equipment	281	1169	813
- Clean hands with gasoline	79	307	216
- Clean hands with mineral spirits	25	168	119
Fiberglass boat repair	74	363	268
Use acetone	52	268	172
Use glue, epoxy or resin	92	393	258
Use glue, epoxy or resin to repair fiberglass boat ^a	59	263	208
Total person-days for each year	10011	43109	34269
Maintenance activity reports per total person-days of fishing	0.04	0.05	0.04

^a Two questions, using glues epoxies and resins and repairing fiberglass boats, were combined to create this variable. The resins and gelcoats typically used for fiberglass boat repair usually contain styrene.

Table I.2. Commonly reported resins used for fiberglass boat repair among commercial fishers (n=119), North Carolina, 2001

Resin System	Number	%	Styrene (% by weight)
Clearcoat Marine Polyester Resin	14	22%	60%
West System Epoxy Resin	8	13%	N/A ^a
Evercoat Marine Polyester Resin	7	11%	40-45%
AOC Resin	2	3%	33-41%
Bondo Resin System	2	3%	15-20%
Other brands of vinylester or polyester resins	4	6%	similar range
Don't Know	31	41%	N/A
Total	68	100%	

^a Not Applicable

Table I.3. Frequency of resin and gelcoat use among commercial fishers who reported doing fiberglass boat repair in the previous year (n=70), North Carolina, 2001-2002

Resin			Gelcoat		
Number of times in the last year	Number	Percent	Number of times in the last year	Number	Percent
0	6	9%			
1-5	43	63%	0	7	24%
6-10	9	13%	1	8	28%
11-50	5	7%	2	8	28%
>50	2	3%	>2	6	21%

Table I.4. Recent studies designed to distinguish acute and chronic effects of organic solvent exposure.

Author	Population	Exposure	Outcome	Results
Morrow et al. 1997	Currently employed painters (n=38) and non-exposed controls (n=36 United Food and Commercial Workers, bakery drivers)	Cumulative Exposure (lifetime) ^a Cumulative Exposure (1 year) Acute v. Chronic: test administered after painting or after an exposure free interval	Neuropsychological tests grouped by functional area ^b : learning and memory (2) spatial (3) attention (4) motor speed (5) general intelligence	Scores on learning and memory tests were significantly lowest among those with longer lifetime cumulative exposure and acute exposure indicating an interaction between cumulative and acute exposure.
Muijser et al. 1996	Currently employed carpet layers (n=89) and age matched controls (n=85 cement floor layers)	Job: carpet layers, controls and carpet layer subgroups: water-based adhesives (toluene), contact adhesives (toluene and other solvents) Acute v. Chronic: AM and PM measurements	NES: Simple Reaction Time, Symbol Digit Substitution, Hand Eye Coordination, Digit Memory Span	No significant differences between carpet layers and controls on AM (before the workday began) tests. No significant differences between carpet layers and controls for differences between AM and PM test scores.
Nasterlack et al. 1999	Painters (n=401) and construction workers (n=209) with at least 10 years of professional experience	Job: painters (exposed), construction workers (unexposed) Lifetime exposure (work history questionnaire/ expert opinion) Recent exposure (1 year)	Neuropsychological tests: verbal intelligence, fluid intelligence, visual retention (Benton), concentration (d2), reaction time (Wiener Reaktionstest) Symptom survey, psychiatric exam	Few significant differences between painters and construction workers (painters performed better on visual retention and concentration). Significantly more symptoms in painters using the lifetime exposure index (not the 1 year).
Eller et al. 1999	Printing workers (n=98)	Toluene exposure groups: (1) unexposed office workers; (2) 1-12 years of exposure <20ppm; (3) > 12 years of exposure with 75% exposed to >100ppm 10+ years Current exposure similar for groups 2 and 3.	Neuropsychological tests (Cognitive Function Scanner Test): Number Learning Test and Word Recognition test, Face Recognition, Figure Drawing Test and Pen to Point, Parallelogram Test, Bourdon Wiersma Test, Continuous Graphics Tests, Reaction Time Tests Symptom survey, medical exam.	Group 3: significantly higher symptom score, lower scores on tests of visuospatial function (Parallelogram Test), number learning and word recognition. No differences in neurological function. No differences between group 2 and group 1.

Table I.4. (continued) Recent studies designed to distinguish acute and chronic effects of organic solvent exposure.

Author	Population	Exposure	Outcome	Results
Daniell et al. 1999	Retired painters (n=67), aerospace workers (n=22) and carpenters (n=126)	Cumulative Exposure (CE) (lifetime) ^a Job: Painters (higher CE relative to aerospace), aerospace workers (higher mean exposure while exposed relative to painters), carpenters selected for no more than 5 years only intermittent exposure	Neuropsychological tests grouped by functional area ^c : (1) language; (2) reasoning; (3) attention; (4) memory; (5) visuomotor speed; (6) motor Symptom survey, psychiatric assessment	Painters had lower mean scores on test measures of motor, memory and reasoning ability. The aerospace workers with moderate to high cumulative exposure had lower mean scores on motor attention memory and reasoning ability. Painters and highly exposed aerospace workers are more likely to have outlier test scores (OR's 3.1 and 5.6 (NS) respectively).
Kiesswetter et al. 2000	Random sample of toluene exposed workers from printing plants in Germany (n=278)	High exposure (printing workers) and low exposure (end processing operators) groups. Stratified by age (<30, 31-40, 41-50, >50).	Neurobehavioral Test Battery (EURO-NES) ^d	The group with the higher exposure and the older age performed better on tests and reported fewer symptoms. Paradoxical results could be explained by differences in intelligence or reversibility of effects from higher exposure early in a career.
Nordling Nilson et al. 2002	Floor layers (n=41) and unexposed carpenters (n=40)	High and low exposure floor layer groups based on interview and measurements	TUFF battery: Synonyms, reasoning, block design, unfolding, digit symbol, identical numbers, dots speed, bolt. Pins, Benton - correct, Benton-error	Older workers (>60) showed a decline in visual memory. The most highly exposed carpet layers deteriorated significantly more than the carpenters.

^a Exposure assessment method considered job task, environment (indoor/outdoor), Personal Protective Equipment (PPE) and ventilation/engineering controls (Fidler et al. 1987).

^b (1) Verbal Paired Associate Learning, Delayed Verbal Learning, Symbol Paired Associate Learning, Delayed Symbol Learning, Recurring Words, Incidental Recall; (2) WAIS-R Block Design, WAIS-R Picture Arrangement, WAIS-R Picture Completion, WMS-R Visual Reproductions, WMS-R Visual Reproduction Delay; (3) WAIS-R Digit Span, WAIS-R Digit Symbol, Trails A, Trails B, Stroop Color Word Interference; (4) Grooved Pegboard Dominant, Grooved Pegboard Non-dominant; (5) WAIS-R Information, WAIS-R Similarities, WAIS-R Comprehension, WAIS-R Arithmetic

^c (1) Aphasia screening, Verbal Fluency Test; (2) Trails B, WAIS-R block design, WAIS-R similarities; (3) d2 Test (error), Stroop Word Test, WAIS-R Digit Span (4) Benton Visual Retention, Rey Auditory Verbal Learning Test (trial VII after interference), WMS-R Logical Memory (immediate), WMS-R Visual Memory (delayed); (5) d2 test (accuracy), Trails A, WAIS-R Digit Symbol; (6) Finger Tapping, Grooved Pegboard, Simple Reaction Time.

^d EURO-NES consists of tests to measure simple motor function, short term memory, eye hand coordination, psychomotor perception and speed and attention (Simple Reaction Time, Symbol Digit Substitution, Digit Span, Switching Attention).

CHAPTER II

Methods

A. Objective and Specific Aims

The overall goal of my doctoral research was to characterize organic solvent exposure among a cohort of commercial fishers and determine the association between this exposure and neuropsychological function. The specific research aims are listed below:

- 1) Measure exposure to fuel emission from boat engines while fishing and determine the predictors of exposure.
- 2) Determine the association between self-reported maintenance activities involving exposure to organic solvents and self-reported symptoms.
- 3) Determine the association between cumulative exposure to organic solvents while performing maintenance activities during the 5-7 month interval between neuropsychological exams and neuropsychological test performance.

The results of this research will be applicable for the evaluation of potential confounders in the study of possible *Pfiesteria* exposure and neuropsychological function. In addition, the results may be relevant for other populations with similar exposures.

B. Population

The study population was made up of 238 commercial fishers and others exposed to marine waters in North Carolina, who were recruited to participate in the longitudinal cohort study, known as the North Carolina Study of Estuaries and Rivers and Cohort Health (NC SEARCH). The majority of the cohort members (97%) listed commercial fishing as their primary or secondary occupation. The majority of the commercial fishers were crabbers, finfishers, clammers and shrimpers. Participants also reported harvesting oysters and scallops and other types of fishing such as trapping eels, turtles, catching bait and flounder. The person-time accumulated during different types of fishing during the 2 and ½ year follow up period is summarized in Table II.1. The variation in rates over the year reflects the seasonal nature of the commercial fishing industry. Figure II.1 shows that the height of the crabbing season extends from the spring to the early fall, while the majority of the finfishing is done in the colder months. Shrimping was done in the summer and fall and, per regulation, oysters are not harvested in the summer months that do not contain the letter “r”.

The fishing gear used did not vary substantially for most types of fishing. More than 90% of the crabbing person-time was accumulated among those using pots to harvest their catch. This method involves baiting and setting pots designed to trap crabs and returning to pull them. Many crabbers have shedding tanks for soft-shelled crabs on their boats. Finfishers most often used gillnets for their work (≈80% of the person-time accumulated during finfishing). Gillnets that are between 100 and 300 yards long, are typically set by hand in shallow water and with a net reel in deeper water. Fish trapped in these nets must be removed almost immediately after capture. Other common finfishing gear included “hook and line” and pound nets. Hook and line fishing involves setting long lines on which hooks are attached at regular intervals. Pound nets are placed permanently near the shoreline and fish are removed periodically. Shell fishers (clams and oysters) typically used rakes and tongs, and there were many reports of using hands and feet. Those who did other types of fishing reported using seine nets, gill nets, rod and reel, spears and pots. Seine nets are pulled through the water rather than set as are gillnets and poundnets.

NC SEARCH was designed to elucidate risk factors and possible clinical disease associated with exposure to estuarine waters contaminated with *Pfiesteria piscicida*. (Moe and others 2001) *Pfiesteria*, a newly discovered dinoflagellate (Burkholder 1999), is believed to produce a toxin that has been associated with neurological dysfunction in laboratory workers exposed to high levels of *Pfiesteria* cultures (Glasgow Jr. and others 1995; Schmechel and Koltai 2001) and one study offers preliminary evidence that exposure to estuarine waters in which *Pfiesteria* is present might adversely affect cognitive function. (Grattan and others 1998) The results of this study, which was conducted among those exposed to estuarine water in Maryland, are summarized in Appendix 5.

A full description of the study design and methods has been published elsewhere. (Moe and others 2001) In summary, participants must have worked on the water at least six months per year for at least 25 hours per week, and believe that they could fulfill the requirements of the study. Specifically, participants agreed to maintain an activity log book and answer questions during a biweekly or weekly telephone interview during the follow-up period that began in April of 1999 and continued until October of 2001. They were also

required to receive a baseline clinical evaluation that included a medical exam, neuropsychological assessment and interview about potentially confounding exposures as well as social and demographic factors. Information was updated during subsequent clinic visits every 5 to 7 months during the 2.5-year follow-up period. All participants were volunteers. Some were randomly selected for recruitment via telephone solicitation from a list of commercial fishers who hold licenses. Others were solicited directly at fishing events or reached through advertisements in local newspapers.

Individuals with health conditions known to affect neurocognitive function were excluded. Specific medical conditions resulting in exclusion included head trauma resulting in loss of consciousness, insulin-requiring diabetes, hospitalization for treatment of drug or alcohol abuse, stroke or transient ischemic attack, brain tumor, seizures, epilepsy, encephalitis, meningitis, Parkinson's disease, Alzheimer's disease, dementia, systemic lupus, Lyme disease, brain surgery, Huntington's disease, multiple sclerosis, narcolepsy, known solvent or pesticide poisoning, reported infection with human-immunodeficiency virus (HIV), antipsychotic or antimanic medication use, or a diagnosis of psychosis. In addition, individuals who had been placed in mentally handicapped classes in school or who had participated in previous or other current studies of health effects possibly related to *Pfiesteria* exposure, were excluded from the cohort.

C. NC SEARCH Data

1. Exposure Data

a) Maintenance Activity Exposures

Data on maintenance activities were collected longitudinally during a total of 15,551 weekly or biweekly telephone interviews. Queries about maintenance activities involving solvent exposure included painting with copper oxide, using tar to coat crab pots, using glues epoxies or resins, repairing a fiberglass boat and doing motor or mechanical equipment work. Fishers were asked whether they did this work inside or outside and how many minutes, hours or days they spent doing the work during the interval between interviews.

2. Measures of Neuropsychological Function

a) Symptoms

Although the symptom questionnaire was designed to address symptoms relating to possible *Pfiesteria* exposure, most of the symptoms queried could also be caused by exposure to organic solvents. Participants were asked whether they experienced any of 22 symptoms including neuropsychological symptoms, gastrointestinal problems, irritant effects, respiratory problems and musculoskeletal disorders during the 15,551 weekly or biweekly telephone interviews that were conducted. The neuropsychological symptoms included were memory loss, poor word and task recall, confusion and poor concentration. The other specific symptoms asked about were headache, diarrhea, crampy belly pain, nausea or stomach sickness, vomiting, eye irritation, nose irritation, skin irritation or burning, skin sores or rash, cough, wheezing shortness of breath, stuffy nose, muscle cramps, unusual tiredness and joint pain. Gastrointestinal problems, irritant effects and respiratory effects have also been observed among solvent exposed populations. (NIOSH 1987) Musculoskeletal problems may be caused by moving heavy objects, repetitive motions or by adopting awkward postures during maintenance work.

b) Neuropsychological Exams

Neuropsychological tests were administered at baseline and every 5-7 months during the 2.5-year follow up period. The test battery consisted of 15 tests to examine executive function, memory and learning, fine motor speed and mood, and eleven of those tests were used in the analyses of solvent exposure. The test battery was selected based on the following criteria:

- 1) Ability to screen the major functional domains of human cognition typically affected by neurotoxic substances, in a standardized fashion;
- 2) ability assess neurocognitive functions with minimal redundancy;
- 3) relevance for the assessment of learning and selective or divided attention;
- 4) well documented reliability and validity data for neurologically impaired populations;
- 5) the availability of age and education stratified normative data; and
- 6) the ability to compare test results with neuropsychological studies of toxic dinoflagellates and other environmental or natural toxins.

The specific neuropsychological tests of executive functions were the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale-III (L-N Sequencing) (Wechsler 1997), the Trail Making Test (TMT) (Reitan 1958), the Symbol Digit Modalities Test (SMDT) (Smith 1982), the Stroop Test (Stroop) (Golden 1978), the Controlled Oral Word Association subtest of the Multilingual Aphasia Examination (COWA) (Benton and Hamsher 1976) and Raven's Progressive Matrices (Raven's Matrices) (Raven and others 1995). The L-N Sequencing test is a mental sequencing subtest requiring the subject to listen to and then reorder in correct sequence successively longer sets of numbers and letters. The first part of the TMT, the Trails A, requires the subject to rapidly sequence a straightforward series. The second part, the Trails B, is a more difficult cognitive flexibility task requiring the subject to follow a sequential pattern while shifting cognitive sets. The SMDT measures nonverbal rapid sequencing of digits and symbols according to a stimulus key. The Stroop measures response inhibition and sensitivity to interference under changing task demands. The COWA is a test of word generation that measures lexical fluency. Raven's Matrices form the basis for an untimed nonverbal test requiring visual pattern matching and reasoning.

The tests of learning and memory were the Rey Auditory Verbal Learning Test (Rey AVLT) (Schmidt 1996) and the Rey-Osterreith Complex Figure Test (Rey-O Copy) (Meyers and Meyers 1995). The Rey AVLT involves five learning trials of a 15-word list, free recall after a brief intervening task, delayed free recall after a 30 minute delay, and recognition memory testing. The two summary scores used in the present study were total learning across the five presentation trials and the percent retained at the delayed recall trial relative to that learned in the last learning trial. The Rey-O Copy assesses visual-constructional ability by requiring the subject to copy a complex figure and nonverbal memory when the subject must reproduce the design from memory after a delay. The score for the copying task and the score for the percent retained at the delayed recall trial relative to the copy score were used in these analyses.

Fine motor skills were assessed using the Grooved Pegboard Test (Klove 1963), which measures both dominant and non-dominant hand fine motor speed, coordination, and

dexterity. Mood and affect were measured using the Beck Depression Inventory (BDI) (Beck and others 1961) and the State-Trait Anxiety Inventory (STAI) (Spielberger 2002). The BDI is a widely used self-rated measure of depression. The STAI uses a multiple-choice format that yields a score for the more situational or transient “state anxiety” and as score the more long-standing quality of “trait anxiety.”

3. Covariates

The association between solvent exposure and neuropsychological function may be confounded or modified by a variety of factors. Data describing covariates considered in these analyses were collected during the baseline and follow-up clinical exams conducted for NC SEARCH. The predictors of neuropsychological function that were evaluated as potential confounders and effect measure modifiers included age, gender, education, drug and alcohol use. Additional predictors specific to neuropsychological test performance are handedness, time of the exam, number of previous times the test was taken and examiner factors (Table II.2). In addition, test score is influenced if subjects show poor effort on the tests. Exclusions were made after initial recruitment if participants exhibited a malingering profile on the Rey 15-item Test (cutpoint < 8) (Loring and Martin 1992).

Self-reported symptoms (O'Donnell and others 1993) and neuropsychological test performance (Lezak 1995) are both influenced by affective disturbances including anxiety and depression. Pre-morbid intelligence is also associated with test performance. Although pre-morbid function is difficult to establish (Hartman 1995), the Wide Range Achievement Test (WRAT-3) (Wilkinson 1993) was used to evaluate equivalency of reading ability across exposure groups. Finally, although BMI is not a predictor of neuropsychological performance, the amount of body fat may modify the measure of association between solvent exposure and neuropsychological function. Organic solvents are highly soluble in lipids and may be stored in the fatty tissue, affecting the body burden of the chemical over time.

D. Fuel Exposure Study

A separate study of personal exposure to fuel emissions from boat engines while fishing or working on motors or mechanical equipment was conducted among a subgroup of NC SEARCH participants. This fuel exposure study was piloted in January of 2001, recruitment began officially on June 17, 2001 and continued through October of 2001. Cohort members who received a clinical examination during the pilot or continuation phase of the study were invited to measure their fuel exposure using a self-monitoring kit developed by Egeghy and colleagues. (Egeghy and others 2000) The recruitment flyer is included in Appendix 2. Informed consent was obtained for those interested in participating during the clinic appointment and an initial monitoring kit was provided. An incentive of \$25.00 was provided for each monitor returned for analysis. Individual results were mailed to each participant and follow-up was conducted to answer questions and to obtain missing data.

Each participant was asked to make at least two measurements. Those who returned the first monitor received a letter with a randomly selected date for a second day of sampling through the projected close of the study (October 31, 2001). When that date approached, attempts were made to contact the participant so that a monitoring kit could be mailed. Similarly, attempts to contact those who returned a second monitor were made so that a third monitor could be mailed. To maximize the number of measurements, we ceased the random selection of dates for repeat measurements at the end of the study and everyone who could be reached by phone was asked to participate in additional monitoring.

The monitoring kit contained a passive monitor, written instructions on how to use the monitor, a questionnaire on work practices and equipment, and a stamped and addressed envelope for returning the monitor for laboratory analysis. The questionnaire consisted of an open-ended work activity log for the monitoring day, a checklist to record the type(s) of fishing performed and questions designed to capture information to help explain observed variation in exposure level. This questionnaire is included in Appendix 3. These questions addressed engine type, use of hazardous chemicals, smoking, boat type and size, refueling,

average boat speed and the amount of time the boat was in motion. The pilot study, conducted in January of 2002, indicated that the self-monitoring methods could be applied successfully among commercial fishers with minimal burden to participants.

The correct use of the monitor was demonstrated when the kit was distributed by the clinician during the exam. The participant was simply required to open the cap, record the time, attach the monitor to his or her shirt collar, then close the cap tightly at the end of the sampling period and record the time. The participant was instructed to use the monitor the next time he or she fished or did mechanical work, measure exposure during a complete workday including lunch and breaks, fill out the work activity questionnaire and mail the monitor back for analysis. Only three measurements were made during mechanical work and were excluded from the analyses of fuel exposure during fishing.

Benzene was used to mark exposure to both evaporative emissions and fuel exhaust generated from boat motors while fishing. Monitoring and analytic methods described by Egeghy and colleagues were employed. (Egeghy and others 2000) Passive monitors consisting of aluminum tubes packed with 0.1 grams of Tenax (SKC Inc., Eighty Four, PA) were assembled. Monitors were initially conditioned at 250° C for 30 minutes using the Perkin Elmer ATD 400 automatic thermal desorption system to clean the reusable sampling medium and remove residual benzene. Prior to distribution for field use, monitors were conditioned again at 225°C for three minutes. Returned monitors were desorbed with the ATD 400 and analyzed with a Hewlett Packard 6890 Series II gas chromatograph (Hewlett-Packard Corp., Palo Alto, CA) with HNU PI-52-02-A photo ionization detector (HNU Systems, Inc., Newton, MA). Separation was accomplished with a megabore DB-1, 60-m x 0.53-mm dimethylpolysiloxane column. (1.5 µm film thickness) (J&W Scientific, Folsom, CA.)

External calibration standards were prepared by drawing known quantities of benzene vapor diluted in zero-grade air through passive monitors at approximately 60 mL/min using a needle valve regulated vacuum line. Calibration curves with at least 5 points were determined by least squares linear regression. The limit of quantitation (LOQ) was estimated

at three times the average size of a residual benzene peak from analysis of a conditioned air sampler.

E. Data Analysis

1. Statistical Analysis

All analyses were conducted using SAS version 8.01. (SAS Institute, Cary, NC) Multivariate methods appropriate for longitudinal data analysis were selected. Where applicable, methods appropriate for repeat outcome measurements that accounted for autocorrelation in the outcomes and time varying exposures, were used. Methods for each specific research aim are described below.

Specific Aim 1: To measure exposure to fuel emission from boat engines while fishing and determine the predictors of exposure.

Repeat measurements of fuel exposure, using benzene as a marker, were made and questionnaire data on potential predictors of exposure were provided by a subgroup of cohort participants. Benzene exposure data were natural log-transformed prior to statistical analyses. A mixed linear regression model, which allowed the estimation of within- and between-subject variation and the prediction of exposure levels, was specified using the MIXED procedure in SAS. Models were fit using methods described by Rappaport and colleagues. (Rappaport and others 1999)

Specific Aim 2: To determine the association between self-reported maintenance activities involving exposure to organic solvents and self-reported symptoms.

The rate ratios describing the association between nine indices of organic solvent exposure during maintenance activities and 21 self-reported symptoms were determined using Poisson regression methods and the GENMOD procedure in SAS. Since this method assumes that each observation is independent, over-dispersion was evaluated prior to application of this model.

Specific Aim 3: To determine the association between cumulative exposure to organic solvents while performing maintenance activities during the 5-7 month interval between neuropsychological and neuropsychological performance.

Regression coefficients describing the effect of cumulative exposure during the 5-7 month interval between neuropsychological exams on neuropsychological test score were determined and recent exposure during the preceding five days was included as a covariate. Longitudinal analysis that accounted for the correlation within individuals was performed with the GENMOD procedure, which uses generalized estimating equations (GEE's) (Liang and Zeger 1986) to determine the model parameters.

In addition, mean neuropsychological test scores across categories of engine type were determined. Linear regression coefficients, simple means and adjusted least square means were determined using the REG, MEANS and GLM procedures in SAS, for the subgroup of commercial fishers who participated in the fuel exposure study (N=50).

2. Conceptual Framework

The conceptual model describing the effect of organic solvents on the central nervous system is shown in Figure II.2. The severity of the effects is determined by duration and intensity of exposure. Acute solvent exposure is known to cause symptoms ranging from drowsiness to narcosis and death. (NIOSH 1987) Permanent or poorly reversible cognitive deficits have been observed after high-level acute exposures. (Hartman 1995; Stollery 1996) Chronic exposure is thought to result in a clinical syndrome known as CTE. (Baker and Seppalainen 1986; WHO 1985) Current workers often experience decrements on neuropsychological tests of memory, psychomotor function and mood but the effects of acute and chronic exposure have not been distinguished in most study designs. (Baker 1994) It has been suggested that many currently employed workers have benefited from the decreasing exposure over time and the effects have been reversible among some populations. (Karlson and others 2000; Kieswetter and others 2000) However, many cases of poorly reversible CTE have been identified. (Baker 1994)

Potential confounders of the association between solvent exposure and CNS effects include age, education, alcohol consumption, drug use, medication use and gender. In addition, the number of times a test is taken, handedness, factors associated with the technician and test site and the time of day may influence performance on specific neuropsychological tests. (Lezak 1995)

Over-adjustment for confounders in neuropsychological studies is often cited as a problem. (Kieswetter and others 2000; Williamson 1996) There are biologically based interactions between solvent exposure, age, alcohol and BMI that may be masked through such adjustment. In addition, although depression and anxiety are often considered as potential confounders, the temporal relationship between solvent exposure, mood and neuropsychological performance has not been firmly established. Organic solvents have been causally associated with mood or affective disorders. (Baker 1994; Baker and others 1986; Kieswetter and others 2000) While pre-morbid function is also known to influence test performance, adjustment for pre-morbid function may not be necessary or desirable. In these analyses, exposure groups were compared with regard to measures of anxiety, depression and reading capacity, but no adjustments were made for these factors.

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Table II.1. Person-time accumulated while fishing during the 2.5-year follow-up, by type of fishing, commercial fishers (n=238), North Carolina, 1999-2001

Type of Fishing	Person-days	Proportion of total person-days
All type of fishing	41913	100%
Crabbing	20018	47.8%
Finfishing	11289	26.9%
Clamming	3812	9.1%
Shrimping	3415	8.1%
Other (i.e. trapping turtle, eels)	2964	7.1%
Oystering	415	1.0%

Figure II.1. Type of fishing as a proportion of the total fishing time, commercial fishers (n=238), North Carolina, 1999-2001

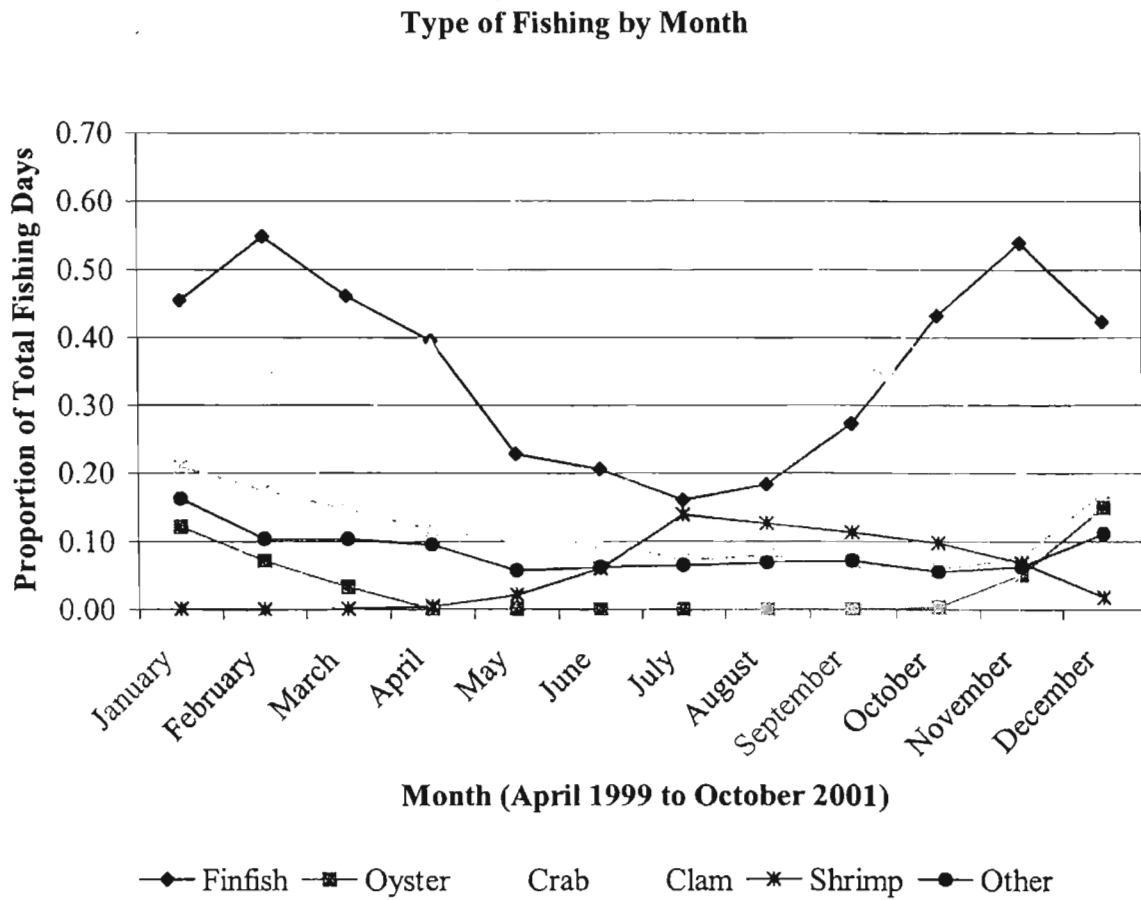


Table II.2. Examples of factors that influence neuropsychological test performance (Lezak 1995)

Neuropsychological Test	Examples of potential confounders
SDMT	Manual speed and agility. Performance decreases with age. Women, right-handed people, those with more years of education perform better.
Trail Making Test	Motor speed and agility. Practice effect. Time increases with age, low education level and possibly by gender. Emotionally disturbed tend to perform more poorly.
Stroop	Practice effects in the second administration but not later ones. Anxiety-producing test environment, gender, age. Vision (particularly color blindness).
COWA	Age, years of education and gender.
Raven's Matrices	Performance declines with age (should not reflect language or academic skills).
L-N Sequencing ^a	Age
Rey AVLT	Performance decreases with age. Women tend to perform better. Scores may differ depending on the word list used.
Rey - O	The copy score does not tend to differ with age but older subjects need more time. Men tend to score better
Grooved Pegboard Test	Slowing with increasing age. Possibly gender and education.

^a This test is new and therefore not described by Lezak and colleagues. Factors that influence performance on this test are less well known.

CHAPTER III

Personal Exposure to Fuel Emissions among Commercial Fishers: Comparison of 2-Stroke, 4-Stroke and Diesel Engines

A. Introduction

Commercial fishers are exposed to unburned hydrocarbon vapors and combustion products present in the emissions from their diesel or gasoline powered boat engines. Both gasoline and diesel fuel are complex hydrocarbon mixtures, but they differ with regard to their vapor pressure, relative proportion of long and short-chained molecules and associated health effects.

Diesel fuel and gasoline contain a host of known and possible neurotoxic substances, while liquid gasoline poses a greater inhalation risk because it is highly volatile. Liquid gasoline typically contains between 25% and 30% aromatic hydrocarbons, many of which are known neurotoxic agents. (Ritchie and others 2001) By contrast, diesel fuel is distilled to exclude the aromatics and has a negligible vapor pressure at normal ambient temperatures. Because most of the hydrocarbons in diesel exhaust tend to have a low vapor pressure, they adsorb onto the particles present in the exhaust emissions. (Muzyka and others 1998) The health hazards typically associated with exposure to the particulate matter in diesel exhaust are lung cancer and respiratory disease. (NIOSH 1988) However, there is increasing concern that the longer chained hydrocarbons in diesel fuel may have a relatively high anesthetic potential based on the pharmacokinetic and animal evidence. (reviewed by Ritchie and others 2001)

In addition to its neurotoxic effects, gasoline exposure has been associated with renal and liver cancer, acute myeloid leukemia (AML), myeloma, heart disease and irritant effects. (Caprino and Togna 1997) Benzene, which is present in liquid gasoline at much higher concentrations than in diesel fuel and is produced during the combustion of both fuels, is causally associated with AML in occupational groups exposed to relatively high levels (>10 PPM). (Infante and others 1982; Savitz and Andrews 1997; Wong 1995)

Although most of the health effects associated with organic solvent mixtures such as fuel, constituents in fuel, and combustion products have been observed among miners, painters and jet fuel workers, the possibility of health effects among workers with lower exposure has not been ruled out. Rather, the health effects associated with low-level

occupational exposure to fuel are difficult to study because an appropriate unexposed comparison group may be impossible to identify. In addition, simultaneous exposure to the many toxic hydrocarbons present in fuel may result in antagonistic, synergistic or additive interactions that remain largely unrecognized.

The objective of this study was to characterize the fuel exposure among commercial fishers over time, and identify the determinants of this exposure. Although we anticipated that commercial fishers would be exposed to relatively low levels of fuel emissions, we expected to observe differences in exposure related to the type of engine used during fishing. Specifically, we expected fishers who use carbureted 2-stroke engines to have higher hydrocarbon exposures than those who use less polluting 4-stroke engines and diesel engines. Two-stroke engines release high levels of hydrocarbons because oil is mixed with the fuel to lubricate the piston and the fuel intake and exhaust ports are open simultaneously during a portion of compression-combustion cycle. Hydrocarbon emissions per kilogram of fuel consumed are approximately 60-100 times greater for the snowmobiles with 2-stroke engines than for gasoline powered cars and diesel buses. (Bishop and others 2001) The United States Environmental Protection Agency (U.S. EPA) estimates that the new generation of 4-stroke and carbureted 2-stroke engines will reduce hydrocarbon emissions by 75% compared to current 2-stroke engines (EPA 1996).

The identification of subgroups with different exposure levels is a necessary step when epidemiological methods are used to study of the health effects of ubiquitous environmental pollutants like fuel emissions. This exposure assessment was conducted in order to identify differences in exposure that may explain variation in neuropsychological test outcomes measured as part of a longitudinal cohort study of commercial fishers. (Moe and others 2001) No previous studies evaluating personal exposure, rather than emissions characteristics, among those using 2-stroke engines were identified through this literature review. Unlike recreational users of 2-stroke engines or those who operate lawnmowers or other power tools with 2-stroke engines, commercial fishers may be at particular risk because they breathe emissions from their boat engines all day, several days per week, during their entire working life.

B. Methods

1. Data Collection

The population for this fuel exposure study consisted of commercial fisher participants throughout the coastal region of North Carolina enrolled in an ongoing longitudinal cohort study conducted by researchers at the University of North Carolina in Chapel Hill. (Moe and others 2001) Each of the 238 participants in the cohort study received a clinical examination every 5-7 months during a nearly 2 ½ year follow-up period. During this exam, clinic staff asked participants if they were interested in measuring their fuel exposure and obtained informed consent for those choosing to participate. The project was piloted in January of 2001 to test the monitoring methods in the field and assess the time burden to participants. The official monitoring period extended from June 17, 2001 through October 10, 2001. The recruitment flyer is included in Appendix 2. An incentive of \$25.00 was offered for each monitor returned for analysis.

An initial self-monitoring kit, adapted from that developed by Egeghy and colleagues (Egeghy and others 2000), containing a passive monitor, written instructions on how to use the monitor, a questionnaire on work practices and equipment, and a stamped and addressed envelope for returning the monitor for laboratory analysis was provided to each participant during the exam. The correct use of the monitor was demonstrated at this time. The participant was simply required to open the cap, record the time, attach the monitor to their shirt collar, then close the cap tightly at the end of the sampling period and record the time. The participant was instructed to use the monitor the next time he or she fished or did mechanical work, measure exposure for a complete workday including lunch and breaks, fill out the work activity questionnaire and mail the monitor back for analysis.

In order to characterize the temporal variation in exposure, participants were asked to make at least two measurements. Those who returned the first monitor received a letter with a randomly selected date (through the projected close of the study on October 31, 2001) for a second day of sampling. When selected date approached, attempts were made to contact the participant so that interest could be assessed and a monitoring kit could be mailed. Similarly, attempts to contact those who returned a second monitor were made so that a third monitor

could be mailed. To maximize the number of measurements made, we ceased the random selection of dates for repeat measurements at the end of the study and everyone who could be reached by telephone was asked to participate in additional monitoring. Individual results were mailed to each participant and follow-up telephone interviews were conducted to answer questions and to obtain missing data.

The questionnaire included in the self-monitoring kit consisted of an open-ended work activity log for the monitoring day, a checklist to record the type(s) of fishing performed and questions designed to capture information to help to explain observed variation in exposure level. This questionnaire is included in Appendix 3. These questions addressed engine type, use of hazardous chemicals, smoking, boat type and size, refueling, average boat speed and the amount of time the boat was in motion.

2. Analysis of Monitors

Benzene was used to mark exposure to both evaporative emissions and fuel exhaust generated from boat motors while fishing. Monitoring and analytic methods described by Egeghy and colleagues were employed. (Egeghy and others 2000) Passive monitors consisting of aluminum tubes packed with 0.1 grams of Tenax (SKC Inc., Eighty Four, PA) were assembled. Monitors were initially conditioned at 250° C for 30 minutes using the Perkin Elmer ATD 400 automatic thermal desorption system to clean the reusable sampling medium and remove residual benzene. Prior to distribution for field use, monitors were conditioned again at 225°C for three minutes. Returned monitors were desorbed with the ATD 400 and analyzed with a Hewlett Packard 6890 Series II gas chromatograph (Hewlett-Packard Corp., Palo Alto, CA) with HNU PI-52-02-A photo ionization detector (HNU Systems, Inc., Newton, MA). Separation was accomplished with a megabore DB-1, 60-m x 0.53-mm dimethylpolysiloxane column. (1.5 μ m film thickness) (J&W Scientific, Folsom, CA.)

External calibration standards were prepared by drawing known quantities of benzene vapor diluted in zero-grade air through passive monitors at approximately 60 mL/min using a needle valve regulated vacuum line. Calibration curves with at least 5 points were

determined by least squares linear regression. The limit of quantitation (LOQ) was estimated as three times the average size of a residual benzene peak from analysis of a conditioned air sampler.

3. Statistical Analysis

Benzene exposure level was natural log-transformed for all statistical analyses. Concentrations at or below the LOQ were assigned a value of 2/3 the LOQ prior to log transformation. A histogram was examined to identify influential outliers and confirm that the distribution of log-transformed benzene levels was approximately normal. Normality was also assessed using the Shapiro-Wilks test for normality (critical p-value = 0.05). The mixed-effect linear regression model described below was specified using the MIXED procedure in SAS version 8.01 (SAS Institute, Cary, NC) to predict benzene level and obtain restricted maximum likelihood (REML) estimates of between- and within-person variance.

Mixed Effect Model

$$Y_{h(ij)} = \ln(X_{h(ij)}) = \mu_y + \alpha_h + \sum_{u=1}^v \delta_u * C_{uh(ij)} + \beta_{hi} + \epsilon_{h(ij)}$$

Where,

- $Y_{h(ij)}$ = the log-transformed exposure level on the j^{th} day for the i^{th} fisher and the h^{th} engine type
- $X_{h(ij)}$ = the untransformed exposure level on the j^{th} day for the i^{th} fisher and the h^{th} engine type
- μ_y = the overall mean log-transformed exposure level for all engine types
- α_h = the fixed effect for engine type h
- δ_u = slope for each covariate (C)
- β_{hi} = random effect for person ($\mu_{yhi} - \mu_{yh}$), $\sim N(0, \sigma_B^2)$
- $\epsilon_{h(ij)}$ = random error for the j^{th} observation on the i^{th} fisher, $\sim N(0, \sigma_w^2)$
- h = 1, 2, ..., g engine types
- i = 1, 2, ..., k workers in the h^{th} engine type
- j = 1, 2, ..., n measurements on the i^{th} fisher in the h^{th} engine type

Models were fit using methods described by Rappaport and colleagues. (Rappaport and others 1999) Engine type (e.g. inboard diesel, 4-stroke gasoline and 2-stroke gasoline) was specified as the main fixed effect and -2 Log Likelihood tests were conducted to determine whether within- and between-person variance could be pooled across engine types.

Nine potential determinants of exposure to benzene in fuel were identified, *a priori*, through a review of the literature. (Egeghy and others 2000; EPA 1996; Moe and others 2001; Wallace 1996; Wixtrom and Brown 1992) These potential determinants were considered for inclusion in the full mixed-effect linear regression model as covariates. They were season, fuel type, refueling car or truck, refueling boat, boat size, having a cabin, type of fishing, smoking and average boat speed. The univariate distributions of each were examined and dichotomous variables were defined. Correlations between covariates were determined using Spearman correlation coefficients and the full model was specified. A backward selection strategy was employed to choose covariates for the final model. Only fixed effects with associated p-values of less than 0.05 were retained in the model. Once the final model was determined, the normality of the random effects was assessed qualitatively by examining the histogram and quantitatively with the Shapiro-Wilks test of normality.

4. Exclusions

Application of the mixed-effect linear regression model requires that the underlying distribution of the data is approximately normal and that random effects are normally distributed with a mean of 0 and a variance of σ_B^2 . If the underlying distribution of the data is found to be approximately lognormal, the mean and variance of the log data can be used to estimate the mean and the variance of the untransformed data. Preliminary univariate analyses of these data indicated the presence of influential outliers that challenged these normality assumptions. Since verification that participants followed the self-monitoring protocol was not possible, observations deemed to be highly improbable were excluded.

All measurements below the LOQ were excluded (n=19). The LOQ for the analytical methods employed is $2 \mu\text{g}/\text{m}^3$ assuming a 4- hour sampling period (Egeghy and others 2002) and by extension $1 \mu\text{g}/\text{m}^3$ for an 8- hour sampling period. The participants who made the measurements that were below the LOQ reported that their monitors were opened between 3.5 and 10.5 hours. These sampling periods should have been adequate to measure rural outdoor levels, which have been estimated at $1.3 \mu\text{g}/\text{m}^3$. (Duarte-Davidson and others 2001) Furthermore, many of the fishers whose measurements were below the LOQ reported activities that should have increased their personal exposure to the detectable limit, such as

refueling their car or boat. Egeghy and colleagues have established the sensitivity of these methods for measuring benzene exposure over the few minutes required to refuel. (Egeghy and others 2000) High outliers (n=3) all contributed by one individual, were also excluded (see Appendix 5). Finally, two monitors that were returned without caps could not be used.

In addition, valid but unusable measurements were excluded (measurements are listed in Appendix 5). These measurements included those that could not be classified with regard to the main effect of engine type (n=2), a measurement taken by a subject who worked a full day as a machinist before beginning his fishing work (n=1), and measurements made while working on boat motors or mechanical equipment (n=3). The benzene levels for these subjects are listed in Appendix 5.

C. Results

The participation rates and number of monitors distributed and returned during different phases in the project are summarized in Table III.1. The initial participation rate, e.g. the proportion of those invited agreeing to participate, was high (88%) during the pilot. Only 50 to 57 percent of those who were provided with a monitor during the pilot returned it for analysis. However, those who returned the monitor reported no difficulties using it, nor did they find the time commitment burdensome. During the continuation phase of the project, an effort was made to emphasize the importance of returning the monitor. During this phase of the project, the participation rate among those recruited at the clinic for their first measurement was lower (32%), while the return rate increased to almost 80%. Overall, a total of 186 fishers were invited to participate in this study and 68 (40%) agreed to measure their fuel exposure. A total of 117 monitors were distributed and 85 (73%) were returned by 50 of the original 68 volunteers. Twenty-four (50%) of those who returned their first monitor made a second measurement and 11 (22%) returned three measurements.

As discussed in the previous section, three measurements made while the participant performed a full day of mechanical work and did not fish were excluded from these analyses. Responses from the open-ended work activity logs describing the workday while fishing (n=82) are summarized in Table III.2. Most participants reported some type of preparatory

or post-fishing work. The other fishing related activities listed in the table appeared to be conducted intermittently during the fishing season. Again, the participant who reported working at a machinist job (see footnote for non-fishing work) while wearing the monitor was excluded from the analysis.

A total of 55 measurements among 37 fishers were included in the final analyses. The underlying distributions of the log-transformed benzene level and the random effects for subject were approximately normal after the above exclusions. The number of subjects, number of measurements and the mean of the log benzene level across engine categories are summarized in Table III.3. As shown in the table, there were no repeated measurements in the diesel engine category and few in the 4-stroke engine category and a larger difference in exposure depending on 2-stroke of 4-stroke engine type is not observable. The within- and between-person variance estimates could not be estimated independently for these groups so their variance components were pooled with the crabber group in the final model.

The distribution of potential predictors of exposure across engine types is described in Table III.4. As shown in this table, the highest benzene levels across all engine types are found when refueling was reported. Benzene levels were highest when crabbing was done compared to other types of fishing. In addition, the results in this table point to an uneven distribution of refueling and type of fishing across engine type categories.

Each of the covariates listed in Table III.4 was included in full model. Cabin and boat size were highly correlated with diesel engine and were not modeled together. The question on average boat speed mentioned in the methods section did not yield useable data because most participants left the question blank. There were no reports of using chemicals during the monitoring day. The fixed effects for season, doing motor work in addition to fishing, and smoking were not significant predictors of exposure. Turning the engine off was not significant. Subjects who oystered or clammed reported turn their motor off for relatively long periods (335 minutes on average) compared to finfishers (148 minutes on average) and shrimpers and crabbers who infrequently reported turning their motors off at all.

Yet, a fixed effect for oystering or clamming was not significant. Finally, an interaction term for type of fishing and boat refueling was not significant.

The results from the mixed effects model are in Table III.5. The model was specified without an intercept, thus, the estimates listed in the table are the mean of the log-transformed data in micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) for each of the engine type categories. The between-person variance component estimated by the model was smaller ($\sigma^2_{\text{B}} = 0.25$) than the within-person variance component ($\sigma^2_{\text{w}} = 0.61$) indicating that more variation in exposure could be explained by factors that may change over time such as environmental conditions, work practices or monitor placement. The mean estimates for the untransformed data, which rely on the underlying normality of the log-transformed data and the correct estimation of the total variance ($\sigma^2_{\text{yh}} = \sigma^2_{\text{w}} + \sigma^2_{\text{B}}$) are also listed. The predicted mean personal exposure estimates were $50 \mu\text{g}/\text{m}^3$, $33 \mu\text{g}/\text{m}^3$, and $28 \mu\text{g}/\text{m}^3$ for 2-stroke, 4-stroke and diesel engine categories, respectively, when no car or truck refueling was done. The mean predicted personal exposure estimates were $121 \mu\text{g}/\text{m}^3$, $79 \mu\text{g}/\text{m}^3$ and $67 \mu\text{g}/\text{m}^3$ for 2-stroke, 4-stroke and diesel engine categories, respectively, when car or truck refueling was also done.

D. Discussion

Commercial fishers work alone or in small groups in geographically diverse locations, which poses a challenge for quantitative exposure assessment. To overcome this challenge, fishers enrolled in this study were trained in the use of a passive monitors, provided with monitoring kits and asked to measure their own exposure. This study provides evidence that personal exposure benzene from fuel emissions is higher when operating a boat with a 2-stroke engine compared to personal exposure when operating a 4-stroke engine or a diesel engine. Since 2-stroke engines are known to emit more unburned fuel than 4-stroke or diesel engines, the elevated personal exposure to benzene indicates that fishers are exposed to higher levels of hydrocarbons generally.

Findings from the total Exposure Assessment Methodology (TEAM) studies conducted by the US EPA in the 1980's as well as recent studies have estimated that the

average personal exposure to benzene is approximately $15 \mu\text{g}/\text{m}^3$ in urban areas, while the average urban outdoor concentration is approximately $6 \mu\text{g}/\text{m}^3$. (Wallace 1989; Wallace 1996) The mean outdoor concentration in rural areas has been estimated at $1.3 \mu\text{g}/\text{m}^3$. (Duarte-Davidson and others 2001) The predicted exposure level for commercial fishers using 2-stroke engines ($50 \mu\text{g}/\text{m}^3$) is higher than both the average personal exposure level and average outdoor concentration. In addition, the predicted exposure level was higher than estimates of in-vehicle exposure level including those estimated during rush hour traffic ($40 \mu\text{g}/\text{m}^3$). (Duarte-Davidson and others 2001; Wallace 1996) This study confirms what has been shown by recent studies that refueling is important source of personal exposure even though this activity takes only minutes. (Backer and others 1997; Egeghy and others 2000; Vainiotalo and others 1999)

The effect of gasoline emissions from 2-stroke engines on the nervous system is difficult to gauge. Many constituent compounds such as benzene, butadiene, toluene, ethylbenzene and xylene, in gasoline are known neurotoxic agents. (Burbacher 1993; Ritchie and others 2001) However, the effect of simultaneous exposure to these compounds is not known. Evidence from studies of animals shows the potential for synergistic or additive as well as antagonistic interactions among the individual components in fuel. (reviewed by Ritchie and others 2001)

Exposure to gasoline (not excluding leaded gasoline) among filling station attendants has been associated with effects on intellectual capacity, psychomotor and visuomotor function, immediate and delayed memory and increased mortality from mental disorders. (Burbacher 1993; Kumar and others 1988; Schwartz 1987) Sniffing gasoline vapors is associated with ataxia, tremor and encephalopathic syndrome. (Burbacher 1993; Cairney and others 2002) Personal benzene exposure among filling station attendants has been reported to be about 10 times more than that predicted for fishers operating boats with 2-stroke engines. (Lagorio and others 1994) Acute effects on the CNS from breathing emissions on boats are not likely. The short-term threshold limit value established by the American Conference of Industrial Hygienists (ACGIH) to protect against the acute neurotoxic effects

of gasoline is 1480 mg/m³ total hydrocarbons (gasoline vapor typically consists of less than 1% benzene). (Reese and Kimbrough 1993)

Benzene in fuel is of particular concern because it has been causally associated with acute myeloid leukemia (AML) (Savitz and Andrews 1997). However, the disease risk at levels less than 32 mg/m³ is not certain. There is inconsistent evidence regarding the AML risk for garage mechanics (Hansen 1989; Hotz and Lauwerys 1997; Hunting and others 1995; Loomis and Savitz 1991; Schwartz 1987), whose average personal exposure to benzene is reported to be approximately 100 µg/m³ (Egeghy and others 2002) or twice that predicted for fishers who use 2-stroke engines. Estimates from the mixed-effect linear regression model analyses indicate that, on average, fishers are exposed to about one half the mean personal exposure levels of garage mechanics.

A self-monitoring approach for collecting personal exposure measurements has been used successfully in several previous studies. (Egeghy and others 2000; Liljelind and others 2000; Loomis and others 1994; Rappaport and others 1999; Saarinen and others 1998; Tielemans and others 1999) However, it is not always possible to verify that participants follow the study protocol when self-monitoring methods are employed. Because the LOQ for the analytical methods used for this project is very low, it appeared that some of the monitors were returned without having been opened. The highly improbable measurements that were below the LOQ were deemed invalid and these observations were excluded. In addition, three high outliers that were contributed by one person were excluded. Although these exclusions represented our best effort to include only high quality data, a bias may have been inadvertently introduced. When these observations were included, the predicted benzene levels were similar for 2-stroke and 4-stroke engines and the distribution of the random effects was not approximately normal.

Benzene is not a perfect marker for hydrocarbon exposure. The proportion of benzene relative to other hydrocarbons may vary depending on the season venter and grade. (Wixtrom and Brown 1992) This variation is expected to be minimal because most measurements were made in the summer and fall and a fixed effect for season (comparing

spring and summer levels to fall and winter levels) was not significant. Furthermore, discussions with individual fishers during telephone follow-up indicated that most participants purchased the cheapest fuel so the octane level should be relatively constant across the measurements.

Although exposure to diesel fuel represents a health hazard, comparison of benzene levels across diesel and gasoline engine categories does not relate directly to the corresponding levels of potentially neurotoxic substances. Liquid diesel fuel may contain small quantities aromatics such as benzene, (Muzyka and others 1998) but is distilled to exclude them. Therefore, the predominant source of benzene exposure measured while fishing on a diesel boat is produced through combustion. Most of the organic compounds in diesel exhaust have low vapor pressures and are adsorbed onto the particulate matter. Benzene, which is more volatile, largely remains in the gaseous phase (Muzyka and others 1998) but does not indicate the presence of other volatile aromatic hydrocarbons that are likely to pose an inhalation risk.

More studies with larger numbers of subjects and more repeat measurements are needed to accurately characterize personal exposure to evaporative and exhaust emissions among commercial fishers using different types of engines. Random error that may have been introduced by incorrect monitor placement or varying lengths of time between conditioning (cleaning the monitoring medium to remove residual benzene) and monitor use would tend to attenuate associations, and could be counterbalanced through a larger study size. However, this study suggests that personal exposure to benzene and hydrocarbons are higher while operating a fishing boat equipped with a 2-stroke compared to boats equipped with 4-stroke engines.

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Table III.1. Number of invitees, monitors distributed and monitors returned by fuel study participants (n=50), North Carolina, 2001.

	Dates	1 st Monitor			2 nd Monitor		3 rd Monitor	
		Invited	Accepted	Returned	Contacted / Accepted	Returned	Contacted / Accepted	Returned
Pilot	January 5 to January 15	16	14 (88%)	8 (57%)	4	2 (50%)	2	1 (50%)
Continuation	June 17 to October 10	170	54 (32%)	42 (78%)	30	22 (73%)	13	10 (77%)
Total		186	68 (37%)	50 (74%)	34	24 (71%)	15	11 (73%)

Table III.2. Mean number of hours worked on days described in 82 work activity logs kept by fuel study participants while fishing, North Carolina, 2001

Work Activity	Number re- porting activity	Mean hours per day (SD^a)	Range of hours reported
Total workday ^b	82	8.0 (2.7)	3.3-14.5
Prepwork ^c	49	0.7 (0.6)	0.1-2.3
On the water work ^d	68	6.0 (1.9)	2.8-11.1
Post fishing work ^e	62	1.0 (0.6)	0.1-3.1
Fishing related work ^f	11	3.1 (3.0)	0.4-10.1
Non-fishing work ^g	4	5.5 (5.0)	0.8-11.0

^a Standard Deviation

^b Does not include reported travel to and from dock or non-fishing work

^c Includes loading boat, unloading truck and filling gas tanks

^d Includes motoring to fishing grounds, fishing (pulling pots or nets, rebaiting), setting pots or nets, and working with catch

^e Includes unloading boat, loading truck, separating catch, preparation for the next day, selling catch and fueling boat

^f Includes work-related errands, repairing boats or equipment and seasonal work such as preparing nets, pots, lines or hooks and cutting net stakes

^g Includes housework, work as a machinist and grounds keeping

Table III.3. Number of subjects, measurements and geometric mean benzene personal exposure level across engine type groupings, fuel study participants, North Carolina, 2001

Engine Type	Number of Subjects	Number of Measurements	Geometric Mean (SD) ($\mu\text{g}/\text{m}^3$)
2-Stroke	22	37	3.72 (1.01)
4-Stroke	10	13	3.68 (1.12)
Inboard Diesel	5	5	3.25 (0.50)
Total	37	55	3.67 (1.00)

Table III.4. Distribution of potential determinants of exposure across engine type categories and mean of log-benzene level, fuel study participants, North Carolina, 2001

Determinant of Exposure	Engine Type			All Engines
	2-Stroke (n=37)	4-Stroke (n=13)	Diesel (n=5)	
Refuel car or truck, # (μ_y) ^a	10 (4.26)	8 (4.26)	4 (3.22)	20 (4.16)
Refuel boat with gasoline, # (μ_y)	22 (4.05)	7 (3.79)	N/A	29 (3.99)
Fall and winter ^a , # (μ_y)	19 (3.89)	4 (4.08)	4 (3.15)	27 (3.81)
Did motor work, # (μ_y)	2 (3.68)	1 (3.64)	1 (3.63)	4 (3.66)
Smoked > 10 cigarettes, # (μ_y)	7 (3.46)	2 (2.77)	1 (3.63)	11 (3.37)
Motor off, # (μ_y), average minutes	18 (3.63), 145	6 (3.99), 130	1 (2.82), 45	26 (3.71), 134
Type of fishing				
Crabbing, # (μ_y)	22 (4.00)	10 (3.74)	2 (3.23)	34 (3.87)
Finfishing, # (μ_y)	9 (3.48)	None	2 (3.08)	11 (3.48)
Shrimping, # (μ_y)	3 (3.29)	1 (3.99)	1 (3.63)	5 (3.50)
Clamming or oystering, # (μ_y)	3 (2.90)	2 (3.23)	None	5 (3.03)

^a Number (#) and geometric mean personal benzene exposure (μ_y)

^b Personal exposure to benzene in the fall and winter was expected to be higher than in the summer and spring due to variation of the benzene content in liquid gasoline. (Egeghy and others 2000)

Table III.5. Point estimates, standard errors and p-values for fixed effects that explained a portion of the variance in the log-benzene exposure level (n=35 subjects, n=52 observations), fuel study participants, North Carolina, 2001

Engine Type	Estimate	Standard Error	P-value	Estimated Mean ($\mu\text{g}/\text{m}^3$)	
				Refuel=No	Refuel=Yes
2-Stroke ($\mu y + \alpha 1$) ^a	3.4812	0.1943	<0.0001	50	121
4-Stroke ($\mu y + \alpha 2$) ^b	3.0519	0.3258	<0.0001	33	79
Inboard Diesel ($\mu y + \alpha 3$) ^c	2.8940	0.4301	0.0010	28	64
Refueling car or truck ($\delta 1$) ^d	0.8859	0.2794	0.0059		

^a $\mu y + \alpha 1$ = geometric mean for the 2-stroke engine group

^b $\mu y + \alpha 1$ = geometric mean for the 4-stroke engine group

^c $\mu y + \alpha 1$ = geometric mean for the diesel engine group

^d $\delta 1$ = fixed effect refueling car or truck

^e The predicted mean was estimated using this equation, which relates the mean of the raw data ($\mu_{x,h}$) to the mean and variance of the log transformed data ($\mu_{y,h}$ and $\sigma^2_{y,h}$).

CHAPTER IV

Exposure to Organic Solvents and Neuropsychological Symptoms among Commercial Fishers

A. Introduction

Commercial fishers are reported to have among the highest injury and fatality rates of any occupational group in the United States (CDC 2001), but little has been published about their risk of occupational disease. In addition to handling catch and working with potentially dangerous fishing gear, fishers are exposed to a variety of chemical agents. They do much of their own boat and equipment maintenance and use organic solvents, including gasoline and diesel fuel, resins containing styrene, acetone and, less frequently, fungicidal paints and tar for coating crab pots. The objective of this study was to characterize the association between solvent use during the most frequently reported maintenance activities and self-reported health symptoms among commercial fishers.

Acute exposure to solvent mixtures, such as fuel or paint, can cause central nervous system depression and symptoms ranging in severity from dizziness to unconsciousness and death from respiratory arrest at high levels (Hartman 1995; NIOSH 1987; Reese and Kimbrough 1993) The less severe effects are usually transient (Kulig 1990), but cases of residual cognitive impairment lasting years after an accidental solvent intoxication episode have been reported. (Hartman 1995; Stollery 1996)

The central nervous system effects of low-level chronic exposure to solvents are not well understood. Frequent findings of cross sectional studies of currently employed painters, carpet layers, printers, jet fuel workers and electronics workers include decrements on neuropsychological measures of memory, psychomotor function, attention and mood. (Baker 1994; Baker and Fine 1986; Broadwell and others 1995; Escalona and others 1995; Jang and others 1999; Ohnishi and others 1995; Tsai and others 1997) These findings could reflect acute or chronic effects of solvent exposure, however. Results from more recent studies designed to distinguish acute and chronic effects and establish whether adverse effects on the central nervous system persist after exposure has ceased are inconsistent. (Daniell and others 1999; Eller and others 1999; Morrow and others 1997; Muijsers and others 1996; Nasterlack and others 1999) However, there is clinical evidence to suggest that chronic exposure to

organic solvents can result in mild or severe chronic toxic encephalopathy that may not be reversible. (Baker and White 1985; Hartman 1995)

Both diesel fuel and gasoline contain a host of known and possible neurotoxic substances, but liquid gasoline poses a greater inhalation risk because it is highly volatile and typically contains between 25% and 30% aromatic hydrocarbons, many of which are known neurotoxic agents. (Ritchie and others 2001) By contrast, diesel fuel is distilled to exclude the aromatics and therefore has a negligible vapor pressure at normal ambient temperatures. Most of the hydrocarbons in diesel exhaust tend to have low vapor pressures, and adsorb onto the particles present in the exhaust emissions. (Muzyka and others 1998) The health hazards typically associated with exposure to the particulate matter in diesel exhaust are lung cancer and respiratory disease. (NIOSH 1988) However, there is increasing concern that the longer chained hydrocarbons may have a relatively high anesthetic potential based on the pharmacokinetic and animal evidence. (reviewed by Ritchie and others 2001) In addition, simultaneous exposure to the many neurotoxic hydrocarbons present in fuel and other solvent mixtures may pose unique hazards that remain largely unrecognized. Evidence from animal studies suggests that interactions between the individual constituents in fuel may result in interactions that are synergistic, additive or antagonistic. (reviewed by Ritchie and others 2001)

Based on evidence animal and human chamber studies, a consensus has emerged that styrene can affect the central nervous system at exposure levels higher than 50 ppm. [ACGIH, 2001 #192; (Hartman 1995) There is also evidence from epidemiological studies of working populations that exposure to styrene at these levels can cause poor performance on neuropsychological or neurobehavioral tests (predominantly tests reaction time). (Cherry and Gautrin 1990; Edling and others 1993; Letz and others 1990; Tsai and Chen 1996; Yokayama and others 1992) The American Conference of Governmental Industrial Hygienists (ACGIH) has set the Threshold Limit Value (TLV) to 20 ppm in order to protect against CNS effects as well as irritation of the mucous membranes and respiratory system. (ACGIH 2001) Acetone, the chemical typically used to dissolve styrene-based resins, is considered one of the least toxic solvents. (Hartman 1995)

B. Methods

This research protocol was approved by the University of North Carolina School of Public Health's Institutional Review Board (IRB). At the time of recruitment, the study protocol was explained to the study subjects by the project staff and informed consent was obtained prior to baseline evaluation.

1. Population

Data collected for a longitudinal cohort study of 238 commercial fishers and others exposed to marine waters in North Carolina were used for these analyses. The main purpose of the cohort study was to “elucidate the risks and possible clinical disease” (Moe and others 2001, p.781) associated with exposure to *Pfiesteria piscicida*, a newly discovered genus of dinoflagellate (Burkholder 1999). *Pfiesteria* is believed to produce a toxin that has been associated with neurological dysfunction in laboratory workers exposed to high levels of *Pfiesteria* cultures (Glasgow Jr. and others 1995; Schmechel and Koltai 2001) and one study offers preliminary evidence that exposure to estuarine waters in which *Pfiesteria* is present may adversely affect cognitive function. (Grattan and others 1998)

A full description of the study design and methods has been published elsewhere. (Moe and others 2001) In summary, volunteer participants must have worked at least nine months per year in the fishing trade and believe that they could fulfill the requirements of the study. Specifically, participants agreed to maintain an activity log book and answer questions during a biweekly or weekly telephone interview during the follow-up period that began in April of 1999 and continued until October of 2001. They were also required to receive a baseline clinical evaluation that included a medical exam, neuropsychological assessment and interview about potentially confounding exposures as well as social and demographic factors. Follow-up information was collected during subsequent clinic visits every 5 to 7 months during the two and one half year follow-up period. Some participants were randomly selected for recruitment via telephone solicitation from a list of commercial fishers who hold licenses. Others were solicited directly at fishing events or reached through advertisements in local newspapers.

Individuals with health conditions known to affect neurocognitive function were excluded from the study. Specific medical conditions resulting in exclusion included head trauma resulting in loss of consciousness, insulin-requiring diabetes, hospitalization for treatment of drug or alcohol abuse, stroke or transient ischemic attack, brain tumor, seizures, epilepsy, encephalitis, meningitis, Parkinson's disease, Alzheimer's disease, dementia, systemic lupus, Lyme disease, brain surgery, Huntington's disease, multiple sclerosis, narcolepsy, known solvent or pesticide poisoning, reported infection with human-immunodeficiency virus (HIV), antipsychotic or antimanic medication use, or a diagnosis of psychosis. In addition, individuals who had been placed in mentally handicapped classes in school or who had participated in previous or other current studies of health effects possibly related to *Pfiesteria* exposure, were excluded from the cohort.

2. Exposure Assessment

All exposure data used for these analyses were self-reported. During the weekly or biweekly telephone interview, participants were asked if they did maintenance work that may have exposed them to organic solvents since their previous interview. Specifically, they were asked if they worked on boat motors or other types of mechanical equipment, cleaned their hands or their equipment with gasoline, used glues, epoxies and resins, or repaired a fiberglass boat. For each of these activities, they were further queried about whether they worked inside or outside and how long they spent doing the activity. Time spent on the activity was ascertained by asking how many hours, days or minutes each participant spent on the activity during the entire interval between interviews. Painting and coating crab pots with tar were reported infrequently and, therefore, were not included in these analyses.

Working on boat motors and other mechanical equipment involves exposure to gasoline or diesel fuel. (Egeghy and others 2000) Using glues, epoxies or resins for fiberglass boat repair was assumed to involve exposure to styrene. To confirm that styrene-based resins were used for fiberglass boat repair, additional telephone interviews were conducted with 119 participants to obtain trade names for the epoxies, resins and hardeners they used for fiberglass boat repair projects so that Material Safety Data Sheets (MSDSs) could be

obtained. Most fiberglass repair projects were found to involve styrene-based resins and acetone as a cleaner.

A total of nine indices, designed to distinguish exposures related to respiratory and skin symptoms as well as characterize different levels of exposure to fuel and fiberglass repair chemicals, were developed. Variables were specified indicating (1) motor or mechanical work inside; (2) motor or mechanical work outside; (3) cleaning hands or equipment with gasoline (skin contact); (4) repairing fiberglass boat with glues, epoxies or resins inside; (5) repairing fiberglass boats with glue, epoxies or resins outside. Four additional variables were developed from the self-reported times spent on each maintenance activity to indicate whether fishers who reported doing motor work or fiberglass repair projects during an interview period spent more or less than the median time on those projects. It was expected that exposure inside would be greater than exposure outside due to a lack of ventilation and that the dose or body burden would be higher for longer projects even if the exposure level remained constant.

3. Outcome Assessment

Participants were asked in weekly or biweekly telephone interviews if they experienced any of 21 symptoms since the previous interview contact, the date(s) of the symptom, how many days a symptom persisted, and how they would describe the severity of the symptom. For these analyses, the outcome was dichotomized as the presence or absence of a symptom during an interview period. In addition, symptoms were grouped into the following categories (1) neuropsychological symptoms indicative of cognitive effects; (2) headache and fatigue; (3) cramps, nausea and diarrhea; (4) irritant effects; (5) respiratory symptoms; and (6) musculoskeletal effects. Participants who reported any of the symptoms in a grouping were classified as a member of that group.

4. Covariates

Information on potential confounders and effect modifiers was collected during the baseline clinical exam and updated every 5 to 7 months during the course of the study. Specifically data on age, race, gender, education, height, weight, alcohol consumption,

smoking status, drug use, medications and secondary jobs were collected. Weekly alcohol consumption was categorized using a clinically relevant cutpoint of greater than 20 drinks per week. A continuum of neurocognitive deficits, with mild to moderate deficits for drinkers consuming more than 20 drinks per week and moderate deficits found in alcoholics has been observed. (Parsons 1998) In addition, variables to indicate current and former drug use, high school or greater education, obesity, having a secondary job with the potential for exposure to neurotoxic substances and taking medications that affect the central nervous system were created.

5. Statistical Analysis

Frequencies or descriptive analyses appropriate for continuous data were conducted to describe each variable. A list of covariates known or suspected to confound or modify the association between solvent exposure and neuropsychological symptoms (Hartman 1995; Lezak 1995; Williamson 1996) was compiled and stratified analysis was done to identify sources of potential confounding and effect measure modification. The associations between symptoms and exposure indices were estimated by fitting Poisson regression models to the data. Covariates that were determined to confound or modify the exposure-disease association were included in full models and a backward selection model building strategy was applied. First, interactions were tested using the -2 Log Likelihood Ratio test (p -value < 0.10). Confounding was then assessed using a change in effect criterion of 10%.

Each person-interview was treated as an independent observation in the Poisson regression models. An offset term was included for the log of the person-time at risk, so that the symptom rate during the 2.5-year follow-up period as a function of exposure and covariates could be estimated. Over-dispersion, that may result when there is dependence in serial outcomes, was evaluated using the deviance/degrees of freedom. For all models, this measure of over-dispersion was well below 1 indicating no extra-Poisson variation.

Symptom rates across mechanical work and fiberglass repair work exposure indices were modeled separately. First, the crude rate ratios for each symptom and symptom category across five motor work exposure indices and four fiberglass boat repair exposure

indices were modeled. Exposure indices were collapsed and refined in the final models and rate ratios were adjusted by including covariates in the models and through stratification. The final motor work exposure indices were (1) motor or mechanical work but not cleaning hands or equipment with gasoline; and (2) cleaning hands or equipment with gasoline. The final exposure index describing fiberglass boat repair was using epoxies, resins or glue to do fiberglass boat repair. All statistical analyses were conducted using SAS version 8.01. (SAS Institute, Cary, NC)

C. Results

A total of 13,028 weekly or biweekly telephone interviews and 1001 questionnaires administered during clinic exams were analyzed to produce the results described in this paper. Characteristics of the study participants are summarized in Table IV.1. Cohort members were predominantly white males who ranged in age from 18 to 67 years old. The majority (68%) were high school graduates. Approximately 60% of participants held another job in addition to commercial fishing, and almost 30% worked at additional jobs with a high potential for exposure to fuels, styrene or other neurotoxic substances. These jobs included boat repair, construction, carpentry, work as a mechanic, heavy equipment operation, welding, work as a machinist, farming, dry cleaning and taxidermy.

The number of maintenance activity reports and the proportion of reports as a percentage of the total number of person interviews are shown in columns 3 and 4 of Table VI.1. The 2207 reports of motor or mechanical equipment work were contributed by 203 (85%) of the cohort members. The 516 reports of fiberglass boat repair shown in column 4 were contributed by 123 (52%) of the cohort members. Approximately 80% of the maintenance work (both fiberglass boat repair and mechanical work) was done outside. The median number of hours spent during an interview period was approximately three hours for motor or mechanical equipment work and five hours for fiberglass repair work.

Crude rate ratios describing the association between 5 motor work exposure indices, 21 specific symptoms and 6 symptom groupings are presented in Table IV.2. The referent for motor or mechanical equipment work categories (outside, both inside and outside, below

the median time spent on the project and above the median time spent on the project) was not doing motor or mechanical equipment. Using gasoline to clean hands or equipment was modeled as a dichotomous variable with not using gasoline to clean hands or equipment as the reference group. As shown in the table, most rate ratios are elevated. The rate ratios for symptoms indicative of cognitive effects were distinguished by being among the highest (RR's from 2.2 to 4.1), increasing if the work was done inside (RR=3.7) and increasing with direct skin contact (RR=4.1). There is no evidence that rate ratios increase when greater than the median time was spent on the activity.

Crude rate ratios for exposure to styrene during fiberglass boat repair are presented in Table IV.3. The reference group for the fiberglass boat repair categories was not doing fiberglass boat repair. The rates for most specific symptoms and groups of symptoms are elevated. Rate ratios for symptom groupings range from RR=0.4 to RR=3.2. However, there is no evidence that rate ratios for symptoms indicative of cognitive effects are high, relative to other symptoms, nor is there evidence that rate ratios for indoor exposure increase compared to outdoor exposure. Again, rate ratios do not increase depending on the duration of the project.

Many of the characteristics listed in Table IV.1 may confound the association between solvent exposure and symptoms of neuropsychological dysfunction if they are associated with the exposure and the outcome. Gender was strongly associated with performing maintenance jobs but not with the symptoms. Body Mass Index (BMI) was not strongly associated with either maintenance work category. There were small associations (OR<2.0) between maintenance activities and risk factors for neuropsychological symptoms including alcohol consumption, current drug use and use of medication that adversely affects the central nervous system. Age and education were strong independent predictors of symptom reporting but inclusion of these terms in the models resulted in less than a 10% change in effect for maintenance exposure indices.

Although confounding was minimal, the inclusion of interaction terms for motor work and age and motor work and alcohol consumption improved the fit of the model,

indicating the presence of effect measure modification. A statistical interaction between obesity, defined as Body Mass Index (BMI) ≥ 30 kg/m², and fiberglass boat repair was also observed. In order describe the effect measure modification that was observed in these data, the rate ratios for cognitive effects and maintenance exposures across relevant strata are presented in Table IV.4. Motor work exposure indices were collapsed to form two mutually exclusive indicator variables for (1) motor work without using gasoline to clean hands and equipment; and (2) using gasoline to clean hands and equipment. One term for using glues, epoxies or resins to repair fiberglass boats was modeled.

Rate ratios for both motor work exposure indices are elevated in the lower age group but only the rate ratio for using gasoline to clean hands or equipment is increased in the older age group. The rate ratios in the younger age group are substantially higher than the crude estimates. Alcohol consumption appears to be inversely associated at younger ages but positively associated in the older age group. For styrene exposure, the rate ratio for cognitive effects and fiberglass boat repair work is increased in the highest BMI category only. Again, the stratified estimate is higher than the crude estimates.

D. Discussion

Although studies of health complaints are subject to reporting biases and there may be low to moderate correlation between symptom reports and neuropsychological test results, symptom questionnaires are considered useful in population research if applied and interpreted appropriately (Lundberg and others 1997; O'Donnell and others 1993). Studies that include symptom questionnaires in their outcome assessment protocols often report results that parallel those obtained using objective standardized neuropsychological tests. (Baker 1994; Baker and others 1986; Chen and others 1999; Daniell and others 1999; Hakkola 1994; Hooisma and others 1994; LoSasso and others 2001) Furthermore, symptom checklists are recommended diagnostic tools in clinical settings (White and Proctor 1997), and may indicate the early stages of nervous system disease that cannot be measured by neuropsychological testing. (Hartman 1995) Finally, the pattern of self-reported symptoms offers a direct reflection of the participant perspective of function and is relevant to mood adjustment and quality of life in the population under study.

The findings from this study indicate that commercial fishers report a wide array of symptoms at higher rates during weeks that they do maintenance work compared to weeks when they do not do maintenance work. In general, rate ratios describing the association between exposures generated during motor work, particularly cleaning hands or equipment with gasoline, and cognitive effects are the highest. Exposure to organic solvents is known to cause many of the symptoms reported here, including headache, nausea, fatigue, cramps, diarrhea and irritant effects, (NIOSH 1987) and has been associated with pulmonary dysfunction. (Baker 1994) In addition, the physical demands and postures required during maintenance activities may cause musculoskeletal problems. Acute exposure to solvents may cause vomiting, and skin sores may be confused with contact dermatitis caused by solvents. However, the ACGIH has found insufficient evidence that gasoline poses an additional hazard through skin contact. (ACGIH 2001) Although solvent exposure is known to cause many of the symptoms reported, the fact that most rate ratios are increased with similar magnitudes may point to a reporting or selection bias.

Those who enrolled in the cohort study were volunteers. At the time of recruitment, it was well known that the purpose of the cohort study was to investigate “Possible Estuary-Associated Syndrome (PEAS)” (CDC 1999). PEAS is characterized by an array of neuropsychological effects similar to those experienced by solvent-exposed workers. There was considerable public speculation and controversy about whether this syndrome was real or imagined and whether it was associated with exposure to *Pfiesteria* in estuaries. A well-publicized book (Barker 1997) was written on the subject, and there was concern in the fishing community about the impact of *Pfiesteria* on health, the future of the fishing industry and tourism. A bias may be present if study participants differentially reported symptom during weeks they worked with fuels or fiberglass boat repair chemicals because they believed these materials might be harmful or had a vested interest in influencing the outcome of the study. In addition, because exposure and outcome were queried nearly simultaneously, on one instrument, errors in their ascertainment may be correlated, biasing rate ratios. (Brenner and others 1993)

Over-reporting of symptoms has been associated with affective disturbances such as depression and anxiety (O'Donnell and others 1993) and depression is strongly and consistently related to self-reports of memory loss. (Collins and Abeles 1996; Schmand and others 1997) However, affective disorders (Baker 1994; Baker and others 1986) and personality changes (Chen and others 2001) may be caused by solvent exposure. Although a standardized instrument that included an assessment of changes in mood and personality characteristics was not used to collect these symptoms data, neuropsychological testing was conducted every 5-7 months during the follow-up period. Recent exposure to organic solvents during maintenance work (within 2 days of the neuropsychological testing) was not associated with increases in current depressive symptoms on the Beck Depression Inventory (BDI) and the small increases in symptoms of anxiety on the State Trait Anxiety Inventory (STAI) were not clinically significant. (Kirrane 2002) If reporting symptoms is strongly associated with mood and personality characteristics that were not measured, however, serial correlation in these data cannot be ruled out, despite the fact that such correlation was not observed.

The actual exposure levels for styrene and fuels are not known. The lack of information on exposure levels limits the interpretation of the results because the pattern of symptoms may differ depending on the intensity and duration of exposure. Also, these analyses cannot distinguish acute versus chronic effects of solvents because only symptoms reported within the weekly or biweekly interview period during which maintenance work was done count towards the rate in the exposed. However, longitudinal studies of workers exposed to solvents during intermittent maintenance work are rare and health risks to commercial fishers have not been studied adequately.

This study identified biologically plausible statistical interactions useful for generating hypotheses regarding the risks posed by maintenance activities performed by commercial fishers. These interactions were between motor work exposure and age, motor work exposure and alcohol consumption and fiberglass boat repair and obesity.

The relationship between age, alcohol and organic solvents is complex. Concomitant exposure to organic solvents and alcoholic drinks can result in elevated blood levels due to competition for metabolic pathways whereas blood levels may be lower in chronic ethanol drinkers because enzymes needed for metabolism are induced in this population. (Baker and others 1986) In solvent exposed populations better performance on neuropsychological tests of memory has been observed among those with the highest reported alcohol use. (Williamson 1996) In these data, alcohol consumption was positively associated with symptoms of cognitive effects in the older age group while an inverse association was observed in the younger age group. Neuroanatomical changes that occur during normal aging may exacerbate the effects of solvent exposure or alcoholic consumption. Age may also be associated with over-reporting, however. Regarding the interaction between fiberglass boat repair and BMI, it is known that styrene is stored in the fat when metabolic pathways of elimination are saturated (Hartman 1995; Sumner and Fennell 1994) and the half-time for elimination from adipose tissue is between 2 and 4 days. (ACGIH 2001) More research is needed to determine if these statistical interactions reflect a biological mechanism, however.

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TABLE IV.1. Number and percent of reports of maintenance activities across strata of demographic characteristics or potential risk factors, commercial fishers, North Carolina, 1999-2001

Study Participants		Count of Maintenance Reports in Each Stratum (% of person-interviews in each stratum) N=13,028 person-interviews	
Demographic Characteristic or Risk Factor	N (%)	Motor or mechanical equipment work	Fiberglass boat repair
Total	238 (100%)	2207 (17%)	516 (4%)
Gender			
Male	208 (87%)	2147 (19%)	503 (5%)
Female	30 (13%)	60 (3%)	13 (<1%)
Age category			
> 55	54 (22%)	676 (22%)	159 (5%)
46-55	60 (25%)	576 (17%)	143 (4%)
39-45	51 (21%)	420 (14%)	86 (3%)
<39	73 (30%)	535 (16%)	128 (4%)
Race			
White	237 (>99%)	2204 (17%)	516 (4%)
Non-white	1 (<1%)	3 (4%)	0 (0%)
Education			
High school	163 (68%)	1648 (18%)	389 (4%)
Less than High School	75 (32%)	559 (15%)	127 (3%)
High risk job ^a			
Yes	65 (27%)	225 (15%)	104 (7%)
No	173 (73%)	1979 (17%)	412 (4%)
More than one job			
Yes	146 (61%)	581 (18%)	118 (4%)
No	92 (39%)	1623 (20%)	398 (4%)
Body Mass Index ^a			
≥30 kg/m ²	117 (50%)	1000 (19%)	203 (4%)
< 30 kg/m ²	119 (50%)	1170 (16%)	308 (4%)
Smoking status			
Current	108 (46%)	826 (16%)	187 (3%)
Past	72 (31%)	758 (19%)	161 (4%)
Never	58 (23%)	582 (16%)	166 (4%)
Alcohol consumption			
> 20 drinks per week	33 (14%)	184 (21%)	31 (4%)
≤20 drinks per week	205 (86%)	1996 (17%)	485 (4%)
Current drug use			
Yes (any drug)	46 (19%)	257 (18%)	48 (3%)
No	192 (81%)	1923 (17%)	468 (4%)
Medication			
Moderate to high risk	54 (23%)	273 (16%)	26 (2%)
Low risk	107 (45%)	859 (17%)	241 (5%)
None	77 (32%)	999 (16%)	248 (4%)

^a Potential for exposure to neurotoxic substances. Jobs include boat repair, construction, carpentry, mechanic, heavy equipment operator, welder, machinist, farming, dry cleaning and taxidermy.

Table IV.2. Crude rate ratios describing the association between specific symptoms or groups of symptoms and mechanical work exposure, commercial fishers (N=13,028 person-interviews), North Carolina, 1999-2001

	Fuel Exposure Indices				
	Work on boat motors or other mechanical equipment				
	Outside ^a N=1764	Inside or both inside & outside ^a N=441	≤median time spent ^b N=1262	>median time spent ^b N=945	Use gasoline to clean hands or equipment ^c N=585
Cognitive effects	2.2 (1.6, 3.0)	3.7 (2.4, 5.9)	2.4 (1.7, 3.5)	2.6 (1.7, 3.8)	4.1 (2.9, 6.0)
Memory Loss	2.0 (1.0, 4.1)	2.4 (0.7, 7.9)	2.0 (0.9, 4.5)	2.3 (0.9, 5.4)	5.5 (2.7, 11.5)
Confusion	3.4 (1.8, 6.3)	4.5 (1.7, 11.6)	3.8 (1.9, 7.4)	3.3 (1.5, 7.3)	6.4 (3.3, 12.6)
Poor Concentration	3.5 (2.2, 5.5)	3.9 (1.8, 8.1)	3.7 (2.3, 6.2)	3.4 (1.9, 6.0)	6.2 (3.8, 10.3)
Poor task recall	2.5 (1.6, 3.9)	4.0 (2.2, 7.4)	2.8 (1.8, 4.5)	2.8 (1.7, 4.7)	3.7 (2.2, 6.1)
Poor word recall	2.3 (1.2, 4.4)	3.8 (1.5, 9.7)	2.9 (1.5, 5.8)	2.1 (0.9, 5.0)	3.5 (1.6, 7.8)
Headache or fatigue	1.7 (1.4, 2.0)	1.8 (1.4, 2.5)	1.8 (1.5, 2.2)	1.6 (1.2, 1.9)	1.5 (1.2, 2.0)
Headache	1.8 (1.5, 2.1)	1.8 (1.3, 2.5)	2.0 (1.6, 2.4)	1.6 (1.2, 2.0)	1.5 (1.1, 2.1)
Tiredness	1.6 (1.1, 2.1)	2.1 (1.3, 3.5)	1.6 (1.1, 2.2)	1.8 (1.2, 2.6)	1.9 (1.2, 3.0)
Cramps, nausea or diarrhea	1.7 (1.3, 2.3)	1.8 (1.1, 3.0)	1.5 (1.1, 2.2)	2.1 (1.5, 2.9)	1.9 (1.2, 2.8)
Belly Cramps	1.6 (1.1, 2.4)	1.1 (0.4, 2.6)	1.4 (0.9, 2.3)	1.6 (0.9, 2.7)	1.7 (0.9, 3.1)
Nausea	1.5 (1.0, 2.3)	1.6 (0.7, 3.5)	1.6 (1.0, 2.6)	1.4 (0.8, 2.5)	2.4 (1.4, 4.1)
Diarrhea	1.6 (1.1, 2.4)	2.1 (1.1, 3.8)	1.3 (0.8, 2.1)	2.3 (1.5, 3.5)	1.4 (0.8, 2.6)
Irritant effects	1.8 (1.5, 2.2)	1.7 (1.2, 2.4)	1.9 (1.5, 2.3)	1.6 (1.3, 2.1)	1.6 (1.2, 2.2)
Eye irritation	2.0 (1.6, 2.6)	1.6 (1.0, 2.8)	2.0 (1.5, 2.7)	1.8 (1.3, 2.6)	1.7 (1.1, 2.6)
Nose irritation	2.0 (1.4, 2.8)	1.2 (0.6, 2.6)	2.3 (1.6, 3.3)	1.2 (0.7, 2.1)	2.1 (1.3, 3.4)
Sore throat	1.4 (1.1, 2.0)	2.0 (1.2, 3.3)	1.4 (1.0, 2.0)	1.7 (1.2, 2.5)	1.6 (1.0, 2.5)
Lower respiratory symptoms	1.9 (1.6, 2.3)	1.6 (1.1, 2.3)	2.0 (1.6, 2.5)	1.7 (1.3, 2.2)	1.8 (1.3, 2.4)
Shortness of Breath	2.1 (1.6, 2.7)	1.9 (1.2, 3.2)	2.0 (1.5, 2.8)	2.1 (1.5, 3.0)	1.8 (1.2, 3.7)
Wheeze	2.4 (1.8, 3.2)	1.4 (0.7, 2.7)	1.9 (1.3, 2.8)	2.5 (1.7, 3.6)	3.0 (2.0, 4.5)
Cough	2.1 (1.7, 2.6)	1.7 (1.1, 2.7)	2.2 (1.7, 2.9)	1.8 (1.3, 2.5)	2.0 (1.4, 2.8)
Musculoskeletal effects	1.5 (1.3, 1.8)	2.2 (1.8, 2.8)	1.6 (1.3, 1.9)	1.8 (1.5, 2.2)	1.2 (0.9, 1.6)
Joint pain	1.5 (1.3, 1.8)	2.8 (2.2, 3.5)	1.6 (1.3, 1.9)	2.0 (1.7, 2.5)	1.1 (0.8, 1.5)
Muscle Cramps	1.8 (1.4, 2.3)	1.0 (0.6, 1.8)	1.9 (1.4, 2.5)	1.3 (0.9, 1.8)	1.1 (0.7, 1.8)
Other Symptoms					
Stuffy Nose	1.6 (1.3, 2.0)	1.7 (1.2, 2.4)	1.8 (1.4, 2.2)	1.4 (1.1, 1.8)	1.5 (1.1, 2.1)
Vomit	1.8 (1.0, 3.2)	1.9 (0.7, 5.3)	2.0 (1.1, 3.8)	1.6 (0.7, 3.5)	2.7 (1.3, 5.7)
Sores	1.6 (1.2, 2.2)	2.0 (1.2, 3.3)	1.6 (1.1, 2.3)	1.8 (1.2, 2.6)	1.1 (0.6, 1.9)

^a Outside and inside exposure modeled with two indicator variables such that there is a common referent (person-interviews for those doing no motor or mechanic work)

^b Above and below the median time modeled with two indicator variables such that there is a common referent (person-interviews for those doing no motor or mechanic work)

^c Modeled with a dichotomous exposure variable (person-interview among those not using gasoline to clean hands or equipment is the referent)

Table IV.3 Crude rate ratios describing the association between specific symptoms or groups of symptoms and fiberglass boat repair exposure, commercial fishers (N=13,028 person-interviews), North Carolina, 1999-2001

Symptoms Reported	Styrene Exposure Indices Use resin, epoxy or glue to repair fiberglass boat			
	Outside ^a	Inside or both inside & outside ^a	≤median time spent ^b	> median time spent ^b
	N=402	N=113	N=249	N=267
<i>Cognitive effects</i>	2.4 (1.4, 4.1)	1.7 (0.6, 5.5)	3.2 (1.8, 5.7)	1.5 (0.7, 3.3)
Memory Loss	3.2 (1.2, 9.0)	2.9 (0.4, 21.0)	5.2 (1.9, 14.7)	1.2 (0.2, 8.8)
Confusion	4.5 (1.9, 10.6)	-∞ ∞	4.9 (1.7, 13.5)	2.2 (0.5, 9.3)
Poor Concentration	3.6 (1.8, 7.2)	2.9 (0.7, 11.7)	5.2 (2.5, 10.8)	1.8 (0.6, 5.7)
Poor task recall	2.0 (1.0, 4.4)	2.1 (0.5, 8.4)	2.8 (1.2, 6.5)	1.3 (0.4, 4.1)
Poor word recall	2.7 (1.0, 7.6)	-∞ ∞	2.2 (0.5, 9.1)	2.0 (0.5, 8.4)
<i>Headache or fatigue</i>	1.9 (1.4, 2.5)	2.2 (1.3, 3.6)	1.8 (1.3, 2.7)	2.0 (1.4, 2.8)
Headache	1.8 (1.3, 2.5)	2.4 (1.4, 4.0)	1.8 (1.2, 2.7)	2.1 (1.5, 3.1)
Tiredness	2.0 (1.2, 3.4)	1.8 (0.7, 4.9)	2.1 (1.1, 3.9)	1.9 (1.0, 3.6)
<i>Cramps, nausea or diarrhea</i>	2.2 (1.4, 3.4)	1.5 (0.6, 4.1)	1.2 (0.6, 2.6)	2.8 (1.7, 4.5)
Belly Cramps	2.0 (1.0, 3.9)	0.8 (0.1, 5.6)	1.1 (0.3, 3.4)	2.3 (1.1, 4.9)
Nausea	2.2 (1.1, 4.3)	2.6 (0.8, 8.2)	1.6 (0.6, 4.3)	2.9 (1.4, 6.0)
Diarrhea	1.7 (0.9, 3.3)	1.3 (0.3, 5.4)	0.6 (0.2, 2.4)	2.5 (1.3, 4.9)
<i>Irritant effects</i>	2.5 (1.8, 3.3)	1.6 (0.9, 3.2)	2.6 (1.8, 3.7)	2.0 (1.3, 3.0)
Eye irritation	3.1 (2.1, 4.5)	0.8 (0.2, 3.1)	3.0 (1.8, 4.9)	2.1 (1.2, 3.7)
Nose irritation	2.1 (1.2, 3.8)	3.2 (1.3, 7.7)	2.6 (1.3, 5.1)	2.1 (1.1, 4.3)
Sore throat	2.0 (1.2, 3.3)	3.5 (1.7, 7.1)	2.2 (1.2, 4.0)	2.4 (1.4, 4.2)
<i>Lower respiratory symptoms</i>	2.2 (1.6, 3.1)	2.1 (1.2, 3.9)	2.3 (1.5, 3.4)	2.1 (1.4, 3.1)
Shortness of Breath	2.7 (1.8, 4.2)	1.3 (0.4, 4.0)	3.1 (1.9, 5.1)	1.8 (0.9, 3.3)
Wheeze	3.3 (2.1, 5.1)	1.1 (0.3, 4.3)	3.6 (2.1, 6.1)	2.0 (1.0, 3.9)
Cough	3.0 (2.1, 4.2)	2.2 (1.0, 4.6)	2.7 (1.7, 4.3)	2.9 (1.9, 4.4)
<i>Musculoskeletal effects</i>	1.2 (0.9, 1.6)	0.4 (0.2, 1.1)	1.0 (0.6, 1.5)	1.0 (0.7, 1.5)
Joint pain	1.2 (0.8, 1.7)	0.5 (0.2, 1.4)	1.1 (0.7, 1.8)	0.9 (0.6, 1.5)
Muscle Cramps	0.9 (0.5, 1.6)	-∞ ∞	0.5 (0.2, 1.4)	0.9 (0.4, 1.8)
<i>Other Symptoms</i>				
Stuffy Nose	1.8 (1.3, 2.5)	1.8 (1.0, 3.4)	2.1 (1.4, 3.1)	1.5 (1.0, 2.4)
Vomit	1.4 (0.4, 4.5)	1.7 (0.2, 12.1)	0.8 (0.1, 5.5)	2.1 (0.7, 6.7)
Sores	2.4 (1.5, 3.8)	0.9 (0.2, 3.6)	2.0 (1.1, 3.9)	2.1 (1.1, 3.8)

^a Modeled using two indicator variables for inside and outside work such that there is a common referent (person-interviews for those doing no motor or mechanic work)

^b Modeled with two indicator variables for above and below the median time spent such that there is a common referent (person-interviews for those doing no motor or mechanic work)

Table IV.4. Stratum specific rate ratios for symptoms indicative of cognitive effects and maintenance exposure across age and obesity strata, commercial fishers, North Carolina, 1999-2001

Main effects and covariates	Stratum Specific Rate Ratios (95% Confidence Intervals)	
	Age ≤ 55 years N=9,951	Age > 55 years N=3,011
Fuel Exposure		
Work on boat motors or other mechanical equipment ^a	4.7 (3.0, 7.3)	0.9 (0.5, 1.5)
Use gasoline to clean hands ^a	7.8 (4.5, 13.4)	2.6 (1.5, 4.5)
Weekly drinking ^b	0.4 (0.1, 1.3)	11.9 (7.9, 17.8)
Education ^c	0.3 (0.2, 0.5)	0.5 (0.3, 0.8)
Styrene Exposure		
	BMI < 30 kg/m ² N=7,499	BMI ≥ 30 kg/m ² N=5,314
Use epoxy, resin or glue to repair a fiberglass boat	1.0 (0.4, 2.2)	5.0 (2.7, 9.4)
Age ^d	4.8 (3.4, 6.7)	2.7 (1.7, 4.4)
Education ^c	0.4 (0.3, 0.6)	1.0 (0.6, 1.8)

^a Common referent (person-interviews among those who did not work on boat motors or mechanical equipment nor use gasoline to clean hands or equipment)

^b Dichotomous variable indicating >20 drinks per week

^c Dichotomous variable indicating high school or greater level of education

^d Dichotomous variable indicating age greater than 55 years

CHAPTER V

Exposure to Organic Solvents and Neuropsychological Outcomes

A. Introduction

Although commercial fishers are reported to have among the highest injury and fatality rates of any occupational group in the United States (CDC 2001), little has been published about their risk of occupational disease. In addition to handling catch and working with potentially dangerous fishing gear, fishers are exposed to a variety of chemical agents. They do much of their own boat and equipment maintenance and use organic solvents, including gasoline and diesel fuel, resins containing styrene, acetone, fungicidal paints and tars for coating crab pots. The objective of this study was to determine the association between cumulative exposure (over 5-7 months) to solvents during maintenance work and neuropsychological test performance, while adjusting for acute exposure. The exposure assessment focused on the most frequently reported maintenance exposures, which were repairing fiberglass boats with glues, epoxies or resins and exposure to fuel during motor or mechanical work.

Organic solvents target the lipid rich tissue of the nervous system or interfere with neurochemical processes causing an array of neurotoxic effects. (Hartman 1995) Acute exposure to organic solvents such as fuel and styrene can cause central nervous system depression and symptoms ranging in severity from dizziness to unconsciousness and death from respiratory arrest at high levels. (Hartman 1995; NIOSH 1987; Reese and Kimbrough 1993) The less severe effects are usually transient (Kulig 1990), but cases of residual cognitive impairment lasting years after an accidental solvent intoxication episode have been reported. (Hartman 1995; Stollery 1996)

The central nervous system effects of low-level chronic exposure to solvent mixtures are not well understood. Frequent findings of cross sectional studies of currently employed painters, carpet layers, printers, jet fuel workers and electronics workers include decrements on neuropsychological measures of memory, psychomotor function, attention and mood. (Baker 1994; Baker and Fine 1986; Broadwell and others 1995; Escalona and others 1995; Jang and others 1999; Ohnishi and others 1995; Tsai and others 1997) These findings could reflect acute or chronic effects of solvent exposure. Results from more recent epidemiological studies designed to distinguish acute and chronic effects and establish

whether adverse effects on the central nervous system persist after exposure has ended are inconsistent. (Daniell and others 1999; Eller and others 1999; Morrow and others 1997; Muijser and others 1996; Nasterlack and others 1999) However, there is clinical evidence to suggest that chronic exposure to organic solvents can result in mild or severe chronic toxic encephalopathy that may not be reversible. (Baker and White 1985; Hartman 1995)

Both diesel fuel and gasoline are organic solvent mixtures that contain a host of known and possible neurotoxic substances. Liquid gasoline poses a greater inhalation risk because it is highly volatile and typically contains between 25% and 30% aromatic hydrocarbons, many of which are known neurotoxic agents. (Ritchie and others 2001) By contrast, diesel fuel is distilled to exclude the aromatics and therefore has a negligible vapor pressure at normal ambient temperatures. Most of the hydrocarbons in diesel exhaust tend to have low vapor pressures, and adsorb onto the particles present in the exhaust emissions. (Muzyka and others 1998) Therefore the health hazards typically associated with exposure to the particulate matter in diesel exhaust are lung cancer and respiratory disease. (NIOSH 1988) However, there is increasing concern that the longer chained hydrocarbons may have a relatively high anesthetic potential based on evidence from pharmacokinetic and animal studies. (reviewed by Ritchie and others 2001) In addition, simultaneous exposure to the many hydrocarbons present in fuel may pose unique hazards that remain largely unrecognized. Evidence from animal studies suggests that interactions between the individual components in fuel may be synergistic, additive or antagonistic. (reviewed by Ritchie and others 2001)

Based on evidence animal and human chamber studies, a consensus has emerged that styrene can affect the central nervous system at exposure levels higher than 50 ppm. (ACGIH 2001; Hartman 1995) There is also evidence from epidemiological studies of working populations of decrements on neuropsychological or neurobehavioral measures (predominantly reaction time) among workers exposed to mean levels of less than 50 ppm. (Cherry and Gautrin 1990; Edling and others 1993; Letz and others 1990; Tsai and Chen 1996; Yokayama and others 1992) The American Conference of Governmental Industrial Hygienists (ACGIH) has set the Threshold Limit Value (TLV) to 20 ppm in order to protect

against CNS effects as well as irritation of the mucous membranes and respiratory system. (ACGIH 2001) Acetone, the chemical typically used to dissolve styrene-based resins, is considered one of the least toxic solvents. (Hartman 1995)

B. Methods

This research protocol was approved by the University of North Carolina School of Public Health's Institutional Review Board (IRB). At the time of recruitment, the study protocol was explained to study subjects by the project staff and informed consent was obtained prior to baseline evaluation.

1. Population and Data Collection

Data collected for a longitudinal cohort study of 238 commercial fishers and others exposed to marine waters in North Carolina were used for these analyses. The main purpose of the cohort study was to “elucidate the risks and possible clinical disease” (Moe and others 2001, p.781) associated with exposure to *Pfiesteria piscicida*, a newly discovered genus of dinoflagellate (Burkholder 1999). *Pfiesteria* is believed to produce a toxin that has been associated with neurological dysfunction in laboratory workers exposed to high levels of *Pfiesteria* cultures (Glasgow Jr. and others 1995; Schmechel and Koltai 2001) and one study offers preliminary evidence that exposure to estuarine waters in which *Pfiesteria* is present may adversely affect cognitive function. (Grattan and others 1998)

A full description of the study design and methods has been published elsewhere. (Moe and others 2001) In summary, volunteer participants must have worked on the water for at least six months per year and believe that they could fulfill the requirements of the study. Specifically, participants agreed to maintain an activity log book and answer questions during a biweekly or weekly telephone interview during the follow-up period that began in April of 1999 and continued until October of 2001. They were also required to receive a baseline clinical evaluation that included a medical exam, neuropsychological screening assessment and interview about potential confounders as well as social and demographic factors. Follow-up exams were administered during subsequent clinic visits every 5 to 7 months during the 2.5-year follow-up period. Some participants were randomly

selected for recruitment via telephone solicitation from a list of commercial fishers who hold licenses. Others were solicited directly at fishing events or reached through advertisements in local newspapers.

Individuals with health conditions known to affect neurocognitive function were excluded from the study. Specific medical conditions resulting in exclusion included head trauma resulting in loss of consciousness, insulin-requiring diabetes, hospitalization for treatment of drug or alcohol abuse, stroke or transient ischemic attack, brain tumor, seizures, epilepsy, encephalitis, meningitis, Parkinson's disease, Alzheimer's disease, dementia, systemic lupus, Lyme disease, brain surgery, Huntington's disease, multiple sclerosis, narcolepsy, known solvent or pesticide poisoning, reported infection with human-immunodeficiency virus (HIV), using medications to treat psychosis or mania, or a diagnosis of psychosis. In addition, individuals who had been placed in mentally handicapped classes in school or who had participated in previous or other current studies of health effects possibly related to *Pfiesteria* exposure, were excluded from the cohort.

Additional exclusions were made after enrollment if participants exhibited poor effort on neuropsychological tests, developed diseases that would affect neurocognitive performance or if a history of such a disease was discovered. Two subjects who exhibited a malingering profile on the Rey 15-item Test (cutpoint ≤ 8) (Loring and Martin 1992) administered during the baseline exam were excluded. Selected neuropsychological tests of verbal fluency and memory (COWA and RAVLT) for one additional individual who showed poor effort and invalid grooved pegboard test results for a subject with long fingernails were excluded. Post diagnosis neuropsychological test data for six subjects who developed vascular disease, non-insulin dependent diabetes mellitus (NIDDM), aplastic anemia, possible stroke, amnesia associated with a concussion and multiple sclerosis (MS) were excluded. Two subjects, for whom a history of psychosis or childhood seizures was discovered, were excluded. Two subjects who were enrolled in another study that measured neuropsychological function were excluded. Forty observations (N=40) among 13 participants (all observations excluded for 9 subjects) were excluded after enrollment.

2. Determination of Exposure

All exposure data used for these analyses were self-reported during the 2.5-year follow-up period. During a weekly or biweekly telephone interview, participants were asked if they did maintenance work that may have exposed them to organic solvents since their previous interview. Specifically, they were asked if they worked on boat motors or other types of mechanical equipment, cleaned their hands or their equipment with gasoline, used glues, epoxies and resins, or repaired a fiberglass boat. For each of these activities, they were further queried about how long they spent doing the activity. Time spent on the activity was ascertained by asking how many hours, days or minutes each participant spent on the activity during the entire interval between interviews. Painting and coating crab pots with tar were reported relatively infrequently and, therefore, their effect was not assessed separately.

Working on boat motors and other mechanical equipment is known to involve exposure to gasoline or diesel fuel. (Egeghy and others 2002) Approximately 65% of the reports of working on boat motors or mechanical equipment among cohort members involved skin contact through cleaning hand or equipment with gasoline. Using glues, epoxies or resins for fiberglass boat repair was assumed to involve exposure to styrene. To confirm that styrene based resins were used for most fiberglass boat repair projects, additional telephone interviews were conducted with approximately 119 participants to obtain trade names for the epoxies, resins and hardeners they used for fiberglass boat repair projects so that Material Safety Data Sheets (MSDSs) could be obtained. Approximately 13% of the participants reported using epoxy resins that did not contain styrene and 46% were found to use products containing 15-60 % styrene by weight and acetone as a cleaner. An additional 41% of participants reported that they bought marine resin in bulk and did not know the name of the product they used. In this case, the fisher was asked where he or she purchased the product. Follow-up calls with marine suppliers named by participants revealed that resins sold in bulk were the relatively inexpensive styrene based products.

A total of 13,551 telephone interviews containing information on maintenance work involving solvent exposure were available for these analyses. The most frequently reported

maintenance activities involving solvent exposure, which were the focus of this study, were working on motors or other mechanical equipment and repairing a fiberglass boat with glues, epoxies or resins. Cleaning hands or equipment with gasoline was also reported with relative frequency but this activity was typically conducted in conjunction with mechanical work. Cumulative exposures were estimated by adding the total number of hours (or times for cleaning hands or equipment with gasoline) reported for the maintenance activity during the 5-7 month interval between neuropsychological exams. In addition, the total cumulative hours of exposure to solvents was estimated by combining the number of hours working on boat motors and mechanical equipment, fiberglass boats, painting and applying tar. Recent exposure was indicated by computing the number of days prior to the administration of the neuropsychological exam a maintenance activity was conducted.

Reporting more than 10 cumulative hours working on boat motors or mechanical equipment or repairing fiberglass boats, during the interval between exams was considered highly exposed. This cutpoint corresponded with the 71st and 90th percentiles of duration (among those reporting the activity) for motor work and fiberglass boat repair projects, respectively. A higher cutpoint of 50 hours (85th percentile of exposure) was used for total solvent exposure. Dichotomous variables were used in analyses for cumulative and recent exposure to solvents during maintenance activities. Any report of a maintenance activity involving solvent exposure within 5 days of the neuropsychological exam was considered a recent exposure for fiberglass repair work or mechanical work. The recent exposure variable was refined for assessment of combined maintenance activities to indicate a solvent related maintenance work of at least 4 hours in duration within 2 days of the neuropsychological exam.

3. Outcome

Neuropsychological testing is a highly sensitive means of measuring complex brain-behavior relationships in a standardized and objective fashion. (Lezak 1995) Tests were selected that examined executive skills (e.g. divided attention, cognitive flexibility, concentration, complex problem solving, verbal fluency, sequencing and information processing), memory and learning, fine motor coordination and dexterity, and mood. A total

of 1001 neuropsychological exams administered every 5-7 months during the 2.5-year follow-up period were administered. After excluding baseline exams (N=238) and making post-enrollment exclusions described previously (N=40), 723 of these exams were included in these analyses.

The neuropsychological tests of executive functions were the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale-III (L-N Sequencing) (Wechsler 1997), the Trail Making Test (TMT) (Reitan 1958), the Symbol Digit Modalities Test (SDMT) (Smith 1982), the Stroop Test (Stroop) (Golden 1978), the Controlled Oral Word Association subtests of the Multilingual Aphasia Examination (COWA) (Benton and Hamsher 1976) and Raven's Progressive Matrices (Raven's Matrices) (Raven and others 1995). The L-N Sequencing test is a mental sequencing subtest that requires the subject to listen to and then reorder in correct sequence successively longer sets of numbers and letters. The first part of the TMT, Trails A, requires the subject to rapidly sequence a straightforward series. The second part, Trails B, is a more difficult cognitive flexibility task requiring the subject to follow a sequential pattern while shifting cognitive sets. The SDMT is a brief measure of nonverbal rapid sequencing of digits and symbols according to a stimulus key. The Stroop measures response inhibition and sensitivity to interference under changing task demands. The COWA is a test of word generation that measures lexical fluency. Raven's matrices form an un-timed nonverbal test requiring visual pattern matching and reasoning.

The tests of learning and memory were the Rey Auditory Verbal Learning Test (Rey AVLT) (Schmidt 1996) and the Rey-Osterreith Complex Figure Test (Rey-O Copy). (Meyers and Meyers 1995) The Rey AVLT is based on five learning trials of a 15-word list. Performance of free recall after a brief intervening task, delayed free recall after a 30-minute delay, and recognition memory testing are measured. The two scores used in the present study were total learning across the five presentation trials and the percent retained during the delayed recall trial relative to that learned by the last learning trial. The Rey-O Copy first assesses visual-constructional ability, when the subject must copy a complex figure, and then nonverbal memory when the subject must reproduce the design from memory after a delay.

The Rey O Copy score and the percent retained at the delayed recall trial relative to the Rey O Copy score were used in these analyses.

Fine motor skills were measured using the Grooved Pegboard Test (Klove 1963), which measures both dominant and nondominant hand fine motor speed, coordination, and dexterity. Mood and affect were measured using the Beck Depression Inventory (BDI) (Beck and others 1961) and the State-Trait Anxiety Inventory (STAI) (Spielberger 2002). The BDI is a widely used self-rated measure of depression. The STAI uses a multiple-choice format that yields a score for situational or transient "state anxiety" and the more long-standing quality of "trait anxiety."

The continuous neuropsychological outcomes were transformed as needed to meet the normality assumptions of the statistical methods described in the next section. The 11 neuropsychological tests, 15 derived measures and their transformations used for these analyses are summarized in Table V.1. Also included in the table is the direction indicating poor performance on the test.

4. Covariates

Performance on most neuropsychological instruments is influenced by a number of factors including age, education, gender, number of previous times the test was taken (practice effect), test version, factors associated with the technician, drugs and alcohol use. Performance on neuropsychological tests is also influenced by affective disorders including anxiety and depression as well as pre-morbid function and intelligence.

In order to define these covariates for the purpose of modeling, age was centered at its mean (44 years), education was centered at 12 years (high school) and a variable for previous number of visits was created. Indicator variables were created for each technician administering the test. Medications taken by participants were categorized with regard to their risk to the central nervous system, and a variable dichotomizing those posing a moderate to high risk was specified. Dichotomous variables were created for alcohol consumption (cutpoint > 21 drinks per week), obesity ($BMI \geq 30 \text{ kg/m}^2$), current drug use

and any drug use. Depression, anxiety and reading competency scores were continuous variables.

5. Statistical Analyses

All statistical analyses were performed using SAS software, version 8.01. (SAS Institute Inc., Cary, NC) The goal of the analyses was to determine the association between cumulative and recent exposure to organic solvents during the 5-7 month interval between neuropsychological exams, and performance on the subsequent neuropsychological exam. In order to maximize the difference between exposure groups, reference cell coding was used for cumulative exposure so that the high cumulative exposure group would be compared to the unexposed.

Longitudinal analysis that accounted for the correlation within individuals was performed with the GENMOD procedure, which uses generalized estimating equations (GEE) (Liang and Zeger 1986) to determine the model parameters. The variance was modeled as a function of the mean by specifying the normal distribution. The normality of the test outcomes was qualitatively assessed, by examining histograms. As shown in Table V.1, outcomes were transformed so that they were approximately normal. The compound symmetric covariance structure was specified. This structure is appropriate for repeated measures because the correlation within clusters of individuals is assumed to be equal and the variation between clusters is assumed to be larger than the variation within individuals. Within-subject and between-subject residuals were examined to identify influential outliers. (Stewart 2002)

Estimates produced by GEE were used because the focus of this paper is on the population average effect of solvent exposure. Because less than half of one percent of data was missing data (Stewart 2002) and the number of clusters of individuals (n=238) was large, the parameter estimates produced by GEE are likely to be robust to any misspecification in the covariance structure. (Hu and others 1998)

In order to select covariates for the models, a list of potential predictors of neuropsychological test performance described above was compiled from a review of the literature. Bivariate analysis was conducted to determine whether these predictors had the potential to confound associations between exposure and neuropsychological test performance. Potential confounders, e.g. independent predictors of one or more test outcomes that are also associated with one or more exposure variables, were included in full multivariate models. Correlations between covariates were examined using the Pearson correlation coefficient to assess possible collinearity.

Because the goal of these analyses was to determine unbiased estimates of the main effects (cumulative and recent solvent exposure during maintenance activities), rather than determine predictors of test outcomes, the change in effect (CIE) of the main exposure due to multiple confounding was evaluated. The CIE was determined by comparing estimates from the full multivariate models to estimates from models including only the main effects. Age, alcohol and BMI, which are suspected to modify the association between organic solvent exposure and neuropsychological outcome, were included in separate multivariate models as interaction terms. Confidence intervals were determined to determine the precision of the results. Trends were evaluated by determining the size of the change in test score and its direction. Effects size was determined by comparing the change in test score due to exposure to the standard deviation for that test among the unexposed (those who did not report solvent related maintenance activities). This measure, which is referred to as the %SD in Tables V.3-V.6, describes the size of the change in test score in units of standard deviations.

Mean scores for anxiety and depression were evaluated across exposure categories in order to assess their potential to confound associations observed for tests of executive function, memory and learning and fine motor skills. The equivalency of reading competency as measured by the WRAT-3, across exposure categories was also evaluated. No multivariate adjustment would be made for symptoms of depression or anxiety because these disorders may be caused by solvent exposure. No adjustment for WRAT-3 was planned because test performance as a function of baseline intelligence was of interest.

C. Results

A total of 723 neuropsychological tests among 219 commercial fishers examined between 2 and 9 times were analyzed. (See Appendix 6 for analyses excluding trigger visits.) The demographic and lifestyle characteristics of this group are summarized in Table V.2. The numbers and percentages in the participant column reflect whether a fisher ever reported the factor during the 2.5-year follow-up period, while those in the observation column reflect the time varying nature of the factors as well as the different amount of person-time contributed by each subject.

The average age of the participants during the course of the study was 44 years and the majority (86%) of participants were male. Approximately 70% of participants reported that they had finished high school (range = 6 to 18 years of schooling). Almost 10% report consuming more than 21 drinks per week while the majority (61%) report consuming between 1 and 21 drinks per week (up to 3 drinks per day on average). The drug use reported by participants was predominantly marijuana.

Exposure prevalence and duration are also summarized in Table V.2. Again the numbers and percentages in the participant column indicate whether a fisher ever reported the activity during the follow-up period. Approximately 49% of the participants reported ever doing fiberglass repair work and 85% of the participants reported ever doing motor or mechanical work. Exposure to gasoline occurred through skin contact as well as inhalation during mechanical work. Approximately 56% of the participants contributed 221 reports of cleaning hands or equipment with gasoline. Maintenance activities involving solvent exposure were combined in final analyses and 87% of the participants reported doing any solvent-related maintenance work (mechanical work, fiberglass boat repair, painting or tar application) during the follow-up period. The number of hours spent on maintenance work was highly variable ranging from less than 1 hour to more than 1,000 hours during the follow-up period. Similarly the number of hours spent during the period between neuropsychological exams ranged from less than 1 hour to more than 500 hours.

Covariates identified through stratified analysis, that had the potential to confound one or more of the associations between maintenance work and neuropsychological test performance, were age, gender, number of times a test was taken and technician. Overall, the CIE due to multiple confounding was less than 10% for most outcomes. The exceptions were for the effect of mechanical work on Rey AVLT % retained (CIE=15%) and Rey O % retained (CIE=12%) and the effect of fiberglass repair work on trait anxiety (CIE=12%), the Stroop (CIE=25%) and the Trails B (131%). The results, which were adjusted for age, gender, training effect, education and technician, are tabulated in Appendix 6. The WRAT-3 reading level score was not lower among those reporting that they did mechanical work or fiberglass repair work, making it unlikely that differences in reading competence could explain differences on neuropsychological test performance.

The results of the regressions of neuropsychological test outcomes on maintenance work are summarized in Tables V.3-V.6. Reference cell coding was used so that the reference group for the highest cumulative exposure term is the unexposed (only the highest cumulative exposure term is shown). The beta coefficients for the exposure variables indicate the change in test performance predicted by exposure. Overall, the effect of recent exposure on neuropsychological test performance was not in the expected direction. Recent exposure was associated with increased performance on many neuropsychological tests. With few exceptions, the effect of cumulative exposure on neuropsychological test performance resulted in poorer neuropsychological test performance.

Relatively large ($\geq 5\%$ of the standard deviation in the unexposed) changes in test score are listed below:

1. Cumulative fiberglass boat repair work (≥ 10 hours) was associated with a 0.10 log second (1.1 second) decrease on the Trails B;
2. recent fiberglass boat repair work (within 5 days) was associated with an 11% increase on the Rey AVLT % retained;
3. recent cleaning hands or equipment with gasoline (within 5 days) was associated with a 9% increase in the Rey AVLT % retained;

4. recent combined maintenance exposures (within 2 days) were associated with a 5 point increase on the Stroop;
5. cumulative combined maintenance exposures (>50 hours) were associated with a 3 point decrease on the Rey AVLT;
6. recent combined solvent exposure (within 2 days) was associated with an 8% increase on the Rey AVLT % retained;
7. recent combined solvent exposure (within 2 days) was associated with a 1.4 point increase on the Rey O Copy; and
8. recent combined solvent exposure (within 2 days) was associated with a 6% decrease on the % retained on the Rey O % retained.

The interaction between obesity (BMI >30 kg/m²) and >10 hours per interval of fiberglass boat repair work was tested. No trends regarding the combined effect of solvents and obesity were identified. There was a suggestion that the combined effect of age greater than 55 years and more than 50 cumulative hours of maintenance work would result in a larger than expected decrease on some neuropsychological tests. The models describing the age*maintenance work interaction and performance on the Rey O Copy, the Grooved Pegboard Non-Preferred Hand and STAI score are summarized in Table V.7. An interaction between drinking more than 21 alcoholic drinks per week and cumulative combined solvent exposure of more than 10 hours among those greater than 55 years was also tested. No trend towards poorer performance among the older heavy drinkers was observed, however.

D. Discussion

Organic solvents such as styrene and the aromatics found in gasoline have short half-lives. In fact, they are almost entirely cleared from the body in approximately 4 to 40 hours. (Kulig 1990) Since the recent exposure was defined to include exposures within 2-5 days of neuropsychological testing when acute effects may no longer be observable, non-differential misclassification that would tend to attenuate the observed changes in test score that was anticipated. However, many of the changes in test score were relatively large and few were in the expected direction. Given the well-established link between acute exposure to solvents and neuropsychological impairment (NIOSH 1987), these observed increases in performance

predicted by recent solvent exposure are likely to be explained by chance or an unforeseen bias. The changes in test scores predicted by cumulative exposure were typically in the expected direction. However, the effect sizes were small and we do not consider them clinically significant.

Gasoline is a mixture of approximately 150 hydrocarbons that may result in synergistic, additive or antagonistic interactions. (reviewed by Ritchie and others 2001) The TLV for gasoline has been set at 890 mg/m³ total hydrocarbons, to protect against eye and upper respiratory irritation and the Short Term Exposure Limit (STEL) has been set at 1480 mg/m³ to protect against acute CNS depression. (ACGIH 2001) The personal exposure to gasoline vapors among fishers who engage in motor or mechanical work is not known. The majority of the literature on exposure during mechanical works describes exposure to benzene, which is a human carcinogen. Exposure to benzene while working on diesel engines ranged from 5 to 12 µg/m³ (see Appendix 5). Mean personal exposure to benzene among automobile mechanics working predominantly on gasoline engines has been estimated at 100 µg/m³. (Egeghy 2002) This exposure level is approximately 5 times less than the mean personal benzene exposure reported for filling station attendants (550 µg/m³). (Lagorio and others 1994) Decrements in neuropsychological performance on tests of intellectual capacity, psychomotor and visuomotor function, memory and increased mortality from psychiatric disorders have been observed in this population. (Burbacher, Schwartz Kumar) Mechanical or motor work is conducted intermittently and, thus, fishers are expected to have a lower cumulative exposure than automobile mechanics. Participants who report the greatest number of hours of motor or mechanical work may approach the exposure levels of automobile mechanics if they work on gasoline engines. No studies of neuropsychological performance among automobile mechanics were identified through this literature review, however.

The TLV for styrene, which was set to minimize the neurotoxic effects of this chemical, is 20 ppm (85 mg/m³). (ACGIH 2001) Personal exposure to workers in the boat building industry who use poorly ventilated “open-system” techniques range from 40 to 100 ppm styrene. (ACGIH 2001) The majority of the fiberglass repair jobs performed by

commercial fishers were completed in a few hours and 91% of the jobs were done outside where the ventilation would tend to reduce personal exposure. The participants who do a lot of fiberglass boat repair work using glue, epoxies and resins may have exposures that approach those in the boat building industry. The upper limit of number of hours of fiberglass boat repair work during the interval between neuropsychological exams was 481 hour (approximately 20 hours per week assuming a 6 month interval).

A previous study of neuropsychological symptoms among members of the same cohort of commercial fishers (Kirrane 2002) found an increased rate of self-reported neuropsychological symptoms during weeks when maintenance activities were performed. A comparable association between recent maintenance work and objective standardized neuropsychological test performance was not observed in this study. The appearance of symptoms may precede measurable decrements on neuropsychological tests. (Hartman 1995) However, the associations observed in the previous study of symptoms may have been vulnerable to reporting biases.

Those who enrolled in the cohort study were volunteers. At the time of recruitment, it was well known that the purpose of the cohort study was to investigate “Possible Estuary-Associated Syndrome (PEAS)”(CDC 1999). PEAS is characterized by an array of neuropsychological effects similar to those experienced by solvent-exposed workers. There was considerable public speculation and controversy about whether this syndrome was real or imagined and whether it was associated with exposure to *Pfiesteria* in estuaries. A well-publicized book (Barker 1997) was written on the subject, and there was concern in the fishing community about the impact of *Pfiesteria* on health, the future of the fishing industry and tourism. A bias may be present if study participants differentially reported symptom during weeks they worked with fuels or fiberglass boat repair chemicals because they believed these materials might be harmful or had a vested interest in influencing the outcome of the study. In addition, because exposure and outcome were queried nearly simultaneously, on one instrument, errors in their ascertainment may be correlated, biasing rate ratios. (Brenner and others 1993)

Symptom over-reporting has also been associated with affective disturbances such as depression and anxiety. (O'Donnell and others 1993) In the current analysis, combined maintenance work and fiberglass boat repair are associated with small increases on STAI scores. In addition, the odds ratios (GEE estimates accounting for autocorrelation in the outcomes) describing the association of high cumulative maintenance work with scoring above the 90th percentile on the BDI, state anxiety inventory and trait anxiety inventory were 1.6 (95%CI: 0.7,3.5), 2.3 (95%CI: 1.0, 4.9) and 1.7 (95%CI: 0.8, 3.4) respectively. These results may suggest small associations between affective disturbances and maintenance work. However, depression and anxiety were not considered potential confounders in these analyses because they may be caused by solvent exposure and sustained mood or personality changes are thought to precede deficits on other neuropsychological tests. (Baker and White 1985; WHO 1985)

A trend indicated by large changes in neuropsychological function would have suggested that recent maintenance work or more than 10-50 cumulative hours of maintenance work during the interval between neuropsychological exams produced deficits lasting from weeks to months. Such a finding would have suggested avenues for further study geared toward refining the exposure assessment or determining whether the effects were reversible. The largely negative findings are more difficult to interpret. Personal exposure to fuel and styrene was not measured during maintenance activities. Exposures may have been low enough to preclude any effect on neuropsychological function. Alternatively, misclassification of exposure may have attenuated the observed changes in the test score predicted by maintenance work. Self-reported exposure duration estimates may have been inaccurate, and estimates based on duration may not be adequate because the level or intensity of solvent exposure was not considered. Finally, neuropsychological testing may not be adequately sensitive to measure small changes in the earliest stage of neurological disease or the subtle effects of very low exposures to solvent. A current challenge in neuropsychological testing is the establishment of pre-morbid function. (Hartman 1995) Without the ability to establishing a baseline level of function, comparisons across groups may be confounded.

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Table V.1. Summary of functional domain, neuropsychological tests and measures test performance

<u>Domain</u> Neuropsychological Test	Transformation	Score Indicating Poor Performance
<u>Executive Function</u>		
SDMT	None (# correct)	Low
Trails B	Log seconds	High
Stroop	None (score)	Low
COWA	None (# correct)	Low
Raven's Matrices	None (total correct, 3 sets)	Low
L-N Sequencing	None (# correct)	Low
<u>Learning and Memory</u>		
Rey AVLT	None (total correct, trials 1-5)	Low
Rey AVLT % retained	% Correct at delay	Low
Rey O	None (score)	Low
Rey O % retained	% Correct at delay	Low
<u>Motor</u>		
Grooved Pegboard Preferred	Log ₁₀ (second-30)	High
Grooved Pegboard Non-Preferred	Log ₁₀ (second-30)	High
<u>Mood and Affect</u>		
BDI	None (score)	High
STAI State	None (score)	High
STAI Trait	None (score)	High

Table V.2. Demographic and lifestyle characteristics, exposure prevalence and exposure duration, commercial fishers, North Carolina, 1999-2001

Demographic Characteristic or Risk Factor	Participants (N=219)	Observations Contributed (N=723)
Gender, No. (%)		
Female	30 (14)	116 (16)
Male	189 (86)	607 (84)
Age, Mean (range)	44 (19-66)	45 (18-67)
Education, No. (%)		
High School or Greater	154 (70)	523 (72)
Weekly drinking, No. (%)		
0 per week	65 (30)	279 (38)
1-21 per week	123 (61)	410 (57)
>22 per week	21 (9)	34 (5)
Current drug user, No. (%)	37 (17)	78 (11)
Ever drug user, No. (%)	80 (37)	230 (32)
Moderate to high risk ^a medications, No. (%)	43 (20)	85 (12)
More than one job, No. (%)	106 (48)	184 (26)
High risk job ^b	49 (22)	74 (10)
Exposure Prevalence and Duration		
<u>Fiberglass boat repair</u>		
Reports of activity, No. (%)	108 (49)	182 (25)
Cumulative hours, Median (range)	8 (0.3-1045) ^c	6 (0.2-481) ^d
≥10 hours in interval between exams	43 (20)	65 (9)
Reporting of acute exposure	17 (8)	20 (3)
<u>Motor or Mechanical Equipment Work</u>		
Report of activity, No. (%)	186 (85)	451 (62)
Cumulative hours, Median (range)	24 (0.3-1072) ^c	8 (0.2-257) ^d
≥10 hours in interval between exams	109 (50)	203 (28)
Reports of acute exposure	43 (20)	58 (8)
<u>Combined Solvent Exposure</u>		
Reports of activity, No. (%)	191 (87%)	479 (66)
Cumulative hours, Median (range)	30 (0.25-1184) ^c	11 (0.02-547) ^d
≥50 hours in interval between exams	51 (23)	81 (11)
Reports of acute exposure	22 (10)	26 (4)

^a Medications were classified with regard to their potential risk to the central nervous system.

^b Potential for exposure to neurotoxic substances. Jobs include boat repair, construction, carpentry, mechanic, heavy equipment operator, welder, machinist, farming, dry cleaning and taxidermy.

^c Among fishers reporting the activity, during the entire follow-up period.

^d Among fishers reporting the activity, during the 5-7 month interval between neuropsychological exams

Table V.3. Regression models of the effect of cumulative and recent fiberglass boat repair work exposure on neuropsychological test performance ^a

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
SDMT	Intercept	47.19	45.96	48.42	<0.001		
	≥10 hrs	-0.95	-2.51	0.62	0.234	-3%	Yes
	within 5 days	0.53	-1.36	2.42	0.582	2%	No
Trails B	Intercept	4.18	4.14	4.23	<0.001		
	≥10 hrs	0.10	0.04	0.17	0.002	26%	Yes
	within 5 days	-0.07	-0.18	0.04	0.219	-17%	No
Stroop	Intercept	41.97	40.94	43.01	<0.001		
	≥10 hrs	-2.06	-3.63	-0.50	0.010	-19%	Yes
	within 5 days	2.22	-0.80	5.25	0.150	21%	No
L-N Sequencing	Intercept	10.74	10.44	11.04	<0.001		
	≥10 hrs	-0.49	-0.91	-0.06	0.024	-15%	Yes
	within 5 days	0.61	0.06	1.16	0.029	19%	No
COWA	Intercept	37.49	35.98	39.01	<0.001		
	≥10 hrs	-1.82	-3.42	-0.22	0.026	-11%	Yes
	within 5 days	1.31	-1.22	3.84	0.309	8%	No
Raven's Matrices	Intercept	29.95	29.43	30.47	<0.001		
	≥10 hrs	-0.18	-0.85	0.48	0.587	-2%	Yes
	within 5 days	0.79	-0.15	1.74	0.101	8%	No
Rey AVLT	Intercept	50.32	49.23	51.40	<0.001		
	≥10 hrs	-1.24	-3.56	1.08	0.294	-11%	Yes
	within 5 days	2.14	-1.82	6.10	0.290	19%	No
Rey AVLT % retained	Intercept	82.53	80.76	84.30	<0.001		
	≥10 hrs	-3.48	-7.03	0.06	0.054	-16%	Yes
	within 5 days	11.16	6.12	16.19	<0.001	50%	No
Rey O Copy	Intercept	27.90	27.43	28.37	<0.001		
	≥10 hrs	-0.20	-1.19	0.80	0.699	-4%	Yes
	within 5 days	1.19	-0.22	2.60	0.098	22%	No
Rey O % retained	Intercept	62.71	60.84	64.59	<0.001		
	≥10 hrs	0.92	-2.98	4.83	0.643	4%	No
	within 5 days	-3.23	-8.67	2.21	0.244	-15%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.61	1.65	<0.001		
	≥10 hrs	0.02	0.00	0.05	0.092	13%	Yes
	within 5 days	0.00	-0.04	0.04	0.978	0%	N/A
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	<0.001		
	≥10 hrs	0.00	-0.03	0.03	0.880	1%	Yes
	within 5 days	-0.01	-0.06	0.03	0.584	-8%	No

Table V.3. Regression models of the effect of cumulative and recent fiberglass boat repair work exposure on neuropsychological test performance ^a (Continued)

Neuropsychological Test	Variable	Model			p-value	% SD ^c	DIR ^d
		Prediction of Test Outcome					
		β	95% CI ^b				
BDI	Intercept	4.00	3.45	4.56	<0.001		
	≥10 hrs	0.55	-0.69	1.79	0.381	10%	Yes
	within 5 days	0.14	-2.07	2.34	0.903	2%	Yes
STAI (S)	Intercept	28.51	27.63	29.38	<0.001		
	≥10 hrs	1.97	-0.56	4.51	0.127	21%	Yes
	within 5 days	0.05	-3.25	3.35	0.975	1%	Yes
STAI (T)	Intercept	30.19	29.22	31.16	<0.001		
	≥10 hrs	2.12	0.31	3.92	0.021	20%	Yes
	within 5 days	-0.22	-2.70	2.25	0.860	2%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

Table V.4. Regression models of the effect of cumulative and recent motor or mechanical work exposure on neuropsychological test performance ^a

Neuropsychological Test	Variable	Model					
		Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
SDMT	Intercept	46.86	45.55	48.16	<0.001		
	≥10 hrs	0.91	-0.29	2.11	0.139	3%	No
	within 5 days	-0.37	-1.96	1.23	0.651	-1%	Yes
Trails B	Intercept	4.20	4.16	4.25	<0.001		
	≥10 hrs	-0.02	-0.07	0.03	0.409	-5%	No
	within 5 days	-0.04	-0.11	0.03	0.321	-9%	No
Stroop	Intercept	41.87	40.78	42.96	<0.001		
	≥10 hrs	-0.53	-1.55	0.49	0.305	-5%	Yes
	within 5 days	1.59	0.06	3.13	0.042	15%	No
L-N Sequencing	Intercept	10.72	10.41	11.03	<0.001		
	≥10 hrs	-0.07	-0.40	0.26	0.692	-2%	Yes
	within 5 days	0.12	-0.34	0.58	0.604	4%	No
COWA	Intercept	37.58	36.02	39.14	<0.001		
	≥10 hrs	-0.74	-1.94	0.47	0.232	-4%	Yes
	within 5 days	-0.03	-1.61	1.54	0.968	0%	N/A
Raven's Matrices	Intercept	29.78	29.24	30.33	<0.001		
	≥10 hrs	0.55	0.04	1.06	0.036	6%	No
	within 5 days	-0.01	-0.69	0.67	0.978	0%	N/A
Rey AVLT	Intercept	50.52	49.37	51.67	<0.001		
	≥10 hrs	-1.20	-2.76	0.36	0.132	-11%	Yes
	within 5 days	1.30	-0.31	2.91	0.113	11%	No
Rey AVLT % retained	Intercept	82.17	80.23	84.12	<0.001		
	≥10 hrs	-0.18	-2.59	2.24	0.886	-1%	Yes
	within 5 days	4.79	0.62	8.96	0.024	22%	No
Rey O Copy	Intercept	27.85	27.36	28.34	<0.001		
	≥10 hrs	0.00	-0.55	0.56	0.993	0%	N/A
	within 5 days	0.78	-0.04	1.59	0.063	15%	No
Rey O % retained	Intercept	62.75	60.68	64.82	<0.001		
	≥10 hrs	0.74	-2.14	3.63	0.613	4%	No
	within 5 days	-3.18	-6.23	-0.14	0.041	-15%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.62	1.65	<0.001		
	≥10 hrs	0.00	-0.02	0.02	0.882	1%	Yes
	within 5 days	-0.01	-0.04	0.01	0.358	-7%	No
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	<0.001		
	≥10 hrs	0.00	-0.02	0.02	0.958	0%	N/A
	within 5 days	-0.01	-0.03	0.01	0.419	-6%	No

Table V.4. Regression models of the effect of cumulative and recent motor or mechanical work exposure on neuropsychological test performance ^a (Continued)

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
BDI	Intercept	3.90	3.34	4.46	<0.001		
	≥10 hrs	0.33	-0.38	1.05	0.362	6%	Yes
	within 5 days	0.77	-0.43	1.96	0.210	13%	Yes
STAI (S)	Intercept	28.42	27.52	29.33	<0.001		
	≥10 hrs	0.92	-0.40	2.24	0.174	10%	Yes
	within 5 days	-0.15	-2.13	1.83	0.879	-2%	No
STAI (T)	Intercept	30.18	29.19	31.17	<0.001		
	≥10 hrs	0.56	-0.51	1.63	0.301	5%	Yes
	within 5 days	0.39	-1.16	1.94	0.623	4%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

Table V.5. Regression models of the effect of cumulative and recent skin contact with gasoline via cleaning hands or equipment on neuropsychological performance ^a.

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
SDMT	Intercept	47.13	45.90	48.37	<0.001		
	≥ 3 reports	-0.20	-1.93	1.54	0.823	-1%	Yes
	within 5 days	-0.23	-2.71	2.26	0.858	-1%	Yes
Trails B	Intercept	4.19	4.15	4.23	<0.001		
	≥ 3 reports	0.03	-0.04	0.10	0.477	6%	Yes
	within 5 days	0.03	-0.08	0.15	0.566	8%	Yes
Stroop	Intercept	41.91	40.87	42.94	<0.001		
	≥ 3 reports	-1.50	-3.32	0.32	0.106	-14%	Yes
	within 5 days	1.69	-0.40	3.79	0.114	16%	No
L-N Sequencing	Intercept	10.69	10.40	10.99	<0.001		
	≥ 3 reports	0.20	-0.42	0.82	0.532	6%	No
	within 5 days	0.08	-0.51	0.66	0.793	2%	No
COWA	Intercept	37.35	35.83	38.87	<0.001		
	≥ 3 reports	0.34	-1.33	2.02	0.688	2%	No
	within 5 days	-1.07	-3.03	0.88	0.282	-6%	Yes
Raven's Matrices	Intercept	29.93	29.41	30.45	<0.001		
	≥ 3 reports	0.66	-0.22	1.54	0.141	7%	No
	within 5 days	-1.08	-2.11	-0.05	0.041	-11%	Yes
Rey AVLT	Intercept	50.17	49.09	51.26	<0.001		
	≥ 3 reports	0.38	-2.13	2.89	0.765	3%	No
	within 5 days	1.80	-0.40	4.01	0.108	16%	No
Rey AVLT % retained	Intercept	82.18	80.38	83.97	<0.001		
	≥ 3 reports	0.85	-3.65	5.35	0.711	4%	No
	within 5 days	8.91	3.82	14.01	0.001	40%	No
Rey O Copy	Intercept	27.86	27.40	28.32	<0.001		
	≥ 3 reports	0.42	-0.46	1.31	0.351	8%	No
	within 5 days	0.59	-0.54	1.73	0.305	11%	No
Rey O % retained	Intercept	62.88	60.97	64.79	0.000		
	≥ 3 reports	-1.04	-4.80	2.72	0.588	-2%	Yes
	within 5 days	-2.77	-9.47	3.93	0.418	-4%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.62	1.65	0.000		
	≥ 3 reports	0.02	-0.01	0.05	0.239	1%	Yes
	within 5 days	-0.01	-0.05	0.03	0.619	-1%	No
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	0.000		
	≥ 3 reports	0.01	-0.01	0.03	0.363	1%	Yes
	within 5 days	0.01	-0.03	0.06	0.604	1%	Yes

Table V.5. Regression models of the effect of cumulative and recent skin contact with gasoline via cleaning hands or equipment on neuropsychological performance ^a
(Continued)

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
BDI	Intercept	4.09	3.53	4.64	0.000		
	≥ 3 reports	-0.37	-1.59	0.84	0.548	-9%	No
	within 5 days	0.13	-1.15	1.41	0.844	3%	Yes
STAI (S)	Intercept	28.78	27.91	29.66	0.000		
	≥ 3 reports	-1.33	-3.06	0.40	0.132	-5%	No
	within 5 days	0.66	-1.88	3.20	0.612	2%	Yes
STAI (T)	Intercept	30.35	29.37	31.32	0.000		
	≥ 3 reports	0.12	-1.56	1.80	0.888	0%	N/A
	within 5 days	1.13	-0.94	3.20	0.286	4%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

Table V.6. Regression models of the effect of combined maintenance work on neuropsychological performance^a

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
SDMT	Intercept	47.69	46.22	49.16	0.000		
	≥ 50 hrs	0.04	-2.08	2.15	0.972	0%	N/A
	within 2 days	1.49	-1.53	4.52	0.334	5%	No
Trails B	Intercept	4.17	4.11	4.23	0.000		
	≥ 50 hrs	0.06	-0.03	0.15	0.179	15%	Yes
	within 2 days	-0.01	-0.11	0.09	0.871	-2%	No
Stroop	Intercept	42.69	41.42	43.96	0.000		
	≥ 50 hrs	-1.96	-3.66	-0.25	0.025	-18%	Yes
	within 2 days	4.97	2.01	7.94	0.001	46%	No
L-N Sequencing	Intercept	10.85	10.50	11.20	0.000		
	≥ 50 hrs	-0.17	-0.72	0.39	0.557	-5%	Yes
	within 2 days	0.53	-0.26	1.32	0.191	16%	No
COWA	Intercept	37.39	35.63	39.15	0.000		
	≥ 50 hrs	-1.45	-3.45	0.56	0.157	-9%	Yes
	within 2 days	3.03	0.47	5.59	0.020	18%	No
Raven's Matrices	Intercept	30.17	29.54	30.79	0.000		
	≥ 50 hrs	0.00	-0.77	0.77	0.999	0%	N/A
	within 2 days	0.32	-0.87	1.50	0.600	3%	No
Rey AVLT	Intercept	51.76	50.23	53.29	0.000		
	≥ 50 hrs	-3.00	-5.56	-0.44	0.022	-26%	Yes
	within 2 days	2.23	-0.79	5.26	0.147	20%	No
Rey AVLT % retained	Intercept	83.04	80.23	85.86	0.000		
	≥ 50 hrs	-3.41	-8.20	1.37	0.162	-15%	Yes
	within 2 days	7.82	2.95	12.69	0.002	35%	No
Rey O Copy	Intercept	27.80	27.17	28.43	0.000		
	≥ 50 hrs	-0.03	-0.97	0.90	0.947	-1%	Yes
	within 2 days	1.39	-0.43	3.21	0.134	26%	No
Rey O % retained	Intercept	63.43	61.19	65.68	0.000		
	≥ 50 hrs	0.11	-4.08	4.30	0.959	1%	No
	within 2 days	-6.14	-14.04	1.76	0.128	-29%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.61	1.65	0.000		
	≥ 50 hrs	0.01	-0.03	0.04	0.761	3%	Yes
	within 2 days	0.01	-0.04	0.06	0.659	7%	Yes
Grooved Pegboard Non-Preferred	Intercept	1.68	1.66	1.70	0.000		
	≥ 50 hrs	0.02	-0.01	0.04	0.175	10%	Yes
	within 2 days	0.01	-0.02	0.05	0.437	9%	Yes

Table V.6. Regression models of the effect of combined maintenance work on neuropsychological performance^a (Continued)

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome		p-value	% SD ^c	DIR ^d
		β	95% CI ^b			
BDI	Intercept	3.93	3.18 4.69	0.000		
	≥50 hrs	1.02	-0.39 2.43	0.156	18%	Yes
	within 2 days	0.01	-3.20 3.23	0.993	0%	N/A
STAI (S)	Intercept	28.45	27.23 29.67	0.000		
	≥50 hrs	1.66	-0.50 3.82	0.132	17%	Yes
	within 2 days	0.21	-3.68 4.09	0.918	2%	Yes
STAI (T)	Intercept	29.76	28.50 31.02	0.000		
	≥50 hrs	2.37	0.27 4.48	0.027	23%	Yes
	within 2 days	0.61	-2.06 3.27	0.657	6%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

Table V.7. Regression models suggesting an interaction between age and maintenance, commercial fishers ≥ 55 years old (n=177), North Carolina, 1999-2001 ^a

Variable	β	95% CI ^b		p-value	%SD ^c	DIR ^d
		Lower	Upper			
Rey O Copy						
Intercept	28.19	27.57	28.80	0.000		
>50 hours	0.80	-0.20	1.81	0.117	15%	
Within 5 days	1.19	0.06	2.32	0.040	22%	
1-10 hours	0.35	-0.24	0.94	0.241	7%	
10-50 hours	0.10	-0.62	0.82	0.785	2%	
>55 years	-1.99	-3.16	-0.82	0.001	-38%	
Age*50 hours	-1.18	-2.41	0.05	0.059	-22%	Yes
Grooved Pegboard Non Preferred						
Intercept	1.66	1.64	1.67	0.000		
>50 hours	-0.02	-0.04	0.01	0.284	-10%	
Within 5 days	-0.03	-0.05	0.00	0.092	-16%	
1-10 hours	0.01	-0.01	0.03	0.248	7%	
10-50 hours	0.01	-0.01	0.03	0.158	9%	
>55 years	0.13	0.09	0.17	0.000	80%	
Age*50 hours	0.05	0.01	0.08	0.008	28%	Yes
State Anxiety Inventory						
Intercept	30.23	28.85	31.61	0.000		
>50 hours	-0.07	-2.35	2.21	0.953	-1%	
Within 5 days	-0.72	-2.72	1.28	0.479	-7%	
1-10 hours	0.43	-0.81	1.66	0.498	4%	
10-50 hours	0.90	-0.36	2.16	0.160	9%	
>55 years	-2.09	-4.01	-0.18	0.032	-20%	
Age*50 hours	3.87	1.42	6.33	0.002	37%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

VI. Summary

A. Overview

The overall goal of my research was to characterize occupational exposure to organic solvents among commercial fishers in North Carolina and determine the effect of this exposure on their neuropsychological function. To this end, three studies were carried out that addressed specific research aims. These studies were a fuel emissions exposure assessment (see Chapter III), an analysis of maintenance work involving solvent exposure and self-reported symptoms (see Chapter IV) and an analysis of maintenance work and neuropsychological outcomes (see Chapter V). In addition, a supplemental assessment of the types and uses of fiberglass boat repair chemicals used was conducted (see Chapter I.A.2).

The objective of the fuel exposure assessment study was to characterize exposure to marine engine emissions using benzene as a marker and to determine predicted exposure levels across categories of carbureted 2-stroke, 4-stroke and diesel engines. A self-monitoring approach was used to obtain measurements of personal exposure to benzene over time. Passive monitors packed with Tenax were thermally desorbed and analyzed with a gas chromatograph equipped with a photoionization detector (GC-PID). Personal exposure data were log-transformed and mixed-effect linear regression methods were used to predict exposure levels and determine restricted maximum likelihood estimates (REML) for within- and between-person variance components. Predicted exposure levels to fishers on boats equipped with 2-stroke, 4-stroke, and diesel engines were 50.1, 32.6 and 27.9 $\mu\text{g}/\text{m}^3$, respectively. A significant fixed effect for refueling a car or truck was identified. The between-person variance component was 0.25 and the within-person variance component was 0.61 indicating that the majority of the variation may be attributable to factors related to work practices, monitor placement or environmental conditions that change over time. Despite sample size limitations, this study suggests that personal exposure to benzene is higher when fishing on a boat equipped with a 2-stroke engine compared to a 4-stroke engine. However, no differences in neuropsychological test performance were observed across categories of engine type (see Appendix 4).

The relationship between the most frequently reported maintenance activities involving exposure to organic solvents, such as fuel and styrene, and self-reported

neuropsychological symptoms among commercial fishers was also investigated. Data from a longitudinal cohort study of 238 commercial fishers generating 13,028 person-interviews were analyzed. Crude and adjusted rate ratios for 21 symptoms across 9 different maintenance exposure indices were estimated with Poisson regression methods. Fishers reported higher rates of all symptoms in weeks they did maintenance work involving solvents compared to weeks they did not. Rate ratios describing associations between fuel exposure and neuropsychological symptoms were the highest, ranging from 2.2 (95% CI: 1.4-2.8) to 4.1 (95% CI: 2.9-6.0). Although self-reported symptoms have limitations as measures of disease status, they offer a direct reflection of the participant perception of function and may indicate the early stages of nervous system disease. More research is needed to determine if the associations reported were causal, however.

The objective of the final study was to determine the association of both cumulative (over 5-7 months) and recent solvent exposure during maintenance work with neuropsychological test performance. Again, the most frequently reported maintenance activities, repairing fiberglass boats with styrene based resins and exposure to fuel via inhalation and skin contact during motor or mechanical work, were the focus of the exposure assessment. The effect of all solvent-related maintenance work reported including painting, applying tar, repairing a fiberglass boat, and performing mechanical work combined was also investigated. The analysis dataset consisted of 723 observations among 219 fishers. Multivariate models appropriate for longitudinal data and repeat outcome measures were specified to determine the regression coefficients describing the relationship between exposure and neuropsychological performance. Analyses of maintenance work and neuropsychological function among a potentially sensitive subgroup, those ≥ 55 years old, were conducted. Multiplicative interactions between fuel exposure and alcohol among those ≥ 55 years old, as well as styrene exposure and BMI were tested. No strong or consistent relationship between self-reported exposure to solvents during maintenance work and objective neuropsychological performance was observed.

B. Discussion

1. Exposure Assessment

Exposure to organic solvents including fuel emissions and fiberglass repair chemicals such as styrene was documented in this population, which was predominantly composed of commercial fishers. The predicted personal exposure to benzene from fuel emissions while fishing was increased among fishers operating boats with 2-stroke engines ($50 \mu\text{g}/\text{m}^3$) compared to fishers operating boats with 4-stroke engines ($33 \mu\text{g}/\text{m}^3$) and the general population living in urban areas ($15 \mu\text{g}/\text{m}^3$). (Wallace 1996) Exposure to neurotoxic agents during maintenance work was also documented. The frequency and duration of the maintenance work reported by participants are summarized in Table VI.1. According to estimates based on NC SEARCH weekly or biweekly telephone interviews, approximately one half of the participants reported that they performed motor or mechanical work at least 6 times per year, cleaned equipment or hands with gasoline at least once per year and did fiberglass repair projects at least once per year. Estimates from the qualitative fiberglass repair chemical exposure assessment were higher but they were based on responses from a subgroup of NC SEARCH participants who agreed to participate in a supplemental study of fiberglass repair chemicals. A few people, however, reported solvent related maintenance activities much more frequently (up to 52 times per year). There was a great deal of variation in the cumulative hours of exposure per year with some people spending minutes and others spending more than 1000 hours.

Associations between maintenance work and symptoms indicative of cognitive effects were observed among this cohort of commercial fishes. A multiplicative interaction between age, alcohol and fuel exposure in the study of symptoms and maintenance work was also observed. However, when the association between recent and cumulative hours of maintenance work with neuropsychological function was investigated further using standardized objective neuropsychological test outcomes, no strong or consistent relationship was evident. In addition, no differences in neuropsychological test performance were observed across categories of engine type despite the higher benzene level predicted for 2-stroke engines.

2. Methodological Challenges and Interpretation of Findings

Both the study of maintenance work and symptoms and the study of maintenance work and neuropsychological test performance were analyses of the effects of recent organic solvent exposure. For the symptoms study, the associations between maintenance work and symptoms reported during the same weekly or biweekly interview period were estimated. In order to estimate the association between maintenance work and neuropsychological test score, exposure within 2 to 5 days and cumulative exposure during the 5 to 7 month period preceding the neuropsychological exam were determined.

Acute exposure is known to cause central nervous system depression and involves a range of neuropsychological symptoms from mild reversible cognitive impairment to residual impairment lasting years after an accidental solvent intoxication episode. (Hartman 1995; NIOSH 1987; Stollery 1996) Even though the causal relationship between acute solvent exposure and the symptoms that were reported has been firmly established (Hartman 1995; NIOSH 1987), the question of whether the association is causal in this population is relevant. Symptoms may mark the early stages of disease that cannot be measured by neuropsychological testing. (Hartman 1995) Acute neuropsychological symptoms linked to recent maintenance work may forewarn of solvent-related nervous system diseases in old age, if repeated exposure occurs over a lifetime. Older workers, who experience nerve cell loss related to aging, have a higher susceptibility to both acute and delayed effects of solvent exposure. (Kieswetter and others 2000)

With the exception of acute intoxication episodes that result in permanent neuropsychological impairment, cumulative exposure during a lifetime as well as age during exposure are important determinants of the extent of the central nervous system damage caused by exposure to organic solvents. Cumulative lifetime exposure, which is a function of time-varying personal exposure level and duration of exposure, was not estimated in this study. In fact, accurately estimating this parameter remains one of the greatest challenges in occupational epidemiology. To further complicate research on the neuropsychological effects of solvents, the exposure levels capable of producing reversible versus irreversible effects and the length of time impairments persist is not known. Attempts to define

biologically relevant exposure categories often results in misclassification. Ideally, cumulative exposure should be defined such that higher short-term exposures capable of causing persistent decrements in neuropsychological performance are grouped with longer-term exposures capable causing of similar decrements. Exposure estimates based on duration without documenting the change in exposure level over time, inevitably result in misclassification. Unfortunately, it is prohibitively expensive to measure the time-varying personal exposure over a lifetime so estimation is necessary.

Findings from a recent study of printing plant workers are similar to those observed in this study of commercial fishers. (Kieswetter and others 2000) Kieswetter and colleagues found that symptom reports were increased if high exposure to organic solvents and lead was combined with age greater than 54 years but when they tried to reproduce their results using neurobehavioral test performance as the outcome, the highest exposed and oldest group was observed to perform the best. (Kieswetter and others 2000) These investigators suggest that the oldest toluene exposed population, who had the highest scores on tests of learning and intelligence, may have benefited from reductions in occupational exposures and recovered from any solvent-related decrements in neuropsychological test performance. (Kieswetter and others 2000)

Although p-values were presented in the analyses of maintenance work and neuropsychological test score, the analytical approach involved evaluating the trend by considering both effect size and direction. There is little consensus in the scientific community regarding whether significance testing is appropriate when multiple comparisons are made to describe observational data. (Savitz and Olshan 1998; Thompson 1998) In this study, of the eight largest effects ($\geq 25\%$ of the SD in the unexposed), four were statistically significant using a critical p-value of 0.0125 that is adjusted for multiple comparisons (0.05/4 CNS domains). These effects are listed below:

1. Cumulative fiberglass boat repair work (≥ 10 hours) was associated with a 0.10 log second (1.1 second) decrease on the Trails B;
2. recent fiberglass boat repair work (within 5 days) was associated with an 11% increase on the Rey AVLT % retained;

3. recent cleaning hands or equipment with gasoline (within 5 days) was associated with a 9% increase in the Rey AVLT % retained;
4. recent combined maintenance exposures (within 2 days) were associated with a 5 point increase on the Stroop;

In addition, cumulative fiberglass boat repair work (≥ 10 hours) was significantly associated with a 2-point decrease on the stroop (19% of the SD in the unexposed). The statistically significant effects were among the largest. Given the well-established link between acute exposure to organic solvents such as fuel and styrene (ACGIH 2001; NIOSH 1987; Reese and Kimbrough 1993), the significant effects for recent exposure were not in the anticipated direction. Reliance on significance testing alone and failure to consider the direction of the effect may have lead to spurious conclusions.

Neuropsychological testing to may not be adequately sensitive or specific to measure the subtle effects of chemical exposure. One of the challenges in the field of neuropsychology is how to establishment pre-morbid function so that the effect of exposure can be distinguished. (Hartman 1995) With large study sizes, it is hoped that subjects with different pre-morbid function will be evenly distributed across exposure groups.

Another challenge involves determining how factors associated with personality or mood influence test outcome. The pathway between solvent exposure, affective disorders, and performance on neuropsychological measures of executive function, learning and motor skills has not been firmly established. Over-reporting of neuropsychological symptoms (using neuropsychological testing as the gold standard) is associated with affective disturbances such as such as anxiety and depression. (O'Donnell and others 1993) This association to over-reporting raises questions about whether mood and anxiety may have confounded the association between solvent exposure and reporting symptoms of observed cognitive effects. However, affective disorders and cognitive problems may be coexisting phenomena, both caused by solvent exposure. Measuring personality factors such as trait anxiety as potential confounders has been suggested as a way to distinguish the effects of emotional lability (mood changes and anxiety) caused by solvents from innate personality characteristics. (Persson R and others 2000) However, another study suggests that long-term

exposure to organic solvents may cause personality abnormalities (increased neuroticism). (Chen and others 2001)

Performance on the WRAT-3 and measures of depression and anxiety were not treated as simple confounders in this research. Instead, the approach was to determine whether these factors were equivalent across exposure categories. Performance on the WRAT-3 test of reading ability did not appear to explain the findings. However, there was a tendency toward small decrements on measures of depression and anxiety in the cumulative exposure categories. Regardless of possible confounding effect anxiety and depression, both neuropsychological symptom reports and test performance are relevant to mood adjustment and quality of life.

2. External Validity

Almost all participants in NC SEARCH listed commercial fishing as their primary (88%) or secondary job (9%). The remaining participants worked on the water in another capacity (e.g. engineer, captain or crew on ferries, tug boats or charters). The demographic characteristics of the commercial fisher participants in NC SEARCH are summarized in Table VI.2. Cohort members are compared to North Carolina residents who listed their primary job is fisher and captain of a fishing vessel in the 1990 census. (Bureau of the Census 1992) In general, minorities are under-represented among cohort participants, there is a higher proportion of women and a higher proportion of fishers who report that their job title as captain. In addition, a smaller percentage of cohort participants report completing high school. The source population, commercial fishers in North Carolina, may have different patterns of exposure compared to cohort members due to these differences.

Cohort members may also be different from commercial fishers in North Carolina with regard to their interest in the outcome of the NC SEARCH study. Those who enrolled in the cohort study were volunteers. Biases may be present due to the volunteer aspect of the study and the self-reported nature of much of the data if participants had a vested interest in influencing the outcome of the study.

C. Conclusions

Relatively high personal exposure to fuel emissions among those using boats equipped with 2-stroke engines was documented in the study population. Although, refueling took minutes, the predicted personal exposure levels for those who refueled were more than double that of determined by their engine type alone. The differences in exposure based on boat type may be overwhelmed by other common sources of exposures such as refueling making it difficult to distinguish 24-hour personal exposure of commercial fishers from background. Exposure to fuel and fiberglass repair chemicals during maintenance activities, was also documented. Although personal exposure was not measured, the estimates of frequency and duration indicate that some participants may be highly exposed.

Although, the study of symptoms and maintenance work may have been influenced by reporting bias, the results were biologically plausible and have been reported in other populations. No large decrements predicted by maintenance work were observed when standardized objective neuropsychological testing was used to measure neuropsychological function. Strong and consistent results would have provided information on the effect of solvent exposure during the months preceding the neuropsychological exam. Studies designed to determine resolve issues regarding the chronic effects of solvent exposure and their reversibility should ideally incorporate detailed longitudinal exposure assessment with a retrospective component and lengthy follow up periods including exposure free time.

D. References

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Table VI.1. Frequency and duration of maintenance work among fishers who reported maintenance work during weekly or biweekly telephone interviews, North Carolina, 1999-2001

Maintenance Activity (% reporting)	Frequency		Duration	
	Frequency, median (range)		Cumulative hrs, median (range)	
	Sub-study ^a Times / year	NC SEARCH Times / year	NC SEARCH Avg. per week	NC SEARCH Avg. per year
Fiberglass Work (52-72%)	N/A	3 (1-38)	0 (0-22)	6 (1-539)
Resins (57%)	3 (0-100)	N/A		
Gelcoat (28%)	1 (0-35)	N/A		
Motor or mechanical work (85%)	N/A	10 (1-52)	0 (0-16)	24 (0.5-1072)
Cleaning hands or equipment with gasoline (57%)	N/A	4 (1-37)	0 (0-1) ^a	2 (1-27) ^b

^a Qualitative exposure assessment on fiberglass repair chemicals (see Chapter I.A.2)

^b Since this activity takes only minutes, the numbers listed here are the number of times per week and number of time over 5-7 months.

Table VI.3. Comparison of cohort participants to commercial fishers in North Carolina

	Commercial Fisher Participants, 1999-2001	1990 Census Data
Characteristic	N (%)	N (%)
Total	228 ^a (100%)	3417 (100%)
Gender		
Male	199 (87%)	3207 (94%)
Female	29 (13%)	210 (6%)
Captain	38% ^b	333 (9%)
Fisher	62%	3084 (91%)
Mean Age	43 (18-65)	41 (16-85)
Race		
White	227 (>99%)	3183 (93%)
Non-white	1 (<1%)	234 (7%)
Education		
Completed high school	166 (73%)	3138 (92%)
Less than High School	62 (27%)	279 (8%)

^aNumber of cohort participants included in the analysis

^bData on job title collected for an ongoing study of injuries among commercial fishers (n=119). (Loomis 2001)

APPENDIX 1

Fiberglass Boat Repair Questionnaire

FIBERGLASS BOAT REPAIR CHEMICAL QUESTIONNAIRE

Part I: Fiberglass Work

1. Do you ever do fiberglass boat repair work? Yes.....1 No.....0, skip to Part II, page 3 of Questionnaire (not included)
2. We would like to ask you a few questions about the resins, hardeners, gel coats and cleaners you use for fiberglass repair work. We will ask about four products, please focus on the ones you use most often.

Product 2A	1) What is the name of the product that you use most often for fiberglass repair work?	3) Is this product a: 1=Resin 2=Hardener 3=Gel Coat 4=Cleaner 5=Other 3a) If other, what is it? _____	4) Briefly describe how you use this product, for example: do you apply it with a brush or rag?; do you spray it on?
	2) Who is the manufacturer?		5) How many times in the last year have you used it? _____ (times)
			6) Approximately when did you use this product last? _____ (mm/yy)
			7) Please describe the repair job you did:
8) Do you use any other products for fiberglass boat repair? Yes / No (If NO, prompt for cleaner)			

Product 2B	1) What is the name of the product that you use next most often for fiberglass repair work?	3) Is this product a: 1=Resin 2=Hardener 3=Gel Coat 4=Cleaner 5=Other 3a) If other, what is it? _____	4) Briefly describe how you use this product, for example: do you apply it with a brush or rag?; do you spray it on?
	2) Who is the manufacturer?		5) How many times in the last year have you used it? _____ (times)
		6) Approximately when did you use this product last? _____ (mm/yy)	
		7) Please describe the repair job you did:	
8) Do you use any other products for fiberglass boat repair? Yes / No (If NO, prompt for cleaner)			
Product 2C	1) What is the name of the product that you use next most often for fiberglass repair work?	3) Is this product a: 1=Resin 2=Hardener 3=Gel Coat 4=Cleaner 5=Other 3a) If other, what is it? _____	4) Briefly describe how you use this product, for example: do you apply it with a brush or rag?; do you spray it on?
	2) Who is the manufacturer?		5) How many times in the last year have you used it? _____ (times)
		6) Approximately when did you use this product last? _____ (mm/yy)	
		7) Please describe the repair job you did:	
8) Do you use any other products for fiberglass boat repair? Yes / No (If NO, prompt for cleaner)			

Product 2D	1) What is the name of the product that you use next most often for fiberglass repair work?	3) Is this product a: 1=Resin 2=Hardener 3=Gel Coat 4=Cleaner 5=Other 3a) If other, what is it? _____	4) Briefly describe how you use this product, for example: do you apply it with a brush or rag?; do you spray it on?
	2) Who is the manufacturer?		5) How many times in the last year have you used it? _____ (<i>times</i>)
			6) Approximately when did you use this product last? _____ (<i>mm/yy</i>)
			7) Please describe the repair job you did:

APPENDIX 2

Fuel Study Recruitment Flyer

NC S.E.A.R.C.H. Fuel and Fiberglass Repair Chemical Air Monitoring Project

Exposure to organic solvents can affect learning and memory and some have suggested that the Pfiesteria toxin might produce symptoms similar to those seen in people who have breathed too much organic solvent vapor.

We are launching a new project to measure organic solvents commonly used by commercial fishers to see how much of these solvents get into the air. We also want to know if the measured level of exposure is associated with effects on learning and memory. The organic solvents included in the study are:

- ◆ Gasoline and diesel fuel
- ◆ Styrene found in the resins and gel coats used during fiberglass repair work
- ◆ Acetone used for cleaning styrene based resins

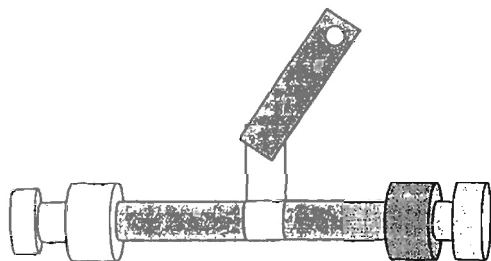
If you would like to participate in this project, we will give you a monitoring device for measuring fuel during your next clinic visit. You would clip the monitor to your shirt the next time you fish, write down some information about your work practices on that day and send the monitor back for analysis. We will send you another monitor by mail on a randomly selected day for a second round of sampling.

If you are planning to do fiberglass repair work within a few weeks of your clinic visit, you may be able to measure the chemicals used during this work as well. The two types of monitors are pictured below.

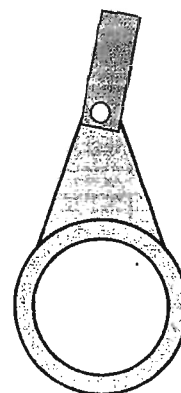
In order to compensate you for the time involved, we will give you \$25.00 for each measurement you complete.

If you have any questions, please call Ellen Kirrane toll free at 1-877-377-7129. Thank you very much for considering the project!

**Fuel Exposure Monitor
(about 4 inches long)**



**Fiberglass Chemicals Monitor
(about 3 inches from top to bottom)**



APPENDIX 3

Fuel Exposure Assessment Questionnaire

Work Activity Questionnaire

Study ID #: _____

1. Date you used the monitor: _____
2. Daily Activity Log: Please list your work activities from the time you opened the monitor at the beginning of your workday until you closed it at the end of the day. Include activities such as driving to the dock, buying bait, loading coolers and ice, motoring out to fishing grounds, fishing, packing fish and sorting catch back on the dock.

Time (circle a.m. or p.m.)	Work Activity
_____ a.m./p.m.	<i>Opened the monitor</i>
_____ a.m./p.m.	1.
_____ a.m./p.m.	2.
_____ a.m./p.m.	3.
_____ a.m./p.m.	4.
_____ a.m./p.m.	5.
_____ a.m./p.m.	6.
_____ a.m./p.m.	7.
_____ a.m./p.m.	8.
_____ a.m./p.m.	9.
_____ a.m./p.m.	10.
_____ a.m./p.m.	<i>Closed the monitor</i>

3a. Answer the questions below about the monitoring day:

If you fished, what type of fishing did you do? (Check all that apply.)	What type of gear did you use? (Check all that apply.)	How much time did you spend fishing with this type of gear?	
Finfishing _____	Gill Netting _____ Pound Net _____ Hook and Line _____ Long Hauling _____ Other _____ Specify: _____	Hours _____	Minutes _____
Oystering _____	Hand Tongs _____ Dredging _____ Other _____ Specify: _____	Hours _____	Minutes _____
Crabbing _____	Pots _____ Trot Lines _____ Dredging _____ Netting _____ Shedding _____ Other _____ Specify: _____	Hours _____	Minutes _____
Clamming _____	Raking _____ Dredging _____ Hand Tongs _____ Other _____ Specify: _____	Hours _____	Minutes _____
Shrimping _____	Trawler _____ Other _____ Specify: _____	Hours _____	Minutes _____
Other Fishing _____ Specify: _____	Seine Nets _____ Other _____ Specify: _____	Hours _____	Minutes _____

3b. Did you work on the boat motor or other mechanical equipment on the day you did the monitoring? Yes ___ No ___

If yes, what mechanical equipment? _____

How long did you spend working on mechanical equipment? ___ hours ___ minutes

Did you use gasoline to clean your hands or equipment? Yes ___ No ___

Did you use mineral spirits to clean your hands or equipment? Yes ___ No ___

4. Did you use any chemicals such as paints or pesticides while you were wearing the monitor? Yes ___ No ___

If yes, what chemicals? _____

5. Did you put fuel in your car or truck while wearing the monitor? Yes ___ No ___

6. On the monitoring day, did you smoke any cigarettes? Yes ___ No ___

If yes, how many? ___ Did you smoke cigars? Yes ___ No ___ A pipe? Yes ___ No ___

7. Do you work full time as a commercial fisher? Yes ___ No ___

8. How long have you worked as a commercial fisher? _____ Years

9. How many years have you worked full time as a commercial fisher? _____ Years

10. Did you have any problems using the monitor? Yes ___ No ___

If yes, please describe the problems:

IF YOU DID ANY FISHING DURING THE MONITORING DAY ANSWER THE FOLLOWING QUESTIONS?

11. Please describe the boat you used (on the monitoring day).

Length _____ (feet)

Type of engine: Outboard ___
Inboard ___ If inboard, gasoline ___ or diesel ___?

Was it a two stroke engine? Yes ___ No ___

Was it a four stroke engine? Yes ___ No ___

Does the boat have a cabin? Yes ___ No ___

What equipment do you have on the boat? (GPS, Mechanical Winch etc.) _____

12. Do you own this boat? Yes ___ No ___

13. Did you put fuel in the boat's tank while wearing the monitor? Yes ___ No ___

If yes, how much? _____ gallons

What size is the fuel tank? ___ gallons

How long were your standing at the pump? _____ minutes

14. Was the boat motor off at any time when you were out fishing? Yes ___ No ___

If yes, how long? ___ hours ___ minutes

15. Was the boat motor on idle at any time when you were out fishing? Yes ___ No ___

If yes, how long? ___ hours ___ minutes

16. On average, how fast did the boat travel? _____

APPENDIX 4

Summary of Finding Reported by Grattan and Colleagues

Table Appendix 4.1. Summary of finding reported by Grattan and Colleagues ^a

Study Population		Outcome	Summary of Results
Exposed Group (n=22)	Unexposed (Comparison) Group (n=8)		
Direct contact with the Pokomoke or other estuaries during fish kill events: high (n=11), moderate (n=7) and low (n=4)	Occupational controls with no exposure	Detailed questionnaire on exposure history and symptoms	Highly exposed group was more likely to complain of neurological symptoms such as forgetfulness and reported significantly higher frequencies of headache, skin lesions, skin burning on contact with water compared to controls. .
High and moderate exposure groups (n=13)	N/A	Medical and laboratory tests	No consistent or unexpected abnormalities. Exposed people showed normal immunological function. Dermatological finding were consistent with reactive erythema or allergic or toxic reaction in 4 of 8 people evaluated.
Group for whom no explanation was available for symptoms (n=19)	Controls matched by age, sex, education and occupation (n=19)	Neuropsychological screening battery ^b	Mean Rey AVLT T-score, Stroop interference T-score and mean grooved pegboard T-score significantly higher among unexposed. Significant linear trend also observed. No significant difference on the mean Trails B.
Participants who returned for follow up (n=10)	Controls who returned for follow up (n=12)	Repeat testing of neuropsychological function after 10-12 weeks	Significant improvement noted on the Rey AVLT and the Stroop interference. Those with the worst initial scores showed the greatest improvement.
Most severely exposed who had residual impairment at 10-12 weeks (n=2)	N/A	Repeat testing of neuropsychological function after 6 months	Improvement on reported memory and normal performance on cognitive measures

^a Grattan L, Oldach D, Perl T, Lowitt M, Matuszak D, Dickson C, Parrot C, Shoemaker R, Kauffman C, Wasserman M and others. 1998. Learning and memory difficulties after environmental exposure to waterways containing toxin-producing *Pfiesteria* or *Pfiesteria*-like dinoflagellates. *The Lancet* 352(9127):532-539.)

^b The neuropsychological tests used by Grattan and colleagues are fully described in Chapter II.B.

APPENDIX 5

Excluded Benzene Personal Exposure Measurements

Table Appendix 5.1. Invalid personal exposure measurements excluded from study of fuel exposure study among commercial fishers, North Carolina, 2001

	Predictor of Exposure		Benzene Personal Exposure Level		
	Engine Type	Refueled	$\mu\text{g}/\text{m}^3$	Log ($\mu\text{g}/\text{m}^3$)	Geometric Mean (SD)
High Outliers	4-Stroke	Yes	3147	8.05	8.13 (0.08)
	2-Stroke	Yes	3386	8.13	
	2-Stroke	Yes	3676	8.21	
Below LOQ ^a	4-Stroke		2.91	1.07	0.53 (1.17) ^b
	4-Stroke		2	0.69	
	Diesel		0.49	-0.70	
	Diesel	Yes	1.97	0.68	
	Diesel		1.04	0.04	
	Diesel		1.51	0.41	
	Diesel	Yes	0.75	-0.29	
	Diesel		1.28	0.24	
	2-Stroke		3.49	1.25	
	2-Stroke		6.11	1.81	
	2-Stroke		2.26	0.81	
	2-Stroke	Yes	13.28	2.59	
	2-Stroke	Yes	2.85	1.05	
	2-Stroke		0.42	-0.85	
	2-Stroke	Yes	0.54	-0.61	
	2-Stroke		0.12	-2.11	
	2-Stroke		14.95	2.70	
2-Stroke		2.4	0.87		
2-Stroke		1.7	0.53		

^a Limit of Quantitation

^b The LOQ varied depending on the analytical run. Tube were conditioned in batches and the peak size of the field blank(s), lab blank(s) (from the day the batch of tubes were conditioned) and recently conditioned monitors used for the zero standards were averaged to determine the LOQ (3 times the average peak).

Table Appendix 5.2. Unusable personal exposure data, excluded from study of fuel exposure study among commercial fishers, North Carolina, 2001

	Benzene Personal Exposure Level		
	$\mu\text{g}/\text{m}^3$	Log ($\mu\text{g}/\text{m}^3$)	Geometric Mean (SD)
Motor Work ^a	11.76	4.35	1.71 (1.53)
	3.77	2.46	
	4.90	1.33	
Engine Type NS ^b	77.77	3.67	N/A ^d
	11.76	4.35	
Worked as machinist	32.16	3.47	N/A ^d

^a Participants were recruited to measure their exposure to fuel while fishing or performing motor work (the most frequent sources of fuel exposure according to preliminary analysis). Since the determinants of exposure are different for fishing and motor work, separate models were to be run for each group. There were too few (n=3) measurements during motor work to fit a separate model, however.

^b Both engines were powered by gasoline but engine type (2-Stroke versus 4-Stroke) was not specified and participants were not reached during follow-up telephone calls.

^c Participant worked a full day as a machinist in addition to fishing.

^d Not Applicable

APPENDIX 6

Additional Analyses on Maintenance Work and Neuropsychological Test Outcomes

Table Appendix 6.1 Regression models of the effect of combined maintenance work, trigger visits excluded (n=442), commercial fishers, North Carolina, 1999-2001 ^a

Neuropsychological Test	Variable	Model			p-value	% SD ^c	DIR ^d
		Prediction of Test Outcome					
		β	95% CI ^b				
SDMT	Intercept	47.96	46.34	49.58	0.000		
	≥ 50 hrs	-1.41	-3.71	0.90	0.233	-5%	Yes
	within 5 days	3.11	0.02	6.21	0.048	11%	No
Trails B	Intercept	4.15	4.08	4.22	0.000		
	≥ 50 hrs	0.08	-0.02	0.19	0.110	21%	Yes
	within 5 days	-0.06	-0.16	0.05	0.276	-15%	No
Stroop	Intercept	43.12	41.60	44.64	0.000		
	≥ 50 hrs	-1.98	-4.02	0.06	0.058	-18%	Yes
	within 5 days	4.84	2.34	7.34	0.000	45%	No
L-N Sequencing	Intercept	10.91	10.46	11.35	0.000		
	≥ 50 hrs	-0.45	-1.13	0.24	0.201	-14%	Yes
	within 5 days	0.75	-0.24	1.74	0.139	23%	No
COWA	Intercept	37.61	35.52	39.71	0.000		
	≥ 50 hrs	-2.22	-4.55	0.12	0.063	-13%	Yes
	within 5 days	3.32	0.71	5.92	0.013	20%	No
Raven's Matrices	Intercept	29.91	29.11	30.71	0.000		
	≥ 50 hrs	0.21	-0.81	1.22	0.686	2%	No
	within 5 days	0.52	-0.45	1.50	0.293	6%	No
Rey AVLT	Intercept	51.51	49.72	53.29	0.000		
	≥ 50 hrs	-3.43	-6.34	-0.52	0.021	-30%	Yes
	within 5 days	2.40	-0.77	5.58	0.138	21%	No
Rey AVLT % retained	Intercept	84.78	81.79	87.78	0.000		
	≥ 50 hrs	-6.24	-11.72	-0.76	0.026	-28%	Yes
	within 5 days	6.92	1.65	12.19	0.010	31%	No
Rey O Copy	Intercept	28.33	27.64	29.02	0.000		
	≥ 50 hrs	-0.36	-1.40	0.68	0.499	-7%	Yes
	within 5 days	0.37	-0.78	1.51	0.529	7%	No
Rey O % retained	Intercept	61.68	58.91	64.46	0.000		
	≥ 50 hrs	2.96	-1.40	7.32	0.184	14%	No
	within 5 days	-2.86	-8.32	2.59	0.304	-14%	Yes
Grooved Pegboard Preferred	Intercept	1.61	1.59	1.64	0.000		
	≥ 50 hrs	0.03	0.00	0.07	0.092	19%	Yes
	within 5 days	-0.01	-0.05	0.03	0.665	-5%	No
Grooved Pegboard Non-Preferred	Intercept	1.68	1.66	1.71	0.000		
	≥ 50 hrs	0.02	-0.01	0.05	0.253	11%	Yes
	within 5 days	-0.01	-0.06	0.03	0.515	-9%	No

Table Appendix 6.1 (Continued)

Neuropsychological Test	Variable	Model Prediction of Test Outcome			p-value	% SD ^c	DIR ^d
		β	95% CI ^b				
BDI	Intercept	3.72	2.81	4.62	0.000		
	≥50 hrs	0.83	-0.76	2.42	0.306	14%	Yes
	within 5 days	0.51	-1.97	3.00	0.685	9%	Yes
STAI (S)	Intercept	27.78	26.28	29.28	0.000		
	≥50 hrs	2.21	-0.40	4.82	0.097	23%	Yes
	within 5 days	-0.67	-3.83	2.49	0.678	-7%	No
STAI (T)	Intercept	29.47	28.07	30.87	0.000		
	≥50 hrs	2.25	-0.07	4.56	0.058	21%	Yes
	within 5 days	-0.58	-3.52	2.35	0.696	-6%	No

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Reference cell coding was used so each beta coefficient represents the change in the test outcome for a 1-unit increase in the exposure variables compared to the non exposed.

^b 95% confidence interval for the beta coefficient.

^c Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^d DIR indicates whether the coefficient is in the expected direction.

Table Appendix 6.2. Regression models of the effect of cumulative and recent motor or mechanical work exposure on neuropsychological test performance ^a

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome				Model 2 (adjusted) ^b Prediction of Test Outcome					DIR ^c	
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c		p-value		% SD ^d
SMDT	Intercept	46.86	45.55	48.16	<0.001		45.01	43.59	46.42	<0.001		
	≥10 hrs	0.91	-0.29	2.11	0.139	3%	0.92	-0.20	2.04	0.106	3%	No
	within 5 days	-0.37	-1.96	1.23	0.651	-1%	-0.75	-2.19	0.69	0.308	-3%	Yes
Trails B	Intercept	4.20	4.16	4.25	<0.001		4.22	4.16	4.28	<0.001		
	≥10 hrs	-0.02	-0.07	0.03	0.409	-5%	-0.03	-0.09	0.02	0.269	-8%	No
	within 5 days	-0.04	-0.11	0.03	0.321	-9%	-0.01	-0.07	0.05	0.699	-3%	No
Stroop	Intercept	41.87	40.78	42.96	<0.001		41.07	39.55	42.59	<0.001		
	≥10 hrs	-0.53	-1.55	0.49	0.305	-5%	-0.34	-1.52	0.84	0.569	-3%	Yes
	within 5 days	1.59	0.06	3.13	0.042	15%	1.15	-0.11	2.40	0.073	11%	No
L-N Sequencing	Intercept	10.72	10.41	11.03	<0.001		11.50	11.05	11.94	<0.001		
	≥10 hrs	-0.07	-0.40	0.26	0.692	-2%	-0.23	-0.57	0.11	0.185	-7%	Yes
	within 5 days	0.12	-0.34	0.58	0.604	4%	0.02	-0.38	0.42	0.928	1%	No
COWA	Intercept	37.58	36.02	39.14	<0.001		36.12	33.93	38.31	<0.001		
	≥10 hrs	-0.74	-1.94	0.47	0.232	-4%	0.03	-1.34	1.40	0.967	0%	Yes
	within 5 days	-0.03	-1.61	1.54	0.968	0%	-0.53	-2.18	1.12	0.531	-3%	Yes
Raven's Matrices	Intercept	29.78	29.24	30.33	<0.001		29.76	29.00	30.51	<0.001		
	≥10 hrs	0.55	0.04	1.06	0.036	6%	0.45	-0.11	1.02	0.117	5%	No
	within 5 days	-0.01	-0.69	0.67	0.978	0%	-0.18	-0.80	0.45	0.584	-2%	Yes
Rey AVLT	Intercept	50.52	49.37	51.67	<0.001		51.86	50.13	53.58	<0.001		
	≥10 hrs	-1.20	-2.76	0.36	0.132	-11%	-0.51	-1.97	0.94	0.489	-5%	Yes
	within 5 days	1.30	-0.31	2.91	0.113	11%	1.02	-0.49	2.52	0.186	9%	No
Rey AVLT % retained	Intercept	82.17	80.23	84.12	<0.001		83.91	80.27	87.54	<0.001		
	≥10 hrs	-0.18	-2.59	2.24	0.886	-1%	1.65	-1.55	4.85	0.312	7%	No
	within 5 days	4.79	0.62	8.96	0.024	22%	5.43	1.16	9.71	0.013	24%	No
Rey O Copy	Intercept	27.85	27.36	28.34	<0.001		28.03	27.23	28.84	<0.001		
	≥10 hrs	0.00	-0.55	0.56	0.993	0%	0.06	-0.59	0.71	0.857	1%	No
	within 5 days	0.78	-0.04	1.59	0.063	15%	0.77	-0.02	1.57	0.057	15%	No

Table Appendix 6.2. (Continued)

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome				Model 2 (adjusted) ^b Prediction of Test Outcome					DIR ^e	
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c		p-value		% SD ^d
Rey O % retained	Intercept	62.75	60.68	64.82	<0.001		57.28	54.00	60.57	<0.001		
	≥10 hrs	0.74	-2.14	3.63	0.613	4%	2.53	-0.33	5.40	0.083	12%	No
	within 5 days	-3.18	-6.23	-0.14	0.041	-15%	-3.72	-6.73	-0.72	0.015	-18%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.62	1.65	<0.001		1.68	1.65	1.70	<0.001		
	≥10 hrs	0.00	-0.02	0.02	0.882	0%	-0.01	-0.03	0.01	0.239	-7%	No
	within 5 days	-0.01	-0.04	0.01	0.358	0%	0.00	-0.02	0.02	0.905	-1%	No
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	<0.001		1.73	1.70	1.75	<0.001		
	≥10 hrs	0.00	-0.02	0.02	0.958	0%	-0.01	-0.03	0.01	0.482	-5%	No
	within 5 days	-0.01	-0.03	0.01	0.419	0%	0.00	-0.02	0.02	0.858	-1%	No
BDI	Intercept	3.90	3.34	4.46	<0.001		4.47	3.41	5.53	<0.001		
	≥10 hrs	0.33	-0.38	1.05	0.362	6%	0.02	-0.84	0.87	0.966	0%	N/A
	within 5 days	0.77	-0.43	1.96	0.210	13%	0.84	-0.32	2.00	0.158	14%	Yes
STAI (S)	Intercept	28.42	27.52	29.33	<0.001		28.41	26.48	30.33	<0.001		
	≥10 hrs	0.92	-0.40	2.24	0.174	10%	0.82	-0.80	2.44	0.323	9%	Yes
	within 5 days	-0.15	-2.13	1.83	0.879	-2%	0.18	-1.81	2.17	0.858	2%	Yes
STAI (T)	Intercept	30.18	29.19	31.17	<0.001		30.61	29.00	32.22	<0.001		
	≥10 hrs	0.56	-0.51	1.63	0.301	5%	0.83	-0.41	2.08	0.190	8%	Yes
	within 5 days	0.39	-1.16	1.94	0.623	4%	0.51	-0.97	1.99	0.501	5%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Each beta coefficient represents the change in the test outcome for a one unit increase in the exposure variables.

^b Model 1 is does not include covariates. Model 2 included covariates for age, gender, training effect, education, and technician. The RAVLT is also adjusted for version.

^c 95% confidence interval for the beta coefficient.

^d Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^e DIR indicates whether the the coefficient is in the anticipated direction.

Table Appendix 6.3. Regression models of the effect of cumulative and recent fiberglass boat repair work exposure on neuropsychological test performance ^a

Neuropsychological Test	Variable	Model 1					Model 2 (adjusted) ^b					DIR ^c
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c		p-value	% SD ^d	
SMDT	Intercept	47.19	45.96	48.42	<0.001		45.10	43.73	46.46	<0.001		
	≥10 hrs	-0.95	-2.51	0.62	0.234	-3%	-0.59	-2.07	0.89	0.433	-2%	Yes
	within 5 days	0.53	-1.36	2.42	0.582	2%	0.34	-1.52	2.20	0.719	1%	No
Trails B	Intercept	4.18	4.14	4.23	<0.001		4.21	4.16	4.26	<0.001		
	≥10 hrs	0.10	0.04	0.17	0.002	26%	0.04	-0.03	0.12	0.240	11%	Yes
	within 5 days	-0.07	-0.18	0.04	0.219	17%	-0.04	-0.13	0.06	0.488	-9%	No
Stroop	Intercept	41.97	40.94	43.01	<0.001		41.29	39.98	42.61	<0.001		
	≥10 hrs	-2.06	-3.63	-0.50	0.010	19%	-1.65	-3.18	-0.12	0.035	-15%	Yes
	within 5 days	2.22	-0.80	5.25	0.150	21%	1.83	-0.76	4.43	0.166	17%	No
L-N Sequencing	Intercept	10.74	10.44	11.04	<0.001		11.36	10.96	11.75	<0.001		
	≥10 hrs	-0.49	-0.91	-0.06	0.024	15%	-0.28	-0.70	0.14	0.195	-8%	Yes
	within 5 days	0.61	0.06	1.16	0.029	19%	0.38	-0.18	0.95	0.185	12%	No
COWA	Intercept	37.49	35.98	39.01	<0.001		36.57	34.59	38.55	<0.001		
	≥10 hrs	-1.82	-3.42	-0.22	0.026	11%	-1.33	-3.10	0.45	0.142	-8%	Yes
	within 5 days	1.31	-1.22	3.84	0.309	8%	0.82	-1.72	3.37	0.525	5%	No
Raven's Matrices	Intercept	29.95	29.43	30.47	<0.001		29.92	29.26	30.57	<0.001		
	≥10 hrs	-0.18	-0.85	0.48	0.587	2%	-0.08	-0.70	0.54	0.807	-1%	No
	within 5 days	0.79	-0.15	1.74	0.101	8%	0.68	-0.34	1.70	0.192	7%	No
Rey AVLT	Intercept	50.32	49.23	51.40	<0.001		51.67	50.20	53.13	<0.001		
	≥10 hrs	-1.24	-3.56	1.08	0.294	11%	-0.32	-2.51	1.87	0.775	-3%	Yes
	within 5 days	2.14	-1.82	6.10	0.290	19%	1.18	-1.94	4.31	0.459	10%	No
Rey AVLT % retained	Intercept	82.53	80.76	84.30	<0.001		84.83	81.71	87.96	<0.001		
	≥10 hrs	-3.48	-7.03	0.06	0.054	16%	-2.92	-6.85	1.02	0.146	-13%	Yes
	within 5 days	11.16	6.12	16.19	<0.001	50%	10.74	5.96	15.52	<0.001	48%	No
Rey O Copy	Intercept	27.90	27.43	28.37	<0.001		28.16	27.43	28.89	<0.001		
	≥10 hrs	-0.20	-1.19	0.80	0.699	4%	-0.11	-1.09	0.87	0.828	-2%	N/A
	within 5 days	1.19	-0.22	2.60	0.098	22%	1.15	-0.20	2.50	0.094	22%	No

Table Appendix 6.3. (Continued)

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome				Model 2 (adjusted) ^b Prediction of Test Outcome				DIR ^e		
		β	95% CI ^c		p-value	% SD ^d	B	95% CI ^c			p-value	% SD ^d
Rey O % retained	Intercept	62.71	60.84	64.59	<0.001		58.80	55.84	61.77	<0.001		
	≥10 hrs	0.92	-2.98	4.83	0.643	4%	1.26	-2.41	4.92	0.501	6%	No
	within 5 days	-3.23	-8.67	2.21	0.244	15%	-3.19	-8.33	1.95	0.224	-15%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.61	1.65	<0.001		1.67	1.64	1.69	<0.001		
	≥10 hrs	0.02	0.00	0.05	0.092	0%	0.02	0.00	0.04	0.116	11%	Yes
	within 5 days	0.00	-0.04	0.04	0.978	0%	0.00	-0.03	0.04	0.893	1%	Yes
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	<0.001		1.72	1.70	1.74	0.000		
	≥10 hrs	0.00	-0.03	0.03	0.880	0%	0.00	-0.03	0.03	0.994	0%	No
	within 5 days	-0.01	-0.06	0.03	0.584	0%	-0.01	-0.05	0.03	0.586	-7%	No
BDI	Intercept	4.00	3.45	4.56	<0.001		4.26	3.40	5.13	0.000		
	≥10 hrs	0.55	-0.69	1.79	0.381	10%	0.45	-0.80	1.70	0.479	8%	Yes
	within 5 days	0.14	-2.07	2.34	0.903	2%	0.13	-1.96	2.22	0.903	2%	Yes
STAI (S)	Intercept	28.51	27.63	29.38	<0.001		28.43	26.96	29.89	0.000		
	≥10 hrs	1.97	-0.56	4.51	0.127	21%	1.55	-1.06	4.15	0.244	16%	Yes
	within 5 days	0.05	-3.25	3.35	0.975	1%	0.39	-2.89	3.66	0.818	4%	Yes
STAI (T)	Intercept	30.19	29.22	31.16	<0.001		30.87	29.47	32.27	<0.001		
	≥10 hrs	2.12	0.31	3.92	0.021	20%	1.88	0.04	3.73	0.046	18%	Yes
	within 5 days	-0.22	-2.70	2.25	0.860	2%	0.00	-2.45	2.44	0.998	0%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Each beta coefficient represents the change in the test outcome for a one unit increase in the exposure variables.

^b Model 1 is does not include covariates. Model 2 included covariates for age, gender, training effect, education, and technician. The RAVLT is also adjusted for version.

^c 95% confidence interval for the beta coefficient.

^d Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^e DIR indicates whether the the coefficient is in the anticipated direction.

Table Appendix 6.4. Regression models of the effect of cumulative and recent skin contact with gasoline via cleaning hands or equipment on neuropsychological performance ^a

Neuropsychological Test	Variable	Model 1				Model 2 (adjusted) ^b				DIR ^c		
		Prediction of Test Outcome			% SD ^d	Prediction of Test Outcome			% SD ^d			
		β	95% CI ^e			p-value	β	95% CI ^e			p-value	
SMDT	Intercept	47.13	45.90	48.37	<0.001	45.19	43.78	46.60	<0.001			
	>=3 reports	-0.20	-1.93	1.54	0.823	-1%	0.45	-0.86	1.75	0.504	2%	N/A
	5 days	-0.23	-2.71	2.26	0.858	-1%	-0.07	-2.14	2.01	0.949	0%	N/A
Trails B	Intercept	4.19	4.15	4.23	<0.001	4.20	4.15	4.26	<0.001			
	>=3 reports	0.03	-0.04	0.10	0.477	6%	-0.01	-0.07	0.05	0.713	-3%	Yes
	5 days	0.03	-0.08	0.15	0.566	8%	0.04	-0.06	0.14	0.431	10%	Yes
Stroop	Intercept	41.91	40.87	42.94	<0.001	41.63	40.30	42.96	0.000			
	>=3 reports	-1.50	-3.32	0.32	0.106	-14%	-1.57	-2.68	-0.45	0.006	-15%	Yes
	5 days	1.69	-0.40	3.79	0.114	16%	2.06	0.53	3.58	0.008	19%	No
L-N Sequencing	Intercept	10.69	10.40	10.99	<0.001	11.39	10.99	11.80	0.000			
	>=3 reports	0.20	-0.42	0.82	0.532	6%	-0.10	-0.53	0.33	0.648	-3%	No
	5 days	0.08	-0.51	0.66	0.793	2%	0.04	-0.49	0.57	0.885	1%	Yes
COWA	Intercept	37.35	35.83	38.87	<0.001	36.62	34.57	38.67	0.000			
	>=3 reports	0.34	-1.33	2.02	0.688	2%	0.39	-1.14	1.92	0.618	2%	No
	5 days	-1.07	-3.03	0.88	0.282	-6%	-1.11	-3.17	0.95	0.292	-7%	Yes
Raven's Matrices	Intercept	29.93	29.41	30.45	<0.001	29.97	29.31	30.63	<0.001			
	>=3 reports	0.66	-0.22	1.54	0.141	7%	0.10	-0.53	0.74	0.746	1%	No
	5 days	-1.08	-2.11	-0.05	0.041	-11%	-0.92	-1.89	0.06	0.066	-10%	Yes
Rey AVLT	Intercept	50.17	49.09	51.26	<0.001	51.52	49.98	53.07	<0.001			
	>=3 reports	0.38	-2.13	2.89	0.765	3%	0.94	-0.69	2.56	0.258	8%	No
	5 days	1.80	-0.40	4.01	0.108	16%	1.41	-0.59	3.41	0.167	12%	No
Rey AVLT % retained	Intercept	82.18	80.38	83.97	<0.001	84.38	81.13	87.64	<0.001			
	>=3 reports	0.85	-3.65	5.35	0.711	4%	1.72	-2.51	5.95	0.427	8%	No
	5 days	8.91	3.82	14.01	0.001	40%	8.54	3.03	14.05	0.002	38%	No
Rey O Copy	Intercept	27.86	27.40	28.32	<0.001	28.29	27.60	28.98	<0.001			
	>=3 reports	0.42	-0.46	1.31	0.351	8%	-0.40	-1.19	0.39	0.318	-8%	No
	5 days	0.59	-0.54	1.73	0.305	11%	0.64	-0.55	1.83	0.290	12%	No

Table Appendix 6.4. Continued

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome				Model 2 (adjusted) ^b Prediction of Test Outcome				DIR ^e		
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c			p-value	% SD ^d
Rey O % retained	Intercept	62.88	60.97	64.79	<0.001		58.44	55.36	61.51	<0.001		
	>=3 reports	-1.04	-4.80	2.72	0.588	-5%	-1.14	-4.58	2.29	0.514	-5%	Yes
	5 days	-2.77	-9.47	3.93	0.418	-13%	-2.39	-8.87	4.09	0.469	-11%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.62	1.65	<0.001		1.67	1.65	1.70	<0.001		
	>=3 reports	0.02	-0.01	0.05	0.239	0%	-0.01	-0.04	0.01	0.186	-9%	Yes
	5 days	-0.01	-0.05	0.03	0.619	0%	-0.01	-0.04	0.03	0.737	-3%	No
Grooved Pegboard Non-Preferred	Intercept	1.69	1.68	1.71	<0.001		1.72	1.70	1.74	<0.001		
	>=3 reports	0.01	-0.01	0.03	0.363	0%	-0.01	-0.02	0.01	0.482	-4%	Yes
	5 days	0.01	-0.03	0.06	0.604	0%	0.01	-0.03	0.05	0.581	7%	Yes
BDI	Intercept	4.09	3.53	4.64	<0.001		4.35	3.47	5.22	<0.001		
	>=3 reports	-0.37	-1.59	0.84	0.548	-6%	-0.26	-1.17	0.65	0.572	-5%	No
	5 days	0.13	-1.15	1.41	0.844	2%	-0.07	-1.31	1.17	0.915	-1%	N/A
STAI (S)	Intercept	28.78	27.91	29.66	<0.001		28.16	26.60	29.72	<0.001		
	>=3 reports	-1.33	-3.06	0.40	0.132	-14%	0.31	-1.35	1.96	0.714	3%	No
	5 days	0.66	-1.88	3.20	0.612	7%	0.03	-2.64	2.69	0.984	0%	Yes
STAI (T)	Intercept	30.35	29.37	31.32	<0.001		30.83	29.39	32.26	<0.001		
	>=3 reports	0.12	-1.56	1.80	0.888	1%	0.58	-0.68	1.85	0.366	6%	Yes
	5 days	1.13	-0.94	3.20	0.286	11%	0.89	-1.20	2.97	0.406	8%	Yes

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Each beta coefficient represents the change in the test outcome for a one unit increase in the exposure variables.

^b Model 1 is does not include covariates. Model 2 included covariates for age, gender, training effect, education, and technician. The RAVLT is also adjusted for version.

^c 95% confidence interval for the beta coefficient.

^d Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^e DIR indicates whether the the coefficient is in the anticipated direction.

Table Appendix 6.5. Regression models of the effect of exposure to solvents during fiberglass boat repair, working on boat motors or mechanical equipment, painting and tar application on neuropsychological performance ^a

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome				Model 2 (adjusted) ^b Prediction of Test Outcome					DIR ^c	
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c		p-value		% SD ^d
SMDT	Intercept	47.68	46.21	49.15	0.000		45.09	43.61	46.57	0.000		
	≥ 50 hrs	-0.02	-2.09	2.05	0.984	0%	0.93	-0.87	2.74	0.310	-3%	Yes
	within 5 days	1.86	-0.18	3.89	0.074	7%	1.38	-0.47	3.23	0.143	5%	No
Trails B	Intercept	4.17	4.11	4.23	0.000		4.22	4.16	4.29	0.000		
	≥ 50 hrs	0.06	-0.03	0.15	0.175	15%	-0.01	-0.08	0.07	0.873	-2%	No
	within 5 days	-0.02	-0.12	0.09	0.763	-4%	0.02	-0.07	0.11	0.613	6%	Yes
Stroop	Intercept	42.70	41.43	43.97	0.000		41.36	39.79	42.93	0.000		
	≥ 50 hrs	-2.16	-3.87	-0.46	0.013	-20%	-1.05	-2.61	0.51	0.186	-10%	Yes
	within 5 days	3.70	1.85	5.54	0.000	34%	2.88	1.25	4.50	0.001	27%	No
L-N Sequencing	Intercept	10.85	10.49	11.20	0.000		11.43	10.98	11.88	0.000		
	≥ 50 hrs	-0.20	-0.74	0.35	0.481	-6%	-0.09	-0.59	0.41	0.725	-3%	Yes
	within 5 days	0.62	-0.02	1.27	0.058	19%	0.46	-0.15	1.07	0.140	14%	No
COWA	Intercept	37.40	35.63	39.17	0.000		35.90	33.66	38.15	0.000		
	≥ 50 hrs	-1.56	-3.55	0.42	0.122	-9%	-0.71	-2.71	1.29	0.488	-4%	Yes
	within 5 days	1.87	-0.21	3.95	0.078	11%	1.25	-0.99	3.48	0.274	7%	No
Raven's Matrices	Intercept	30.16	29.53	30.79	0.000		29.93	29.17	30.69	0.000		
	≥ 50 hrs	-0.01	-0.79	0.76	0.971	0%	0.22	-0.51	0.95	0.557	-2%	Yes
	within 5 days	0.52	-0.17	1.22	0.142	6%	0.25	-0.52	1.02	0.518	3%	No
Rey AVLT	Intercept	51.77	50.23	53.30	0.000		51.91	50.13	53.68	0.000		
	≥ 50 hrs	-3.08	-5.68	-0.49	0.020	-27%	-0.97	-3.24	1.29	0.400	-9%	Yes
	within 5 days	1.42	-0.63	3.46	0.175	12%	0.54	-1.21	2.29	0.543	5%	No
Rey AVLT % retained	Intercept	83.03	80.22	85.84	0.000		83.89	80.10	87.67	0.000		
	≥ 50 hrs	-3.90	-8.74	0.94	0.114	-18%	-1.01	-5.95	3.92	0.687	-5%	Yes
	within 5 days	8.46	4.14	12.78	0.000	38%	8.45	4.33	12.56	0.000	38%	No
Rey O Copy	Intercept	27.80	27.17	28.43	0.000		27.96	27.10	28.81	0.000		
	≥ 50 hrs	-0.10	-1.03	0.84	0.835	-2%	0.07	-0.85	0.99	0.881	1%	Yes
	within 5 days	1.20	0.03	2.36	0.044	23%	1.12	0.08	2.16	0.036	21%	No

Table Appendix 6.5. Continued

Neuropsychological Test	Variable	Model 1 Prediction of Test Outcome					Model 2 (adjusted) ^b Prediction of Test Outcome					DIR ^e
		β	95% CI ^c		p-value	% SD ^d	β	95% CI ^c		p-value	% SD ^d	
Rey O % retained	Intercept	63.43	61.19	65.68	0.000		57.83	54.46	61.19	0.000		
	≥50 hrs	0.37	-3.81	4.55	0.862	2%	2.30	-1.71	6.30	0.262	11%	No
	within 5 days	-4.78	-9.53	-0.02	0.049	-23%	-5.12	-9.36	-0.88	0.018	-24%	Yes
Grooved Pegboard Preferred	Intercept	1.63	1.61	1.65	0.000		1.67	1.65	1.70	0.000		
	≥50 hrs	0.00	-0.03	0.04	0.806	3%	-0.01	-0.04	0.02	0.516	-6%	No
	within 5 days	-0.02	-0.06	0.01	0.130	-14%	-0.01	-0.04	0.01	0.348	-8%	No
Grooved Pegboard Non-Preferred	Intercept	1.68	1.67	1.70	0.000		1.72	1.70	1.75	0.000		
	≥50 hrs	0.02	-0.01	0.04	0.207	10%	0.00	-0.03	0.02	0.807	-2%	No
	within 5 days	-0.03	-0.06	0.00	0.085	-17%	-0.02	-0.04	0.01	0.265	-9%	No
BDI	Intercept	3.93	3.18	4.68	0.000		4.51	3.37	5.64	0.000		
	≥50 hrs	1.00	-0.41	2.42	0.165	17%	0.65	-0.77	2.06	0.370	11%	Yes
	within 5 days	0.31	-1.49	2.11	0.735	5%	0.43	-1.34	2.20	0.636	7%	Yes
STAI (S)	Intercept	28.46	27.24	29.68	0.000		28.59	26.63	30.55	0.000		
	≥50 hrs	1.71	-0.46	3.88	0.122	18%	1.35	-0.77	3.46	0.211	14%	Yes
	within 5 days	-0.86	-3.47	1.76	0.521	-9%	-0.59	-3.15	1.98	0.653	-6%	No
STAI (T)	Intercept	29.78	28.51	31.04	0.000		30.64	28.97	32.32	0.000		
	≥50 hrs	2.38	0.27	4.49	0.027	23%	2.10	0.06	4.13	0.043	20%	Yes
	within 5 days	-0.82	-2.79	1.16	0.418	-8%	-0.64	-2.54	1.26	0.509	-6%	No

^a The GENMOD procedure in SAS was used to fit a longitudinal population average model. The intercept is the mean of the continuous test outcome transformed as shown in table V.1. Each beta coefficient represents the change in the test outcome for a one unit increase in the exposure variables.

^b Model 1 is does not include covariates. Model 2 included covariates for age, gender, training effect, education, and technician. The RAVLT is also adjusted for version.

^c 95% confidence interval for the beta coefficient.

^d Beta coefficient as a proportion of the standard deviation (SD) among the unexposed.

^e DIR indicates whether the the coefficient is in the anticipated direction.

APPENDIX 7

Mean Neuropsychological Test Score across Engine Type Categories

Table Appendix 6. Mean neuropsychological test score across engine type categories

Neuropsychological Test	Mean ^a (SD)		Range	
	2-Stroke	4-Stroke/Diesel	2-Stroke	4-Stroke/Diesel
SMDT	48.3 (9.0)	51.0 (10.6)	29-64	36-77
Trails B (log seconds)	4.1 (0.32)	4.1 (0.39)	3.6-4.7	3.5-5.3
Stroop	43.4 (7.2)	42.9 (7.0)	32-55	26-60
L/N Sequencing	10.2 (2.3)	10.6 (2.8)	7-15	6-17
COWA	40.0 (10.5)	40.7 (12.8)	28-68	18-76
Raven's Matrices	31.0 (3.2)	29.4 (4.8)	24-36	14-36
Rey AVLT	54.6 (10.4)	53.6 (10.1)	39-71	33-70
Rey AVLT % retained	82.3 (17.4)	85 (20.6)	50-100	0-100
Rey O copy	27.8 (3.6)	26.9 (4.1)	17.5-33	16-33
Rey-O % retained	62.9 (12.5)	67.3 (20.1)	39-83	31-114
Grooved Pegboard Preferred (log(sec-30))	1.6 (0.13)	1.6 (0.17)	1.4-2.0	1.4-2.2
Grooved Pegboard Non-preferred (log(sec-30))	1.6 (0.13)	1.6 (0.17)	1.4-2.0	1.4-2.2
BDI	3.3 (4.8)	2.7 (3.7)	0-18	0-13
STAI State	31.5 (9.0)	27.4 (6.9)	20-50	20-41
STAI Trait	32.5 (9.1)	29.2 (7.7)	20-51	20-46

^a Least mean square estimates, which were adjusted for practice effect, age, gender and education, were not substantially different from the estimates reported above. 2-Stroke engine did not predict test performance in multivariate regression models.