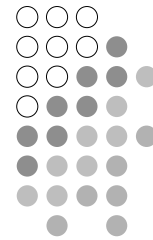


The Pesticide Cognition Study in Gulf War Veterans

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Boston University School of Public Health



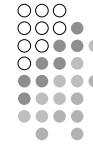
Collaborators and acknowledgements



- Roberta White, Ph.D. – BU School of Public Health
- William Bradford, MS – Parsons corp.
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- Callie Comtois – BU School of Public Health
- Terri Thompson – BU School of Public Health
- DOD Force Health Protections and Readiness office

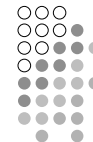
Funding – DoD Congressionally Directed Medical Research Program

Background: What do we know?



- Reports from our lab and others have indicated that many GW veterans have experienced adverse changes in health since their return from the war.
- Reported symptoms include: fatigue, memory disturbance, concentration difficulties, joint pain, gastrointestinal problems, skin rash and headache.
- In addition to health symptoms, research reports have documented differences in mood, motor speed, memory, attention and visuospatial functioning.

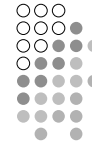
Why Study Pesticides?



- The RAND report suggested that acetylcholinesterase inhibitors including OP pesticides and pyridostigmine bromide (PB) may have contributed to the ill health effects of GW veterans.
- Institute of Medicine (IOM) report concluded that there is limited/suggestive evidence of an association between organophosphorus insecticide exposure and long term neurobehavioral effects at doses sufficient to cause poisoning.
- DoD Environmental Exposure Report- Pesticides concluded that 41,000 Gulf War veterans could have been over-exposed to pesticides during the war.

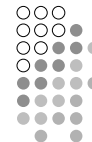
EER-pesticides http://www.gulflink.osd.mil/pesto/pest_exec_summary.htm

Health Symptoms and Cognitive Deficits in pesticide applicators



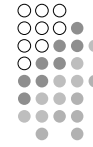
- Agricultural workers exposed to pesticides have shown deficits in cognitive domains similar to those in GW veterans including psychomotor slowing, visuospatial deficits, and mood complaints (Stephens, 1995; Steenland, 1994; Bazylewicz-walckzak, 1999).
- The Agricultural Health Study (AHS) reported significant associations between pesticides and reported neurological symptoms, respiratory problems and lung cancer in pesticide applicators (Lee, 2004; Kamel, 2005; Hoppin, 2006) .
- The AHS also reported the risk of suicide and accidental deaths were increased 2-fold in the highest pesticide exposed categories (Lee, 2007).

Acute Overexposure Effects



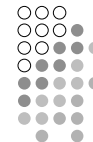
- Acute effects of organophosphate and carbamate pesticide overexposure can result in:
 - Nausea and vomiting
 - Dizziness, ataxia
 - Muscle cramps and weakness
 - Rashes and itching
 - Breathing difficulties
 - Convulsions, coma and death

Chronic Overexposure Effects



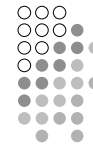
- Long term or chronic effects from OP and Carbamate overexposure include:
 - Cognitive and mood effects
 - Motor slowing
 - Fatigue
 - Joint and muscle pain
 - Sleep problems

What about chronic low to moderate level pesticide exposure?



- Several studies suggest that chronic low to moderate level exposures can result in permanent effects without an acute poisoning event.
- This can sometimes present as flu-like symptoms as with sheep dipping farmers
(Davies, 2000; Pilkington, 2001).

What about Gulf War veterans?



- The question remained whether exposures to acetylcholinesterase inhibitors including OP pesticides and/or PB could have caused lasting neurobehavioral deficits in GW veterans without overt poisoning?

How many pesticides were in Gulf War Theatre?



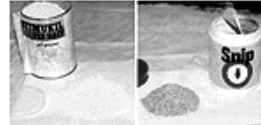
- Pesticides were used widely in the Gulf War to protect the troops from pests such as sand flies, mosquitoes and fleas that can carry infectious diseases.
- US forces used pesticides in areas where they worked, slept and ate. In fact, on any given day during their deployment GW veterans could have been exposed to at least 15 pesticide products of concern with 12 different active ingredients.

How were pesticides used in Gulf War Theatre?



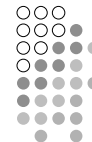
- Troops used pesticides for personal use on skin and uniforms and as:

- Insect repellants
- As area sprays and fogs
- In pest strips and fly baits
- As delousing agents for POWs

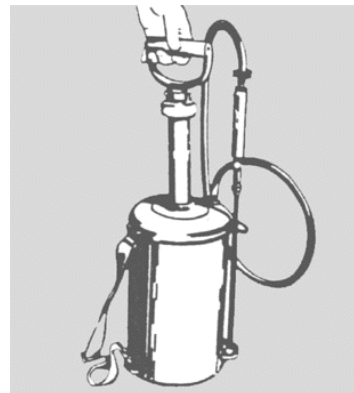


- Those who applied the pesticides were likely exposed to more pesticide products and at higher doses.
- They were also much more knowledgeable about pesticide types and usages therefore making them an ideally suited group to study.

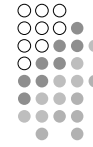
DoD Environmental Exposure Report - Pesticides



- These widespread common uses of pesticides contributed to the DoD's decision to investigate pesticide exposure as a possible contributor to unexplained illnesses in GW veterans and began by performing a health risk assessment.

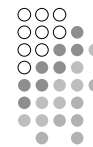


Health Risk Assessment



- The DoDs health risk assessment (HRA) for pesticides included a toxicity assessment to determine which GW exposures likely exceeded levels of concern for toxicity.
- For General military personnel, fly baits, pest strips, sprayed liquids, and sprayed powders likely exceeded levels of concern for toxicity for some individuals.
- For pesticide applicators, additional exposures of concern included fogs (organophosphates) and delousing of prisoners of war (Lindane)
- The HRA concluded that 41,000 Gulf War veterans could have been overexposed to pesticides and recommended an epidemiological study of GW pesticide applicators to further assess these potential over-exposures.

General Military population exposures which exceeded the levels of concern



Pesticide Type	Affected Group	Active Ingredient/Class	Exposure Scenario
Fly baits	Only individuals who handled (applied) fly baits	Azamethiphos (OP) *	Medium, High
		Methomyl (C)	High
Pest strips	General military population	Dichlorvos (OP)*	Low, Medium, High
Sprayed Liquids	General military population	Chlorpyrifos (OP) *	High
		Diazinon (OP)*	High
		Malathion (OP)*	High
Sprayed Powders	General military population	Bendiocarb (C) *	Medium, High

OP = Organophosphate C = Carbamate

*Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.

Source: Environmental Exposure Report – pesticides

Applicator personnel additional exposures which exceeded the levels of concern



Pesticide	Active Ingredient/Class	Exposure Scenario
Sprayed liquids	Chlorpyrifos (OP)*	High
	Diazinon (OP)*	Medium, High
	Malathion (OP)*	High
Sprayed powders	Bendiocarb (C)	Low, Medium, High
Fogs	Chlorpyrifos (OP)*	High
	Malathion (OP)*	High
Delousing	Lindane (OC)*	Medium, High

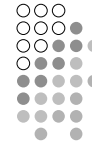
OP = Organophosphate C = Carbamate OC = Organochlorine
*Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.
Source: Environmental Exposure Report - pesticides

Environmental Exposure Report - Pesticides



- The DoD Environmental Exposure Report – pesticides (EER) identified five major classes of pesticides of potential concern (POPC) during their health risk assessment (Winkenwerder, 2003)

Pesticides of Potential Concern



Repellents	Pyrethroids	Organophosphates	Carbamates	Organochlorines
DEET	Permethrin	Azamethiphos*	Methomyl	Lindane*
	D-Phenothrin	Chlorpyrifos*	Propoxur	
		Diazinon*	Bendiocarb*	
		Dichlorvos*		
		Malathion*		

*Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.
Source: Environmental Exposure Report - pesticides

Pesticides currently used in Iraq and Afghanistan



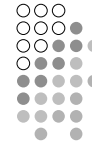
- Why aren't OIF/OEF veterans showing the same symptoms as GW veterans?
- Different pesticides are now being used than in the Gulf War.

Pesticide Use and Application Overview					
Use	Designation	Purpose	POPCs, Active Ingredient	Application Method	User or Applicator
General Use Pesticides	Repellents	Repel flies and mosquitoes	DEET 33% cream/stick	By hand to skin	Individuals
			DEET 75% Liquid	By hand to skin, uniforms or netting	
			Permethrin 0.5% (P) Spray	Sprayed on uniforms	
	Area Spray	Knock down spray, kill flies and mosquitoes	d-Phenothrin 0.2% (P) Aerosol	Sprayed in area	
	Fly Baits	Attract and kill flies	Methomyl 1% (C) Crystals Azamethiphos 1% (OP) Crystals	Placed in pans outside of latrines, sleeping tents	Individuals, Field Sanitation Teams, Certified Applicators
Pest Strip	Attract and kill mosquitoes	Dichlorvos 20% (OP) Pest Strip	Hung in sleeping tents, working areas, dumpsters		
Field Use Pesticides	Sprayed Liquids (emulsifiable concentrates, ECs)	Kill flies, mosquitoes, crawling insects	Chlorpyrifos 45% (OP) Liquid	Sprayed in corners, cracks, crevices	Field Sanitation Teams or Certified Applicators
			Diazinon 48% (OP) Liquid	Sprayed in corners, cracks, crevices	Certified Applicators
			Malathion 57% (OP) Liquid		
			Propoxur 14.7% (C) Liquid		
	Sprayed Powder (wetable powder, WP)	Kill flies, mosquitoes, crawling insects	Bendiocarb 76% (C) Solid		
	Fogs (Ultra-Low Volume Fogs, ULVs)	Kill flies, mosquitoes	Chlorpyrifos 19% (OP) Liquid	Large area fogging	Certified Applicators
Malathion 91% (OP) Liquid					
Delousing Pesticide	Delousing Pesticide	Kill lice	Lindane 1% (OC) Powder	Dusted on EPWs, also available for personal use	Certified Applicators, Military Police, Medical Personnel

Pesticide Cognition Study

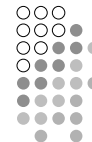
- The pesticide Cognition study was devised to follow up on EER-pesticides recommendation to conduct an epidemiological assessment of GW pesticide applicators for potential chronic health and cognitive effects.

Purpose of the Present Study



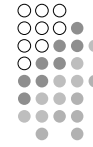
- In this study, we assessed CNS functioning and health symptoms in GWI veterans who have been exposed to multiple pesticides as part of their military occupational specialty (MOS) or occupational designation.
- The study focuses on analysis of low level chemical exposures in pest control interviewees (PCI) from the EER-pesticides report and comparison of neuropsychological functioning among high and low exposed groups. Differences in health symptom report and diagnostic outcomes were also examined.

Specific Aims



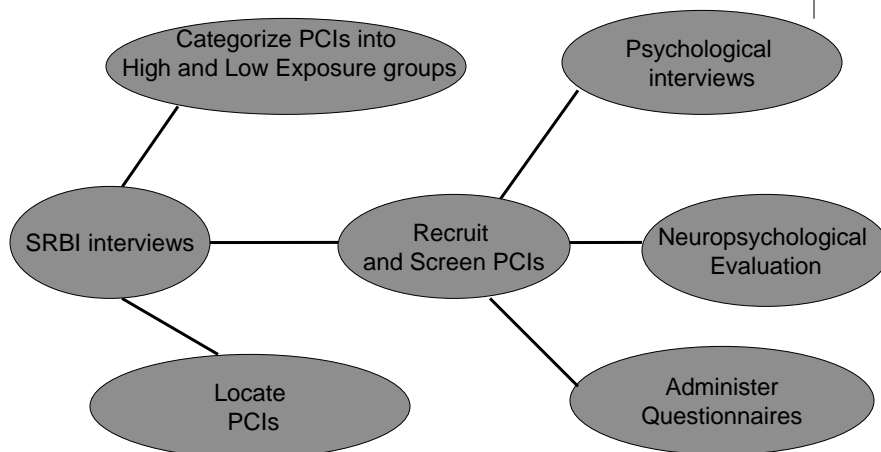
- 1.) determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans
- 2.) determine the cognitive and neurological effects of pyridostigmine bromide (PB) exposure in specific groups of GW veterans
- 3.) to assess for additive/synergistic effects in GW veterans with multiple chemical exposures.

Study Design



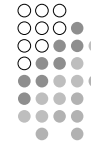
- Two hundred and ninety eight (298) pesticide control interviewees (PCIs) were interviewed regarding pesticide exposures during GWI by the DoD in 1997-1998 are the subjects in this study.
- This sample includes, physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police and other pest controllers.
- Out of the 298 interviewees, a sample of one hundred and fifty nine (159) individuals were recruited for neuropsychological examination during a four year time period. This group were then divided into four groups, based on self reported exposure to pesticides and to PB during the GW.

Pesticide Study Assessment Method



Assessment Instruments

Neuropsychological test battery



DOMAINS

TESTS

Attention/Executive

Wisconsin Card Sort
Trail making Test
Continuous Performance Test

Language

Boston Naming Test

Psychomotor

Finger Tapping, Grooved Pegboard,
mean reaction time on CPT

Visuospatial

Rey-Osterrieth Complex figure
Hooper Visual Organization Test

Memory

California Verbal Learning Test
Stanford Binet copying task
Rey-Osterrieth Complex figure

Mood

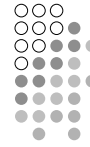
POMS

Other Assessments



- Psychological Assessment:
 - SCID
 - CAPS-DX
- Environmental Exposure Assessment
 - Pesticide Exposure Assessment questionnaire
 - SNAC

Pesticide Group Determinations



Low exposure

- An individual is assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below.

High exposure

- PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, at least once. A general statement, such as "became ill".
- PCI applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits (≥ 2 pounds handled), and/or fogs.
- PCI was present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.
- PCI spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.
- PCI applied DEET to self at least 30 times.

PB group determinations



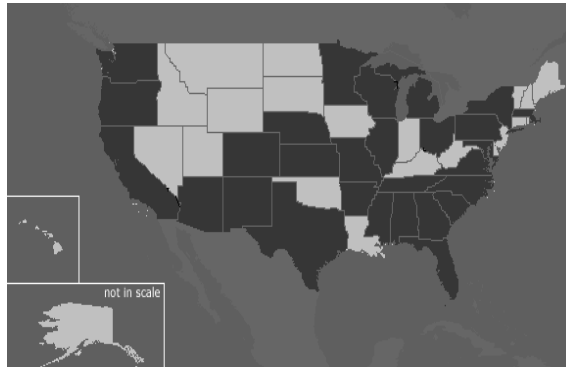
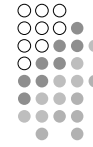
Low exposure

- 1) The individual reported not using PB.
- 2) The total dose reported was less than or equal to 180 mg PB active ingredient
- 3) The PCI reported using PB, but could not recall sufficient details to conclude that the dose was probably greater than 180 mg PB.

High exposure

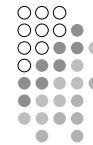
- 1) The total dose was greater than 180 mg PB active ingredient.
- 2) The individual reported taking any PB and also reported experiencing acute signs and/or symptoms of exposure.

Research Protocol



Study participants were seen during multiple field trips convenient to PCI current residence locations in 28 states.

Subject Demographics



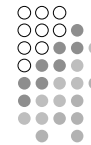
- One-hundred and fifty nine participants were recruited and completed the study protocol (cognitive evaluation, psychological interviews and exposure questionnaires).
- Analyses have been completed on 159 study participants (F = 20, M = 139).
- Mean age is 48
- Mean education is 16 years

Exposure Assessment for Pesticides of Potential Concern



Pesticide	low Exposed	High Exposed	% high Exposed
DEET	90	69	43
Permethrin	121	38	24
d-phenothrin	155	4	3
Azamethiphos	139	20	13
Chlorpyrifos	114	45	28
Diazinon	119	40	25
Dichlorvos	103	56	35
Malathion	111	48	30
Methomyl	92	67	42
Propoxur	146	13	8
Bendiocarb	126	33	21
Lindane	116	43	27

Pyridostigmine Bromide Exposure Categories



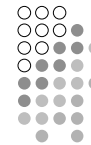
PB Dosage (total tablets)	N	Percent
0-5	71	45
6-20	46	28
21-40	21	13
41-92	22	14
Total	159	100

Pesticide Exposure Groups

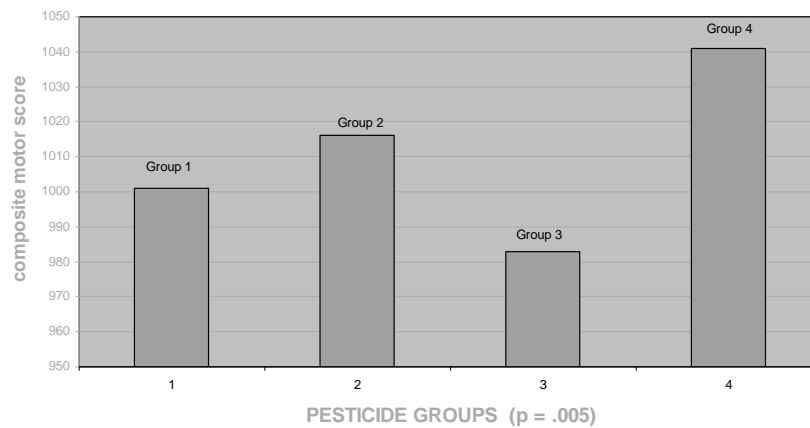


<u>Group</u>	<u>Pesticide Category</u>	<u>N</u>
Group 1	Low Pesticide, low PB	24
Group 2	High Pesticide, low PB	50
Group 3	Low pesticide, high PB	18
Group 4	High Pesticide, high PB	67

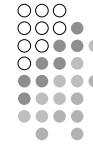
Results for cognitive Domains:



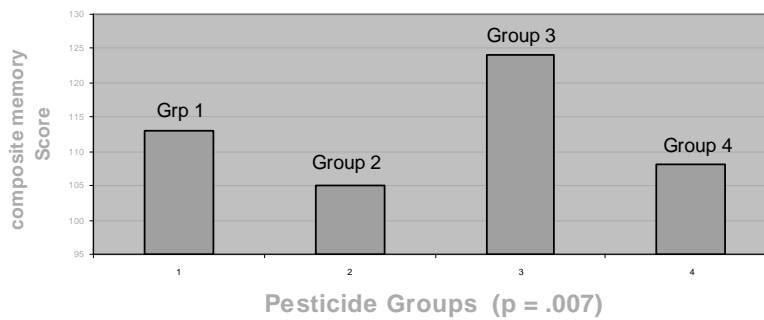
PSYCHOMOTOR DOMAIN BY PESTICIDE GROUPS



Results for cognitive domains



Memory Domain by Pesticide Groups



Results of Cognitive Tests in the Four Exposure Groups

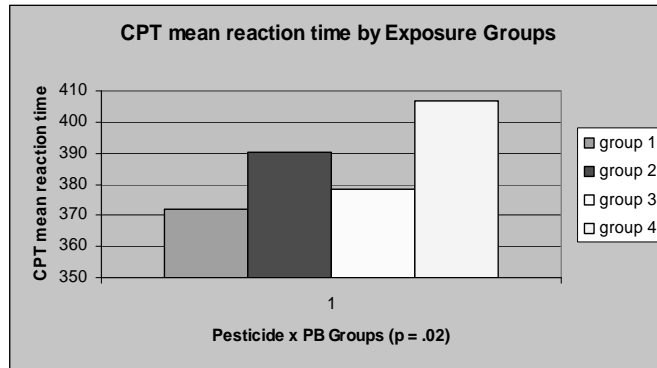
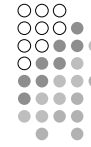


Domain

Test

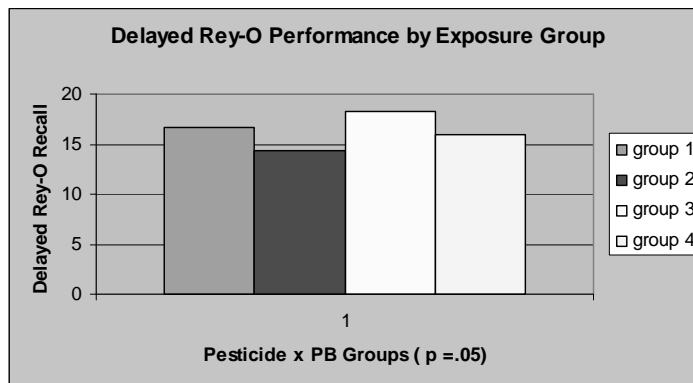
- Psychomotor Continuous Performance Test (p = .007)
- Visual Memory Rey-Osterreith Complex Figure
Immed (p = .003), delay (p = .03)
- Health Symptoms Chronic MultiSymptom Illness (p = .02),
Mood cognition (p = .003), Fatigue (p = .03)

Continuous Performance Test by Pesticide Exposure Groups

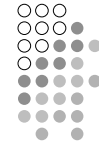


Individual comparisons among the groups showed a significant difference between exposure Group 1 (low/low) and Group 4 (high/high) at $p=.007$.

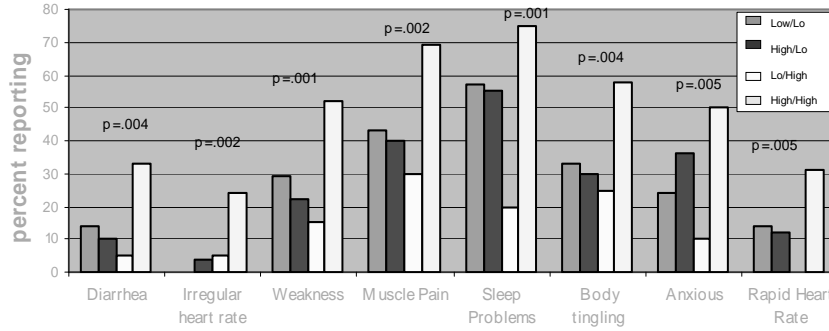
Visual memory by Pesticide Exposure Groups



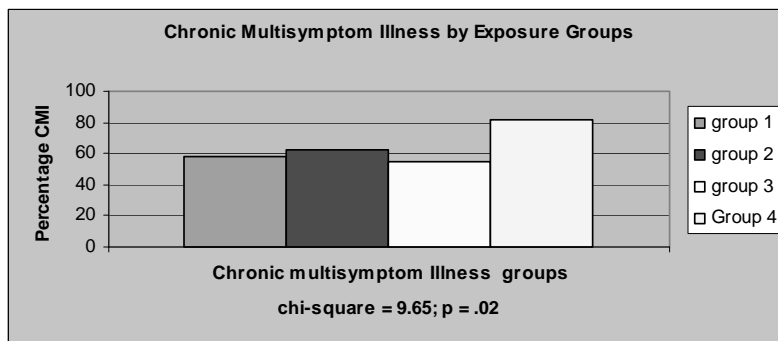
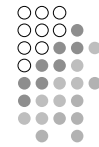
Health Symptom Results



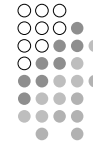
Health Symptoms by Pesticide Groups



CMI and Pesticide Groups



Conclusions



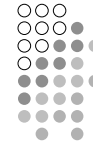
- Combined pesticide and PB exposures associated with reduced performance in mean reaction times, mood and health symptoms including CMI in this study cohort.
- Chronic effects from combinations of moderate level exposure to OP and carbamates appear present in this group of GW veterans.

Conclusions (2)



- Results support the hypothesis that multiple chemical exposures have contributed to the chronic ill health in some GW veterans.
- Findings correlate with studies of professional pesticide applicators, greenhouse workers, and sheep dipping farmers suggesting similar subtle effects on cognition and mood with chronic low-level exposures.
- Results consistent with the conclusion of the DoD pesticides health risk assessment and the RAND report which suggested that the AchE inhibiting pesticides could be among the contributing factors to some of the undiagnosed illnesses in GW veterans.

Future Directions



- Continued analyses with individual pesticides of concern (POPC) and relation to chronic cognitive and health effects.
- Neuroimaging study with a subgroup of PCIs to assess for brain behavior relationships.

Thank You

