

Presentation 2 – Lea Steele

**The Gulf War and Gulf War Illnesses:  
An Overview of Research  
Reviewed by the RAC-GWVI**

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**Lea Steele, Ph.D.  
May 16, 2006**

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Research Advisory Committee to Gulf War Veterans' Illnesses

**The Gulf War and Gulf War Illnesses:  
Overview of the Research Review Process So Far**

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- **The Gulf War and Gulf War Illnesses**
- **The work of the RAC**
- **Highlights of research findings and conclusions**

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## The Gulf War and Gulf War Illnesses: Overview of the Research Review Process So Far

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## 1990-1991 Gulf War: Operations Desert Shield/Desert Storm

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Aug 2, 1990 - Iraq invaded Kuwait

Jan 16, 1991 - Air strikes began

Feb 24, 1991 - Ground combat began

Feb 28, 1991 - Cease fire declared



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**1990-1991 Gulf War: Operations Desert Shield/Desert Storm  
Circumstances Very Different from Current Iraq War**

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- ~700,000 U.S. troops deployed
- War ended after 6 weeks of heavy air strikes, 4-day ground war
- Decisive victory, few casualties (< 150 battle-related deaths)



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**Gulf War Illnesses:  
Chronic Symptoms in the Wake of Desert Shield/Desert Storm**

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- After the 1991 war, widespread reports of unexplained health problems in Gulf War veterans, typically included:
  - *Chronic headaches*
  - *Joint pain, muscle pain*
  - *Dizziness, memory problems*
  - *Mood problems, cognitive difficulties*
  - *Unexplained fatigue*
  - *Persistent diarrhea*
  - *Respiratory problems*
  - *Unusual skin rashes*



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## Gulf War Illnesses (GWI)

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- Little progress in understanding or treating GWI for many years; in 1998, Congress directed Committee be appointed
- RAC appointed in 2002, charged with reviewing Gulf War research and federal research programs, making recommendations



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## Research Advisory Committee on Gulf War Veterans' Illnesses

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- RAC charter identifies central objective of all GWI research:

***to improve the health of ill veterans***



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## **The Gulf War and Gulf War Illnesses: Overview of the Research Review Process So Far**

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- **Big picture: The Gulf War and Gulf War Illnesses**
- **The work of the RAC**
- **Highlights of research findings and conclusions**



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**Comprehensive review of scientific and other  
information relevant to the health of Gulf War  
veterans**

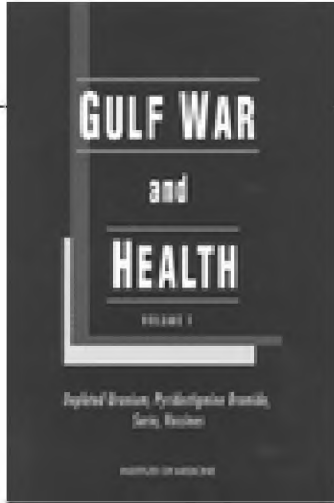
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***The Committee has considered evidence  
from diverse sources .....***



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- Reports from DOD, VA, CDC, NIH
- Series of reports commissioned by DOD, VA (RAND, IOM)
- Congressional reports
- Special panels (e.g. PAC, PSOB)
- Reports from foreign governments, special panels



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Research Activity Committee of the National Academies

**April 2003 Report from DOD Special Assistant for Gulf War Illnesses**

## **Environmental Exposure Report**

### **Pesticides**

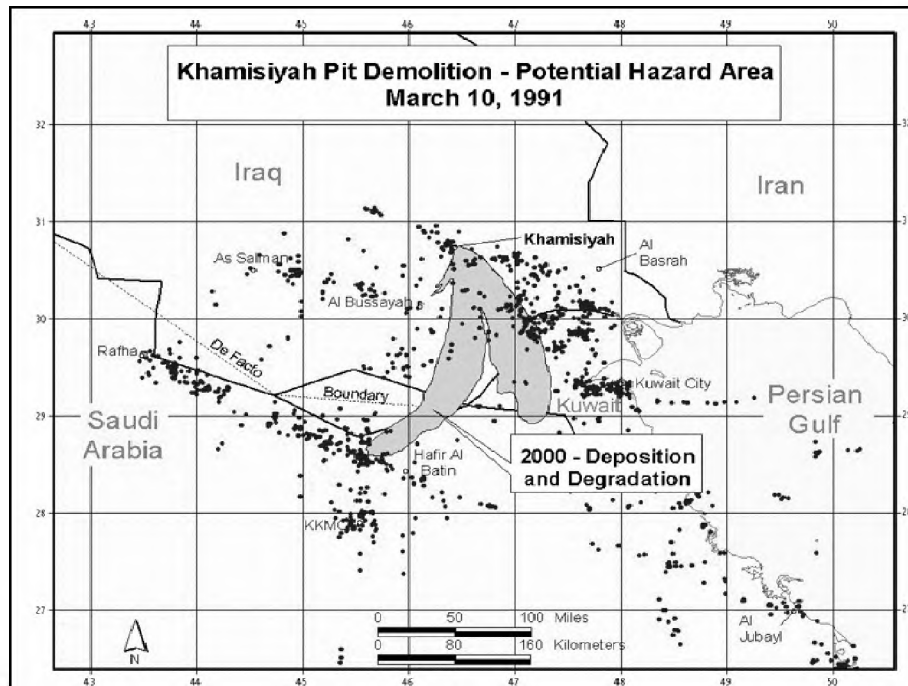
Environmental Exposure Reports are reports of what we know today about certain events of the 1990-1991 Gulf War. This particular environmental exposure report focuses on the use of pesticides by US military personnel and the resulting exposures to these compounds. Our goal is, to the extent possible, to determine if the pesticides used during the Gulf War contributed to unexplained illnesses reported by some Gulf War veterans. This is an interim, not a final, report. We hope that you will read this and contact us with any information that would help us better understand the events reported here. With your help, we will be able to report more accurately on the events surrounding pesticide use and exposures. Please contact my office to report any new information by calling:

**1-800-497-6261**

Dale A. Vesser  
Acting Special Assistant for Gulf War Illnesses, Medical Readiness, and Military Deployment  
Department of Defense

2003-10-20/040608/01  
Ver 1.1

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**Primary focus has been on the now large body of relevant scientific research**

***The Committee has considered evidence related to a wide variety of Gulf War-related experiences and exposures .....***



### Large amount of laboratory, clinical, and epidemiologic research related to Gulf War exposures of potential interest

- Deployment-related stressors
- Chemical weapons
- Pesticides/repellants
- PB
- Vaccines
- Depleted uranium
- Oil well fires
- Infectious diseases
- Tent heaters
- Particulates
- Fuel exposures
- Solvents, CARC paint

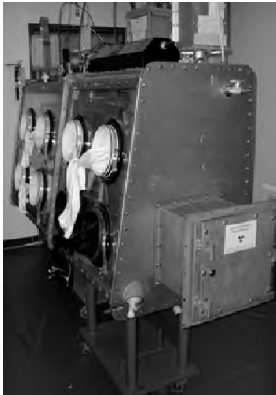


Table 7. Studies of Chronic Effects of Low-Dose Sarin Exposure in Animals

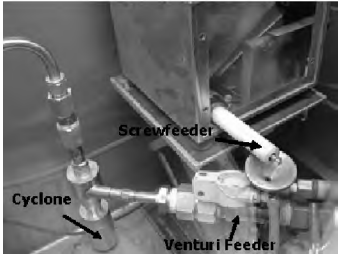
Study	Year	Animal Model	Major Finding
Berchiel <sup>44</sup>	1976	monkey	Persistent effects on electroencephalograph readings
Husain <sup>120</sup>	1993	mouse	Delayed development of spinal cord lesions
Jones <sup>149</sup>	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa <sup>165</sup>	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa <sup>167</sup>	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa <sup>166</sup>	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa <sup>161</sup>	2001	rat	Impaired spatial memory
Conn <sup>87</sup>	2002	rat	No persistent effects on reported indices of temperature regulation and motor activity
Henderson <sup>113</sup>	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Hule <sup>130</sup>	2002	guinea pig	Persistent failure to habituate on functional test battery
Soremin <sup>163</sup>	2002	rat	Persistent increase in cerebral blood flow in specific areas
Katra <sup>161</sup>	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson <sup>164</sup>	2002	guinea pig	Chronic depression of AChE activity, persistent behavioral changes (disordered activity, increased rearing behavior)
Husain <sup>127</sup>	2003	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BChE activity, NTE activity in various tissues
Soremin <sup>162</sup>	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa <sup>162, 164</sup>	2003 2004 2004	mouse	Chronic alteration in immune function (increase in CD19 cells, decrease in CD4 cells, decrease in mitogen-induced lymphoproliferation, increased NK cell activity)




**Glove Box Enclosure System**



**Aerosol Generation System**

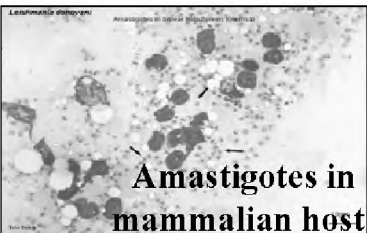


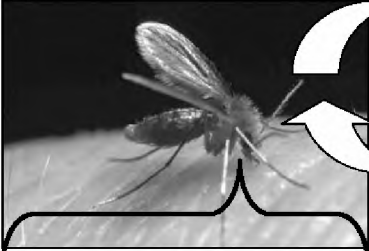



**96-Port Nose-Only Exposure Chamber**



Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures. Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

***Leishmania* Parasite Life Cycle**



**Promastigotes in sand fly**

**Amastigotes in mammalian host**

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

**Table 10. Population Studies Assessing Relationships of Multiple Exposures in Theater to Gulf War Veterans' Illnesses**

Population Studied	Sample Size	Health Measure	Association with Self-Reported Exposures		
			Chemical Weapons	PB	Pesticide Use
*Air Guard veterans <sup>222</sup>	1,002	severe CMI	+	+	+
		mild/moderate CMI	+	+	+
*Army veterans from New England, New Orleans <sup>224</sup>	291	neurological and musculoskeletal symptoms	+	-	+
Australian veterans <sup>224</sup>	1,456	functional impairment	+	+	+
Iowa veterans <sup>138</sup>	1,896	cognitive dysfunction	+	+	+
*Navy Seabees <sup>20</sup>	11,869	CMI (modified)	+	+	+
*Navy construction battalion <sup>187</sup>	249	1 or more of 3 defined syndromes	+	+	+
*New England Army veterans <sup>211</sup>	1,290	CMI (modified)	na	+	na
*Pacific Northwest veterans <sup>201</sup>	354	unexplained illnesses	-	+	+
UK male veterans <sup>201</sup>	2,735	CMI (modified)	+	+	+
*UK veterans <sup>52</sup>	7,871	symptom severity	na	+	+

CMI: chronic multisymptom illness as defined by Fukuda et al.<sup>18</sup>  
 + = statistically significant association; - = association not statistically significant; na = association not assessed  
 \* Indicates analyses controlled for possible confounding due to concurrent exposures

### Diverse types of scientific studies considered ....

- **Published scientific research**
  - > **Epidemiologic studies of Gulf War-era veterans**
  - > **Clinical studies of Gulf War veterans**
  - > **Occupational health studies related to exposures**
  - > **Animal studies**
  - > **In vitro studies**
  
- **Research-in-progress**



## Information Synthesis/Analysis

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- > *Compare findings from different studies: how are they similar? how are they different?*
  
- > *Evaluate strength of evidence related to each health finding and exposure of interest*

**What does all this information tell us about the nature of Gulf War illnesses?**



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## The Gulf War and Gulf War Illnesses: Overview of the Research Review Process So Far

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- **Big picture: The Gulf War and Gulf War Illnesses**
  
- **The work of the RAC**
  
- **Highlights of research findings**
  - *Overview, emphasis on epidemiologic findings*
  - *Dr. Abou-Donia: Toxicological studies*
  - *Dr. Haley: Neurological findings*



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## Epidemiologic Studies: General Findings

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- **Mortality:** no overall increase in disease-related mortality; higher rate of brain cancer mortality in relation to Khamisiyah
- **Hospitalizations:** no overall increase; some differences with nondeployed
- **Diagnosed medical conditions**
  - Excess rate of ALS
  - Excess rates of skin conditions, "dyspepsia"
  - Excess rates of chronic fatigue syndrome, fibromyalgia
  - Possible excess rate of asthma for oil-fire exposed
  - Cancers?
- **Psychiatric conditions**
  - Higher rates of PTSD, depression than in non-deployed veterans
  - Overall rates of psych conditions are low (e.g. PTSD: 2 – 10%)
  - Higher PTSD rates associated with combat, other psych stressors during deployment



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### Epi findings:

**Symptoms, symptom complexes significantly elevated in Gulf War veterans compared to nondeployed era veterans**

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### Gulf War Illnesses

- Symptoms in multiple domains  
GW veterans have more symptoms, more types of symptoms, more severe symptoms
- Nonrandom distribution  
Rates vary by branch of service, deployment location
- Prevalence of GWI depends on definition



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**Table 3. Prevalence Estimates of Multisymptom Illness in Gulf and Non-Gulf Veterans**

<b>Group Studied</b>	<b>Case Definition Used</b>	<b>Prevalence in Gulf War Veterans</b>	<b>Prevalence in Non-Gulf Veterans</b>	<b>Excess Illness in Gulf Veterans</b>
Pennsylvania Air Guard <sup>265</sup>	CMI	45%	15%	30%
U.K. male veterans <sup>349</sup>	CMI (modified)	62%	36%	26%
Kansas veterans <sup>265</sup>	KS Gulf War Illness	34%	8%	26%
Kansas veterans <sup>265</sup>	CMI (modified)	47%	20%	27%
New England Army veterans <sup>243</sup>	CMI (modified)	65%	33%	32%

CMI: chronic multisymptom illness, as defined by Fukuda et al.<sup>85</sup>

## Gulf War Illnesses

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### Gulf War Illnesses

Epidemiologic studies also find GWI rates significantly associated with veteran-reported exposures

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### **Epidemiologic Studies: General Findings**

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- **Epidemiologic studies typically identify significant associations between GWI and most self-reported exposures**
- **Has led to observations that:**
  - *Veterans with GWI more likely to overreport every exposure*
  - *All epidemiologic findings are result of reporting bias*
  - *Epidemiologic results not informative; no exposure clearly implicated in GWI*



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### **Basic Problem with This Assessment (Epidemiology 101)**

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- **Complex exposure scenario: multiple exposures in theater; exposures highly correlated**
- **When data analyses do not account for this, expect results to be highly confounded, even nonsensical**
- **Relatively few Gulf War epidemiologic studies have been analyzed to address this**



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## **Weighing the Evidence from Epidemiologic Studies**

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- **When analyses control for effects of multiple exposures, studies typically identify only a limited number of “risk factors” for GWI**
- **With an eye to this and other study strengths/weaknesses, epidemiologic information can be a valuable resource in understanding GWI**
- **Important to consider consistency of epidemiologic findings across different studies**



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## **RAC Analysis: Comparing the Weight of Evidence for GWI in Relation to Different Wartime Exposures**

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- **Big picture**                      extent and patterns of exposure during deployment
- **Known toxic effects**        info from toxicological, occupational health studies
- **Epidemiologic studies of Gulf War veterans**



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# Psychological Stressors During Deployment

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## Psychological Stressors Associated with Gulf War Deployment

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- Big picture: exposures
- Known toxic effects
- GW epidemiologic studies



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## →Big Picture Psychological Stressors

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- ◆ Many types reported, from less severe to extremely traumatic
- ◆ How common?
  - Chemical alerts 66 %
  - SCUD exploded nearby 43 %
  - Participation in combat 27 %
  - Witnessed deaths 26 %
  - Family problem 7 %
  - Sexual assault 1 %
- ◆ Some more common among ground troops
- ◆ Many of these were not unique to 1990-91 Gulf War



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## →Known Toxic/Adverse Effects Psychological Stressors

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- ◆ Severe trauma associated with PTSD, other psychiatric conditions
- ◆ PTSD, other psych conditions associated with higher levels of somatic symptoms
- ◆ Less is known re:
  - Persistence of somatic symptoms many years after lower-level stressors?
  - Somatic symptoms after trauma in the absence of psych illness?



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**→Known Toxic/Adverse Effects  
 Psychological Stressors**

- ◆ Animal studies have shown that stress can alter effects of other Gulf War-related exposures
  - Can increase adverse effects of PB, DEET, permethrin combinations
  - Effects on blood brain barrier?
  - May modulate neurotoxic effects of DU

**→Epidemiologic Findings in Gulf War Veterans  
 Psychological Stressors in relation to GWI**

	<u>Unadi OR</u>	<u>Adi OR</u>	<i>Ref</i>
Chemical alerts	2.6*	1.2	GG
	2.2*		CU
	1.9*, 2.7*	ns	JW
SCUD exploded nearby	1.6*		CU
Participated in combat	2.6*	1.3	GG
High combat stress		(2.5)	PS
Witnessed deaths	3.1*	1.3	GG
	1.6*		CU
Family problem	1.7*	1.6	RN
Sexual assault	8.3*		HK
"Combat stress index"	p = 0.02	ns	RH, syn 1

## →Epidemiologic Findings Psychological Stressors

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- ◆ All significantly associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.6 – 3.1
- ◆ High crude OR (8.3) for sexual assault in Kang study
- ◆ None significant in studies adjusting for other wartime exposures



# Vaccines

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**→Big Picture  
 Vaccines**

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◆ Self-reported exposures:

- Anthrax 41%
- Typhoid 44%
- Botulinum 3%
- Plague 15%
- Meningococcus 6%
- 10 shots or more 34%

◆ Combat troops reported most likely to have received anthrax, botulinum toxoid

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**→Epidemiologic Findings in Gulf War Veterans  
 Individual Vaccines**

	<u>Unadi</u>	<u>Adi</u>	<i>Ref</i>
Botulinum	1.8*		KB
	4.9*	1.4	GG
Meningococcus	1.6		
	3.0*	1.3*	GG
Anthrax	1.5*, 1.9*	1.5*	JW
	1.7*		KB
	3.7*	1.0	GG
	1.3		MH(post)
	1.5*	0.9	CU
Plague	1.3		KB
	3.2*	0.9	GG
	0.9		MH(post)
	1.3*		CU

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**→Epidemiologic Findings in Gulf War Veterans  
 Number of Vaccines**

	<u>Unadi</u>	<u>Adi</u>	<i>Ref</i>
Post deploy:			
0-1	1.0		
2	2.2*		<i>MH</i>
3	2.4*		
4	2.2*		
5+	5.0*		
Symptom score/# vaccines		p<.001	<i>NC</i>
0	1.0		<i>Austr</i>
1-4	0.9		
5-9	1.3*		
10+	1.2*		

**NAPP Pills  
 (Pyridostigmine  
 Bromide)**

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## →Big Picture PB Exposures

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- ◆ Self-reported exposures:
  - Used PB 49 - 60%
  - Seabees study 32%
  - Used NAPS > 14 days 60% (UK)
- ◆ More commonly reported by ground troops; Guard use may be higher than active
- ◆ Widespread use of PB unique to 1990-91 Gulf War



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## →Known Toxic Effects PB

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- ◆ Used for many years to treat myasthenia gravis, considered safe in clinical use
- ◆ Acute side effects (mostly GI) reported to have affected about 1/3 with PB use during the Gulf War
- ◆ Animal studies indicate synergism with DEET, permethrin
- ◆ Preliminary evidence of PB causing severe difficulty for individuals with low BChE activity



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**→Epidemiologic Findings in Gulf War Veterans  
 PB use in relation to GWI**

	<u>Unadi</u>	<u>Adi</u>	<i>Ref</i>
Took PB tablets	3.0*	1.5*	<i>GG</i>
	1.4*		<i>Aust</i>
	1.4*, 3.0*	1.6*, 2.9*	<i>RN</i>
	2.6*		<i>CU</i>
	ns	ns	<i>SP</i>
Took 1-21 PB pills	1.9*, 2.3*	1.4	<i>JW</i>
22 + PB pills	2.5*, 3.7*	2.1*	
Took > 21 PB tablets	4.44*	2.2*	<i>PS</i>
No. of days took NAPs		p<.001*	<i>NC</i>
Side effects from NAPs		p<.001*	<i>NC</i>
Advanced PB side effects	p<.001*	p<.001*	<i>RH syn2,3</i>
Used PB	p<.001*		<i>Iowa</i>

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- Epidemiologic Findings  
 PB**
- 
- ◆ PB variables sign. associated with GWI in studies that adjust for other wartime exposures, ORs ~ 1.5 – 2.9 (not in Ft. Devens study or at lower level in 2<sup>nd</sup> Ft. Devens study)
  - ◆ 3 studies indicate a dose/response effect
  - ◆ 2 studies support association with acute side effects of PB
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## Putting It All Together

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### Weight of Evidence Relating Individual Wartime Exposures to GWI

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### Gulf War Exposures in relation to GWI: Summary of Epidemiologic Evidence

	<u>Unadi</u>	<u>Adi</u>	<u>Adi Results Consist</u>	<u>Dose/ resp</u>
Psychological stressors	1.6-3.1	ns	yes	-
Pesticides	1.9-3.8	1.7-8.7	yes	yes
NAPP/PB pills	1.4-4.4	1.5-2.9	yes	yes
Chemical weapons	1.9-6.3	2.3-7.8	~	-
DU	4.5*	no studies	-	-
Oil well fires	1.8-4.5	2.1	no	yes
Vaccines: anthrax meningococcus	1.5-3.7 3.0	1.5 1.3	little info	-
Number of vaccines	3 sign	1 sign	little info	yes

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### **Exposures and GWI: *Evidence Supports Association***

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- > **Strongest evidence from epidemiologic studies supports pesticides and PB as causal factors in GWI**
  - **Animal studies support plausibility, especially when PB combined with other exposures**
  - **Overall pattern of exposures consistent with association**
  
- > **Two studies support positive associations with s/r exposure to chemical weapons, but s/r exposure questionable**
  - **Unknown if exposures extensive enough to explain large proportion of cases**



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### **Exposures and GWI: Little/Poor Evidence**

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- > **Very little useful information concerning associations between vaccines and GWI**
  - **Significant associations generally modest**
  - **Little animal or human research informs plausibility**
  
- > **Almost no epi information concerning associations between DU and GWI**
  - **Animal studies suggest possible neuro effects**
  - **Unknown if similar conditions seen in other deployments with comparable DU exposures**



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## Exposures and GWI

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- > Oil well fires, overall, unlikely to be primary cause of GWI
  - 2 studies suggest higher exposure levels may be problematic
  - May be associated with diagnosed asthma
  
- > Consistent epi findings that psych stressors are not associated with GWI
  - Animal studies suggest possible synergism w/exposures
  - Epi studies consistently identify association of psych stressors with PTSD, other psych diagnoses



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## Gulf War Illnesses: General Observations

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- Studies have identified consistent patterns of excess symptomatology in Gulf War veterans; not associated with objective signs, tests
- Substantial proportion of veterans affected
- A number of dx conditions elevated, but affect far fewer veterans. CFS, FM account for small % of veterans with GWI.



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### **Gulf War Illnesses: General Observations**

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- **Epidemiologic findings indicate consistent associations with neurotoxic exposures, little/no association with psychological stressors**
- **Clinical studies have identified a variety of indicators of CNS impairment in veterans with GWI; other findings limited**
- **Toxicological studies indicate synergism between some Gulf War-related exposures**



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### **Broad Spectrum of Evidence Considered by the Committee Thus Far**

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**Gulf War  
experiences  
and  
exposures**

**Gulf War  
Illnesses**



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