

Scientific Progress in Understanding Gulf War Veterans' Illnesses: 2004 Report and Recommendations

Research Advisory Committee on Gulf War Veterans' Illnesses

**Lea Steele, Ph.D.
Scientific Director**



RAC-GWVI
Research Advisory Committee on Gulf War Veterans' Illnesses

Research Advisory on Gulf War Veterans' Illnesses: 2004 Report and Recommendations

- **Background**
 - Gulf War veterans' illnesses
 - The Committee
 - The Report
- **Key Findings of the Report**



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1990-1991 Gulf War: Operations Desert Shield/Desert Storm Circumstances Differ from Current Iraq War

Aug 2, 1990 - Iraq invaded Kuwait
Jan 16, 1991 - Air strikes began
Feb 24, 1991 - Ground combat began
Feb 28, 1991 - Cease fire declared

- War ended after 6 weeks of heavy air strikes, 4-day ground war
- Decisive victory, relatively few casualties



Gulf War Veterans' Illnesses (GWVI)

- After the 1991 war, widespread reports of unexplained health problems in Gulf War veterans
- Consistent pattern of multiple symptoms typically included:
 - *Chronic headaches*
 - *Joint pain, muscle pain*
 - *Dizziness, memory problems, cognitive difficulties*
 - *Mood changes*
 - *Unexplained fatigue*
 - *Persistent diarrhea*
 - *Respiratory problems*
 - *Unusual skin rashes*
- These multisymptom illnesses are commonly referred to as "Gulf War Veterans' Illnesses" (GWVI)



Research Advisory Committee on Gulf War Veterans' Illnesses

- Little progress in understanding or treating GWVI for many years
- In 1998, Congress directed VA to appoint a committee to review government research, provide recommendations
- Committee appointed by Secretary Principi in 2002; members include veterans, scientists with expertise in Gulf War research



Research Advisory on Gulf War Veterans' Illnesses: 2004 Report and Recommendations

The Report

- 1st major report, focuses on specific topics covered in Committee's first 2 years of work
- Additional topics will be addressed in future reports
- Committee reviewed hundreds of scientific studies, government reports, presentations by scientific experts, consulted with outside scientists
- **10 key findings, associated research recommendations**



Research Advisory Committee on Gulf War Veterans' Illnesses: 2004 Report and Recommendations

- **Highlights**

- Recent research has provided important insights about nature of Gulf War illnesses and the effects of Gulf War-related exposures
- Gulf War illnesses affect a substantial proportion of veterans and are not explained by deployment stress or psychiatric illness
- Growing body of evidence indicates an important component of GWVI is neurological, supports a probable link with neurotoxic exposures during the war



2004 Report and Recommendations

"Scientific Progress in Understanding Gulf War Veterans' Illnesses"

- Large number of scientific studies in recent years have provided important new insights with respect to:
 - the nature of GWVI
 - biological effects of Gulf War-related exposures
- These findings call into question earlier assumptions about GWVI, mandate fundamentally different conclusions than those of earlier government panels



1. A substantial proportion of Gulf War veterans are ill with conditions not explained by wartime stress or psychiatric illness

- How many veterans have multisymptom illness as a result of Gulf War service? Answer depends on how “GWVI” is defined.
- Can estimate by seeing how illness rates and patterns in Gulf veterans differ from those of veterans who did not serve in the Gulf War
- Population studies consistently find that 25-32% of Gulf War veterans are affected by multisymptom illness (over and above rates in veterans who did not deploy to the Gulf War)



1. A substantial proportion of Gulf War veterans are ill with multisymptom conditions

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

Group Studied	Case Definition Used	Prevalence in Gulf War Veterans	Prevalence in Non-Gulf Veterans	Excess Illness in Gulf Veterans
Pennsylvania Air Guard ⁸⁵	CMI	45%	15%	30%
U.K. male veterans ³⁴⁹	CMI (modified)	62%	36%	26%
Kansas veterans ²⁸⁵	KS Gulf War Illness	34%	8%	26%
Kansas veterans ²⁸⁵	CMI (modified)	47%	20%	27%
New England Army veterans ²⁴³	CMI (modified)	65%	33%	32%

CMI: chronic multisymptom illness, as defined by Fukuda et al.⁸⁵



1. A substantial number of Gulf War veterans are ill with conditions not adequately explained by wartime stress or psychiatric illness

Studies consistently find that the large majority of ill Gulf War veterans do not have psychiatric conditions

- Less than 4 % of veterans in VA Gulf War Registry have post traumatic stress disorder (PTSD)
- PTSD rates in Gulf veterans are much lower than other wars, similar to PTSD rates in the general population
- Brief war: most Gulf veterans did not engage in combat, were not in combat areas, did not witness casualties



1. Gulf War illnesses not explained by wartime stress or psychiatric illness

Recent Example: 2002 British study conducted psychiatric evaluations of ill Gulf veterans

- Found only 24 % of disabled Gulf veterans have any psychiatric disorder (similar to rates of disabled veterans who didn't serve in the Gulf War)
- 76 % of disabled Gulf veterans have no identifiable psychiatric conditions
- Concluded that "alternative explanations for persistent ill health in Gulf War veterans are needed"

- K Ismail et al. The mental health of UK Gulf War veterans BMJ 2002;325:576



3. Research indicates an important component of GWVI is neurological in character

- Similar patterns of neurological symptoms identified in numerous studies of ill Gulf War veterans
- Studies indicate that Gulf veterans have developed ALS (Lou Gehrig's disease) at twice the rate of veterans who didn't serve in the Gulf War
- Diverse objective measures of neurological pathology and impairment in ill veterans



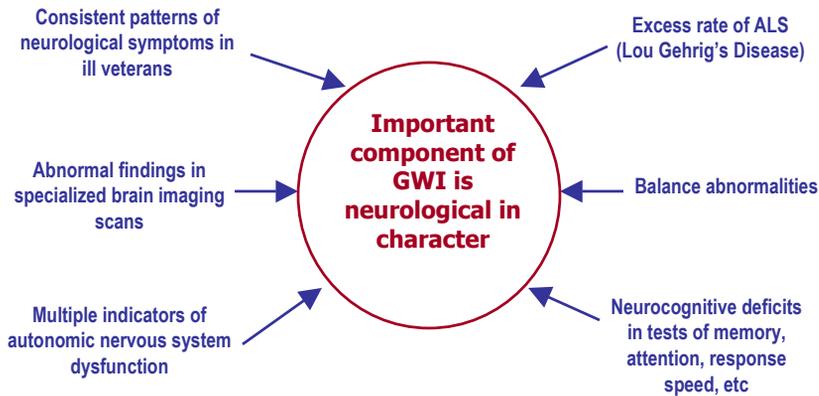
3. Research indicates an important component of GWI is neurological in character

Objective measures of neurological damage, impairment

- Studies using specialized brain scans have identified cell damage in several specific regions of the brain of ill Gulf veterans
- Multiple studies have identified dysfunction of the autonomic nervous system, using different tests and measures
- Abnormalities related to dizziness, balance identified using audiovestibular tests, measures of postural sway
- Neurocognitive deficits demonstrated in tests of memory, attention, response speed



**Multiple lines of evidence converge:
An important component of GWI is neurological in character**



4. Evidence supports a probable link between exposure to neurotoxins and the development of Gulf War veterans' illnesses

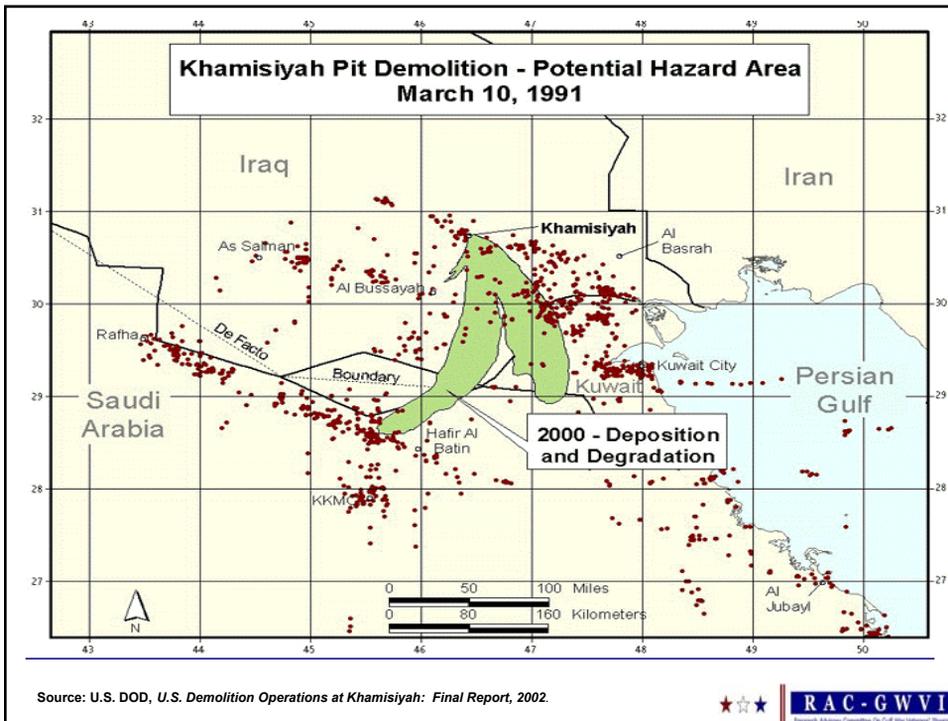
- Gulf veterans were exposed to a variety of substances that can negatively effect the nervous system
- Several of these compounds have a similar mode of action: they interfere with regulation of acetylcholine, an important nerve signaling chemical

- *Chemical nerve agents*
- *PB pills, taken to protect against nerve gas*
- *Pesticides and insect repellants*



Neurotoxic exposures in the Gulf War: Low-level exposure to nerve agents

- DOD reports indicate that about 100,000 veterans were downwind when a large munitions storage area at Khamisiyah, Iraq, was destroyed in March, 1991
- Destroyed bunkers and the demolition plume contained the nerve agents sarin and cyclosarin



GAO

United States General Accounting Office

Testimony

Before the Subcommittee on National Security,
Emerging Threats, and International Relations,
Committee on Government Reform, House of
Representatives

For Release on Delivery
Expected at 1:00 p.m. EDT
Tuesday, June 1, 2004

GULF WAR ILLNESSES

DOD's Conclusions About U.S. Troops' Exposure Cannot Be Adequately Supported

Statement of Keith Rhodes, Chief Technologist
Center for Technology and Engineering, Applied Research
and Methods

Low-level exposure to nerve agents in the Gulf War

- **2003, 2004 GAO reports concluded more veterans may have been exposed to chemical agents than indicated by DOD Khamisiyah models**
 - **Khamisiyah plume models seriously flawed**
 - **Evidence that there were additional demolitions, bombing sites that released chemical weapons to which troops may have been exposed**
 - **Concluded that exposures may have been widespread; GWI studies based on Khamisiyah models not likely to be reliable**



Recent Studies Identify Effects of Low-level Nerve Agent Exposure

- Long-held belief that nerve agent exposures too low to cause immediate symptoms do not cause long-term adverse effects
- Recent studies challenge this assumption:
 - 15 animal studies since 2000 show persistent neurological, immunological effects after low-level exposures to sarin



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

Study	Year	Animal Model	Major Finding
Burchfiel ¹¹⁴	1976	monkey	Persistent effects on electroencephalograph readings
Husain ¹²⁶	1993	mouse	Delayed development of spinal cord lesions
Jones ¹⁴⁹	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa ¹⁶⁶	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa ¹⁶⁷	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa ¹⁶⁸	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa ¹⁶¹	2001	rat	Impaired spatial memory
Conn ⁶⁷	2002	rat	No persistent effects on reported indices of temperature regulation and motor activity
Henderson ¹¹³	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Hulet ¹²⁶	2002	guinea pig	Persistent failure to habituate on functional test battery
Scremin ³⁶³	2002	rat	Persistent increase in cerebral blood flow in specific areas
Kalra ¹⁵¹	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson ²⁵⁴	2002	guinea pig	Chronic depression of AChE activity, persistent behavioral changes (disordered activity, increased rearing behavior)
Husain ¹²⁷	2003	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BCHE activity, NTE activity in various tissues
Scremin ³⁶²	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa ¹⁶²⁻¹⁶⁴	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)

Neurotoxic Exposures in the Gulf War: PB

- **PB (pyridostigmine bromide) pills**
 - “Investigational drug” used in Gulf War to protect against nerve gas
 - Used by more than half of all personnel, amounts varied widely
 - Chronic effects as used in the Gulf War are not known
 - Epidemiologic studies consistently link PB use with increased rates of GWVI
 - Animal studies indicate that PB toxic effects can be enhanced when combined with other Gulf War-related exposures



Neurotoxic Exposures in the Gulf War Pesticides, insect repellants

- **Pesticides and Insect Repellants**
 - Gulf War desert environment teeming with pests and biting insects; posed serious disease risks
 - Liberal use of multiple pesticides: on skin, clothing, in tents, sprayed in camp. Government reports indicate that more than 37 pesticide ingredients were used
 - DOD reports that 41,000 troops were overexposed to pesticides in the Gulf War
 - Epidemiologic studies consistently link higher GWVI rates to use of pesticides



Combinations of Exposures

- Studies consistently find that Gulf veterans were commonly exposed to multiple neurotoxic substances of potential concern
- Dozens of animal studies in recent years have shown that combinations of Gulf War-related exposures can act synergistically, yielding toxic effects greater than individual exposures, for example:
 - *PB*
 - *DEET (repellant, used on skin)*
 - *Permethrin (repellant, used on uniforms)*



Epidemiologic Findings Consistently Implicate Neurotoxic Exposures

- Many Gulf veteran studies have evaluated illness rates in relation to long list of self-reported exposures
- Most prominent and consistent findings:
significantly higher illness rates found in veterans who report greater use of PB pills, pesticides, and possible exposure to chemical weapons

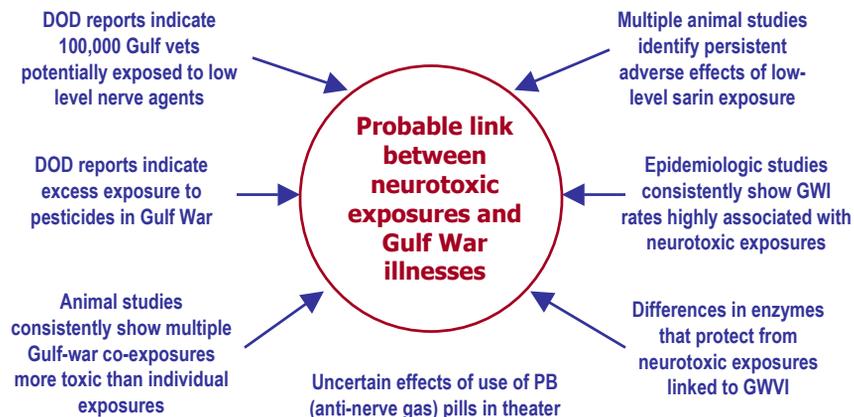


Biochemical Differences May Have Made Some Individuals More Vulnerable to Neurotoxins

- Individuals differ in their ability to inactivate neurotoxins, due to genetic variability, differences in certain enzyme levels
- Studies have found ill Gulf War veterans have lower levels of PON1, an enzyme that neutralizes nerve agents, pesticides
- These and related findings may help explain why some veterans developed chronic problems after the war, others did not



Multiple lines of evidence converge: Probable link between neurotoxic exposures and Gulf War illnesses



2004 Report and Recommendations: Additional Findings

- **Treatments for Gulf War illnesses are urgently needed**
 - **Little is currently known about what treatments are effective for Gulf War illnesses**
 - **Committee has designated identification of effective treatments for GWVI to be the highest research priority**



2004 Report and Recommendations: Additional Findings

- **Other Gulf War exposures may have contributed to GWVI**
 - **Future reports will provide findings and recommendations on additional topics (e.g. oil well fires, depleted uranium, vaccines)**
- **Research on Gulf War veterans' illnesses has important implications for current deployments and homeland security**



Research Advisory Committee on Gulf War Veterans Illnesses: 2004 Report and Recommendations

- **Key Points**

- Recent and accumulated research have provided important insights about nature of Gulf War illnesses and the effects of Gulf War-related exposures
- Gulf War illnesses affect a substantial proportion of veterans and are not explained by deployment stress or psychiatric illness
- Growing body of evidence indicates an important component of GWVI is neurological, supports a probable link with neurotoxic exposures during the war

