

**Presentation 5 – Lea Steele**

**2007 RAC Report**  
**Discussion of Committee Recommendations**

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**Lea Steele, Ph.D.**  
**April 24-25, 2007**

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Research Advisory Committee On Gulf Air Waters' Status

**2007 RAC Report**

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- **Report Overview and Outline**
- **Timeline**
- **Review/ Discussion of Recommendations**

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### **Excerpts from the RAC-GWVI Charter: Committee Charge and Activities**

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- The RAC shall provide advice and make recommendations to the Secretary on research related to understanding and treating the health consequences of military service during the Persian Gulf War.
- The Committee shall assess the overall effectiveness of government research to answer central questions on the nature, causes, and treatments of Gulf War-associated illnesses.
- The Committee shall review all relevant funded research, investigations, and processes for funding research and assess their methods, results, and implications.



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### **RAC-GWVI Charter: Committee Charge and Activities**

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The guiding principle shall be the premise that the fundamental goal of Gulf War-related research is to improve the health of Gulf War veterans.



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## 2007 RAC Report

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- First comprehensive RAC Report released in October, 2004 (covered topics considered by RAC in 2002, 2003, and some information from 2004)
  
- 2007 RAC Report:
  - Will cover, in detail, new topics considered by the RAC from 2004 through 2006 (and limited info from 2007)
  
  - Will summarize and update topics covered in 2004 RAC Report



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## 2004 RAC Report: Topics Addressed

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- Epidemiologic research on Gulf War veterans
- Treatment research
- Neurological abnormalities in Gulf War veterans
- Neurotoxins (PB, pesticides/repellants, low-level sarin) and GWI
- Minimal info on other exposures (prelim info and recs re: vaccines)
- Need for additional information on diagnosed diseases, mortality
- Birth defects and the health of GWV family members
- Need for coordination of GW data resources among federal agencies
- Implications of GWI research for other deployments, homeland security
- Focus and effectiveness of federal GW research programs



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### **2007 RAC Report: Topics Addressed 2004-2006**

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- Depleted uranium
- Oil well fires
- Other petroleum exposures
- Vaccine topics
- Infectious diseases
- Particulates, sand
- Solvents
- CARC paint
- Multisymptom illness (CFS, FM, MCS)
- Cancer research in GWV
- Immune function in GWV
- Health, exposures of GW troops from allied countries
- Synthesis/analysis of findings on GWI etiologic factors



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### **2007 RAC Report: Summary/Update of Topics Previously Addressed**

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- Epidemiologic research on GW veterans, family members
- Psych exposures and illness in Gulf War veterans
- Treatment research
- Neurological abnormalities in Gulf War veterans
- Neurotoxins
- Federal GW research programs



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## **2006-2007: New Direction in RAC Activities**

### **Toward a Better Understanding of the "Nature" of GWI**

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#### **Considering Physiological Mechanisms Potentially Underlying GWI**

- **Introductory discussions: neuroinflammation, neuroplasticity, biology of multisymptom illness, mitochondrial injury**
- **Potential role of CNS proinflammatory processes, autonomic dysregulation in GWI**



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## **2007 RAC Report: Overview**

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- **2007 RAC Report:**
  - **Will cover, in detail, topics considered by the RAC from 2004 through 2006 (and limited info from 2007)**
  - **Will summarize and update topics covered in 2004 RAC Report**



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## **2007 RAC Report: Intent**

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- **To accurately synthesize the broad range of information considered by the RAC**
- **To accurately reflect committee discussions and recommendations associated with this information**
- **To collate and analyze the information in order to provide meaningful insights**



## **2007 RAC Report: Primary Objective**

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- **To recommend research with the best potential for improving the health of ill Gulf War veterans**
- **To provide recommendations that reflect a synthesis of what is known about the nature, causes, and treatments for Gulf War illness**



## 2007 RAC Report: Primary Focus

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- Primary focus is Gulf War illness (GWI)
- Report will also describe findings, recommend research re: other Gulf War-related health issues of concern
  - Diagnosed conditions (ALS, cancer, other)
  - Health of family members



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## 2007 RAC Report: Why Focus on GWI?

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Previous panel reports have not focused specifically on GWI and research related to the nature and causes of GWI

- Early reports (DHSB, PAC, NIH): little research available
- More recent panel reports:
  - PSOB: focus on DOD exposure reports, little scientific review
  - IOM Gulf War Reports:
    - primary focus on diagnosed diseases, evidence from occupational health studies
    - minimal consideration of GWI, self-reported symptoms, links with Gulf War exposures
    - minimal consideration of toxicological research



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## 2007 RAC Report: The Need to Address GWI

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**GWI is the most prominent health issue affecting Gulf War veterans**

**Gulf War Illness research is complex, challenging to study, and difficult to make sense of**

- **Diverse exposures of possible concern; almost no measured exposures**
- **GWI associated with multiple concurrent symptom types, few objective diagnostic findings**



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## 2007 RAC Report: The Need to Address GWI

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- **Vast amount of relevant information now available**
- **Options:**
  - *Disregard information if it isn't the type preferred or because it is difficult to integrate?*
  - *Collate available information, determine if conclusions can be drawn from consistent patterns, parallel findings from different sources*



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## **Draft/Outline: Organization**

### **5 sections**

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- 1) **GWV and the Health of GW veterans**
- 2) **What Caused GWV?**
- 3) **The Nature of GWV**
- 4) **Federal Research on the Health of GW veterans**
- 5) **Research Priorities and Recommendations**



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## **Draft/Outline**

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- **Draft chapters provided for most of the topics “new” to the 2007 Report, other chapters outlined**
- **Additional background information on each topic in meeting minutes; many were summarized in Dec 2005**



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## Statistical Analyses?

- Gulf War illness research usually involves evaluation of multiple possible “causal” factors
- Some of the most prominent Gulf War epidemiologic studies have great samples and data collection, but overly simplistic data analyses



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## Are All Exposures Associated with Gulf War Illness?

Example: Data from Kansas study

	GWI cases	GWI controls	OR (unadj)
Used PB	72%	44%	3.2*
DU	60%	36%	2.6*
Contact with POWs	59%	35%	2.6*
Contact with dead animals	54%	34%	2.2*
SCUD w/in 1 mile	48%	31%	2.1*
Ground combat	32%	25%	1.8
Pesticide-treated uniforms	27%	9%	3.7*



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**After Adjusting for Confounding:**

**Few Exposures Are Associated with Gulf War Illness**

	<b>GWI cases</b>	<b>GWI controls</b>	<b>OR</b>
<b>Used PB</b>	<b>72%</b>	<b>44%</b>	<b>2.9*</b>
<b>Contact with dead animals</b>	<b>54%</b>	<b>34%</b>	<b>1.4</b>
<b>DU</b>	<b>60%</b>	<b>36%</b>	<b>1.3</b>
<b>Contact with POWs</b>	<b>59%</b>	<b>35%</b>	<b>1.4</b>
<b>SCUD w/in 1 mile</b>	<b>48%</b>	<b>31%</b>	<b>2.2*</b>
<b>Ground combat</b>	<b>32%</b>	<b>25%</b>	<b>0.6</b>
<b>Pesticide-treated uniforms</b>	<b>27%</b>	<b>9%</b>	<b>2.9*</b>



**Important to Consider How Data Were Collected and Analyzed**

- **Overly simple analyses can generate erroneous conclusions about exposures and GWI**
- **Many factors assessed in RAC evaluation of results from epi studies; analytic methods figure prominently**



<b>Gulf War Exposures in Relation to GWI: Summary of Epidemiologic Evidence</b>					
	<u>Unadi</u>	<u>Adj</u>	<u>Adj Results</u> <u>Consist</u>	<u>Dose/</u> <u>resp</u>	<u>S/R</u> <u>variable</u>
Psychological stressors	1.6-3.1	ns	yes	-	+
Chemical weapons	1.9-6.3	2.3-7.8	~	-	↓
Pesticides	1.9-3.8	1.7-8.7	yes	yes	+
NAPP/PB pills	1.4-4.4	1.5-2.9	yes	yes	+
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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<b>Gulf War Exposures in relation to GWI: Summary of Evidence</b>		
	Pattern of Exposure Compatible with Patterns of GWI?	
	Higher in ground troops?	Greater exp in 1990-91 PGW?
Psychological stressors	yes	no
Chemical weapons	yes	yes
Pesticides	yes	?
NAPP/PB pills	yes	yes
DU	yes	no
Oil well fires	yes	yes
Vaccines: anthrax	yes	no
Number of vaccines	no	no

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### **The Process: Handling Drafts Circulated for Committee Review**

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- Complete drafts will be provided in hard copy to each member
- Members asked to return hard copies, with comments, to RAC office
- Committee members asked not to share drafts or contents with nonmembers
- Final report provided first to Secretary, then will be publicly released



### **2007 RAC Report: Proposed Timeline**

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- Current meeting: Review and discuss report recommendations
- Mid June: Members receive 1<sup>st</sup> draft for detailed review and comment; return to RAC office by early July (~3 wks)
- July 18-19 RAC meeting: Discuss proposed changes to be incorporated into 2<sup>nd</sup> draft
- Early August: Members receive 2<sup>nd</sup> draft for review, comment; return to RAC office (~2 wks)
- Final report to Secretary by late August/early September
- October 22-23 RAC Meeting: Public Release of 2007 RAC Report



**Today's Meeting:  
Review, Discuss Recommendations**

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- Review for some members, others not present for presentations/discussions of individual topics
- The majority of members have been involved in generating most individual draft recommendations



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**Today's Meeting:  
Review, Discuss Recommendations**

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**Development of draft recommendations:**

- Recommendations included in 2004 report
- Recommendations discussed at the time topic was presented
- Recommendation discussions at Dec 2005 RAC "synthesis" meeting
- Research recommendations provided by RAC to VA in early 2006
- Committee discussions 2006-2007



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# **RAC 2007 Report**

## **Discussion of Recommendations**

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### **Section 1**

#### **GWV and the Health of Gulf War Veterans**

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- **Summary: background of GWV issue**
- **Summary: Epidemiologic studies, GWV characteristics and prevalence**
- **Longitudinal assessment of veterans with GWV**
- **Summary: GWV treatment research, lack of systematic info on effective treatments**
- **Other health issues of concern for Gulf War veterans**

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## **Recommendations: Section 1 (i)**

### **GWV and the Health of Gulf War Veterans**

**Because of the urgent need for treatments that substantially improve the health of veterans with Gulf War illness, the Committee reiterates its previous recommendation that research focused on identifying and evaluating treatments for Gulf War illness be vigorously pursued and given highest priority**



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## **Recommendations: Section 1 (ii)**

### **GWV and the Health of Gulf War Veterans**

**To provide information on other health issues of concern for Gulf War veterans, the Committee recommends the following:**

- **Epidemiologic research to identify rates of diagnosed neurological diseases (including multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, and brain cancers), as well as central nervous system abnormalities that are difficult to precisely diagnose, in Gulf War veterans and appropriate comparison groups**
- **Continuation of current research comparing cancer rates in Gulf War and nondeployed era veterans, and longitudinal assessment of cancer rates in Gulf War era veterans by repeating these studies at regular intervals**



**RAC - G W V I**

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### **Recommendations: Section 1 (iii)**

#### **GWI and the Health of Gulf War Veterans**

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To provide information on other health issues of concern for Gulf War veterans, the Committee recommends the following:

- Regular evaluation of overall and cause-specific mortality rates in Gulf War veterans, including deaths in subgroups of Gulf War veterans identified by deployment locations, branch, and exposures reported in the National Survey of Gulf War Era Veterans
- Use of innovative study designs to evaluate risk of specific types of birth defects and other health problems in children of Gulf War veterans



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### **Recommendations: Section 1 (iv)**

#### **GWI and the Health of Gulf War Veterans**

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The Committee recommends the following principles in collecting and analyzing data on Gulf War illness and the health of Gulf War veterans:

- Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups
- Research findings reported from studies of Gulf War veterans should not be limited to results that combine all deployed veterans into a single group, but should include results for subgroups of Gulf War veterans defined according to veterans' locations in theater, exposures, or other deployment characteristics potentially relevant to outcomes of interest
- Evaluation of associations between deployment-related exposures and health outcomes in Gulf War veterans should use analytic methods that appropriately control for effects of confounding introduced by multiple exposures in theater



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## **Section 2: What Caused GWI? Scientific Findings on Gulf War Experiences and Exposures**

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- Psychological stressors
- Kuwaiti oil well fires
- Depleted uranium
- Vaccines
- Neurotoxic chemicals: PB, pesticides, nerve agents
- Infectious diseases
- Other exposures: sand, tent heaters, solvents, jet fuel, CARC, contaminated food and water



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## **Section 2 Recommendations**

### **Psychological stressors and the health of GW veterans**

**Evidence from multiple studies consistently indicates that Gulf War illness was not caused by psychological stressors during the war and the large majority of ill Gulf War veterans do not have psychiatric conditions.**

**The Committee therefore recommends that federal funding for Gulf War illness research not be provided for studies of posttraumatic stress disorders or other psychiatric conditions, or studies that focus on psychological factors as the central cause of Gulf War illness.**



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## Section 2 Recommendations

### Kuwaiti Oil Well Fires (i)

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Based on available research and exposure information, the Committee finds that Kuwaiti oil well fires are not likely to be a primary cause of Gulf War multisymptom illness for the majority of affected veterans. However, additional information is required to determine if oil well fire exposures may have contributed to the risk of GWI or diagnosed medical conditions in identifiable subsets of Gulf War veterans.

To address remaining questions relating to long-term health effects of the Kuwaiti oil fires, the Committee recommends the following research:

- Analyze data collected from completed and ongoing epidemiologic studies to determine whether the subset of Gulf War veterans with the highest level exposures to smoke, oil, and particulates from the Kuwaiti oil well fires have elevated rates of multisymptom illness. Such analyses should properly adjust for confounding effects of other Gulf War exposures.



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## Section 2 Recommendations

### Kuwaiti Oil Well Fires (ii)

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- Conduct additional analyses of existing data from the U.S. National Survey of Gulf War veterans to determine if rates of chronic respiratory diseases, pulmonary function abnormalities, or other medical conditions are significantly associated with modeled or self-reported levels of oil fire exposures.
- Continue monitoring cancer rates in Gulf War veterans, including assessment of cancer rates among subsets of veterans identified by modeled levels of oil fire exposures, self-reported oil fire exposure levels, and/or locations and time periods of deployment



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## Section 2 Recommendations

### Depleted Uranium (i)

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Preliminary evidence from animal studies that DU accumulates in the brain and can cause adverse physiological and behavioral effects is of great interest and deserves further elaboration.

However, the Committee finds that specifically with respect to the health of Gulf War veterans, the primary issues of concern are whether DU is a cause or contributor to Gulf War multisymptom illness, cancer, or mortality.

Therefore, prior to making recommendations relating to specific toxicological studies to evaluate effects of DU, additional research is needed to evaluate rates of GWI, as well as other health outcomes of concern, in an expanded cohort of individuals exposed to DU during the Gulf War.



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## Section 2 Recommendations

### Depleted Uranium (ii)

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To address priority questions concerning health effects related to depleted uranium in the Gulf War, the Committee recommends the following research:

- Conduct a comprehensive study of health parameters in Gulf War veterans who had the greatest exposure to depleted uranium during deployment, and an appropriate comparison group.



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## Section 2 Recommendations

### Depleted Uranium (iii)

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The exposed cohort should include, at minimum, all locatable Gulf War veterans who were exposed to DU in relation to friendly fire incidents, who served in units tasked with processing Iraqi or Allied vehicles struck by DU munitions, and U.S. and Canadian Gulf War veterans exposed to DU in relation to the Camp Doha fire and subsequent cleanup activities.

Health measures should include, in addition to laboratory measures evaluated in the Baltimore VA DU Follow up Study, detailed information on symptoms, GWI, functional status, neurological and neuropsychological assessments, all diagnosable medical and psychiatric conditions including cancer, and reproductive outcomes.



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## Section 2 Recommendations

### Depleted Uranium (iv)

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- In current and future studies of Gulf War veterans, assess possible DU exposures by querying veterans in detail about experiences most likely to have resulted in DU exposures, including their involvement in friendly fire incidents and the extent of their exposure to vehicles destroyed by U.S. munitions
- Continue monitoring cancer rates and mortality in Gulf War veterans, including assessment of cancer and mortality rates among subsets of veterans identified as being exposed to DU and veterans who served in areas where the highest concentrations of DU munitions were fired.



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## Section 2

### Vaccines

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- Information on number and types of vaccines received by Gulf War veterans
- Health effects of vaccines used in the Gulf War: acute side effects, AVA studies, animal studies, questions re: squalene antibodies, receipt of multiple vaccines
- Findings from studies of Gulf War veterans



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## Section 2 Recommendations

### Vaccines (i)

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- Commission a case-control study to provide clear answers concerning possible associations between GWI and squalene antibodies.

The study should, at minimum, analyze blinded samples from ill and healthy Gulf War veterans for the presence of squalene antibodies using each of the assays developed for this purpose. The project should be organized and overseen by qualified investigators not affiliated with either the federal government or with civilian scientists whose initial work raised concerns in relation to squalene.



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## Section 2 Recommendations

### Vaccines (ii)

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- In current and future epidemiologic studies of Gulf War veterans, analyze data on associations between GWI and individual vaccines, combinations of vaccines, and number of vaccines received using methods that control for potential confounding by other Gulf War-related exposures
- **\*\*Evaluate the association of AVA with chronic symptoms and multisymptom illness by conducting a retrospective cohort study of military personnel known to have received/not received AVA in the early years of the AVIP program**



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## Section 2

### Neurotoxins: PB, Pesticides, Nerve Agents

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- **PB: patterns of exposure, health effects, findings from studies of Gulf War veterans**
- **Pesticides and insect repellants: patterns of exposure, health effects, findings from studies of Gulf War veterans**
- **Nerve agents: new information on exposure, health effects, findings from studies of Gulf War veterans**
- **Combined exposure to neurotoxins**



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## Section 2 Recommendations

### Neurotoxins: PB, Pesticides, Nerve Agents

During the 1990-1991 Gulf War, military personnel were widely exposed to a variety of neurotoxic compounds that included pyridostigmine bromide pills, different types and dosages of pesticides and insect repellants, and low-level exposure to nerve agents. The chemical action of many of these compounds involves inhibition of the enzyme acetylcholinesterase and the buildup of the neurotransmitter acetylcholine.

Animal studies have consistently found that these neurotoxins, in combination with one another and other Gulf War-related exposures, can have synergistic effects that exceed the effects of individual exposures.

Epidemiologic studies that have assessed independent effects of multiple exposures in the Gulf War have consistently found that use of pyridostigmine bromide and use of pesticides are significant risk factors for Gulf War illness. Self-reported information concerning nerve agent exposures in relation to Gulf War illness is less consistent and reliable but several studies have reported excess pathology in Gulf War veteran subgroups who were downwind from the Khamisiyah chemical munitions demolitions.



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## Section 2 Recommendations

### Neurotoxins: PB, Pesticides, Nerve Agents

Due to the consistency of findings relating GWI to neurotoxic exposures during the war, the Committee gives high priority to studies that further characterize specific effects of Gulf War-related neurotoxic exposures, and recommends the following research:

- Studies that evaluate and characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides, insect repellants, and low-level sarin
- Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This might include studies that utilize technologies capable of detecting toxins or secondary metabolites retained for many years following exposure, studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxin exposure, and studies that identify persistent changes in the central nervous system and autonomic function associated with exposure to Gulf War-related neurotoxins.



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## Section 2

### Infectious Diseases

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- Exposure to infectious pathogens in the Gulf War
- Chronic health effects potentially associated with GW-associated pathogens
- Research on infectious disease in relation to chronic symptoms in Gulf War veterans



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## Section 2 Recommendations

### Infectious Diseases

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Because of unanswered questions related to possible associations between GW and persistent intracellular infections in Gulf War veterans, the Committee recommends the following research:

- Using the most reliable assay method available, determine the rate of latent and/or active leishmania infection in veterans with Gulf War illness and healthy controls
- Using the most reliable assay method available, determine the rate of mycoplasma infection in veterans with Gulf War illness and healthy controls



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## Section 2

### "Other" Exposures in Theater

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- Sand and particulates
- Tent heaters
- Solvents
- Jet fuel
- CARC
- Contaminated food and water



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## Section 2 Recommendations

### Other Exposures (i)

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A number of exposures in theater are unlikely to have been primary causes of Gulf War illness in the majority of ill veterans, but may have contributed to illness risk in identifiable subsets of Gulf War veterans.

To better understand the potential contributions of two of these exposures, CARC paint and unvented tent heaters, the Committee recommends the following research:



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## Section 2 Recommendations

### Other Exposures (ii)

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- Conduct an epidemiologic investigation to determine if personnel who served with the Army National Guard's 325th Maintenance Company in the Gulf War suffer excess health problems in comparison to nondeployed personnel, to describe the nature of any excess problems, and to evaluate the degree to which problems are associated with veterans' exposure to CARC during deployment, alone or in combination with other Gulf War-related exposures.
- In existing and future epidemiologic studies of Gulf War veterans, analyze data collected relating to exposure to unvented tent heaters during the Gulf War using analytic methods that control for the effects of other exposures in theater, to determine whether tent heaters contributed to the risk of Gulf War illness, particularly among Army veterans in theater during winter months.



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## Section 3: The Nature of GWI

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- The biology of GWI
- GWI in relation to multisymptom conditions in the general population
- Future directions in understanding physiological mechanisms underlying GWI



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### **Section 3:**

#### **The Biology of GWI**

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- **CNS abnormalities associated with GWI**
- **Autonomic function in Gulf War veterans**
- **Little indication of sensory neuropathy in GW veterans**
- **Neuroendocrine findings in GW veterans**
- **Immune findings associated with GWI**
- **Relationship of GWI to genotype/activity of enzymes that neutralize effects of neurotoxins**



### **Section 3 Recommendations**

#### **The Biology of GWI (i)**

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**The Committee places a high priority on identification of biological markers for GWI and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing associations between Gulf War illness and neurological, immune, endocrine, and enzyme abnormalities, the Committee recommends the following research:**



### **Section 3 Recommendations**

#### **The Biology of GWI (i)**

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- **Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with GWI, including illness or exposure subgroups, from healthy Gulf War veterans**
- **Comprehensive evaluation of autonomic nervous system function associated with GWI, as well as illness and exposure subgroups**



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### **Section 3 Recommendations**

#### **The Biology of GWI (iii)**

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- **Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures**
- **Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups**



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### **Section 3 Recommendations**

#### **The Biology of GWI (iv)**

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- **Comprehensive evaluation of hypothalamic-pituitary-adrenal axis parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups**
- **Studies that utilize new technologies (proteomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, as well as illness and exposure subgroups**



### **Section 3 Recommendations**

#### **GWVI in Relation to Multisymptom Conditions in the General Population (i)**

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**Research studies have demonstrated both differences and similarities between GWI and defined multisymptom conditions found in the general population.**

**Symptom complexes consistent with defined chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS) are found in Gulf War veterans at elevated rates, but account for only a fraction of the excess morbidity affecting Gulf War veterans.**

**Research related to these conditions may provide important insights and clues regarding biological processes that underlie veterans' symptoms, treatment interventions that may benefit ill veterans, and research methodologies useful in studying syndromes defined primarily by symptoms. The Committee therefore recommends the following research:**



### **Section 3 Recommendations**

#### **GWVI in Relation to Multisymptom Conditions in the General Population (ii)**

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- **Studies that determine the extent to which physiological characteristics that distinguish CFS, FM, and MCS patients from healthy controls are also associated with Gulf War illness.**

**Such studies should include identification of cerebrospinal fluid levels of neuropeptides associated with central pain processing, comprehensive evaluation of autonomic function and hypothalamic-pituitary-adrenal parameters in ill veterans, studies of immune and inflammatory parameters potentially associated with multisymptom illnesses, and genomic and proteomic evaluation of blood and cerebrospinal fluid of veterans with GWI.**

**Emerging research related to CFS, FM, and MCS should also be monitored on a continuing basis to identify new findings potentially useful in understanding Gulf War illness.**



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### **Section 3 Recommendations**

#### **GWVI in Relation to Multisymptom Conditions in the General Population (iii)**

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- **Pilot studies and, where indicated by adequate evidence, clinical trials to determine whether veterans with GWI benefit from therapies shown to improve the health of patients with FM, CFS, and MCS.**
- **Coordination of federal GWI research programs with other federal research programs focused on multisymptom conditions such as CFS and FM.**



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### Section 3

#### **Future Directions in Identifying Physiological Mechanisms Underlying GWI**

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- **Physiological processes considered in brief (neuroinflammation, neuroplasticity, pathophysiology of CMI)**
- **Potential role for central neuroinflammatory processes and autonomic dysregulation in GWI**



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### Section 3 Recommendations

#### **Future Directions in Identifying Physiological Mechanisms Underlying GWI**

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**After reviewing evidence concerning potential interrelationships between Gulf War-related exposures, persistent neuroinflammatory processes, cholinergic dysregulation, and the chronic symptoms of Gulf War illness, the Committee supports additional studies in this area and recommends the following research:**

- **Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by Gulf War illness**
- **Animal studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs**



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## **Section 4**

### **Federal Research on GWI and the Health of GW Veterans**

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- **Background: Federal GW Research Programs**
- **Federal GW Research in 2004-2005**
- **Recent developments in Federal GW Research: DOD**
- **Recent Developments in Federal GW Research: VA**



## **Section 4 Recommendations (i)**

### **Federal Research on GWI and the Health of GW Veterans**

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The committee welcomes recent funding and programmatic developments related to federal Gulf War research, and urges Congress to allocate no less than 45 million annually for VA and DOD Gulf War research programs, consistent with annual funding levels committed for federal Gulf War research between 1999 and 2001.

Specifically, the Committee recommends:



#### **Section 4 Recommendations (ii)**

##### **Federal Research on GWI and the Health of GW Veterans**

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- That Congress appropriate a minimum of \$30 million annually to the Department of Defense for the Gulf War Veterans' Illness Research Program managed by the Congressionally Mandated Medical Research Program for research primarily focused on evaluating the effectiveness of available treatments for Gulf War illness, and identification of objective measures that distinguish ill from healthy veterans.
- That Congress continue to appropriate a minimum of \$15 million annually to the Department of Veterans Affairs for the Gulf War Research Center at the University of Texas Southwestern for a comprehensive program focused primarily on identifying treatments and diagnostic markers by determining specific mechanisms underlying Gulf War illness, in accordance with priorities identified by the Committee.



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#### **Section 4 Recommendations (iii)**

##### **Federal Research on GWI and the Health of GW Veterans**

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- That the Department of Veterans Affairs Office of Research and Development continue to solicit and fund additional GWI research studies consistent with recommendations in this report through Gulf War-specific funding announcements and general funding solicitations.
- That VA continue to fund the ALS Registry and brain tissue bank, focused more specifically on data, materials, and projects related to Gulf War era veterans, with both programs expanded to include Gulf War era veterans with other diagnosed neurological diseases and difficult-to-diagnose neurological conditions



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## **Section 4 Recommendations (iv)**

### **Federal Research on GWI and the Health of GW Veterans**

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- That the Department of Defense and the Department of Veterans Affairs coordinate Gulf War research efforts to avoid duplication of effort and ensure that priority research objectives are satisfactorily achieved



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## **Section 5**

### **Research Priorities and Recommendations**

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- Summarizes, prioritizes research recommendations from the entire report
- Two research priority groups, individual topics within groups numbered sequentially
- Recommended guidelines relating to clinical and epidemiologic research on Gulf War veterans



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**Section 5: Research Priorities and Recommendations:  
Two Priority Groups**

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**Highest Priority Gulf War Research Topics**

1. Identification of effective treatments for GWI
2. Identification of objective measures that distinguish veterans with GWI from healthy veterans
3. Studies that characterize effects of neurotoxic exposures associated with GWI
4. Epidemiologic research to determine if Gulf War veterans are affected by excess rates of neurological disease



**Section 5: Research Priorities and Recommendations:  
Research Guidelines**

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**Other Research Areas of Importance for Addressing GW Health Issues**

1. Epidemiologic Research: General
2. Studies to further characterize effects of Gulf War exposures



## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

##### 1. Identification of Effective Treatments for Gulf War Illness.

The highest priority research on the health of Gulf War veterans will advance efforts to identify beneficial treatments for Gulf War illness. The primary objective is the conduct of well-designed clinical trials of treatments that hold promise for providing substantial benefit for veterans with Gulf War illness. Gulf War illness treatment research should include:



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## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

##### 1. Identification of Effective Treatments for Gulf War Illness:

- Studies that identify and empirically evaluate treatment outcomes associated with currently available therapies. Preliminary research should include observational studies and pilot trials that provide systematic information on treatment outcomes in order to identify promising treatments suitable for larger clinical trials
- Research to identify pathophysiological mechanisms underlying Gulf War illness that are likely to be amenable to treatment intervention



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## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

#### 2. Identification of Objective Measures that Distinguish Veterans with Gulf War illness from Healthy Veterans.

The Committee places a high priority on identification of biological markers for Gulf War illness and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing associations between Gulf War illness and neurological, immune, endocrine, genetic, and biochemical alterations, the Committee recommends the following research:



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### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

#### 2. Identification of Objective Measures that Distinguish Veterans with Gulf War illness from Healthy Veterans

- Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with Gulf War illness, including illness or exposure subgroups, from healthy Gulf War veterans
- Comprehensive evaluation of autonomic nervous system function associated with Gulf war illness, as well as illness and exposure subgroups



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### Research Priorities and Recommendations

#### Highest Priority Gulf War Research Topics

#### 2. Identification of Objective Measures that Distinguish Veterans with Gulf War illness from Healthy Veterans.

- Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures
- Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by GWI



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### Research Priorities and Recommendations

#### Highest Priority Gulf War Research Topics

#### 2. Identification of Objective Measures that Distinguish Veterans with Gulf War illness from Healthy Veterans.

- Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups
- Comprehensive evaluation of hypothalamic-pituitary-adrenal axis and other neuroendocrine parameters in association with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups
- Studies that determine the extent to which other physiological characteristics that distinguish CFS, FM, and MCS patients from healthy controls are also associated with GWI



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## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

#### 2. Identification of Objective Measures that Distinguish Veterans with Gulf War illness from Healthy Veterans.

- Studies to determine rates of latent or active leishmania and mycoplasma infection in veterans with Gulf War illness and healthy controls
- Studies that utilize new technologies (proteomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, as well as illness and exposure subgroups



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## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

#### 3. Studies that Characterize Effects of Neurotoxic Exposures Associated with GWI.

Due to the consistency of findings relating Gulf War illness to neurotoxic exposures during the war, the Committee gives high priority to studies that further characterize specific effects of Gulf War-related neurotoxic exposures, and recommends the following research:



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### Research Priorities and Recommendations

---

#### Highest Priority Gulf War Research Topics

#### 3. Studies that Characterize Effects of Neurotoxic Exposures Associated with GWI.

- Studies that evaluate and characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.
- Studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs



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## Section 5

### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

#### 3. Studies that Characterize Effects of Neurotoxic Exposures Associated with GWI.

- Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans.

This might include studies that utilize technologies capable of detecting toxins or secondary metabolites retained for many years following exposure, studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxin exposure, and studies that identify persistent changes in the central nervous system and autonomic function associated with exposure to Gulf War-related neurotoxins.



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### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

**4. Epidemiologic Research to Determine if Gulf War Veterans Are Affected by Excess Rates of Neurological Disease.**

Research studies indicating that Gulf War veterans have a significantly higher rate of amyotrophic lateral sclerosis than their nondeployed peers raise concerns about other chronic neurological conditions for which no studies have been conducted.

The committee therefore recommends the following:



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### Research Priorities and Recommendations

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#### Highest Priority Gulf War Research Topics

**4. Epidemiologic Research to Determine if Gulf War Veterans Are Affected by Excess Rates of Neurological Disease.**

- Epidemiologic studies to identify rates of diagnosed neurological diseases (including multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, and brain cancers), as well as central nervous system conditions that are difficult to precisely diagnose, in Gulf War veterans and a nondeployed comparison group
- Refocus VA's ALS Registry and brain tissue bank more specifically on projects related to Gulf War era veterans, and expand both programs to include Gulf War era veterans with other diagnosed neurological diseases as well as difficult-to-diagnose neurological conditions



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## Section 5

### Research Priorities and Recommendations

#### Other Research Areas of Importance for Addressing Gulf War Health Issues

##### Epidemiologic Research: General

- Continue current research evaluating cancer rates in Gulf War era veterans, and assess cancer rates among subsets of veterans identified as being exposed to chemical nerve agents, depleted uranium, and oil well fires
- Regular evaluation of overall and cause-specific mortality rates in Gulf War veterans, including deaths in subgroups of Gulf War veterans identified by deployment locations, branch, and exposures reported in the National Survey of Gulf War-era Veterans



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### Research Priorities and Recommendations

#### Other Research Areas of Importance for Addressing Gulf War Health Issues

##### Epidemiologic Research: General

- Conduct additional analyses of available data from existing large population-based studies to more thoroughly evaluate rates of multisymptom illness, cancer, respiratory conditions, and other health outcomes in relation to self-reported and modeled exposures, appropriately controlling for effects of other exposures in theater
- Use of innovative study designs to evaluate risk of specific types of birth defects and other health problems in children of GW veterans



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## Section 5

### Research Priorities and Recommendations

#### Other Research Areas of Importance for Addressing Gulf War Health Issues

##### Studies to Further Characterize Effects of Gulf War Exposures

- Conduct a comprehensive study of health parameters in an expanded cohort of Gulf War veterans who had the greatest exposure to depleted uranium during deployment, and an appropriate comparison group
- Commission a case-control study to determine whether Gulf War illness is associated with elevated levels of squalene antibodies



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### Research Priorities and Recommendations

#### Other Research Areas of Importance for Addressing Gulf War Health Issues

##### Studies to Further Characterize Effects of Gulf War Exposures

- \*\*\*Evaluate the association of anthrax vaccine adsorbed with chronic symptoms and multisymptom illness by conducting a retrospective cohort study of military personnel known to have received/not received AVA during the Gulf War and/or in the early years of the AVIP program



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### Research Priorities and Recommendations

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#### Other Research Areas of Importance for Addressing Gulf War Health Issues

##### Studies to Further Characterize Effects of Gulf War Exposures

- Conduct an epidemiologic investigation to determine if personnel who served with the Army National Guard's 325th Maintenance Company in the Gulf War suffer excess health problems associated with exposure to CARC paint during deployment, alone or in combination with other Gulf War-related exposures
  
- *In vivo* and *in vitro* studies that characterize molecular, cellular, systemic, and behavioral effects of other compounds to which Gulf War veterans were exposed during the war, individually and in combination



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## Section 5

### Research Priorities and Recommendations

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- Two research priority groups
  
- Recommended guidelines relating to clinical and epidemiologic research on Gulf War veterans



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## Section 5

### Research Priorities and Recommendations

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#### Guidelines for Clinical and Epidemiologic Research on Gulf War Veterans

- Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups
  
- Research findings reported from studies of Gulf War veterans should not be limited to results that combine all deployed veterans into a single group, but should also include results for subgroups of Gulf War veterans defined according to veterans' locations in theater, exposures, or other deployment characteristics potentially relevant to outcomes of interest



## Section 5

### Research Priorities and Recommendations

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#### Guidelines for Clinical and Epidemiologic Research on Gulf War Veterans

- Evaluation of associations between deployment-related exposures and health outcomes in Gulf War veterans should use analytic methods that appropriately control for effects of confounding introduced by multiple exposures in theater
  
- Research studies whose principle focus is on psychiatric disorders such as posttraumatic stress disorder or effects of psychological stressors are not directly relevant to Gulf War illness and should not be considered Gulf War illness research Two research priority groups

