

Appendix A

Presentation 1 – Lea Steele

Exposures and Gulf War Illnesses

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Approaching the Big Picture

- > Context for understanding potential relationship between wartime exposures and Gulf War veterans' health

- > The work of the RAC-GWVI: *Where we've been and where we're going*

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Work of the RAC-GWVI: Identify Research Priorities for Gulf War Illnesses

Research to address questions related to:

- > *Nature of*
- > *Causes of,*
- > *Treatments*

for Gulf War veterans' illnesses

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Why Address the Causes of Gulf War Illnesses?

- > To shed light on the physiological nature of veterans' conditions

- > To assist in identifying treatments

- > To prevent similar problems in future deployments

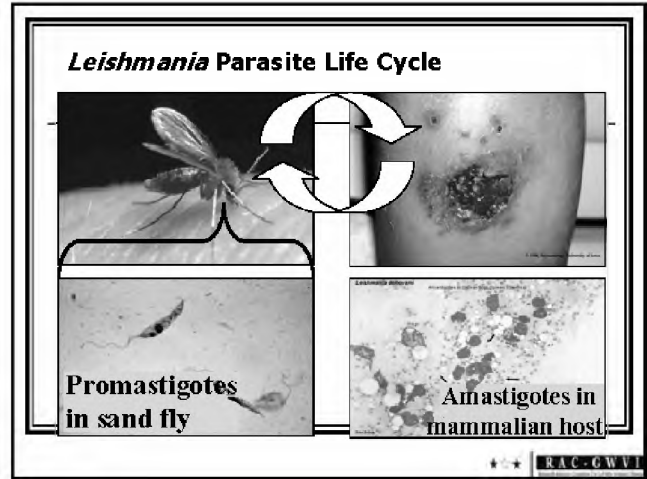
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Systematic review of exposure-related topics

The Committee has considered evidence related to a variety of exposures in theater

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Committee has reviewed large amount of information on exposures potentially relevant to Gulf War veterans' health

Major types of Gulf War-related exposures considered thus far:

- > Pyridostigmine bromide
- > Nerve agents
- > Pesticides/repellants
- > Vaccines
- > Oil well fires
- > Depleted uranium
- > Infectious agents

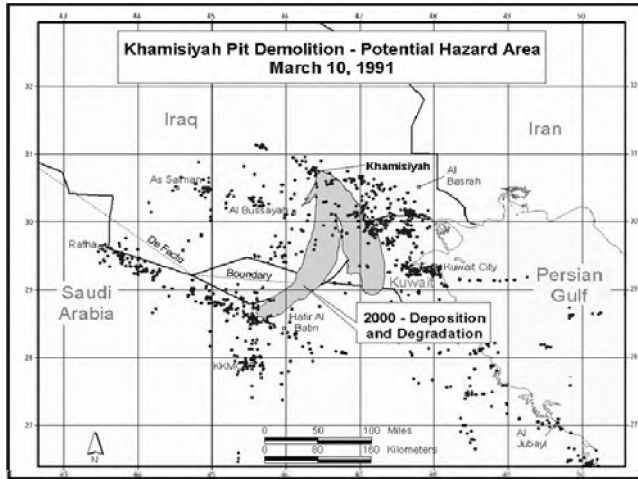
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Table 10. Population Studies Assessing Relationships of multiple Exposures in Theater to Gulf War Veterans' Illnesses

Population Studied	Sample Size	Health Measure	Association with Self-Reported Exposures		
			Chemical Weapons	PB	Pesticide Use
*Air Guard veteran ²⁰²	1,002	severe CMI	+	+	+
		mild/moderate CIM	+	+	+
*Army veterans from New England, New Orleans ²⁴⁴	291	neurological and musculoskeletal symptoms	+	--	+
Austrian veterans ²⁴	1,456	functional impairment	+	+	+
Iowa veterans ¹³⁸	1,896	cognitive dysfunction	+	+	+
*Navy Seabees ⁹⁸	11,868	CMI (modified)	+	+	+
*Navy construction battalion ¹⁰⁷	249	1 or more of 3 defined syndromes	+	+	+
*New England Army veterans ²⁸¹	1,290	CMI (modified)	na	+	na
*Pacific Northwest veterans ²⁰¹	354	unexplained illness	-	+	+
UK male veterans ¹⁹	2,735	CMI (modified)	+	+	+
*UK veterans ⁹²	7,971	symptom severity	na	+	+

CMI: chronic multisymptom illness as defined by Fukuda et al. 28
 *statistically significant association; --: association not scientifically significant na association not assessed
 *indicates analyses controlled possible confounding due to concurrent exposures

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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

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

Study	Year	Animal Model	Major Finding
Bunford ¹⁰	1978	monkey	Persistent effects on electroencephalograph readings
Hussain ¹¹	1980	mouse	Delayed development of spinal cord lesions
Jones ¹²	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa ¹³	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa ¹⁴	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa ¹⁵	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa ¹⁶	2001	rat	Impaired spatial memory
Coen ¹⁷	2002	rat	No persistent effects on reported indices of temperature regulation and motor activity
Henderson ¹⁸	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Huler ¹⁹	2002	guinea pig	Persistent failure to habituate on functional test battery
Sorensen ²⁰	2002	rat	Persistent increase in cerebral blood flow in specific areas
Kata ²¹	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson ²²	2002	guinea pig	Chronic depression of AChE activity, consistent behavioral changes (spontaneous activity, increased rearing behavior)
Hussain ²³	2002	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BChE activity, NTE activity in various tissues
Sorensen ²⁴	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa ²⁵⁻²⁸	2003-2004	mouse	Chronic alteration in immune function (increase in CD19 cells, decrease in CD4 cells, decrease in mitogen-induced lymphoproliferation, increased NK cell activity)

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Glove Box Enclosure System

Aerosol Generation System

96-Port Nose-Only Exposure Chamber

Diverse sources of research information considered

- **Published research**
 - > Epidemiologic studies of Gulf War-era veterans
 - > Clinical studies of Gulf War veterans
 - > Occupational health studies related to exposures
 - > Animal studies
 - > Tissue studies
- **Research-in-progress**
- **Government reports**
 - > Various agencies (e.g. DOD, VA, HHS, GAO)
 - > Various committees (e.g. Congressional, PAC, PSQB, NIH)
 - > Foreign governments
 - > Topics related to exposures (measured and modeled), health risk assessments
- **Nongovernmental reports**
 - > RAND
 - > ICM
 - > Other

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Moving From Information Review to Identifying Research Needs and Priorities

- Assemble and analyze information from different sources
 - > Compare findings from different studies: how are they similar? how are they different?
 - > Weigh strengths/weaknesses of individual studies
 - > Evaluate nature and strength of evidence related to health effects of each type of exposure of interest – alone and in combination with other exposures

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Moving From Information Review to Identifying Research Needs and Priorities

- Committee Findings and Conclusions:
 - > What we know from existing research
 - Re: Health of Gulf War veterans
 - Re: Effects of exposures
 - > What we don't know
 - > Research priorities for addressing unanswered questions and health needs of ill Gulf War veterans

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Considerations in "weighing the evidence"

- **Complex illnesses:**
 - > Clinical presentations vary: different veterans have different symptoms, signs, diagnosed conditions
 - > Illnesses may reflect different pathophysiological processes in different veterans

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Considerations in "weighing the evidence"

- **Complex etiology:**

- > Multiple "causative" factors? not one cause → one disease

- **Single causes in some individuals?**

- Varies with dosage
 - Varies with individual susceptibility
 - Different single causes in different individuals?

- **Multiple causes in some individuals?**

- Combinations of exposures vary between individuals
 - Dosages in those combinations vary
 - Individual susceptibility to combinations likely to vary

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Current Meeting: Exposures to be Considered

- Petroleum combustion products
- Particulates
- Solvents
- Jet fuel
- Misc other

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Exposures: Questions to Consider

What evidence is there re: the potential for "Exposure X" to have contributed to the chronic symptoms affecting Gulf War veterans?

- > Potential role as a single exposure?
- > Potential role in combination with other exposures?
- > Potential for a subset of individuals to have been particularly affected due to their location or occupation?
- > Potential for some individuals to have greater susceptibility to this exposure?

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