Presentation 7 – Lea Steele

Wartime Exposure in Relation to Gulf War Illnesses:

Summary of Evidence

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December 12, 2005

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December 12-13, 2005
A Working Meeting

- Review, summarize information on topics covered in 2004-2005 RAC Meetings
- Synthesize, compare strength of evidence for each exposure in relation to Gulf War illnesses
- Outline 2006 RAC Report

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RAC 2006 Report

- Findings, recommendations re: topics reviewed in 2004 and 2005
- Update on topics covered in 2004 RAC Report
- **Synthesis and analysis of findings, identification of research priorities**

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Comparison of evidence re: Exposures

- **Stressful exposures**
- **Chemical weapons**
- **Pesticides/repellants**
- **PB**
- **Vaccines**
- **Depleted uranium**
- **Oil well fires**
- **Tent heaters, combustion products**
- **Particulates**
- **Fuel exposures**
- **Solvents, CARC paint**
- **Infectious diseases**

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Considering the Degree and Weight of Evidence for Gulf War-related Exposures

- Primary interest is likely relationship between exposure and "Gulf War Syndrome" multisymptom illnesses
- In some cases, evidence may suggest association with other health issues

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Considering the Degree and Weight of Evidence for Gulf War-related Exposures

→ Big picture: extent and patterns of exposure during deployment

→ Known toxic effects of exposure

→ Epidemiologic studies of Gulf War veterans

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Rating the Evidence

➔ For all sources of information, consider strength and reliability of methods used

➔ GW epidemiologic research: evaluate strength of findings on key parameters

- Sample *(size, representativeness, etc)*
- Methods, measures
- Statistical analyses

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Statistical Analyses?

➔ Gulf War illness research usually involves:

- *Complex of multiple causal factors*
- *Complex of multiple symptoms in multiple systems*
- *No objective indicators of "disease"*

➔ Some of the most prominent Gulf War epidemiologic studies have great samples and data collection methods, but overly simplistic data analyses

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Important to Consider How Data Were Collected and Analyzed

➔ **Overly simple analyses can generate erroneous conclusions about exposures and GWI**

➔ **Complex exposures require consideration of:**

- ***Effects of "grouped" exposures***
- ***Different risk factors in different subgroups***
- ***Effects of combinations of exposures***

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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 veterans[30]	1,002	severe CMI	+	+	+
		mild/moderate CMI	+	+	+
*Army veterans from New England, New Orleans[24]	251	neurological and musculoskeletal symptoms	+	–	+
Australian veterans[34]	1,456	functional impairment	+	+	+
Iowa veterans[138]	1,896	cognitive dysfunction	+	+	+
*Navy Seabees[46]	11,868	CMI (modified)	+	+	+
*Navy construction battalion[107]	249	1 or more of 3 defined syndromes	+	+	+
*New England Army veterans[31]	1,290	CMI (modified)	na	+	na
*Pacific Northwest veterans[26]	354	unexplained illness	–	+	+
UK male veterans[34]	2,735	CMI (modified)	+	+	+
*UK veterans[32]	7,071	symptom severity	na	+	+

CMI: chronic multisymptom illness as defined by Fukuda et al.[8]
+ : statistically significant association; – : association not statistically significant; na: association not assessed
*Indicates analyses controlled for possible confounding due to concurrent exposures

Comparison of evidence re: Exposures

- Psychological stressors related to deployment
- Chemical weapons
- Pesticides/repellants (various)
- PB
- Vaccines
- Depleted uranium
- Oil well fires
- Tent heaters, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Infectious diseases

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Gulf War Exposures:

Summary Areas of Consideration

➔ Big picture re: extent and patterns of exposure

➔ Known toxic effects

➔ GW epidemiologic studies

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Psychological Stressors During Deployment

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Psychological Stressors Associated with Gulf War Deployment

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

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➔Big Picture
Psychological Stressors

- 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; similar in UK
- Many of these were not unique to 1990-91 Gulf War

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➔Known Toxic/Adverse Effects
Psychological Stressors

- Severe trauma associated with PTSD, other psychiatric conditions
- PTSD, other psych conditions associated with higher levels of s/r somatic symptoms
- Lower–level stressors associated with short-term immune alterations
- Less is known re:
  - Somatic symptoms after trauma in the absence of psych illness?
  - Persistence of somatic symptoms many years after lower-level stressors?

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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

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→Epidemiologic Findings in Gulf War Veterans Psychological Stressors

	Unadi	Adi	*Ref*
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*

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➔Epidemiologic Findings Psychological Stressors

- 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

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Exposure to Chemical Weapons

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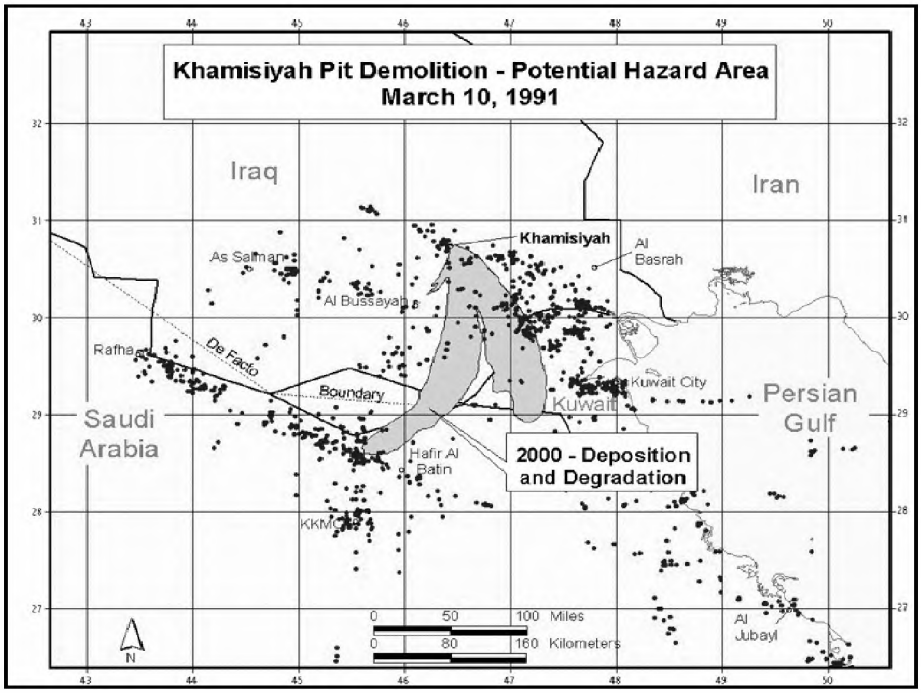
Chemical Weapons

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies



→ Big Picture
Chemical Weapons

- Actual extent of exposure unknown
- OSAGWI report indicates potential for very low-level exposures to ~100,000 following Khamisiyah demolitions
- Multiple reports of other incidents; 80% of chemical targets destroyed
- Self-reported exposures:
  - Chemical alerts 66 %
  - SCUD exploded nearby 43 %
  - CBW 22-24%
  - Chemical warfare agents 5-10%
- More commonly reported by ground troops; similar in UK
- Exposure is fairly unique to 1990-91 Gulf War

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➔Known Toxic Effects Chemical Weapons

- High-level exposures deadly
- Little known re: low-level, chronic effects in humans
  - Japanese studies indicate chronic symptoms, subtle neuro effects in sarin attack survivors
- Animal studies have identified persistent neuro, immune effects following low-level exposures
- Few animal studies have evaluated interaction of sarin with other Gulf War-related exposures

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

Study	Year	Animal Model	Major Finding
Burchfiel[44]	1976	monkey	Persistent effects on electroencephalograph readings
Husain[120]	1993	mouse	Delayed development of spinal cord lesions
Jones[48]	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa[155]	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa[157]	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa[156]	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa[141]	2001	rat	Impaired spatial memory
Conn[57]	2002	rat	No persistent effects on repeated indices of temperature regulation and motor activity
Henderson[11]	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Hulet[130]	2002	guinea pig	Persistent failure to habituate on functional test battery
Soremin[153]	2002	rat	Persistent increase in cerebral blood flow in specific areas
Kaira[151]	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson[104]	2002	guinea pig	Chronic depression of AChE activity, persistent behavioral changes (disinhibited activity, increased rearing behavior)
Husain[121]	2003	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BChE activity, NTE activity in various tissues
Soremin[152]	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa[52,164]	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)

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➔Epidemiologic Findings in Gulf War Veterans
Chemical Weapons

	Unadi	Adi	Ref
Chemical alerts	2.6*	1.2	GG
	2.2*		CU
	1.9*, 2.7*	ns	JW
Poison gas	6.3*		JW
Likely chem attack		7.8*	RH, syn 2
Poor prot/chem attack	3.2*		PS
In Sector 7 Jan 20		4.3*	RH, syn 2
Nerve gas	15.1*		HK
Chem/bio weapons	2.5*, 6.0*	2.3*, 3.5*	RN
Chemical warfare agents	p<.001		Iowa

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➔Epidemiologic Findings
Chemical Weapons

- All CW variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 2.0 – 6.3
- High crude OR (15.1) for "nerve gas" exposure in Kang study
- CW variables (except "chemical alert" questions) are sign. associated with GWI in studies that adjust for other wartime exposures: ORs ~ 2.3 – 7.8
- Brain cancer mortality sign. elevated among veterans in Khamisiyah plume area; few other assoc. with modeled Khamisiyah proximity

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Pesticides, Insect Repellants

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Pesticides, Insect Repellants

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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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

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

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➔Big Picture
Pesticide Exposures

- Multiple compounds used; DOD-identified 37; 15 of possible concern
- Diverse applications: skin, uniforms, tents, bedding, area fogging, delousing
- OSAGWI report indicates 41,000 potentially overexposed to pesticides
- Studies indicate highly correlated use of multiple pesticides, i.e., those who used high levels of one pesticide most likely to use higher levels of others
- RAND study found higher pesticide use correlated with higher PB use

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→Big Picture
Pesticide Exposures

- Self-reported exposures:
  - Insecticide spray 35%
  - Insect repellant 28-35%
  - Personal pesticides 48%
  - Insecticide cream/spray 26-28%
- More commonly reported by ground troops; Reserve/Guard use may be higher than Active
- Similar usage in UK
- Levels, pattern of use unique to 1990-91 Gulf War?

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→Known Toxic Effects
Pesticides

- Acute poisoning produces diverse symptoms, delayed neuro syndrome
- Large body of toxicological research on adverse effects of different compounds on multiple systems
- Community and occupational studies indicate chronic, low level exposures associated with higher symptom levels
- Animal studies demonstrate synergistic effects of DEET, OP, and permethrin
- Genetic variation (PON1, BCHE, NTE) linked to individual susceptibility to pesticide exposures

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→Epidemiologic Findings in Gulf War Veterans
Pesticides

	Unadi	Adi	Ref
Pesticides	3.5* 2.2*	1.9*	*GG* *CU*
Flea collar	3.8*	1.3 8.7*	*GG* *RH, syn 1*
Treated uniform	3.4* 3.6* 1.9*	1.2	*GG* *PS* *CU*
Insect repellant	1.9*, 3.4* 3.3*	1.7*, 2.4* ns	*RN* *PS*
Pesticides	p<.001* p<.001*	p<.001*	*SP;n+ms* *IA, all*
Insect repellant > 14 days	p<.001*	p<.001*	*NC*
Amt skin repellant	p<.001*	p<.001*	*RH, syn 3*

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→Epidemiologic Findings
Pesticides

- All pesticide variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.9 – 3.8
- Pesticide variables are sign. associated with GWI in studies that adjust for other wartime exposures (except 2 variables in Navy Seabee study, 1 in NW vets): ORs ~ 1.7 – 8.7
- Some evidence of dose-response relationship
- "Handling of pesticides" sign. associated with non-disease related mortality in UK veterans

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NAPP Pills (Pyridostigmine Bromide)

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Pyridostigmine Bromide

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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→Big Picture
PB Exposures

- Orders to use and implementation varied by unit; commander discretion
- Recommended use: 3 x 30 mg tables per 24 hour period
- RAND study indicates use varied widely; higher pesticide use correlated with higher PB use

→Big Picture
PB Exposures

- 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
- Similar usage in UK
- Exposure to PB unique to 1990-91 Gulf War

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→Known Toxic Effects
PB

- 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

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

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→Epidemiologic Findings
PB

- PB variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.4 – 4.4
  (1 exception: 1st Ft. Devens study)
- PB variables sign. associated with GWI in studies that adjust for other wartime exposures, ORs ~ 1.7 – 8.7
  (not in Ft. Devens study or at lower level in 2nd Ft. Devens study)
- 3 studies indicate a dose/response effect
- 2 studies support association with acute side effects of PB

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Vaccines

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Vaccines

- Big picture
- Known toxic effects
- GW epidemiologic studies

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→Big Picture
Vaccines

- 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

	Unadi	Adi	Ref
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

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

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→Epidemiologic Findings
Vaccines

- Unadjusted analyses: variable results for individual vaccines
  anthrax: 4 positive (OR ~1.5-3.7); 1 neg
  botulinum: 2 positive (OR~1.8-4.9); 0 neg
  plague: 2 positive (OR~1.3-3.2); 2 neg
- Very few studies have looked at vaccine-associated risk while controlling for effects of other exposures in theater
  anthrax: 1 pos (OR = 1.5); 1 neg
  mening: 1 pos (OR = 1.3)
  plague: 1 neg
- Number of vaccines: Only UK and Australia studies
  2 studies show positive association without adjusting for other exposures:
  Cherry study found positive association in adjusted analysis (p<.001)

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Depleted Uranium

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Depleted Uranium

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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➔Big Picture
Depleted Uranium

- No clear estimate of total number exposed
- Small cohort with shrapnel, larger number exposed by inhalation
- Self-reported exposures low, problematic question in epi studies
  - Kang 10%
  - Wessely 10%
  - Gray 2%
- DU also used in Kosovo, current deployments

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➔Epidemiologic Findings in Gulf War Veterans
Depleted Uranium

	Unadj	Adj	*Ref*
Depleted uranium	ns		*RH (all syn)*
	4.5*		*PS*
	2.3		*Dan, neuro*

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➔Epidemiologic Findings Depleted Uranium

- Very few epidemiologic studies have looked at DU exposures
- Those that did didn't solicit information likely to be reflective of actual DU exposures
- VA DU cohort (Baltimore study) does not report results re: symptoms, multisymptom illness

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Oil Well Fires

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Oil Well Fires

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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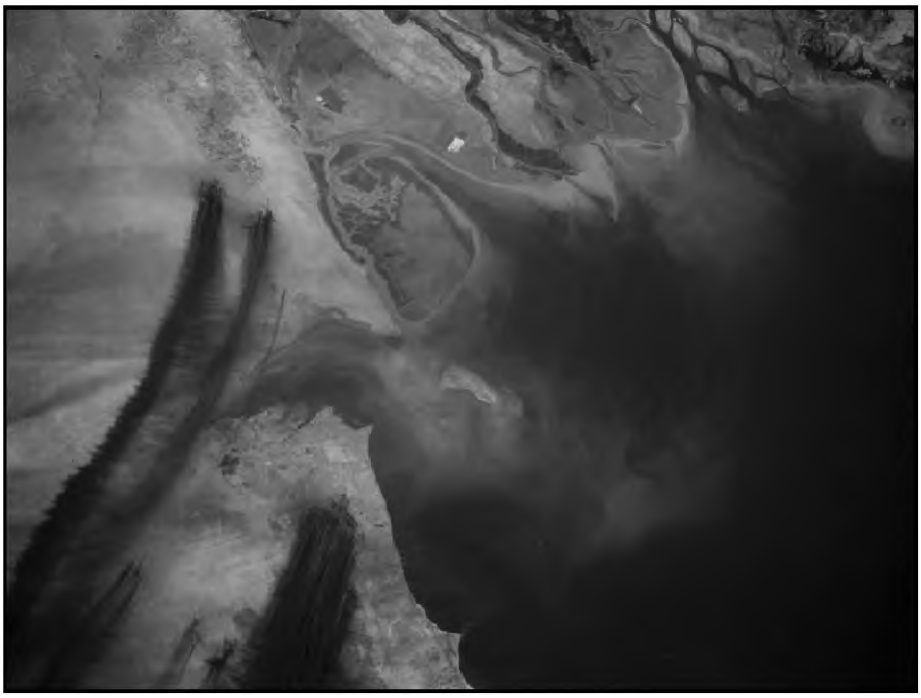

→Epidemiologic Findings in Gulf War Veterans
Oil Well Fires

	Unadi	Adi	Ref
s/r Oil fire smoke	1.9*, 3.4*	1.3, 1.5	*RN*
	1.8*		*CU*
	2.2*	1.2	*GG*
Modeled oil fire smoke	1.5*	0.4	*GG*
Odor from burning wells		2.1*	*JW*
Consumed food cont w/oil	10.6*		*HK*
Eye irr/ smoke: 1-5 days 6+days	2.64* 4.47*		*PS*
Number days exposed		p<.001*	*NC*
Smoke, combustion	p<.001*		*Iowa*

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→Epidemiologic Findings
Oil Well Fires

- All variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.5-4.5
- Oil well fire variables sign. associated with GWI in 2 studies that adjust for other wartime exposures OR = 2.1
  Not sign associated in Seabees study, Air Guard study
- 3 studies suggest dose/response effect
- Kang neuro factor sign associated with oil-contaminated food (OR=10.6)
- No association in study that used modeled exposure to smoke (Seabees study)

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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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Exposures: Additional consolidation of information

- *More detailed breakdown where possible, e.g. pesticide types and combinations*
- *Calculate attributable risk where possible*
- *Compare findings from different studies: how are they similar? how are they different?*
- *Patterns related to branch of service, location, types of case definitions, exposure questions?*

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

	Unadi	Adi	Adi Results Consist	Dose/ resp	S/R variable
Psychological stressors	1.6-3.1	ns	yes	-	
Chemical weapons	1.9-6.3	2.3-7.8	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	+
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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Gulf War Exposures in relation to GWI: Preliminary Summary of Evidence

	Known Toxic Effects: Possible Relation to GWI?		Evidence of synergism w/other GW exposures?
	Human/ Occup	Animal	
Psychological stressors	yes	yes	yes
Chemical weapons	~	yes	
Pesticides	yes	yes	yes
NAPP/PB pills	?		yes
DU	?	yes	yes
Oil well fires	no	?	?
Vaccines: anthrax	?	?	?
Number of vaccines	no	?	?

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Gulf War Exposures in relation to GWI: Preliminary Summary of Evidence

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

Psych stressors	Evidence consistently indicates not associated
Chemical weapons	Two studies support sign association, higher OR with more severe illness; s/r exposure problematic
Pesticides	Consistent sign assoc, dose response
NAPP/PB pills	Consistent sign assoc, dose response
DU	Almost no useful information
Oil well fires	Results inconsistent, may relate to proximity/duration
Vaccines, individual	Very little clear information; s/r problematic, little control for confounding
Number of vaccines	Little info, 1 strong study suggests association

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Exposures and GWI: Preliminary Conclusions Strongest Evidence

- Strongest evidence from epidemiologic studies supports pesticides and PB as causal factors in GWI
  - Animal studies support plausibility, especially when PB combined with other compounds
  - Overall pattern of exposures also support association
- Two studies support positive associations with chemical weapons, but s/r exposure questionable in one
  - Unknown if exposures extensive enough to explain large proportion of cases
  - Brain cancer/Khamisiyah findings could be due to nerve agents, confounding by other exposures?

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Exposures: Preliminary Conclusions Little/Poor Evidence

- Very little useful information concerning likely associations between vaccines and GWI
  - Significant associations generally modest
  - Little animal or human research informs plausibility
- Almost no information concerning likely 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: Preliminary Conclusions

- Oil well fires, overall, unlikely to be primary cause of GWI
  - 2 studies identifying higher exposure levels show sign association.
  - Little information re: possible synergism with other exposures
  - May be associated with diagnosed asthma, other resp conditions
- Consistent findings that psych stressors are not associated with GWI
  - Animal studies suggest possible synergism w/exposures

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