Presentation 2- Lea Steele

RAC 2006 Report:

Overview of Materials Considered in 2004-2005

Lea Steele, Ph.D.

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
- Outline findings and recommendations in key areas
- Synthesize, compare strength of evidence for each exposure in relation to Gulf War illnesses

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

Areas Addressed in 2004 RAC Report

- Nature and prevalence of Gulf War illness symptom complex
- Urgent need for treatments for GWI
- Evidence of neurological pathology in Gulf veterans
- Links between GWI and neurotoxic exposures
- Possible links with other exposures
- Birth defects and health of family members
- Need for coordination of federal data resources
- GWI research relates to current deployments, domestic security
- Focus, funding of federal GW research programs

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
  - Cell culture studies
- *Research-in-progress*
- *Government reports*
  - Various agencies (e.g. DOD, VA, HHS, GAO)
  - Various committees (e.g. Congressional, PAC, PSOB, NIH)
  - Foreign governments
  - Topics related to exposures (measured and modeled), health risk assessments
- *Nongovernmental reports*
  - IOM
  - RAND
  - Other

Major Topics Covered in 2004 and 2005 RAC Meetings

- Depleted uranium
- Oil well fires, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Vaccines
- Infectious diseases

- Chronic multisymptom illnesses in the general population
- Epidemiologic studies of multisymptom illness in Gulf veterans
- Respiratory conditions
- Cancer
- Immunological, neurological findings in Gulf veterans

- Treatments
- VA Research Programs

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

Review of 2004-2005 Exposure Topics

- Review highlights of information presented
- Summarize what is known/not known in each area in relation to Gulf War veterans' health
- Discuss findings, recommendations

2004-2005 Exposure Topics

- Depleted uranium
- Oil well fires, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Vaccines
- Infectious diseases

Depleted Uranium

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Major Reports on the Health Effects of DU

- RAND (1999)
- IOM (2000)
- Royal Society (UK, 2002)
- USACHPPM

Major Reports on the Health Effects of DU: General Conclusions

- **Chemical (heavy metal) toxicity of greater concern than radiological effects of DU**
- **Concern about increased cancer risk**
  - Minimal concern re: possible increase in overall cancer risk (primarily lung)
  - Occupational studies of uranium exposures often too small to provide information re: less common cancers
- **Concerns about renal toxicity**
  - Transient effects demonstrated, but minimal concern re: longer-term kidney effects except with large exposures (e.g., Gulf veterans with significant amount of embedded shrapnel)
  - Solubility of uranium affects outcomes in animal studies
- **Little research available re: possible damage to other systems and organs (cardiovascular, hematological, respiratory, neurological, immunological, etc)**

Depleted Uranium: Information Considered by RAC in 2004-2005

- Efforts to estimate levels of DU exposure
- Animal studies to evaluate effects of DU exposures via different routes, in different systems
  - Ingested, injected
  - Embedded pellets
  - Inhaled
- Epidemiologic studies to evaluate associations between DU exposure and health outcomes in Gulf War veterans

Estimates of Exposure/ Modeled Health Risks

Depleted Uranium

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DU Exposure: OSAGWI Report

DOD has identified 3 levels of DU exposure in Gulf War veterans

- Level 1: ~ 150 people with high exposures associated with friendly fire incidents and rescue
- Level 2: ~ 750 people exposed during cleanup operations following the Doha fire, and cleanup of destroyed U.S. vehicles
- Level 3: unknown numbers exposed to smoke from Doha fire, burning U.S. and Iraqi tanks, entered DU-contaminated equipment

Preliminary Assessment of DU Munitions Health Effects.

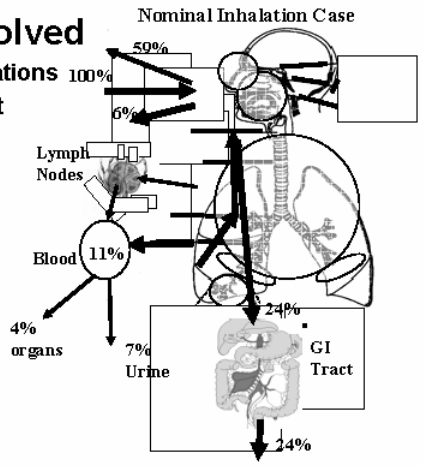
Al Marshall

National Security Studies Department
Sandia National Laboratories
Presented to RAC Gulf War Veteran's Illness
Washington DC
February 24, 2004

Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Basic distribution of inhaled DU.

- **Basic equations solved**
  - **Coupled differential equations**
  - **Compute time-dependent**
    - Transport
    - Blood absorption
  - **Each compartment**
  - **Rapid and slow blood**
- **Equations couple to**
  - **Other organ models**
  - **Urine elimination**



Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Preview of Preliminary Findings.

- Inhaled DU mass exceeds DoD estimates
- Fragment dose contribution significant
- DU radiological effect insignificant
- DU in Kidney high for max case, chemical heavy metal: consequences uncertain
- Other DU heavy metal effects possible, significance uncertain

Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Depleted Uranium
CAPSTONE Aerosols Study
and Human Health Risk Assessment

LTC MARK A. MELANSON, Ph.D., CHP
Program Manager, Health Physics
US Army Center for Health Promotion and Preventive Medicine

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Military Unique Exposures

- For over 30 years, the DoD has evaluated the safety of DU munitions and armor with this most recent assessment in 2004
- U.S. used DU for the first time in combat during Operation Desert Storm in 1991
- Fratricide ("friendly fire") involving six Abrams tanks and fourteen Bradley Fighting Vehicles in 1991
- As reported in the USACHPPM 2000 Report, existing data were not robust enough for modeling doses to personnel inside Abrams and Bradleys perforated by DU munitions

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

DU CAPSTONE Aerosol Study and Human Health Risk Assessment

- $ 6 Million Project
- 5 years to complete
- Rigorous science
- External Peer Review
- Transparent process
- Unlimited release of data

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Estimating Depleted Uranium Aerosol Doses and Risks:

An Overview of the Capstone Depleted Uranium Aerosol Study

and the Capstone Human Health Risk Assessment

Research Advisory Committee on Gulf War Veterans' Illnesses
April 7, 2005

Mary Ann Parkhurst
Battelle/Pacific Northwest National Laboratory
Richland, Washington

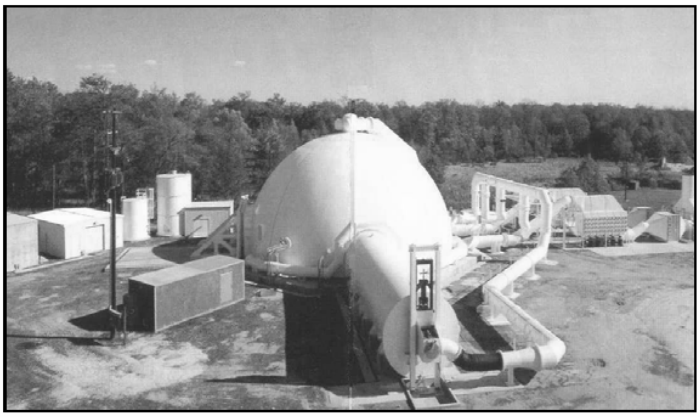
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Capstone DU Aerosol Study

- Large-scale field testing of aerosols generated by perforation of armored vehicles with depleted uranium (DU) penetrators
- Highest priority on aerosols created inside vehicle at time of and immediately after perforation
- Fired at ballistic turrets and hulls
- Collected aerosol and deposited particulate material
- Characterized chemical composition and particle size collected over first 2 hours

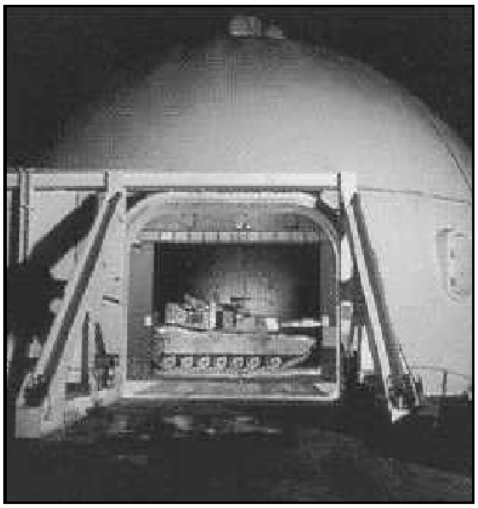
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

ATC SUPERBOX FACILITY



Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

ATC SUPERBOX SHOT



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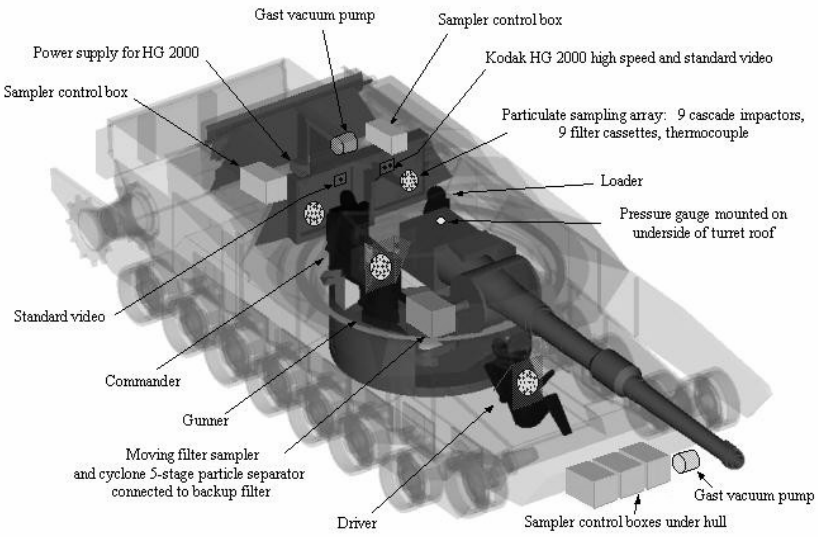

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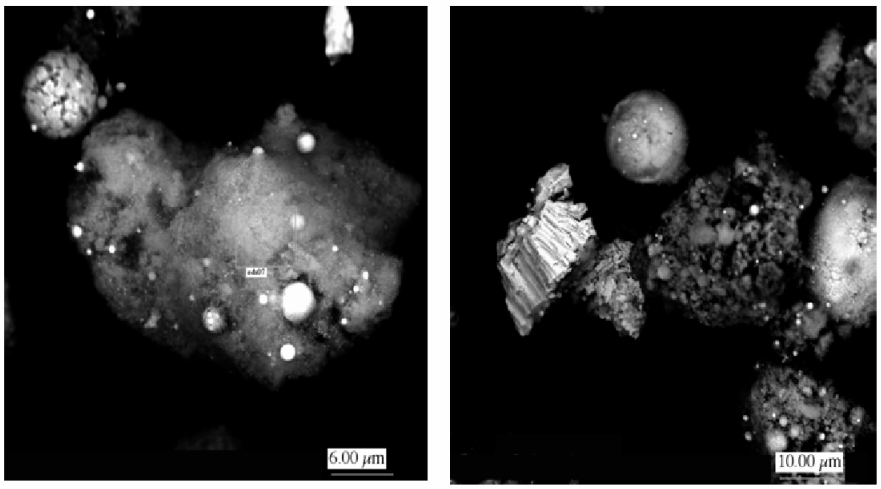
DU Aerosol Analysis

- 8,000 samples collected
- Analysis performed by 4 laboratories

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Less Dense Aggregates



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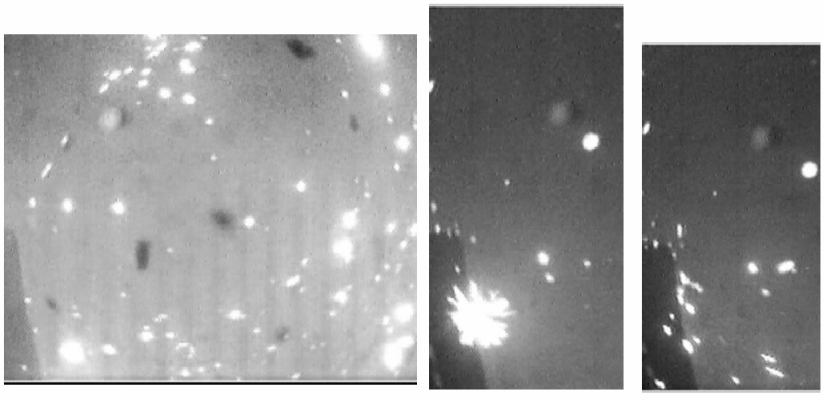
Transient Fireflies



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Median 50-yr Committed Effective Doses

Scenarios	E(50), rem			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, EC/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	2.0	2.2	0.090	0.59
B - Crew, exit in 5 min	3.7	6.0	0.44	1.7
E - First responders	0.92	1.9	0.41	0.89
Upper Bound				
C - Crew, exit in 1 h	4.8	8.3	1.02	2.1
D - Crew, exit in 2 h	5.0	8.7	1.20	2.4

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Median Lifetime Risk Increase of Fatal Cancer from DU Inhalation

Scenario	Lifetime Risk Increase of Fatal Cancer (%)			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, EC/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A – Crew, exit in 1 min	0.11	0.12	0.0049	0.034
B – Crew, exit in 5 min	0.20	0.32	0.025	0.099
E – First responders	0.050	0.10	0.023	0.052
Upper Bound				
C – Crew, Exit in 1 h	0.27	0.44	0.057	0.12
D – Crew, Exit in 2 h	0.28	0.45	0.065	0.14

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

The Bottom Line—Radiological Effects

- For all vehicle configurations and modeled exposure times, except for the *unventilated* Abrams tank perforated through DU armor, predicted radiation doses were within U.S. (routine) occupational limits.
- For the *unventilated* Abrams tank perforated through DU armor, short exposures (about 1 min) were within routine occupational limits, and exposures up to 2 h were within the emergency or planned special exposure limits.
- *For all vehicle configurations and exposure times modeled (up to 2 h), predicted radiation doses are not likely to cause adverse health effects*.

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The Bottom Line—Toxicological Effects

- In the case of the *unventilated* Abrams tank perforated through conventional armor, the potential exists for short-term adverse kidney effects for exposures 5 min or longer.
- In all other cases, *predicted uranium concentrations in the kidney are not likely to cause adverse chemically-induced health effects*.

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Animal Studies: Effects of DU exposures via different routes, on different biological systems

Depleted Uranium

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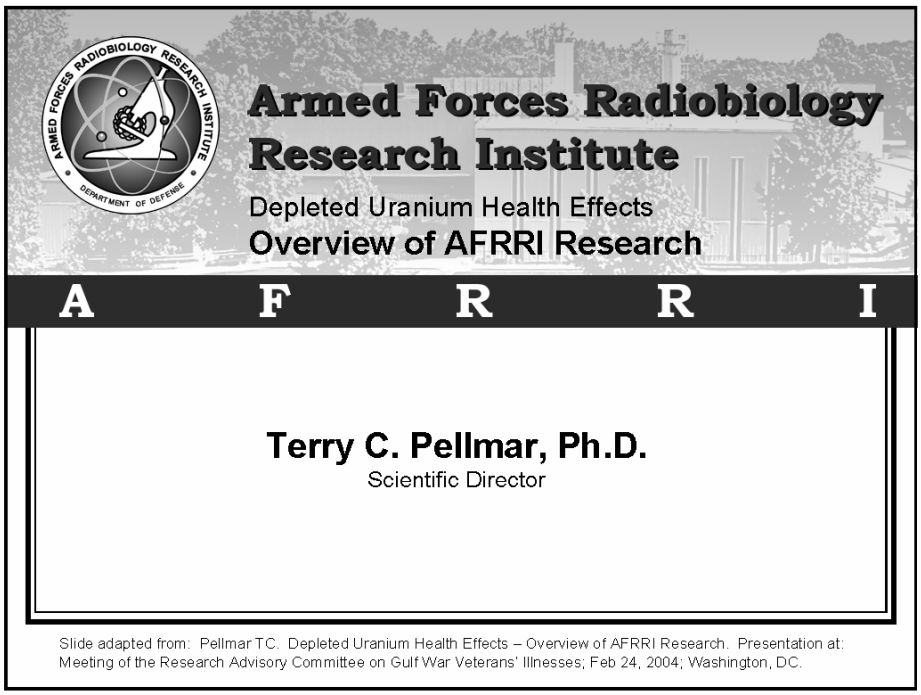
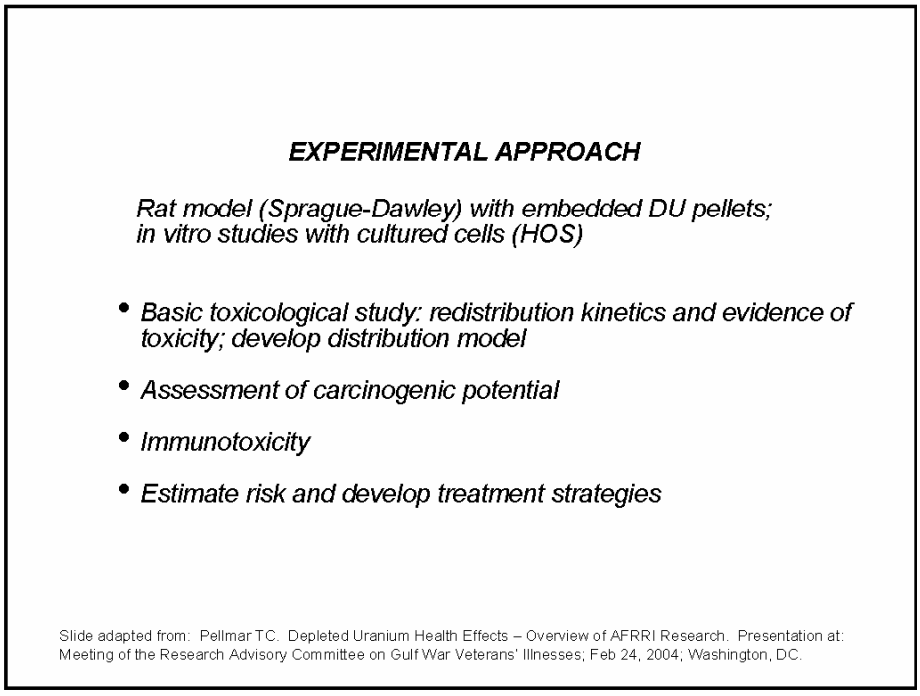
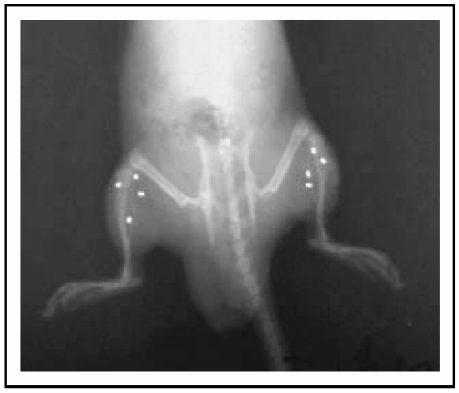

Armed Forces Radiobiology Research Institute
Depleted Uranium Health Effects
Overview of AFRRI Research
A F R R I
Terry C. Pellmar, Ph.D.
Scientific Director
Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.


EXPERIMENTAL APPROACH
Rat model (Sprague-Dawley) with embedded DU pellets; in vitro studies with cultured cells (HOS)
• Basic toxicological study: redistribution kinetics and evidence of toxicity; develop distribution model
• Assessment of carcinogenic potential
• Immunotoxicity
• Estimate risk and develop treatment strategies
Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Implanted DU pellets



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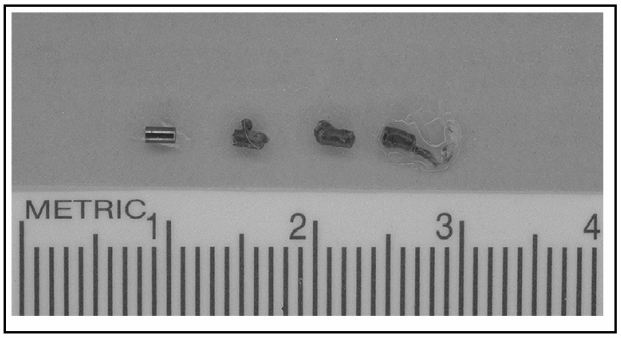
DU Distribution and Toxicity...

DU pellet implants: new and 90 days



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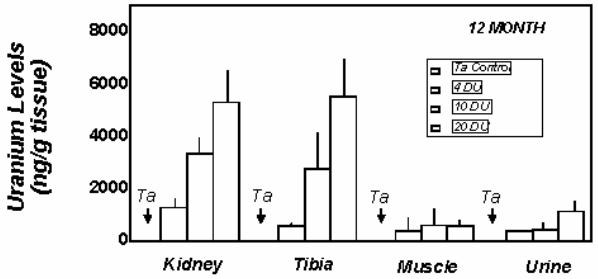
DU Distribution and Toxicity...

Uranium Distribution in Rat Tissue after DU Pellet Implantation



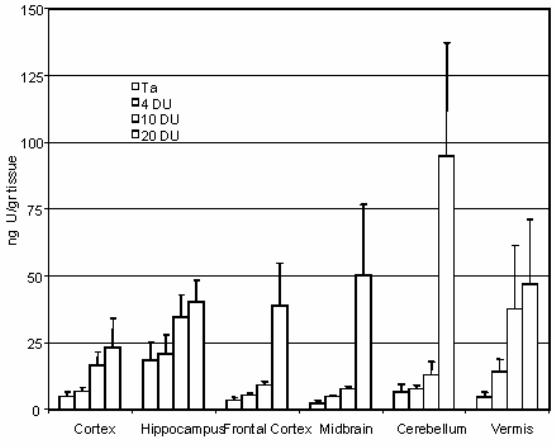
- ***Uranium redistributes with time to various organs and tissues, especially bone and kidney. Uranium also distributes to brain, lymph nodes, and testes.***
- ***No apparent changes in kidney or bone histology***

Pellmar et al., Toxicol. Sci. 49, 29-39 (1999)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

DU Distribution and Toxicity...

- ***Non-homogeneous distribution of uranium in the brain***



Pellmar et al., Neurotoxicol. 20, 785-792 (1999)

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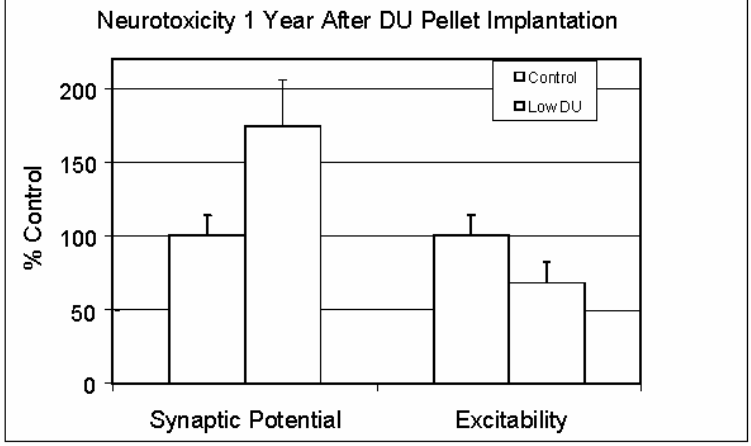


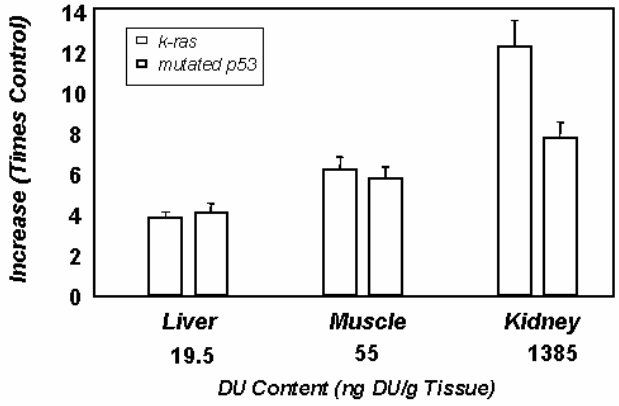
- *DU altered electrophysiological activity in the hippocampus*
- *No gross behavioral changes were observed*

Pellmar et al., Neurotoxicol. 20, 785-792 (1999)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

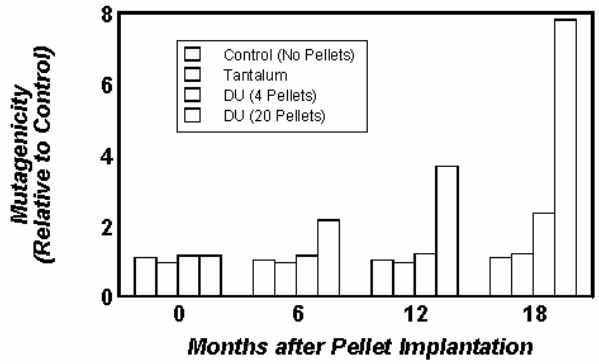
Increased Oncogenes



- *DU induces oncogenes known to be involved in carcinogenesis*

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...



- *Urine from DU animals is mutagenic*

Miller et al., Mutagenesis, 13, 643-648 (1998)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

- *DU and tungsten alloy metals induce genetic changes to extent similar to known carcinogens beryllium and nickel*

	DU (Soluble)	DU (Insoluble)	WNiCo*	Be	Ni
Micronuclei Induction	↑	↑	↑	↑	↑
Sister Chromatid Exchange	↑	↑	↑	↑	↑
DNA Single-Strand Breaks	↑	↑	↑	(not done)	↑
Dicentric Formation	↑	↑	(not done)	(not done)	No Change

*WNiCo: reconstituted metal mixture of tungsten (W), nickel (Ni), and cobalt (Co) typical of tungsten military alloy

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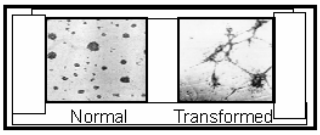
Transformation, Mutagenicity, Carcinogenicity...



Normal and DU-Transformed HOS Cells

	Untreated	Tungsten	Tungsten/Nickel Cobalt	Nickel	Lead	Soluble DU	Insoluble DU	DU/Phenyl Acetate
Transformation Rate*	4.2	28.2	121.5	29.9	21.1	40.2	115.9	4.7
Tumorigenicity**	0 (0/82)	.33 (8/24)	.83 (10/12)	.29 (7/24)	.10 (2/20)	.44 (11/25)	.65 (13/20)	0 (0/12)

** Number of transformed cells per 500,000 surviving cells*
***Number of tumors formed when 1 million transformed cells injected into immune compromised mice*

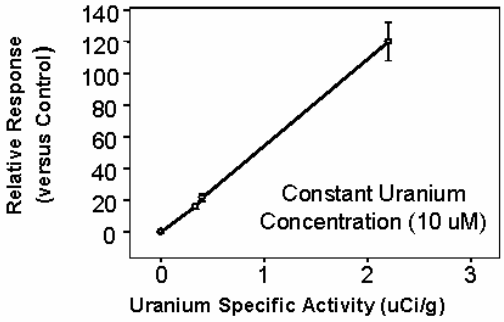
- ***DU transforms cells to a tumorigenic phenotype; cells form tumors in mice***

Miller et al., Environ. Health Persp. 106, 465-471 (1998); Miller et al., Radiat. Res. (In Press)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

Radiation vs. Chemical Toxicity of DU
Neoplastic Transformation Assay



- ***DU-induced transformation rate is influenced by radioactivity of DU, not just chemical toxicity***

Miller et al.,Radiation Protection Dosimetry, submitted

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Immunotoxicity

Principal Investigators: David McClain, Ph.D. and John Kalinich, Ph.D.

- *Immune system is represented in a variety of tissues*
- *Other heavy metals have been shown to be immunotoxic*
- *AFRRI DU Distribution and Toxicity study determined there are alterations in several immune system parameters in DU-implanted rats*

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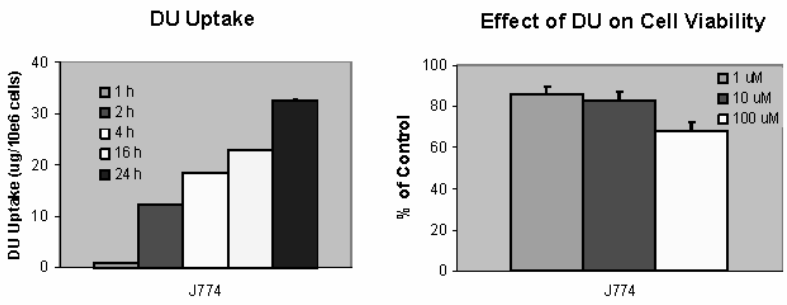
Immunotoxicity



- ***Soluble DU is taken up and concentrated by cultured macrophages, affecting their metabolic viability, and eventually leading to their death***

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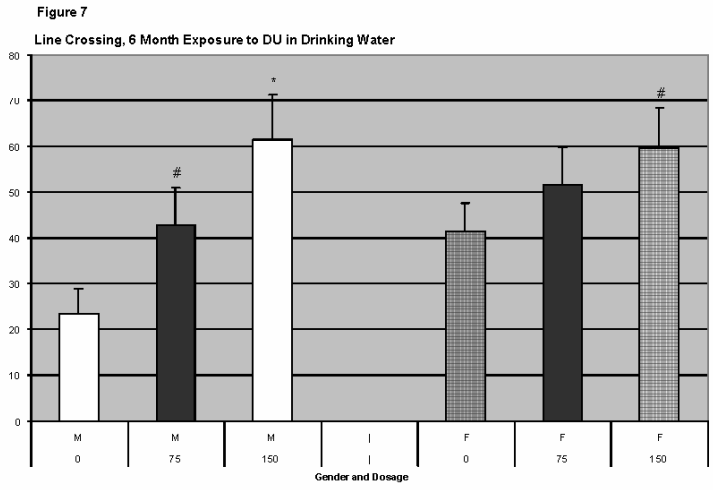
Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure

Wayne Briner
Jennifer Murray

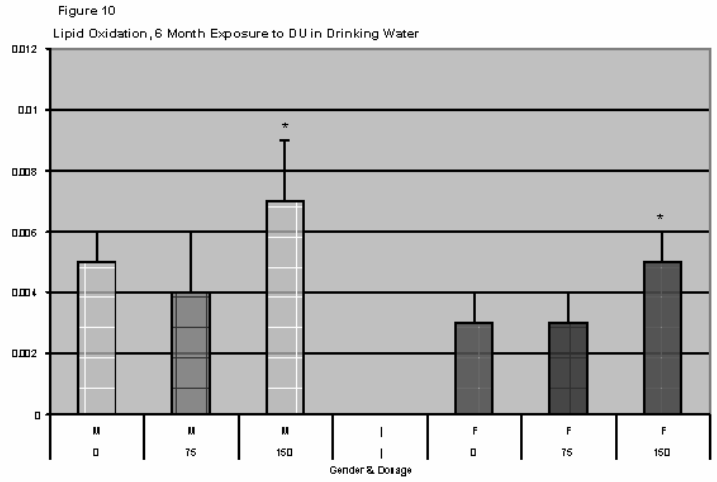
University of Nebraska Kearney

Line Crossing, 6 months



Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Lipid Oxidation (adult, 6 months)

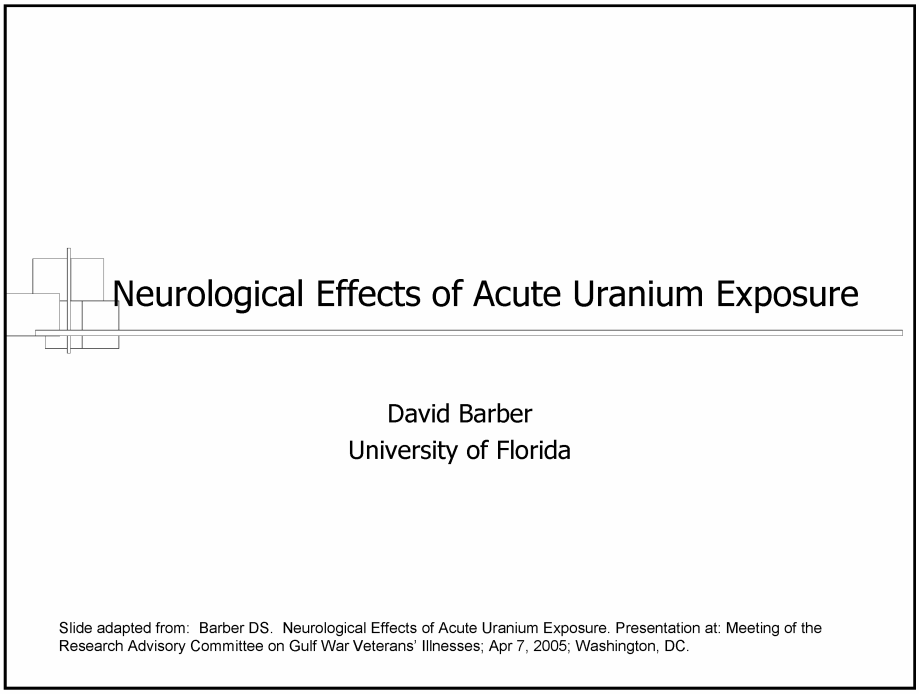


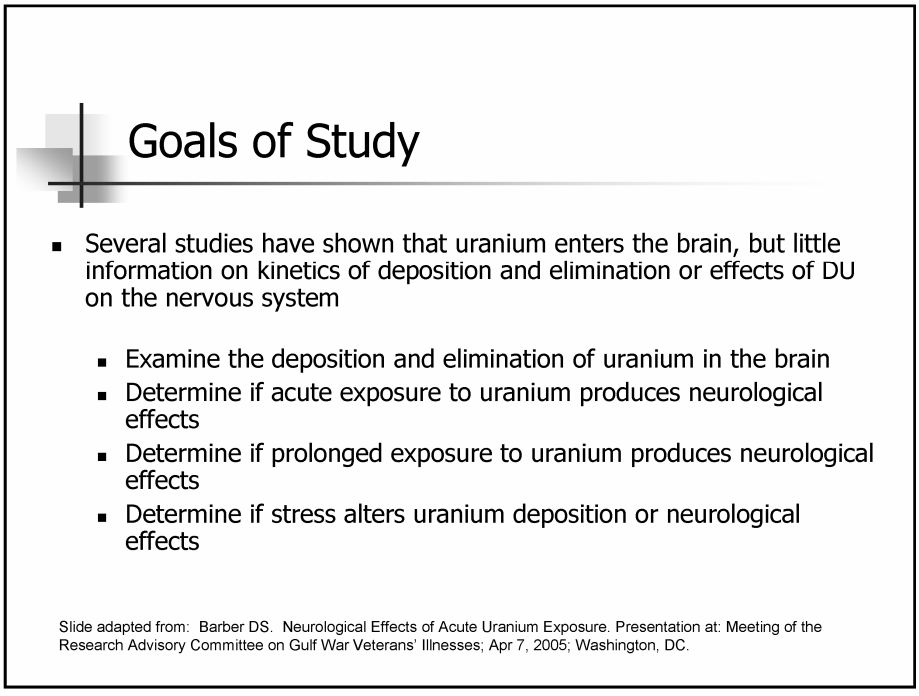
Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

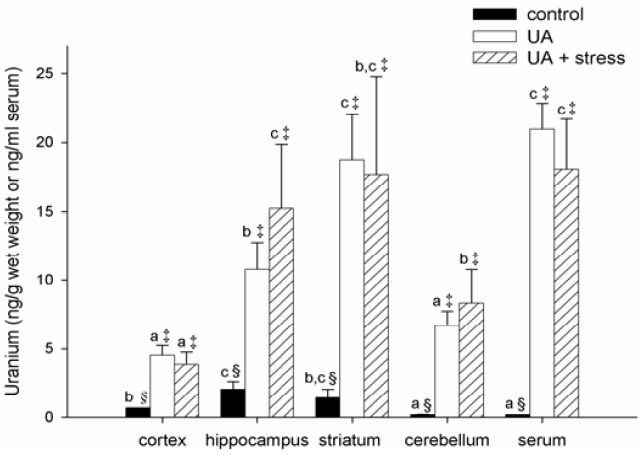
Overview

- Behavioral changes in adults and developing animals
- Changes seen in two species
- Produces lipid oxidation in CNS (direct/indirect?)
- Lipid oxidation related to behavioral alterations
- Complex effects on midbrain neurotransmitter profile

Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Neurological Effects of Acute Uranium Exposure
David Barber
University of Florida
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Goals of Study
Several studies have shown that uranium enters the brain, but little information on kinetics of deposition and elimination or effects of DU on the nervous system
Examine the deposition and elimination of uranium in the brain
Determine if acute exposure to uranium produces neurological effects
Determine if prolonged exposure to uranium produces neurological effects
Determine if stress alters uranium deposition or neurological effects
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.



Barber et al., 2005

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

- This study demonstrated that:
  - There are regional differences in brain uranium distribution
  - There are several phases of uranium elimination from the brain with the last phase being very long
  - Prior stress did not exacerbate the entry of uranium into the brain, if anything increased its elimination

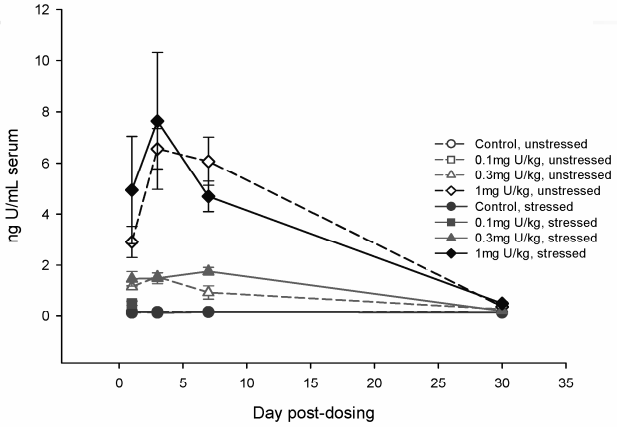
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Experimental Design

- Male Sprague Dawley rats
- Stress applied for 5 days prior to uranium exposure (restraint + swim)
- 0, 0.1, 0.3, and 1.0 mg uranium/kg administered as uranyl acetate by i.m. injection
- Tissue samples taken at 1, 3, 7,and 30 days for uranium levels, neurotransmitters, GSH, receptor number, and histopathology
  - Rats perfused with cold saline
  - Cerebral cortex, hippocampus, striatum, hypothalamus and cerebellum removed
  - Whole body perfusion fixation for histopathology

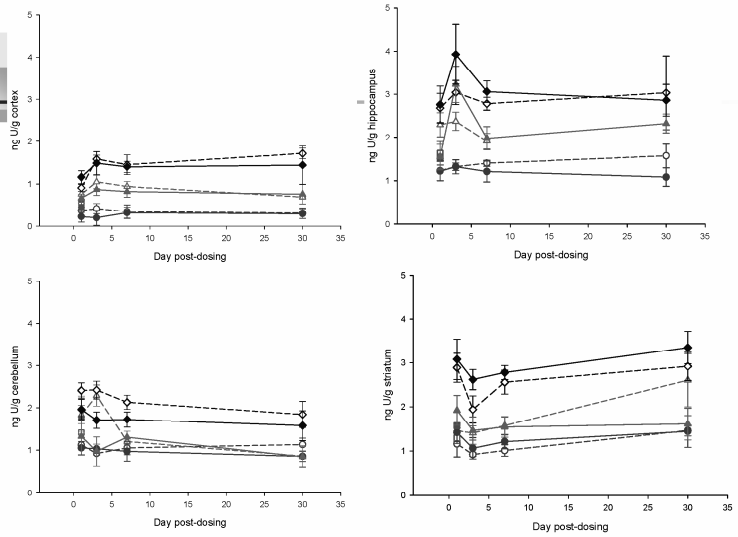
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Serum uranium



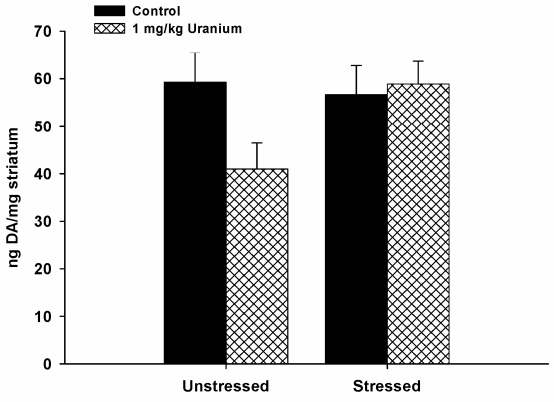
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Brain Uranium



Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

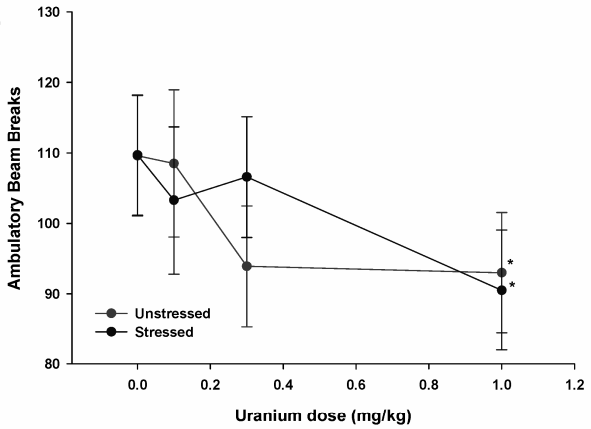
Striatal Dopamine on PD 3



Uranium exposure decreases striatal dopamine in unstressed rats. Values are mean ± SD (N=5). * indicates values that are significantly different from control ($p<0.05$).

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Ambulatory activity on PD 27



Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Uranium exposure decreases forelimb grip strength

Day post-dosing	Uranium dose (mg/kg)	Forelimb Grip Strength (kg)	
		Unstressed	Stressed
6	0	1.83 ± 0.04	1.81 ± 0.05
	0.1	1.87 ± 0.04	1.79 ± 0.05
	0.3	1.79 ± 0.03	1.76 ± 0.03
	1.0	**1.70 ± 0.07**	1.79 ± 0.04
13	0	1.96 ± 0.04	1.94 ± 0.04
	0.1	2.01 ± 0.02	2.05 ± 0.03
	0.3	1.91 ± 0.04	1.96 ± 0.04
	1.0	**1.86 ± 0.04**	1.93 ± 0.03
20	0	2.01 ± 0.06	1.98 ± 0.05
	0.1	1.98 ± 0.07	2.06 ± 0.04
	0.3	1.90 ± 0.04	1.94 ± 0.05
	1.0	**1.87 ± 0.06**	1.96 ± 0.04
27	0	2.06 ± 0.06	2.08 ± 0.05
	0.1	2.08 ± 0.03	2.09 ± 0.07
	0.3	1.99 ± 0.04	2.10 ± 0.04
	1.0	**1.91 ± 0.05**	1.99 ± 0.04

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Summary

- A single intramuscular injection of uranyl acetate increased brain uranium for at least 30 days. Hippocampus and striatum accumulated higher uranium levels than cortex and cerebellum.
- A single exposure to uranyl acetate is capable of producing neurological effects that last for at least 27 days after exposure
- Stress at the time of uranium exposure had little effect on uranium levels, but did alter some behavioral and neurochemical parameters
  - Dose dependent decreases in ambulatory activity were observed. These effects were not significantly altered by prior stress.
  - A transient decrease in striatal dopamine was observed. This was ameliorated by prior stress
  - Small dose dependent decreases in forelimb grip strength were observed. These were ameliorated by prior stress.

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

- All doses produced some degree of uremia. It is difficult to separate direct neurological effects of uranium from secondary effects due to uremia.
- The timing, duration, and effect of stress suggest that effect on dopamine and forelimb grip strength may be direct effects of uranium.

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

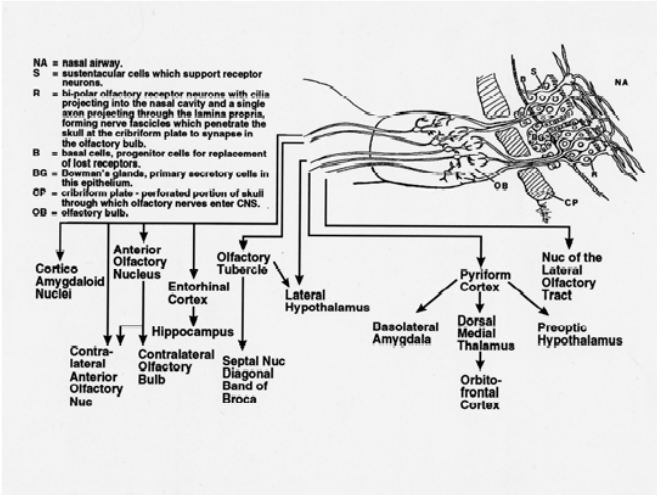
Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney

Johnnye Lewis, Ph.D., DABT
Director, Community Environmental Health Program, University of New Mexico Health Sciences Center

Co-Investigators:
Graham Bench, Ph.D., CAMS, Lawrence Livermore National Laboratory
Fletcher Hahn, DVM, Ph.D., DACVP, Lovelace Respiratory Research Institute
Jenny Karlsson, Ph.D., Community Environmental Health Program, UNM HSC
Ed Barr, MSEE, Lovelace Respiratory Research Institute

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

Nose-Brain Barrier



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

DU as a contributor

- **Potential for exposures to DU aerosols**
  - **Tank-Impact – High concentration, acute (15 min) exposure**
  - **March-Through – Low concentration – single day**
  - **Clean-up – Low concentration – up to 30 day**
  - **Maintenance – Very low concentration – longer duration**
- **Aerosols resulted from impact, combustion, resuspension**
  - **Estimates of exposure inconsistent**
    - **Varied from 300 micrograms to >25 grams**
    - **Estimates of solubility and respirability varied**
  - **Respirable fraction could move suspended for hours**
- **Other heavy metals neurotoxic and neuroimmunotoxic**

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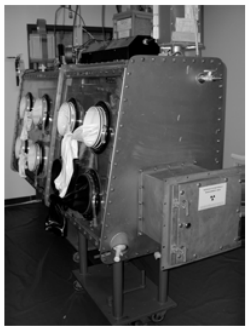
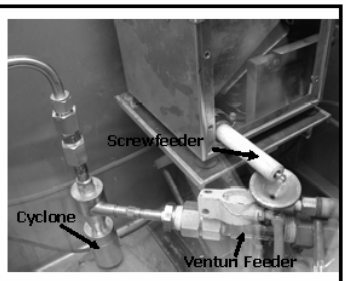
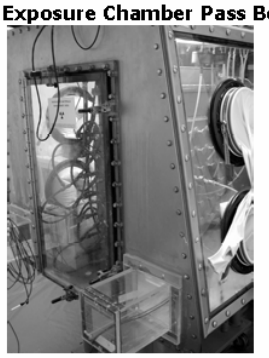
Glove Box Enclosure System



Aerosol Generation System



Exposure Chamber Pass Box



96-Port Nose-Only Exposure Chamber

EXPOSURE

Ed Barr, MSEE

Lovelace Respiratory Research Institute

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

Pathology at 4 hr post-exposure

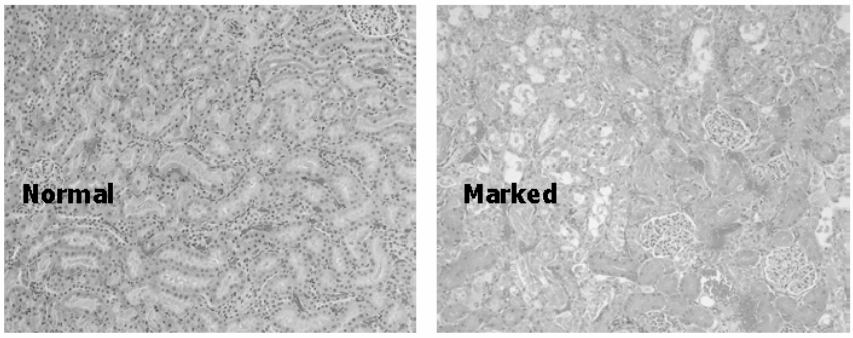
Tank-Impact Scenario

(Moribund sacs & deaths at <14 d included)

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

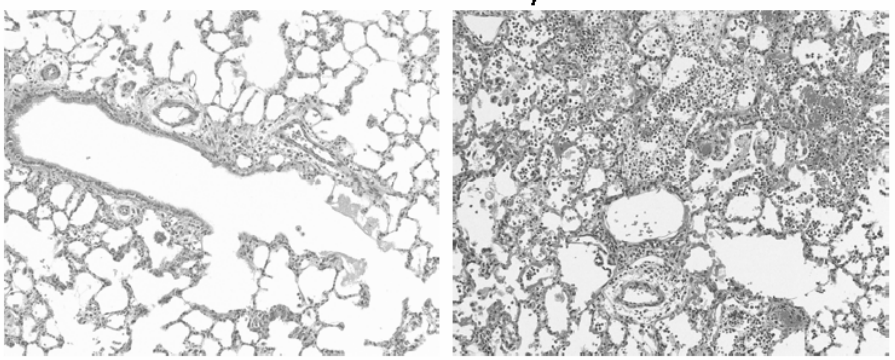
Renal Tubular Necrosis

More soluble UO_3 resulted in renal tubular necrosis and uremia



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

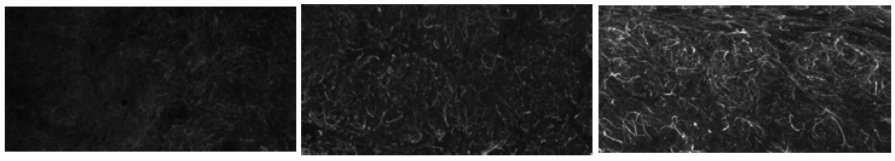
Uremic Pneumonia
Mild vs. Marked, Fatal



- **Uremic pneumonia was the immediate cause of death**
- **Females had a higher death rate**

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

GFAP 4 hours post 15 min high dose exposure *Tank-impact Scenario*



Control DUOx UO3

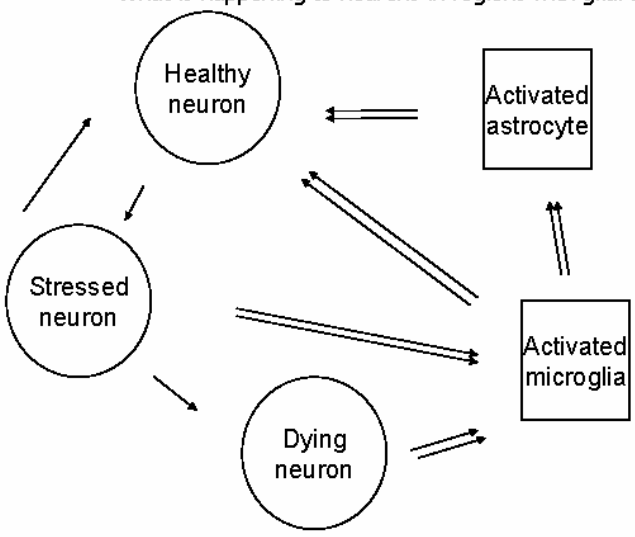
Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Brain inflammation – GFAP data
Tank-impact scenario

- **Solubility related increase in GFAP**
- **Females appear to show greater response**
- **Time x gender x exposure interaction**
- **Endotoxin increases GFAP response in all exposures**
  - **Females show greater increase with U exposure**

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

What is happening to neurons in regions with glial activation?



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

Conclusions

- **Very Short/High Dose – *Tank-Impact* scenario**
  - **no detectable CNS uptake regardless of solubility**
  - **Solubility-related neuroinflammation**
  - **Most soluble forms result in extensive renal deposition and renal toxicity**
  - **Females more sensitive to CNS & renal toxicity**
- **Short-term/ Moderate Dose – *March-Through* Scenario**
  - **Nasal inflammation increases the probability of CNS deposition and transport with low dose inhalation for 6 hr durations**
- **Longer-duration/ Moderate Dose – *Clean-Up* Scenario**
  - **No uptake observable in animals without inflammation**

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

Epidemiologic Studies: Associations between DU exposure and health outcomes in Gulf War veterans

Depleted Uranium

★☆★ RAC-GWVI

Epidemiologic Studies: Association of DU With GWI-related Health Outcomes

Study	Exposure	Outcome	OR
Haley, 1997 (249 Seabeas)	s/r DU exposure	any of 3 defined syndromes	ns
Spencer, 2001 (241 GWI cases, 113 controls)	s/r DU exposure	GWI case CMI case	OR = 3.69 (1.54 – 8.81) OR = 4.46 (1.74 – 11.40)
Suadicini, 1999 (686 Danish Gulf War vets)	s/r DU exposure	3+ neuro-psych symptoms	OR = 2.3 (0.95-5.7)
Australian study (1,456 Australian vets)	s/r contact with DU shell casings	functional impairment in prior 2 weeks	OR = 1.1 (0.8-1.6)

HEALTH EFFECTS OF DEPLETED URANIUM IN EXPOSED GULF WAR VETERANS – A TEN-YEAR FOLLOW-UP

Melissa A. McDiarmid, M.D., M.P.H.
VA Maryland Health Care System
Baltimore Division

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

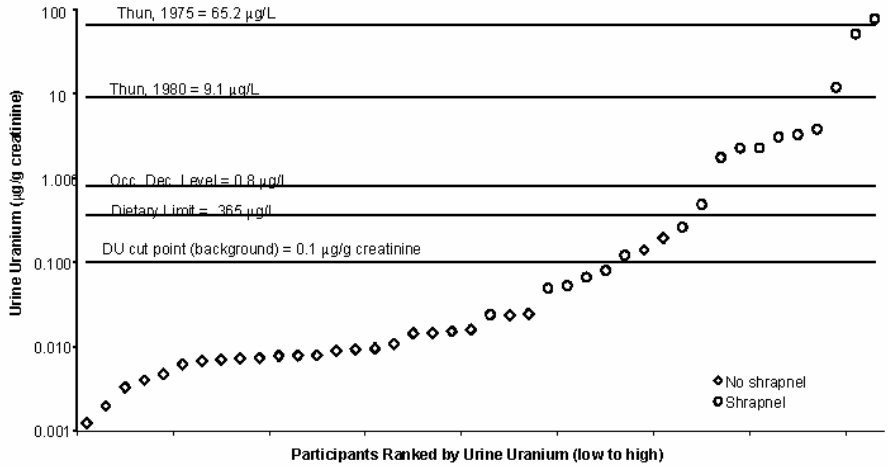
Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Summary of Surveillance Visits

Year	Cases	Non-exposed	Total
1993-4	33		33
1997	29	38	67
1999	21+29 new		50
2001	31+8 new (17 original cases)		39
2003	32		32

A total of 70 individuals involved in friendly fire incidents have been evaluated at Baltimore.

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.



Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Hematologic Parameters Summary (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
White Blood Cells (4.8-10.8 K/cm^2)	6.53 ± 0.41	5.85 ± 0.45	0.36
Hematocrit (4252%)	**44.60 ± 0.43**	**42.59 ± 0.80**	**0.03**
Hemoglobin (1418 g/dL)	**15.40 ± 0.15**	**14.79 ± 0.32**	**0.07**
Platelets (140-440 K/cm^2)	254.54 ±13.82	234.08 ± 13.73	0.21
Lymphocytes (%) (15-45%)	36.87 ± 1.99	36.07 ± 1.81	0.80
Neutrophils (%) (40-75%)	50.95 ± 2.09	51.83 ± 1.97	0.74
Basophils (%) (0-2%)	0.78 ± 0.10	0.65 ± 0.07	0.54
Eosinophils (%) (0-4%)	3.60 ± 0.35	3.51 ± 0.44	0.85
Monocytes (%) (2-12%)	7.79 ±0.37	7.94 ± 0.48	0.99

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Renal Function Parameters (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
Serum creatinine (0.5-1.1 mg/dL)	**0.95 ± 0.03**	**0.85 ± 0.03**	**0.03**
Serum uric acid (3.4-7 mg/dL)	5.94 ± 0.23	5.85 ± 0.51	0.45
Serum calcium (8.4-10.2 mg/dl)	9.17 ± 0.006	9.27 ± 0.137	0.67
Serum PO4 (2.7-4.5 mg.dl)	3.82 ± 0.101	3.82 ± 0.148	0.63
Urine calcium (100-300 mg/24 hr)	183.50 ± 23.8	214.50 ± 26.3	0.35
Urine PO4 (0.4-1.3 g/24 hr)	1.03 ± 0.008	1.15 ± 0.107	0.40

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Neuroendocrine and Thyroid Hormone Parameters (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
Prolactin (2.1- 17.7 ng/mL)	**18.84 ± 1.60**	**14.70 ± 2.76**	**0.06**
FSH[c] (.9-15 IU/ml)	4.39 ± 0.50	4.51 ± 0.74	0.95
LH[c] (1.5-9.3 mIU/ml)	5.09 ± 0.51	5.13 ± 1.04	0.48
Testosterone (3-10 ng/ml)	5.64 ± 0.49	4.77 ±0.47	0.28
TSH[c] (0.49-4.67 µIU/ml))	1.99 ±0.24	2.28 ± 0.50	0.89
Free thyroxine (0.7-1.85 ng/dL)	**1.66 ± 0.35**	**1.08 ± 0.07**	**0.02**

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)
[c] FSH, follicle - stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Genotoxicity Parameters (2001)

Laboratory test	Low Uranium Group[a] (mean ± SE(n))	High Uranium Group[b] (mean ± SE(n))	Mann - Whitney Test (p)
Mean aberrations/cell	**0.003 ± 0.001 (26)**	**0.01 ± 0.004 (13)**	**0.027**
Mean SCE[c] untreated	5.07 ± 0.32 (25)	4.39 ± 0.37 (13)	0.199
Mean SCE w/Bleomycin 2 µg/ml	5.42 ± 0.32 (23)	5.95 ± 0.71 (11)	0.663
Mean SCE w/Bleomycin 4 µg/ml	6.31 ± 0.60 (20)	5.30 ± 0.42 (11)	0.197
HPRT MF[d]	10.97 ± 0.97 (26)	19.84 ± 4.89 (13)	0.105

[a] < 0.10 µg/g creatinine
[b] ≥ 0.10 µg/g creatinine
[c] SCE, sister chromatid exchange
[d] HPRT MF, hypoxanthine phosphoribosyl transferase mutation frequency

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Recent Publication from VA DU Cohort

Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **Reports on physical exams and lab evaluations of 32 Gulf veterans with embedded DU shrapnel; 5th exam**
- **Found that urine uranium continues to be elevated in this cohort 12 years after first exposure**
- **Paper concludes that "no clinically significant uranium-related health effects were observed in blood count, blood chemistries, neuropsychological measures, semen quality, or genotoxicity measures."**

Epidemiologic Studies
Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **13 veterans with "high level" urine uranium (>0.10 ug/g creatine) and 19 with lower levels of urinary uranium (<0.10 ug/g creatine)**
- **Significant differences reported include:**
  - Serum phosphate levels (high)
  - Uranium levels sign assoc with neurocogn accuracy index (intellectual level)
- **Differences approaching significance include:**
  - Urine retinol binding protein (high)
  - Neurocognitive accuracy measure (more impairment)
  - Mutation frequencies
- **Low and high U groups had elevated serum prolactin levels**

Epidemiologic Studies
Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **Concerns:**
  - **Comparisons between "low urine uranium" and "high urine uranium" groups, not between those with/without uranium, or exposed/not exposed**
  - **Small sample limits ability to detect significant differences**
  - **Differences that are identified are minimized**
  - **No information on chronic symptoms, symptom complexes**
  - **No information on tumors**

Depleted Uranium: Information Considered by RAC in 2004-2005

- DU exposure levels/modeled health risks
- Animal studies
- Epidemiologic studies

DU: Summary of Information Considered

DU exposure levels/modeled health risks

- Experimental and modeled DU exposure levels generally indicate no/minimal expected increases in known health risks
- Models focused on expected risks associated with renal effects, common cancers

DU: Summary of Information Considered

Animal Studies

- All exposure routes produce renal toxicity at higher doses
- DU from embedded pellets, injected U accumulate in the brain differentially by region; long-term effects on synaptic potential/ excitability in hippocampus
- Embedded DU pellets associated with chromosomal and mutagenic changes associated with tumor development; immunological changes
- Ingested, injected uranium associated with short-term changes in dopamine levels, longer-term changes in behavioral measures
- Inhaled DU can produce systemic effects, neuroinflammation ; direct brain penetration enhanced by nasal inflammation

DU: Summary of Information Considered

Epidemiologic Studies

- Little information from the large epidemiologic studies
- Baltimore VA cohort study suggests veterans carrying DU shrapnel continue to excrete DU over time, possible alterations in cognitive function, kidney function, hormonal levels (prolactin, thyroxin)
- Baltimore study does not provide information on tumors, symptom rates, Gulf War multisymptom illness

Unanswered Questions
DU and the Health of Gulf War Veterans

- Reports and epi studies have not specifically addressed questions re: possible links between DU and multisymptom illnesses in Gulf War veterans
- Little epidemiologic information concerning possible association of DU exposure with cancer
- No research comparing health outcomes in DU-exposed to DU-not exposed populations

Recommendations?

Animal/Toxicological Research:

- **Carcinogenic effects, including brain tumors**
- **Neurotoxic effects: neurochemistry and behavioral studies**
- **Penetration and effects of inhaled exposures**

Epidemiologic Studies:

- **Expand epidemiologic research/surveillance of DU-exposed veterans**
  - e.g., 900 veterans with Level 1 and Level 2 exposures vs. nonexposed
  - e.g., existing data: map health outcomes with DU locations
- **Evaluate/report all health outcomes in expanded cohort:**
  - GWI symptom complex
  - Tumors, cancers
  - Lab measures