

Presentation 11 – Terry Pellmar



**Armed Forces Radiobiology
Research Institute**
Depleted Uranium Health Effects
Overview of AFRI Research

A F R R I

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Health Effects of Depleted Uranium: AFRI Research

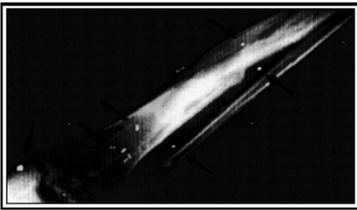
Background

- *Gulf War involved first combat use of munitions made with depleted uranium (DU); only Coalition forces used DU; DU casualties resulted from friendly-fire incidents.*
- *Standard surgical guidelines dictate metal fragments be left in place if risk of surgery is greater than potential damage fragments may cause later.*
- *Given demonstrated effectiveness of DU munitions, U.S. can expect adversaries will use such weapons in future conflicts, resulting in much larger numbers of DU casualties.*
- *AFRI research: are existing fragment removal guidelines appropriate for a metal with the unique chemical and radiological properties of DU?*



Health Effects of Depleted Uranium: AFRI Research

DU shrapnel in lower leg

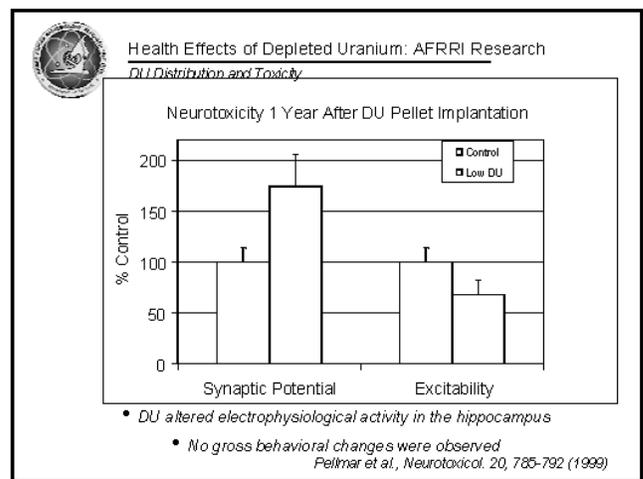
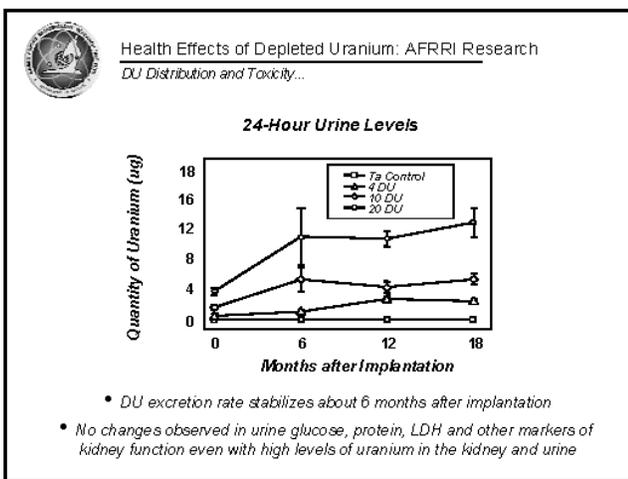
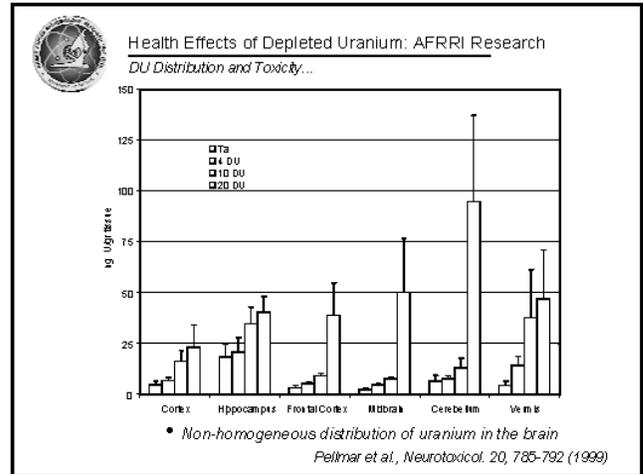
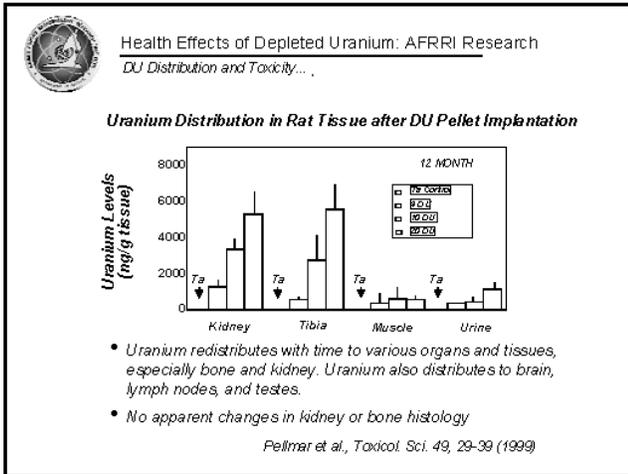


Health Effects of Depleted Uranium: AFRI Research

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*



 Health Effects of Depleted Uranium: AFRRI Research

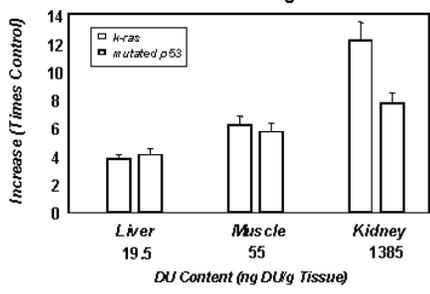
Transformation, Mutagenicity, Carcinogenicity

Principal Investigator: Alexandra Miller, Ph.D.

- Other heavy metals have been shown to be mutagenic and have the capacity to confer tumorigenic potential to exposed cells
- Determine whether exposure to embedded DU presents a long-term risk of cancer
- *In Vivo*: assess oncogene expression in DU-implanted animals; assess genetic instability in lymphocytes from implanted animals
- *In Vitro*: standard methodologies in cultured cells to assess both mutagenic and tumorigenic potential of exposure to DU

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 Transformation, Mutagenicity, Carcinogenicity...

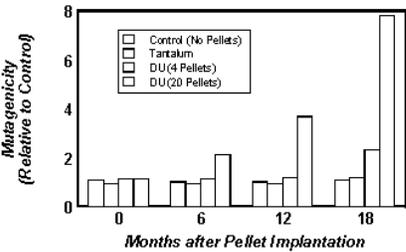
Increased Oncogenes



Organ	DU Content (ng DU/g Tissue)	H-ras (Times Control)	mutated p53 (Times Control)
Liver	19.5	~4.0	~4.5
Muscle	55	~6.5	~6.0
Kidney	1385	~12.5	~8.0

- DU induces oncogenes known to be involved in carcinogenesis

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Months	Control (No Pellets)	Tantalum	DU (4 Pellets)	DU (20 Pellets)
0	1.0	1.0	1.0	1.0
6	1.0	1.0	1.5	2.0
12	1.0	1.0	1.5	3.5
18	1.0	1.0	1.5	7.5

- Urine from DU animals is mutagenic

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

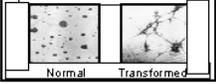
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 Transformation, Mutagenicity, Carcinogenicity...

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

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

**WNI^{Co}: 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/Pheny 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)

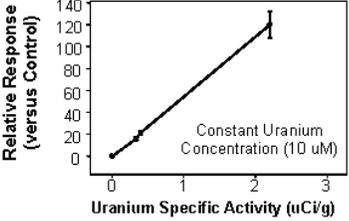
* Number of transformed cells per 500,000 surviving cells
** Number of tumors formed when 1 million transformed cells injected into in mice on prostrated in ice

- 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)

Health Effects of Depleted Uranium: AFRRRI Research
Transformation, Mutagenicity, Carcinogenicity...

**Radiation vs. Chemical Toxicity of DU
Neoplastic Transformation Assay**



Relative Response (versus Control)

Uranium Specific Activity (uCi/g)

Constant Uranium Concentration (10 uM)

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

Miller et al., *Radiation Protection Dosimetry*, submitted

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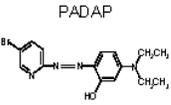
Immunotoxicity

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

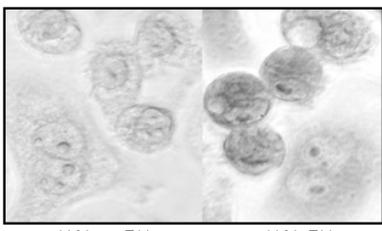
- Immune system is represented in a variety of tissues
- Other heavy metals have been shown to be immunotoxic
- AFRRRI DU Distribution and Toxicity study determined there are alterations in several immune system parameters in DU-implanted rats

Health Effects of Depleted Uranium: AFRRRI Research
Immunotoxicity

PADAP Staining of DU-treated J774 Cells

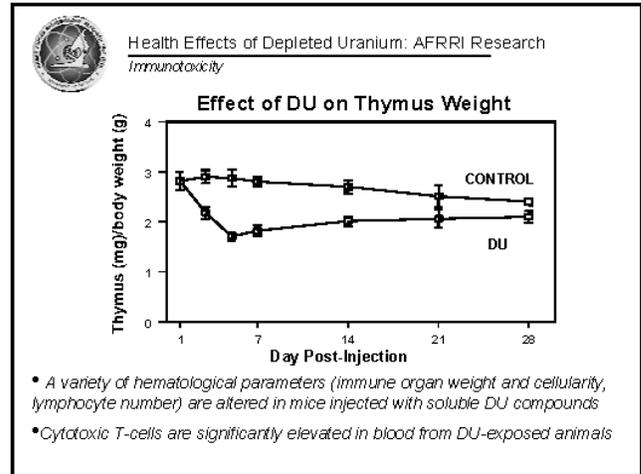
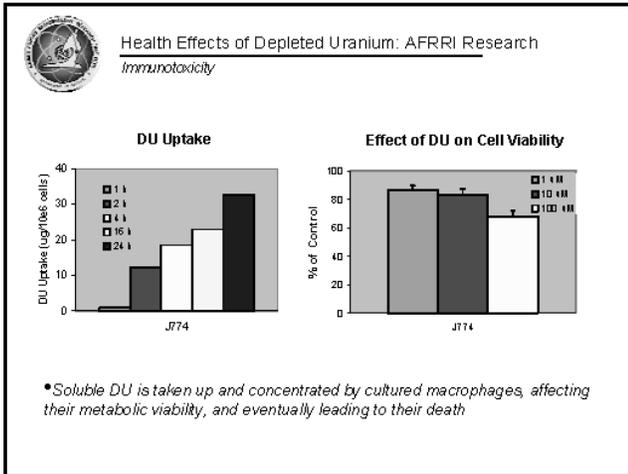


2-(5-Bromo-2-pyridylazo)-5-diethylaminophenol



Without DU With DU

- Uranium-specific dye labels cells that take up the metal



Health Effects of Depleted Uranium: AFRRRI Research
Immunotoxicity

Future Directions

- Expand DU carcinogenicity study (in vitro and in vivo); include other heavy metals of military interest
- Expand in vivo immunotoxicity assessment
- Evaluate transgenerational effects of in vivo exposure to DU in both male and female rodents

Health Effects of Depleted Uranium: AFRRRI Research
Immunotoxicity

AFRRRI DU Research Team

David McClain PhD	Alexandra Miller PhD
John Kalinich PhD	LT Blaise LeBlanc PhD
Christy Emond	Tom Dalton
SSgt Michael Stewart	Vilmar Villa
Kia Brooks	LT Shelly Hakspiel