Presentation 11 – Terry Pellmar

Armed Forces Radiobiology Research Institute

Depleted Uranium Health Effects
Overview of AFRRI Research

A F R R I

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Health Effects of Depleted Uranium: AFRRI 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.*
- *AFRRI research: are existing fragment removal guidelines appropriate for a metal with the unique chemical and radiological properties of DU?*

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DU shrapnel in lower leg

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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*

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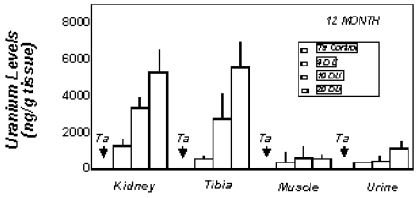
DU Distribution and Toxicity...

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)

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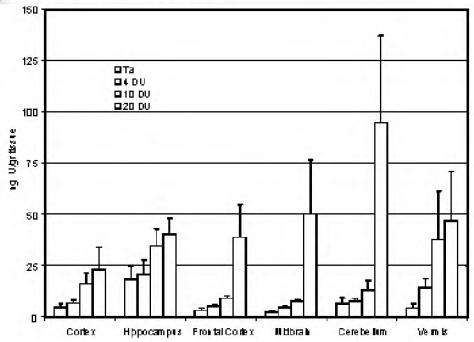
DU Distribution and Toxicity...



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

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

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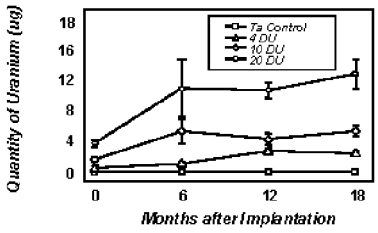
DU Distribution and Toxicity...

24-Hour Urine Levels



- *DU excretion rate stabilizes about 6 months after implantation*
- *No changes observed in urine glucose, protein, LDH and other markers of kidney function even with high levels of uranium in the kidney and urine*

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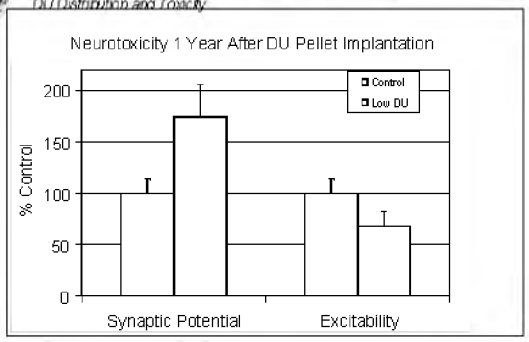
DU Distribution and Toxicity



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

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

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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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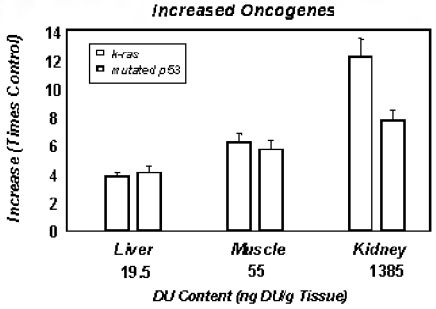
Transformation, Mutagenicity, Carcinogenicity...



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

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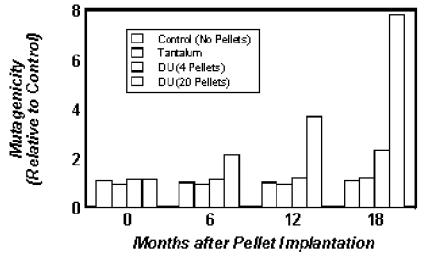
Transformation, Mutagenicity, Carcinogenicity...



- *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)	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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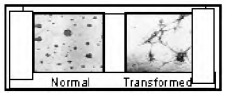
Transformation, Mutagenicity, Carcinogenicity...



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)

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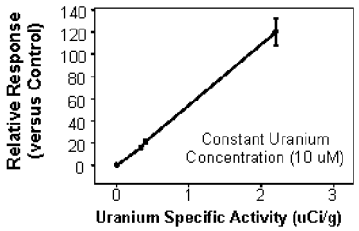
Transformation, Mutagenicity, Carcinogenicity...

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

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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*
- *AFRRI DU Distribution and Toxicity study determined there are alterations in several immune system parameters in DU-implanted rats*

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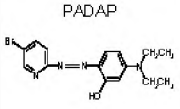
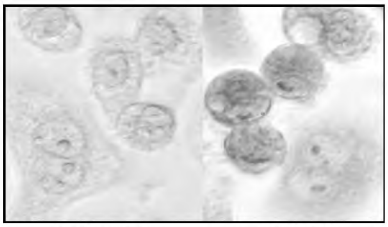
Immunotoxicity

PADAP Staining of DU-treated J774 Cells

PADAP



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



Without DU With DU

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

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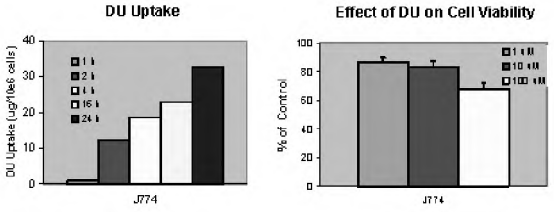
Immunotoxicity



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

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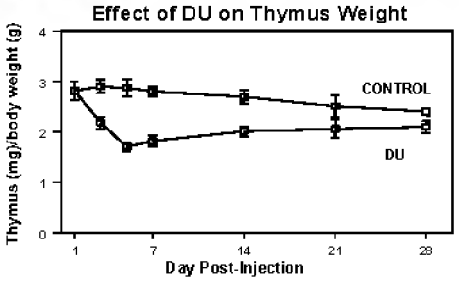
Immunotoxicity



- *A variety of hematological parameters (immune organ weight and cellularity, lymphocyte number) are altered in mice injected with soluble DU compounds*
- *Cytotoxic T-cells are significantly elevated in blood from DU-exposed animals*

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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*

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AFRRI DU Research Team

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