The Use of Uranium Isotopes To Evaluate Depleted Uranium Health Effects

Alexandra C. Miller, PhD
Uniformed Services University
Armed Forces Radiobiology Research Institute

The work presented represents the opinion of the author and is not the opinion of the U.S. Department of Defense or the U.S. Government.
The AFRRI Mission

• To conduct research in the field of radiobiology and related matters essential to the operational and medical support of the U.S. Department of Defense and the Military Services.

• To provide training to medical personnel.

• Advisory
Low-Level Radiation (LLR) Exposure Facility runs at pulses of up to 2,500 Megawatts and at a steady rate of 1 Megawatt.
Depleted Uranium

- Used in military munitions/tanks
- Uranium with less than 0.2% by weight of U$^{235}$ (natural uranium has 0.72%)
- Reduced U$^{234}$, no daughter products, e.g., Radium, radon

Chronic internal exposure: US Soldiers injured with DU Shrapnel 1991 Gulf War, British soldiers Iraq 2003

Potential for inhalation exposure
**Comparison of the Relative Contribution of Uranium Isotopes**

(natural and depleted)

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Specific Activity (µCi/g)</th>
<th>DU SA by WT% (µCi/g)</th>
<th>Natural Uranium SA by WT% (µCi/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{238}\text{U}$</td>
<td>0.333</td>
<td>0.332</td>
<td>0.331</td>
</tr>
<tr>
<td>$^{236}\text{U}$ (not naturally occurring)</td>
<td>63.6</td>
<td>0.0001</td>
<td>0</td>
</tr>
<tr>
<td>$^{235}\text{U}$</td>
<td>2.2</td>
<td>0.0044</td>
<td>0.051</td>
</tr>
<tr>
<td>$^{234}\text{U}$</td>
<td>6200</td>
<td>0.093</td>
<td>0.310</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.4295</strong></td>
<td><strong>0.692</strong></td>
<td></td>
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</table>

*Contribution of the daughter products is not included.*
DU Program Overview at AFRRI

- Acute and Late Biological Effects of Embedded Fragments
- Chemoprevention and Decorporation Procedures
- Transgenerational Effects
- Militarily-Relevant Metals
- Mechanistic Studies
- Model System Development
- Exposure Biomarkers
Short-Term Carcinogenicity Tests:
Relative Comparison of DU, Nickel, and Alpha Particles
Using DU-Uranyl Nitrate

Published *In vivo* Results

- Leukemia
- Mutagenicity
- Genomic Instability
- Genotoxicity
# How to Answer Question Regarding DU Radiation Specific Effects??

## Uranium Isotope Comparison Model System

<table>
<thead>
<tr>
<th>Uranium Isotopes:</th>
<th>Specific Activity</th>
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<tbody>
<tr>
<td>$^{235}\text{U}$</td>
<td>2.2</td>
</tr>
<tr>
<td>DU</td>
<td>0.43</td>
</tr>
<tr>
<td>$^{238}\text{U}$</td>
<td>0.33</td>
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</table>
Does DU Cause Radiation Specific Damage?

Radiation Effects of DU: *In vitro* studies

![Dicentric Chromosomes](image)

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<tr>
<th>Endpoint</th>
<th>DU</th>
<th>238U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutagenicity (HPRT Loci)</td>
<td>5.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Transformation (Morphology)</td>
<td>10.0</td>
<td>20.0</td>
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</tbody>
</table>

**Uranium Isotopes:**
- DU: 0.43
- 238U: 0.33

Radiation Specific Effects in Vitro: Heavy Metal Mutagenicity, Genotoxicity Neoplastic Transformation: Comparison of DU and $^{238}$U at Equal Concentrations

Unpublished data.
Use of Uranium Isotopes to Evaluate *In vivo* Effects

**Model to Assess Transgenerational Effects of Radiation or Heavy Metals**

**“Big Blue” Mutation and Offspring Assessment Assay**

**Assay:**
- Exposed Parent
- F1 Offspring

- **Suspected mutagen**
- Mouse transgenic for a vector contain lac (the lac repressor gene)
- Extract DNA from tissues
- Vector DNA
- Isolate vector and insert into bacteriophage lambda
- Infect *E. coli* with the bacteriophage
- Place on agar containing substrate that turns blue when hydrolyzed by beta-galactosidase

- **Vector DNA**
- **Extract DNA from tissues**
- **Isolate vector and insert into bacteriophage lambda**
- **Infect *E. coli* with the bacteriophage**
- **Place on agar containing substrate that turns blue when hydrolyzed by beta-galactosidase**

**Cells with unmutated lac gene produce repressor so no beta-galactosidase is synthesized**

**Cells with mutated lac gene produce defective lac repressor so beta-galactosidase is synthesized**

- **Colorless plaques**
- **Mutation frequency**
- **Blue plaques**

**Number of blue plaques**

**Total number of plaques**
Transgenerational Effects of Depleted Uranium: Involvement of Radiation

Miller et al., 2010 *Health Physics*, epub Aug 30, 2010
Conclusions

In vitro
1. DU induces neoplastic transformation, mutagenicity, and genotoxicity \textit{in vitro}.

2. Radiation effects are associated with DU-induced neoplastic transformation, mutagenicity, and chromosomal damage.

In vivo
1. Radiation Effects are associated with transgenerational genomic instability.
## Acknowledgements

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<thead>
<tr>
<th>AFRRI – My Lab</th>
<th>Columbia University</th>
<th>University Of Paris</th>
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<td>Rafael Rivas</td>
<td>David Brenner</td>
<td>Robert Merlot</td>
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<td>Mike Stewart</td>
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<tr>
<td>Tim Whittaker</td>
<td>Catherine Mitchell</td>
<td>Lillian Crepin</td>
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<td>Jiaquan Xu</td>
<td>Steve Mitchell</td>
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