Long-Term Health Effects of Embedded Depleted Uranium

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<tr>
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The Embedded Pellet Rat Model

X-ray of pellets implanted in gastrocnemius muscle
Experimental Approach

- Two-year longevity study to determine whether intramuscularly implanted DU or tungsten alloy pellets are carcinogenic.

- Six treatment groups of Fisher 344 rats
  - Two groups with 4 or 20 DU pellets
  - Two groups with 4 or 20 tungsten alloy pellets (91% W, 6% Ni, 3% Co)
  - One nickel group (positive control)
  - One tantalum group (negative control)

- One set of pellet-implanted rats for duration of study. Second set includes rats euthanized at selected times after pellet implantation to provide tissues for histopathology, assessment for metal content and immunotoxicity testing.

- USAMRMC Award DAMD17-01-1-0821
Body Weight Gain After Pellet Implantation

Body Weight (gm) vs. Time Post-Implantation (weeks)
Survival After Pellet Implantation

Percent Survival

Time Post-Implantation (weeks)

- NS
- TC
- DL
- DH
DU pellet implants: new and 12 weeks
Spleen Uranium Levels

Concentration (ng/gm tissue)

Implantation Group

NS  TC  DL  DH
Fibrotic Capsule from DU Implantation Site (13 weeks)
DU Implantation Site – 13 weeks
Popliteal Lymph Node Uranium Levels

Concentration (ng/gm tissue)

Implantation Groups

1M
3M
6M
12M
18M
## Tumor Distribution Based on Gross Necropsy Examination

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<tr>
<th></th>
<th>6 Month (n = 20)</th>
<th>12 Month (n = 20)</th>
<th>18 Month (n = 10)</th>
<th>24 Month (n = 16)</th>
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<tr>
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<td>None</td>
<td>1-abdominal</td>
<td>8-testicle</td>
<td>7-testicle</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-abdominal</td>
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<tr>
<td>Tantalum</td>
<td>2-abdominal</td>
<td>None</td>
<td>8-testicle</td>
<td>9-testicle</td>
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<td></td>
<td></td>
<td></td>
<td>2-abdominal</td>
<td>5-abdominal</td>
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<tr>
<td>DU Low Dose</td>
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<td>8-testicle</td>
<td>10-testicle</td>
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<td></td>
<td></td>
<td></td>
<td>1-abdominal</td>
<td>1-adrenal</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-kidney</td>
</tr>
<tr>
<td>DU High Dose</td>
<td>None</td>
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<td>6-testicle</td>
<td>9-testicle</td>
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<td></td>
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<td></td>
<td>2-abdominal</td>
<td>2-lung</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1-kidney</td>
<td>8-kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-muscle (leg)</td>
</tr>
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</table>
Renal Tubule Carcinoma – High-Dose DU (104 weeks)
Renal Tubule Carcinoma – High-Dose DU (104 weeks)
Urine Uranium Levels

Concentration (ng/mg creatinine)

1 M  3 M  6 M  12 M  18 M  24 M
Kidney Uranium Levels

- DL
- DH

- U Concentration (ng/gm tissue)

- 1M
- 3M
- 6M
- 12M
- 18M
- 24M
Correlation of Kidney and Urinary Uranium Levels

Kidney Uranium Levels (ng U/gm tissue)

Urine Uranium Levels (ug/gm creatinine)

TC (24)
DL (24)
DH (24)
Uranium Levels in Rats with and without Renal Tumors

- Kidney Uranium Levels (ng U/gm tissue)
- Urine Uranium Levels (ug/gm creatinine)

Graph showing the comparison of uranium levels between rats with and without renal tumors.
Summary

- DU-implanted rats did not exhibit tumors at the pellet implantation sites.

- High-dose DU rats, in the 24 month group, had an increased incidence of renal neoplasias.

- Urine uranium levels in DU-implanted rats increased over time in a dose-dependent manner.

- Uranium levels in the kidney also increased over time, reaching 3 µg/g tissue by 18 months in the high-dose DU group.
Current Work

• Continue histopathology assessment of renal carcinomas

Future Directions

• Identify early serum or urinary biomarkers of DU-induced neoplastic renal changes
• Investigate molecular mechanisms associated with DU-induced renal effects
• Tier-testing approach for assessing potential health effects of embedded metal fragments
The “Team”

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Histopathology

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QUESTIONS

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