Long-Term Health Effects of Embedded Depleted Uranium

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**1. REPORT DATE**
NOV 2010

**2. REPORT TYPE**

**3. DATES COVERED**
00-00-2010 to 00-00-2010

**4. TITLE AND SUBTITLE**
Long-Term Health Effects of Embedded Depleted Uranium

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**6. AUTHOR(S)**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**
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**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

**10. SPONSOR/MONITOR’S ACRONYM(S)**

**11. SPONSOR/MONITOR’S REPORT NUMBER(S)**

**12. DISTRIBUTION/AVAILABILITY STATEMENT**
Approved for public release; distribution unlimited

**13. SUPPLEMENTARY NOTES**
Presented at the Depleted Uranium Symposium, held November 4, 2010, at the Armed Forces Radiobiology Research Institute

**14. ABSTRACT**

**15. SUBJECT TERMS**

**16. SECURITY CLASSIFICATION OF:**

<table>
<thead>
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<th>a. REPORT</th>
<th>b. ABSTRACT</th>
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**17. LIMITATION OF ABSTRACT**
Same as Report (SAR)

**18. NUMBER OF PAGES**
22

**19a. NAME OF RESPONSIBLE PERSON**

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Standard Form 298 (Rev. 8-98)
Prepared by ANSI Std Z39-18
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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 Gain After Pellet Implantation versus Time Post-Implantation (weeks). The graph shows the body weight (in grams) over time for different groups, labeled as NS, TC, DL, and DH. The y-axis represents body weight in grams, ranging from 0 to 600, while the x-axis represents time post-implantation in weeks, ranging from 0 to 98.
Survival After Pellet Implantation

Percent Survival vs. Time Post-Implantation (weeks)

Lines represent different groups:
- NS
- TC
- DL
- DH

Survival rates decrease over time, with some groups showing a steeper decline than others.
DU pellet implants: new and 12 weeks
Spleen Uranium Levels

- **Concentration (ng/gm tissue)**

- **Implantation Group**
  - NS
  - TC
  - DL
  - DH

- **Legend**
  - 1 Month
  - 3 Month
  - 6 Month
  - 12 Month
  - 18 Month

The graph shows the concentration of uranium in spleen tissue across different implantation groups and time periods.
Fibrotic Capsule from DU Implantation Site (13 weeks)
DU Implantation Site – 13 weeks
Popliteal Lymph Node Uranium Levels

Implantation Groups

Concentration (ng/gm tissue)

DL

DH

1M
3M
6M
12M
18M
<table>
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<tr>
<th>Group</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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<td>1-abdominal</td>
<td>8-testicle</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Tantalum</td>
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<td>9-testicle</td>
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<td></td>
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<td></td>
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<td>1-muscle (leg)</td>
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<td></td>
<td></td>
<td>1-adrenal</td>
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<td></td>
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<td>8-kidney</td>
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<td></td>
<td>1-muscle (leg)</td>
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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)

- DL
- DH

Legend:
- 1 M
- 3 M
- 6 M
- 12 M
- 18 M
- 24 M
Kidney Uranium Levels

U Concentration (ng/gm tissue)

- **DL**: 1M, 3M, 6M, 12M, 18M, 24M
- **DH**: 1M, 3M, 6M, 12M, 18M, 24M
Uranium Levels in Rats with and without Renal Tumors

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

- **Tumor**
- **Non-Tumor**
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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QUESTIONS

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