Depleted Uranium (DU) Follow-Up Program Update

Melissa A. McDiarmid, MD, MPH, DABT
Katherine S. Squibb, PhD
VA Maryland Health Care System
University of Maryland
Baltimore, USA
Report Documentation Page

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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
   Depleted Uranium (DU) Follow-up Program Update

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)
   University of Maryland , 620 W. Lexington St, Baltimore, MD, 21201

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:
   a. REPORT
      unclassified
   b. ABSTRACT
      unclassified
   c. THIS PAGE
      unclassified

17. LIMITATION OF ABSTRACT
   Same as Report (SAR)

18. NUMBER OF PAGES
   31

19a. NAME OF RESPONSIBLE PERSON

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18
Gulf War Exposures to DU

- Friendly-fire incidents exposed US soldiers to:
  - DU shrapnel
  - Aerosolized DU oxides
    - Inhalation, ingestion, wound contamination

- Burning of munitions storage facility
- Decontamination of military equipment
Purpose of DU Surveillance Program

• Determine DU-related health effects, if any, in exposed soldiers
• Develop methods to measure uranium exposure
  – Inhalation exposure/wound contamination
  – Embedded fragment
• Examine medical and surgical management of fragments
Measurements of DU Exposure

- Urine uranium concentrations
  - Relation between fragment status and elevated urinary uranium levels first observed in 1994 visit
  - Confirmed in all 7 subsequent visits
- Developed analytical method for measuring DU vs total U
  - $^{235}\text{U}/^{238}\text{U}$ isotopic analysis
## Summary of Surveillance Visits

<table>
<thead>
<tr>
<th>Visit Year</th>
<th>Gulf War I</th>
<th>OIF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-4</td>
<td>DU-exposed</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>29</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>1999</td>
<td>21 + 29 new</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>2001</td>
<td>31 + 8 new</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>2003</td>
<td>32</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>2005</td>
<td>30 + 4 new</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>2007</td>
<td>32 + 3 new</td>
<td>2 (1 new)</td>
<td>37</td>
</tr>
<tr>
<td>2009</td>
<td>38 + 2 new</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>

79 unique cases have been evaluated from Gulf War I.
4 unique cases have been evaluated from OIF.
Mean Urine Uranium Values (1993-2007, N=77)

- Thun, 1975 = 65.1 µg U/L
- Dietary Limit = 0.365 µg
- DU Cut point = 0.1 µg U/g creatinine
- NHANES 95th percentile = 0.043 µg U/g creatinine
- NHANES geometric mean = 0.008 µg U/g creatinine

Participants Ranked from Low to High Mean Urine Uranium
Individual Participant’s with 4 or More Visits Mean uU with Minimum and Maximum uU Values (n=35)
Correlation between Urine and Blood Uranium When Urine U >0.1 µg/g Creatinine

Blood Uranium (µg/L) vs. Urine Uranium (µg/g creatinine)

$\rho=0.95$

$p<.01$
Blood Uranium Values from the 2007 Cohort

Fisene and Perry 1985 = 0.14 µg U/L

Blood Uranium (µg/L)

Blood Uranium Values Ranked from Low to High

- Insufficient total uranium to measure isotopes
- DU present
- No DU

Fisene and Perry (1985) Mean U concentration in blood of residents of NYC with no known occupational exposure to U
Radiation Dose Estimate from Whole Body Counting

- Nine veterans with whole body measurements above background
- Radiation dose estimates calculated using ICRP 30 Biokinetic model for U
  - 0.01 to 0.11 rem/year
  - 0.61 to 5.33 rem/50 years
- Public dose limit: 0.1 rem/year
- Occupational limit: 5 rem/year
Health Surveillance Results from 2009 Visit
# Demographic Characteristics of the 2009 Participants Compared to All Participants

<table>
<thead>
<tr>
<th>RACE</th>
<th>2009 Cohort (n = 35)</th>
<th>All GWI Participants (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%*</td>
</tr>
<tr>
<td>African American</td>
<td>12</td>
<td>34%</td>
</tr>
<tr>
<td>Asian American</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>20</td>
<td>57%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>Native American</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

**AGE**

- 2009 Cohort: $43.62 \pm 5.35$
- All GWI Participants: $43.12 \pm 4.80$

* May not add to 100% due to rounding

** Mean age at a time of 2009 evaluation (± standard deviation)
Health Surveillance Protocol

- Complete history (medical, social, family, reproductive, occupational exposure, partner)
- Extensive laboratory studies (hematology, serum chemistry, neuroendocrine, urinalysis, urine, semen and blood uranium, renal markers, semen analysis, bone metabolism)
- Chromosomal analysis (HPRT, PIG-A, FISH, micronuclei)
- Neurocognitive testing
- Dermatologic testing for hypersensitivity to U
- Focus group/risk communication
Summary of Renal Effect Measures
## Proximal Tubule Markers – 2009 Cohort

<table>
<thead>
<tr>
<th>2009 Laboratory test (normal range)</th>
<th>Low Mean Uranium Group&lt;sup&gt;a&lt;/sup&gt; (mean ± SE)</th>
<th>High Mean Uranium Group&lt;sup&gt;b&lt;/sup&gt; (mean ± SE)</th>
<th>Mann-Whitney p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine β&lt;sub&gt;2&lt;/sub&gt; microglobulin (0-0.3 mg/L)</td>
<td>0.10 ± 0.02</td>
<td>0.10 ± 0.01</td>
<td>0.50</td>
</tr>
<tr>
<td>Urine intestinal alkaline phosphatase (IAP) (&lt;2 U/g creatinine)</td>
<td>0.20 ± 0.04</td>
<td>0.22 ± 0.04</td>
<td>0.79</td>
</tr>
<tr>
<td>Urine N-acetyl-β-glucosaminidase (NAG) (&lt;5 U/g creatinine)</td>
<td>0.68 ± 0.23</td>
<td>0.45 ± 0.05</td>
<td>0.74</td>
</tr>
<tr>
<td>Urine total protein (1-150 mg/24 h)</td>
<td>110.24 ± 18.15</td>
<td>127.43 ± 16.80</td>
<td>0.15</td>
</tr>
<tr>
<td>Urine micro-albumin (&lt;25 mg/g creatinine)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.36 ± 1.24</td>
<td>4.39 ± 2.48</td>
<td>0.39</td>
</tr>
<tr>
<td>Urine retinol binding protein (&lt;610µg/g creatinine)</td>
<td>33.23 ± 4.32</td>
<td>35.51 ± 8.37</td>
<td>0.79</td>
</tr>
</tbody>
</table>

<sup>a</sup> < 0.10 µg/g creatinine (n=21)

<sup>b</sup> ≥ 0.10 µg/g creatinine (n=14)

<sup>c</sup> Low n = 18, High n = 12
## Summary of Renal Parameters 1994-2009

<table>
<thead>
<tr>
<th>Renal parameter</th>
<th>1994</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine creatinine</td>
<td>ns</td>
<td>ns</td>
<td>&gt;h¹</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine calcium</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine PO4</td>
<td>ns</td>
<td>ns</td>
<td>&gt;h²</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine β-2 microglobulin</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>h&gt;l</td>
</tr>
<tr>
<td>Urine intestinal alkaline phosphatase (IAP)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine N-acetyl-β-glucosa-minidase (NAG)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine total protein</td>
<td>ns</td>
<td>ns</td>
<td>H&gt;L</td>
<td>&gt;h²</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Urine microalbumin</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Retinol binding protein (RBP)</td>
<td>ns</td>
<td>ns</td>
<td>H&gt;L</td>
<td>h&gt;L²</td>
<td>ns</td>
<td>ns</td>
<td>h&gt;L²</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>L&gt;H</td>
<td>ns</td>
<td>ns</td>
<td>L&gt;H</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Serum PO4</td>
<td>ns</td>
<td>ns</td>
<td>H&gt;L</td>
<td>&gt;h²</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>-</td>
</tr>
</tbody>
</table>

L = Low urine uranium group (U < 0.1 µg/g creatinine)
H = High urine uranium group (U > 0.1 µg/g creatinine)
ns = no significant differences between groups
¹ Lower case letters = non-significant findings
² High uranium group 80.5 µg/g creatinine ± 51.4, low uranium group 27.3 µg/g creatinine ± 3.1, p=.54
Predicted Kidney Uranium Concentrations

[U] in micrograms/gram

- Ten years
- Twenty years

Individual Participants

1 2 3 4 5 6 7
Summary of Genotoxicological Measures
## Summary of Differences in Genotoxicity Parameters across Evaluations

<table>
<thead>
<tr>
<th>Genotoxicity Parameter</th>
<th>1994</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sister chromatid exchange (SCE)</td>
<td>l&gt;h*</td>
<td>ns</td>
<td>H&gt;L**</td>
<td>l&gt;h</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromosomal aberrations (CA)</td>
<td>ns</td>
<td>ns</td>
<td>H&gt;L</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypoxanthine-guanine phosphoribosyl transferase (HPRT)</td>
<td>h&gt;l</td>
<td>ns</td>
<td>h&gt;l</td>
<td>h&gt;l</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mutation frequency</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mutation frequency adjusted for cloning efficiency</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mutation frequency adjusted for cloning efficiency and age</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Fluorescent in-situ hybridization (FISH); Mean number of total mutations per subject in chromosomes 5, 7, 11, and 13</td>
<td>h&gt;l</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIG-A</td>
<td>l&gt;h</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronuclei</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low urine uranium group (U < 0.1 µg/g creatinine)
High urine uranium group (U ≥ 0.1 µg/g creatinine)

ns = no significant differences between groups
* lower case letters = non-significant findings
** upper case letters = significant findings (p ≤ 0.05)
Other Clinical Findings

- No clinically significant differences detected between low and high uranium exposure groups for
  - Semen characteristics
  - Neuroendocrine measures
  - Neurocognitive measures
Summary

• Subtle health effects observed in DU exposed veterans are most likely the result of chemical effects of U
  - Decreased reabsorption of filtered proteins in renal proximal tubules
  - Subtle changes in bone metabolism

• Weak genotoxicity results are consistent with epidemiological studies examining carcinogenicity in U millers and miners
  - Mechanisms of DU genotoxicity may be a mix of chemical and radiologic effects
  - Potential for foreign body reaction in vicinity of embedded fragments is a concern
2nd Mission of the DU Follow-Up Program

- Since 1998:
  To provide biologic monitoring by mail for uranium for all GWI and OIF veterans
Purpose of the Urine Biomonitoring Program

- Determine urine uranium concentration in veterans from GWI and forward
- Passively survey for exposure scenarios linked to DU exposure other than friendly fire
- Provide assistance to veterans’ primary care providers in interpreting results and answering veterans questions
Comparison of Urine Uranium Values from DUP, GWI and OIF (as of 10/31/10)

Samples for Low to High Urine Uranium (µg U/g creatinine)

- Mean uU thru 2007 for 2009 cohort; no DU (n=21)
- Mean uU thru 2007 for 2009 cohort; DU (n=15)
- Gulf War mailin; no DU (n=820)
- Gulf War mailin; isotopic not done (n=469)
- Gulf War mailin; DU (n=1)
- OIF/OEF mailin; no DU (n=1899)
- OIF/OEF mailin; DU (n=3)

- Thun, 1975 65.1 µg U/g creatinine
- Thun, 1980 9.1 µg U/g creatinine
- Occ. Dec. Level 0.8 µ/L
- Dietary limit 0.365 µ/L
- DU program (Mail In) cut point 0.05 µ U/g
- NHANES 95th% 0.34 µ U/g creatinine
Results of OIF Urine Surveillance
(as of 31 October 2010)

Samples processed
3192

Gulf War I (n=1290)
- Isotopic signature for natural uranium
  820
- Isotopic signature for DU 1*

OIF/OEF (n=1902)
- Isotopic signature for natural uranium
  1899
- Isotopic signature for DU 3*
- Isotopic analysis not done
  469

*All with DU signature were invited to enter the DU Follow-up Program. Two from OIF/OEF declined but may be interested in future follow-up.
Outstanding Questions

• Will health effects of DU develop in the cohort as it grows older?

• What are the health effects of concern related to effects of DU embedded fragments on adjacent tissues?

• Should even small pieces of DU shrapnel be removed?
Fate of DU Metal Fragments in Rat Muscle *in Situ*

Correlation of radiographic appearance with histologic appearance. (A) Thick fibrotic capsule with shards of corroded DU in lumen; (B) thick cellular capsule lined by squamous metaplasia, particles, and shards of corroded DU in wall and lumen; (C) particles and shards of disintegrated DU fragment scattered throughout a soft tissue sarcoma (Hahn et al, 2002).
Development of *in Situ* Surveillance Protocol

- Objective: To identify and manage (prevent) health effects related to fragment retention
  - Risk of the development of tumors at fragment sites
    - Foreign body effects?
      - Medical implants (hip, knee joints; dental implants, etc)
    - Bullets
  - Chemical effects?
In Situ Imaging Methods for Surveillance of Fragments and Surrounding Tissue

- Currently using x-ray films to look for changes in the shape and other physical characteristics of the fragments

- Exploring other available imaging methods for identifying pre-neoplastic lesions or primary stage tumors
  - Ultrasound
  - MRI
  - PET/CT