

# Depleted Uranium (DU) Follow-Up Program Update



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# 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
  - $U^{235}/U^{238}$  isotopic analysis

# Summary of Surveillance Visits

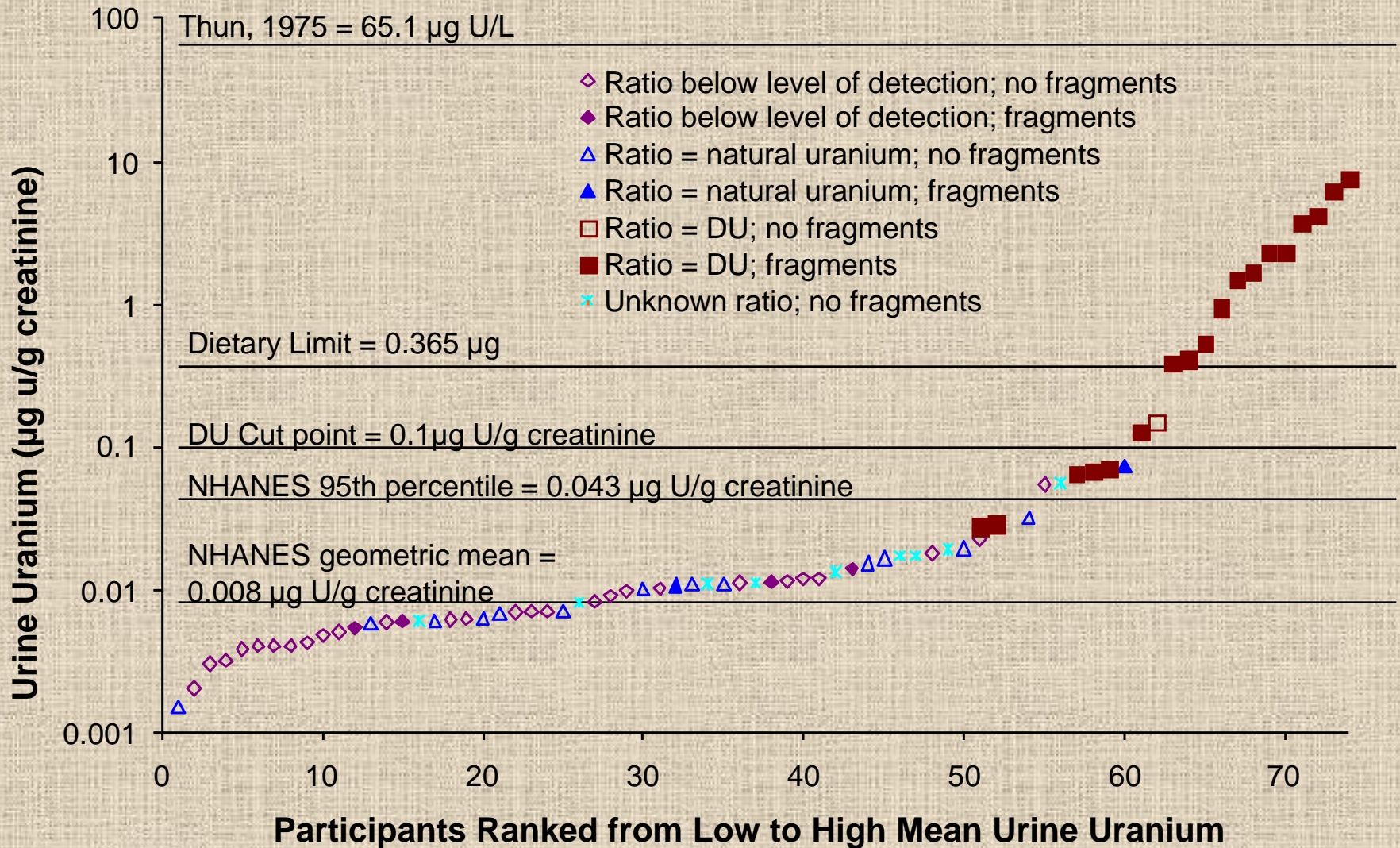
<u>Visit Year</u>	<u>Gulf War I</u>		<u>OIF</u>	<u>Total</u>
	<u>DU-exposed</u>	<u>Non-exposed</u>	<u>DU-exposed</u>	
1993-4	33			33
1997	29	38		57
1999	21 + 29 new			50
2001	31 + 8 new			39
2003	32			32
2005	30 + 4 new		3	37
2007	32 + 3 new		2 (1 new)	37
2009	38 + 2 new		2	40

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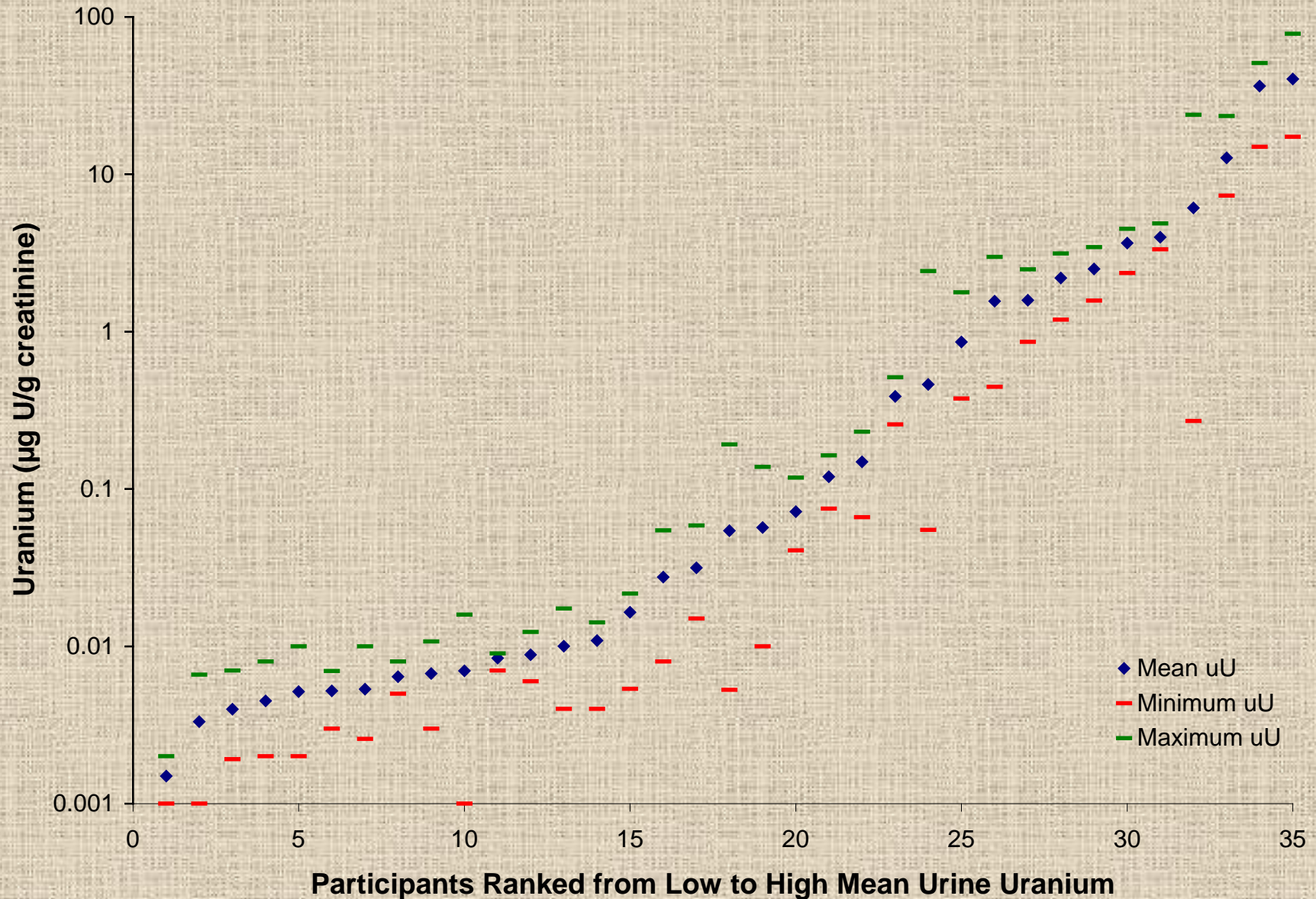
79 unique cases have been evaluated from Gulf War I.

4 unique cases have been evaluated from OIF.

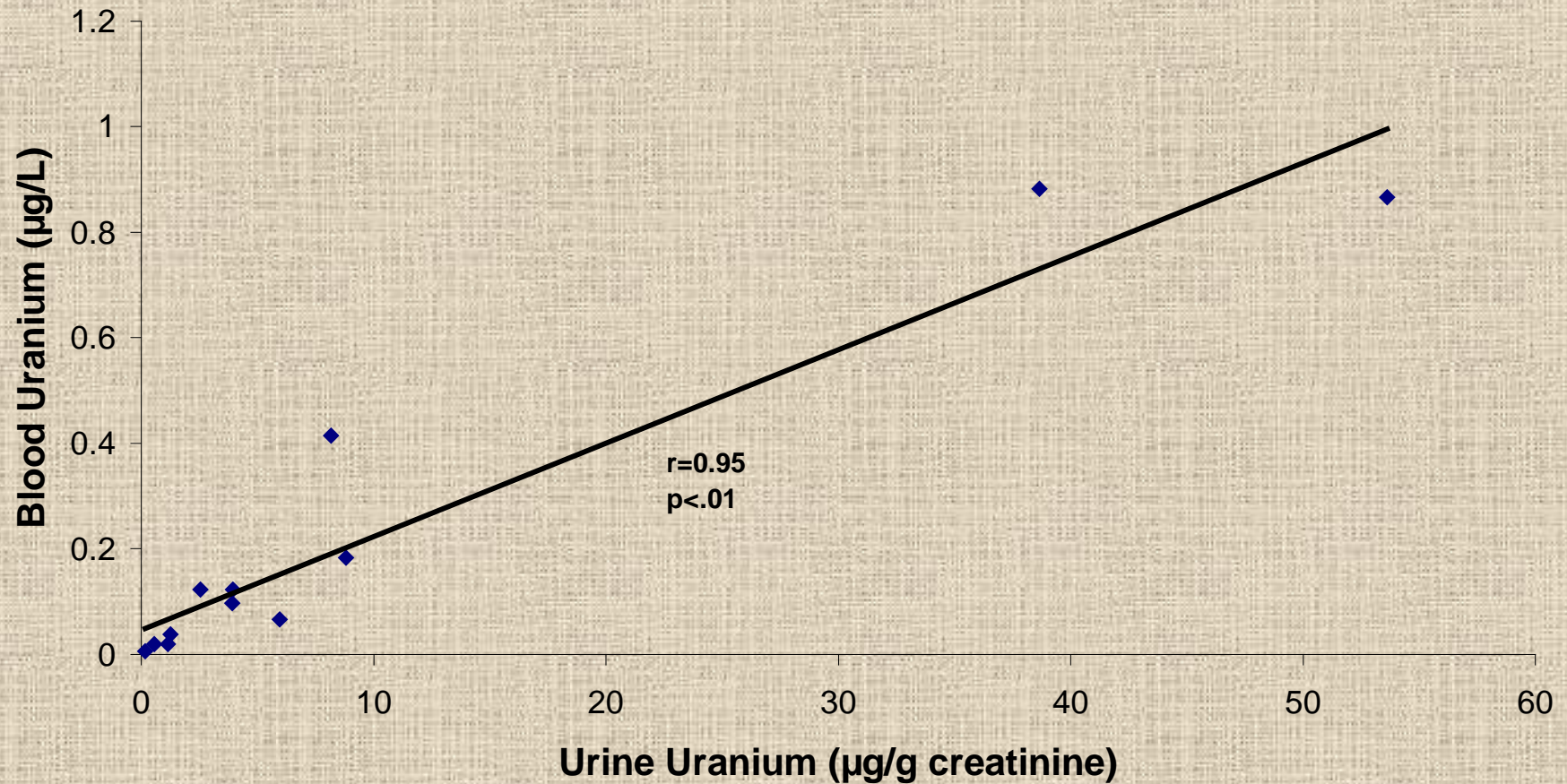
# Mean Urine Uranium Values (1993-2007, N=77)



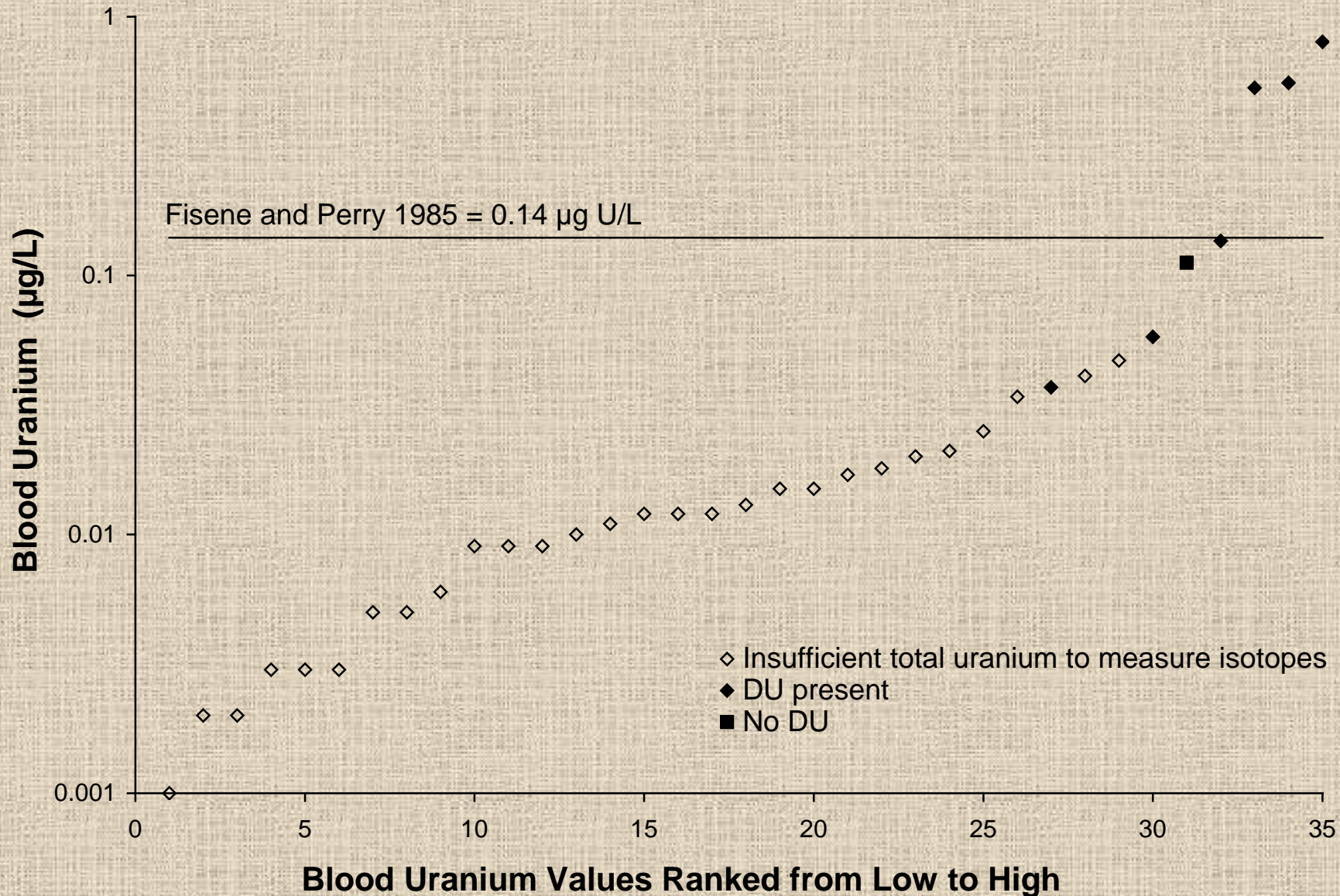
# Individual Participant's with 4 or More Visits Mean uU with Minimum and Maximum uU Values (n=35)



# Correlation between Urine and Blood Uranium When Urine U > 0.1 $\mu\text{g/g}$ Creatinine



# Blood Uranium Values from the 2007 Cohort



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

	2009 Cohort (n = 35)		All GWI Participants (n = 79)	
	N	%*	N	%
<b>RACE</b>				
African American	12	34%	24	30%
Asian American	1	3%	1	1%
Caucasian	20	57%	45	57%
Hispanic	2	6%	8	8%
Native American			1	1%
<b>AGE**</b>	43.62 ± 5.35		43.12 ± 4.80	

\* May not add to 100% due to rounding

\*\* Mean age 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, micronulcei)
- Neurocognitive testing
- Dermatologic testing for hypersensitivity to U
- Focus group/risk communication

# Summary of Renal Effect Measures

# Proximal Tubule Markers – 2009 Cohort

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

<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

Renal parameter	Evaluation Year						
	1994	1997	1999	2001	2003	2005	2007
Urine creatinine	ns	ns	l>h <sup>1</sup> (p=.07)	ns	ns	ns	ns
Urine calcium				ns	ns	ns	ns
Urine PO <sub>4</sub>				ns	ns	l>h (p=.10)	ns
Urine β-2 microglobulin	ns	ns	ns	ns	ns	ns	h>l (p=0.11)
Urine intestinal alkaline phosphatase (IAP)			ns	ns	ns	ns	ns
Urine N-acetyl-β-glucosa-minidase (NAG)			ns	ns	ns	ns	ns
Urine total protein		ns	ns	H>L	l>h (p=.21)	ns	ns
Urine microalbumin					ns	ns	ns
Retinol binding protein (RBP)		ns	ns	h>l (p=.06)	h>l ns <sup>2</sup>	ns	h>l (p=.07)
Serum creatinine	ns	ns	ns	L>H	ns	ns	L>H
Serum calcium				ns	ns	ns	ns
Serum PO <sub>4</sub>				ns	H>L	l>h ns	-
Serum uric acid	ns	ns	ns	ns	ns	ns	-

L = Low urine uranium group (U < 0.1 µg/g creatinine)

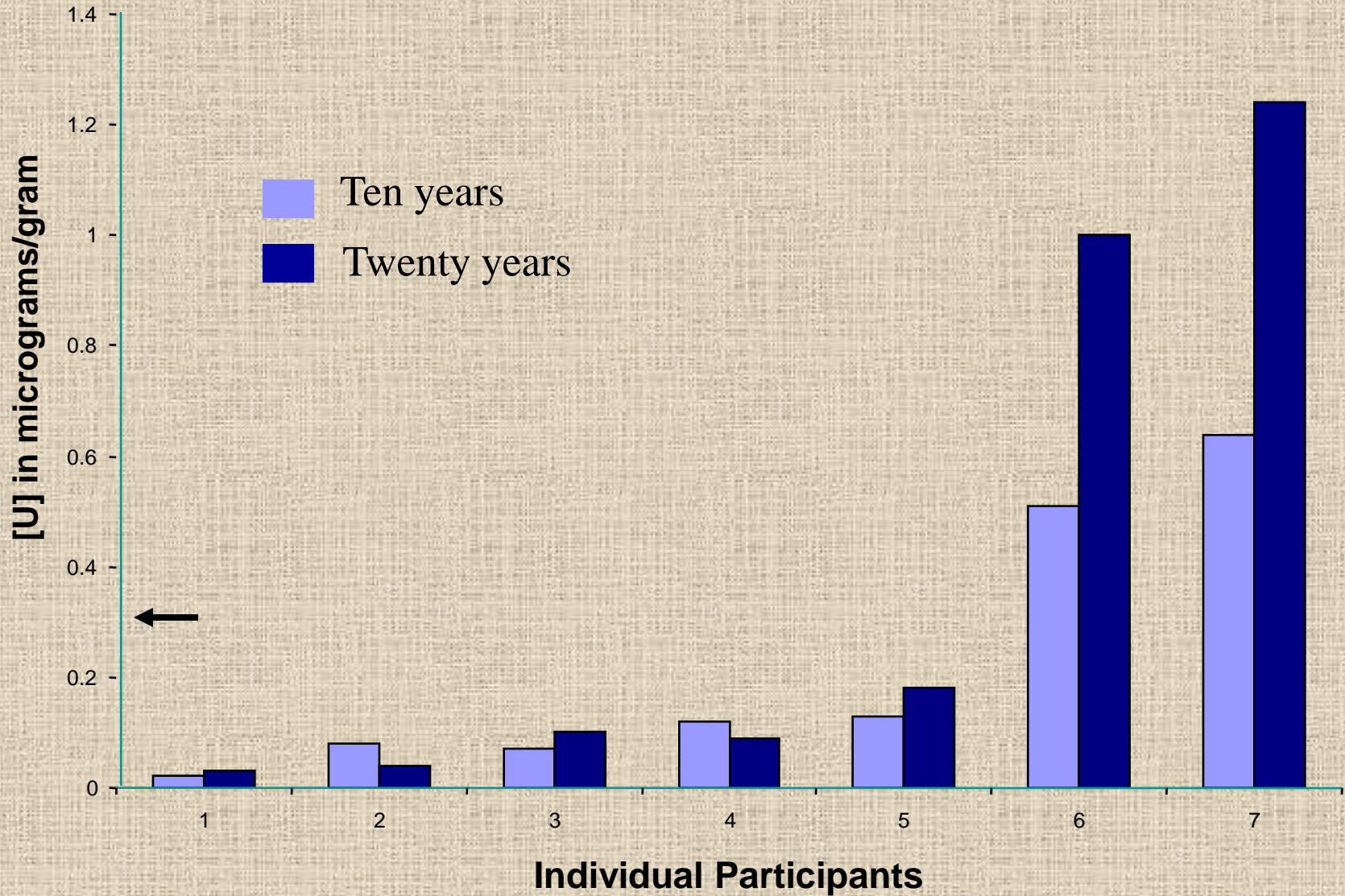
H = High urine uranium group (U > 0.1 µg/g creatinine)

ns = no significant differences between groups

<sup>1</sup> Lower case letters = non-significant findings

<sup>2</sup> 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



# Summary of Genotoxicological Measures

# Summary of Differences in Genotoxicity Parameters across Evaluations

Genotoxicity Parameter	Evaluation Year							
	1994	1997	1999	2001	2003	2005	2007	2009
Sister chromatid exchange (SCE)		l>h* ns	H>L**	l>h ns	ns	-	-	-
Chromosomal aberrations (CA)		ns	ns	H>L	ns	ns	ns	-
Hypoxanthine-guanine phosphoribosyl transferase (HPRT)				h>l ns	h>l ns	h>l ns	ns	ns
Mutation frequency								
Mutation frequency adjusted for cloning efficiency					ns	ns	ns	ns
Mutation frequency adjusted for cloning efficiency and age					ns	ns	ns	ns
Fluorescent in-situ hybridization (FISH); Mean number of total mutations per subject in chromosomes 5, 7, 11, and 13						h>l p=.08	ns	ns
PIG-A								l>h p=.08
Micronuclei								ns

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 epi 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

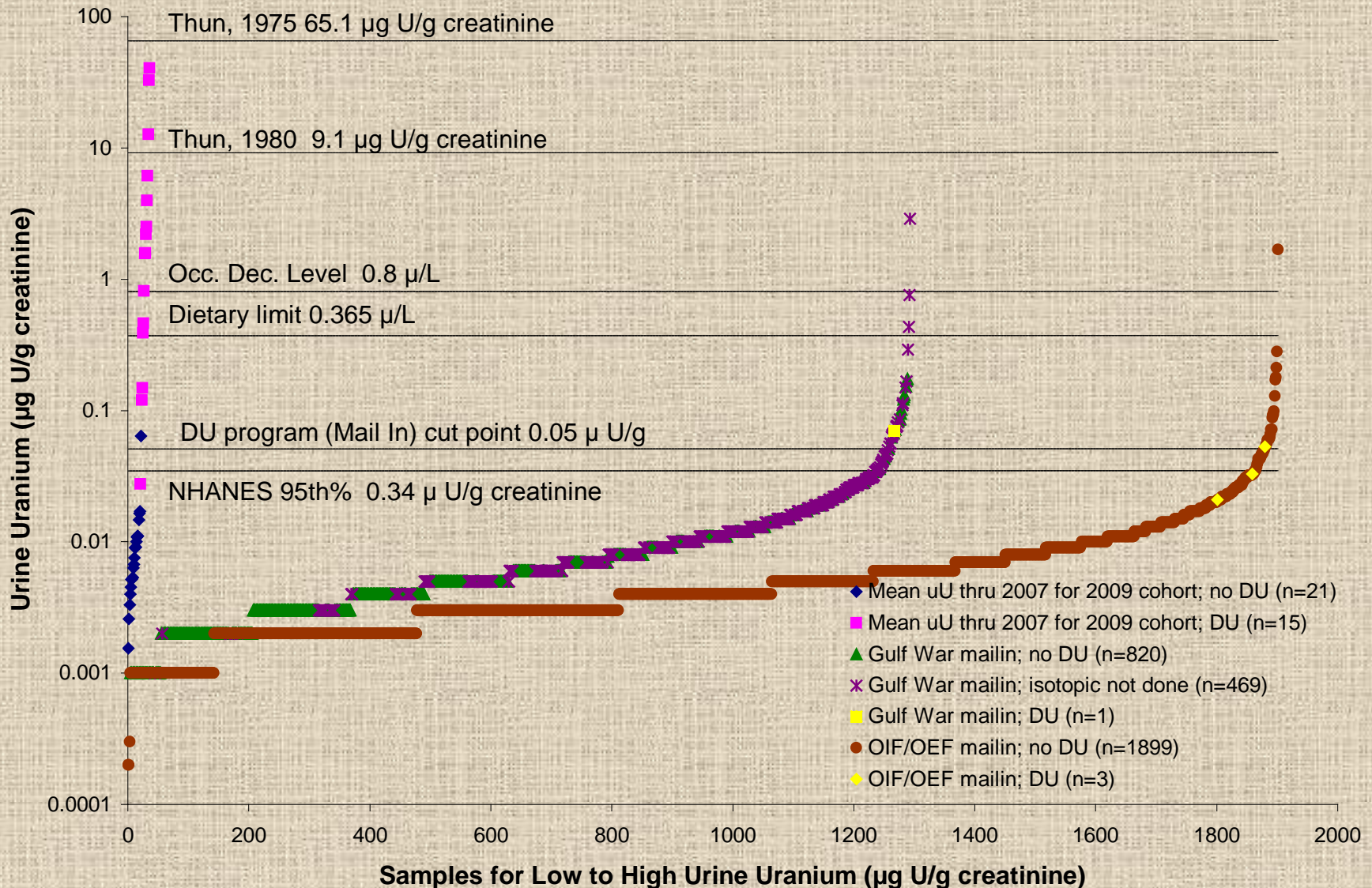
# 2<sup>nd</sup> Mission of the DU Follow-Up Program

- Since 1998:  
To provide biologic monitoring by mail for uranium for all GWI and OIF veterans

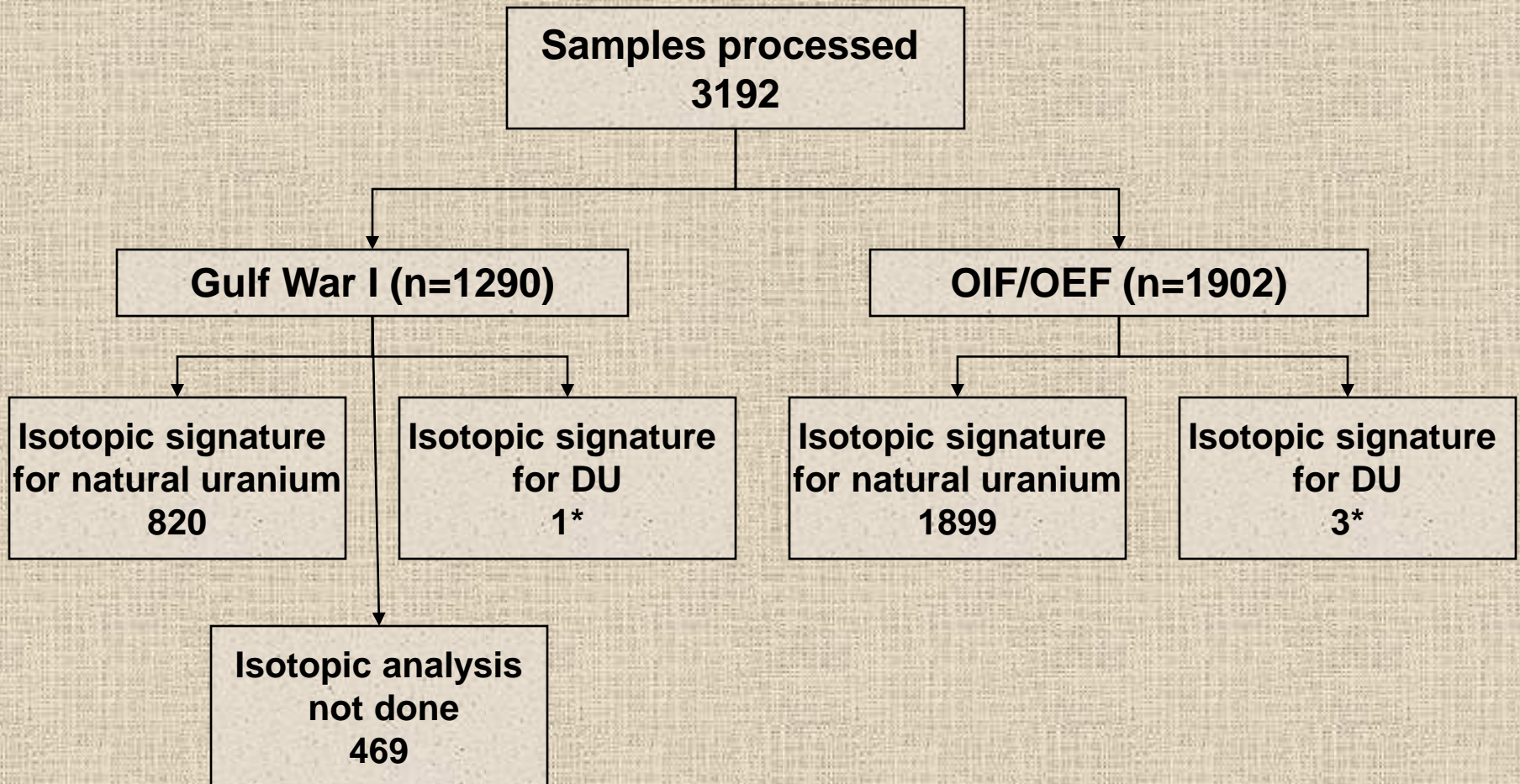
# Purpose of the Urine Biomonitoring Program

- 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)



# Results of OIF Urine Surveillance (as of 31 October 2010)

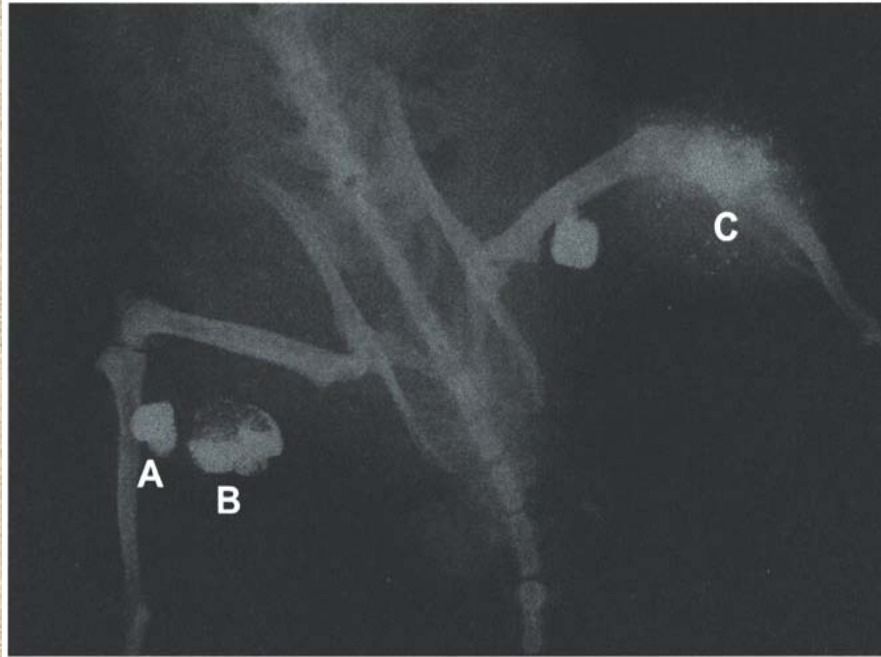


**\*All with DU signature were invited to enter the DU Follow-up Program.  
Two from OIF/OEF declined but may be interested in future follow-up.**

# 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).

1995 film



2001 film



# 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