

Patch Testing with Uranyl Acetate in Veterans Exposed to Depleted Uranium during the 1991 Gulf War and the Iraqi Conflict

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Background: The Depleted Uranium Follow-Up Program is a clinical surveillance program run by the Baltimore Veterans Affairs Medical Center since 1993 for veterans of the Gulf and Iraqi wars who were exposed to depleted uranium (DU) as a result of “friendly-fire” incidents.

Objectives and Methods: In 2009, 40 veterans from this cohort were screened for skin reactivity to metals by patch-testing with extended metal series and uranyl acetate (0.25%, 2.5%, and 25%). A control arm comprised 46 patients without any known occupational exposures to DU who were seen at the University of Maryland Dermatology Clinic for evaluation of allergic contact dermatitis.

Results: Excluding irritant reactions, no patch-test reactions to uranyl acetate were observed in the participants. Irritant reactions to DU were more common in the clinic cohort, likely reflective of the demographic differences between the two arms of the study. Biologic monitoring of urine uranium concentrations in the DU program participants with 24-hour urine samples showed evidence of percutaneous uranium absorption from the skin patches.

Conclusion: We conclude that dermatitis observed in a subset of the veterans was unrelated to their military DU exposure. Our data suggest that future studies of skin testing with uranyl acetate should utilize 0.25%, the least irritating concentration.

DEPLETED URANIUM (DU) is a heavy metal that has been used by the Department of Defense in the manufacture of armor-piercing munitions (“DU sabot rounds”) and as shielding in heavy armored tanks and other vehicles.^{1,2} DU is a major by-product of the uranium enrichment process, in which two uranium isotopes—uranium-234 (²³⁴U) and uranium-235 (²³⁵U) are removed from natural uranium, creating a “depleted” form of uranium metal with a lower ²³⁵U/²³⁸U isotopic ratio. Natural uranium has a ²³⁵U/²³⁸U isotopic ratio of 0.0072, whereas the isotopic ratio for DU used by the military is approximately 0.002. This DU metal is converted into a titanium-based alloy used for manufacturing munitions.³ Owing to its high melting point, density, tensile strength,

reduced radioactivity, and ability to self-sharpen and ignite on impact, DU has had multiple military applications.^{4,5} Most recently, DU-containing weapons were used in Operation Iraqi Freedom and during the Kosovo peace-keeping mission.^{6,7} The highest level of exposure of US personnel to DU during the Gulf War occurred as a result of “friendly-fire” incidents involving Abrams tanks and Bradley Fighting Vehicles, when US soldiers were mistakenly fired upon by other US troops.⁸ Because DU self-sharpens and burns as it penetrates tank armor, fine DU oxide particles were formed. The routes of exposure during these incidents included inhalation of DU-aerosolized particles of uranium oxide, wound contamination with DU particles, and soft-tissue penetration by shrapnel metal fragments.

The Department of Veterans Affairs (VA) Depleted Uranium Follow-Up Program is a medical surveillance program organized in 1993 to follow up US military veterans exposed to DU in friendly-fire incidents in the Gulf War in 1991 to determine if health effects that are related to DU exposure have developed in this population. Members of this cohort are invited to come to the Baltimore VA Medical Center every 2 years for a comprehensive health evaluation. During earlier visits, veterans with metal fragments embedded in soft tissue were identified through skeletal plain-film radiography.

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Findings from biennial evaluations in 1993, 1997, 1999, 2001, 2003, 2005, and 2007 have been published.^{9–13} Long-term systemic exposure to DU has been determined by measuring urine uranium concentrations at each visit. Veterans with embedded fragments have had consistently elevated urine uranium levels for the past 18 years. Several small differences in health outcomes for veterans with low urine uranium concentrations versus those with high urine uranium concentrations have been observed during the past 18 years; however, these differences have not been clinically significant and have not been consistent over time.

One of the goals of the 18-year postwar follow-up visits (in 2009) was to test for skin reactivity to uranium, which would induce a type IV hypersensitivity reaction. The rationale behind this study was that systemic exposure to some metals in medical implants is known to initiate such reactivity, and patch-test reactivity would be an indication that the long-term exposure to uranium experienced by this cohort may have led to an immune response to the uranium. Precedent for this idea is the observation that some patients who have been implanted with medical devices that contain metals can experience adverse reactions that correlate with positive patch-test reactions to the metals contained in these devices.^{14,15}

Materials and Methods

Cohorts

Forty veterans in the Baltimore VA Medical Center (VAMC) DU-exposed cohort who were exposed to DU during friendly-fire incidents in either the 1991 Gulf War or the current war in Iraq were examined between April 2009 and June 2009. A control arm comprised 46 patients with no known occupational exposures to DU who were seen at the University of Maryland Dermatology Clinic for evaluation of allergic contact dermatitis from July 2009 to December 2009. The demographic characteristics of the DU and clinic cohorts are presented in Table 1. Each participant gave fully informed written consent before enrollment in this study. The study was reviewed and approved by the Institutional Review Board of the University of Maryland School of Medicine and the Baltimore VAMC research service.

Uranium Exposure Assessment: Urine Uranium Analysis

Total uranium concentration and the ²³⁵U/²³⁸U isotopic ratio of 24-hour urine samples collected during the 2009

Table 1. Demographic Characteristics of the Depleted Uranium and Clinic Cohorts

Characteristic	DU Cohort (N = 40)	Clinic Cohort (N = 46)
Mean age ± SD* (yr)	42.97 ± 5.63	43.45 ± 19.57
Male sex (%)	100	26
Female sex (%)	0	74
Dermatitis (%)	25	100
Other cutaneous findings (%)	25	8.7

DU = depleted uranium.

*At 2009 evaluation.

surveillance visits were measured by the Armed Forces Institute of Pathology's Department of Environmental Toxicologic Pathology (Washington, DC), as previously described,¹² with the inductively coupled plasma dynamic reaction cell mass spectrometry method developed by Ejnik and colleagues.¹⁶ To correct for urine dilution, urine uranium concentrations were standardized on the basis of urine creatinine concentrations to obtain micrograms of uranium per gram of creatinine (μg U/g creatinine).^{17,18}

Medical Evaluation

A thorough medical history of each subject was taken, and a physical examination evaluating many aspects of the participant's mental status, physical health, and combat experience was conducted. We discovered a number of cases of incident cutaneous rashes and service-related skin lesions (Table 2). Biomarkers of renal function and bone metabolism were also measured because the kidneys and bones are major target organs for heavy metals.^{3,19–21}

Patch Testing

All participants in the DU cohort (*n* = 40) underwent patch testing with extended metal series comprising 42 reagents (Dormer Laboratories, Inc., Toronto, Ontario, Canada) and with uranyl acetate (SPI Supplies and Structure Probe, Inc., West Chester, PA) in three concentrations (0.25%, 2.5%, and 25% weight per volume in petrolatum). Fourteen subjects were patch-tested with nickel, cobalt, and chromium (the prevalent allergens for the general population).^{22,23} One veteran was patch-tested with six substances from the North American tray (mercaptobenzothiazole 1%, phenylenediamine 1%, carba mix 3%, thiuram mix 1%, mixed dialkyl thioureas 1%, and

Table 2. Cutaneous Rashes in the Depleted Uranium Cohort (*n* = 10)

<i>Participant ID</i>	<i>Findings</i>
1	Subacute dermatitis on anterior upper thighs
3	Subacute dermatitis on anterior lower abdomen Pustular folliculitis on upper back Seborrheic keratosis on right lower extremity
8	Stasis dermatitis on bilateral lower extremities
10	Subacute dermatitis Acne on back Dermatitis below waistline
15	Rosacea on nose Chronic recurrent dermatitis on chest, back, and neck, in remission
18	Lichenoid purpura on dorsum of right foot Nummular eczema
31	Acne Multiple nevi on upper back Venous insufficiency resulting from multiple surgeries for shrapnel extraction; complicated by leg ulcers and hyperpigmented plaques on lower extremities
32	Seborrheic dermatitis on bilateral external ears and ear canals Keratosis pilaris
38	Dyshidrotic dermatitis on bilateral hands
39	Follicular eczema on bilateral arms and chest

ID = identification number.

ethyleneurea/melamine formaldehyde mix 5%), and three DU-group participants were tested with a full 50-reagent set of the standard North American series (Dormer Laboratories) to evaluate active dermatitis noted during that visit.

Clinic patients (*n* = 46) underwent diagnostic patch testing with the standard North American series. Uranyl acetate in three concentrations (the same concentrations used in the DU study: 0.25%, 2.5%, and 25%) was also added to establish the rate of reactivity in this cohort.

With both cohorts, the substances were applied to the patient's back in 8 mm Finn Chambers (Epitest Ltd Oy, Tuusula, Finland); patches were applied to the upper thorax of several patients who had extensive tattoos or body hair. The results were interpreted with the standard grading system at 48 and 72 hours. Digital photographs of local reactions were taken for each reading. Some selected participants in the DU cohort (*n* = 10) e-mailed photographs of their patch-test sites if they experienced any late crescendo or persistent patch-test reactions.

Results

Uranium Exposure

As at previous surveillance visits, members of the DU-exposed veteran cohort underwent biologic monitoring of ongoing uranium exposure by measurement of urine uranium concentrations in 24-hour urine samples. Each veteran was placed in either a "low" or "high" uranium-exposure group; a cutoff level of 0.10 µg of uranium per gram of creatinine was used to separate low exposure from high exposure (Fig 1). Urine uranium excretion is a standard measure used to monitor recent uranium exposure in the workplace.¹ Existing surveys measuring urine uranium in the general population were used as comparison data. Internalization of natural uranium from the environment occurs from exposure through diet and drinking water and accounts for the natural uranium normally measured in urine. A value of 0.354 µg/L has been reported as the upper limit of normal levels caused by dietary exposure.²⁴ According to the National Health and Nutrition Examination Survey, the urine uranium concentration at the ninety-fifth percentile for the normal US population aged 20 years and older is 0.031 µg per gram of creatinine.²⁵

Testing performed during previous visits indicated that DU-exposed soldiers with embedded shrapnel were excreting high concentrations of uranium in their urine as compared with DU-exposed soldiers without embedded shrapnel. The latter had normal levels of natural uranium and no detectable DU in their urine (as measured by determining the ²³⁵U/²³⁸U ratio of the urine uranium), with the exception of two soldiers who might have had undetected embedded shrapnel or were exposed to DU via other routes (such as wound contamination, inhalation, or ingestion). A few veterans with embedded fragments also had low urine uranium levels, likely because the fragments did not contain DU or because of the extrusion of superficial DU fragments. To account for these exceptions, the participants were always compared on the basis of their urine uranium levels in lieu of their fragment status. All of the participants' urine uranium concentrations remained similar between surveillance visits.²⁶

Uranyl Acetate Reactions

No allergic patch-test reactions ("uncertain" through ++ reactions) to uranyl acetate (0.25%, 2.5%, or 25%) were observed in either the veterans or the clinic patients.

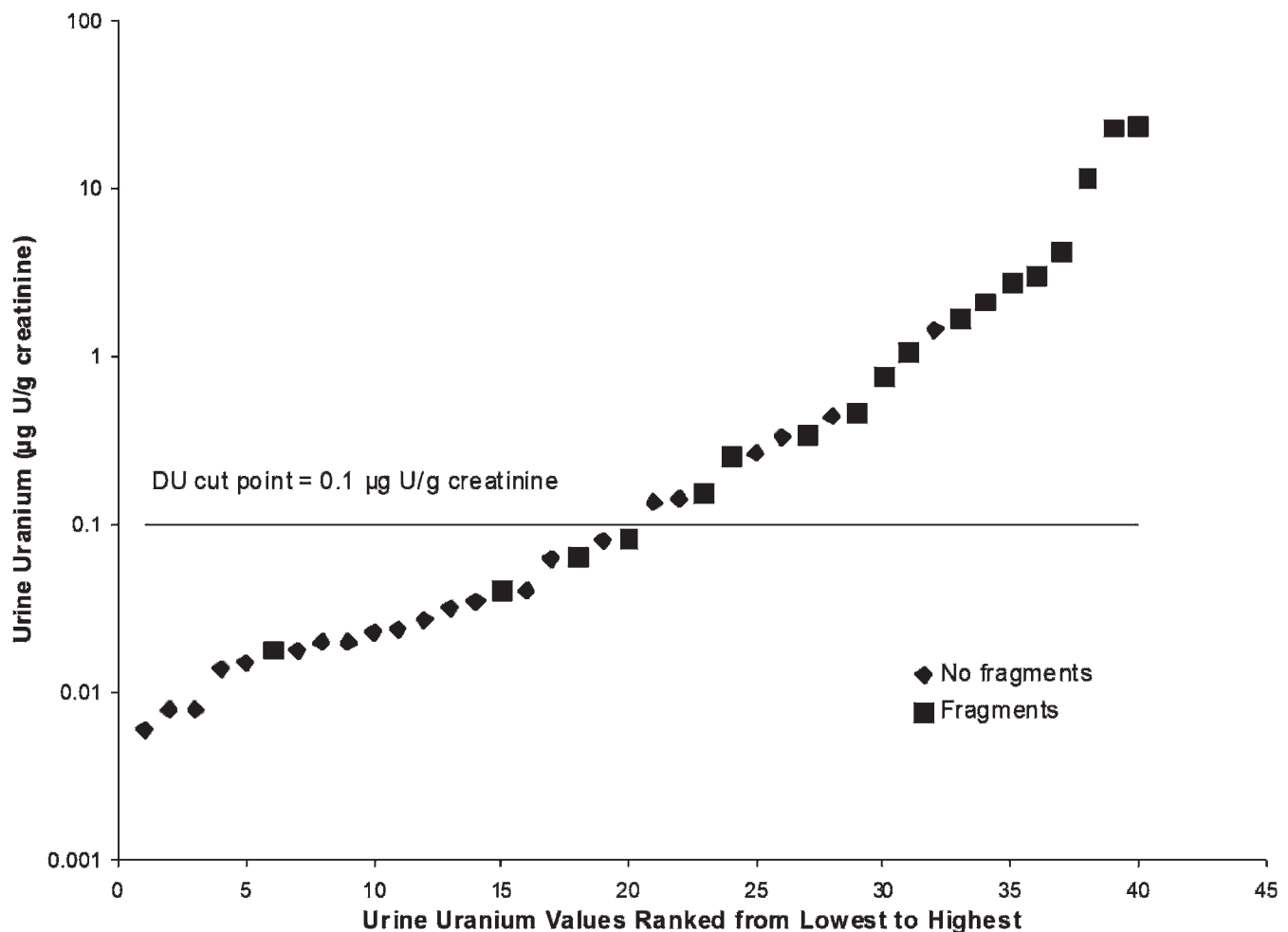


Figure 1. Distribution of urine uranium concentrations for participants in the Depleted Uranium (DU) Follow-Up Program 2009 surveillance visit. The urine uranium concentrations of the participants are plotted along the x-axis from low to high. The DU program cutoff for dividing the participants into two groups (low vs high urine uranium) was set at 0.1 µg of uranium per gram of creatinine, based on literature values.¹³ Participants whose urine uranium concentrations are designated by diamonds had no radiographic evidence of embedded shrapnel. Participants whose urine uranium concentrations are designated by boxes either had had or still had one or more embedded fragments. Most of the veterans with fragments had high urinary uranium values, indicating that their fragments contained uranium. (U = uranium.)

However, irritant reactions to uranyl acetate at higher concentrations were observed in a small number of the participants (Fig 2 and Table 3). There were more irritant reactions with the 25% DU patches. A higher rate of irritant reactions was seen at 48 hours, consistent with a concentration-dependent irritant contact dermatitis (ICD).

Irritant Reactions

Irritant reactions were observed more frequently in the clinic cohort than in the DU-exposed cohort (45% vs 12% after 48 hours) (see Table 3). This may be related to demographic differences in the two arms of the study:

females made up 74% of the clinic cohort, whereas all of the veterans were males. The rate of irritant reactions was higher in the clinic cohort than in the DU cohort (20% vs 10% after 72 hours); by the Fisher exact test, however, the difference was not statistically significant ($p = .09$). Although there are no major differences between the sexes in regard to allergic contact dermatitis,²⁷ a number of study articles have reported female predominance in regard to ICD.^{28,29} Some attribute the higher prevalence of irritant reactions to the nature of exposure, which is more likely to occur in female-dominated occupations, particularly those that involve “wet work.”³⁰ In our study, this would have been an unlikely confounding factor as men had a higher incidence of exposure to DU.

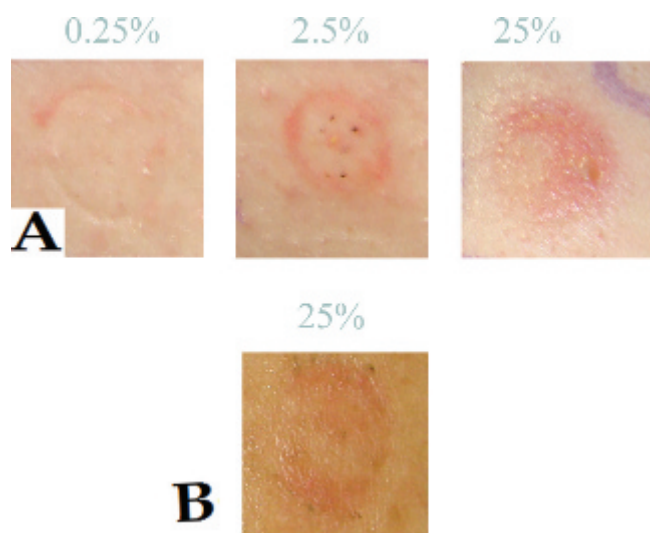


Figure 2. Two types of irritant reactions to patch tests with 0.25%, 2.5%, and 25% uranyl acetate at 48 hours in two clinic patients. A, Pustular reactions to 0.25%, 2.5%, and 25% uranyl acetate in patient 31. B, Rim reaction to 25% uranyl acetate in patient 45. Similar irritant reactions were observed in the Veterans Affairs cohort.

Percutaneous Uranium Absorption from Skin Patches

Sixteen veterans with low urinary uranium in 2007 took part in the 2009 follow-up study. Urine collection started about 20 hours after patches were placed, and continued for 24 hours (ie, an estimated 44 hours after the patches were applied). As shown in Table 4, the mean urine uranium concentration in these 16 individuals increased from 0.016 μg per gram of creatinine in 2007 to 0.167 μg per gram of creatinine in 2009. This small increase was not detectable in the subjects who excreted high urinary uranium concentrations owing to the presence of embedded DU fragments, but it was detectable in the group with low urinary uranium concentrations (see Fig 1). We also noticed that participants who normally excrete only natural uranium (ie, who do not have DU in their urine) did excrete DU during the 2009 visit when the patch

testing was done. More than 80% of the subjects in the low urinary uranium group had only natural uranium in their urine in 2007, which is consistent with what was seen in previous years. In 2009, however, only 25% had natural uranium in their urine, whereas 75% had DU in their urine. This finding indicates that uranium from the skin patches was absorbed across the skin surface, since the commercially purchased soluble uranyl acetate used in the skin patches was determined to be DU, based on its $^{235}\text{U}/^{238}\text{U}$ isotopic ratio of 0.003.

Because of this evidence of dermal absorption of uranium from these patches, it is unlikely that the negative results observed for hypersensitivity to uranium were due to a lack of exposure to uranium during patch testing; in 16 veterans, however, there was evidence of percutaneous absorption and excretion in the urine.

Relation of Dermatitis to Uranium Exposure

We observed dermatitis in 25% of the veterans in the DU group. These cases of dermatitis were unlikely to be due to ongoing exposure to uranium because these men did not exhibit allergic reactivity to uranium compounds when patch-tested.

Discussion

Dermal absorption of uranium compounds in humans has not been well described. Animal studies show that soluble uranium compounds can be effectively absorbed across the skin. Dermal application of water-soluble uranium compounds to rabbits has been reported to cause a number of pathologic abnormalities in skin, ranging from epidermal atrophy, swelling, inflammation, and vacuolar changes, to coagulation necrosis in the epidermis, damage to hair follicles and sebaceous glands, and severe dermal ulcers.^{31–33} The irritant reactions observed in both the DU and clinic

Table 3. Allergic and Irritant Patch-Test Reactions to Uranyl Acetate

Concentration (%)	Allergic Reactions*				Irritant Reactions			
	DU Cohort		Clinic Cohort		DU Cohort		Clinic Cohort	
	48 hr	72 hr	48 hr	72 hr	48 hr	72 hr	48 hr	72 hr
0.25	0/40	0/40	0/40	0/40	0/40	0/40	1/40	0/40
2.5	0/40	0/40	0/40	0/40	1/40	0/40	5/40	1/40
25.0	0/40	0/40	0/40	0/40	4/40	4/40	12/40	7/40
Total	0/40	0/40	0/40	0/40	5/40 (12%)	4/40 (10%)	18/40 (45%)	8/40 (20%)

DU = depleted uranium.

*“uncertain” through ++ reactions.

Table 4. Uranium Concentration and Presence of Depleted Uranium in Urine Collected at Surveillance Visits

No. (Year) of Surveillance Visit	Patch Testing at Visit	Urine Uranium* ($\mu\text{g per gram Cre}$)		Urine Samples Positive for DU (n = 16)
		Mean $\pm$ SD	Range	
7 (2007)	No	0.016 $\pm$ 0.025	0.001–0.075	2 (13%)
8 (2009)	Yes	0.167 $\pm$ 0.363	0.006–1.465	12 (75%)

Cre = creatinine; DU = depleted uranium.

*n = 16.

cohorts are consistent with the cutaneous toxicities seen in rabbits.

Prior to the Depleted Uranium Follow-Up Program, there was no literature describing the health effects of combat exposure to DU. Background literature on heavy-metal toxicology and studies of workers engaged in uranium processing and purification (miners and millers of uranium) provided the basis for the specific protocol components of the DU group's health surveillance visits. DU is a heavy metal that is 160% denser than lead and can remain in the body for many years, slowly oxidizing and releasing uranium ions. The fact that urinary uranium excretion remains high in soldiers with embedded fragments decades after the initial exposure suggests a slow release of DU from embedded fragments that oxidize in situ and account for slow systemic uranium absorption and eventual elimination in urine.¹⁵ It has been standard practice to leave embedded fragments undisturbed unless they are easily removed or are causing harm, particularly if their removal poses a high risk of injury to healthy muscle tissue. Yet, the long-term effects of retained fragments are largely unknown.³⁴ Studies reported to date have failed to find any association between DU and skin cancers.¹ Experiments in rats demonstrated that DU fragments implanted in soft tissues can lead to localized proliferative reactions and even sarcoma formation.³⁵ However, similar effects were not observed in another study of surgically implanted DU pellets in rodents.³⁶ It is possible that rats are more implant- and radiation-sensitive than humans.³⁵ There is one previous report of hand eczema in two men who prepared uranium for an atomic energy plant.³⁷

Conclusions

The goal of this component of the 2009 depleted uranium follow-up study was to screen veterans with known exposure to DU for skin-patch reactivity to metals, including uranyl acetate. Results were analyzed by comparing the rates of patch-test reactivity to uranium compounds in the DU-exposed cohort with rates in the

general population in the context of urinary uranium, exposure history, and physical examination findings.

Despite evidence of percutaneous absorption of the uranyl acetate into the systemic circulation via patch tests, there was no allergic skin reactivity in either veterans or clinic patients. Irritant reactions were observed with higher concentrations of uranium only. We conclude that the internal depots of DU-containing fragments did not generate a sufficient number of memory effector T cells to mediate "detectable" cutaneous reactivity to uranium derivatives. Uranium is a heavy metal and, like other heavy metals, can cause irritant contact dermatitis but not allergic reactions. This is in contrast to transition metals such as nickel, cobalt, and chromium, which can cause both allergic contact dermatitis and irritant contact dermatitis. We suggest that future studies of skin testing with uranyl acetate use a 0.25% concentration (the least irritating concentration).

Our patch tests with the metal series indicated that the veterans in the DU cohort indeed reacted with other selected transition metals (data not shown). This will be the subject of another report.

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