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TECHNICAL REPORT

Assessment of the Risks from Imbedded Fragments of Depleted Uranium



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BRP

27 March 1992

MEMORANDUM FOR DIRECTOR, PROFESSIONAL SERVICES, OFFICE OF THE
SURGEON GENERAL (SGPS-PSP)

SUBJECT: Research Request; Health Effects of Depleted Uranium Imbedded in Tissue

Reference: Brigadier General Ronald R. Blanck (SGPS-PSP) letter of 26 February 1992

In response to your letter of 26 February 1992, subject as above, AFRRI has conducted a detailed review of the pertinent scientific literature regarding the health effects of depleted uranium (DU) fragments which are imbedded in tissue. In addition, we have consulted with a wide range of scientists with expertise in this area. A summary of our findings is attached.

It is clear from our analysis that there are several areas in which there is little or no scientific data which would enable more definitive risk assessments to be made. Nevertheless, in order to meet your operational requirements, attachment (1) addresses each of the issues raised in your letter. To address areas in which there remains substantial scientific uncertainty, attachment (1) also identifies specific research needs.

Based on available data, in almost all cases, we recommend that standard medical criteria should be used to determine the advisability of the removal of imbedded DU fragments without regard to the radiological characteristics of the fragment. More specific guidance is provided in attachment (1).

Point of contact is Lieutenant Colonel Eric G. Daxon, Chief, Operational Dosimetry Division, Radiation Biophysics Department, 301-295-2299.

Attachment:
as stated


ROBERT L. BUMGARNER
Captain, MC, USN
Director

AFRRI Technical Report 93-1

**ASSESSMENT OF THE RISKS
FROM IMBEDDED DEPLETED URANIUM
FRAGMENTS**

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March 1993

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Assessment of the Risks From Imbedded Depleted Uranium Fragments

1. General

a. Authority

Letter, Office of The Army Surgeon General, (SGPS-PSP), Subject: Research Request; Health Effects of Depleted Uranium Imbedded in Tissue, 26 February 1992.

b. Mission

Assess the health risks associated with implanted DU fragments in the body to provide medical guidance for current and future patients with these fragments, and provide recommendations for future research.

2. Background

The primary conclusion of the review of the uranium literature¹⁻¹⁶ and discussions with others¹⁷⁻²⁶ in the field is that this situation is radiologically and toxicologically unique. The health risks of allowing depleted uranium (DU) fragments or any other radioactive heavy metal to remain imbedded in an organ have not been studied. The uranium literature reviewed is focused on inhaled or ingested uranium compounds. There is only one reported instance of a DU fragment accidentally injected subcutaneously in a patient. This case, as reported by Cole,^{22,27} provides little information for long-term effects because the fragment was surgically removed after 8 months.^{22,27}

3. Chemical Toxicity

The toxicological effects of uranium are well known. The target organ for uranium heavy metal toxicity is the kidney. The literature concerning the acute effects of uranium heavy-metal poisoning on the kidney is extensive and is summarized in recent articles by Leggett¹², Diamond¹³ and Kocher.¹⁴ While the generally accepted threshold level for kidney toxicity is from 1-3 μg of uranium per gram of kidney mass,^{1,13,14} there is considerable discussion in recent literature concerning this limit.^{12,13,14}

A review of uranium toxicology conducted by USAEHA¹¹ concluded that, while there was substantial toxicologic data for inhaled and ingested uranium compounds, there was little or no data for the metabolic behavior of implanted DU fragments. Key uncertainties include organ specific solubilities; organ specific retention functions; the metabolic impact of a source term other than the lung or GI tract; the potential for chronic kidney toxicity; the impact of fibrotic encapsulation, if it occurs; and the chemical form of the imbedded fragment.

The potential for wound contamination (the injection of small sub-millimeter fragments) and for spallation of small fragments from large fragments introduces two additional dispersal mechanisms - macrophage transport and the physical movement of intact particles by the blood stream. The impact of both is an increase in the rate at which uranium is deposited in the kidney and other organs. De Rey et al.² found insoluble UO₂ particles in the kidney 6 to 48 hours after injection of 4 to 40 micrometer diameter UO₂ micro-spheres into the subcutaneous tissue of the dorsal skin of female rats. This is significantly quicker than predicted by standard metabolic transfer models for insoluble compounds of uranium.

These limitations and uncertainties preclude a definitive assessment of the toxicologic risks of allowing DU fragments to remain in the body for extended periods of time.

4. Radiological Effects

The literature is extensive concerning the deterministic and stochastic effects of acute and chronic exposure to inhaled and ingested uranium compounds.^{1,28-32} The lack of data for imbedded uranium fragments precluded a direct determination of the potential long-term radiological effects of these fragments. An estimate of the potential effects was obtained by reviewing the literature available for plutonium, Thorotrast, and hot-particles.

The plutonium (Pu) literature³³⁻⁴⁴ reviewed also focused on inhalation and ingestion, but there were several studies that dealt with injected plutonium compounds. Lushbaugh^{19,34,42} and Langham et al.⁴² summarize the findings of studies of eight patients with injected plutonium. Lagerquist et al.⁴³ and Carbaugh et al.⁴⁴ discuss patients with plutonium contamination of puncture wounds. While these studies are somewhat useful, their usefulness is limited because the exposure duration was relatively short (the longest was 5-8 years), the particle sizes were small, and in each case the wounds were debrided to removed the injected plutonium. For both the animal and human studies, the plutonium injected was in the form of the fine particulates expected from injection wounds caused by contaminated, sharp tools.

The Thorotrast literature is extensive^{1,34,47-62} and important because of the radiological similarities with the situation under study. Thorotrast is a colloidal suspension of thorium dioxide (ThO₂) that was used as an intravenously-injected contrast agent for radiographic imaging from the late 1920's until the late 1950's when its long-term radiologic health effects became apparent.^{45,46} The Thorotrast literature provides the most definitive evidence that both clinically-significant deterministic and stochastic effects are possible from long-term irradiation of low dose-rate α and β emitting radionuclides.

However, the differences in particle size and chemical properties between Thorotrast and DU are significant enough to preclude a direct application of the data. The ThO₂ particles in Thorotrast were small enough (nanometers in size) to be engulfed by both the mobile and fixed macrophages in the reticuloendothelial (RE) system which led to a time dependent, selective concentration in the liver and spleen. This time dependence makes dose-dependent extrapolations from Thorotrast data to a DU fragment difficult. In addition, the selective retention by the RE system limited the exposure to the organs in this system.

Although directed specifically at the radiation effects on the skin of a highly radioactive, beta-emitting particle, the hot-particle research literature⁶³⁻⁷⁰ provides valuable information concerning the differences between the highly nonuniform irradiation that results from an imbedded fragment and the results of the uniform organ irradiation upon which assessments of radiation risk are based. Specifically, the hot particle research sheds light on the relationship between the fraction of an organ system irradiated and the dose required to produce both deterministic and stochastic effects. The primary conclusion of this work is that the radiation risk of both endpoints is dependent upon dose and the number of cells irradiated.

Based upon this review, the following radiobiological effects are possible from imbedded DU fragments.

a. Granuloma Production

Cole's^{22,27} experience and Lushbaugh's^{19,34,42} work indicate that granuloma production in the muscle and fatty tissue will probably occur and will occur in all other tissue types that elicit similar cellular responses to foreign bodies. It is still questionable whether this encapsulation is permanent or will undergo the degradation-regeneration cycle suggested by Lushbaugh for the plutonium cases he studied.

The data to date are insufficient to allow a determination of whether Thorotrastoma-like growths are possible. A Thorotrastoma is a large growth that appears at the sites of extravascular Thorotrast with a latent period of from 5-35 years postinjection.^{17,47,48,53,60} These granulomas grow to large sizes; in a few cases, clinically significant blood vessels and/or nerves were enveloped, resulting in fatal conditions.²⁴ While a strictly chemical causation cannot be dismissed, there is sufficient evidence to suggest a radiogenic mechanism.

b. Local Tissue Necrosis

The results of the Thorotrast, lung inhalation studies, and animal studies showed that local tissue necrosis followed by fibrosis was possible from the long-term irradiation of tissues by a low dose-rate, α and β emitting radionuclide.

Dose estimates made at AFRRRI based upon published data^{71,72,73,74} indicated that the probability of deterministic effects at distances greater than 1-3 mm from the surface of any fragment is negligibly small. Depth-dose calculations indicated that at the distances from the surface of all particle sizes studied (1-4 mm in diameter) the dose-rates were less than the repopulation dose-rate for non-proliferative cells provided by the ICRP²⁸ (1-5 mGy/d). The assumption in this analysis is that at distances greater than this, deterministic effects will not occur because cell repopulation will compensate for cell death for most tissue types. The most notable exception to this assumption is mature neural tissue, the neurons of which do not usually have a proliferative potential.

The clinical significance of necrosis at distances closer to the fragment is dependent upon the location of the fragment and the body's response to the fragment. Lushbaugh,³⁴ in his analysis of cases of injected plutonium, found that "...metallic plutonium implanted in the skin in minute amounts elicits a foreign-body reaction of the granulomatous type, which after subsiding in cellular activity becomes fibromatous." As time progressed, the collagen in the vicinity of the fragment liquified.

Lushbaugh speculated that the "pointed" nature of the granulomas he found and the fact that the granulomas became more superficial, suggested that the altered collagen might induce a cycle of inflammatory reaction followed by a reorganization and re-liquefaction of the collagen.

c. Whole-Organ Deterministic Effects

The potential for multiple fragments in a single organ led to the examination of the potential for whole-organ deterministic effects. A whole-organ deterministic effect is defined as one in which there is a clinically significant compromise of organ function due to the ionizing radiations emitted by one or more DU fragments.

The appearance of whole-organ deterministic effects from acute, high dose rate exposure is well documented. Mettler and Mosely,⁷⁵ Conklin and Walker,⁷⁶ and ICRP 41²⁸ provide excellent summaries with extensive bibliographies for whole-organ deterministic effects based primarily on examination of the Japanese atomic bomb survivors, radiation accident victims, and radiation therapy patients. Direct extrapolation from high dose rate, acute exposure to low dose rate protracted exposure is difficult because of the dose rate dependence of the threshold dose required to produce a deterministic effect.²⁸

The results of inhalation studies with uranium and plutonium summarized in ICRP 31³⁰ and in other references^{6,7,33,39} show that whole organ deterministic effects are possible from inhaled particulates. The Thorotrast studies^{1,34,47-62} provide the clearest evidence that deterministic effects are possible from protracted exposures to low dose rate internal alpha emitting isotopes. These studies showed that both fibrosis of the spleen and cirrhosis of the liver could be related to the radiation emitted by the thorium dioxide (ThO₂) in the Thorotrast. The latent period for the onset of clinically significant liver cirrhosis was on the order of 20 years after Thorotrast administration.⁵⁷ The latent period for significant spleen fibrosis was not reported but is assumed to be comparable.

A dose calculation, made using similar methodology as described above, showed that the risk of whole-organ stochastic effects do not become significant until the fragment density in the organ exceeds one fragment per cm³ of organ volume for the fragment sizes considered (1-4 mm diameter). At particle densities greater than this, the average dose rate in the organ will exceed the repopulation dose rate for non-proliferative cells.

d. Stochastic Effects

The standard ICRP stochastic-risk-estimation methodology⁷⁷ is directly applicable for systemic DU but can be used only with caution when assessing the risks of imbedded DU fragments. There are several unknowns that could cause this and similar procedures to either overestimate or underestimate the stochastic risks. Included are these specifics:

(1) The hot-particle research indicates that the risk from an imbedded fragment could be significantly less because fewer cells are irradiated. ICRP methodology assumes that the dose is uniformly distributed over all of the cells in the organ while a DU fragment will irradiate only the cells within a finite range of the fragment.

(2) The Thorotrast experience showed evidence that the constant irradiation of the same cell population could increase the risk by adding necrosis-regeneration as an additional cancer induction mechanism. This mechanism is not considered in the ICRP models or cancer risk estimates.

An estimate of the stochastic risk posed by an implanted, insoluble fragment was made by calculating the effective dose equivalent (H_E) for a range of fragments (1-4 mm) for each organ listed in ICRP 60.³¹ The actual organ weights were used to calculate the dose as were the actual weighting factors (w_T). The calculation was performed assuming that alpha dose could be ignored because the energy of these particles will be expended producing lethal damage to the cells adjacent to the fragment and thus contribute nothing to the stochastic risk.

For the largest fragment size evaluated (4 mm), the highest H_E is in the thyroid because of its relatively small mass. In this case, H_E is 1 mSv/y (100 mRem/y). Using current risk estimates,³² these values represent an increase in lifetime risk of fatal cancer of 0.3%. The value for other organs will be substantially lower because of their larger masses.

At this point in the discussion, it is important to recognize that this risk estimate is based upon a single, insoluble fragment imbedded in an organ and does not include the risk from systemic DU.

5. Conclusions

a. Chronic kidney toxicity is a potentially clinically significant health effect from imbedded DU fragments. While the toxicology of uranium in the kidney is well known, little is known about the toxico-kinetic behavior of imbedded uranium. This information is required to make definitive estimates of both the toxicological and radiological risk.

b. Based upon the literature reviewed, the potential exists for both stochastic and deterministic radiation effects from the long-term exposure to imbedded DU fragments.

(1) The most clinically significant, radiogenic effect is the potential for a Thorotrastoma-like growth to form at the site of single or multiple imbedded-fragments. The risk, if any, of this growth formation cannot be estimated. It is still uncertain whether this is a radiation effect or an effect due to the chemical nature of the Thorotrast colloid.

(2) The risks of fragments near neural tissues should be carefully assessed because of the nonproliferative nature of these cells.

(3) The potential does exist for whole-organ deterministic effects but only for organs with a large number of imbedded fragments. The point at which this effect is likely to occur requires a detailed estimate of the dose to the organ from all sources of DU. First order, dose estimates indicate that particle densities greater than one fragment per cm^3 of organ volume are required as long as the fragments are insoluble and there are no other sources of DU in the body. Fragment sizes considered in this calculation range in diameter from 1-4 mm.

(4) Using the best risk estimation procedures available, the estimated increased lifetime risk of fatal cancer from a single, insoluble, DU fragment in any organ is at most 0.3%. Scaling this risk for multiple fragments or fragments with systemic DU is difficult and should be done on a case-by-case basis after assessing the total DU content in the patient.

c. The toxicological and radiological unknowns are significant enough to warrant both follow-up of current patients and research to more clearly define the long-term risks associated with these fragments. This is especially important in light of the latent periods noted for both deterministic and stochastic radiogenic effects.

6. Clinical Recommendations

a. The primary clinical recommendation is to continue to use standard medical criteria for fragment removal. Include consideration of the potential impact of a granuloma or a Thorotrastoma-like growth as a part of the decision making process for fragment removal as well as the potential for tissue necrosis for fragments lodged in or within 1-3 mm of neural tissue.

b. Determine the total amount of DU in the patient and continue to monitor patients with confirmed DU fragments for signs of kidney toxicity and any of the radiological endpoints discussed. Monitoring is required primarily because of the toxicological but also because of the radiological uncertainties.

c. If fragments are excised based upon accepted clinical criteria, save the fragment and surrounding tissue for further analysis.

7. Research Recommendations

a. Epidemiology

Establish a registry that will allow for the efficient acquisition, cataloging, and analysis of the results of patient monitoring. This effort should include

(1) periodic examinations to watch for and catalogue signs of chronic kidney toxicity, granuloma induction, and cancer;

(2) periodic bioassay and whole-body counting to determine the metabolic behavior of the internalized DU and to provide information concerning the solubility of the DU; and

(3) a program for tissue analysis if fragments are subsequently removed for medical reasons.

b. Animal Model Experimentation

The primary objective of animal model experimentation is to allow a detailed observation and study of the pathology of these fragments under controlled conditions. The specific objectives of this experimentation should include the following steps:

(1) Accurately assess the toxico-kinetic properties of the various chemical forms of DU that could be imbedded in patients.

(2) Investigate whether there are DU specific cancer induction mechanisms similar those observed in Thorotrast-specific liver cancers.

(3) Determine whether the radiogenic deterministic effects noted above occur and, if they do, at what fragment densities and latent periods.

(4) Assess the impact of long-term, low-dose-rate irradiation of specific tissues such as those of the nervous system.

(5) Determine the potential for chronic nephrotoxicity as a function of organ in which the DU is implanted

(6) Conduct pathological studies of the tissue surrounding the fragment.

c. Dosimetry

Perform definitive absorbed dose calculations using advanced techniques to determine the significance of particle size and shape.

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