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14. ABSTRACT A variety of tungsten alloys and other unusual metals have begun to enter U.S. military arsenals as substitutes for depleted uranium (DU) in munitions. There are questions about the health effects of exposure to the tungsten alloys that are similar to those originally surrounding DU, especially for embedded shrapnel exposures. The Armed Forces Radiobiology Research Institute (AFRRI) recently performed research that showed one of the militarily promising tungsten alloys to be a potent carcinogen when implanted in rats. The need to confirm the carcinogenicity of such alloys in another rodent species is an important second step required in biological as well as regulatory terms to better assess the cancer risk in humans. Results of this work will help in formulating policies for military surgeons who must treat personnel wounded by fragments of the alloys. Indications of unacceptable risks of exposure will also help determine the advisability of deploying (or developing) similar munitions. Planned timelines for the first year of the project have been disrupted when unanticipated difficulties procuring the custom pellets required for implantation were encountered, including added costs and metallurgical problems associated with the manufacture of pellets. Pellet deliveries are now expected early within the second year of the project.					
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INTRODUCTION

A variety of tungsten alloys and other unusual metals have begun to enter U.S. military arsenals as substitutes for depleted uranium (DU) in munitions. Many other nations around the world, some of which are unfriendly to the U.S., also possess munitions made with these alloys. As a result, opportunities for exposure are increasingly likely. There are questions about the health effects of exposure to the tungsten alloys that are similar to those originally surrounding DU, especially for embedded shrapnel exposures. The Armed Forces Radiobiology Research Institute (AFRRI) recently performed research that showed one of the militarily promising tungsten alloys to be a potent carcinogen when implanted in rats. The need to confirm the carcinogenicity of such alloys in another rodent species is an important second step required in biological as well as regulatory terms to better assess the cancer risk in humans. Results of this work will help in formulating policies for military surgeons who must treat personnel wounded by fragments of the alloys. Indications of unacceptable risks of exposure will also help determine the advisability of deploying (or developing) similar munitions. The National Toxicology Program (NTP) Two-Year Study Protocol carried out in two rodent species is the recommended approach in the U.S. for identifying human carcinogens. This investigation aims to confirm the previous AFRRI data in rats by carrying out a two-year protocol in mice based upon NTP guidelines. The uses the B6C3F1 hybrid mouse, a strain commonly used in carcinogenicity and toxicity assessment studies, implanted with pellets of tungsten alloys, the individual component metals of the alloys, tantalum (negative control), or nickel (positive control). The protocol includes serial collection of tissues 3, 6, and 12 months post-implantation aimed at identifying early changes relevant to the development of carcinogenic endpoints.

BODY

The specific aims (tasks) of the project are:

Aim 1: Apply the NTP two-year carcinogenicity protocol to determine whether the alloys tungsten/nickel/cobalt and tungsten/nickel/iron cause cancer in mice. Include in the protocol mice embedded with pellets of the individual metals composing the alloys and the various metal combinations (blended with biologically inert tantalum at the same percentages present in the alloys).

Aim 2: Sacrifice mice at various times after alloy implantation to detect early signs of tumor development.

Aim 3: Measure tissue levels of the various metals that compose the alloys to correlate metals levels with tumor development.

The Year 1 milestones were as follows:

- a. Implant 24-month exposure animals (1200 mice)
- b. Begin implanting 12-month exposure animals (150 mice)

A delay in obtaining the custom-fabricated metal alloy pellets for implantation prevented us from meeting these milestones. When the project began, it was anticipated that we would be able to procure the pellets approximately 6 months into the project--around September 2006. The procurement was initially delayed when a key Task Order that was in place between the U.S. Army Armament Research, Development and Engineering Center (ARDEC) at Picatinny Arsenal, New Jersey, and Aerojet Ordnance Tennessee, in Jonesborough, TN, the intended vendor for the pellets, expired between the time our project was proposed and when we initiated efforts to obtain the pellets. The chance to use this Task Order was important because it provided a mechanism for purchasing the pellets at a greatly discounted price--approximately \$31K, the price budgeted in our project, versus the unsupported, commercial cost of approximately \$71K.

Mr. Gregory O'Connor of ARDEC made numerous efforts over the next several months to get the Task Order with Aerojet reinstated or find another procurement path that would allow us to obtain the pellets for a price close to the amount budgeted. However, new procedures in place this fiscal year that would have required ARDEC to pay the administrative cost of setting up a new Task Order (in excess of \$30K) prevented ARDEC from assisting us further.

We initiated an appeal to USAMRMC for a supplement to our budget to account for the increased costs of the pellets, but the

USAMRMC turned down the request. Their view was that we were early enough in the project to be able to absorb those costs along the way. With no other pricing options available, we initiated procurement of the pellets from Aerojet in November 2006. To decrease costs, we reduced the number of spare pellets we planned to order, thereby reducing our expense from \$71K to approximately \$60K.

After overcoming a number of technical problems with the production of the pellets resulting from their unusual compositions required, Aerojet delivered test samples of the pellets this month (March 2007). The pellets appear to meet our standards and pending a few additional assessments, we expect soon to authorize the full production run.

The consequence of these delays is that the initiation of the implantation surgeries has been pushed into the second year, which will result in an overall project timeline delay of 6-8 months. Aside from the timeline shift, we anticipate that modification in our future work schedule will allow us ultimately to complete the entire project within the allotted time.

Despite the delay, we have made good use of the time available as we worked the pellet procurement issues. We identified and purchased large volumes of supplies and small equipment required for the project, including radio frequency chips and readers that are critical for animal identification and animal data collection. We have practiced radiofrequency chip implantation in animals and trained for the application of the readers with our project. We have also refined and improved the methods we will require for tissue metal measurements using our inductively coupled plasma mass spectrometry instrument. This includes a more efficient and effective sample processing procedure that relies on a muffler furnace-based decomposition of tissues to improve sample solubility before analysis.

KEY RESEARCH ACCOMPLISHMENTS

None to date.

REPORTABLE OUTCOMES

Abstract Presentation

McClain DE (2006) Carcinogenicity of embedded tungsten alloys in mice. Military Health Research Forum, San Juan, Puerto Rico, May 2006, p. 8.

CONCLUSIONS

The delayed project timelines will resume in the next few months with final delivery of the implantable metal pellets. Modifications in the schedule over the time period allotted for the project should still allow completion of project aims.

REFERENCES

None to date.