Status of Health Concerns about Military Use of Depleted Uranium and Surrogate Metals in Armor-Penetrating Munitions

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ABSTRACT

The use of depleted uranium in armor-penetrating munitions remains a source of controversy because of the numerous unanswered questions about its long-term health effects. Although there are no conclusive epidemiological data correlating depleted uranium exposure to specific health effects, studies using cultured cells and laboratory rodents continue to suggest the possibility of genetic, reproductive, and neurological effects from chronic exposure. Until issues of concern are resolved with further research, the use of depleted uranium by the military will continue to be controversial. Meanwhile, there are military programs to find substitutes for depleted uranium in munitions. Although a wide variety of alloys are being evaluated by munitions developers, certain alloys of tungsten have been developed that demonstrate properties very close to the ones that make depleted uranium useful in armor-penetrating munitions. One hundred and fifty years of industrial experience suggest that tungsten and tungsten alloys are not a significant health risk except in certain industrial exposure scenarios. However, recent research has shown that some of the most promising militarily relevant alloys of tungsten exhibit unexpected long-term toxicities as embedded shrapnel. Rats implanted in their leg muscles with pellets made from a particular alloy of tungsten, nickel, and cobalt, considered a promising surrogate for depleted uranium in munitions, develop aggressive rhabdomyosarcomas within 6 months of implantation that metastasize to the lung and necessitate euthanasia of the animals. One hundred percent of the tungsten alloy-implanted rats were affected. Immune system changes independent of tumor development were also observed. These findings amplify the need to investigate substances of questionable toxicity early in munitions development, especially with regards to the unusual kinds and levels of exposure that might be expected by the military.

1.0 INTRODUCTION

Advances in metallurgy and weapons design in the past several decades have led to new munitions whose effectiveness has provided tactical advantages on the battlefield and consequently, saved lives of personnel. However, decisions to deploy these munitions have sometimes outpaced our knowledge of how they impact the health of those exposed to them.

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Depleted uranium (DU) kinetic energy penetrators are perhaps the best-known example of these advanced munitions, primarily because of their outstanding, well-publicized performance against enemy armor in the 1991 Persian Gulf War. DU munitions were again used in the NATO military actions in Bosnia-Herzegovina (1995) and Kosovo (1999) and, more recently, coalition actions in Iraq.

Depleted uranium (DU) munitions were used only by Coalition forces during the 1991 Gulf War, but their use led to DU fragment injuries among Coalition forces as a result of friendly fire incidents. Other personnel were exposed via inhalation/ingestion after working around vehicles struck by DU munitions. Such exposures were not considered especially dangerous at the time, because numerous epidemiological studies of uranium miners and millers working with natural uranium had shown few concrete health effects from exposure; and DU has 40% less radioactivity than natural uranium. However, the exposure of wounded personnel to uranium as embedded fragments had no medical precedent, so the earlier studies dealing primarily with inhalation or ingestion exposures in miners were of uncertain utility. As a result, questions were soon raised as to whether it was wise to leave in place fragments possessing the unique radiological and toxicological properties of DU, especially when considering that exposures might extend as long as the 40-50 years remaining in the individuals' lives. As these treatment questions were being addressed, a growing public concern about the long-term health and environmental impact of using a radioactive metal like DU on the battlefield fueled forceful national and international efforts to ban the use of DU in munitions.

The medical and political controversies surrounding the use of DU played an important part in stimulating a search for substitute metals in armor-penetrating munitions. A wide variety of alloys have been and are being investigated, but recent developments in tungsten metallurgy have led to new alloys of tungsten/nickel/cobalt and tungsten/nickel/iron that rival DU in armor-penetrating performance. They have become among the leading candidates to replace DU in selected munitions, and ordnance containing these alloys has already been deployed, although on a relatively small scale.

This report aims to summarize the current status of knowledge about the health effects of DU and the general class of tungsten alloys currently being considered as surrogates for DU in munitions. DU toxicity at moderate exposure levels appears to be low in most cases, but significant questions have been raised about the toxicity of the tungsten alloys. Our present understanding and experience reinforces the advisability of including more effective health effects testing early in weapons development programs. The relatively insignificant cost of such testing would be paid back many times over by helping to redirect expensive engineering programs to more acceptable alternatives earlier in the development process.

2.0 DEPLETED URANIUM

2.1 Background

Uranium was discovered in the mineral pitchblende in 1789 by the German chemist Martin Heinrich Klaproth. Uranium does not exist in pure metallic form in nature because it is quickly oxidized in air. It occurs most commonly as U_3O_8, uranium oxide, in ores such as pitchblende. Refined uranium metal used in reactors is in the form of UO_2, uranium dioxide.

A sample of uranium was used by the French physicist Henri Bequerel in his discovery of the concept of radioactivity in 1896. Natural uranium has three predominant natural isotopes, ^{234}U, ^{235}U, and ^{238}U, all of which are radioactive; other uranium isotopes can be produced artificially in a reactor. The half lives of the natural isotopes are: 2.44×10^5 years for ^{234}U, 7.10×10^8 years for ^{235}U, and 4.5×10^9 years for ^{238}U; and their com-

position in natural uranium by mass is: 0.005% ^{234}U, 0.711% ^{235}U, and 99.284% ^{238}U. Considering the isotope half lives and their mass percentages, it can be calculated that 48.9% of the radioactivity of natural uranium is derived from the isotope ^{234}U, 2.2% from ^{235}U, and 48.9% from ^{238}U [ATSDR 1999]. Thus, ^{234}U contributes as much to the radioactivity of natural uranium as does ^{238}U, despite the fact it is 20 thousand times less abundant. Natural uranium has a low specific radioactivity of about 0.68 µCi/g or 1.8 x 10^7 Bq, which means natural uranium is considered only a weakly radioactive element.

All isotopes of uranium, natural or manmade, decay by emission of alpha particles of various energies, a process by which the uranium is transformed into another element that is also radioactive. The decay series continues until reaching a non-radioactive isotope of lead. Alpha particles have very low penetrating power but deposit large amounts of energy during penetration. Thus, alpha particles represent little hazard when on the surface of the skin, but are potentially a significant hazard if inhaled or ingested, whereupon they come in close contact with sensitive tissues [Hartmann 2000]. Beta and gamma radiation are also emitted during certain transformations, but those radiation levels are lower. Workers exposed to natural uranium could receive radiation exposures to all of the isotopes in the transformation series.

The use of uranium as nuclear fuel or in nuclear weapons requires enrichment of the fissionable isotope ^{235}U. The enrichment process concentrates ^{235}U in the metal to specific activities required to sustain nuclear reactions. The by-product of enrichment is uranium with reduced levels of the ^{235}U isotope, or “depleted” uranium. The Nuclear Regulatory Commission considers the specific activity of DU to be no more than 0.36 µCi/g, but more aggressive enrichment processes can drive this value slightly lower (~0.33 µCi/g) [ATSDR 1999]. This means DU has roughly 50% of the radioactivity of natural uranium. Even though DU has less specific radioactivity than natural uranium, it retains all of its chemical properties. The large-scale production of enriched uranium for nuclear weapons and fuel over the decades has resulted in an abundance of cheap DU, a factor that has played a role in its use in a wide variety of applications (e.g., radiation shielding, compact counterweights, armor, kinetic energy weapons). The properties of DU that make it useful as an armor-penetrating munition are its density (1.68 times that of lead) and the ability to engineer into it a molecular structure that facilitates entry into a hardened target by “shedding” outer layers of the metal during penetration.

2.2 Uranium Toxicity and Health Effects

Toxicology studies of uranium relevant to understanding DU health effects are numerous, beginning with the first reported observations of uranium-induced kidney abnormalities in the middle 1800s (see [Hodge 1973b]). Most of our detailed knowledge of uranium toxicity is derived from studies in the 1940s and early 1950s as the Manhattan Project and the need for enriched uranium for reactors led to a requirement to understand better the occupational hazards presented to uranium workers. Much of that original work is described in the classic multi-volume monographs of Voeglen and Hodge [Voeglen 1949; Voeglen 1953) and in Hodge *et al.* [Hodge 1973a], which are often together considered the definitive compilations of toxicology and pharmacokinetic data for uranium in animals and humans.

Additional biological information about uranium has accumulated since then that has reinforced our understanding of both uranium and DU health effects. The Agency for Toxic Substances and Disease Registry (ATSDR) has produced a very thorough reference that summarizes what is known and not known about the toxic effects of uranium exposure [ATSDR 1999]. The controversy surrounding the use of DU during and after the 1991 Gulf War led to a number of other excellent literature reviews of uranium and DU health effects [Institute of Medicine 2000; The Royal Society 2001, 2002].

2.2.1 Cancer

2.2.1.1 Epidemiological Studies

A series of significant epidemiological studies of nuclear industry workers and uranium miners and millers carried out since the mid 1960s have added a wealth of data to the uranium health effects database. Several investigations of uranium millers [Wagoner 1965; Archer 1973; Waxweiler 1983], workers whose occupation exposes them to uranium dust inhalation in the workplace, used death certificates and in some cases health records to investigate cancers and other diseases (e.g., renal) as a cause of death. These studies failed to clearly identify a link between uranium exposure and any specific health effects, including cancer. Studies have also been carried out of workers at the Y-12 nuclear processing plant in Oak Ridge, Tennessee [Dupree 1995; Loomis 1996] The studies, which often included controls for age, race, gender, radiation dose, other chemical exposures, and medical history (when available) showed no association between cancer and occupational exposure to radiation from external and internal sources. The relatively small sizes of these epidemiological studies, uncertainties about the amount of uranium workers were exposed to, and the impact of confounding factors such as parallel exposures to agents such as radon, silicates, and other toxic metals (e.g., arsenic) lead to large statistical errors in the results, so caution should be exercised in over-interpreting the results of such studies.

In the 1991 Gulf War, an unknown number of personnel were exposed to DU aerosols (primarily uranium oxides) after being in vehicles that were struck by DU munitions, rescuing personnel in struck vehicles, reclaiming or investigating struck vehicles, or moving through areas where DU dusts were left in the environment. Even though satisfactory exposure model exists for such personnel, it is generally considered that the brief exposures to DU dust experienced by personnel would have been far below exposures experienced by uranium miners and millers in earlier studies, so no cancers would be expected by any route of exposure. McDiarmid *et al.* [McDiarmid 2004] calculated radiation dose estimates of personnel carrying DU shrapnel in their bodies as a result of fragment injuries. Whole body radiation counting using the ICRP 30 biokinetic model for uranium yielded an upper dose limit of 0.1 rem/year, a dose is not considered particularly dangerous.

2.2.1.2 Cancer in Laboratory Animals

Experiments with laboratory animals have expanded our understanding of the carcinogenic potential of uranium and DU. Not long after the 1991 Gulf War, in an effort to understand more about the potential health effects in personnel wounded in that conflict by DU shrapnel, Pellmar *et al.* [Pellmar 1999a] carried out a toxicological investigation using Sprague-Dawley rats implanted with various numbers of DU pellets (cylinders 1 mm in diameter and 2 mm long) to mimic shrapnel injuries in humans. Although cancer was not specifically designed as an endpoint in these studies, necropsies of subject rats showed no increased number of tumors in DU-implanted rats compared to tantalum pellet-implanted controls. The high levels of spontaneous tumor development typical of Sprague-Dawley rats confounded the interpretation of that data, however.

In similar studies, Hahn *et al.* [Hahn 2002] implanted male Wistar rats with either pellets or thin foils (1 × 2 or 2 × 5 mm) of DU. They showed that there was a slightly elevated risk of cancer in the DU foil- versus tantalum foil-implanted rats. Implanted DU pellets similar to those used in research by others [Pellmar 1999a] did not produce tumors. Interpretation of these data were complicated by the fact that rats are prone to developing tumors around implanted foreign bodies shaped like the foils used, irrespective of the object's chemical composition. In experiments assessing the carcinogenic potential of DU and a tungsten alloy proposed as a surrogate for DU in armor-penetrating munitions, Kalinich *et al.* [Kalinich 2005] demonstrated DU pellets (1 x 2

mm cylinders) implanted into the leg muscles of Fisher 344 rats for 18 months caused no cancer development.

2.2.1.3 Uranium Genotoxicity

There have been very few studies comparing uranium exposure in humans to genotoxic endpoints. Such studies are relevant because destabilization of the genome can indicate an increased susceptibility to cancer development. Martin *et al.* [Martin 1991] reported that levels of chromosomal aberration, sister chromatid exchange, and dicentrics measured in nuclear fuel workers increase proportionally with uranium exposure. McDiarmid *et al.* [McDiarmid 2004], in their 10-year follow-up of thirty-nine veterans exposed to DU in friendly fire incidents during the 1991 Gulf war, reported that study participants exposed to the highest levels of DU showed a statistically significant increase in chromosomal aberrations compared to the low-exposure groups. HPRT mutation frequencies were also significantly higher in the high-DU groups, but sister chromatid exchanges were not.

Even though uranium appears to pose only a minor risk of cancer in both man and animals, the consistent observation of uranium-induced genetic changes remains a cause for concern since they are known to precede cancer development. Hu and Zhu [Hu 1990] injected uranyl fluoride into the testes of mice and showed that chromosomal aberrations in spermatogonia and primary spermatocytes are dependent on the amount of injected uranium. In experiments in which rats were implanted with pellets of DU and/or the biologically inert metal tantalum, urine and serum mutagenicity levels increased in a DU dose-dependent manner [Miller 1998a].

Experiments with cultured cells have also demonstrated the capacity of uranium to induce genotoxic changes. [Lin 1993] showed that uranyl nitrate increased frequencies of micronuclei, sister chromatid exchange, and chromosomal aberrations in Chinese Hamster Ovary (CHO) cells. Miller *et al.* [Miller 1998b] observed transformation of human osteoblast (HOS) cells to a tumorigenic phenotype after exposure to uranyl chloride. Treated cells demonstrated anchorage-independent growth, increased levels of the *k*-ras oncogene, decreased levels of Rb tumor suppressor protein, and an increase in sister chromatid exchange. Transformation rates were 9.6 times that of untreated controls, and transformed cells formed tumors in nude mice. Miller *et al.* [Miller 2002a] showed that incubating HOS cells with uranyl nitrate solutions at a fixed uranium concentration but increasing specific radioactivity resulted in increasing transformation rates and dicentrics. Results demonstrated that uranium toxicity results from both chemical and radiological toxicity. Miller *et al.* [Miller 2003] showed that uranium can activate gene expression through several signal transduction pathways that may be involved in the uranium toxicity and tumorigenicity.

The fact that human studies have yet to demonstrate a conclusive association between uranium exposure by any route and cancer [ATSDR 1999] is significant, but it should not discount the relevance of in vitro experiments showing genetic changes consistent with cancer development. The BEIR IV report [BIER IV 1988] on radon and other alpha particle emitters states that large statistical uncertainties in most of the epidemiological studies looking for cancer in uranium workers may be hiding small populations of adversely affected individuals; it cautions against minimizing the risk until more studies are available.

2.2.2 Nephrotoxicity

The review by Hodge [Hodge 1973b] of uranium toxicity prior to the Manhattan Project (1824-1942) shows that it has long been known that uranium is toxic to humans, animals, and other living things. Kidney toxicity of uranium was first recognized in animals around the middle of the 19th century, and kidney toxicity remains the primary basis for the regulation of uranium exposure. Limits for inhalation and ingestion of uranium are

aimed at not allowing uranium content in the kidney to exceed a set value, which for most countries is set at a maximum of 3 µg of uranium per gram of kidney tissue; effects caused by exposure of the kidneys at these levels are considered to be minor and transient.

The pharmacokinetics and pharmacodynamics of uranium and, therefore, DU are well established [Wrenn 1985; Leggett 1994; Taylor 1997; ICRP 1995; Leggett 2003]. There have been many studies that have investigated the results of uranium exposure in laboratory animals [Morrow 1982; La Touche 1987; Ortega 1989; Wren *et al.*, 1989]. Once absorbed it circulates in the blood primarily as the stable uranyl ion UO_2^{2+} bound to bicarbonate, albumin, or proteins [Diamond 1989; Kocher 1989; Leggett 1989]. At the kidney, uranium is filtered through the glomerulus and most is excreted within 24 h. Renal kidney toxicity occurs when residual uranium is subsequently taken up by the proximal tubules and causes damage by forming complexes with phosphate ligands and proteins in the tubular walls, thereby impairing kidney function [Blantz 1975].

Pellmar *et al.* [Pellmar 1999a] showed that DU from pellets implanted in muscle of rats can be measured in their urine within one day after pellet implantation. Over the course of the 18-month experiment, kidney uranium content reached levels well above 5 µg/g of kidney tissue, a concentration that, if reached in an acute exposure, would normally prove lethal to the animal. The findings suggested that the kidney adapted to the high levels during the chronic exposure.

2.2.3 Uranium and Bone

Bone is a major site of uranium deposition. Neuman and colleagues, in a series of early articles designed to understand how uranium interacts with normal bone metabolism, published the first observation demonstrating that bone has a high affinity for uranium. Twenty to thirty percent of a toxic does of intravenous uranium could be found in the bones of male rats within 2.5 hours after administration, and 90% of the uranium retained by the body after 40 days was in bone [Neuman 1948a]. They showed that young growing rats or rats deficient in dietary calcium incorporated greater amounts of uranium than controls [Neuman 1948b]. They also showed that uranium is preferentially incorporated in areas of active calcification and becomes more refractory to resorption as new calcification covers areas of uranium deposition [Neuman 1948c].

Uranium incorporates itself into the bone matrix by displacing calcium to form complexes with phosphate groups in the matrix [Domingo 1992; Guglielmotti 1989]. Bone-bound uranium establishes a equilibrium with uranium in the blood, and as the circulating uranium is excreted by the kidneys, bone-bound uranium slowly returns it to the circulation over time [Wrenn 1985]. Pellmar *et al.* [Pellmar 1999a] demonstrated that DU from implanted pellets rapidly distributes throughout the body and accumulates at high levels in the bone, though histological examination showed no bone lesions as a result.

2.2.4 Uranium Neurological Effects

The neurophysiological effects of uranium exposure have been investigated for many decades. Among the early findings was the observation that uranyl ions potentiate the twitch response of frog sartorious muscles by prolonging the active state of contraction. The fact this effect was reversed by administration of phosphate ions suggested that uranium prolongs the action potential [Sandow 1996]. In a study of uranium workers, Kathren and Moore [Kathren 1986] showed individuals excreting up to 200 µg U per liter urine manifested abnormal mental function. High doses of oral (210 mg/kg) or subcutaneous (10 mg/kg) uranyl acetate caused tremors in rats [Domingo 1987]. It was also shown that uranium applied at high concentrations to the ileal longitudinal muscle of guinea-pig [Fu 1985] and mouse phrenic nerve-diaphragm preparation [Lin 1988] en-

hanced muscle contraction.

In a study investigating the toxicology of embedded pellets of DU in rats to mimic shrapnel wounds in wounded 1991 Gulf war veterans, Pellmar *et al.* [Pellmar 1999b] demonstrated that DU crosses the blood brain barrier and accumulates in the hippocampus, where electrophysiological changes were observed. Briner and Murray [Briner 2005] tested behavioral effects and brain lipid peroxidation in rats exposed to various concentrations of uranyl acetate in drinking water for 2 weeks or 6 months. Open-field behavior was altered in male rats receiving the highest dose of DU after two weeks of exposure; female rats demonstrated behavioral changes after 6 months of exposure. Lipid peroxidation levels increased in the brain and correlated with some of the behavioral changes, but the correlation was ambiguous. Barber *et al.* [Barber 2005] sought to determine the kinetics of uranium content in the brains of rats following a single intraperitoneal injection of uranyl acetate (1mg/kg). They found that uranium content in all areas of the brain tested increased rapidly after injection and remained elevated for 7 days post-injection. Interestingly, rats stressed by daily forced swimming before uranium injection accumulated less uranium in their brains and had lower levels than unstressed animals 7 days after exposure.

2.2.4 Uranium Reproductive/Developmental Effects

Despite nearly a century of studies of uranium toxicity, there were few detailed studies of uranium reproductive and developmental toxicity until the late 1980s [Domingo 1995]. In most exposure scenarios, including exposure to DU, the chemical toxic effects from uranium compounds appear to occur at lower exposure levels than radiological toxicity [Hartmann 2000], and this is thought to be the case for reproductive effects as well [Domingo 1995]. In the early 1980s, Domingo and his colleagues began extensive investigations of uranium reproductive toxicity, and they have provided most of our current knowledge on the subject to date. There are only a few and preliminary studies investigating the reproductive and developmental health effects of DU specifically. Given the likelihood that uranium chemical toxicity plays the major role in any reproductive and developmental toxicity, it is reasonable to assume that uranium and DU reproductive health effects are similar.

Early studies [Maynard 1949] identified uranium as a possible reproductive toxicant in rats. Male and female rats fed diets containing 2% uranyl nitrate hexahydrate for 7 months followed by normal diets for 5 months produced fewer litters with fewer pups per litter than control rats [Maynard 1949]. However, it was difficult to determine in these experiments whether uranium toxicity or nutritional effects arising from retarded weight gain in the uranium-fed rats caused the decreased reproductive success. In follow-up studies, rats fed diets containing 2% uranyl nitrate hexahydrate for a single 24-h period after weaning also produced fewer litters with fewer pups per litter than control rats with no signs of maternal toxicity [Maynard 1953], an observation that strengthened the connection between uranium exposure and reproductive toxicity.

Llobet *et al.* [Llobet 1991] showed that male mice continuously receiving water containing uranyl acetate dihydrate and mated with untreated females resulted in a significantly decreased, but dose-unrelated, pregnancy rate; but testicular function and spermatogenesis were unaffected. Domingo *et al.* [Domingo 1989] showed that pregnant female mice given uranyl acetate dihydrate (0.05-50 mg/kg per day) by oral gavage from gestational day 13 through postnatal day 21 demonstrated no significant decrease in litter size, pup litter size, and pup viability except at the highest dose (50 mg/kg; about 1/5 of the oral LD_{50}). On the other hand, injection of 1/40 to 1/10 the subcutaneous LD_{50} dose (20 mg/kg) into pregnant female mice between gestational days 6-15 produced both maternal and fetal toxicity [Bosque 1993]. Some of the malformations noted in pups could have occurred as a result of maternal toxicity, but defects such as cleft palate and certain other variations are not known to be associated with maternal toxicity and were interpreted to be the result of

uranium developmental toxicity [Domingo 2001].

Reports of the health status of military veterans the 1991 Gulf War have provided certain insight into the possible health effects of DU. A follow-up examination of DU-exposed individuals (via embedded DU fragments and/or inhaled DU dusts) showed that there were no significant differences in semen and sperm characteristics among veterans with high or low DU urine concentrations [McDiarmid 2000; McDiarmid 2004). As of 1999, fifty of the Gulf War veterans in the McDiarmid studies had fathered thirty-five children since the conflict, and none had birth defects [McDiarmid 2001]. The relatively small number of individuals involved in these studies and the end points that were possible limit their contribution towards understanding reproductive health effects.

2.3 Summary of Depleted Uranium Health Effects

Since internalization of uranium in any form will result in a combined chemical and radiation exposure, there exists the potential for subtle differences in health effects between DU and uranium. Recent developments in cell biology technology and understanding are providing more sensitive approaches towards understanding those differences (see [Miller 2001]). Although it is doubtful that future findings will alter the view that moderate exposures to either DU or uranium present a significant toxicological threat, the new information could help improve current risk assessments of DU exposure.

3.0 TUNGSTEN ALLOYS

3.1 Background

Tungsten metal has been used for many centuries in a variety of applications. Tungsten alloys are, as their name implies, primarily tungsten, and they can include a wide variety of other metals. The first effective use of tungsten in combat dates back to German and Allied munitions (mostly tungsten carbide) in World War II. Pure tungsten metal is hard, brittle, and very difficult to machine, but when it is mixed with various other metals, including nickel, iron, and cobalt, a variety of alloys can be produced, some of which have characteristics especially useful for military applications.

Based upon a small number of studies, prevailing theory is that elemental tungsten or insoluble tungsten compounds have only limited toxicity [Leggett 1997]. For example, tungsten coils implanted into the subclavian artery of rabbits rapidly degrade, leading to elevated serum tungsten levels as early as 15 minutes after implantation. However, after 4 months, no signs of local or systemic toxicity were observed [Peuster 2003].

Studies on health effects of nickel and cobalt are more numerous. Intramuscular injections (28 mg) of soluble metallic nickel or cobalt result in formation of rhabdomyosarcomas at the injection site. With nickel, 100% of injected rats develop a tumor within 41 weeks [Heath 1964], while administration of cobalt results in tumor formation in 40% of the rats with a latency period of 71 weeks [Heath 1954; Heath 1956]. However, intramuscular implantation of rods or pellets composed of various nickel or cobalt alloys used in orthopedic prosthetics results in no excessive tumor formation [Gaechter 1977; Sunderman 1989]. A variety of other nickel compounds, including nickel subsulfide, nickel oxide, and nickel monosulfide, have been tested for carcinogenic potential via intramuscular administration [Gilman 1962; Sunderman 1976; Sunderman 1977]. Tumors (rhabdomyosarcoma and fibrosarcoma) were found in many cases at the injection site, with tumor yield dependent on solubility and concentration of the administered compound. It has been postulated that the yield of localized tumors is inversely related to the rate of solubilization of the nickel-containing compound [Kasprzak

1983]. This hypothesis does not appear to hold for cobalt compounds [Lison 2001].

Weinbren *et al.* [Weinbren 1978] reviewed the evidence that injected iron compounds of various kinds can cause local cancers in man. Only sporadic cancers of various types (mostly sarcomas) were discovered in the medical literature. The International Agency for Research on Cancer (IARC), focusing on a particular injectable iron compound, iron-dextran complex, determined that there is inadequate evidence for carcinogenicity in man [IARC 1987], but the evidence for carcinogenicity of iron dextran complex in animals suggested that it is reasonably anticipated to be a human carcinogen. Huang [Huang 2003] reviewed evidence of iron as a carcinogen and concluded that the influence iron can have on various oxidative mechanisms known to cause cancer suggests that iron can contribute to cancer development either as an cancer initiator or promoter. Until the mechanisms by which iron induces cancer are better understood, it remains uncertain whether iron or iron bearing compounds are carcinogenic.

When metals such these are alloyed, alloy-specific effects are observed that complicate understanding of the alloy's toxicity. Investigations of hard-metal disease have shown that either tungsten carbide or cobalt alone has limited toxicity on lung tissue [Lasfargues 1992]. However, when the metals are alloyed, the tungsten carbide/cobalt mixture increases the observed toxicity synergistically. It is not known whether this is due to the combined toxicity of the tungsten carbide/cobalt mixture or to an increase in the bioavailability of the known toxicant, cobalt [Lison 1997].

Studies performed by the Armed Forces Radiobiology Research Institute (AFRRI) with cultured human osteoblast sarcoma (HOS) cells, using tungsten, nickel, and cobalt or iron in proportions equivalent to the makeup of armor-penetrating munitions, demonstrated that the mixtures induce a metal dose-dependent malignant transformation [Miller 2000, 2001, 2002a; Kalinich 2005]. This neoplastic transformation was associated with genotoxic damage, including sister chromatid exchange, micronuclei induction, and DNA single-strand breaks [Miller 2000, 2001]. Data from these studies are summarized in Table 1. The data demonstrate that, like the studies of Lasfargues *et al.* [Lasfargues 1992], the metal combinations produce toxicity greater than the sum of the toxicities produced by the individual metals.

Table 1. Effect of tungsten alloy and alloy components on neoplastic transformation of HOS cells and tumorigenicity of those transformed HOS cells in athymic mice.

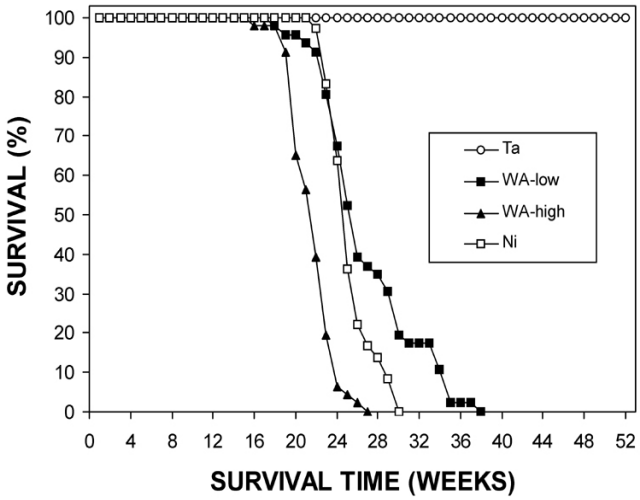
Treatment	Transformation Frequency of HOS Cells	Tumorigenicity (%) of Transformed HOS Cells
None	4.2	0
Co	4.8	0
Fe	5.1	0
Ni	9.5	0
W	6.9	0
W/Ni/Co	37.6	50
W/Ni/Fe	40.1	58

3.2 AFRRI Embedded Tungsten Alloy Studies in Rats

In 2001, AFRRI initiated a project funded by the United States Army Medical Research and Materiel Command (USAMRMC) to assess the carcinogenicity and immunotoxicity of DU and one of the tungsten-nickel-

cobalt alloys of special interest to the military [Kalinich 2001]. In this study, rats received a low dose (4 pellets; cylinders 2 mm long and 1 mm in diameter) or a high dose (20 pellets) of the tungsten alloy implanted in the gastrocnemius muscles. The number of pellets used was within the range of doses that might be expected in wounded personnel, with 4 pellets representing about 2 ounces of shrapnel in man. Other rats received implants of the biologically inert metal tantalum as a control for pellet implantation. Results of this study [Kalinich 2005] showed that tumors developed in 100% of the tungsten alloy-implanted rats. Figure 1 shows that aggressive tumor development forced euthanasia of all of the alloy-implanted rats 37 weeks after implantation, with the higher dose of alloy forcing euthanasia as early as 16 weeks.

Figure 1. Survival times of pellet-implanted rats. Rats were implanted with either 20 pellets of W/Ni/Co tungsten alloy ("WA-high"), 4 pellets of tungsten alloy (plus 16 pellets of the biologically inert metal tantalum; "WA-low"), 20 pellets of tantalum ("Ta"), or 20 pellets of pure Nickel ("Ni"). Rats were sacrificed only when became moribund.



Gross examination of the tumors showed most to contain a tungsten alloy pellet embedded within it, while tantalum pellet-implanted rats showed no tumors (Figure 2). Tumors were malignant and characterized as extremely aggressive pleomorphic rhabdomyosarcomas (Figure 3). Furthermore, muscle tumor-derived metastases developed in the lungs of all alloy-implanted rats (Figure 4). No rats receiving tantalum pellets developed tumors. Interestingly, neither did the DU-implanted animals.

Figure 2. Effect of implanted W/Ni/Co pellets on F344 rats. (a) Gross appearance of Ta-implanted hind leg. (b) Dissected area around implanted Ta pellet (arrow indicates pellet). (c) Gross appearance of tungsten alloy-implanted hind leg with tumor(s). (d) Dissected area around implanted tungsten alloy pellet with tumor surrounding pellet (arrow indicates pellet).

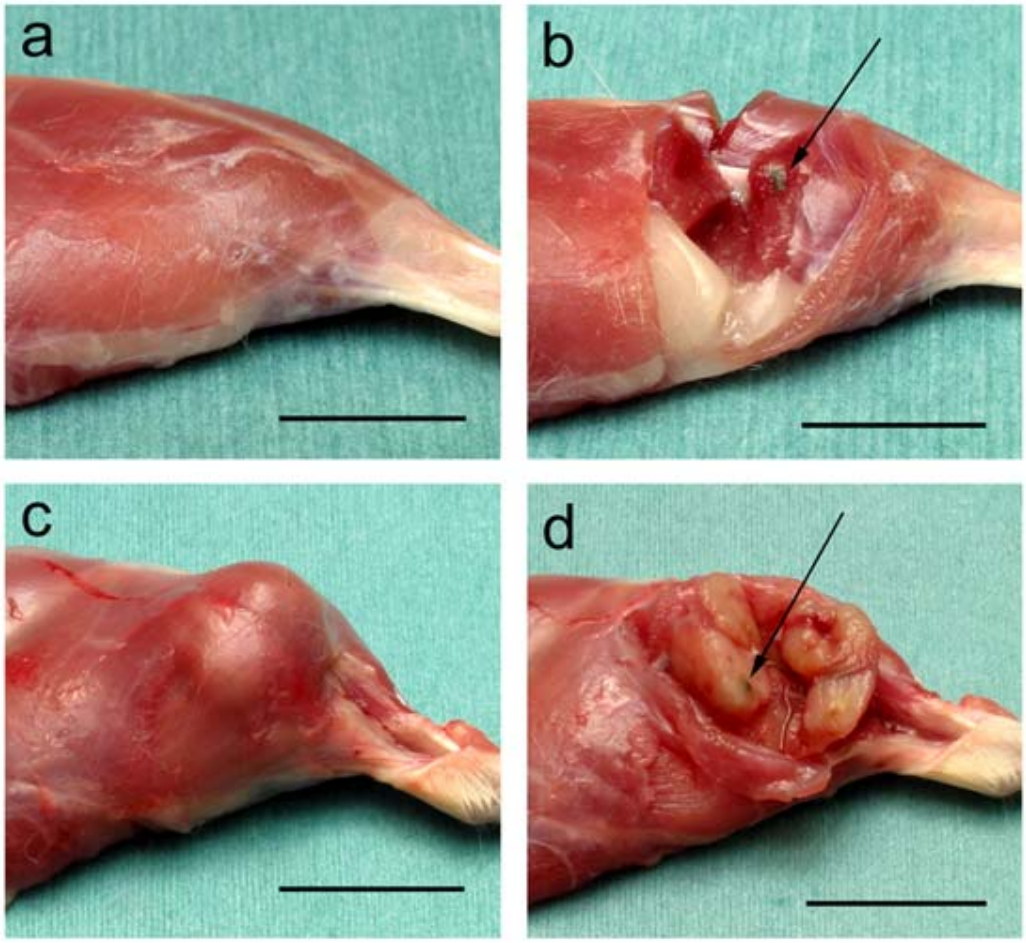


Figure 3. Histopathological examination of leg tumor surrounding W/Ni/Co pellet. (a) Hematoxylin and eosin (H&E) stained section of leg tumor from F344 rat showing tungsten alloy pellet hole (P), scale bar = 500 µm. (b) H&E stained tumor section showing neoplastic infiltration of preexisting muscle fibers (MF), scale bar = 200 µm. (c) H&E stained tumor section showing neoplastic cells with numerous mitoses (arrows) and bizarre mitotic figures (BZ), scale bar = 100 µm. (d) H&E stained tumor section showing pleomorphic cell (arrow), scale bar = 100 µm. (e) Desmin staining of leg tumor showing neoplastic cells (NC) and muscle fibers (MF), scale bar = 500 µm. (f) Desmin staining of neoplastic cells, scale bar = 50 µm.

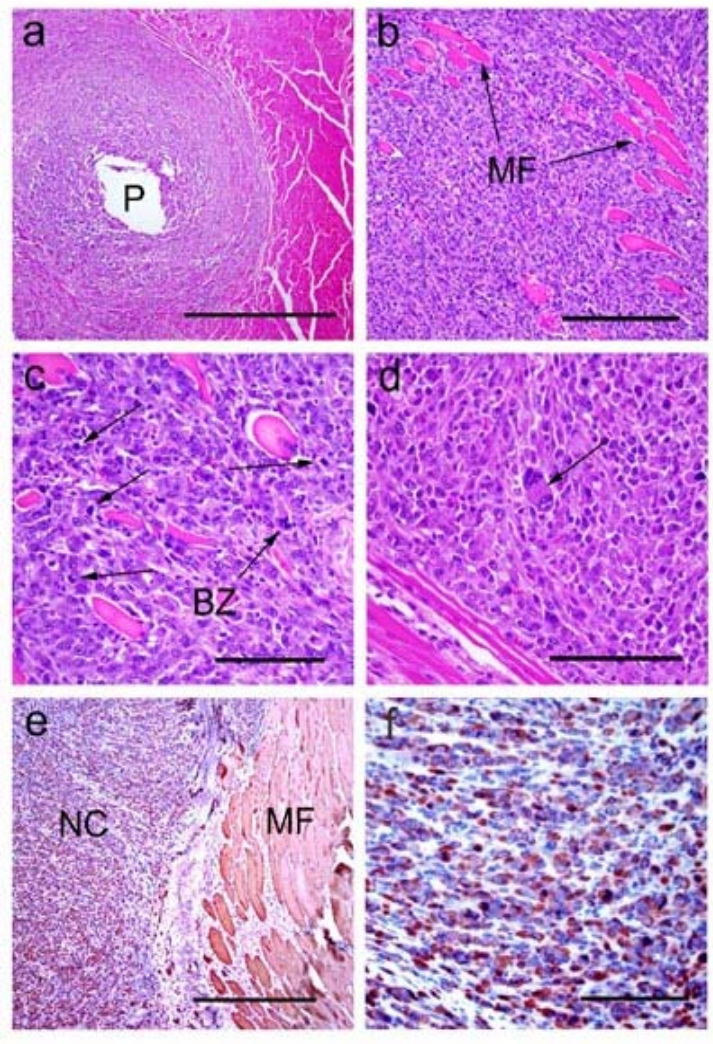
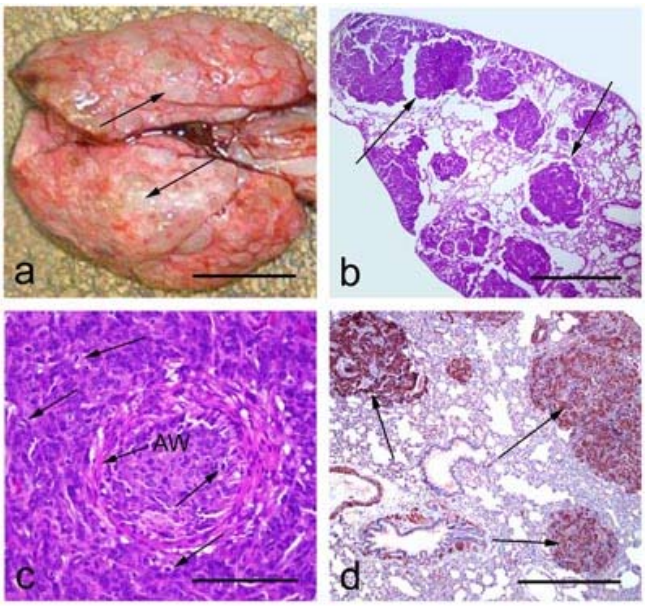


Figure 4. Lung metastases from W/Ni/Co-implanted F344 rats. (a) Gross appearance of pulmonary metastases from tungsten alloy-implanted rat (arrows indicate metastatic foci). (b) H&E stained section of pulmonary metastases (arrows), scale bar = 1 mm. (c) H&E stained section of an occluded pulmonary arteriole (arrow indicates vascular smooth muscle wall (AW)) showing neoplastic cells with numerous mitoses (arrows), scale bar = 50 µm. (d) Desmin staining of pulmonary metastases (arrows), scale bar = 500 µm.



The mechanism of tumor induction with embedded WA pellets remains unclear. The AFRRI study did not include a full assessment of the individual metals composing the tungsten-nickel-cobalt alloy, since funding was limited and the study focused on DU at a time when questions of tungsten alloy toxicity were only beginning to be raised [Miller 2000, 2001, 2002a]. However, it included experiments with one of the alloy component metals, nickel, a known carcinogen used as a positive control to validate the experimental system. The nickel–implanted rats (20 pellets) developed tumors, pleomorphic rhabdomyosarcomas, but the tumors developed significantly slower than those of the high-dose tungsten alloy groups (Figure 1; [Kalinich 2005]) and no lung metastases were observed. Nickel exposure in rats receiving the pure nickel pellets was presumably much higher than that in rats implanted with tungsten alloy pellets, which contained 6% nickel.

Despite the smooth and impermeable surface of the pellets, foreign body or solid-state carcinogenesis is unlikely because of the intramuscular, rather than subcutaneous, location of the implanted pellets [Bates 1966; Brand 1975]. In addition, implanted tantalum pellets of an identical geometry resulted in no tumor formation. One possibility is that free-radical reactions at the interface of the pellet and tissue could result in damage leading to carcinogenesis.

3.3 Summary of Tungsten Alloy Health Effects

For years, exposure to tungsten was thought to be of little consequence to health. In fact, tungsten is occasionally found as a minor component (5-15%) in some of the various alloys used to produce medical implant devices such as artificial hips and knees. Since the alloy used in WA munitions usually contains greater than 90% tungsten, along with smaller amounts of other metals, it was also assumed that exposure to these alloys would present little or no health risk.

As is shown here, this is not the case in the rat. Embedded WA pellets not only resulted in aggressive, metastatic, pleomorphic rhabdomyosarcomas, but also caused significant hematopoietic changes well before the carcinogenic effect was observed. It seems unlikely that these adverse health effects can be attributed solely to the small amounts of nickel and/or cobalt present in the alloy. Recent *in vitro* studies have demonstrated a synergistic effect in terms of damage when tungsten is present with these metals [Miller 2001, 2002a] that may play a role in WA carcinogenicity.

4.0 CONCLUSIONS

In many ways the development of substitutes for DU in munitions has followed a pattern similar to that for DU deployment, in that incomplete toxicological information was available prior to their release. In terms of the new tungsten alloys, it was assumed that many years of industrial use of tungsten and alloys such as tungsten carbide, which showed common exposures to the metals (e.g., inhalation, ingestion, or skin contact) represents a manageable risk, meant they could be used as safely in armaments. However, until recently, limited toxicological studies had ever been carried out with many of the alloys of specific military interest, and there has been no meaningful prior experience with exposures of special interest to the military, such as via embedded fragments. Recent research into the health effects of embedded pellets of a tungsten/nickel/cobalt alloy have led to those assumptions being questioned.

The health effects of tungsten metal exposure is receiving a new look in other circumstances as well. Environmental testing of the leukemia cluster around Fallon, Nevada, in the western United States showed slightly elevated levels of several heavy metals including uranium and cobalt, but significantly elevated levels of tungsten [CDC 2003]. Although no definitive link between elevated tungsten levels and cancer has been established, because of the uncertainty surrounding this issue, the U.S. National Toxicology Program recently added tungsten to their list of compounds to be assessed for adverse health effects. Further study of the health effect of tungsten and tungsten alloys is clearly indicated.

Our present understanding and experience reinforces the advisability of including more effective health effects testing early in weapons development programs. The relatively insignificant cost of such testing would be paid back many times over by helping to redirect expensive engineering programs to more acceptable alternatives earlier in the development process.

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