ELSEVIER

The Science of the Total Environment 274 (2001) 115–118

the Science of the Total Environment

www.elsevier.com/locate/scitotenv

Biological effects of embedded depleted uranium (DU): summary of Armed Forces Radiobiology Research Institute research

D.E. McClain[a,*], K.A. Benson[b], T.K. Dalton[a], J. Ejnik[c], C.A. Emond[a], S.J. Hodge[a], J.F. Kalinich[a], M.A. Landauer[a], A.C. Miller[a], T.C. Pellmar[d], M.D. Stewart[a], V. Villa[a], J. Xu[a]

[a]*Armed Forces Radiobiology Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5603, USA*
[b]*Food and Drug Administration, Division of Oncologic Drug Products, HFD-150, 5600 Fishers Lane, Rockville, MD 20857, USA*
[c]*Navy Drug Screening Laboratory, 320B 'B' Street, Bldg 38-H, Great Lakes, IL 60085, USA*
[d]*National Academy of Sciences / Institute of Medicine, 2101 Constitution Ave., N.W., Washington, DC 2041833, USA*

Received 20 June 2000; accepted 4 October 2000

Abstract

The Persian Gulf War resulted in injuries of US Coalition personnel by fragments of depleted uranium (DU). Fragments not immediately threatening the health of the individuals were allowed to remain in place, based on long-standing treatment protocols designed for other kinds of metal shrapnel injuries. However, questions were soon raised as to whether this approach is appropriate for a metal with the unique radiological and toxicological properties of DU. The Armed Forces Radiobiology Research Institute (AFRRI) is investigating health effects of embedded fragments of DU to determine whether current surgical fragment removal policies remain appropriate for this metal. These studies employ rodents implanted with DU pellets as well as cultured human cells exposed to DU compounds. Results indicate uranium from implanted DU fragments distributed to tissues far-removed from implantation sites, including bone, kidney, muscle, and liver. Despite levels of uranium in the kidney that were nephrotoxic after acute exposure, no histological or functional kidney toxicity was observed. However, results suggest the need for further studies of long-term health impact, since DU was found to be mutagenic, and it transformed human osteoblast cells to a tumorigenic phenotype. It also altered neurophysiological parameters in rat hippocampus, crossed the placental barrier, and entered fetal tissue. This report summarizes AFRRI's depleted uranium research to date. Published by Elsevier Science B.V.

Keywords: Depleted uranium; Uranium; Toxicity; Health effects

* Corresponding author. Tel.: +1-301-295-1344; fax: +1-301-295-0292.
E-mail address: mcclain@mx.afrri.usuhs.mil (D.E. McClain).

0048-9697/01/$ - see front matter Published by Elsevier Science B.V.
PII: S0048-9697(01)00734-3

1. Background

During the Persian Gulf War there were a small number of friendly fire incidents that resulted in military personnel being wounded by fragments of depleted uranium (DU) munitions (McDiarmid et al., 2000). Following long-standing fragment removal policies in effect at that time, fragments not immediately threatening the health of the individual were left in place. Soon after the Gulf War, questions arose as to whether such a policy remains appropriate for fragments with the unusual chemical and physical properties of DU.

DU is a radioactive, pyrophoric, heavy metal approximately 1.7 times the density of lead (19 g/cm^3 vs. 11.35 g/cm^3) (Livengood, 1998). DU is used by the military primarily as armor and as kinetic energy penetrators to defeat armored vehicles. It is a byproduct of the enrichment process for reactor- and weapons-grade uranium (^{235}U). ^{235}U and ^{234}U are reduced from 0.72 and 0.006%, respectively, in natural uranium to 0.2 and 0.001% in DU. The remainder is ^{238}U (approx. 99.8%). DU emits alpha, beta, and weak gamma radiations. Although DU emits less radiation than natural uranium, its chemical properties are identical.

DU presents minimal external chemical or radiation hazards. Its radioactivity is very low, and the fraction of penetrating radiation emitted per decay (< 1%) is small. However, internalization of DU, which more intimately exposes sensitive tissues, enhances its potential chemical and radiological hazard.

Combat use of DU can lead to its internalization by several routes. When a DU penetrator breaches a vehicle there is a spalling of metal (derived potentially from the penetrator and/or DU armor) that can introduce high-velocity shards into the vehicle interior, thereby producing shrapnel wounds. DU dust produced by the impact can also be inhaled and ingested, and small particles produced by penetration can contaminate open wounds.

Our knowledge of the health consequences of exposure to DU has been derived primarily from the large body of data from animal experimentation and human epidemiological studies of uranium miners, uranium millers, nuclear weapons workers, and nuclear fuel workers, especially between the early 1940s and through the early 1970s. There have also been several literature reviews addressing the health and environmental risks of DU penetrators (ATSDR, 1999; BEIR IV, 1988; JTCG/ME, 1974). Existing literature allows a fairly comprehensive appraisal of the hazards of inhalation and ingestion, but it does not allow a dependable assessment of the consequences of internalization by wound contamination or fragment injuries that are of special additional interest to the military.

It is important to note that the military's concern about DU toxicity is an issue potentially much broader than that concerning the relatively small number of individuals accidentally wounded during the Gulf War. During that conflict, only Coalition forces possessed and used DU munitions, but the dramatic effectiveness demonstrated by these weapons has since led other nations — many unfriendly to the US — to initiate programs to obtain and/or develop their own DU weaponry. We can therefore logically presume that future conflicts could easily result in dramatic increases in numbers of US casualties wounded by DU.

Responding to concerns about the Army fragment removal policy, the Army Surgeon General in 1992 requested that the Armed Forces Radiobiology Research Institute (AFRRI) review the potential hazards of embedded DU. That report, completed in 1993, concluded there were sufficient uncertainties about the long-term chemical and radiological effects of embedded DU to: (a) warrant medical follow-up of Gulf War veterans wounded by DU fragments; and (b) initiate pilot animal toxicology studies of the biological effect of embedded DU fragments (Daxon and Musk, 1993). After a competitive grant proposal process, AFRRI was awarded late in 1994 funding from the US Army Medical Research and Material Command (USAMRMC) (Pellmar et al., 1995) to perform a toxicological study of embedded DU using a rat model. AFRRI subsequently received additional funding from the Women's Health Program of the USAMRMC to investigate the fetal and developmental effects of maternally em-

bedded DU (Benson and Pellmar, 1997). Those studies, along with other research performed with AFRRI in-house funding have produced a large body of research findings that have already played a role in updating the military fragment removal policies (Department of the Army, 1999). The goal of this paper is to provide a brief summary of those research findings.

2. AFRRI depleted uranium research

2.1. Experimental design

The initial AFRRI studies were in the form of a basic toxicological assessment of embedded DU pellets, and the results derived from several parts of that study have been published (Miller et al., 1998a,b; Pellmar et al., 1999a,b). In these experiments, DU pellets (1-mm cylinders, 2 mm in length) were experimentally implanted in the gastrocnemius muscle of rodents. Biologically inert tantalum pellets served as a negative control. Various times after implantation, uranium levels were measured in a variety of tissues (using kinetic phosphorescence analysis and inductively coupled plasma mass spectrometry). Histological and functional assessments were performed in selected target tissues.

The AFRRI research has also employed in vitro assays using cultured human cell lines exposed to both soluble and insoluble forms of DU.

3. Results

Within days of DU pellet implantation, uranium was detected in tissues far-removed from the site of implantation, including bone, kidney, muscle, and liver. Most tissues continued to accumulate uranium throughout the 18-month course of the experiments. Uranium appeared in the urine of DU-implanted rats within 24 h after implantation, and a significant excretion of urine uranium continued for the duration of the study. One of the most interesting observations made in this research was that the uranium content of kidney tissue reached levels well above that known to be nephrotoxic after acute exposure. However, no histological or functional evidence of kidney or other organ toxicity was observed in DU-implanted animals, indicating that, in the short term at least, the body may adapt to high levels of uranium with chronic exposure (Pellmar et al., 1999a).

The toxicology study also provided preliminary evidence of potential health problems that might be associated with exposure to embedded fragments of DU. A carcinogenic potential of embedded DU was suggested from a number of the AFRRI experiments. Kidney, liver, and proximal muscle tissue tested various times after implantation showed elevation in the expression of several oncogenes known to be involved in carcinogenesis (Livengood, 1998). DU was shown to be mutagenic, as indicated by the Ames bacterial reversion test, as was urine from DU-implanted rodents (presumably as a result of its uranium content) (Miller et al., 1998a). Incubation of a cultured human osteoblastic sarcoma (HOS) cell line with soluble and insoluble compounds of DU transformed the cells and conferred upon them tumorigenic potential (Miller et al., 1998b). Interestingly, it was observed that alloys of tungsten, which have often been suggested as an alternative to DU in munitions, transformed HOS cells at a greater frequency than DU and was even more tumorigenic (Miller et al., 1998b). In preliminary experiments designed to test agents that could block the effect of DU on HOS cells, phenylacetate was shown to be very effective (Miller et al., 2000).

AFRRI studies have also provided evidence that DU may have neurotoxic properties (Pellmar et al., 1999b). This can be concluded from observations that DU from embedded fragments penetrated the blood/brain barrier, accumulated in regions throughout the brain, and induced changes in normal neurophysiological parameters in the hippocampus, a region of the brain involved in memory and learning. There was no indication that behavioral parameters were affected in these animals. However, these studies used a functional observation battery of behav-

ioral tests, which are fairly coarse indicators. More sensitive studies to assess motivation and learning in DU-implanted animals are currently planned.

Additional studies are currently assessing reproductive behavior in DU-implanted female rats. Preliminary results indicate that DU from implanted pellets penetrated the placenta of pregnant rats and accumulated in the fetus, although at very low levels. Preliminary results also indicated that the longer one waits to breed the female after DU pellet implantation, the greater the chance for decreased litter size.

4. Conclusion

The AFRRI results to date indicate a need for further study of the potential health effects from embedded DU. Many of these experiments are either already underway or planned. Once completed, they will provide data that will allow military planners to address more knowledgeably the risks vs. benefits of DU use in the military.

References

ATSDR (Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, Public Health Service). Toxicological Profile for Uranium (Update). 1999:398.

BEIR IV (Committee on Biological Effects of Ionizing Radiation. Study IV). Health Risks of Radon and Other Internally Deposited Alpha-Emitters. Washington, DC: National Academy Press, 1988.

Benson KA, Pellmar TC. Evaluation of the health risks of embedded depleted uranium (DU) shrapnel on pregnancy and offspring development. US Army Medical Research and Materiel Command Contract Number DAMD17-96.

Daxon EG, Musk JH. Assessment of the risks from embedded fragments of depleted uranium. AFRRI Technical Report 93-1, 1993.

Department of the Army. United States Army Medical Command. Policy for the Treatment of Personnel Wounded by Depleted Uranium Munitions, April 9, 1999.

JTCG/ME. (Joint Technical Coordinating Group for Munitions Effectiveness). Ad Hoc Working Group for Depleted Uranium. Medical and Environmental Evaluation of Depleted Uranium, Vol I, 1974.

Livengood DR. Health effects of embedded depleted uranium: an Armed Forces Radiobiology Research Institute (AFRRI) Workshop. AFRRI Special Publication 98-3. AFRRI, 1998.

McDiarmid MA, Keough JP, Hooper FJ, McPhaul K, Squibb K, Kane R, DiPino R, Kabat M, Kaup B, Anderson L, Hoover D, Brown L, Hamilton M, Jacobson-Kram D, Burrows B, Walsh M. Health effects of depleted uranium on exposed Gulf War veterans. Environ Res 2000;82:168–180.

Miller AC, Fuciarelli AF, Jackson WE, Ejnik EJ, Emond C, Strocko S, Hogan JB, Page N, Pellmar TC. Urinary and serum mutagenicity studies with rats implanted with depleted uranium or tantalum pellets. Mutagenesis 1998a;13:643–648.

Miller AC, Blakely WF, Livengood D, Whittaker T, Xu J, Ejnick J, Hamilton M, Parlette E, St. John T, Gerstenberg HM, Hsu H. Transformation of human osteoblast cells to the tumorigenic phenotype by depleted uranium–uranyl chloride. Environ Health Persp 1998b;106:465–471.

Miller AC; Xu J; Whittaker T; Stewart M; McClain D. Suppression of depleted uranium-induced neoplastic transformation of human cells by the phenyl fatty acid phenylacetate. Radiat Res 2000;155:163–170.

Pellmar TC, Hogan JB, Benson KA, Landauer M. Toxicological evaluation of depleted uranium in rats. U.S. Army Medical Research and Material Command Contract Number 95MM5530, 1995.

Pellmar TC, Fuciarelli AF, Ejnik JW, Hamilton M, Hogan JB, Strocko S, Emond C, Landauer M. Toxicological evaluation of depleted uranium in rats implanted with depleted uranium pellets. Toxicol Sci 1999a;49:29–39.

Pellmar TC, Keyser DO, Emery C, Hogan JB. Electrophysiological changes in hippocampal slices isolated from rats embedded with depleted uranium fragments. Neurotoxicol 1999b;20:785–792.