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Chemical and Radiological Toxicity of Depleted Uranium

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A by-product of the uranium enrichment process, depleted uranium (DU) contains approximately 40% of the radioactivity of natural uranium yet retains all of its chemical properties. After its use in the 1991 Gulf War, public concern increased regarding its potential radiotoxicant properties. Whereas in vitro and rodent data have suggested the potential for uranium-induced carcinogenesis, human cohort studies assessing the health effects of natural and DU have failed to validate these findings. Heavy-metal nephrotoxicity has not been noted in either animal studies or Gulf War veteran cohort studies despite markedly elevated urinary uranium excretion. No significant residual environmental contamination has been found in geographical areas exposed to DU. As such, although continued surveillance of exposed cohorts and environments (particularly water sources) are recommended, current data would support the position that DU poses neither a radiological nor chemical threat.

Introduction

Fear of radiation is prevalent in modern society.' Anxiety and distress are the most pronounced primary health effects after most radiation accidents.[1-5] Depleted uranium (DU) has been linked in the lay-press to cancer, the Gulf War syndrome, and the Balkans syndrome. It continues to foment confusion and controversy. The U.S. Armed Forces Radiobiology Research Institute explicitly declared that "DU is neither a radiological nor chemical threat. It is not a weapon of mass destruction."[6] However, the United Nations Subcommission on Prevention of Discrimination and Protection of Minorities passed a resolution declaring "weaponry containing depleted uranium" a weapon of mass destruction and called for the end of its use.[7]

Multiple reports have emphatically stated a lack of cancer risk from exposure to DU .[8-11] Yet, a recent report by the Royal Society suggested the possibility of a twofold increase in lung cancer in individuals exposed to DU munitions. [12.11] The purpose of this study was to evaluate the current knowledge and understanding of DU and its potential for both chemical and radiological toxicity.

What Is DU?

Uranium, the heaviest naturally occurring element, is a ubiquitous soil component found at an average concentration of 3 μg/g soil. A typical plot of soil 1 square mile in area and 1 foot deep contains 4 tons of uranium.[8-14] Naturally occurring uranium is composed of three isotopes, ^{234}U ^{235}U, and ^{238}U, in the following proportions, respectively : 0.005%, 0.711% and 99.283%.[15] During the process of nuclear fuel and weapons production, naturally occurring uranium is processed to increase the percentage of available ^{235}U. This "enriched uranium" contains more than 0.711% ^{235U} by mass. The by-product of the enrichment process is DU, which by definition contains less than 0.711% ^{235}U by mass. [15] DU typically contains 70% less 235U and 80% less ^{234}U than naturally occurring uranium. [14.15] DU manufactured from spent uranium fuel rods additionally may contain trace levels of plutonium, neptunium, americium, technetium, and ^{236}U. These impurities are found in parts per billion concentrations, and increase radioactivity by less than 1%.[16]

Sources of DU Exposure

DU has been used in both civilian and military technology with particular emphasis placed upon its military use. DU has several properties that make it useful as a military kinetic penetrator munition. Uranium is the heaviest naturally occurring element, approximately 1.7 times denser than lead. In addition, DU is pyrophoric and has self-sharpening properties.[15.17] These properties make DU an ideal munition with which to defeat protective armor. In contrast, other armor-piercing incendiary munitions such as tungsten tend to mushroom and become blunt upon armor penentration.[18]

During the 1991 Gulf War, DU rounds were extensively deployed by the United States. In addition to 288 DU-containing Tomahawk cruise missiles, between 14,000 and 940,000 armor-piercing incendiary rounds were fired.[19] More recently, U.S. military aircraft fired 10,000 30-mm DU rounds (approximately 3.3 tons of DU) at 12 sites in Bosnia-Herzegovina between 1994 and 1995 and another 31,000 DU rounds (10.2 tons) at 85 sites in Kosovo in 1999.[18.19]

Although less well publicized, DU is used commercially as ballast in yachts and wide-body commercial jet liners, including the DC-10 and 747.[20] The Boeing 747 involved in the 1992 Amsterdam accident reportedly contained 282 kg of DU counterweights.[21] DU has also been used as shielding in radiation therapy.

Chemical Characteristics of DU

DU is unique in that it possesses both potential chemical and radiological toxicant properties. Based upon reports by both the Agency for Toxic Substances and Disease Registry and the World Health Organization, the major health concern from DU is toxicological rather than radiological.[8.11]

Chemically, uranium causes toxicity as a heavy metal with characteristics similar to the alkaline earth metal ions.[14] The principal target organ is the kidney.[8.11.22] Toxicity is dependent upon the solubility of the uranium compound.[19-23] Soluble compounds, such as halides and urinates, demonstrate absorption rates from the gastrointestinal and respiratory tracts 10- to

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20-fold greater than insoluble uranium oxides (U_3O_8, UO_2, UO_3), and demonstrate increased nephrotoxicity.[23]

Once absorbed in the blood stream, uranium circulates as the uranyl ion (UO_2^{2+}), forming uranium-carbonate and uranium-albumin complexes.[24] Approximately 90% of a single uranium exposure is renally eliminated in the first 24 hours.[14] The remaining 10% is rapidly redistributed to the bones and other organs. Sixty-six percent of the total uranium body burden resides in the skeleton, where the uranyl ion codeposits with calcium.[14.20] The average human body contains approximately 100 μg of uranium.[14] The kidney, liver, and muscle are the major extraskeletal sites of uranium deposition with the kidney potentially acting as a second site of long-term storage.[24 25] Normal urinary uranium excretion levels range from 0.04 to 0.5 μg/L urine.[14]

Radiobiological Characteristics of DU

The radiological effects of DU are considered a "negligeable hazard."[14] Because of the very long half-lives of the individual radioisotopes (^{234}U, 245,000 years; ^{235}U, 704 x 10^6 years; and ^{238}U, 4,470 X 10^6 years), the specific activity of uranium is low.[20.26] The predominant radioisotope, ^{238}U, also has the longest half-life and therefore the lowest specific activity. Placed in perspective, radon has a specific activity 10,000 times greater than naturally occurring uranium. By its very nature, DU contains only 50% to 60% of the radioactivity of naturally occurring uranium.[19.20.26] DU is approximately 3 million times less radioactive than Ra-226 found in luminous clocks and watches and 10 million times less radioactive than Am-241 found in fire detectors."

Uranium emits α, β, and γ ionizing radiation.[27.28] Although α particles are the primary radiation hazard, these particles are unable to penetrate the superficial layers of dead skin and so do not pose any external radiation risk.[9] These α particles do pose a potential hazard upon inhalation, ingestion, or contamination of open wounds. β and γ radiation, although present in much lower activities, do represent a potential external radiation hazard. Calculated potential whole body radiation doses in tank crew members have demonstrated levels of 0.00001 to 0.00013 rem/h (0.001-0.013 Sv/h) above ambient background.[23] The maximum possible annual whole body radiation dose in a scenario involving continuous exposure would be 2.6 rem (260 Sv), which is one-half the current annual occupational exposure limit. Direct contact with DU ammunition produces a skin dose rate of 0.2 rem/h, predominantly through β particle emissions.[23] Direct skin contact for 250 hours per year would be required to exceed current occupational skin dose limits.

DU and the Kidney

Chronic exposure to natural uranium has been demonstrated to affect kidneys in a dose-dependent manner.[29] Acute exposure in the range of 70 to 100 μg/kg body weight has been demonstrated to produce chemical damage to the proximal renal tubule.[14] In 1959, the International Commission on Radiological Protection set the maximal permissible organ concentration standard for uranium at 3 μg/g for the kidney.[19.23]

A rodent model of implanted DU pellets in the rat demonstrated dose-dependent elevated uranium levels in the kidney and urine. Despite urinary uranium levels as high as 674±156 μg/L, no renal injury was noted.[24] The authors concluded that chronic exposure from embedded DU fragments was not as nephrotoxic as predicted from acute uranium exposure studies.

During Operation Desert Storm, approximately 120 soldiers, were believed exposed to DU through "friendly-fire" incidents.[30.31] In accordance with prevailing military doctrine at the time, embedded DU fragments were left in place unless deemed to be a current or future health threat.[15] Because of subsequent concerns about the health risks of DU, the Department of Veterans Affairs has performed an ongoing health assessment of a cohort of these individuals. Veterans with retained DU shrapnel continued to excrete elevated levels of urinary uranium 9 years after first exposure.[32] These individuals were subsequently classified into low- or high-urinary uranium excretion groups based upon excreted levels of <0.10 μg/g and ≥0.10 μg/g, respectively. No disturbances were noted in renal function, including functional measures of the proximal tubule, despite urinary uranium levels as high as 30.7 μg/g.[30.33]

DU and Malignancy

Urine from rats implanted with DU pellets had enhanced mutagenic activity in Salmonella strain TA98 and Ames II mixed strain (TA7001-7006). The mutagenic activity increased in a dose-dependent manner with excreted urinary uranium concentration.[34]

In vitro studies using the soluble DU compound uranyl chloride ($DU\text{-}UO_2Cl_2$) demonstrated an ability to transform the human osteosarcoma cell line HOS to a tumorigenic phenotype.[34] Use of DU-uranyl chloride resulted in a 9.6 ± 2.8-fold increase in transformation frequency, compared with the known carcinogen nickel sulfate (7.1 ± 2.1-fold increase). The insoluble DU compound $DU\text{-}UO_2$ was similarly capable of transforming the immortalized HOS cell line to a neoplastic phenotype [35] Although nickel induced a 9.5 ± 0.9-fold increase in tumorigenic transformation, $DU\text{-}UO_2$ resulted in a 25.5 ± 2.8-fold increase. The studies conflicted on whether the chemical or radiological nature of DU accounted for the increased tumorigenesis.

Rats implanted with large DU squares manifested a significant increase in soft tissue sarcomas, including malignant fibrous histiocytomas, fibrosarcomas, and osteosarcomas.[36] A small, nonsignificant increase in soft tissue sarcomas was noted in rats containing small DU squares, whereas rats implanted with DU pellets demonstrated no increased tumor frequency. The tumors were directly associated with the implant locations, suggesting a lack of systemic carcinogenesis. These results suggested that DU fragments of sufficient size are locally carcinogenic in rats. However, care must be taken in extrapolating this data to humans.[37] The proliferative tissue reactions noted in this study are seen with many materials in rodents and may not occur in humans. Rats are susceptible to foreign body carcinogenesis, and in fact, the physical nature of the implant may be more important than the actual chemical composition in determining carcinogenesis.[38-41]

Multiple human studies on malignancy risks in uranium miners have been performed. To date, no evidence exists to suggest that any form of uranium is carcinogenic in humans.[26.42] The conclusion of the National Research Council Committee on the Biological Effects of Ionizing Radiation was that exposure to

radon and its progeny, as opposed to uranium, was the cause of lung cancer in these miners.[43] The National Academy of Sciences evaluation of uranium-related industries, including mill workers, enrichment workers, and laboratory workers concluded that there is "limited/suggestive evidence of no association between exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy."[44] Levels of 25 cGy are equivalent to environmental exposure in a dusty uranium workshop for 1 full year .[45] U.S. Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry concluded "no significant differences in cancer was found between workers who are occupationally exposed to uranium and control populations."[8]

No increased frequencies of lung cancer or leukemia have been noted in Gulf War veterans.[20.30.31.33] Although bone is a storage depot for uranium, no increase in bone cancer rates has been noted in cohort studies .[33] One member of the low-urinary uranium excretion group developed Hodgkin's disease 4 years after service in the Gulf War. This was felt to be unrelated to DU exposure, as Hodgkin's disease is not thought to have any major risk factors. An analysis of British Gulf War veterans demonstrated that there are fewer deaths attributable to malignancy in this cohort compared with a control group.[20]

A Chiefs of Military Medical Services in NATO investigation initiated after a report of increased frequencies of leukemia in Italian peacekeepers concluded that no causal relationship between DU and leukemia or other malignancy in Balkans veterans existed.[18.46] Upon analysis, the Italians confirmed 28 cases of malignancy among 39,450 veterans, which was fewer than the 53 cases statistically predicted. Of 17 cases of leukemia identified by The Netherlands Military Medical Service Agency, only 4 cases involved personnel deployed to the Balkans.

DU and Neuropsychiatric Effects

Although low-dose uranium does not penetrate the central nervous system, higher doses result in brain levels comparable to those found in the liver and bone.[24] Rats given high doses of oral or subcutaneous uranyl acetate developed tremors. Mouse studies have demonstrated neuropathies and motor end plate abnormalities associated with uranium exposure.[47] Although no behavioral changes were noted in mice with implanted DU seeds, hippocampal neurons demonstrated decreased excitability in the high-dose DU group at 6 months.[24]

Neurological effects, including cognitive impairment, have been reported in uranium workers excreting up to 200 µg/L uranium in their urine.[48] Only 10.3% of DU-exposed veterans in the Gulf War Veterans Affairs Medical Center cohort study reported nervous systems problems, as opposed to 52.4% of non-exposed veterans. A total of 24.1% of DU-exposed and 24.0% of non-DU-exposed veterans reported active psychiatric problems.[30] Neuropsychiatric studies of these veterans initially demonstrated a statistically significant relationship between elevated urinary uranium excretion and decline in performance efficiency.[30] At the 8-year follow-up, the relationship between elevated urinary uranium excretion and performance measures was no longer statistically significant.[33] Epidemiological and medical investigations of the Gulf War syndrome have failed to detect any relationship between DU and reported symptoms.[9]

Reproductive and Genotoxic Effects of DU

The placenta does not serve as a barrier to limit transfer of maternal uranium to the fetus.[49] In rats implanted with DU seeds, uranium levels in the placenta and whole fetus increased in a dose-dependent manner with increasing maternal dose. However, increasing uranium levels resulted neither in increased infertility nor in increased pregnancy loss rates. In utero exposure of gravid mice to uranium produced no embryo lethality. Fetal toxicity, including intrauterine growth retardation and developmental anomalies, was noted.[28.50.51] The most sensitive time for uranium-induced embryotoxicity was gestational day 10.[28]

Mouse studies investigating chronic exposure to naturally occurring uranium demonstrated a significant but nondose-related decline in male fertility. Testicular function was not affected by uranium at any concentration. It was speculated that behavioral changes may have accounted for the differences in fertility.[28.52] However, studies in male rats have suggested a direct gonadotoxic effect of DU. resulting in testicular atrophy and germ cell depletion.[28] DU implant studies demonstrated significant redistribution to the testicles as early as 1 day after implantation of seeds.[15]

Reproductive studies of the VAMC Gulf War cohort have demonstrated that semen characteristics, including physical parameters and motility. were not significantly different between the high- and low-urinary uranium excretion groups.[30] Within the exposed cohort, 50 veterans fathered 35 children since returning from service in the Gulf War, none of whom had congenital defects.[33]

DU and Environmental Impact Studies

At least 13 countries have performed environmental assessments in the Balkans, analyzing soil, air, water, vegetation, and food samples.[18] Environmental monitoring found small amounts of DU within 1 m of the munition impact sites. In most cases, detectable levels of DU were limited to the impact hole. An assessment of Red Cross and Red Crescent aid workers in Kosovo demonstrated 24-hour excreted urinary uranium levels of 3.5 to 26.9 ng/L.[53] No increased exposure to DU occurred in individuals residing in areas of DU munitions deployment who did not spend time in close proximity to targets such as destroyed vehicles. United Nations Environment Program conducted an analysis of 11 sites in Kosovo in 2000 with samples analyzed in five independent laboratories. No DU contamination of the water, milk, or buildings in Kosovo was discovered.[18.54] It has still been recommended that, despite the apparent low risks from DU, environmental monitoring be performed for assurance purposes in areas with high DU burdens.[26]

After the 1992 Amsterdam Boeing 747-258F crash, individuals reported a vast array of physical and mental health complaints, all of which were attributed to toxic substances released in the crash and subsequent fire.[21] The plane was known to contain 24 pieces of DU used as counterbalance weights with a total weight of 282 kg. After the accident, only 130 kg of DU was recovered. It was postulated that some, if not all, of the remain-ing DU might have been oxidized in the fire and dispersed throughout the environment. Risk assessments performed 6

years after the accident determined that it was improbable that DU was responsible for the various health complaints.

Conclusions

Despite nearly 50 years of accrued information on the health effects of natural uranium, concern still exists regarding its potential hazard as a radiotoxicant.[13.26] Reports linking DU to the Gulf War syndrome and leukemia in Balkans peacekeeping forces have been widely disseminated in the lay press. Although in vitro and rodent data suggest the potential for uranium-induced carcinogenesis, cohort studies assessing the health effects of natural and DU have failed to validate these findings in humans.[20,24.30.33-36] Recent reports have explicitly stated the lack of an association between DU and malignancy.[8-11] Even the Royal Society report, which suggested a small link between DU, stated that "except in extreme circumstances any extra risks of developing fatal cancers as a result of radiation from internal exposure to DU arising from battlefield conditions are likely to be so small that they would not be detectable above the general risk of dying from cancer over a normal lifetime."12

Whereas much of the fear surrounding DU has focused upon its radiation properties, its principal toxicological effects stem from its properties as a heavy metal.[8.11] Studies with natural uranium have demonstrated dose-dependent nephrotoxicity.[29] However, both animal studies and a continuing cohort study performed by the U.S. Army Department of Veterans Affairs has documented normal renal function despite markedly elevated urinary uranium excretion.[24.30.33]

Environmental sampling of the Balkans, where more than 10 tons of DU was employed during the military conflict, has demonstrated no evidence of residual contamination in soil. water, or milk.[18.54]

As such, although continued surveillance of exposed cohorts and environments (particularly water sources) is recommended, current data would support the position of the Armed Forces Radiobiology Research Institute that "DU is neither a radiological nor chemical threat."[6]

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