

Emerging Picture of Uranium's Health Risks

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Uranium, including depleted uranium (DU), is usually most dangerous to people when it gets inside the body, whether through ingestion, inhalation, or through breaks in the skin (though prolonged contact can also result in significant external radiation dose). Inside the body, uranium creates risks both as a toxic heavy metal and as a radioactive material. Additionally, there are some indications that synergisms might exist between these two types of health effects.

Current federal safe drinking water regulations limit the concentration of uranium in drinking water to 30 micrograms per liter ($\mu\text{g/L}$) based primarily on its chemical toxicity. For natural uranium, this limit translates into 20 picocuries per liter (pCi/L) of radioactivity from uranium. For depleted uranium, the drinking water limit translates into about 12 pCi/L of uranium activity. Federal regulations limit uranium inhalation based on cancer risk and limit drinking water intake based mainly on kidney toxicity.

Exposure to uranium in water is regulated for chemical toxicity largely because uranium is known to be nephrotoxic (toxic to the kidneys). The kidneys are responsible for controlling the composition of blood and eliminating wastes. Important uncertainties remain as to the level of sensitivity of human kidneys to depleted uranium. Animal studies have shown toxic thresholds that differ by more than an order of magnitude between experiments on rabbits (more sensitive) and rats (less sensitive).

The science surrounding uranium's effects on the body is rapidly expanding due in large part to the concerns that have arisen in the wake of the 1991 Gulf War, the 1999 NATO bombing campaign in the former Yugoslavia, and the gradual recognition of the many health problems that have come to be known as Gulf War Syndrome. We discuss below the *emerging* picture from this research.

Ionizing radiation risks

Ionizing radiation is a known carcinogen; as such, exposure to it increases the risk of a variety of cancer types. The current best understanding of low-dose radiation effects, and that which forms the basis of regulatory practice in the United States and Europe, is that every increment of radiation exposure produces an incremental increase in the risk of cancer. This is known as the linear no-threshold hypothesis.²

In general, the estimated risks per unit of exposure have increased with time as more is learned about the interaction of radiation with living tissue. As a result, the maximum permissible doses have been decreased. For example, in 1954 the AEC set the radiation limit at 15 rem per year.³ This was a significant reduction from the 0.1 roentgen *per day* limit that had been adopted in 1942 during the Manhattan Project. In 1959, the dose limit for the public was lowered to 0.5 rem per year and was then lowered again in 1990 to 0.1 rem per year.⁴

The *non-cancer* effects discussed below (other than kidney toxicity) are indicated by laboratory research, which is often done at elevated levels of exposure. These effects have not been definitively established for human beings in terms of quantitative health risks. Also, some of the experiments we cite were conducted with uranium directly injected into animals or with depleted uranium in metallic form embedded under the skin, which are pathways different than what would be expected from environmental exposures from the disposal of depleted uranium oxide. Also, it has not been established whether some non-cancer effects have thresholds, in contrast to the well-accepted no-threshold hypothesis for cancer risk of ionizing radiation.

An additional element of radiological protection that has evolved over time is the understanding of the relative risks to women and men. Currently, the overall risk to women of developing a fatal cancer from exposure to low-dose, low-LET (Linear Energy Transfer) radiation is estimated to be nearly 50 percent greater than that for men. Nearly 45 percent of the additional risk to women per unit of exposure is due to the significant radiosensitivity of the female breast.⁵ If cancer *incidence* is considered, irrespective of

¹ This article is based on the IEER report, *Costs and Risks of Management and Disposal of Depleted Uranium from the National Enrichment Facility Proposed to be Built in Lea County New Mexico by LES*, prepared for Nuclear Information and Resource Service (NIRS) and Public Citizen. Detailed references can be found in the report, which is available online at www.ieer.org/reports/du/LESrptfeb05.pdf.

² See National Council on Radiation Protection and Measurements. *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation*. NCRP report no. 136. Bethesda, MD: June 4, 2001.

³ For a summary of historical annual regulatory dose limits for workers in the U.S., see SDA vol. 9 no. 1, December 2000, on the web at www.ieer.org/sdfiles/vol_9/9-1/dosetbl.html.

⁴ U.S. Dept. of Energy, Office of Environmental Safety and Health. *Radiation protection of the public and the environment*. Order: DOE 5400.5, Washington, DC: February 8, 1990. Section II.1.a.

⁵ The overall cancer risk per person-Gray of exposure to women from low-dose, low-LET uniform irradiation is estimated to be 6.83×10^{-2} while the risk to men is 4.62×10^{-2} . The female breast has the second highest risk per unit of exposure of any individual organ listed for either men or women in this EPA guidance document and is higher than any individual

fatality, the comparison is grows slightly worse, with women having more than a 58 percent greater risk of developing some form of cancer from radiation exposure than men.

Current research on DU

The understanding of the risks of cancer due to radiation exposure from depleted uranium and of kidney damage due to its heavy metal properties has expanded greatly in recent years. In addition, evidence is amassing that raises serious concerns regarding the impact of chronic exposure to DU in relation to a number of other health issues. Studies in humans and animals have shown that uranium can concentrate to varying degrees in the skeleton, liver, kidneys, testes, and brain. In addition, rats implanted with DU pellets have shown uranium concentrating in the heart, lung tissue, ovaries, and lymph nodes among other tissues.

As noted above, some research has also provided indications that there may be a synergistic effect between the heavy metal aspect of exposure to uranium and its radioactive effects. Research on the hazards of the heavy metal cadmium indicated a potential synergistic response when exposures were combined with gamma radiation. Work on these kinds of combined exposures has shown that the direct damage to DNA from radiation exposure was likely combined with an inhibition of DNA repair by certain heavy metals. A double whammy, so to speak.

Research at the Armed Forces Radiobiology Research Institute (AFRRI) in Bethesda, Maryland has shown that depleted uranium can cause oxidative DNA damage and thus provides the first indication that uranium's radiological and chemical affects might potentially play both a tumor-initiating and a tumor-promoting role. We will discuss some of these potential aspects of depleted uranium's health effects that are emerging from a wide range of research.

Mutagenic and tumorigenic effects

Since the late 1990s there has been a growing body of evidence from *in vitro* and *in vivo* studies that indicates depleted uranium may be genotoxic, mutagenic, and tumorigenic. A significant amount of this work is currently being conducted at the AFRRI under the direction of Dr. Alexandra Miller.

Miller and her colleagues demonstrated for the first time that internalized depleted uranium could result in "a significant enhancement of urinary mutagenicity," a common biomarker of exposure to a genotoxic agent.⁶ They also demonstrated for the first time that exposure to DU can transform human cells into cells capable of producing cancerous tumors in mice with suppressed immune systems. They found that exposures to equal chemical concentrations of uranium with different isotopic composition caused "a specific activity dependent increase in neoplastic transformation frequency" which further suggested "that radiation can play a role in DU-induced biological effects *in vitro*."

Miller *et al.* also found in other experiments that DU was capable of inducing "oxidative DNA damage in the absence of significant radioactive decay." In light of their other work showing the potential for the radiological aspect of DU to contribute to genotoxic effects *in vitro*, they note that "it is tempting to speculate that DU might exhibit both a tumor 'initiation' and 'promotion' component." This potential dual role could result from, for example, the alpha particle radiation causing the cancerous mutation (tumor initiation) followed by a build up of oxidative damage from either or both the heavy metal and radiation properties of uranium aiding the spread of the cancer (tumor promotion), or vice versa.

The relative role of the radiological and chemical components of the genetic damage caused by the depleted uranium is a significant question given that DU is currently regulated for drinking water with a primary focus

Definitions

Cytotoxic: Toxic to cells.

Genomic instability: An increased tendency of DNA to not repair itself correctly, typical of cancer cells.

Genotoxic: Damaging to DNA.

In vitro: experiments conducted outside the body

In vivo: experiments conducted inside the body

Micronuclei: Chromosome fragments that are not incorporated into the nucleus at cell division.

Mutagenic: Causing or contributing to inheritable genetic mutations.

Neoplastic transformation: The conversion of normal cells into tumor cells.

Progeny: Offspring.

Tumorigenic: Tumor-causing.

organ risk for men. (Keith F. Eckerman, Richard W. Leggett, Christopher B. Nelson, Jerome S. Puskin, Allan C.B. Richardson. *Cancer Risk Coefficients for Environmental Exposure to Radionuclides: Radionuclide-Specific Lifetime Radiogenic Cancer Risk Coefficients for the U.S. Population, Based on Age-Dependent Intake, Dosimetry, and Risk Models*. Federal Guidance Report No. 13. EPA 402-R-99-001. Oak Ridge, TN: Oak Ridge National Laboratory; Washington, DC: Office of Radiation and Indoor Air, United States Environmental Protection Agency, September 1999.)

⁶ Unless otherwise stated, this and the rest of the research referenced in this section refers to a number of papers by Miller *et al.* published between 1998 and 2003. For full references, see pages 10-13 of the IEER report on which this article is based, *Costs and Risks of Management and Disposal of Depleted Uranium from the National Enrichment Facility Proposed to be Built in Lea County New Mexico by LES*, online at www.ieer.org/reports/du/LESrptfeb05.pdf.

on its chemical hazard with the implicit assumption that its radiation hazard can generally be treated as a secondary concern in the environment.

A final example of the work being conducted at the AFRRRI on these issues comes from a 2003 Miller *et al.* publication concerning the potential for DU to induce genomic instability in human cells. It is worth noting here that DU emits alpha particles during radioactive decay. In this work the authors initially note that:

Studies with DU in our laboratory demonstrated neoplastic transformation of human cells under conditions where approximately 14% of the DU-exposed cells were transformed even though less than 5% were traversed by an alpha particle. These findings suggest that factors other than direct or "targeted" damage to the DNA may be involved in the transformations. Chemical effects of DU and "non-targeted" effects of radiation may also play a role. Non-targeted effects can result in damage in cells not traversed by an alpha particle. The overall level of transformation observed may result from contributions by any or all of these factors.

In order to gauge the impact of radiation and heavy metal toxicity separately, the effects of depleted uranium were compared to that of nickel (Ni) and to gamma irradiation. From the results of their experiments, Miller *et al.* concluded:

In summary, we have presented data showing the production of genomic instability in the progeny of human cells exposed to DU. The findings demonstrate that DU can induce delayed cell death and genetic alterations in the form of micronuclei. Compared to gamma radiation or Ni, DU exposure resulted in a greater manifestation of genomic instability. Although animal studies are needed to address the effect of protracted DU exposure and genomic instability *in vivo*, results obtained from our *in vitro* system can play a significant role in determining risk estimates of DU exposure.

Effects on children and the embryo/fetus

Children as well as the embryo/fetus are likely to be at higher risk in relation to the mutagenic and carcinogenic nature of uranium. The International Commission on Radiological Protection (ICRP) notes that:

It is very well known that ionising radiation interferes to a high degree with cell proliferation. Therefore, biological systems with a high fraction of proliferating cells show high radiation responsiveness. High rates of cell proliferation are found throughout prenatal development. However, although cell proliferation is a key process for the development of radiation effects, the sensitivity of the embryo and fetus is also determined through processes of differentiation and cell migration, and the radiation effects on these biological processes.

...

Tissues such as brain, thyroid, bone, and breast appear to be more susceptible if exposed during normal periods of rapid growth (i.e. early childhood or puberty).⁷

Acknowledging these larger risks to children from radiation exposure, the 2002 supplement to the U.S. Environmental Protection Agency's Federal Guidance Report 13 introduced mortality and morbidity coefficients per becquerel of intake for various age groups including 0 to 5 years old. For the three uranium isotopes present in DU, the risk of developing a fatal cancer per unit of intake for a child under five is roughly six to eight times greater than the age-averaged risk currently used by the EPA for dietary and drinking water intake respectively.

Taken together, these considerations – increased risk per unit of intake combined with the unique exposure pathways for children to environmental contaminants such as DU, and the fact that uranium is known to be capable of crossing the placental barrier and concentrating in the embryo/fetus – make it plausible that far stricter requirements for the disposal of DU will need to be adopted in the event that uranium is concluded to be more carcinogenic than currently believed, and particularly if children's health is to be protected in that event.

Reproductive effects

Investigations of the reproductive effects of uranium exposure in animals were reported as far back as the 1940s, however, these early studies do not appear to have been systematically followed up on by other researchers in the United States until many decades later. Even today, there are substantial gaps in the understanding of uranium's effects on human and animal reproduction.

In the 1940s experiments, it was found that continuous feeding or even just a single one time feeding of uranium to rats could detrimentally affect the animal's reproductive success. The impact of continuous

⁷ International Commission on Radiological Protection. *Biological effects after prenatal irradiation (embryo and fetus)*. Annals of the ICRP, v. 33, no. 1-2. ICRP publication 90. Kidlington, Oxford; Tarrytown, NY: Pergamon, 2003.

feeding was significantly greater than that of the one time ingestion, but the authors noted their surprise at finding an impact on the rat's reproductive success even 9 months after a single exposure to uranium.⁸

Why these provocative early studies do not appear to have been carried forward or more widely reported is not clear. However, the work that has been done recently on uranium has expanded these early findings and has resulted in the identification of two distinct areas of concern in regard to the potential impact of uranium on reproductive health. The first area relates to the risks associated with exposures of men while the second relates to exposures of women.

Uranium is found to concentrate in the testes and has been found in the sperm of Gulf War veterans at elevated levels. While no epidemiological data yet demonstrates an impact on reproductive success from the veteran's exposure, the Royal Society (of Britain) noted that the concentration of DU in the testes was a potential concern given the possible synergistic effects between uranium's ability to damage DNA through both chemical oxidative stress and ionizing alpha radiation. In addition, the World Health Organization has noted the observation of "unspecified degenerative changes in the testes" of rats as a result of chronic ingestion of soluble uranium compounds.

Although still very limited, somewhat more work has been done on the reproductive effects of uranium exposure on females. Uranium has been shown to cross the placental barrier and concentrate in fetal tissue. Experiments with animals have demonstrated that exposure to uranium either through ingestion or injection can cause "[d]eferred fertility, embryo/fetal toxicity including teratogenicity, and reduced growth of the offspring." These findings have been demonstrated in both rats and mice, and provide evidence (at least at the levels of uranium ingestion examined) that uranium exposure can adversely affect the reproductive success of females. The one reported experiment to use depleted uranium did not find statistically significant effects on "maternal weight gain, food and water intake, time-to-pregnancy, or the percentage of litters carried to terms," however, higher numbers of implanted DU pellets were found to lead to increasing concentrations of uranium in the placenta and whole fetus of rodents.

While there are still many unknowns as to the effects of uranium on reproductive success, a number of potential radiological and non-radiological mechanisms have been proposed to help explain the effects that have been observed. These proposed mechanisms include hormonal or enzymatic disruption and behavioral changes. In addition, we have already noted the ICRP's conclusions regarding the greater general radiosensitivity of the developing embryo/fetus as well as of young children which may also play a potential role in DU's effects on reproductive success.

Neurotoxic effects

Limited evidence linking uranium to neurological damage dates back to at least the mid-1980's. While these early reports have a number of problems that have hampered their usefulness in drawing solid inferences regarding the neurological risks of depleted uranium, they provided an impetus for further research. Research that started in the 1990s began to raise new concerns about the potential toxic effects of DU on the brain. One of the major concerns connected to this recent work centers around the fact that uranium's primary chemical form in the body is the uranyl cation (UO_2^{2+}) which is a toxic heavy metal chemically analogous to the lead cation (Pb^{2+}) which has a well-documented and tragic history as a neurotoxin and is a particular concern in relation to children's health.

In 1999 Pellmar *et al.* at the AFRRRI showed that depleted uranium implanted in mice concentrated in various regions of the brain with higher concentrations at higher levels of exposures. From these results they concluded that "[t]he accumulation in brain, lymph nodes, and testicles suggest the potential for unanticipated physiological consequences of exposure to uranium through this route."⁹

In additional research, Pellmar *et al.* were able to further show that the "exposure to DU fragments caused neurophysiological changes in the hippocampus." The hippocampus was chosen for analysis because it is the region of the brain involved in memory and learning. Reviews of these AFRRRI experiments have concluded that their results provide important evidence of the potential for depleted uranium to display neurotoxic effects.

Other researchers have shown that following ingestion, uranium concentrated in the brains of mice and of rats. Some of the experiments in mice have shown effects on the brain with potential neurotoxicological importance at levels of uranium exposure that were not found to cause discernable damage to the kidneys.

⁸ References for this section can be found on pp. 13-14 of IEER's report on LES.

⁹ Unless otherwise indicated, references for this section can be found on pp. 14-16 of the IEER LES report.

A recent study found observable behavioral changes in rats after 2 weeks exposure to DU in drinking water.¹⁰

A specialized computer test designed to assess “performance efficiency” has been used to look for potential neurological effects in veterans who were exposed to depleted uranium munitions during the Gulf War. These tests, conducted at the Baltimore VA Medical Center, observed a statistically significant correlation between uranium concentration in the veteran’s urine and poorer performance on the computerized neurocognitive tests. However, no measurable effects were found in this same group using traditional neurocognitive tests. It is important to recall in this case that the soldiers were exposed as adults, and that these tests do not provide information on the impacts of uranium exposures during the more sensitive stages of early childhood when the brain is undergoing rapid growth and development or when the blood-brain barrier is not yet fully formed.

In addition to the potential for uranium to play a chemically neurotoxic role analogous to lead, radiation is also known to adversely affect the nervous system of the embryo/fetus. From a review of the Japanese atomic bomb survivor data, the ICRP, in the same publication referenced earlier, concluded:

There is a clear constellation of effects of prenatal irradiation on the developing central nervous system – mental retardation, decreased intelligence scores and school performance, and seizure disorders.

The ICRP elaborated further on why the prenatal period is of particular concern for radiation damage to the nervous system and why it is so important to consider in assessing risks:

Development of the central nervous system starts during the first weeks of embryonic development and continues through the early postnatal period. Thus development of the central nervous system occurs over a very long period, during which it is especially vulnerable. It has been found that the development of this system is very frequently disturbed by ionising radiation, so special emphasis has to be given to these biological processes.

Prenatal exposures to lead and mercury have also shown an indication that they are capable of doing neurological damage during this period of rapid development. However, the early years of childhood are generally considered to be the most critical time period for exposure to heavy metals given babies’ greater potential for environmental exposures. As with a number of other emerging risks discussed above, there is also the potential for synergisms between uranium’s chemical and radiological effects on the nervous system.

It is important to note that even relatively small changes in average IQ, spread over a large number of children, will “dramatically increase the proportion of children below any fixed level of concern, such as an IQ of 80, and decrease the proportion above any ‘gifted’ level, such as 120.” Thus the effect of neurotoxic agents, even at very low levels, on an exposed population as a whole can end up being quite significant even if the effect on an “average” or “typical” member of that population does not appear so.

Skeletal effects

As with the brain, the fetal period and other periods of rapid development (i.e. in early childhood and during puberty) are times of heightened sensitivity for the skeleton. In experiments on rats, it has been demonstrated that both acute and chronic intakes of uranium can cause damage to bones, and the Royal Society has recommended that, in light of the fact that uranium crosses the placental barrier, “the effects of maternal exposure to DU on skeletal development in the foetus may also need to be considered.” The World Health Organization and the National Research Council have also recommended studies to determine what effect, if any, uranium integrated into the bone has on the bone marrow and thus on the production of new blood cells. A new study that exposed dogs to daily doses of uranyl nitrate from a young age found that uranium accumulated in the marrow as much as in the bone, contrary to results obtained with single, acute doses.¹¹

Uranium: Radioactive lead?

There are clear indications that uranium toxicity for at least some effects, including its neurotoxic effects on fetuses and young children, might be better understood if uranium was considered to be analogous to a kind of radioactive lead, in which the damage from the alpha radiation occurs in conjunction with heavy metal induced damage to produce a variety of health problems at relatively low levels of exposure. This analogy between uranium and lead was made in 2003 by Lemerrier *et al.* in reporting their study demonstrating the

¹⁰ Wayne Briner and Jennifer Murray, “Effects of short-term and long-term depleted uranium exposure on open-field behavior and brain lipid oxidation in rats.” *Neurotoxicology and Teratology*, v. 27 (2005). pp. 135-144.

¹¹ Arrudo-Neto *et al.* “Long-term accumulation and microdistribution of uranium in the bone and marrow of beagle dog.” *Int. J. Radiat. Biol.*, vol. 80, no. 8 (2004), pp. 567-575.

concentration of uranium in the brain of rats.¹² While this way of thinking has obvious limitations in regards to understanding the detailed biological mechanisms involved in the damage caused by uranium as compared to lead, the ability of uranium to chemically induced oxidative stress, to cross the blood-brain barrier and alter electrical activity in parts of the higher brain, and to potentially interrupt neurotransmitters through chemical replacement of calcium in the interneuron gaps all in combination with the high levels of local cellular damage caused by alpha radiation raises significant warning signs about the potential impact of uranium on a child's developing brain.

In light of the uranium-lead analogy, it should be noted that despite evidence of lead's damaging effect on the brain dating back nearly two millennia and lead poisoning being first clinically recognized in children as early as the 1890's, it was not until 1979 that leaded gasoline was finally taken off the U.S. market after being widely sold for several decades. As with the general trend in radiation protection standards, the Centers for Disease Control (CDC) has chosen to lower the guideline it considers to be an indicator of "elevated" levels of lead in the blood of children four times since the late 1960s. The level today is one-sixth of where it stood 35 years ago. In addition, the CDC has adopted the position that there is no safe level of exposure to lead, and that any intake will thus result in some level of harm.

Unfortunately, despite significant reductions in exposure since 1979, the current levels of lead in children's blood are still roughly 100 to 1,000 times larger than the estimated pre-industrial levels, and as of the year 2000 the CDC estimated that nearly half a million children in the U.S. still exceeded their guideline for elevated levels of lead in the blood. Adding to these concerns, continuing research on the effects of lead shows that children's intellectual function is adversely affected by exposures roughly half of the CDC/WHO level of concern, further supporting the conclusion that there is likely no threshold for lead's damaging effects.

In addition to lead's neurotoxicity, recent research has also shown that both prenatal and postnatal exposure to lead is associated with retarded growth in animals and humans and that exposure to lead can also alter sex hormone production and delay puberty in rats. An epidemiological study published in 2003 has shown that even relatively low average levels of lead (roughly a third of the CDC/WHO level of concern) caused a measurable delay in puberty in African-American and Mexican-American girls, while no statistically significant delay in Caucasian girls was found. This effect on the girl's sexual development was attributed, at least in part, to potential "alterations in endocrine function." Many questions as to how lead caused the observed delay and whether or not the children had been exposed to higher levels in the past, before the study's screening began, remain unanswered. Nevertheless, the potential for uranium to play an analogous role in effecting hormonally-mediated processes in developing children could add further to its list of health concerns and add significant new avenues for potential synergisms with its other chemical and radiological health effects.

The lessons of lead's tragic history in relation to children's health – including the decades-long denial of the risks by industries producing lead-based products, as well as the systematic and progressive tightening of health guidelines specifically targeting children once the guidelines were finally introduced – should be closely examined in relation to the direction uranium research is now unfolding.

¹² Lemerrier, *et al.* "Study of uranium transfer across the blood-brain barrier." *Radiation protection dosimetry*, v. 105, nos. 1-4 (2003). pp. 243-245.