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Medical Effects of Internal Contamination with Uranium*Asaf Durakoviæ*

Department of Nuclear Medicine, Georgetown University School of Medicine, Washington D.C., USA

The purpose of this work is to present an outline of the metabolic pathways of uranium isotopes and compounds, medical consequences of uranium poisoning, and an evaluation of the therapeutic alternatives in uranium internal contamination. The chemical toxicity of uranium has been recognized for more than two centuries. Animal experiments and human studies are conclusive about metabolic adverse affects and nephro-toxicity of uranium compounds. Radiation toxicity of uranium isotopes has been recognized since the beginning of the nuclear era, with well documented evidence of reproductive and developmental toxicity, as well as mutagenic and carcinogenic consequences of uranium internal contamination. Natural uranium (^{238}U), an alpha emitter with a half-life of 4.5×10^9 years, is one of the primordial substances of the universe. It is found in the earth's crust, combined with ^{235}U and ^{234}U , alpha, beta, and gamma emitters with respective half-lives of 7.1×10^8 and 2.5×10^5 years. A special emphasis of this paper concerns depleted uranium. The legacy of radioactive waste, environmental and health hazards in the nuclear industry, and, more recently, the military use of depleted uranium in the tactical battlefield necessitates further insight into the toxicology of depleted uranium. The present controversy over the radiological and chemical toxicity of depleted uranium used in the Gulf War warrants further experimental and clinical investigations of its effects on the biosphere and human organisms.

Key words: actinides; carcinogens; dose-response relationship, Gulf War syndrome; mutagenesis; mutation; nuclear decay; radioactivity; radiobiology; uranium

General Concepts

Uranium, the ninety-second element of the periodic system, has 15 isotopes, with mass numbers 227 through 240. Two of these, ^{235}U and ^{238}U , are considered the primordial substances of the universe by their half lives of 7.1×10^8 and 4.49×10^9 years, respectively. The relative relationships of ^{235}U and ^{238}U are 0.72% and 99.27%, with the difference in abundance due to ^{234}U which exists in nature as one of the decay products of ^{238}U . When a uranium nucleus reaches a state of excitation in order to cross the fission barrier, it undergoes a process of nuclear fission, either by interaction with neutrons, electrons, photons, mesons, or charged particles such as deuterons and protons. If a nucleus penetrates through the fission barrier, it encounters a spontaneous fission. In either process a nucleus splits into predominantly two large particles of a similar size, with the emission of neutrons or, less commonly, alpha particles. Occasionally, the nucleus splits into three or more fragments of fast-excited nuclei with a kinetic energy of 70-100 MeV. These nuclei emit neutrons, beta particles, x-rays, or gamma rays and remain radioactive even after reaching their ground state. Uranium fission releases a total energy of ~ 200 Mev (1). Uranium may decay by spontaneous fission, whereas the induced fission is a more probable mode of decay for uranium isotopes. Inducing fission is a factor of utmost importance in reactor technology and its probability is related to reactor-induced cross sections for uranium isotopes (^{233}U , ^{235}U , ^{238}U) and thermal neutrons (2). The energy released in fission is the sum of all component energies of fragments, neutrons and photons of the fragments, and neutrons, electrons, photons, and antineutrinos emitted by the fragments. The usual two fragments per fission in a large number of events results in different mass distribution of fragments of uranium isotopes interacting with thermal fission or high energy neutrons. Fission neutrons emitted in the fission itself, deexcitation of the fragments, or in the process of radioactive decay are referred to as scission neutrons or delayed neutrons, respectively. The number of fission neutrons is determined

by the energy of incident neutrons (3).

Uranium is the fourth element in the actinide group ($Z=89-103$) and the first in the uranide group. It can be produced in a metallic form by various methods, including the reduction of uranium oxides, halides and thermal disintegration of uranium halides. The most common method, calcium or magnesium reduction of uranium metal from uranium ore, has been extensively studied and described in detail in numerous texts and references (4). Uranium is a dense metal. The physical properties of its three allotropic forms depend on microstructure, sample purity, and metallurgic origin. Uranium reacts with most non-metallic elements as a strong reducing agent. Pyrophoric properties of uranium have been extensively studied (5). It may spontaneously ignite at room temperature in air, oxygen, and water. At 200-400 °C, uranium may spontaneously ignite in a carbon dioxide or nitrogen atmosphere. Pyrophoricity is related to the heat produced in the micropores of the metal. The oxidation of uranium may result in explosion. The lower limit for explosion of uranium dust clouds is 55 mg/L. Aluminum and zirconium, mixed with uranium as a powder, may be both pyrophoric and explosive. Uranium compounds with more metallic elements have been extensively studied for their use as nuclear fuels. They include uranium hydride, fluorides (group IIIA), carbides, silicides (group IVA), nitrides, phosphides and arsenides (group VA), oxides, sulfides, selenides, and tellurides (group VIA), fluorides, chlorides, bromides and iodides (group VIIA), uranium salts (carbonates, phosphates, halides) with polyatomic anions of uranium, uranates, and peruranates. Uranium solutions are relatively stable in an inert atmosphere. The stability is dependent on the acid concentration and the chemical nature of the acid. Hydrochloric acid solutions increase in stability with increased acid concentration, whereas uranium ions are rather unstable in any concentration of perchloric or sulfuric acid (6).

Uranium ions form complexes with organic ligands such as ethylene diamine tetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTA), and hexaethylene diamine tetraacetic acid (HDTA) (7). These complexes are stable. The complexing properties of uranium in aqueous solutions are well known. Uranium in body fluids interacts with a wide range of complexing agents competing for uranium ions. Of particular importance is a complex of uranium and bicarbonate ions, which increases the solubility of uranium in serum. This compound is rather insoluble in water due to the complex ion formation between uranium and bicarbonates. This mechanism determines the transport of ultrafilterable uranium from the sites of contamination to the tissues and target organs (8). In blood, the uranium-bicarbonate complex establishes an equilibrium with non-filterable protein-bound uranyl ions, with 60% of uranium bicarbonate-formed and 40% protein-formed (9). In other studies, 74% of uranium in blood was present in the inorganic compartment of plasma, 32% was protein-formed, whereas 20% was associated with red blood cells (10). Uranyl salt complexes with bicarbonates are less stable than uranous salt complexes. Reduction of uranium in plasma is not probable, while the uranous salts can be reduced in the intracellular environment (11). Uranous (IV) retention sites are the bone and kidney, whereas uranyl (VI) ions accumulate in the liver and spleen prior to their redistribution in the renal and skeletal system. Sixty percent of intravenously administered uranium is excreted in urine within 3 days, with bone mineral phase being the principal site of retention. Each of the uranyl ions are complexed by two phosphate ions on the surface of bone crystals, with simultaneous release of two calcium ions. The uranous ion produces a toxic effect on the living cells by inhibiting the processes of metabolism of carbohydrates by the inhibition enzyme systems, particularly hexokinase at the sites of ATP surface-building through magnesium-hexokinase mechanism. The adsorption process results in the sixth glucose carbon atom interacting with a phosphate atom of ATP, with negatively charged glucose-6-phosphate re-entry inhibition through a negatively charged point of entry at the cell surface. A uranyl ion replacing a magnesium ion binds the ATP molecule to hexokinase. ATP-uranyl-hexokinase complex blocks the release of phosphate to glucose, inhibiting its first step of metabolic utilization with non-metabolized glucose in the extracellular environment (12). Several mechanisms have been studied for the purpose of reducing the effects of uranium contamination. These include: 1) adding phosphate or polyphosphate ions to the system; 2) adding complexing agents to remove uranium adsorbed on the phosphate groups; and 3) removing the uranium already incorporated in the target organs. Among the potential therapeutic agents, including bicarbonate, citrate, lactate, fumarate, and ion removal was best achieved by bicarbonate. It is likely due to the fact that most complexing agents are metabolized, leaving alkaline residue in the form of bicarbonate. The toxic effects of uranium on rats were reduced as late as 12 hours after uranium administration (13). The mortality rate of rats pretreated by bicarbonates 2-3 days prior to the administration of uranium was reduced from 80% to zero.

Other agents studied for the removal of uranium include hydroxyaspartate and citrate (14), catechol disulfonate (15), calcium salts of polyphosphates (16), and chelating agents. The polyphosphates, although reducing mortality rate of uranium poisoning, were associated with metabolic acidosis and hypocalcemia (16), rendering their use impractical in therapy of uranium poisoning. The effects of EDTA have been demonstrated as beneficial in the treatment of uranium poisoning, with a toxicity of 3.8 g/kg in rats (16). Single injections were less effective than multiple parenteral injection of Ca-EDTA prior to intraperitoneal injection of uranyl nitrate. Ca-EDTA did not reduce uranium retention after incorporation in the bone (17). Other chelating agents used in experimental rodents include diethylene triamine pentaacetic acid (DTPA), triethylene tetraamine hexaacetic acid (TTHA), diamino diethylether tetraacetic acid (DDETA), and ethylene diamine tetraacetic acid (EDTA), with greater effectiveness of DTPA compared to other chelating agents (18). Russian studies reported an increase of elimination of uranium in vivo with the use of diamino diethylthioether tetraacetic acid (DDETA) in rats (19). Other actinides whose impact may be a significant contamination of the biosphere include plutonium and transplutonium elements. While uranium toxicity has been studied for over a century, plutonium was postulated in theory as element 94 until 1941 when it was isolated by Glenn Seaborg and Edwin McMillan at the University of California at Berkeley. No element in the periodic system attracted as much attention and controversy as plutonium. Its original quantity of 0.5 mg in March of 1941, has reached tens of thousands of kilograms in today's world of strategic nuclear arsenal and plutonium reactors. Although the reference to plutonium as the most toxic substance known to man had been suggested (20), there is ample experimental evidence of its carcinogenic properties (21), particularly osteogenic sarcoma (22). Other actinides of importance in terms of their medical effects include americium produced by neutron capture from ^{239}Pu to form ^{241}Pu and ^{241}Am by separating the mass 241 fraction in a sample of plutonium. Its half-life of 458 years, monoenergetic alpha emissions of high energy ($E=5.44\text{-}5.49\text{ MeV}$) and monoenergetic gamma emission ($E=59.6\text{ KeV}$). The production of hundreds of kilograms per year present risks in internal contamination (23). Pulmonary, hepatic, and skeletal deposition of ^{241}Am place it next to plutonium in terms of the radiological hazards of actinides (24). Other actinides of interest include thorium (^{227}Th - ^{232}Th), with reference to its biological effects in the lung, liver, bone, and kidney (25). Other transplutonium elements of interest include curium (element 96), berkelium (element 97), californium (element 98), einsteinium and fermium (elements 99 and 100), mendelevium (element 101), and nobelium (element 102), with subsequent controversial elements of lawrencium, rutherfordium, hahnium, and future heavy and superheavy elements, being only of theoretical interest.

Historical Aspects

Early studies (Gmelin 1824) at the University of Tübingen on the biological effects of uranium indicated that uranium salts given by mouth present a hazard as a feeble poison, but facilitating death after intravenous injection. This work with pure uranium oxide prepared from pitchblende in the form of uranyl citrate, sulfide, and chloride was performed on experimental dogs and rabbits by oral and intravenous administration of uranium salts. The oral administration of uranium in the form of sulfate (300 mg) or nitrate (900 mg) did not demonstrate any immediate symptoms, whereas 4 g of uranyl nitrate produced emesis in dogs. Chloride salt given by a gastric tube (2 g) produced death in a rabbit in 52 hours. Pathomorphological examination showed diffuse gastric inflammatory changes with leukocyte extravasation. Intravenous administration of 600 mg of uranyl nitrate or 180 mg of chloride killed a dog within a minute, with autopsy findings of coagulated blood in the right ventricle and great vessels, as well as considerable pericardial effusion. Only 3 out of 18 metals reported in Gmelin's work produced similar findings: barium, palladium, and uranium (26).

Thirty years after Gmelin's work was first published, Leconte reported the unique effects of uranium in the form of acetate and nitrate on the uropoietic system. Uranium salts consistently produced anuria, oliguria, and glucosuria (27) in dogs, with a lethal dose of 0.6-1 g in rabbits (27). This work also confirmed Gmelin's findings of pathological changes in the stomach, heart, and great vessels, and postulated asphyxia as a leading cause of death. The interpretation of anuria was the impairment of renal circulation, and of glycosuria as an impairment of sugar metabolism due to hepatic alterations induced by uranium. Leconte's findings were instantly used in homeopathic medicine, with all attempts to provide a cure for diabetes mellitus in humans (28). Uranium was subsequently studied in humans suffering from diabetes and renal disorders (29). It was observed that polydipsia, polyuria, and glycosuria were reduced in >80% of cases after oral administration of uranyl nitrate. This use continued as late as 1930, with the last commercial preparation of vin urané for treatment of diabetes.

Commercial preparations of uranium were discontinued after more attention was focused on the associated renal pathology and considerable side effects, including dyspepsia, diarrhea, increased uric acid excretion, and weight gain. It was finally discontinued as a dangerous drug, contraindicated in diabetes.

Uranium toxicity was recognized early. This led to its wide use in experimental pathophysiology, mainly in producing experimental glomerulonephritis. Renal damage, both structural and functional, is confined to the terminal third of the proximal convoluted tubule, even after small doses of uranium salts, whereas glycosuria, initially considered a consequence of liver injury, was later thought to be of renal origin. This is also true for hematuria, albuminuria, hyaline and granular casts, azotemia, and tubular necrosis (30). Experimental work showed that parenteral administration of uranium causes extreme toxicity and some authors referred to it as the most toxic metal (31). It was also observed that uranium-damaged tubular epithelium demonstrates a remarkable rate of atypical tubular regeneration (32). The toxic effects of uranium were shown to be enhanced by the administration of calcium (33) or ephedrine (34), whereas the administration of adrenaline produced less severe toxic effects (35). Studies on uranium toxic effects on the renal system have been conducted since the mid-nineteenth century. For over 100 years, experimental models and pathoanatomy and clinical studies demonstrated the association of uranium poisoning and chronic Bright's disease, ranging from nephromegaly with tubular and glomerular alterations to the small granular kidneys, with the functional pattern of polyuria, albuminuria, tubular casts, glycosuria, oliguria, and terminal anuria (36). These studies provided conclusive evidence that uranium, as one of the toxic agents affecting renal tubules, was a major kidney poison in the category of tubular toxins, with action similar to mercury and chromium. Later studies demonstrated glomerular changes in uranium poisoning (37). This presented evidence that nephrotoxicity of uranium is not limited to the tubular system. Small doses of uranium caused glomerular injury, with coagulation necrosis glomerular and capsular edema, efferent vessels obstruction, and hyaline degeneration (38). Uranium-damaged tubular system had a rapid regeneration, with the appearance of large nuclei, meiotic activity, and replacement of the damaged cells, paralleled by proliferation of the connective tissue. Regeneration originated in the narrow part of the loop of Henle, terminal portion of the proximal convoluted tubule and upper position of the descending part of the loop. Regenerated epithelium was equally vulnerable to uranium poisoning as the original epithelium before the uranium injury (39). With larger and repeated doses of uranium exposure, renal tissue demonstrated resistance to uranium toxic effects (40). This resistance was associated with atypical cells of regenerated tubular epithelium (41). However, if the process of repair has not been completed and if damaged tubular epithelium was repaired by non-damaged tubular cells, there was no resistance to the subsequent uranium-induced poisoning. The exact mechanism of this resistance has not been totally clarified (42). Uranium-induced granular tubular obstruction and hyaline and granular casts do not appear to be a consequence of altered blood chemistry but seem to be uranium-specific (43). Regarding alternations of renal histomorphology, numerous studies have confirmed altered kidney function (44) and changes in the acidity and excretion of acetone, keton bodies, and organic acids, in animals (45) and workmen with occupational exposure to uranium (46). Other functional changes – increased urine specific gravity, initial increase and delayed decrease of chlorine excretion, and similar pattern of sodium and potassium excretion acidosis with altered urinary composition, have been well documented as consequences of uranium poisoning (47). The blood changes in uranium exposure have been well demonstrated. These include: 1) increased nitrogen retention (48); 2) a decrease of serum albumin (49) and largely unchanged serum proteins; and 3) increased serum ammonia creatinine, blood urea nitrogen, and uric acid. Sodium and chloride concentrations were lowered, calcium, potassium, phosphate and magnesium were not changed, whereas total lipids and cholesterol, as well as blood glucose, appear to be elevated in uranium poisoning (50). Uranium effects on the liver have been inconclusive, although fatty degeneration was consistently observed in experimental animals in chronic uranium poisoning with centrilobular necrosis, dilated and congested sinusoids and granular degeneration, described as an entity resembling hepatophoric disease (44). Biliary excretion in uranium poisoning does not seem altered, although uranium is excreted in bile (51). The effects of uranium on the nervous system have been described as paralysis of the hind legs, blindness, and loss of coordination in rabbits in the terminal phase of intoxication (52). The effects of uranium on the muscular tissue have been unremarkable, although in the heart perfusion studies uranium was reported to depress contractility when added as UNO₃ in the Ringer solution (53).

Chemical toxicity of uranium has been known for over 200 years and its radiation toxicity for over one century,

since the discovery of radioactivity in 1896. Special attention of basic and medical research was focused on uranium toxic properties during the Manhattan project. This was a turning point in the production and use of uranium in various physical and chemical forms in the military and industrial programs. Toxicological hazards of uranium have been classified in three groups of transportability: highly, moderately, and slightly transportable uranium. High transportability includes uranium compounds with a biological half-life of days, the moderate group has a biological half-life of weeks to months and the slightly transportable group has a biological half-life of months to years. Transportability is determined by the kinetic of uranium mobilization from the target organ to the extracellular fluid and the blood stream. Other classifications of uranium toxicity are based on the percent of ^{235}U in the uranium materials and their origin in reactor processing (54). Materials with >5-8% of ^{235}U are considered a serious nephrotoxic risk if it is in a highly transportable form, whereas the same isotopic ratio in a less transportable form would not present an equal hazard to the kidney or lungs. Some uranium materials with ^{235}U concentration less than 5-8% may present a significant risk of radiation exposure even as an external hazard. This is mainly due to the first and second decay products of ^{238}U , ^{234}Th and ^{234}Pa (UX, and UX2), which are potent beta emitters. In circumstances of high temperatures, such as in processing of molten uranium or during the impact of a missile, these isotopes may cause an external radiation risk to the personnel, whose exposure should be minimized by adequate protective clothing. The materials of >5-8% ^{235}U are of less concern as radiation hazards. Environmental monitoring is an essential prerequisite for the correct assessment of exposure risks, including air concentration, amount of uranium released in the biosphere and confinement of uranium materials to the area of incident, sampling of surface contamination, and personnel monitoring, including bioassays, in vivo monitoring, and target tissue analysis.

Exposure to the isotopes of uranium produces both chemical and toxic hazards to humans and have been studied extensively from the early data on uranium miners to the most recent controversy of depleted uranium in the Gulf War. Radioactive ore dust inhalation and its risk due to internal contamination with ^{238}U , ^{234}U , ^{230}Th and ^{226}Ra , have been well documented in the literature in studies from different parts of the world (55), with particular reference to the exposure to radon and radon daughters ^{213}Po , ^{214}Pb , and ^{214}Po , formed in radon decay processes in mines (56). Three major areas of uranium-related medical concerns are the responsibility of the US Uranium Registry, funded by the Department of Energy and operated by the Hanford Environmental Health Foundation. The uranium registry, which was established about 20 years ago, defined three major uranium-related areas of registry: 1) survey of uranium facilities; 2) survey of epidemiological studies; and 3) human internal deposition of uranium and its decay products (57).

The US Transuranium Registry (USTR) was another program established in 1968 as the National Plutonium Registry. It conducted studies on human biodistribution of actinides (58). Most recent studies indicate significantly higher prevalence of malignant diseases in uranium workers (59), with increased mutations in underground miners (60) and connective tissue disease, including lupus erythematosus (61). Reproductive toxicity of uranium in a recent Chinese study includes chromosome aberrations in spermatogonia, causing DNA alterations in the spermatocytes and strand breakage in sperm (62). This has implications in the current controversy of depleted uranium and Desert Storm Syndrome (63) and Al-Eskan disease (64) as related to depleted uranium ammunition and armor.

Metabolic Pathways of Uranium

Early observations from the beginning of the 19th century reported nephrotoxicity caused by uranium poisoning, with predominant changes described by necrosis in the proximal convoluted tubule and a moderate degree of inflammatory and fibrotic changes, resulting in scarred kidney (65). In cases of non lethal poisoning damaged tubular epithelium rapidly regenerated (66), with subsequent tolerance to large doses of uranium (67).

Regenerated epithelium was of a metaplastic histologic type, different from the normal epithelium, and the postulated tolerance mechanism was the inability of uranium compounds to interact with renal tubular cells (68). Toxic effects were also observed in the liver (69), central nervous system (70), and blood (71). The turning point, which brought uranium studies to the high level of scientific attention, was the advent of World War II. It resulted in the most comprehensive experimental investigation of any poison conducted in a relatively short time (72). This was carried out as part of the Manhattan Project. The Research Center at the University of Rochester was predominantly concerned with inhalational studies of uranium dust, whereas research projects at the University of Chicago studied uranium pathways and toxicology after ingestion or parenteral administration in various

animal models and on human volunteers (73). Animal studies were conducted after oral, intravenous, or intraperitoneal administration, application to the eye and the skin, and after inhalational exposure. There are three major routes of internal contamination with uranium: 1) gastrointestinal system; 2) skin and wounds; and 3) inhalation and transalveolar transfer to the blood stream.

Gastrointestinal Absorption

Gastrointestinal absorption of uranium isotopes is relatively low in the adult human organism but still presents a considerable biomedical hazard because of their long half-lives, nephrotoxicity, and retention in skeletal tissue. Whereas ^{234}U and ^{235}U have a high potential of inducing malignant alteration in the bone and hematopoietic tissues, the hazards of depleted uranium (DU) are predominantly its nephrotoxicity and its general metabolic toxicity (102). Its radiological hazards depend on its mechanism of entry and retention in the body.

The oral exposure pathways have been studied since the beginning of the 20th century. It was recognized that, although uranium predominantly enters the animal or human organism by the respiratory route, it may be swallowed, gaining entry to the gastrointestinal system (74). In one of the research studies nine uranium compounds were tested on rats, mice, rabbits, and dogs. Metabolic pathways were studied in various experimental designs, with studies of histopathology and mortality. Although death resulted at different time intervals, depending on the dose of uranium, animal sex, age, and dietary status, all experimental groups exhibited renal damage. Ingestion of uranium compounds resulted in a higher concentration in kidney and skeletal tissue if the animals were fed with soluble materials. In experiments on rats, it was found that a dietary content of 0.5% UO_2F_2 fed for 1-2 years resulted in a skeletal retention of 60 g/kg, while uranyl intake under similar experimental protocol, resulted in bone retention of 150-200 g/g of the bone mineral phase. These results are of an exceedingly significant importance in view of the radiological risk of uranium retention in bone, where the maximum permissible dose was considered 25 g/g of wet bone, which would deliver an approximate dose of 0.45 rem (<0.5 mSv)/24 hr. Since the studies were conducted on rodents with a short life span, these findings are of considerable interest in human toxicology in view of the longer turnover of nonexchangeable bone minerals. Actinide absorption is rather low in the gastrointestinal tract, being higher in young than in mature experimental animals and considerably lower in the form of insoluble oxides than of non soluble nitrates (75). This was consistent in all experimental species – mice, rats, guinea pigs, dogs, and pigs. Increased absorption was observed for uranium that was ingested with the food of animal origin, whereas its association with the plant diet also enhanced absorption in comparison with absorption in the form of solution. The absorption of uranium was also enhanced by fasting (76). Oral administration of uranium in humans has been studied for over 150 years. It was originally used in the treatment of diabetes mellitus (77). Then it was used as a metabolism-stimulating drug, administered in increasing doses from 30-60 mg to 1.8 g of uranyl nitrate in water (78). Uranium oral administration in humans was finally discontinued in 1936, when its toxicological risks were declared to outweigh any of the dubious and indefinite health benefits (79). Subsequent oral administration continued on uranium workers. They were given an oral dose of uranyl nitrate in water, their excretion pattern was studied, with findings of less than 1% of uranium absorbed and renal excretion of 66% of absorbed dose (80). The studies conducted on hospital patients included volunteers with no history of gastrointestinal or renal disease. Metabolic pathways of uranium were studied after oral administration of 10 mg of uranyl nitrate. Urinary and fecal contents were analyzed and urinary excretion was found to be in the range of 0.3-3.0% of the ingested dose, with about 30% of the absorbed uranium incorporated in the skeletal tissue and kidney. The distribution and retention of uranium in the internal body environment, particularly kidney and bone, appears similar in human and experimental animals. The gastrointestinal pathway of internal contamination of uranium results in adverse clinical symptoms, including diarrhea and vomiting, resulting in the low intestinal absorption (81). The gastrointestinal pathway presents the least adverse pathway of uranium poisoning.

Intravenous Administration

Animal experiments conducted over a span of 150 years demonstrated that small doses of several micrograms per kg of uranium compounds administered intravenously result in the urinary elimination of 60-80% within the first 24 hours. Uranous hexavalent salts, complexed with proteins, phosphates, citrates, or bicarbonates are filtered in the glomerular system, while a smaller amount of 10-20% is retained in the skeleton (82). In the metabolic studies on humans, blood, urine, and fecal samples and renal function tests were analyzed, the excretion curves indicated a rapid early elimination of 50% of hexavalent uranium, whereas 14-30% was

excreted slowly days after administration. Acute parenteral toxicity was studied in much larger doses in experimental animals with different uranium compounds. Uranium fluoride was found to be more toxic than nitrate or tetrachloride compounds, with the lethal dose of 2 g/kg. In human experiments conducted in Massachusetts General Hospital and Boston Veterans Administration Hospital by the Oak Ridge National Laboratory team, the patients receiving intravenous injections of uranium were suffering from terminal diseases of the central nervous system and almost all were in a coma at the time of injection. The dose of intravenous uranium ranged from 72-907 m/kg. The 24 hour excretion was an average of 56.2%, while fecal excretion was less than 0.03%. Most of the retained uranium was present in the kidney and bone with minimal retention in 21 other tissues and organs (83). The intravenous experimental use of uranium in humans has been used as a database for the evaluation of a variety of bone disorders. This is based on the verified ability of uranyl ion to form stable compounds with phosphate groups in bone crystals in both the exchangeable and the nonexchangeable phase (84).

Contamination through Skin and Wounds

Internal contamination through the wounds and DU entry into the systemic circulation was encountered in the Gulf War (1991). Although the soldiers with shrapnel wounds containing DU fragments have been identified, there is no current data regarding this patient population. However, studies on biomarkers of carcinogenesis demonstrated a significant up to 1,000-fold increase of uranium levels six months after uranium pellet implantation in rats. The alteration of the oncogene expression was found to be DU dose and time dependent. These results indicate that depleted uranium may be a critical contributing factor to the induction of malignant disease in humans. These results of DU-induced transformation to the tumorigenic cell phenotype at a rather low radiation dose (0.13 Gy) were indicative of both the chemical and radiotoxic properties of DU in cellular oncogenic expression (103).

Dermal exposure to soluble uranium compounds causes severe poisoning and death, with extensive experimental evidence of significant quantities of uranyl nitrate, fluoride, pentachloride, trioxide, sodium and ammonium diuranate in the bloodstream after absorption through the skin. Insoluble uranium oxides (UO₂, UO₄, U₃O₈) and uranium tetrafluoride (UF₄) do not appear a significant toxic risk when applied through the skin. There is a dramatic interspecies difference in the lethal effect of dermally applied uranium compounds, with decreasing susceptibility of rabbits, rats, guinea pigs, and mice. Toxicological manifestations of cutaneous contamination with uranium compounds included renal alterations, body weight loss and death, which are similar in all species tested. Repeated exposure to uranium compounds by dermal application results in tolerance to cumulative doses, which would produce a lethal effect if applied initially in a single dose.

Inhalation

The inhalation pathway of internal contamination with depleted uranium is the most important route of entry to the extracellular fluid via the bronchoalveolar tree. Inhaled DU particles are absorbed in the upper bronchial tree, and on the alveolar surface. If soluble, they gain access into systemic circulation.

Bronchoalveolar deposition of radioactive particles has been actively studied for decades (104). The radiation hazard of inhaled radioactive particles was studied with different actinides (105) and the general model of their metabolic behavior in the respiratory system was introduced in 1955 by the International Commission of Radiation Protection (ICRP), with recommendations of the parameters for studies of respiratory contamination pathways (106). The experimental model was later revised, with an emphasis on uranium, plutonium, and their fission products (107). According to this model, about 25% of the radioactive particles are deposited in the bronchial tree, 25% are immediately exhaled, whereas 50% are translocated to the nasopharynx and swallowed, with subsequent handling by the mechanisms of gastrointestinal absorption. The intestinal absorption of DU is negligible, placing the respiratory pathway in the category of major radiotoxicological hazard. One of the therapeutic aims in internal DU contamination should include the movement of the inhaled particles to the extrapulmonary pathways. The deposition of DU particles on the alveolar surfaces will result in their absorption, depending on their solubility, with approximately 10% of the particles retained in the lungs and reaching systemic circulation, and the remaining 15% ascending to the nasopharynx by expectoration and ending in the gastrointestinal tract. Soluble components of uranium absorbed from the pulmonary tree are deposited in the skeleton within a few weeks, with a biological half-life in the lungs of 120 days. A considerably longer pulmonary retention of 1,470 days is expected in the case of inhalation of uranium oxides. Fatal cases of uranium poisoning

by the respiratory route have been described in humans with nephrotoxic syndrome, including glomerular and tubular damage, azotemia, albuminuria, and tubular necrosis. Less soluble uranium compounds are not as readily absorbed in the respiratory system (108). The compartmental analysis, kinetics, and autopsy data have not been defined for either animal or human exposure to depleted uranium. Further understanding of the toxicity of DU will have to be addressed by animal studies and data of human exposure to depleted uranium. The airborne fraction of DU ranges from 0.9% to 70%, depending on penetration size, velocity, and target material (109). An impact of a 150 mm DU penetrator releases 2.4 kg of airborne DU. Half of the airborne DU particles sampled during the testing of 105 mm DU projectiles were in the respirable range. They reached the non-ciliated portion of the bronchial tree (110). In other studies, 70% of airborne DU particles upon impact were less than 7 μ m in size, thus considered respirable. An aerodynamic equivalent diameter (AED) of 10 μ m is considered non-respirable, 5 μ m being 25%, 3.5 μ m 50%, 2.5 μ m 75%, and 2.0 μ m 100% respirable (110). Larger particles of $>5 \mu$ m and very small particles of $<0.2 \mu$ m are not significant as inhalational hazards. Those particles in the respirable range may be retained in the lung, producing local radiation injury or deposited into the target organs after absorption in the blood stream. Retention is determined by the particle concentration, density, size, shape, and breathing pattern of the exposed person. Soluble compounds of DU have quick access to the blood stream and primarily exert a toxic effect on the kidney as a chemical rather than a radiological toxic agent. Insoluble compounds remain in the lungs, with a biological half-life of 120 days and present a radiation hazard by irradiating alveolar tissue. One study reported that 60% of insoluble uranium was retained in the lung tissue for 500 days (111). Uranium oxide is considered relatively insoluble, whereas uranium dioxide is moderately soluble. Although the bronchoalveolar pathway is the single most important point of entry of uranium in the internal environment of the human organism, there has been very few controlled exposures of man to uranium compounds by inhalation. The size of the dust particles in uranium mining or other dust concentration in the uranium industry were considered too large to reach the micro-bronchiolar and alveolar compartment of the human lung. It was assumed that these particles would be deposited in the nasopharyngeal region, where they could be swallowed and eliminated by the gastrointestinal tract (85). In uranium plants, sampling of the particle size indicated a probability of up to 99% of the dust being concentrated in the upper respiratory tract. An experiment, named "a miniature cyclone", simulated the distribution of uranium dust particles between the upper and lower respiratory pathways. The urinary excretion after single exposure inhalation shows the half-time of the rapid decrease of about 7 hours. The half-time for the slower decrease is about 100 hours. The average uranium particle size in the respirable dust was much larger than the size of a UO₃ aerosol particle. Since over 85% of UO₃ in the micro-bronchial and alveolar tree is in the form of UO₃, which is excreted by the kidney, it has been postulated that uranium is mobilized from the lungs into systemic circulation, over 60% ending in the bone and kidney and 40% excreted in urine (86). The industrial exposure to uranium dust involves particles that vary in size and uniformity. Postmortem studies on uranium workers provided a basis of differentiation between inhaled soluble uranium in bone and insoluble uranium in the tracheobronchial tree. Uranium oxide retained in bronchoalveolar tree was studied for its dissolution kinetics by the alveolar macrophages (87). Radiation and chemical toxicity in the respiratory (contamination) pathway involving radiation toxicity has been known for several decades; the respiratory pathway involving chemical toxicity has been known for two centuries. Recent evidence of a high incidence of systemic sclerosis in the lungs of German uranium miners further confirms the significance of the respiratory pathway of contamination (88). The most recent reports confirm the association between the uranium mining environment and squamous cell carcinoma (89). This factor necessitates reconsideration of the ratio between genetic and environmental cancer.

Depleted Uranium

Depleted uranium is natural uranium in which ²³⁵U isotopic content is reduced from 0.7% to 0.2%. The enrichment process which allows the use of uranium in power reactors and nuclear weapons results in a by-product, partially depleted ²³⁵U to about one third of its original content in natural uranium. Uranium is present in the environment in low concentrations in all parts of the world, the most abundant deposits being in sedimentary rocks. The main areas of the world with rich uranium deposits are the Colorado plateau in Wyoming in the United States, Blind River and Beaver Lodge districts in Canada, the Erz Mountains in central Europe, the Ural Mountains in Russia, the Rand Mountains in South Africa, the French Alps, Radium Hill in Australia and the Pirinean Mountain range in Spain. Open pit mining has been the preferred way of uranium production, but some

deposits are too deep for this type of mining because it necessitates deep underground mining. The range of uranium content of the most ores is between 0.1-1.0% of U₃O₈. However, much higher grades are frequently found, presenting higher radiation hazards to miners from beta radiation from the ore and inhalation of uranium dust suspended in the air of the mining environment. Uranium toxic effects after inhalation largely depend on the size of respirable particles. It is the portion of inhaled dust deposited in the non-ciliated portion of the lung. Particles of 10 μ m in size are not respirable, while particles of 2 μ m have almost complete access in the alveolar compartment. Commonly encountered aerosols associated with uranium oxide are much larger in AED than the sand in the Arabian desert, and over 80% are deposited in the alveolar portion of the lungs, 10% in the thoracic lymph nodes, whereas the rest is deposited in the upper respiratory tree. This illustrates the significance of the respiratory port of entry in the Gulf War. Studies of the Persian Gulf Syndrome and Al-Eskan disease points to the small size (<1 μ m) and uniformity of fine dust particles in the Arabian desert as a contributing factor in the Desert Storm Illness.

Radiation estimates from uranium mines in Japan, Australia, France, Spain, and Mexico are in a range of 0.02 to 4.0 mrem per hour, although in the areas of rich deposits gamma radiation may reach 20 mrem/hr (94). The primary radiation risks to the lung tissue in uranium mines are from Radon-222 and its daughters ²¹⁸Po, ²¹⁴Pb, and ²¹⁴Po (95). Depleted uranium, a by-product of the enrichment of natural uranium, presents an internal hazard by its parenteral entry in extracellular fluid and ultimately by its incorporation in the uranium target organs, i.e., the skeletal tissue for the uranyl salts (VI) and the kidney for uranous compounds (IV). While less soluble compounds of uranium primarily cause long-term deposition risk in the bone, soluble uranium compounds are predominantly nephrotoxic in the proximal convoluted tubules (96) (Table 1).

Table 1: Isotopic composition of natural, enriched, and depleted uranium. [[view this table](#)]

The enrichment process increase the percent of fissionable fuel in the reactor core, leaving the residual depleted uranium with reduced content of ²³⁵U and ²³⁴U, which is not a fissible material. The chemical and metallic properties of depleted uranium (DU) are largely identical with natural uranium ore of uranium oxides. Natural uranium has a specific activity of 6.77×10^{-7} A/g, whereas depleted uranium has a specific activity of 3.6×10^{-7} A/g of uranium material. The isotopic content of ²³⁸U in natural uranium is 99.27%; ²³⁵U is 0.72 percent, and ²³⁴U is 0.006%. The isotopic composition of enriched uranium is ²³⁸U=97.01%, ²³⁵U=2.96% and ²³⁴U=0.03%. DU contains ²³⁸U=99.75%, ²³⁵U=0.25% and ²³⁴U=0.005%. All three isotopes decay in a cascade of daughter products. However, most of the decay products of ²³⁸U are removed in the gaseous diffusion process (97). Radon is unlikely to be a contamination risk for personnel exposed to the impact of DU penetrators, although it is a component of ²³⁸U decay (98) (Table 2).

Table 2: Decay scheme of U-238a. [[view this table](#)]

The high density of DU (19 g/cm³) makes it a superior armor-penetrating material (99). In the US Air Force DU is alloyed with 0.75% titanium. The US Navy has used the alloy of 2% of molybdenum, whereas the Army has used an alloy (QUAD), containing 0.5% titanium, 0.75% molybdenum, 0.75% zirconium, and 0.75% niobium. DU metal does not differ from natural uranium in its chemical properties and internal contamination with DU poses the same chemical toxic hazard as natural uranium. It oxidizes at room temperature as well as in water vapor, which necessitates the use of aluminum protective coating (100).

The US Nuclear Regulatory Commission classifies DU as a source material, governed by general and specific licenses. General license governs the use and transfer of DU in the amount of a maximum of 15 pounds at a given time and a maximum of 150 pounds in a calendar year. The specific license applies to larger quantities of DU. The licensing requirements include written documentation of the intended use of DU equipment, environment and health and safety compliance as well as the training of personnel (101).

Medical concerns of internal contamination with DU are similar to the metabolic pathways, chemical and radiation toxicology of natural uranium. The radiation effects of internally deposited DU depend on the quantity,

particle size, solubility, portal of entry, and physiological pathways that determine its metabolic fate. High organo-specificity of DU may result in radiation and chemical damage to the target organs, namely the kidney and bone, with its excretion determined by the biological half-life and kinetics of elimination from the contaminated organism. Since DU is an osteotrophic radioactive material, its incorporation in the crystals of non-exchangeable bone will result in long biological retention. This results in a high probability of malignant alterations of the radiosensitive components of target organs, due to its long physical half-life and particulate radiations (alpha and beta).

Alpha radiation from DU is not a significant external hazard because of its short range and low specific radioactivity of ^{238}U . However, beta radiation is the predominant component of the DU penetrator, with the most energetic particle of 2.29 MeV (^{234}Pa) and maximum range of 0.5 cm in aluminum. Approximately 91% of beta particles are from ^{234}Pa and 8% from ^{234}Th . Both are effectively shielded by the metallic component of the DU round, without any significant Bremsstrahlung component. Gamma rays are the main type of radiation in the completed round, with photon energies of 700 KeV to 1 MeV. The surface of a bare 120 mm DU ($1\text{R}=2.58\times 10^{-4}\text{ LC/kg}$) penetrator produces a beta exposure of $217\pm 20.4\text{ mR/hr}$, and a gamma exposure of $26\pm 2.7\text{ mR/hr}$. The surface of an unshielded DU metal produced an exposure of 225 mR/hr, only 1% from gamma radiation. A bare phalanx penetrator produces a beta exposure of 52.2 mR/hr and gamma exposure of 2.5 mR/hr (112). These exposure rates are similar to natural uranium. Although x-rays and gamma rays are always detectable in the immediate environment of DU ammunition, it is less than ten times background levels and does not constitute an external hazard. The primary DU hazard is from internal contamination.

The impact of a depleted uranium penetrator exposes the attending personnel to a radiation hazard which exceeds the maximum permissible dose, with an average aerosol concentration after impact of a 120 mm round exceeding $47\times 10^{-8}\text{ Ci/mL}$ ($1\text{ Ci}=3.7\times 10^{10}\text{ Bq}$) two minutes after firing (112). Because of radiation hazards, the NRC regulatory limits determine the maximum permissible air concentration of $7\times 10^{-11}\text{ Ci/mL}$ for soluble DU and $1\times 10^{-10}\text{ Ci/mL}$ for insoluble DU in order not to exceed 15 rem in the lungs and kidneys during a working life of 50 years (101).

Depleted uranium penetrators do not present a significant chemical hazard in the solid metallic form. However, they may present significant risk of heavy metal poisoning, by their nephrotoxic action after reaching circulation from the respiratory portal of entry, if the particles are of a respirable size. Threshold limits values (TLV) for the chemical toxicity of DU have been determined by the Occupational Safety and Health Administration (OSHA) and range from 0.25 mg/cm³ for insoluble and 0.05 mg/cm³ for soluble depleted uranium. However, the airborne concentrations of 69-1664 mg/cm³ detected in the vicinity of the DU penetrator testing sites have been extremely above the TLV limits. It has been recommended that range controls should be implemented to ensure safe radiological conditions at the timing ranges. The special emphasis on personal control includes personnel dosimetry, respiratory protection, protective clothing, standard operation procedures and record keeping. All persons involved in the military use of DU should be radiologically monitored with TLD dosimeters for the skin and total body exposure, while bioassay (urine) and pulmonary monitoring should be routinely performed. All personnel dealing with DU should receive annual radiation safety training on DU hazards. Environmental samples of water and soil, swipe, and air analysis for alpha and beta radiation and waste disposal should be analyzed by health physicists, with accurate documentation. These measures should be observed by both the civilian and military when using depleted uranium.

Chemical and Radiation Toxicity

Medical concerns regarding exposure to uranium can be traced to European silver mines, mainly those in the Erz Mountains, Schneeberg and Joachimstall (Jachmov, now in Germany). Long before the discovery of radioactivity in 1896, it was observed for over five centuries that mine workers were dying of "black lung disease". Medical studies of this century reported a 50% incidence of lung cancer in these areas (113). The current radiation hazards on those sites is estimated at about $2.9\times 10^{-9}\text{ Ci}$. The earlier estimated hazard was higher, in the range of $1.5\times 10^{-8}\text{ Ci}$. Canadian data on uranium miners in Newfoundland reported that 51 out of 142 cancer deaths were due to lung cancer in workers who spent 2,000 hours in the underground mines. Uranium was the only oncological hazard identified in that study (114). The United States studies on biological effects of uranium exposure in Colorado mines reported that of 4,146 miners 509 died during the eighteen year observation period, with an expected 386 deaths in that population (115). The deaths were caused predominantly by lung cancer

and renal disease. Similar findings have been reported from different parts of the world, such as the recent studies of reproductive toxicity in Chinese uranium workers (62), silicosis and lung cancer incidence in New Mexico (116), recent German studies on uranium miners describing changes of immune system (88), and alterations of chromosomal and endocrine alterations in Namibian miners (117). All studies are in general agreement regarding the toxic properties of uranium compounds for the human population.

Chemical Toxicity

Uranium heavy metal toxicity has been extensively studied for two centuries. The main parameter in the assessment of its toxic effect were mortality studies and LD50 at different quantities in a single dose or as a function of time. Other parameters extensively studied include survival time, the effects on the life span, growth and development, excretion of uranium in the urine, deposition in tissues and organs and general and local health effects. During the Manhattan Project, acute toxicity studies were conducted at different National Centers in the United States, with the most intensive investigation done at the University of Rochester with a rat model, mainly with uranyl nitrate, uranyl fluoride, and uranyl tetrachloride given parenterally.

Further preparation of UF₆ by oxidation or fluoridation provides the basis of combination between UF₆ and the metal fluorides. Uranyl fluoride was found to be more toxic than uranyl nitrate or uranium tetrachloride, with a lethal dose of uranyl nitrate being 2 mg/kg by subcutaneous or 0.4 mg/kg by intravenous injection. Oral toxicity of insoluble UO₂, U₃O₈, and UF₄ was found to be non-toxic in rats, while six other soluble components were of a considerable toxicity. Uranyl nitrate had a more dramatic effect on the mature than on the newborn rats. The main chemical toxicity was observed in the proximal convoluted tubule of the kidney. Experiments on dogs with oral administration of 0.2 mg/kg of soluble UO₂F₂ to 10 mg/g of insoluble UO₂, as well as uranyl nitrate at 0.2 g/kg and 0.05 g/kg of uranium tetrachloride, demonstrated renal cortical tubular changes with very little evidence of necrosis. Renal pathology was a common finding with several chemical compounds of uranium tested parenterally.

Percutaneous application of uranium was studied with soluble compounds including uranyl nitrate fluoride, pentachloride, trioxide, sodium, and americium diuranate. All of the tested components were absorbed through the skin into the blood stream and in excessive amounts were able to produce severe poisoning and death. In contrast, insoluble uranium compounds, such as oxides and tetra fluoride, did not cause significant poisoning when applied to the skin. There is a considerable species difference in susceptibility to dermal toxicity of uranium compounds. Rabbits are the most sensitive followed by rats, guinea pigs and mice. There is up to one hundred-fold difference of LD50 between rabbits and mice. The main poisoning site was the kidney, with similar changes seen in other types of parenteral toxicity.

Uranium application to the eye has been studied as a possible port of uranium entry in the internal environment of the living organism because of the hazards of ophthalmic exposure to uranium workers. Application of uranium compounds in the conjunctival sac in rabbits, guinea pigs, and rats included uranium peroxide, dioxide, tetra fluoride, nitrate, fluoride, and sodium and ammonium diuranate. Local damage occurred in animals, ranging from conjunctivitis to corneal ulceration. Of all tested compounds, the most severe reactions were encountered with dry uranium penta- chloride. Necrosis of periorbital tissue occurred followed by death in 50% of animals. Uranyl nitrate, fluoride, and Na-diuranate were absorbed from the conjunctiva and caused systemic poisoning. Uranium tetrafluoride and diuranate caused systemic poisoning with very little local irritation.

Chemical poisoning with uranium compounds after respiratory exposure has been studied extensively in order to establish safety standards for the control of health hazards related to uranium dust. Experimental studies of the respiratory aspects of heavy metal poisoning have been performed with various experimental designs (118). Eleven uranium compounds studied in elaborate experimental designs, from the Manhattan project to recent reports, suggest that soluble uranium compounds are definitely toxic with frequent fatal (0.2 m/m³) outcomes, mainly because of the lung and renal damage. The less soluble dusts such as UF₄ and high grade ore produce little renal damage, at the 2.5 mg/m³ level. Tritaoxide (U₃O₈) produced no systemic effect. Toxicity, mortality, and renal damage vary greatly between different species. Chronic toxicity studies on dogs, rats, rabbits, mice, and guinea pigs using uranyl nitrate hexahydrate, hexafluoride, tetrachloride dioxide, and tetrafluoride, revealed no significant abnormalities in the experimental design of a low concentration of compounds given for a year. Two years of exposure revealed chronic renal injury. In the five years of follow-up studies there was evidence of malignant tumors in the lungs, including adenomas and adenocarcinomas (119), mostly reported in the chronic

studies on dogs and monkeys.

Radiation Toxicity of Uranium

Natural uranium contains 99.28% of ^{238}U , 0.72% of ^{235}U and 0.006% of ^{234}U . Uranium-238 decays into thorium (^{234}Th), which further decays to protactinium (^{234}Pa), followed by uranium-234. Physical half-lives of ^{238}U is 4.5×10^9 , $^{235}\text{U} = 7.1 \times 10^8$ and $^{234}\text{U} = 2.5 \times 10^5$ years. Uranium isotopes and their decay products are alpha, beta, and gamma emitters, with spontaneous fission below the level of criticality. Alpha emitting radon (^{222}Rn), a decay product of ^{238}U , presents a considerable inhalation hazard in uranium mines. Uranium ore (U_3O_8) is obtained from the mines, concentrated, and processed to americium diuranate, which is fluorinated and, when enriched, may be used for fuel in power reactors and nuclear weapons. The by-product of the enrichment process is depleted uranium. All steps in the mining and processing of uranium isotopes may be associated with radiation hazards and internal contamination.

In the decay process of ^{238}U , its daughter products ^{234}Th and ^{234}Pa reach secular equilibrium with their parent isotope in approximately 6 months, decaying at the same rate as ^{238}U . They emit alpha and beta particles and gamma rays. Gamma radiation interacts with the internal environment of the organism by Compton and photoelectric reactions, which may pass through layers of several hundred cells, producing radiation-induced tissue alterations. The beta particles of protactinium-234 ($E = 2.29 \text{ MeV}$) have potent ionizing radiation. They can pass through several hundred cells. Alpha particles, although of a short range, present high radiation risk because of their mass, positive charge, and powerful ionization capacity. The alpha particles may present a considerable genetic or carcinogenic risk when incorporated in the vicinity of non-differentiated, highly radiosensitive cells, such as the pluripotent stem cell. All three modes of decay present a biological risk in internal contamination, mainly when inhaled or entering the body through damaged skin or missile fragment wounds.

Radiation interactions of uranium decay products interact with the internal environment of the organism by direct ionization as charged particles and by indirect interaction as electromagnetic radiation, with a transfer of energy in the tissue by both ionization and excitation, as well as the formation of free radicals. Structural changes in the molecules include hydrogen bond breakage, molecular disintegration and molecular cross linking. Structural alterations of the molecular integrity lead to functional changes with consequent metabolic changes, which may alter genetic transcription and translation of the macromolecular codes in both DNA and RNA. This happens mainly in the nucleus, the main target of lethal effects of ionizing radiation. According to the target hypothesis, several alpha particles delivering a dose of 25 cGy may kill the cell if delivered to the nucleus, whereas a dose of alpha radiation would have to be 2-4 thousand times higher to kill the cell if delivered to cytoplasm. Whereas a single radiation exposure may result in a repair mechanism in 97% of DNA, the constant exposure by the internally deposited alpha emitters may result in chromosome aberrations, resulting in mutations or malignant alterations.

Radiation-induced alterations by uranium compounds are well documented. Lung cancer in uranium miners has been linked with internal contamination with uranium decay products (120). Animal data on the radiotoxicology of uranium compounds has been used to simulate environmental exposure of the general human population. Beagle dog was used as an appropriate model from which extrapolation with reference to uranium in the internal organs of humans can be studied (121). Synergistic effects of inhaled uranium and cigarette smoking has been reported (122).

The relationship between enriched uranyl fluoride and DNA damage in the spermiogenic stages of mice was studied for the UO_2F_2 doses of 6 mg/kg administered parenterally (123). Mitotic damage was found. Ovarian genetic toxicity of uranyl nitrate has been recently reported to have potential teratogenic effects in the fetal stages of mice (124). Carcinogenic effects of ionizing radiation were recently reported in a study of increased non-melanoma skin cancer among uranium miners (125). Bronchopulmonary precancerous conditions have recently been reported in a German study of uranium workers, implying that uranium is one of the occupational carcinogenic agents (126).

Cancer susceptibility of uranium-exposed human population, assessed by genetic polymorphism and host-reactivation assays in a mutator phenotype, indicates that uranium may be one of the mutagens causing abnormal DNA repair (127). These studies emphasize the need for further epidemiological studies to better understand the radiation risks of cancer incidence in the nuclear industry, specifically in uranium mining (128).

Radiation protection criteria have been established to limit personal and population exposure to uranium, in reference to quarterly and annual dose to the radiation worker. Principles of radiation protection include both the cumulative lifetime exposure and averages for quarterly and annual limits, usually expressed in Ci (Sv)/yr. The tolerance dose rate of 0.05 rem/24 h, corresponding to uranium retention of 24 g/g of tissue, depends on the multiple static and dynamic parameters, leading to wide fluctuations of dose limits. The aim of radiological protection is to control and limit delayed radiotoxicological effects of uranium radiotoxicological effects of uranium such as necrosis of the tissue, life shortening, altered homeostasis, and cancer. Although the individual exposures are frequently low, the corpuscular radiation organ-specificity and long physical and biological half-life render uranium a radiological hazard with no threshold effects in the internal environment of the contaminated organism. In spite of the extensive literature on maximum permissible levels, protection criteria, occupational standards, and elaborate methods of setting limits when radiological toxicity is the critical end point, uranium is still an inadequately understood chemical and radiological hazard to the biosphere and human organism, with increasing relevance to the human population in its less strictly controlled use in modern industry and, recently, in modern warfare.

The association of depleted uranium with human mutagenesis, carcinogenesis, and diseases of the immune system has been postulated in the environmental measurements of radioactivity at the DU testing ranges in the United States. Whereas the surface contamination levels are strictly regulated for the decommissioning of the facilities for unrestricted use, with a maximum permissible level of 35 pCi/g, the surface contamination levels found after the testing of DU penetrators routinely exceeded the maximum permissible dose of soil contamination. The radiation toxicity of DU has to be considered an inherent aspect of DU exposure risks. The most conservative MPC for DU of 7×10^{-11} Ci/mL air was not exceeded in the controlled environment of DU firing ranges. Compliance with decontamination criteria is a time-consuming and costly operation. Decontamination of a DU penetrator manufacturing facility requires 40 thousand man hours and costs about US\$ 4 million (129). The weight of the average DU penetrator in one study (129) of 60-75 g of DU produced activity of 8.6×10^{-9} Ci/mL of air. However, other examples demonstrate a noncompliance with radioactivity limits, such as the National Lead Industry Plant, Colonie, New York, which exceeded by 150 Ci the New Yorks state radioactivity limits for the release of DU in a month. 150 Ci corresponds to 387 g of DU metal, which compares with 272 g of DU in a single 30 mm common round (130). The size of a respirable DU particle (uranium dioxide) is 10 μ m in diameter. It was estimated that in the Gulf War 300 metric tons of DU were deposited in the battlefield. Three to six million grams of DU aerosol particles would become airborne even if 1-2% of this DU burned up. Radioactivity as a result of the decay progeny of ^{238}U poses a radiation hazard of inhalation. One milligram of DU generates over a billion alpha and beta particles per year, which, together with gamma emitted radionuclides of ^{238}U progeny (^{234}Th , ^{234}Pa), causes internal radiation hazards.

The reality of the legacy of DU waste and its use in the recent tactical warfare warrants detailed studies regarding its effect on the biosphere and the human population.

Treatment of Uranium Contamination

The principal aim in the therapeutic management of patients with internally deposited uranium is to prevent the absorption from the site of entry and eliminate uranium from the blood stream or target organs. Regardless of the therapeutic alternatives planned, it is of utmost importance to initiate therapy soon after exposure. It should consist of the prevention and reduction of uranium absorption from the portal of entry, treatment with agents which eliminate uranium compounds from the sites of their initial deposition, and therapy that facilitates their excretion via the gastrointestinal system, renal pathway, or respiratory tract. Finally, medical intervention in uranium internal contamination includes the use of chemical agents that bind inorganic ions to non-ionized complexes and facilitate their urinary excretion when they are present in soluble form.

Although the gastrointestinal absorption of uranium is low, it is of utmost importance to reduce its entry in the systemic circulation and its deposition in the target organs.

There are various methods of decreasing the intestinal absorption of uranium and actinides and facilitating their elimination. They include the use of emetics, gastric lavage, ionic exchange agents, antacids which contain aluminum salts, barium sulfate, sodium fitate, and salts of glucoric and manuronic acid.

The method of gastric lavage is very useful in therapy or early exposure by ingestion. It is accomplished by the placement of a nasogastric tube in the stomach and washing it several times with water or physiological saline by

negative pressure, until the aspirate is declared free of the contaminant. These procedures require proper medical skills in order to achieve total washout of the gastric contents and prevent aspiration of contaminated fluid into the respiratory system.

The use of emetics is complementary to gastric lavage, although it may be performed as a separate procedure. This method is used only after very careful diagnostic evaluation of the contaminated patient. It is clearly contraindicated in patients who are in a state of shock or confusion, or after ingestion of petroleum and corrosive substances. The most common uses of emetics include subcutaneous administration of apomorphine or oral preparations of ipecac. These interventions require sound clinical understanding of the procedure. The most common method is the administration of an emetic after the patient drinks 250 mL of water. Apomorphine primarily acts by stimulating the vomiting center in the area postrema of the medulla oblongata. It is used in a single dose of 5-10 mg subcutaneously, while preparations of ipecac can be used in several doses until vomiting is induced. Both drugs are readily available. Side effects include nausea, weakness, tachypnea, tachicardia, and hypotension. They may not require special clinical management and may be treated by symptomatic therapy. The use of laxatives is a common therapeutic approach in reducing internal contamination. Purgative agents may be given in different forms, as agents which act by the release of linoleic acid, stimulating peristalsis in the small intestine. Sustained use of laxatives inhibit absorption of actinides by the formation of insoluble salts. Their hypertonic action causes water extraction in the intestinal mucosa with the cathartic elimination of the intestinal contents. Clinical assessment and detailed understanding of the type and quantity of the contaminant is required prior to the use of laxative therapy. Laxative use is contraindicated in acute abdominal syndrome or non-diagnosed pain in the stomach. Numerous side effects include tachypnea, dyspnea, tachiarhythmias, intestinal irritation, exanthema, and syncopal attacks, which require professional medical attention.

Treatment of patients who have been contaminated by inhalation of uranium compounds includes the use of therapeutic agents which decrease viscosity of endobronchial mucosa. The use of mucolytic substances, which have the effect on mucopolysaccharides and nucleoproteins in the respiratory tree, enable the elimination of actinides by expectoration. However, these substances, such as pancreatic dornase, triton, Tween-90, and F-68 have not been found satisfactory for practical use.

The mobilization of uranium and actinides from the skeleton by the parathormone was studied in various experimental models but this method of decrease in the body burden of uranium contamination does not offer a practical alternative. Actinides are not controlled by the homeostatic mechanisms. Radioisotopes of the alkaline earths series can be eliminated from the bone by PTH-induced resorption, together with uranium bound to the bone crystals. This process of demineralization of the bone has been proven as a mechanism of reduced uranium retention. However, it is of no practical value in the treatment of internal contamination. This applies to all actinides (¹³¹), whether mineral-bound (uranium) or sialoprotein-bound (plutonium, which is retained on the endosteal surfaces of the bone).

Treatment of uranium internal contamination by complexing agents is based on the ability of a ligand to form non-ionized ring complexes with inorganic ions, which are subsequently eliminated by the kidney. This treatment has to be instituted as soon as possible, before uranium incorporation in the target organs. These substances are not useful in binding the actinides which are deeply incorporated in the cells because of their hydrophylic properties. Present investigations are focused on the synthesis of lipophylic chelating agents, capable of reaching radionuclides from the cells and facilitating their excretion through the kidneys.

Among the numerous complexing agents which have been tested in clinical trials, only several appear of practical concern in uranium contamination.

Ethylenediaminetetraacetic acid (EDTA) has been used in experiments on animals and in human medicine for the treatment of poisoning with inorganic substances. It was proven useful and effective in the treatment of lead, zinc, copper, chromium, manganese, and nickel poisoning and in contamination with transuranic elements (¹³²). EDTA is administered intravenously as an infusion in 5% glucose in water or physiological saline. It is essential to evaluate kidney function before the beginning of the treatment because its use is contraindicated in patients with renal disease. Na-EDTA is used in a dose of 50 mg/kg. The total quantity should not exceed 300 mg during 6 days of treatment. It is not administered by oral or intramuscular application. Parenteral use of Na-EDTA may lead to hypocalcemia. The use of Ca-EDTA in the therapeutic dose of 15-30 mg/kg does not have a hypocalcemic effect.

Diethylenetriaminopentacetic acid (DTPA) is a chelating agent of polyaminocarboxylate series, which, after parenteral use, binds many polyvalent radionuclides of heavy metals. It forms very stable complexes, which are soluble in water and are excreted by the kidney. The Food and Drug Administration (FDA) approves the use of calcium and zinc salts of DTPA in cases of human contamination with transuranium elements.

Ca-DTPA is successful in the treatment of actinide contamination (133). The therapeutic effectiveness of both Ca-DTPA and Zn-DTPA depends on the chemical form and solubility of transuranic elements. Both agents are useful in the elimination of soluble uranium salts, such as nitrates or chlorides, but have a rather low efficiency in poorly soluble compounds such as oxides (134). Both drugs are used by intravenous injection, intravenous infusion, intramuscular injection, or via inhalation in the form of an aerosol. The mode of administration depends on the given circumstances of uranium poisoning, its chemical form, and the pathway of contamination. Ca-DTPA is more efficient than Zn-DTPA if used early after contamination (135), but they do not differ in efficacy if administered at later time intervals. DTPA therapy has been associated with a loss of trace elements, which is a reversible process, without reported harmful effect on the organism. The injection of 1 g of Ca-DTPA per week in long-term treatment did not cause toxic effects in patients contaminated with actinides (136). In contrast, a constant infusion of Ca-DTPA was shown to cause severe toxic effects in experimental animals, leading to death after several days (137). The toxicity of Zn-DTPA was demonstrated to be 30 times less than Ca-DTPA in fractionated use, not leading to the loss of micro elements and not demonstrating teratogenic effects (138). In early decontamination therapy of contamination with transuranium elements in humans, Ca-DTPA is the treatment of choice, whereas in the planning of a long-term treatment, Zn-DTPA is preferentially used because of its lesser effect on trace metals. It is also used for patients with renal disease, depressed activity of the bone marrow, and pregnancy, where Ca-DTPA is contraindicated.

Other agents used in internal contamination with actinides include desferoxamine (DFOA), which was demonstrated to be effective in oral, intramuscular, and intravenous administration. Its therapeutic effect is enhanced when used together with DTPA, but it has to be used with caution because of the side effects, including exanthema, tachycardia, and hypotension (139). Biscarboxy-*l*-methylamino diethyl ether (BAETA) is another agent shown to be effective in transuranic contamination, but less than DTPA. From the viewpoint of elimination of most hazardous radionuclides of the transuranic series, DTPA outweighs other agents, including the recently studied sulfonated tetrameric catecholamines (LICAM-C and LICAM-S), which have been found effective in contamination. However, their use has been limited because of the toxicity (140).

There have been numerous attempts to produce a lipophilic chelating agent that would allow better access to the intracellular environment through the fatty layers of the cell membrane. Among the compounds of this category, a lipophilic agent Puchel, produced at Harwell, England, was found more effective than DTPA by the inhalational administration (141), with better therapeutic effects in their combined use.

Recent studies of liposomes as possible agents of choice in the internal contamination with actinides focused on specific sites such as the reticuloendothelial system (142). In addition to the recent studies of synthetic catecholamines (143), natural chelates have also been isolated from cultures of different microorganisms, such as natural chelates of the *Pseudomonas aeruginosa* (144). Recent studies of multidentate catecholate and hydroxypyridinonate ligands for *in vivo* chelation of soluble uranyl ions appear promising because of their low toxicity, effectiveness, and reasonable cost (145). Siderophore analogue chelating agents (LIHOPO compounds) have been recently reported as a most significant advance in the early treatment of uranium contamination (146).

Summary

The medical and environmental consequences of contamination with uranium compounds present both a moral and legal requirement to control uranium exposure to levels below those causing pathological alterations or death, either by its immediate or long-term action. The increased use of uranium compounds in industry, and more recently in warfare in the form of depleted uranium, necessitates a further look into the complex biomedical aspects of internal contamination with uranium and its toxicological consequences both as a heavy metal and radiological hazard. Whereas it is theoretically possible to reduce uranium contamination to an as low as reasonably achievable level, the emerging evidence of increasing industrial and military access of uranium to the biosphere requires a sound understanding of physical, chemical, and toxicological properties of uranium. In the current times of its higher levels and anticipated risks such understanding is necessary to provide protection against somatic and genetic injury. The aim of this review was to provide an outline of uranium physical,

chemical, radiological, and toxicological properties as an actual contaminant of the environment and the human organism. The possible role of the medical profession in this interdisciplinary field requires an understanding of the current concerns of the medical and environmental consequences of uranium poisoning, which are currently far beyond the mere theoretical interests of conventional toxicology.

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Correspondence to:

Asaf Duraković

Department of Radiology and Nuclear Medicine

Georgetown University School of Medicine

3430 Connecticut Avenue

Washington, DC 20008, USA

ASAF@compuserve.com

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