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REVIEW ARTICLE

HUMAN HEALTH AND ENVIRONMENTAL URANIUM

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Summary

Uranium from the environment enters the human body by ingestion with food and drink and by inhalation of respirable airborne uranium-containing dust particles or aerosols. A 70 kg, non-occupationally exposed 'Reference Man' living in Europe or in the United States has an estimated total body uranium content of about 22 micrograms. Uranium is absorbed from the intestine or the lungs, enters the bloodstream, and is rapidly deposited in the tissues, predominantly kidney and bone, or excreted into the urine. In the bloodstream, uranium is associated with red cells, and its clearance is relatively rapid. Renal toxicity is a major adverse effect of uranium, but the metal has toxic effects on the cardiovascular system, liver, muscle, and nervous system as well. Any possible direct risk of cancer or other chemical- or radiation-induced health detriments from uranium deposited in the human body is probably less than 0.005% in contrast to an expected indirect risk of 0.2% to 3% through inhaling the radioactive inert gas radon, which is produced by the decay of environmental uranium-238 in rocks and soil and is present in materials that are used to build dwellings and buildings where people live and work.

Key words: Environmental uranium; environmental disease; chemical hazard; radiological hazard

INTRODUCTION

Uranium (U) is a naturally occuring heavy metal that is both radioactive and ubiquitous (Jiang and Aschner, 2006). Small amounts of U are found in rock, soil, air, water and food. Uranium from the environment enters the human body by ingestion with food and drink and by inhalation of respirable airborne uranium-containing dust particles or aerosols.

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Daily intake of uranium in food and water varies from approximately 1 to approximately 5 micrograms U/day in uncontaminated regions to 13-18 micrograms/day or more in uranium mining areas (Taylor and Taylor, 1997). Total annual intake of U by human adults approximates 460 micrograms by ingestion of food and water, and 0.6 micrograms by inhalation (Fiesenne et al., 1988). Total body uranium content of a 70 kg, non-occupationally exposed person, is about 22 micrograms of U (Fiesenne et al., 1988).

Use of depleted uranium (DU) ammunition has resulted in contamination of the near-surface environment with penetrator residues. DU contamination changed the concentration of this radioactive element in the earth's crust in some areas and increased the risk of human exposure (Patočka et al., 2004;

Eckerd, 2013, Crean et al., 2014). Contamination of soils with DU from ammunition occurs in conflict zones and at test firing sites (Fathi et al., 2013; Yousefi and Najafi, 2013). Uranium rich particles with characteristic spherical morphologies were observed in soils, consistent with other instances of DU munitions contamination (Crean et al., 2013). More studies demonstrate that substantial alteration of DU residues can occur, which directly influences the health and environmental hazards posed by this contamination (Fathi et al., 2013; Vidic et al., 2013), especially when many studies show that DU is primarily associated with macromolecules in dissolved fraction (Harguindeguy et al., 2013). The aim of this article is to provide an integrated view of the potential impact of uranium in the environment on the environmental health.

URANIUM IN ENVIRONMENT

Results of Kraemer and Evans (2012) showed significant uranium bioaccumulation in the lake impacted by historical mining activities. Uranium accumulation was 2-3 orders of magnitude higher in invertebrates than in the fish species. In fish, uranium was measured in operculum (bone), liver and muscle tissue and the accumulation followed the order: operculum>liver>muscle. There was a negative relationship between stable nitrogen ratios ((15)N/(14)N) and U bioaccumulation, suggesting uranium biodilution in the foodweb. Uranium bioaccumulation in all three tissues (bone, liver, muscle) varied among fish species in a consistent manner and followed the order: bluegill (*Lepomis macrochirus*) > yellow perch (*Perca flavescens*) > smallmouth bass (*Micropterus dolomieu*). Collectively, gut content and stable isotope analysis suggest that invertebrate-consuming fish species (i.e. bluegill) have the highest uranium levels, while fish species that were mainly piscivores (i.e. smallmouth bass) have the lowest uranium levels.

The accumulation and toxicity of uranium in water are dependent on water hardness. Markich (2013) has shown that water hardness reduces the accumulation and toxicity of U in a freshwater macrophyte (*Ceratophyllum demersum*). A 20-fold increase in water hardness resulted in a 4-fold decrease in U toxicity (median effect concentration EC_{50}=134 μg/L at 20 mg CaCO3/L hardness, increasing to 547 μg/L at 400 mg $CaCO_3$/L hardness.

Pacheco and Havel (2001) showed significant complexation of uranium (VI) with humic acids. Complex formation greatly reduces the mobility of uranium in the environment.

CHEMICAL AND RADIOLOGICAL HAZARDS OF URANIUM

Uranium presents both chemical and radiological hazards, but there are some problems with the comparison of these hazards (Ebinger and Hansen, 1994). Different reports on the health hazard of DU munitions have concluded that this metal used on the battlefield probably did not lead to any measurable excesses of cancers. The explosion of uranium missile can kill everyone caught in the tank, but radioactive uranium aerosol is able to disperse in the air, tens of kilometres from the point of release. It can be also stirred up in dust and resuspended in the air with wind or human movement. Following the inhalation exposure, very small uranium particles can stay in the human body for years, irradiating the tissue with powerful alpha particles within about a 30 micron sphere, causing damage to cells. Uranium can also be ingested and cause damage to the gastrointestinal tract. In addition, it penetrates through lung tissue to the blood stream and can be stored in liver, kidney, bone or other tissues for years, irradiating all tissues located near its storage place. There is a serious suspicion that exposure to U might be associated with neurotoxic health sequelae (Jiang and Aschner, 2006). It has also an influence on the blood cells that are the important part of immune system, and can damage the renal system when eliminated into urine. It can also initiate cancer or promote cancers which have been initiated by other carcinogens. This radiological toxicity is combined with chemical toxicity of uranium, comparable with the toxicity of other heavy metals, for example with lead or nickel.

TOXICOKINETICS AND TOXIDYNAMICS OF URANIUM

Adsorption

Ingestion

The absorption of uranium across the gastrointestinal (GI) tract is related to the solubility

of the compound and generally increases with increased solubility. Only a small fraction is absorbed of even the relatively soluble uranium compounds (Harrison and Stather, 1981). Lang and Raunemaa (1991) showed that uranium could not be detected in liver, kidney, muscel, bone, brain, blood, and urine, and that uranium was not absorbed or retained significantly in the epithelial cells of the intestinal wall.

Inhalation

Animal and human research indicate that inhalation of insoluble uranium dioxide is associated with general damage to pulmonary tissue, usually non-cancerous damage to alveolar epithelium. This pulmonary damage can lead to emphysema or pulmonary fibrosis (Cooper et al., 1982; Dungworth, 1989). Animal studies demonstrate uranium compounds to cause adverse haematological disturbances (Dyggert, 1949; Cross et al., 1981).

The soluble compounds of uranium, such as uranium hexafluoride, uranyl fluoride, uranium tetrachloride, uranyl nitrate hexahydrate, can penetrate the blood from the alveolar pockets in the lungs within days of exposure (Puncher et al., 2008). Although inhalation products are also transported through coughing and mucocilliary action to the gastro-intestinal tract, only about 2 percent of this fraction is actually absorbed into the body fluids through the intestines. Therefore, all of the research papers on acute effects of uranium describe the inhalation exposure to these soluble uranium compounds. The main acute effect of inhalation of soluble uranium compounds is damage to the renal system (Thun et al., 1985). The bone seems to be the main long term storage place of these compounds in the human body (Kathren et al., 1989).

Particles of uranium smaller than 2.5 microns are usually deposited in the lungs and pulmonary lymph nodes where they can remain for years (Igarashi et al., 1987). Studies have shown that only small uranium particles less than 10 micrometer in diameter will reach and accumulate in the bronchioles and alveoli, while larger particles are effectively cleared by mucocilliary clearance (Harley et al., 1999; Gwiazda et al., 2004; Petitot et al., 2013). These particles do present a potential health hazard from uranium inhalation, but studies have shown than less than 1% of inhaled uranium actually reaches the kidneys (Morris et al., 1990; Lang et al., 1994; Gwiazda et al., 2004). It has been also demonstrated that of the inhaled uranium, 75% is exhaled and 25% is retained in the respiratory tract and lungs. Of the retained uranium fraction in the lungs, 80 % is removed by bronchial clearance, 15% is deposited in lymph nodes, and 5% actually enters the blood (Spencer et al., 1990; Harley et al., 1999).

According to research done in the British National Radiation Protection Board, ceramic uranium is formed when uranium ignites through friction, as happened in the Gulf War. In this form, uranium usually penetrates the lungs to the blood twice slower than non-ceramic uranium. A very small portion of inhaled uranium (2%) can be transported to the gastro-intestinal tract, where it is absorbed through the intestines. This fraction of the inhaled compound can damage the GI tract as it passes through because it emits alpha particles with statistical regularity. The residence time of the insoluble uranium compounds in the GI tract is estimated in years (Stradling et al., 1988).

Dermal

In animal studies, soluble uranium compounds (ammonium uranyl tricarbonate or uranyl nitrate hexahydrate) have been shown to penetrate the skin of rats within 15 min of application. Two days after exposure, dermally absorbed uranium was no longer localized in the epithelium, and rats had either significant weight loss or had died. No penetration through the skin was observed when uranium dioxide, a more insoluble form, was applied (de Rey et al., 1983). Other uranium compounds (uranium tetrachloride or tetrafluoride, uranium trioxide) are absorbed through the skin of mice, rats, and guinea pigs at a rate of 0.1% of dermally applied uranium, a relatively low absorption rate (Orcutt, 1949). Also other studies show that soluble uranium compounds can be absorbed through the skin (Petitot et al., 2007, 2010), however, the concentrations of uranium applied to the skin were extremely high, and it is unlikely that humans would typically experience such exposures.

Distribution

Distribution of uranium has been studied in laboratory animals (Ellender et al., 1995; Monleau et al., 2005). The distribution data in humans were obtained from several random instances of people who had worked in the environment burdened by the presence of uranium. The results of these more or less random observations are very similar. The uranium content in the various tissues of the body followed a rank order

lung > skeleton > liver > kidney. The concentration of uranium in the kidney tissue was approximately 2.0 ng/g, about 3 orders of magnitude less than the generally accepted threshold level for permanent kidney damage (Galibin, 1974; Igarashi et al., 1987; Dang et al., 1995; Russell and Kathren, 2004; Spencer et al., 2007).

Metabolism and Excretion

The average gastrointestinal uptake of uranium is limited and ranges from 1 to 5% in adult humans (Legged and Harrison, 1995). Absorption generally increases with increasing solubility of uranium salt. Uranium absorption takes place predominantly in the small intestine, with no absorption from the large intestine, oral cavity or stomach (Dublineau et al., 2005).

The predominant form of uranium in blood is a bicarbonate complex, the stability of which is highly dependent on the pH of the solution (Chevari and Likhner, 1968). In the kidneys, the bicarbonate complex is filtered at the renal glomerulus and excreted into the urine (Adams and Spoor, 1974; Bowman and Foulkes, 1970; Blantz, 1975). Nevertheless, approximately 90% of the ingested uranium in humans is excreted into the feces (Spencer et al., 1990).

TOXICITY

Immediately following entering of uranium dioxide into the blood, hexavalent uranium is formed, which is also a systemic chemical toxicant. The slow excretion rate of the uranium oxide is favourable for the kidney and tubule repair and regeneration. Moreover, much uranium is still being stored in the body and has not yet passed through the kidneys because of the long biological half-time. The direct damage to lungs and kidneys by uranium compounds is thought to be the result of their combined radiation and chemical properties. It is difficult to distinguish a portion of the damage to these separate factors because they cannot be separated in life (Stradling et al., 1988).

The chemical action of all isotopic mixtures of uranium (depleted, natural and enriched) is identical. Current evidence from animal studies suggests that the chemical toxicity is largely due to its chemical damage to kidney tubular cells, leading to nephritis. Uranium poisoning is characterized by generalized health impairment (Briner, 2010; Guseva Canu et al., 2011). The element and its compounds produce changes in the kidneys, liver, lungs and cardiovascular, nervous and haemopoietic systems, and cause disorders of protein and carbohydrate metabolism (Brugge and Buchner, 2011). The differences in toxicity based on the solubility of the uranium compound are more striking: water soluble salts are primarily renal and systemic chemical toxicants; insoluble chemical compounds are primarily lung chemical toxicants with systemic radiological hazard.

Although human experience with uranium spans more than 200 years, the LD_{50} for acute intake in humans has not been well established (Kathren and Burklin, 2008). Large acute doses of uranium can produce death from chemical toxicity in rats, guinea pigs, and other small experimental animals, with variation in sensitivity among species. However, there has never been a death attributable to uranium poisoning in humans, and humans seem to be less sensitive to both acute and chronic toxic effects of uranium than other mammalian species studied. Highly relevant data on uranium toxicity in humans are available from the experience of persons administered large doses of uranium for therapy of diabetes and from acute accidental inhalation intakes. Although the data on which to establish oral and inhalation acute LD_{50} for uranium in humans are sparse, they are adequate to conclude that the LD_{50} for oral intake of soluble uranium compounds exceeds several grams of uranium and is at least 1.0 g for inhalation intakes. For intakes of uranium compounds of lesser solubility, acute LD_{50} values are likely to be significantly greater. It is suggested that 5 g be provisionally considered the acute oral LD_{50} for uranium in humans. For inhalation intakes of soluble compounds of uranium, 1.0 g of uranium is proposed as the provisional acute inhalation LD_{50}.

Nephrotoxicity

Kidney is known as the most sensitive target organ for uranium toxicity in comparison to other organs (Jiang and Aschner, 2006; Vicente-Vicente et al., 2010). In the kidneys, the site of action is the proximal tubule where proton secretion degrades the bicarbonate complex of the uranyl ion (Homma-Takeda et al., 2013). Uranium can then react with apical cell membranes of the tubule epithelium (Carrière et al., 2004). Nephrotoxicity of uranium is clearly associated with exposure to this metal and has

been documented in many animal studies (Leggett, 1989; Sztajnkrycer MD, Otten, 2004; Malard et al., 2009; Arzuaga et al., 2010; Shaki et al., 2012).

Notwithstanding in vitro studies on renal cells demonstrated a concentration-dependent uranium toxicity (Carriere et al., 2004; Thiebault et al., 2007; Shaki et al., 2012), any observed uranium nephrotoxicity results from acute exposure.

Genotoxicity

Studies on mammals have shown that uranium is genotoxic. Miller et al. (1998a) followed the mutagenicity of urine of rats, to which DU pellets were implanted subcutaneously. Authors found a dose- and time- dependent increase of urine mutagenicity, as was tested by Ames Salmonella typhimurium test by strains TA 98 and mixed strains TA – 7001 – 7006. During the Persian Gulf War several US military personnel were wounded by shrapnel fragments containing DU. Analyses indicated a significant increase in urine uranium levels above nature background levels. The examination of potential mutagenicity of DU internalisation is necessary in understanding of the etiology in potential disease development DU- uranyl chloride has the capacity to transform human osteoblastoma cells (Miller et al., 1998b). DU internalisation presents a unique toxicological problem, because it combines chemical toxicity with radiological exposure.

Genotoxic effect of DU may be comparable to other heavy metal compounds (Lourenço et al., 2013). This mechanism might be connected with an inhibition of DNA repair in heavy – metal treated cells. This hypothesis seems to be supported by studies (Au et al. 1995, 1998) that found a decreased DNA repair capacity in individuals residing near uranium mining facilities

Carcinogenicity

The uranium risk is not well established and additional research is needed on the metabolism of U in humans and its carcinogenicity in laboratory animals. These estimates assume linear dose responses. However, if incidence varies with the square of dose, virtually no induced cancers would be expected from these levels of radioactivity (Mays et al., 1985). The risk is likely to change when uranium ammunition began to be used and some war areas were contaminated with uranium (Hahn et al., 2002).

Bones are the secondary target organ of uranium toxicity. The majority of absorbed uranium, which mimics calcium, is stored in the bones, and could induce death of bone cells (Rodrigues et al., 2013). It is still unclear if the mutagenic and carcinogenic affects are a result of the chemical or radiological effects of uranium, but it is believed that these effects are primarily due to the latter. Osteosarcoma risk has clearly been demonstrated to be related to the amount of radiation exposure and there is a lot of *in vitro* studies on bone cells and in animal models (Miller et al., 2003, 2005; Ibrulj et al., 2004, 2007).

However, many scientists believe that the amount of radiation emitted by DU is insufficient to raise a significant risk in humans, but may be more of a concern for children whose bones are growing rapidly (Brugge et al., 2005; Jiang and Aschner, 2006, 2010).

Lungs and tracheobronchial lymph nodes are the major sites od uranium accumulation for large particles and relatively insoluble forms of uranium, and fibrotic changes in the lung tissue have been observed suggesting radiation injury (Leach et al., 1970, 1973). These insoluble particles deposited in the lungs have a long residual time and may result in an increased risk of cancer (Hartmann et al., 2000).

According to Voeghtlin and Hodge (1949, 1953), typical health effects seen in uranium inhalation studies are the development of pneumonia and chemically irritated passages, which are considered as early signs of lung cancer. Although there is a relatively large amount of experimental material as well as clinical observation, the exact mechanisms associated with lung injury in uranium exposure are not well understood (Periyakaruppan et al., 2007). Several studies have established the deleterious effect of DU on cytokine secretion and on the proteasome-ubiquitin system (Gazin et al., 2004; Mallard et al., 2005), on viability, micronuclei, chromosomal instability, and sister chromatid exchanges in cells (Lin et al., 1993; Wolf et al., 2004). Numerous studies on the effects of prolonged exposure of the Gulf War veterans to DU showed that genotoxic damages are believed to be due to the radiological properties of uranium more than to the chemical effects (Bakhmutsky et al., 2011, 2013; McDiarmid et al., 2011, 2013).

Reproductive and Developmental Toxicity

The reproductive effects of uranium have been recently studied in various animal models (Arfsten

2001, 2005, 2006, 2009; Hao et al., 2012). Uranium has been shown to be a reproductive and developmental toxicant when given orally or subcutaneously, resulting in decreased fertility, embryo/fetal toxicity including teratogenicity, and reduced growth of offspring following uranium exposure at different gestation periods (Domingo et al., 1989; Llobet et al., 1991; Bosque et al., 1993; Domingo, 2001; Arfsten DP, et al, 2001, 2005; Sánchez et al., 2006 ; Feugier et al., 2008; Arfsten et al., 2009; Homma-Takeda et al., 20013).

In humans, studies have evaluated the reproductive effects in male miners, uranium processors, and Gulf War veterans and show that these individuals have uranium in their semen, but do not otherwise show any detrimental reproductive effects (Domingo, 2001; Arfsten et al., 2006; Squibb et al., 2006).

Neurotoxicity

Up to date, there are limited data on the neurotoxicity of uranium. Animal studies demonstrated that uranium crosses the blood-brain barrier (BBB) and readily accumulates in the brain (Lemercier et al., 2003; Fitsanakis et al., 2006; Paquet et al., 2006; Houpert et al., 2007; Barillet et al., 2011). Studies in rats and follow-up studies in Gulf War veterans suggested that DU may cause subtle changes in CNS function without any corresponding nephrotoxicity (McDiarmid , 2001; McDiarmid et al., 2000, 2001, 2002; 2004, 2007). The public concern regarding the potential neurotoxic effects of DU has purred recent novel scientific research to extensively evaluate if there are reasons to be concerned about DU exposure and neurotoxicity.

TOLERABLE DAILY INTAKE (TDU) OF URANIUM

TDU of uranium is dependent on the route of administration because pharmacotoxic parameters are different in the case of inhalation or ingestion.

TDU for Inhalation

The study ATSDR (1997) reviews all published data on animal studies dealing with uranium toxicity. For the hazard from chronic inhalation of soluble forms of uranium, a study performed by Stokinger et al. (1953) on dogs has been used: it showed that uranium concentrations of 0.15 mg U/m^3 in air produced no observable adverse effect. From this figure, a "minimal risk" inhalation level for humans of 1 µg/m^3 is derived, applying a number of safety factors. In another review (Jacob et al., 1997), performed for the German Federal Environmental Agency, a study written by Stokinger et al. (1953) on rats has been used: The rat study showed slight impacts to the kidneys at uranium resorption rates of 2.6 µg per kg per day. This rate corresponds to uranium concentrations of 40 µg per m^3 in the air. Applying a number of safety and conversion factors, the authors obtain a "tolerable" level of 0.07 µg/m^3 uranium in air; this is 14 times lower than the above mentioned ATSDR level.

TDU for Ingestion

The "minimal risk" level for intermediate-duration ingestion proposed by ATSDR (1997) is an oral uptake of 1 µg of uranium per kg body weight per day. This is based on adverse effects observed by Ortega et al. (1989) in rats at uptakes of 1.1 mg per kg per day. Jacob et al. (1997) proposes a "tolerable" uptake of 0.7 µg per kg body weight per day. This value is based on adverse effects observed by McDonald-Taylor et al. (1992) in kidneys of rabbits at resorption rates of 3.2 µg U per kg body weight per day. The WHO has established a TDI for uranium of 0.6 µg/kg body weight per day (WHO, 1998). This is based on adverse effects observed by Gilman (1998) in kidneys of rats at uptakes of 60 µg U per kg body weight per day.

CONCLUSIONS

Uranium from the environment enters the human body by ingestion with food and drink and by inhalation of respirable airborne uranium-containing dust particles or aerosols. Uranium is absorbed from the intestine or the lungs, enters the bloodstream, and is rapidly deposited in the tissues, predominantly kidney and bone, or excreted into the urine. Renal toxicity is a major adverse effect of uranium, but the metal has toxic effects on the cardiovascular system, liver, muscle, and nervous system as well. According to Taylor and Taylor (1997) possible direct risk of cancer or other chemical- or radiation-induced health detriments from uranium deposited in the human body is probably less than 0.005% in contrast to an expected indirect risk of 0.2% to 3% through inhaling the radioactive inert gas radon, which is produced by the decay of environmental

uranium-238 in rocks and soil and is present in materials that are used to build dwellings and buildings where people live and work.

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