Chapter 17
Biological Effects of Uranium and Its Decay Products on Soil Microbes, Plants, and Humans

Chanda Siddoo-Atwal

Abstract In this atomic age, exposure to toxins in the environment ranges from radioactive heavy metals to chemical pesticides, and detoxification has become an issue of considerable importance. Recently, many parts of the world have been contaminated with radioactive waste from depleted uranium bombs and projectiles including the Arabian Gulf, Iraq, Syria, Bosnia, Serbia, and Afghanistan. In addition, other areas of the globe have been contaminated by nuclear testing sites and accidents at nuclear power plants involving radioactive uranium and its decay products. There are three naturally occurring uranium isotopes that are of major significance with regard to mining of this element and the nuclear industry. These include uranium-238 (U-238), which comprises the majority of this element in the Earth's crust, uranium-235 (U-235), and uranium-234 (U-234), which together comprise a much smaller portion. The half-lives of these isotopes are approximately 4500 million years, 703 million years, and 246,000 years, respectively. The transfer of radionuclides of the uranium decay series through the environment is important for assessing the impact of nuclear weapons use, nuclear power plant leaks, and the mining and milling of uranium ores. The pathway from soil through plants to humans contributes significantly to the overall radiation dose. The transfer of mobilized radionuclides within the environment is determined by weathering rate, which, in turn, depends on particle composition and chemical conditions such as pH of the soil after deposition. Specific geographical sites that have been contaminated with uranium attract specific bacterial species that display resistance to the metal. Moreover, various plant species exhibit substantial differences in the soil-plant transfer factor for uranium and other related radionuclides. The biological effects of environmental radionuclides in humans (particularly depleted uranium) have been documented as part of the Gulf War syndrome and Balkan syndrome and comprise a complex set of seemingly unrelated symptoms. Some of these include incapacitating fatigue, musculoskeletal and joint pains, headaches, neuropsychiatric disorders, confusion, visual problems, changes of gait, loss of memory, lymphadenopathies, respiratory impairment, impotence, and urinary tract morphological and functional alterations. Moreover, the overall incidence of breast and lung cancer, leukemia, and

C. Siddoo-Atwal (✉)
Moondust Cosmetics Ltd., West Vancouver, BC, Canada

A. Varma et al. (eds.), *Plant Microbe Interface*,
https://doi.org/10.1007/978-3-030-19831-2_17

lymphoma has doubled or tripled in certain areas of Iraq contaminated with depleted uranium during the Gulf War. An association with lung cancer has also been found in uranium miners. Thus, soil remediation, plant selection, phytoremediation, and human detoxification are the main issues to be considered in relation to environmental contamination with uranium and its decay products.

17.1 Introduction

In this atomic age, exposure to toxins in the environment ranges from radioactive heavy metals to chemical pesticides, and detoxification has become an issue of considerable importance. It is something of note particularly for official governmental agencies dealing with the cleanup of environmental pollution and setting regulatory health standards for such hazards in the surrounding environment. Recently, many parts of the world have been contaminated with radioactive waste from depleted uranium bombs and projectiles including the Arabian Gulf, Iraq, Bosnia and Serbia, Afghanistan, and Syria (Durakovic 2001, 2003; Obralic et al. 2004; Briner 2006; Middle East Eye). Depleted uranium (DU) is a by-product of the uranium enrichment process employed in nuclear reactors. It has been used to make depleted uranium bombs and to coat bullets, which are effective armor-piercing projectiles, since the 1990s. Other areas of the globe have also been contaminated by nuclear testing, such as Nevada and the Bikini Islands, and accidents at nuclear power plants, such as Three Mile Island, Chernobyl, and Fukushima. Heavy metal exposure can occur in humans potentially through the air, water, and soil via food chain (Figs. 17.1, 17.2, and 17.3). However, depleted uranium exposure is most likely to occur via inhalation (Bleise et al. 2003).

Natural uranium consists of three isotopes that are of significance with regard to mining of this element and the nuclear industry. These include uranium-238 (U-238), which comprises approximately 99.3% of this element by mass; uranium-235 (U-235), which comprises 0.72% by mass; and uranium-234 (U-234), which comprises 0.006% by mass. The half-life of U-238 is approximately 4.5 billion years, while those of U-235 and U-234 are estimated at 703 million and 246,000 years, respectively (Priest 2001). U-235 is fissile, and, therefore, it is used to trigger nuclear fission in atomic bombs and to power steam turbines which generate electricity at nuclear power plants (World Nuclear Association 2017). The process of uranium enrichment alters the relative percentages of the three isotopes to produce more U-235, and depleted uranium with a higher percentage of U-238 is a by-product. The decay products of U-238 form the "uranium-radium decay chain" and include uranium, protactinium, thorium, actinium, radium, francium, radon, astatine, polonium, bismuth, lead, and thallium. The decay products of U-235 form the similar, but distinct, "actinium decay chain." Lead (Pb) is the end product for both the uranium and actinium decay chains (Pb-206 and Pb-207, respectively) (Thoennessen 2016).

Fig. 17.1 Bosnia-Herzegovina is an example of a country that has been bombed with depleted uranium (DU) weapons (photo of Trebinje, Bosnia and Herzegovina)

Fig. 17.2 It is quite possible that the soil in Bosnia is contaminated with radioactive uranium isotopes and these may accumulate in plants (photo of an olive and olive tree in Trebinje, Bosnia)

The transfer of radionuclides of the uranium decay series through the environment is important for assessing the impact of nuclear weapons use, nuclear power plant leaks, and the mining and milling of uranium ores. The pathway from soil through plants to humans contributes significantly to the overall radiation dose received (Sheppard and Evenden 1988). Size distribution pattern, radionuclide and matrix composition, morphology, and structure are all important factors in studying weathering, mobilization, and biological uptake of radionuclides when radioactive particles are released into the environment. The particle characteristics are dependent on the radiation source which will determine release, dispersion, and deposition. For example, high-temperature releases like Chernobyl can result in varying

Fig. 17.3 The water sources in Bosnia may also be contaminated with uranium, and these may affect the local wildlife (photo of waterfowl in Trebinje, Bosnia)

composition, morphology, and structure of uranium fuel particles, while low-temperature releases like Windscale may result in flake-like uranium fuel particles that are significantly different. In fact, the release of radioactive particles from nuclear sources occurs more frequently than expected. In order to predict transport, ecosystem transfer, and radiation dose, experimental information is also required with respect to factors such as radionuclide speciation and association with other particles and colloids that influence mobility and biological uptake (Salbu and Krekling 1998).

The transfer of mobilized radionuclides within the environment is determined by weathering rate, which, in turn, depends on particle composition and chemical conditions such as pH of the soil after deposition. It has been found that soil pH is highly linearly correlated with log sorption ratios as a probable consequence of different uranium chemical complexes as a function of soil pH. For example, there is such a great difference in sorption behavior between uranium carbonate complexes that other effects of soil properties on uranium sorption are hidden (Echevarria et al. 2001).

Prokaryotes and eukaryotes contribute actively to geological phenomena including the transformation of metals. Microbes have a variety of properties that can effect changes in metal speciation, toxicity, and mobility, as well as mineral formation or deterioration. Such mechanisms are important components of natural biogeochemical cycles for metals as well as associated elements. Bacteria and fungi are the most important organisms for reclamation, immobilization, or detoxification of metallic and radionuclide pollutants (Gadd 2010).

Geographical sites that have been contaminated with uranium attract specific bacterial species that display resistance to the metal. This may manifest as radiation resistance as in the case of *Deinococcus radiodurans*, the most radioresistant organism known, or chemical resistance as in the case of *Arthrobacter*. As an example, one acidic uranium-contaminated site was found to contain heterotrophic *Arthrobacter* species. These included gram-positive bacteria, one of which was closely related to *Arthrobacter ilicis*. It accumulated uranium intracellularly as precipitates associated with polyphosphate granules. The authors interpreted this as a biochemical detoxification mechanism. However, *D. radiodurans* was vulnerable to uranium chemical toxicity under the same conditions in this particular environment (Suzuki and Banfield 2004). In fact, certain experiments have shown that an *Arthrobacter* strain (G975) is the fastest growing and most uranium-tolerant strain, which removes up to 90% of the uranium from growth media. Various *Arthrobacter* strains, including this one, have been isolated from Hanford site soil (Katsenovich et al. 2013).

Element-specific concentration ratios (CR) are used to model the impact of radionuclides like uranium on the environment. These CR values decrease significantly as the corresponding soil concentrations increase. Interestingly, CR values can differ significantly among some soil and plant types (Sheppard and Evenden 1988). Moreover, various plant species exhibit substantial differences in the soil-plant transfer factor for certain radionuclides. For example, Indian mustard has the smallest root/shoot (R/S) ratio for both radium-226 and thorium-232, while clover has the smallest R/S ratio for uranium-238, when grown on soils from southeastern China contaminated with uranium mine tailings. Chinese mustard also has a low uranium-238 uptake (Chen et al. 2005).

The biological effects of environmental radionuclides in humans via inhalation (particularly depleted uranium), skin contact, and potential ingestion via the food chain including drinking water (for natural uranium) have been noted. The effects of DU have been described as part of the Gulf War and Balkan syndromes, and both comprise a complex set of seemingly unrelated symptoms. Some of these include incapacitating fatigue, musculoskeletal and joint pains, headaches, neuropsychiatric disorders, confusion, visual problems, change of gait, loss of memory, lymphadenopathies, respiratory impairment, impotence, and urinary tract morphological and functional alterations (Durakovic 2001, 2003). In addition, there have been reports of an increased incidence of birth defects in Iraq (Alaani et al. 2011). The overall incidence of breast and lung cancer, leukemia, and lymphoma has doubled or tripled in certain areas of Iraq contaminated with DU during the Gulf War (Fathi et al. 2013; Busby et al. 2010). An association with lung cancer has also been found in uranium miners (Grosche et al. 2006). It is strongly linked to exposure with radon that is one of the decay products of natural uranium. Miners are at risk as a result of exposure to radioactive alpha, beta, and gamma emissions from uranium, which may act as a carcinogen or cocarcinogen, as well (National Academies Press 2012).

Thus, soil remediation, plant selection and phytoremediation, and human detoxification are the main issues to be considered in relation to environmental contamination with uranium.

17.2 Soil Remediation and Soil Conservation

The remediation of uranium and other radionuclide-contaminated soils is a complex and expensive undertaking that depends on a variety of factors. These include the quantitative and qualitative aspects of the contaminant present, the structure and dynamics of the indigenous microbial community, and the geological and chemical conditions at the contaminated site. Bioremediation with microorganisms appears to be one of the most cost-effective and ecologically appealing strategies available. Bacteria, specifically, utilize various mechanisms to sequester uranium including biosorption at the cell surface, intracellular accumulation, bioprecipitation or biomineralization, and redox transformations (oxidation/reduction) (Merroun and Selenska-Pobell 2008).

In order to analyze native microbial populations in any given contaminated environment, PCR-based cloning techniques can be useful for assessing their density and structure. Using this technology, it has been determined that microbial diversity decreases with increasing uranium-associated nitrate and aluminum groundwater contamination when compared with control samples and favors bacteria metabolically adapted to the particular contaminant that is most abundant (Fields et al. 2005). Nitrate-reducing bacteria including phylotypes related to *Proteobacteria* (*Alpha-*, *Beta-*, *Delta-*, and *Gammaproteobacteria*), *Bacteroidetes*, *Actinobacteria*, *Firmicutes*, and *Planctomycetes* have been found to be the most metabolically active microbial communities in uranium-contaminated subsurface sediments using DNA/RNA amplification techniques (Akob et al. 2007). Sulfate-reducing bacteria such as *Desulfobacterales* and *Desulfovibrionales*, which can cause the reductive transformation of metals like uranium into more insoluble forms or form metal sulfides, have also been detected in a former uranium-mining area (Sitte et al. 2010).

Moreover, various *Arthrobacter* strains including *Arthrobacter* strain (G975) have been isolated from Hanford site soil and may be metabolically suited for use in the remediation of such uranium-contaminated sites. In fact, in laboratory tests, *Arthrobacter* strain (G975) is the fastest growing and most uranium-tolerant strain, which removes up to 90% of the uranium from growth media. In other experiments, *Bacillus* and *Rahnella* bacterial strains exhibiting phosphatase-positive phenotypes indicative of constitutive phosphatase activity were found to liberate sufficient phosphate to precipitate 73% and 95% of total soluble uranium added as uranyl acetate, respectively (Martinez et al. 2007). Another potential methodology for the remediation of uranium-contaminated soils involves a three-step process including extraction with citric acid, biodegradation of several metal-citrate complexes with *Pseudomonas fluorescens* resulting in the bioprecipitation and recovery of other toxic metals, and photodegradation of uranyl citrate upon exposure to light since it is resistant to biodegradation (Francis and Dodge 1998). This technique might be well suited to a site with mixed contamination. Another approach exploits the decrease in solubility following the reduction of U (VI) to U (IV), which produces the insoluble mineral uraninite. A variety of bacteria exhibit this reductive capacity via uranium reductases and may be suitable for bioremediation (Wall and Krumholz 2006). In

fact, through a concerted program of biostimulation of bioreducing bacteria, organisms belonging to genera known as U (VI) reducers including *Desulfovibrio*, *Geobacter*, *Anaeromyxobacter*, *Desulfosporosinus*, and *Acidovorax* spp. were detected in sediments from a highly uranium-contaminated site (Cardenas et al. 2008).

At the same time, microorganisms are difficult to control and can mutate relatively easily. There is also a possibility that uranium may be mutagenic in bacteria according to the Ames test (Hudcová et al. 2013). Conceivably, a monumental health hazard could be created by adopting such a bioremediation practice at contaminated sites over too wide an area, especially if these bacteria were to outcompete plants, animals, and humans. Currently, a vast swathe of Eurasia may be contaminated with uranium or its decay products due to wars and nuclear accidents, so a degree of caution should be exercised in making recommendations. Thus, bioremediation with microorganisms may be a strategy best reserved for specialized use for large areas of soil and water contaminated with low concentrations of uranium and is not appropriate for every situation (Li and Zhang 2012).

Soil remediation should aim to remove the contaminant from the substratum or reduce the risk posed by the contaminant by diluting exposure. Although there are many remediation techniques available for contaminated soils, relatively few are applicable to heavy metal contamination. In some cases, a combination of more than one technique may be applied effectively. For example, soil amendments may be combined with phytostabilization, which involves the selection of tolerant plant species and genotypes, to decrease soil metal bioavailability (Vassilev et al. 2004). In practice, an integrated set of modern remediation methods should be utilized to remove uranium from contaminated environments thoroughly and efficiently with the objective of avoiding the production of secondary pollution and causing least disturbance to the ecosystem (Li and Zhang 2012).

Some of the conventional methods that have been used in the past for the treatment of uranium-contaminated soils include removal of a top soil layer or soil excavation and transfer to designated repositories, encapsulation, size separation, soil washing, leaching with chelating agents, electrokinetics, and ion exchange (Dushenkov 2003). Such methods result in the generation of solid and liquid wastes and can damage the local ecosystem by reducing soil quality. Soil components like soil microorganisms and nutrients that are essential for plant growth may also be removed in the process (Malaviya and Singh 2012).

Soil amendments convert soluble and pre-existing high-soluble solid phase forms to more stable solid phases resulting in reduced bioavailability and plant toxicity of heavy metals. Commonly used amendments include liming agents, phosphates, metal oxyhydroxides, and organic compounds such as sludge or compost. Synthetics like ammonium thiocyanate and natural zeolites have also yielded promising results (Prasad and Freitas 2003). A combination of metal immobilization and subsequent phytostabilization, which involves the use of metal-tolerant plants and/or plants tolerant to the growing conditions of a given site, can be effective. For example, grasses and fast-growing plants that are easy to care for can provide complete surface coverage and a large network of shallow roots to stabilize soil and take up soil water.

The main objectives for successful heavy metal remediation are to change the trace element speciation of the soil, to stabilize the vegetation cover and limit trace element uptake by crops, to reduce direct exposure of living organisms, and to enhance biodiversity. However, there is no standardized system for classifying the effectiveness of soil treatment, and the remedial strategy must be evaluated on a case to case basis (Vassilev et al. 2004).

Phosphate fertilizers are another major source of uranium contamination of agricultural land largely due to impurities in the phosphate rock used for fertilizer manufacture. Fertilizers contaminated with uranium (U) can significantly elevate the uranium content of fertilized soils. For example, in Germany, the cumulative use of phosphate fertilizers from 1951 to 2011 has led to an average distribution of approximately 1 kg of uranium per hectare (Schnug and Lottermoser 2013). Several German mineral waters also have a tendency toward higher than average uranium concentrations. This could be due to leaching from natural deposits, or it may be related to the extensive use of phosphate fertilizers in the region (Schnug et al. 2005). As a result, the Federal Ministry of Food, Agriculture and Consumer Protection asked its scientific advisory panel (UBA) on soil conservation matters to make recommendations in this regard. Labelling for phosphate fertilizers containing 20 mg or more of uranium per kilogram of phosphate and a limit value of 50 mg per kg of phosphate is now recommended (European Commission Brussels 2016). Thus, imposing such a regulatory control may serve to dilute pre-existing uranium contamination and limit future contamination of agricultural soil and groundwater proving to be an important initiative in environmental conservation. If labelling is not available, in certain soils, it is possible to estimate the average concentration of uranium in superphosphate fertilizers between samplings using this formula (Taylor 2007):

$$c = iAdp/f$$

where

c = concentration of U in fertilizer in μg g^{-1}
i = average annual increase in U in soil in μg g^{-1}
A = area of 1 ha in m
d = sample depth in m
ρ = bulk density in total m^3
f = annual fertilizer application to 1 ha in kg

17.3 Plant Selection and Phytoremediation

Uranium is known to be highly toxic to plants. Plants experience oxidative stress in response to heavy metals resulting in cellular damage and disruption of cellular homeostasis similar to animals and humans. As a result, they have evolved

detoxification mechanisms mainly involving chelation and subcellular compartmentalization to minimize the toxic effects of heavy metal exposure. Phytochelatins (PCs) are an important class of heavy metal chelators in plants which are synthesized from reduced glutathione (GSH) in a transpeptidation reaction catalyzed by the enzyme phytochelatin synthase (PCS). So, glutathione availability is essential for heavy metal detoxification in plants (Singh et al. 2011). Organic acids also play a key role in the metal tolerance of plants. In a process of metal detoxification, organic acids can form complexes with metals (Prasad and Freitas 2003).

Phytoremediation is the use of green plants to remove pollutants from the environment or to deactivate them and is based on exploiting the metabolic diversity of plants. This technology has been applied to a number of radionuclide-contaminated sites around the world. There are four main aspects of radionuclide phytoremediation including phytoextraction, rhizofiltration, phytovolatilization, and phytostabilization. Phytoextraction involves using high-biomass radionuclide-accumulating plants to transport and concentrate radionuclides from the soil into shoots above the ground; rhizofiltration involves using plant roots to precipitate and concentrate radionuclides from polluted effluents; phytovolatilization involves using plants to extract volatile radionuclides from soil and volatilize them from the foliage; and phytostabilization involves using plants to stabilize radionuclides in soils by metabolizing them (Dushenkov 2003). However, more basic research is required in this emerging new field to maximize the metabolic differences between detoxification pathways in plants and to understand the complex interactions of metals, soil, plant roots, and soil microbes such as bacteria and mycorrhizal and non-mycorrhizal fungi for decontaminating metalliferous substrates in the environment. There are significant interactions between metals and mycorrhizal fungi and macrofungi that may result in the amelioration of plant phytotoxicity and metal accumulation. Some of the mechanisms of metal fungitoxicity include extracellular precipitation and complexation, binding to cell walls, metal-binding proteins and peptides, vacuolar compartmentation, and metal transformations such as organometalloid synthesis (Gadd 1993).

Currently, up to 400 plants that hyperaccumulate metals have been reported. Most notably different genera of Brassicaceae are known to accumulate metals, such as Indian mustard, which is effective in the removal of heavy metals including cadmium, chromium, and lead. Sunflower has been found to be effective for the removal of uranium, cesium, and other radionuclides in hydroponic solutions. Plants can be raised hydroponically for transplantation into polluted water or soil where they can absorb and concentrate metals in unexposed parts like their roots for rhizofiltration. As the plant roots become saturated with metal contaminants, roots or whole plants are harvested for disposal. Alternatively, synthetic cross-linked polyacrylates or hydrogels can protect plant roots from heavy metal toxicity by preventing the entry of toxic metals into the roots during phytoextraction. Then, after sufficient plant growth and metal accumulation, the above-ground portions of the plant are harvested and removed resulting in permanent removal of metals from the site. Certain aquatic plant species also have the ability to remove heavy metals from

water including water hyacinth, pennywort, and duckweed (Prasad and Freitas 2003).

It should be noted that phytostabilization is not a technology for cleaning up contaminated soil but a management strategy for stabilizing or inactivating potentially toxic trace elements, possibly as a follow-up to rhizofiltration and/or phytoextraction. Thus, along with soil amendments, the plant cover can provide pollution control and stability to the soil. Phytostabilization may be adapted to different metal contaminants and soil types by the careful selection of plants displaying maximum uptake of the contaminant in most abundance and adopting specific cropping schemes (Vassilev et al. 2004).

Plants that have been used in the phytoremediation of uranium-contaminated soils include Chinese cabbage, Swiss chard, and maize among various other species (Malaviya and Singh 2012). Uranium accumulates mainly in the roots of plant species, and uranium remediation of soils by plants can be largely influenced by soil type. For example, plant performance is affected by uranium contamination rates, particularly in calcareous soils. Plant roots grown in soils with high carbonate-uranium content accumulate the most uranium, while the lowest plant accumulation occurs in clayey acid soils with high iron, manganese, and organic uranium content (Shahandeh and Hossner 2002).

Conversely, crops grown on partially remediated sites should be simultaneously selected for minimum radionuclide uptake since vegetable and fruit plants can accumulate uranium. As an example, Indian mustard displays low accumulation for both radium-226 and thorium-232, while clover has low accumulation of uranium-238, when grown on soils from southeastern China contaminated with uranium mine tailings. Chinese mustard also has a low uranium-238 uptake (Chen et al. 2005). Therefore, Chinese mustard and clover would be two good crop choices in a uranium-contaminated area following a degree of remediation to reduce uranium levels to nontoxic levels according to international standards such as those currently being set in Germany. Similarly, Indian mustard would be suitable for soils contaminated with uranium decay products, radium, and thorium.

Quite recently, a very interesting use has been made of transgenic plants, which detoxify/accumulate cadmium, lead, mercury, arsenic, and selenium, for the purposes of phytoremediation (Eapen and D'Souza 2004). Similarly, specific plants could be genetically engineered to selectively uptake uranium and its decay products like radium and thorium in order to remediate polluted environments.

17.4 Human Cancer Risk and the Potential for Uranium Detoxification

17.4.1 Biochemical Detoxification of Uranium

No unique biochemical pathways have been elucidated for uranium detoxification in mammals, and the existing data is limited. In rats, hydrogen sulfide has been demonstrated to attenuate uranium-induced acute nephrotoxicity through oxidative stress and the inflammatory response via the Nrf2 and NF-κB pathways. Sodium hydrosulfide administration restores glutathione levels and antioxidant enzyme activities like superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase in rat kidneys (Zheng et al. 2015). These results may indicate that uranium toxicity is ameliorated in mammals through the induction of antioxidant defense following an initial reduction in activity similar to that observed in certain fish species (Barillet et al. 2007). Interestingly, different patterns of antioxidant activity have been observed for depleted uranium (DU) and enriched uranium (EU) in the cerebral cortex of rats. Lipid peroxidation increased significantly after EU exposure, but not after DU exposure. The gene expression or activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) increased significantly after chronic DU exposure in drinking water, while oral EU administration induced a decrease in these antioxidant enzymes (Lestaevel et al. 2009). Experiments have also shown that uranium can alter xenobiotic-metabolizing enzymes such as *CYP3A* (cytochrome P450, family 3, subfamily A) in the rat liver or kidneys after either acute or chronic exposure causing high gene expression for several months (Gueguen et al. 2014). In addition, uranium administration has been associated in several studies with decreases in creatinine clearance congruent with an increase in the plasma concentration of creatinine and blood ureic nitrogen indicating a reduction in glomerular filtration rate (GFR). Moreover, it has been demonstrated that several species undergo some degree of renal damage in a dose-dependent and route-independent manner following uranium exposure (Vicente-Vicente et al. 2010).

In humans, nephrotoxicity has been studied the most extensively. Acute uranium intoxication appears to affect the reabsorption of filtered solutes and the excretion of other solutes leading to kidney impairment of varying degrees depending on the initial dose (Vicente-Vicente et al. 2010). Reduced creatinine clearance, increased serum nonprotein nitrogen, and a higher rate of uranium excretion have been observed in humans. Increases in the urinary excretion of proteins (Friberg et al. 1986; Lu and Zhao 1990), amino acids (Lu and Zhao 1990), and urinary catalase (Bassett et al. 1948; Friberg et al. 1986) have also been noted. Thus, in both humans and animals, acute intoxication with uranium leads to nephrotoxicity in a dose-dependent manner suggesting that the kidneys are a major site for biochemical detoxification. However, the potential role of route of exposure remains largely unexplored for these findings in humans.

17.4.2 Biochemical Mechanisms of Uranium Toxicity

Uranium (U) mainly exists in the U (+IV) or U (+VI) oxidation states in water systems depending on their reduction-oxidation potential. Uranium is present in the soil primarily in the U (+VI) state as the uranyl cation. This is the most mobile form of uranium, and it is highly soluble in this state, while U (+IV) is much less soluble. In both soil and water, uranium can form complexes with sulfate, phosphate, carbonate, and hydroxide. These complexes also increase the total solubility of uranium. However, the linear uranyl oxycation and carbonate complexes of uranium are the dominant species in solution. In body fluids, uranium is dissolved as the uranyl ion, an ionic form that may react with biological molecules (Shahandeh and Hossner 2002). Absorption of DU into the blood and deposition in tissues and organs depend mostly on particle size and solubility of the uranium-containing particle. Solubility determines the rate of absorption from the lungs. Soluble chemical forms of uranium are absorbed within days, while insoluble forms can take from months to years. Insoluble particles deposited in the lung and lymph nodes and retained for extended periods of time are more likely to be associated with the radiation effects of uranium, while more soluble forms are associated with toxic chemical effects. In the blood, uranium can form a complex with bicarbonate and bind to plasma proteins or erythrocytes, and up to 90% of the dissolved uranium is excreted in urine within the first few days of exposure. The remaining 10% is deposited in the bones, kidneys, and other organs from where it is mobilized over a longer period of time (Malaviya and Singh 2012). Long-lived isotopic U is not well absorbed from the gastrointestinal (GI) tract in humans, and uranium oxide absorption is estimated at 1–2% with the bulk passing through the GI tract in feces (Wrenn et al. 1985; Lawrence et al. 2014). However, in rats, U-233 absorption from the GI tract takes place in the small intestine, probably via a transcellular pathway (Dublineau et al. 2005). The chemical speciation of uranium may play a role in this process.

It appears that different isotopic compositions of uranium like many other heavy metals can penetrate to the subcellular level resulting in bioaccumulation and initiation of oxidative stress in zebrafish tissues (Barillet et al. 2007). At subtoxic concentrations (>100 μm), depleted uranium precipitates mainly in the nucleus of the human kidney, liver, and neuronal cell lines (Rouas et al. 2010). Chemically, uranium can activate oxygen species in the course of redox reactions via the redox chemistry of transition metals (Yazzie et al. 2003) and enhance free radical production via the ionization phenomenon induced by alpha particle emissions to produce DNA damage in the form of double-strand breaks (Miller et al. 2002a; National Academies Press 2012). Although uranium can emit alpha, beta, and gamma radiation, alpha particle emissions are of the greatest relevance in relation to depleted uranium (Hon et al. 2015). Thus, uranium is capable of initiating chemotoxicity and radiotoxicity (Ng et al. 2015) via the generation of free oxygen species and possibly via other more direct mechanisms in cells. Both biochemical pathways can stimulate cell death or apoptosis, which has been linked to carcinogenesis in various cancer

models. The loss of equilibrium between cell proliferation and cell death in a tissue may play a crucial role in tumor formation (Siddoo-Atwal 2009; Siddoo-Atwal 2017a).

17.4.3 Cancer Risk Assessment

Although the cancer data on depleted uranium alone is still sparse, it is possible to analyze the combined carcinogenic potential of uranium isotopes based on the existing data according to a new method of cancer risk assessment that relies on epidemiology, animal data, and cell studies. Recently, it has become apparent that the pathogenesis of cancer is closely connected with aberrantly regulated apoptotic cell death and the resulting deregulation of cell proliferation (Denmeade AND Isaacs 1996; Martin 2006). In fact, the initiation of uncontrolled apoptosis in a tissue can serve as the trigger for carcinogenesis (Siddoo-Atwal 2017b, 2019).

A distinct biological effect on wildlife has been observed for various isotopes of uranium. An irregular distribution of U-234 and U-238 has been found in the tissues of marine birds from the Polish area of the southern Baltic Sea. The highest accumulation occurs in the liver and other organs along with the feathers, while the smallest accumulation occurs in the skin and muscles with apparent interspecies differences (Boryko et al. 2010). Depleted uranium can cause adverse reproductive effects in terrestrial animals, and the likelihood of this occurring can range from 0.1% to 44% between various species (Fan et al. 2005).

Epidemiologically, there have been reports of an increased incidence of birth defects and, possibly, infant mortality in Iraq since the advent of the Gulf War (Alaani et al. 2011). In addition, an increased incidence of congenital anomalies and perinatal mortality has been reported in Kuwaiti newborns, and birth defects have been reported in the newborns of Gulf War veterans (Araneta et al. 1997, 2000, 2003; Doyle et al. 2004). A statistically significant relationship was also found between birth defects and the mother's proximity to uranium tailings among Native American Navajo in a uranium-mining area of the United States (Shields et al. 1992).

Some studies with US Gulf War veterans have reported cancers of the upper aerodigestive tract, lymphoma, and leukemia as health consequences of DU exposure (Bertell 1999; McDiarmid et al. 2000; Cannova 1998). WHO statistics for the years 1998–2000 suggest an elevation in lymphoma and leukemia incidence for the Eastern Mediterranean region affected by the Gulf War (Shawky 2003). The overall incidence of breast and lung cancer, leukemia, and lymphoma has doubled or tripled in certain areas of Iraq contaminated with DU during the Gulf War (Fathi et al. 2013; Busby et al. 2010). Interestingly, according to WHO, there also appears to be an elevated incidence in cancers of the trachea, bronchi, and lungs in Europe during the years 1998–2000 possibly due to other regional wars (Shawky 2003). DU weapons were deployed in Bosnia and Serbia, as well.

In addition, an association with lung cancer has been found in uranium miners (Grosche et al. 2006). It is strongly linked to exposure with radon, which is one of the

decay products of natural uranium. Miners are also at risk as a result of exposure to radioactive *alpha*, *beta*, and *gamma* emissions from uranium, which may act as a carcinogen or cocarcinogen in this model (National Academies Press 2012).

Moreover, in South Carolina, it has been found that regions with elevated groundwater uranium and more groundwater use may have an increased incidence of certain cancers, including kidney, breast, colorectal, and prostate (Wagner et al. 2011).

In animal studies, reproductive toxicity and teratogenicity have been observed in mice following maternal uranium exposure at different gestation periods (Domingo 2001). Like other heavy metals, depleted uranium in drinking water has estrogenic activity and acts like estrogen in the reproductive tract of female mice leading to an increased risk of fertility problems (Raymond-Whish et al. 2007). In addition, DU exposure of wild-type and metallothionein-deficient mice has been shown to result in ROS production and cell apoptosis in the kidney. The MT-deficient mice were more susceptible to both effects suggesting a protective role for metallothionein in DU nephrotoxicity (Hao et al. 2015). Implantation of DU metal fragments in rats led to the development of soft tissue sarcomas (Hahn 2002).

In cell studies, depleted uranium-uranyl chloride has been found to induce apoptosis in mouse J774 macrophages (Kalinich et al. 2002). In rat lung epithelial cells, uranium induces significant oxidative stress followed by a decrease in antioxidant potential of the cells and a decreased proliferation rate (Periyakaruppan et al. 2007). Mitochondrial membrane collapse, mitochondrial swelling, and cytochrome c release associated with apoptosis have been observed following uranyl acetate treatment of isolated rat kidney mitochondria (Shaki et al. 2012). Studies with human osteosarcoma cells (HOS) demonstrate that DU exposure results in genomic instability manifested as delayed reproductive death and micronuclei formation (Miller et al. 2003). DU exposure also causes neoplastic transformation of immortalized HOS cells (Miller et al. 2002b). Particulate DU is cytotoxic and clastogenic in human bronchial fibroblasts (Wise et al. 2007). In human kidney cells (HK-2), pre-treatment with zinc significantly inhibits DU-induced apoptosis. It does this by reducing reactive oxygen species (ROS) production in cells and increasing catalase (CAT) and glutathione (GSH) concentrations, suppressing the DU-induced soluble FAS receptor and FAS ligand overexpression, suppressing caspase activation, and suppressing the release of cytochrome c and apoptosis-inducing factor (AIF) translocation from mitochondria to cytoplasm and nucleus, respectively. AIF is involved in the caspase-independent apoptotic pathway and can act directly to cause chromatin condensation and DNA breaks. In fact, all these events inhibited by zinc are linked to biochemical pathways for triggering cellular apoptosis via caspase-dependent or caspase-independent mechanisms (Hao et al. 2014).

17.4.4 Heavy Metal Chelation Therapy

In the 1940s, animal studies found that citrate salts like sodium citrate administered intravenously or orally provided significant protection from uranium poisoning. Subsequently, it was reported that uranium can be precipitated with citric acid by forming a metal-citrate complex (uranyl citrate) under certain chemical conditions. This may still be the most practical treatment to employ in conflict areas where DU weapons have been used and metal chelation therapy is not available. Citric acid and/or citrate consumption could be recommended to individuals exposed to the easily inhaled uranium oxide aerosols resulting from DU penetrators since it seems to be effective even when taken orally (Lawrence et al. 2014).

Later, metal chelation agents were tested for their capacity to increase urinary excretion of the uranyl ion and included tiron, gallic acid, diethylenetriaminepentaacetic acid (DTPA), p-aminosalicylic acid, sodium citrate, EDTA, 5-aminosalicylic acid, and ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA). These eight substances were tested as antidotes for acute uranium poisoning in mice and significantly increased survival rate (Ortega et al. 1989).

EDTA and DMSA have both been used as chelation agents for uranium and other heavy metal detoxification in humans. EDTA (ethylenediaminetetraacetic acid) is a synthetic amino acid food preservative that binds to various heavy metals in the body and removes them through the urine. It is administered intravenously and has been in use for nearly 50 years to treat heavy metal toxicity (Dean 2018a). Na-Ca-EDTA chelates are rapidly excreted and, generally, cause greater losses of essential minerals from the body than DMSA. EDTA has been found to be most effective in removal of lead, cadmium, and mercury (Sears 2013). DMSA (meso-2,-3-dimercaptosuccinic acid) is a sulfhydryl-containing, water-soluble, nontoxic, orally administered metal chelation agent. It has been used to treat heavy metal toxicity, particularly lead and mercury poisoning, since the 1950s. The low toxicity and efficacy of DMSA makes it the primary metal chelator of choice for removal of mercury and other heavy metals. It is also very safe and causes few side-effects. The DMSA-metal conjugates are expelled through the urine (Dean 2018b). Oral absorption of DMSA is approximately 20% with most DMSA in the blood plasma being bound to protein, mainly albumin (95%). 10–25% of orally administered DMSA is excreted in the urine, mostly within 24 h of administration. Excretion of trace elements including zinc, iron, calcium, and magnesium is much less than with Na-Ca-EDTA. Copper may be an exception (Sears 2013).

However, the individual efficacies of EDTA and DMSA for uranium detoxification are not widely documented since they have not been specifically engineered as uranium chelators. Nevertheless, an approximation of their relative efficiencies may be gained by considering the results of a case study (*in press*) in which 90 ug of uranium was completely cleared from a subject's body after two metal chelation treatments with EDTA (1900 mg) and DMSA (500 mg). According to the WHO, approximately 90 μg of uranium exist in the human body on average from normal intakes of water, food, and air (https://www.who.int/ionizing_radiation/pub_meet/

en/DU_Eng.pdf?ua=1). So, these results are not staggering, especially since the average body burden of uranium was found to be 100 times greater than the normal range in urine samples collected from a civilian population in Eastern Afghanistan following the use of depleted uranium bombs by Allied Forces in 2002 (Durakovic 2005). In some cases, uranium concentrations up to 200 times higher than in the control population were detected in affected districts (Durakovic 2003).

Moreover, metal chelation therapy is a lengthy, unpleasant, and costly treatment for patients to undergo. It is inefficient and depletes the body of essential micronutrients. Therefore, it is necessary to develop more efficient chelating agents that are specifically engineered for targeting uranium. Some interesting preliminary experiments in DU-poisoned human renal proximal tubule epithelium (HK-2) cells with Cu^{2+}-imprinted chitooligosaccharides have shown that these molecules can selectively chelate DU outside cells and reduce cellular DU accumulation in a dose-dependent manner. They also significantly reduce loss of cell viability induced by DU by preventing its cellular internalization. In addition, treatment with these chitooligosaccharides appears to increase the activity of antioxidant enzymes and to reduce membrane damage and DNA damage caused by DU oxidant injury as compared to a control drug (Zhang et al. 2011).

17.4.5 Zinc Supplementation and Metallothionein

Metallothioneins (MTs) are small, cysteine-rich proteins that bind heavy metals and participate in an array of protective stress responses (Ruttkay-Nedecky et al. 2013). Inside the cell, the harmful effects of free radicals are balanced by the antioxidant action of antioxidant enzymes and nonenzymatic antioxidants. MTs are found in bacteria, plants, invertebrates, and vertebrates. There are four main mammalian MT isoforms (MT-1–MT-4) with distinct roles in different tissues. Aerobic organisms are susceptible to damage by reactive oxygen species (ROS) and reactive nitrogen species (RNS). MT protects cells from exposure to various free radical species like the hydroxyl, peroxyl, alkoxyl, and superoxide anion radical and the nitric oxide and nitric dioxide radicals, which react readily with sulfhydryl groups. MT is also important for the regulation of zinc levels and the distribution of this metal in the extracellular space. Since zinc cannot pass easily through membranes, zinc-transporting proteins, ZIPs (Zrt-Irt-like protein or zinc iron permease), and ZnTs (zinc transporters) help to facilitate this process. The presence of zinc(II) within the cell causes an increase in the major zinc-binding protein metallothionein, and it binds to MTs forming a thermodynamically stable complex. MT can be activated by various stimuli including heavy metal ions, cytokines, growth factors, and oxidative stress within the cell. Cells that display high MT production are resistant to heavy metal toxicity by cadmium, whereas cell lines that cannot synthesize MTs are sensitive to the toxic effects of cadmium (Ruttkay-Nedecky et al. 2013).

One fascinating study with rats indicated that pre-treatment with zinc has protective effects against depleted uranium toxicity. Posttreatment with zinc also had a

protective effect but to a lesser extent. In fact, the pre-treated group had a 60% higher rate of survival than the untreated group. Blood urea nitrogen, creatinine, and urine *N*-acetyl-β-D-glucosaminidase concentrations were significantly decreased. The gene expression levels of metallothionein (MT) in kidney tissues were significantly increased, and catalase levels were increased, as well. Thus, the protective mechanism that alleviated DU toxicity appeared to be related to the induction of MT synthesis and the enhancement of antioxidant function (Hao et al. 2012). It is quite possible that this result could extend to humans given that these multifunctional proteins are so well-conserved from nematodes to mammals (Isani and Carpene 2014) and zinc fortification may be worth investigating.

In rats, rice fortified with zinc oxide or zinc carbonate is a feasible vehicle for zinc absorption, although zinc oxide displays lower bioavailability than zinc carbonate (Lucia et al. 2014). In young adults, zinc absorption from supplemental zinc citrate is comparable with that from zinc gluconate but higher than from zinc oxide (Wegmuller et al. 2014).

17.5 Conclusions

The biochemical detoxification of uranium in humans is still not completely understood. It appears to activate various antioxidant enzyme activities in mammals including superoxide dismutase, catalase, and glutathione enzymes, although, the results between treatment with depleted uranium and enriched uranium are not always comparable and may vary between tissues. Nevertheless, it is known that depleted uranium/natural uranium chemotoxicity and radiotoxicity can occur through the generation of free radical species and initiation of DNA damage (double-strand breaks) within the cell resulting in apoptosis. Apoptotic deregulation is increasingly viewed as a major mechanism for carcinogenesis.

Epidemiological data suggests that uranium is implicated in the etiology of lymphoma, leukemia, renal, and respiratory tract cancers. Animal studies indicate reproductive toxicity and teratogenicity as a result of uranium exposure. DU displays estrogenic activity leading to an increased risk of fertility problems in mice, and it can cause cell apoptosis in mouse kidney. Cell studies show that depleted uranium-uranyl chloride causes apoptosis in mouse macrophages and uranium promotes oxidative stress in rat lung epithelial cells which can also induce apoptosis. Events associated with apoptosis have been observed following uranyl acetate treatment of isolated rat kidney mitochondria. In human osteosarcoma cells, DU exposure results in genomic instability, and, in human kidney cells, DU induces apoptosis. DU is cytotoxic and clastogenic in human bronchial fibroblasts. Therefore, according to the new approach to cancer risk assessment, it is highly likely that certain uranium isotopes including those of depleted uranium are implicated in respiratory disorders and lung cancer in humans. DU is also nephrotoxic in nature resulting in various renal effects such as chronic kidney disease, and it has the potential for causing renal cancer via the initiation of apoptosis. Additionally, it is probable that uranium can

cause lymphoma and leukemia. Apoptotic assays should be carried out in human lymphocytes and other white blood cells to further test the carcinogenic potential of isotopic uranium in these tissues.

Metal chelation therapy and citrate and zinc supplementation may represent possible methods of uranium detoxification. There is no published data relating to the effectiveness or viability of these treatments in patients with 100 or 200 times the normal body burden of uranium. Since metal chelation depletes the body of micronutrients, which need to be replenished, and only removes a limited quantity of toxic elements, which can be redistributed from less accessible to more accessible body compartments following therapy, such a course of treatment might extend over a period of several years. Therefore, a more practical solution like the development of uranium-specific chelating agents is necessary.

Traditional methods of soil remediation are costly and labor-intensive (a typical project can cost more than $200–300 billion), while phytoremediation represents a newer, more economic, and environmentally friendly approach to cleaning up heavy metal and radionuclide contamination. On the downside, the latter has low extraction efficiency, generates large quantities of contaminated biomass, and requires long periods to complete the decontamination process. The aim of soil amendments is mainly metal immobilization and/or inactivation, while the main aim of phytoremediation is metal hyperaccumulation in various plant parts, and a combination of these two methods can be effective in the remediation of contaminated agricultural soils. However, few reports of the application of such combined techniques to cases of uranium contamination appear in the scientific literature suggesting that it is a relatively new field of research. Therefore, it is not possible to judge their efficacy for uranium removal as yet. Other biotechnological approaches that are currently being tested and may be applied to this type of pollution in the future include biomineralization (mineral synthesis by living organisms or biomaterials), biosorption (via dead microbial and renewable agricultural biomass), dendroremediation (growing trees in polluted soils), biostimulation (stimulating living microbial populations adapted to accumulating the pollutant), mycoremediation (stimulating living fungal/mycelial ultrafiltration), cyanoremediation (stimulating algal mass for remediation), and genoremediation (stimulating specific genes for remediation through selection or genetic engineering of transgenic plants) (Mani and Kumar 2014).

Uranium contamination due to the continued use of depleted uranium weapons and nuclear accidents has potentially far-reaching consequences for humans and wildlife populations. In fact, DU could prove to be an unprecedented ecological hazard. Moreover, the remediation of uranium and other related radionuclide contamination is an extremely complex and expensive biological and environmental problem. Currently, there is limited data available on effective remediation methods for the removal of uranium in contaminated areas. Furthermore, remediation measures are of indeterminate efficiency as the ratio of uranium contamination to soil, uptake by plant species, and the total body burden in humans increases. As a primary health and ecological measure, it is suggested that an immediate global ban should

be placed on the use and manufacture of DU weapons. Violators of the ban should be made to bear all remediation and public health costs.

Acknowledgments I am grateful for discussions with a bright, young geologist, Talya Grewal, that helped to shape this chapter.

References

Akob DM, Mills HJ, Kostka JE (2007) Metabolically active microbial communities in uranium-contaminated subsurface sediments. FEMS Microbiol Ecol 59:95–107

Alaani S, Savabieasfahani M, Tafash M, Manduca P (2011) Four polygamous families with congenital birth defects from Fallujah, Iraq. Int J Environ Res Public Health 8:89–96

Araneta MRG, Moore CA, Olney RS, Edmonds LD, Karcher JA, McDonough C, Hiliopoulos KM, Schlangen KM, Gray GC (1997) Goldenhar syndrome among infants born in military hospitals to Gulf War veterans. Teratology 56:244–251

Araneta MRG, Destiche DA, Schlangen KM, Merz RD, Forrester MB, Gray GC (2000) Birth defects prevalence among infants of Gulf war veterans born in Hawaii, 1989–1993. Teratology 62:195–204

Araneta MR, Schlangen KM, Edmonds LD, Destiche DA, Merz RD, Hobbs CA, Flood TJ, Harris JA, Krishnamurti D, Gray GC (2003) Prevalence of birth defects among infants of Gulf War veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989–1993. Birth Defects Res A Clin Mol Teratol 67:246–260

Barillet S, Adam C, Palluel O, Devaux A (2007) Bioaccumulation, oxidative stress, and neurotoxicity in *Danio rerio* exposed to different isotopic compositions of uranium. Environ Toxicol Chem 26:497–505

Bassett SH, Frenkel A, Cedars N, Van Alstine H, Waterhouse C, Cusson K (1948) The excretion of hexavalent uranium following intravenous administration. II. Studies on human subjects. The University of Rochester, Rochester, URB37, Washington, DC

Bertell R (1999, May) Gulf war veterans and depleted uranium. Hague peace conference

Bleise A, Danesi PR, Burkart W (2003) Properties, use and health effects of depleted uranium (DU): a general overview. J Environ Radioact 64:93–112

Boryko A, Skwarzec B, Fabisiak J (2010) Bioaccumulation of uranium ^{234}U and ^{238}U in marine birds. J Radioanal Nucl Chem 284:165–172

Briner WE (2006) The evolution of depleted uranium as an environmental risk factor: lessons from other metals. Int J Environ Res Public Health 3:129–135

Busby C, Hamdan M, Ariabi E (2010) Cancer, infant mortality and birth sex-ratio in Fallujah, Iraq 2005–2009. Int J Environ Res Public Health 7:2828–2837

Cannova JV (1998) Multiple giant cell tumors with Gulf War syndrome. Mil Med 163:184–185

Cardenas E, Wu W-M, Leigh MB, Carley J, Carroll S, Gentry T, Luo J, Watson D, Gu B, Ginder-Vogel M, Kitanidis PK, Jardine PM, Zhou J, Criddle CS, Marsh TL, Tiedje JM (2008) Microbial communities in contaminated sediments, associated with bioremediation of uranium to submicromolar levels. Appl Environ Microbiol 74:3718–3729

Chen SB, Zhu YG, Hu QH (2005) Soil to plant transfer of ^{238}U, ^{226}Ra and ^{232}Th on a uranium mining-impacted soil from southeastern China. J Environ Radioact 82:223–236

Dean W (2018a) Chelation with EDTA: a food additive with many remarkable properties. Anti-aging and life extension medicine

Dean W (2018b) DMSA and detoxifying heavy metals. Anti-aging and life extension medicine

Denmeade SR, Isaacs JT (1996) Programmed cell death (Apoptosis) and cancer chemotherapy. Cancer Control 3:303–309

Domingo JL (2001) Reproductive and developmental toxicity of natural and depleted uranium: a review. Reprod Toxicol 15:603–609
Doyle P, Maconochie N, Davies G, Maconochie I, Pelerin M, Prior S, Lewis S (2004) Miscarriage, stillbirth and congenital malformation in the offspring of UK veterans of the first Gulf war. Int J Epidemiol 33:74–86
Dublineau I, Grison S, Baudelin C, Dudoignon N, Souidi M, Marquette C, Paquet F, Aigueperse J, Gourmelon P (2005) Absorption of uranium through the entire gastrointestinal tract of the rat. Int J Radiat Biol 81:473–482
Durakovic A (2001) On depleted uranium: Gulf war and Balkan syndrome. Croat Medl J 42:130–134
Durakovic A (2003) Undiagnosed illnesses and radioactive warfare. Croat Medl J 44:520–532
Durakovic A (2005) The quantitative analysis of uranium isotopes in the urine of the civilian population of eastern Afghanistan after operation enduring freedom. Mil Med 170:277–284
Dushenkov S (2003) Trends in phytoremediation of radionuclides. Plant Soil 249(1):167–175
Eapen S, D'Souza SF (2004) Prospects of genetic engineering of plants for phytoremediation of toxic metals. Biotechnol Adv 23:97–114
Echevarria G, Sheppard MI, Morel J-L (2001) Effect of pH on the sorption of uranium in soils. J Environ Radioact 53:257–264
European Commission Brussels, 17.3.2016 SWD (2016) SWD 2016_64_F1_IMPACT_ASSESMENT_EN_V6_P2_839082.pdf
Fan M, Thongsri T, Axe L, Tyson TA (2005) Using a probabilistic approach in an ecological risk assessment simulation tool: test case for depleted uranium (DU). Chemosphere 60:111–125
Fathi RY, Al-Salih HS, Matti LY, Godbold DL (2013) Environmental pollution by depleted uranium in Iraq with special reference to Mosul and possible effects on cancer and birth defect rates. Med Confl Surviv 29:7–25
Fields MW, Yan T, Rhee S-K, Carroll SL, Jardine PM, Watson DB, Criddle CS, Zhou J (2005) Impacts on microbial communities and cultivable isolates from groundwater contaminated with high levels of nitric acid–uranium waste. FEMS Microbiol Ecol 53:417–428
Francis AJ, Dodge CJ (1998) Remediation of soils and wastes contaminated with uranium and toxic metals. Environ Sci Technol 32:3993–3998
Friberg L, Nordberg GF, Vouk VBGFBN, Nordberg M, Friberg L (1986) General aspects, handbook on the toxicology of metals, vol 1. Elsevier, Amsterdam
Gadd GM (1993) Interactions of fungi with toxic metals. New Phytol 124:25–60
Gadd GM (2010) Metals, minerals and microbes: geomicrobiology and bioremediation. Microbiology 156:609–643. https://doi.org/10.1099/mic.0.037143-0
Grosche B, Kreuzer M, Kreisheimer M, Schnelzer M, Tschense A (2006) Lung cancer risk among German male uranium miners: a cohort study, 1946–1998. Br J Cancer 95:1280–1287
Gueguen Y, Rouas C, Monin A, Manens L, Stefni J, Delissen O, Grison S, Dublineau I (2014) Molecular, cellular, and tissue impact of depleted uranium on xenobiotic-metabolizing enzymes. Arch Toxicol 88:227–239
Hahn FF, Guilmette RA, Hoover MD (2002) Implanted depleted uranium fragments cause soft tissue sarcomas in the muscles of rats. Environ Health Perspect 110:51–59
Hao Y, Ren J, Liu J, Luo S, Ma T, Li R, Su Y (2012) The protective role of zinc against acute toxicity of depleted uranium in rats. Basic Clin Pharmacol Toxicol 111:402–410
Hao Y, Ren J, Liu C, Li H, Liu J, Yang Z, Li R, Su Y (2014) Zinc protects human kidney cells from depleted uranium-induced apoptosis. Basic Clin Pharmacol Toxicol 114:271–280
Hao Y, Huang J, Gu Y, Liu C, Li H, Liu J, Ren J, Yang Z, Peng S, Wang W, Li R (2015) Metallothionein deficiency aggravates depleted uranium-induced nephrotoxicity. Toxicol Appl Pharmacol 287:306–315
Hon Z, Osterreicher J, Navratil L (2015) Depleted uranium and its effects on humans. Sustainability 7:4063–4077

Hudcova H, Badurova M, Rozkosny M, Sova J, Funkova R, Svobodova J (2013) Quality and mutagenicity of water and sediment of the streams impacted by the former uranium mine area Olší–Drahonín (Czech Republic). J Environ Radioact 116:159–165

Isani G, Carpene E (2014) Metallothioneins, unconventional proteins from unconventional animals: a long journey from nematodes to mammals. Biomolecules 4:435–457

Kalinich F, Ramakrishnan N, Villa V, McClain DE (2002) Depleted uranium–uranyl chloride induces apoptosis in mouse J774 macrophages. Toxicology 179:105–114

Katsenovich Y, Carvajal D, Guduru R, Lagos L, Li C-Z (2013) Assessment of the resistance to uranium (VI) exposure by *Arthrobacter* sp. isolated from Hanford site soil. Geomicrobiol J 30:120–130

Lawrence GD, Patel KS, Nusbaum A (2014) Uranium toxicity and chelation therapy. Pure Appl Chem 86(7). https://doi.org/10.1515/pac-2014-0109

Lestaevel P, Romero E, Dhieux B, Bensoussan H, Berradi H, Dublineau I, Voisin P, Gourmelon P (2009) Different pattern of brain pro-/anti-oxidant activity between depleted and enriched uranium in chronically exposed rats. Toxicology 258:1–9

Li J, Zhang Y (2012) Remediation technology for the uranium contaminated environment: a review. Procedia Environ Sci 13:1609–1615

Lu S, Zhao FY (1990) Nephrotoxic limit and annual limit on intake for natural U. Health Phys 58:619–623

Lucia CMD, Santos LLM, da Cruz Rodrigues KC, da Cruz Rodrigues VC, Martino HSD, Sant'Ana HMP (2014) Bioavailability of zinc in wistar rats fed with rice fortified with zinc oxide. Nutrients 6:2279–2289

Malaviya P, Singh A (2012) Phytoremediation strategies for uranium-contaminated environments: a review. Crit Rev Environ Sci Technol 42:2575–2647

Mani D, Kumar C (2014) Biotechnological advances in bioremediation of heavy metals contaminated ecosystems: an overview with special reference to phytoremediation. Int J Environ Sci Technol 11:843–872

Martin KR (2006) Targeting apoptosis with dietary bioactive agents. Exp Biol Med 231:117–129

Martinez RJ, Beazley MJ, Taillefert M, Arakaki AK, Skolnick J, Sobecky PA (2007) Aerobic uranium (VI) bioprecipitation by metal-resistant bacteria isolated from radionuclide- and metal-contaminated subsurface soils. Environ Microbiol 9:3122–3133

McDiarmid MA, Keogh JP, Hooper FJ, McPhaul K, Squibb K, DiPino R et al (2000) Health effects of depleted uranium on exposed Gulf War veterans. Environ Res 82:168–180

Merroun ML, Selenska-Pobell S (2008) Bacterial interactions with uranium: an environmental perspective. J Contam Hydrol 102:285–295

Middle East Eye -#SyriaWar - US Pentagon confirms it used depleted uranium in Syria; www.middleeasteye.net

Miller AC, Stewart M, Brooks K, Shi L, Page N (2002a) Depleted uranium-catalyzed oxidative DNA damage: absence of significant alpha particle decay. J Inorg Biochem 91:246–252

Miller AC, Xu J, Stewart M, Brooks K, Hodge S, Shi L, Page N, McClain D (2002b) Observation of radiation-specific damage in human cells exposed to depleted uranium: dicentric frequency and neoplastic transformation as endpoints. Radiat Prot Dosim 99:275–278

Miller AC, Brooks K, Stewart M, Anderson B, Shi L, McClain D, Page N (2003) Genomic instability in human osteoblast cells after exposure to depleted uranium: delayed lethality and micronuclei formation. J Environ Radioact 64:247–259

National Academies Press (2012) Uranium mining in Virginia: scientific, technical, environmental, human health and safety, and regulatory aspects of uranium mining and processing in Virginia. Chapter 5: Potential human health effects of uranium mining, processing, and reclamation. https://www.ncbi.nlm.nih.gov/books/NBK201047/

Ng CY, Pereir S, Cheng SH, Adam-Guillermin C, Garnier-Laplace J, Yu KN (2015) Combined effects of depleted uranium and ionising radiation on zebrafish embryos. Radiat Prot Dosim 167:311–315

Obralic N, Gavrankapetanović F, Dizdarević Z, Duric O, Sisic F, Selak I, Balta S, Nakas B (2004) Regional comparison of cancer incidence. Radiol Oncol 38:145–151
Ortega A, Domingo JL, Gomez M, Corbella J (1989) Treatment of Experimental Acute Uranium Poisoning by Chelating Agents. Pharmacol Toxicol 64:247–251
Periyakaruppan A, Kumar F, Sarkar S, Sharma CS, Ramesh GT (2007) Uranium induces oxidative stress in lung epithelial cells. Arch Toxicol 81:389–395
Prasad MNV, Freitas HMO (2003) Metal hyperaccumulation in plants - biodiversity prospecting for phytoremediation technology. Electron J Biotechnol 6. https://doi.org/10.2225/vol6-issue3-fulltext-6
Priest ND (2001) Toxicity of depleted uranium. Lancet 357:244–246
Raymond-Whish S, Mayer LP, O'Neal T, Martinez A, Sellers MA, Christian PJ, Marion SL, Begay C, Proper CR, Hoyer PB, Dyer CD (2007) Drinking water with uranium below the U.S. EPA water standard causes estrogen receptor–dependent responses in female mice. Environ Health Perspect 115:1711–1716
Rouas C, Bensoussan H, Suhard D, Tessier C, Grandcolas L, Rebiere F, Dublineau I, Taouis M, Pallardy M, Lestaevel P, Gueguen Y (2010) Distribution of soluble uranium in the nuclear cell compartment at subtoxic concentrations. Chem Res Toxicol 23:1883–1889
Ruttkay-Nedecky B, Nejdl L, Gumulrc J, Zitka O, Masarik M, Eckschlager T, Stiborova M, Adam V, Kizek R (2013) The role of metallothionein in oxidative stress. Int J Mol Sci 14:6044–6066
Salbu B, Krekling T (1998) Characterisation of radioactive particles in the environment. Analyst 123:843–850
Schnug E, Lottermoser BG (2013) Fertilizer-derived uranium and its threat to human health. Environ Sci Technol 47:2433–2434
Schnug E, Steckel H, Haneklaus S (2005) Contribution of uranium in drinking waters to the daily uranium intake of humans - a case study from Northern Germany. Landbauforschung Völkenrode 55:227–236
Sears ME (2013) Chelation: harnessing and enhancing heavy metal detoxification – a review. Sci World J 2013:219840. https://doi.org/10.1155/2013/219840
Shahandeh H, Hossner LR (2002) Role of soil properties in phytoaccumulation of uranium. Water Air Soil Pollut 141:165–180
Shaki F, Hosseini M-J, Ghazi-Khansari M, Pourahmad J (2012) Toxicity of depleted uranium on isolated rat kidney mitochondria. Biochim Biophys Acta 1820(12):1940–1950. – [BBA] general subjects
Shawky S (2003) Causes of death in the Eastern Mediterranean Region during the years 1998–2000. Saudi Med J 24:380–387
Sheppard SC, Evenden WG (1988) Critical compilation and review of plant/soil concentration ratios for uranium, thorium and lead. J Environ Radioact 8:255–285
Shields LM, Wiese WH, Skipper BJ, Charley B, Benally L (1992) Navajo birth outcomes in the Shiprock uranium mining area. Health Phys 63:542–551
Siddoo-Atwal C (2009) AT, apoptosis, and cancer: a viewpoint. Indian J Ecol 36:103–110
Siddoo-Atwal C (2017a) Heavy metal carcinogenesis: a possible mechanistic role for apoptosis. Vegetos 30(Special). https://doi.org/10.5958/2229-4473.2017.00046.5
Siddoo-Atwal C (2017b) A New Approach to Cancer Risk Assessment: An Overview. Publishing, Lambert Academic
Siddoo-Atwal C (2019) An approach to cancer risk assessment and carcinogenic potential for three classes of agricultural pesticide. In: Natural resource management: ecological perspectives. Springer, Cham, pp 109–132
Singh R, Gautam N, Mishra A, Gupta R (2011) Heavy metals and living systems: An overview. Indian J Pharm 43:246–253
Sitte J, Akob DM, Kaufmann C, Finster K, Banerjee D, Burkhardt E-M, Kostka JE, Scheinost AC, Buchel G, Kusel K (2010) Microbial links between sulfate reduction and metal retention in uranium- and heavy metal-contaminated soil. Appl Environ Microbiol 76:3143–3152

Suzuki Y, Banfield JF (2004) Resistance to, and accumulation of, uranium by bacteria from a uranium-contaminated site. Geomicrobiol J 21:113–121

Taylor MD (2007) Accumulation of uranium in soils from impurities in phosphate fertilisers. Landbauforschung Völkenrode 2:133–139

Thoennessen M (2016) The discovery of isotopes – a complete compilation. Springer, Cham

UBA website – website of the German Crop Protection Association (Fertilizer)

Vassilev A, Schwitzguebel J-P, Thewys T, van der Lelie D, Vangronsveld J (2004) The use of plants for remediation of metal-contaminated soils. Sci World J 4:9–34

Vicente-Vicente L, Quiros Y, Pérez-Barriocanal F, López-Novoa JM, López-Hernández FJ, Morales AI (2010) Nephrotoxicity of uranium: pathophysiological, diagnostic and therapeutic perspectives. Toxicol Sci 118:324–347

Wagner SE, Burch JB, Bottai M, Puett R, Porter D, Bolick-Aldrich TT, Wilkerson RC, Vena JE, Hebert JR (2011) Groundwater uranium and cancer incidence in South Carolina. Cancer Causes Control 22:41–50

Wall JD, Krumholz LR (2006) Uranium reduction. Annu Rev Microbiol 60:149–166

Wegmuller R, Tay F, Zeder C, Brnic M, Hurrell RF (2014) Zinc absorption by young adults from supplemental zinc citrate is comparable with that from zinc gluconate and higher than from zinc oxide. J Nutr 144:132–136

WHO – Depleted uranium sources, exposure, and health effects (online monograph)

Wise SS, Thompson WD, Aboueissa A-M, Mason MD, Wise JP (2007) Particulate depleted uranium is cytotoxic and clastogenic to human lung cells. Chem Res Toxicol 20:815–820

World Nuclear Association Website (updated 2017) What is Uranium? How does it work?

Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET, Willis DL (1985) Metabolism of ingested U and Ra. Health Phys 48:601–633

Yazzie M, Gamble SL, Civitello ER, Stearns DM (2003) Uranyl acetate causes DNA single strand breaks in vitro in the presence of ascorbate (vitamin C). Chem Res Toxicol 16:524–530

Zhang X-F, Ding C-J, Liu H, Liu L-H, Zhao C (2011) Protective effects of ion-imprinted chitooligosaccharides as uranium-specific chelating agents against the cytotoxicity of depleted uranium in human kidney cells. Toxicology 286:75–84

Zheng J, Zhao T, Yuan Y, Hu N, Tang X (2015) Hydrogen sulfide (H_2S) attenuates uranium-induced acute nephrotoxicity through oxidative stress and inflammatory response via Nrf2-NF-κB pathways. Chem Biol Interact 242:353–362