toxics

Review

The Chemistry and Toxicology of Depleted Uranium

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Abstract: Natural uranium is comprised of three radioactive isotopes: ^{238}U, ^{235}U, and ^{234}U. Depleted uranium (DU) is a byproduct of the processes for the enrichment of the naturally occurring ^{235}U isotope. The world wide stock pile contains some 1½ million tons of depleted uranium. Some of it has been used to dilute weapons grade uranium (~90% ^{235}U) down to reactor grade uranium (~5% ^{235}U), and some of it has been used for heavy tank armor and for the fabrication of armor-piercing bullets and missiles. Such weapons were used by the military in the Persian Gulf, the Balkans and elsewhere. The testing of depleted uranium weapons and their use in combat has resulted in environmental contamination and human exposure. Although the chemical and the toxicological behaviors of depleted uranium are essentially the same as those of natural uranium, the respective chemical forms and isotopic compositions in which they usually occur are different. The chemical and radiological toxicity of depleted uranium can injure biological systems. Normal functioning of the kidney, liver, lung, and heart can be adversely affected by depleted uranium intoxication. The focus of this review is on the chemical and toxicological properties of depleted and natural uranium and some of the possible consequences from long term, low dose exposure to depleted uranium in the environment.

Keywords: depleted uranium; DU chemistry; DU toxicology; DU munitions; DU friendly fire

1. Introduction

Natural uranium is comprised of three radioactive isotopes: ^{238}U, ^{235}U, and ^{234}U. The current generation of nuclear power reactors is based on the controlled fission of the ^{235}U in the fuel at concentrations enriched to some five fold greater than that occurring in nature. The residue from the enrichment process is the depleted uranium. The world wide stock pile of depleted uranium contains

more than 1½ million tons. Some of it has been used to dilute weapons grade uranium (~90% ^{235}U) down to reactor grade uranium (~5% ^{235}U) [1]. Among the other uses found for depleted uranium is the fabrication of munitions. Such weapons were used in the Persian Gulf, in the Balkans and elsewhere. The use of depleted uranium in armor-piercing bullets and missiles during wartime has resulted in environmental contamination and human exposure. The chemical properties and the toxicological behavior of depleted uranium are very similar to those of the natural uranium. The chemical and radiological toxicity of depleted uranium can injure biological systems. Normal functioning of the kidney, liver, and lung can be adversely affected by depleted uranium intoxication. This review describes depleted uranium munitions and focuses on the chemistry of depleted and natural uranium, their toxicological effects on several systems in the mammalian body and some consequences of long term, low dose environmental exposure. This review does not resolve the apparent divergence of opinions expressed a decade ago in the reviews prepared by Legget and Pellmar [2] and by Bleise, *et al*. [3] on the biological fate of depleted uranium shrapnel embedded in the soft tissue of wounded military personnel. It does, however, update some of the information in the subsequent reviews prepared by Craft *et al*. [4] and by Briner [5].

2. Occurrence of Uranium

Of the two and a half dozen known uranium isotopes, only three occur in nature. They are ^{234}U, ^{235}U, and ^{238}U. The radiological properties of these three as well as those of the other uranium isotopes have been compiled at Karlsruhe Kernforchungszentrum [6] and at Brookhaven National Laboratory [7]. These radiological properties are listed in Table 1.

Table 1. Uranium isotopes [a,b].

Naturally occurring isotopes			
Isotope	**Abundance ***	**Half life**	**Principle decay**
^{234}U	0.00054%	2.455×10^5 years	α: 4776 MeV
^{235}U	0.07204%	4.468×10^8 years	α: 4.398 MeV
^{238}U	99.2742%	4.468×10^9 years	α: 4.197 MeV
Other known isotopes			
Isotope	**Half life**		**Principle decay**
^{217}U	16 ms		α
^{218}U	1.5 ms [a]		α: 8.27 MeV
^{218}U	0.51 ms [b]		α
^{218m}U	0.56 ms		α
^{219}U	~42 μs		α: 9.68 MeV
^{220}U			
^{221}U	700 ns [b]		
^{223}U	18 μs		α: 8.78 MeV
^{224}U	0.7 ms		α: 8.47 MeV
^{224}U	0.9 ms [b]		α
^{225}U	95 ms		α: 7.88, 7.82 MeV
^{226}U	0.2 s		α: 7.57, 7.42 MeV
^{226}U	0.35 s [b]		α

Table 1. *Cont.*

Other known isotopes		
Isotope	**Half life**	**Principle decay**
^{227}U	1.1 min	α: 6.86, 7.06, 6.74 MeV
^{228}U	9.1 min	α: 6.68, 6.59 MeV
^{229}U	58 min	α: 6.36, 6.33, 6.30 MeV
^{230}U	20.8 days	α: 5.89, 5.82 MeV
^{231}U	4.2 days	α: 5.46, 5.47, 5.40 MeV
^{232}U	68.9 years	α: 5.32, 5.26 MeV
^{233}U	1.59×10^5 years	α: 4.82, 4.78 MeV
^{234}U	2.46×10^5 years	α: 4.77, 4.72 MeV
^{235}U	7.04×10^8 years	α: 4.40 MeV
^{236}U	2.34×10^7 years	α: 4.49, 4.45 MeV
^{237}U	6.75 days	β⁻: 0.2 MeV
^{238}U	4.47×10^9 years	α: 4.20 MeV
^{239}U	23.5 min	β⁻: 1.2. 1.3 MeV
^{240}U	14.1 h	β⁻: 0.4 MeV
^{242}U	16.8 min	β⁻: 1.2 MeV

* Isotopic abundance; [a] G. Phennig, H. Klewe—Nebenius, W. Seelmann—Eggebert, Karlsruher Nuklidkarte, 6 Auflage 1995, korrigierten 1998, Institut für Instrumentelle Analytic, 1998, Karlsruhe; [b] Chart of the Nuclides, National Nuclear Data Center, Brookhaven National Laboratory, Upton, NY. α = radioactive decay is by alpha emission, β⁻ = radioactive decay is by negatron emission.

Some of the primary and secondary uranium minerals are listed in Table 2. Major deposits of uranium ores are found in Canada and the U.S.A., in Brazil, in the Russian Federation, in Kazakhstan and Uzbekistan, in Namibia and South Africa and in Australia. The global distribution of uranium in the crust of the earth is approximately 2.3 mg/kg making it as common as tin, 2.1 mg/kg [8]. The mining, milling, refining and enriching of uranium as well as the security issues and the waste management strategies are beyond the scope of this review.

Table 2. Uranium ores.

Some primary uranium minerals	
Branneritem	UTi_2O_6
Coffinite	$U(SiO4)_{1-4}(OH)_{4-1}$
Davidite	$(REE)(Y,U)(Ti,Fe)_{20}O_{38}$
Pitchblende	U_3O_8
Urainnite	UO_2
Some secondary uranium minerals	
Autunite	$Ca(UO_2)_2(PO_4)_4 \cdot (8 \text{ to } 12)H_2O$
Camolite	$K_2(UO_2)_2(VO_4)_2 \cdot (1 \text{ to } 3)H_2O$
Seleeite	$Mg(UO_2)_2(PO_4)_2 \cdot 10H_2O$
Torbernite	$Cu(UO_2)_2(PO_4)_2 \cdot 12H_2O$
Tyuyamunite	$Ca(UO_2)_2(VO_4)_2 \cdot (5 \text{ to } 8)H_2O$
Uranocircite	$Ba(UO_2)_2(PO_4)_2 \cdot (8 \text{ to } 10)H_2O$
Uranophane	$Ca(UO_2)_2(HSiO_4)_2 \cdot 5H_2O$
Zeunerite	$Cu(UO_2)_2(AsO_4)_2 \cdot (8 \text{ to } 10)H_2O$

3. Physical Properties of Uranium

Elemental uranium is a dense, malleable and ductile, silvery-white metal. Typically depleted uranium contains as much as 70% less ^{235}U and as much as 80% less ^{234}U than does naturally occurring uranium. The enrichment process reduces the radioactivity of depleted uranium to approximately half of that of natural uranium. The isotopic distributions and their respective contributions to the radioactivity are summarized in Table 3 [9]. These data show the radioactivity of natural uranium is 25,280 Bq g^{-1}, and that of 3.5% enriched uranium is 81,508 Bq g^{-1} while that of depleted uranium from the 3.5% enrichment is only 14,656 Bq g^{-1}. This corresponds to a reduction of 42% in total radioactivity. The data presented by Bleise *et al.* [3] also show a reduction of 42% in the total radioactivity of depleted uranium compared to the radioactivity of natural uranium.

The physical properties of uranium are summarized in Table 4.

Table 3. Isotopic distributions in natural uranium, enriched uranium and depleted uranium [9].

Natural uranium			
	^{234}U	^{235}U	^{238}U
Mass %	0.0053	0.711	99.284
Radioactivity %	48.9	2.2	48.9
Activity, Bq g U^{-1}	12356	568	12356
Enriched (3.5%) uranium			
	^{234}U	^{235}U	^{238}U
Mass %	0.02884	3.5	96.471
Radioactivity %	81.8	3.4	14.7
Activity, Bq g U^{-1}	66703	2800	12500
Depleted uranium			
	^{234}U	^{235}U	^{238}U
Mass %	0.0008976	0.2	99.799
Radioactivity %	14.2	1.1	84.7
Activity, Bq g U^{-1}	2076	160	12420

Table 4. Physical properties of uranium metal.

Density (highly purified)	19.05 ± 0.02 gm cm^{-3}
Density (industrial grade)	18.85 ± 0.20 gm cm^{-3}
Melting Point	$1132 \pm 1\,°C$
Boiling Point	$3811 \pm 3\,°C$
Heat of Fusion	19.7 J mole^{-1}
Vapor Pressure at 1600 °C	10^{-4} mm
Thermal Conductivity at 70 °C	0.297 J (cm s °C)$^{-1}$
Electrical Resistivity at 25 °C	35×10^6 ohm cm^{-3}
Enthalpy at 25 °C	6364 J mole^{-1}
Entropy at 25 °C	58.2 ± 0.2 J (mole °C)$^{-1}$

4. Chemical Properties of Uranium

Gindler's [10] monograph provides much information on the chemistry of uranium and its compounds, and Roberts *et al.* [11] subsequently reported detailed analytical methodologies for the determination of uranium. Grenthe *et al.* [12] contributed a comprehensive chapter on the chemical and physical properties of uranium to a larger work on the chemistry of the actinides. This chapter includes descriptions of the processing and refining of uranium ores as well as material on the chemistry of uranium in solution.

In compounds, the oxidation number of uranium can range from 2 to 6. The oxidation-reduction chemistry of uranium is reflected by the standard reduction potentials listed in Table 5 [10,12].

Table 5. Standard reduction potentials.

Acidic solution	Gindler [10]	Grenthe *et al*. [12]
$UO_2^{2+} + e \rightarrow UO_2^{1+}$	0.05 V	0.0878 ± 0.0013 V
$UO_2^{1+} + 4\,H^{1+} + e \rightarrow U^{4+} + 2\,H_2O$	0.62 V	
$UO_2^{2+} + 4\,H^{1+} + 2\,e \rightarrow U^{4+} + 2\,H_2O$	0.334 V	0.2673 ± 0.0012 V
$U^{4+} + e \rightarrow U^{3+}$	−0.61 V	-0.553 ± 0.004 V
$U^{3+} + 3\,e \rightarrow U$	−1.80 V	
$U^{4+} + 4\,e \rightarrow U$	−1.38 V	
Alkaline solution		
$UO_2(OH)_2 + 2\,e \rightarrow UO_2$	−0.3 V	
$UO_2 + e \rightarrow U(OH)3$	−2.6 V	
$U(OH)_3 + 3\,e \rightarrow U$	−2.17 V	

In aqueous solutions of low pH, hexavalent uranium exists primarily as the yellow uranyl or dioxouranium (VI) ion, UO_2^{2+}. Some of its typical salts are: the nitrate, $UO_2(NO_3)_2$, the acetate, $UO_2(CH_3COO)_2$ and the sulfate, UO_2SO_4. Complexes of the uranyl ion with inorganic ligands include $[UO_2(NH_3)_2]^{2+}$, $[UO_2(CN)_4]^{2-}$, $[UO_2(CO_3)_2]^{2-}$, and $[UO_2F_3]^{1-}$ [13].

Complexes with bioligands are more relevant to the distribution of uranium in biological systems. The transport of uranium species in the blood most likely takes place as complexes with plasma proteins, erythrocytes and/or low molecular mass species. Gutowski *et al.* [14] suggested the histidine residues in plasma proteins were responsible for binding of the uranyl ion. On the basis of infrared spectroscopy, Raman spectroscopy, single crystal, X-ray crystallography and computational methods, they determined the binding of the uranyl ion with 1-methylimidazole (meimid) to form a complex of the type $UO_2(meimid)_2(CH_3COO)_2$. Coordination of the uranyl ion is at the nitrogen atoms with bond lengths of 2.528 Å. The lengths of the uranium-oxygen bonds are 1.775 Å.

Vanengelen *et al.* [15] reported the coordination of the uranyl ion with pyrroloquinoline quinone (PQQ) cofactor and its potential as an inhibitor of flavoproteins. Using ultraviolet-visible spectroscopy and electrospray ionization mass spectroscopy as well as density functional theory computations for geometric structural optimizations, a complex having the general formula of $UO_2(CO_3)(H_2O)_x(PQQ)$ with bonding of the uranyl ion to the carbonyl oxygen, the pyridine nitrogen and the quinone oxygen of the pyrroloquinoline quinone cofactor was proposed. They suggested, "…UO_2^{2+} may also coordinate with enzymes or enzyme cofactors responsible for Mn(II) oxidation." Previously,

Chinni *et al*. [16] reported the oxidation of UO_2 by biogenic MnO_2, and they suggested the possibility of a catalytic enhancement of UO_2 oxidation-MnO_2 reduction. Such a cycling would impact the environmental fate of tetravalent uranium compounds by formation of more mobile hexavalent uranium compounds.

Pible *et al*. [17] employed computational tools to identify calcium-dependent interactions between proteins and small molecules likely to be inhibited by complexation of the uranyl ion. Four proteins were selected for experimental evaluation: C-reactive protein (P02741), fructose-binding lectin PA-ILL (Q9HYN5), 3,4-dihydroxy-2-butanone 4-phosphate synthatase (Q60364) and Mannose-binding protein C (P08661). Biochemical experiments confirmed the predicted binding site for UO_2^{2+}, and surface Plasmon resonance assays demonstrated the binding of UO_2^{2+} prevented the calcium mediated binding of phosphorylcholine. Experiments such as these partially elucidate the toxicological responses to uranium and the understanding of uranium toxicity.

The basic uranyl unit is thought to be retained in the uranates, Na_2UO_4, $CaUO_4$, *etc*. X-ray diffraction studies indicate each uranium atom is bonded to two uranyl oxygen atoms by shorter (1.9 Å) bonds and oxide oxygen atoms by longer (2.3 Å) bonds [18]. Diuranates such as $(NH_4)_2U_2O_7$ are analogous to the dichromates. Uranyl salts are the usual product of uranate hydrolysis; *i.e.*,

$$UO_4^{2-} + 4\ H^{1+} \leftrightarrows UO_2^{2+} + 2\ H_2O \text{ and}$$

$$UO_2^{2+} + 4\ OH^{1-} \leftrightarrows UO_4^{2-} + 2\ H_2O$$
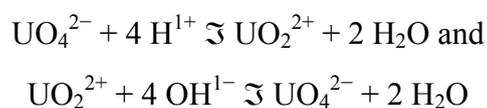
Pentavalent uranium is oxidized by atmospheric oxygen. In the absence of air, pentavalent uranium undergoes disproportionation to hexavalent and tetravalent compounds; *i.e.*,

$$U_2O_5 \rightarrow UO_2 + UO_3.$$

Tetravalent uranium compounds include the oxide, UO_2, the binary halides as well as the acetate, the sulfate and the perchlorate. Tetravalent uranium also exists as basic salts such as $UOCl_2$, $UO(NO_3)_2$ and $UO(CH_3COO)_2$. Aqueous solutions of tetravalent uranium compounds are green in color, and the tetravalent uranium compounds are stable in the absence of air. Carbonato- and oxalato-complexes are more stable.

Trivalent uranium compounds are red in color. In aqueous media, trivalent uranium compounds are readily oxidized with the liberation of hydrogen. Among the trivalent compounds are UCl_3 and $UH(SO_4)_2$. Typical examples of compounds containing U(III) are the so called double chlorides such as $RbUCl_4$ and complexes with 1-phenyl-2,3-dimethyl-5-pyrazolone [19].

Some of the divalent uranium compounds described by Grenthe *et al.* [12] are UO and US.

Elemental uranium is an active metal. It dissolves readily in hydrochloric acid and nitric acid but slowly in sulfuric acid. Uranium metal is unreactive with sodium hydroxide solutions. Finely divided uranium metal is pyrophoric. The metal can spontaneously ignite in air. A mixture of uranium oxides is produced in this combustion.
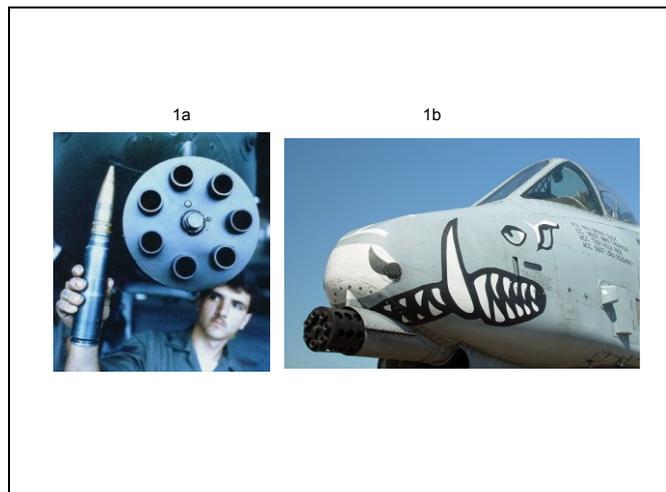
5. Depleted Uranium Penetrators

The pyrophoricity of uranium is among the properties considered in the selection of depleted uranium for the fabrication of high energy penetrators. A variety of depleted uranium munitions have

been developed and deployed. These depleted uranium penetrators are hardened by reducing the carbon content and by alloying with 0.75 percent by mass titanium during fabrication [3]. The high temperature generated by the impact with steel ignites the surface of a depleted uranium penetrator, and the projectile sharpens as it melts making it better able to pierce heavy armor. Depleted uranium projectile impacts are often characterized by round entry holes.

The 30-mm depleted uranium rounds were among the depleted uranium munitions used by the United States Air Force when Desert Shield became Desert Storm. They were able to pierce steel armor up to a thickness of 9 cm. This depleted uranium 30-mm ammunition consists of a conical penetrator 95 mm in length, 16 mm in diameter at the base and approximately 280 g in mass. The penetrator shown in Figure 1a is fixed in aluminum casing or jacket having a diameter of 30 mm and a length of 60 mm. The A-10 aircraft shown in Figure 1b is equipped with one gun capable of firing 3900 rounds per minute. A typical burst of fire from this gun usually has a duration of 2–3 s and involves between 130 and 190 rounds. Normally the depleted uranium ammunition is present in about 75% of the rounds. The remainder is traditional ammunition. The shots hit the ground in a straight line. Depending on the angle of approach, the shots hit the ground 1–3 m apart and cover an area of about 500 m^2. The number of penetrators striking the ground depends upon the type of target. Frequently, not more than 10% of the penetrators hit the target. When the penetrator hits a hard object such as an armored vehicle, the penetrator pierces the metal armor, generally leaving the jacket behind [20].

Figure 1. (**a**) Depleted uranium round (30 mm); (**b**) A-10 Warthog.

Among the munitions fired by the M1A1 Abrams tanks were 120 mm depleted uranium penetrators. The depleted uranium content of these munitions was 4.7 kg. The 120 mm ammunition consisted of a family of kinetic energy rounds and a family of high explosive anti-tank rounds. The kinetic energy rounds used a high length over diameter ratio sub-caliber projectile with a depleted uranium fin-stabilized rod as the penetrator element. Traveling at supersonic speed, this penetrator concentrated an extremely high level of kinetic energy over a relatively small surface area of the target. The high specific energy on target enabled the kinetic energy round to penetrate even the most resistive armor plates. All 120 mm rounds used a common combustible case which structurally combined the ammunition's components prior to firing and is completely consumed during firing. The combustible

case is the primary reason for the superior interior ballistics performance of the 120 mm ammunition [20].

The fires and explosions resulting from hard-target penetrations of depleted uranium munitions produce UO_2 and U_3O_8. As the uranium oxides weather in the environment, some UO_3 may be formed. Mitchel and Sunder [21] reported an X-ray diffraction analysis of the dust obtained from live firing of depleted uranium munitions showing the uranium was present as 47% U_3O_7, 44% U_3O_8 and 9% UO_2. The composition of the oxides is most likely variable, and it will change over time as weathering takes place.

Individual particles of depleted uranium collected from different sites in Kuwait were examined by scanning electron microscopy with X-ray fluorescence spectrometry for microanalysis and with synchrotron radiation based X-ray absorption near edge spectroscopy. The particles collected at the holes made in armored vehicles by depleted uranium penetrators had a median size of 13 μm. The median size of those collected at the site of a fire at a storage facility for depleted uranium munitions was 44 μm. The compositions of the smaller particles corresponded to UO_2 and U_3O_8 while the mu-XANES (micro X-ray absorption near edge structure) spectra of the larger particles indicated the presence of uranyl compounds [22].

The products from live fire tests with depleted uranium munitions against hard and soft targets and from unfired uranium munitions buried in soils for corrosion studies were collected and examined. On the basis of electron microscopic and X-ray spectrometric examinations, three classes of particles were identified: depleted uranium aerosol particulates with diameters ranging form 1 to 20 μm composed mainly of UO_2 and U_3O_8, fused uranium particles containing iron (most likely from the targets) having diameters between 200 and 500 μm and deposits on particles of sand up to 500 μm in diameter. Particles in the first two classifications were thought to be derived from live fire impacts while those in the last classification originated from corrosion of buried, unfired munitions [23].

A dust of uranium oxides is often formed during impact. This dust can be dispersed and contaminate the environment. An estimated from 10% to 35% of the depleted uranium penetrator can become aerosolized on impact or when the depleted uranium ignites [3].

Depleted uranium dust is black. Many sites impacted by depleted uranium ammunition frequently show this black dust on and around the target. After an attack with depleted uranium ammunition, this black dust this can be deposited on the ground and other surfaces as partially oxidized depleted uranium fragments of different size, and as uranium oxide dust. Most of the depleted uranium dust is deposited within 100 m of the hit target.

The majority of the penetrators impacting sand or clay usually remain intact after penetrating the ground to a depth of more than 50 cm. Those striking soft targets such as unarmored or lightly armored vehicles do not generate significant dust contamination. Weathering of intact and fragmented depleted uranium penetrators and the black dust produced from their detonation is variable depending on the chemical properties of surrounding soils and rocks. In quartz sand, granite, or acidic volcanic rock, solubilization rates may be high enough to lead to local contamination of groundwater. The actions of wind and water may redistribute the fine depleted uranium dust. However, following a sand storm in south western Iraq, Yousefi and Najafi [24] collected and analyzed air and soil samples to determine the transport of depleted uranium dust from Iraq to Iran. None was found. Adsorption onto soil particles, mainly clay particles and organic matter, can reduce mobility and the danger of

re-aerosolization. However, concern remains for the potential contamination of ground water after weathering of intact penetrators or large penetrator fragments.

Depleted uranium ordnance has been employed in at least three recent conflicts: the 1991 Iraq-Kuwait conflict, the 1995 Bosnia-Herzegovina conflict and the 1999 Kosovo-Serbia conflict. A summary of the depleted uranium weapons fired in these conflicts is presented in Table 6 [25]. This summary indicates that some 325 tons of depleted uranium have been introduced into the environment.

Table 6. Depleted uranium munitions deployed in recent military actions.

Action	Munitions	Total mass, tons
1991 Iraq-Kuwait	US Air Force 30 mm rounds	259
1991 Iraq-Kuwait	US Army 120 mm tank rounds	50
1991 Iraq-Kuwait	US Marine aviation rounds	11
1991 Iraq-Kuwait	UK 120 mm tank rounds	1
1995 Bosnia-Herzegovina	NATO 30 mm rounds	3
1999 Kosovo-Serbia	NATO 30 mm rounds	10

6. Exposure to Depleted Uranium

The isotopic composition of depleted uranium, as shown in Table 3 is dominated by ^{238}U at 99.977%. The percentages of ^{235}U and ^{234}U are 0.2% and 0.0008976%, respectively, which are below the natural values. All are long-lived alpha emitters as shown in Table 1. Like all radioactive nuclides, ^{238}U undergoes radioactive decay, and, within about six months, very small amounts of ^{234}Th, ^{234m}Pa, ^{234}Pa and ^{234}U are formed. They exist in a complicated equilibrium system with the ^{238}U. The decay scheme for ^{238}U and its progeny is shown in Figure 2. The progeny undergo sequential radioactive decays involving α and β emissions with some concurrent γ emissions to eventually become a stable isotope of lead, ^{206}Pb. The quantities of the intermediates are small, and their radiations like the α radiation from the parent ^{238}U present little, if any, external exposure hazard.

Figure 2. Decay chain for uranium-238.
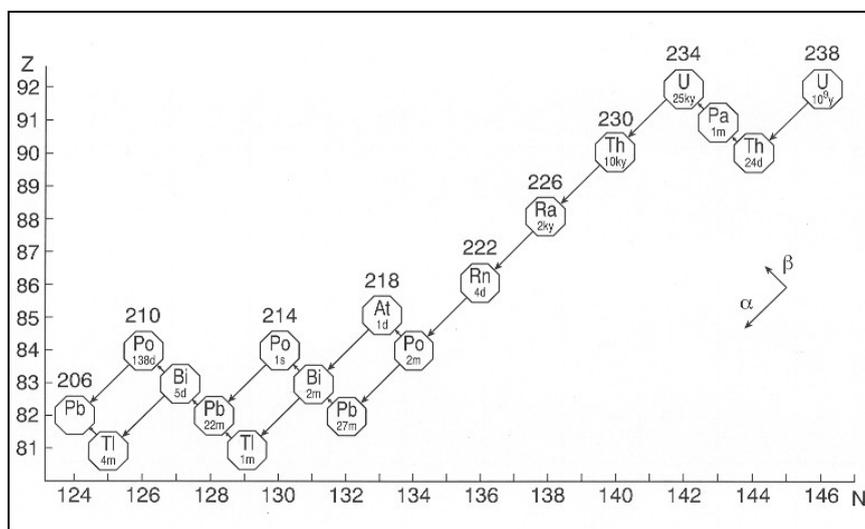
Depleted uranium can become an internal exposure hazard by inhalation, by ingestion, by percutaneous absorption, and by dermal penetration of shrapnel or other explosion fragments. Tasat and her collaborators [26] have conveniently classified these as the inhalation route, the oral route, the dermal route, and the subcutaneous entry route. The US EPA [27] considers inhalation to be the most likely route for the intake of depleted uranium. Likewise, the World Health Organization [28] considers inhalation to be "…the most likely route of intake during or following the use of depleted uranium munitions in conflict or when depleted uranium in the environment is resuspended in the atmosphere by wind or other disturbances Accidental inhalation may also occur as a consequence of fire in a depleted uranium storage facility, an aircraft crash or the decontamination of vehicles from within or near areas of conflict." The World Health Organization [28] has pointed out that ingestion can occur in a large section of a community or population if drinking water or food supplies become contaminated with depleted uranium. Using thermal ionization mass spectrometry, Sahoo *et al.* [29] determined the uranium contamination of surface and ground water in South Serbia as of both natural and anthropogenic origins. The annual effective dose due to ^{238}U was estimated to be in the range of 9.2×10^{-5} to 2.1×10^{-3} mSv. The hand to mouth ingestion by children of soil contaminated with the black dust could become an additional potential pathway for the ingestion of uranium. The World Health Organization [28] considered dermal contact as a "… relatively unimportant type of exposure since little of the depleted uranium will pass across the skin into the blood". A similar statement, "Dermal contact is considered unimportant since little of the DU will pass across the skin into the blood" was made by the US EPA [27]. The Toxicological Profile for Uranium [30] contains the tabulated results of numerous animal experiments on the dermal toxicity of many uranium compounds. A large majority of these animal experiments were conducted with water soluble uranium compounds. Evidence for the percutaneous absorption of uranium in the human has been reported [31]. In the course of patch testing veterans exposed to depleted uranium during the Gulf Wars for dermal sensitivity using aqueous uranyl acetate solutions, the detection of elevated uranium concentrations in 24 h urine samples was interpreted as evidence for percutaneous absorption. The uranium in the black dust resulting from the detonation of depleted uranium munitions is of low solubility in water. However, elevated concentrations of uranium in the urine of 32 Gulf war veterans who were known to have been injured by depleted uranium munitions some 12 years earlier were attributed to fragments of depleted uranium that remained imbedded in the tissues [32]. The environmental weathering of unexploded depleted munitions or the *in vivo* corrosion of depleted uranium shrapnel could result in the formation of soluble and physiologically active forms of uranium.

6.1. The Inhalation Route

In his review on the toxicity of depleted uranium, Briner [5] has written about a cloud of particles, ranging in size from 0.2 to 15 μm in median aerodynamic diameter and containing a variety of oxides, being produced when a depleted uranium penetrator is detonated. He wrote, "When these particles are inhaled, they are either trapped in the oropharynx, where they are eventually swallowed, or they reach the lower airways where they are subject to alveolar absorption. Alveolar absorption appears to occur in two phases. There appears to be an early rapid phase which results in peak plasma levels and then a decline followed by a prolonged period of steady absorption. It is unclear what accounts for this

biphasic pattern. It could be due to the heterogeneous chemistry of depleted uranium particles in the black dust. Some components may be more soluble than others. It could be due to the various sizes of inhaled particulates with those of a greater surface area to volume ratio dissolving quickly leaving behind those that dissolve more slowly. It may be due to an inflammatory response of the lung tissue that begins to retard absorption after a few days. Whatever the cause, the inhaled depleted uranium appears to have a pulmonary half life of about 4 years". Earlier Durakovic *et al*. [33] determined the minimum value for the biological half life of ceramic depleted uranium oxide in the lungs as 3.85 years. Valdéz [34] developed a linear model for estimating the lung burden of depleted uranium from measurement of depleted uranium in the urine. This model considered the intercellular dissolution of depleted uranium particles as well as the precipitation of a significant fraction of the dissolved depleted uranium as uranyl phosphate. Once desorbed from the lung, uranium becomes widely distributed throughout the body.

6.2. The Ingestion Route

Ingestion of depleted uranium is an additional exposure pathway. Uptake of uranium with drinking water is one of the major pathways for exposure to natural uranium, and possible for exposure to depleted uranium. Drinking water can become contaminated with depleted uranium from the black dust, munitions' fragments or penetrators buried in soil. Such contamination is strongly dependent on the chemical form of the depleted uranium, and the acidity and oxidation-reduction properties of the contaminated soil and ground water. Correlations between the ^{234}U to ^{238}U ratios in drinking water and the ^{234}U to ^{238}U ratios in the hair, nails, and urine have been reported for a group of 45 subjects who consumed from 0.2 to 2775 µg of uranium per day [35]. However, consuming up to 3000 µg of uranium per day in drinking water was not found to have cytotoxic effects on the kidney [36]. In addition to exposure to uranium in drinking water, direct ingestion of contaminated soil by children must be taken into consideration. Samples of soil from Kuwait and Kosovo known to be contaminated with depleted uranium were subjected to simulated gastric digestion with 0.16 M HCl. Between 73% and 96% of the depleted uranium particles in these soils were dissolved within one week indicating the potential for bioavailability by way of the ingestion route [37].

6.3. The Dermal Route

Percutaneous absorption is possibly one of the routes whereby uranium can intoxicate the body systemically. However, the amount of uranium absorbed depends on factors such as the solubility of the uranium compound, the length of time of exposure, the size of the area that is exposed, and other physical and physiological conditions. As described above, percutaneous absorption is not thought to be a major route to systemic intoxication.

6.4. The Subcutaneous Route

Wound contamination can occur during combat activities or later in the case of accidentally abrading of skin on contaminated surfaces. In the latter case, wound cleaning will be effective decontamination, and the resulting exposure to depleted uranium can be expected to be negligible.

However, embedded fragments not removed by surgical means can result in chronic, internal exposure. Sixty-two American soldiers, wounded with depleted uranium shrapnel when their tanks or armored vehicles were hit by friendly fire during the Gulf War were studied for the effects of embedded fragments of depleted uranium shrapnel in their bodies [38]. It was shown that the depleted uranium metal slowly solubilized in the body fluids, and that several years after the war, blood and urine levels of uranium were elevated by up to two orders of magnitude [39].

7. Toxicokinetics of Depleted Uranium

Leggett [40] reported on the development of the, International Commission on Radiological Protection (ICRP) age specific biokinetic model for uranium. The compartments for this model are shown in Figure 3 [41]. This model describes the deposition of uranium from the blood into various, compartments, the return of uranium to the blood, and the eventual excretion of uranium. In keeping with ICRP's move towards physiological realism in its models, the uranium model includes recycling, *i.e.*, the possibility for material to pass from compartment to compartment via the blood stream [42]. The model is based on a number of sources which include data from both animal experiments and studies on humans. Clearly human data is preferred, and for uranium, ICRP can draw on a large database. In particular, there are data from the so-called Boston Subjects, a group of terminally ill patients who were injected with uranium in the 1950s. A brief overview of the human data that support the ICRP model is given in ICRP-69 [35]. Other reviews are provided by Leggett and Harrison [43] and Leggett [44].

Figure 3. Biokinetic model for uranium [41].
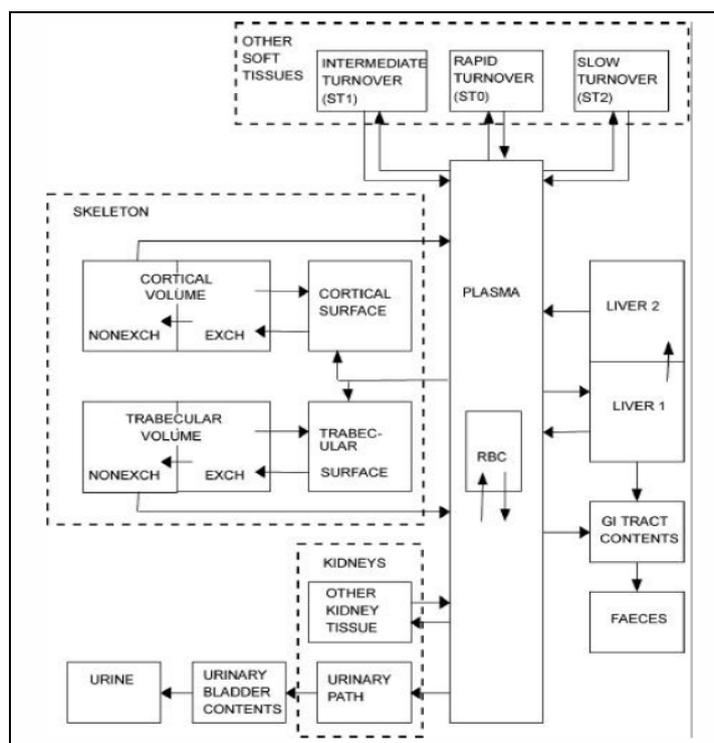
The principal sites of uranium deposition in the body are the kidneys, the liver, and the bones. In addition, some material is deposited in various other tissues generally at lower concentrations than the

main sites of deposition. These are usually referred to as "soft tissues". Of the amount absorbed into the blood stream, the ICRP model assigns 30% to soft tissues (rapid turnover, ST0 in Figure 3). This represents a pool of activity distributed throughout the body which exchanges rapidly with the blood stream. The remaining activity is apportioned as follows; kidneys 12%, liver 2%, bone 15%, red blood cells 1%, soft tissue (intermediate turnover, ST1 in Figure 3) 6.7%, soft tissue (slow turnover, ST2 in Figure 3) 0.3%, with 63% being promptly excreted in urine via the kidneys.

Some of the uranium initially deposited in these organs and tissues can be returned to the blood stream, and some can be transferred to other organs or tissues (Figure 3). For example, uranium in the soft tissue compartments can be returned only to the blood while uranium in the liver can be exchanged with blood or transferred to other regions of the liver (Liver 2 in Figure 3). The bone warrants additional comment. Uranium is initially deposited on the bone surface (either trabecular or cortical), from where it can be transferred to bone volume (exchangeable) or returned to the blood stream. Uranium which does reach the exchangeable bone volume can be buried deeper in the bone volume (non-exchangeable) or returned to the surface. Uranium in the non-exchangeable volume can be transferred slowly to the blood. All the pathways used in the model are illustrated in Figure 3. In time, most of the systemic uranium is excreted in urine via the kidneys. A small fraction is also excreted in the feces. The length of time material remains in these compartments is partly governed by a removal half time, *i.e.*, the time that it takes to remove half of the material present. This time varies from organ to organ. For example, the removal half time for ST0 is as little as two hours, while for ST2 it is one hundred years. The net or apparent time that it takes to halve the amount of material in an organ, however, can be very different from the removal half-time, since uranium is continually being re-deposited by the recycling nature of the model. The net half time thus results from a combination of removing existing uranium and depositing new uranium from the blood stream.

8. Toxicology of Depleted Uranium

The potential for the toxicity of uranium lies in its properties as a heavy metal and as a radioactive substance. It is difficult to distinguish between the chemical toxicity of uranium and its radiotoxicity. The very small amounts of ^{234}Th, ^{234m}Pa, ^{234}Pa and ^{234}U formed during the first few months by the radioactive decay of ^{238}U are most likely of little toxicological consequence. However, radiation-specific damage from depleted uranium has been demonstrated *in vitro* using human osteoblast cells. Significant elevations in dicentric frequency were observed after 24 h exposures to depleted uranium as 50 μM $UO_2(NO_3)_2$ compared to parallel exposures using 50 μM solutions of nickel and tungsten as the nitrates. Exposures to 50 μM ^{238}U-$UO_2(NO_3)_2$ (0.33 μCi g^{-1}), 50 μM DU-$UO_2(NO_3)_2$ (0.44 μCi g^{-1}) and 50 μM ^{235}U-$UO_2(NO_3)_2$ (2.2 μCi g^{-1}), showed that at equivalent micro-molar concentrations (50 μM) of $UO_2(NO_3)_2$, there was a specific activity (μCi g^{-1}) dependent increase in neoplastic transformation frequency suggesting that α radiation can play a role in depleted uranium induced biological effects [45]. This observation, however, does not negate the chemical toxicity of uranium. The ATSDR Toxicological Profile for Uranium [30] states, "The health effects associated with oral or dermal exposure to natural and depleted uranium appear to be primarily chemical in nature and not radiological, while those from inhalation exposure may also include a slight radiological component, especially if the exposure involves prolonged exposure to insoluble uranium

compounds. This profile is primarily concerned with the effects of exposure to natural and depleted uranium, but does include limited discussion regarding enriched uranium, which is considered to be more of a radiological than a chemical hazard. Also, whenever the term "radiation" is used, it applies to ionizing radiation and not to non-ionizing radiation". Some examples of the impact on enzyme systems of uranium, as uranyl salts, are the reversible inhibition of glucose-hexosediphosphate fermentation [46], the inhibition of S-adenosylmethionine synthetase [47], the inhibition of lactate dehydrogenase, pyruvate carboxykinase and glucose-6-phosphatase [48] and the inhibition of xenobiotic-metabolizing enzymes, CYP3A in particular [49].

8.1. Toxicity to the Lung

Inhalation studies with rats using 38-nm CMD nanoparticles in a nose-only exposure system showed that uranium was deposited in the respiratory tract and distributed to the blood, brain, skeleton, and kidneys. Of the uranium deposited in the lungs, some 20% was cleared with a half time of 2½ h, but the majority of the deposited uranium were cleared more slowly, $t_{1/2}$ = 141½ days [50]. The occurrence of lung cancer among uranium miners has been attributed to radon gas rather than uranium dust. There is a causal relationship between lung cancer and radon exposure among uranium miners even though there is a cancer mortality deficit among all workers exposed to uranium [51]. In the natural state, radon gas is a part of the ^{238}U decay scheme. This is shown in Figure 2. Uranium has been shown to induce oxidative stress in rat lung epithelial cells, decrease the antioxidant potential of these cells, and reduce their proliferation [52]. Human lung epithelial cells lost contact inhibition and anchorage independent growth when exposed to depleted uranium. Cytogenetic analysis showed that exposure to depleted uranium induced neoplastic transformations in more than half of the cells [53]. Orona and Tasat [54] reported generation of the superoxide anion when rat alveolar macrophages were exposed to uranyl nitrate.

8.2. Renal Toxicity

High levels of uranium have been reported to accumulate in renal tissue [55]. At higher doses of uranium, kidney damage is the primary concern and the most immediate threat to patient health and survival. A human population of nearly 200 subjects continuously exposed to uranium in drinking water at concentrations as high as 1500 μg L^{-1} showed no evidence of renal damage. No statistically significant differences between the exposed population and age- and gender-matched controls were found for indicators of nephortoxicity in the urinary the levels of calcium, phosphate, glucose, creatinine, *N*-acetyl-gamma-D-glucosamididase, alkaline phosphatase, gamma-glutamyltransfertase, glutathione-*S*-transferase and lactate dehydrogenase as well in the serum levels of calcium, phosphate, glucose and creatinine [36]. A subsequent review of the literature, however, reported some evidence of adverse renal effects from exposure to uranium in drinking water as assessed by biomarkers of proximal tubular damage. In addition, indicators of proximal tubular effects, as evidenced by increased urinary β(2)-microglobulin and retinol binding protein levels, were reported in Desert Storm veterans exposed to depleted uranium [56]. It was previously reported that urinary uranium concentrations of veterans with embedded depleted uranium shrapnel ranged from 10 to over 500 times normal levels and that high urinary uranium concentrations were consistent with biomarkers of renal proximal

tubular cell function and cytotoxicity associated with elevated urinary protein excretion, and it was proposed that these results supported basing the health protection guidelines for depleted uranium on chemical rather than radiological toxicity [57]. Chronic low dose exposures of up to 12 months to surgically-implanted depleted uranium in the rat has been reported to produce subtle pathologic changes in the kidneys along with blood chemistry changes suggesting renal dysfunction with accompanying anemia due to aberration of the kidneys' erythropoitic function [58]. The uranium concentrations in the bone, 21.64 ± 3.68 μg g^{-1}, and in the kidney, 17.79 ± 2.87 μg g^{-1}, at 360 days post implant were significantly greater than those in other tissues [59]. Using mitochondria isolated from the rat kidney, the nephrotoxicity of uranyl acetate, at concentrations of 50, 100 and 200 μM, was shown to disrupt the electron transfer chain at complex II and III leading to the generation of reactive oxygen species and subsequent oxidative stress [60]. It was further shown by Shaki and Pourahmad that beta-glucan offered some degree of protection against mitochondrial damage by uranyl acetate *in vitro* [61].

Roszell *et al*. [62] have concisely and succinctly described the renal toxicity of uranium. They wrote, "Whether the route of exposure is through inhalation or ingestion, after absorption the kidney is considered to be the target organ for uranium chemical toxicity". Uranium is transported in the blood as complexes with carbonate or bicarbonate, or with transferrin, or with other ligands. The uranium is either deposited in other compartments or excreted by the kidney. The carbonato complexes are filtered in the kidney at the glomerulus. These complexes dissociate as the glomerulate filtrate passes along the proximal tubule and becomes more acidic. The uranyl ion released from the complex can react with components of the filtrate or with components of the tubular membrane. The former may remain dissolved in the filtrate, and the latter may become bound at the ionic sites of the brush border membrane of the proximal tubule. The soluble forms of uranium can pass into the bladder and be eliminated, but the bound forms can alter or destroy renal tubular cells. Roszell *et al*. [62] cited one suggested mechanism for renal damage by which the binding of uranium altered cellular permeability to sodium which, in turn, interfered with the transport of glucose, amino acids, and phosphates and resulted in increased excretion of these compounds. Other possible cellular events could include changes to the plasma membrane, which could in turn affect membrane transport and permeability, lysosomal damage, mitochondrial dysfunction, and DNA damage leading to apoptosis. In preparing their assessment, they recognized the formation of oxides when depleted uranium ammunition impacts upon a hard target, and they recognized their limited solubility in aqueous media. They proposed inhalation as the major route of uranium intake.

Arzuaga, *et al* [56] have also reviewed the renal effects of uranium, and they too have described mechanisms for renal toxicity. One of the studies they described used proximal and distal tubular cell lines (MD CK and LLC PK1) and suggested the dependence of renal toxicity on the formation of complexes such as $UO_2(PO_4)^{-1}$ and $UO_2(HPO_4)$ with their subsequent uptake by the sodium dependent co-transporter NaPi-II and absorptive endocytosis. They described another study in which isolated human and murine kidney cortex tubules exposed to uranium showed inhabitation of cellular ATP and glucogenesis due to inhabitation of lactate dehydrogenase, pyruvate carboxylase, glucose 6-phosphatase and phoshonolpyruvate carboxykinase. Additional studies suggested uranium exposure of human renal HEK293 cells altered expression of genes associated with calcium-dependent cell signaling such as IP3 cascade kinases PI4K11 and PIK3R1, the intercellular calcium receptor

calmodulin and calmodulin-dependent proteins and cell trafficking pathways such as the potassium channel ABC subunits ATP6V1A1 and ABCCC8. Also described are some *in vitro* and *in vivo* studies showing uranium exposure depleted glutathione and glutathione reductase activity, increased reactive oxygen species production and DNA damage and promoted apoptosis. The final description was of studies reporting chronic exposure to uranium enhances the expression of genes associates with oxidative stress responses such as superoxide dismutase 1 and ion transports including NaPi-II and S1c34A1. The involvement of the oxidative stress responses is a factor Lestaevel *et al.* [63] considered in their work on neurotoxicological disturbances attributed to depleted uranium exposure (See section 8.3). Neither Arzuaga *et al.* [56] nor Roszell and her collaborators [62] make mention of radiotoxicity in their overviews on the mechanisms of renal toxicity.

8.3. Neurological Toxicity

Houpert *et al.* [64] reported a study comparing neurophysiological and behavioral changes in rats exposed to enriched uranium and depleted uranium. Exposure was with mineral water containing 40 mg U (from uranyl nitrate) L^{-1} as either enriched (95.74% ^{238}U, 4.24% ^{235}U, 0.02 ^{234}U) uranium having a specific activity of 66.3 kBq g^{-1} or depleted (99.74% ^{238}U, 0.026% ^{235}U, 0.001 ^{234}U) uranium having a specific activity of 14.7 kBq g^{-1}. The control rats received the same mineral water. After 45 days of exposure, electroencephalographic (EEG) activity was recorded, and spatial working memory was assessed. The rats were sacrificed at the end of the exposure, and the uranium contents of kidneys, adrenals bones and brains were determined by ICP-MS. The EEG activity of the rats exposed to the enriched uranium showed increased paradoxical sleep episodes relative to the control rats while the rats exposed to the depleted uranium showed no such changes in sleep architecture. In assessing spatial working memory by spontaneous alternation examination, it was observed that the rats exposed to the enriched uranium demonstrated decreased activity while the activity of those exposed to the depleted did not differ from the control rats. As might be expected, the uranium concentrations in the kidneys of the rats exposed to the enriched uranium and the depleted uranium did not differ and both were approximately ten fold greater that those of the control rats. Surprisingly, the mean concentrations of uranium in the hippocampus and hypothalamus of the brain and in the adrenals of the rats exposed to the enriched uranium were significantly greater than those of the rats exposed to the depleted uranium. While the accumulation of uranium in the adrenals and in some brain structures was correlated with decreased neurobiological functions, the differential between the enriched and the depleted uranium remain intriguing.

Jaing and Aschner [65] have described several neurobiological consequences of exposure to depleted uranium in their review on its neurotoxicity. Among these were: differences in electrophysiological studies in hippocampal slices from rats implanted with depleted uranium, increased acetylcholinesterase activity in the cortex of rats receiving intramuscular injections of uranyl acetate at doses of 1 mg kg^{-1} and differences in brain lipid oxidation in rats treated with depleted uranium.

Jaing *et al.* [66] recognized the gap in the understandings of the specific effects of uranium on cells of the central nervous system and the potential molecular changes resulting from exposure to depleted uranium. Using primary cortical neuron cultures as targets for exposure to depleted uranium (as uranyl

acetate), they observed: little if any effect on cell viability and morphology; little if any effect on thiol metabolite levels, redox potential or high energy phosphates; and little if any effect on lipid peroxidation. Neuro degradation was not observed when *Caenorhabditis elegans* was the target for the depleted uranium exposure. One of the conclusions drawn from these observations was the neurotoxic potential of depleted uranium as uranyl acetate was low. No speculations were made regarding the chemical form of the depleted uranium encountered under military combat, fuel processing or other conditions.

Lestaevel *et al*. [63] reported further on the double toxicity, chemical and radiological, of uranium. Rats were to uranyl nitrate as cited above for Houpert *et al*. [64]. The cerebral cortex of those exposed to the enriched uranium showed enhanced lipid peroxidation. Increases in the activities of superdioxide dismutase, catalyse and glutathione peroxidase were observed in the cerebral cortex of the rats exposed to the depleted uranium. These results were interpreted as a demonstration that depleted uranium induced increases in several antioxidants while exposure to enriched uranium was associated with oxidative stress, and the reactive oxygen species associated with oxidative stress could induce neurotoxicological disturbances attributed to uranium exposure. Lestaevel *et al*. [67] also reported decreases of the cholesterol and the acetylcholine in the entorhinal cortex of nice exposed to depleted uranium, and suggested exposure to depleted uranium could modify the pathology of the apolipoprotein E associated with Alzheimer's disease.

8.4. Reproductive/Developmental Toxicity

A literature review published a decade after the deployment of depleted uranium munitions in Operation Desert Storm reported no data was available on the reproductive effects of embedded depleted uranium shrapnel [68]. Subsequent studies using the offspring of female and male rats surgically implanted with depleted uranium pellets revealed no gross physical abnormalities attributable to prenatal uranium exposure. Elevations of the urinary uranium concentrations, confirming *in vivo* solubilization of the implanted pellets, were observed in the parent generation. Neurodevelopment and immune function assessments of the first generation offspring were normal [69]. In a follow up study of the second generation offspring, development was normal, and no gross abnormalities were observed. As with the first generation offspring, no instances of rib cage malformation were observed at necropsy. Histopathology of kidneys, spleen, thymus, bone marrow and ovaries and testes did not differ from control rats for both the first and second generation offspring. In the necropsy of the parent rats, marked inflammatory responses were observed in the soft tissues surrounding the implanted depleted uranium pellets. The mean heart masses of the first and second generation offspring of the rats receiving the highest doses of depleted uranium were greater than those of the corresponding control animals. In general, it appears that imbedded depleted uranium is not a reproductive or developmental hazard. However, the elevated heart masses of the first and second generation offspring suggest conservatism in totally discounting the possibility of teratogenic effects [70].

As was the observation of the increased masses of hearts in offspring from parents receiving the highest doses of depleted uranium pellets, the mutation frequency in vector recovered from the DNA in bone marrow cells of the offspring of transgenic male mice exposed to depleted uranium also

showed a dose dependent increase. In addition, a dose dependent (in terms of specific activity) mutation increase was observed in the offspring of male mice exposed to either enriched or depleted uranium in drinking water as uranyl nitrate at a total uranium concentration of 50 µg L^{-1} [71].

8.5. Carcinogenicity

Increased cancer incidence is one of the many concerns about exposure to depleted uranium. A British study involving surveillance for the ten years following the conflict of 52,721 Gulf War veterans and 50,755 age- and gender-matched military personnel who had not been deployed to the Gulf revealed no excesses in site specific cancers in the former cohort. There were 270 incidences of cancer among those who had served in Iraq and 269 incidences of cancer in the control cohort [72]. Four bone cancers among the 20,012 Danish Balkan War veterans exceeded expectations [73]. A review of twelve epidemiological studies found no evidence of excess cancer risk among veterans of military operations in Iraq and Kosovo except for the apparent increased risk of bone cancer in the Danish cohort [74]. In a subsequent study comparing 18,175 male Dutch soldiers who had been deployed to the Balkans with 1,365,355 male members of the Dutch military who had not served in this region, the cancer incidence in the former was 17% lower than that of the later [75].

8.6. Twenty-Year Surveillance

In the heat of combat, some three dozen U.S. servicemen were killed by friendly fire, and almost twice that number were wounded. Of the wounded, more than half were left with fragments of depleted uranium embedded in their bodies. They have been under periodic medical surveillance during the two decades following the cessation of hostilities in early 1991.

Eight years after hostilities ended, urinary uranium levels of Gulf War veterans with retained depleted uranium shrapnel were between 0.018 and 39.1 µg per g creatinine while uranium in the urine from other veterans without imbedded shrapnel ranged from 0.002 to 0.231 µg per g creatinine. The persistently elevated urinary uranium excretion was interpreted as an indication of continued mobilization and chronic low dose exposure. This was correlated with an increase in sister chromatid exchange in peripheral lymphocytes [76]. Continued surveillance confirmed the elevated urinary uranium concentrations [77]. Application of the ICRP biokinetic model described above suggested the possibility of renal damage from both the chemical and radiological toxicity of uranium. However, markers for changes in renal glomerular and tubular function did not differ significantly between those with embedded depleted uranium shrapnel and their controls. The absence of firm evidence for renal effects, despite the kidney's reputation as the critical organ, may be attributed to a relatively low uranium burden compared to uranium exposures in the occupational sector. However, measures of renal tubular function and structural integrity have yielded results suggestive of, though not statistically significant for, an early effect from exposure to depleted uranium. Genotoxicity endpoints continued to yield mixed results [32]. On follow up, the concentrations of retinol binding protein, a marker for renal proximal tubular function, in the exposed group showed no significant differences from those of the controls, but evidence of a weak genotoxic effect was reported [78]. Sixteen years after being wounded by friendly fire, military personnel continue to excrete uranium at concentrations proportional to the depleted uranium shrapnel burden in the body. Although subtle trends emerge in

renal proximal tubular function and bone formation, the wounded veterans exhibited few of the clinically significant health effects associated to uranium intoxication [79]. Two years later, these parameters showed little change. The elevated urinary excretion of uranium by those with the embedded shrapnel continued. No significant evidence of clinically important changes was observed in kidney and bone, the two principle uranium target organs [80]. Compared with uninjured Gulf War veterans, those with embedded depleted uranium showed no increased frequency of micronuclei formation in the peripheral blood lymphocytes [81]. Likewise, chronic exposure from the embedded depleted uranium did not induce chromosomal aberrations in the peripheral blood lymphocytes [82]. Pulmonary health assessments of veterans with high body burdens of depleted uranium, who most likely sustained inhalation exposure during the friendly fire incidents, were within normal clinical expectations. No significant respiratory symptoms, abnormal pulmonary function values or prevalence of chest CT scan abnormalities were observed [83]. McDiarmid *et al.*, [84] observed few clinically significant health effects related to long-term, low-dose depleted uranium exposure from embedded shrapnel. Renal biomarkers showed minimal effects on proximal tubular function and cytotoxicity, and pulmonary functions remained within the normal clinical ranges.

8.7. Collateral Injuries

While American soldiers wounded with shrapnel from depleted uranium penetrators showed few, if any, symptoms or signs of injury due to uranium intoxication during twenty years of observation, increased incidences of congenital birth abnormalities and of cancers have been reported in Iraq. Of 6049 births recorded at the Fallujah General Hospital in 2009, there were 291 instances of congenital abnormality, which corresponds to a rate of 48 per thousand. This frequency of congenital abnormality is higher than the 12½ per thousand reported in neighboring Kuwait, the 8 per thousand reported in the United Arab Emirates and the 32 per thousand reported in Egypt. The higher rates of congenital abnormality in Iraq were attributed to prenatal environmental exposures of the parents to genotoxic agents such as uranium [85]. Environmental exposures to depleted uranium of the Iraqi parents of children with congenital abnormality were assessed by monitoring soil and drinking water and by analyzing scalp hair. (Hair is considered by many to be a bio-indicator of occupational or environmental exposure to toxic elements.) The average uranium concentration for two dozen scalp hair samples from parents of children born with major congenital abnormalities at the Fallujah General hospital were between two to three times higher than that obtained with samples from a hundred residents of southern Israel. The average values were 0.16 *versus* 0.062 mg kg^{-1}, respectively. The uranium concentration of six soil samples collected in different districts of Fallujah ranged from 0.1 to 1.5 mg kg^{-1}, and the concentrations of uranium in tap water, well water and water from the Euphrates River were 2.28, 2.72 and 2.24 μg L^{-1}, respectively. The high concentrations of uranium in the scalp hair from the Fallujah subjects could not be attributed to either the soil or the water concentrations of uranium. "… these results support the belief that the effects in Fallujah follow the development of a uranium-based weapon or weapons of some unknown type" [86]. However, a subsequent review of the literature on congenital abnormalities in Iraq concluded, "As no [*sic*] enough data on pre 1991 Gulf War prevalence of birth defects in Iraq are not available, the ranges of birth defects reported in the reviewed studies from Iraq most probably do not provide a clear indication of a

possible environmental exposure including DU or other teratogenic agents although the country has faced several environmental challenges since 1980" [87]. In addition, the frequency of congenital abnormalities among infants born to U.S. service personnel who had served in Iraq between 1990 and 1991 did not differ from that among infants born to members of the U.S. military who were not deployed to Iraq. A slight increase in the prevalence of birth defects was observed among infants born to male war fighters who were deployed for between 153 and 200 days compared to those deployed to Iraq for between 1 and 92 days [88].

A report on a questionnaire designed to substantiate media coverage of increased birth defects and incidences of cancer attributed to the use of depleted uranium weapons in Fallujah did little to clarify the issues. In the words of the authors, "… the results reported here do not throw any light upon the identity of the agent(s) causing the increased levels of illness, and although we have drawn attention to the use of depleted uranium as one potential relevant exposure, there may be other possibilities and we see the current study as investigating the anecdotal evidence of increases in cancer and infant mortality in Fallujah" [89].

Elevated blood uranium concentrations among leukemia victims have been reported in the Basrah-Muthanna-Dhi Qar region south east of Fallujah [90]. The blood uranium concentrations were determined by a track-etch technique based on the neutron induced fission of ^{235}U. The mean blood uranium concentrations with their standard errors for 30 leukemia victims and 30 control subjects matched for gender, age and domicile were 2.87 ± 0.11 and 1.43 ± 0.07 μg L^{-1}, respectively. The higher uranium concentrations in the blood samples from the leukemia victims were attributed to military activities during the Gulf Wars. No environmental data are presented to confirm their exposure, nor is any explanation offered for the lower values in the control subjects who shared this environment. Studies on frequencies of childhood leukemia over time in the Basrah region disagree on the trends. Hagopian *et al.* [91] maintain the rates have doubled over the fifteen year period from 1993 to 2007 while others [92] observed no temporal increases during the six year period from 2004 to 2009. The former cited an annual rate of 12.2 per 100,000 population for 2006 while the 2006 annual rate reported by the latter was 4.49 per 100,000 population. The latter rate is several orders of magnitude less that that cited above for 2009 in Fallujah 2009 [85]. Greiser and Hoffmann [93] challenged the former report citing the work of a WHO mission that found no increase in childhood leukemia for the governorate of Basrah. The authors [94] response was based on uncertainties in the accuracy of the population statistics and did little to resolve the discrepancy. In addition, instances of further increased cancer rates due to depleted uranium have been reported in the northern Iraq city of Mosul [95].

Polarized views from different interest groups maintain a somewhat sustained controversy about the collateral effects of depleted uranium weapons. The issues are sometimes more in the realm of the public media than they are in the scientific community. Regardless of the orientation, the growing body of evidence should encourage putting the problem and its solution high on the list of priorities.

9. Some Concluding Comments

Some 325 tons of depleted uranium munitions were detonated during the conflicts in the Persian Gulf and in the Balkans, and additional quantities of depleted uranium were released into the

environment during incidents such as the explosion and fire on 11 July 1991 at the ammunition storage depot known as Camp Doha. Uranium is an α emitting radioactive element having both radiological and chemical toxicity. The release of uranium and its decay products into the environment (air, soil, and water) presents a threat to human health and environmental quality. Uranium can enter the body by inhalation, ingestion, transdermal absorption, or injection from injuries. The primary route of entry into the body is inhalation. Research on inhaled, ingested, and/or dermally absorbed industrial uranium compounds has shown that solubility influences the target organ, the toxic response, and the mode of uranium excretion. The overall clearance rate of uranium compounds from the lung reflects both mechanical and dissolution processes depending on the morphological and chemical characteristics of uranium particles. Three kinds of uranium can be considered: natural uranium, enriched uranium, and depleted uranium. While the chemical and radiological toxicities of natural uranium and enriched uranium have been the subject of extensive research for more than a half century, depleted uranium is a relatively new arrival on the scene. The radiological and chemical properties of natural uranium and depleted uranium are similar. In fact, natural uranium has essentially the same chemical toxicity as depleted uranium, but the radiological toxicity is some 60% higher for the former. Depleted uranium has been used in military conflicts, and it has been claimed to contribute to health problems.

The United Nations Environment Programme (UNEP) [96] post conflict environmental assessment of depleted uranium was conducted at 11 locations in southwestern Kosovo along the border with Albania. These sites were selected from among the 112 targets where NATO air strikes fired 30 mm depleted uranium munitions. This assessment concluded, "There was no detectable widespread contamination of the ground surface by depleted uranium. …. The corresponding radiological and toxicological risks are insignificant or even non-existent. Detectable ground surface contamination by DU is limited to areas within a few meters of penetrators and localized points of concentrated contamination caused by penetrator impacts. … There is no significant risk related to these contamination points in terms of possible contamination of air, water of plants. …." None the less, Nafezi, *et al*. [97] have reported radon levels ranging from 82 to 432 Bq m^{-3} in 15 dwellings in the village of Planej, one of the 11 sites selected for the UNEP assessment.

During the conflict, Serbs held positions in and around this village. In November 2000, there was heavy fighting in the area, and the village was largely destroyed. According to NATO, the village was attacked on 31 May 1999 by A-10 aircraft which fired 970 rounds. The size of the targeted area is not known. Many penetrators may remain hidden in the ground. Eventually these could dissolve, with the depleted uranium entering the ground water. There is, consequently, a possibility that the drinking water in some nearby wells could become contaminated. The drinking water in nearby wells should be kept under surveillance by taking samples at appropriate intervals for uranium testing.

The UNEP has conducted additional post conflict environmental assessments of depleted uranium in Serbia, Montenegro and Bosnia and Herzegovina [98,99]. The large majority of the NATO air strike targets were in Kosovo. These are considered in the preceding paragraphs. Investigations were made at five of the 11 sites targeted in Serbia and Montenegro. As was the case in Kosovo, the primary concern in Serbia was for the potential contamination of ground water with depleted uranium from the sub-surface corrosion of buried penetrators. In Bosnia and Herzegovina, 10 sites near the cities of Sarajevo and Gorazde were investigated. It is important to point out this investigation was conducted seven years after hostilities ended. Surface β/γ radiation was detected at some 300 sites of depleted

uranium penetrator air strikes. Analysis of air samples taken at some of these sites indicated no significant risk was expected to arise from these sites by inhalation of soil particulate matter. Recovery of buried depleted uranium penetrators revealed they were corroded, and the soil in contact with the buried depleted uranium penetrators was contaminated with as much as 45 g of uranium per kilogram of soil. Uranium concentration in the soil 10 cm below the penetrator was some hundred times less, and it was reduced by another factor of ten within the next 30 cm. The low mobility of corroded uranium in the soil does not preclude the contamination of ground water. Traces of depleted uranium were found in two samples of drinking water by mass spectrometry. Although the mobility of depleted uranium corrosion products in soil is low, the potential for drinking water contamination should undergo further monitoring.

The corrosion of depleted uranium and the subsequent transport of the corrosion products were studied in column experiments simulating a sand rich environment with field moist conditions. The depleted uranium was oxidized to metaschoepite, $(UO_2)_8O_2(OH)_{12}$, at a rate of 100 ± 12 mg cm^{-2} years^{-1} [100]. The rate at which buried depleted uranium munitions corroded at the Kirkcudbright and Eskmeals live fire test ranges was reported to be from 130–1900 mg cm^{-2} years^{-1}, and the time for complete corrosion was estimated as between 2½ and 48 years [101]. Experimental remediation of contaminated soil at the latter site showed extraction with citric acid removed between 30 and 42 percent of the depleted uranium while extraction with ammonium bicarbonate solution removed between 42 and 50 percent of the depleted uranium. Sequential extraction with ammonium bicarbonate and then with citric acid improved uranium removal from soil at the Eskmeals site to between 68 and 87 percent [102]. Both of these extractants are environmentally friendly, but after use, they would require management as hazardous wastes.

The results from *in vivo* and *in vitro* investigations on both natural and depleted uranium and the renewed efforts to understand the chemistry and the toxicology of depleted uranium appear to have been compromised somewhat by the political agendas of special interest groups at the national and international levels. The presence of the depleted uranium in the environment, the routes of its entry to the body and its impact on human health and environmental quality will occupy the scientific community and the political arena for decades to come.

Conflicts of Interest

The author declares no conflict of interest.

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