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Biodistribution of Uranium in Mice and Influencing Factor Preliminary Discussion

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The general objective of our work was to preliminary discuss the relationship between uranium(VI) distribution in mice and the speciation of uranium in blood plasma and urine. The results show that, mice were injected with depleted uranium (DU) (5 mg/kg), the important uranium deposit sites are bones, kidneys, liver and spleen. Excretion of uranium mainly through kidney and the concentration of uranium in the liver and spleen have two peaks with time passed. Computer simulation shows that the major uranium species were uranium complex ions at normal blood plasma pH value, which explain the animal experiment phenomenon that uranium removed faster in the blood and the species of uranium in the plasma blood related to the total uranium concentration. The formation of soluble uranyl ion with phosphate radical is high solubility solid material, resulting in uranium long-term deposition in bone. Computer simulation also shows the solid phase as $(\text{UO}_2)_3(\text{PO}_4)_2 \cdot 4\text{H}_2\text{O}$ appeared in the urine, which are toxic to kidneys.

Keywords: Uranium, Computer simulation, Speciation, Biodistribution.

INTRODUCTION

Assessment of the risk of impact from most radionuclides is based on the total radiological dose rate to the organism of concern. However, for DU there can be greater risk from chemical toxicity than radiological toxicity. DU has recently been widely used in counterweights, radiation protection and military activities¹. However, unregulated release of DU into the environment could become a threat to human health²⁻³. Although DU emits less radiation than natural uranium, its chemical properties are identical which lead to renewed efforts to assess the environmental consequences and the health impact of the use of DU.

The effects of uranium contamination on human health have been largely studied in experimental animals. It is now well established that the observed toxicity of naturally occurring uranium is essentially due to the action of this element, mainly on the kidneys but also on skeleton. Scott *et al.*⁴ has described UF_6 , UO_3 , uranium sulfates and carbonate as highly transportable from the lungs, whereas UO_2 , U_3O_8 , uranium carbides and hydrides are only slightly transportable. Yapar *et al.*⁵ showed that ginkgo leaf extract significantly improved liver and kidney functions in mice after uranium ingestion. McClain *et al.*⁶ confirmed the liver is the main organ for possible metal metabolic reduction and therefore one of the most important site for its toxicity. Sutton and Burastero⁷ has described the speciation of uranium(VI) in a number of simulated elemental human body fluids by using chemical

thermodynamics speciation and solubility modeling using methods previously described to study beryllium speciation in body fluids. But the relationship of the speciation and the chemistry toxicity of uranium are not well investigated.

To evaluate the effects of U(IV) on different tissue samples in mice which were injected DU from tail vena. After DU entering *in vivo*, the chemical form of U(IV) plays a decisive role on its absorption, distribution, deposition and excretion in different tissues and its mechanism and impact of the results were significantly different. Therefore, we conducted a preliminary study were, (1) to establish the acute toxicity of U(IV) and to measure the mice of distribution of the metal; and (2) to establish models to simulated the speciation of U(IV) in the plasma as very little is known about the ecotoxicological mechanisms of U(IV) in mice, which is the foundation to evaluate the toxicity of U(IV) in plasma and design chelating agent.

EXPERIMENTAL

Kunming mice weighting 20 ± 2 g were purchased from West China Center of Medical Science (Sichuan University, China) and maintained on a light/dark cycle in the central animal facility before use. The protocol was carried out according to the "Guide for the Care and use of Laboratory Animals at the National Institute of Radiological Sciences" and Use of Laboratory Animals and was approved by Chinese legislation regarding the ethical use of animals.

Treatments: The mice were randomly divide into two groups: **(i) DU group:** The mice were fixed in the cylindrical plastic tube and exposed tail through which injected with DU (The source and constituent of DU was as the previous study⁸, with $U^{238} = 99.75\%$, $U^{235} = 0.20\%$, trace U^{234}) in the form of uranyl nitrate ($pH = 6.9-7.1$) at a single dose of 5 mg/kg body -weight; **(ii) Control group:** Compared with the DU group, the mice were injected with equal volume of saline in place of DU.

DU group consisted of 49 animals and the testes were as follows: Seven mice per group were killed by rapid decapitation at different time points (as 5 min, 30 min, 6 h, 12 h, 24 h, 72 h and 144 h) after DU injection. Uranium content was measured in the blood, hearts, livers, spleens, kidneys, lungs, meat and bones by Luminescence-ultraviolet pulse trace uranium analyzer.

Sample preparation: Tissue samples were initially put in the crucible and dried in a muffle furnace at 150 °C for 2 h. The samples were then converted into ash at 450-500 °C for another 8 h until the samples were no black carbon particles (white or gray), then put in desiccators. Ashes in the crucible were wet-ashed with 16 M nitric acid solution and evaporated at 140 °C on the furnace. Then adding 2 mL H_2O_2 , the samples were heated to a white loose-like and transferred into 50 mL beaker. Samples were wet-ashed with 15 mL deionized water and 2 g sodium persulfate and then dry-ashed in the electric panel for the second time. Then, a mixture of 5 mL nitric acid and 5 mL ultrapure water was added to the resulting samples and finally the samples were made up to 50 mL with ultrapure water.

Computer models and methods

Methods and approaches: The computational approach to chemical speciation assessment is based upon the principles of chemical equilibrium, laws of thermodynamics and aqueous complexation chemistry. The JESS program, developed by May and Murray, simulates all the possible labile interactions between basic primitive components (*i.e.* metal ions and ligands) present in a simulated chemical or biochemical environment, identifies the extent of reaction between components and predicts the predominance of these species under specific conditions, *e.g.* temperature, ionic strength and pH, as a percentage of the total metal or ligand concentration. It calculates the percentage predominance of each chemical species through many types of simultaneous mathematical equations, which are solved using a Newton-Raphson style iterative approach. These equations are based upon a number of known variables such as the total concentrations of the basic components and the log K_{MLH} for each possible species (obtained from the JESS database) and one unknown variable, *i.e.* the species percentage predominance. All log K_{MLH} values listed in the JESS database are original source values, quoted at the temperature (T) and ionic strength (I) of measurement. JESS considers the T and I of the system under investigation and corrects the original source values, either using traditional correction methods or by using its own unconditional correction coefficient (UCC) extrapolation method in which all data sets for all the T and I values for each reaction are considered and built into a mathematical equation, which enables log K_{MLH} to be calculated for

the required T and I of the system under investigation. Further, all log K values quoted in the JESS database have been critically assessed by May and Murray, using a strict quality control procedure and have been weighted zero (poor) to ten (excellent) by the program developers, thus assuring that all possible avenues of unreliability in the data have been explored and assessed. This allows researchers to evaluate the thermodynamic data required for their own specific studies and to remove any unreliable constants from their simulation database prior to calculation. (Few of the constants present in the database have a weighting > 5.)

Table-1 shows the overall log K values for the major uranium(VI) species predicted to be formed in human blood plasma; The thermodynamic data in the THERMO.DBS database⁹ that accompanies the MINTEQA2v4 model were compared for compatibility and updated with critically reviewed chemical thermodynamics data from the NIST database¹⁰⁻¹¹ and Nuclear Energy Agency (NEA) thermodynamic uranium data set¹².

TABLE-1
OVERALL FORMATION CONSTANTS FOR THE
MAJOR URANIUM (VI) SPECIES PREDICTED TO
FORM IN HUMAN BLOOD PLASMA AT pH = 7.4

Species	log K
$[UO_2(OH)]^+$	-5.45
$UO_2(OH)_{2(aq)}$	-12.15
$[UO_2(OH)_3]^-$	-19.6
$[UO_2(OH)_4]^{2-}$	-34.23
UO_2CO_3 (cr)	9.68
$[UO_2(CO_3)_2]^{2-}$	16.94
$[UO_2(CO_3)_3]^{4-}$	21.6
$[(UO_2)_3(CO_3)_6]^{6-}$	54
$[UO_2Ca(CO_3)_3]^{2-}$	27.18
$UO_2Ca_2(CO_3)_3(aq)$	30.7
UO_2SO_4 (cr)	3.185
$[UO_2PO_4]^-$	13.23
UO_2HPO_4 (cr)	-22.712
$(UO_2)_3(PO_4)_2$ (cr)	-46.4
$[(UO_2)_2(H_2PO_4)_2]^{2+}$	43.28
$UO_2(H_2PO_4)_2$	-42.14

Modelling components: Fixed total concentration values for all the metal ions and ligands involved in the blood plasma, urine and systems (Table 2 and 3¹³⁻¹⁴) are assumed for models, which was set at temperature of 37 °C and the ionic strength of 0.15 mol dm⁻³ in order to be biologically realistic. All modelling was carried out using an aqueous system with no solids percent. Table-1 contains the equilibrium constants calculated by JESS, under these conditions for UO_2^{2+} species.

RESULTS AND DISCUSSION

Uranium speciation and distribution in blood plasma:

The uranium distribution (ID % g⁻¹) in blood plasma are shown in Table-4. From Table-4 they are apparent that uranium distribution in the blood reached the maximum about 5.601 ID % g⁻¹ at 5 min after injecting the mice and then quickly decreased to 0.193 ID % g⁻¹ at 12 h. The uranium distribution at 72 h was close to background values (0.068 mg U g⁻¹) which indicated that the uranium excreted quickly in the blood with the body's metabolic energy. Initial studies of the chemical

TABLE-2
TOTAL-LIGAND CONCENTRATIONS IN HUMAN BLOOD
PLASMA USED IN THE COMPUTER SIMULATIONS

Component	Concentration (mol L ⁻¹)	Component	Concentration (mol L ⁻¹)
Alanine	3.7×10^{-4}	Carbonate	2.5×10^{-2}
Aminobutyrate	2.4×10^{-5}	Phosphate	1.6×10^{-3}
Arginine	9.5×10^{-5}	Thiocyanate	1.4×10^{-5}
Aspartate	5.5×10^{-5}	Silicate	1.4×10^{-4}
Aspartate	5.0×10^{-6}	Sulphate	2.1×10^{-4}
Cysteinate	2.3×10^{-5}	Ammonia	2.4×10^{-5}
Cystinate	4.0×10^{-5}	Citrate	1.1×10^{-4}
Citrullinate	2.7×10^{-5}	Lactate	1.8×10^{-3}
Glutamate	4.8×10^{-5}	Malate	3.5×10^{-5}
Glutamine	5.2×10^{-4}	Oxalate	1.2×10^{-5}
Glycinate	2.4×10^{-4}	Pyruvate	9.5×10^{-5}
Histidinate	8.5×10^{-5}	Salicylate	5.0×10^{-6}
Histamine	1.0×10^{-8}	Succinate	4.2×10^{-5}
Hydroxyproline	7.0×10^{-6}	Ascorbate	4.3×10^{-5}
Isoleucinate	6.5×10^{-5}	OH ⁻	1.2×10^{-6}
Leucinate	1.2×10^{-4}	Ca ²⁺	1.1×10^{-3}
Lysinate	1.8×10^{-4}	Mg ²⁺	5.2×10^{-4}
Methionate	2.9×10^{-5}	Cu ⁺	1.0×10^{-17}
Ornithinate	5.8×10^{-5}	Cu ²⁺	1.0×10^{-20}
Phenylalaninate	6.4×10^{-5}	Fe ²⁺	1.0×10^{-11}
Prolinate	2.1×10^{-4}	Fe ³⁺	1.0×10^{-23}
Serinate	1.2×10^{-4}	Pb ²⁺	1.0×10^{-14}
Threoninate	1.5×10^{-4}	Mn ²⁺	1.0×10^{-12}
Tryptophanate	1.0×10^{-5}	Zn ²⁺	1.0×10^{-9}
Tyrosinate	5.8×10^{-5}	Ni ²⁺	1.0×10^{-18}
Valinate	2.3×10^{-4}	pH	7.4

TABLE-3
COMPOSITION AND pH VALUE OF HUMAN URINE

Component	Concentration (mol L ⁻¹)	Component	Concentration (mol L ⁻¹)
Al ³⁺	2.733×10^{-5}	Li ⁺	1.0273×10^{-4}
AsO ₄ ³⁻	1.72×10^{-6}	Mg ²⁺	4.68111×10^{-3}
B(OH) ₄ ⁻	7.944×10^{-5}	Mn ²⁺	1.099×10^{-5}
Ba ²⁺	5.2×10^{-7}	MoO ₄ ²⁻	6.6×10^{-7}
Be ²⁺	1.444×10^{-5}	Na ⁺	1.74075×10^{-1}
Br ⁻	4.911×10^{-5}	NbO ₃ ⁻	3.88×10^{-6}
Ca ²⁺	5.285×10^{-3}	Ni ²⁺	1.85×10^{-6}
Ce ³⁺	2.3×10^{-7}	PO ₄ ³⁻	1.882×10^{-2}
Cl ⁻	1.4667×10^{-1}	Pb ²⁺	2.3×10^{-7}
Co ²⁺	3.8×10^{-7}	Rb ⁺	2.657×10^{-5}
Cr ³⁺	5×10^{-7}	SO ₄ ²⁻	3.3125×10^{-2}
Cs ⁺	1.2×10^{-7}	Sn ²⁺	2.2×10^{-7}
Cu ²⁺	7.7×10^{-7}	Sr ²⁺	2.56×10^{-6}
F ⁻	8.421×10^{-5}	TeO ₄ ²⁻	4.15×10^{-6}
Fe ²⁺	5.67×10^{-6}	Ti ³⁺	8.66×10^{-6}
Ga ³⁺	6×10^{-7}	V ²⁺	4.4×10^{-7}
Ge ²⁺	1.928×10^{-5}	WO ₄ ²⁻	1.6×10^{-7}
I ⁻	2.02×10^{-6}	Zn ²⁺	6.91×10^{-6}
K ⁺	6.4851×10^{-2}	pH	4.2-8.0

speciation of uranium(IV) in the human blood plasma under the concentration of 1×10^{-3} mol dm⁻³ and between 6 and 8 predicted that element appeared to exist mainly as negatively charged $[\text{UO}_2\text{Ca}(\text{CO}_3)_3]^{2-}$, electrically net-neutral $[\text{UO}_2\text{Ca}_2(\text{CO}_3)_3]_{(\text{aq})}$ and U(IV) with the formation of other amino acids in the form of complex ions at pH = 7.4. Fig. 1 shows that uranium circulates in blood as the uranyl ion and is mainly distributed between bicarbonates, ascorbic acid salts and proteins complexes which are excreted within a short time^{15,16}.

Fig. 1. Uranium speciation with varying pH at $[\text{U}] = 1 \text{ mm}$

Uranium speciation and distribution in bones: Table-4 shows the accumulation of uranium in the bones at 0.5 h to reach the peak and then decreased. After injection of uranium in mice, uranium maintain large amount of accumulation in the bones from 6 h and at 72 h uranium content in bones more than uranium content in kidney, which demonstrated that a large number of uranium in bone accumulation and long residence time, not easy to be excreted through the metabolism of organisms¹⁷. Further investigation were made to assess the influence of the concentration of uranium upon the prevailing chemical speciation of Ca²⁺ (1.1×10^{-3} mol dm⁻³) in human blood plasma. Fig. 2 shows the speciation profile for the concentration of uranium ranging from 1×10^{-4} mol dm⁻³ to 1×10^{-3} mol dm⁻³ and clearly illustrates that at pH 7.4, solid phase $\text{Ca}_3(\text{PO}_4)_2$ contented in the plasma began to decline rapidly. When the concentration of uranium increased to 1×10^{-3} mol dm⁻³, solid phase $\text{Ca}_3(\text{PO}_4)_2$ were almost completely disappeared

TABLE-4
BIODISTRIBUTION OF URANIUM IN MICE

Time	Percentage of the injected dose per gram of tissue mass/(ID % g ⁻¹)							
	Blood	Heart	Liver	Spleen	Kidney	Lung	Muscle	Bone
Blank	0.068±0.036	0.162±0.034	0.040±0.012	0.305±0.099	0.051±0.017	0.174±0.077	0.072±0.020	0.194±0.030
5 min	5.601±1.767	4.471±0.471	2.236±0.399	2.206±0.263	74.623±6.036	6.347±0.754	2.563±0.976	12.344±4.921
0.5 h	1.307±0.476	2.037±0.399	0.902±0.517	1.572±0.586	131.843±14.728	2.836±0.993	1.700±0.673	40.262±4.153
6 h	0.762±0.160	1.832±0.769	2.104±0.544	4.187±1.263	150.109±49.817	2.536±0.754	1.328±0.458	18.883±3.367
12 h	0.193±0.065	0.651±0.121	2.368±0.515	1.267±0.509	92.498±27.970	0.819±0.224	0.764±0.239	15.736±4.724
24 h	0.091±0.036	0.252±0.137	1.154±0.244	0.254±0.015	63.291±16.488	0.586±0.081	0.219±0.079	22.706±4.013
72 h	0.074±0.038	0.302±0.151	1.112±0.322	1.068±0.264	18.927±6.304	0.384±0.118	0.192±0.058	17.246±3.435
144 h	0.026±0.010	0.351±0.101	0.918±0.307	1.137±0.294	15.423±2.508	0.296±0.107	0.318±0.042	23.626±2.218

Fig. 2. Influence of the concentration of uranium on the speciation of calcium ion ($[Ca^{2+}] = 1.1 \text{ mM}$) in human blood plasma model, pH = 7.4

and the major species of uranium as $[UO_2Ca(CO_3)_3]^{2-}$ and $[UO_2Ca_2(CO_3)_3]_{(aq)}$ complexes. The results indicated the uranium may participate in the process of bone calcification, UO_2^{2+} take the place of Ca^{2+} in the bone mineral phase surface and then chelated with the two phosphate ions near the crystal surface, so that the calcium ion release from the bone mineral surface causing bone injury. This is consistent the study of Kurtio *et al.*¹⁷. They observed that about 80 to 90 deposition product of uranium in the bones deposited in the mineral structure of bone and deposition of the mechanism of uranium is UO_2^{2+} interacted with the bone mineral phase¹⁸.

Uranium speciation and distribution in urine: After entering the animal body, uranium was distributed unevenly amongst different tissues, with the content in kidney tissues being the highest (Table-4) and the kidney is the most sensitive target organ for uranium toxicity. The peak time of uranium accumulation in the kidney was 6 h after injection DU and significantly decreased from 72 to 144 h. The result indicated that the uranium which was injected in mice mostly retention in the kidneys and excreted through the urine. Distribution of uranium in the kidney is far more than other tissues and organs. Our result are similar to those of Ribera *et al.*¹⁹ after an accidental acute exposure, uranium enters the human body by ingestion, inhalation, or through the skin and 80 % of the initial dose is excreted in the urine during the first 24 h after contamination. A small part of the initial dose is retained in the body, deposited in bones and kidneys. After DU injection, the uranium is carried by blood as a soluble anionic complex enter the glomerulus and pass into the peritubular capillaries or the tubular lumen where it is subsequently filtered into the urine or bound by the brush border membranes of epithelial cells. The speciation of uranium(IV) in urine was simulated at pH = 6.5, the concentration of uranium ranging from $1 \times 10^{-5} \text{ mol dm}^{-3}$ to $1 \times 10^{-4} \text{ mol dm}^{-3}$ and the concentration of phosphate radical at $1.882 \times 10^{-2} \text{ mol dm}^{-3}$. Fig. 3 shows that at lower concentrations of uranium, the species of uranium mainly as negatively charged $[UO_2PO_4]^-$, electrically net-neutral aqueous

Fig. 3. Influence of the concentration of uranium on the speciation of phosphate radical ($[PO_4^{3-}] = 1.882 \times 10^{-2} \text{ M}$) in human urine model, pH = 6.5

$[UO_2HPO_4]$ and solid species $[(UO_2)_3(PO_4)_2 \cdot 4H_2O]$ were predicted to occur in urine under the higher concentration of uranium. The results clearly demonstrate that uranium and phosphorus containing crystals are formed within the LLC-PK1 cells by precipitation of uranium and the crystals found in extra-cellular spaces were liberated from renal cells. Meanwhile, UO_2^{2+} is combined with phosphate form deposition which accumulated in renal proximal tubular damaged to kidneys²⁰.

Uranium speciation and distribution in liver and spleen: Table-4 shows the overall values for the distribution of uranium in the liver and spleen which were fluctuated in the metabolism. After uranium injection and with the blood circulation, uranium were accumulated in the liver and spleen reached the first peak at 5 min and then decreased. The accumulation of uranium in the liver and spleen reached the second peak (maximum) at 6 h and the trend to stability. Fig. 4 shows when the concentration of uranium(IV) in computer simulation increased to the concentration equal to the mice blood plasma which exposed to uranium(IV) ($[UO_2^{2+}] \approx 1.7 \times 10^{-4} \text{ mol dm}^{-3}$ to $2.8 \times 10^{-4} \text{ mol dm}^{-3}$) at pH = 7.4. The species of uranium mainly as negatively charged $[UO_2Ca(CO_3)_3]^{2-}$ and electrically net-neutral $[UO_2Ca_2(CO_3)_3]_{(aq)}$. Because of aqueous $[UO_2Ca_2(CO_3)_3]$ is relatively stable, it is difficult to enter cells through the cell membrane and accumulated into the liver and spleen with the blood circulation. The result demonstrated that the liver has a large capacity to accumulate uranium²¹ which gradually eliminated from the body through the intestines and uranium accumulation in the spleen are considered related to macrophages which swallow solid particles of uranium and take them to the corresponding lymph nodes which gradually deposited solid particles of uranium into the spleen²².

Conclusions

(1) Uranium excreted quickly in the blood with the body's metabolic energy and the negatively charged $[UO_2Ca(CO_3)_3]^{2-}$, electrically net-neutral $[UO_2Ca_2(CO_3)_3]_{(aq)}$, U(IV) with the

Fig. 4. Influence of the concentration of [U] on the speciation of UO_2^{2+} in human blood plasma model, pH = 7.4

formation of other amino acids in the form of complex ions are the major species of uranium(IV) in the human blood plasma at pH = 7.4.

(2) A large number of uranium in bone accumulation and long residence time, not easy to be excreted through the metabolism of organisms and the computer simulation demonstrated when the concentration of uranium increased to $1 \times 10^{-3} \text{ mol dm}^{-3}$, solid phase $\text{Ca}_3(\text{PO}_4)_2$ were almost completely disappeared and the major species of uranium as $[\text{UO}_2\text{Ca}(\text{CO}_3)_3]^{2-}$ and $[\text{UO}_2\text{Ca}_2(\text{CO}_3)_3]_{(\text{aq})}$ complexes.

(3) Kidney is the primary reservoirs for uranium(IV) and the most sensitive target organ for uranium toxicity which is mainly accumulated in kidneys. The species of uranium mainly as negatively charged $[\text{UO}_2\text{PO}_4]^-$ and aqueous $[\text{UO}_2\text{HPO}_4]$. At a higher concentration, solid phase $(\text{UO}_2)_3(\text{PO}_4)_4 \cdot 4\text{H}_2\text{O}$ began to exist in the urine, which formed within the LLC-PK1 cells by precipitation of uranium and that the crystals found in extracellular spaces were liberated from renal cells. Meanwhile, UO_2^{2+} is combined with phosphate form deposition which accumulated in renal proximal tubular damaged to kidneys.

(4) The distribution of uranium in the liver and spleen with fluctuating trends in the metabolism. The species of uranium mainly as negatively charged $[\text{UO}_2\text{Ca}(\text{CO}_3)_3]^{2-}$ and electrically neutral $[\text{UO}_2\text{Ca}_2(\text{CO}_3)_3]_{(\text{aq})}$. Because of aqueous $[\text{UO}_2\text{Ca}_2(\text{CO}_3)_3]$ is relatively stable, it is difficult to enter cells through the cell membrane and accumulated into the liver and spleen with the blood circulation.

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