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Acute chemical toxicity of uranium

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ACUTE CHEMICAL TOXICITY OF URANIUM

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Abstract—Although human experience with uranium spans more than 200 years, the LD₅₀ for acute intake in humans has not been well established. Large acute doses of uranium can produce death from chemical toxicity in rats, guinea pigs, and other small experimental animals, with variation in sensitivity among species. However, there has never been a death attributable to uranium poisoning in humans, and humans seem to be less sensitive to both acute and chronic toxic effects of uranium than other mammalian species studied. Highly relevant data on uranium toxicity in humans are available from the experience of persons administered large doses of uranium for therapy of diabetes and from acute accidental inhalation intakes. Although the data on which to establish oral and inhalation acute LD₅₀ for uranium in humans are sparse, they are adequate to conclude that the LD₅₀ for oral intake of soluble uranium compounds exceeds several grams of uranium and is at least 1.0 g for inhalation intakes. For intakes of uranium compounds of lesser solubility, acute LD₅₀ values are likely to be significantly greater. It is suggested that 5 g be provisionally considered the acute oral LD₅₀ for uranium in humans. For inhalation intakes of soluble compounds of uranium, 1.0 g of uranium is proposed as the provisional acute inhalation LD₅₀.

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Key words: uranium; ingestion; inhalation; injection

INTRODUCTION

General aspects of acute uranium toxicity

Although more than two centuries have passed since the discovery of uranium in 1789 by German apothecary chemist Martin Heinrich Klaproth, the toxicology of this naturally occurring heavy metal is still incompletely understood. Indeed, despite the long experience with uranium, there is no established or generally accepted level for acute toxicity in humans. The first studies of uranium toxicity were carried out in 1824 by Christian Gottlieb Gmelin, some 17 years before the metal was purified and 72 years before uranium was discovered to be radioactive. Death occurred in a rabbit given a rather

massive for its size, 2 g dose of uranium chloride by gastric lavage, but no deaths or observable effects were noted in dogs fed up to 0.9 g of various uranium compounds, including the nitrate. Emesis was observed in a dog fed 4 g of uranyl nitrate in 30 cc of water, and death occurred within a minute in dogs intravenously injected with 180 and 600 mg of uranyl nitrate. On the basis of his experimental results, Gmelin concluded that uranium ingested orally was “a feeble poison,” but that injection would produce death by blood coagulation and irritability of the heart, a property shared with only two other metals—barium and palladium—whose toxicity he also studied (Hodge 1973).

The initial experiments by Gmelin have been followed by numerous other studies, several hundred alone having been carried out prior to the Manhattan District and an even greater number during and subsequent to the effort to build an atomic bomb. In recent years, interest in uranium toxicity has been heightened by the use of depleted uranium (DU) in munitions used in Iraq and Kosovo. Despite intensive effort and hundreds of scientific papers and reports devoted to the study of uranium in recent years, there is still no definitive or even generally agreed upon acute toxic level in humans. Indeed, what is well known and agreed upon is that uranium is both a chemical and radioactive toxin, with chemical toxicity dominant at enrichments below about 7 to 20% (ICRP 1968; Stannard 1988; Brodsky 1996). As enrichment decreases, so does the radiotoxicity, while chemical toxicity remains constant. Thus, at lower enrichments such as DU (0.2%), the toxic effect is overwhelmingly from chemical and not radiological effects.

Chemical toxicity is independent of enrichment and simply a function the mass of uranium that gets into the blood and other tissues, which in turn is a function of the route of entry and solubility of the specific uranium compound taken into the body. Solubility is thus an important parameter in determining the acute toxic level of uranium. Animal study data indicate a wide variation in toxicity among various uranium compounds. The relatively insoluble compounds of uranium, specifically UO₂, U₃O₈, and UF₄,

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are nontoxic even when given orally in large doses on a daily basis. The more soluble UO_3 and UCl_4 are toxic in large doses, while soluble compounds of uranium such as $\text{Na}_2\text{U}_2\text{O}_7$, $\text{UO}_3(\text{NO}_3)_2$, and UO_4 are toxic in moderate doses. Because of fluoride content and associated effects, particularly following inhalation, UO_2F_2 and UF_6 are chemically toxic at still lower doses (Tannenbaum and Silverstone 1951).

Radiotoxicity is a function of the specific activity that increases with increasing enrichment; the primary concern with radiotoxicity is stochastic effects—i.e., increased probability of carcinogenesis. Because of the large amount of uranium necessary to exceed the threshold for deterministic effects, these are for all practical purposes not of concern with respect to low enrichment uranium intakes. Although the two types of toxicities produce different biological effects, there may well be overlapping cytogenetic and carcinogenetic effects and it is not possible from the available data to determine what fraction of a particular effect was attributable to the metal toxicity vis-à-vis the radiotoxicity. Moreover, the increased radiotoxicity of high uranium enrichments may potentiate the heavy metal chemical toxicity. However, irrespective of enrichment, acute effects and certainly acute toxicity will be dominated by the chemical toxicity as the quantity of even highly enriched uranium needed to produce deterministic effects or a radiation dose in the LD_{50} range is likely many fold greater than the mass of uranium that would produce a fatal chemotoxic effect.

Natural uranium has a ^{235}U content of 0.71% by weight, and typical light water reactor fuels have enrichments of 2–5 weight percent. DU is 0.2% by weight ^{235}U . Soluble compounds with enrichments of 5% or less are potentially far more hazardous chemically than radiologically, and it is the potential effects on the kidney produced by chemical toxicity that serves as the basis for the various protective limits and concentrations for natural uranium that have been put forth by national regulatory bodies such as the U.S. Environmental Protection Agency (EPA) and the U.S. Nuclear Regulatory Commission (NRC) and other standards setting bodies such as the International Commission on Radiological Protection (ICRP) and National Council on Radiation Protection and Measurements (NCRP). For high enrichment uranium, the standards are based on possible stochastic effects (i.e., carcinogenesis) from radiation exposure. Because of the paucity of human data, protection standards for occupational exposure and intakes by members of the general public have of necessity been primarily based on animal studies, which may not be fully relevant or applicable to humans. Also, the standards established for protection are by and large concerned with long-term chronic exposures as contrasted

with acute intakes and hence not necessarily applicable or relevant to the acute toxicity of uranium in man.

Acute toxicity in animals

There are considerable interspecies differences among animals with respect to uranium toxicity; more than 50 years ago Orcutt (1949) proposed the following order of species sensitivity on a per kilogram of body weight basis to the toxic effects of uranium: rabbit > rat > guinea pig > pig > mouse. Based on comparative evaluation of toxic effects, the dog would seem to fall at the lower end of the level of susceptibility scale; the cat at the higher end. This is consistent with the observations of Tannenbaum and Silverstone (1951) who observed that on a per kilogram of body weight basis, the relative sensitivity of mouse, dog, and rabbit was 40:10:1; in other words, per kilogram of body weight, the mouse was 40 times less sensitive to the toxic effects of uranium as the rabbit. For a given intake of uranium, acute results will not only vary with species but also are dependent upon the specific uranium compound. Not unexpectedly, the more soluble uranium compounds exhibit greater uranium toxicity. Uranium hexafluoride is a special case as the compound rapidly reacts with water to produce hydrofluoric acid, which in itself has highly irritating and toxic properties particularly when inhaled.

Comprehensive reviews of the extensive literature of published animal toxicity studies have been performed by Hodge (1973), Durbin and Wrenn (1975), Yuile (1973), Stannard (1988), ATSDR (1999), and Bailey and Davis (2002) and reveal relatively few studies of acute oral toxicity from a single dose. The earliest studies, carried out in the late nineteenth and early twentieth centuries, clearly demonstrated heavy metal toxicity on the kidneys by whatever route of entry in experimental animals but did not provide adequate or unequivocal data with which to establish an acute LD_{50} . What these studies did establish with respect to acute toxicity was the “marked individual variation in response, especially in rabbits” and the apparent high chemical toxicity of uranium administered parenterally (Hodge 1973). A relatively recent (1987) study by Domingo et al., cited by ATSDR (1999), indicates that the acute oral LD_{50} in rats and mice for a single intake is at least 100 mg kg^{-1} , based on instillation of uranium acetate (soluble) by gastric lavage. If directly and linearly extrapolated to man, this is equivalent to a single oral dose of 7 g or more.

Considerably more data are available for longer term oral intakes. In 30-d oral feeding studies in rats with various uranium compounds carried out during the Manhattan District days, relatively insoluble uranium compounds, specifically UO_2 , U_3O_8 , and UF_4 , were nontoxic even at levels of up to 20% by weight in the diet while six

other water soluble uranium compounds resulted in 100% mortality at levels of 2 to 10% in the diet (Maynard and Hodge 1949). Oral LD₅₀ values in rats were estimated to be as small as 540 mg kg⁻¹ d⁻¹ for uranyl fluoride (soluble) with more typical values for this and other soluble uranium compounds studied in the intake range of 1,000 mg kg⁻¹ d⁻¹. By linear extrapolation based on weight, the 540 mg kg⁻¹ d⁻¹ level corresponds to a daily intake of 37.8 g of the compound for a 70 kg reference man, which equates to a daily intake of 29.2 g of uranium, or 876 g over a 30-d period. Assuming for illustrative purposes the validity of the extrapolation to humans, this corresponds to a peak kidney burden of 794 mg or a peak concentration of 2.6 mg g⁻¹ of kidney as calculated using the proprietary Integrated Modules for Bioassay (IMBA-URAN)[†] (James 2002). To achieve this same peak kidney burden would require an acute inhalation intake of 31.6 g of this compound (24.4 g of uranium) in the form of Type F material.

For inhaled uranium, the lethal concentration (LC) is determined by several factors including the specific species, chemical form of the uranium, and length or time of exposure. Such studies as have been done are generally protracted exposures over a period of weeks to years. In short term exposure studies in rats and guinea pigs exposed to UF₆, the LC₅₀ for a 2-min exposure was estimated at 35 g of uranium per cubic meter; in rats, the LC₅₀ for a 5-min exposure was estimated at 26 g per cubic meter. Longer exposure times resulted in concomitantly lower LC₅₀ values, but the relationship of exposure time and LC₅₀ was inversely related although not necessarily linear. Although pulmonary effects attributable to HF were observed, death was primarily from kidney damage (ATSDR 1999). What is clear from these animal studies is that inhaled uranium can be fatal, but that massive air concentrations and short term exposures are required to produce death.

The dermal LD₅₀ value following application of uranyl nitrate to the skin for 4 h before removal by washing was 4.29 and 1.19 g U per kg body weight, respectively, in mice and guinea pigs (Orcutt 1949). The LD₅₀ value could not be established for rats because of insufficient data, but the mortality curve for rats was intermediate between that of the mice and the guinea pigs. When applied to the skin of rabbits in a lanolin vehicle, water soluble uranium compounds exhibited the greatest toxicity and resulted in some deaths from kidney failure; animals similarly treated with insoluble compounds UO₂, U₃O₈, and UF₄ yielded no deaths in the experimental group.

[†] Jointly developed by ACJ and Associates, Inc. and the U.K. National Radiological Protection Board.

Acute human exposure to uranium

It is highly significant to note that there have been no reports of deaths in humans following acute or chronic intakes of uranium by whatever route of entry during mankind's more than two centuries of experience with uranium (ATSDR 1999), and humans as a species seem to have a lower order of sensitivity to the toxic effects of uranium than the other mammalian species that have been studied. Since at least the late nineteenth century until after the discovery of insulin by Canadians Frederick Banting and Charles Best and their coworkers in 1921–1922, uranium was used therapeutically in the treatment of diabetes mellitus. An excellent summary and discussion of uranium administered orally for this purpose has been put forth by Hodge (1973).

Reference to the original literature reveals a total of approximately two dozen cases treated by administration of uranyl nitrate (soluble) by mouth, typically thrice daily in individual doses ranging to a reported 30 grain (2 g) for a total daily intake of 5.8 g, sometimes for extended periods of months or even years (Bond 1898; Bradbury 1896; Duncan 1897; West 1895, 1896; Wilcox 1917). No fatalities were observed among the group so treated, nor was kidney pathology reported. Wilcox (1917) indicated that no untoward symptoms were seen in diabetic patients treated for extended periods of months to years with up to 200 mg of uranium daily. Using the IMBA-URAN software, the kidney burdens from the oral intakes were estimated. Kidney burdens for the patients increased over time, and close to peak burdens may have been sustained for some patients for long periods. Acute inhalation intakes of soluble uranium required to produce the same peak kidney burden were estimated using ICRP 66 defaults for absorption fractions for Type F materials, and ICRP 66 default aerosol characteristics (ICRP 1994a).

Equivalent acute inhalation intakes were calculated for the 11 patients with the greatest uranium intakes and are shown in Table 1. For these 11 cases, the calculated acute inhalation required to produce an equivalent kidney burden ranged from 730 mg to 3.8 g of uranium. In several of these cases, calculated acute inhalation intakes exceeding a gram of soluble uranium were required to produce equivalent peak kidney burdens. Some of the patients may have had higher peak kidney burdens than listed, but the description was inadequate to include the additional exposures. Still other patients receiving high oral doses were not included because of uncertainties of the oral intake quantity. In the most recent of these older studies, Wilcox (1917) stated "In all instances in which I have employed uranium nitrate I have never noted any untoward gastric or intestinal symptoms nor any signs of blood or renal disturbances; careful observation has been

Table 1. Calculated peak kidney burdens and equivalent inhalation intake of Type F material from cases involving large oral intakes of soluble uranium.

Reference	Case number	Estimated oral intake (g U)	Calculated peak kidney burden from ingestion (mg U)	Calculated acute inhalation required to produce equivalent kidney burden (mg U)
Bond (1898)	Case 1	268	25	750
Bond (1898)	Case 9	1,329	120	3,800
Duncan (1897)	Case 1	40	24	740
Duncan (1897)	Case 2	31	33	1,000
Duncan (1897)	Case 3	94	65	2,000
Duncan (1897)	Case 4	111	51	1,600
Duncan (1897)	Case 5	50	32	990
West (1895)	Case 1	101	52	1,600
West (1895)	Case 3	38	39	1,200
West (1896)	Case 3	27	24	730
Bradbury (1896)		178	38	1,200

especially directed toward the early detection of the latter." Wilcox patients were treated for extended periods of months to years with up to 200 mg of uranyl nitrate daily.

For the patient with the highest intake, which included an oral intake in excess of one and a quarter kilograms of soluble uranium in 1 year, the peak kidney burden is estimated to be about 123 mg or about 0.4 mg kg⁻¹ of kidney. To achieve a comparable kidney burden by inhalation would require an acute inhalation intake of 3.8 g, which corresponds to 0.4 g U per cubic meter of air for a single 8-h (=1 working day) exposure, some three orders of magnitude greater than the occupational Derived Air Concentration (DAC) assuming 5% enriched soluble uranium and ICRP 66 and 68 parameters (ICRP 1994a and b).

Several planned administrations of uranium have been carried out under controlled conditions. The first of these was a study of uranium metabolism carried out as a part of the Manhattan Project at the University of Rochester in the 1940's (Bassett et al. 1948). Six subjects were injected with doses of 70% enriched uranyl nitrate ranging from 6.3 to 70.9 μg kg⁻¹ of body weight. One subject also received a subsequent dose of 54.5 μg kg⁻¹ of body weight. Ignoring the second dose to this subject, the injections correspond to a dose of 0.44 to 4.96 mg for a 70-kg man. A comparable amount administered by mouth would be about 20 to 250 mg based on a gut absorption fraction of 0.02 (ICRP 1996). There was no mortality and the only effects were noted in the highest exposed individual who exhibited a transient slight rise in urinary catalase and protein, suggestive of minor kidney effects. About 70% of the injected uranium was excreted within 24 h.

A second planned administration—the so-called Boston Injection Cases—was a study to determine the potential value of partially enriched uranium as a treatment for malignancies. If enriched uranium concentrated in tumor tissue, subsequent irradiation of that tissue with

a beam of thermal neutrons would induce fissions in the uranium, and in particular in the higher cross section 235 isotope, producing fission fragments which in turn would produce high doses localized in the tumor tissues. The experiment involved injection of eight comatose persons ranging in age from 26 to 63 y, terminally ill with severe central nervous system diseases (Struxness et al. 1956; Leussenhop et al. 1958; Hursh and Spoor 1973). Six of the patients were injected with soluble uranyl nitrate, the doses ranging from 72 to 907 μg kg⁻¹ or 5 to 51.4 mg in total (Hursh and Spoor 1973). The other two patients were injected with 573 and 700 μg kg⁻¹ corresponding to a total of 41.1 and 44.2 mg of the less soluble tetravalent UCl₄. Survival times ranged from 2.5 to 566 d post-injection, but in all cases deaths were attributable to the terminal central nervous system disease and not to the uranium.

An obvious difference between the two compounds injected was the 24-h excretion, which averaged 69% of the injected dose for the six cases injected with uranyl nitrate but only 20 and 16.9% for the two cases injected with the less soluble UCl₄. A similar but less striking effect occurred with respect to total uranium excretion; the six cases injected with the more soluble uranyl nitrate excreted an average of 82% of the dose while the two cases injected with the less soluble uranium tetrachloride excreted 68 and 57%.

There was no correlation between survival time and dose of uranium. The physician who reviewed the extensive clinical test data used to evaluate kidney function concluded that the minimum single dose required to produce caltalaris and albuminuria was about 0.1 mg kg⁻¹, equivalent to about 7 mg in a 70-kg adult male (Leussenhop et al. 1958). However, at autopsy, none of the injected group showed evidence of any pathology, including kidney damage, attributable to uranium. IMBA-URAN was used to calculate the peak kidney burdens and then to determine the acute intakes of

Table 2. Calculated kidney burden from experimental injection of uranium.^a

Paper	Calculated peak kidney burden from injection (mg U)	Calculated acute inhalation of Type F uranium required to produce equivalent kidney burden (mg U)
Hursh and Spoor—Boston		
Injection Experiment Case 6	3.5	110
Injection Experiment Case 7	2.9	97
Injection Experiment Case 8	3.2	90

^a Note: For cases 7 and 8, the actual oral intake was Type M material, but the acute inhalation intake was calculated for Type F material. This is because IMBA-URAN calculates the same kidney burden for a given activity in the urine regardless of the type of material.

soluble uranium required to produce equivalent peak kidney burdens. It should be noted that when uranium is injected, the resulting peak kidney burdens are the same regardless of the solubility of the uranium if the urine concentrations are the same. Based on the IMBA calculation (James 2002), the upper dose limit in this series of subjects would produce a maximum kidney burden equivalent to an acute inhalation of 108 mg of soluble uranium salts (Table 2). Using the data from the injection cases and a scaling factor derived from published experimental data in rabbits, Leussenhop et al. (1958) estimated the lethal intravenous injection dose for humans to be 1 mg kg⁻¹ or 70 mg for 70-kg reference man. Assuming a gut uptake of 0.02 per ICRP (1996), this corresponds to a single oral intake of 3.5 g, in reasonable agreement although somewhat lower than what was obtained with the human cases.

A third planned administration involved oral administration of 10.8 mg of uranium as uranyl hexahydrate dissolved in Coca-Cola to four hospital patients. With this relatively low dose, the patients reported no subjective symptoms, and no urine abnormalities were noted, indicative of no kidney damage (Hursh and Spoor 1973). Also, in a planned inhalation study, a volunteer inhaled uranium for short periods on 17 different days during a period of 23 d, resulting in an estimated lung deposition of 9.5 mg of uranium without ill effect (Harris 1961).

Butterworth (1955) described a controlled experiment in which a volunteer subject ingested a single intake of 1 g of uranyl nitrate (equivalent to 0.47 g of uranium) in 200 mL of water. Following the intake, the subject experienced violent vomiting, diarrhea, and mild albuminuria. Peak urinary concentrations of uranium, based on two 30 mL specimens, was estimated as 8 mg U per liter. Symptoms cleared within 24 h of the intake. Based on an uptake fraction of 0.02 via the gut, the uptake in this case would have been 9.4 mg. This dose was, of course, not lethal, and the symptoms experienced

by the subject may have been attributable to unusual susceptibility on the part of the subject, or to psychological reasons as the subject was aware that he was ingesting a toxic substance (Hursh and Spoor 1973).

In addition to the planned administrations described above is a clinical report from Australia of a deliberate ingestion of 15 g uranium acetate, equivalent to 8.4 g of uranium, along with an unknown quantity of benzodiazepine, by an individual attempting suicide (Pavlakakis et al. 1996). Based on 2% uptake via the gut, this would correspond to an uptake of 168 mg; ATSDR (1999) estimated the dose to be 131 mg U kg⁻¹ corresponding to an intake of 9.1 g U for a 70-kg reference man. Chelation therapy with both Ca EDTA and Ca DTPA, the former given in conjunction with sodium bicarbonate, failed to significantly increase urinary U excretion. The individual, who survived, suffered from rhabdomyolysis as evidenced by increased serum creatinine kinase, refractory anemia, myocarditis, liver dysfunction with a disproportionate coagulopathy, paralytic ileus, acute renal failure treated by dialysis for two weeks, and glycosuria. Six months after the acute intake, significant renal impairment was present along with a persistent incomplete Fanconi's syndrome. Fanconi's syndrome is an impairment of proximal tubule function characterized by excess amounts of glucose, bicarbonate, phosphates, uric acid, potassium, sodium, and certain amino acids being excreted in the urine. Fanconi's syndrome is relatively rare and may be hereditary and associated with certain genetic defects, or a result of medications or heavy metal poisoning.

Although it is not known whether the individual would have survived without treatment, given his medical history, it is likely that other than the kidney effects and glycosuria, the effects observed in this case were primarily if not wholly attributable to other causes. The observed kidney effects attributed to uranium may have been exacerbated by other medical conditions or potentiated by drugs, as was noted by Pavlakakis et al. (1996): "In view of his established history of gastrointestinal ulceration, it is likely that an impaired mucosal barrier aided absorption and significantly increased his toxic insult." His rather extensive medical history included established diagnoses of hyperlipidemia, muscle enzyme deficiency, hypertension, and hypogonadism; he also indicated that suffered from chronic peptic ulcer, asthma, gout, migraine, and more significantly, from renal calculi and urinary tract infections. This patient had been diagnosed with a borderline personality disorder and had undergone psychotherapy for more than 20 y. Perhaps even more notably, he was an admitted self-medicator and abuser of prescription drugs, having regularly taken some 14 drugs orally in the 12 mo preceding his suicide

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