Paper

ACUTE CHEMICAL TOXICITY OF URANIUM

Ronald L. Kathren* and Richard K. Burklin†

Abstract—**Although human experience with uranium spans more than 200 years, the LD_{50} 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 LD_{50} for uranium in humans are sparse, they are adequate to conclude that the LD_{50} for oral intake of soluble uranium compounds exceeds several grams of uranium and is at least 1.0 g for inhalation intakes. For intakes of uranium compounds of lesser solubility, acute LD_{50} values are likely to be significantly greater. It is suggested that 5 g be provisionally considered the acute oral LD_{50} for uranium in humans. For inhalation intakes of soluble compounds of uranium, 1.0 g of uranium is proposed as the provisional acute inhalation LD_{50}.**

Health Phys. 94(2):170–179; 2008

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 Gottleib 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 UO_2, U_3O_8, and UF_4,

* Washington State University at Tri-Cities, Richland, WA 99357; † Areva Corporation, Richland, WA 99357.

For correspondence contact: Ronald L. Kathren, 137 Spring, Richland, WA 99354-1651, or email at kathren@bmi.net.

(*Manuscript accepted* 20 *August* 2007)

0017-9078/08/0

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 Na_2U_2O, $UO_3(NO_3)_2$, 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 metalotoxicity 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 LD_{50} 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 UF_6, the LC_{50} for a 2-min exposure was estimated at 35 g of uranium per cubic meter; in rats, the LC_{50} for a 5-min exposure was estimated at 26 g per cubic meter. Longer exposure times resulted in concomitantly lower LC_{50} values, but the relationship of exposure time and LC_{50} 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 LD_{50} 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 LD_{50} 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 UO_2, U_3O_8, and UF_4 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 $\mu g\ kg^{-1}$ of body weight. One subject also received a subsequent dose of 54.5 $\mu g\ kg^{-1}$ 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 $\mu g\ kg^{-1}$ or 5 to 51.4 mg in total (Hursh and Spoor 1973). The other two patients were injected with 573 and 700 $\mu g\ kg^{-1}$ corresponding to a total of 41.1 and 44.2 mg of the less soluble tetravalent UCl_4. 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 UCl_4. 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 caltalasuria 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 benzodiazipine, by an individual attempting suicide (Pavlakis 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 Pavlakis 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

attempt in addition to using a number of topical agents including antifungals and steroid creams, and topical eye drops. In particular, the Fanconi's syndrome is known to be induced by certain medications (Izzedine et al. 2003). The effect of benzodiazipine, which was taken with the uranium, or any of the other drugs which the individual had taken, on the toxic effects of uranium is unknown, and given his medical and psychological history, even the amount of uranium ingested is open to question as he could have taken doses prior to the reported ingestion. Thus, limited credence should be placed on this case.

Acute accidental occupational exposures provide additional data relative to acute uranium toxicity. Three men who received a massive airborne exposure to UF_6 in 1944 were evaluated 38 y after their exposure and found to have no apparent long term health effects, including kidney toxicity, attributable to their exposure. The "best" estimate of initial lung deposition of uranium in the three cases was about 40–50 mg, but the range was very broad: 1.21 to 110 mg, 1.3 to 480 mg, and 2.1 to 827 mg in the three cases (Kathren and Moore 1986). The intake, of course, was considerably higher than the initial lung deposition since most of the inhaled material would likely never reach the lungs, being removed in the upper respiratory tract, indicating that an acute inhalation intake of tens to a few hundred milligrams of uranium is well below the LD_{50}. In another acute inhalation exposure also involving UF_6, 31 workers received acute intakes estimated to range from 0.47 to 24 mg with no long-term health effects or significant short-term effects other than possibly mild and reversible effects on the proximal tubules of the kidney (Fisher et al. 1990).

Zhao and Zhao (1990) describe the case of an individual in China who suffered an acute accidental inhalation of natural UF_4 powder. Various renal effects including proteinuria, elevated non-protein nitrogen, and aminoaciduria were observed 1 wk post exposure. Urinary excretion characteristics of this case were quite unusual and not in consonance with recognized biokinetic models for uranium. The case described by Zhao and Zhao (1990) shows a more or less constant initial urinary excretion of about 125 μg for the first 10 d, dropping to 85 μg day 15 and then rapidly increasing to a peak of 3,174 μg at post-exposure day 63. After post-exposure day 63, urinary levels of uranium followed an exponential decrease with a half-life of 11.75 d, declining to normal background level 3 y after exposure.

This unusual urinary excretion pattern is indicative of gradual or slowed clearance from the lung to the blood and it is interesting albeit perhaps a bit speculative to note that the exponentially increasing urinary excretion during the first 2 mo post exposure is reflective of a gradual release of the acutely inhaled uranium from the lungs to the blood, or in other words a holdup in the lungs. Indeed, the excretion curve for this case is rather similar although on a much larger scale to what was observed by Kathren and Moore (1986). In the three of four males acutely exposed to tens of milligrams of UF_6 who exhibited symptoms of pulmonary edema, the initial urinary output dropped to below detection limits on day 5 or 6, followed by a resumption of excretion on post-exposure day 8 in two cases and day 10 in the third. Kathren and Moore (1986) attributed this unusual excretion pattern to a temporary retention of a portion of the U inhaled in a metabolic pool or compartment, likely from the edema resulting from inhalation of corrosive chemicals and physical irritants, specifically including HF, which is produced by the decomposition of UF_6 when combined with water or tissue fluids.

Total urinary excretion for this case is reported as 86.7 mg, which was also considered to be the "estimated inhaled dose." However, to achieve this level of urinary excretion, intake would have to be significantly greater. Using the total urinary excretion of 86.7 over a 1,065-d period, as reported by Zhao and Zhao (1990), and the current ICRP model for U, the intake is calculated as 1.46 g, truly a remarkably large amount. A similar analysis was performed by Bailey and Davis (2002) using the earlier ICRP 30 indicated an inhalation intake of 600 mg.

A second case was originally reported by Jia-Mei and Ji-Xiong in 1982 in the Chinese literature and briefly described by Zhao and Zhao (1990). A worker was burned over 71% of his body with a hot (108°C) mixture of uranyl nitrate and uranium oxide. Urine monitoring from day 1 to 7.5 y post exposure indicated a total excretion of 130 mg of uranium, plus 22 mg excreted in the first 24 h after the accident. This indicates an intake of at least 152 mg, likely mostly through dermal absorption, although inhalation intake could have been significant but is not known. Oliguria began on post-exposure day 1; only 100 mL of urine was excreted on that day, dropping to a nadir of 10 mL on post-accident day 7. Renal function began to improve at post-exposure day 8 as evidenced by increased urinary output, returning to normal 1 mo post exposure and remaining normal throughout the 7.5 y post-accident follow up period. Renal tubule dysfunction was evident in early laboratory studies, which showed grade 3+ proteinuria and elevated non-protein nitrogen and carbon dioxide combining power. It is entirely likely that the oliguria and biomarkers in the urine were mainly, if not entirely, attributable to the severe burns suffered by this individual and the associated loss of water through wound effusion, and not to his intake of uranium.

McGuire (1991) examined the literature and calculated LD_{50} values for uranium derived from reports by Just (1984) and Just and Emler (1984) that he cites. For uranium in a 70-kg person, Table 2 in McGuire (1991) gives 114 mg of uranium in a 70-kg person as the LD_{50} which presumably refers to systemic uranium and thus is in the middle of the range of 70–140 mg for the $LD_{50/30}$ in a reference man put forth a few years earlier in an unpublished work by Lincoln and Voelz (1988; cited in Fisher et al. 1990). McGuire's value is equivalent to an acute oral intake of 5.7–11.4 g based on a gut uptake factor of 0.01–0.02 (Wrenn et al. 1985; Dang et al. 1992; Harduin et al. 1994; Medley et al. 1994; ICRP 1996; Limson Zamora et al. 2002). This is approximately the upper level of therapeutic doses of uranium given daily for treatment of diabetes without apparent ill effect, as discussed above, and thus might be considered a lower limit of the actual acute oral LD_{50}, which is likely several fold greater but indeterminate with the available data.

For inhaled uranium, McGuire uses the 114 mg LD_{50} value for systemic uranium and the now obsolete ICRP 30 lung model to obtain a value of 230 mg for uranium intake by a 70-kg person, defining "intake" as the total amount of material inhaled into the body, and basing his calculation on the following: "For 1-micron (sic) uranium particles in soluble form, about 49% of the intake will be excreted through the kidneys according to ICRP 30 models" (McGuire 1991). However, unlike the ICRP model, McGuire assumes that all the uranium entering the urine over the course of the next 50+ years enters the kidney instantaneously. Thus, relative to the model, NUREG 1391 significantly overestimates the fraction of inhaled soluble particulates that will get into the systemic circulation at any instant in time yielding a conservative underestimate of the LD_{50} based on intake.

This assumption in NUREG 1391 thus ignores the kinetics and assumes that a single inhalation intake that results in a total systemic burden of 114 mg of uranium over the lifetime of the individual is equivalent to the LD_{50}. However, using the current ICRP lung model (ICRP 1994a, 1994b) for a single acute intake of a 5 μm Activity Median Aerodynamic Diameter (AMAD) aerosol, which is the default value, the comparable fraction is 27.6% resulting in a calculated intake 1.77 times greater than that obtained by McGuire (1991) or about 410 mg using his methodology as shown: assuming the 114 mg systemic uranium deposition in a 70-kg person to be in fact the LD_{50}, and accounting for the trivially small additional fraction absorbed from the larger fraction of inhaled material cleared via the gut, suggests that the LD_{50} for an acute inhalation intake of soluble uranium is 410 mg for a 5 μm AMAD aerosol. If inhaled over a single 8-h workday, this corresponds to a mean air concentration of 43 mg m^{-3}. This is, of course, a conservative lower limit on the LD_{50} for inhaled soluble material. The actual LD_{50} for inhaled uranium is likely to be much larger given the actual human data presented in Table 1. Even the example cited above assumes a single intake with essentially immediate and full transfer to the systemic body which of course is not the case. The inhaled uranium will be gradually absorbed into the systemic circulation, and most of it (approximately 70–80%) excreted within 24 h. Thus, the buildup of systemic uranium will be dictated by the kinetics of absorption from the lung and excretion of the absorbed material via the kidneys.

Note that the above assumes that a systemic deposition of 114 mg in a 70-kg person to be the LD_{50} as determined by McGuire (1991) based on the data put forth by Just (1984) and Just and Emler (1984). Reference to the original work by Just is illuminating, and raises the question of whether it provides an adequate basis on which to establish a human LD_{50} for acute intake of uranium. The basis for the LD_{50} proposed by Just (1984) and Just and Emler (1984) was developed as follows:

1. A panel of five scientists—four from the University of Rochester and one from the University of Utah—with expertise in the chemical toxicity of uranium was assembled to develop preliminary guidelines for estimating the toxicity of soluble uranium and HF;
2. This led to a series of toxicity experiments with guinea pigs and rats completed some three years later; and
3. Using primarily data from the animal toxicity experiments, plus limited human data primarily from the injection cases, a panel of four of the original five scientists used the Delphi method to develop, first independently and then by consensus, toxicity levels for soluble uranium and HF.

The expert panel concluded that for soluble uranium absorption 1.63 mg U per kg of body weight was the LD_{50} level. The members of the panel differed on the level, 1.63 mg being the average. The expert panel also put forth an LD_{50} exposure level, defined as the product of air concentration and exposure time of 35,000 mg U per cubic meter-minutes for inhaled uranium based on up to 60 min of exposure and a breathing rate of 7.5 L min^{-1}. This corresponds to a total intake of 15.75 g, a rather significant amount nearly two orders of magnitude greater than that computed by McGuire (1991), and an order of magnitude greater than that calculated using the current ICRP lung model and taking the kinetics into account. Unlike McGuire (1991), who clearly defined the aerosol parameters, the

expert panel report was mute with respect to fractional uptake from inhalation of this quantity of soluble uranium.

The expert panel also examined the chemical toxicity of insoluble uranium compounds, specifically uranium tetrafluoride, but did not come up with a specific LD_{50} value, noting that as insoluble uranium compounds are less toxic than soluble ones, the methodology and values used for soluble uranium compounds could be conservatively applied to insoluble compounds.

Finally, it bears mention that epidemiology studies in human populations, whether occupationally exposed or chronically exposed via high natural uranium levels in drinking water, have revealed no definitive evidence linking uranium exposure to human deaths (ATSDR 1999).

Threshold for chemotoxic effects on the kidney

It has long been generally known and accepted that the kidney is the most sensitive organ for chemotoxic effects of uranium, which manifest as proximal tubule effects with possible glomerular effects at higher exposures. Biomarker indications of kidney damage are many and include glucosuria, albuminuria, elevated beta-2 microglobulin and elevated blood creatinine levels, with specific types of damage indicated by specific biomarkers. The nephrotoxic threshold limit for chronic low-level exposure is typically taken to be 3 μg of uranium per gram of kidney (Alexander 1984; ATSDR 1999; Brodsky 1996; Kathren and Weber 1988; Leggett 1989; Spoor and Hursh 1973; Stannard 1988).

Some have indicated that this level may be too high and recommend additional study if not outright lowering of this nephrotoxic threshold level. Morrow et al. (1982) recommended a five-fold reduction to 0.6 μg U g^{-1} kidney based on animal studies carried out in his laboratory. For prudence, Leggett (1989) proposed a ten-fold reduction to 0.3 μg U g^{-1} kidney ". . . until more is known about subtle physiological effects of small quantities of U in the kidneys" based on a comprehensive review of the literature. Zhao and Zhao (1990) suggested the permissible kidney burden should not exceed 0.26 μg U g^{-1} kidney, basing this on a single case with an apparently massive acute inhalation intake of UF_4 powder. This case, which was only sketchily reported and was reviewed briefly above, had an atypical urinary excretion pattern and did not exhibit biomarkers of kidney damage until 68 d post exposure, at which time urinary excretion levels were approximately at their peak, some 20-fold greater than on the first day post accident and indicative of a kidney content of several tens of μg U g^{-1} kidney.

More recently, Brodsky (1996) reviewed the literature and concluded that a 3 μg U g^{-1} kidney concentration was ". . . unlikely to cause kidney damage over a lifetime." Brodsky's conclusion appears to be consistent with recent comprehensive studies and evaluations that have been done, including those by the ATSDR (1999), the U.S. National Academies (Fulco et al. 2000) and British Royal Society (Baily and Davis 2002). Also of interest, a very recent NRC guidance document for personnel responding to radiological emergencies stated "There are no known long term chemical injuries from uranium intakes that are sublethal," which would seem to imply that intakes of uranium no matter how large that did not cause death would not result in permanent kidney damage and further notes that permanent renal damage has never been observed in humans (Athey et al. 2007).

McGuire (1991) also provides an estimate for the threshold intake required for permanent kidney damage. This question was put to the same expert scientific panel described above, but only one member ventured an estimate relative to permanent kidney damage. The estimate of this single scientist was 0.3 mg U kg^{-1} body weight, which corresponds to a body burden of 21 mg for a 70-kg reference man or an inhalation intake of about 40 mg based on ICRP Publication 30 (ICRP 1979) or 75 mg based on the current ICRP model (ICRP 1994a, 1996), and the highly conservative assumption that all the uranium that passes into the urine over the next 50+ years enters into the kidney instantaneously. Assuming the fraction reaching the kidney is 0.12, this corresponds to a peak kidney burden of 8.4 μg U g^{-1} kidney.

Review of the high level acute intake cases described above and especially Table 1 indicates peak kidney burdens of tens of milligrams of uranium, and peak concentrations an order of magnitude or more greater than the 3 μg U g^{-1} kidney considered to be the threshold for permanent kidney damage, apparently incurred without significant or long lasting ill effects. This suggests that the 3 μg U g^{-1} kidney concentration is adequate and quite likely has a safety factor of 10 to 100, as has been suggested by its framers.

CONCLUSION

In summary, large acute doses of soluble uranium can produce death in experimental animals, with variation in sensitivity among species. Insoluble uranium compounds are reportedly nontoxic. 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. Although the data on which to establish oral and inhalation acute LD_{50} for uranium in humans are sparse, they are generally consistent and adequate to conclude that the LD_{50} for oral intake of

soluble uranium compounds exceeds several grams of uranium and is at least 0.41 g, and likely greater, for inhalation intakes of soluble compounds of uranium. It is suggested that 5 g be provisionally considered the acute oral LD_{50} for uranium in humans; for inhalation intakes of soluble compounds of uranium, 1.0 g of uranium is proposed as the provisional acute inhalation LD_{50}.

Acknowledgments—The authors wish to thank Robert A. Goyer for his prepublication review and helpful suggestions.

REFERENCES

Agency for Toxic Substances and Disease Registry. Toxicological profile for uranium (update). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 1999.

Alexander RE. Biokinetics model for uranium inhalation/excretion, uranium mill workers. In: Moore RH, ed. Biokinetics and analysis of uranium in man. Richland, WA: United States Uranium Registry; Report USUR-05, HEHF-47; 1984.

Athey GF, McGuire SA, Van Ramsdell J Jr. RASCAL 3.0.5 workbook. Washington, DC: U.S. Nuclear Regulatory Commission; 2007.

Bailey M, Davis K. The health hazards of depleted uranium munitions, Part II. Annexe A: Estimations of kidney uranium concentrations from published reports of uranium intakes in humans. London: The Royal Society; 2002.

Bassett SH, Frenkel A, Cedars N, Van Alstine H, Waterhouse C, Cusson K. The excretion of hexavalent uranium following intravenous administration. II. Studies on human subjects. Washington, DC: U.S. Atomic Energy Commission; Report UR-37, University of Rochester Atomic Energy Project; 1948.

Bond CH. Remarks upon the value of uranium nitrate in the control of glycosuria. The Practitioner Vol. viii:257–264; September 1898.

Bradbury JB. Case of diabetes mellitus treated by uranium nitrate. Brit Med J II:847; 1896.

Brodsky A. Review of radiation risks and uranium toxicity. Hebron, CT: RSA Publications; 1996.

Butterworth A. The significance and value of uranium in urine analysis. Trans Assoc Industrial Med Officers 5:36–43; 1955.

Dang HS, Pullat VR, Pillai KC. Gastrointestinal absorption factor for uranium incorporated in diet. Radiat Protect Dosim 40:195–197; 1992.

Duncan E. The treatment of diabetes mellitus by nitrate of uranium. Brit Med J II:1044–1047; 1897.

Durbin PW, Wrenn ME. Metabolism and effects of uranium in animals. In: Conference on Occupational Health Experience with Uranium, Arlington, Virginia, 28–30 April 1975. Washington, DC: U.S. Energy Research and Development; Administration Report ERDA-93; 1975: 67–129.

Fisher DR, Swint MJ, Kathren RL. Evaluation of health effects in Sequoyah Fuels Corporation (SFC) workers from accidental exposure to uranium hexafluoride. Washington, DC: U.S Nuclear Regulatory Commission/Pacific Northwest Laboratory; Report NUREG/CR-5566 (PNL-7328); 1990.

Fulco CE, Liverman CT, Sox HC. Gulf War and health. Volume 1. Depleted uranium, pyridostigmine bromide, sarin, and vaccines. Washington, DC: Institute of Medicine, National Academies Press; 2000.

Harduin JC, Royer Ph, Piechowski J. Uptake and urinary excretion of uranium after oral administration in man. Radiat Protect Dosim 53:245–248; 1994.

Harris WB. Experimental clearance of uranium dust from the human body. In: Davies CN, ed. Inhaled particles and vapours. Proceedings of an International Symposium held in Oxford, 29 March–1 April 1960. London: Pergamon Press; 1961: 209–215.

Hodge HC. A history of uranium poisoning (1824–1942). In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium plutonium transplutonic elements. Handbook of experimental pharmacology XXXVI. New York: Springer-Verlag; 1973: 5–68.

Hursh JB, Spoor NH. Data on man. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium plutonium transplutonic elements. Handbook of experimental pharmacology XXXVI. New York: Springer-Verlag; 1973: 197–239.

International Commission on Radiological Protection. Report of Committee IV on evaluation of radiation doses to body tissues from internal contamination due to occupational exposure. Oxford: Pergamon Press; ICRP Publication 10; 1968.

International Commission on Radiological Protection. Limits for intakes of radionuclides by workers. Oxford: Pergamon Press; ICRP Publication 30, Annals of the ICRP 2(3/4); 1979.

International Commission on Radiological Protection. Human respiratory tract model for radiation protection. Oxford: Pergamon Press; ICRP Publication 66, Annals of the ICRP 24(1–3); 1994a.

International Commission on Radiological Protection. Dose coefficients for intakes of radionuclides by workers. Oxford: Pergamon Press; ICRP Publication 68, Annals of the ICRP 24(4); 1994b.

International Commission on Radiological Protection. Age-dependent doses to members of the public from intake of radionuclides: Part 5, compilation of ingestion and inhalation dose coefficients. Oxford: Pergamon Press; ICRP Publication 72, Annals of the ICRP 26(1); 1996.

Izzedine H, Launay-Vacher V, Isnard-Bagnis C, Deray G. Drug-induced Fanconi's syndrome. Am J Kidney Dis 41:292–309; 2003.

James AC. User manual for IMBA-URAN, Framatone ANP Edition (Version 3.0). Richland, WA: ACJ and Associates, Inc.; 2002.

Just RA. Report of toxicological studies concerning exposures to UF_6 and UF_6 hydrolosis products. Oak Ridge, TN: U.S. Department of Energy Oak Ridge Gaseous Diffusion Plant; Report K/D-5573, Revision 1, Martin Marietta Energy Systems; 1984.

Just RA, Emler VS. Generic report on health effects for U.S. gaseous diffusion plants. Oak Ridge, TN: U.S. Department of Energy Oak Ridge Gaseous Diffusion Plant; Report K/D-5050-Sect. 8-Pt. 1, Martin Marietta Energy Systems; 1984.

Kathren RL, Moore RH. Acute accidental inhalation of U: a 38 year follow up. Health Phys 51:609–619; 1986.

Kathren RL, Weber JL. Ultrasensitive techniques for measurement of uranium in biological samples and the nephrotoxicity of uranium. Proceedings of a public meeting in Washington, DC, 4–5 December 1985. Washington, DC: U.S. Nuclear Regulatory Commission; Report NUREG/CP-0093; 1988.

Leggett RW. The behavior and chemical toxicity of U in the kidney: a reassessment. Health Phys 57:365–384; 1989.

Leussenhop AJ, Gallimore JC, Sweet WH, Struxness EG, Robinson J. The toxicity in man of hexavalent uranium following intravenous injection. Am J Roentgenol Radium Ther Nucl Med 79:83–100; 1958.

Limson Zamora M, Zielinski JM, Meyerhof DP, Tracy BL. Gastrointestinal absorption of uranium in humans. Health Phys 83:35–45; 2002.

Maynard EA, Hodge HC. Oral toxicity of uranium compounds. In: Voegtlin C, Hodge C, eds. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series VI. New York: McGraw-Hill Book Company; 1949: 309–376.

McGuire SA. Chemical toxicity of uranium hexafluoride compared to acute effects of radiation. Washington, DC: U.S. Nuclear Regulatory Commission; Report NUREG-1391; 1991.

Medley DW, Kathren RL, Miller AG. Diurnal urinary volume and uranium output in uranium workers and unexposed controls. Health Phys 67:122–130; 1994.

Morrow PE, Gelein RM, Beiter HD, Scott JB, Picano JJ, Yuile CJ. Inhalation and intravenous studies of UF_6/UO_2F_2 in dogs. Health Phys 43:859–873; 1982.

Orcutt JA. The toxicology of compounds of uranium following application to the skin. In: Voegtlin C, Hodge HC. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series VI. New York: McGraw-Hill Book Company; 1949: 377–414.

Pavlakis N, Pollock CA, McLean G, Bartrop AR. Deliberate overdose of uranium. Nephron 72:313–317; 1996.

Spoor NL, Hursh JB. Protection criteria. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium plutonium transplutonic elements. Handbook of experimental pharmacology XXXVI. New York: Springer-Verlag; 1973: 241–270.

Stannard JN. Radioactivity and health: a history. Columbus, OH: Battelle Press; 1988.

Struxness EG, Leussenhop AJ, Bernard SR, Gallimore JC. The distribution and excretion of hexavalent uranium in man. In: Proceedings of the International Conference of the Peaceful Uses of Atomic Energy, Volume 10, held in Geneva, 8–20 August 1955. New York: United Nations; 1956: 186–196.

Tannenbaum A, Silverstone H. Factors affecting uranium poisoning. In: Tannenbaum A, ed. Toxicology of uranium. New York: McGraw-Hill; 1951: 11–15.

West S. The treatment of diabetes mellitus by uranium nitrate. Brit Med J II:467–472; 1895.

West S. Further contribution on the treatment of diabetes mellitus by uranium nitrate. Brit Med J II:729–730; 1896.

Wilcox RW. The theraputics of uranium nitrate. Med Rec (NY) 92:361–364; 1917.

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

Yuile CL. Animal experiments. In: Hodge HC, Stannard JN, Hursh JB, eds. Uranium plutonium transplutonic elements. Handbook of Experimental Pharmacology XXXVI. New York: Springer-Verlag; 1973: 165–196.

Zhao S, Zhao F-Y. Nephrotoxic limit and annual limit on intake for natural U. Health Phys 58:619–623; 1990.

■ ■