ACUTE CHEMICAL TOXICITY OF URANIUM WITH APPLICATION TO 10 CFR 70.61

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Executive Summary

Requirements for licensure of special nuclear material applicable to uranium are specified in Title 10 Code of Federal Regulations Part 70 (10 CFR 70) and include three levels of specific risk criteria defined by biological effects and whether the exposed individual is a worker or a member of the public; these are in order of decreasing severity life endangerment, irreversible or serious long lasting effects, and mild transient health effects. This report provides a brief overview and necessary background of the properties, distribution, biokinetics and chemical toxicity of uranium and recommends threshold levels or standards for accidental acute inhalation and ingestion of levels for application to acute accidental exposure to uranium to comply with 10 CFR 70.

To date, the Nuclear Regulatory Commission (NRC) has been relying on "Chemical Toxicity of Uranium Hexafluoride Compared to Acute Effects of Radiation, NUREG-1391, U.S. Nuclear Regulatory Commission, February 1991." NUREG 1391 was developed largely on animal data and expert judgment. It is also focused only on the inhalation pathway. In 2007, it was recognized by NRC and the fuel cycle industry that a technical basis could be developed to support an increase in the soluble uranium intake criteria in 10 CFR 70.61 and that NRC had authorized increased limits on a licensee-by-licensee basis. As a result, an NRC and industry working group was formed to develop a report that could support the needed technical basis for a different regulatory limit. This report satisfies that need. The data in this report is based on known human ingestion and inhalation of soluble uranium. Unfortunately, the human data represents a scatter graph rather than a precise fit, however even with a scatter graph, a very conservative use of the data provides greater accuracy than NUREG 1391. It is also important to note that the exposure limit for uranium hexafluoride is constrained by the chemical toxicity of hydrogen fluoride (HF), a product formed when uranium hexafluoride reacts with moisture in the air, to a worker This report does not address hydrogen fluoride chemical toxicity.

The proposed threshold levels were primarily based on human exposure experience as reported in the peer reviewed scientific and medical literature and correlated with kidney concentrations calculated with a generally accepted biokinetic model. For life endangerment, the proposed thresholds are 2500 mg and 500 mg, respectively, for acute oral and inhalation intakes, although the former could be increased by a factor of 3 based on peak kidney concentration. Acute intake thresholds for irreversible or serious long lasting health effects are 1400 mg and 100 mg, respectively, for ingestion and inhalation and 410 and 30 mg, respectively for ingestion and

inhalation for minor transient health effects. Based on peak kidney concentration, 3 μg U per gram of kidney is considered to be the threshold for measurable kidney effects and 50 μg U per gram of kidney is conservatively selected as having life endangerment possibilities.

Introduction

The report provides a brief overview and necessary background of the properties and chemical toxicity of uranium for application to regulatory limits generally and acute accidental exposures specifically as called out in Title 10 Code of Federal Regulations Part 70.61 (10 CFR 70.61) based primarily upon available human data as reported in the open peer reviewed medical and scientific literature. As such it parallels and expands the previous work on the same topic published in August 2008 (Kathren and Burklin 2008a, 2008b) providing additional discussion and support for the recommendations put forth in that peer reviewed paper, drawing upon recently developed knowledge as well as long standing knowledge of the biological effects of exposure to uranium, and discusses and evaluates areas of uncertainty.

Uranium is a heavy metal and thus exhibits chemical toxicity as is true of all heavy metals. In addition, uranium is also radiotoxic as all isotopes of uranium are radioactive. The three naturally occurring isotopes – U-234, U-235, and U-238 -- are only weakly radioactive, having very long half-lives and hence low specific activity. It is generally well accepted that the chemical nephrotoxicity of ingested or inhaled soluble uranium exceeds the radiotoxicity and is more limiting for U-235 enrichments less than 20 per cent (Brodsky 1996; Fisher et al. 1994; Fulco, Liverman and Sox 2008; ICRP 1991; NRC 2008; Stannard 1988; The Royal Society 2001, 2002). Radiotoxicity is generally thought to exceed chemical toxicity only from inhalation of insoluble compounds which deposit in the respiratory tract and are retained there for long periods producing a stochastic risk of radiation induced carcinogenesis proportional to the dose delivered by the deposited material.

Although the chemical toxicity dominance is recognized by the International Commission on Radiological Protection (ICRP), it has put forth protection standards for uranium based solely on radiotoxicity (Fisher et al.1994). Thus, this review considers only acute chemotoxic effects of acute exposures to uranium. And since basic to chemical toxicity is absorption into or uptake by the body, the review is primarily applicable to soluble uranium compounds. Long term chronic chemotoxic effects of uranium exposures and radiation induced stochastic effects such as

carcinogenesis, as might be determined from epidemiologic studies of exposed worker populations, or from inhalation of insoluble aerosols, are outside the purview of this report.

Properties and Uses of Uranium

In 1789, the German apothecary chemist Martin Heinrich Klaproth, often referred to as the father of analytic chemistry, identified a new metallic element in a precipitate of the mineral pitchblende. He named this new element uranium after the planet Uranus that had only recently been discovered by Sir William Herschel. The newly discovered metal was not purified for 17 more years, and more than a century passed before it was found to be radioactive. Uranium, element number 92 in the periodic table of elements, is the heaviest naturally occurring element having an atomic weight of 238.03 atomic mass units. Its density of 19.1 grams per cubic centimeter (g/cm^{-3}) is nearly twice that of lead. Pure uranium is a silvery gray weakly radioactive metal that is chemically reactive with several valence states, forming a variety of compounds and oxidizing readily. Freshly separated uranium metal reacts with the oxygen in air to form a black oxide coating on the surface of freshly separated metal and in finely divided form, metallic uranium is pyrophoric.

As found in nature, uranium is a mixture of three weakly radioactive (i.e. low specific activity) radioisotopes: U-234 (0.0054% by weight); U-235 (0.71% by weight) and U-238 (99.28% by weight) with half-lives of 245,500; 704 million; and 4.5 billion years, respectively. The specific activity of natural uranium is about 685 nanocuries (25.3 kBq) per gram as compared with naturally occurring radium-226 which contains one curie (3.7×10^{10} Bq) per gram. Each uranium isotope decays by emission of an alpha particle, and thence through a series of radioactive decays to ultimately end up as an isotope of stable lead, a process which takes hundreds of thousands to billions of years given the long half lives of the various uranium isotopes. The progeny, or radioactive daughter or decay products, are usually found in association with uranium as it is found in nature but not necessarily in equilibrium amounts.

The primary value of uranium lies in the fissile nature of the 235 isotope which makes it capable, given the right circumstances, of supporting a self-sustaining nuclear chain reaction. The

fraction or weight percentage of U-235 may be increased by treatment of natural uranium by methods such as gaseous diffusion or centrifugation, a process known as enrichment. Enrichments to a level of a few percent of U-235 are used as fuels in light water cooled and moderated nuclear reactors used for production of electrical power, while high enrichments to 93 percent or even greater are used for nuclear weapons and for specialized reactor applications. Enrichments greater than 85 % U-235 are considered weapons grade. The residuum of the enrichment process is uranium depleted (i.e. having a lower weight percentage) in its U-235 content as compared with the 0.71 % in natural uranium. Depleted uranium (DU) is extensively used in munitions because of its superior armor piercing capabilities attributable in part to its high density, hardness, pyrophoricity, and self-sharpening properties as it penetrates armored vehicles. DU is also used to armor tanks and other combat vehicles.

Over and above its use in weapons and for power generation, uranium has a number of commercial and industrial applications. DU is used as counterweights in aircraft and ballast in ships, and, as it is only weakly radioactive, as shielding material for penetrating radiations such as x- and gamma rays. It is useful as an alloying material in special steels, and, in the form of the compound uranyl acetate finds applications in analytical chemistry. It has been used in the past in optical glasses, dental porcelain, and to produce colorful yellow and orange glazes for pottery and ceramic materials. This latter use reportedly dates back more than 2000 years.

Distribution of Uranium in Man and the Environment

Uranium is ubiquitous throughout the natural environment, being present to a greater or lesser degree in all soils, rocks, fresh and salt waters, and all living things. Crustal rocks typically contain a few parts per million (ppm) of natural uranium, averaging about 2.8 ppm, but some rocks, notably phosphates sometimes used as fertilizers may contain in excess of 100 ppm of natural uranium (Eisenbud and Gesell 1997). Uranium concentrations in natural fresh waters are highly variable, ranging from a few hundredths to a few hundred micrograms per liter, while sea water contains a more or less uniform concentration of 2 to 3.7 microgram per liter or about 3.2 ppb on average (Faure and Mensing 2005). The natural uranium content of the human body is variable, influenced primarily by the dietary intake of uranium and concentrations in drinking

water. An adult typically ingests on average about 1.9 μg of natural uranium per day, largely from food, excreting about the same amount, largely via the feces (1.4-1.8 μg/day), plus 0.05-0.5 μg in the urine, and 0.02 μg in the hair (ICRP 1975). Thus the individual is in equilibrium with respect to uranium intake and excretion. Uranium is not known to be an essential trace element and hence there is no recommended daily allowance.

On average, an adult human contains about 90 μg of uranium (ICRP 1975; ATSDR 1999) resulting in an average tissue concentration of about 1.29 μg U/kg tissue based on a 70 kg Reference Man. Uranium is found in all tissues of the body, but concentrations of natural uranium in the various tissues are quite variable among individuals, ranging over more than an order of magnitude in the tissues of two male whole body tissue donors completely analyzed by the United States Transuranium and Uranium Registries (Kathren1997). The skeleton is the primary depot for uranium, containing about two thirds of the natural uranium content in the body (ICRP 1975), and indicative of a concentration of about 6 to 7 μg U/kg of skeleton. Soft tissue concentrations are typically about an order of magnitude lower than those in the skeleton; using Reference Man values (ICRP 1975), the average concentration of natural uranium in the soft tissues is calculated as 0.5 μg/kg, somewhat lower than but still entirely consistent with what was observed in the two USTUR whole body cases. The highest tissue concentrations – on the order of 20 to 30 μg U/kg in the USTUR cases -- are found in the lymph nodes, particularly those associated with the respiratory tract, but because of the small mass of these tissues their total uranium content is but a small fraction of the whole body content.

The kidney is typically considered a secondary depot as indicated by various biokinetic models and by Reference Man data (ICRP 1975; ATSDR 1999) and the kidney concentration reported by Reference Man is about 20 μg U/kg, a factor of 40 greater than for the average of all soft tissues and an order of magnitude or more greater than in any other soft tissue listed. The elevated kidney uranium concentration reported for Reference Man is at variance with what has been reported elsewhere in the literature based on postmortem tissue analysis. In the two whole bodies it analyzed, the USTUR found kidney concentrations of natural uranium to be approximately the average of the soft tissues as a whole (Kathren 1997); like observations were made in postmortem tissue analysis of members of the general public by Welford, Baird and

Fisenne (1976), Wrenn and Singh (1982), New York City residents by Fisenne and Welford (1986), in the UK (Hamilton 1972) and world wide by Singh (1990), among others. Similarly, neither have grossly elevated kidney concentrations of U been reported in cases of persons occupationally exposed to uranium whose tissues were analyzed postmortem (Wrenn et al. 1985; Kathren et al. 1989; Russell and Kathren 2004).

It bears mention that these postmortem tissue measurements were made at long times after exposure in the case of those occupationally exposed or with persons seemingly at intake-excretion equilibrium in the case of members of the general public, and thus mitigate against the kidney serving as a long term storage depot for uranium. However, they do not preclude the existence of a short or intermediate term kidney compartment of up to perhaps 1,000 to 1,500 days as has been proposed in various biokinetic models for uranium that have put forth over the years (Russell and Kathren 2004).

Biokinetics and Biokinetic Models

The just concluded discussion of the distribution of uranium in the tissues serves as an important segue into the discussion of the biokinetics of uranium. Uranium may enter the body by one of three routes: inhalation, ingestion, or through the skin (percutaneous). Biokinetics refers to the uptake or absorption of uranium by the body and its subsequent deposition, translocation, and removal from the various body tissues, and is essential to predicting biological consequences of intakes and to understanding the toxicity. The biokinetics of uranium is complex and influenced by a number of factors, including the route of entry, the solubility and other physicochemical characteristics of the uranium, and not well known despite a history of human experience with uranium spanning more than 200 years (NRC 2008, p. 23). Individual physiological characteristics, diet, age and medications of the individual also may significantly influence biokinetics.

Biokinetic models are typically mathematically based representations of the movement, deposition, fate and excretion of substances within the body that basically convert exposure or intake into uptake and excretion, considering such factors as the fractional absorption of the

material via the route of entry, uptake and residence time in various tissues and organs, chemical and physical factors such as solubility and particle size distribution, and clearance kinetics from the body. There is wide individual variability among people, and uptake, retention and excretion can be affected by a host of environmental and other variable including water and dietary intake, temperature and sweating, medications, and exercise. As such, the biokinetics characterize what tissues are likely to be affected or to concentrate or serve as depots, and the residence time in these tissues and hence the concentration as a function of time, important factors in establishing toxicity. Moreover the models themselves are mathematical representations of complex biological phenomena, typically based on a few human cases providing fragmentary and incomplete data and extrapolations from animal data, and have inherent large and unknown uncertainties. The latter is particularly true if the human case(s) used to develop the model were metabolically atypical or if the model is applied to a metabolically atypical individual, or if the solubility of the material in biological fluids is not well known.

Despite the limitations, a number of basically similar systemic biokinetic models and refinements to models have been put forth over the years (Bernard and Struxness 1957; Durbin 1974; Fisher, Kathren and Swint 1991; Harduin, Royer and Piechowski 1994; ICRP 1977, 1979, 1988, 1994, 1995a; Leggett 1992, 1994; Leggett and Harrison 1995; Leggett and Pelmar 2003; Lipsztein 1981; Wrenn et al. 1985a, 1989a). Generally, all the models indicate that only a small fraction of the uranium taken into the body is absorbed into the systemic circulation of the body by whatever route of entry. Most of the small fraction of uranium that has been absorbed into the blood is quickly excreted, primarily via the urine. About two thirds of what has been absorbed into the blood is excreted in the first 24 hours after intake and another 10 % in the next few days (ICRP 1995a). Most of the remainder is also quickly excreted but a small amount of the uranium in the blood may be taken up by and incorporated into certain specific tissues, remaining there for various lengths of time before being excreted; this is the so-called systemic deposition. Most of the uranium in the body is resident in the skeleton which is considered the primary depot; in part this is because of the large mass of the skeleton relative to the other tissues and organs in the body. A recent study in which the uranium content of all the tissues of the body from two male whole body donors was chemically analyzed confirmed that bone was the primary depot and further revealed that uranium was well distributed throughout and found in all

the soft tissues of the body although with the exception of the lymph nodes typically at concentrations an order of magnitude lower than those in bone (Kathren 1997).

The biokinetic models developed by the International Commission on Radiological Protection (ICRP) represent the consensus of a committee of experts that has exhaustively examined the scientific literature and are generally the most widely accepted and used, serving as the basis for the development of radiation protection standards for uranium. The most recent ICRP model (ICRP 1994, 1995a) is a recycling model in which uranium is taken up from the blood and held by various compartments (i.e. tissues or organs) before being released back to the blood. The major tissue compartments are the skeleton, liver, kidneys, and a generic soft tissue compartment. The skeleton, liver and kidneys are each modeled as two separate compartments, for the skeleton, one compartment represents trabecular bone and the other cortical bone. About 15% of the uranium removed from the blood is taken up by the skeleton and released back to it with a half-life of 30 days or less. The liver and kidneys are also modeled as two compartments, one short term and the other longer term. About 1.5% of the uranium leaving the blood is taken up by the liver. Most of the liver uptake is rapidly released back to the blood with a half time of one week; the remainder of the liver uptake is to a second liver compartment that releases the uranium back to blood with a half time of 10 years. One of the two kidney compartments is a rapid urinary excretion pathway. The other receives only 0.05% of the uranium leaving the blood and retains it with a half time of 5 years. The remainder of the soft tissues are included in a generic soft tissue compartment subdivided into three compartments based on retention time (rapid, intermediate, slow turnover).

Uranium is not well absorbed via the gut with the overwhelming fraction of ingested uranium excreted via the feces. The fraction of ingested soluble uranium that is absorbed into the blood via the gut is on the order of 1-2 per cent, and about an order of magnitude less (~ 0.1%) for the insoluble oxide forms (Harduin, Royer and Piechowski. 1994; Leggett and Harrison 1995; Medley, Kathren and Miller 1994; Wrenn et al. 1895a, 1989a). The current ICRP model uses 2 and 0.2 per cent, respectively, as the uptake fractions from the gut for soluble and highly insoluble forms of uranium, the latter being specified as uranium dioxide (UO_2) and triuranium octoxide (U_3O_8) (ICRP 1994, 1995a).

Uptakes via the lungs are a complex function of particle size and solubility requiring sophisticated mathematical models and computer solutions to characterize them. Only a small fraction of inhaled uranium is deposited in the lungs. Most of the particles in the respirable range (typically taken to be particles with AMAD $\leq$ 20 μm) that are taken into the lungs are directly exhaled or cleared via the mucociliary escalator and the gut. Material deposited in the deep lung spaces may be absorbed into the systemic circulation over time depending on solubility. Insoluble particulates may be phagocytized and cleared from the lungs via the lymphatic system and deposition in the mediastinal or pulmonary lymph nodes where they may be retained for years, undergoing gradual dissolution, or excreted via the liver into the feces.

Regulatory Requirements: 10 CFR 70.61

Uranium of any enrichment is considered a special nuclear material, and as such, regulatory control of uranium falls under the purview of the Nuclear Regulatory Commission (NRC). Uranium is both radioactive and, as a heavy metal, chemically toxic. Requirements for domestic licensure of special nuclear material are specified in Title 10, Code of Federal Regulations, Part 70 (10 CFR 70). Specific safety performance requirements or risk limitations are specified in Paragraph 70.61 (b)(4) and 70.61 (c)(4), and reproduced below:

High consequence events are those internally or externally initiated events that result in:

(b)(4) An acute chemical exposure to an individual from licensed material or hazardous chemicals produced from licensed material that:

(i) Could endanger the life of a worker, or

(ii) Could lead to irreversible or other serious, long-lasting health effects to any individual located outside the controlled area identified pursuant to paragraph (f) of this section. If an applicant possesses or plans to possess quantities of material capable of such chemical exposures, then the applicant shall propose appropriate quantitative standards for these health effects, as part of the information submitted pursuant to § 70.65 of this subpart.

. . .

Intermediate consequence events are those internally or externally initiated events that are not high consequence events that result in:

(c)(4) An acute chemical exposure to an individual from licensed material or hazardous chemicals produced from licensed material that:

(i) Could lead to irreversible or other serious, long-lasting health effects to a worker, or

(ii) Could cause mild transient health effects to any individual located outside the controlled area as specified in paragraph (f) of this section. If an applicant possesses or plans to possess quantities of material capable of such chemical exposures, then the applicant shall propose appropriate quantitative standards for these health effects, as part of the information submitted pursuant to § 70.65 of this subpart.

The three levels of health effects put forth in 10 CFR 70.61 are summarized below based on their severity:

1. Life endangerment (b)(4)(i)
2. Irreversible or other serious long lasting health effects (c)(4)(i) and (b)(4)(ii)
3. Mild transient health effects (c)(4)(ii)

However, the description of each level as given in the regulation is quite general, vague and nondefinitive, and subject to wide and overlapping differences in interpretation, and the temporal aspects are not specified nor is acute exposure is defined. For example, consider the phrase "irreversible or other serious long lasting health effects". Certainly the word "irreversible" is unequivocal, but what is a "serious" health effect? And, what period of time defines "long lasting"? And what is the difference between a mild transient health effect and a serious long lasting health effect? In which of the three levels does a mild long lasting health effect fall? And what constitutes an acute exposure?

The last question is relatively easily answered. Acute exposures are customarily assumed to be of short duration, typically minutes or less, but in no case lasting longer than 24 hours. But the phrase "could endanger the life of a worker" is not so easily defined and raises a number of questions, particularly if the exposure has occurred in conjunction with some other insult such as physical injury from an explosion or exposure to other chemicals that may produce an additive effect. Then too there is the situation of exposure to uranium hexafluoride, which hydrolyses to HF and may result in acid burns to the skin or potentially fatal pulmonary edema if inhaled. There is also the question of treatment; in theory at least, one might incur an acute exposure that if untreated would prove fatal, but if treated could fall into a lower category.

In an attempt to resolve or at least minimize potential questions of interpretation and ambiguities in the discussion pertaining to uranium toxicity, the following set of definitions was developed for use in this report.

1. *Life endangerment* refers to the effects of an acute exposure that, if untreated, would in and of itself result in the death of the exposed individuals, or result in life shortening of one year or greater based on actuarial life expectancy.
2. *Irreversible or other serious health effects* are clinically observable and result in diminished functional capability, either physical or physiological, lasting more than one year postexposure.
3. *Mild transient health effects* are symptomatic changes or physical effects perceptible to the exposed individual lasting no longer than 10 days post exposure, are without long term consequences, excluding psychological effects such as those arising from fear or anxiety, and require no treatment. This level is analogous to the lowest observed adverse effects level (LOAEL) in toxicological studies.

Note that all of the above categories are concerned with clinical effects, more specifically deterministic somatic effects and not stochastic or probabilistic effects such as cancer or genetic effects. Somatic effects typically have a threshold dose that needs to be exceeded if they are to manifest and such effects usually occur shortly after exposure. The severity and indeed the onset time of deterministic effects are directly related to the dose. Thus if the dose is sufficiently large, and deterministic effects known to be caused by exposure to uranium are manifested, then such effects are likely attributable to the chemical toxicity of uranium. By contrast, stochastic effects are generally associated with exposure to ionizing radiation, do not have a threshold for occurrence although their probability of occurrence is related to the dose, and do not manifest for many years, if at all.

It is important to note that irrespective of the isotopic mix or specific activity of the uranium, the chemical toxicity is constant. Thus as the fraction of U-234 and U-235 decrease, so does the specific activity of the mix of uranium isotopes and hence the radiotoxicity while chemical toxicity remains constant irrespective of enrichment. Based on animal studies, it is generally accepted that chemical toxicity dominates at enrichments below about 7 to 20 percent (ICRP

1968; Stannard 1988; Brodsky 1996, p. 157). Since the bases of chemical toxicity and radiotoxicity differ, the former being based on deterministic effects and the latter on stochastic effects, it is not truly possible to determine the ratio of chemical to radiological toxicity since in effect the comparison is between apples and oranges. However, one recent study has indicated that for depleted uranium, the chemical toxicity based on subcellular effects is a million fold greater than the radiotoxicity (Miller 2002).

The four levels presented above are not absolute and mutually exclusive, but rather represent a continuum which could change with time after exposure. Indeed, it may be difficult in many instances to transition among them and to decide in which level a specific effect belongs. This can be illustrated by the familiar if simplistic example of a minor cut to a finger. To which level should such a cut be assigned? One could make a case for the lowest or fourth level since there are likely to be no discernable health effects. The small cut on the finger produces no functional impairment and will quickly heal, perhaps leaving no scar and hence evidence of injury behind.

A case could also be made for assignment to the third level. Certainly even a very small cut will likely be perceptible to the affected individual through his own senses, and may even affect the functional of the affected finger so slightly but would likely be fully healed within 10 days. So, perhaps the minor cut to a finger properly belongs in the third category.

But there is also the possibility that the finger may become infected resulting in diminished capacity and pain to the individual. This is clearly a second level effect, and could, if untreated, result in endangerment to life or even death from infection, which would raise it to first level status.

Chemical Toxicity of Uranium

The discussion in this section is not a comprehensive review or evaluation of the voluminous literature pertaining to the toxicity of uranium in man and animals. Rather it is a brief presentation of the historical development of chemical toxicity studies and the salient points relative to the toxicity of uranium derived from those studies. A number of detailed comprehensive reviews of the literature pertinent to uranium toxicity are available (ATSDR

1999; Brodsky 1996; Fulco, Liverman and Sox 200; Hodge, Stannard and Hursh 1973; Leggett 1989; The Royal Society 2001, 2002; NRC 2008) and should be consulted for more in depth toxicological information.

Historical

In 1824, some 35 years after its discovery, Christian Gottleib Gmelin carried out the first uranium toxicity studies. A rather massive dose of 2 g of uranium relative to the size of the animal, administered as a chloride by gastric lavage, produced death in a rabbit. No deaths or observable effects in larger dogs fed up to 0.9 g of various uranium compounds, including the nitrate. Gmelin concluded that uranium was "a feeble poison", an observation confirmed by numerous animal studies carried out over subsequent years (Hodge 1973; Stannard 1988, ATSDR 1999). No less than 330 published studies from the peer reviewed literature, many carried out by German, French and British investigators, dating from Gmelin's original work until 1942, were documented by Hodge (1973).

The year 1942 marks the start of the Manhattan Engineering District (MED) efforts to create an atomic bomb and a watershed year with respect to biomedical studies of uranium. The recognition that the MED activities would involve handling and processing of massive quantities of uranium on a scale never before realized led to extensive comprehensive research into all aspects of uranium, with biomedical studies starting ". . . almost immediately after the organization of the Medical Section of the Manhattan Project" (Stannard 1988, p. 85). Pilot tracer studies had in fact been initiated in 1942 by Joseph G. Hamilton at the University of California (Stannard 1988, p. 87), and by late 1942 toxicological and other biomedical studies on uranium were being carried out at Medical Research Institute of Michael Reese Hospital and the Metallurgical Laboratory of the MED in Chicago under the direction of Albert Tannenbaum (Tannenbaum 1951). The Chicago program was largely concerned with mechanisms and routes of entry. But great expansion was in the works; and the next few months saw the organization and implementation of a far larger and more extensive research program with a staff of more than 300 at the University of Rochester Medical School under the direction of Harold C. Hodge.

Initially, the focus at Rochester was on acute toxicity, including inhalation toxicology, but soon was expanded into a much broader effort that studied the effects of a number of uranium compounds in several species of animals. Among the questions that the Rochester group in particular sought to answer were which uranium compounds were the most toxic, and how to best determine uranium induced kidney damage in man. A relatively unknown aspect of the work at Rochester involving human subjects was carried out during the 1940s. Two studies with humans are known to have been carried out; these were a metabolic study on six hospital patients injected with soluble uranium that took place during the war (Bassett et al. 1948) and another injection study in the early years after the war in seven subjects to validate animal data that suggested that uranium might be a suitable indicator of skeletal metabolic disorders (Terepka et al. 1965).

The MED work with uranium at Rochester was reported in four large volumes of papers entitled *Pharmacology and Toxicology of Uranium Compounds* published as part of the National Nuclear Energy Series (Voegtlin and Hodge 1949 and 1953). The four volumes, which encompassed more than 2400 pages of text, described the animal work in great detail along with efforts to establish standards for workers, but were oddly mute on the human experiments. The work at Chicago was described in a single volume entitled *Toxicology of Uranium*, also published as part of the National Nuclear Energy Series (Tannenbaum 1951).

After the war, experimental studies of uranium toxicology and metabolism waned but continued. Animal studies with the higher specific activity isotopes of uranium were carried out at several laboratories but the focus was on acquiring human data, specifically from occupational experience with uranium. The earliest studies with animals, verified, buttressed and expanded by the MED studies showed that the kidney was the organ most likely to be affected by uranium and this served as the basis for protection standards for both workers and the general public. Since airborne uranium and excretion of uranium in the urine of workers were routinely measured at industrial facilities handling uranium, a large database was available and the urinary excretion of uranium could be compared with biomarkers associated with kidney damage. Evaluation of the worker data was reported and discussed at two symposia, one sponsored in 1958 Atomic Energy Commission (AEC) that was held at the Health and Safety Laboratory (HASL) in New York

City (AEC 1959) and the other by the Energy Research and Development Administration (ERDA 1975) in 1975 (ERDA). The occupational health data, coupled with reports of a few accidental exposures and a few additional human administration studies with very limited postmortem tissue analysis in a few cases rather clearly indicated and were leading investigators to conclude that soluble uranium was less avidly retained in the body and also less nephrotoxic to humans than indicated by the animal data. Furthermore, the indications were that the chemical toxicity of uranium to humans was relatively low.

But as was pointed out by Eisenbud at the 1975 ERDA symposium, there was a plethora of animal data and a paucity of human data (Eisenbud 1975). It was with this in mind that the U.S. Uranium Registry, patterned after its decade older sister plutonium registry and now combined with it as the United States Transuranium and Uranium Registries (USTUR) at Washington State University, was created in 1978 (Kathren 1995; 1999). The Uranium Registry is a postmortem tissue analysis program concerned with the biokinetics, dosimetry and possible health effects of persons exposed to uranium. Epidemiologic studies of uranium worker and other populations had yet to begin in earnest, but would during the decade of the 1980's; generally these studies supported the growing conclusion that uranium was of a low order of chemical toxicity.

A second spike in research activity related to uranium toxicity was brought about by the use of depleted uranium munitions in Gulf War I (1990-91) and II (2003) and by NATO forces in Kosovo in 1999. Unlike the first spike represented by the MED studies, the emphasis was now on human studies rather than animal studies, an emphasis made possible by the availability of exposed military personnel with exposures to depleted uranium by inhalation and by contaminated wounds and fueled by allegations in the media and elsewhere that illness among Gulf War and Kosovo veterans – the so called Gulf War Syndrome -- and indeed civilian populations in the battle areas was directly attributable to exposure to depleted uranium. Reviews of the toxicologic and radiologic risks of depleted uranium were undertaken by various learned bodies including the World Health Organization, the British Royal Society, and the National Research Council of the National Academies in the United States and provided important comprehensive reviews of the literature and toxicological insights and evaluations (Fulco, Liverman and Sox 2001; NRC 2008; The Royal Society 2001, 2002; WHO 2001).

Ongoing in depth studies of exposed veterans are continuing along with animal studies using highly sensitive modern analytical techniques such as FISH, cytogenetics, and recognition and identification of biomarkers that did not exist in past years to look for even the most minimal of biological or biochemical effects relatable to uranium exposure. By comparison with modern capabilities, the early animal studies were crude and limited to observation and identification of rather obvious biological changes. Many of the effects recently being evaluated, such as reproductive and developmental effects, genotoxicity, and immune system effects were only casually studied (if at all) previously, in part due to a lack of sufficiently techniques and funding, and less concern with the possibility of effects at very low doses. The epidemiologic studies of worker populations begun in the 1980's have expanded to include general population studies in area with high levels of natural uranium in drinking water, and also to include the cohort of veterans exposed in the Gulf and in Kosovo. Thus far these ongoing recent studies have failed to identify significant toxicology associated with uranium, but tend to confirm what had been observed and concluded from the earlier and less sophisticated studies.

Summary of Animal Study Findings

Early studies of uranium toxicity in animals were relatively unsophisticated, largely limited to observations of gross effects from large acute doses, and to a considerable extent concerned with determination of the lethal concentration (LC) or lethal dose (LD_{50}). The early studies did, however, quickly establish a number of important aspects of uranium toxicity. Uranium was typically found to be poorly absorbed regardless of the route of entry, and that once absorbed in the blood is relatively quickly excreted via the kidneys. The small fraction of absorbed uranium was distributed throughout all the tissues, with preferential deposition in the bone and kidney (ATSDR 1999).

The very earliest animal studies quickly and conclusively determined that the kidney was be the most sensitive organ to uranium toxicity, with the degree of injury largely dependent upon the solubility and route of entry. Acute nephrotoxic effects in animals are characterized by dose dependent injury and necrosis of cells in the proximal tubules characterized by glycosuria,

increased excretion of amino acids and transient enzymuria of a number of enzymes along with histologic changes. In animals, the lowest observed adverse effect level (LOAEL) was typically in the range 0.7-1.4 μg of U per g of kidney, with peak effects occurring in the concentration range of 3.4-5.6 μg U per g of kidney (ATSDR 1999; NRC 2008, p. 38). In the earliest studies by Gmelin showed that intravenous injection of uranium was far more toxic than the oral route of intake producing instant death in a rabbit only 200 mg (3 grains) intravenously (Hodge 1973). Much larger doses of uranium were required to produce death after a few days when administered orally.

An important early observation related to observations of considerable interspecies differences among animals with respect to uranium toxicity. Thus, established toxicity levels and toxic effects were in fact species dependent even when normalized in the standard fashion of dose per kg of body weight (Orcutt 1949; Tannenbaum and Silverstone 1951). Orcutt (1949) compared uranium toxicity in several mammalian species; the amount of U per kilogram of body weight needed to produce toxic effects was greatest in the rabbit, followed by the rat and guinea pig, and least in the mouse, or rabbit > rat > guinea pig > pig > mouse. In other words, since it took a much larger dose per kilogram of body weight to induce toxic effects in the rabbit than it did in the mouse, the mouse was actually more sensitive to the toxic effects of uranium than the rabbit. Tannenbaum and Silverstone (1951) reported that the relative sensitivity of mouse, dog, and rabbit was 40:10:1; in other words, for a given unit dose per kilogram of body weight the mouse was 40 times as sensitive to the toxic effects of uranium as the rabbit. Based on comparative evaluation of toxic effects, the dog would seem to fall at the lower end of the level of susceptibility scale along with the rabbit; the cat at the higher end. For a given intake of uranium, acute results will not only vary with species but also are dependent upon the specific uranium compound with greater toxicity exhibited by the more soluble uranium compounds, likely because of their greater uptake to the blood.

Summary of Uranium Toxicity in Humans

Before the discovery of insulin in the first quarter of the twentieth century, diabetes mellitus was a formidable and often fatal disease with no effective treatment. The apparent low toxicity of

uranium derived from animal studies coupled with the observation of glycosuria in dogs following oral administration led to the use of uranium as a therapeutic agent for diabetes mellitus early in the nineteenth and twentieth centuries (Hodge 1973; Kathren and Burklin 2008). Kathren and Burklin (2008) examined data from the original literature on approximately two dozen cases of diabetics treated by oral administration of uranyl nitrate, sometimes for periods of months or even years with daily intakes reported to be as large as 5.8 g of U. No fatalities attributable to uranium were reported in any of this cohort. For 11 cases, it was possible to make reasonably reliable estimates of the total oral intake of uranium which ranged from 27 to 1329 g of uranium; these data are summarized in Table 1 along with calculated peak kidney burdens of uranium as reported by Kathren and Burklin (2008a). Largely on the basis of the data from these cases plus other human exposures from planned and accidental intakes, Kathren and Burklin (2008a) concluded that the acute LD_{50} for uranium for oral intake of soluble compounds "exceeds several grams of uranium and is at least 1.0 g for inhalation intakes", with values for insoluble compounds of uranium likely to be significantly greater. On the basis of their study, they suggested conservative provisional values of 5 g and 1g as the LD_{50} for acute oral and inhalation intakes, respectively, noting that the actual values are likely higher but could not be supported by the available data.

The use of uranium as a treatment for diabetes clearly established that at least for oral intakes of gram quantities of uranium as the nitrate on a daily basis there were no significant untoward effects. In fact, many patients were helped by this therapeutic regimen. Wilcox (1917) reported reduced thirst and polyuria, along with glycosuria in 46 of 54 diabetic patients so treated over extended periods of months to years with daily doses of up to 200 mg of uranyl nitrate. With respect to toxic or other adverse side effects of the treatment, he flatly stated:

> "In all instances in which I have employed uranium nitrate I have never noted any untoward gastric or intestinal symptom nor any signs of blood or renal disturbances; careful observation has been especially directed toward early detection of the latter." (Wilcox 1917).

Table 1. Calculated Peak Kidney Burdens and Equivalent Inhalation Intake of Type F Material from Cases Involving Large Oral Intakes of Soluble Uranium¶

Original Reference	Case Number	Estimated Oral Intake (g U)	Calculated Peak Kidney Burden from Oral Intake* (mg U)	Calculated Kidney Concentration from Oral Intake (mg U/kg)	Calculated Acute Inhalation** Required to Produce Equivalent Kidney Burden (mg U)
Bond 1898	Case 1	268	25	81	750
Bond 1898	Case 9	1329	120	387	3800
Duncan 1897	Case 1	40	24	77	740
Duncan 1897	Case 2	31	33	106	1000
Duncan 1897	Case 3	94	65	210	2000
Duncan 1897	Case 4	111	51	165	1600
Duncan 1897	Case 5	50	32	103	990
West 1895	Case 1	101	52	168	1600
West 1895	Case 3	38	39	126	1200
West 1896	Case 3	27	24	77	730
Bradbury 1896		178	38	123	1200

¶ Reproduced from Kathren and Burklin 2008a with addition of kidney concentrations
* Uptake from gut taken as 0.02 per ICRP 1994
**Type F solubility, AMAD = 5 μm; GSD = 2.5; shape factor = 1.5; $\rho = 3$ g cm^{-3}

While granted Wilcox did not have available to him the sophisticated modern tests currently available to assess or infer kidney damage, and indeed in none of the cases presented in Table I was long term followup reported and observations were largely limited to gross effects, they are nonetheless significant and strongly support the conclusion that uranium is not of a particularly high order of acute toxicity and that man ranked low in the toxicity sensitivity scale. The above conclusion is buttressed by the fact that despite what would considered by many to be massive oral or accidental inhalation intakes there has never been a documented death in a human attributable to intake of uranium by whatever route of intake (ATSDR 1999, pp. 27, 93, 138) and, as has been pointed out by Kathren and Burklin (2008), ". . . and man as a species seems to have a lower order of sensitivity to the toxic effects of uranium than the other mammalian species that have been studied."

Largely by analogy with animal data and the very limited data available from human accidental intake cases, the kidney has long been considered the primary target organ following acute and chronic exposures to soluble U compounds. The nephrotoxic threshold limit in man for chronic low level exposure is generally accepted as 3 μg of uranium per gram of kidney (Alexander 1984; ATSDR 1999; Brodsky 1996, p 157-8; Kathren and Weber 1988; Leggett 1989; Spoor and Hursh 1973; Stannard 1988). Nephrotoxicity is indicated by various biomarkers including glucosuria, albuminuria, elevated beta-2 microglobulin and elevated blood creatinine level.

The origins of the 3 μg/g threshold for kidney damage are rooted in animal studies, and although this limit has stood for decades, and has virtually assumed the status of a paradigm, its acceptance within the scientific community, while widespread, has not been unanimous. More than 25 years ago, Morrow and his coworkers (1982) recommended a fivefold reduction to 0.6 μg U/g kidney based on inhalation and intravenous studies of UF_6/UO_2F_2 in dogs carried out in his laboratory. This recommendation was based solely on the animal data and apparently did not take into account differences in interspecies sensitivity. A few years later, Leggett (1989), based on his comprehensive review of the literature, conservatively proposed a ten fold reduction to 0.3 μg U/g kidney ". . . until more is known about subtle physiological effects of small quantities of U in the kidneys". From a single case with an apparently massive acute inhalation intake of UF_4 powder, Zhao and Zhao (1990) suggested the permissible kidney burden should not exceed 0.26 μg U/g kidney. This sketchily reported case had an atypical urinary excretion pattern and did not exhibit biomarkers of kidney damage until 68 days post exposure suggesting that this case is an atypical outlier.

On the other hand, Brodsky (1996) reviewed the literature and concluded that a 3 μg U/g kidney concentration was ". . . unlikely to cause kidney damage over a lifetime", a conclusion consistent with recent comprehensive studies and evaluations that have been done, including the ATSDR (1990), the Institute of Medicine (IOM) (Fulco, Liverman and Sox 2000), the National Research Council (NRC 2008) and British Royal Society (Baily and Davis 2002). The Royal Society report, however, acknowledged that minor transient kidney effects were present in some persons with kidney uranium concentrations as low as 1 μg /g (Bailey and Davis 2002). An important and potentially definitive study of military personnel exposed to depleted uranium

aerosols from munitions used in the Gulf War (Guilmette et al. 2005) was the Capstone Study. The Capstone Report identified four so-called Renal Effects Groups (REGs) which correlated uranium kidney concentrations with acute effects on the kidney and predicted outcomes as shown in Table 2.

Table 2. Renal Effects from Depleted Uranium per Capstone Report

Renal Effects Group (REG)	Kidney Uranium Concentration µg U/g kidney	Acute Renal Effects	Predicted Outcome
0	≤ 2.2	No detectable effects	No detectable effects
1	> 2.2 to ≤ 6.4	Possible transient indicators of renal dysfunction	Not likely to become ill
2	> 6.4 to ≤ 18	Possible protracted indicators of renal dysfunction	May become ill
3	> 18	Possible severe clinical symptoms of renal dysfunction	Likely to become ill

Source: Guilmette et al. 2005

The predicted outcomes in the Capstone Report were derived from published data of acute accidental exposures or planned administrations in 27 cases with intakes reported in the range of 4.3 mg to 8.5 g of U. In 13 of the 14 cases with intakes < 10 mg U, there were no detectable effects – renal or otherwise; one case with an injected dose of 5.9 mg U as the nitrate showed minor and transient biochemical indicators of kidney effects. The calculated peak kidney concentration in this case was 2 µg U/g kidney; the two other cases in this experimental uranyl nitrate injection study had intakes of 5.5 and 4.3 mg U, with calculated (modeled) peak concentrations of 2 and 1.5 µg U/g kidney (Luessenhop et al. 1958, Guilmette et al. 1995).

The Capstone Report was quite recently evaluated by the National Academies Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat which concluded that minimal, transient effects such as proteinuria and albuminuria may occur at concentrations as low as 1 µg U/g kidney (NRC 2008, pp. 3-4, p 42). Apparent minor transient kidney effects in the form of urinary biomarkers such as proteinuria and albuminuria have been observed at kidney concentrations of about 1 µg U/g kidney in some, but by no means

all, chronically exposed workers (Thun et al. 1985) and in Gulf War veterans with embedded depleted uranium fragments (Squibb, Leggett and McDiarmid 2005).

In medical studies of Gulf War military personnel with inhalation or ingestion intakes of depleted uranium, or with DU wound contamination, McDiarmud and her coworkers (2000, 2004, 2006, 2007) separated study subjects into high and low exposure groups using urinary uranium excretion of 0.10 μg U/g creatinine as the cutoff criterion between the two groups. They examined several renal function indices in both groups – serum creatinine, beta 2 microglobulin, retinal binding protein, serum uric acid, urinary creatinine and protein -- and found results between the high and low exposure groups to be quite similar and renal function to be generally within normal limits.

In its comprehensive study of the health effects of the Gulf War, the Institute of Medicine initially concluded that there is "Limited/Suggestive evidence of no association" between exposure to uranium and clinically significant renal effects. Most recently, a committee of the Institute of Medicine of the National Academies provided an updated review of the literature pertinent to depleted uranium and associated health effects, concluding (IOM 2008, p. 207):

> ". . . there is inadequate/insufficient evidence to determine whether an association between exposure to uranium and nonmalignant renal disease exists".

The IOM committee could not rule out renal effects after exposure of any magnitude but also could not determine at what levels effects might occur or place quantitative limits on dose because of the uncertainties in the uranium exposure levels and methodological differences in the relatively few available human studies. The IOM committee further noted that the available research evidence is ". . . inadequate to support a conclusion about depleted uranium as a cause of nonmalignant renal disease" and that available studies in humans occupationally exposed to uranium, or exposed via high natural levels in groundwater, and the relatively small numbers of exposed military personnel do not indicate renal toxicity (IOM 2008, pp. 207-208).

Although effects at what might be considered low exposure levels based on modeled kidney concentrations of ≥ 3 µg U/ g kidney are equivocal at best and if present limited to transient urinary biomarkers without clinical significance, at still higher kidney uranium concentrations, irreversible or serious long lasting health effects in humans as defined above would expectedly occur, at least based on animal studies, posing the question of at what level might such effects occur. There is a paucity of human exposure data, acute or otherwise, from which to develop such a level (Athey, McGuire and Ramsdell 2007; ATSDR 1999; Brodsky 1996) and extrapolation from animal data poses well known problems related to interspecies differences. Indeed whether such a level can even be established is questionable, for a recent Nuclear Regulatory Commission guidance document stated "There are no known long term chemical injuries from uranium intakes that are sublethal" and further noted that permanent kidney damage has never been seen in humans (Athey, McGuire and Ramsdell 2007, p138-9). This implies that intakes of uranium will either produce no effect, transitory reversible minor effects, or, if sufficiently high, death.

However, in attempting to answer the question posed above, Fisher and coworkers (1994) acknowledged that the limiting value for uranium toxicity in man should be based on the concentration of uranium in the kidneys, and reaffirmed the 3 µg U/g kidney tissue as the threshold for minimal nephrotoxic effects, further noting that that the degree of tissue damage ranged from minimal at a concentration of 3 µg U/g kidney to complete loss of function at "much higher concentrations". These higher concentrations were not specified, but based on a review of animal data, Fisher et al. (1994) concluded with respect to more serious nephrotoxic effects:

> "The threshold for severe injury in humans is thought to be about 70 µg U/kg of body weight, between that for dogs and rats. This value corresponds to a renal injury threshold concentration of 16.3 µg U per gram of human kidney and is well above the 3 µg U per gram level."

Although Fisher et al. did not specify or define what was meant by severe injury, their conclusion is generally consistent with other studies. A peak kidney concentration of about 16.3 µg/g falls near the upper end of the range given for Capstone REG 2 (Table 2) and is equivalent

to an acute oral intake of about 2250 mg or an acute inhalation intake of about 150 mg for an aerosol with AMAD = 5 μm, GSD = 2.5, ρ = 3, and shape factor = 1.5. These are approximately 2 to 3 fold and 7 fold lower than the conservative provisional LD_{50} values for ingestion and inhalation intakes, respectively, proposed by Kathren and Burklin (2008a). Also, the observation of Fisher et al. (1994) of a renal injury threshold concentration of 16.3 μg U per gram of human kidney is consistent with the observation of Hursh and Spoor (1973) that a peak kidney concentration of about 10 μg U/g kidney will produce temporary, but not permanent, damage in persons experimentally administered uranium compounds (Hursh and Spoor 1973).

Examination of the data from the few available acute accidental exposure cases in man reveals no irreversible or serious long lasting health effects in humans in any of these cases. Therefore, the level of intake in these cases would presumably be below the threshold for long term effects and hence could be used as a conservative level or baseline for irreversible or serious long lasting health effects in humans. Zhao and Zhao (1990) reported a case with an acute inhalation intake estimated to in the range of several hundred mg of U to 1.46 g as the tetrafluoride. Initially, some renal dysfunction was noted in this case, including the presence of proteinuria, elevated NPN, and other kidney markers, with kidney function returning to normal 18 months postexposure. Zhao and Zhao (1990) reported another case with an estimated intake of 152 mg U as uranyl nitrate via dermal absorption following a thermal burn, producing an estimated peak kidney burden of about 50 μg/g. Initial renal tubular dysfunction was marked but returned to normal by one month postexposure.

Looking at the available acute intake data another way, it is noted that 17 cases were accidental acute inhalation intakes of UF_6 with intakes estimated to range from 6 mg to 40-50 mg and corresponding to calculated peak kidney concentrations of 0.62 to 4 μg U/g. Minor kidney effects in the form of transient biochemical indicators of renal dysfunction were noted only in the four cases in this group of 17 with the larges intakes, all estimated to be 24 mg or greater, with corresponding kidney uranium concentrations in the range of 1.5 to 4 μg/g.

As noted, there have been no deaths attributable to acute or chronic uranium poisoning in man. There is, however, a case report 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 (Pavlakis et al. 1996). Assuming 1-2 per cent uptake via the gut, this would correspond to an uptake in the range of 84-168 mg. The peak renal concentration for this case has been estimated at 100 µg U/g (NRC 2008, p. 28, Bailey and Davis 2002; Guilmette et al. 2005). ATSDR (1999) estimated the dose to be 131 mg U/kg corresponding to an intake of 9.1 g U for a 70 kg reference man.

The individual ingesting this large dose of uranium was hardly typical and unarguably in poor health, suffering from various conditions and taking various medications which may have exacerbated his response to the ingested uranium. Established diagnoses included hyperlipidemia, muscle enzyme deficiency, hypertension, and hypogonadism and he also indicated that suffered from chronic peptic ulcer, asthma, gout, migraine, as well as from renal calculi and urinary tract infections. He had been diagnosed with a borderline personality disorder and had undergone psychotherapy for more than 20 years prior to his suicide attempt. He was an admitted self-medicator and abuser of prescription drugs, having regularly taken some 14 drugs orally in the 12 months preceding his suicide attempt in addition to using a number of topical agents including antifungals and steroid creams, and topical eye drops.

He was chelated with Ca EDTA plus bicarbonate and Ca DTPA which failed to significantly increase urinary U excretion. Following the intake, he 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, a relatively rare and possibly hereditary condition associated with certain genetic defects, or with medications or heavy metal poisoning (Izzedine et al. 2003) which is characterized by impairment of proximal tubule function with excess amounts of glucose, bicarbonate, phosphates, uric acid, potassium, sodium, and certain amino acids being excreted in the urine.

The many abnormal aspects of this attempted suicide case limit its value from a toxicological standpoint. Given the medical and drug abuse history of the case, it is likely that other than the

kidney effects and glycosuria, many of the other observed abnormal physiological effects were largely or even wholly attributable to other causes. The observed nephrotoxicity was quite likely properly attributed to uranium but may have been aggravated or reduced by his preexisting medical conditions or enhanced by drugs, as was noted by Pavlakis et al. (1996) in the case report: "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." The simultaneous ingestion of benzodiazepine, a class of antianxiety drugs, may also have affected his uptake and excretion of uranium. Other drugs may have been ingested as well shortly before the intake of uranium that could also have affected uptake and excretion. Even the amount of uranium ingested is uncertain as he could have ingested oral doses of uranium prior to the reported single ingestion.

Certainly by comparison with the several cases described above who were therapeutically treated with oral uranium for diabetes the renal effects noted in this case were much more severe and indeed life threatening even though the dose and peak kidney concentrations were not appreciably different than that estimated for the diabetes therapy cases. However, this needs to be tempered with the fact that this individual was suffering from preexisting kidney disease and other significant health problems at the time of his suicide attempt. The former would expectedly render the kidneys more susceptible to damage from heavy metal toxicity and the latter, and in particular his peptic ulcer, would result in increased uptake from the gut.

Threshold Values for Acute Effects

The peak concentration of uranium in the kidney following acute exposure is generally used as the basis for bioeffects. Kidney concentrations are typically determined with the aid of biokinetic models and there is undoubtedly and not unexpectedly a great deal of uncertainty in the specific levels of peak kidney concentration at which acute effects are likely to occur which may account at least in part for the variations in the reported observations of effects relative to modeled kidney concentrations in exposed persons. The uncertainties of extrapolation from animals to humans, paucity of human exposure data with concomitant uncertainty in intakes in these cases, and the applicability and accuracy of the biokinetic models used to calculate peak

kidney concentration are the major reasons for this uncertainty. Nonetheless, the available human data are sufficient to develop prudent and conservative estimates of the peak kidney concentration and associated acute and predicted long term effects as presented in Table 3 for six different levels of acute effects based on peak uranium concentration in the kidney ranging from no effect to severe and irreversible renal dysfunction possibly leading to death if untreated.

Table 3. Peak Kidney Concentration Thresholds for Effects from Acute Uranium Exposure

Peak Kidney Uranium Concentration µg U/g kidney	Acute Effects	Predicted Outcome	References
<1	No detectable effects	No detectable effects	Bailey and Davis 2002 Boback 1975 Butterworth 1955 Guilmette 2002 McDiarmid et al. 2000, 2004, 2006, 2007
1	Possible mild transient indicators of renal dysfunction such as albuminuria and glycosuria	Observed indicators may be a result of stress or other causes; not likely to become ill or have any indication of dysfunction; no long term effects	Butterworth 1955 Fisher et al 1990 Guilmette et al. 2005 Leussenhop et al. 1958
3	Possible mild transient asymptomatic changes of renal dysfunction or physical effects likely not perceptible to the exposed individual and discernable via urinalysis.	Clinical effects lasting no longer than 10 days post exposure; no significant dysfunction or long term consequences; no treatment necessary.	Butterworth 1955 Fisher et al. 1990 Kathren and Moore 1986 Leussenhop et al. 1958
10	Possible protracted indicators (signs)of renal dysfunction	May experience clinical renal dysfunction effects that may require treatment and may be perceptible to the individual; treatment may be indicated	Butterworth 1955 Guilmette et al. 2005 Zhao and Zhao 1990
18	Severe clinical symptoms of renal dysfunction	Likely to become ill and require medical treatment; may be long term effects	Guilmette et al. 2005 Zhao and Zhao 1990
100	Severe and possibly irreversible clinical symptoms of renal dysfunction	Possibly fatal without treatment.	Bailey and Davis 2002 Pavlakis et al. 1996 NRC 2008

Table 3 and the associated discussion and basis from which it was developed fully support the proposed toxicological threshold levels for acute intakes of soluble uranium based on chemical toxicity recently put forth by Kathren and Burklin (2008b) as meeting the requirements of 10

CFR 70.61 and underscore the high degree of conservatism inherent in them. The levels proposed by Kathren and Burklin are given in Table 4 and represent the lowest levels at which the associated effects might occur based on the literature pertinent to humans and in consideration of the uncertainties therein. Until additional data become available, the level proposed in Table 4 would seem to incorporate an adequate margin of safety and thus be wholly appropriate and prudent for application to 10 CFR 70.61.

Toxicological thresholds presented in Table 4 for the two lower risk levels were directly derived from calculated peak kidney concentrations below which specific observed health effects were absent. This was possible to do because there exists a body of literature in which observed effects could be correlated with peak kidney uranium concentrations. In other words, the acute ingestion and inhalation thresholds levels for the two lower risks were calculated via the biokinetic model from the peak kidney concentration below which the health effects would not occur. However, this could not be done with respect to the highest risk level – life endangerment – since no deaths in humans attributable to uranium poisoning have been reported in the literature. Hence, unlike the lower two levels, less direct methods with highly conservative assumptions were used by Kathren and Burklin (2008a) to derive provisional LD_{50} values for acute intake of uranium, and these values were further reduced by half on the assumption that there would be no mortality at this level (Kathren and Burklin 2008b). It was from these values that the peak uranium concentrations in the adult kidney were modeled.

This resulted in an apparent inconsistency in that calculated peak kidney concentrations differing by a factor of three were calculated for inhaled and ingested uranium. This apparent inconsistency is largely an artifact of the conservative assumptions used by Kathren and Burklin (2008a) in putting forth a provisional LD_{50} for acute oral and inhalation intakes of uranium. A simpler and far less conservative approach would have been to assume, not unreasonably, that since no deaths resulted in persons with oral intakes of uranium resulting in peak kidney concentrations ranging up to 387 μg U per g of kidney (Table 1), that the lethal dose was greater than the intake needed to produce this kidney concentration, or at least 53 g for acute ingestion and 3.8 g for acute inhalation. This clearly illustrates the high degree of conservatism in the levels for life endangerment proposed in Table 4. The fact that the peak kidney concentrations

for the two routes of entry differ by a factor of three is simply an artifact of the way in which the highly conservative levels were determined by Kathren and Burklin (2008a), perhaps coupled with uncertainties and differences in the model for inhaled and ingested uranium.

The threshold levels for acute intakes of soluble uranium for adults proposed in Table 4 should be adequate for protection of the fetus as well and hence applicable to adult pregnant women as well, inasmuch as placental transfer of uranium is quite small (ICRP 2002; NCRP 1998; Sikov and Hui 1996). Based on analogy with very limited human data for plutonium which, like uranium, is also an actinide, has a large ionic radius, and is likewise not a necessary trace element and, the placenta may discriminate against passage of uranium from mother to fetus (Russell et al. 2004).

Smaller permissible threshold levels are indicated for children because of their smaller size and possibly higher degree of sensitivity to uranium toxicity and other factors, factors which are offset to some extent by a reduced breathing volume and hence smaller intake in the case of inhaled soluble uranium, and smaller daily intakes of water and food. The permissible fraction of the adult threshold level have been calculated by Kathren and Burklin (2008b) for children in five different age groups ranging from 3 months to 15 years of age using the methodology put forth by the ICRP for determining radiological dose from intakes based on age that takes into account the smaller size of children and which presumably could be applied to chemical toxicity of uranium as well (ICRP 1989, 1995a, 1995b). These age specific fractions of the proposed adult levels are given in Table 5; adult intake levels presented in Table 4 can be converted to those suitable for a younger person simply by multiplying the appropriate adult intake level by the proper factor from Table 5. No adjustment has been made for the possible different sensitivity of the younger age groups as compared with adults as there are no known or readily available data in this regard.

Table 4. Proposed Toxicological Threshold Levels for Acute Intakes of Soluble Uranium¶

Risk	Acute Ingestion Dose* (mg)	Acute Ingestion Dose (mg U/kg)	Acute Inhalation Dose* (mg)	Acute Inhalation Dose (mg U/kg)	Peak concentration in adult kidney (µg U/g)	Comments
Life endangerment	>2500	>36	>500	>7.1	>18 >52	No reported deaths in humans from calculated kidney concentrations of ≤ ~380 µgU/g
Irreversible or serious long lasting health effects	>1400	>20	>100	>1.4	>10	No reported permanent kidney damage in humans from calculated kidney concentration of ~50 µgU/g indicating permanent damage may not occur at sub-lethal doses.
Mild transient health effects	410	5.9	30	0.5	3	Totally reversible effects with no acute or long term functional impairment detectable only by urinary biomarkers.

¶ Table reproduced from Kathren and Burklin 2008b.

* Normalized to 70 kg adult male, values rounded.

Table 5. Permissible Fraction of Proposed Adult Threshold Limits for Acute Intake of Soluble Low Enrichment Uranium¶

Age	**Permissible Fraction of Proposed Adult Limit**	
	Inhalation	**Ingestion**
3 months	0.19	0.13
1 year	0.26	0.38
5 years	0.46	0.56
10 years	0.67	0.66
15 years	0.91	0.67
Adult	1.00	1.00

¶ Table reproduced from Kathren and Burklin 2008b.

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