Influence of Nephrotoxicity on Urinary Excretion of Uranium

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ABSTRACT

Measurements of urinary excretion are being used to assess previous potential exposures to depleted uranium following its use in recent conflicts. High concentrations of uranium in kidneys are known to affect kidney function, and some studies of uranium biokinetics in rats have shown changes in the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations.

As part of a project to estimate overall uncertainties in the assessment of intakes, radiation doses, and peak uranium kidney concentrations from urine samples taken at long times (100-10,000 days) after intake, a review of the scientific literature was carried out to provide information on (i) measured indicators of kidney damage following human exposures to uranium (ii) biokinetic studies giving data on the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations. Particular attention was paid to human experimental studies in which uranium solutions were intravenously injected. This report complements reports considering uncertainties in the ICRP (International Commission on Radiological Protection) respiratory tract model as applied to depleted uranium and the ICRP model that describes the behaviour of uranium after entry to the blood.

The correlations between peak uranium kidney concentration and measured indicators of kidney damage in humans reported by the Royal Society Working Group (RSWG) on the Health Hazards of Depleted Uranium Munitions were extended with additional results. They support the RSWG conclusions that acute exposures that lead to concentrations of about 1 µg uranium g^{-1} of kidney have been associated with minor kidney dysfunction, and that chronic levels that lead to minor kidney dysfunction are not well established, but are likely to be below 0.3 µg uranium g^{-1} of kidney.

Available measurements in humans of the ratio of uranium urinary excretion to kidney concentration show no obvious change in this ratio up to kidney concentrations of at least 3 µg uranium g^{-1} of kidney.

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EXECUTIVE SUMMARY

Measurements of urinary excretion are being used to assess previous potential exposures to depleted uranium following its use in recent conflicts.

High concentrations of uranium in kidneys are known to affect kidney function.

Some studies of uranium biokinetics in rats have shown changes in the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations.

As part of a project to estimate overall uncertainties in the assessment of intakes, radiation doses, and peak uranium kidney concentrations from urine samples taken at long times (100-10,000 days) after intake, a review of the scientific literature was carried out to provide information on

(i) measured indicators of kidney damage following human exposures to uranium

(ii) the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations.

Studies involving the intake of uranium by inhalation, ingestion or wounds are difficult to interpret because an estimate of the mass of uranium entering the circulatory system must be made to assess the mass of uranium reaching the kidneys and urine. Therefore in this study particular attention was paid to human experiments in which uranium solutions were intravenously injected because a known mass of uranium was delivered directly into the circulatory system.

The results of this study support the conclusions of the Royal Society Working Group report on “The health hazards of depleted uranium munitions Part II” that

- acute exposures that lead to concentrations of about 1 μg uranium g^{-1} of kidney have been associated with minor kidney dysfunction
- chronic levels that lead to minor kidney dysfunction are not well established, but are likely to be below 0.3 μg uranium g^{-1} of kidney.

Based on the available data in the literature, the results of this study also indicate that, for humans, the ratio of uranium urinary excretion to kidney concentration shows no obvious change up to kidney concentrations of at least 3 μg uranium g^{-1} of kidney.

This report complements reports that consider uncertainties in the ICRP (International Commission on Radiological Protection) respiratory tract model as applied to depleted uranium and the ICRP model that describes the behaviour of uranium after entry to the blood.

CONTENTS

1 INTRODUCTION

Measurements of uranium in urine are used with the current biokinetic models of the International Commission on Radiological Protection (ICRP) to assess past uranium exposures. Uranium is known to be nephrotoxic but traditionally it has been assumed that no kidney damage will occur in humans at or below a kidney threshold concentration of 3 μg uranium g^{-1} of kidney tissue. As the threshold concentration was derived entirely on radiation dose and not nephrotoxicity (see section 2) this assumption is questionable. Furthermore studies in rats have shown changes in the ratio of urinary excretion to kidney concentration of uranium at kidney concentrations of 1 μg uranium g^{-1} kidney tissue. If uranium excretion is altered as a result of damage to the kidney, estimates of exposure will be in error (Stradling et al, 2002).

Since the nephrotoxic effects of uranium are due to its chemical properties, rather than its radioactivity, no distinction needs to be made between the mass of depleted uranium (DU), natural uranium (U-nat) or enriched uranium which enters the systemic circulation after inhalation, ingestion, injection or from wounds.

As part of a project to estimate overall uncertainties in the assessment of intakes, radiation doses, and peak uranium kidney concentrations from urine samples taken at long times (100-10,000 days) after intake, a review of the scientific literature was carried out to provide information on (i) measured indicators of kidney damage following human exposures to uranium (ii) biokinetic studies giving data on the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations. Particular attention was paid to human experimental studies in which uranium solutions were intravenously injected.

This report complements those considering uncertainties in the ICRP human respiratory tract model (HRTM) as applied to DU (Bailey and Puncher, 2007) and the ICRP model that describes the behaviour of uranium after entry to the blood (Harrison et al, 2007).

2 DERIVATION OF THRESHOLD KIDNEY CONCENTRATION FOR NEPHROTOXIC EFFECTS

2.1 Derivation of threshold concentration

In the early 1950's Hodge et al (Voegtlin and Hodge, 1949-1953) examined the effect of inhaling three soluble uranium compounds on four different animal species and recommended a tentative mean air concentration for soluble uranium compounds in the work environment of 50 μg uranium m^{-3}. They concluded that inhaling soluble uranium dust at this concentration presented a negligible radiological hazard to bone and only rarely produced very minor kidney damage in a small number of very susceptible animals. As a consequence of discussions between Committee 2 of the ICRP and the National Committee on Radiation Protection and Measurements (later to become the National Council on Radiation Protection and Measurements, NCRP) subcommittee 2,

the chemical toxicity for long lived isotopes of uranium was identified as the limiting criterion for exposure with the kidney as the critical organ and a threshold concentration of 3 μg uranium g^{-1} of kidney was proposed (NCRP, 1959; ICRP, 1959; Spoor and Hursh, 1973).

This concentration was not listed as such by ICRP in Publication 2 (ICRP, 1959), but could be derived from four other listed values at that time (Spoor and Hursh, 1973). These were:

- for a dose of 5 rem (50 mSv) in one year, which was the recommended dose limit at that time, the maximum permissible content of natural uranium in the total body (the so called q value) with kidney considered to be the critical organ, was 5.10^{-3} μCi (0.185 kBq) (ICRP Publication 2, Table 1, for ^{238}U)
- the fraction of uranium in the kidneys relative to that in the total body (the so called f_2 value) was 0.065 (ICRP Publication 2)
- a kidney mass of 300 g (ICRP Publication 2)
- the specific activity of natural uranium, 0.33 μCi g^{-1} (12.21 kBq g^{-1}).

Hence, the permissible concentration of natural uranium in the kidney was calculated to be

$(5.10^{-3}$ μCi x 0.065) / (300 g x 0.33 μCi g^{-1}) = 3.3 10^{-6} g g^{-1} = 3.3 μg g^{-1}

Thus, the derivation of the threshold limit value was based entirely on radiation dose and not nephrotoxicity.

The evidence available from animal studies conducted by the late 1950's showed that mild to moderate kidney damage occurred in a variety of species at concentrations up to an order of magnitude lower than this. It has been suggested that the Committees of ICRP and NCRP were less influenced in the choice of a safe kidney concentration by the animal data than by the experience of many years of occupational exposure where there was no apparent evidence of permanent kidney dysfunction even in workers exposed at levels in excess of the above derived threshold limit value (Spoor and Hursh, 1973).

The procedure adopted by NCRP Committee 2 for deriving the exposure limit is shown in Table 2.1 (Stokinger et al, 1949-1953; Spoor and Hursh, 1973; Stopps and Todd, 1982). The value derived for the maximum permissible concentration in air (MPC_a) for soluble uranium compounds (0.2 mg m^{-3}), now referred to as the time weighted average (TWA) Threshold Limit Value (TLV), is still recommended by the American Conference of Government Industrial Hygienists (ACGIH, 2005). The National Institute for Occupational Safety and Health, recommend a lower value of 0.05 mg m^{-3} (NIOSH, 2005). The values for the PEL recommended by various organisations in the intervening years are summarised elsewhere (Stradling et al, 1997; 2002).

It is noteworthy that a fairly recent American National Standard has reaffirmed the 3 μg uranium g^{-1} kidney concentration limit as a basis for designing and interpreting biossay programmes (ANSI, 1996).

Table 2.1 Derivation of the permissible daily intake and $(MPC)_a$ for soluble natural uranium by NCRP Committee II (Spoor and Hursh, 1973).

Assumption		Source
1)	A maximum permissible concentration of 3 µg uranium g^{-1} of kidney	Animal experiment results (Voegtlin and Hodge, (1949-1953); Committee judgment decision)
2)	An average kidney mass of 300 g	Standard Man (ICRP Publication 2, (ICRP, 1959))
3)	An effective half-life of 15 days for uranium in the kidney, ie 0.693/15 = 0.0462 x the kidney burden is excreted per day	Animal experiments: Voegtlin and Hodge, (1949-1953), Chapter 11. Experiments on man: Butterworth and McLean, 1955; Struxness et al, 1956*
4)	That 2.8 percent of the uranium inhaled was deposited in the kidney (f_a as denoted by ICRP-NCRP)	The lung model (ICRP Publication 2 (ICRP, 1959)) specifies that the 25% deposited in the pulmonary lung is absorbed into the body for soluble compounds. The 50% deposited in the upper respiratory tract is transferred to the gut and because of the low absorption of uranium can be neglected. Of the systemic uranium, 78% is rapidly excreted and the remaining 22% is divided equally between bone and kidney, f_a = 0.25 x 0.11 = 0.028)
5)	That a worker breathes in an average of 6.9 x 10^6 cm^3 air per working day	Standard Man (ICRP Publication 2 (ICRP, 1959))

*Reference corrected from mistake in original source table

3 REVIEW OF SCIENTIFIC LITERATURE

A review of the scientific literature was carried out to provide information on

(i) measured indicators of kidney damage following human exposures to uranium

(ii) the ratio of uranium urinary excretion to kidney concentration, at high uranium kidney concentrations.

Studies involving the intake of uranium by inhalation, ingestion or wounds are difficult to interpret because an estimate of the mass of uranium entering the circulatory system must be made to assess the mass of uranium reaching the kidneys and urine. Therefore in this study particular attention was paid to human experiments in which uranium solutions were intravenously injected because a known mass of uranium was delivered directly into the circulatory system.

3.1 Human data

Animal studies have identified the kidney as the most sensitive target organ of uranium toxicity, especially to its soluble compounds. The renal effects observed in animals also occur in humans, however differences in sensitivity between the species have been observed (Luessenhop et al, 1958). There is also a general consensus among toxicologists that data derived from studies with animals should be treated with caution and that whenever available, human data should be considered (eg Royal Society 2002). There are relatively few reports on the nephrotoxicity of uranium in humans and

information from unintentional or occupational intakes of uranium must be treated cautiously, as the investigator had to make assumptions about the exposure. The assumptions for many of the reported human cases were reviewed by the Royal Society in Part II of their report on "The health hazards of depleted uranium munitions" (Royal Society, 2002) and this review was extended by the Capstone report (Guilmette et al, 2004), see Table 3.4. However, neither of these reviews appear to have been exhaustive and a further review has been carried out here.

Only administration of the material by intravenous injection eliminates the need for further conjecture on the exposure. Two intravenous injection studies conducted between 1945 and 1960 are particularly noteworthy as they provide the best available human data to date. A third intravenous injection study using lower doses of uranium, conducted by Terepka et al (1964), provides additional information on the urinary excretion in hospital patients with normal kidney and bone function. However, renal toxicity was not studied. Hursh and Spoor (1973) and Stopps and Todd (1982) provide useful précis of these studies.

Renal toxicity is detected by the presence of different biomarkers in the urine. These biomarkers are mentioned in the main text of the report and are explained in Appendix A.

3.1.1 Acute Intravenous Data

3.1.1.1 University of Rochester Intravenous Injection studies (Bassett et al, 1948)

This study, conducted between August 1946 and January 1947, had 3 objectives:

- To determine the dose level of soluble uranium at which renal injury was barely detectable. The levels of urinary catalase and protein were used in each case to monitor for renal damage. Other urine tests used occasionally included the ratio of amino nitrogen to creatinine nitrogen, glomerular filtration of mannitol, renal plasma flow, maximum tubular excretion capacity and urea clearance.
- To measure the clearance rate of soluble uranium from the blood. Total urine and faecal collection was made from all subjects. Urine was collected as individual voidings on the day of injection and thereafter in pools of 24 hours.
- To observe the effect of treatment aimed at altering the rate of excretion. Three experiments were performed, intravenous administration of citrate, low calcium diet and production of acidosis (a decrease in alkali relative to acid in bodily fluids) with ammonium chloride.

Highly enriched uranium (uranium-234 and uranium-235) was administered intravenously as uranyl nitrate in amounts ranging from 6.3 to 70.9 μg uranium kg^{-1} of body weight. The six subjects were hospital patients, four males and two females, ranging in age from 24 to 61 years (see Table 3.1). The lower amounts were given to the younger patients to minimise the possibility of late radiation effects, and at levels approaching 50 μg uranium kg^{-1} of body weight, the preparation was diluted with natural uranium acetate to reduce the specific activity and limit radiotoxic effects. The subjects were selected from a large group on the basis they had reasonably good kidney function

and would benefit from continued hospitalisation and medical care. However, all had medical conditions such as malnutrition, alcoholism or heart disease.

Five subjects received a single injection, increasing in dose from 6.3 to 42.0 µg uranium kg^{-1} of body weight with no measurable kidney damage. Slight kidney tissue toxicity was measured for Subject 6 who had received a dose at the 70.9 µg uranium kg^{-1} of body weight level. This was deemed to be the human tolerance level. Ammonium chloride was administered to render this patient acidotic before he received a second dose of 56.6 µg uranium kg^{-1} of body weight. Of the three treatments tried only this affected urinary excretion, it reduced the early rate.

The authors concluded that;

- the tolerance level for systemic uranium in humans was about 70 µg uranium kg^{-1} of body weight
- systemic uranium is excreted mainly through urine
- between 70 to 85 percent of the injected dose was eliminated in the first 24 hours
- acidosis decreased the rate of uranium excretion

Data for the six patients from this study are summarised in Table 3.1 and their cumulative urinary excretion is shown in Figure 3.1. Table 3.1 also includes the predicted peak kidney concentration calculated using the current ICRP systemic model (ICRP, 1995a) and ICRP value for mass of the kidney (275 g for females and 310 g for males) (ICRP, 1975; 2002).

Table 3.1. Patient data and predicted peak kidney concentration (µg uranium g^{-1} of kidney tissue) from Rochester intravenous injection experiments

Patient	1	2	3	4	5	6[a]	6[b]
Sex	male	female	female	male	Male	male	male
Age (years)	32	40	24	42	51	61	61
Weight (kg)	60.5	72.8	37.0	64.0	65.3	55.2	55.2
Dose (µg uranium kg^{-1} of body weight)	6.4	6.5	15.8	30.0	48.9	70.8	57.4
Urinary excretion							
First 24 hours (%)	82.3	84.7	69.2	66.6	75.3	77.6	57.3
By 5 days (%)	86	87	71.5	74.3	76.3[c]	87.6	79.5
Predicted peak kidney values from intake							
Content (µg uranium)	44	54	67	219	313	446	418[d]
Concentration (µg uranium g^{-1} of kidney)	0.14	0.20	0.24	0.71	1.01	1.44	1.35[d]

[a,b]Patient received 2nd injection 26 days later

[c]Collected 4 days only

[d]Includes residual uranium from 1st injection

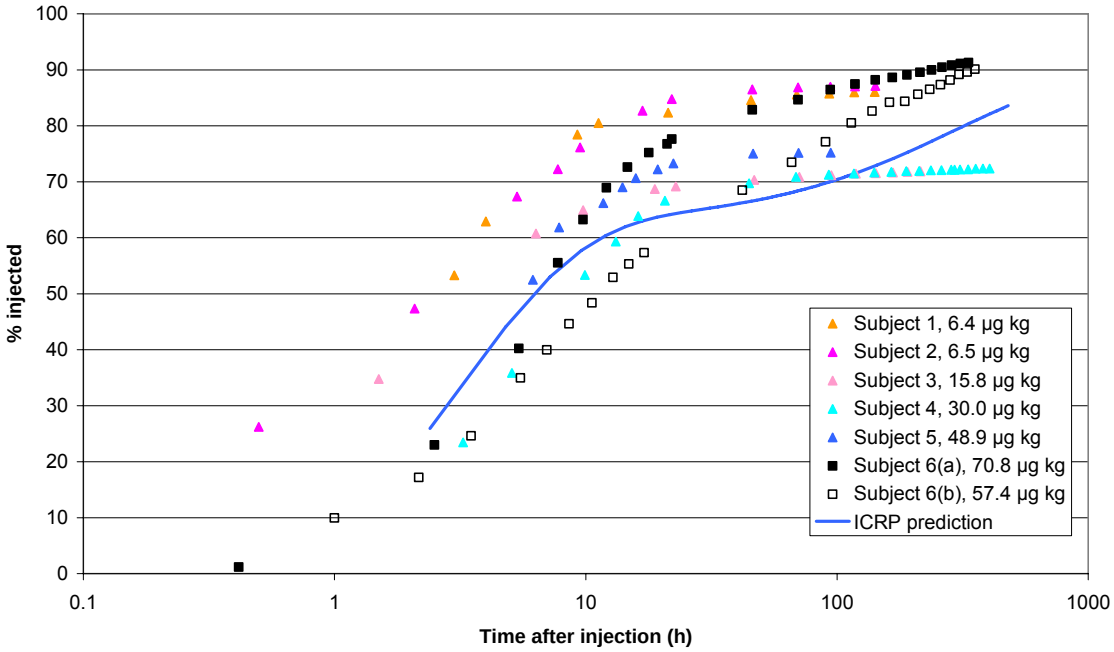

Figure 3.1 Cumulative urine excretion data for Rochester patients

It is worth noting that patient 6, who received the two higher level doses within a 26 day period, displays diminished urinary output after the second injection. At the time the authors attributed this to acidification of the blood, but it could also be interpreted that kidney efficiency had been transiently impaired. Figure 3.1 also shows the cumulative urinary excretion predicted by the ICRP model for uranium (ICRP, 1995a). It appears to be generally representative of urinary excretion by the patients.

3.1.1.2 The Boston Intravenous Injection Experiment (Bernard et al, 1957; Bernard and Struxness, 1957; Bernard, 1958; Luessenhop et al, 1958; Struxness et al, 1956; Leggett, 1994)

This was a collaborative study between doctors in Massachusetts General Hospital, Boston, appraising the value of neutron capture therapy, and Oak Ridge National Laboratory, studying the tissue distribution and excretion of uranium. The subjects were patients diagnosed as being in the terminal phase of severe irreversible central nervous system disease (cancer). In all, eleven patients were used in this study, nine were intravenously injected with hexavalent uranyl nitrate and two with tetravalent uranium tetrachloride. The original papers on this work, those before 1960, provided details on the first eight patients, and there were inconsistencies between the source references. Leggett (1994) provides limited data on patients 9, 10 and 11, so most of the following is only applicable to patients 1 to 8 (Table 3.2).

The patients, ranged in age from 26 to 63 years, were considered near death, and all but one was comatose at the time of injection. Patients 1 to 6 and 9 to 11 received hexavalent uranyl nitrate enriched in ^{235}U and ^{234}U, patients 7 and 8 received tetravalent uranium tetrachloride (UCl_4). The lowest injected dose was 4 mg (72 µg uranium kg^{-1} of body weight) and the highest was 50 mg (907 µg uranium kg^{-1} of body weight). The highest dose was very close to what was later proposed, by some of the authors (Luessenhop et al, 1958), to be the lethal dose limit for uranium (1000 µg uranium kg^{-1}

of body weight). Blood and excreta samples were collected at regular intervals until the patients' death. Twenty different organ or tissues samples were obtained from 6 of the subjects at autopsy.

Table 3.2. Data and predicted peak kidney concentration (µg uranium g^{-1} of kidney tissue) for 8[a] patients from Boston intravenous injection experiments

Patient	1	2	3	4	5	6	7	8	9[a]	10[a]	11[a]
Compound	Nitrate	nitrate	nitrate	nitrate	nitrate	nitrate	UCl_4	UCl_4	nitrate	nitrate	nitrate
Sex	Male	male	male	female	male	male	NR	male	NR	NR	NR
Age (years)	26	47	34	63	39	60	NR	NR	NR	NR	NR
Weight (kg)	55.9	57.4	60	67.7	55.9	56.7	71.8	63.2	NR	NR	NR
Survival (d)	2.5	74	566	136	139	18	228	21	25	94	28
Dose (µg uranium kg^{-1} of body weight)[b]	99	103	72	165	283	907	573	700	NR	NR	NR
Urinary excretion											
First 24 hours (%)	59.4	78	83.8	77.2	66.5	49.1	20	16.9	80	80	60
Total (%)	69	92	98	85	85	63	68	57	NR	NR	NR
Kidney content (%)											
At death	16.6	0.7	0.4	NR	1.2	7.2	NR	1.1	1.7	0.8	1.6
ICRP model	10.0	0.2	<0.1	0.1	0.1	2.6	0.7	2.0	1.7	0.1	1.3
Peak kidney values											
Content (µg uranium)	631	674	492	1273	1803	5861	4689	5042			
Conc. (µg uranium g^{-1} of kidney)	2.0	2.2	1.6	4.6	5.8	18.9	15.1[c]	16.3			

NR – Not analysed or reported

[a]Data not fully reported for patients 9, 10 and 11. No details on dose of uranium administered

[b]Calculated from mass of uranium given and body mass. Values inconsistent between references

[c]Assumed to be male

Author's conclusions pertinent to this report include;

- that systemic uranium is rapidly cleared via the urine, but the rate is dependent on valence and mass injected. During the first 24 hours after injection, the uranyl nitrate patients excreted on average 70 % of the injected dose while the uranium tetrachloride patients averaged less than 20 %. The authors suggested that the very early urinary excretion rate, during the first 4 hours post injection, increased with increasing mass of uranyl nitrate injected, however the opposite was found for the 24 hour rate. This was further substantiated by comparing the daily urinary excretion rate for uranyl nitrate from this study with that found for the patients from the Rochester study (described above).

- although the kidneys were said to be in a 'parlous clinical state', the minimal dose producing a nephrotoxic syndrome was determined to be 0.1 mg uranium kg^{-1} bodyweight. Using the current ICRP values for body and kidney mass (ICRP, 1975;

ICRP, 2002) and the systemic model for uranium (ICRP, 1995a) , this dose equates to a peak kidney concentration of about 2.7 μg uranium g^{-1} of kidney tissue. The traditional concentration limit for uranium in the kidney is 3 μg uranium g^{-1} of kidney tissue (see section 2.1).

The data from this study are summarised in Table 3.2. The current ICRP systemic model (ICRP, 1995a) and the value for the mass of the kidney (275 g for females and 310 g for males) (ICRP, 2002) have been used here to predict the peak kidney concentration and the kidney concentration at death from the individual patient data.

Figure 3.2 shows the cumulative urinary excretion for all eleven of the patients in the Boston study and for comparison the predicted excretion using the current ICRP model for uranium (ICRP, 1995a). Note that two of the patients, Patients 7 and 8, were injected with the tetravalent uranium tetrachloride. All the other patients received the hexavalent uranyl nitrate. There appears to be no correlation between urinary output and age or sex. There is a possible dose effect with uranyl nitrate as the patient receiving the highest dose produced the least uranium in urine. A distinct difference is observed between the two compounds administered. The tetravalent compound is eliminated at a much slower rate (about 20 % of injected) during the first day than the hexavalent nitrate. Interestingly, the authors provide figures that suggest that at later times, between 4 and 40 days, tetrachloride is excreted more efficiently than the nitrate, but unfortunately these data are not tabulated.

The kidney content at death (% of injected) of nine of the patients, eight injected with uranyl nitrate and one injected with uranium tetrachloride, is presented in Figure 3.3. For comparison, the kidney content predicted by the ICRP systemic model (ICRP, 1995a) is also shown. The ICRP model underestimates kidney content at all dose levels for patients injected with uranyl nitrate. This is understandable given that uranium is nephrotoxic, and the high levels administered.

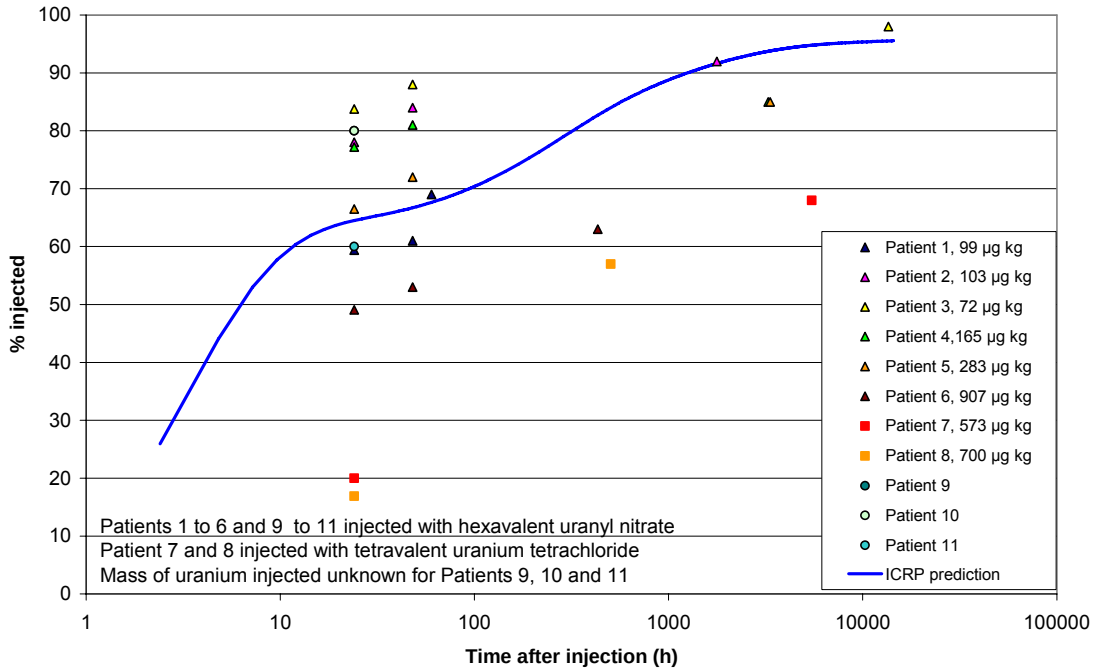

Figure 3.2 Cumulative urinary excretion for Boston patients (injected dose unknown for Patients 9, 10 and 11)

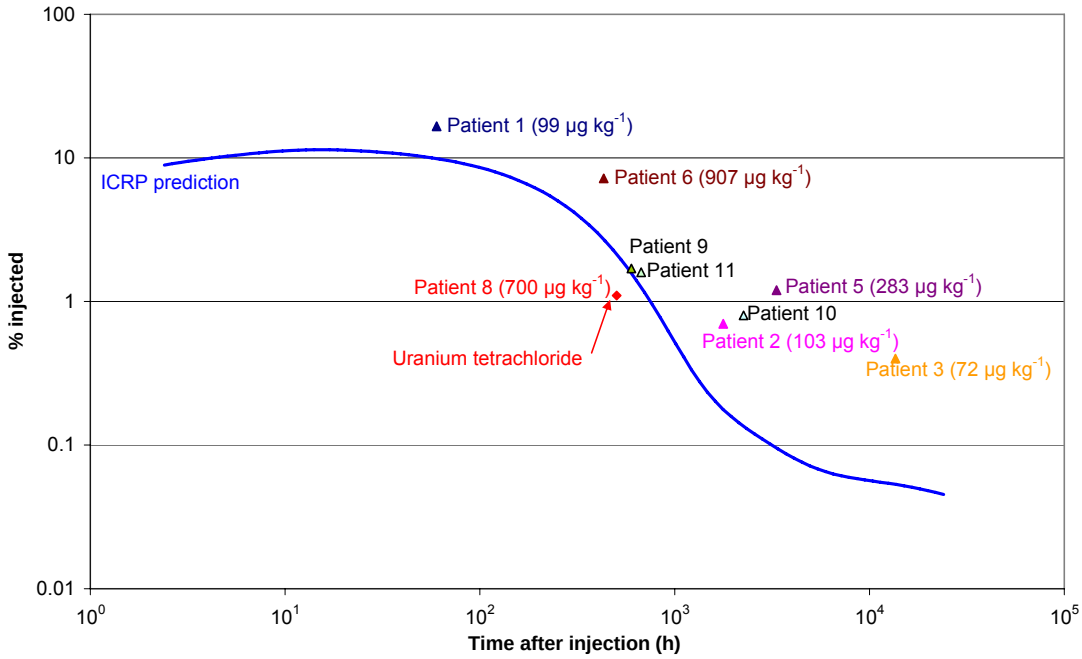

Figure 3.3 Kidney content (percentage of injected activity) at death for Boston patients (patient identification and injected dose, dose unknown for Patients 9, 10 and 11)

3.1.1.3 Study of the Metabolism of Natural Uranium in the Human Skeleton (Terepka et al, 1964; Terepka, 1965a, b)

The motivation for this study was from animal experiments that suggested that about 70 % of injected soluble uranium was rapidly excreted via the urine and that the remainder was retained in the bone. Once again some details are unclear but it appears the experiments were conducted on 12 patients at the University of Rochester between 1960 and 1964. The subjects included three control patients (without clinical, laboratory or x-ray evidence of bone disease), four patients with bone disease (osteoporosis or osteomalacia), one with Paget's disease of the bone, one with hyperparathyroidism plus a parathyroid adenoma, and one with hypoparathyroidism. Data for these patients are given in Table 3.3 and Figure 3.4. Data could not be found for the remaining two subjects. Each patient was injected intravenously with about 1.5 to 2.0 milligrams (at a dosage of 30 μg uranium kg^{-1} of body weight) of natural uranium as the hexavalent nitrate form following breakfast. Some of the subjects received multiple uranium injections over time. Measurements were later made to determine the rates of urinary uranium excretion by the subjects. Serum calcium was also measured to determine the effect of uranium on blood calcium levels. The early urinary excretion rates of the uranium for the three controls are in good agreement with the Boston and Rochester studies.

Table 3.3. Data for patients from intravenous injection experiments conducted by Terepka (Table taken from Hursh and Spoor (1973)

				Daily urinary excretion rate (% of injected)					
Patient	Age	Sex	Condition	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
CM	53	male	Normal	61.5	3.8	1.5	0.7	0.6	0.4
RW	53	male	Normal	64.3	3.1	1.5	0.6	0.5	-
JP	72	male	Normal	61.5	6.1	2.1	1.3	0.4	0.4
CW	53	male	Paget's disease	16.0	5.6	1.1	0.6	0.6	0.6
CW*	53	male	Paget's disease	18.6	7.2	1.5	-	-	-
CS	58	male	Hyperthyroidism	31.0	-	-	-	-	-
AK	71	female	Hypothyroidism	63.3	6.9	-	-	-	-
MC	60	female	Osteomalacia	34.2	5.0	2.6	2.1	1.3	1.1
JL	62	male	Osteomalacia	32.6	7.1	-	-	-	-
MC	74	female	Osteoporosis	59.5	6.3	1.9	1.2	0.9	0.5
AH	81	female	Osteoporosis	60.1	6.1	2.1	0.9	0.8	0.6

*Received second dose after treatment with Prednisone (5 mg twice daily)

Using the current ICRP systemic model (ICRP, 1995a) and a kidney mass of 310 g for a 70 kg male (ICRP, 1975; 2002) with the amount of uranium administered (1.5 to 2 mg), the peak kidney concentration for the three controls is predicted to be between 0.5 and 0.7 μg uranium g^{-1} of kidney tissue. Unfortunately no information was provided relating to the kidney function of any of the patients.

Figure 3.4 suggests that the health status of the individual can greatly affect the excretion of uranium via the urine. Patients identified as CM, RW and JP were considered controls for this study as all the other participants had diseases expected to alter uranium metabolism.

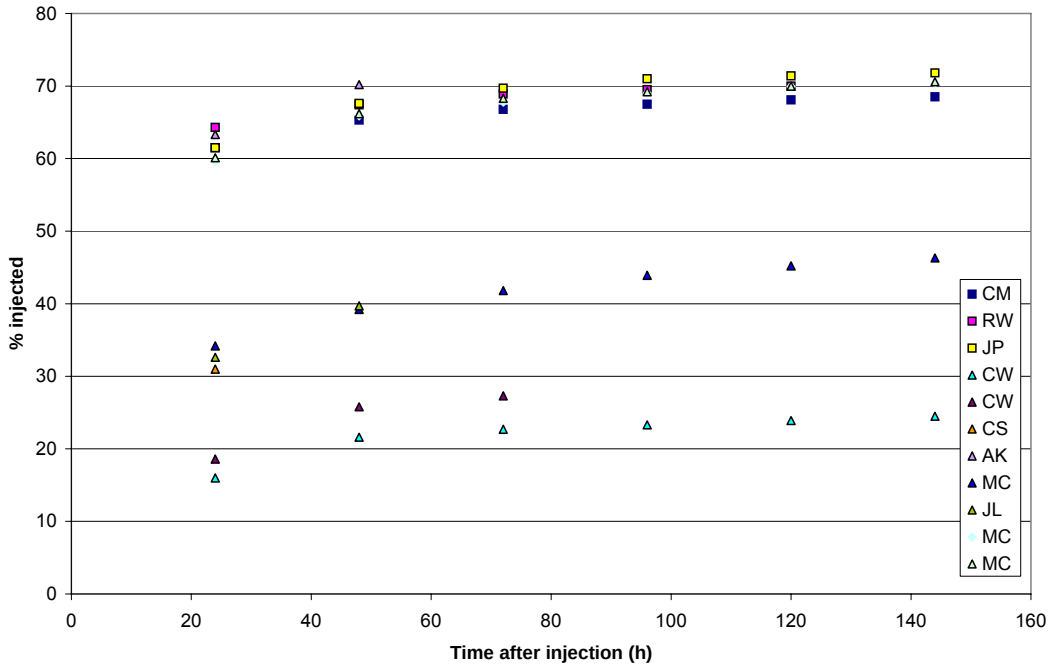

Figure 3.4 Cumulative urinary excretion for intravenously injected Patients from studies conducted by Terepka

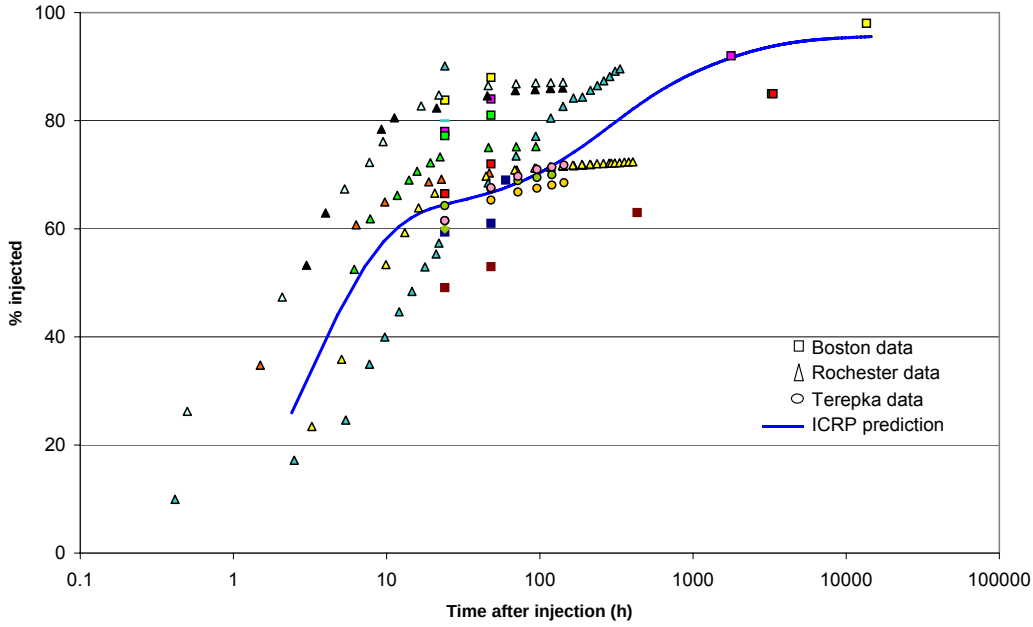

Figure 3.5 Cumulative urinary excretion from patients intravenously administered uranyl nitrate

The cumulative urinary excretion data from the three injection studies described above is shown in Figure 3.5. Only the patients whose condition was described as 'normal' have been included from the Terepka studies. The data from the three studies show excellent agreement and there appears to be no correlation with patient age or sex. For comparison, the cumulative urinary excretion predicted by the ICRP model for uranium (ICRP, 1995a) is also shown and appears to be generally representative of urinary excretion of systemic uranyl nitrate.

3.1.2 Acute Ingestion Data

3.1.2.1 Oral Ingestion of Uranyl Nitrate (Hursh et al, 1969)

An oral absorption study of uranium nitrate was conducted on 4 elderly patients in 1969. The purpose of this experiment was to validate the then recently ICRP adopted absorption factor of 1 % for soluble uranium compounds. Each patient, ranging in age from 56 to 78, received 10.8 mg of uranium nitrate dissolved in 100 ml of a proprietary brand of cola after fasting. Crucially, the kidney function was confirmed as being 'normal' for each patient before and during the experiment. As expected, uptake of uranium was low and led to highly variable urinary excretion rates. The authors suggested that the data tended to support the increase in the value for the absorption factor and also that, on general biological grounds, younger subjects would have been preferable. Using the current ICRP model (ICRP, 1995a), the value for the mass of the kidney (275 g for females and 310 g for males) (ICRP, 1975; 2002) and parameter values for soluble uranium compounds, the estimated peak kidney concentrations following ingestion of 10.8 mg uranyl nitrate is 0.08 μg uranium g^{-1} of kidney. No proteinuria was found indicating that the absorbed uranium had not caused kidney damage.

3.1.2.2 Ingestion of uranyl nitrate by a volunteer (Butterworth, 1955)

In 1955, 1.0 g of uranyl nitrate was administered orally to a volunteer in 200 cm^3 of water. Urinary excretion of uranium was followed continuously for 7 days and then at intervals up to 30 days after administration, at which time uranium was still measurable in the samples. The estimated uptake of uranium into the body was 1% of the ingested material, i.e. 10 mg. Assuming a 10 mg uptake, the excretion as a percentage of absorbed uranium was approximately 22% at 1 day and 24% by 5 days after administration. However, the volunteer suffered from acute nausea, vomiting and two attacks of diarrhoea within the first 12 hours of the study. Albuminuria was detected on two occasions when the uranium excretion was at its highest indicating transient kidney damage (Butterworth, 1955). Leggett and Harrison (1995) did not consider that it was possible to reliably estimate the uptake of uranium into the body under these conditions. Bailey and Davis (2002) estimated the peak kidney concentration from the urine data to be 1 μg uranium g^{-1} of kidney using the ICRP Publication 69 uranium systemic model (ICRP, 1995a) for the Royal Society study: see Table 3.4.

3.1.2.3 Ingestion exposure of uranium acetate (Pavlakis et al, 1996)

In October 1993 a male was admitted to hospital having attempted suicide by deliberately ingesting 15 g of "stable" uranium acetate and an unknown quantity of benzodiazepine. Quoting directly from the literature report "His past history included established diagnoses of hyperlipidaemia, muscle enzyme deficiency, hypertension and hypogonadism. He also described having chronic peptic ulcer disease, asthma, gout, renal calculi, urinary tract infection and migraine". He also admitted to self-medicating and abusing prescription drugs and had taken a wide range of drugs in the previous 12 months. Initially he underwent endotracheal intubation and nasogastric aspiration, which recovered a quantity of yellowcake followed by lavage with 50 g activated charcoal. His liver function was normal. 16 hours after admission he was referred to a nephrologist and diagnosed with acute nephrotoxicity due to heavy metal poisoning. He was treated daily with 1 g of calcium ethylene diamine tetra-acetic acid (Ca EDTA) intravenously for 5 days plus 8.4% sodium bicarbonate intravenously as required to maintain urinary pH above 7 and mannitol to promote diuresis. Despite these measures urine excretion dropped rapidly and on day 4 haemodialysis was started. By about 8 days after admission urine output ceased but then began to recover and dialysis was finally stopped 2 weeks after its initiation. After dialysis had ceased he was again treated with intravenous Ca EDTA for 5 days. He also suffered from a number of other problems including anaemia. He was discharged 32 days after admission.

Subsequently he was re-admitted 54 days after his initial admission because he was excreting unusually high levels of glucose and phosphate and required 18.5 g of bicarbonate supplement per day to counteract renal tubular acidosis, all of which indicated that renal function had not returned to normal. He was given a single 1 g intravenous injection of Ca EDTA but this failed to increase uranium excretion. Over the next 8 weeks his renal function failed to improve and his anaemia persisted. He was therefore given a single 1 g intravenous injection of calcium diethylene triamine penta-acetic acid (Ca DTPA) but this also failed to significantly enhance urinary excretion.

He was followed up again 6 months after his initial admission but although his haemoglobin had improved and there was no residual manifestation of muscle, liver or cardiac toxicity he still had renal function problems (Pavlakis et al, 1996). Unfortunately it is difficult to assess the patient's uranium intake because some of the uranium was recovered by aspiration and because his uranium absorption was possibly higher than normal due to the presence of an ulcer. Bailey and Davis (2002) estimated the peak kidney concentration from the urine data to be 100 μg uranium g^{-1} of kidney using the ICRP Publication 69 uranium systemic model (ICRP, 1995a) for the Royal Society study: see Table 3.4.

3.1.3 Acute Inhalation exposure data

3.1.3.1 Inhalation of Uranium Tetrafluoride (Zhao and Zhao, 1990)

A 23 year old uranium worker wearing protective clothing, gloves and a special gauze mask was working on a clogged furnace when a large quantity of pure uranium tetrafluoride (composed of natural uranium) dust was accidentally released from the furnace filling the room in which he was working. The worker was exposed for

approximately 5 minutes. He was hospitalised immediately. Initially he was fine but suffered from a number of problems between day 6 and day 9. He was released from hospital on day 30 at which point his kidney and liver function tests, urinary protein and urine analysis were all within normal limits. His urine was analysed regularly from day 1 immediately after the accident to day 1065. In the first 24 hours he excreted 156.8 µg of uranium in his urine and this gradually rose peaking at day 60 and then returning to normal by day 1065. The authors' estimate of the mass of uranium inhaled, based on ICRP 30 models, was 87 mg (assuming an aerosol particle size of 1 µm AMAD). From this value they estimated his kidney content at day 1 to be 804.2 µg or approximately 2.6 µg uranium g^{-1} kidney assuming a kidney weight of 310 g. His kidney function showed a number of abnormalities during urine monitoring. The phenolsulfonphthalein excretion became abnormal from day 78, followed by the non-protein nitrogen at day 82, the amino acid/creatinine ratio at day 451 and the urinary protein excretion by day 455. All of these gradually returned to normal.

Bailey and Davis (2002) estimated the intake and peak kidney concentration to be 10 µg uranium g^{-1} of kidney from the urine data for the Royal Society study (see Table 3.4.) using the ICRP Human Respiratory Tract Model (ICRP, 1994) and the ICRP Publication 69 uranium systemic model (ICRP, 1995a). However, the analysis presented particular difficulties because of the increasing urinary excretion rate, peaking at 60 days after intake.

3.1.3.2 Rupture of a tank releasing 400 lb of uranium hexafluoride (Voegtlin and Hodge, 1949-1953; Kathren and Moore, 1986)

In 1944 a number of workers were accidentally exposed to natural uranium hexafluoride gas plus steam when a large tank ruptured releasing around 400 pounds (180 kg) of uranium hexafluoride. The average estimated exposure was about 17 seconds. Three of the staff were seriously injured and were retained in hospital for 10-14 days after the incident. In all three cases urinary excretion was transitorily suppressed for 3 days after the accident (Voegtlin and Hodge, 1949-1953). Two of the three workers, (cases 4 and 5), were subjected to a medical follow up 38 years after the accident. At that time it was estimated that the initial lung deposit as a result of the accident was 40-50 mg of uranium in both cases (Kathren and Moore, 1986). In the immediate aftermath of the accident case 4 had a number of problems, including severe burns, lung damage and nausea and vomiting. Within the first 24 hours he began excreting trace amounts of albumin which rose to 100 mg albumin per 100 ml of urine by day 5 and then disappeared by the 10^{th} day after the accident. He also had casts in his urine on a number of occasions. By three weeks after the accident he had recovered well and his general condition was considered to be excellent. Case 5 also had severe burns, lung damage and nausea and vomiting. He showed transient albuminuria and fine granular casts were detected in his urine once on the 18^{th} day after the accident. He was discharged from hospital 10 days after the accident (Voegtlin and Hodge, 1949-1953). The urinary suppression, albuminuria and the presence of casts in the urine all indicate that both workers suffered kidney damage and the disappearance of the albuminuria and the casts indicate that the kidney probably began to recover fairly quickly. In the follow up medical examination 38 years later the kidney, liver and bone functions and

the urine analysis for both men were within the normal clinical limits and no uranium was detected in the urine (Kathren and Moore, 1986). The initial insult to the kidney does not appear to have had any long term effects.

Bailey and Davis (2002) estimated the intake and peak kidney concentration from the urine data for the Royal Society study (see Table 3.4.) using the ICRP Human Respiratory Tract Model (ICRP, 1994) and the ICRP Publication 69 uranium systemic model (ICRP, 1995a). The peak kidney concentration ranged from 1.2 to 4 µg uranium g^{-1} of kidney.

3.1.3.3 Accidental release of 3800 lb of uranium hexafluoride (Boback, 1975)

Employee G was engulfed in a cloud of uranium hexafluoride when a valve from a heated 10 ton uranium hexafluoride cylinder was inadvertently removed releasing 3800 lbs (1730 kg) of UF_6. He was hospitalised immediately and continuous urine collections were instigated at the hospital. The urine samples were returned to the plant for analysis. The first voiding at 2.5 hours after the incident contained 1.8 mg uranium l^{-1} of urine. Total uranium excretion was 3.36 mg at 25.5 hours and 3.65 mg at 211.6 hours after exposure. A total of 6 urine samples were collected during the 211.6 hour period and all were negative for protein indicating that there was no kidney damage. Continuous collection was therefore stopped. More urine samples were taken including a sample supplied when the employee returned to work 38 days after the accident. These were also free from protein (Boback, 1975; Moore and Kathren, 1985).

Bailey and Davis (2002) estimated the intake and peak kidney concentration (1 µg uranium g^{-1} of kidney) from the urine data for the Royal Society study (see Table 3.4.) using the ICRP Human Respiratory Tract Model (ICRP, 1994) and the ICRP Publication 69 uranium systemic model (ICRP, 1995a).

3.1.3.4 Inhalation exposure of 31 workers from the rupture of a cylinder of uranium hexafluoride (Fisher et al, 1990; 1991; Spitzberg, 1988)

In 1986, 31 workers accidentally inhaled UF_6, and its hydrolysis products UO_2F_2 and HF, when a cylinder of UF_6 ruptured (Fisher et al, 1990; 1991; Spitzberg, 1988). Urine measurements were instigated for these workers from between 4 to 8 hours after the accident until the urine content had fallen to the limit of detection (3-5 µg uranium l^{-1} urine) at about 15 days after the accident. Estimates of the uranium intake for the 31 workers ranged from about 0.47-24 mg uranium and the estimated maximum concentration in the kidney ranged from 0.048-2.5 µg uranium g^{-1} of kidney (Fisher et al, 1991). Spitzberg (1988) quotes a broader range of intakes from 0.14 to 34.2 mg uranium. Eight of the workers exceeded the 9.6 mg soluble uranium limit for a 40 hour working week laid down by the United States Nuclear Regulatory Commission at that time. These 8 cases are quoted in Table 3.4 below. Eleven workers tested positive for protein in excess of the normal range in at least one urine specimen during the first 20 days after the exposure. Only one subject (Worker E-26) showed positive protein (>200 mg dL^{-1}), glucose and cells in the first two urine samples submitted 4 days after the accident. This individual was estimated to have had the highest intake of 24 mg uranium

and the highest maximum kidney uptake of 2.5 µg uranium g^{-1} of kidney. The protein, glucose and cell content of the urine for worker E-26 returned to normal 13 days after the exposure. E-26 continued to show trace amounts of protein in his urine for the next 9 months. E-26 also experienced concurrent urinary tract infections during these episodes and this can also lead to the presence of protein in the urine. Therefore based on a review of a clinical analysis of the urinary results it was concluded at the time that there was insufficient evidence of transitory or long term damage for either worker E-26 or any of the other workers involved in the accident (Fisher et al, 1990).

3.1.4 Acute Burn absorption data

3.1.4.1 Severe burn with a mixture of uranium compounds (Zhao and Zhao, 1990)

In 1973 a 19 year old man was splashed with a mixed solution of uranyl nitrate and uranium oxide at 108°C resulting in burns to 71% of his body surface. The skin was highly contaminated and the worker was washed repeatedly for 5 hours until, with the exception of the deeper burn regions, the skin activity was reduced to background levels. He was hospitalised immediately. His urine was analysed immediately after the accident and regularly for 7.5 years. In the first 24 hours he excreted 22 mg of uranium in his urine. Daily urinary output dropped to 100 ml on day 1 post accident and was down to 25 ml by day 6 and 10 ml by day 7 by which time the patient was in a critical condition. There was also protein in the urine. By day 8 urinary output began to rise and renal function gradually began to return to normal. Within 1 month of the accident his laboratory tests were giving normal results. His progress was followed for 7.5 years after the accident during this time he excreted a total of 130 mg of uranium in his urine. Zhao and Zhao concluded that at least 130 mg reached the transfer compartment and that the kidney uranium content reached 12% of this value, equivalent to 50.3 µg uranium g^{-1} of kidney. His kidney function over the follow up period was within normal limits (Zhao and Zhao, 1990).

Bailey and Davis (2002) estimated the peak kidney concentration to be 35 µg uranium g^{-1} of kidney from the urine data using the ICRP Publication 69 uranium systemic model (ICRP, 1995a) for the Royal Society study: see Table 3.4 assuming that the man received an acute injection of 130 mg of uranyl nitrate.

3.1.4.2 Severe burn from uranyl nitrate solution (Butterworth, 1955)

In 1955 (Butterworth, 1955), a worker received severe burns over an area of 900 cm^2 of skin from exposure to uranyl nitrate solution. No urine samples were obtained for the first week after exposure. The results of later urine measurements indicated that uranium excretion may be more prolonged after absorption from injured skin than after absorption from the alimentary tract. Butterworth (1955) postulated that this difference was due partly to slower absorption through skin and also partly due to prolonged retention in the damaged skin. Albuminuria was reported in this case, indicating kidney damage, persisting until the beginning of the third week after exposure. Butterworth (1955) compared the case with observations on previous cases and found that the case was unusual in showing prolonged absorption, excretion and kidney damage.

Bailey and Davis (2002) estimated the intake and peak kidney concentration from the urine data for the Royal Society study (see Table 3.4.) using the ICRP Human Respiratory Tract Model (ICRP, 1994) and the ICRP Publication 69 uranium systemic model (ICRP, 1995a). The peak kidney concentration was estimated at 3 μg uranium g^{-1} of kidney

3.1.5 Chronic inhalation data

3.1.5.1 Inhalation of soluble forms of uranium by uranium mill workers (Thun et al, 1985)

Kidney function was compared for 39 uranium mill workers and 36 local cement plant workers of equivalent age, sex and race. Excretion of β_2-microglobulin and five amino acids (dicarboxylic amino acids and the methionine sub group of neutral amino acids: methionine, cystathionine, ornithine, aspartic acid and arginine) by the uranium workers was significantly higher than the reference group indicating impaired tubular reabsorption. The production of β_2-microglobulin was also higher in the uranium workers. Increased excretion was associated with length of exposure to soluble uranium compounds and the authors concluded that this was consistent with uranium induced nephrotoxicity. Although levels of increased protein excretion were mild there was a dose-effect relationship between clearance of β_2-microglobulin, relative to creatinine and the length of time workers had spent in the yellowcake drying and packaging area and the work area with the highest exposures to soluble uranium. The authors concluded from the results of the study that renal proximal tubule reabsorption of amino acids and low molecular weight proteins was reduced consistent with uranium toxicity (Thun et al, 1985).

Bailey and Davis (2002) estimated the peak kidney concentration from the urine data using the ICRP Publication 69 uranium systemic model (ICRP, 1995a) for the Royal Society study: see Table 3.6.

3.1.5.2 Inhalation exposure to uranium ore concentrate (Boback, 1975)

Employee D was exposed to airborne uranium ore concentrate in three incidents in January, February and June 1972 as a result of clearing jams on a conveyor system. Despite wearing respiratory protection he had a significant intake on the third occasion. The first urine sample recorded, was voided about 16 hours after the intake and contained 2.85 mg uranium l^{-1} of urine. A sample voided the following day contained 0.22 mg uranium l^{-1} of urine. No evidence of kidney damage was found in any of the urine samples given by Employee D for the whole of 1972 either before or after these incidents (Boback, 1975).

Bailey and Davis (2002) estimated the peak kidney concentration from the urine data using the ICRP Publication 69 uranium systemic model (ICRP, 1995a) for the Royal Society study, see Table 3.6, assuming that employee D had a series of acute intakes.

3.1.6 Chronic wound data

3.1.6.1 Chronic exposure of USA service personnel wounded in the 1991 Gulf War to depleted uranium resulting from shrapnel retained in the body (Hooper et al, 1999; McDiarmid et al, 2000; 2001; 2004; 2006; Squibb et al, 2005; Squibb and McDiarmid, 2006)

During the first Gulf war in 1991 a number of American service personnel were exposed to depleted uranium when their Bradley fighting vehicles or Abrams tanks were hit by depleted uranium penetrators as a result of friendly fire. Some of the personnel received wounds from shrapnel containing depleted uranium and were possibly also exposed to depleted uranium by inhalation and ingestion due to the generation of depleted uranium aerosol in the vehicle. In many cases the shrapnel has been left in the body and therefore these men are being chronically exposed to depleted uranium as the shrapnel dissolves in the body. Since 1993 a number of these personnel plus personnel who served in the war but were either exposed to depleted uranium by inhalation and/or ingestion but not by wound or were unexposed have been monitored for a wide range of biological parameters including uranium urinary excretion and renal function. The number of personnel involved in the study has also increased over time as more of them have been contacted (Hooper et al, 1999; McDiarmid et al, 2000; 2001; 2004; 2006; Squibb et al, 2005; Squibb and McDiarmid, 2006).

The estimated concentration of uranium in the kidney at the time of the last available urine measurement and the estimated maximum kidney concentration between the intake in 1991 and the last available urine measurement were estimated for 16 soldiers containing shrapnel (Squibb et al, 2005). In eight cases the calculated kidney concentration had peaked before the last urine measurement and was falling indicating that uranium build up in the kidney had ceased. However, in the other eight cases the two values coincided (including the two highest values 0.63 and 0.95 μg uranium g^{-1} kidney) indicating that kidney concentration is still increasing in these cases. To date the results of all the renal function tests, made within the period over which monitoring has occurred, for all of the exposed group fall within the normal clinical range and there is no indication of kidney damage. Regular monitoring of this group is continuing because the kidney concentration in these soldiers is still increasing (Hooper et al, 1999; McDiarmid et al, 2000; 2001; 2004; 2006; Squibb et al, 2005; Squibb and McDiarmid, 2006).

3.1.7 Studies on populations chronically exposed to uranium in drinking water

The ICRP systemic model and f_1 value for soluble uranium have been used to provide estimates of the kidney concentrations for the following studies (ICRP, 1995a; b; 2002; Limson Zamora et al, 2003). Because of the wide range of values for the consumption data, the maximum value for has been taken to obtain the highest value for uranium concentration in the kidney.

3.1.7.1 Exposure of a Canadian population (Limson Zamora et al, 1998)

Limson Zamora et al (1998) investigated the effect of chronic low level exposure to uranium on renal function by comparing two groups of local Canadian residents that had been exposed for between 3 and 59 years through drinking water. The “low level” group

(7 males and 13 females) received municipal drinking water containing less than 1 µg uranium l^{-1} and consumed between 0.34 and 20 µg uranium d^{-1} from drinking water and food combined. The "high level" group (10 males and 20 females) received drinking water from privately drilled wells which contained between 2 and 781 µg uranium l^{-1}. They consumed between 3 and 570 µg uranium d^{-1} from drinking water and food combined. The authors measured glucose, creatinine, protein and β_2-microglobulin excretion to assess kidney function and alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and N-acetyl-β-D-glucosaminidase (NAG) as markers of cell toxicity. The authors pooled the data for the high and low level groups to look for relationships between uranium intake and the presence of biomarkers. They found that

- excretion of glucose, β_2-microglobulin and ALP were significantly associated with uranium intake for pooled male and pooled female data
- there was no observed association between creatinine, total protein, NAG or GGT excretion

When the high and low dose groups were compared against each other, only glucose excretion (which was greater in the high dose group) and LDH excretion (which was greater in the low dose group) were significantly different. It was concluded from the study that chronic ingestion of uranium at the levels measured here result in damage to the proximal tubule but not the glomerulus of the human kidney.

3.1.7.2 Exposure of a Finnish population (Kurttio et al, 2002)

Kurttio et al (2002) measured the renal function of 325 people in Finland whose supply of drinking water came from 194 drilled wells containing water with a median uranium concentration of 28 µg uranium l^{-1} (range 0.001 to 1920 µg uranium l^{-1}). The median daily intake was 39 µg uranium per person (range 7 to 224 µg) and the average exposure period was 13 years (range 1-34 years). They measured β_2-microglobulin, glucose, calcium and phosphate levels in urine to assess proximal tubule function and albumin and creatinine clearance to assess glomerular function. They found that

- increased fractional calcium excretion was significantly associated with increased uranium in urine and in drinking water and with uranium intake
- increased fractional phosphate excretion was significantly associated with increased uranium in urine
- the tendency for increased uranium exposure to increase glucose excretion was not statistically linked
- there was no observed association between creatinine, albumin or β_2-microglobulin excretion

The results showed that for chronic low level exposure, uranium affects tubular function but not glomerular function. The effects on tubular function were modest in magnitude and it was not possible to identify from this study a threshold level below which the effects would not occur.

3.2 Compilation of Human data

A Working Group of the Royal Society (2002) identified cases of uranium exposure reported in the research literature. They described the cases and presented the medical findings along with up to date estimates of intake and kidney concentration using the most recent biokinetic models recommended by ICRP (Bailey and Davis, 2002). This work was further extended in the Capstone Report (Guilmette et al, 2004; Parkhurst et al, 2004). Summaries of these data, and those identified above, obtained at early times after acute exposure, are given in Table 3.4. Information resulting from long term follow-up of some of these cases is given in Table 3.5. Data on chronic exposures are given in Table 3.6.

The data in Table 3.4 show that after acute exposure:

- transient elevation of biochemical indicators of renal dysfunction occur above a kidney concentration of 3 μg uranium g^{-1} of kidney and have occasionally been observed as low as 1 μg uranium g^{-1} of kidney
- protracted elevation of biochemical indicators of renal dysfunction have been seen above 3 μg uranium g^{-1} kidney tissue and more severe conditions have been observed at higher concentrations

Table 3.4. Acute human exposures to uranium resulting in effects on the kidney measured at early times after exposure

Intake route	Chemical form	Subjects	Intake mg uranium[d]	Peak kidney μg uranium g^{-1} of kidney[d]	Effect[*]	Reference
Ingestion	Acetate	1	8500	100[e]	+++	Pavlakis et al (1996)
Dermal (burn)	Nitrate	1	130	35[e]	+++	Zhao and Zhao (1990)
Injection	Nitrate	1	51.4	19[f]	NR	Bernard and Struxness (1957)
Injection	Tetrachloride	1	44.2	16.3[f]	NR	Bernard and Struxness (1957)
Injection	Tetrachloride	1	41.1	15.1[f]	NR	Bernard and Struxness (1957)
Inhalation	Tetrafluoride	1	920[e]	10[e]	++	Zhao and Zhao (1990)
Injection	Nitrate	1	16	6	+	Luessenhop et al (1958)
Injection	Nitrate	1	11	5	+	Luessenhop et al (1958)
Inhalation	Hexafluoride	2	40-50[e]	4[e]	+	Kathren and Moore (1986)
Dermal (burn)	Nitrate	1	10[e]	3[e]	++	Butterworth (1955)
Inhalation	Hexafluoride	1	24	2.5	+[c]	Fisher et al (1990)
Injection	Nitrate	1	5.9	2	+	Luessenhop et al (1958)
Injection	Nitrate	1	5.5	2	-	Luessenhop et al (1958)
Inhalation	Hexafluoride	1	18	1.9	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	18	1.9	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	17	1.8	-	Fisher et al (1990)
Injection	Nitrate	1	4.3	1.5	-	Luessenhop et al (1958)
Inhalation	Hexafluoride	1	15	1.5	-	Fisher et al (1990)
Injection	Nitrate	1[a]	3.91	1.4[f]	+	Bassett et al (1948)
Injection	Nitrate	1[a]	3.17	1.4[bf]	NR	Bassett et al,(1948)
Inhalation	Hexafluoride	1	40-50[e]	1.2[e]	+	Kathren and Moore (1986)
Inhalation	Hexafluoride	1	12	1.2	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	11	1.1	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	11	1.1	-	Fisher et al (1990)
Injection	Nitrate	1	2.746	1.0[f]	-	Bassett et al (1948)
Ingestion	Nitrate	1	470[e]	1.0[e]	+	Butterworth (1955)
Inhalation	Hexafluoride	1	20[e]	1.0[e]	-	Boback (1975)

Intake route	Chemical form	Subjects	Intake mg uranium[d]	Peak kidney µg uranium g^{-1} of kidney[d]	Effect*	Reference
Inhalation	Hexafluoride	1	8.7	0.9	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	7.4	0.76	-	Fisher et al (1990)
Injection	Nitrate	1	1.918	0.7[f]	-	Bassett et al (1948)
Inhalation	Hexafluoride	1	6.0	0.62	-	Fisher et al (1990)
Inhalation	Hexafluoride	1	6.0	0.62	-	Fisher et al (1990)
Injection	Hexavalent	10	1.5-2.0	0.5-0.7[f]	NR	Terepka et al (1964)
Injection	Nitrate	1	0.584	0.2[f]	-	Bassett et al (1948)
Injection	Nitrate	1	0.477	0.2[f]	-	Bassett et al (1948)
Injection	Nitrate	1	0.385	0.1[f]	-	Bassett et al (1948)
Ingestion	Nitrate	4	10.8	0.08[f]	-	Hursh et al (1969)

[a]Same patient received second (lower) dose 26 days later.
[b]Peak kidney concentration includes residual from first dose.
[c]Reported as negative in the original accounts of the accident

[d]Values for intake and peak kidney concentration are taken from the original literature reference(s) except:-

- [e]Calculated by Bailey and Davis (2002) using current ICRP models
- [f]Calculated by authors using current ICRP models

*Clinical symptoms of renal dysfunction (eg oliguria, anuria, rhabdomyolysis, acute renal failure):
+++ Severe .
Biochemical indicators of renal dysfunction:
++ Protracted (eg albuminuria, glycosuria, casts)
+ Transient (eg non-protein nitrogen, β_2-microglobulin)

– No detectable effects (ie Biochemical tests on urine negative)

NR Not analysed or reported

Table 3.5. Long term follow-up on humans acutely exposed to uranium (From Capstone report Attachment 3 Table 6.4 (Guilmette et al, 2004; Parkhurst et al, 2004))

Intake mg uranium	Peak kidney µg uranium g^{-1} of kidney	Renal function* Early	Late	Follow-up time	Reference
8500	100	+++	+++	6 mon	Pavlakis et al (1996)
130	35	+++	-	7 yr	Zhao and Zhao (1990)
86	10	++	-	7 yr	Zhao and Zhao (1990)
24	2.5	+	-	2 yr	Fisher et al (1990)
40-50	4	+	-	38 yr	Kathren and Moore (1986)
40-50	1.2	+	-	38 yr	Kathren and Moore (1986)

*Clinical symptoms of renal dysfunction (eg oliguria, anuria, rhabdomyolysis, acute renal failure):
+++ Severe .
Biochemical indicators of renal dysfunction:
++ Protracted (eg albuminuria, glycosuria, casts)
+ Transient (eg non-protein nitrogen, β_2-microglobulin)

– No detectable effects (ie Biochemical tests on urine negative)

The data in Table 3.5 suggest that for an acute exposure giving a peak kidney concentration about ten times the traditional limit of 3 µg uranium g^{-1} of kidney tissue, normal renal function can recover with time. There is insufficient evidence to ascertain if the time required for the kidney to recover normal renal function is dependent on the mass of uranium to which it is exposed.

The data in Table 3.6 suggest that after chronic exposure renal dysfunction can occur below concentrations of 1 µg uranium g^{-1} of kidney.

Table 3.6. Chronic human exposures to uranium resulting in effects on the kidney

Intake route	Chemical form	Subjects	Kidney concentration µg uranium g^{-1} of kidney[a]	Effect*	Length of exposure (years)	Reference
Inhalation[f]	Ore Concentrate	1	3[b]	-	1.1 to 23	Boback (1975)
Inhalation	Yellowcake	27	up to ~1[b]	++	4.7 to 16.1	Thun et al (1985)
Intramuscular	Uranium Metal	16	up to ~0.95	-	12	Squibb et al (2005)
Ingestion	Total diet	30	up to ~0.14[cd]	++	3 to 59	Limson Zamora et al (1998)
Ingestion	Drinking water	101	Up to ~0.05[ce]	++	1 to 34	Kurttio et al (2002)

[a]Values for peak kidney concentration are taken from the original literature reference except:-

[b]Calculated by Bailey and Davis (2002) using current ICRP models

[c]Calculated by authors using current ICRP models

[d] Assumes max. consumption – 570 µg uranium d^{-1}, over 59 y, female (275 g kidney)

[e] Assumes max. consumption – 224 µg uranium d^{-1}, over 34 y, female (275 g kidney)

[f] Multiple acute intakes over a period of months

*Biochemical indicators of renal dysfunction:
++ Protracted
+ Transient
- No detectable effects

3.3 Animal data

There is a great deal of data relating to the effect of uranium on the kidney in different animal species and strains in the research literature and it would be impossible to cover it in detail in the time available for this project. In view of possible species differences, emphasis has been placed on the available human data, as it was in recent major assessments (Royal Society, 2002; Guilmette et al, 2004; Parkhurst et al, 2004). A review of uranium concentrations and effects in the kidneys of several animal species based on experiments carried out in the early 1950s has been undertaken (Spoor and Hursh, 1973). In these experiments the animals were exposed periodically to low concentrations of uranium for periods up to 1 year. The data are presented in Table 3.7.

Table 3.7 shows that changes ranging from borderline to mild or moderate could be identified at kidney concentrations below 3 µg uranium g^{-1} of kidney.

As shown in Table 3.7, the qualitative effects of uranium exposure in mammals are similar and therefore similar effects may be expected in humans. However, it has been shown that sensitivity to uranium varies between mammalian species (Luessenhop et al, 1958; Spoor and Hursh, 1973; Spitzberg, 1988). Therefore the extrapolation of the quantitative effects of uranium toxicity from mammals to humans should be undertaken with caution.

TABLE 3.7 Uranium concentration and effects in the kidney observed at one year after continuous inhalation exposure to soluble uranium compounds for one year* (from Spoor and Hursh (1973))

Uranium dust concentration		Dogs†		Rats†		Rabbits†		Guinea Pigs†		
$\mu g\ m^{-3}$	Compound	**No.**	**‡µg uranium g^{-1}**	**No.**	**‡µg uranium g^{-1}**	**No.**	**‡µg uranium g^{-1}**	**No.**	**‡µg uranium g^{-1}**	Kidney injury
2000	$UO_2(NO_3)_2.6H_2O$	5	1.7 (1.2-2.3)	24	5.6 (1.9-11.3)	3	1.4 (0.8-2.2)	10	0.5 (0.3-0.8)	Mild to moderate
250	$UO_2(NO_3)_2.6H_2O$	15	1.0 (0.1-1.9)	23	1.6 (0.1-4.4)	5	0.9 (0.4-1.9)	10	0.1 (0.1-0.2)	Occasional changes
200	UF_6	10	0.4 (0.0-0.7)	23	2.7 (0.0-5.8)	7	0.3 (0.0-0.8)	-	-	Mild
200	UCl_4	13	0.2 (0.0-0.5)	12	0.4 (0.1-1.9)	10	0.4 (0.2-0.6)	10	0.1 (0.0-0.3)	Borderline
150	$UO_2(NO_3)_2.6H_2O$	11	0.5 (0.2-1.0)	23	1.4 (0.6-3.3)	-	-	-	-	None
50	UF_6	12	0.3 (0.0-0.5)	26	0.9 (0.1-2.0)	-	-	10	0.2 (0.1-1.1)	Extremely mild-very few animals
50	UCl_4	15	0.2 (0.9-0.5)	7	0.4 (0.1-0.9)	-	-	-	-	Generally none-mild, few animals
40	$UO_2(NO_3)_2.6H_2O$	17	0.4 (0.1-1.0)	25	0.4 (0.1-2.0)	-	-	-	-	none

*Data compiled from Hodge HC, Stokinger HE, Neuman WF, Suggested maximum allowable concentration of soluble uranium compounds in air. In Pharmacology and Toxicology of Uranium Compounds, pp 2170-2256 (C Voegtlin and HC Hodge Eds), New York: McGraw-Hill 1953.

†Exposure period was 7-9 months.

‡Measured kidney concentration at autopsy (range of values in parentheses)

4 EFFECT OF URANIUM ON BIOKINETICS OF EXCRETION

Hodgson et al (2000; 2001) related the amount of uranium excreted or retained by the kidneys of rats to the mass of uranium absorbed into the blood. At very low mass levels, such as those used in intravenous distribution studies, the ratio of urine excretion to urine excretion plus kidney content (u/(u+k)), at one day, was 0.85 (Figure 4.1). In experiments where larger amounts of uranium were absorbed into the blood the value of (u/(u+k)) decreased to 0.5. The results indicate that there may be a threshold effect on excretion for uranium toxicity for rats at or near 1 µg uranium g^{-1} of kidney. Above this concentration (1 µg uranium g^{-1} kidney tissue) urine output is reduced and retention in the kidney increased on the first day that the kidney is exposed to uranium. However, this conclusion should be treated with caution because the results are from a wide range of studies, using different chemical forms of uranium, that were not designed to examine uranium nephrotoxicity.

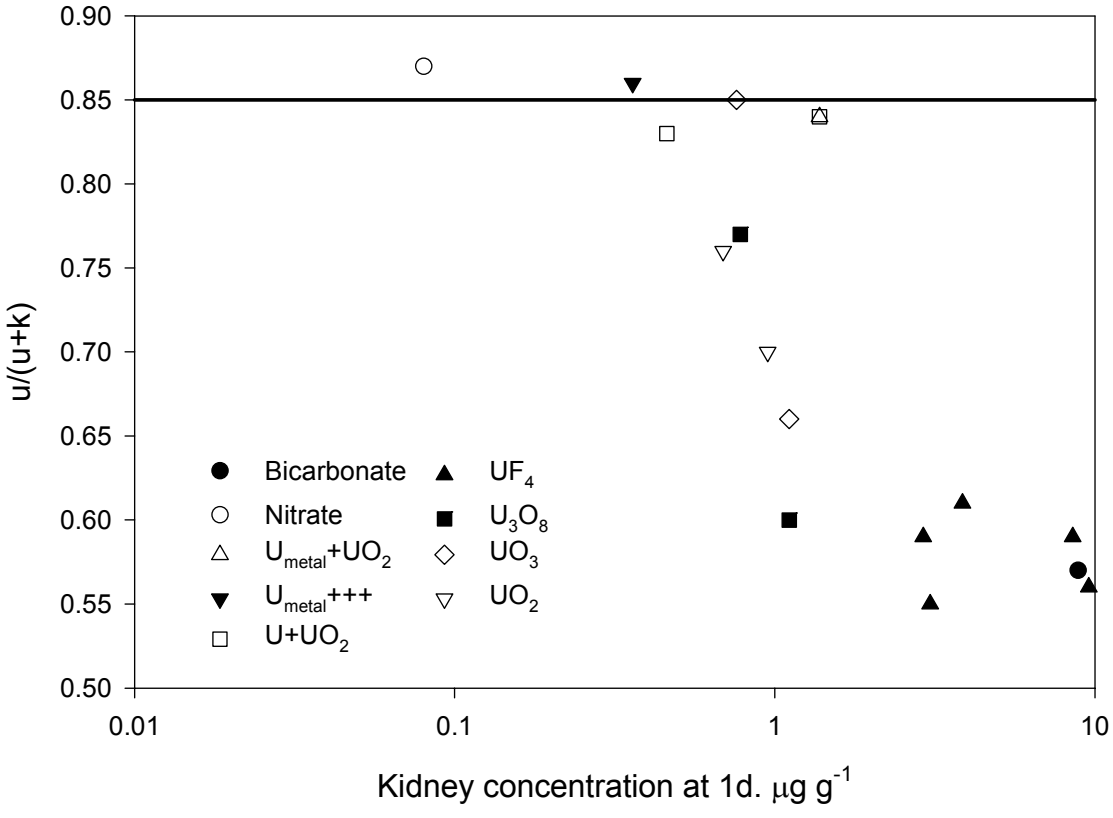

Figure 4.1 The effect of uranium mass deposited in the rat kidney on urine/(urine+kidney) ratio

In experiments in which UF_4 was instilled into the lungs of 300g male Sprague Dawley rats, kidney damage was reported in animals that received 301 µg (high exposure group) of uranium instilled into the lungs but not in those that received 32 µg (low

exposure group) (Houpert et al, 1999). The average uptake of uranium to blood in the first 24 hours for both groups of animals was approximately 18% (range 16.5 and 19.9%) and the percentage of this material reaching the kidneys was approximately 24% and 18% for the low and high exposure groups respectively. Assuming that the kidney mass for a 300 g rat is approximately 3 g, the rats which received 32 µg of uranium had an approximate total kidney content of 1.5 µg, a kidney concentration of 0.5 µg uranium g^{-1} of kidney and a (u/(u+k)) value of 0.66. Animals receiving 301 µg uranium had an approximate total kidney content of 9.0 µg, a kidney concentration of 3.0 µg uranium g^{-1} of kidney and a (u/(u+k)) value of 0.72. These results are in contrast with the findings of (Hodgson et al, 2000; 2001).

In experiments in which UO_4 was instilled into the lungs of rats, Houpert et al (1999) observed that the ratio of (k/(u+k)) remained essentially constant at about 0.36 (ie (u/(u+k)) ~ 0.64) when the uranium concentration in the kidney varied between 0.02 and 12.5 µg uranium g^{-1} of kidney. Further research is required to clarify this issue.

It is worth noting that the same ratio (u/(u+k)) predicted by the ICRP Publication 67 (ICRP, 1993) human biokinetic model for uranium is also 0.85, and that (Luessenhop et al, 1958) suggested that kidney sensitivity in man is similar to that for the rat. However, a similar figure can be constructed from the Rochester and Boston human intravenous injection study (Figure 4.2). Although the data are more variable, they appear to show that the urinary excretion of uranium is normal after intakes giving peak kidney concentrations up to about 3 µg uranium g^{-1} kidney tissue.

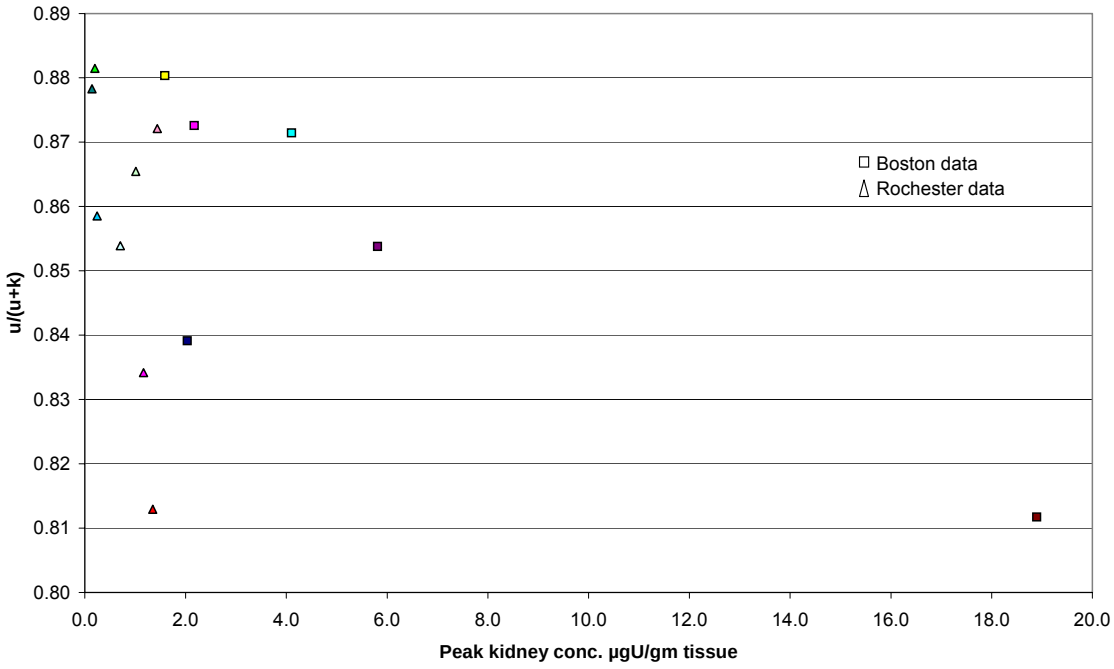

Figure 4.2 The effect of uranium mass deposited in the kidney on urine/(urine+kidney) ratio for the Rochester and Boston intravenous injection studies

5 CONCLUSIONS

A review of the scientific literature has been carried out to provide information on

- measured indicators of kidney damage following human exposures to uranium
- biokinetic studies giving data on the ratio of uranium urinary excretion to kidney concentration in humans

Particular attention was paid to human experimental studies in which uranium solutions were intravenously injected and several human studies have been identified here that were not considered in the Royal Society Working Group report on "The health hazards of depleted uranium munitions Part II".

The results of this study support the conclusions of the Royal Society Working Group that

- acute exposures that lead to concentrations of about 1 μg uranium g^{-1} of kidney have been associated with minor reversible kidney dysfunction
- chronic levels that lead to minor kidney dysfunction are not well established, but are likely to be below 0.3 μg uranium g^{-1} of kidney.

Based on the available data in the literature, the results of this study also indicate that, for humans, the ratio of uranium urinary excretion to kidney concentration shows no obvious change up to kidney concentrations of at least 3 μg uranium g^{-1} of kidney.

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APPENDIX A Comments on biomarkers for assessing nephrotoxicity

The measurement of biomarkers in urine has been used often to assess the potential nephrotoxicity of uranium (Spoor and Hursh, 1973; Leggett, 1989; Diamond, 1989; Limson Zamora et al, 1998; Royal Society, 2002).

Two types of biomarkers have been used.

Indicators used to identify loss of kidney function include creatinine, glucose, total protein, and β_2-microglobulin (BMG). Creatinine (MW 113 Daltons), is a metabolic waste product that is filtered by the glomerulus, passes through the tubular system with little or no re-absorption and is excreted in urine. Glucose (MW 180 Daltons) is filtered by the glomerulus and is completely or almost completely re-absorbed into the blood in the proximal tubules of the kidneys. Under normal conditions only small amounts of protein are excreted in urine. Small increases in glomerular permeability will lead to large increases in the urinary excretion of high molecular weight serum proteins such as albumin (MW 69,000 Daltons) which can be used as an indicator of glomerular damage (Lillehoj and Poulik, 1986).

Cell toxicity markers include the urinary excretion of the enzymes alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and N-acetyl-β-D-glucosaminidase (NAG) produced in kidney tissue. The diagnostic potential of urinary enzymes is enhanced by the simultaneous assay of more than one enzyme. GGT is maximal in the membrane of the proximal tubules and the loop of Henle (Albert et al, 1961). ALP is present in the membrane of epithelial cells of the proximal tubules (Butterworth et al, 1965) and is located more superficially in the membrane than GGT (Jung et al, 1993). NAG is found in lysosomes and is present in greatest concentration in the glomerulus and proximal tubules (Bourbouze et al, 1984). LDH is found in the cytoplasm and is maximal in the distal tubule (Bonting et al, 1960).

There is little doubt that such biomarkers can be of value for identifying nephrotoxic effects in the kidneys as illustrated by the human data summarised in Tables 3.4 to 3.6. In general terms, the data from animal studies is consistent with the human data (Spoor and Hursh, 1973; Leggett, 1989; Diamond, 1989; Limson Zamora et al, 1998).

However, the results of studies in humans and animals should be treated with caution since:

- kidney dysfunction may not be specific for uranium
- wide fluctuations can occur in urinary excretion with time. For example, after an industrial accident involving the inhalation of natural uranium tetrafluoride (Zhao and Zhao, 1990) clinical effects such as anorexia, diarrhoea and blood in the faeces were observed during the first 9 d after exposure. After 30 d the results of a full blood count, urinalysis and renal and liver function were within normal limits. Follow up studies over seven years provided evidence of abnormal phenolsulfonphthalein excretion at 78 d and an abnormal amino acid nitrogen/creatinine ratio at day 82; substantially enhanced protein excretion

occurred between days 455 and 590 and at day 1695 before returning to normal values.

- the increased concentrations of biomarkers in urine are transient phenomena and early and late insult to the kidney may not be detected. Functional abnormalities may not appear until 3-5 d after exposure and may subside about 7 d later, so that urine samples collected within days after exposure or after several weeks may give misleading information (Diamond, 1989).
- animal studies have shown that concentrations of albumin and glucose were normal at maximum kidney concentrations of 0.8-2 µg uranium g^{-1} of kidney when mild to moderate kidney damage was identified (Houpert et al, 1999; Gilman et al, 1998a; b; c; Hodgson SA et al, 2001). However glucosuria has been identified at kidney concentrations between 2.9 and 14 µg uranium g^{-1} of kidney (Houpert et al, 1999).