THE ROYAL SOCIETY

The health hazards of depleted uranium munitions, part II

Annexe A: Estimations of kidney uranium concentrations from published reports of uranium intakes in humans

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A1 Introduction

A number of cases are reported in the literature of measurements of kidney function, and in some cases of observations of kidney damage following substantial intakes of uranium. This annexe gives the results of calculations performed to estimate kidney concentration in these cases as a function of time, and in particular

- the maximum kidney concentration, ${}^{max}[U]_k$, and the time at which it occurred
- the time for which the kidney concentration was above 3 μg of uranium per gram of kidney (μgU/gK).

These calculations do not take into account the medical toxicology assessments of exposures, which vary with issues such as nutritional status, age, sex and current health status as well as possible concomitant chemical exposures. The models used in these assessments are described in Part I, Appendix 1, Annexe A, to which the reader is referred for further information.

In addition to software mentioned in Part I, a recent version of the software IMBA (Birchall et al 1998) was used for some of the calculations. IMBA implements the ICRP Publication 66 human respiratory tract model (ICRP 1994a), the ICRP Publication 69 uranium systemic model (ICRP 1995) and ICRP Publication 78 uranium excretion model (ICRP 1997), which is based on the Publication 69 uranium systemic model. IMBA has three features that make it particularly useful for this purpose.

- Assessment of multiple intakes: the user specifies the intake pattern (the dates on which acute intakes occurred, and between which chronic intakes occurred) and IMBA applies a maximum-likelihood method to find the set of intakes with the highest probability of giving the observed excretion data.
- The maximum-likelihood method, which provides an unbiased assessment from measurements reported as 'below the limit of detection'.
- The facility to calculate uranium concentration in the kidneys at a series of times.

A2 Chronic (protracted) exposures

Several studies are considered in which kidney function has been tested in groups of people exposed chronically to elevated levels of uranium intake by various routes. If the rate of intake of uranium is assumed to be constant then the rate of uptake of uranium to blood will similarly be constant. Because most uranium that enters the blood is excreted in urine, if the intake is

protracted the rate of uptake to blood is approximately equal to the urinary excretion rate. Although about 10% of uranium that is absorbed into blood goes to the kidneys, most of it only remains for a few weeks, and so with a continuous uptake the kidney concentration initially rises quickly but after a week or so increases only slowly. Table A1 (Table D11 of Part I, Annexe D) gives results calculated for continuous constant uptake of 1 µg per day over 50 years. Results for up to 10,000 days are also plotted in Figure A1 (Figure D8 of Part I, Annexe D).

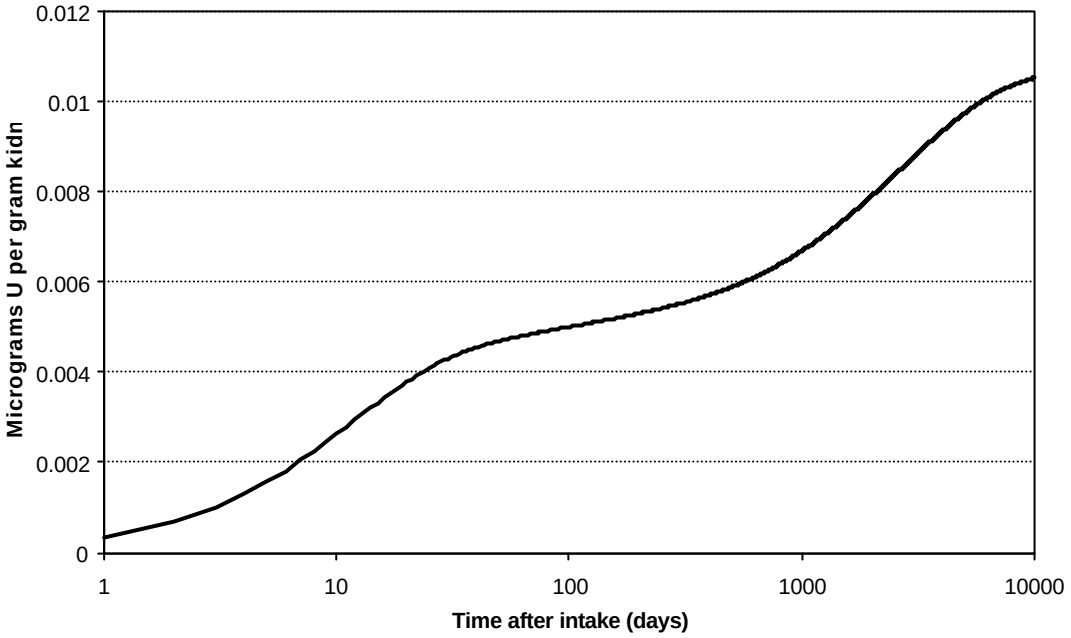
Initially the amount in the kidney is about 0.1 µg (10% of the daily uptake), and builds up over the first few weeks to about 1.5 µg (150% of the daily uptake). Thereafter, although the predicted amount in the kidneys continues to increase, it does so only slowly, eventually reaching about 3 µg (three times the daily uptake). This represents a diminishing fraction of the total uptake, eventually less than 0.1%.

Figure A1 and Table A1 show that after one year of constant uptake to blood of 1 µg per day, the level of uranium is predicted to reach 0.0056 µg per gram kidney (µgU/gK) and after 50 years it is predicted to reach 0.011 µgU/gK. For uranium in soluble form it is generally assumed that for adults 2% of ingested uranium is absorbed into blood (ICRP 1995; Part I, Appendix 1, Annexe A). Thus it is predicted that these levels would be reached from constant ingestion of 50 µg per day of soluble uranium.

Table A1. Predicted kidney content and concentration of uranium from constant uptake to blood of 1 µg per day

Time after start of intake	Kidney content (µg)	Kidney concentration (µg uranium per gram kidney)	Total uptake (µg)	Kidney content/ total uptake (%)
1 day	0.106	0.0003	1	10.6
2 days	0.21	0.0007	2	10.5
5 days	0.49	0.0016	5	9.8
10 days	0.8	0.0026	10	8.1
20 days	1.2	0.0038	20	5.9
50 days	1.5	0.0047	50	2.9
100 days	1.6	0.0050	100	1.55
200 days	1.6	0.0053	200	0.82
365 days	1.8	0.0056	365	0.48
2 years	1.9	0.0061	730	0.26
5 years	2.4	0.0077	1825	0.13
10 years	2.8	0.0090	3650	0.077
20 years	3.2	0.010	7300	0.044
50 years	3.3	0.011	18250	0.018

Figure A1. Predicted concentration of uranium in kidneys (µgU/gK) from constant uptake to blood of 1 µg per day.



A2.1 Ingestion of uranium in drinking water: Limson Zamora et al (1998) (Appendix 1, Section 4.4)

Limson Zamora et al (1998) studied the chemical effects on the human kidney of chronic ingestion of uranium in drinking water. They compared two communities, one that used mains water (<1 µg per litre) and another that used water from private wells (2–780 µg per litre). The highest intake was estimated to be 570 µg per day. As noted above, constant ingestion of 50 µg per day of soluble uranium is predicted to result in a kidney concentration of about 0.01 µgU/gK (0.0056 µgU/gK after one year and 0.011 µgU/gK after 50 years). These values can be scaled up to estimate the levels of uranium in the kidneys of the individual with the highest average daily intakes of soluble uranium (570 µg of uranium per day). After one year of chronic exposure, the level of uranium is predicted to reach 0.06 µgU/gK and after 50 years of daily exposure it would reach 0.13 µgU/gK.

A2.2 Inhalation of yellowcake: Thun et al (1985) (Appendix 1, Section 4.2.3)

Thun et al (1985) studied renal toxicity in a group of uranium mill workers who were exposed in the yellowcake drying and packaging areas. The report (p 84) states that in 1975–9 monthly average air concentrations in the yellowcake area were up to eight times the current occupational standard of 3.7 Bq per cubic metre. The text (and Table 1 of Thun et al) also states that 21% of measurements of uranium in urine exceeded the action level of 30 µg per litre, ie about 50 µg per day, assuming about 1.5 litres urine per day. (The ICRP Reference Man value is 1.4 litres urine per day (ICRP 1975)). If at equilibrium, then the rate of uptake to blood is approximately the same. From Figure A1, 1 µg per day gives about 0.005 µgU/gK after a year of exposure. Thus 50 µg per day would give about 0.25 µgU/gK. Table 1 of Thun et al gives a 95th percentile of 120 µg per litre in 1975, indicating that kidney concentrations were up to about 1 µgU/gK.

A2.3 Embedded DU shrapnel: Hooper et al (1999) (Appendix 1, Section 4.2.5)

US soldiers involved in 'friendly fire' incidents who have retained DU shrapnel are excreting elevated levels of uranium in urine (Hooper et al 1999; McDiarmid et al 2000).

Hooper et al 1999 (Table 3) give average values in soldiers with confirmed shrapnel of 4.47 and 6.4 μg per gram creatinine in 1993/4 and 1995, respectively. Values were up to 22.48 μg per gram creatinine in 1993/4. McDiarmid et al (2000) (p. 171) refers to values up to 30.74 μg per gram creatinine. Creatinine excretion is used to normalise urine samples to 24-hour excretion rates. A value of 1.7 g creatinine per day is often assumed (Jackson 1966), although Fetter and von Hippel (1999; notes 40 and 41) use 2.2 g creatinine per day. Taking 2 g creatinine per day as a rounded value gives excretion rates in those with embedded shrapnel as typically about 10 μg per day and ranging up to about 60 μg per day. Rates of uptake of uranium to blood can be assumed to be the same.

From Table A1 and Figure A1 an uptake rate of 1 μg per day gives kidney concentrations of 0.0056 μgU/gK at one year and 0.0090 μgU/gK at ten years. Hence predicted levels for 10 μg per day are about 0.06 μgU/gK at one year and 0.1 μgU/gK at ten years, and for 60 μg per day they are 0.3 μgU/gK at one year and 0.5 μgU/gK at ten years.

A3 Acute (short) exposures

A number of cases of acute intakes of uranium have been reported and in some of these cases the levels of uranium in the kidney can be estimated. In some cases there were multiple acute intakes.

A3.1 Ingestion of 'uranium acetate': Pavlakis et al 1996 (Appendix 1, Section 4.1)

It was reported that 15 g of 'uranium acetate' were ingested. Uranyl acetate has the formula $UO_2(C_2H_2O_2)_2.2H_2O$ and a molecular weight (MW) of 422.19 (CRC 1984). Hence 15 g contains 15*(238/422) = 8.5 g uranium. Data on urinary excretion at times between 20 and 95 days after intake are given in Figure 3 of Pavlakis et al.

A3.1.1 Simple assessment based on amount ingested

For a soluble form of uranium it is generally assumed that the fraction absorbed from the gut to the blood (f_1 value) = 0.02 (ICRP 1995). Hence 0.02*8.5 = 0.17 g or 170 mg is absorbed into blood. Of this, about 10% goes to the kidneys, ie 17 mg or 17,000 μg. Mass of kidneys = 310 g, hence concentration = 17,000/310 = 55 μgU/gK.

A3.1.2 Intake assessment based on urinary excretion

Figure 3 of Pavlakis et al gives uranium in urine concentrations in μmol per day. Using a molecular weight of 238 for uranium, convert to μg per day (Table A2):

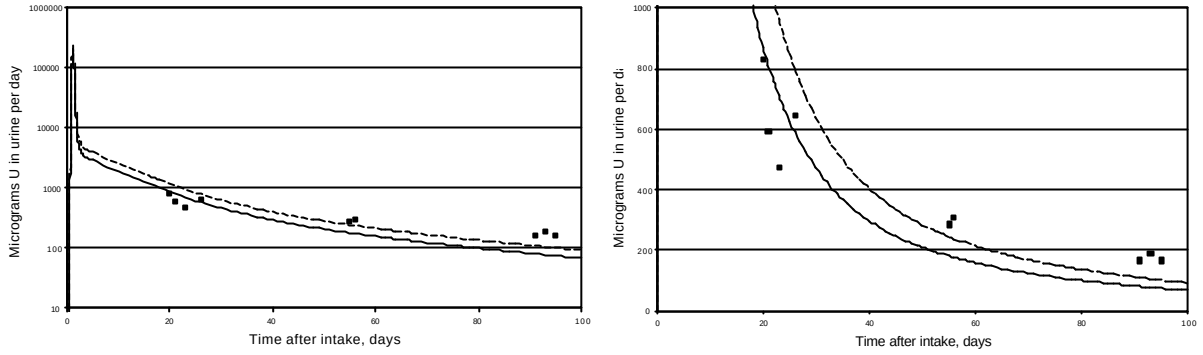
Table A2. Uranium urinary excretion data after ingestion of uranium acetate

Day	μmol per day	μg uranium per day
20	3.5	833
21	2.5	595
23	2	476
26	2.7	643
55	1.2	286
56	1.3	309
91	0.7	167
93	0.8	190
95	0.7	167

A modified version of the computer program LUDEP (Jarvis et al 1996), in which the ICRP Publication 69 uranium systemic model and the ICRP Publication 78 excretion model are implemented, was used to estimate the intake from the urinary excretion data. The assessment involves two stages. In the first stage, information about the intake is entered, in this case an acute ingestion, with f_1 (the unknown quantity) set to 0.01. This is combined with the urinary excretion function from ICRP Publication 78 (urinary excretion as a function of time following unit uptake to blood) to give a bioassay output function (urinary excretion as a function of time following unit acute ingestion with f_1 = 0.01).

In the second stage the bioassay output function is scaled to fit the data, by minimising the weighted sum of the squares of the differences between each data point and the scaled bioassay output function. Thus in Figure A2, the shape of the curves is determined by the time course of uptake to blood following ingestion, and the ICRP Publication 78 uranium excretion function. The weighting applied is determined by the errors on the data, ie the difference between each data point and the bioassay output function is measured in terms of the error on that point. Where (as here) measurement errors are not given, LUDEP provides several options in the assumed errors. Two were applied here: uniform relative errors (the error is assumed to be proportional to the value of the data point) and logarithmic errors (the error is assumed to be proportional to the logarithm of the value of the data point). The results of both are shown in Figure A2. These gave estimated intakes of 20 and 27 g (assuming f_1 = 0.01), ie uptake to blood of 200 mg and 270 mg, respectively. Since the amount ingested is known to be 8.5 g U, these results correspond to f_1 values of 0.023 and 0.031, respectively.

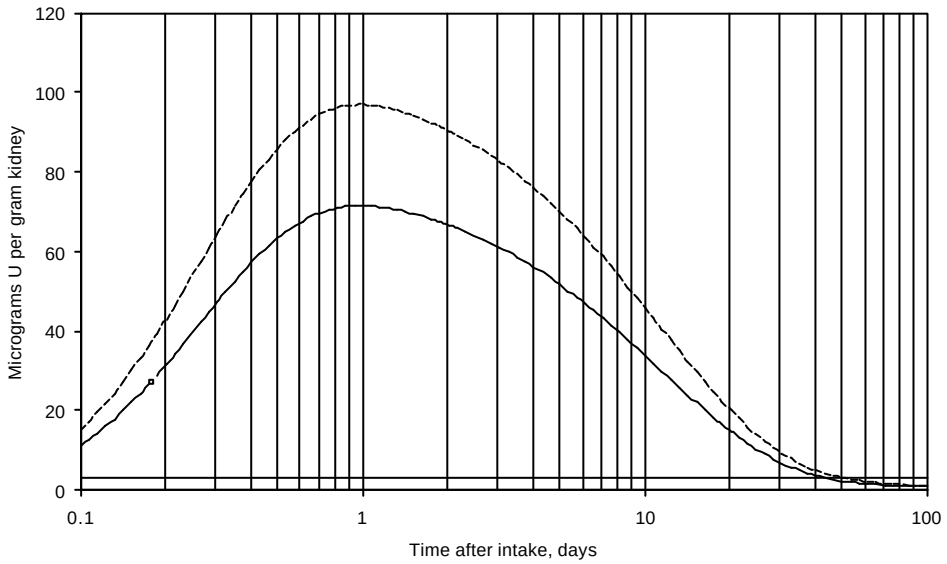
Figure A2. Fits to urinary excretion data after ingestion of uranium acetate. Lower curve fit with uniform relative errors (f_1 = 0.023); upper curve fit with logarithmic errors (f_1 = 0.031). (a) Logarithmic y-axis showing the predicted initial high excretion rate; (b) linear y-axis showing data and fits in more detail. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at 20 days is the excretion between 19 and 20 days after intake.



(a) (b)

Using the same models and parameter values (intake of 8.5 g with f_1 values of 0.023 and 0.031), the concentration in the kidneys was then calculated, assuming a mass of 310 g, using IMBA. The results are shown in Figure A3. It was predicted that the maximum concentration was about 100 µgU/gK, and that it remained above 3 µgU/gK for about 50 days.

Figure A3. Predicted uranium concentration in kidneys after ingestion of uranium acetate. Lower curve for f_1 = 0.023; upper curve for f_1 = 0.031; horizontal line at 3 µgU/gK.



A3.2 Inhalation of uranium tetrafluoride (UF_4): Zhao and Zhao (1990), Case one (Appendix 1, Section 4.2.1)

It was reported that the patient, a 23-year-old man, had been working with uranium for 3.5 years before the accident. During UF_4 production, the top of the furnace became clogged with UF_4 powder (natural uranium). During overhaul a large amount of pure UF_4 powder escaped into the room and filled it for five minutes. The patient was working on the furnace, wearing protective clothing, a special gauze mask and gloves.

Urinalysis for uranium began on day one and continued to day 1065. Results given in Figures 1 and 2 of Zhao and Zhao (1990) are tabulated in Table A3. The excretion rate increases gradually to a peak at about 60 days and returns to normal by about 1060 days. It was estimated that the total excreted was about 87 mg.

Table A3. Uranium urinary excretion data after inhalation of UF_4

Day	µg uranium	Day	µg uranium	Day	µg uranium
1	117	56	1973	118	36
4	129	58	2369	125	47
7	130	63	3174	129	44
10	129	67	506	215	44
15	85	72	1406	350	32
22	124	75	443	438	21
26	218	79	1460	509	19
36	329	84	119	570	4
40	469	89	663	811	2
48	1336	99	107	1060	1
54	1321	107	64		

A3.2.1 Assessment of kidney concentration by Zhao and Zhao (1990)

From this result the authors estimated the uranium kidney content. They assumed an intake by inhalation of 87 mg, an activity median aerodynamic diameter (AMAD) of 1 µm, and using the ICRP Publication 30 model calculated a kidney content on post-accident day one of 804 µg; assuming a kidney weight of 310 g, they obtained a concentration of 2.6 µgU/gK.

In ICRP Publication 30 (ICRP 1979), for an aerosol of AMAD 1 µm, deposition in the nasopharyngeal (N-P), tracheobronchial (T-B) and pulmonary (P) regions is 30%, 8% and 25% of the inhaled amount, respectively. UF_4 is assigned to inhalation Class W, for which the amounts absorbed rapidly into blood from the N-P and T-B regions are 10% and 50%, respectively. Hence of the inhaled amount (0.3 x 0.1) + (0.08 x 0.5) = 0.07 is absorbed rapidly. In addition, 90%, 50% and 40% of the deposits in the N-P, T-B and P regions are rapidly cleared to the gastrointestinal (GI) tract. For Class W uranium f_1 was taken to be 0.05, and so a further 0.05(0.3x0.9 + 0.08x0.5 + 0.25x0.4)= 0.0155 is absorbed from the GI tract. Hence the total amount absorbed rapidly is 0.0855 of the amount inhaled. Thus if 87 mg were inhaled, the amount absorbed rapidly would be about 7.4 mg. Of this, about 12% is assumed to transfer to the kidneys, ie 0.9 mg. Hence with a kidney mass of 310 g, this gives a concentration of 2.9 µgU/gK, close to that obtained by Zhao and Zhao.

Apart from the use of models from ICRP Publication 30, which have now been superseded, there are two problems with this assessment. The first problem is that only a fraction of the amount inhaled is absorbed into blood and excreted in urine. Thus since 87 mg was excreted, a larger amount must have been inhaled. In addition to the rapid absorption addressed above, in the ICRP Publication 30 model 15% of the deposit in the P region is absorbed with a half-time of 50 days. As shown by Silk et al (1997), the fraction eventually transferred to blood for a Class W compound is 0.12 + 0.51f_1. For Class W uranium f_1 was taken to be 0.05, and hence the total amount absorbed is 0.1455. Most of this is excreted in urine and therefore the amount inhaled is about 87/0.1455, ie about 600 mg. Using the same calculation, the kidney concentration would be about 20 μgU/gK.

The second problem is that the urinary excretion pattern is qualitatively different from that predicted by the ICRP Publication 30 model. As described above, about half of the absorption to blood takes place rapidly, and the rest with a half-time of 50 days. Since most of the uranium absorbed into blood is rapidly excreted in urine, this should be reflected in the urinary excretion pattern, ie it should be highest on the first day or so after inhalation and decrease with time, rapidly at first then more slowly. The reported excretion pattern is quite different, and quite extraordinary, increasing exponentially to a sharp peak at about 60 days after the accident, then decreasing exponentially.

A3.2.2 Assessment of kidney concentration using current ICRP models

In ICRP Publication 68 (ICRP 1994b), UF_4 is assigned to absorption type M in the Human Respiratory Tract Model (HRTM; ICRP 1994a), because it was assigned to inhalation Class W in ICRP Publication 30. Specific absorption parameter values have been derived from the results of experiments in which it was administered to the lungs of rats. Results are given in Table A4, and are consistent across the three studies. For the present exercise, take rounded central values of f_r = 0.5, s_r = 0.15 d^{-1} and, s_s = 0.005 d^{-1}.

Table A4. Absorption parameter values for uranium tetrafluoride from in vivo studies

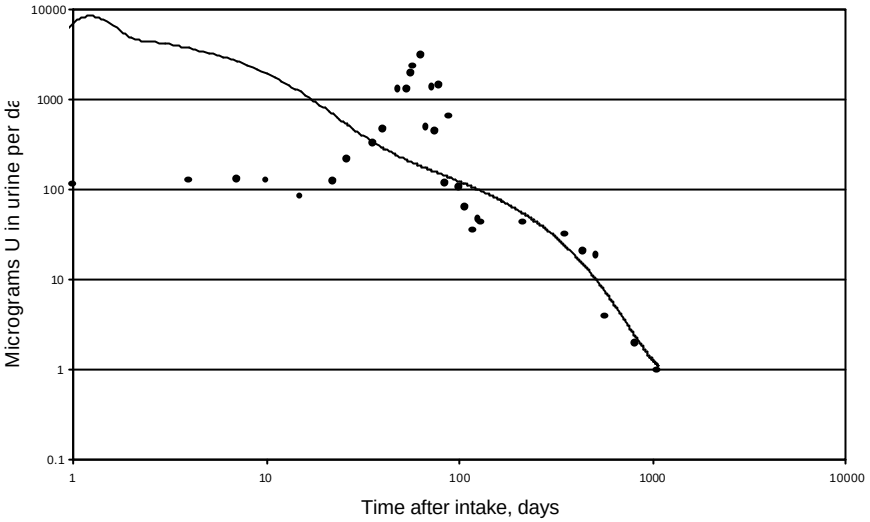
Reference	Absorption parameters		
	f_r	s_r, d^{-1}	s_s, d^{-1}
Ansoborlo et al 2001	0.58	0.21	0.0026
Hodgson et al 2000, 2001	0.51	0.10	0.0074
Hodgson et al 2000, 2001	0.52	0.11	0.0039
Defaults (ICRP Publication 68)			
Type F	1	100	-
Type M	0.1	100	0.005
Type S	0.001	100	0.0001

Figure A4 shows urinary excretion predicted by the HRTM, assuming an AMAD of 1 μm, and inhalation by a Reference Worker at Light Work. The intake has been scaled (to 915 mg uranium), to give the same total urinary excretion of 87 mg. As discussed above for the ICRP Publication 30 model, the excretion pattern is quite different from that observed. Excretion is predicted to be highest in the first day or two and then to decrease monotonically, whereas the observed excretion increases to a sharp peak around 60 days. Interestingly, however, the observed pattern from 200 days onwards is well predicted.

Consider two possibilities:

- absorption of uranium from the lungs to blood is as expected for UF_4, but most of the uranium, instead of being excreted promptly, is retained in the kidneys for a few weeks.
- the absorbed uranium behaves as predicted by the uranium systemic model, whereas absorption from the lungs is not as expected, but increases with time then decreases. This seems more likely as kidney effects were not seen until day 80.

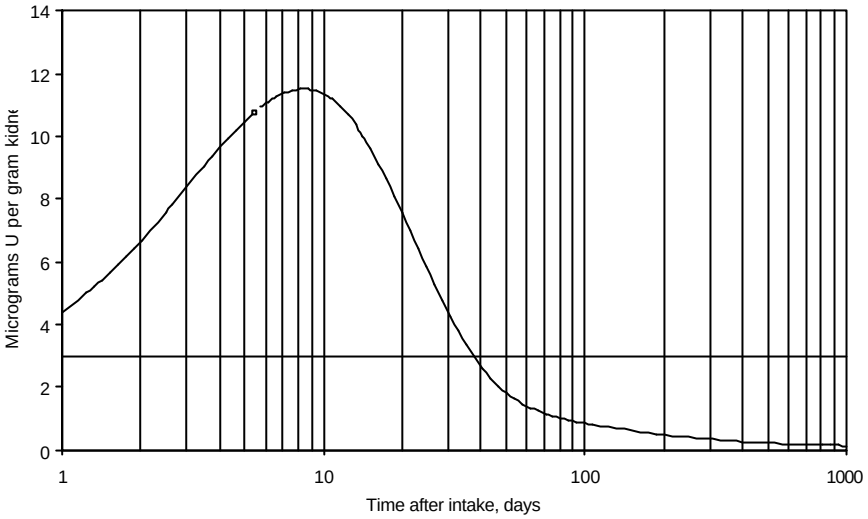
Figure A4. Urinary excretion of uranium predicted for intake of 915 mg UF_4 compared with data



A3.2.2.1 Absorption of uranium from lungs to blood as expected for UF_4

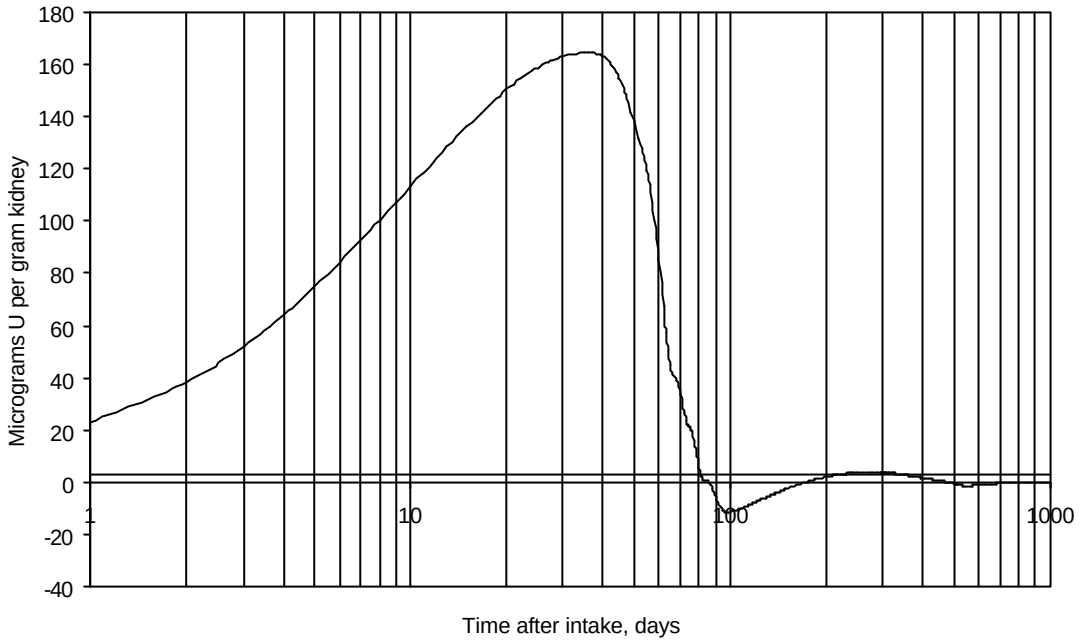
For this assessment it is assumed that absorption of uranium from the lungs to blood is as expected for UF_4 using the HRTM, assuming an AMAD of 1 µm, and inhalation of 915 mg by a Reference Worker at Light Work, with $f_r = 0.5$, $s_r = 0.15\ d^{-1}$ and $s_s = 0.005\ d^{-1}$. Figure A5 shows kidney concentration as predicted by the ICRP models, corresponding to the predicted urinary excretion in Figure A4. A maximum concentration of about 10 µgU/gK is reached (similar to that predicted by the ICRP Publication 30 models) at about ten days after intake and remains above 3 µgU/gK for about 40 days.

Figure A5. Kidney concentration based on predicted absorption from intake of 915 mg UF_4 with retention in kidneys based on the ICRP Publication 69 uranium model. Horizontal line at 3 mgU/gK.



However, most of the excretion occurs not in the first few days, but between about 40 and 90 days after intake. To take account of this, assume that the uranium was absorbed into blood as predicted, but that most of the uranium that is expected to be excreted in urine is retained in the kidneys instead. To obtain an approximate estimate of the effect, the amount in the kidneys at a given time was calculated from the total predicted urinary excretion minus the total measured urinary excretion (with linear interpolation between the data to estimate the amounts excreted on days on which it was not measured). (Note that this does not take account of the expected deposition in the kidneys, recycling of uranium deposited in bone, etc) Results are shown in Figure A6: the kidney concentration exceeds 20 µgU/gK after one day and continues to increase up to about 50 days (during which predicted excretion exceeds observed excretion in Figure A4). It reaches a maximum of about 150 µgU/gK, then falls rapidly to zero by about 90 days.

Figure A6. Kidney concentration based on predicted absorption from intake of 915 mg UF_4 and observed excretion. Horizontal line at 3 mgU/gK.



A3.2.2.2 Absorption of uranium from lungs to blood based on observed urinary excretion

For this assessment it is assumed that the absorbed uranium behaved as predicted by the uranium systemic model, whereas absorption from the lungs is not as expected for UF_4, but increases with time then decreases. The HRTM can be used to represent absorption from the lungs that increases with time (ICRP 1994a). Attempts to do so were made, but did not succeed in producing a peak as sharp as that observed.

As an alternative approach, the uptake to blood as a function of time after the intake was estimated directly from the excretion data. The observed urinary excretion as a function of time can be considered mathematically as the convolution of the uptake from the respiratory tract to blood as a function of time with the excretion rate as a function of time after a single instantaneous uptake to blood. Let:

A(t)dt be the amount (μg) absorbed from the respiratory tract to blood between times t and t+dt after intake;
E(t) be the amount (μg) excreted in urine per day at time t after uptake of 1 μg to blood;
U(T) be the amount (μg) excreted in urine per day at time T after the intake.

Then:

$$U(T) = \int_{o}^{T} A(t)E(T-t)dt$$

The resulting kidney concentration can be calculated directly from A(t), which is determined by 'deconvolution'. To obtain this, the uptake to blood was modelled as a series of injections to give a similar pattern of excretion, using IMBA. A reasonable fit was obtained with a series of 14 injections (Figure A7), scaled to give the same total urinary excretion of 87 mg. These were then used to calculate the corresponding kidney concentration (Figure A8). As for the urinary excretion,

this shows a sharp peak at about 60 days, with a maximum at about 10 µgU/gK, and remains above 3 µgU/gK between about 40 and 80 days.

Figure A7. Urinary excretion of uranium predicted for a series of injections compared with data after inhalation of UF_4.

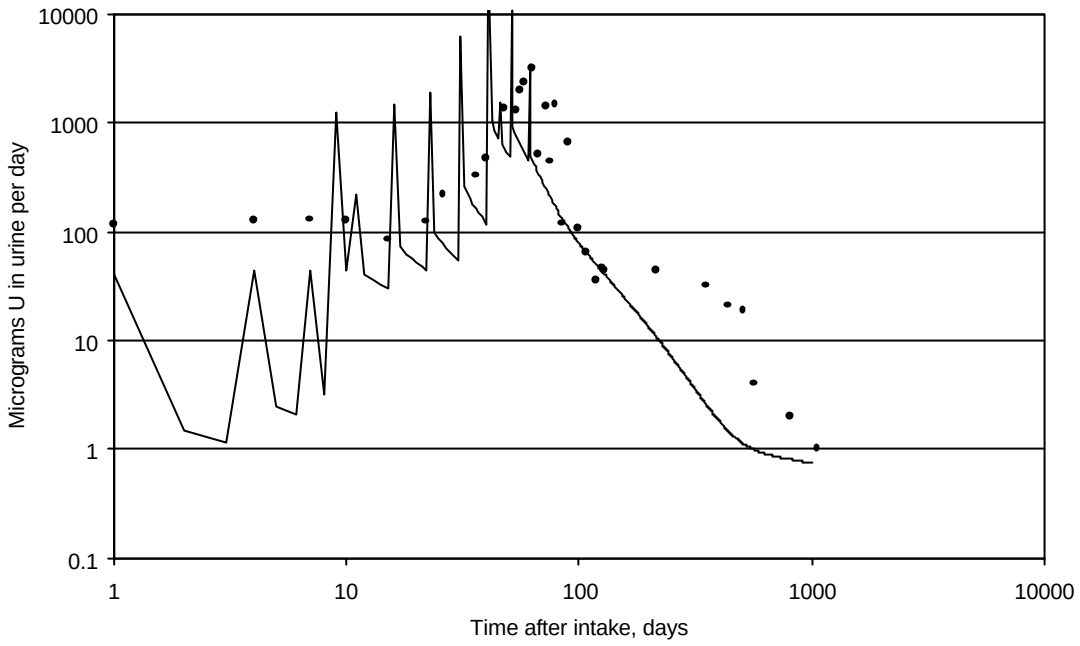
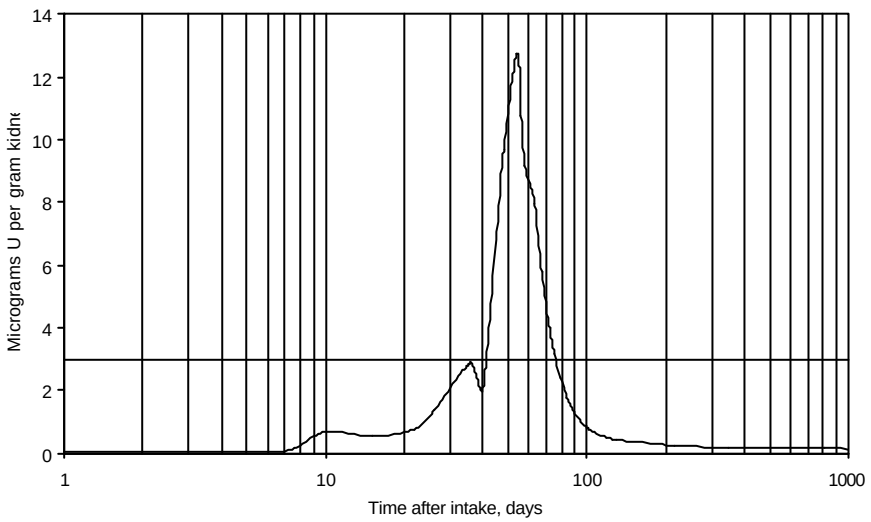


Figure A8. Kidney concentration after inhalation of UF_4 based on predicted absorption from a series of injections giving urine excretion in Figure A7.



A3.2.3 Summary and conclusions

A very unusual urinary excretion pattern was reported in this case, with the excretion rate increasing gradually to a peak at about 60 days and returning to normal by about 1000 days. The total amount of uranium excreted over this period was about 87 mg, indicating that the total intake by inhalation was about 500 – 1000 mg (depending on assumptions about the aerosol

characteristics). For such an intake of UF_4, the kidney concentration would be expected to reach a maximum of about 10 μgU/gK, and remain above 3 μgU/gK for several weeks. However, based on both the current and previous ICRP biokinetic models, and on studies of the behaviour of UF_4 administered to the lungs of rats, the urinary excretion pattern would be quite different from that reported. The difference might result from the specific characteristics of the material or abnormal biokinetics resulting from the large intake. Two possibilities were considered:

- that the lung clearance was as expected but that the uranium was retained in the kidneys before being excreted. This would lead to a much higher predicted kidney concentration, rising from about 20 μgU/gK on day one to a peak of about 150 μgU/gK, then falling rapidly to a low level by about 90 days after the intake.
- that excretion of uranium that entered the blood was as expected, but absorption from the lungs increased with time to a peak, as reflected in the urinary excretion. For this, it was predicted that the uranium kidney concentration reached a maximum of about 10 μgU/gK, and remained above 3 μgU/gK between about 40 and 80 days after the intake.

The latter seems more likely as kidney effects were not seen until about day 80, and were not severe.

A3.3 Uranyl nitrate burn: Zhao and Zhao (1990), Case two (Appendix 1, Section 4.2.2)

A 19-year-old man was badly burned by a hot mixture of uranium nitrate solution and uranium oxide. Urinary excretion of uranium was reported to be 22 mg in the first 24 hours, and 130 mg total in 7.5 years of follow-up. Since most of any uranium uptake is excreted in the urine within a few years, the total uptake will be approximately 130 mg. From this, and assuming that 12% of the uptake went to the kidneys (15.6 mg), the authors assessed that the maximum kidney concentration was 50 μg per gram kidney.

A3.3.1 Assessment of kidney concentration using current ICRP models

A3.3.1.1 Instantaneous uptake to blood

The intake was represented as an acute injection of 130 mg, and using the ICRP Publication 69 systemic model implemented in IMBA the uranium concentration in the kidney was calculated. As shown in Figure A9, it increases rapidly to a peak of about 50 μg per gram kidney (as calculated by Zhao and Zhao), and remains above 3 μg per gram kidney for about 35 days.

A3.3.1.2 Gradual uptake to blood

It was noted that the predicted urinary excretion in the first 24 hours following injection of 130 mg is 83 mg, but only 22 mg was observed (26.5%). To represent a gradual uptake, retention at the wound site was represented by a single exponential function with a rate constant of transfer to blood of s d^{-1}. Let $A(t)$ be the amount remaining at the wound site at time t (days), then:

$$A(1) = A(0)\exp(-st)$$

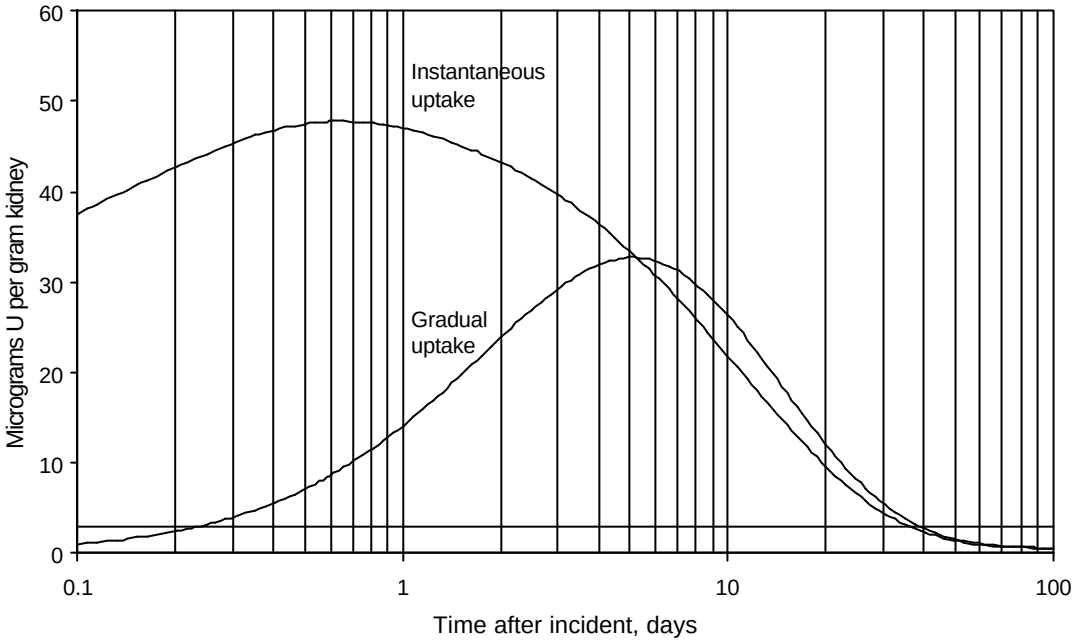
If there is 26.5% uptake in one day, 73.5% remains:

$$0.73 = 1 \exp -s*1$$

$$s = 0.31\ d^{-1}$$

To model this in LUDEP, the intake was represented by 100% alveolar deposition with f_r = 1 and s_r = 0.31. This gave 18.7 mg excreted in urine in one day. By iteration, s_r was adjusted to give 22 mg excreted in one day, for which its value was 0.38 d^{-1} (this takes account of the delay between uptake to blood and excretion in urine). Using these parameter values for the uptake, the uranium concentration in kidney was calculated. As shown in Figure A9, it increases to a peak of about 35 µgU/gK after a few days, and remains above 3 µgU/gK for about 40 days.

Figure A9. Kidney concentration after uranyl nitrate burn based on uptake of 130 mg uranium, with retention in kidneys based on ICRP Publication 69 uranium model. Horizontal line at 3 µgU/g kidney.



A3.4 Butterworth (1955), Case one (Appendix 1, Section 4.3)

It was reported that 1 g of uranyl nitrate solution was ingested by a volunteer. Uranyl nitrate has the formula $UO_2(NO_3)_2.6H_2O$, and a molecular weight (MW) of 502.13 (CRC 1984). Hence 1 g contains 1(238/502) = 0.47 g uranium. Uranium excretion in urine was measured for about a month, but only during the first seven days were measurements above the limit of detection (Table VIII of Butterworth (1955)). The case is also mentioned in Butterworth (1958), but little additional information is given.

A3.4.1 Simple assessment based on amount ingested

For a soluble form of uranium it is generally assumed that the fraction absorbed from the gut to the blood (f_1 value) = 0.02 (ICRP 1995). Hence 0.02*0.47 = 0.0095 g or 9.5 mg is absorbed into blood. Of this, about 10% goes to kidneys, ie 0.95 mg or 950 µg. Mass of kidneys = 310 g, hence concentration = 950/310 = 3 µgU/gK.

A3.4.2 Intake assessment based on urinary excretion.

Data on urinary excretion at times between one and seven days after intake are given in Table IX of Butterworth (1955) and Table A5 here.

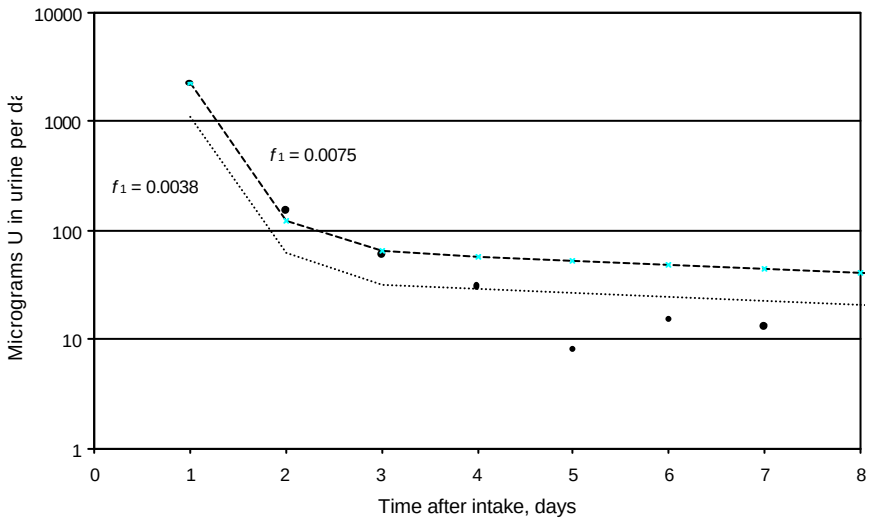
Table A5. Uranium urinary excretion data after ingestion of uranyl nitrate

Day	mg uranium per day
1	2.20
2	0.15
3	0.06
4	0.03
5	0.008
6	0.015
7	0.013

The total excreted during the first seven days is thus 2.476 mg. According to the ICRP Publication 69 uranium systemic model, of uranium injected into blood, 74.6% is predicted to be excreted in urine in seven days (ICRP Publication 78 (1997)). Hence it is predicted that 2.476/0.756 = 3.32 mg was absorbed into blood. Since the amount of uranium ingested was 470 mg, this gives an f_1 value of 3.32/470 = 0.0071.

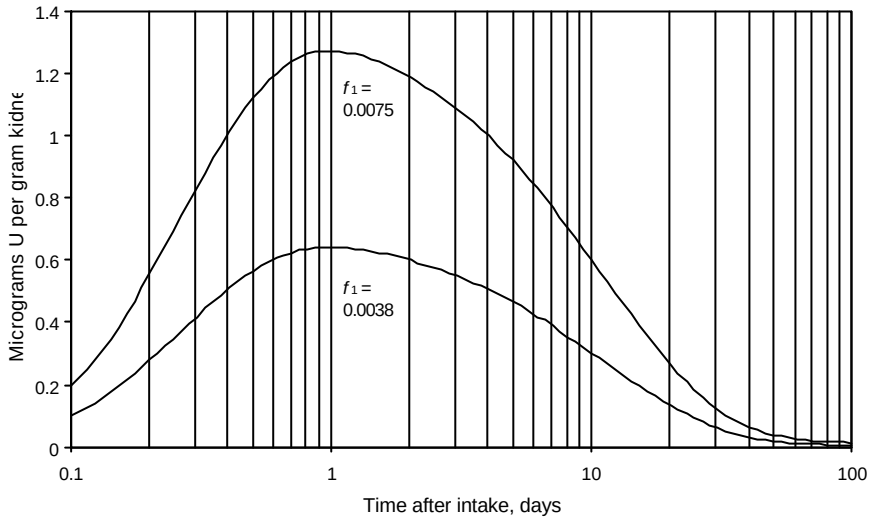
A modified version of the computer program LUDEP (Jarvis et al 1996), in which the ICRP Publication 69 uranium systemic model and ICRP Publication 78 excretion model are implemented, was used to estimate the intake from the urinary excretion data. (For details of the procedure see Section A3.1.2.) Two error assumptions were made here: uniform absolute errors (the same error is assumed for each data point) and logarithmic errors (the error is assumed to be proportional to the logarithm of the value of the data point). The results of both are shown in Figure A10. These gave estimated intakes of 0.18 and 0.35 g (assuming f_1 = 0.01), ie uptake to blood of 1.8 and 3.5 mg, respectively. Since the amount ingested is known to be 0.47 g uranium, these results correspond to f_1 values of 0.0038 and 0.0075, respectively. The latter is more consistent with the total amount of uranium excreted.

Figure A10. Fits to urinary excretion data after ingestion of uranyl nitrate. Lower curve fit with logarithmic errors (f_1 = 0.0038); upper curve fit with uniform absolute errors (f_1 = 0.0075). Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at two days is the excretion between one and two days after intake.



Using the same models and parameter values (intake of 0.47 g with f_1 values of 0.0038 and 0.0075), the concentration in the kidneys was then calculated, assuming a mass of 310 g, using IMBA. The results are shown in Figure A11. It was predicted that the maximum concentration was about 1 μgU/gK

Figure A11. Predicted uranium concentration in kidneys after ingestion of uranyl nitrate. Lower curve for f_1 = 0.0038; upper curve for f_1 = 0.0075.



A3.5 Uranyl nitrate burn: Butterworth (1955), Case 2 (Appendix 1, Section 4.2.2)

A worker received severe burns from uranyl nitrate solution. Uranium concentrations were measured in urine samples obtained between seven and 62 days. Results (μg uranium/litre) are given in Table X of Butterworth (1955). Twenty-four hour samples were obtained between days 12 – 26 and 28 – 35. The average volume collected on these days was 1708 ml and this volume was used to estimate daily excretion on the days when collection was not complete. Butterworth (1955) also gives the results of measurements on 53 routine samples collected over several months before the accident. The average of these (8 μg/litre) was assumed to represent a background and was subtracted from the measured concentrations in Table X. Table A6 here gives the daily uranium excretion derived from the data presented.

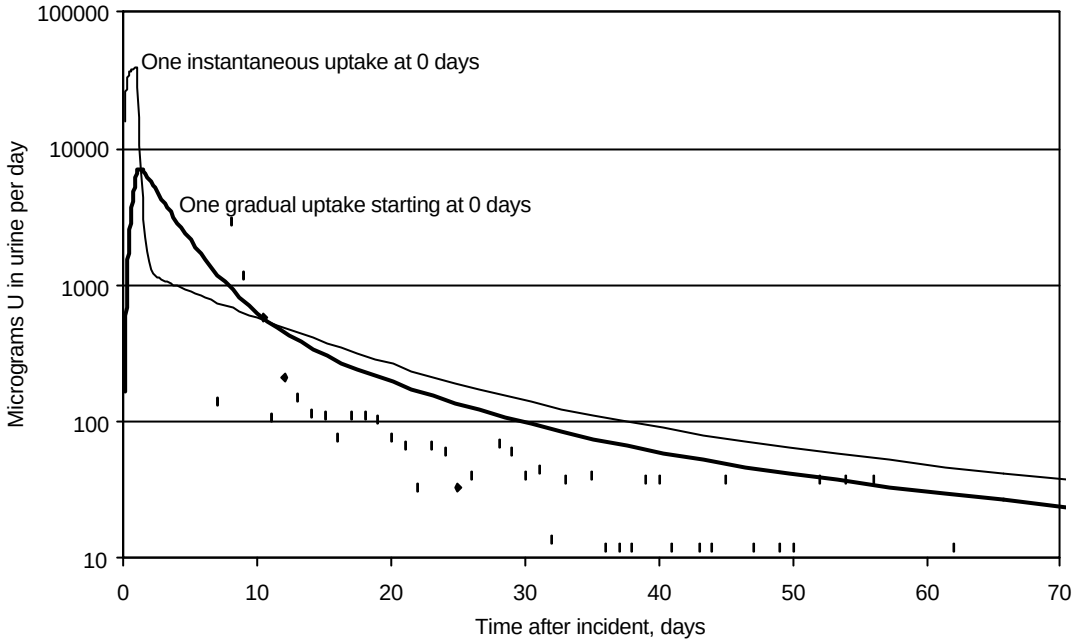
Table A6. Uranium urinary excretion data after uranyl nitrate solution burn

Day	µg uranium per day	Day	µg uranium per day	Day	µg uranium per day
7	140	22	33	38	12
8	2890	23	66	39	38
9	1182	24	61	40	38
10	584	25	33	41	12
11	106	26	40	43	12
12	213	28	69	44	12
13	148	29	60	45	38
14	114	30	40	47	12
15	112	31	44	49	12
16	76	32	14	50	12
17	112	33	37	51	0
18	112	34	0	52	38
19	104	35	40	54	38
20	78	36	12	56	38
21	67	37	12	62	12

The case is difficult because of the lack of data during the first week and because the first measurement (on day seven) was much lower than the subsequent measurements. Kathren and Moore (1986) noted that in the three cases of inhalation of UF_6 the urinary excretion was 'abnormal', in that it fluctuated widely during the first week after the intake (see below, especially Case five). In discussion they considered that the most plausible explanation was temporary retention in a 'metabolic pool or compartment', possibly resulting from pulmonary oedema caused by inhalation of hydrofluoric acid. If that is the case, it might be expected that fluctuations in excretion would be seen after a wound as here, possibly resulting from fluctuations in absorption from the wound site.

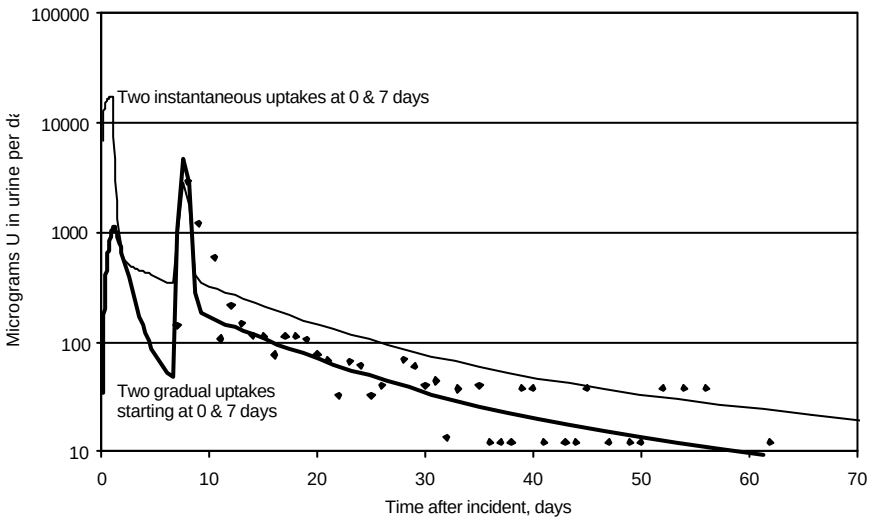
The uptake to blood was assessed using IMBA (all fits made with uniform absolute errors). The first attempt was to represent the uptake by an instantaneous injection at time zero, but the fit (intake of 60 mg) was poor, especially over the peak at 7 – 12 days (Figure A12). The effect of these high values was to lead to overestimates of the later data. To model a slower uptake, a similar approach was taken as with Zhao and Zhao, Case 2 (Section A3.3). The uptake was modelled by a single exponential function. To achieve this, the intake was represented by 100% alveolar deposition with $f_r = 1$ and s_r was varied. A value of $s_r = 0.4\ d^{-1}$ (intake of 36 mg) gave the best fit obtainable in this way but was still not considered satisfactory.

Figure A12. Fits to urinary excretion data after uranyl nitrate burn for single intake at 0 days, instantaneous and gradual (s_r = 0.4 d^{-1}). Both were fit with uniform absolute errors. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at eight days is the excretion between seven and eight days after intake.



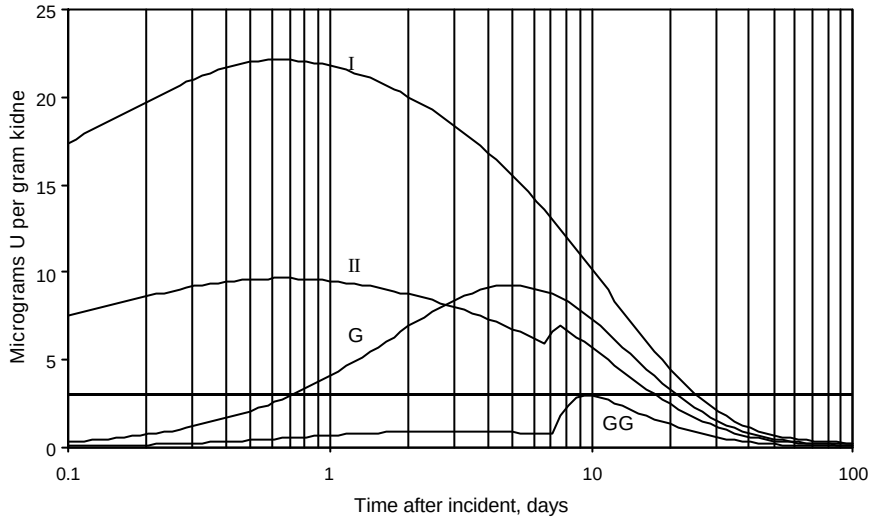
To take account of the low first measurement, the exposure was represented by two intakes: one at time 0 and one on day seven. Initially, it was represented by two injections (26 and 4.0 mg, respectively), and then by two gradual uptakes with the same value of s_r (Figure A13). In this case a satisfactory fit was obtained with s_r = 1 d^{-1} with intakes of 3.0 and 7.6 mg, respectively.

Figure A13. Fits to urinary excretion data after uranyl nitrate burn for two intakes at 0 and seven days, instantaneous and gradual (s_r = 1 d^{-1}). Both were fit with uniform absolute errors. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at eight days is the excretion between seven and eight days after intake.



Using the same models and parameter values, the concentration in the kidneys was then calculated, assuming a mass of 310 g, using IMBA. The results are shown in Figure A14. For the best fit to the data (two gradual uptakes) it was predicted that the maximum concentration was about 3 µgU/gK. The predictions of the other fits are also shown for comparison and show that depending on the pattern of intake the maximum concentration could have been up to about 10 µgU/gK and could have remained above 3 µgU/gK for ten – 20 days.

Figure A14. Predicted uranium concentration in kidneys after uranyl nitrate burn: I, single instantaneous uptake; II, two instantaneous uptakes at 0 and seven days; G, single gradual uptake; GG, two gradual uptakes, starting at 0 and seven days. Horizontal line at 3 µgU/gK.



A3.6 Inhalation of uranium hexafluoride (UF_6): Boback (1975), Cases F – M (Appendix 1, Section 4.2.1)

An accidental release of 3800 pounds of uranium as UF_6 occurred when 'employee G' inadvertently removed the valve from a heated ten-ton UF_6 cylinder. He was immediately engulfed in a cloud containing hydrolysed UF_6 (UO_2F_2) and hydrofluoric acid. He was hospitalised for six days, but returned to work nine days after the incident. While hospitalised all urine was collected and analysed for uranium content. (Clinical findings, including analysis for protein in urine were negative.) The uranium in urine data are given (in milligrams per litre) up to about 51 hours after the exposure in Table 7 of Boback (1975). Data for employee G were collated and converted to milligrams per day by Moore and Kathren (1985), who refer to Boback (1975) and also to a personal communication from Boback (1985). Presumably they obtained additional data since they report measurements up to eight days (Table A7).

Table A7. Uranium urinary excretion data after inhalation of UF_6 (Boback Case G, as reported by Moore and Kathren (1985))

Day	mg uranium per day
1	2.79
2	0.36
3	0.085
4	0.051
5	0.029
6	0.025
7	0.023
8	0.015
9	0.016

Note that these measurements are similar to those for Butterworth Case one (Section A3.4), and therefore a similar kidney concentration (about 1 μgU/gK) is expected.

In this case the intake was represented by an acute inhalation, with default ICRP parameter values for occupational exposure (5 μm AMAD; Reference Worker at Light Work). In ICRP Publication 30 UF_6 is assigned to Class D and therefore in ICRP Publication 68 it is assigned to Type F. The magnitude of the intake was assessed using IMBA, but the value of s_r was varied iteratively from its default value of 100 d^{-1} to obtain a better fit (the value of f_r was fixed at 1.0). It has been found in other studies with uranium compounds, including soluble forms such as uranyl nitrate, that the value of s_r is much lower than the ICRP default, typically around 1 d^{-1} (Ansoborlo et al 2001; Hodgson et al 2000, 2001).

A satisfactory fit was found with s_r = 1.5 d^{-1} (Figure A15). In this case three assumptions about the distribution of errors were made:

(A) errors normally distributed, uniform absolute errors

(B) errors normally distributed, uniform relative errors (20%)

(C) errors log-normally distributed, geometric standard deviation = 2 (corresponds to uniform relative errors of 200%). This assumption, which gave the best fit, is suitable for use with measurements reported as being below the limit of detection. Although there are no such measurements in this case, there are in the UF_6 cases reported by Kathren and Moore (Section A3.7), and it was considered desirable to use a consistent approach to all the UF_6 cases.

Note that these three error assumptions provide a range of fits spanning the data (Figure A15). The uniform absolute error assumption (A) fits the first, highest value best. The uniform relative error assumption (B) fits the later, lower values best, and the log-normal error assumption is central. Corresponding estimated intakes were 66, 21 and 32 mg for assumptions A, B and C, respectively.

Figure A15. Fits to urinary excretion data after inhalation of UF_6 (Boback 1975; Case G), with s_r = 1.5 d^{-1}: (A) uniform absolute errors; (B) uniform relative errors; (C) log-normal errors. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at two days is the excretion between one and two days after intake.

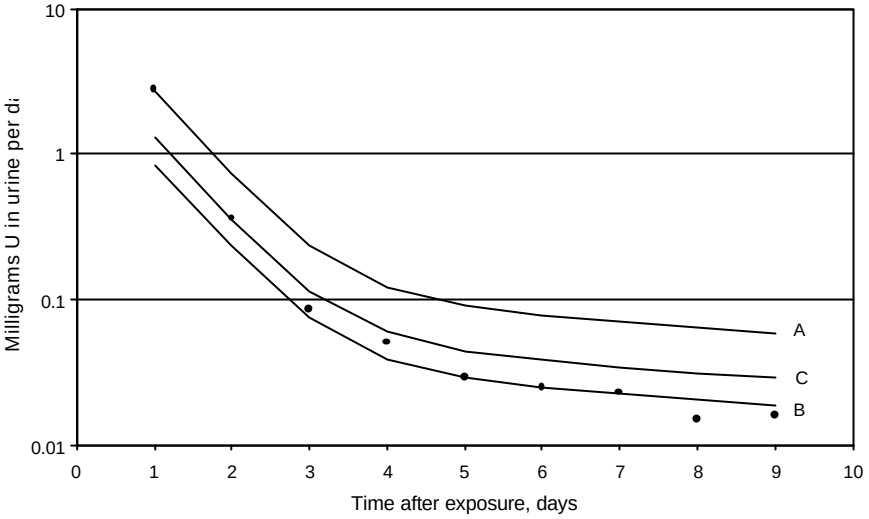
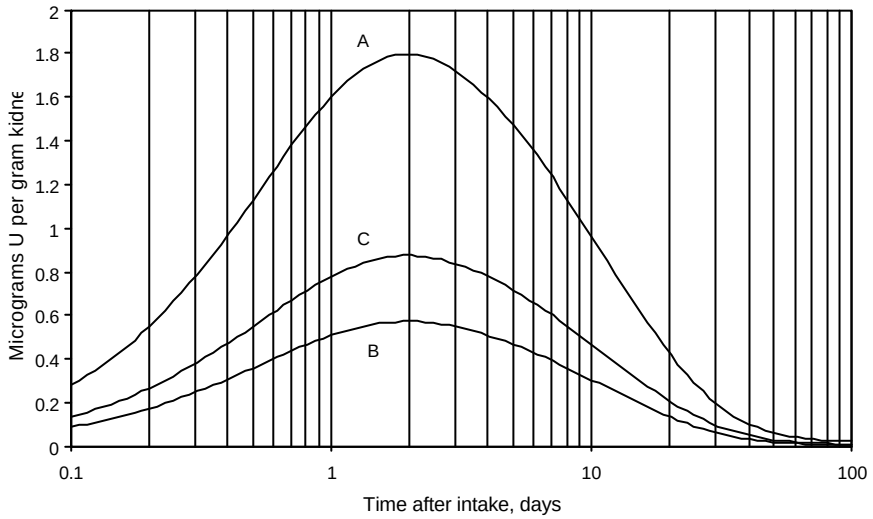


Figure A16 shows the corresponding predicted kidney concentrations. The maximum is predicted to be about 1 µgU/gK.

Figure A16. Predicted uranium concentration in kidneys after inhalation of UF_6 (Boback 1975; Case G) with s_r = 1.5 d^{-1}: (A) uniform absolute errors; (B) uniform relative errors; (C) log-normal errors.



Boback (1975) notes that in this incident 280 employees submitted over 1000 urine samples, most of which were analysed for uranium as well as protein, sugar, white and red blood cells and casts. There were no findings that indicated kidney damage. Over 65 samples contained more than 0.1 µg uranium/litre, and six contained more than 1 µg uranium/litre. Boback gives urinary excretion data for five other employees (H – M) in Tables 8 – 13. Because they are similar to, but somewhat lower than, those for Case G, they have not been assessed here.

Boback also gives data (in Table 7) for employee F, who was exposed to UF_6 in separate incidents. No evidence of kidney damage was found, and again, because the uranium excretion data are similar to, but somewhat lower than, those for Case G, they have not been assessed here.

A3.7 Inhalation of uranium hexafluoride (UF_6): Kathren and Moore (1986), Cases three, four and five (Appendix 1, Section 4.2.1)

An accident in 1944 resulted in the release of about 180 kg of UF_6, which with steam formed a dense cloud of UF_6 and its hydrolysis products (uranium oxyfluoride, UO_2F_2, and hydrofluoric acid, HF), and which enveloped everything within about 100 m (Moore and Kathren 1985; Kathren and Moore 1986). Twenty individuals were exposed to varying degrees, of whom two died and three (Cases three, four and five) were seriously injured. For these three, uranium was measured in urine samples collected between days three and 19 (the accident occurred on day one). Kathren and Moore analysed the data and estimated daily excretion (using 1.4 litres of urine per day; ICRP 1975) for those days when the volume was not given. The results are given in Table A8.

Table A8. Uranium urinary excretion data after inhalation of UF_6 (Kathren and Moore, Cases three, four and five)

	Urinary excretion (mg uranium per day)		
Day[1]	Case three	Case four	Case five
1	–[2]	–	–
2	–	–	–
3	0.00	0.51	0.21
4	0.13	0.36	0.16
5	0.30	0.70	0.00
6	–	–	–
7	–	–	–
8	0.10	0.14	0.00
9	0.19	0.14	0.00
10	0.19	0.10	0.29
11	0.15	0.20	0.22
19	0.07	0.00	0.03

[1]Accident occurred on day one.
[2]Data not available.

Kathren and Moore used the uranium excretion model from ICRP Publication 10 (1968) to estimate the initial lung deposit from the urinary excretion for each case. Whereas the method used here (as implemented in IMBA or LUDEP) is to fit a model excretion function to all the data simultaneously, the procedure used by Kathren and Moore was to estimate the intake from each measurement separately, and then take an average to obtain the best estimate. In this way they estimated initial lung deposits of 36, 38 and 27 mg of uranium for Cases three, four and five, respectively. They also noted, however, that the excretion rate did not show the gradual monotonic decrease with time predicted by the model, or shown by Boback's (1975) Case G (Section 3.6), whose data they analysed in the same way, and for whom they estimated an initial lung deposit of about 5 mg of uranium. Instead the excretion rate fluctuated, especially over the first few days, with low values followed by higher ones, especially for Case five. This was discussed in detail, and the authors considered that the most plausible explanation was temporary retention in a 'metabolic pool or compartment', possibly resulting from pulmonary oedema caused by inhalation of HF.

Kathren and Moore did not estimate the resulting kidney concentrations. However, since their estimates of lung deposits were about six times higher than that of Case G, for whom the maximum kidney concentration was estimated to be about 1 µgU/gK, it is expected that they would be in the range of 5 – 10 µgU/gK.

Intakes were assessed with IMBA using the same parameter values as for Case G (Section A3.6): default ICRP parameter values for occupational exposure (5 µm AMAD; Reference Worker at Light Work), with $f_r = 1$ and $s_r = 1.5\ d^{-1}$. In each of these cases, however, one or more measurements is given as zero. Such points were here taken to be below the limit of detection (LOD), and the errors were assumed to be log-normally distributed with geometric standard deviation = 2. Kathren and Moore (p. 612) note that the technique used for detecting uranium in urine was valid for concentrations of 0.01 – 20 µg uranium/litre (*sic*), presumably meaning 0.01 – 20 mg uranium/litre, because the lowest measurement in Table A8 is 0.03 mg per litre (30 µg uranium/litre). Hence, assuming about 1.4 litres of urine per day, the LOD was taken to be 0.015 mg. Because the measurements fluctuated, the intake was represented by up to four intakes, set at time one day (time of the accident), and at subsequent times before each increase in excretion. IMBA was then used to find the magnitude of the intakes with the maximum likelihood of giving the observed results.

A3.7.1 Case three

Figure A17 shows the fits for:

- one intake (164 mg at one day),
- two intakes (154 and 1.0 mg at one and four days) and
- three intakes (73, 4.9 and 6.5 mg at one, four and 8.5 days).

Figure A18 shows the corresponding predicted kidney concentrations. The maximum is predicted to be about 3 µgU/gK.

Figure A17. Fits to urinary excretion data after inhalation of UF_6 (Kathren and Moore 1986; Case three), with $s_r = 1.5\ d^{-1}$ and log-normal errors. Solid circles represent measurements above the limit of detection. Open square represents the point given as 0.00 and here taken to be below the limit of detection of 0.015 mg per day. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at four days is the excretion between three and four days after intake.

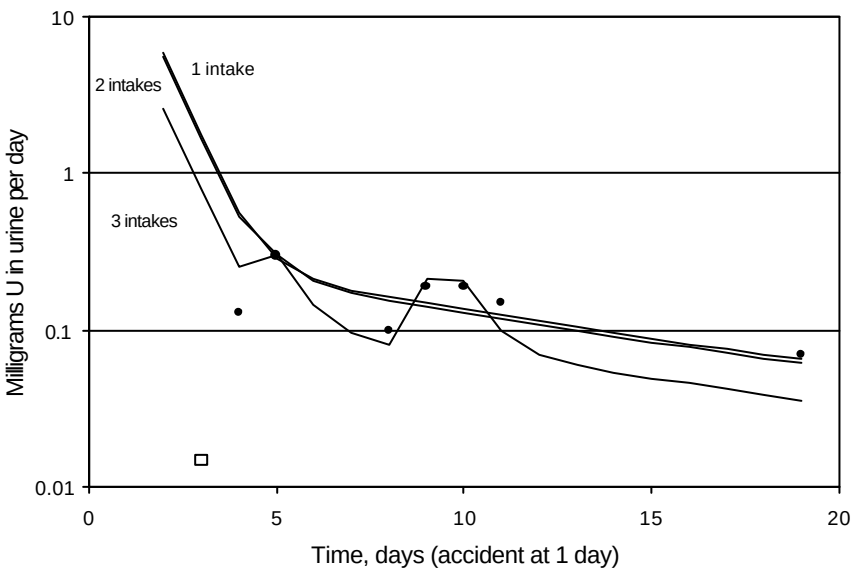
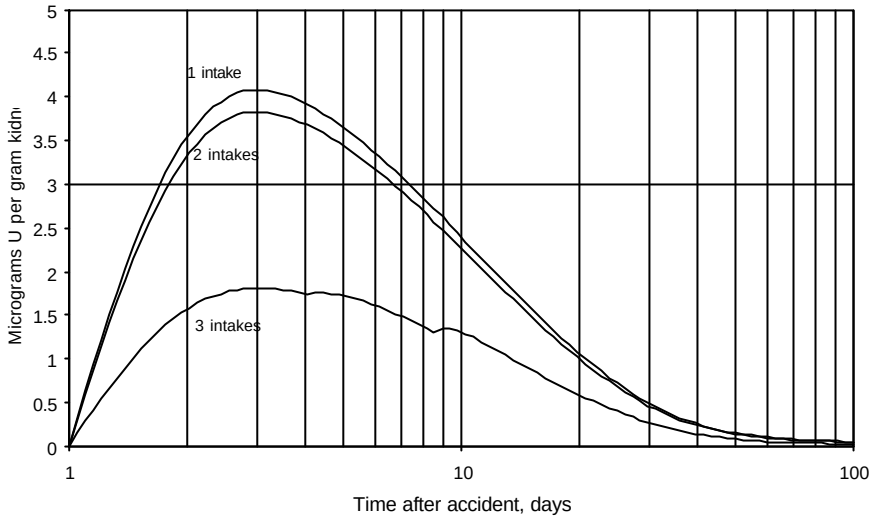


Figure A18. Predicted uranium concentration in kidneys after inhalation of UF_6 (Kathren and Moore 1986; Case three), with s_r = 1.5 d^{-1} and log-normal errors. Horizontal line at 3 µgU/gK.



A3.7.2 Case four

Figure A19 shows the fits for:

- one intake (47.6 mg at one day)
- two intakes (47.2 and 19.8 mg at one and four days)
- three intakes (47.2, 18.3 and 4.2 mg at one, four, and seven days) and
- four intakes (47.2, 17.5, 3.1 and 4.1 mg at one, four, seven and ten days).

Figure A20 shows the corresponding predicted kidney concentrations. The maximum is predicted to be about 1 µgU/gK.

Figure A19. Fits to urinary excretion data after inhalation of UF_6 (Kathren and Moore 1986; Case four), with s_r = 1.5 d^{-1} and log-normal errors. Solid circles represent measurements above the limit of detection. Open square represents the point given as 0.00 and here taken to be below the limit of detection of 0.015 mg per day. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at three days is the excretion between two and three days after intake.

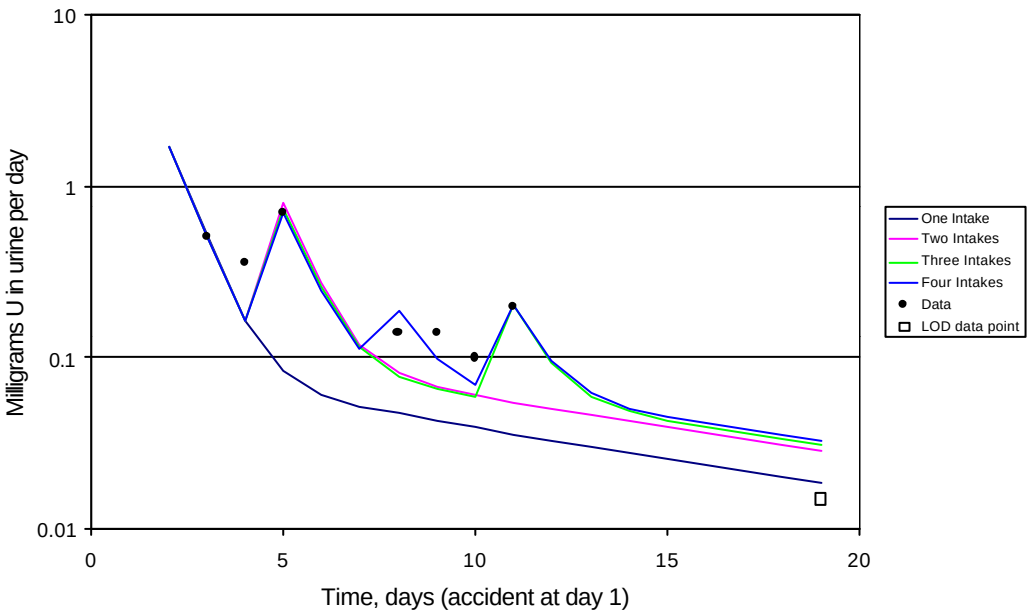
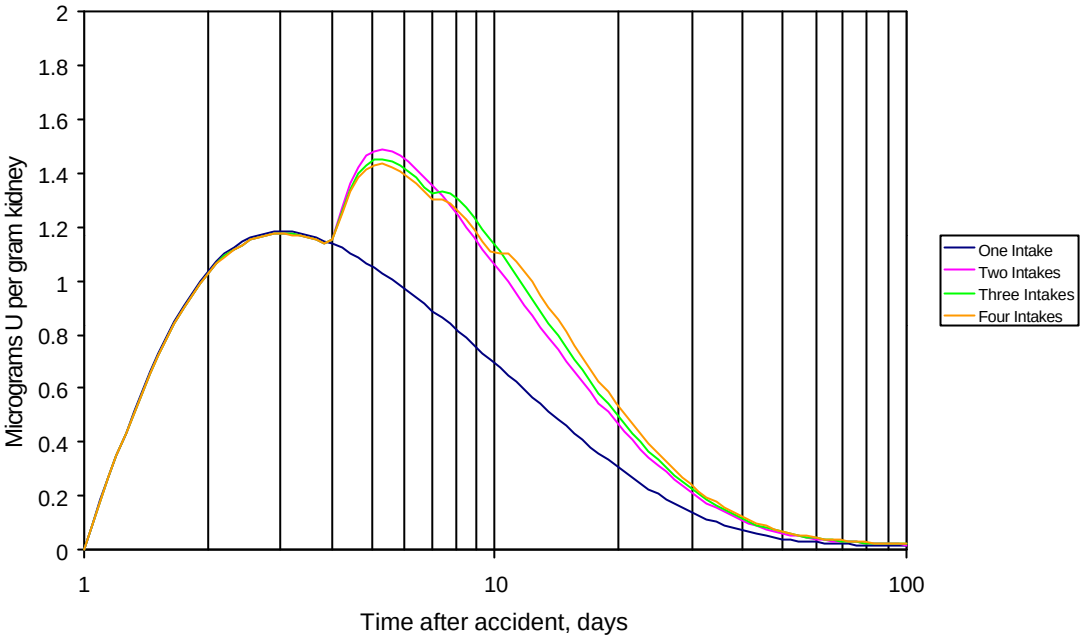


Figure A20. Predicted uranium concentration in kidneys after inhalation of UF_6 (Kathren and Moore 1986; Case four), with s_r = 1.5 d^{-1} and log-normal errors.



A3.7.3 Case five

Figure A21 shows the fits for:

- one intake (161 mg at one day) and
- two intakes (37 mg at one day and 9.1 mg at nine days).

Figure A22 shows the corresponding predicted kidney concentrations. The maximum is predicted to be about 2 µgU/gK.

Figure A21. Fits to urinary excretion data after inhalation of UF_6 (Kathren and Moore 1986; Case five), with s_r = 1.5 d^{-1} and log-normal errors. Solid circles represent measurements above the limit of detection. Open squares represent points given as 0.00 and here taken to be below the limit of detection of 0.015 mg per day. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at three days is the excretion between two and three days after intake

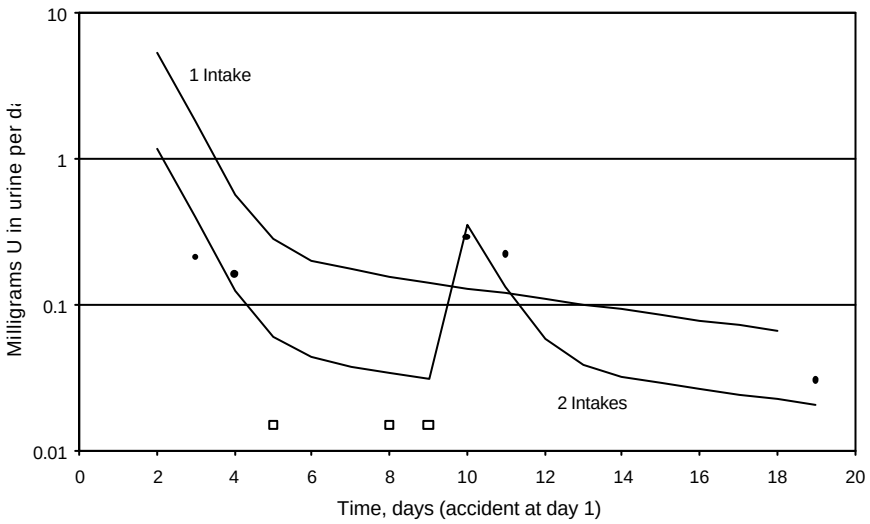


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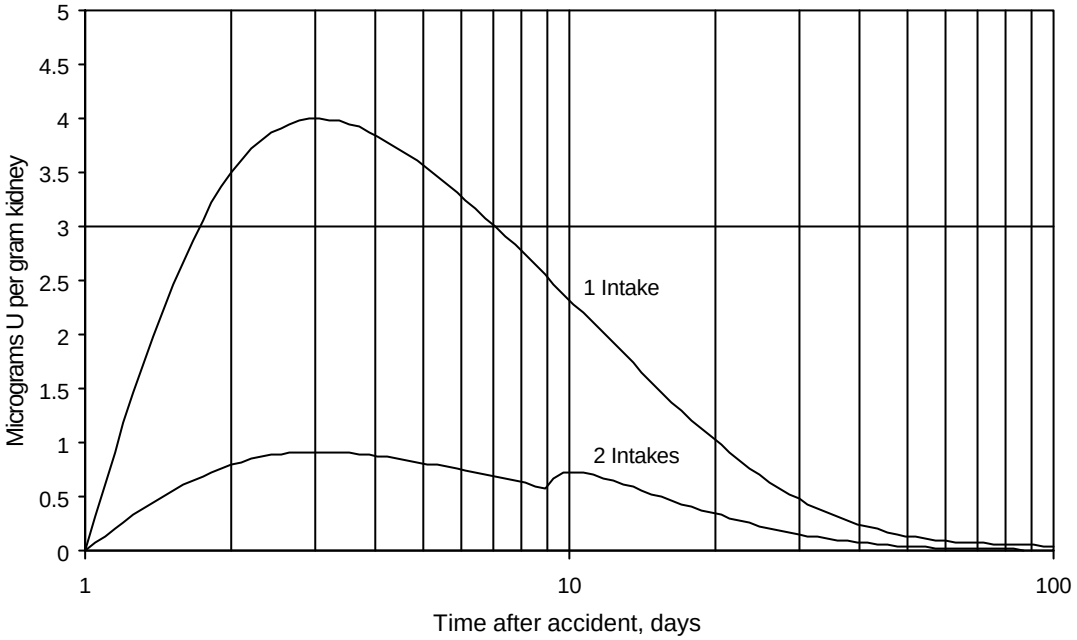
Figure A22. Predicted uranium concentration in kidneys after inhalation of UF_6 (Kathren and Moore 1986; Case five), with s_r = 1.5 d^{-1} and log-normal errors. Horizontal line at 3 µgU/gK.



A3.8 Inhalation of uranium ore concentrates: Boback (1975), Cases A – D

Several workers were exposed to relatively high levels of uranium ore concentrates, during a period when a screw conveyor became blocked and had to be dismantled to clear the blockage. According to Boback (1975), most of the concentrates were sodium or uranium diuranates, but some had been roasted and were mixtures of uranium oxides. Boback gives uranium urinary excretion data for four workers (A – D) in Tables 1 – 4. Only Case D is assessed here, as his data contain the highest concentration in Boback's report (2.85 mg/litre). The other datasets are similar, but with lower values. No signs of kidney dysfunction were found in any of the four subjects. Table A9 gives the uranium urinary excretion data for Case D, converted to mg uranium per day, assuming a urinary output of 1.4 litres per day (ICRP 1975).

Table A9. Uranium urinary excretion data after inhalation of uranium ore concentrates (Boback 1975; Case D)

Day	mg uranium per day	Day	mg uranium per day
1	0.052	92	0.031
26	0.17	164	0.022
27	0.076	173	4.00
28	0.17	174	0.31
29	0.17	180	0.62
43	0.067	183	0.24
44	0.028	242	0.043
45	0.14	296	0.022
64	0.029	304	0.018

Neither sodium nor ammonium diuranate is assigned to a default inhalation class or absorption type in ICRP Publications 30 or 68. Specific absorption parameter values have been derived from the results of experiments in which ammonium diuranate was administered to the lungs of rats.

Results are given in Table A10, and are consistent across the two studies. For the present exercise, rounded central values of f_r = 0.8, s_r = 0.7 d^{-1} and s_s = 0.01 d^{-1} were taken.

Table A10. Absorption parameter values for ammonium diuranate from in vivo studies

Reference	Absorption parameters		
	f_r	s_r, d^{-1}	s_s, d^{-1}
Ansoborlo et al 2001	0.71	0.61	0.019
Hodgson et al 2000, 2001	0.85	0.78	0.005
Defaults (ICRP Publication 68)			
Type F	1	100	-
Type M	0.1	100	0.005
Type S	0.001	100	0.0001

It is clear from the description and data that a series of intakes occurred. It was assumed that an intake occurred before each measurement that was higher than the previous measurement. IMBA was used to estimate the intakes, which were represented by acute inhalations, with default ICRP parameter values for occupational exposure (5 µm AMAD; Reference Worker at Light Work). Log-normally distributed errors were assumed with geometric standard deviation = 2 (corresponds to uniform relative errors of 200%) as in Section A3.6. Initially it was assumed that the intake occurred at the mid-point in time between the measurement and the previous measurement (Fit one in Figure A23). This is the usual assumption made in the absence of information (ICRP 1997). The total intake was predicted to be 580 mg (Table A11). However, in two cases (at about 13 and 80 days) there are predicted peaks in excretion which are not supported by data nearby (Figure A23). To avoid overestimating the kidney concentration, the corresponding intakes were taken to occur at somewhat later times (Fit two in Figure A23). In this case the total intake was predicted to be 325 mg (Table A11).

Table A11. Calculated intakes (Boback 1975; Case D)

Fit one		Fit two	
Day	mg	Day	mg
0	2.3	0	2.8
12.5	240.3	25	8.6
27.5	3.5	27.5	13.7
44.5	6.9	44.5	13.8
78	51.3	90	4.5
168.5	189.3	168.5	195.1
177	85.8	177	86.5
Total	579		325

Corresponding predicted kidney concentrations are shown in Figure A24. The maximum is predicted to be about 3 µgU/gK.

Figure A23. Fits to urinary excretion data after inhalation of uranium ore concentrates (Boback 1975; Case D), with log-normal errors. Intakes listed in Table A11. Note that the data and fits represent one-day integrated urinary outputs, ie the result shown at 27 days is the excretion between 26 and 27 days after the start of the series of intakes.

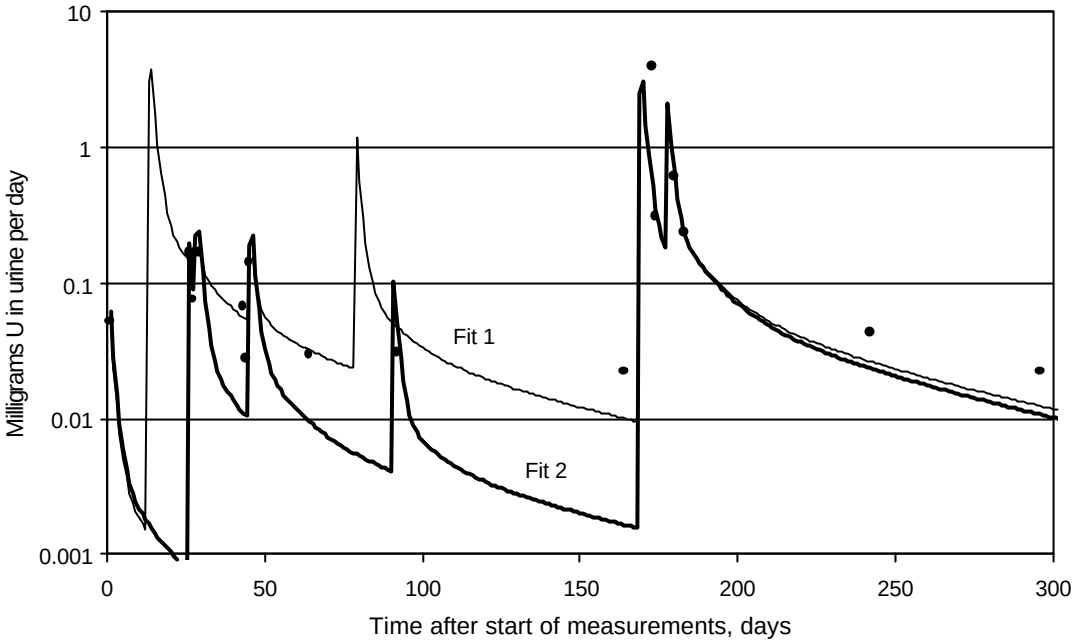
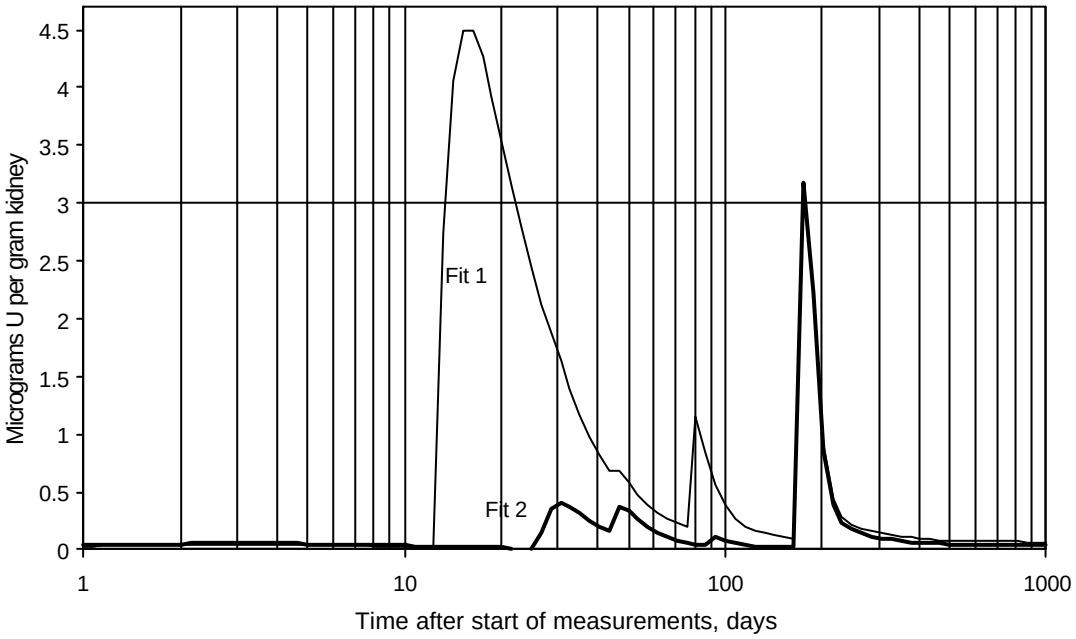


Figure A24. Predicted uranium concentration in kidneys after inhalation of uranium ore concentrates (Boback 1975; Case D). Intakes listed in Table A11.

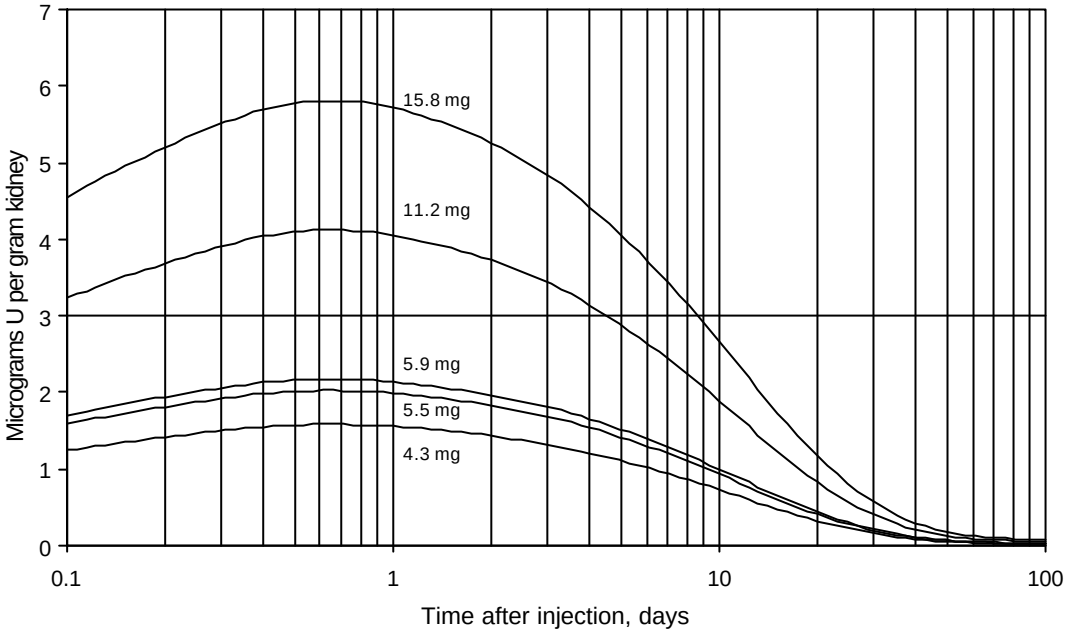


A3.9 Uranyl nitrate injections: Luessenhop et al (1958) (Appendix 1, Section 4.3)

In studies with terminally ill patients, single intravenous injections of uranium nitrate (5.5, 5.9, 4.3, 11.2 and 15.8 mg uranium in Patients I, II, III, IV and V, respectively) produced proteinuria and increased catalase excretion (Luessenhop et al 1958; Berlin and Rudell 1986). Since about 10% of this goes to the kidneys (mass 310 g) the initial (maximum) concentration from injection of 1 mg is

about 0.3 µgU/gK. Hence for injections of 4.3 – 15.8 mg, it would be 1.5 – 5 µgU/gK. LUDEP was used to calculate the concentration as a function of time using the ICRP Publication 69 uranium systemic model. As shown in Figure A25, for the largest injection the concentration is predicted to have a maximum at about 6 µgU/gK, and to remain above 3 µgU/gK for about ten days.

Figure A25. Predicted uranium concentration in kidneys after uranyl nitrate injections of uranium masses indicated (Luessenhop et al 1958).



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