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Biological Characterization of Radiation Exposure and Dose Estimates for Inhaled Uranium Milling Effluents

Final Report

Prepared by A. F. Eidson

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Prepared for
U.S. Nuclear Regulatory Commission

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PREVIOUS DOCUMENTS IN SERIES

Biological Characterization of Radiation Exposure and Dose Estimates for Inhaled Uranium Milling Effluents, Annual Progress Report, March 1979-March 1980, NUREG/CR-1669, LMF-76.

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ABSTRACT

The problems addressed are the protection of uranium mill workers from occupational exposure to uranium through routine bioassay programs and the assessment of accidental worker exposures. Comparisons of chemical properties and the biological behavior of refined uranium ore (yellowcake) are made to identify important properties that influence uranium distribution patterns among organs. These studies will facilitate calculations of organ doses for specific exposures and associated health risk estimates and will identify important bioassay procedures to improve evaluations of human exposures.

Samples of airborne uranium from operating mills and deposition models were used to predict appreciable deposition rates in the upper respiratory tract of workers, if respiratory protection were not used.

Laboratory analyses of commercial yellowcake, and inhalation studies in rats, showed that inhalation of yellowcake aerosols might be considered to be inhalation of variable mixtures of ammonium diuranate and U_3O_8. Studies of yellowcake clearance from rats after wound contamination showed that uranium behavior *in vivo* could not be quantitatively related to chemical composition.

A biokinetic model of retention and excretion of yellowcake inhaled by Beagle dogs was developed. Comparison of the results with available data from human exposures showed that organ burdens in an exposed worker can be estimated from urinary bioassay results and *in vivo* counting, if the chemical composition, or soluble fraction, of the inhaled yellowcake is known.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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It should be emphasized that a listing such as this is rarely comprehensive in acknowledging all the individuals who have made important contributions to the research. In the unnamed category are the many highly skilled animal care, maintenance, shop, administrative, and secretarial personnel whose efforts are essential to the continuation of a productive research project. The authors acknowledge the friendly and helpful participation of the employees and management of the uranium mills studied. Research is performed in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. Research is sponsored by the U. S. Nuclear Regulatory Commission under an interagency agreement via U. S. Department of Energy Contract Number DE-AC04-76EV01013.

EXECUTIVE SUMMARY

The purpose of this project is to provide scientific information to the U. S. Nuclear Regulatory Commission for its consideration in determining radiation protection guides and standards. This will ensure that the standards will protect adequately the health and welfare of mill workers and the public without placing unduly restrictive and expensive regulations on mill operators.

U. S. Nuclear Regulatory Commission guides for worker protection in uranium mills, including requirements for bioassay programs at uranium mills (R. E. Alexander, "Applications of Bioassay for Uranium," WASH-1251, 1974), are based on information derived from accidental human inhalation exposures to single chemical forms of uranium, such as UO_2, U_3O_8, UF_4 or UF_6. Recommended procedures have since been revised to include more recent information, provided by this research program and others, that describes the composition of yellowcake as variable mixtures of ammonium diuranate and U_3O_8, which vary in their solubility properties (U. S. Nuclear Regulatory Commission, "Bioassay at Uranium Mills," Regulatory Guide 8.22, Revision 1, 1988).

Much of the information used in the proposed procedures was derived from studies of yellowcake dissolution conducted in vitro using simulated biological fluids (D. R. Kalkwarf, NUREG/CR-0530, 1979; A. F. Eidson and J. A. Mewhinney, Health Phys., 39, 893, 1980; N. A. Dennis, H. M. Blauer and J. E. Kent, Health Phys. 42, 469, 1982). There is inadequate information available from accidental worker exposures to authentic yellowcake materials to evaluate the proposed procedures. It remains, then, to be shown how such information derived from experiments conducted in vitro can be used to predict the behavior of uranium inhaled by a mill worker.

The most important problem addressed in this project is the protection of uranium mill workers from occupational exposure to uranium, specifically through bioassay programs to assess the adequacy of worker protection. An additional consideration is the assessment of accidental exposures of workers and use of results to re-evaluate and modify protection programs, if necessary.

This final report presents results of research conducted according to a four-phase approach to the problem.

First, limited sampling during milling operations was conducted to determine the properties of aerosols that a worker might inhale. The results (described in paper 1) were related to specific packaging steps and led to predictions of appreciable rates of deposition in the upper respiratory tract for the aerosols, if inhaled. Second, laboratory analyses of yellowcake were used to quantify the range of composition variability of commercial yellowcake and to illustrate the use of such results in interpreting the results of animal studies or human bioassay data. These results are described in papers 2-4.

Third, short-term studies using laboratory rats exposed to selected yellowcake powders were completed. An inhalation study using rats was conducted to compare the behavior of inhaled yellowcake aerosols in vivo with chemical composition and dissolution results obtained in laboratory analyses (paper 5). Results showed that yellowcake can be considered as a mixture of pure uranium compounds.

An additional study designed to investigate the in vivo behavior of yellowcake deposited in a wound (paper 6) showed that retention and clearance were qualitatively related to yellowcake solubility, but the behavior of subcutaneously implanted yellowcake could not have been quantitatively predicted from knowledge of its chemical composition or in vitro dissolution rate, as could the retention of inhaled yellowcake. An additional study (paper 7) showed, for the first time, that 3 to 5 days of acclimation of laboratory rats to cages are required before valid uranium nephrotoxicity results can be obtained.

In the fourth phase, a study of yellowcake aerosols inhaled by Beagle dogs (paper 8) was conducted. Distribution, retention, excretion data, and a biokinetic simulation model were used to compare the results with available data from human exposures. The results showed that dose estimates should include knowledge of the chemical composition, or soluble fraction, of uranium to estimate organ burdens from bioassay results.

Uranium mills are identified alphabetically in this project. Identifying letters were assigned to each mill (Mills A through F) in the order we obtained their products and do not relate to the name of the mill, its location, or the parent company.

1. PREDICTED INHALATION DEPOSITION RATES OF URANIUM YELLOWCAKE AEROSOLS SAMPLED IN URANIUM MILLS

PRINCIPAL INVESTIGATORS
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Abstract — Uranium aerosols generated during normal yellowcake packaging operations were sampled at four uranium mills. Samplers located in the packaging area were operated before, during and after drums of yellowcake were filled and sealed. Median aerosol concentrations in the packaging areas ranged from 0.04 μg U/L to 0.34 μg U/L. The aerosols were heterogeneous and included a broad range of particle sizes such that 14% to 76% (by weight) of the airborne uranium was in particles with aerodynamic diameters greater than 12 μm. Air concentrations and particle size distributions varied with time as larger particles settled or more aerosols were suspended. Aerosol characteristics could often be related to individual packaging steps. The results show that appreciable amounts of airborne uranium would be expected to deposit in the nasopharyngeal compartment of the respiratory tract if inhaled by a worker not wearing respiratory protection.

Commercial uranium ore processing schemes used in the U. S. differ among mills. However, there are process steps common to all mills: (1) ore crushing and grinding, (2) ore leaching, (3) uranium recovery from leach solutions and (4) drying and packaging of yellowcake. The dustiest operations are crushing and grinding of ore and the yellowcake drying and packaging operations. These have received the greatest attention with regard to minimizing airborne uranium.

Because inhalation is the most common mode of occupational exposure at uranium mills, it is necessary to sample uranium aerosols produced during milling operations to allow predictions of their potential for inhalation by workers. The objectives of the sampling studies were to characterize particle size distributions of yellowcake aerosols produced under normal milling conditions and to relate the results to potential exposure of workers in the packaging operation if adequate respiratory protection is not used.

Sampling efforts described here concentrated on aerosols produced during the final drying and packaging processes, since airborne yellowcake dust contains uranium in the most concentrated and refined form and represents the greatest potential toxicity if inhaled.

Packaging operations at four mills were sampled. Three mills employ an acid leach process and the fourth uses an alkaline leach process. The final process at all four mills includes precipitation of yellowcake, drying the precipitate to a specified moisture content and packaging as a powder in 55 gallon drums, each containing approximately 1000 pounds (450 kg) of yellowcake.

MATERIALS AND METHODS

Yellowcake Packaging

The sequence of steps for yellowcake packaging is common to all four mills sampled. They are:

1. No Activity - includes times when no other activity is occurring or has occurred for at least two hours prior. Generally, the mill was shut down for maintenance or all available dried yellowcake was packaged during a previous shift. Workers are generally not present in the packaging area during this time.
2. Drum Loading - occurs when the drum is in place as shown in Figure 1.1 with yellowcake falling into the drum and safety ventilation operating. The duration of drum loading can vary from a few minutes to several hours depending on the drying rate of the drier and the inventory of dried yellowcake in the hopper. When there is a large inventory of

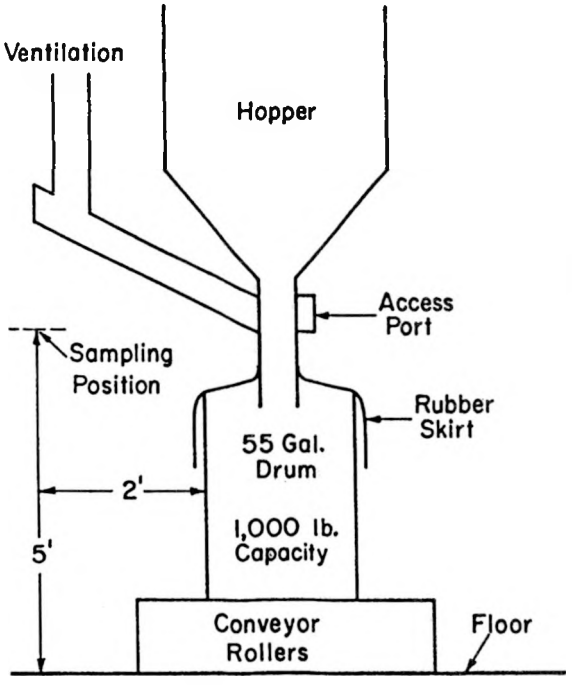

Figure 1.1 Samplers were located in the packaging area to simulate the location of the worker. The figure shows typical packaging equipment, although more than one drum can be loaded simultaneously at some mills.

dried yellowcake in the hopper, the operator fills drums relatively rapidly until the hopper is emptied. In other circumstances, the drum can stand while yellowcake falls into the drum as it is dried.

The amount of time an operator spends in the packaging area varies. During times when the drum is filling slowly, the operator often works at other tasks and intermittently monitors the progress of the loading. At other times, he is in the packaging area constantly while filling drums more rapidly.

Two of the mills loaded more than one drum simultaneously while we sampled. The drums were filled at different rates and the aerosols were probably mixed between packaging steps.

3. Drum Uncovering - occurs when the filled drum is removed from beneath the protective ventilation shown in Figure 1.1 and rolled a few feet away. At some mills, the drum is vibrated to compact the yellowcake prior to uncovering the drum. The drum then remains uncovered for a few minutes while the operator (wearing a respirator) prepares to seal the drum.
4. Powder Sampling - occurs when the operator takes a sample (approximately 100 g) of yellowcake to analyze for moisture content. This step usually requires less than one minute per drum.
5. Lid Sealing - occurs when the operator places a lid on the drum and seals it with a metal band and bolt. This step requires approximately five minutes. The operator is necessarily present during steps 3, 4 and 5.
6. Average of Sampling and Sealing Steps - after the drum is uncovered, a yellowcake sample is taken and the lid is sealed within 10 to 20 min (steps 3, 4, and 5) such that the resulting aerosols include a mixture of particles suspended during each of the separate steps. Aerosol sampling during separate steps was sometimes possible, however. At one mill, four drums were loaded in succession and powder samples were taken from each before they were all sealed; and it was possible to sample aerosols generated by yellowcake sampling alone (step 4). When the drums were later sealed, an additional set of samplers was run to sample aerosols generated in the drum sealing step (step 5).

7. Other Activities - include hosing with water to clean the area, maintenance and possible yellowcake releases. Hosing the packaging area is a routine operation at mills. Aerosol sampling during this operation was done only once. Maintenance operations cannot be generalized. They can require from an hour to a day or more of worker time depending on the nature of the problem. We sampled during a maintenance operation only once and cannot relate our results to a general worker exposure. We sampled during one small release of yellowcake when approximately 50 g of yellowcake fell from the inside of the hopper as a drum was being removed. As with maintenance operations, each occurrence is different and generalizations cannot be made.

Sampling Methods

Lovelace multijet impactors (Ref. 1.1), point-to-plane electrostatic precipitators (Ref. 1.2), and membrane filters were located in the packaging area to simulate the location of a worker standing near the drum loading station or nearby where the lid was applied. The location of the samplers shown in Figure 1.1 is representative of sampling at all four mills. The sampling position simulated the location of a worker performing packaging steps that require constant attention and require respiratory protection but continue for only a few minutes, e.g., applying the lid and sealing the drum. Other packaging steps, such as drum loading, do not necessarily require that the operator be in this location or in the packaging area. As such, these samplers represent a worst case of a worker standing at this work station during the entire operation.

Uranium Analysis

Aerosols collected on membrane filters were heated in a muffle furnace for 16 h at 550°C. The residue was dissolved in 10 mL of 16 M HNO_3, evaporated to dryness and heated for 16 h at 550°C. The residue was dissolved and diluted to the desired volume with 2 M HNO_3. Aerosols collected on glass substrates in cascade impactors were removed by washing with chloroform, dried and processed as above. Uranium content was determined by reflectance fluorimetry of a fused NaF-LiF salt pellet containing an aliquot of yellowcake dissolved in 2 M HNO_3 (Ref. 1.3).

Data Reduction

Data from cascade impactor measurements were analyzed by plotting mass as cumulative probability versus the stage effective cutoff aerodynamic resistance diameters (D_{ar}; Ref. 1.1). Cumulative mass distribution plots of cascade impactor data generally did not correspond to lognormal particle size distributions (Figure 1.2). Figure 1.2 is representative of plots that departed from a lognormal distribution in the larger and smaller particle size ranges of the curve. The fraction of airborne uranium contained in particles > 20 μm aerodynamic diameter (D_{ar}) was estimated using the results of filter and impactor samplers by a successive approximation method (Appendix 1A). The mean and standard error for the percentages of uranium in particles > 20 μm was 17% ± 3% for 18 estimates. The upper size limit for particles deposited on stage 1 of the Lovelace impactors was taken to be 20 μm D_{ar} in the respiratory tract deposition rate calculations.

The nonlinear curve and the collection of more than half of the uranium on the first impactor stage (Figure 1.2) shows that the aerosol was heterogenous with a broad range of particle sizes and could not be represented by a single lognormal function. Results were interpreted by classification of the percentages of airborne uranium associated with particles of 0-1 μm, 1-3 μm, 3-6 μm and 12-20 μm aerodynamic diameter. The size classifications were chosen to correspond to regions of the respiratory tract where deposition of that particle size range would predominate (Refs. 1.4, 1.5). According to this model, particles in the 0-1 μm D_{ar} size range deposit preferentially in the pulmonary compartment, but with significant deposition in the nasopharyngeal compartment. Particles in the 1-3 μm D_{ar} size range deposit significantly in the pulmonary and nasopharyngeal compartments, but deposition in the latter compartment predominates. Sixty to 80%

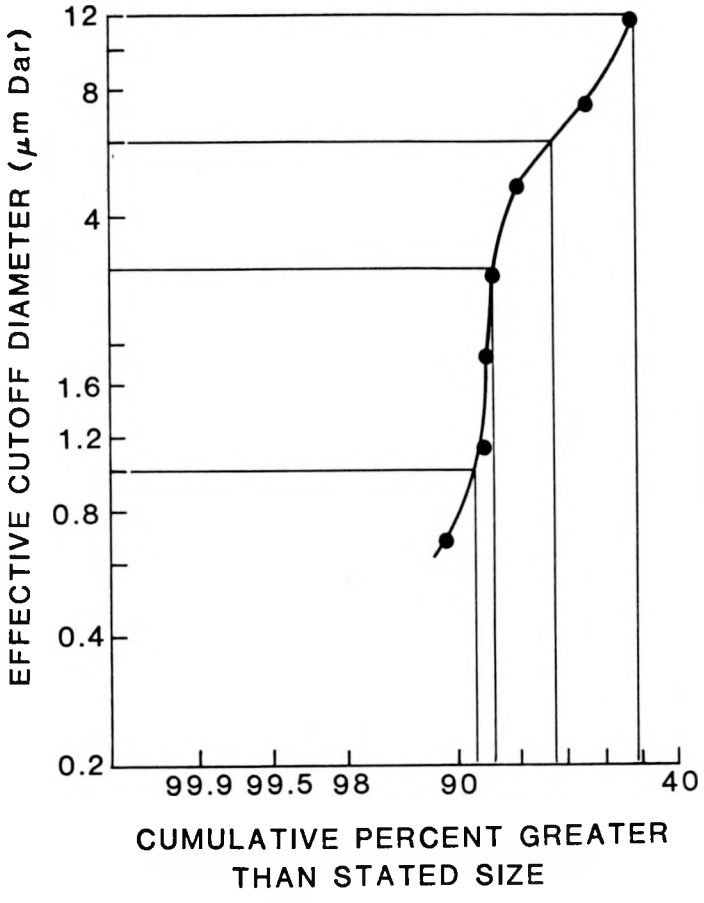

Figure 1.2 Cumulative mass probability plot of yellowcake aerosols sampled by a cascade impactor during yellowcake packaging operations at one mill.

of particles between 3 and 6 μm D_{ar} are expected to be deposited in the nasopharyngeal compartment and < 8% of the particles 6 to 12 μm D_{ar} in size range are expected to be deposited in the pulmonary compartment. Particles in the 12 to 20 μm D_{ar} size range deposit primarily in the nasopharyngeal compartment. The expected deposition fraction in the tracheobronchial compartment is approximately 8% or less for all particles in the 0.2 to 20 μm D_{ar} size range.

The percentages of particles in the five size classes of yellowcake aerosols were determined from the cumulative mass distribution plots as shown by the horizontal and vertical lines in Figure 1.2 and are summarized in Table 1.1.

The expected deposition rate in each compartment of the respiratory tract was estimated by the equation:

$$R_{s,c} = F_{s,c} \times F_{a,s} \times C_a \times V \times f \qquad (1)$$

where

$R_{s,c}$ is the expected deposition rate of particles of size range s (Table 1.2) in compartment c of the respiratory tract (Ref. 1.4), in μg U/min,

$F_{s,c}$ is the deposition fraction of aerosol particles of size s in compartment c,

$F_{a,s}$ is the fraction of airborne uranium in size range s (Table 1.1)

C_a is the airborne uranium concentration in μg U/L,

V is the tidal volume in liters per breath (1.450 L for normal breathing) and

f is the breathing frequency in breaths/minute (15 min for normal breathing, Ref. 1.4).

Table 1.1 Characteristics of aerosols required for estimating respiratory tract deposition of uranium produced in uranium yellowcake packaging operations

Packaging Step	Airborne Uranium Concentration (μg/L)		% Airborne Uranium < 20 μm D_{ar}[a]				
			< 0-1 μm	1-3 μm	3-6 μm	6-12 μm	12-20 μm
No Activity	Median	0.040	14	23	17	23	21
	Maximum	0.051	19	35	28	28	32
	Minimum	0.027	10	14	12	16	14
Drum Loading	Median	0.17	7	12	12	17	46
	Maximum	1.4	22	42	20	31	73
	Minimum	0.021	0.2	8	5	6	26
Powder Sampling	Median	0.081	7	10	9	10	64
	Maximum	0.10	16	17	20	22	76
	Minimum	0.018	4	5	5	7	32
Lid Sealing	Median	0.34	3	8	11	15	61
	Maximum	0.639	14	17	20	26	72
	Minimum	0.11	0	2	6	11	28
Average of Sampling and Sealing Steps	Median	0.051	7	12	9	15	49
	Maximum	1.4	42	37	21	21	73
	Minimum	0.021	0.1	2	5	5	19
Small Spill	Median	2.9	0.5	5	11	20	65
	Maximum	3.0	1	6	13	33	74
	Minimum	1.9	0.3	3	9	13	49
Hosing Area	Single Measurement	0.12	1	5	9	13	72
Repair Conveyor Track	Single	0.10	17	25	14	30	14

[a]Aerodynamic resistance diameter.

Values of $F_{s,c}$ were calculated using a computer program based on the aerosol deposition model described in ICRP Publication 30 (Ref. 1.6). Deposition fractions were calculated for particles of 0.5 μm, 2 μm, 4 μm and 16 μm D_{ar}. These sizes are the linear midpoints of the five size ranges shown in Figure 1.2.

The total expected deposition rate for the respiratory tract is then:

$$R_{total} = \sum_{s=0.5\ \mu m}^{16\ \mu m} (R_{s,NP} + R_{s,TB} + R_{s,P}) \qquad (2)$$

where NP, TB and P indicate the nasopharyngeal, tracheobronchial and pulmonary compartments of the respiratory tract, respectively.

It was possible at one of the four mills to relate changes in particle size distributions to the different packaging steps outlined above. The changing particle size distributions were shown by data from cascade impactors operated according to a staggered schedule (Figure 1.3). The percentages of uranium in the four size classes of the aerosol sampled by each impactor were plotted versus time after the drum was uncovered and removed from the hopper. Points were plotted on the horizontal axis at the midpoint of each impactor's sampling duration (denoted by horizontal bars). The vertical bar indicates the precision of the percentage estimates as the coefficient of variation of the mean of values measured by three impactors operated simultaneously.

Table 1.2 Estimated respiratory tract deposition rates of uranium dusts during yellowcake packaging

Packaging Step		Estimated Deposition Rates in Respiratory Tract Compartments (μg U/min) NP	TB	P	Total
No Activity	Median	0.56	0.061	0.11	0.73
	Maximum	1.0	0.11	0.20	1.3
	Minimum	0.26	0.028	0.049	0.33
Drum Loading	Median	2.6	0.21	0.29	3.1
	Maximum	40	3.7	6.2	50
	Minimum	0.17	0.012	0.016	0.20
Lid Sealing	Median	6.0	0.41	0.44	6.9
	Maximum	16	1.3	1.8	19
	Minimum	0.97	0.065	0.055	1.1
Average of Sampling and Sealing Steps	Median	0.80	0.061	0.084	0.95
	Maximum	38	3.9	8.0	50
	Minimum	0.12	0.0080	0.0075	0.14
Small Spill	Median	55	3.6	3.2	62
	Maximum	71	4.8	4.3	80
	Minimum	27	1.7	1.4	30
Hosing Area	Single Measurement	2.3	0.14	0.12	2.6
Repair Conveyor Tract	Single Measurement	1.4	0.16	0.30	1.9

NP = nasopharyngeal
TB = tracheobronchial
P = pulmonary

The points plotted at t = 0 min represent the particle size distribution sampled for 26 min prior to removal of the drum from the hopper. This particle size distribution was typical for aerosols sampled while the covered drum was loaded under the hopper. After the drum was uncovered, a lid was placed over the drum, hammered into place, and sealed with a metal band. During this time the aerosol contained primarily large particles with less uranium in 6 to 12 μm and smaller particles; and with < 1% in the 0 to 1 μm size class. This change did not reflect preferential removal of small particles, but the mechanical suspension of larger particles by hammering the lid on the drum. After the drum was sealed, the aerosol changed to one more similar to that observed at t = 0 min.

The changes in aerosol characteristics with different packaging steps cannot always be so simply related. Drums are often filled simultaneously or in rapid succession so that yellowcake aerosols are continuously resuspended. In addition, there were drafts in some packaging rooms and mixing of aerosols caused by the worker moving around the room.

The aerosols associated with each of the packaging steps were grouped for all mills sampled. Table 1.1 shows the aerosol concentrations that occurred during each of the packaging steps listed above that could be sampled separately. Table 1.1 also summarizes the impactor data expressed as the percentage of airborne uranium concentration within the five categories described above. The results of samplers run during steps 3, 4 and 5 combined are entered as the "average of sampling and sealing". Figure 1.4 summarizes the particle size distributions for aerosols associated with the average of sampling and sealing steps. The combined data from individual impactors were plotted as cumulative mass probability plots (Figure 1.2) and the maximum, minimum and median

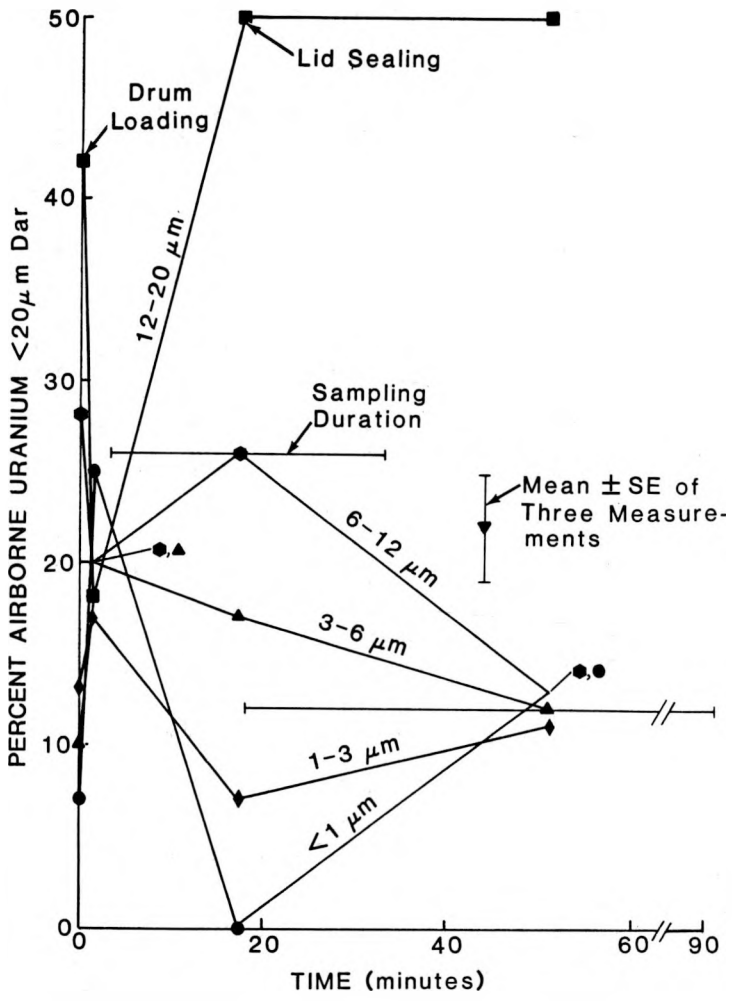

Figure 1.3 Variation of particle size distribution of aerosols produced during packaging of a drum at one mill.

percentages were plotted for each impactor stage. Each curve in Figure 1.4 does not represent a separate impactor but the maximum, minimum and median of the data points. Figure 1.4 also shows individual data points from three representative impactors. The figure shows the median and range in particle size distributions for aerosols that the operator might inhale if not wearing respiratory protection while sealing a filled drum.

Deposition rates estimated using Eqs. (1) and (2) are shown in Table 1.2. Since the worker must be present during the average of sampling and sealing steps, the estimated deposition rates in each respiratory tract compartment and the total are shown in Figure 1.5 and are compared with those for aerosols produced during periods of drum loading, powder sampling and no activity.

Each group of predicted deposition rates was estimated using the median and range of all aerosols measured in the four mills for the specified activity (Table 1.1). Values in Table 1.2 do not estimate deposition of a single aerosol, but they represent median estimates within the ranges shown. An exposure of a worker (without respiratory protection) to an aerosol present in the four mills during a period of no activity was estimated to result in a median deposition rate in the nasopharyngeal compartment of 0.56 μg U/min within a range of 0.26 to 1.0 μg U/min. Deposition in the tracheobronchial compartment was estimated to range from 0.028 to 0.11 μg U/min and deposition in the pulmonary compartment was estimated to be from 0.049 to 0.20 μg U/min.

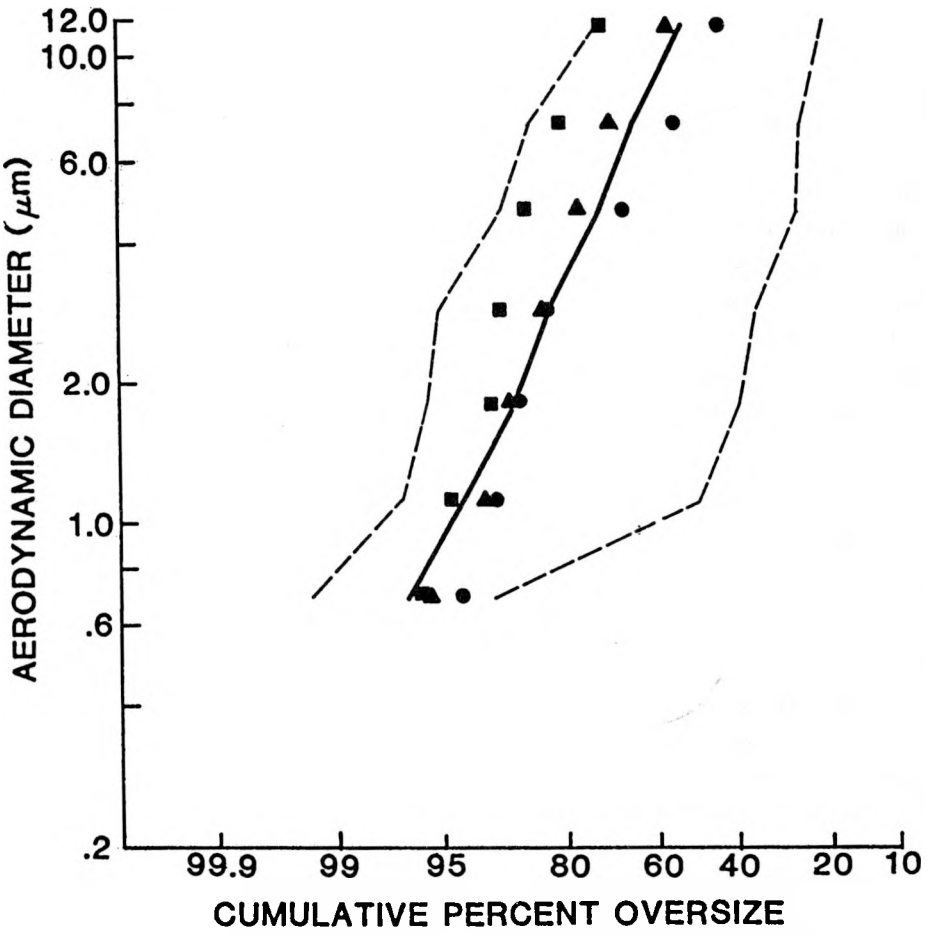

Figure 1.4 Cumulative mass probability plots of yellowcake aerosols generated during the average of sampling and sealing steps at four mills. Individual points indicate data from three separate impactors. Median percentages of airborne uranium on each cascade impactor stage are connected by the solid line. The ranges for each stage are connected by dashed lines.

Thus, the median total deposition rate in the respiratory tract was estimated at 0.73 μg U/min within a range of 0.33 to 1.3 μg U/min.

When there was no activity in the packaging area, the median airborne concentration was lowest and particles < 6 μm D_{ar} predominated. Although the particle size distributions were more uniform than for later steps, the deposition rate in the nasopharyngeal compartment would be expected to predominate.

During the drum loading steps, the median concentration increased slightly and the range increased considerably, although the range included values of the no activity step. The particle size distribution shows that larger particles were generated during drum loading.

The data for powder sampling indicate that the concentration was more similar to the lower concentrations of aerosols measured during periods of no activity than during the drum loading or lid sealing steps. These data were taken while one operator sampled the yellowcake and the aerosol sampled might reflect his individual work style rather than represent this operation at all mills. Estimated deposition rates indicate that reaching into an open drum to sample yellowcake need not be a uniquely hazardous operation.

During lid sealing, the median concentration was higher than during the drum loading or other packaging steps, but within the ranges for the other steps. There was also an increased suspension of larger particles and deposition in the nasopharyngeal compartment would be expected to predominate.

DISCUSSION

Aerosols sampled during the average of sampling and sealing steps represent a weighted average of all the aerosols generated during the time between removing a filled drum from the hopper and sealing with the lid. As expected, ranges in concentrations and particle size distributions (Table 1.1) were greatest for this combination of aerosols. These data might serve as a limiting case for potential worker exposure in normal packaging operations because the worker is constantly present and they show the most variable predicted deposition rates for the routine packaging steps. As such, they estimate a median total deposition rate for a worker without respiratory protection of 0.95 μg U/min, within a range of 0.14 to 50 μg U/min.

Three nonroutine operations were sampled. Data measured during the small spill are probably not representative of all possible accidents. The aerosol concentration was higher, but not greatly above the concentration range for other activities, and the airborne uranium was in larger particles as expected. Hosing the packaging area is a routine but less frequent operation. Aerosols generated (Table 1.1) probably included liquid droplets that contained partly dissolved yellowcake. Note the predominance of large particles. The conveyer track repair step (Table 1.1) was nonroutine maintenance work which was similar to that produced during the drum loading and powder sampling steps.

It is difficult to estimate the duration of worker exposure during packaging operations. The drum loading step required the operator to be present when the drums were loaded in rapid succession to empty a filled hopper. At other times when drums were filling slowly, there was no general pattern to the operator's activities. The operator must work close to the drum during the powder sampling and lid sealing steps. Therefore, results were expressed as expected deposition rate rather than total expected exposure.

Estimated deposition rates (Table 1.2, Figure 1.5) show deposition in all respiratory tract compartments. Although normal breathing was assumed, deposition rates during exertion might be used in Eqs. (1) and (2), if desired. Deposition rates in the nasopharyngeal region contributed the greatest fraction of the total expected deposition rate for all steps considered, within the range of concentrations observed. This was caused by the predominance of larger particles in airborne yellowcake dusts that masked the differences in deposition efficiency among the respiratory tract compartments.

Biological Implications for Man

The variability in concentration and particle size distribution of aerosols generated during yellowcake packaging is reflected in the ranges of expected deposition rates (Table 1.2). Even within this variability, deposition in the nasopharyngeal compartment is expected to predominate. Generally, absorption of uranium deposited in the pulmonary compartment is considered to be most significant as the result of greater absorption efficiency in lung tissues; and uranium deposited in the nasopharynx is considered to clear rapidly and be excreted via the gastrointestinal tract with low absorption efficiency (Ref. 1.4). However, the availability of a uranium compound deposited in the nasopharynx for absorption is determined by its solubility. Research (paper 4, this report) has shown that yellowcake from commercial mills can be predominantly ammonium diuranate, a soluble (Class D) form (Ref. 1.4). The predominant deposition in the nasopharynx indicates that absorption of soluble uranium compounds through the nasopharyngeal tract tissues might become appreciable because of the greater fraction of yellowcake deposited there.

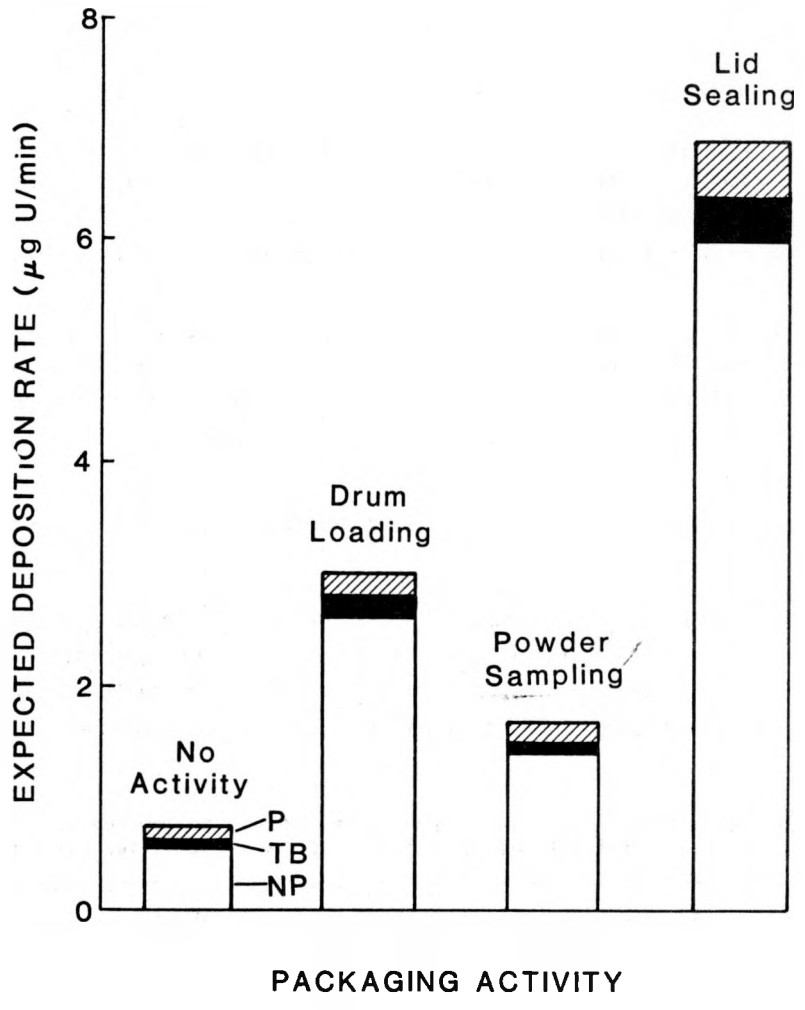

Figure 1.5 Median estimated deposition rates in the nasopharyngeal (NP), tracheobronchial (TB) and pulmonary (P) compartments of the respiratory tract for a worker without respiratory protection hypothetically exposed during periods of no activity, drum loading, powder sampling and lid sealing steps.

APPENDIX

Estimation of the Percentage of Airborne Uranium Contained in Particles > 20 μm D_{ar}

The percentage of airborne uranium contained in particles greater than any given size can be estimated using a cascade impactor to measure the particle size distribution and filter samplers to measure airborne concentration without respect to particle size. An example of the iterative procedure is given below for one impactor and filter sampler pair operated simultaneously in the same location (Table 1.A).

The concentrations of uranium in particles < 12 μm D_{ar} (C_i, μg U/L) were calculated using the total uranium deposited on each of the stages 2-8 of the impactor and the volume of air sampled (Table 1.A). The total airborne concentration (C_T) was calculated from the filter sampler. The percentage of airborne uranium in particles less than 12 μm D_{ar} is

$$A_i = \frac{100\ C_i}{C_T}, \text{ where } i = \text{the stage number 2 through 8.} \qquad \text{(A1)}$$

The percentages [Eq. (A1)] on each of stages 2-8 were calculated (Column 4, Table 1.A) and plotted as a cumulative mass distribution vs. stage effective cutoff diameter. A straight line was fitted by hand to the points and extrapolated to an effective cutoff diameter of 20 μm D_{ar} (Figure 1.A). The extrapolation estimates that E = 1.2% of airborne uranium was contained in particles > 20 μm D_{ar}.

Table 1.A Results of simultaneous sampling of airborne yellowcake dust using Lovelace multijet cascade impactor and membrane filter samplers

Stage Number	Effective Cutoff Diameter (μm D_{ar})	Uranium Mass (μg)	Initial Estimate	First Iteration
1	11.7	13.9	-	S_1 = 11.7[a]
2	7.3	2.0	1.9	13.6
3	4.7	1.3	3.1	14.8
4	2.9	1.3	4.3	16.0
5	1.8	0.88	5.1	16.8
6	1.1	1.1	6.1	17.8
7	0.68	1.2	7.2	18.9
8	0	0.54	7.7	19.4

Total uranium mass = 22.2 μg
Flow rate = 18.8 L/min
Sampling time = 25 min
Volume - 470 L

Membrane Filter Sampler

Uranium mass = 5.37 μg
Flow rate - 1.0 L/min
Sampling time - 24 min
Airborne uranium concentration = 0.23 μg U/L

[a]Calculated from Eq. (A2).

The amount of uranium deposited on stage 1 contained in particles between 12 μm and 20 μm D_{ar} was estimated using the above extrapolated value and the values given in Table 1.A according to the equation:

$$S_1 = P-E \qquad (A2)$$

where P is the percentage of airborne uranium concentration > 12 μm, E is the extrapolated percentage > 20 μm (above) and S_1 is the percentage of airborne uranium on stage 1 that is > 12 μm but < 20 μm. For the example shown in Table 1.A.

$$P = \frac{13.9\ \mu g\ U}{470\ L \times 0.23\ \mu g\ U/L} \times 100 = 12.9\% \qquad (A3)$$

and S_1 = 12.9% - 1.2% = 11.7% (see Figure 1.A). The cumulative percentages for stages 1-8 were recalculated using the estimated value for S_1 (Table 1.A, Column 5) and the data were plotted as shown in Figure 1.A. A straight line was fitted to the data points and extrapolated giving a new estimate of the percentage of uranium > 20 μm D_{ar} (E = 10.5%, Figure 1.A). The new value of E = 10.5% was used to calculate a new value of S_1 [Eq. (A2)] and the data were replotted (Figure 1.A). Successive iterations were used until estimates of E converged to a value 6% < E < 7%. The percentage of airborne uranium contained in particles > 20 μm D_{ar} was estimated to be 6.5% for the aerosol sampled by the filter and impactor samplers shown.

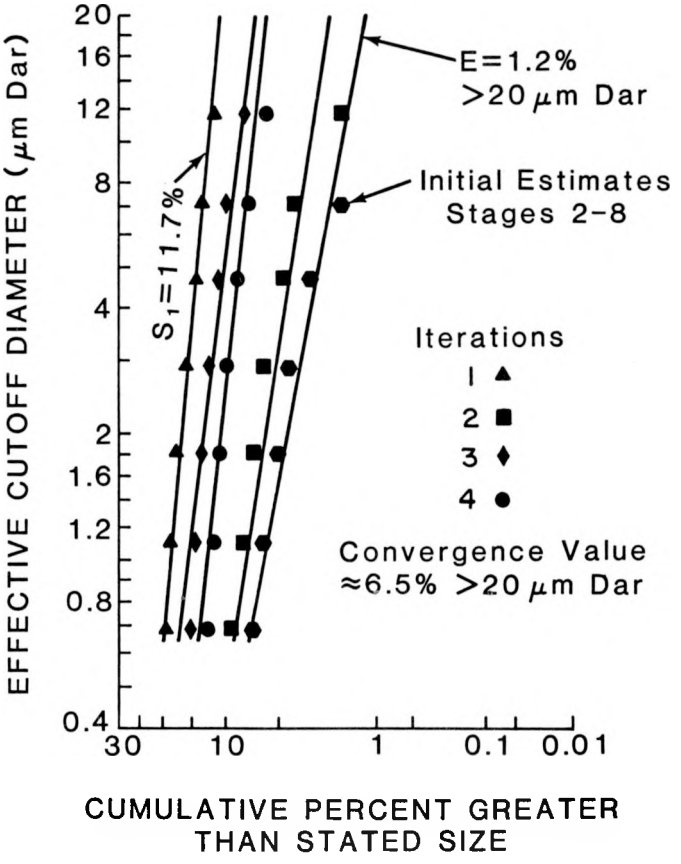

Figure 1.A Estimation of the percentage of airborne uranium contained in particles > 20 μm D_{ar}.

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2. QUANTITATIVE DETERMINATION OF URANIUM IN BIOLOGICAL SAMPLES

PRINCIPAL INVESTIGATORS
A. F. Eidson
D. H. Gray
R. A. Guilmette

Abstract — Laser phosphorimetry has been applied to uranium assay of generally nonbiological matrices, except for urine and vegetation. The method was expanded to allow assay of a wider variety of biological matrices using a Scintrex UA-3 uranium analyzer to measure uranium phosphorescence. The revised method employs standard addition or tri-n-octylphosphine oxide extraction techniques to analyze digests containing large amounts of dissolved ionic species and high acid concentrations. Recoveries from spiked solutions of bone residues, tissue, or fecal ash using the laser phosphorimeter and the standard addition technique were quantitative within ± 4%. Analytical results were comparable with those of LiF + NaF pellet fusion fluorimetry and laser phosphorimetry was simpler than reflectance fluorimetry.

The fluorimetric method of determining uranium in fused LiF + NaF pellets is widely used for the assay of uranium (Ref. 2.1). It has been used routinely in our laboratory for assay of biological samples from animals that inhaled uranium-bearing aerosols. These samples include soft tissue, bone, feces, or urine from Beagle dogs or rodents, and contain large amounts of ions dissolved in 2 M HNO_3. Reflectance fluorimetry is reliable and relatively interference free, however, it is time-consuming and labor-intensive. These disadvantages result in slow data acquisition and increased cost per uranium determination. Laser phosphorimetry offers simpler methodology (Figure 2.1) and has been successfully applied by a number of workers to the determination of uranium in a variety of matrices (Refs. 2.2 to 2.6). Because the only biological matrices previously studied have been urine (Refs. 2.2, 2.6) and plant tissue (Ref. 2.4), we developed methods which could be used to assay a wider range of biological materials by laser phosphorimetry. This paper describes application of reflectance fluorimetry and laser phosphorimetry to the wide range of biological matrices encountered in this project.

METHODS

Sample Digestion

Samples from laboratory animals that inhaled yellowcake ranged in weight from a few grams to several hundred grams (wet weight). All samples were prepared as acid digests according to the method of Keough and Powers (Ref. 2.7). Briefly, the sample was heated to 500°C and wet-ashed in hot concentrated HNO_3 + 30% H_2O_2. Wet and dry ashing of bone tissue usually results in solid residues of undissolved bone mineral, and fecal ash residues usually include undissolved silicates that were ingested by the animal. These residues were transferred to Teflon® beakers and dissolved with concentrated HF. Teflon beakers were required since it was found that dissolution of residues by HF in glass beakers also leached natural uranium from glass beakers. Boric acid (0.2 M) was added to those samples treated with HF and the solutions were heated to dryness. All chemicals were reagent grade. The digests were then dissolved in 2 M HNO_3, and typically ranged in volume from 100 to 250 mL with uranium concentrations of 5 to 1000 ng per mL.

Reflectance Fluorimetry

Because the range of uranium masses in our samples was greater than the dynamic range of the Jarrell Ash Model 2600 fluorimeter, the samples were screened determine the course of further treatment. Three assay techniques were used. First, a direct determination of a 0.2 mL aliquot from the 2 M HNO_3 acid digest was made in a 0.4 g pellet of 2% LiF + 98% NaF flux. Each pellet

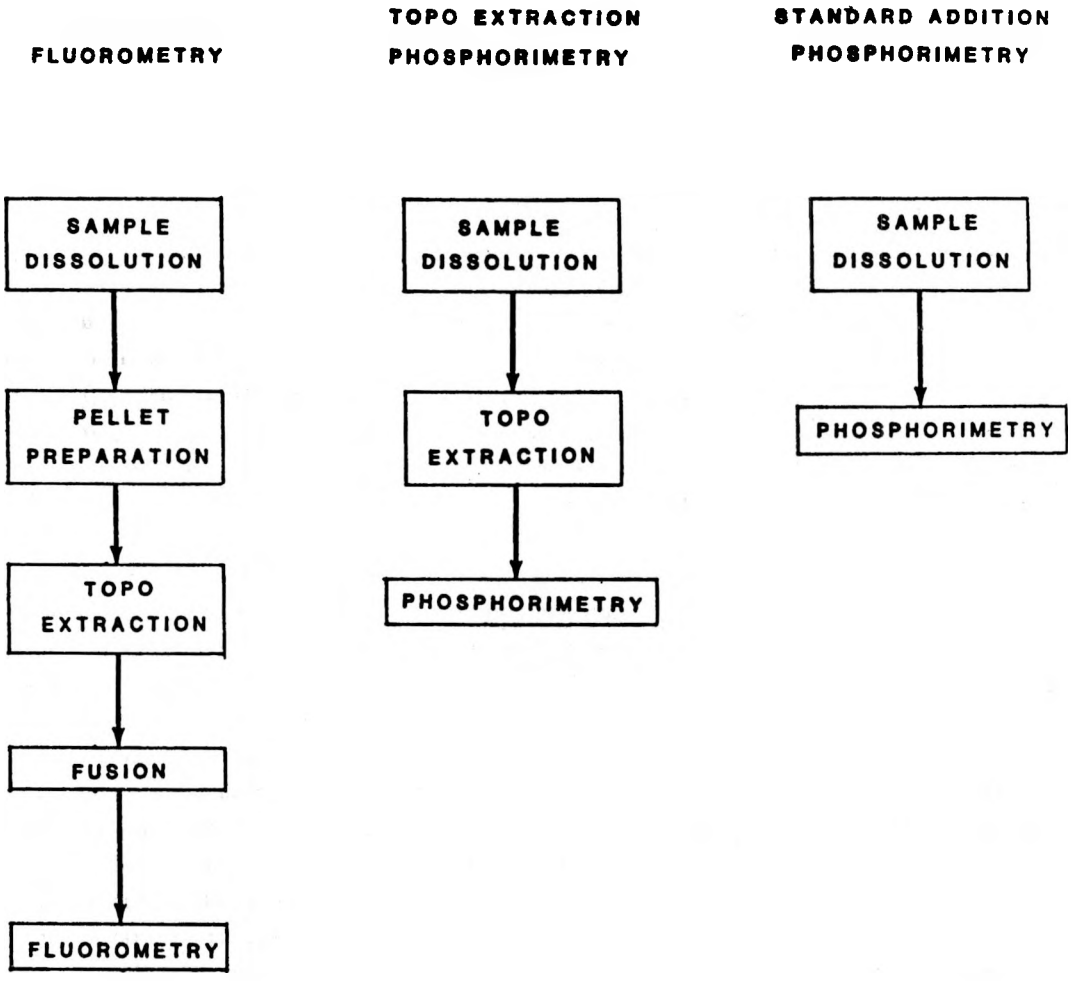

Figure 2.1 Comparison of methodology for pellet fusion fluorimetry, tri-n-octylphosphine oxide (TOPO) extraction, and standard addition phosphorimetry.

was dried under a heat lamp, fused at 1100°C on a rotary fusion burner (Geoco, Inc.), annealed at 850°C, and allowed to cool to room temperature. Second, where levels of uranium were high, one or more serial dilutions were made using 2 M HNO_3, followed by pellet fusion. Third, when uranium levels were low, a concentrating step was done by extracting uranium from 2 M HNO_3 into a solution 0.1 M tri-n-octylphosphine oxide (TOPO) in cyclohexane. Aqueous-to-organic phase ratios of 10 to 20 (v/v) were normally used, although ratios as high as 50 were found satisfactory for urine samples. Following phase separation, 0.2 mL of the organic phase was added to the LiF-NaF flux, dried under a heat lamp, and fused. Increases in sensitivity of 10 to 50 times that of a direct determination were achieved by the TOPO extraction. The average recovery of standard uranium (99.93% U_3O_8, New Brunswick Laboratory, Standard #114) spiked into a total of 80 tissue samples that were processed with experimental samples was 101 ± 4%.

Laser Phosphorimetry

Phosphorescence measurements were made with a Scintrex UA-3 Uranium Analyzer (Scintrex Ltd., Concord, Ontario, Canada). This instrument uses a pulsed nitrogen laser for excitation, and gating circuitry to minimize positive interferences from the emission intensity from fluorescent organic materials. The laser pulses 15 times per second and an integrator sums the readings from 60 pulses. At the end of each 4-sec measurement cycle, the integrated signal is displayed until another measurement cycle is complete. The theory and principles of operation of the instrument

have been described in detail (Ref. 2.8). The 7 mL quartz sample vials supplied with the instrument were used for all measurements. The pH of each solution was measured with a Corning Model 5 pH meter and an Orion Model 91-15 semi-micro combination pH electrode.

A working standard containing 250 ng U mL^{-1} in distilled water was prepared from the standard solution of U_3O_8. The concentration of the working standard was verified by comparison with the primary standard solution. All samples were assayed in 2 M HNO_3. A stock solution of the FLURAN reagent, which is the proprietary phosphorescence-enhancing reagent supplied with the instrument, was prepared by diluting 167 mL of FLURAN to 1 liter with distilled water. The extraction reagent was prepared by dissolving 38.6 g of reagent grade TOPO (Fisher Scientific, Fair Lawn, NJ) in 1 L of cyclohexane.

Two different procedures were applied to specimens prior to laser phosphorimetry; a standard addition method, and extraction with TOPO. Acid digests of soft tissue, bone or fecal samples in 2 M HNO_3 were used to evaluate both procedures.

Standard Addition Method

Each sample aliquot was transferred directly to a quartz vial and 5.8 mL of FLURAN stock solution was added. The action produced by the addition of FLURAN solution was sufficient to mix the sample completely. The quartz vial was then inserted into the instrument and readings were obtained immediately upon stabilization of the meter needle. It has been noted (Ref. 2.3) that during the course of measurement, the meter reading tends to decrease slightly from laser heating of the solution. Therefore, the meter needle was considered to have stabilized when it showed steady or very slightly decreasing values for three successive 4-sec measurement cycles. The maximum of the three values was recorded. The quartz vial was removed and an aliquot of a neutral uranium standard solution was added. This was sufficient to increase the scale reading by at least 0.5 to 1.0 scale units. The solution was mixed by capping the quartz vial with Teflon® caps and inverting 10 to 12 times. The vial was then replaced in the instrument sample holder and a second reading obtained after the needle had stabilized.

Tri-n-octylphosphine Oxide Extraction Method

Uranium was extracted from a 10-mL aliquot of the acid digest with 2 mL of 0.1 M TOPO in cyclohexane. Three 0.2-mL aliquots of the organic phase were evaporated to dryness at low heat on a heating plate and heated at 550°C for 16 h in a Thermolyne (Thermolyne Corporation, Dubuque, IA) muffle furnace. The cooled residue was dissolved in 0.5 mL of 2 M HNO_3 after ashing. The resulting solution was neutralized with 2 M NaOH and 5.8 mL of the FLURAN stock solution was added. The pH was measured using an Orion semi-micro pH probe and adjusted to pH 6 to 7 with 2 M NaOH, if necessary. The solution was then shaken for 15 min on a mechanical shaker to ensure complete mixing before transfer to the quartz vial for the uranium determination. A calibration curve for the TOPO extraction procedure was obtained from aliquots of standard uranium solutions in 2 M HNO_3 that were neutralized, mixed with the FLURAN solution and measured in the quartz vials.

RESULTS AND DISCUSSION

The use of FLURAN as the phosphorescence enhancing reagent was complicated by its interaction with the sample solutions. Assay of neutral solutions was desired to avoid quenching of phosphorescence intensity at low pH, and aliquots taken for analysis were neutralized before addition of the FLURAN. Bone or fecal sample solutions, which contain relatively high concentrations of calcium often formed a white precipitate that could be redissolved by addition of acid to pH < 2. Efforts to inhibit precipitation of calcium by addition of 0.1 M EDTA in the FLURAN were successful; however, uranium phosphorescence was quenched to approximately 20% of the intensity of a pH = 7.0 standard uranium solution. Substitution of H_3PO_4 for FLURAN as the

phosphorescence-enhancing reagent resulted in about the same degree of quench caused by pH reduction. Therefore, the relatively high amount of calcium in bone or fecal sample digests precluded assay of neutral solutions. Many of these biologically derived solutions could contain significant amounts of iron, another fluorescence quencher (Ref. 2.3). We investigated the standard addition technique and TOPO extraction to separate uranium from iron as approaches to solve these problems.

Blanks for all three matrices were determined using solutions assayed by the pellet fusion method and shown to contain only background levels of uranium (Table 2.1). These bone, soft tissue and fecal samples were from animals that were never exposed to uranium. The relatively high and variable levels of uranium shown in feces have been observed previously (Ref. 2.9). The detection limits were derived by applying the American Chemical Society definition of the detection limit as the blank value plus three times its standard deviation (Ref. 2.10).

Recoveries were determined using both techniques for digests of samples representing those normally prepared in our laboratory: bone, soft tissue, and fecal ash solutions in 2 M HNO_3. These solutions were shown to contain only background uranium concentrations by the fluorimetric method. Aliquots of these were spiked with uranium standard solutions so that the final solution contained 1000 ng U mL^{-1} and were assayed by the standard addition and TOPO-extraction techniques. The results are summarized in Table 2.2. Care was taken to ensure that the uranium standards used in the standard addition method had no effect on the FLURAN solution pH.

Table 2.1 Phosphorimetric assay for background uranium content in sample digests

Sample	N	Mean ± 1 SD (ng U mL^{-1})	Detection Limit[a] (ng U mL^{-1})
(a) Standard Addition Method			
Bone	8	2.9 ± 1.2	6.5
Feces	10	31.8 ± 4.5	45.4
Soft Tissue	9	4.8 ± 1.0	7.8
(b) TOPO-Extraction Method			
Bone	6	5.5 ± 0.6	7.3
Feces	10	29.9 ± 7.8	53.3
Soft Tissue	7	2.7 ± 2.6	10.5

[a]Detection limit = mean + 3 SD.

Following the method of Zook et al. (Ref. 2.3), the uranium concentration, C (ng U mL^{-1}), in solutions assayed by the standard addition method was calculated according to Eq. (1):

$$C = \frac{A\, R_1 S_1}{B(R_2 S_2 - R_1 S_1)} \qquad (1)$$

where A is the amount of standard uranium spike in ng; B is the aliquot volume in mL; R_1 and R_2 are the instrument readings (dimensionless units) before and after the addition of the standard, respectively; and S_1 and S_2 are solution volumes before and after addition of the standard, respectively. The previously determined blanks (Table 2.1) were used to correct these concentration values.

For the TOPO-extraction experiments, the reagent blank, which consisted of 0.5 mL of HNO_3 neutralized as above, did not yield an observable needle deflection. Earlier experiments using neutral uranium standards in the absence of any quenching agents demonstrated a linear instrument response over the expected concentration range up to 2000 ng U mL^{-1} in the original solution.

The low recoveries in fecal and soft tissue samples (Table 2.2) by the TOPO-extraction method were investigated further. It was found that if the solutions in the quartz vials were retained in capped vials and remeasured during one week following the initial measurement, the recoveries increased steadily until essentially quantitative recoveries were observed after one week. Factors that might influence this rate by change in the results were not investigated. We recommend that the TOPO-extraction method as described here be used only when standard addition is precluded by very high concentrations of quenchers, and when a suitable waiting period for measurements can be determined.

Table 2.2 Measured percentage recovery from sample digests spiked with 1000 ng U mL^{-1} (mean ± 1 SD)

Matrix	Standard Addition		TOPO Extraction	
	N	% Recovery	N	% Recovery
Bone	9	98.1 ± 4.1	10	97.1 ± 3.0
Feces	10	99.0 ± 9.9	10	83.1 ± 8.5
Soft Tissue	10	97.6 ± 4.0	10	70.6 ± 10.5

These results indicate that the Scintrex UA-3 Uranium Analyzer and the standard addition method can be used to accurately determine uranium in bone, fecal, and soft tissue samples. The methodology is simpler than reflective fluorimetry, requires less time, and produces similar results at a reduced cost per sample.

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3. INFRARED ANALYSIS OF REFINED URANIUM ORE

Abstract — Infrared assay of refined uranium ore (yellowcake) is described and the results are related to worker protection measures. Eleven standard mixtures of ammonium diuranate and U_3O_8 were prepared that contained 0% ammonium diuranate (pure U_3O_8) through 100% ammonium diuranate (no U_3O_8) in 10% intervals. Assay of these mixtures (0.30% in KBr) showed that ammonium diuranate could be accurately assayed within ± 7% standard error of the mean (n = 8), and U_3O_8 to within 12%. For specimens that contained only one of the uranium forms, the percentage of ammonium diuranate was overestimated by 16 ± 4% and U_3O_8 was underestimated by 24 ± 2%. Fifty-six commercial samples from 10 mills were assayed. The results were applied to the use of urinalysis data to estimate the amount of uranium in the body of a worker after a hypothetical inhalation of dust from an assayed sample. It was shown that the uncertainty in body burden estimates could be reduced from a factor of 100 to a factor of 10 with 95% confidence. Infrared assay results also showed that the ammonium diuranate and U_3O_8 content of a specific yellowcake sample cannot be predicted from the dryer temperature alone.

PRINCIPAL INVESTIGATOR
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Uranium ore is refined in uranium mills to produce the commercial product known as yellowcake. Leaching from ore is accomplished using H_2SO_4 or $Na_2CO_3/NaHCO_3$ solutions. Uranium is dissolved in H_2SO_4, removed by solvent extraction or ion exchange and precipitated from solution by ammonia, as ammonium diuranate. Ammonium diuranate (often written as $(NH_4)_2U_2O_7$) is actually a variable mixture of $UO_3 \cdot xNH_3 \cdot yH_2O$ compounds with their composition dependent on the pH during precipitation. Four stoichiometric forms can be crystallized by shaking under an ammonia atmosphere for two weeks (Ref. 3.1); but these conditions do not occur in industry. Uranium dissolved in $Na_2CO_3/NaHCO_3$ is precipitated by NaOH. Sodium diuranate is generally dissolved and reprecipitated by ammonia. Prior to packaging, ammonium diuranate precipitate is dried at temperatures chosen to either dehydrate it or convert it to U_3O_8. Partial or incomplete conversion often occurs.

Routine urinalysis for uranium is used to monitor protection measures so that workers who might inhale yellowcake dust do not accumulate dangerous amounts of internally deposited uranium. It is necessary, then, to quantitatively measure ammonium diuranate and U_3O_8 in yellowcake to interpret urinalysis data, either as part of routine monitoring, or to evaluate accidental exposures. Dissolution studies in vitro are useful for studies of a few selected samples, such as a sample of a lot involved in an accident, but they are too time consuming for use in a survey of yellowcake samples (Refs. 3.2-3.4). X-ray diffraction techniques were considered for yellowcake assay (Ref. 3.5); however, industrial products often include large fractions of poorly crystallized or amorphous ammonium diuranate, precluding accurate assay. Infrared absorption measurements were chosen to assay the two uranium forms regardless of crystallinity.

The objectives of this study were to describe the assay of mixtures of standard ammonium diuranate and U_3O_8 by infrared absorption, and to assay commercial samples obtained from operating mills.

METHODS

Ammonium diuranate was prepared in the laboratory by dropwise addition of 15% aqueous NH_4OH to an aqueous solution of $UO_2(NO_3)_2$ with stirring at room temperature. When the pH increased to 7.5, NH_4OH addition was stopped and the resulting yellow precipitate was stirred for 16 h, filtered, washed with cold water, acetone and air dried at room temperature.

Ammonium diuranate prepared as above was ground with U_3O_8 (New Brunswick Laboratory, Argonne, IL) using a Wigl-Bug® grinder (Crescent Dental Mfg. Co., Chicago, IL) to prepare eleven mixtures that contained from 0% ammonium diuranate (pure U_3O_8) through 100% ammonium diuranate (no U_3O_8 present) in 10% intervals. Weighed aliquots of the mixtures were added to 1 g of spectral grade KBr to prepare standard mixtures that were 0.30 ± 0.01%, 0.50 ± 0.01%, and 1.00 ± 0.01% in KBr. All masses were measured to within ± 0.05 mg. Duplicate pellets were prepared by pressing 200 mg of the ground mixture at 2000 psi for 5 min. Pellets were 0.052 ± 0.001 cm thick.

Fifty-six yellowcake samples were obtained from 10 commercial mills and KBr pellets that contained 0.3% sample in KBr were prepared as above. There was no pretreatment of yellowcake samples prior to grinding with KBr. Prior to use, KBr was heated at 100°C and stored in a desiccator. All pellets were stored in desiccators, but were not reheated to avoid decomposition of ammonium diuranate. Mill designations A-G and I-K do not identify the mills.

Infrared absorption measurements were obtained using a Perkin-Elmer Model 283B infrared spectrophotometer equipped with a microprocessor control unit and programs for quantitative analyses of mixtures using the Beer-Lambert law. Absorbance measurements were made at wavenumbers assigned in the literature to U_3O_8 and to the uranyl moiety of UO_3 and at an intermediate frequency chosen to represent the remaining sample matrix. Baseline points were chosen at 970 ± 5 cm^{-1} and 635 ± 5 cm^{-1} as the relative minima of the standard spectra. They represent the minimum of several overlapping absorptions, rather than wavelengths of 100% transmittance, but are the best available wavelengths in the 200 cm^{-1} to 1500 cm^{-1} range (Figure 3.1).

The eleven standard ammonium diuranate plus U_3O_8 mixtures were used to calibrate the instrument. One duplicate standard pellet of each mixture was selected randomly. The absorbances

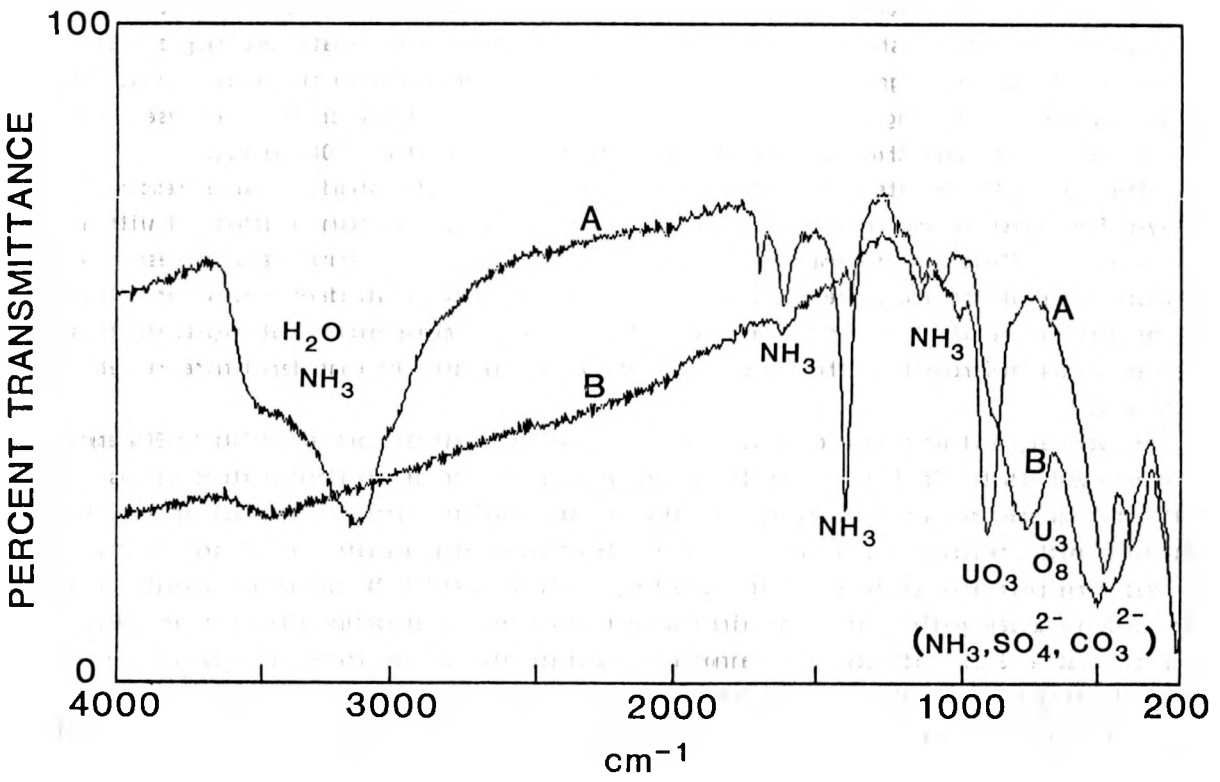

Figure 3.1 Infrared transmittance spectra of a yellowcake specimen from Mill B before (A) and after (B) heating at 150°C for 16 h, showing partial conversion of ammonium diuranate to U_3O_8. The band identified as UO_3 represents the uranyl moiety absorption (Ref. 3.7).

of these pellets were used to obtain the absorbtivity array that described the entire range of ammonium diuranate and U_3O_8 percentages in a mixture. The remaining pellets of each pair were then analyzed as unknowns. The process was then reversed to provide an analysis of all standard pellets as if they were unknowns.

The absorptivity array derived in this manner includes mixture and pellet preparation errors, and instrumental errors between individual spectra obtained during the same analysis session. The array does not include instrumental errors introduced by changing settings for analysis of other materials and resetting the instrument for yellowcake analysis.

RESULTS

Changes in the infrared transmittance spectrum of a commercial yellowcake specimen upon thermal conversion to U_3O_8 are shown in Figure 3.1. The unheated specimen spectrum (A) shows the presence of NH_3, H_2O and a band assigned to the asymmetric uranyl stretching frequency of UO_3 at 920 cm^{-1} (Ref. 3.6). Spectrum B was measured after the specimen was heated at 150°C for 16 h. It shows nearly complete loss of NH_3 and H_2O, and the appearance of a band near 740 cm^{-1} corresponding to U_3O_8 (Ref. 3.7).

Absorptions by NH and OH species in the sample are the major interferences in the 600 cm^{-1} to 1000 cm^{-1} region of interest (Figure 3.1) (Ref. 3.8). Sulfate ion and carbonate ion can also interfere (Ref. 3.8), but SO_4^{2-}, which can represent from 1% to 7% of yellowcake and CO_3^{2-} (< 1%) (Refs. 3.2, 3.3) are of secondary importance. Figure 3.2 shows both pure ammonium diuranate and U_3O_8 absorbance spectra superimposed on the same axes with a specimen from Mill D.

Standard mixture assay results (Table 3.1) are expressed as the difference between the analyzed and known percentages in the mixture, so that an ideal result would be 0.0% ± 0.0%. The accuracy of the results shows that the percentages of ammonium diuranate and U_3O_8 are slightly overestimated, but not significantly so when compared with the precision of the estimates. The 22 values arose from measuring duplicate pellets from 11 mixtures. Based on these analyses, results of the 0.3% pellets were shown to be more precise than for the 0.5% or 1.0% pellets.

After the 0.3% pellets were chosen for unknown assays, the standards were rescanned and assayed four times during the subsequent work; and the results are shown in Table 3.1 with n = 8. The results of these four separate assays of the 0.3% pellets, with error bars representing the standard error of the mean, are shown in Figure 3.3. The greater standard errors for 8 than for 22 measurements resulted not only from the smaller number of measurements but represent possible changes in the instrument or the standard pellets with time and are considered more reliable for routine work.

The accuracy and precision of results are greatest for mixtures containing 10% to 90% ammonium diuranate and 30% to 70% U_3O_8. Given the accuracy and precision of standard mixture assays (Table 3.1), unknown specimen assays showing less than ≃ 13% ammonium diuranate (± 2 SE) or less than ≃ 24% U_3O_8, might indicate the presence of only U_3O_8 or ammonium diuranate. A calibration curve was derived from peak area analyses of 0% (pure KBr), 0.3% 0.5% and 1.0% ammonium diuranate or U_3O_8, and used to assay pellets that contained only 0.35% standard ammonium diuranate or U_3O_8. The results (Table 3.2) indicate that ammonium diuranate was overestimated by 16% and U_3O_8 was underestimated by 24%. The diminished accuracy of analyses that included 0.5% and 1.0% standards in the working curve was attributed to bias introduced by the sloping baselines of standard spectra, and to NH and OH interferences that were more pronounced at the higher concentrations in KBr.

The spectrum of a sample from Mill D (curve C, Figure 3.2) illustrates a typical commercial sample assay. The analytical approach used was to assume that an unknown sample was a mixture of

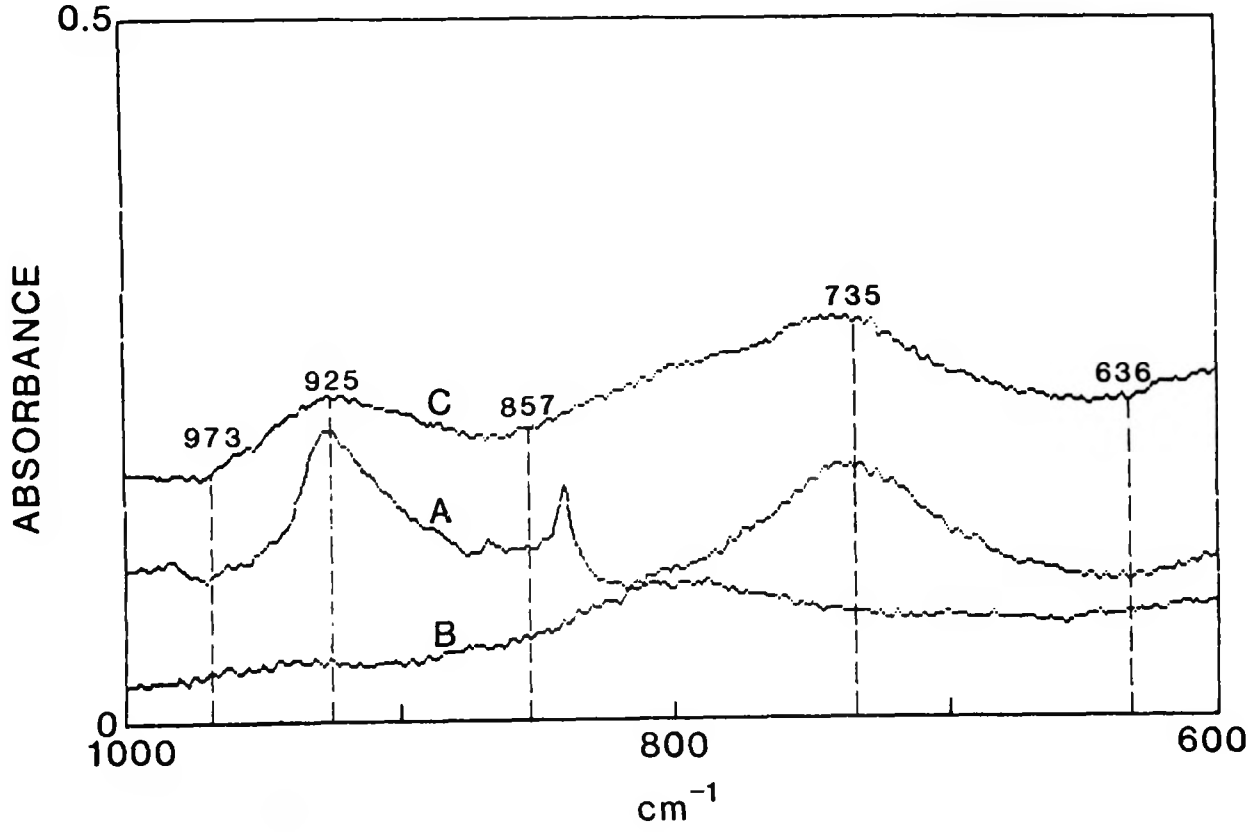

Figure 3.2 Infrared absorbance spectra of pure ammonium diuranate (A), pure U_3O_8 (B) and a yellowcake from Mill D (C). All specimens were 0.30 ± 0.01 wt % in KBr. Mill D curve is offset for clarity. Analyses were done using wavelengths specified.

Table 3.1 Assay of standard mixtures of ammonium diuranate and U_3O_8 in KBr pellets

Wt % Mixture in KBr ± 0.01	Deviation (Analyzed % - Known Wt % in Mixture) Mean ± Standard Error (n)	
	Ammonium Diuranate	U_3O_8
0.30	0.40 ± 2.6 (22)	0.48 ± 2.6 (22)
	0.070 ± 6.6 (8)[a]	-0.13 ± 12 (8)a
0.50	0.068 ± 3.4 (22)	-0.34 ± 4.8 (22)
1.00	-0.36 ± 3.2 (22)	0.22 ± 3.8 (22)

[a]0.3% standard mixtures were assayed four times during the study of commercial samples. These values are considered more reliable for routine assays.

ammonium diuranate, U_3O_8, and other interfering milling products. If the results indicated the yellowcake contained only ammonium diuranate or U_3O_8 (and the spectrum showed only one form present), the sample was reanalyzed using calibration data from the single component standards (Table 3.2).

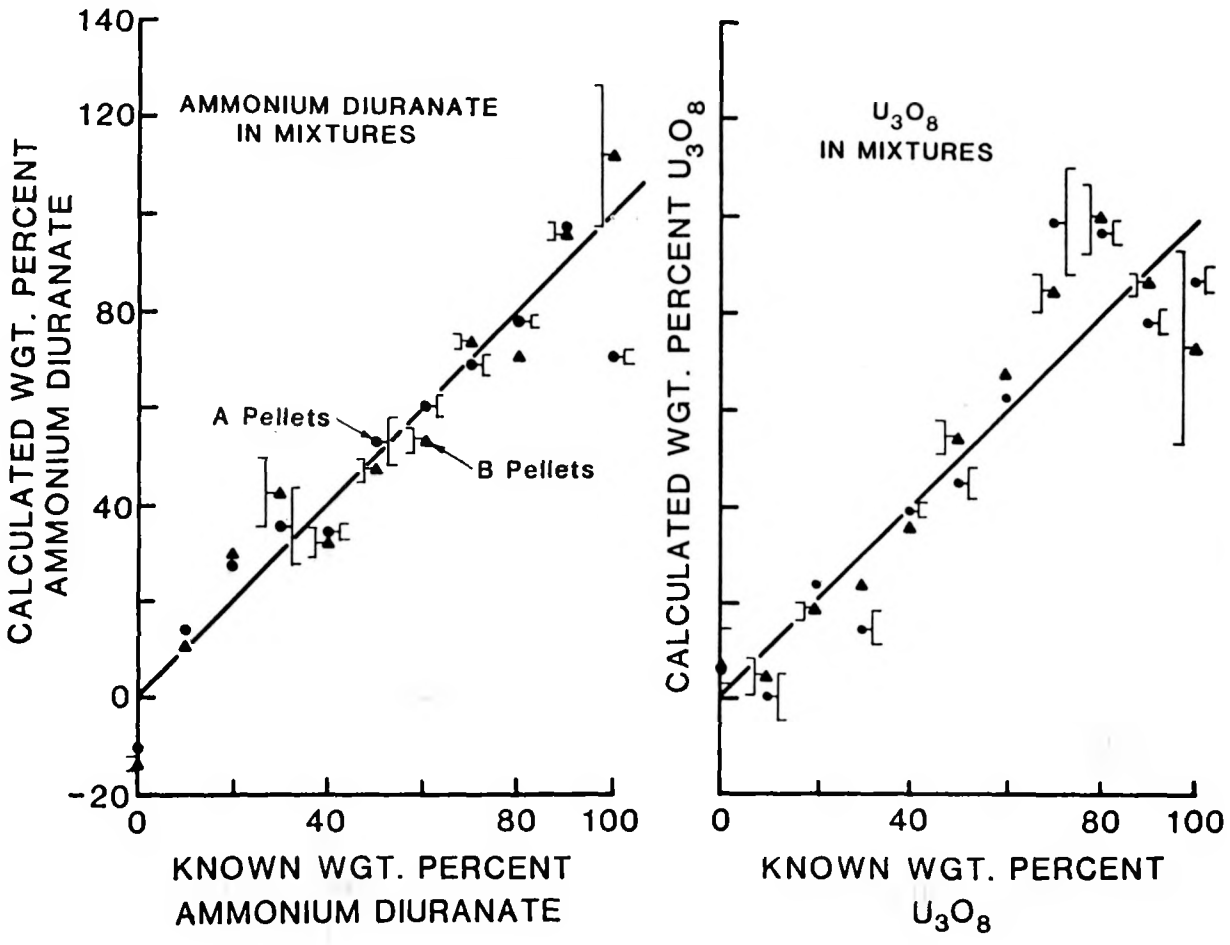

Figure 3.3 Results of assays of known ammonium diuranate and U_3O_8 mixtures. Duplicate pellets of each mixture were prepared and one of each pair was selected randomly (A Pellets) for calibration. The remaining B Pellets were analyzed as unknowns. The B Pellets were then used to calibrate the instrument for analysis of A Pellets as unknowns. The straight line indicates the ideal result of calculated value = known value.

Table 3.2 Assay of standard pellets that contained either ammonium diuranate or U_3O_8 in KBr

Wt % Component in KBr	Deviation (Analyzed % - 100%) Mean ± Standard Error (n = 8)	
	Ammonium Diuranate	U_3O_8
0.30 ± 0.01	15.5 ± 3.8	-24.1 ± 2.1

Table 3.3 shows assay results of samples taken from the mills studied. Results of analyses of unknown samples containing only one uranium compound were corrected for the systematic errors shown in Table 3.2. Results that indicated greater than 108% ammonium diuranate in a specimen were reported as containing only that form of uranium. Figure 3.4 illustrates the most extreme variability observed, which occurred among grab samples from two drums of Mill E Lot #55. Both spectral bands in the drum #42 sample can be assigned to peaks from ammonium diuranate (Ref. 3.7) and the spectrum shows no U_3O_8 absorbance. Mills C, D and J produced yellowcake that was partially converted to U_3O_8. The Mill I sample was a special case. It was collected from the

Table 3.3 Assay of unknown yellowcake samples from ten mills

Mill	Mean Wt % ± Standard Error (n)[a]	
	$UO_3 \cdot xNH_3 \cdot yH_2O$	U_3O_8
A	100	b
B	92 ± 11 (18)	b
C	64 ± 23 (5)	43 ± 29
D	30 ± 11 (6)	77 ± 20
E	94 ± 10 (17)	b
F	100 ± 5 (2)	b
G	100	b
I	50	b
J	24	87
K	b	100

[a]n = number of samples obtained from specified mill, if > 1.

[b]No absorption bands for this form observed.

floor of the packaging area and represents a mixture of production lots and other dusts generated in the overall milling process that might be resuspended and inhaled by a worker. Note that, although no U_3O_8 was present, the specimen was not pure ammonium diuranate. This information would be valuable in assessing the consequences of an accidental inhalation of this material.

Ammonium diuranate variability of the type shown in Figure 3.4 also complicated the analysis of mixtures (Figure 3.5). Such specimens were analyzed using the same 11 standard pellets used in all other assays, but wavenumbers were chosen to correspond to the U_3O_8 maximum, the minimum between the U_3O_8 and ammonium diuranate peaks, and the wavenumber at the "crossover" between the ammonium diuranate standard and the unknown spectrum. The accuracy and precision were similar to those shown in Table 3.1; mean and standard error (n = 11) were ammonium diuranate -2.3 ± 2.7% and U_3O_8 -2.0 ± 3.9%.

DISCUSSION

Infrared analysis can accurately assay ammonium diuranate in the presence of U_3O_8 to within ± 7% standard error of the mean, and U_3O_8 content to within ± 12%. For specimens suspected to contain only one of the uranium oxide forms and reanalyzed accordingly, the percentage of ammonium diuranate was overestimated by 16 ± 4% and U_3O_8 was underestimated by 24 ± 2%.

Commercial yellowcake composition or its biological behavior cannot be reliably predicted from its drying temperature alone (Figure 3.6). The range in drying temperatures, obtained from mill records, indicates the temperatures at the top of the dryer, where the ammonium diuranate is initially heated, and the bottom. The line connects points representing the median ammonium diuranate percentages and the average dryer temperature; dotted lines show the temperature range for formation of U_3O_8 from ammonium diuranate (Refs. 3.6, 3.9). Because the capacity of the dryer is large, sufficient information on the temperature history of a minute aliquot of yellowcake that might be inhaled (Paper 1, this report) is not available to predict its biological behavior. For this reason, yellowcake drying temperature alone should not be used to establish health protection regulations.

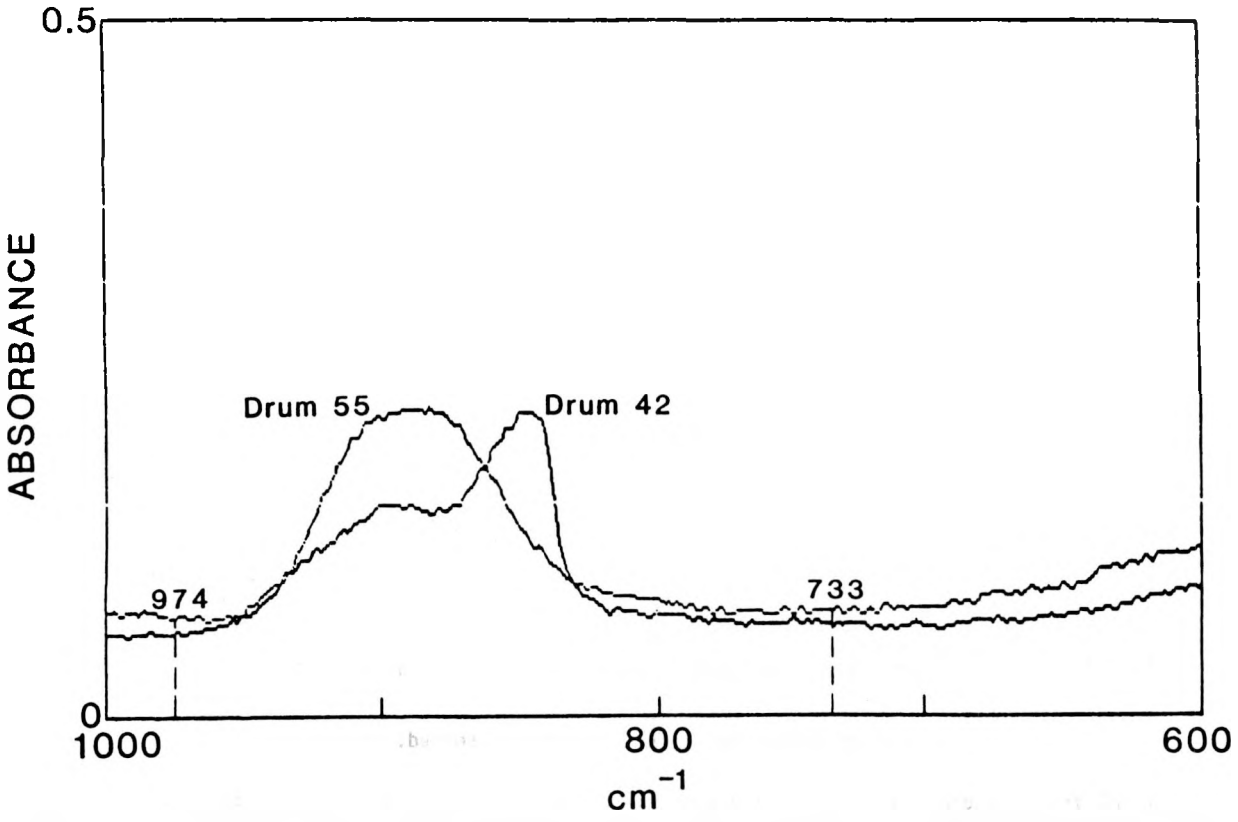

Figure 3.4 Spectra of 0.30 ± 0.01% specimens taken from two drums from lot #55 produced by Mill E. The illustrates the variable nature of ammonium diuranate produced during apparently similar conditions.

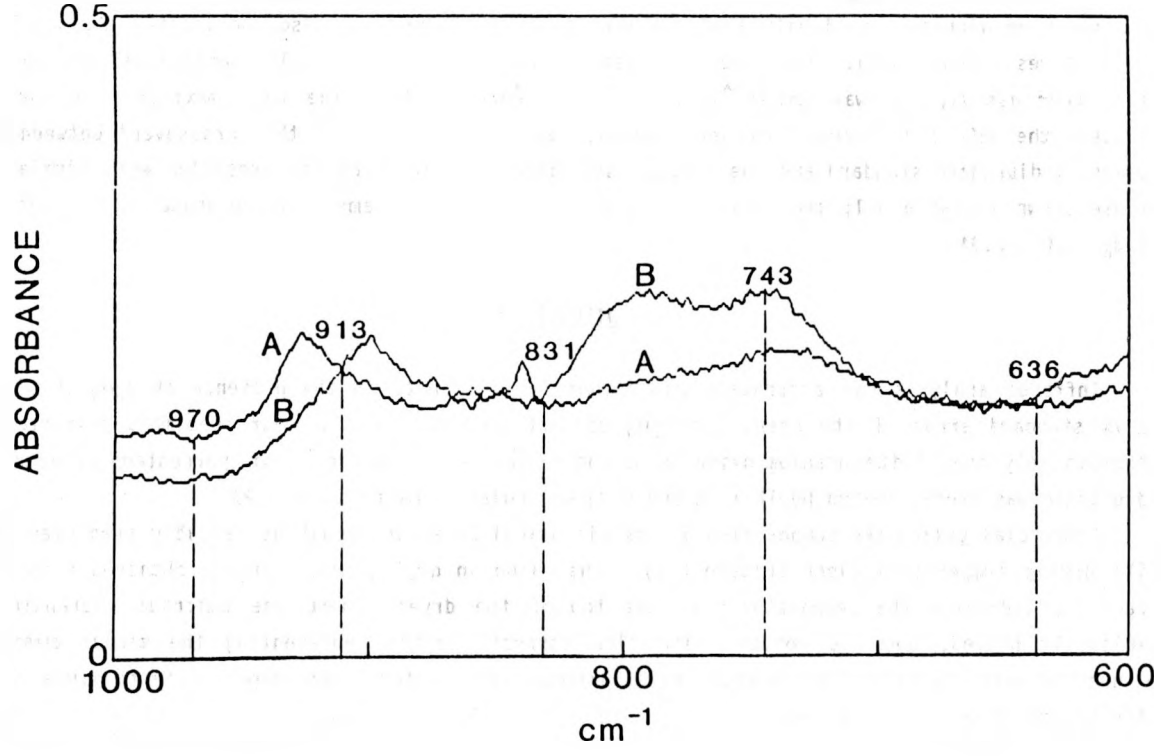

Figure 3.5 Spectra of Mill D sample containing variable forms of ammonium diuranate (A) and binary mixture of 50% ammonium diuranate plus 50% U_3O_8 standard (B). The instrument was recalibrated for assay of this specimen using absorbances of the 11 standard mixtures at these new wavenumbers. Results were similar to those shown in Table 3.1.

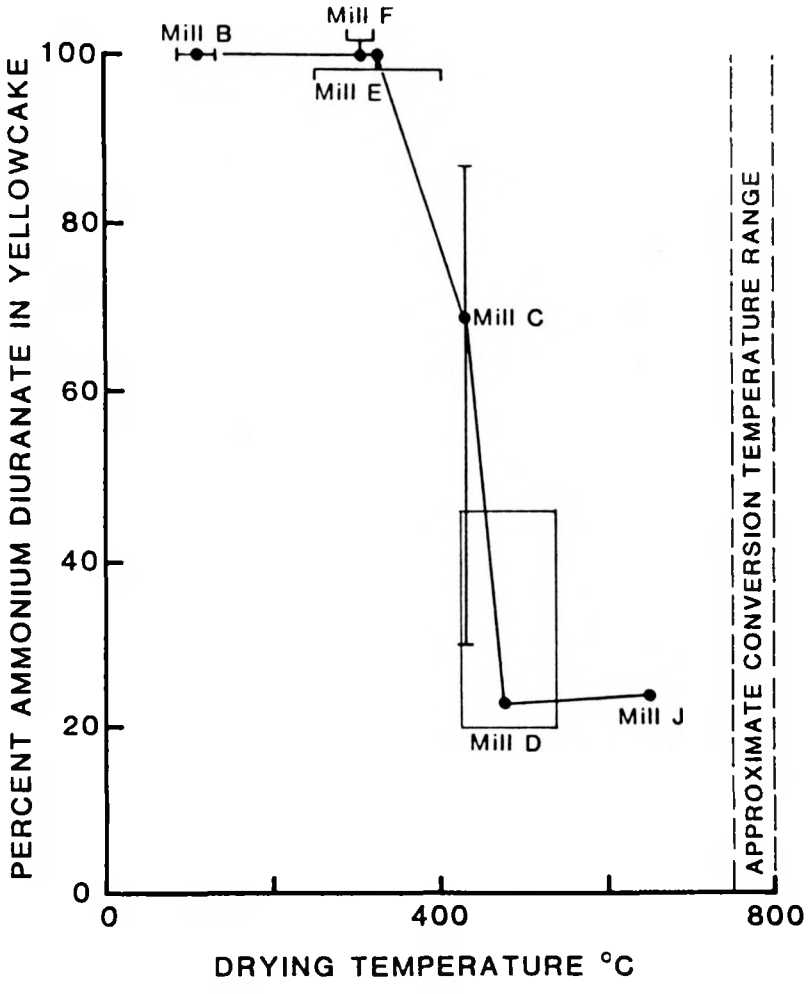

Figure 3.6 Comparison of medians and ranges of the ammonium diuranate concentration in commercial yellowcake with their reported drying temperatures and the temperature of complete conversion to U_3O_8.

The following actions are recommended for those wishing to apply this technique to yellowcake analysis:

1. Standard and unknown pellets should be scanned at the same time or without turning off the instrument.
2. A dried but unheated sample of yellowcake precipitate from each mill should be used as the ammonium diuranate standard.
3. If experience shows that the spectra of successive lots from one mill are excessively variable (see Figure 3.4), then a library of spectra of ammonium diuranate forms mixed with U_3O_8 should be maintained.

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4. TECHNIQUES FOR YELLOWCAKE DISSOLUTION STUDIES IN VITRO AND THEIR USE IN BIOASSAY INTERPRETATION

PRINCIPAL INVESTIGATORS
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Abstract __ The high variability in solubility of yellowcake produced by different mills complicates the interpretation of routine bioassay data. A simple in vitro dissolution test is needed for yellowcake to improve this interpretation. A series of experiments was designed to evaluate the relative importance of solvent composition, method, pH and temperature in determining yellowcake dissolution according to a model developed from the known composition of a test yellowcake and data from inhalation exposures of humans to UO_3 or U_3O_8. Useful in vitro dissolution results can be obtained using either simulated serum ultrafiltrate or simulated lung fluid as the solvent if dissolved and undissolved yellowcake are separated by a membrane filter. In vitro dissolution experiments estimated the soluble portion of the test yellowcake within ± 6% (mean ± 2 standard errors) and showed that the dissolution rates of the more soluble and less soluble portions corresponded to Class D and Class Y compounds, respectively. It was not necessary to maintain physiological pH or temperature conditions to approximate the "human" model. The greatest utility of in vitro dissolution results was in the estimation of the more soluble fraction of the yellowcake and to indicate whether prior excretion of a Class D uranium compound and possible kidney damage could have occurred before detection of an exposure. Some guidelines for the use of in vitro dissolution data in bioassay interpretation are suggested based on ICRP Publication 30 recommendations.

If a uranium mill worker is involved in an accident, analysis of excreta for uranium content and in vivo counting methods (Refs. 4.1, 4.2) are used to estimate the extent of the possible exposure and to predict the pattern of uranium distribution among tissues. Interpretations of urinary excretion data are based on studies of human exposures to single uranium compounds including soluble UO_3, UO_2F_2 and UF_6 and less soluble UO_2, U_3O_8, and UF (Ref. 4.3). Yellowcake is a complex and variable mixture of UO_3-NH_3-H_2O adducts (ammonium diuranate, ADU) and their thermal conversion product, U_3O_8. The variability in composition of yellowcake from different mills (Paper 3, this report) complicates the interpretation of bioassay data from individuals that might have inhaled any single yellowcake material.

A simple test system would be useful to estimate the dissolution behavior of a particular yellowcake aerosol inhaled by a worker and aid the interpretation of bioassay data collected before and after an accident. A series of experiments was conducted for this purpose. The objectives of these studies were to: (1) develop specific criteria for comparing in vitro dissolution systems, (2) to use the criteria to evaluate solvents, methods, temperature and pH conditions used in previous studies (Refs. 4.4-4.6) and (3) to illustrate the utility of in vitro dissolution results in the interpretation of bioassay data.

One approach for developing an in vitro test system to aid bioassay interpretation would be to use data from accidental human exposures to commercial yellowcake. Such exposures are not predictable and the nature of the yellowcake involved is usually not well known so that little useful information is available for developing in vitro tests.

Because little information is currently available from commercial yellowcake inhalation to evaluate the in vitro results, a preliminary model of yellowcake dissolution in lung was constructed from cases in which humans were exposed to single uranium compounds known to be in yellowcake (Ref. 4.7). Dissolution techniques were tested using the same sample of yellowcake and the results are evaluated according to the preliminary model.

The alveolar environment of the lung is complex and requires the interaction of many physical and chemical processes for its function (Ref. 4.8). Many methods that vary in their complexity have been developed to simulate these processes and each has advantages and limitations (Ref. 4.9). The in vitro techniques are judged in this report according to their performance in comparison with the expected behavior of uranium compounds in vivo, rather than how they might simulate the lung environment as it is understood today. Parallel study of in vitro results and in vivo dissolution patterns in animals will be required to ensure that in vitro tests provide an accurate assessment of in vivo behavior (Paper 8, this report).

MATERIALS AND METHODS

Materials

The powder used in the tests was taken from one lot of yellowcake obtained from a commercial uranium mill. The same powder was previously designated as Mill D in Ref. 4.5 and Mill 2 in Ref. 4.4. The ammonium diuranate content was measured by infrared absorption to be 25% ± 1% (Ref. 4.5). The precision of infrared results was based on analyses of three subsamples of the Mill D powder and includes errors associated with powder homogeneity. Therefore, the Mill D yellowcake was sufficiently homogeneous to serve as a test sample to compare other experimental factors for dissolution in vitro.

Solvents

Previous yellowcake dissolution studies in vitro used simulated lung fluid (SLF) (Refs. 4.4, 4.6) and simulated blood serum ultrafiltrate (SUF) (Ref. 4.5). The SLF solvent was chosen to simulate the composition of lung fluid as closely as practical (Ref. 4.10). The SUF solution has been used in studies of inhaled ^{239}Pu aerosols (Ref. 4.11) and of $^{241}AmO_2$ in Beagle dogs (Ref. 4.12).

The compositions of the two biological fluid simulants used are compared in Table 4.1. Major differences are that SLF contains Mg^{2+} and a higher Ca^{2+} concentration than SUF and that SUF contains ammonium ion. Both solvents include protein substitutes; citrate and acetate are used in SLF, while citrate, amino acids and the chelating agent diethylenetriaminepentaacetic acid (DTPA) are used in SUF. The presence of phosphate ion in both solvents offers the possibility of uranyl phosphate precipitate formation after initial dissolution of UO_2^{2+}. Because this would not reflect the initial dissolution properties of the sample, DTPA was used in SUF to mitigate phosphate precipitate formation.

Modified solvent compositions were prepared to study the importance of phosphate, DTPA and amino acids in yellowcake dissolution. Solutions of SUF (Table 4.1) were prepared without DTPA (SUF-DTPA) and without amino acids (SUF-amino acids). No solution excluded both DTPA and amino acids. The SLF solutions were prepared with DTPA (SLF + DTPA) and without phosphate (SLF-PO_4). No SLF-based solution contained DTPA and not phosphate. All chemicals used were reagent or analytical grade and were dissolved in distilled water. Solvents were prepared in 10-L reservoirs using the recommended mixing order (Ref. 3.10) and were stirred until clear before use - generally for 24 h. The reserve solutions were stirred throughout the experiments.

Methods

Four experimental methods have been used for yellowcake dissolution testing: the static method (Ref. 4.5), the batch/filter method (Ref. 4.4), the batch method (Ref. 4.6) and the pass-by method (Ref. 4.4).

In the "static method" a weighed portion of yellowcake is placed between two 0.1 μm pore size membrane filters (Millipore Corp.) and the filter sandwich secured with a circular Teflon® clamp. The assembly is placed in 200 mL of solvent, covered and allowed to stand without stirring.

Table 4.1 Compositions of biological fluid simulants used

Species	Molar Concentration[a] Simulated Serum Ultrafiltrate SUF[b]	Simulated Lung Fluid SLF[c]
KCl	-	0.004
NaCl	0.116	0.145
$MgCl_2$	-	0.001
NH_4Cl	0.010	-
$NaHCO_3$	0.027	0.024
Glycine	0.005	-
L-Cysteine	0.001	-
Na_3 Citrate	0.0002	0.0003
Na Acetate	-	0.007
$CaCl_2$	0.0002	0.0025
H_2SO_4	0.0005	-
Na_2SO_4	-	0.0005
Na_2HPO_4	-	-
NaH_2PO_4	0.0012	-
DTPA[d]	0.0002	-
ABDC[e]	50 ppm	-

[a]Aqueous solution

[b]Ref. 4.5

[c]Refs. 4.4, 4.6

[d]Diethylenetriaminepentaacetic acid, not present in blood serum.

[e]Alkylbenzyldimethylammonium chloride, an antibacterial agent not present in blood serum.

Periodically the assembly is transferred to fresh solvent and the used solvent analyzed for uranium.

The "batch method" (Ref. 4.6) involves the direct suspension of weighed powder in 20 mL of solvent in centrifuge tubes sealed with screw caps. An ultrasonic water bath is used to disperse any agglomerates and the suspension is then shaken continuously. Periodically the tubes are centrifuged to remove suspended particles and the supernatant liquid is removed with a pipette and analyzed for uranium. Fresh solvent is added after which the centrifuge tube is shaken by hand and sonicated to redisperse the particles. The schedule for changing solvents during the 30-day study was generally the same for both procedures and is shown by the data points in Figure 4.1.

The "batch/filter" method (Ref. 4.4) involves direct suspension of the sample in the solvent, as in the batch method, but the dissolved and undissolved yellowcake are separated by filtration rather than centrifugation. Because the static and batch/filter methods both use a membrane filter to separate the liquid and solid phases, the batch/filter method was not used in this study. The "pass-by" method involves impractically large volumes of solvent (Ref. 4.4) and was not considered further. Other methods using flowing solvents were not considered for the same reason.

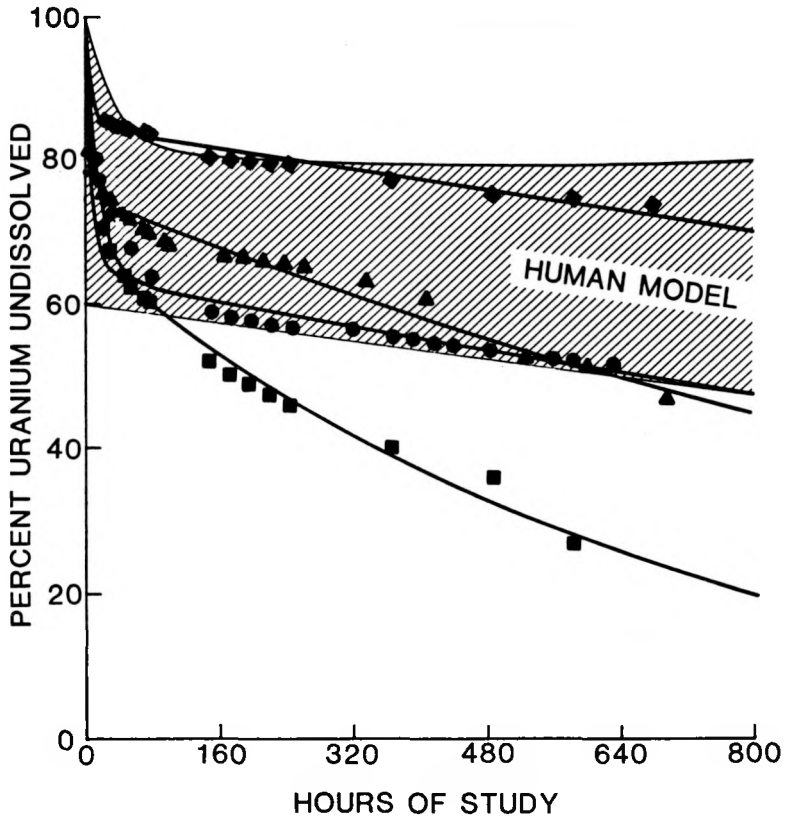

Figure 4.1 Comparison of dissolution curves with a model of yellowcake dissolution in the human lung. The upper curve of the human model was calculated from Equation 1 where; A_1 = 20%, λ_1 = -0.693/1 day, A_2 = 80% and λ_2 = -0.693/4000 days. Similarly the lower curve represents; A_1 = 40%, λ_1 = $-\infty$ (immediate dissolution), A_2 = 60% and λ_2 = -0.693/100 days. (Δ) Exp 1, (◇) Exp 2, (□) Exp 3, (●) Exp 4.

Effects of pH and temperature of the solvents on yellowcake dissolution were investigated by conducting both static and batch procedures under physiological and nonphysiological conditions. In experiments using the static method the filter sandwich was allowed to stand in a constant temperature bath at either 37°C or at room temperature of ~ 20°C. The suspensions used for the batch method were shaken gently, either in a constant temperature bath at 37°C or at room temperature. In some experiments physiological pH conditions were approximated by adjusting the pH of each fresh solution to 7.3 at the time of transfer. Other workers readjusted the pH to 7.3 as it slowly drifted upward (Ref. 4.6) or at least weekly (Ref. 4.4). The pH of each solvent composition used was measured potentiometrically using a glass electrode.

Uranium Analysis and Data Reduction

Each solution collected during an experiment and the undissolved yellowcake were dried and the residue heated at 550°C for 16 h. The resulting ash was dissolved in 2 M HNO_3. The uranium concentration was determined by reflectance fluorimetry (Paper 2, this report). Each modified solvent described above was used to prepare blank and spiked quality control samples for the uranium analyses in each corresponding experiment. The average recovery of uranium spiked into the salt solutions was 105% ± 6% (mean ± 1 standard deviation).

Table 4.2 Results of yellowcake dissolution experiments conducted in simulated serum ultrafiltrate (SUF)

Experiment Number	Solvent (Table 1)	pH Adjusted to 7.3	Temp.	Method	Criteria I More Soluble Percentage ± 2%[a]	Criteria II More Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± 0.04[a] (days)	Less Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± SE (days)	Precipitation	Criteria Satisfied
1	SUF	Yes	37°C	Static	25	0.08	46 ± 4	No	I, II
2	SUF	Yes	Room[b]	Static	16 ± 3%	0.13	130 ± 20	No	II
3	SUF	No	37°C	Static	32	0.17	19 ± 2	No	I, II
4	SUF	No	Room	Static	36	0.46 ± 0.08	78 ± 20	No	I, II
E	SUF	No	Room	Static	26	0.13	300	No	I, II
6	SUF-DTPA	No	Room	Static	30	0.17	74 ± 4	Yes	I, II
7	SUF-amino acids	Yes	37°C	Static	31	0.71 ± 0.08	27 ± 3	No	I, II
8-1	SUF	Yes	37°C	Batch	2	0.83 ± 0.5	900 ± 200	Yes	II
8-2	SUF	Yes	37°C	Batch	32	0.08	170 ± 40	Yes	I, II
9-1	SUF	Yes	Room	Batch	2	0.54 ± 0.3	1400 ± 500	Yes	II
9-2	SUF	Yes	Room	Batch	33	0.04	160 ± 20	Yes	I, II
10	SUF	No	Room	Batch	15	0.08	22 ± 1	No	II

[a]The precision was calculated from the nonlinear squares fit to the data. The values at the top of the column apply unless specified below.

[b]~ 20 to 24°C.

E = Ref. 4.5.

Table 4.3 Results of yellowcake dissolution experiments conducted in simulated lung fluid (SLF)

Experiment Number	Solvent (Table 1)	pH Adjusted to 7.3	Temp.	Method	Criteria I More Soluble Percentage ± 2%[a]	Criteria II More Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± 0.04[a] (days)	Less Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± SE (days)	Precipitation	Criteria Satisfied
11	SLF	No	Room[b]	Static	35	0.17	130 ± 20	Yes	I, II
12	SLF	Yes	37°C	Static	39	0.23 ± 0.4	60 ± 10	Yes	I
13	SLF	Yes	Room	Static	31	0.17	19 ± 2	No	I, II
14	SLF	Yes	37°C	Batch	55	0.08	30 ± 5	No	II
K	SLF	Yes	37°C	Batch/ Filter	36	0.79[K] (0.40-0.90)[K]	237 (213-267)[K]	Not Noted	I, II
D	SLF	Yes	37°C	Batch	16.0[D] (13.5-18.5)	0.14[D] (0.13-0.16)	224 (90.9-321.3)	Not Noted	I, II
17	SLF	Yes	Room	Batch	28	0.04	37 ± 3	Yes	I, II
18	SLF	No	37°C	Batch	39	0.17	21 ± 1	Yes	I, II
19	SLF	No	Room	Batch	38	0.08	31 ± 6	No	I, II
20	SLF + DTPA	No	37°C	Batch	25	0.04 ± .01	7 ± 1	Yes	I, II
21	SLF - PO_4	No	37°C	Batch	38	0.08	37 ± 3	Yes	I, II

[a]The precision was calculated from the nonlinear squares fit to the data. The values at the top of the column apply unless specified below.

[b]~ 20 to 24°C.

K = Results of dissolution of powder taken from the same lot used in this report. Values in parenthesis are 90% confidence limits (Ref. 4.4).
D = Mean and 95% confidence limits for dissolution of yellowcake from 10 lots from Mill D. A second component corresponding to an additional 16.5% (12.6-20.4) dissolving with a half-time of 4.4 (3.8-5.0) days was also reported.

Dissolution data were represented by nonlinear least squares fits using two-component negative exponential equations of the form;

$$\% \text{ U undissolved} = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} \quad (1)$$

where A_i are the percentages of the total sample dissolved in each component with $A_1 + A_2 = 100\%$, $\lambda_i(day^{-1})$ are the corresponding dissolution rate constants and t is the elapsed time of the study in days.

Estimates of uranium body burdens were calculated using equations given in ICRP Publication 30 (Ref. 4.13). Maximum and minimum values were calculated using program E04JAF obtained from the Numerical Algorithms Group, Downers Grove, IL.

Criteria for Interpretation of Results

The criteria used to interpret the experimental results were derived from the known ammonium diuranate content of the test yellowcake and available data from human exposures to other uranium oxides. The test yellowcake was shown by infrared analysis to contain 25% ammonium diuranate, a form of UO_3, and the remaining uranium was primarily U_3O_8 (Ref. 4.5). Uranium trioxide is more soluble *in vivo* than U_3O_8 (Ref. 4.7). The primary criteria for a useful *in vitro* dissolution test system are, (1) to determine whether the more soluble fraction of the test yellowcake agrees with the infrared value (25%), and (2) to verify that it dissolves at a rate similar to UO_3 in humans.

Previous research reported the soluble fraction to be 36% (Ref. 4.4) and 26% (Ref. 4.5). The mean of the two values is 31%, and the range is 10% (and includes the infrared value of 25%). The criterion for judging estimates of the soluble percentage of the test yellowcake was chosen to be 20% and 40% and requires that the repeatability of the results will equal or improve precision.

A dissolution half-time of 14 h was calculated using urinary excretion date for a human exposed to UO_3 aerosol (Ref. 4.7). Inhaled UO_3 probably dissolves more rapidly in lung than indicated by the excretion rate. Therefore, a range in dissolution half-times of approximately zero days - immediate dissolution and transfer to blood (Ref. 4.13) - to 1 day was chosen for the second criterion.

The U_3O_8 dissolution rate in humans is variable with half-times ranging from 121 to 4000 days (Ref. 4.7). We do not consider clearance half-times of greater than 1000 days to be reliably estimated by 30-day *in vitro* dissolution experiments, because accumulated errors are propagated far beyond the duration of the experiment. Considering the variability among humans, any agreement between long-term dissolution rates estimated for an individual exposed worker and an *in vitro* study would be fortuitous. Therefore, half-times for U_3O_8 dissolution *in vitro* were calculated but were not used to evaluate a specific experimental technique. Note, however, that in Eq. (1) the intercept of the long-term dissolution component is independent of its slope and contributes to estimates of the relative fractions of more soluble and less soluble yellowcake.

The two criteria were used to construct a model for dissolution of the test yellowcake in lung as if it were inhaled by a worker. *In vitro* test results were considered to approximate the model if: (I) the soluble percentage was estimated to be within 20% and 40%, and (II) the dissolution half-time of the more soluble percentage was less than 1 day. The model is shown graphically in Figure 4.1.

Because the model could not include data from humans that inhaled actual yellowcake, the criteria should be considered only as useful tools to compare previous results and to guide future experiments but should not be rigidly applied. The two criteria are numbered in the order of importance for bioassay data interpretation.

RESULTS

Comparisons of all dissolution rates with the two criteria are shown in Tables 4.2 and 4.3. The relative importance of solvent composition, precipitation, pH, temperature and method for yellowcake dissolution studies are discussed below.

Effect of Solvent Composition

Solvent composition was a major factor in yellowcake dissolution *in vitro*. The SUF solution without DTPA (Table 4.2, Experiment 6) remained cloudy throughout the experiment indicating precipitation of calcium salts. The SUF solvent without amino acids (Experiment 7) agreed with both criteria without precipitate formation. Precipitates were also observed in SLF containing DTPA (Table 4.3, Experiment 20). Because modified solvents generally formed precipitates, the remainder of the paper concerns primarily SLF and SUF (Table 4.1).

Precipitation

When SLF was used with the static method (Table 4.3), a visible precipitate formed on the filter sandwich within the first hour. Although a clear SLF solution could be maintained in the 10 L reservoirs (Table 4.1) by constant stirring, the filter material apparently provided a matrix for precipitation in the presence of yellowcake. Precipitates also formed when SUF was used with the batch method. In Experiments 8 and 9 (Table 4.2), less than 2% of the total uranium dissolved in 30 days. The two experiments were repeated and the results satisfied both criteria. Thus, results obtained in solvents that contained precipitates were considered unreliable and disregarded as discussed below.

Effect of Temperature

Table 4.2 summarizes the results of experiments using SUF. When the static method was used, the results generally satisfied the two criteria regardless of temperature, except for Experiment 2. Comparison of Experiment 1 with Experiment 2 suggests that the lower temperature caused a 9% difference in the more soluble percentage when pH was adjusted. Comparison of Experiments 3, 4 and E shows a 10% range in the more soluble percentage rate when the pH was not adjusted. There was no trend in the dissolution half-time (criterion II) with temperature. Thus, any temperature effects in the ~ 20°C to 37°C range were masked by other factors.

Comparison of results using the batch method (Table 4.2, Experiments 8 and 9) are complicated by precipitation; however, precipitate formation was not related to temperature. Experiment 10 shows that although no precipitate formed, the percentage of the more soluble yellowcake was underestimated. Table 4.2 shows that the combination of solvent and method had a greater influence on yellowcake dissolution than did temperature.

Table 4.3 summarizes the results of experiments using SLF. When SLF was used with the static method (Experiments 11-13) precipitates formed on the membrane filters regardless of temperature or pH conditions, showing that the combination of solvent and method was the primary factor that influenced dissolution. When SLF was used with the batch method and the pH was adjusted (Experiments 14 and 17), precipitate formed at room temperature. When the pH was not adjusted (Experiments 18 and 19) precipitates formed at 37°C, but not at room temperature. Clearly, solvent temperature was not related to precipitate formation. There was no clear trend in the more soluble percentage dissolved (criterion I) with temperature (Table 4.3), nor was there a clear trend in the dissolution half-time (criterion II) with temperature.

Effect of pH

The pH of both solvents was measured to monitor changes that occurred at room temperature after the pH was readjusted to 7.3. The pH increased to greater than 8.0 within 24 h (Figure 4.2) as CO_2 evolved. After 2 to 3 h, the pH was greater than the physiological range of 7.25 to 7.45 (Ref. 4.14) for both solvents. The rapid increase in pH during the first 2 to 3 h was observed

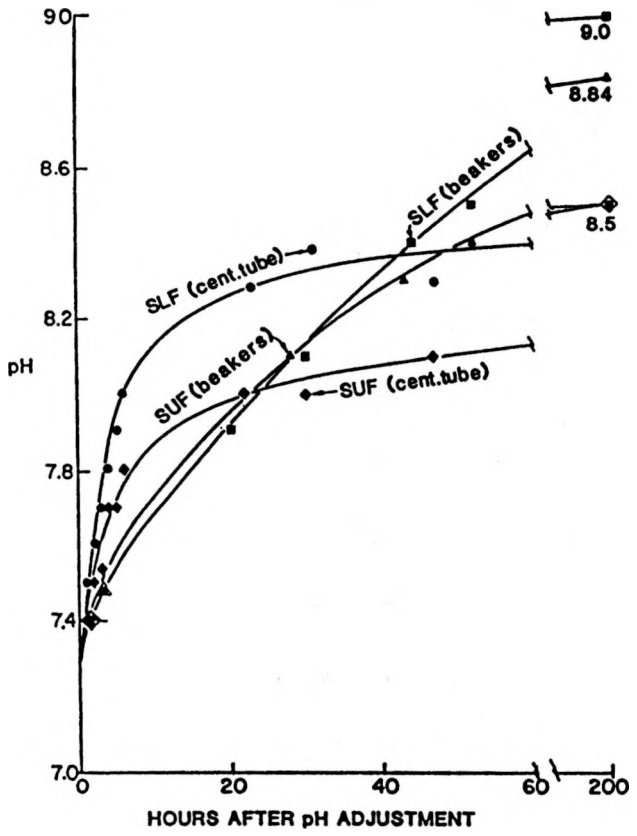

Figure 4.2 Changes in pH of biological fluid simulants with time.

for solvents in both the static and batch methods. Thus, physiological pH cannot be maintained unless the pH is adjusted to 7.25 to 7.45 every 2 to 3 h or the experiments are conducted in a 5% CO_2 atmosphere (Refs. 4.4, 4.11).

The pH of both SLF and SUF approached an equilibrium value of 8.5 as CO_2 evolved in the sealed centrifuge tubes used in the batch method (Figure 4.2). Higher values were approached for the same solvents in beakers that were covered but not sealed (static method). Either SLF or SUF generally approximated the more soluble fraction and its dissolution rate in humans - criteria I and II - regardless of pH. Results of Experiments 2 and 10 (Table 4.2) and 12, 13 and 14 (Table 4.3) did not agree with both criteria, but this was not related to whether the pH was adjusted.

Combination of Solvent and Method

The combination of solvent and method was the most important factor in determining yellowcake dissolution in vitro. Experiments that used SUF with the batch method (Table 4.2, Experiments 8-10), or SLF with the static method (Table 4.3, Experiments 11-13) either formed precipitates or did not satisfy both criteria, regardless of temperature or pH conditions.

Summary of Results

The results may be summarized as follows:

1. The combination of solvent and method was the most important factor; SLF formed precipitates when used with the batch method,
2. Only one of the modified solvents (SUF without amino acids, Table 4.2) did not form precipitates and agreed with both criteria,
3. Within 2-3 h of adjusting the pH to 7.3, it was no longer in the physiological range. However, the experiments generally gave results that satisfied criteria I and II even without adjustment of pH,
4. Temperature between ~ 20°C to 37°C was not an important factor.

DISCUSSION

Precipitation

Except for the irreversible loss of CO_2, changes in the solution composition were limited to shifts in the ionic species distribution that could be readily reversed by readjusting the pH to 7.3 if desired. The changes were not severe and criteria I and II were generally satisfied. Precipitation indicated changes in solution composition that were not readily reversed by stirring for several days at pH 7.3. Experimental results obtained from solvents that formed precipitates were disregarded for three reasons. First, the results obtained from two experiments that formed precipitates were not repeatable. Second, formation of precipitates can introduce errors by interfering with the diffusion of dissolved uranium through the membrane filters used in the static method, or by coprecipitation or postprecipitation of dissolved uranium in either the batch or static method. Third, the errors could not be readily corrected since precipitation was not readily reversible.

Recommended Techniques for Yellowcake Dissolution Experiments

We recommend the following techniques for using in vitro tests to estimate the dissolution properties of yellowcake possibly inhaled by a worker. Since yellowcake lots from the same mill might vary in solubility, the sample studied must be as representative of the inhaled material as possible and should be taken from the same lot or container that the worker handled.

Method

The batch/filter method allows complete separation of the undissolved yellowcake from the mixture (Ref. 4.4). The batch method requires special care to obtain a clear supernatant solution by centrifugation and to avoid removing suspended particles in the pipette; and it is not recommended for the inexperienced user. The static system combines the advantage of better separation of dissolved and undissolved yellowcake with a simpler procedure for changing solvents. The addition of fresh solvent requires only careful transfer of the filter sandwich to fresh solvent in a different beaker. The simplicity of the static method is especially important when a large number of experiments is in progress.

Combination of Solvent and Method

Unmodified SUF or SLF solvents (Table 4.1) gave results that agreed with the human model if SUF was used with the static method or if SLF was used with the batch or batch/filter methods. Either unmodified solvent is recommended, although Experiment 7 (Table 4.2) shows that amino acids might be excluded from SUF. The SUF solvent was more easily maintained as a clear solution.

Temperature and pH

Temperature was not a factor for yellowcake dissolution and it need not be maintained at 37°C. Changes in pH (Figure 4.2) probably contributed to the variability in observed dissolution half-times. The methods for maintaining physiological pH used in previous work were ineffective. If a constant physiological pH is desired, a CO_2-enriched atmosphere should be used (Refs. 4.10, 4.11). However, if results of the experiment are used to interpret bioassay data for yellowcake as shown below, the more soluble fraction can be measured accurately under nonphysiological conditions.

The results obtained using the techniques recommended above are summarized in Table 4.4. Experiment 2 was included although it did not strictly agree with criterion I; but all results must be considered if SUF is recommended for study of unknown yellowcake samples. Temperature and pH conditions were omitted from Table 4.4 for clarity.

Table 4.4 Summary of results obtained using recommended techniques

Experiment Number	Solvent (Table 1)	Method	Criteria I More Soluble Percentage ± 2%[a]	Criteria II More Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± 0.04[a] (days)	Less Soluble Uranium Dissolution Half-Time $T_{1/2}$ ± SE (days)	Criteria Satisfied
1	SUF	Static	25	0.08	46 ± 4	I, II
2	SUF	Static	16 ± 3%	0.13	130 ± 20	II
3	SUF	Static	32	0.17	19 ± 2	I, II
4	SUF	Static	36	0.46 ± 0.08	78 ± 20	I, II
E	SUF	Static	26	0.13	300	I, II
K	SLF	Batch/	36	0.79	237	I, II
		Filter		(0.40 ± 0.90)	(213-267)	
D	SLF	Batch/	16.0	0.14	224	I, II
			(16.5)	(4.39)	(90.9-321.3)[b]	

	Criterion I (%)	Criterion II (days)	Less Soluble Uranium Dissolution Half-Time (days)
In Vitro Repeatability:			
Excluding Study D	29 ± 7[c]	0.2	93
		(0.03-1.5)[d]	(12-741)[d]
Including Study D	29 ± 6[c]	0.4	105
		(0.1 - 1.8)[d]	(14-786)[d]

E = Ref. 4.5.
K = Results of dissolution of powder taken from the same lot used in this report. Values in parentheses are the 90% confidence limits on the dissolution half-times (Ref. 4.4).
D = Mean values for dissolution of yellowcake from 10 lots from Mill D, not including the lot used in this report. Values in parentheses indicate a second dissolution component (Ref. 4.6).

[a]The precision was calculated from the nonlinear least squares fit to the data. The values at the top of the column apply unless specified below.

[b]Mean and 95% confidence limits (Ref. 4.6).

[c]Arithmetic mean ± 2 standard errors.

[d]Geometric means and 95% confidence limits.

Repeatability of Results

The precision of an analytical method must be less than the variability in the measured property of the analyte when all sources of error are included. Further, the method should give repeatable results when applied by different users if it is to be useful.

The standard errors shown in Tables 4.2 and 4.3 were calculated from the curve fitting procedure and represent the degree of agreement between the fitted curve and those data, but do not include the precision of solvent preparation or of the different uranium assay methods used: spectrophotometry (Ref. 4.4) or reflectance fluorimetry (Refs. 4.5, 4.6, and this work). The repeatability of *in vitro* yellowcake dissolution experiments was estimated as shown in Table 4.4 and its influence on bioassay interpretation is discussed below.

Experiment D (Table 4.3) shows mean values for the dissolution rate parameters for 10 yellowcake lots from Mill D (Ref. 4.6), but not including the same lot studied in Refs. 4.4 and 4.5. As such, the values reflect the variability in yellowcake production conditions as well as the conditions of the dissolution experiments and do not strictly reflect the repeatability of in vitro tests. However, because the results agreed with both criteria and all 10 lots dissolved similarly within experimental precision (Ref. 4.6), they were included in Table 4.4. The dissolution curves include a component in addition to those shown in Table 4.3 corresponding to dissolution of 16.5% of the yellowcake with an average half-time of 4.39 days. Including the results of Experiment D (with or without the additional component) did not significantly alter the in vitro test repeatability. The values in Table 4.4 include results obtained by different experimenters using different methods and solvents and, therefore, reflect the overall repeatability of in vitro yellowcake dissolution results. Note that the variability in measured percentage of more soluble material (± 6%) is less than that observed in yellowcake from different mills (Refs. 4.4, 4.5).

The Utility of In Vitro Yellowcake Dissolution Results

Results of routine urinalysis for uranium content might be interpreted according to the revised lung model proposed by the ICRP Task Group on Lung Dynamics in which the in vivo behavior is related to solubility (Ref. 4.13). The equations given in ICRP Publication 30 (Ref. 4.13a) were derived primarily for health physics planning purposes rather than to describe excretion rates of inhaled radionuclides by humans. However, the formulations given specifically for uranium (Ref. 4.13b) were derived from experience gained from human exposures to uranium compounds of different solubilities. Therefore, use of ICRP Publication 30 equations to estimate general trends in urinary excretion by humans that might inhale yellowcake seems justified at this time. Such estimates (particularly at early times after inhalation) will require substantial validation by comparison with results of accidental human exposures or yellowcake inhalation studies using animals (Paper 8, this report).

The kinetic model for inhaled uranium given in ICRP Publication 30 is reproduced in Figure 4.3 with minimal modification. The dashed line in Figure 4.3 indicates a simplifying assumption that clearance from the indicated compartments is to excretion. This assumption recognizes that the model for uranium (Ref. 4.13b) does not address excretion except for direct excretion of a fraction of uranium in skeleton, kidney and other tissues to urine without returning to the transfer compartment. This description is necessary since the equations for uranium metabolism are given as retention equations and include recycle through the transfer compartment.

Lung retention parameters in this model are a function of the clearance classification of the inhaled material. Uranium compounds are classified in ICRP Publication 30 according to clearance half-time as Class D ($T_{1/2}$ < 10 days), Class W ($T_{1/2}$ = 10 to 100 days) or Class Y ($T_{1/2}$ > 100 days). Ammonium diuranate contains ammonia and water adducts of UO_3, a Class D compound (Refs. 4.7, 4.15); and U_3O_8 is a Class Y compound (Ref. 4.13b).

The results of in vitro dissolution experiments using the test yellowcake (Table 4.4) can be expressed as:

$$\% \text{ U undissolved} = (29 \pm 6\%)e^{-0.693\ t/0.4\ \text{days}} + (71\% \pm 6\%)e^{-0.693\ t/105\ \text{days}} \qquad (2)$$

showing that (29 ± 6%) of the test yellowcake dissolved with a half-time that corresponded to a Class D compound and the remaining (71% ± 6%) corresponded to a Class Y compound.

The model shown in Figure 4.3 was used to determine the influence of uranium classification on the appearance of uranium in urine samples and its interpretation for bioassay purposes. The

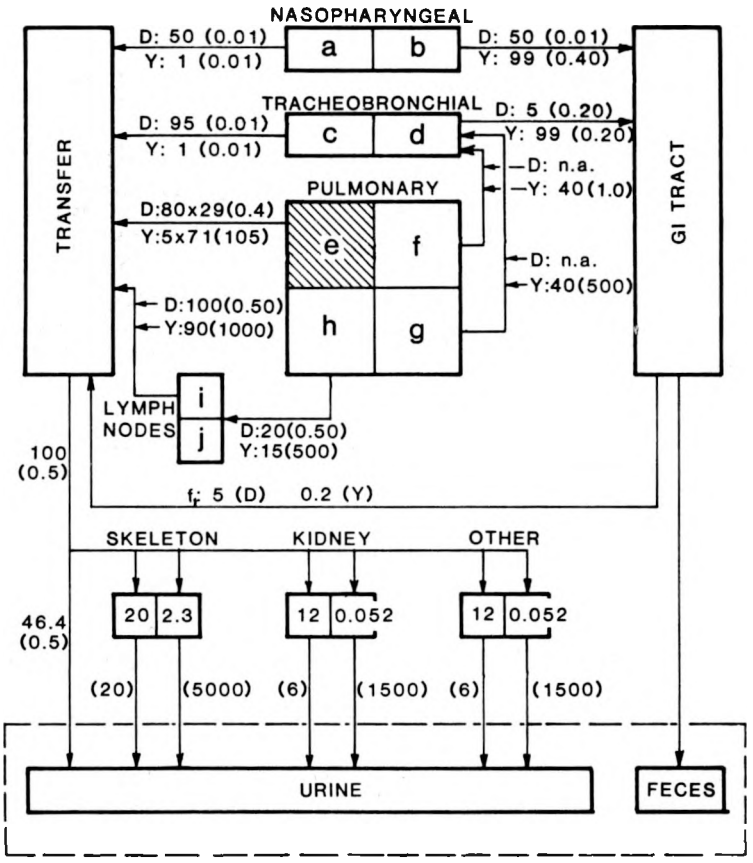

Figure 4.3 Application of ICRP Publication 30 model. Values shown represent the percentages of uranium transferred from each compartment, ( ) indicate transfer half-time in days. Values for transfer from the shaded pulmonary compartment are shown in Table 4.4.

corresponding Class D and Class Y curves (Figure 4.4) represent the estimated uranium body burden for a worker that might have inhaled either of the pure forms. Body burdens were calculated assuming a hypothetical 1 μg uranium/L of urine detected at some time within 100 days after inhalation of yellowcake. The calculations assumed 1.4 liters of urine excreted per day (Ref. 4.3). Thus, if 1 μg uranium/L were measured in a urine sample from a worker 20 days after inhalation of Class Y uranium, the estimated body burden would be 12 mg of uranium. During the first 100 days after inhalation, the estimated body burdens of Class Y and Class D yellowcake differ by a factor of approximately 1000 for the same amount of uranium excreted in urine.

Test results were used to estimate the uranium body uranium body burden for a worker if he inhaled the test yellowcake: a mixture of (29% ± 6%) Class D and (71% ± 6%) Class Y uranium (shaded compartment of Figure 4.4). Separate body burden curves were calculated based on the percentages in each class and the corresponding ICRP clearance classifications for half-times of 0.4 and 105 days (Eq. 2). The two curves were summed and shown in Figure 4.4.

The shaded region shows the effect of the variability of *in vitro* dissolution results on body burden estimates. The maximum and minimum curves were calculated using the 95% confidence limits of Eq. (2) (see Table 4.4). The *in vitro* dissolution model curve, then, represents the estimated body burden within 100 days after inhalation and the shaded region represents the 95% confidence limits of the estimates. Interpretation of bioassay data with the aid of *in vitro* dissolution results avoids the necessity to assume that the worker inhaled either a pure Class D or Class Y uranium compound; and the urinalysis data can be interpreted with greater certainty (Figure 4.4).

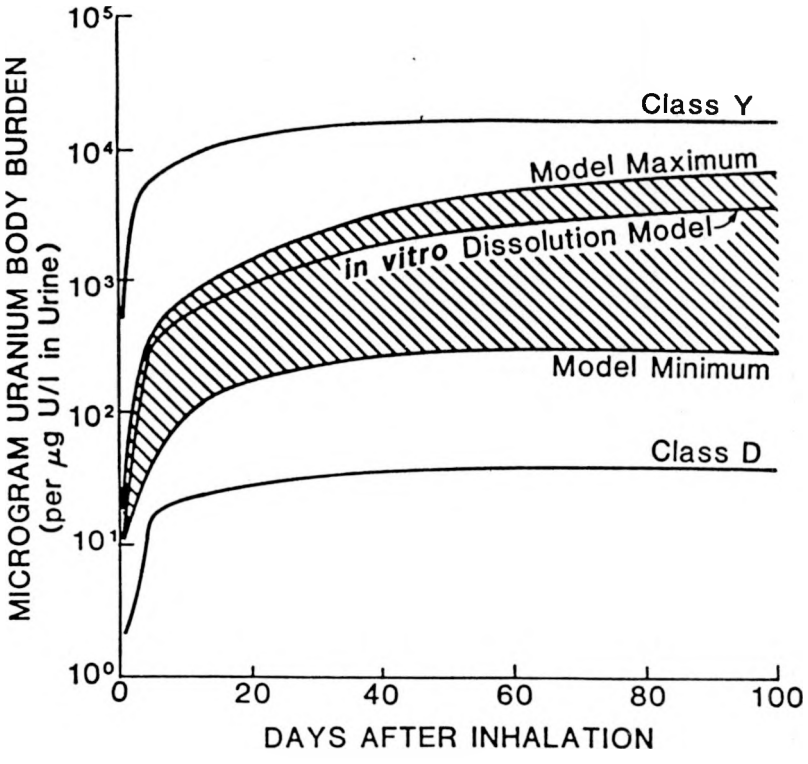

Figure 4.4 Estimated body burdens of the test yellowcake in a hypothetical worker based on in vitro dissolution results compared with ICRP Publication 30 Class D and Class Y models.

The use of in vitro dissolution data could reduce the probability that potential kidney damage would be overlooked in cases where the exposure date is unknown.

The greatest utility of in vitro dissolution results for bioassay interpretation is to estimate the more soluble fraction of the yellowcake in the initial lung deposit by differential dissolution. Dissolution half-times measured in the experiments are useful in confirming that the more soluble and less soluble fractions should be considered as Class D, W or Y compounds. Greater importance should not be given to the in vitro dissolution half-times because the variability among individuals in long-term clearance rates is large.

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5. COMPARISON OF EARLY LUNG CLEARANCE OF YELLOWCAKE AEROSOLS IN RATS WITH IN VITRO DISSOLUTION AND INFRARED ANALYSIS

Abstract — Retention of uranium in lung was determined in rats that inhaled aerosols of commercial yellowcake powders obtained from two mills (Mill A and Mill D) and whose chemical composition and solubilities in vitro were significantly different. Analysis by infrared absorption indicated Mill A yellowcake contained 82% ammonium diuranate (ADU) and 18% U_3O_8. The Mill D powder contained 25% ADU and 75% U_3O_8. In vitro dissolution studies indicated for the Mill A sample, ~ 85% of the uranium had a dissolution half-time ($T_{1/2}$) of < 1 day, with the remainder dissolving with a half-time of 500 days. For the Mill D sample, 25% had $T_{1/2}$ < 1 day and 75% had $T_{1/2}$ of 300 days. Groups of 50 rats were exposed by nose-only inhalation to aerosols of either Mill A or Mill D yellowcake. Rats were sacrificed in groups of 5 at intervals through six months after exposure. Selected tissues and excreta samples were assayed by fluorimetry to determine their uranium contents. For the Mill A yellowcake, 78% initial lung burden cleared with $T_{1/2}$ of 0.5 days, and 22% with $T_{1/2}$ of 240 days. For the Mill D yellowcake, 25% of the initial lung burden cleared with a $T_{1/2}$ of 3.5 days and 75% with $T_{1/2}$ of 110 days. Thus, the lung clearance of uranium in the rat mimicked the in vitro dissolution data and supported classification of ADU as a Class D compound ($T_{1/2}$ = 0.5 days) and U_3O_8 as a Class Y ($T_{1/2}$ > 100 days) material.

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The most likely route of exposure for uranium mill workers is by inhalation of refined uranium ore (yellowcake) which usually consists of a variable mixture of ammonium diuranate (ADU) and U_3O_8. The objective of the experiments described here was to compare the in vivo behavior of uranium in inhaled yellowcake with results of infrared assay data and in vitro dissolution rate data (Papers 3 and 4, this report). Laboratory rats were exposed by inhalation to aerosols of two yellowcake samples that differed widely in chemical composition and dissolution rate. The translocation and retention parameters for the uranium deposited in lung were compared to the ADU and U_3O_8 compositions and in vitro dissolution properties of the two yellowcake samples.

MATERIALS AND METHODS

Animals

A total of 144 (72 males and 72 females) laboratory-raised, specific pathogen-free, F344/Crl rats, 10 to 12 wk-old at exposure were used. The means and standard deviations of the body weights at the time of exposure were 240 ± 30 g for males and 160 ± 10 g for females. The rats were housed individually in polycarbonate cages (45 cm x 25 cm x 20 cm) containing a bedding of aspen wood shavings (American Excelsior, Oshkosh, WI). Food (Lab Blox®, Allied Mills, Chicago, IL) and water were available to the rats at all times. The cages were cleaned weekly and the water bottles changed twice weekly. During collection of excreta samples, rats were housed individually in stainless steel, wire bottom metabolism cages (18 cm x 18 cm x 25 cm; Wahman's Manufacturing Co., Timonium, MD). Animal rooms were maintained on a 12 h light cycle (0600 h to 1800 h) at temperatures of 20-23°C and a relative humidity of 40 to 60%.

Yellowcake Samples

Two commercial yellowcake samples obtained from acid-leach process uranium mills (Mill A and Mill D) were used. Quantitative infrared analysis indicated the Mill A sample contained 82% ADU and 18% U_3O_8; the Mill D sample contained 25% ADU and 75% U_3O_8 (Ref. 5.1).

Aerosol Generation and Characterization

Polydisperse aerosols were generated from the yellowcake powders using a DeVilbiss Model 175 powder blower fixed to a mechanical shaker (Ref. 5.2). The aerosol was sampled for particle size measurement by cascade impactors (Ref. 5.3) and for aerosol concentration determination by 0.45 μm pore-size, 25 mm diameter membrane filters during the course of the rat exposures.

Animal Exposures

Fifty rats (25 males and 25 females) were simultaneously exposed by nose-only inhalation to either of the two yellowcake aerosols using a Lovelace multiport chamber (Ref. 5.4).

Sacrifice Schedule

Five rats exposed to each aerosol were sacrificed at 2 h, 1, 2, 3, 4, 8, 16, 35, 73 and 179 days after exposure. Sacrifices were accomplished by intraperitoneal injection of 1 mL (50 mg) of sodium pentobarbital followed by exsanguination. The five rats were divided approximately equally between the sexes (i.e., 3 males and 2 females were sacrificed at the first time period and 2 males and 3 females at the second time period, etc.).

Tissue samples taken for assay of uranium were the head pelt, remaining pelt, blood collected at sacrifice by heart puncture, head and trachea, lung, kidney, liver, gastrointestinal tract and contents, spleen, tracheobronchial lymph nodes, femurs and remaining carcass. A central section, cut longitudinally from one of the kidneys of each rat, was fixed in 10% neutral buffered formalin and processed by standard procedures for histopathological examination.

Unexposed Control Rats

Fourteen unexposed rats were used as a control group. The control rats were sacrificed singly at approximately 2 h, 1, 2, 3, 4, 8, 16 and 32 days after the starting date of the study and in groups of three at 64 and 180 days. Tissues and excreta from the control rats were analyzed for uranium content to determine the biological background levels. Sections of kidneys of control rats were fixed and processed as described above for histopathological examination.

Excreta Collections

Urine, feces, and cage-wash samples were collected from three of the rats in both the 35-day and the 179-day sacrifice groups. The samples were collected daily for four days after exposure and then one 3-day collection was made each week until sacrifice in the 35-day sacrifice group and through 60 days in the 179-day sacrifice group. One 3-day collection was made each month thereafter until sacrifice at 179 days in the latter group. Excreta samples from two control rats were collected on the same schedule as the 179-day sacrifice group.

Uranium Analysis

All biological samples were assayed for uranium content by reflectance fluorimetry (Paper 2, this report). Endogenous uranium levels in rats are measurable and can be highly variable, both among and within sample types. Therefore, uranium assay was done on tissues and excreta of rats which were not experimentally given uranium compounds and were of similar age to the experimental animals. The results of these analyses are summarized in Table 5.1. The mean uranium content of both tissue and excreta samples were used as biological matrix blanks and were subtracted from the values measured in the experimental-treated animals. Because no correlation between uranium content and the age, sex, or size of the rats could be found, the intersample variability could not be reduced.

Data Analysis

The mean amount of uranium in the lungs of the five rats sacrificed 2 h (0.08 day) after exposure was used to represent the initial lung burdens of all rats exposed to the same aerosol. The initial lung burden is considered here to be the amount of uranium deposited in the bronchial and alveolar regions of the lungs. The lung burdens at later sacrifice times after exposure were then expressed as percentages of the initial lung burden defined in this way. The mean amount of

Table 5.1 Uranium content of tissue and excreta samples from control rats ranging in age from 10 to 36 weeks

Sample	Number	Uranium Content, ng per Sample	
		Mean	Standard Deviation
Lung	26	180	80
Liver	25	240	100
GI Tract and Contents	26	7900	3700
Kidney	26	130	66
Femur	23	61	31
Urine	17	92	81
Feces	6	5700	3800

uranium in all of the tissues (including the gastrointestinal tract) of the five rats sacrificed 2 h after exposure was taken as the initial body burden of all rats exposed to the same aerosol.

Two-component negative exponential retention curves [Eq. (1)] were fitted to the lung burden data by a nonlinear least squares technique (Ref. 5.5):

$$\% \text{ initial lung burden retained } (t) = A_1 e^{-0.693t/T_1} + A_2 e^{-0.693t/T_2} \quad (1)$$

where A_1 and A_2 are early and late retention components in percent, and t is time after exposure in days. T_1 and T_2 are the clearance half-times (in days) for components A_1 and A_2, respectively. Levels of significance of differences between uranium retention curves for organs of rats exposed to the two materials were determined by an F test. Lung clearance curves for the separate sexes exposed to the same yellowcake material were not significantly different ($p > 0.05$) and therefore the data for both sexes were combined.

RESULTS

Aerosol Characteristics

The Mill A yellowcake aerosol had a mass median aerodynamic diameter (MMAD) of 1.6 μm, and a geometric standard deviation (σ_g) of 2.7. The Mill D yellowcake aerosol had a MMAD of 1.4 μm and a σ_g of 2.7. Particle size distribution measurements indicated these aerosols had heterogenous particle size distributions similar to those reported previously for yellowcake aerosols sampled in uranium mills (Paper 1, this report).

Uranium Retention in the Lung

The mean and standard error of the initial lung burdens for rats exposed to Mill A yellowcake was 0.014 ± 0.002 mg U/kg of body weight. The initial lung burden for rats exposed to Mill D yellowcake was 0.12 ± 0.04 mg U/kg body weight. These lung burdens were well below the 30-day LD_{50} value of 48 mg U/kg for rats exposed by inhalation to soluble uranium compounds (Ref. 5.6). Lung burdens of uranium in rats serially sacrificed after exposure to the two aerosols were expressed as percentages of initial lung burdens for each exposure group. The parameters for the equations of the resulting retention curves are compared to the *in vitro* dissolution data in Part I of Table 5.2 The lung retention curves for the two materials were significantly different ($p < 0.005$).

It seemed likely that the difference in the slopes of the lung burden curves was not significant and that the statistically significant difference between the curves actually resulted from the difference in the percentages of the more soluble component associated with the two materials. Therefore, regressions having common slopes were fitted to the lung burden data (T_1 and T_2 of Eq. (1) for the Mill A material are equal to T_1 and T_2 for the Mill D material). The resulting curves are shown as the solid lines in Figure 5.1 and the parameters for the equations of these curves are presented in Part II of Table 5.2. The increase in the deviations of the data points from the curves fitted in this way was not significant ($p > 0.25$). Therefore, the curves (solid lines in Figure 5.1) and retention parameters presented in Part II of Table 5.2 adequately represent the data.

These curves were compared to curves that might be expected, based on the ADU and U_3O_8 percentages of the two yellowcake materials as determined by infrared analysis and the *in vitro* dissolution rates (Ref. 5.1). Retention curves having more rapid and more slowly cleared components equivalent to the ADU and U_3O_8 percentages, respectively, were fitted to the lung burden data. The resulting curves are shown as the dashed lines in Figure 5.1. The lung retention parameters (listed on the figure and in Part III of Table 5.2) are for the dashed-line

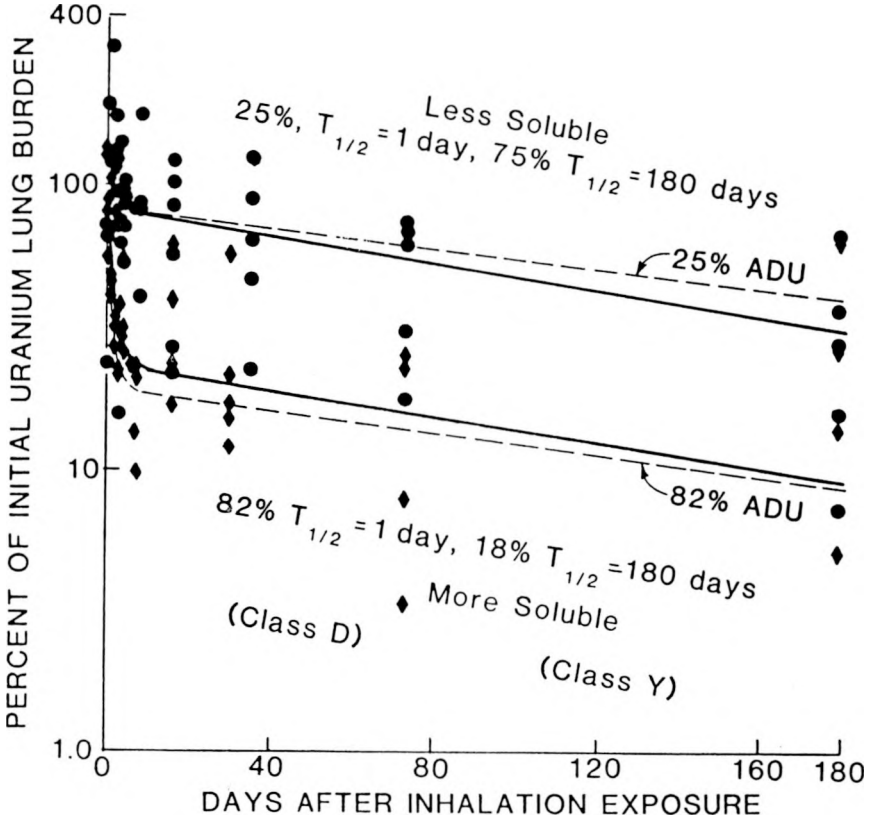

Figure 5.1 Uranium lung retention curves (solid lines) with common negative exponentials fitted to the lung burden data for rats exposed to yellowcake aerosols. The dashed lines represent the regressions having early components equivalent to the ADU percentage composition of the two yellowcake materials (25% for the Mill D and 82% for the Mill A yellowcake). The regression parameters listed on the figure are for the dashed lines. The lung retention parameters for the solid lines are listed in Section II of Table 5.1.

curves. The regressions represented by the dashed lines were not significantly different from those represented by the solid lines ($p > 0.10$). Therefore, the retention parameters shown in Figure 5.1 adequately represent the *in vivo* retention of yellowcake in lung and agree with the results of infrared analyses and *in vitro* dissolution studies (Ref. 5.1). The *in vitro*

Table 5.2 Lung retention parameters[a] for rats that inhaled aerosols of yellowcake compared to *in vitro* dissolution rate parameters and infrared analysis of yellowcake composition[b]

Yellowcake Aerosol	Retention[a] or Dissolution[b] Parameters A_1 (%)	T_1 (days)	A_2 (%)	T_2 (days)
Part I. Lung Retention Parameters from Individual Curve Fits Compared to *In Vitro* Dissolution Rate Parameters:				
Mill A				
Lung Retention	78 ± 6[c]	0.5 ± 0.2[c]	22 ± 6[c]	240 ± 130[c]
In Vitro[b]	86 ± 14	0.08 ± 0.83	15 ± 10	500 ± 300
Infrared[b]	82% ADU		18% U_3O_8	
Mill D				
Lung Retention	25 ± 18[c]	3.5 ± 2.3[c]	75 ± 18[c]	110 ± 30[c]
In Vitro[b]	26	0.13	75	300
Infrared[b]	25% ADU		75% U_3O_8	
Part II. Lung Retention Parameters From Curve Fits With Common Slopes:				
Mill A	76	0.5[d]	24	130[d]
Mill D	22	0.5[d]	78	130[d]
Part III. Lung Retention Parameters from Curve Fits with Common Slopes and Percentages Selected to Agree with Infrared Data[e]:				
Mill A	82	1.0[d]	18	180[d]
Mill D	25	1.0[d]	75	180[d]

[a] $\%ILB\ (t) = A_1 e^{-0.693t/T_1} + A_2 e^{-0.693t/T_2}$.

[b] *In vitro* dissolution rate parameters and infrared analysis from Ref. 5.1.

[c] Mean and standard deviation.

[d] The retention half-times for the two materials were constrained to be equal by the computer program used.

[e] Percentages for early and late retention components preselected to agree with infrared analysis of yellowcake composition (Ref. 5.1).

dissolution studies, supported by the bronchoalveolar lung clearance rate, indicate that ADU can be considered as a Class D compound ($T_{1/2}$ < 10 days) and U_3O_8 behaves as Class Y ($T_{1/2}$ > 100 days) or (within the precision of the data) possibly Class W ($T_{1/2}$ = 10-100 days) material (Ref. 5.7, 5.8).

Excretion of Uranium

The background levels of uranium in the feces of unexposed control rats were high and variable (Table 5.1). The fecal excretion of uranium for both groups of rats exposed to yellowcake approached background levels by 4 to 8 days after exposure. Figure 5.2 shows the daily rate of urinary excretion of uranium for the two groups of rats. Because of the wide deviations of the data points, the data are presented without fitted excretion rate curves. However, the data show that the urinary excretion rate was generally higher in rats exposed to the Mill A yellowcake than

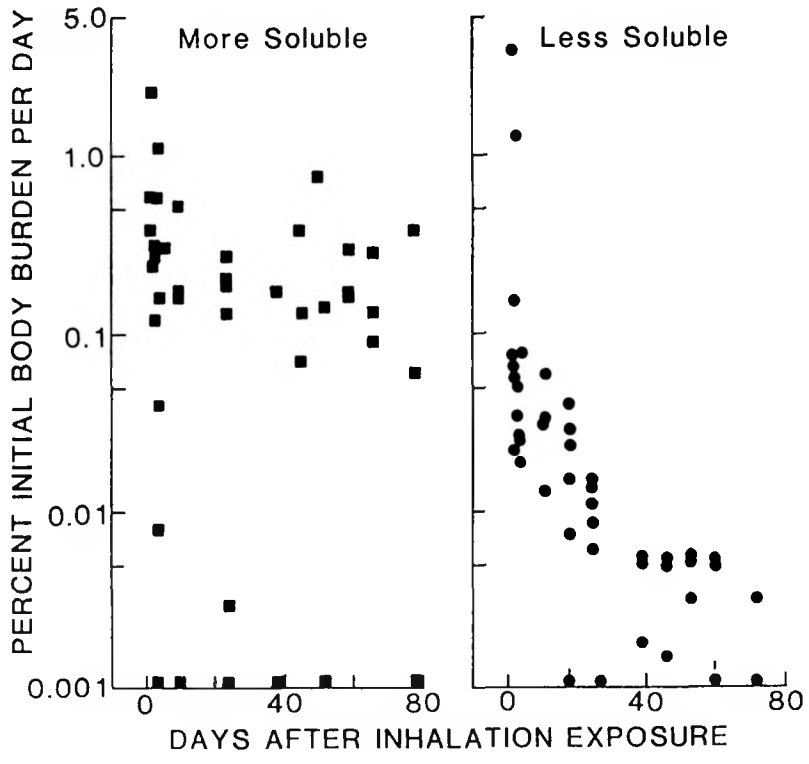

Figure 5.2 Urinary excretion of uranium in rats exposed to yellowcake aerosols.

in those exposed to the Mill D yellowcake, especially during the period from 20 to 80 days after exposure.

Tissue Distribution of Uranium

The initial body burden of uranium was 0.14 ± 0.03 (mean ± standard error) mg U/kg of body weight for rats exposed to the Mill A yellowcake and 4.6 ± 1.6 mg U/kg for those exposed to the Mill D powder. The soluble (ADU) portion of the initial body burden was 0.12 mg U/kg for the rats exposed to the Mill A yellowcake (85% ADU) and 1.15 mg U/kg for those exposed to the Mill D (25% ADU) material. Thus, the body burden of soluble uranium compound (ADU) was 10 times higher in the rats exposed to the Mill D yellowcake aerosol than those exposed to the Mill A material.

The uranium concentration in kidney reached a maximum value of 13.5 ± 7.5 µg/g of wet tissue for rats exposed to the Mill D yellowcake and 1.4 ± 1.7 µg U/g for those exposed to the Mill A material. Thus, the difference in concentration of uranium in the kidneys of the two groups of rats correlates with the difference in the soluble portion of the initial body burden of yellowcake. Very little uranium was detected in the femurs of rats in either group, even though the endogenous levels of uranium were low (Table 5.1).

Histopathological Observations

Significant renal lesions seen were in the rats that exhibited the highest concentration of uranium in the kidneys. Focal acute tubular necrosis in the proximal tubules near the corticomedullary junction of the kidneys of these rats was first seen at 3 days after exposure. By 8 days after exposure, the lesions were the most severe of any sacrifice time. Tubular necrosis was present as well as cellular and protein casts in the tubules. There was also a hyperplasia of the tubular epithelial cells in the damaged areas, indicating repair of the lesions. Although these lesions at 8 days were notable, they were not widespread. By 16 days after exposure, the proliferation of tubular epithelial cells was still present but there were no

acute lesions of necrosis. By 35 days after exposure, no lesions were seen. No lesions were seen in 12 unexposed control rats.

DISCUSSION

The percentages of uranium in the two yellowcake samples that cleared from the lungs with a shorter half-time or with a longer half-time agreed well with the ADU and U_3O_8 percentage composition of the two yellowcake samples as indicated by results of infrared analysis (Table 5.2). Galibin and Parfenov (Ref. 5.9) reported results of studies of retention of uranium following inhalation exposure of albino rats to aerosols of ADU, U_3O_8 or UF_4. These investigators used pure compounds rather than mixtures. They noted that one year after a single inhalation exposure, the lung content of U_3O_8 was five times more than that of ammonium diuranate. Results of our studies indicate that retention of uranium from inhaled yellowcake aerosols consisting of variable mixtures of ADU and U_3O_8 is determined by the composition of the inhaled yellowcake. The U_3O_8 is retained longer than ADU when inhaled as a mixture.

The lung clearance classification (Ref. 5.7) of ammonium diuranate (Class D, W or Y) is not given in ICRP Publication 30, although UO_3 is assigned to Class W (Ref. 5.8). Results of *in vitro* dissolution studies indicated that ADU should be placed in Class D along with UO_3 (Paper 4, this report). Morrow *et al.* reported a lung retention half-time of 4.7 days for UO_3 inhaled by dogs (Ref. 5.10). Results presented here indicate that the ammonium diuranate portion of yellowcake aerosol inhaled by rats cleared with a half-time of 0.5-3.5 days and supports classification of ADU as a Class D material. The U_3O_8 portion of the inhaled yellowcake cleared from the rat lung with a half-time of 110-240 days and agreed with results of *in vitro* dissolution studies indicating it should be considered as a Class Y material (Paper 4, this report). It has long been recognized that the lung clearance half-times for insoluble particles inhaled by rats is much shorter than the 500 day half-time generally used in calculations for clearance of Class Y material from the human lung (Refs. 5.8, 5.11). Thus, rat data do not adequately represent the human case in regard to the mechanical clearance of particles.

Excretion of uranium in urine could not be quantitatively related to ADU content or *in vitro* dissolution rate although it was generally greater for rats exposed to the Mill A yellowcake. Thus, while these studies have indicated that lung clearance of uranium from inhaled yellowcake depends upon composition of the material, additional studies using the Beagle dog were initiated to provide a basis for interpretation of bioassay data (Paper 8, this report).

CONCLUSIONS

These results support the following conclusions: (1) the lung retention of uranium in rats exposed to yellowcake aerosols is related to the ratio of the ADU to U_3O_8 composition of the inhaled material. (2) The *in vivo* results agreed with previous *in vitro* results. (3) Yellowcake can be considered for health protection purposes to be a mixture of ADU and U_3O_8. Its composition can be determined by *in vitro* analysis. (4) Histological changes in the kidneys of rats exposed to yellowcake were similar to those reported for rats exposed to pure uranium compounds and occurred at similar tissue concentrations of uranium (Ref. 5.6). (5) Clearance of ADU from rat lungs approximates that of a Class D compound.

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6. EARLY CLEARANCE OF URANIUM FROM SIMULATED WOUNDS CONTAMINATED BY YELLOWCAKE IN THE RAT

Abstract — A study to assess the early translocation and retention of uranium from wounds contaminated with yellowcake was conducted by implanting yellowcake samples subcutaneously in rats. Whole-body retention of uranium was related qualitatively to the solubility of the implanted yellowcake. Whole-body clearance of uranium from relatively soluble yellowcake consisting of 82 to 100% ammonium diuranate (ADU) and 0 to 18% U_3O_8 was faster than that of uranium from relatively insoluble yellowcake consisting of 25% ADU and 75% U_3O_8. For the more soluble yellowcake, 77% of the initial body burden of uranium (IBB) cleared with a half-time ($T_{1/2}$) of 2 days; the remaining 23% IBB cleared with a $T_{1/2}$ of 15 days. For the less soluble material, 52% IBB cleared with a half-time of 0.6 days; the remaining 48% IBB cleared with $T_{1/2}$ of 29 days.

PRINCIPAL INVESTIGATORS
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A. F. Eidson

Uranium mill workers can be exposed to uranium compounds by inhalation, ingestion, wound contamination or by absorption from the eyes or mucous membranes. Studies recently completed using rats (Paper 5, this report) and Beagle dogs (Paper 8, this report), evaluate the lung retention and translocation of uranium from inhaled yellowcake aerosols. Although toxicologic studies on dermal absorption of uranium compounds have been conducted (Ref. 6.1), absorption of yellowcake powder or uranium compounds from contaminated wounds has not been investigated. The objective of this study is to determine the rate of absorption and the patterns of retention, translocation and excretion in rats exposed to one of two types of yellowcake powder administered via subcutaneous implantation.

MATERIALS AND METHODS

Yellowcake Powders

Two yellowcake materials having known solubility properties were selected to provide data on retention and translocation of uranium from wounds contaminated with yellowcake powders that differed widely in composition and solubility (Ref. 6.2). The less soluble powder was obtained from Mill D and contained 25% of its uranium as more soluble ammonium diuranate (ADU) and 75% as less soluble U_3O_8. The more soluble material was composed of ~ 82% ADU and ~ 18% U_3O_8 or of ~ 100% ADU obtained from Mill B. The Mill B yellowcake was used because the yellowcake sample from Mill A was exhausted before completion of the studies. Because the *in vitro* solubilities of the Mill A and the Mill B samples were similar (Ref. 6.2), the clearance data for these two materials were combined and reported below as clearance rates for "more soluble" yellowcake powder.

Animals

Fifteen male, F344/Crl, specific pathogen-free, laboratory-reared rats, 10-12 wk of age, were used to complete the retention studies of each yellowcake material. The mean ± 1 SE of the body weights was 269 ± 6 g. Rats were fed Lab Blox (Allied Mills, Chicago, IL) and watered *ad libitum*. Water bottles were changed two times a week. Rats were housed in polycarbonate cages (45 x 25 x 20 cm) containing a bedding of hardwood chips from birth until selection for the study. For this study, rats were individually housed in stainless steel wire-mesh bottom cages (18 x 18 x 25 cm, Wahman's Manufacturing Co., Timonium, MD) during a 14-day conditioning period before implantation and until sacrifice following implantation with yellowcake. Animal rooms were maintained on a 12 h light cycle (0600 to 1800 h) at temperatures of 20-23°C and a relative humidity of 40 to 60%.

Yellowcake Implantations

Anesthesia was induced in rats with a 5% mixture of halothane (Halocarbon Laboratories, Inc., Hackensack, NJ) vaporized in 95% O_2 at a flow rate of 0.6 liter/min and maintained with 2% halothane via a face mask. Hair was clipped from the dorsal thoracic area and a 1 cm incision was made through the skin on the dorsal midline between the scapulae. The dorsal midline was chosen for the implant to prevent the rat from removing the sutures. A weighed dose of yellowcake was subcutaneously implanted and the skin was sutured with VETAFIL BENGEN (S. Jackson, Inc., Washington, DC). The incision was then sprayed with Aeroplast plastic dressing (Parke-Davis and Co., Greenwood, SC). Fourteen rats were implanted with either material at a dose of 10 mg U/kg body weight. Two of the 14 rats in each group were sham implanted and retained as controls to provide data on background levels of uranium in the tissues of unexposed rats.

Sacrifice Schedule

Rats implanted with each material were sacrificed in groups of 3 at intervals of 4, 12, 24 and 72 h after implantation. Sacrifices were accomplished by intraperitoneal injection of 1 mL (50 mg) of sodium pentobarbital followed by exsanguination by heart puncture. Rats were weighed prior to sacrifice and the individual organs were weighed at necropsy.

Fluorimetric assay for uranium (paper 2, this report) was conducted on the following tissues from each rat:

1. Section of soft tissue surrounding the site of the implantation (2 x 2 cm excised to the depth of the vertebral column),
2. Kidney,
3. Gastrointestinal tract,
4. Pelt,
5. Soft tissue (all remaining viscera),
6. Remaining carcass (muscle, brain and skeleton).

Two 2.6 mg of the dry powder of each yellowcake material were analyzed to determine the percentage of uranium recovered by the analytical procedures used.

Analysis of Retention Data

The sum of the uranium contents of the tissues of sacrificed rats was expressed as a percentage of the uranium implanted initially, i.e., the initial body burden (IBB). Two-component negative exponential functions [Eq. (1)] were fitted to the whole-body retention data by a nonlinear least squares technique (Ref. 6.3):

$$\%IBB(t) = A_1 e^{-0.693t/T_1} + A_2 e^{-0.693t/T_2} \quad (1)$$

where A_1 and A_2 are early and late retention components in percent, t is time after exposure in days and T_1 and T_2 are the clearance half-times for components A_1 and A_2, respectively.

Retention functions for the rats exposed to the more soluble and less soluble yellowcake powder were compared to determine effects of composition of the implanted yellowcake powder on uranium retention. Levels of significance of differences between uranium retention curves for the two groups were determined by an F test (Ref. 6.3).

RESULTS

Figure 6.1 shows the uranium retention curves fitted to all of the whole-body retention data for the two yellowcake samples, and the fitted parameters for the retention functions are listed in Table 6.1. For the more soluble yellowcake, 77% IBB cleared with a half-time of 2 days; the remaining 23% IBB cleared with $T_{1/2}$ of 15 days. For the less soluble yellowcake, 52% IBB cleared

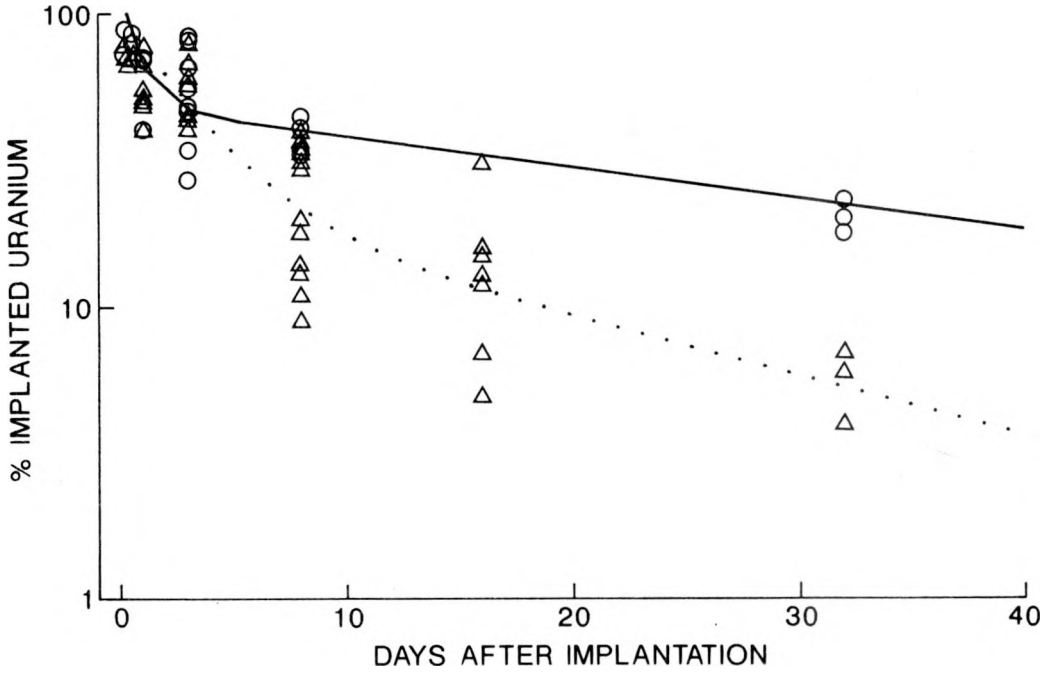

Figure 6.1 Whole-body retention of uranium in rats subcutaneously implanted with less soluble yellowcake (solid line, data points as circles) or with more soluble yellowcake (dotted line, data points as triangles).

Table 6.1 Retention of the initial whole-body burden (IBB) of uranium in rats receiving subcutaneous yellowcake implants

Yellowcake Sample	Retention Parameters[a] A_1 (%)	T_1 (days)	A_2 (%)	T_2 (days)
More Soluble Yellowcake:				
Whole-body	77 ± 10[b]	2.1 ± 0.9	23 ± 10	15 ± 10
Less Soluble Yellowcake:				
Whole-body	52 ± 5	0.6 ± 0.3	48 ± 5	29 ± 6

[a] $\%IBB(t) = A_1 e^{-0.693t/T_1} + A_2 e^{-0.693t/T_2}$

[b] Parameter ± one SD

with a half-time of 0.6 days; the remaining 48% IBB cleared with $T_{1/2}$ of 29 days. Whole-body retention functions for the two yellowcake samples were significantly different ($p < 0.005$).

DISCUSSION

Whole-body uranium clearance half-times were significantly shorter for rats implanted with the more soluble yellowcake than for those implanted with the less soluble material. The differences in percentages for the two components of the clearance functions for the two powders were in qualitative agreement with differences in chemical composition of the yellowcake powders, but did not agree quantitatively.

The generally shorter retention half-time of the more soluble yellowcake indicates that solubility is a factor in the whole-body retention of subcutaneously implanted yellowcake. However, the lack of quantitative agreement between the percentage of more soluble yellowcake and the percentage cleared in the rapid component indicate that mechanical clearance, regardless of solubility, is also a major clearance mechanism. Results from this study indicate that wounds contaminated with yellowcake represent a significant route of entry of uranium into the body. Those responsible for protection of the health and safety of uranium mill workers must be aware of this potential risk.

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7. EFFECT OF ANIMAL CAGING ON NEPHROTOXIC RESPONSE OF RATS TO URANIUM FROM SUBCUTANEOUSLY IMPLANTED YELLOWCAKE

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Abstract — Animal studies of the toxicity and metabolism of radionuclides and chemical substances usually require housing rats in metabolism cages during excreta collection. Response of rats to toxic substances may be affected by environmental factors related to the type of cage used. Dose-response studies were conducted to assess the effects of two types of cages on the nephrotoxic response of rats to uranium from implanted refined uranium ore (yellowcake). The $LD_{50/21}$ days was 6 mg of yellowcake per kilogram body weight (6 mg/kg). The 95% confidence interval (CI) was 3-8 mg/kg for rats housed in metabolism cages beginning on the day of implantation (naive rats). For rats housed in metabolism cages for 21 days before implantation (acclimated rats) the $LD_{50/21}$ days was 360 mg U/kg (CI = 220-650 mg U/kg), which was the same value obtained for rats housed continuously in polycarbonate cages. This significant difference ($p < 0.01$) in response of naive rats compared to response of acclimated rats appeared related to a significantly lower water consumption by the naive rats.

Information on the influence of environmental factors, such as housing, on the response of laboratory animals to toxic agents is essential for proper design, interpretation, and use of animal toxicity test data (Refs. 7.1-7.3). This study was conducted after it was observed that F344/Crl rats, reared in polycarbonate cages, then housed in metabolism cages immediately after subcutaneous implantation of refined uranium ore (yellowcake) at a dose of 10 mg U/kg body weight, died from uranium toxicity within 8 days of the implantation. Identically exposed rats maintained in polycarbonate cages showed no overt toxic effects (Ref. 7.4).

The study reported here compared toxicity after implantation of yellowcake into rats that were: (1) housed only in polycarbonate cages, (2) housed in metabolism cages during a 21-day period of acclimation before implantation with yellowcake, or (3) initially housed in polycarbonate cages then housed in metabolism cages immediately after implantation with uranium (naive group). The amount of food and water consumed and changes in body weight were assessed for rats housed in the two cage types.

MATERIALS AND METHODS

Refined Uranium Ore

Powders containing the soluble compound ammonium diuranate (ADU) as the major component were used. The powder consisted of 82-100% ADU and 0-18% U_3O_8 (Ref. 7.5).

Animals

One hundred twenty-two male F344/Crl, specific pathogen-free, laboratory-raised rats, 10-12 wk of age, with initial body weights of 260 ± 4 g (mean ± SEM) were used. Rats were weighed twice weekly from 3 wk before implantation until death or sacrifice 21 days after implantation. Rats were fed Lab Blox (Allied Mills, Chicago, IL) and water ad libitum. Water bottles were changed two times a week.

From birth until entry into the study, all rats were housed in polycarbonate cages (45 x 25 x 20 cm) fitted with filter caps and containing a bedding of hardwood chips or aspen wood shavings (American Excelsior, Oshkosh, WI). Cages and bedding were changed weekly. Animal rooms were maintained on a 12 h light cycle at temperatures of 20-22°C and a relative humidity of 20 to 60%.

Experimental Design

Before implantation of the uranium, rats were divided into three groups (Fig. 7.1). Group 1 (30 rats) was housed individually in stainless steel, mesh-bottomed metabolism cages (18 x 18 x 25 cm, Wehman's Manufacturing Co., Timonium, MD) beginning on the day of implantation and until death or sacrifice 21 days after implantation. Group 2 (45 rats) was housed individually in metabolism cages for 21 days of acclimation before implantation of uranium and was housed in this cage type until death or sacrifice 21 days after implantation. Group 3 (47 rats) was housed individually in polycarbonate cages for 21 days before implantation and until death or sacrifice 21 days after implantation.

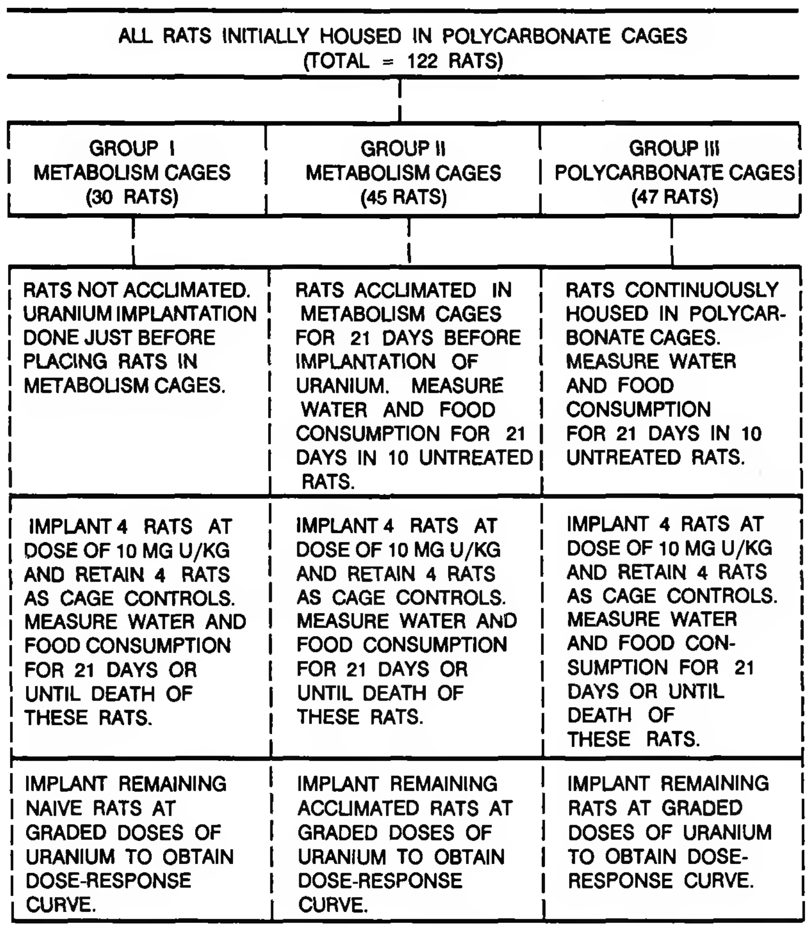

Figure 7.1 Experimental design to study effect of animal caging on nephrotoxic response.

Water and Food Consumption

Water and food consumption were measured daily for 10 untreated rats in Groups 2 and 3 during the 21-day period of acclimation. Water was supplied *ad libitum* in 100 mL graduated bottles fitted with sipper tubes. Water remaining in the bottle was measured each morning, daily water consumption was calculated and bottles were refilled to the 100 mL mark. Food consumption was measured by supplying 100 g of food and weighing the amount of food remaining each morning. Body weights for these subgroups of rats were measured twice per week during this period.

Four rats in each group were then exposed to uranium (10 mg U/kg) by subcutaneous implantation, and four unexposed rats in each group were retained as cage controls. Water

consumption was measured daily from the day of implantation until death or sacrifice 21 days after implantation. The remaining rats were then implanted with graded doses of uranium to obtain dose-response curves for each group. Doses were increased in units of approximately 0.11 log unit until mortality occurred in each group within 4 to 21 days after implantation.

Yellowcake Implantations

Rats were anesthetized with halothane and subcutaneously implanted with uranium. Anesthesia was induced with a 4% mixture of halothane (Halocarbon Laboratories, Inc., Hackensack, NJ) vaporized in 95% O_2 at a flow rate of 0.6 L/min and then maintained with 2% halothane by means of a face mask. Hair was clipped from the dorsal thoracic area and a 1 cm-long incision was made on the dorsal midline between the scapulae. The uranium dose was subcutaneously implanted and the skin was sutured with VETAFIL BENGEN™ (S. Jackson, Inc., Washington, DC). The incision was sprayed with Aeroplast™ spray-on plastic dressing (Parke-Davis and Co., Greenwood, SC). Control rats were sham implanted (subjected to the anesthesia and surgical procedures, but no uranium was implanted).

Rats were observed at least twice daily for morbidity or mortality through 21 days after implantation. Surviving rats were sacrificed by use of an intraperitoneal injection of 1 mL of euthanasia solution (T-61, National Laboratories Corp., Somerville, NJ) administered 21 days after implantation. Necropsies were performed on all rats; thoracic and abdominal viscera were examined grossly, and photographs were taken of the kidneys. Kidneys were assayed for uranium content by reflectance fluorimetry (Paper 2, this report). A section of kidney from each rat was fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 6 μm, stained with hematoxylin and eosin, and examined by light microscopy for histopathological alterations.

Data Analysis

Dose-response data for the three groups of rats were analyzed by probit analysis of the lethality data (Ref. 7.6). The $LD_{50/21}$ days and associated 95% confidence intervals (CI) were derived from the probit regressions and 95% fiducials.

Food and water consumption and changes in body weight of rats in the three groups were compared by analysis of variance, and significance of differences between groups was determined by the F test or the Student's t test (Ref. 7.7). Differences were considered to be significant if $p < 0.05$.

RESULTS

Mortality

The $LD_{50/21}$ days for rats housed in polycarbonate cages (Group 3) was 340 mg U/kg with 95% CI of 190-640 mg U/kg; and for "Acclimated Rats" housed in metabolism cages (Group 2), it was 440 mg U/kg with 95% CI of 200-2050 mg U/kg. The difference between the LD_{50} values for these two groups was not statistically significant. Data for these two groups of rats were pooled to obtain the dose-response curve for acclimated rats shown in Figure 7.2 (LD_{50} = 360 mg U/kg and 95% CI of 220-650 mg U/kg). The $LD_{50/21}$ days for naive rats housed in metabolism cages was significantly lower ($LD_{50/21}$ days = 6 mg U/kg, with 95% CI of 3-8 mg U/kg) than for the acclimated rats ($p < 0.01$). The mean time to death of rats that died after implantation with uranium was 8 days for all 3 groups the range was 4 to 20 days. None of the sham-implanted control rats died.

Body Weight, Water, and Food Consumption

Figure 7.3 summarizes body weight data for untreated rats housed in metabolism cages compared with those housed in polycarbonate cages. It shows changes in mean body weight for 10 rats in each group through 21 days after the rats were first placed in metabolism cages. At the end of 21 days, six rats from each group were removed for use in the dose-response phase of the study. Body

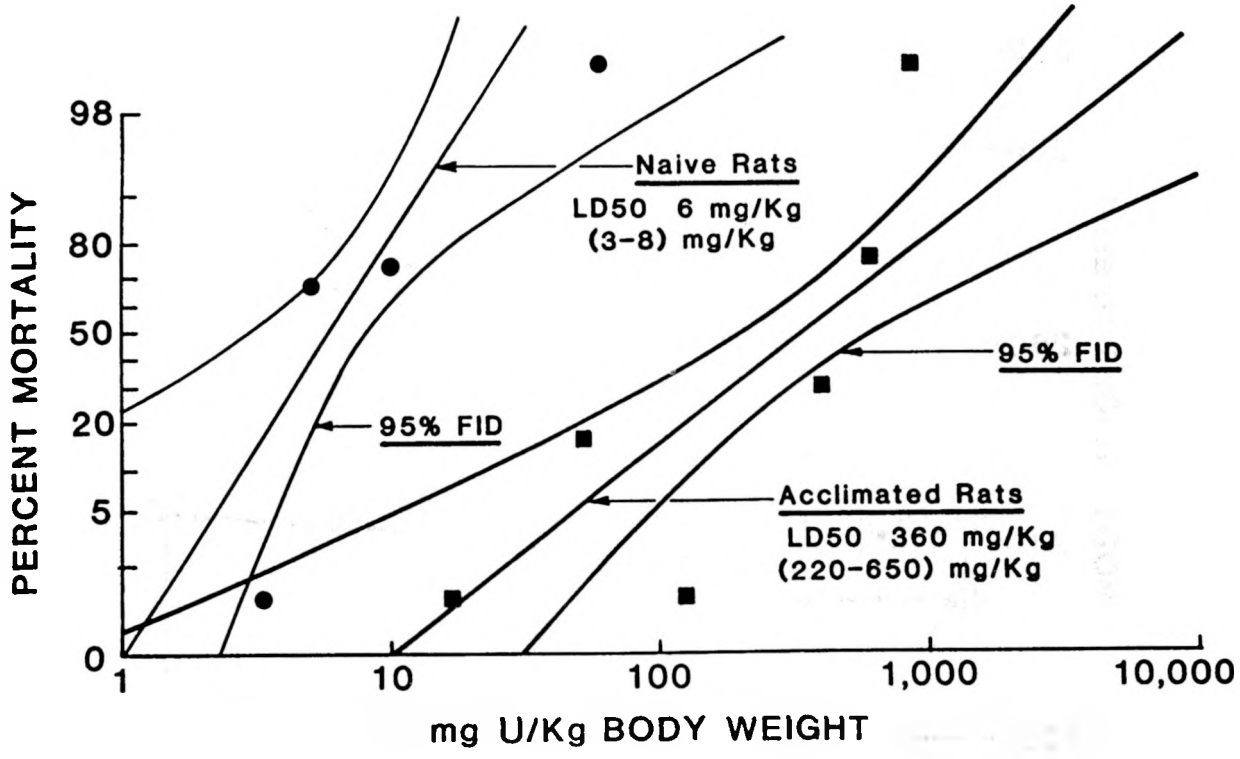

Figure 7.2 Dose-response curves for rats housed in metabolism cages beginning on the day of yellowcake implantation (Naive Rats, circles) or for rats housed in polycarbonate cages or in metabolism cages beginning 21 days before yellowcake implantation (Acclimated Rats, squares). LD_{50} values (and 95% confidence limits) are for 21-day mortality.

weights shown after 21 days are for the remaining four rats in each group. Rats placed in metabolism cages initially lost weight, and the subsequent gain in body weight for these rats was significantly lower than for those housed in polycarbonate cages throughout the period of observation. Food consumption by rats placed in metabolism cages (data not shown) initially dropped, but by day 3, food consumption was not significantly different for the two groups, despite the body weight differences observed.

Rats in metabolism cages drank significantly less water than those housed in polycarbonate cages throughout the period of observation. Because of the increasing difference in body weight for the two groups of rats (Figure 7.3), water consumption was normalized to body weight. When this was done, the normalized water consumption of the two groups was not significantly different after day 5 (Figure 7.4). Figure 7.5 summarizes water consumption data for four rats in each group from 2 days before implantation until 21 days after implantation with uranium at a dose of 10 mg U/kg. The naive rats housed in metabolism cages drank significantly less water than acclimated rats or rats housed in polycarbonate cages until day 8 after implantation.

Histopathological Observations

Kidneys of these rats had a widespread massive necrosis of tubular epithelial cells, and it involved essentially all tubules and the proximal and distal portion of each individual tubule. Nearly all tubular epithelial cells were necrotic and sloughed. Massive casts of necrotic cells, mineralized debris, and protein filled the tubules. The glomeruli were relatively spared. Two of the four rats died with signs of uranium nephrotoxicity 8 or 10 days after implantation. Data

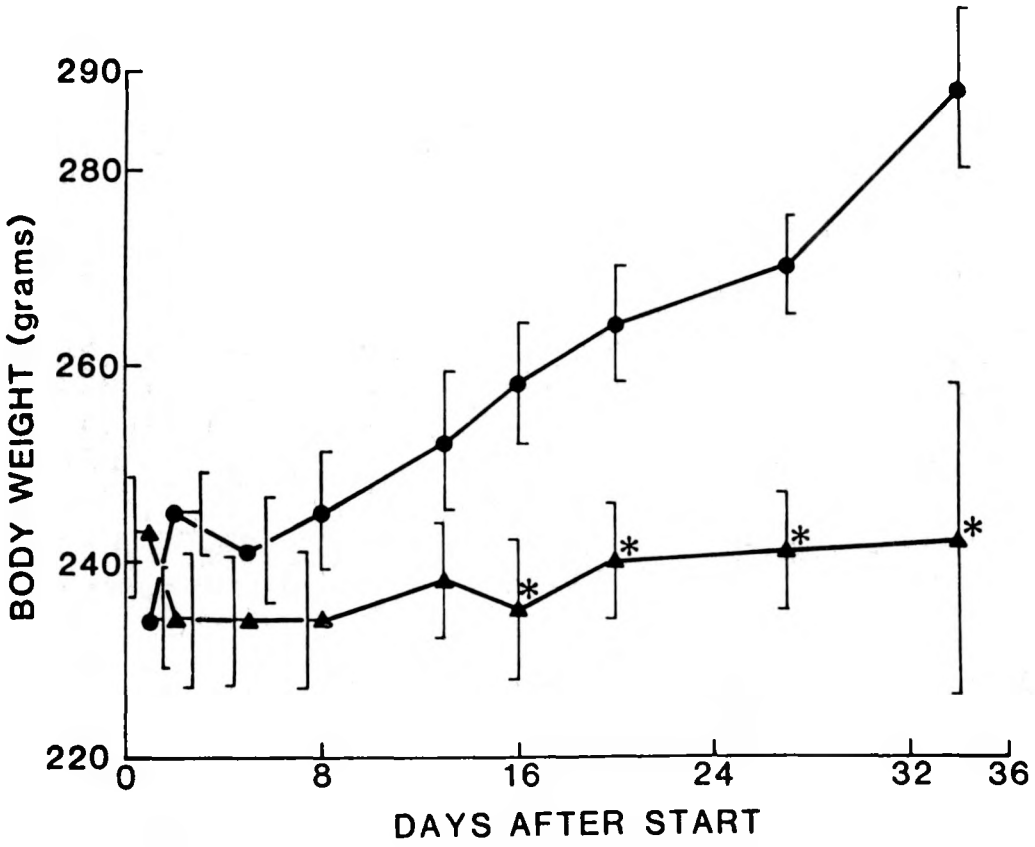

Figure 7.3 Mean body weight of unexposed rats housed in metabolism cages (triangles) or in polycarbonate cages (circles). Error bars represent ± 1 SEM for 10 rats per group thru 21 days and 4 rats per group thereafter. Asterisks (*) indicate points where means are significantly different ($p < 0.05$).

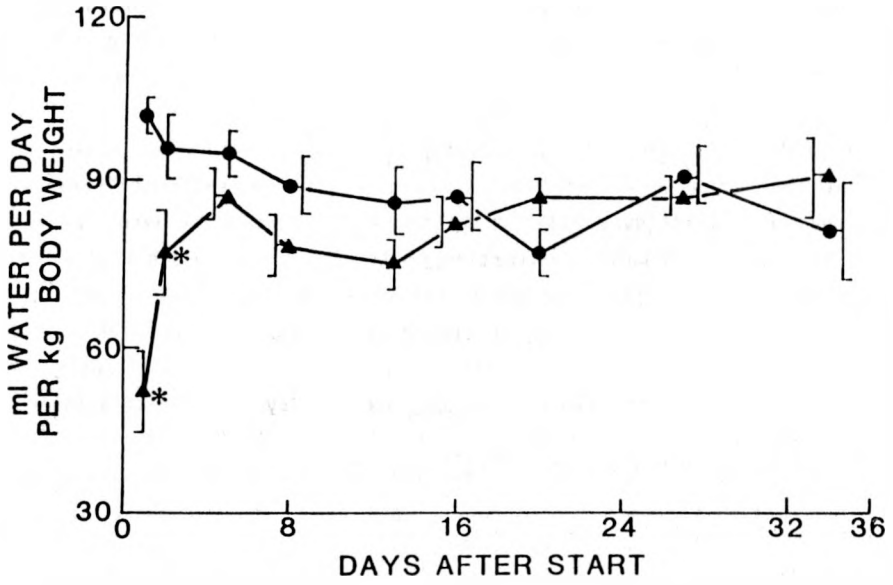

Figure 7.4 Mean water consumption (mL/kg body weight) for unexposed rats housed in metabolism cages (triangles) or in polycarbonate cages (circles). Error bars represent ± 1 SEM for 10 rats per group thru 21 days and 4 rats per group thereafter. Asterisks (*) indicate points where means are significantly different ($p < 0.05$).

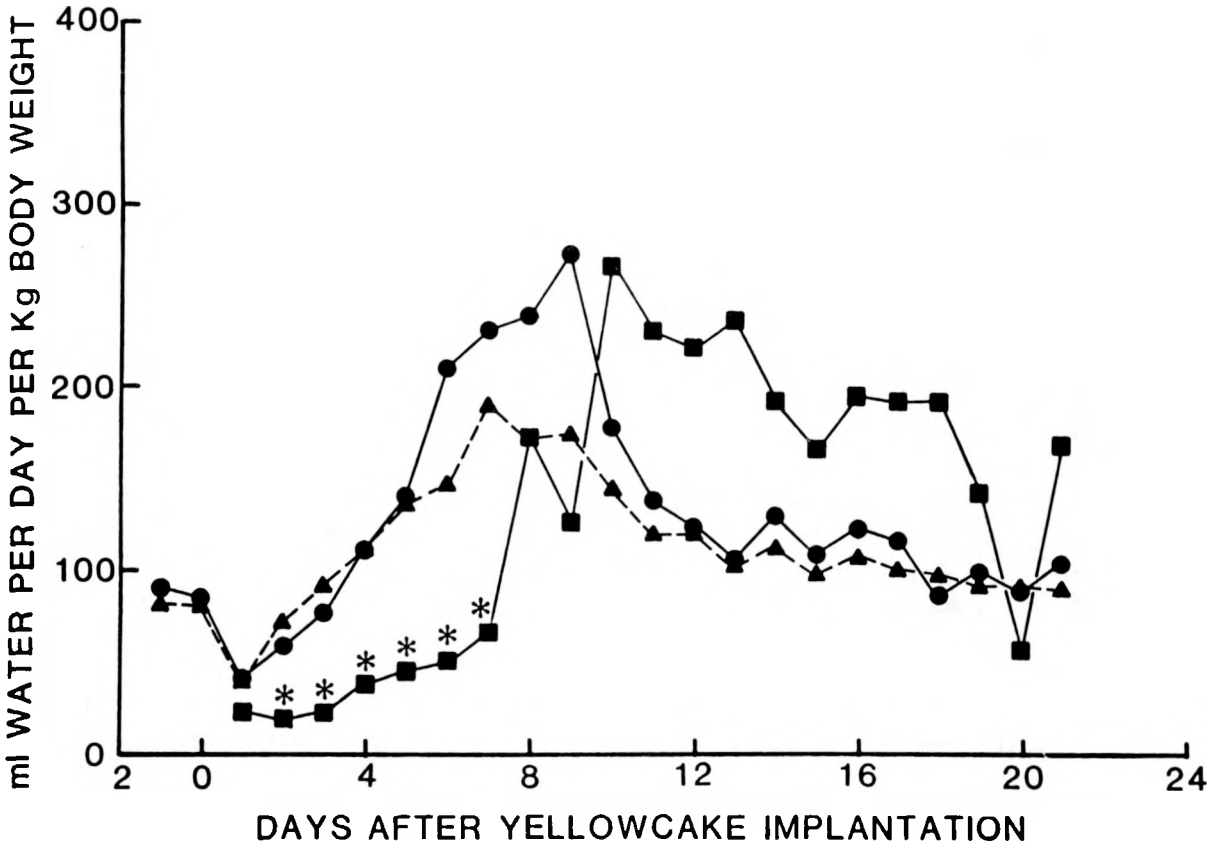

Figure 7.5 Mean water consumption by rats implanted with 10 mg uranium/kg body weight. Square symbols indicate naive rats housed in metabolism cages; triangles indicate rats acclimated to metabolism cages, and circles indicate rats housed in polycarbonate cages (4 rats per group). Asterisks (*) indicate points where means are significantly different ($p < 0.05$).

beyond day 10, shown in Figure 7.5 for this group, are for the two surviving rats. None of the rats in the other two groups implanted at this dose level (10 mg U/kg) died.

DISCUSSION

The histopathological observations noted for rats that died were generally similar to those reported by others for rats after oral or parenteral administration of uranyl nitrate (Refs. 7.8, 7.9). In earlier studies of toxicity from parenteral administration of soluble uranium compounds to animals, rats were usually housed in wire cages in groups of five or fewer (Refs. 7.8, 7.10). Haven and Hodge reported $LD_{50/48}$ h and $LD_{50/21}$ days values of 86 mg U/kg and 2.5 mg U/kg, respectively, for male Wistar rats housed in wire cages after a single intraperitoneal injection of uranyl nitrate hexahydrate. The $LD_{50/21}$ days value (6 mg U/kg with 95% confidence limits of 3-8 mg U/kg) reported here for naive F344/Crl rats housed in metabolism cages after implantation was not significantly different from the literature value.

The lower tolerance to the acute effects of implanted uranium exhibited by naive rats housed in metabolism cages may be related to reduced water consumption by these rats during the first 4 to 7 days after uranium implantation (Figure 7.5). Rats housed in polycarbonate cages or rats acclimated to metabolism cages for 21 days before uranium implantation consumed significantly more water during this time than did the naive rats.

The lower tolerance to uranium toxicity exhibited by naive rats housed in metabolism cages compared to rats housed in polycarbonate cages was associated with a higher concentration of uranium in the kidneys of the naive rats than in those housed in polycarbonate cages. The concentration of uranium in the kidneys of four rats that died 8 days after implantation with uranium at a dose of 10 mg U/kg was 72 ± 18 μg U/g. This value was significantly higher than that reported previously for five surviving rats (16 ± 4 μg U/g) housed in polycarbonate cages and sacrificed 8 days after implantation at this same dose level (Ref. 7.11).

The difference in uranium concentration in kidney of the two groups of rats was probably related to differences in water consumption. Water consumption by rats acclimated to metabolism cages was equal to that of rats housed in polycarbonate cages, and the response of these two groups of rats to the acute effects of uranium was similar (Figure 7.5).

It has generally been recognized that a period of acclimation must be provided for laboratory animals placed in a new environment before undertaking toxicity studies. However, the period required for acclimation of rats to metabolism cages has not been determined previously. Data presented here indicate that a minimum of 3 days or 5 days of acclimation are required for food or water consumption to return to normal after placing rats in a different cage type. However, rate of body weight change for rats housed in metabolism cages was less than that for rats housed in polycarbonate cages throughout the 34-day period of observation. After 21 days of acclimation, rats housed in metabolism cages showed no significant difference in response to the acute effects of uranium from those housed in polycarbonate cages.

Additional studies on the effects of environment on the results of toxicity studies are certainly needed. This study illustrates that a sudden change of cage type markedly decreased the $LD_{50/21day}$ for rats implanted with uranium. At a minimum, a 3- or 5-day period of acclimation was necessary for food and water consumption to return to levels observed for rats not changed to a new cage type. With 21 days of acclimation to the different cage type, no difference in the acute toxicity of implanted uranium was observed.

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8. A MODEL FOR SCALING THE RESULTS OF URANIUM EXCRETION RATE STUDIES IN BEAGLE DOGS TO MAN

PRINCIPAL INVESTIGATORS
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Abstract — A biokinetic model was used to simulate retention and excretion of two forms of uranium: ammonium diuranate (ADU), a relatively soluble form, and U_3O_8, a relatively insoluble form. These two uranium forms represent those most probably encountered in the uranium milling industry. The simulation model was compared with results from a study of aerosols of commercial refined uranium ore inhaled by laboratory animals. Beagle dogs were exposed by inhalation to ADU aerosols to achieve a median initial body burden of 0.058 mg U kg^{-1} body weight, (within a range of 0.016 to 0.64 mg U kg^{-1}), or to U_3O_8 aerosols to achieve a median retained body burden of 0.28 mg U kg^{-1} (0.030 - 0.81 mg U kg^{-1}). The simulation model accurately described the accumulation of nephrotoxic concentrations of uranium in kidneys of animals exposed to ADU. Very small fractions of the initial body burden of U_3O_8 were translocated to kidney, and these fractions were overestimated by the model. The model showed general agreement with results of other laboratory animal studies, and with available information from human exposures to ammonium diuranate, UF_6, or U_3O_8.

Workers in the uranium industry might be exposed to a variety of uranium compounds. These compounds vary widely in chemical composition, oxidation state, and physical form, but can be divided into two general solubility categories: the more soluble industrial compounds, including UO_3, $UO_2(NO_3)_2$, UF_6, and UO_2F_2; and the less soluble compounds, including UF_4, U_3O_8, and UO_2 (Ref. 8.1).

Inhalation exposures of humans to the soluble compounds UO_3 (Ref. 8.2), uranium concentrates (ammonium diuranate, ADU) (Ref. 8.3), and UF_6 (Refs. 8.3, 8.4) have been reported. Studies have also been published of workers who accidentally inhaled relatively insoluble compounds such as U_3O_8-bearing fumes from machining (Refs. 8.5, 8.6) or ingot casting (Refs. 8.2, 8.7), and aerosols released during conversion of $UO_2(NO_3)_2$ to U_3O_8 (Refs. 8.3, 8.8). Chest burdens and excretion rates for three workers who inhaled U_3O_8 have been measured up to 16 yr after exposure (Refs. 8.9-8.11).

Assessment of accidental uranium exposure is difficult. The major health protection concern for exposure to highly enriched uranium is irradiation of lung or bone tissue. If the uranium is not enriched, chemical toxicity to kidney is a primary concern. Intake is estimated within a short time after a suspected exposure using external chest counting and urinary bioassay measurements. Urinary bioassay is useful, assuming that 80% of the absorbed U is excreted within 24 h (Ref. 8.12). Both techniques are also used to monitor U retention at later times, but provide no direct information on kidney toxicity. Sensitive biochemical indicators of nephrotoxicity are useful, if appropriate pre-exposure values are known and the results are not confounded by concurrent renal infection or inflammation from other causes. If it is suspected that the worker inhaled a mixture of U compounds, the exposure material can be analyzed in the laboratory if specimens are available. Often, available information must be reviewed long after the suspected exposure might have occurred. Accident assessment can be made easier if results from many complementary techniques can be interpreted using a model of U biokinetics.

Although information on human exposures is available, the data are incomplete and the biokinetics of inhaled U in humans is still uncertain. For example, urinary excretion data from UO_3 or ADU inhalation exposures (Refs. 8.2, 8.3) are not complemented by lung and kidney retention

data. Urinary excretion and kidney retention rates after injection (Refs. 8.13, 8.14) are not complemented by pulmonary absorption data. Our experiments were designed to measure the retention and excretion of U in Beagle dogs exposed by inhalation of ADU or U_3O_8 for the purpose of developing a biokinetic model to facilitate assessments of accidental human exposures.

MATERIALS AND METHODS

Refined uranium ore (yellowcake) samples were obtained from operating uranium mills. Two samples were chosen, based on infrared analysis (Ref. 8.15) to represent the two extremes of yellowcake products: 100% ADU and > 99% U_3O_8. Twenty Beagle dogs from the Institute's colony, 10 male and 10 female, 2 to 6 yr of age were exposed by pernasal inhalation (Ref. 8.16). Aerosols were generated from dry powders using a DeVilbiss Model 175 powder blower fixed to a mechanical shaker (Ref. 8.17). The aerosols were sampled using cascade impactors to measure particle size distribution (Ref. 8.18), and 0.45 μm pore size membrane filters to measure airborne uranium concentration. The aerosol particle size distributions were described by log normal functions with characteristics shown in Table 8.1. The aerosol concentration was 80 to 160 μg U L^{-1}.

Table 8.1 Properties of aerosols for inhalation exposure of dogs to ammonium diuranate (ADU) or uranium octoxide

Property	ADU	U_3O_8
MMAD (μm)[a]	3.27 ± 0.51	2.55 ± 0.56
σ_g[b]	1.46 ± 0.23	1.58 ± 0.13
MMD (μm)[c]	1.87	1.18
Density (g cm^{-3})	2.94	4.32
a_s/a_v[d]	30	30

[a]Mass median aerodynamic diameter.

[b]Geometric standard deviation.

[c]Mass median geometric diameter.

[d]Shape factor ratio [Eq. (3)), approximate value based on measurements of other actinide oxide aerosols (Ref. 8.19).

Dogs were sacrificed according to the following schedule: the day of exposure (1 dog), 2 days after exposure (1), 4 days (2), 8 days (1), 32 days (1), 64 days (2), and 180 days (2). Tissues taken at necropsy included blood, skull, turbinates, trachea, lung, kidney, gastrointestinal tract (including esophagus and stomach), liver, spleen, tracheobronchial lymph nodes, femur, and lumbar vertebrae. Urine and feces were collected daily from 2 days through 16 days after exposure, then three daily collections were made every two months until 180 days after exposure. Tissue and excreta samples were analyzed for uranium content by reflectance fluorimetry (Ref. 8.17).

The initial body burdens (IBB) of U inhaled by individual dogs were reconstructed as the sum of U measured in tissues and U excreted between exposure and sacrifice, less the amount excreted in feces during the first 4 days after exposure. Uranium excreted in feces during the first 4 days was excluded from the initial body burden, because it represented rapid clearance of

insoluble particles deposited initially in the upper respiratory tract and contained U that was not absorbed by the body. Exponential functions were fitted to data sets using nonlinear least squares techniques (Ref. 8.20). Total U excreted was estimated as the integrals of these functions.

The empirical simulation model used (Figure 8.1) has been described in detail elsewhere (Ref. 8.21). Briefly, mass balance among all compartments is assumed. Any U removed from one organ compartment is added to another, or to an excretion compartment, so that the sum of all compartments equals the IBB at all times. The model uses time-dependent rate functions to simulate mechanical and dissolution clearance mechanisms for material deposited in the respiratory tract. Because these functions operate simultaneously, the two clearance mechanisms always compete for material remaining in each respiratory tract compartment. This approach provides for changing clearance rates, and avoids the previous assumption of constant clearance rates for each mechanism (Ref. 8.1). The model assumed that all dissolved U behaves the same, regardless of whether its source was ADU or U_3O_8. Similarly, mechanical clearance rates of all undissolved U was assumed to be the same.

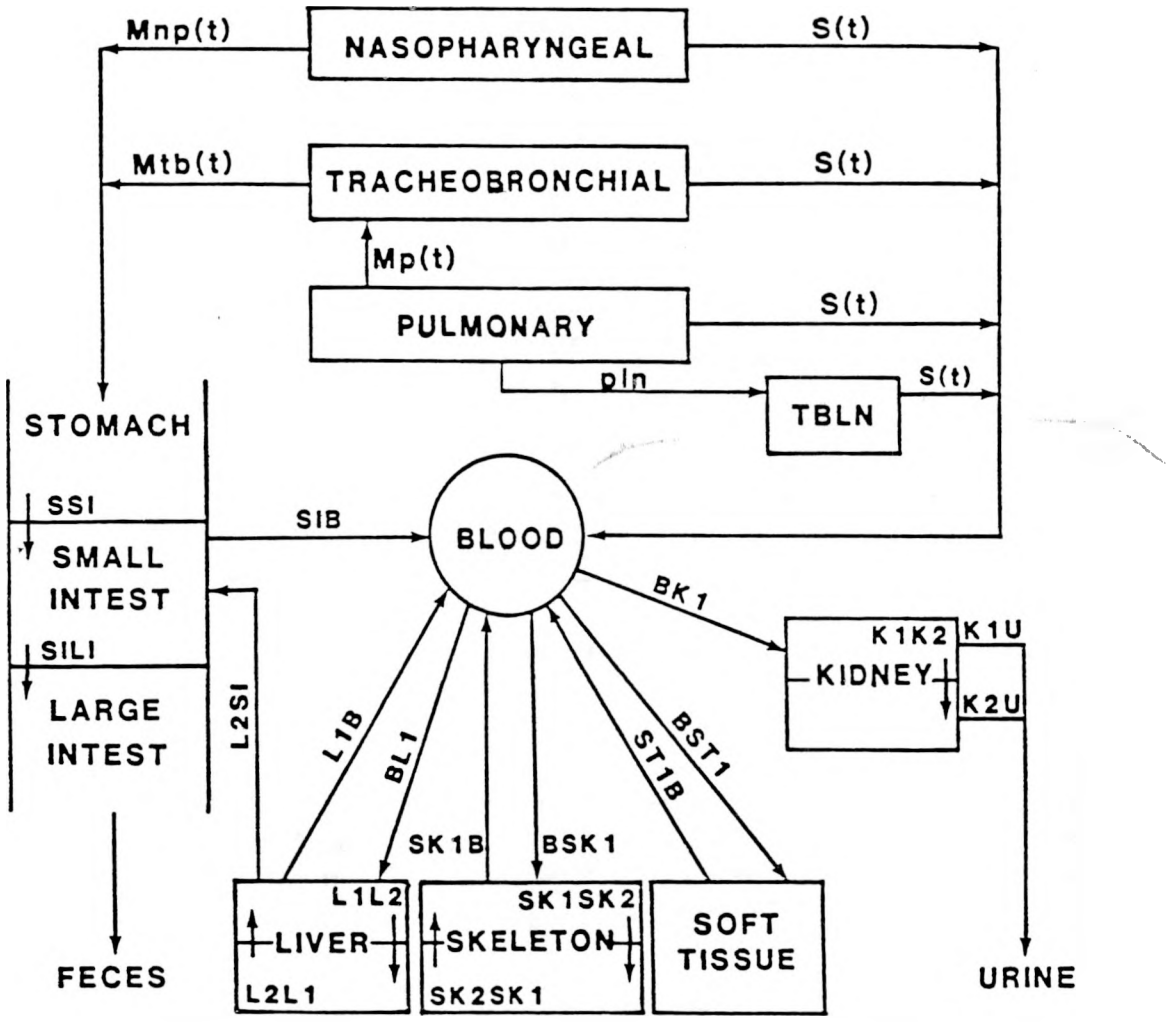

Figure 8.1 Schematic representation of the simulation model (Ref. 8.21) modified for use with uranium compounds. Rate constant abbreviations used are defined in Table 8.3.

Clearance from the pulmonary compartment was simulated according to the equation

$$\frac{dP(t)/dt}{P(t)} = -M_p(t) - \frac{dS(t)/dt}{S(t)} - p\ln \qquad (1)$$

where P(t) is the percentage of the retained body burden in the pulmonary compartment at time t in days after inhalation exposure. Mechanical clearance to the gastrointestinal tract is simulated by time-dependent equation $M_p(t)$ (Table 8.2).

Table 8.2 Rate expressions for clearance by mechanical and dissolution mechanisms (time is expressed in days)

Mechanical Translocation Rates
Nasopharyngeal Compartment
$M_{np}(t) = 2.86$
Tracheobronchial Compartment
$M_{tb}(t) = 2.86$
Pulmonary Compartment
$M_p(t) = 0.014\ e^{-0.14t} + 0.014\ e^{-0.014t}$
Dissolution Functions
Ammonium Diuranate (ADU)
$S_{ADU}(t) = 0.35\ e^{-0.90t} + 0.65\ e^{-0.023t}$
$T_{1/2} = 0.8$ days $\quad T_{1/2} = 30$ days
Uranium Octoxide
$S_{U_3O_8}(t) = 0.01\ e^{-0.25t} + 0.99\ e^{-0.00030t}$
$T_{1/2} = 2.7$ days $\quad T_{1/2} = 2300$ days

Dissolution was simulated according to the rate function S(t):

$$S(t) = f(\sigma_g, b_1, b_2). \qquad (2)$$

Eq. (2) describes dissolution as a function of the aerosol properties according to the surface area dissolution model (Ref. 8.22). The variable σ_g is the geometric standard deviation of the aerosol particle size distribution. The variables b_1 and b_2 represent the two components of the inhaled mixture, and are of the form

$$b_i = \frac{a_s k_i t}{a_v r\ D_m},\ i = 1,2, \qquad (3)$$

where a_s = the surface shape factor,

a_v = the volume shape factor,

r = the density of the particles (g cm^{-3}),

D_m = the mass median diameter (cm)

k_i = the dissolution rate constant of one of the two uranium forms (g cm^{-2} day^{-1}).

It was assumed in Eqs. (2) and (3) that the dissolution rate constant was the only significant difference between the two components of the inhaled aerosol, and that the aerosol properties (Table 8.1) were constant during the simulation.

The model simulates instant transport of dissolved U to blood, without accumulation in respiratory tract tissues. Transfer of dissolved U among blood and other compartments is simulated using linear combinations of first-order rate equations. This assumes that the U ion concentration is negligible compared to the concentration of biological transport molecules in vivo, so that higher order rate equations can be treated as pseudo-first-order rates (Ref. 8.23). Urinary excretion pathways in the Mewhinney and Griffith model were modified to describe U uptake in kidney and release to urine (Ref. 8.24).

The model was solved using the GASP IV simulation language (Ref. 8.25) and was programmed in FORTRAN IV. Mechanical clearance rate constants were obtained using respiratory tract retention and fecal excretion results from animals exposed to the U_3O_8 aerosol. These rate constants were not varied when used to model results from animals exposed to the more soluble ADU aerosol. Transfer constants for dissolved U were likewise obtained from tissue content and urinary excretion data from animals exposed to the ADU aerosol and used to model results from U_3O_8-exposed dogs.

RESULTS

The median IBB received by dogs that inhaled ADU was 0.058 mg U kg^{-1} body weight (within a range of 0.016 to 0.64 mg U kg^{-1}) and was 0.28 mg U kg^{-1} body weight (0.030-0.81 mg U kg^{-1}) for dogs that inhaled U_3O_8. Results of simulation modeling are shown in Figures 8.2 and 8.3. Functions that describe mechanical clearance and dissolution rates are shown in Table 8.2, and rate constants that describe transfer of uranium among compartments are shown in Table 8.3. A greater percentage of the IBB was cleared from the lungs and was transferred to other organs of dogs that inhaled ADU than of those that inhaled U_3O_8, as expected.

Excretion of uranium in urine was highly variable among individual animals, and no clear distinctions can be made between the urinary excretion of dogs that inhaled either ADU or U_3O_8 (Figure 8.3), although uranium excretion by dogs that inhaled the ADU aerosol appears to be somewhat greater. Fecal excretion rates were similar for the two groups of dogs.

When uranium translocates rapidly from lung to blood, it can cause chemical toxicity to the kidney if sufficient concentrations accumulate. The uranium concentration in kidneys during the first 64 days after exposure (Table 8.4) shows that dogs that inhaled ADU aerosols had higher concentrations than those exposed to U_3O_8, although the median initial body burden of the U_3O_8-exposed group was greater. Histopathologic examination of kidney tissues showed no significant abnormalities in dogs exposed to U_3O_8 aerosols. However, dogs exposed to ADU showed proximal tubular necrosis typical of heavy metal nephrotoxicity. At 2 days after exposure, few renal changes were seen. At 4 to 8 days, there was focal necrosis of cortical proximal tubules and sloughing of proximal tubular cells, but lesions were neither severe nor widespread, and there was obvious regeneration. At 64 days, the tubules in atrophic foci were shrunken and surrounded by fibrous tissue. These observations are consistent with a proximal tubular necrosis that reached its peak between 4 and 8 days after exposure and was subsequently repaired. Our results agree with those of Morrow et al. (Ref. 8.26) whose inhalation and intravenous injection studies

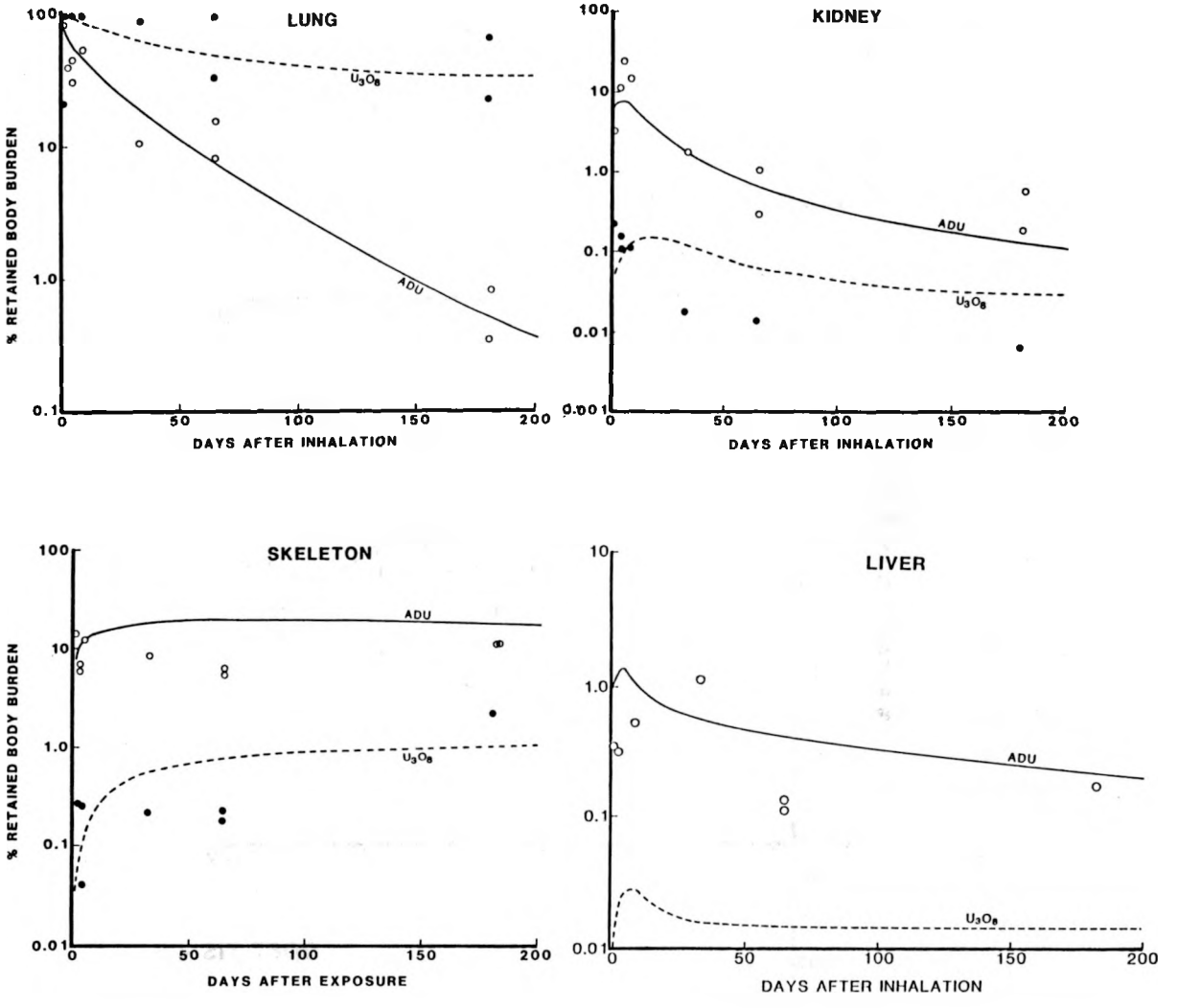

Figure 8.2 Simulated retention of uranium in tissues of Beagle dogs that inhaled ammonium diuranate (ADU) or U_3O_8 aerosols. No uranium was detected in liver tissues from dogs exposed to U_3O_8.

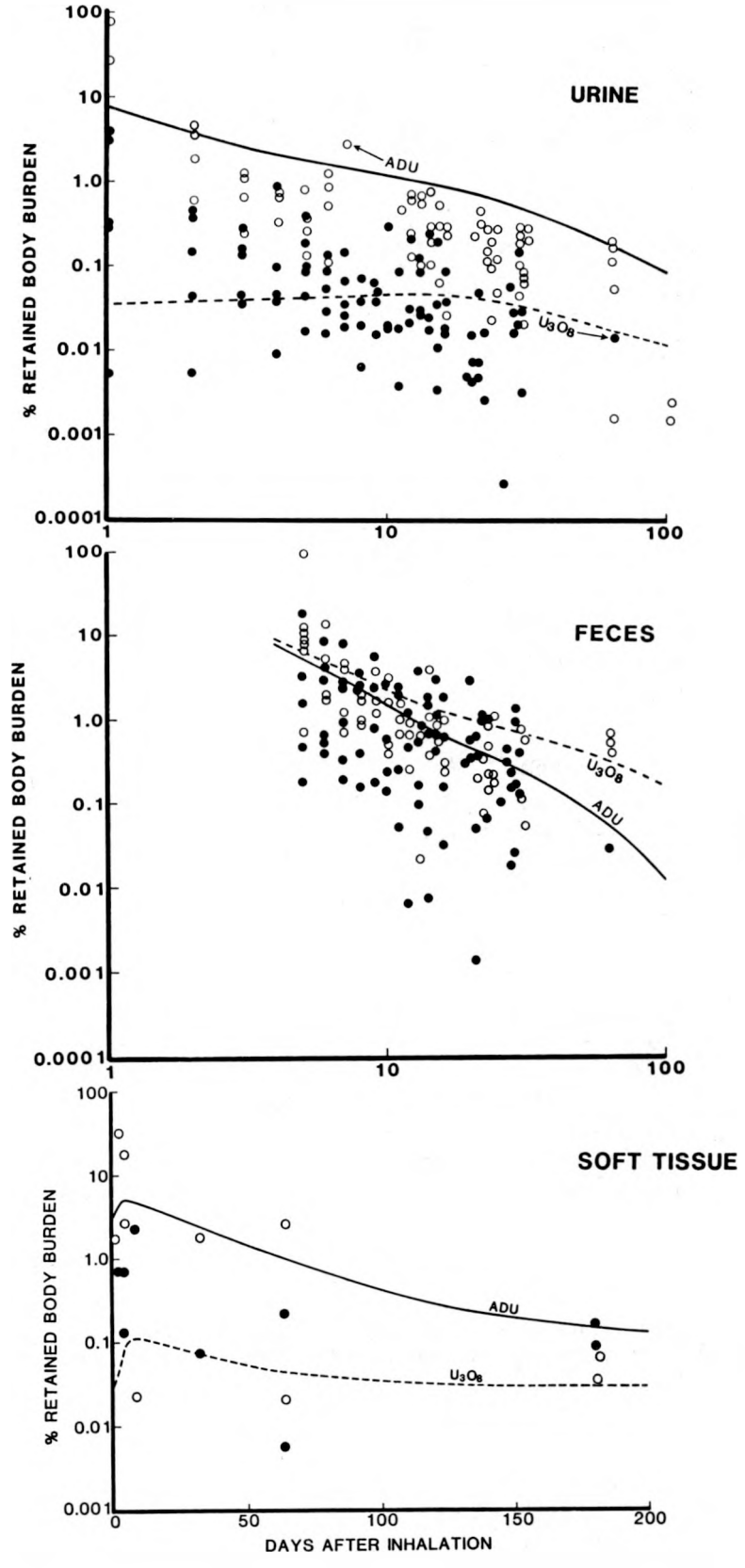

Figure 8.3 Simulated retention of uranium in soft tissues and excreta of Beagle dogs that inhaled ammonium diuranate (ADU) or U_3O_8 aerosols.

Table 8.3 Rate constants for translocation and excretion of uranium by dogs exposed to either ammonium diuranate or U_3O_8 aerosols

Translocation of Dissolved Uranium			
From Compartment	To Compartment	Symbol[a]	Rate Constant (day^{-1})
Pulmonary	Lymph Nodes	pln	0.000014
Stomach	Small Intestine	ssi	0.43
Liver-2	Small Intestine	l2si	0.00014
Small Intestine	Large Intestine	sili	1.86
Small Intestine	Blood	sib	0.01
Blood	Kidney-1	bk1	8.57
Kidney-1	Urine	klu	5.71
Kidney-2	Urine	k2u	0.14
Kidney-1	Kidney-2	klk2	5.71
Blood	Soft Tissue-1	bst1	2.14
Soft Tissue-1	Blood	st1b	0.071
Blood	Skeleton-1	bsk1	4.29
Skeleton-1	Blood	sk1b	0.014
Skeleton-1	Skeleton-2	sk1sk2	0.071
Skeleton-2	Skeleton-1	sk2sk1	0.014
Blood	Liver-1	bl1	0.71
Liver-1	Blood	l1b	0.14
Liver-1	Liver-2	l1l2	0.014
Liver-2	Liver-1	l2l1	0.0071

[a]See Figure 8.1.

Table 8.4 Concentration of uranium in kidneys of individual dogs at selected times of the exposure

Days After Inhalation	Concentration ($\mu g\ U\ g^{-1}$ kidney)[a]	
	ADU[b]	U_3O_8
0	0.6	0.1
2	0.3[c], 3.5	0
4	1.6[c], 0.9[c], 0.6, 1.0	0.05, 0.2
8	0.8[c], 0.8	0.08
32	0.08	0.02
64	0.2, 0.07	0, 0.02

[a]Wet tissue weight.

[b]Ammonium diuranate.

[c]Dog was removed from the biokinetic modeling group after urine samples were lost during analysis. The uranium concentration in kidney tissue and histopathologic conclusions were not affected.

in Beagle dogs at 1.5 and 1.6 μg U g^{-1} kidney, respectively, also show that kidney damage results from inhalation of the soluble aerosol.

Simulated Retention of Uranium in Dogs Exposed to Ammonium Diuranate (ADU)

Explicit differential equations used in the simulation model and the transfer rate constants can be simplified to compare our results with others. The pulmonary compartment burden, P(t), was simulated according to Eq. (1). The first term of the ADU dissolution function (Table 8.2) represents a half-time of 0.8 days and reflects the rapid transfer to other organs during the first 4 days after inhalation. After the first 4 days, the slower dissolution rate predominates, which corresponds to a lung retention half-time of 30 days. For bioassay interpretation, the two portions of the pulmonary burden of ADU could be considered solubility Class D and W compounds, respectively (Ref. 8.1), although such assignments could not be made without physical and chemical composition data.

Other organ burdens can be approximated as shown below for kidney. After 4 days,

$$\text{kidney}(t) \cong 0.11\exp(-0.14t) + 0.050\exp(-0.023t). \quad (4)$$

The first term of Eq. (4) describes clearance of the kidney burden with a half-time of 5 days, whereas the second term describes clearance from kidney according to the dissolution rate of ADU in lung. The skeletal burden can be similarly approximated to have a retention half-time of 50 days.

Excretion in urine can be described by inspection of the dissolution function (Table 8.2) and Eq. (4). Prior to 4 days after exposure, the simulated uranium clearance by dissolution from the pulmonary compartment occurred at a rate of 0.90 day^{-1} ($T_{1/2}$ = 0.8 days). As a result, a bolus of uranium translocated to kidney at a faster rate than the kidney clearance rate (0.14 day^{-1}, $T_{1/2}$ = 5 days), resulting in accumulation of ~ 10% of the IBB in kidney (Figure 8.3). After 4 days, the model predicts dissolution from the pulmonary compartment with a half-time of 30 days, resulting in a reduction of the kidney compartment content.

Simulated Retention of Uranium in Dogs Exposed to U_3O_8

Dissolution of the less soluble U_3O_8 aerosol in lung was simulated by $S_{U_3O_8}(t)$ (Table 8.2) to occur with half-times of 2.7 days for 1% of the uranium, and 2300 days for the remaining 99%. The long-term dissolution rate is consistent with estimated dissolution rates (Ref. 8.27) for U_3O_8 in five exposed workers (Ref. 8.11). Unlike ADU, long-term clearance of U_3O_8 from lung was not dominated by the dissolution rate. Both the competing dissolution and mechanical clearance pathways can be approximated by

$$\frac{dP(t)/dt}{P(t)} \cong -0.014\exp(-0.14t) - 0.00030. \quad (5)$$

According Eq. (5), the overall clearance half-time from lung changes with time from an initial value of about 26 days, increasing to 70 days at 1 mo, 490 days at 6 mo, and 1800 days at 1 yr.

After translocation of a negligible bolus from lung to kidney (1% IBB) and clearance from kidney with a half-time of 5 days, both the kidney burden and the fecal excretion rates decreased with these above changing half-times as the lung burden decreased by mechanical clearance. Thus, no accumulation in kidney was simulated for the U_3O_8-exposed animals.

Simulated excretion of uranium in feces (Figure 8.3) was similar for both the more soluble and less soluble uranium forms, as required by the constraints applied. At later times, the simulated fecal excretion rate of the more soluble material decreased, reflecting the depletion of the pulmonary burden caused by dissolution and excretion in urine.

DISCUSSION

Application of the Simulation Model to Beagle Dog Experiments

The simulation model results agreed well with the pulmonary retention of ADU and U_3O_8 in dogs, and with the kidney, skeleton, liver, and soft-tissue retention in ADU-exposed dogs. There was less agreement between the model and kidney and skeleton retention in the dogs exposed to U_3O_8. The model developed to simulate translocation of 1% to 20% of an initial body burden was less accurate at simulation of 0.001% to 0.01% of a body burden. The lack of agreement for very low fractions of the IBB probably indicates that uptake and release of small amounts of U are more complex than previously believed. The possibility of dose dependent kidney retention has been considered; however, available data do not allow a clear conclusion (Ref. 8.24). The same is true for U uptake and release by skeleton. The model simulates the rapid deposition of U on bone surfaces and slower incorporation into bone volumes (Ref. 8.28) by using two skeleton compartments. More experimental results at low U doses would be required to develop a more complex bone model, however.

The simulation model accurately described accumulation of uranium in kidney during the first 4 days after inhalation, rather than immediate excretion in urine. Histopathology results indicated that kidney damage reached its peak during this period of accumulation. The slower clearance of uranium from lungs containing U_3O_8 prevented accumulation in kidney and formation of kidney lesions. This accumulation of uranium to toxic concentrations has important bioassay implications. It shows that the amount of uranium that is excreted in urine does not necessarily indicate the kidney burden at the time of kidney damage.

Histopathology results observed in dogs at maximum kidney concentration of 0.3 to 3.5 μg U g^{-1} kidney (Table 8.4) indicate greater sensitivity of dogs than humans to nephrotoxicity. No unusual kidney histopathology was observed in humans injected with $UO_2(NO_3)_2$ at 0.1 mg U kg^{-1} body weight (~ 6 μg U g^{-1} kidney) (Ref. 8.14, 8.29).

Comparison of Simulation Model With Results of Other Animal and Human Exposures

Retention in Lung

Ammonium diuranate, $UO_3 \cdot xH_2O \cdot yNH_3$ (Ref. 8.30), would be expected to mimic UO_3 absorption and translocation *in vivo*. Simulation model rates for ADU-exposed dogs (Table 8.5) agree with pulmonary retention of UO_3 compounds in dogs (Ref. 8.26). There are no similar data in humans for comparison, although accidental exposures to UO_3 or ADU have been reported (Refs. 8.2, 8.3).

Five workers who inhaled material characterized as U_3O_8 have been studied extensively (Refs. 8.9-8.11). The increasing retention half-times calculated by the simulation model are within the range of those measured by chest counting of these workers (Table 8.5), although there is variability among the five individuals.

Studies of other workers exposed to uranium machining fumes (Refs. 8.5, 8.6), ingot casting fumes (Ref. 8.7) or to uranium generated in the conversion of uranyl nitrate to U_3O_8 (Ref. 8.8) indicate somewhat more rapid clearance of the pulmonary burden than calculated by the simulation model. It is possible that the oxides inhaled were not pure U_3O_8. Because the uranium-oxygen system is highly complex (Ref. 8.31), oxide mixtures with differing solubility properties would be expected for fumes formed under uncontrolled conditions. This emphasizes the need for thorough characterization of suspected exposure materials and use of a biokinetic model in accident assessment.

Retention in Kidney

Results of simulated retention of uranium in kidney can be compared with results of injection studies in humans and animals (Table 8.6). Sixteen percent of soluble uranium injected into human patients cleared with a half-time of 16 days (Ref. 8.14). Adams and Spoor (Ref. 8.32) reviewed

Table 8.5 Comparison of simulation model lung clearance results with inhalation exposures of humans and dogs

Exposure Compound	Species	Reference	In Vivo Result % IB[a]	In Vivo Result Half-time (days)	Simulation Result for Dogs % IBB[b]	Simulation Result for Dogs Half-time (days)
			Soluble Compounds			
UO_3	Dog	8.26	85	4.7	35	0.8
			15	34	65	30
			Insoluble Compounds			
U_3O_8	Human	8.11			1	2.7
	Y-1		100	600	99	time varying
	Y-2		75	725		26 initially
			25	Infinite		70 at 1 mo
	Y-3		100	380		490 at 6 mo
	Y-4		60	644		1800 at 1 yr
			40	Infinite		
	Y-5		60	382		
			40	Infinite		
Metal fume (U_3O_8)	Human	8.6		7		
		(8.5)		70		
				39		
Metal fume (U_3O_8)	Human UR-2	8.7		380		
Uranyl nitrate conversion	Human	8.8				
	K-1			245		
	K-2			209		
	K-3			27		
				119		

[a]Initial burden reported in references cited.

[b]Initial body burden defined in these experiments.

these results and proposed that, for an acute exposure, 16% of the injected uranium was cleared with a half-time of 12 days, and 1% with an 1100 day half-time. For chronic exposure, they proposed that 12% would clear with a half-time of 6 days. These results are in general agreement with the simulation model values.

Simulation model results are also in general agreement with uranium clearance rates from kidneys of rats exposed to ADU aerosols (Ref. 8.33) (Table 8.6). Dogs injected with uranyl nitrate cleared 15% of the injected amount with a half-time of 79 days (Ref. 8.28). The clearance rate was slower than observed for humans or predicted by the simulation model, possibly as a result of nephrotoxicity in the dogs exposed to uranyl nitrate. The maximal uranium concentration in the dogs was 14 μg U g^{-1} kidney, but it was ~ 1 μg U g^{-1} kidney in this study (Table 8.4).

Retention in Skeleton

Simulation model predictions of skeletal retention half-times were in closer agreement with injection studies in the human and rat than in the dog (Table 8.7). The simulated clearance half-time, 50 days, is somewhat longer than the value of 15-28 days for retention in humans (Ref. 8.32), but is similar to the 40-45 day value observed in rats injected with uranyl nitrate (Ref. 8.34). Note that all of these experiments were substantially shorter than the median lifetime of the species studied. The human bone retention half-times were obtained from studies of terminally

Table 8.6 Comparison of simulation model kidney clearance results with human and animal exposures

Compound	Exposure Route	Species	Reference	In Vivo Result % IB[a]	In Vivo Result Half-time (days)	Simulation Result for Dogs % IBB[b]	Simulation Result for Dogs Half-time (days)
Uranyl Nitrate	Injection	Human	8.13	16	16	11	5
			8.32				
			(acute)	16	12		
				1	1100		
			(chronic)	12	6		
				0.052	1500		
		Dog	8.28	15	79		
ADU	Inhalation	Rat	8.33	18	6.7		

[a]Initial burden reported in references cited.

[b]Initial body burden defined in these studies.

ill patients, and the values are probably not relable indicators of bone retention in healthy individuals. Data obtained through the U. S. Uranium Registry, and further research in animals, will be required to refine the rate constants for retention in bone.

Excretion

Comparison of simulated urinary excretion rates with those measured for humans exposed by inhalation (Table 8.8) shows agreement within the variability of excretion rates among humans exposed to uranium concentrates (ADU). Half-times were calculated in our laboratory using nonlinear least squares fitting methods (Ref. 8.20) to tabulated data (Ref. 8.3). Workers exposed to UF_6 gas (Refs. 8.3, 8.4) excreted uranium in urine with half-times ranging from 0.5-11 days, in reasonable agreement with the 5-day simulated clearance half-time of uranium accumulated in kidney.

Workers exposed to U_3O_8, or aerosols thought to contain U_3O_8, excreted uranium with half-times ranging from 8-2140 days (Table 8.8). The long-term excretion half-time, however, ranged from 69 to 2140 days and reflects the total mechanical and dissolution clearance rate from lung (Eq. 5). Excretion rates of uranium in feces by humans exposed to U_3O_8 (Ref. 8.10) are within this range, although there were fewer fecal excretion data than chest counting data available (Table 8.9).

Scaling to Man

The foregoing comparisons show that the simulation model results agree with pulmonary clearance rates from humans exposed to U_3O_8 and from dogs exposed to UO_3. The simulation model kinetics were also in general agreement with previous studies in humans and laboratory animals of uranium uptake in kidney and bone and excretion in urine. Thus, if the properties of the inhaled material are known, the simulation model results can be combined with urinary bioassay measurements to estimate organ content of uranium in accidentally exposed workers. If the aerosol properties are not known, and cannot be determined, the model can be used to estimate maximum and minimum organ burdens by applying maximum and minimum estimates of aerosol properties (Table 8.1) and dissolution rates (Table 8.2).

Urinary excretion of uranium by four workers exposed to ADU (Ref. 8.3) was highly variable (Ref. 8.5). The four data sets were normalized to the amount excreted on the first day of elevated uranium excretion, and the simulation model curve was normalized to the value calculated on the first day after exposure. The simulation model agrees within the variability; however, the need for continuing urinary bioassay for long times after exposure is obvious. Individual

Table 8.7 Comparison of simulation model skeleton clearance results with human and animal exposures

Compound	Exposure Route	Species	Reference	In Vivo Result % IB[a]	In Vivo Result Half-time (days)	Simulation Result for Dogs % IBB[b]	Simulation Result for Dogs Half-time (days)
Uranyl Nitrate	Injection	Human	8.13	6	28	20	50
			8.32				
			(acute)	10	15		
				1	3200		
			(chronic)	20	20		
				0.23	5000		
		Dog	8.28	7.7	883		
		Rat	8.34	30	40-45		

[a]Initial burden reported in references cited.

[b]Initial body burden defined in these experiments.

measurements, or even a series of measurements, might be uncertain by a factor of 10. However, if the inhaled material is unknown and a simulation model is not applied, the results would be uncertain by a factor of 1000 (Paper 4, this report).

In assessments of recent accidental exposures, or in retrospective assessments, it is desirable to estimate organ burden from urinary excretion results. These estimates will include the individual variability shown in Figure 8.4, and must be made cautiously. Ratios of organ burdens of ADU-exposed dogs to the simulated daily urinary excretion rate (Figure 8.5) show that the ratio of lung burden to urine was simulated as 30 to 45 between 8 and 100 days after exposure. The same ratio for kidney burden to urinary excretion rate was 3.5 to 4.5 during the first 200 days. The bone burden was estimated to be 580 times the urinary excretion rate at 180 days.

Similar ratios for dogs exposed to U_3O_8 (Figure 8.6) show that the lung burden/urinary excretion rate ratio was approximately 2900. Individual data points indicate ratios of *in vivo* chest counts to radioactivity excreted in urine for workers exposed to U_3O_8 (Ref. 8.10). There is good agreement for measurements obtained after ~ 30 days. The ratio of kidney burden to urinary excretion was approximately 3.5, and the corresponding ratio for skeleton approached 130 at 180 days.

CONCLUSIONS

The simulation model provides a useful tool for assessing the consequences of accidental uranium inhalation exposures, especially during the first 16 days after exposure when kidney damage might occur. Assessments using this model must also include knowledge of the chemical composition, or the soluble fraction, of the inhaled uranium to estimate organ burdens from urinary bioassay results.

Because the simulation model was developed using both soluble and insoluble uranium forms, it estimates the ranges of organ burdens that might be expected for exposures to unknown uranium compounds. As such, it can be used for conducting retrospective assessments of earlier inhalation exposures, and for correlation of future data obtained through the U. S. Uranium Registry.

Table 8.8 Comparison of simulation model urinary excretion clearance results with human exposures by inhalation

Exposure Compound	Species	Reference	In Vivo Result Half-time (days)	Simulation Result for Dogs Half-time (days)
		Soluble Uranium		
UO_3	Human	8.2	0.58 43	5 30 (lung)[a]
ADU (Uranium Concentrates)	Human A	8.3	65 (46-109)[b]	
	B		80 (52-172)	
	C		67 (53-92)	
	D		45 (26-150)	
UF_6	Human F	8.3	2.3	5[c]
	G		1.8	(kidney)
	H		0.5	
	I		4.9	
	K		2.5	
	L		5.3	
	M		0.87	
UF_6	Human Case 3	8.4	11	5[c]
	Case 4		3.5	(kidney)
		Insoluble Uranium		
U_3O_8	Human Y-1	8.10	360	time varying 26 initially
	Y-2		440	70 at 1 mo
	Y-4		2140	490 at 6 mo
	Y-5		pos. slope	1800 at 1 yr
Metal fume (U_3O_8)	Human	8.6 (8.5)	8 85 240	
	Human UR-2	8.7	12 69	
	E	8.3	24	
Uranyl nitrate conversion (U_3O_8)	Human K-1	8.8	138	
	K-2		103	
	K-3		27 119	

[a]Urinary excretion rate determined by dissolution rate in lung after 4 days.

[b]95% confidence interval.

[c]Urinary excretion rate for accumulated uranium in kidney.

Table 8.9 Comparison of simulation fecal excretion results with human and animal exposures by inhalation

Exposure Compound	Species	Reference	In Vivo Result Half-time (days)	Simulation Result for Dogs Half-time[a] (days)
U_3O_8	Human	8.10		time varying
	Y-1		330	26 initially
	Y-2		600	70 at 1 mo
	Y-4		450	490 at 6 mo
	Y-5		340	1800 at 1 yr
Metal fume (U_3O_8)	Human	8.6 (8.5)	104 392	
	Human UR-2	8.7	70	
Uranyl nitrate conversion	Human K-1	8.8	144	
	K-2		71	
	K-3		12	
			383	

[a]Time dependent.

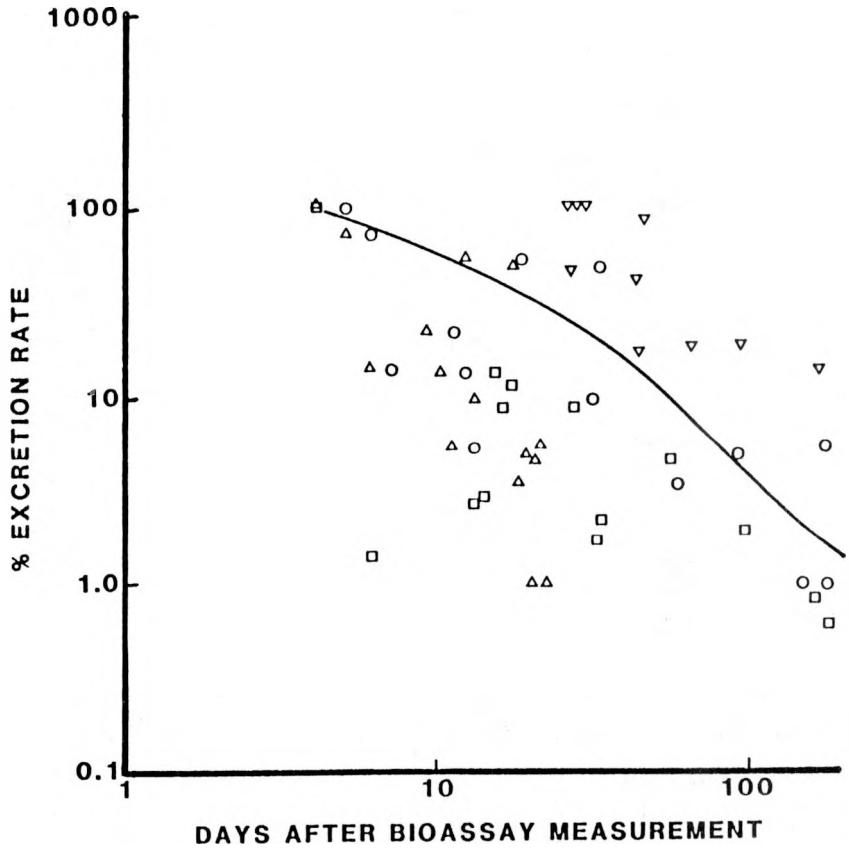

Figure 8.4 Simulated excretion rates of uranium in urine by four workers exposed to uranium concentrate aerosols (Ref. 8.2). Worker A (square), Worker B (circle), Worker C (triangle), Worker D (inverted triangle), simulation model (——).

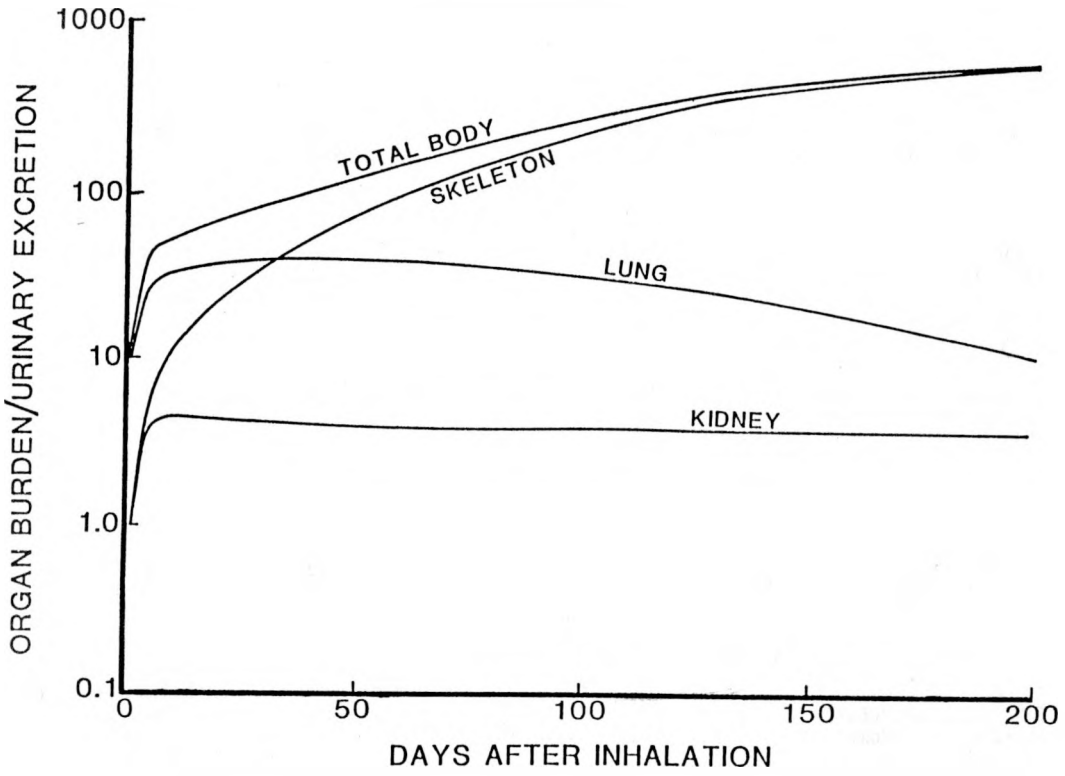

Figure 8.5 Ratio of % IBB in organ to % IBB excreted in urine after inhalation of ammonium diuranate (ADU).

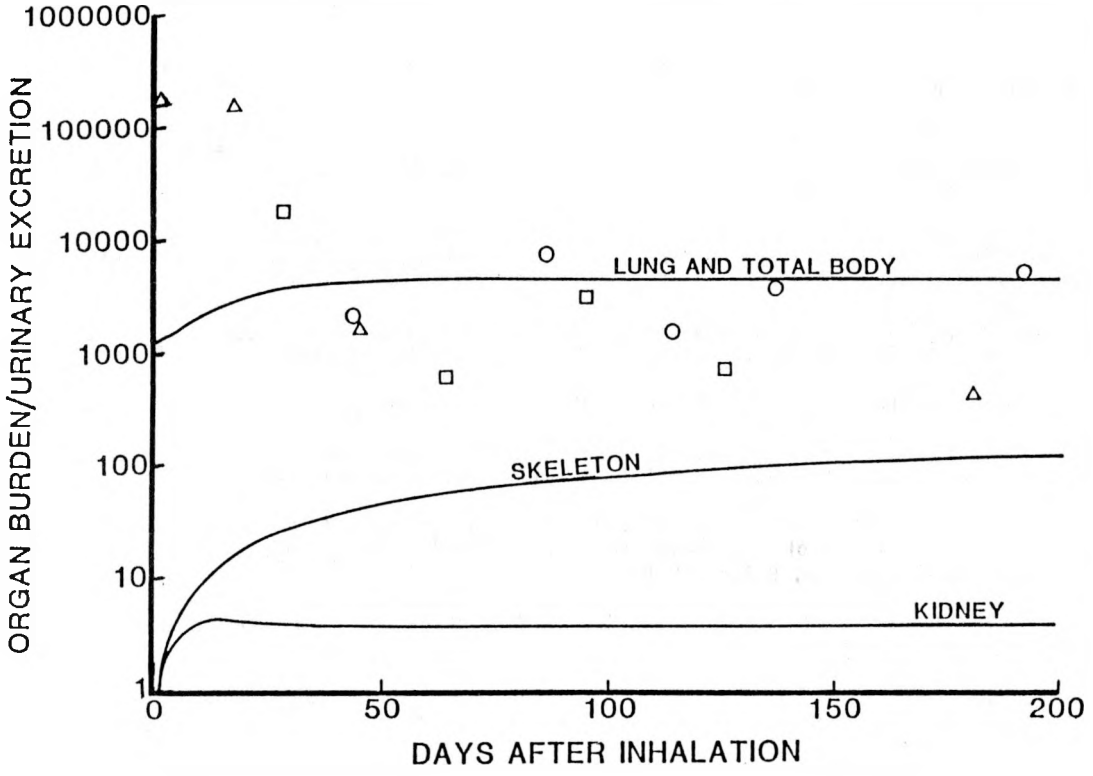

Figure 8.6 Ratio of % IBB in organ to % IBB excreted in urine after inhalation of U_3O_8 (Ref. 8.10); Worker Y-2 (square), Worker Y-4 (triangle), and Worker Y-5 (circle).

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PRESENTATIONS DERIVED FROM THIS RESEARCH

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11. ABSTRACT *(200 words or less)*

Protection of uranium mill workers from occupational exposure to uranium through routine bioassay programs and the assessment of accidental worker exposures are addressed. Comparisons of chemical properties and the biological behavior of refine uranium ore (yellowcake) are made to identify important properties that influence uranium distribution among organs. These studies will facilitate calculations of organ doses after exposures and associated health risk estimates and will identify important bioassay procedures to improve evaluations of human exposures.

Samples of airborne uranium from operating mills and deposition models were used to predict appreciable deposition in the upper respiratory tract of workers, if respiratory protection were not used.

Laboratory analyses of commercial yellowcake, and inhalation studies in rats, showed that inhalation of yellowcake aerosols might be considered to be inhalation of variable mixtures of ammonium diuranate and U_3O_8. Studies of yellowcake clearance from rats after wound contamination showed that uranium behavior in vivo could not be quantitatively related to chemical composition.

A biokinetic model of yellowcake inhaled by Beagle dogs was developed. Comparison with available data from human exposures showed that organ burdens in an exposed worker can be estimated from urinary bioassay results and in vivo counting, if the chemical composition, or soluble fraction, of the inhaled yellowcake is known.

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