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This document was prepared primarily for preliminary or internal use. It has not received full review and approval. Since there may be substantive changes, this document should not be considered final.

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RADIATION DOSE ESTIMATES AND HAZARD EVALUATIONS FOR INHALED AIRBORNE RADIONUCLIDES

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and
J. A. Mewhinney, Project Coordinator

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Prepared For

Division of Safeguards, Fuel Cycle and Environmental Research
Office of Nuclear Regulatory Research
U. S. Nuclear Regulatory Commission
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INTERIM REPORT

NRC Research and Technical Assistance Report

PROJECT STATUS SUMMARY

This quarterly report presents detailed information from radiobiological studies in two areas within the project which have attained a level of maturity sufficient for such presentation. Considerable effort was also given to several other areas of ongoing research. These latter areas will be highlighted here to familarize the reader with their present status. They will receive detailed analysis in subsequent reports as suitable stages in the work are reached which will allow for succinct summary.

The two research areas presented in detail in this quarterly report are, (1) an update on the status of the two pilot inhalation studies, including an analysis of the patterns of excretion of these materials, in which Fischer-344 rats were exposed to "pure" PuO_2 or to mixed oxides of U and Pu coated with an organic binder and (2) a summarization of the pathology observed to date in animals in all studies underway in this project.

The schedule for the progress of three long-term radiation dose pattern studies, as well as the pilot studies mentioned above, is illustrated in Figure 1. These studies are progressing on schedule. During this quarter, the scheduled sacrifice of animals at one year after inhalation exposure was carried out and subsequent radiochemical analysis of tissues initiated. Radiochemical analysis of excreta samples obtained from these animals was emphasized in order to obtain estimates of the initial lung burdens at an early date. Animals that died during this quarter other than at scheduled sacrifice times included one long-term reserve monkey which died due to gastric torsion, a not altogether rare occurrence, which was not related to its radiation exposure. One rat that was exposed to mixed U and Pu oxides coated with an organic binder material died with lung masses at 453 days after inhalation exposure.

Substantial progress was made during this quarter on the physical chemical characterization of materials collected from the Babcock and Wilcox facility. Emphasis in this area was on the production of powder x-ray diffraction data, as well as continuing work on *in vitro* solubility information for correlation with the *in vivo* lung retention data being developed. A visual representation of progress on the work for each industrial material collected to date is presented in Figure 2 through Figure 8. Figures 2-8 may be interpreted as described below.

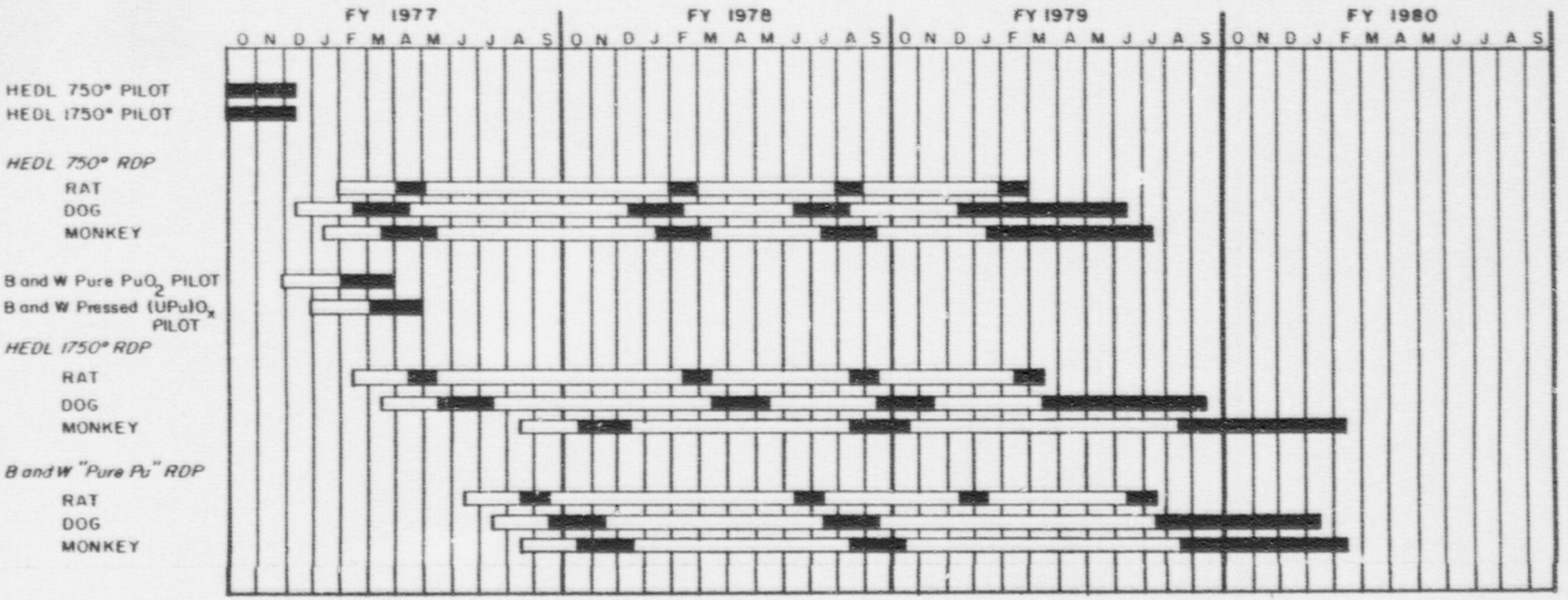

Figure 1. Progress of Nuclear Regulatory Commission Project animal studies for fiscal years 1977, 1978, and projected progress for 1979 and 1980. Each bar represents the time sequence of the indicated animal study from the time of inhalation exposure through the complete evaluation of results. The shaded areas within each bar indicate the sacrifice times and the period for analytical radiochemical effort required to produce radiation dose pattern data. The shaded areas serve to emphasize the continuing nature of data accumulation and evaluation for each study and how continuing comparisons between studies can be made.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

750°C $(U,Pu)O_x$ HEDL
AFTER BALL MILLING

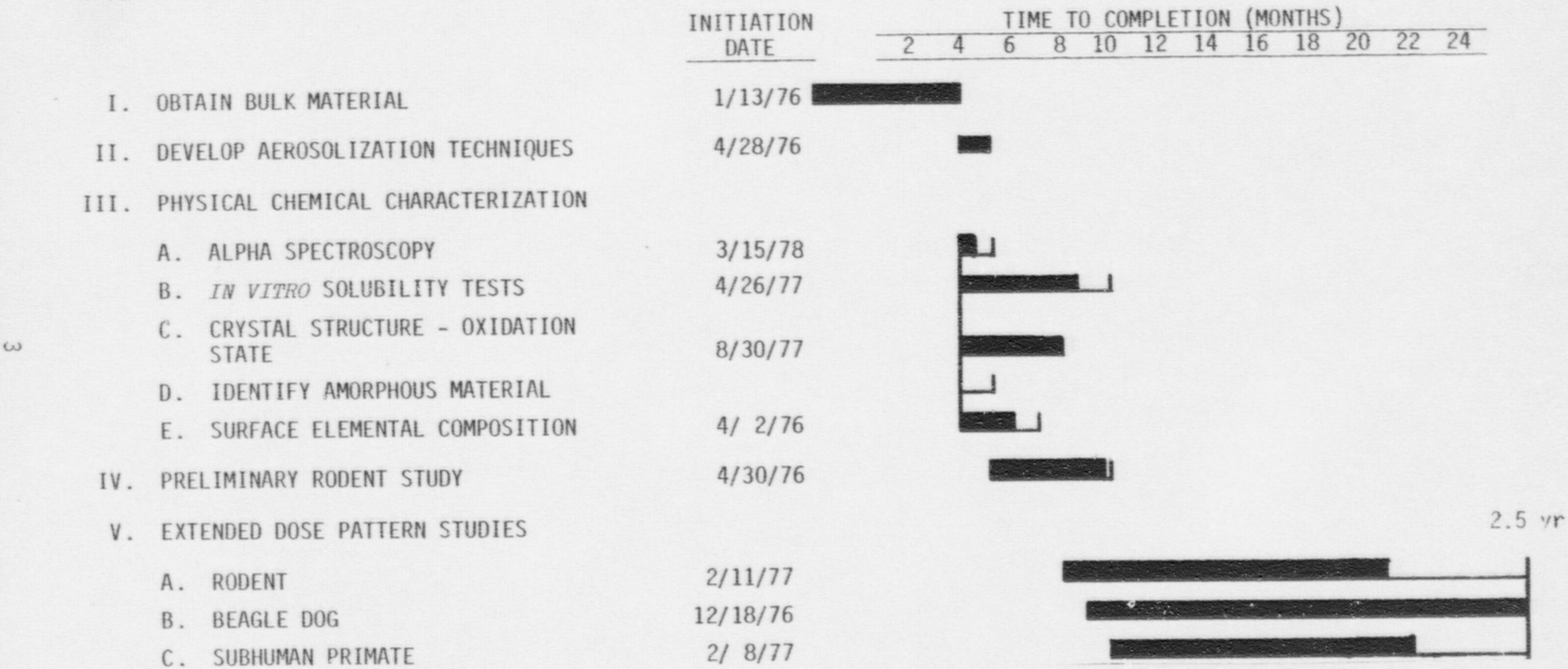

Figure 2. Current status of experiments using 750°C-treated U, Pu mixed oxides obtained from the ball milling process at HEDL.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

1750°C $(U,Pu)O_x$ HEDL
CENTERLESS GRINDING

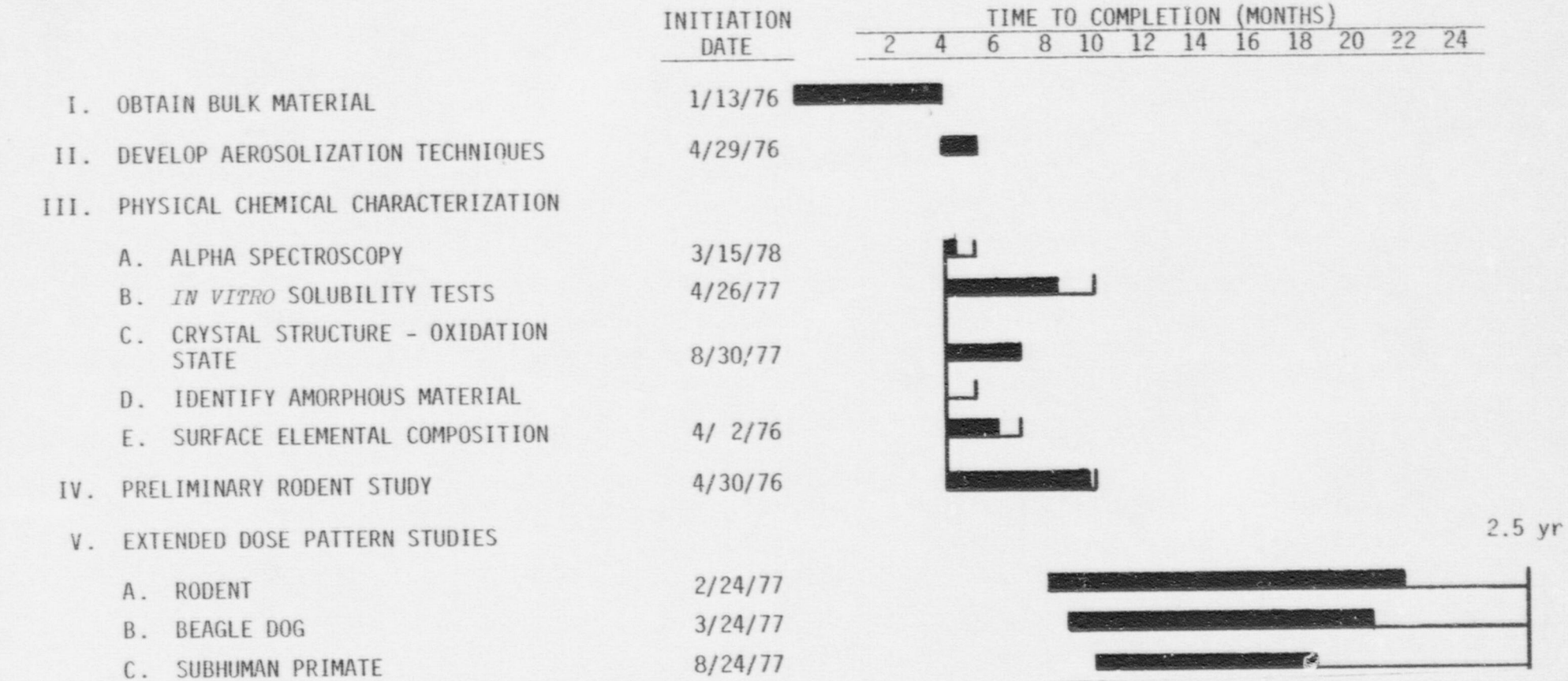

Figure 3. Current status of experiments using 1750°C-treated U, Pu mixed oxides obtained from the centerless grinding operation at HEDL.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

850°C PuO_2 B&W
V-MIXING

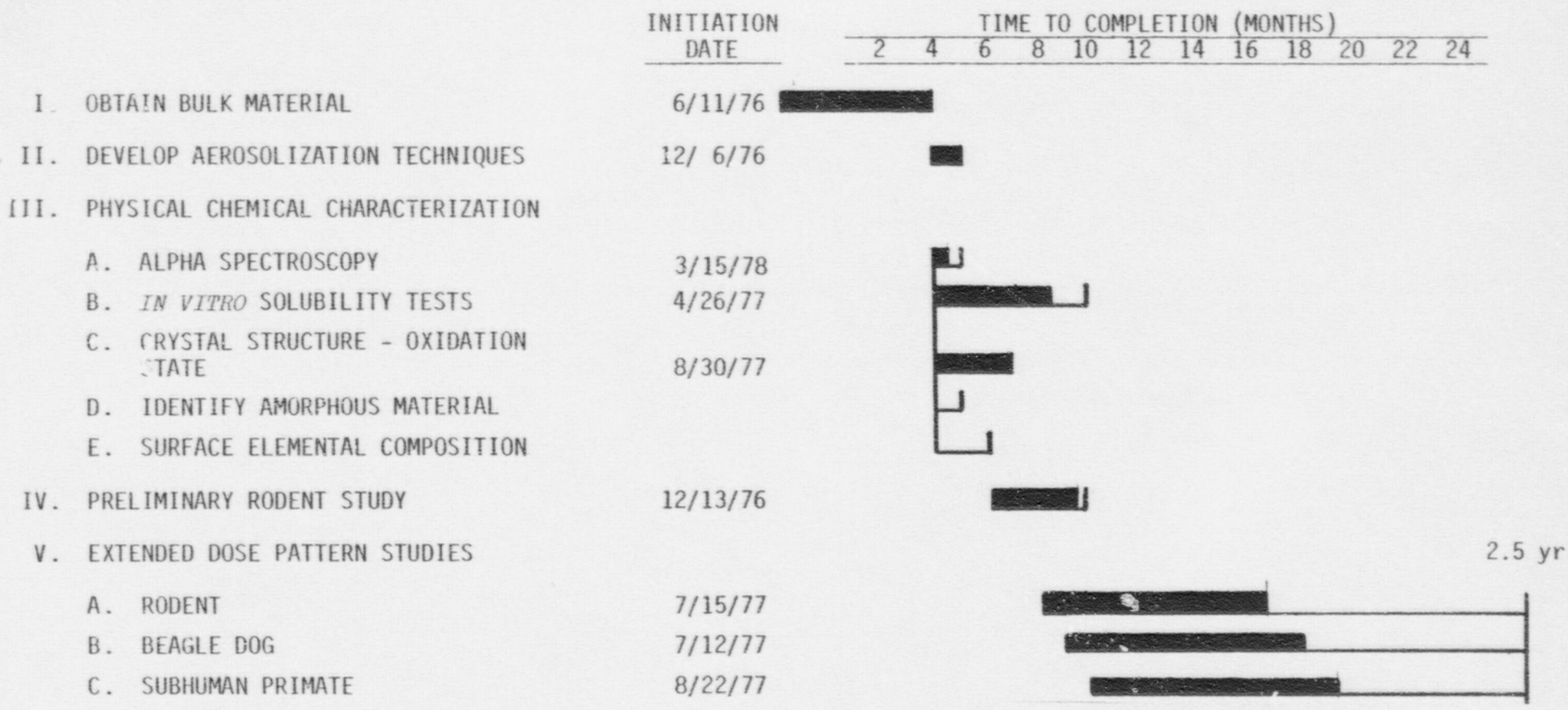

Figure 4. Current status of experiments using 850°C-treated PuO_2 obtained from the V-mixing process at B&W.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

850°C B&W WITH BINDER

$(U,Pu)O_x$ PELLET PRESS

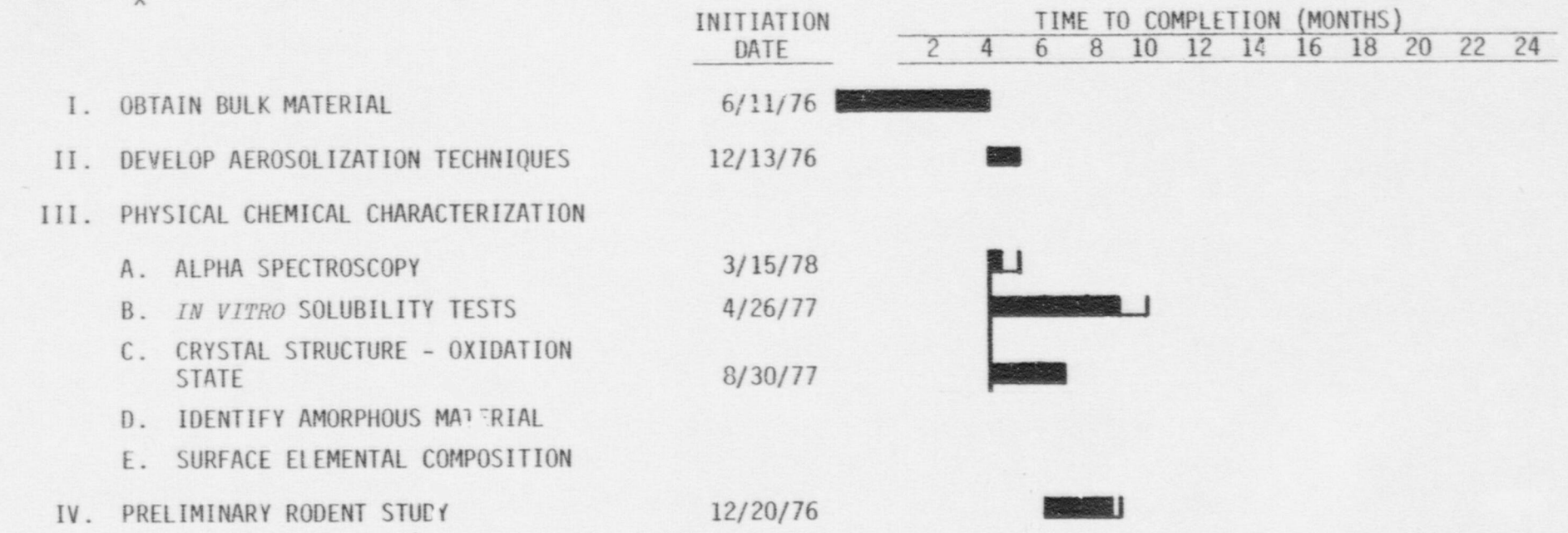

Figure 5. Current status of experiments using 850°C-treated U, Pu mixed oxides with organic binder obtained from the pellet pressing operation at B&W.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

750°C $(U,Pu)O_x$ HEDL
BEFORE BALL MILLING

	INITIATION DATE	TIME TO COMPLETION (MONTHS) 2 4 6 8 10 12 14 16 18 20 22 24
I. OBTAIN BULK MATERIAL	1/13/76	[redacted]
II. DEVELOP AEROSOLIZATION TECHNIQUES		
III. PHYSICAL CHEMICAL CHARACTERIZATION		
A. ALPHA SPECTROSCOPY		
B. *IN VITRO* SOLUBILITY TESTS		
C. CRYSTAL STRUCTURE - OXIDATION STATE	12/5/77	[redacted]
D. IDENTIFY AMORPHOUS MATERIAL		
E. SURFACE ELEMENTAL COMPOSITION		
IV. PRELIMINARY RODENT STUDY		
V. EXTENDED DOSE PATTERN STUDIES		
A. RODENT		
B. BEAGLE DOG		
C. SUBHUMAN PRIMATE		
VI. COMPARISON WITH LABORATORY DATA		
VII. CALCULATION OF DOSE ESTIMATES		

Figure 6. Current status of experiments using 750°C-treated U, Pu mixed oxides obtained before the ball milling process at HEDL.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

1750°C $(U,Pu)O_x$ B&W
CENTERLESS GRINDING

	INITIATION DATE	TIME TO COMPLETION (MONTHS) 2 4 6 8 10 12 14 16 18 20 22 24
I. OBTAIN BULK MATERIAL	6/11/76	[redacted]
II. DEVELOP AEROSOLIZATION TECHNIQUES		
III. PHYSICAL CHEMICAL CHARACTERIZATION		
A. ALPHA SPECTROSCOPY		
B. *IN VITRO* SOLUBILITY TESTS		
C. CRYSTAL STRUCTURE - OXIDATION STATE	12/12/77	[redacted]
D. IDENTIFY AMORPHOUS MATERIAL		
E. SURFACE ELEMENTAL COMPOSITION		
IV. PRELIMINARY RODENT STUDY		
V. EXTENDED DOSE PATTERN STUDIES		
A. RODENT		
B. BEAGLE DOG		
C. SUBHUMAN PRIMATE		
VI. COMPARISON WITH LABORATORY DATA		
VII. CALCULATION OF DOSE ESTIMATES		

Figure 7. Current status of experiments using 1750°C-treated U, Pu mixed oxides obtained from the centerless grinding operation at B&W.

NRC EXPERIMENT STATUS

TYPE AND SOURCE OF MATERIAL

850°C PuO_2 B&W
SIEVING

	INITIATION DATE	TIME TO COMPLETION (MONTHS) 2 4 6 8 10 12 14 16 18 20 22 24
I. OBTAIN BULK MATERIAL	6/11/76	
II. DEVELOP AEROSOLIZATION TECHNIQUES	12/ 3/76	
III. PHYSICAL CHEMICAL CHARACTERIZATION		
A. ALPHA SPECTROSCOPY		
B. *IN VITRO* SOLUBILITY TESTS		
C. CRYSTAL STRUCTURE - OXIDATION STATE	12/28/77	
D. IDENTIFY AMORPHOUS MATERIAL		
E. SURFACE ELEMENTAL COMPOSITION		
IV. PRELIMINARY RODENT STUDY		
V. EXTENDED DOSE PATTERN STUDIES		
A. RODENT		
B. BEAGLE DOG		
C. SUBHUMAN PRIMATE		
VI. COMPARISON WITH LABORATORY DATA		
VII. CALCULATION OF DOSE ESTIMATES		

Figure 8. Current status of experiments using 850°C-treated PuO_2 obtained from the sieving process at B&W.

One figure is given for each material on hand at ITRI and a list of physical, chemical, biological and mathematical tests which might be employed to assess the radiobiological effect of each material. An initiation date is shown for each test and a line to indicate the estimated time to completion once the experiment is initiated. The shaded bar associated with each line represents the status of each experiment to date. Tests VI and VII will be initiated for all materials when sufficient data becomes available from radiobiological studies. Other experiments, specifically experiments IV and V may never be initiated for some materials unless information from an ongoing study shows that these materials are unique in some respect such that radiobiological studies would be warranted. Results from these efforts will be reported in the Annual Report to be prepared at the end of the next quarter.

The remainder of this quarterly report presents detailed information on two specific areas of the research. The first is a report on the results obtained from two pilot inhalation studies in which Fischer-344 rats received inhalation exposures to materials collected at the Babcock and Wilcox Mixed Oxide Fuel Fabrication Facility. The second area of detailed presentation concerns the long term biological effects (specifically lung tumors) that have been observed in all studies in this project to date including, where possible, the radiation dose to lung.

During the next quarter, the research effort will continue along present lines with emphasis on the development of preliminary comparisons in two areas. First, work on the physical chemical characterization accomplished on the several materials under study will be summarized with emphasis being given to alpha spectroscopy and *in vitro* solubility studies. The second area will emphasize comparisons among the several animal inhalation studies which have been underway at least one year.

SHORT TERM RADIATION DOSE PATTERNS IN FISCHER-344 RATS FOLLOWING INHALATION OF PuO_2 OR MIXED OXIDES OF U AND Pu COATED WITH AN ORGANIC BINDER

The studies were initiated to determine the radiation dose pattern in Fischer-344 rats following inhalation of either PuO_2 or mixed oxides of U and Pu coated with an organic binder. The materials were collected from glove boxes at the Babcock and Wilcox Mixed Oxide Fuel Fabrication Facility at Apollo, PA during normal operations. The PuO_2 material was collected during operation of a V-blender. This operation serves to blend PuO_2 powder from several batches to a uniform feed material for later mixture with U oxides in the fuel fabrication process. The mixed oxides of U and Pu were obtained during a V-blending operation after the material had passed through several stages of processing, one of which served to coat the particles of U and Pu oxides with an organic binder to aid in the subsequent pellet pressing operation.

Sufficient material of both types was collected from the glove boxes and returned to ITRI. This material was then re-aerosolized using a powder blower for inhalation exposure of groups of Fischer-344 rats. Groups of five animals were sacrificed at 0, 8, 16, 32 and 64 days after the inhalation exposure and selected tissues were analyzed radiochemically to determine their Pu and Am content. Routine collections of fecal and urinary excretions, as well as of the wash water collected during cleansing of their cages, were made during the course of these two experiments to allow reconstruction of initial lung burdens. Urine, feces and cage wash samples were collected every day for three animals in the 16-day sacrifice group for both experiments. Collections were also made every day for three animals in the 64-day sacrifice group through two weeks after inhalation exposure and pooled collections every three days thereafter. Earlier reports on these experiments were based on determination of relative content of Pu or Am in the tissues of sacrificed animals. These values were expressed as a percentage of the initial lung burden (ILB) based on the lung content of Pu and Am in animals sacrificed at one hour after inhalation exposure. Results of radiochemical analysis of excreta and cage wash samples collected during the study are now available which allow a refinement of the ILB values reported earlier.

The excreta data were used to construct revised individual estimates of the initial lung burdens of Am and Pu for the animals in the following manner. The activity of each isotope in feces, urine and cage wash samples from collected animals was plotted versus collection time after exposure. Equations of the form: nanocuries excreted/day = $A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$ were then fit to the data using a non-linear least squares method. The initial lung burden (ILB) of each animal was calculated according to Equation (1):

$$ILB = SBB + \int_{4d}^{sac\ d} A_f(t)dt + \int_{4d}^{sac\ d} A_u(t)dt \int_{4d}^{sac\ d} A_w(t)dt \qquad (1)$$

where SBB refers to the total sacrifice body burden, d represents days after exposure, sac d = day of sacrifice and $A_f(t)$, $A_u(t)$ and $A_w(t)$ represent functions of the form $A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$ for feces, urine and cage wash, respectively. The lower limit of integration in each case was chosen as four days after inhalation exposure. The fecal excretion data indicated that material excreted from 0 to 4 days after exposure represented material initially deposited in the upper respiratory tract and gastrointestinal tract. This amount of excreted activity does not contribute to the initial lung burden. During the time interval from four days to 64 days after exposure, the excreta plus cage wash represented about 39% of the initial lung burden (the rest comprising the sacrifice body burden) and of this 39%, 96.5% was contributed by the feces, 0.5% by the urine and 2.9% by the cage wash.

The initial lung burdens of other rats in the same study that were not subject to excreta collection were determined by combining their respective sacrifice body burdens with a curve giving the ratio of sacrifice body burden to initial lung burden as a function of time after exposure derived from the collected animals. This type of a construct required making the assumptions that : (1) all animals in the study excreted activity at the same rate and (2) the ratio of sacrifice body burden to initial lung burden at a given time was the same for all animals in the study. Using this method, the mean initial lung burdens of plutonium and americium for the two studies were calculated and are shown in Table 1.

Three measurements of Am/Pu ratio are shown in Table 1 and compared for each material. The first value represents the ratio of the americium and plutonium initial lung burdens as given in the table and determined by summing the activity in the excreta with that found in the animal at sacrifice. The second value is the americium to plutonium ratio in the aerosol material sampled during the inhalation exposure of each group of rats. These ratios were determined by alpha spectroscopy of aerosols deposited on filters. The third value is calculated from radiochemical analyses of the americium and plutonium content of the lungs of animals sacrificed on the day of exposure.

It should be noted that although the Am/Pu ratios as an activity balance determined from deposition and excretion data agree with those determined by alpha spectrsocopy and with those determined from lung content on the day of exposure, within the error of the measurements, the mean values determined by alpha spectroscopy appear to be somewhat higher than the exposure day radiochemistry values. The reasons for this are not obvious at this time. Ideally, one would expect the ratios determined from the original aerosol material to agree closely with those found by examination of the lungs on the day of exposure since no potential effects of differential solubility or metabolism of americium vs plutonium need be taken into account for this comparison. This problem is receiving continuing examination. As expected, there is more variability observed in the ratios determined by activity balance than by the other methods. This is due to the fact that there are more sources of error in this determination, i.e., errors in the curve fitting of excreta data and errors in applying excreta data obtained from six animals to the entire exposed population.

These initial lung burdens were then used to calculate the tissue data as percentages of the initial lung burden to arrive at lung retention curves. Figures 1-4 show the retention of americium and plutonium in the lung as a function of time after exposure. Each point on the retention curves, except for the 0-day values, represents the mean of five animals in that sacrifice group. The 100% value on day 0 is an assumed value placed on the graphs for reference. In the case of plutonium, the slopes of the retention curves appear to be significantly different with biological halftimes of 173 days and 50 days, respectively, for the PuO_2 and mixed oxides with binder. However, it must be remembered

Table 1

Initial Lung Burdens of Americium and Plutonium in Fischer-344 Rat After Inhalation of Aerosols of Industrial Nuclear Fuel Materials

Material, Process, Temperature History	Number of Rats	ILB Pu[a] (nCi)	ILB Am[a] (nCi)	Am/Pu		
				[b]	[c]	[d]
PuO_2 V-Mixing 850°C	30	60 ± 36	5.5 ± 4.5	0.092 ± 0.090	0.177 ± 0.025	0.049 ± 0.022
$(U,Pu)O_x$ + Organic Binders Pellet Pressing 850°C	30	110 ± 60	7.8 ± 3.9	0.071 ± 0.053	0.162 ± 0.047	0.049 ± 0.038

[a] Mean ± 1 standard deviation.

[b] Determined as the sum of excreted activity and activity found in animal at sacrifice.

[c] Determined by alpha spectroscopy on exposure aerosol material.

[d] Determined by radiochemical analysis of lungs from animals sacrificed on day of exposure.

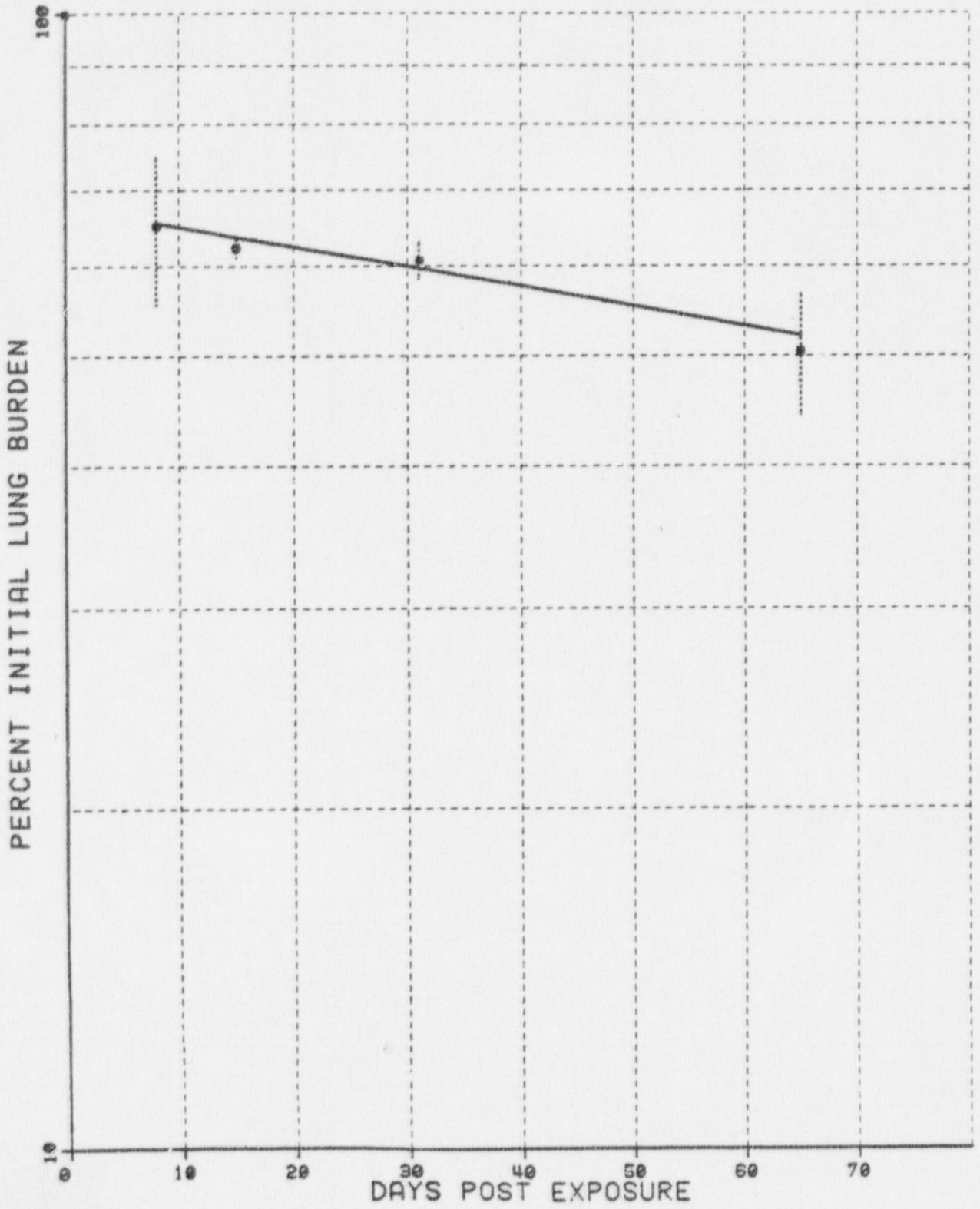

Figure 1. Lung retention of plutonium in Fischer-344 rats of 850°C heat treated PuO_2 obtained from the V-blending operation at the Babcock and Wilcox Nuclear Fuel Fabrication Facility. Error bars represent 1 standard deviation.

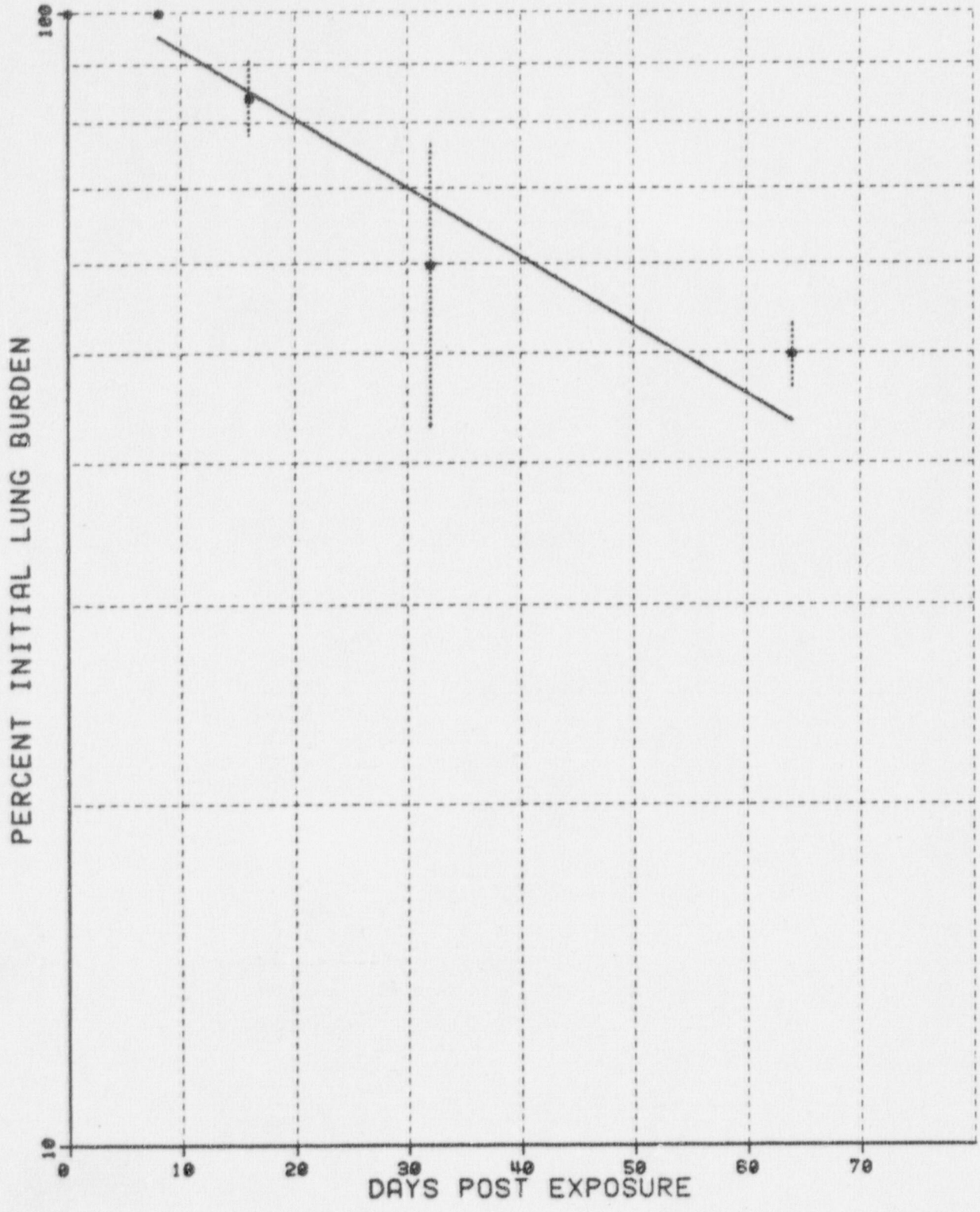

Figure 2. Lung retention of plutonium in Fischer-344 rats of 850°C heat treated mixed uranium and plutonium oxides with binders obtained from the pellet pressing operation at the Babcock and Wilcox Nuclear Fuel Fabrication Facility. Error bars represent 1 standard deviation.

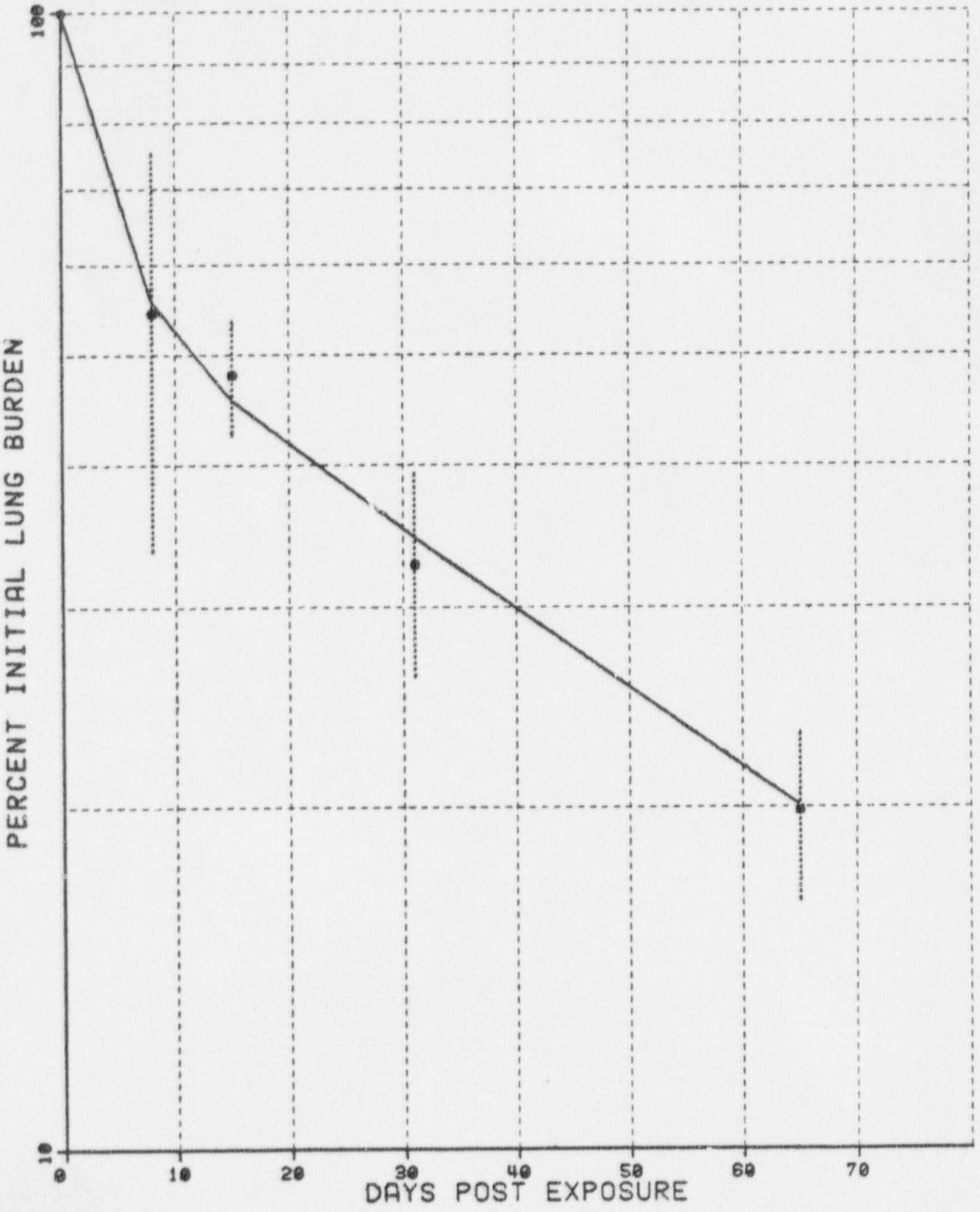

Figure 3. Lung retention of americium in Fischer-344 rats of 850°C heat treated PuO_2 obtained from the V-blending operation at the Babcock and Wilcox Nuclear Fuel Fabrication Facility. Error bars represent 1 standard deviation.

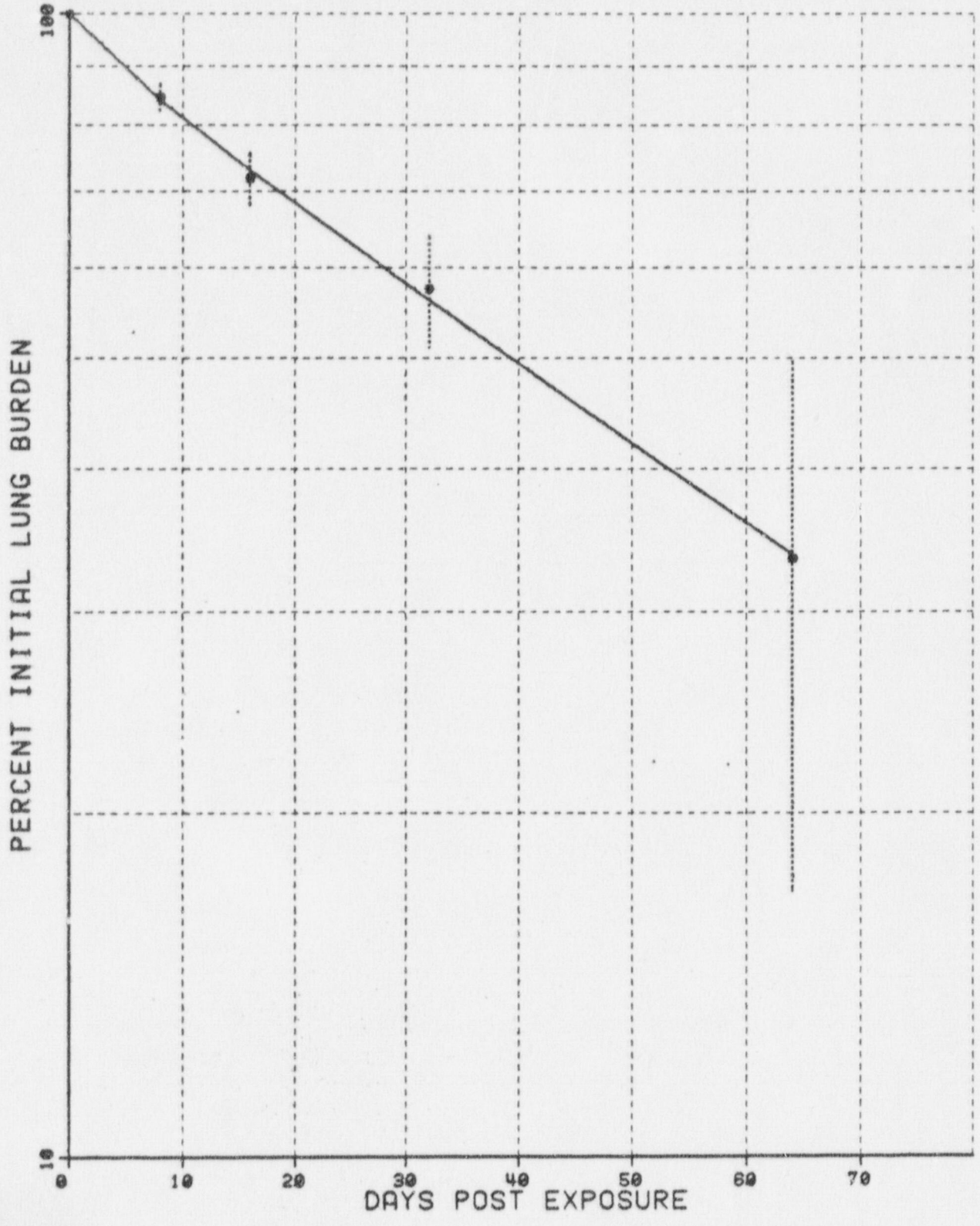

Figure 4. Lung retention of americium in Fischer-344 rats of 850°C heat treated mixed uranium and plutonium oxides with organic binders obtained from the pellet pressing operation at the Babcock and Wilcox Nuclear Fuel Fabrication Facility. Error bars represent 1 standard deviation.

that the length of the study was only 64 days. Experience with longer term studies suggests that these differences are simply small pertubations in the short term component of a longer study. This will be examined in greater detail in longer term studies.

There are two important features of these retention curves. First, it can be seen by comparing the americium and plutonium curves for each study that in the case of both studies the americium appears to have left the lung at a faster rate than the plutonium did, suggesting that the *in vivo* solubility of americium in these materials was greater than that of plutonium. This greater solubility was borne out by *in vitro* solubility results on these materials which will be reported in detail in the forthcoming Annual Report for the period July 1, 1977 - June 30, 1978. Second, by comparing the americium retention curves of the two materials, it can be seen that the americium in the PuO_2 left the lung much more rapidly at early times than did the americium in the material with the binder. At longer times the rates appeared to be the same, however. A possible explanation for this is that the binder material may have interferred with the early dissolution of americium. A similar effect can be seen by comparing the two plutonium curves although the effect does not appear as dramatic.

The organ distribution of plutonium and americium for these two pilot studies at 64 days after inhalation exposure were calculated and are summarized in Table 2.

It has been determined from these studies that the only organs other than the lung showing significant uptake of plutonium and americium from these materials are the liver and the skeleton. These data also show that, in general, americium tends to leave the lung at a faster rate than does plutonium and to appear in other tissues at a faster rate than plutonium, thus giving another indication of its greater *in vivo* solubility.

The results from these pilot studies will be integrated with the data from the long term studies using the same materials. In the case of lung retention curves, the superposition of these pilot study data on those from the long term experiments will help to better define the lung retention curves and will yield additional information about early clearance. The information obtained from these pilot studies will also give an indication of just how useful pilot studies are in predicting the behavior of these materials in various animal species.

Table 2

Plutonium and Americium Distribution in Lung, Liver and Skeleton of Laboratory Rats at 64 Days After Inhalation Exposure to Aerosols of Industrial Nuclear Fuel Materials

Material, Process, Temperature History	Lung[a] (% SBB)		Liver (% SBB)		Skeleton[b] (% SBB)	
	Pu	Am	Pu	Am	Pu	Am
PuO_2 V-Mixing 850°C	91.3	76.8	3.6	6.2	1.4	10.7
$(U, Pu)O_x$ + Binder Pellet Pressing 850°C	93.9	83.5	0.2	0.9	2.1	11.2

[a]Sacrifice Body Burden.

[b]Sum of values from femur, skull and carcass.

Aside from their potential use for better definition of the results from the respective long term studies, these pilot studies provide information useful in such areas as bioassay. In this respect, for example, making use of the knowledge gained from these studies concerning the differential solubility of americium versus plutonium allows the health physicist to more intelligently interpret his bioassay data. And, finally, combining the results of these pilot studies with the final results of the completed long term studies will provide the data base for mathematical modeling of the behavior of these materials *in vivo* and allow the formulation of intelligent risk estimates.

SUMMARY OF PATHOLOGY OBSERVED TO DATE IN ANIMALS IN ALL STUDIES UNDERWAY IN THIS PROJECT

Six rats exposed to aerosols of the materials under study in this project have died from abnormal causes to date. Five of these have undergone histopathological examination. In each case, an attempt was made to calculate as accurately as possible the accumulated radiation dose to lung at the time of death. This dose was calculated by assuming a uniform distribution of activity in lung and making use of available lung retention data along with a knowledge of the initial lung burden to calculate the dose according to the following equation:

$$\text{Cumulative rads} = \frac{51.2\ \bar{E}F}{M} \int_0^t R(t)dt \qquad (2)$$

where $\bar{E}$ is the average energy per disintegration of the isotope, F is the fraction of the energy emitted which is absorbed in tissue, M is the mass of the lung, R(t) is the lung retention function and 51.2 is a conversion constant. The integral is taken from the day of exposure to the death date and R(0) is taken to be the initial lung burden.

The assumptions used in making these dose calculations were as follows:

1. A "standard rat" was used, i.e., a total body weight of 360g was assumed for an adult male rat and 190 g for an adult female and the lung weight was assumed to be 1% of total body weight in each case. These assumptions were made because the large tumor masses in an animal added significantly to organ weights while body weights were frequently less than expected for a healthy animal, making observed weights useless for these calculations.

2. Most of the dose was due to the alpha emissions from ^{239}Pu with an average energy of 5.16 MeV/disintegration based on available iostopic composition data.

3. A [illegible] alpha particles emitted are absorbed in the lung.

The form [illegible]ung retention equation R(t) was straightforward in the case of animals from the long term studies in which retention data exist through

one year after exposure. In the case of the 64-day pilot studies, however, information from the appropriate long term studies was used to aid in determining the form of R(t).

Results of radiation dose calculations and of histological examination of these animals are summarized in Table 1. Six rats being held for long-term sacrifice died or were euthanized before their scheduled sacrifice time. Three of these rats, 1933-21, 1933-29 and 1933-31, had large masses in the lungs which were primary lung tumors. Two rats died with radiation pneumonitis and pulmonary fibrosis and one rat was euthanized because of a subcutaneous tumor.

Animal number 1933-31 died 216 days after exposure to an aerosol of $(U,Pu)O_2$ containing organic binders with a radiation dose of 860 rads. This is a revision of the dose estimate given for this animal in the last Annual Report (NUREG/CR-0010) in the light of new data obtained since the time of that report. Large masses were present in the lung which spread out into the pleural cavity and infiltrated the mediastinum and thoracic wall. The tumor was an adenosquamous carcinoma of the lung which was characterized by sheets of large anaplastic cells interwoven with a connective tissue stroma. In a few areas, small tubular or acinar structures were formed which were lined by large anaplastic cuboidal cells. The lumina were filled with necrotic debris. In a lesser number of areas, squamous epithelium lined the tubular structures. In all areas, the tumor completely obliterated the normal architecture of the lung, invading vessels, pleura and airways. Some large foci of necrosis were present where the tumor had outgrown its blood supply. In the more normal areas of lung, a focal septal fibrosis with radiation pneumonitis was found. Centrolobular necrosis in the liver was probably caused by a passive congestion of the liver due to an inability to perfuse blood through the badly damaged lung. No significant lesions were noted in the other major organs. Radioisotope was found only in the lung with autoradiographs.

A second animal, 1933-29, died 369 days after exposure to the same aerosol with a dose to lung of 1100 rads. Large masses were found in the lung. It was not examined histologically, but it most likely was also a primary lung tumor.

Animal 1933-21 died 453 days after exposure to this same aerosol with a dose to lung of 2100 rads. A large firm whitish mass filled one lung lobe.

Table 1

Summary of Pathology Observed in Fischer-344 Rats Exposed by Inhalation to Industrial U, Pu Mixed Oxides

Animal Number	Exposure Material	Death Date (DPE)[a]	Cumulative Lung Dose to Death (rads)	Histopathologic Diagnosis[b]
1933-31	$(U,Pu)O_2$[c] + Binders	216	860	Adenosquamous carcinoma, lung
1933-29		369	1100	Large lung mass[d]
1933-21		453	2100	Squamous cell tumor
2086-08	$(U,Pu)O_2$[e]	207	210	Mammary tumor[f]
2086-25		212	400	Radiation pneumonitis, pulmonary fibrosis
2086-24		284	450	Radiation pneumonitis, pulmonary fibrosis

[a] DPE - days after exposure.

[b] See text for complete diagnosis.

[c] PuO_2 which had been heat treated at 850°C before mixing with UO_2 and organic binder material. Powder was obtained from the pellet pressing operation at the Babcock and Wilcox facility.

[d] Gross appearance was that of a primary lung tumor.

[e] PuO_2 which had been calcined at 750°C before mixing with UO_2. Powder was obtained from the ball milling operation at the Hanford Engineering and Development Laboratory.

[f] Not radiation induced.

Histologically, the mass had the characteristics of a squamous cell tumor. The mass appeared to be slow growing and compressed surrounding lung parenchyma. Most of the mass was composed of necrotic cells which were sloughed into the center of the tumor. There was no evidence of metastasis or invasion. It could not be classified as malignant, but it did replace a large portion of the lung lobe and, if given enough time, may well have invaded other organs or metastasized. No significant lesions were noted in other organs.

Rat 2086-08 was euthanized because of a large, superficial tumor 207 days after exposure to an aerosol of $(U,Pu)O_2$ which did not contain organic binders with a radiation dose to lung of 210 rads. The tumor was a fibrosarcoma apparently arising from subcutaneous tissue under the skin or possibly from remnants of mammary tissue. However, the histologic features were strictly that of a sarcoma, with many anaplastic irregular or spindle-shaped cells and abundant formation of collagen. Although the tumor did not metastasize, the anaplasia of the cells and the numerous mitotic figures were evidence of malignancy. Fibrosarcomas of the subcutis are a common tumor in aged Fischer-344 rats (1). This, plus the fact that essentially no transuranics are translocated to these tissues indicates that this tumor was spontaneous and not directly related to radiation injury. Throughout the lung there were foci of radiation pneumonitis and fibrosis characterized by thickening of the alveolar septa with connective tissue and mononuclear cells and alveolar collections of mononuclear cells. Many of the alveolar macrophages contained radioisotope as indicated by autoradiographs. Most of the foci were concentrated near the pleural or outer regions of the lungs.

Rat 2086-24 died 284 days after exposure to an aerosol of $(U,Pu)O_2$ with a radiation dose to lung of 450 rads. Grossly, the lung was darkened with granular foci scattered over the surface. Histologically, it was determined that this appearance was due to a widespread radiation pneumonitis and pulmonary fibrosis that was most severe in the subpleural or peripheral portions of the lung. There was a thickening of the subpleural alveolar septa and the pleura with connective tissue in large foci of the lung which in some areas formed large scars. Some chronic inflammatory cells were present but fibrosis predominated.

Rat 2086-25 died 212 days after exposure to an aerosol of $(U,Pu)O_2$ with a radiation dose to the lung of 400 rads. The lungs were pitted with small pale

foci. The thorax was filled with blood. Histologically, a severe, widespread radiation pneumonitis and pulmonary fibrosis was present. Alveolar septa in large areas of the lung were greatly thickened with connective tissue. The alveoli contained many macrophages which were laden with hemosiderin and radioisotope. In addition, an acute vasculitis with thrombosis was present which involved small arteries and arterioles and probably accounted for the hemorrhage and hemothorax.

Conclusions based on this small number of premature spontaneous deaths would be speculative at best. However, it may be noted that the aerosol of $(U,Pu)O_2$ containing organic binders induced lung tumors at doses of ≈ 1000 to 2000 rads in three of thirty rats exposed. The aerosols of $(U,Pu)O_2$ which did not contain organic binders induced radiation pneumonitis and pulmonary fibrosis at a cumulative lung doses of 200-450 rads in two of thirty rats. These dose levels and related histopathology findings will be compared with results of studies where pure isotope laboratory produced aerosols were used in an effort to determine whether the industrial mixed oxides are comparable in their radiobiological effects. Similar analysis will be performed if similar premature spontaneous deaths occur in beagle dogs or cynomolgus monkeys exposed to aerosols of the same materials.

REFERENCE

1. Coleman, G. L., Barthold, S. W., Osbaldiston, G. W., Foster, S.J. and Jonas, A. M., "Pathological Changes During Aging in Barrier-Reared Fischer-344 Male Rats," *J. of Gerostology*, 32, 258-278, 1977.