COMPARATIVE DISPOSITION OF FOUR TYPES OF PLUTONIUM DIOXIDES INHALED BY DOGS*

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Abstract—Groups of three dogs were given single inhalation exposures to dry aerosols of one of four different plutonium dioxides to compare retention, translocation, and rates of excretion. Two of the plutonium dioxides were prepared by calcining the oxalate at 350°C and at about 1000°C. Two others were produced by ignition of the stabilized delta metal at 450°C and by slow oxidation of the pure metal at 123°C. The lung retention half-time of the oxalate calcined at 350°C was about one year, half that of the other oxides. This was due to greater accumulation of plutonium in the bronchial lymph nodes rather than greater clearance via the mucus-ciliary pathway or a relatively high rate of solubility. The metal oxidized at 450°C was cleared via the mucus-ciliary route to a lesser extent than the other oxides. This same oxide also showed a selective loss of ^{241}Am, relative to ^{239}Pu, in lung and bronchial lymph node tissue which was not evidenced by the other oxides. The oxalate calcined at 1000°C showed the least translocation to tissues outside the respiratory tract. These results indicate that the physical-chemical state of inhaled plutonium dioxide influences its disposition in the body.

INTRODUCTION

Earlier studies in this laboratory[1-3] indicated that the disposition of inhaled plutonium dioxide in beagle dogs was influenced by the particle size characteristics of the aerosol. Inhalation studies with cerium in dogs showed that oxides prepared by chemical precipitation were more rapidly translocated and excreted in the urine than oxides calcined at approximately 400°C.[4, 5] Therefore, it seemed possible that inhaled plutonium dioxides having different physical and chemical properties, such as those that might occur as a result of the method of formation, could have dissimilar fates in the body. Because of the increasing possibility for human exposures to plutonium dioxides from several different sources and treatments, such as oxidation of the metal in air, high explosive detonation and incineration of nuclear weapons, fallout from nuclear detonations, calcination of oxalates, or as ceramics formed in a very high temperature plasma jet, it is desirable to know whether and how the origin of the plutonium dioxide might influence its disposition in the body and its subsequent biologic effects. In this study the retention, distribution, and excretion rates of four different plutonium dioxides inhaled by dogs were compared. The plutonium dioxides ranged from metal oxidized at 123° to oxalate calcined at about 1000°. In general all oxides, except one which was prepared by calcining the oxalate at 350°, showed similar pulmonary retention, translocation, and excretion rates during the first three months after exposure.

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METHODS

A. Materials

The experimental protocol is shown in Table 1. The plutonium dioxides prepared by calcining the oxalates were obtained from the Hanford Plant. The oxalate calcined at 350° was an aliquot of that used in most of our previous studies since 1958. Another aliquot was

recalcined at a temperature between 950° and 1000°. The oxides prepared from plutonium metal were obtained from the United Kingdom Atomic Energy Authority through the courtesy of Dr. K. Stewart.† One type was produced by the ignition at 450° of the stabilized delta metal and the other by the slow oxidation of the pure metal at 123°C. In both cases the oxide was the residue remaining after the oxidation of the metal. The oxides were sieved to obtain the fractions with particle size less than 50 μ. According to Dr. Stewart the 123° oxide was very friable, tending to break down into particles of less than 3 μ, and could agglomerate on standing.[6]

laboratory.[8] Training of the dogs eliminated the need for anesthesia or tranquilizers. The aerosol chamber was a 2-ft vertical section of 8-in. (O.D.) lucite pipe. The aerosol was introduced at the top of the chamber, exhausted at the bottom and sampled with membrane filters and a Walkenhorst type thermal precipitator. The respiratory rates and volumes were monitored throughout the 10–20 min exposures with a calibrated respiratory sensor.[9]

The aerosols were produced by directing dry air at a rate of 100 cc/min through a small diameter tube attached as a side arm to a 25 ml flask containing the dry plutonium dioxide dust. The flask was vibrated with an electric

Table 1. *Experimental Protocol*

Group No.	Dog No.	PuO_2 inhaled	Particle size CMD (μ)	Particle size MMD	Percent ultra-filterability
I	1*, 2+, 3*	Oxalate calcined at 1000°	.51	2.8	0.04
II	4△, 5, 6+	Oxalate calcined at 350°	.45	2.8	0.02
III	7+, 8△, 9	Metal oxidized at 450°	.50	4.8	0.006
IV	10△, 11, 12	Metal oxidized at 123°	.46	1.3	0.006

*, +, △ Litter mates.

Female beagle dogs, about three years old, weighing from 8 to 12 kg were used. All dogs were raised in our colony and had complete clinical histories including radiographs. A number of the dogs were litter mates as indicated in Table 1.

B. Aerosol Exposures

For the inhalation exposures the dogs were fitted with masks and required to inhale the aerosol from the chamber through an electronically operated fast-acting three-way respiratory valve[7] by a method previously used in our test tube shaker to keep the dust in motion. The top of the flask was connected to the top opening of the aerosol chamber by flexible tubing. The aerosol concentrations ranged from 10^{-2} to 10^{-3} μCi/cc. These relatively high aerosol concentrations were required to assure that the dogs deposited enough plutonium to excrete detectable levels in the urine. The results of earlier studies indicated that these deposition levels would cause some pathology in the lungs during the three-month period selected for this study, but would not markedly influence the rates of excretion and translocation.

Particle size distributions of the aerosols inhaled by the dogs were determined with the Zeiss Particle Size Analyzer from electron-micrographs of thermal precipitator and mem-

† United Kingdom Atomic Energy Authority, Atomic Weapons Research Establishment, Aldermaston, Berkshire, England.

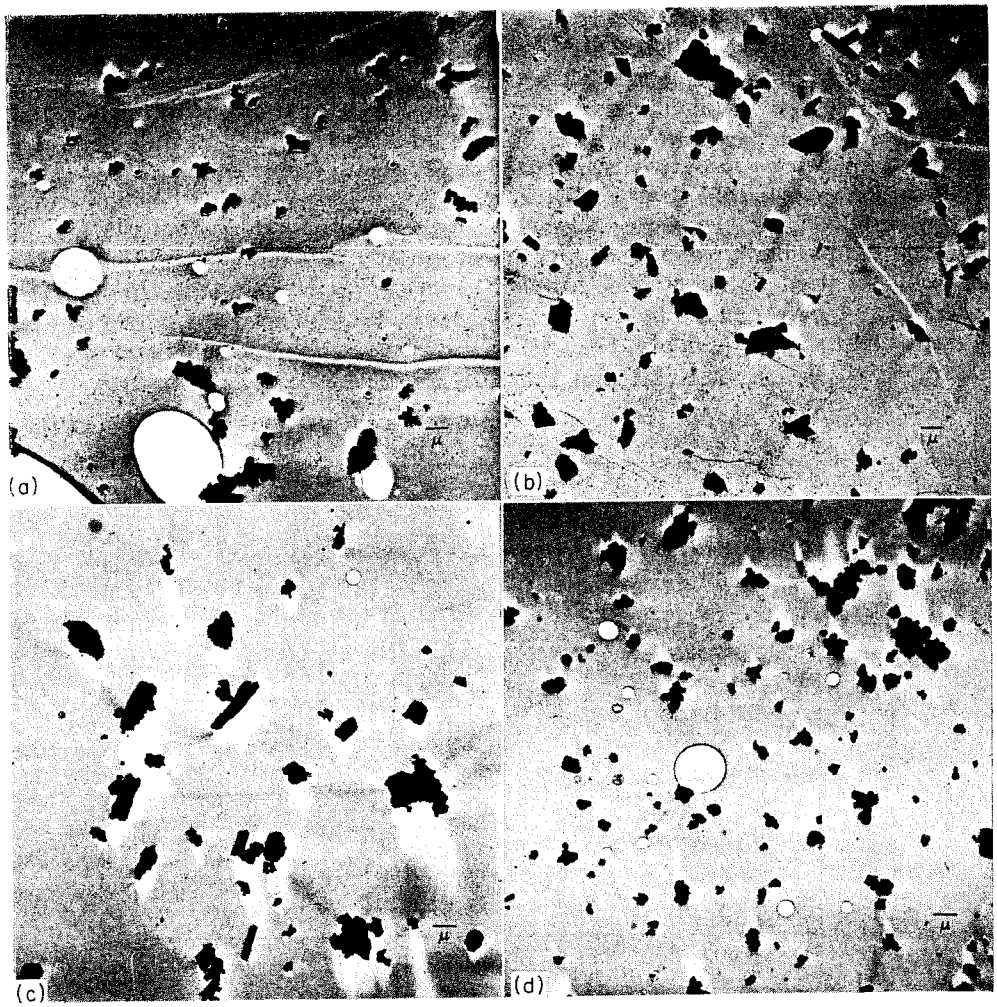

FIG. 1. Electromicrographs of PuO_2 particles (shadowed with chromium at 20°). (a) Plutonium oxalate calcined at 1000°. (b) Plutonium oxalate calcined at 350°. (c) Plutonium metal oxidized at 450°. (d) Plutonium metal oxidized at 123°.

brane filter samples. The values given in Table 1 are means of samples collected from three dog exposures in each group. Unfortunately for the comparative purpose of this study the Mass Median Diameter of the metal oxidized at 450° was greater than, and that of the metal oxidized at 123° was less than the MMD's of the calcined oxalates. The low MMD of the metal oxidized at 123° may reflect the friable nature of the material.

Representative electronmicrographs of the four aerosols are given in Fig. 1. The oxalate calcined at 1000° (Fig. 1(a)) is distinguished by rounded corners and the apparent fusion of several smaller particles. The particles of metal oxidized at 123° (Fig. 1(d)) are all irregular in shape, many of which appear to be aggregates. The oxalate calcined at 350° and the metal oxidized at 450° contain many particles of similar shape and are essentially indistinguishable.

X-ray diffraction analyses of the four plutonium compounds confirmed that all were crystalline PuO_2.

The ultrafilterabilities of the four oxides were determined by the method of Lindenbaum.[10] The results, Table 1, indicate that the calcined oxalates were somewhat more filterable than the oxidized metals.

Immediately following exposure to the aerosols and after 1, 2, 7, and 14 days and 1, 2, and 3 months, blood samples were collected from all dogs for plutonium analyses. Other samples were collected at monthly intervals for hematology. The dogs were maintained in metabolism cages for daily collection of urine and feces for plutonium analyses. After three months all dogs were sacrificed by exsanguination under anesthesia for plutonium analyses and histology of about 40 tissues. Microscopic distributions of plutonium particles in lungs and bronchial lymph nodes were determined from autoradiographs. The dogs also were counted frequently with a multi-detector scintillation counter.[11] The histology, autoradiography, and the results of the whole-body counting study will be reported separately.

RESULTS

A. Retention

The total quantity of plutonium deposited in each dog was determined from the analyses of all urine and feces collected daily and all tissues at necropsy. Whole-body clearance curves were constructed for each dog by subtracting cumulative excretion values from the total quantity of plutonium deposited.[1, 2] An example is given in Fig. 2. Extrapolation of the clearance curve to the ordinate at zero time gives an estimate of the fraction of the deposited plutonium that was deposited below the ciliated epithelium of the terminal bronchioles and was, therefore, unavailable for early clearance by ciliary processes. This fraction was assumed to have been deposited in the alveoli and accounted for the longterm retention of plutonium in the dogs. Since subsequent clearance of the fraction deposited in the alveoli was exponential with time, the expression, $p = Ae^{-bt}$, was evaluated empirically for each dog. Here p is the quantity of plutonium present in the dog at a given time,

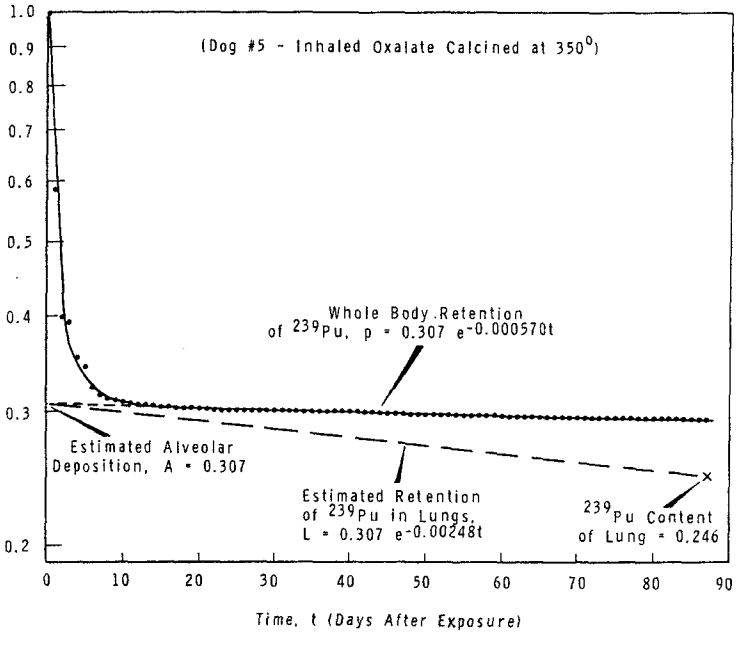

FIG. 2. Whole-body and lung retention of ^{239}Pu.

t, after exposure; A is a constant related to the quantity initially deposited in the alveoli; and b is a constant describing the rate of clearance and excretion in urine and feces of the plutonium deposited in the alveoli.

The amount of plutonium found in the lung at time of sacrifice was expressed as a fraction of the total amount initially deposited. Assuming the clearance of plutonium was exponential with time, an expression for lung retention, $L = Ae^{-b_L t}$, similar to the whole-body retention equation, was obtained for each dog.

Values for the constants in these equations are given in Table 2. The percent of the total deposited plutonium that was deposited in the alveoli varied from 20% to about 45% for all but two dogs which had alveolar depositions less than 10%. Apparently the fractions deposited in the alveoli were independent of the type of PuO_2 inhaled and the total quantity deposited.

The slopes of the whole-body and lung-retention curves are also expressed as retention half-times for convenience of discussion. The whole-body retention half-times ranged from about 1000 days to more than 3400 days, the larger values being observed for the dogs in Group III which inhaled metal oxidized at 450°. The lung retention half-times were in the 600 to 1000 day range for all except the dogs in Group II which inhaled oxalate calcined at 350°. For these dogs the lung retention half-times were about one year, similar to those we observed in previous studies using the same type of PuO_2.[12]

It is to be noted that the lung retention half-times for Group II dogs were about half those for the other groups of dogs although the whole-body retention half-times were not significantly less than those for dogs in Groups I and IV. Also, the lung retention half-times for dogs in Group III were not markedly greater than for dogs in Groups I and IV, although the whole-body retention half-times were generally greater. These differences are reflected in the tissue distribution and excretion data.

Table 2. Whole Body and Lung Retention of Inhaled PuO_2

PuO_2 inhaled	Dog No.	A (% deposited in alveoli)	Whole body		Lung		Total ^{239}Pu deposited (μCi)
			b	T 1/2 (days) retention half-time	b_L	T 1/2 (days) retention half-time	
I Oxalate calcined at 1000°	1	24.3	0.000583	1190	0.00095	730	14.1
	2	39.9	0.000463	1500	0.00072	960	4.8
	3	23.6	0.000730	950	0.00109	640	27.4
II Oxalate calcined at 350°	4	44.6	0.000630	1100	0.00160	430	19.2
	5	30.8	0.000570	1220	0.00248	280	99.4
	6	27.1	0.000406	1710	0.00180	390	75.6
III Metal oxidized at 450°	7	3.7	0.000333	2080	0.00071	980	29.3
	8	25.7	0.000260	2670	0.00078	890	30.0
	9	20.5	0.000201	3440	0.00109	640	25.4
IV Metal oxidized at 123°	10	8.1	0.000516	1350	0.00129	540	18.0
	11	26.1	0.000333	2080	0.00107	650	77.5
	12	20.2	0.000510	1360	0.00078	890	37.0

B. Tissue Distribution

Approximately 40 tissues including total skeleton, muscle, and skin from each dog were assayed for ^{239}Pu at necropsy three months after exposure. The ^{239}Pu contents of the tissues having the highest levels are given in Table 3. The dogs in Group II had smaller percentages of the total body burdens in their lungs than the other dogs. This correlates with the difference in lung retention rates shown in Table 2. The low lung values of Group II dogs occurred

Table 3. Tissue Distribution of ^{239}Pu in Dogs 3 Months after Inhalation of PuO_2
(% of total body burden)

PuO_2 inhaled	Dog no.	Lung*	Bronchial lymph nodes†	All other lymph nodes‡	Bone	Muscle	Kidneys	Spleen	Liver	Gall bladder	Heart	G.I. tract	Trachea	Upper nasal passages
I Oxalate	1	96.9	2.76	0.007	0.026	0.033	0.0002	0.0001	0.004	0.0002	0.007	0.014	0.038	0.0002
calcined	2	98.1	1.73	0.007	0.021	0.028	0.0001	0.0002	0.011	0.0003	0.002	0.007	0.026	0.0003
at 1000°	3	96.9	2.88	0.014	0.055	0.040	0.0001	0.0001	0.059	0.0002	0.0002	0.003	0.010	0.0002
II Oxalate	4	91.6	8.00	0.005	0.18	0.036	0.002	0.001	0.083	0.016	0.002	0.004	0.015	0.016
calcined	5	84.2	15.20	0.046	0.11	0.023	0.003	0.016	0.20	0.002	0.019	0.023	0.029	0.002
at 350°	6	88.9	10.50	0.032	0.19	0.049	0.003	0.002	0.19	0.002	0.002	0.015	0.011	0.002
III Metal	7	96.6	2.51	0.27§	0.19	0.070	0.002	0.0007	0.085	0.0001	0.0003	0.025	0.003	0.0001
oxidized	8	95.3	4.45	0.007	0.091	0.058	0.001	0.001	0.047	0.00001	0.001	0.011	0.004	0.00001
at 450°	9	92.3	7.39	0.022	0.094	0.056	0.001	0.001	0.042	0.00001	0.0004	0.014	0.050	0.00001
IV Metal	10	97.3	2.35	0.024	0.15	0.083	0.0008	0.001	0.047	0.00001	0.0001	0.015	0.029	0.00003
oxidized	11	93.7	6.10	0.01	0.038	0.029	0.0006	0.0005	0.032	0.00001	0.002	0.011	0.032	0.00005
at 123°	12	97.6	1.88	0.14§	0.072	0.029	0.0005	0.002	0.031	0.00001	0.0003	0.086	0.020	0.00001

* Total for all lobes of lung.
† Bronchial and mediastinal lymph nodes.
‡ Total of all other lymph nodes in the body which could be dissected.
§ Cervical and mandibular lymph nodes accounted for the high values.

almost entirely as a result of greater translocation to the bronchial and mediastinal lymph nodes rather than translocation to other tissues or excretion from the body. Thus, the whole-body retention of ^{239}Pu was not significantly different from Groups I and IV dogs, Table 2. nodes. Otherwise, translocation in Group III dogs, which showed a tendency toward longer whole-body retention times, did not differ greatly from Groups I and IV dogs with the exception that the kidneys contained a somewhat larger percentage of the body burden.

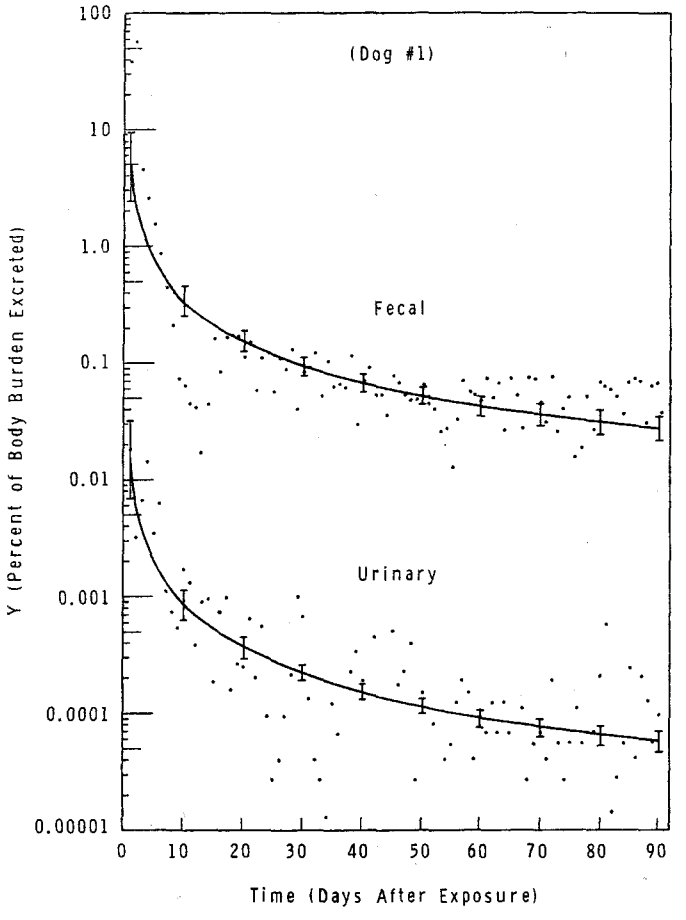

FIG. 3. Daily excretion of ^{239}Pu after inhalation of plutonium oxalate calcined at 1000°.

Translocation of ^{239}Pu to bone and muscle was not significantly greater in Group II dogs than in the other dogs. However, translocation to soft tissues such as kidneys, spleen, liver, heart, etc. was generally highest in Group II dogs. Dog No. 7 in Group III showed a relatively high level of translocation, but this was essentially accounted for by two tissues, the upper nasal passages and the mandibular lymph

C. Excretion

The amount of ^{239}Pu excreted each day in urine and feces was expressed as the percent of the body burden of plutonium at the beginning of the 24-hr period during which the excretion occurred. These data were programmed for curve fitting by least squares analyses using a digital computer. Curves were fitted to each set of data for individual dogs and to daily mean

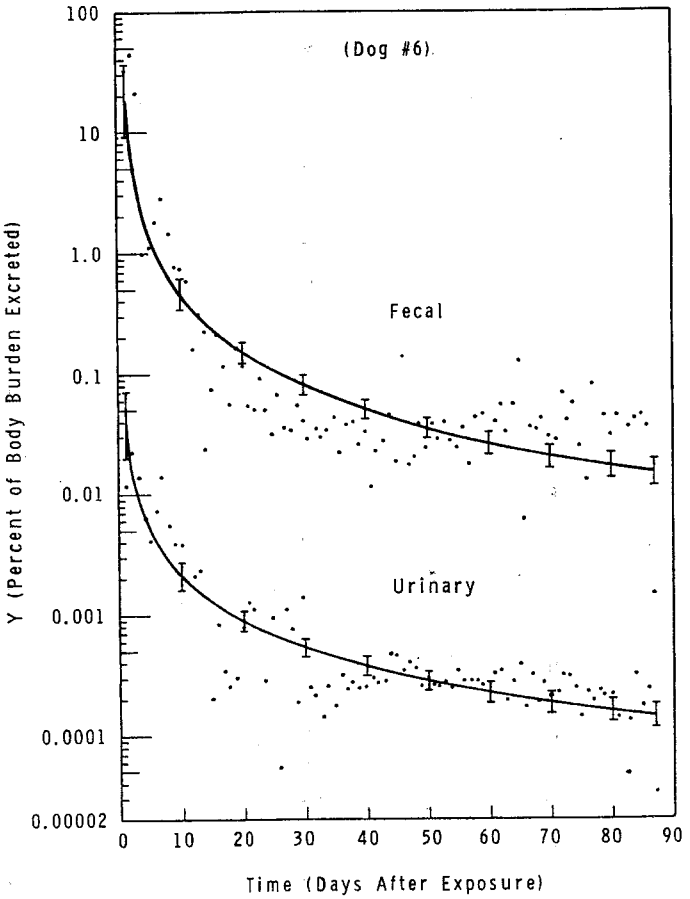

FIG. 4. Daily excretion of ^{239}Pu after inhalation of plutonium oxalate calcined at 350°.

values for the three dogs in each group to obtain equations representing the mean excretion rates for each dog and each group of dogs, respectively. Logarithmic equations of the form $Y = At^b$, where Y is the percentage of plutonium excreted each day in urine or feces, were fitted to all data. Power functions did not always provide the best visual fit, but are probably adequate to compare the four plutonium dioxide aerosols.

Excretion data are shown for representative dogs from each group in Figs. 3–6. Figure 7 is the curves with 95% confidence levels fitted to the mean daily values of all three dogs in each group. The plots of individual excretion values for each of four dogs shows the daily fluctuations in levels of ^{239}Pu in urine and feces. Comparison of these excretion data for representative dogs from the four groups and the constants in Table 4 for the power function equations fitted to the individual and combined excretion data for all of the dogs indicates that there were only minor differences. These differences are more clearly seen in Fig. 7 which shows the curves fitted to the combined data for each group. After the first 20 days the rate of fecal excretion tended to be slightly less for dogs in Group III than for the other dogs. This correlates with the generally longer whole-body retention half-times calculated for these dogs. The rate of excretion of plutonium in urine tended to be greater for Groups II and III dogs than for Groups I and IV dogs.

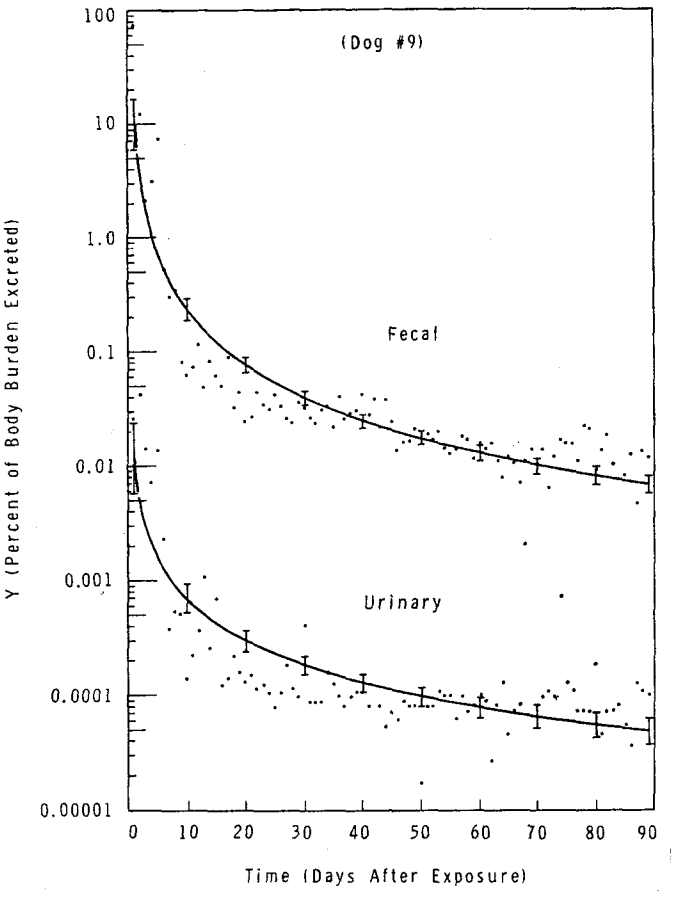

FIG. 5. Daily excretion of ^{239}Pu after inhalation of plutonium metal oxidized at 450°.

D. Disposition of Alveolar Deposited Plutonium

In Table 5 the disposition of ^{239}Pu deposited in the alveoli is shown. Values for amounts deposited in the alveoli of each dog are those shown in Table 2. The fraction of the alveolar deposited ^{239}Pu excreted in urine and feces was estimated by subtracting from the total amount excreted the fraction that was excreted during about the first week after exposure, which brought the body burden down to about the level of the estimated alveolar deposition. In making these calculations certain assumptions were made. For example, since it was found that total blood levels of ^{239}Pu immediately after exposure were considerably less than 0.01% of the total plutonium deposited, it was assumed that the fraction of inhaled plutonium absorbed by the blood immediately after exposure contributed an insignificant amount to the total translocated plutonium found in tissues after three months or excreted in urine during the 1-week to 3-month postexposure period and that practically all of that which was absorbed was excreted in the urine the first few days after exposure. It was also accepted that these calculations might underestimate the clearance and excretion of truly alveolar deposited plutonium since early clearance of some alveolar deposited plutonium probably occurred within the first few days after exposure. However, these calculations probably provide reasonable estimates of the disposition of the fraction of plutonium deposited in the alveoli which was not available for early clearance and which accounted for

*Table 4. Constants for ^{239}Pu Excretion Equations**

PuO_2 inhaled	Dog No.	Urine		Feces	
		A	b	A	b
I Oxalate calcined at 1000°	1	0.015	−1.24	4.7	−1.15
	2	0.035	−1.48	4.9	−1.22
	3	0.0018	−0.86	7.7	−1.143
	Combined†	0.017	−1.27	4.3	−1.11
II Oxalate calcined at 350°	4	0.017	−1.03	4.7	−1.16
	5	0.0037	−0.75	23.0	−1.61
	6	0.038	−1.26	18.0	−1.60
	Combined	0.027	−1.14	16.0	−1.49
III Metal oxidized at 450°	7	0.27	−1.60	22.0	−1.72
	8	0.0034	−0.89	4.5	−1.34
	9	0.012	−1.23	9.9	−1.63
	Combined	0.12	−1.54	16.0	−1.66
IV Metal oxidized at 123°	10	0.036	−1.38	0.15	−0.22
	11	0.0020	−0.85	3.9	−1.23
	12	0.0009	−0.70	2.2	−0.96
	Combined	0.031	−1.43	16.0	−1.47

* With the form $Y = At^b$, where Y is % of body burden excreted on a given day, t, after exposure.
† The arithmetic means for the three dogs in each group were fitted by least square analysis.

Table 5. Disposition of Alveolar Deposited ^{239}Pu 3 Months after Exposure

PuO_2 inhaled	Dog No.	% of alveolar deposited plutonium					
		Excreted		Total body burden	Lung	Bronchial and mediastinal lymph nodes	All other tissues
		Urine	Feces				
I Oxalate calcined at 1000°	1	0.019	5.5	94.5	91.6	2.7	0.18
	2	0.014	4.2	95.8	94.0	1.7	0.12
	3	0.011	6.6	93.4	90.5	2.7	0.18
II Oxalate calcined at 350°	4	0.063	5.0	95.0	87.0	7.6	0.36
	5	0.017	4.7	95.4	80.3	14.5	0.58
	6	0.049	3.5	96.5	85.8	10.1	0.56
III Metal oxodized at 450°	7	0.093	2.9	97.0	93.7	2.4	0.88
	8	0.012	2.5	97.5	93.0	4.3	0.24
	9	0.012	1.7	98.4	90.8	7.3	0.31
IV Metal oxidized at 123°	10	0.023	7.5*	92.4	89.8	2.2	0.36
	11	0.0084	3.0	97.1	91.0	5.9	0.19
	12	0.0083	4.7	95.3	93.0	1.8	0.54

* 3.6% was excreted in last 12 days. (Three other values were excluded because they were several orders of magnitude above the average values, suggesting contamination of the samples.)

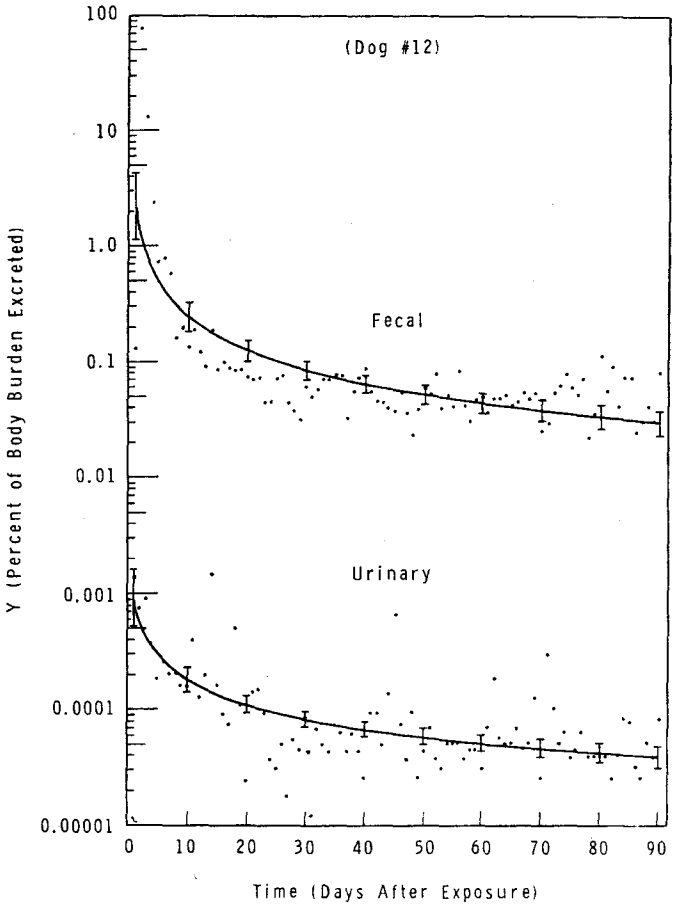

FIG. 6. Daily excretion of ^{239}Pu after inhalation of plutonium metal oxidized at 123°.

the long-term retention and excretion of plutonium.

The values given in Table 5 are generally consistent for the dogs within each group, with the exception of the urine data.

In the case of the fecal data, Group III dogs excreted less than the other dogs suggesting that the mucus-ciliary pathway was least effective for pulmonary clearance of the plutonium metal oxidized at 450°. This assumes that the biliary secretion of plutonium into the gastrointestinal tract was either insignificant or of the same order of magnitude for all dogs.

Three months after exposure greater than 90% of alveolar deposited plutonium was retained in the lungs of all dogs except those that inhaled the oxalate calcined at 350°, Group II. In these dogs, only 80% to 87% was retained and, as indicated above, the difference was in the amount collected in the bronchial and mediastinal lymph nodes.

The fraction of alveolar deposited plutonium translocated to other tissues was apparently less for dogs which inhaled the oxalate calcined at 1000° than for other dogs.

E. ^{239}Pu–^{241}Am Ratios

The dogs were counted with a multi-detector scintillation counter to detect the low energy X-rays and gammas from ^{239}Pu and from the ^{241}Am which is a daughter product of ^{241}Pu, a common contaminant of most ^{239}Pu preparations.

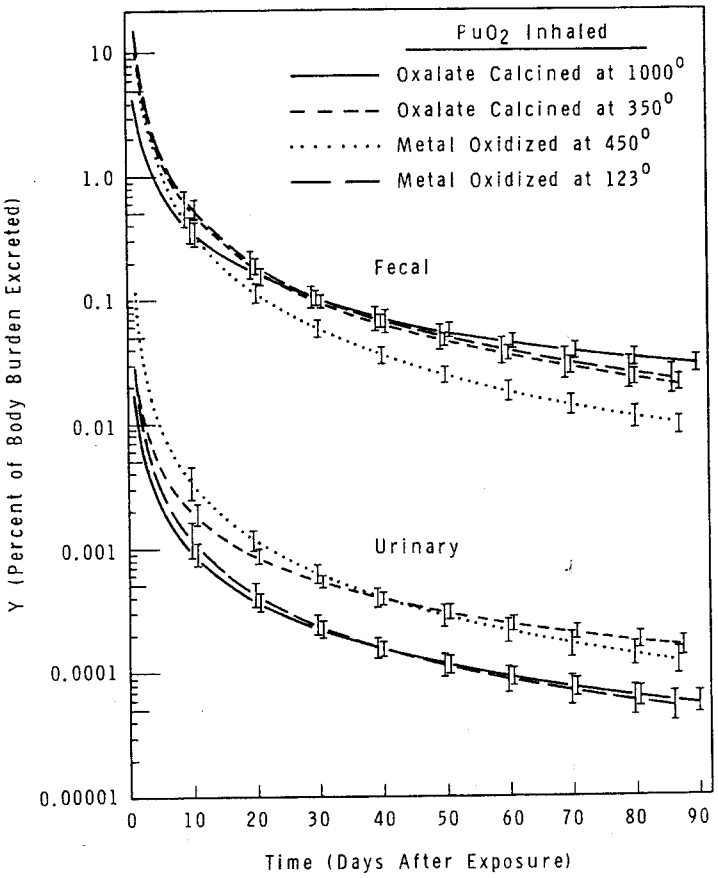

FIG. 7. Comparative excretion of ^{239}Pu following inhalation of four different plutonium dioxides. Curves were fitted to means of daily values for three dogs in each group exposed to one of four different plutonium dioxide aerosols.

Since the whole-body counting data contribute nothing to the comparison of the four different types of PuO_2 in this study, it will not be reported here. However, in evaluating the whole-body counting data it was necessary to determine whether ^{241}Am separated from the ^{239}Pu in the body. Therefore, the ^{239}Pu–^{241}Am ratios in lung and bronchial lymph nodes were examined in respect to the ratios in the material inhaled. Acid dissolved samples of these tissues and the membrane filters used to collect aerosol samples during exposures were counted on platinum disks with a germanium diode alpha detector which had a resolution of 40 keV compared with the 5.15 MeV ^{239}Pu alpha-particles and 5.30 MeV ^{241}Am alphas. The results of these alpha energy analyses are given in Table 6.

The ^{239}Pu–^{241}Am ratios in the inhaled materials were different: the PuO_2 used for Groups I and II dogs was considerably older than the PuO_2 used for Groups III and IV and, thus, contained a greater quantity of ^{241}Am. In Groups I, II, and IV there appeared to be no significant differences between the ratios in the aerosols and the tissues. However, in Group III dogs there was an increased ratio in both lung and lymph nodes. This is interpreted as indicating that there was a selective loss of ^{241}Am relative to the ^{239}Pu, or conversely a selective retention of ^{239}Pu relative to the ^{241}Am, in

the lung and lymph node tissues of the dogs which inhaled the metal oxidized at 450° but not in those dogs which inhaled the other oxides.

F. Biological Effects

To assure adequate levels of plutonium in the excreta and tissues for maximum analytical accuracy, quantities of plutonium were deposited which caused some pathology during the three-month period. In fact, the doses were large enough in most dogs to have caused death within about a year from pulmonary insufficiency as a result of irradiation of the lung tissue.[13] However, previous studies[12] indicated that the levels used in this experiment would not produce changes severe enough to significantly interfere with excretion and translocation of the inhaled plutonium during the three-month duration of this study. Nevertheless, it is important to document the clinical changes seen for the possible bearing they might have on the results observed. Histologic and autoradiographic studies of the tissues collected in this study are in progress and will be reported later.

In other studies in our laboratory it was found that decreasing levels of circulating lymphocytes were the first clinical indications of toxicity following plutonium inhalation.[12-14] This occurred at levels which did not involve major lung pathology. Extensive lung pathology was usually preceded and accompanied by loss of body weight and increasing respiratory rates. In Table 7 are given mean pre-exposure and three-month postexposure lymphocyte counts, body weights and resting respiratory rates and minute volumes. All 12 dogs showed a decreased lymphocyte count, the degree of which was related to the quantity of plutonium in their bodies. However, none of the dogs showed an appreciable weight loss or an increased respiratory rate, with the possible exception of Dog No. 11. Therefore, it is assumed that although some biological damage occurred as a result of the plutonium inhalation, it was not sufficient to markedly alter the disposition of the plutonium and thus invalidate the comparison of the four plutonium dioxides. Further, while the levels of plutonium in the dogs varied from 2 to 29 μCi, there was overlapping of levels among the four groups.

Table 6. ^{239}Pu—^{241}Am Ratios in Aerosols and Dog Tissues

PuO_2 inhaled	Ratio: ^{239}Pu to ^{241}Am		
	Aerosol	Lung	Bronchial lymph nodes
I Oxalate calcined at 1000°	13.8 ± 0.3	13.4 ± 0.3	11.6 ± 0.6
II Oxalate calcined at 350°	12.0 ± 0.2	13.0 ± 1.2	14.2 ± 0.1
III Metal oxidized at 450°	31.0 ± 1.9	37.8 ± 1.5	36.1 ± 1.2
IV Metal oxidized at 123°	31.0 ± 0.6	31.5 ± 1.0	30.0 ± 0.9

DISCUSSION

The results of this study provide further evidence for the relatively long-term pulmonary retention of inhaled PuO_2, its gradual accumulation in bronchial and mediastinal lymph nodes and the accompanying low rate of translocation and urinary excretion of plutonium. Similar findings have been reported from this as well as other laboratories.[1-3, 12-19] None of the four types of plutonium oxides tested in this study showed significant deviations from these earlier studies, although certain differences among them were apparent. Major differences include:

1. The lung retention half-time of the oxalate calcined at 350° was about one year, half of that of the other oxides. This was due to greater accumulation of plutonium in the bronchial and mediastinal lymph nodes rather than greater clearance via

the mucus blanket of the ciliated tracheobronchial pathway or a relatively high rate of solubility.

2. The metal oxidized at 450° appeared to be cleared via the mucus-ciliary route to a lesser extent than the other oxides. This same oxide showed a selective loss of ^{241}Am, relative to ^{239}Pu, in lung and bronchial lymph node tissue which was not evidenced by the other oxides.
3. The oxalate calcined at 1000° showed the least translocation to tissues outside of the lung and bronchial-mediastinal lymph nodes.

These results are of interest to the biologist as well as to the health physicist because biological processes apparently discriminated between the four types of plutonium oxides, all of which were in the crystalline state when inhaled. Their only apparent differences were the Mass Median Diameters of the aerosol particles and the ultrafilterabilities. In considering an explanation for the relatively high accumulation in the bronchial lymph nodes of the oxalate calcined at 350°, none of these observed differences in physical–chemical properties seem to provide a clue. The particle size and ultrafilterability were similar to the oxalate calcined at 1000° and the shapes of the particles closely resembled those of the metal oxidized at 450°. However, there may be a correlation between accumulation of plutonium in bronchial lymph nodes and the total amount of plutonium deposited in the alveoli, Fig. 8. This is especially apparent at the higher alveolar depositions. In an earlier study[2] we found some variation of plutonium lymph node accumulation with the MMD of the inhaled PuO_2 (oxalate calcined at 325°), but there was no positive indication that the fraction of plutonium accumulated in the lymph

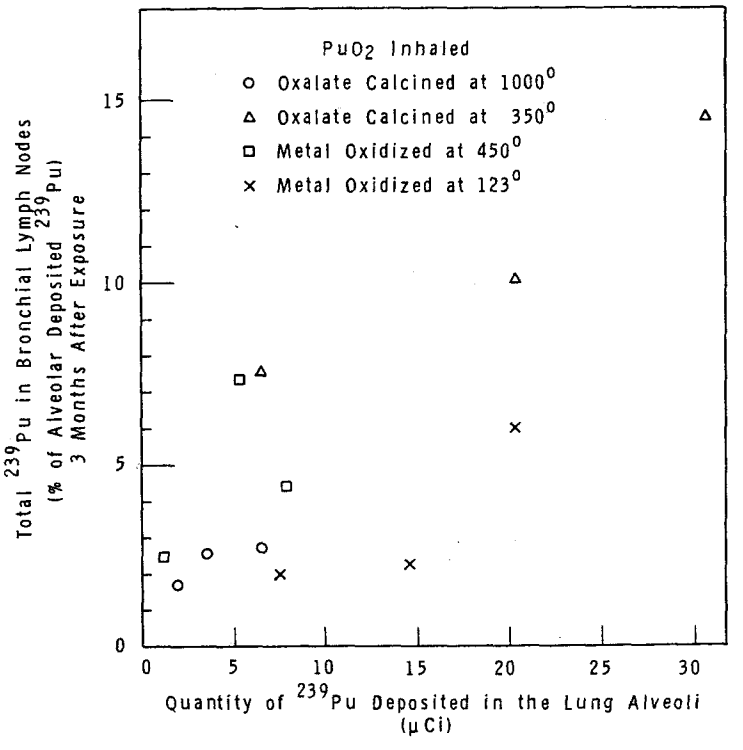

FIG. 8. Relationship between accumulation of ^{239}Pu in bronchial lymph nodes and the total quantity of PuO_2 deposited in the lung alveoli.

Table 7. Clinical Observations

PuO_2 inhaled	Dog No.	^{239}Pu body burden (μCi)	Body weight (Kg)		Respiratory rate (resp/min)*		Minute volume (L)		Lymphocyte count (10^3 per ml)	
			Initial	Final	Initial	Final	Initial	Final	Initial	Final
I Oxalate calcined at 1000°	1	3.2	8.4	8.0	20	21	2.8	2.6	2.47	1.15
	2	1.8	11.1	11.0	18	19	2.3	1.9	2.71	1.78
	3	6.0	9.6	10.0	27	25	3.1	2.9	3.30	1.43
II Oxalate calcined at 350°	4	6.1	9.9	10.8	15	31	4.8	3.6	2.75	1.19
	5	29.0	9.9	11.0	34	32	5.8	5.0	2.50	0.83
	6	20.0	8.5	9.0	22	33	3.4	3.7	3.20	0.73
III Metal oxidized at 450°	7	1.0	10.0	12.4	27	19	5.2	4.8	2.08	1.77
	8	7.5	12.3	11.6	19	18	4.3	4.1	3.23	1.37
	9	5.1	10.2	9.7	22	21	5.5	3.9	3.62	0.84
IV Metal oxidized at 123°	10	1.3	12.6	12.6	23	23	6.0	5.6	2.46	1.87
	11	20.0	8.0	7.3	24	53	3.0	2.4	2.75	0.46
	12	7.1	11.0	10.7	38	32	5.4	3.5	3.00	1.53

* Normal values for dogs in our colony range between 15 and 40; the mean is 20 to 25.

† Mean of 2 and 9 week pre-exposure counts.

nodes one month after exposure increased with the amount of PuO_2 deposited in the alveoli. In another study,[18] 39 weeks after two dogs inhaled PuO_2 prepared by calcining the oxalate at 350°, bronchial lymph node levels were about 11% and 50% of the 0.5 and 1.4 μCi, respectively, initially deposited in the alveoli. However, these results are not adequate proof that the fraction of plutonium accumulating in the bronchial lymph nodes was dependent upon the quantity deposited in the alveoli of the dogs in this study.

There does not seem to be any obvious explanation for the lower rate at which metal oxidized at 450° was cleared from the lung by the mucus-ciliary pathway or the apparent selective loss of ^{241}Am relative to ^{239}Pu in lung and lymph node tissue. Additional alpha energy analyses of tissue and excreta samples from the dogs in the group may show a relationship between these two findings, but none can be identified as yet. The fact that the oxalate calcined at 1000° showed somewhat less translocation from the respiratory tract than the other oxides seems reasonable since the high temperature might be expected to decrease its solubility, yet this material did not show the lowest ultrafilterability. On the other hand it was expected that the metal oxidized at 123° would show the greatest translocation because of its friability and its small mass median diameter. However, this did not occur.

The results of this study have certain radiation protection implications although the differences in behavior of the four types of oxide in the body cannot be considered large. The possible difference in the fraction of plutonium that accumulated in the bronchial lymph nodes can be an important finding. Most animal experimentation with inhaled PuO_2 that has been reported was probably done with oxides prepared by calcining the oxalate at temperatures less than 500°. In the present study the greatest accumulation of ^{239}Pu in the bronchial lymph nodes occurred with this type of PuO_2. In a long-term study[19] with dogs, inhalation of this type of PuO_2 has resulted in a high proportion of animals with primary lung cancer, but despite the heavy accumulation of ^{239}Pu in the bronchial lymph nodes no primary tumors have been identified as originating in this tissue although some metastases to the lymph nodes occurred. If the accumulation of ^{239}Pu in the bronchial lymph node is a desirable phenomenon in respect to the hazard associated with inhaled PuO_2, the inhalation of the types of PuO_2 which show minimal accumulation in the lymph nodes and consequently longer retention times in the lung, where it is known to be carcinogenic, would be more hazardous than inhalation of the low-temperature calcined oxalate. Therefore, it seems that long-term studies of inhaled plutonium metal oxides or high temperature calcined oxalates are required to compare the biological effects with the results of current studies using plutonium oxalate calcined at 350°.[19]

Although the excretion rates of ^{239}Pu in this study suggested some differences among the four types of oxides inhaled, the differences were probably not great enough to cause much concern in interpreting human bioassay data. It is planned to further assess the excretion data collected in this study in terms of the many proposed models.[20-26]

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