CONF-751205--8

IAEA-SR-6/101

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RECENT ANIMAL STUDIES ON THE DEPOSITION, RETENTION AND TRANSLOCATION OF PLUTONIUM COMPOUNDS

BNWL-SA-5626

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INTRODUCTION

Since the first IAEA meeting on Diagnosis and Treatment of Radioactive Poisoning in Vienna in 1962, the volume of research on plutonium and other transuranics has expanded enormously. For example, in 1962 only 5 of the 20 papers presented dealt with plutonium and only 2 of these described animal experiments. At this meeting, at least 33 of the approximately 50 papers to be presented deal with plutonium and other transuranics, and a large percentage of these describe animal experiments.

In the early 1960's the primary transuranic of concern was plutonium, especially PuO_2, because it was the most likely form to be encountered after an accidental release. Animal experiments had demonstrated that inhaled PuO_2 was largely retained in the lungs and thoracic lymph nodes; thus, the need for therapeutic measures to remove insoluble particles from the lungs was emphasized. In recent years, with the availability of other transuranics for research and the emphasis on nuclear power development, americium and curium, as well as plutonium, have been recognized as potential health problems. And, additional research with animals has indicated that the lungs and the thoracic lymph nodes are not the only tissues of concern following inhalation of transuranium elements. Other tissues, such as the liver and skeleton, may be of even greater concern. These results reemphasize the need for measures to remove alpha-emitting transuranics deposited throughout the body.

This paper is based on work performed by Battelle, Pacific Northwest Laboratories, for the U.S. Energy Research and Development Administration under contract E(45-1)-1830.

DISCLAIMER

In this review, I have selected from the literature examples that illustrate the major findings from recent animal experiments. I have also identified additional areas in which animal research is needed.

ABSORPTION FROM THE GASTROINTESTINAL TRACT AND THE INTACT SKIN

Experiments confirm that most transuranic compounds are not readily absorbed from the gastrointestinal tract. Table I gives values for the absorption of uranium and several transuranic elements in newborn and adult rats. Neptunium nitrate was most readily absorbed, nearly 1 percent. The least absorbed was PuO_2, 0.0001 percent. Grastointestinal tract absorption was one or two orders of magnitude greater in the newborn rat than in the adult rat.

Americium, curium, berkelium and einsteinium were at least ten times more readily absorbed than plutonium compounds. The only exception was an aqueous suspension of a plutonium-sodium aerosol, which showed 0.01 percent absorption in rats. (Brightwell)

Percutaneous absorption has been studied for only two transuranic elements. Results from experiments with plutonium indicate that absorption through intact skin is relatively insignificant (Table II). The highest absorption value, 2 percent, was obtained in rat skin exposed to $Pu(NO_3)_4$ in 10 N HNO_3 for 5 days. All other experiments gave values of less than 1 percent. About 0.05 percent of einsteinium, the other transuranium element for which data are available, was absorbed over a period of 7 days through rat skin. Results of these animal experiments and human contamination incidents indicate that the intact skin is an effective barrier to the entry of plutonium and einsteinium, and probably to other transuranium elements as well.

RETENTION OF TRANSURANICS IN LUNG

Several laboratories (especially the University of Rochester, the Lovelace Foundation, and Battelle, Pacific Northwest Laboratories) have measured the deposition of inhaled radionuclides in rats and dogs. Most of these experiments have been directed toward perfecting aerosol exposing techniques, rather than developing information that might be extrapolated to human beings. (Craig, 1972.) Moreover, few of the studies have involved the transuranium elements. This research has shown, however, that the respiratory tract is an effective route for the entry of transuranium elements to the body. And, since human contamination incidents have been rare, these animal experiments have provided the bulk of our information about retention of transuranics in the lung, their translocation to other tissues in the body, and their excretion from the body.

Plutonium deposited in the upper respiratory tracts of dogs, including the tracheal-bronchial region, is cleared with a half-time of about 2 days. (Marrow 1967.) However, plutonium and other transuranics deposited in the lower respiratory tract or pulmonary region are retained for much longer periods. Table III is a compilation of published values for the retention of plutonium compounds in the pulmonary region in several animal species, including man. The retention half-times for organic complexes of plutonium, plutonium nitrate and plutonium fluoride range from about 30 to 300 days in rats, hamsters and dogs. The retention half-times for $^{239}PuO_2$ are substantially longer, from 150 to 500 days in rodents and 300 to 1000 days in dogs.

These values for experimental animals can be compared with measurements from several human beings accidentally exposed to plutonium aerosols. Values reported for these retention half-times range from 240 to 650 days.

Studies with $^{238}PuO_2$ in rodents and dogs indicate a much shorter lung retention time than is observed for $^{239}PuO_2$ particles, possibly because of radiolysis in tissue fluids.

The physical properties of inhaled plutonium particles affect their retention in the lung, as illustrated in Figure 1. Retention half-times are given in days for several plutonium oxides. Each bar represents data from one dog. Plutonium oxide calcined at 1000° was retained with a half-time of 650 to 950 days, compared with 300 to 400 days for an oxide calcined at 350°. Oxides prepared from metal powder at 123° to 450° were retained in lung longer than the low fluid oxide. Particle size is also important; for oxides of various-sized particles calcined at similar temperatures, retention half-times were generally less for the aerosols comprised of smaller particles.

Americium, curium and einsteinium compounds are cleared from the lungs of rats and dogs more rapidly than $^{239}PuO_2$, probably because they are more soluble (Table IV). Rather large portions of inhaled curium appeared to be translocated from the lungs of dogs soon after exposure, but the curium remaining in the lungs showed long retention half-times ranging from 250 to 1400 days.

Figure 2 shows comparative retention half-times for inhaled transuranics in rats and Figure 3 shows similar data for beagle dogs. In rats,

both ^{241}Am and ^{242}Cm nitrate were cleared much more rapidly than ^{238}Pu and ^{239}Pu nitrates. Autoradiograms from this rat study indicated that the ^{241}Am and ^{242}Cm were dispersed more widely throughout the lung than the ^{238}Pu and ^{239}Pu.* In another experiment the rate of clearance of intratracheally instilled einsteinium chloride was found to be similar to that reported for ^{242}Cm nitrate. The results of beagle dog studies compared favorably with those of rat studies.

TRANSLOCATION FROM LUNGS TO OTHER TISSUES

The circulating blood distributes transuranic compounds from the lung among the body tissues. The relative distribution by this process is essentially the same for all transuranics but differs quantitatively, depending upon the chemical and physical properties of the inhaled material.

Soluble Transuranics

Distribution patterns for a number of inhaled soluble plutonium compounds are shown in Table V. Inhaled plutonium citrate and plutonium nitrate are translocated from lung to bone and, to a somewhat lesser extent, to liver. Smaller quantities are deposited in lymph nodes, kidney, spleen, and other soft tissues. The difference between the distribution of plutonium nitrate and citrate is small, considering that plutonium complexed with citrate is less likely to form colloidal polymers. Plutonium fluoride is less rapidly translocated from the respiratory tract than the citrate or the nitrate; the table shows the greatest accumulation of fluoride in the thoracic lymph nodes.

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* Private communication--Dr. J. Lafuma 1974.

In beagle dogs within several months after inhalation of $^{239}Pu(NO_3)_4$, the fraction of plutonium remaining in lung decreased to 40 percent or less of the amount deposited in the lower respiratory tract (Figure 4). About 30 percent of plutonium translocated from lung accumulated in bone and about 10 percent in liver. A small amount was found in spleen, lymph nodes, and other soft tissues and the remainder was excreted in urine and feces.

Comparative data for whole-body retention of $^{238}Pu(NO_3)_4$ and $^{239}Pu(NO_3)_4$ in rats are given in Table VI. Retention of $^{238}Pu(NO_3)$ given by inhalation and by intramuscular injection (Morin) was greater at both 30 and 45 days than for $^{239}(Pu(NO_3)_4$. This was primarily accounted for by greater retention in lungs and greater deposition in the skeleton. Following intramuscular injection ^{238}Pu was translocated from the injection site much more readily than ^{239}Pu; again the skeleton accumulated the major portion.

Ballou ( ) compared these compounds and $^{253}Ea(NO_3)_3$ given to rats by inhalation (Figure 5) and obtained results similar to those of Morin et al. for ^{238}Pu in the skeleton. However, Ballou observed greater retention of ^{239}Pu than of ^{238}Pu in the lungs for nearly 200 days past exposure. Ballou calculated retention parameters for all three compounds (Table VII) and attributed the varying behaviors of the three compounds to differences in their masses. These differences must have resulted in varying degrees of colloid formation following deposition in lung (or in muscle, in Morin's study), because there is no reason to expect ^{238}Pu and ^{239}Pu to have different chemical properties.

Other plutonium compounds have been studied in rats (Table VIII). Plutonium citrate, sodium plutonyltriacetate, ammonium plutonium pentacarbonate,

and plutonium chloride were all more readily translocated from lung than plutonium nitrate. These studies of plutonium citrate and plutonium nitrate show less total retention in rats than has been observed in dogs (Table VI), but this may be because different methods were used to estimate initial lung burden.

Stather and Howding ( ) compared the retention and translocation of several plutonium compounds in rats 7 days after pulmonary intubation (Table IX). The data are expressed as percentage of the administered dose. The values for $^{239}PuO_2$ suggest that a rather large percentage of the dose was cleared from the body through the feces. A large fraction of the oxalate was retained in the lung but 27 percent was translocated to other tissues in the body. The results of the citrate and nitrate experiments were similar to those already mentioned. However, plutonium administered as a DTPA complex was almost entirely cleared from the body, suggesting the possible effectiveness of early administration of DTPA to remove inhaled $Pu(NO_3)_4$.

Nearly all of the studies of inhaled transuranics have involved single short-duration exposures of animals to aerosols. In a study in which rats inhaled plutonium citrate daily for 160 days, the lungs and bone accumulated equal amounts of plutonium during the first 80 days. During the next 80 days, the bone burden was double the lung burden. After the daily exposures were stopped, clearance from lung was more rapid (half-time = 93 days) than from bone (half-time = 583 to 816 days).

In a similar experiment with ammonium plutonium pentacarbonate, more plutonium accumulated in lung than in bone. The rate of clearance from lung

(half-time = 148 days) was less than for the citrate but still greater than for bone (which was the same as after inhalation of plutonium citrate). In both experiments the concentrations of plutonium in the tracheobronchial lymph nodes were as high as those in the skeletons. (Lyubchansky 1972.)

Animal experiments have shown that curium and americium oxides must be included among the relatively soluble transuranic compounds. McClellan et al. ( ) compared $^{244}CmO_{1.73}$ and $^{244}CmCl$ (Table X). There was no difference in the translocation of these compounds. Both were largely deposited in liver and skeleton and within 2 months the lung burdens were less than 10 percent of the amount initially deposited. Results obtained by Craig et al. ( ) with inhaled $^{244}CmOx$ (Table X were similar, except that the lung burden did not drop as much. This may have been due to the different methods used to prepare the oxides in the two studies, which resulted in homogeneous spherical particles in one ( ) and heterogeneously shaped particles in the other ( ). However, the difference could also have been due to differences in the amounts initially deposited in the lung. For example, Sanders ( ) (Table XI) found that the retention of $^{244}CmOx$ in lungs and the amount translocated to skeleton were dependent upon the quantity deposited, being greater at higher doses than at lower doses. Possibly this is because increased pathology at high doses interfered with clearance processes.

Studies with beagle dogs indicate that inhaled $^{241}AmO_2$, like CmOx, is translocated to liver and skeleton in comparable amounts (Table XII). Data from two laboratories are similar even though the different methods used to

prepare the AmO_2 resulted in spherical particles in one ( ) and heterogeneously shaped particles in the other ( ). Almost 90 percent of the body burden of ^{241}Am was distributed between the liver and skeleton within about a year after exposure. The Thoracic lymph nodes, as in the case of Cm and other related soluble transuranics, accumulated less than 1 percent of the body burden.

Insoluble Transuranics

Animal experiments have shown that PuO_2 is really the only transuranic compound that can be considered insoluble when inhaled. However, experiments have also shown that under some conditions even PuO_2 appears to be relatively soluble, but not to the extent observed for CmOx and AmO_2.

Data from a 11-year study with beagle dogs illustrates the relative insolubility of $^{239}PuO_2$ (Figure 6). After 5 years the lungs and thoracic lymph nodes each contained about 30 percent of the plutonium initially deposited in the pulmonary region of the respiratory tract. After 11 years the amount in the thoracic lymph nodes had accumulated to 40 percent. Translocation of plutonium from lung resulted in levels in liver of about 10 percent, in bone of about 5 percent, and in the abdominal lymph nodes of about 7 percent. The average concentration of plutonium in the thoracic lymph nodes was over 1000 times and in the abdominal lymph nodes over 100 times the average concentration in the lungs.

In the beagle experiment there was a high incidence of lung cancer. Nearly all lungs showed extensive pathology, which could have resulted in greater retention of plutonium than occurs at lower doses. For example,

Sanders ( ) found that hamsters retained a larger percentage of $^{238}PuO_2$ and $^{239}PuO_2$ at higher initial lung burdens than at lower lung burdens (Table XIII). In this experiment the initial lung burden ranged from 3 to 200 nCi and the amount in the lungs after 3-12 months ranged from a low of 4 percent at 3 nCi to 41 percent at 160 nCi. Sanders ( ) found similar in rats (Table XIV). Current experiments at Lovelace and Battelle will indicate whether the pulmonary retentions of $^{238}PuO_2$ and $^{239}PuO_2$ in beagle dogs are also dose-dependent.

At the first IAEA meeting on Diagnosis and Treatment of Radioactive Poisoning in 1962, I reported that the particle size of the inhaled $^{239}PuO_2$ aerosol influenced the translocation of plutonium from lungs to other tissues. This is summarized in Figure 7. These data indicated that translocation and urinary excretion were greatest for the aerosol with the smallest mass median diameter. Few experiments have tested these findings. Recently Stather and Howden ( ) reported preliminary results of pulmonary intubation with a $^{239}PuO_2$ suspension that had been passed through a series of four filters. After 1 week 22 percent of the PuO_2 had been translated from the lungs to other tissues, much as had occurred in their experiments with plutonium nitrate and citrate. In a current experiment at Lovelace with monodisperse $^{238}PuO_2$ particles in dogs, the results after exposure do not suggest a particle size effect (Table XV).

Two experiments indicate that the behavior of inhaled $^{239}PuO_2$ varies with the method of preparing the compound ( ). (Data from these experiments are compiled in Table XVI.) Methods of preparation ranged from

oxidation of the metal in air at 123° to calcining the oxalate at 1000° and passing $PuCl_4$ aerosol through a quartz tube at 1150°. The aerosols produced by passing $PuCl_4$ through a heated quartz tube were comprised of spherical particles, while those produced from air-oxidized and calcined plutonium were comprised of heterogeneously shaped particles. In general, the oxides prepared at the lowest temperatures were more rapidly translocated to liver and bone than those prepared at 900° and above. The accumulation in the thoracic lymph nodes appeared to be greater for the heterogeneously shaped particles than for the spherical particles. However, this could be partially accounted for by the fact that the animals in this series were sacrificed after 90 days compared to 56 days for those that inhaled the spherical particles.

A number of experiments indicate that $^{238}PuO_2$ behaves differently from $^{239}PuO_2$. This was first reported in rats by Stuart et al. in 1968 ( ) and has been confirmed in both rats and dogs. Results from Stuart et al. are reproduced in Table XVII. Rats were exposed to either the $^{238}PuO_2$ or $^{239}PuO_2$ aerosols; both were prepared by the same method and had similar particle size characteristics. The rats exposed to $^{238}PuO_2$ showed a relatively high rate of translocation to skeleton: 11 percent of the body burden at 20 days and as much as 20 percent a year or more after exposure. The translocation to spleen and kidney was also greater than in rats exposed to $^{239}PuO_2$. Accumulation of plutonium in thoracic lymph nodes was about the same for the two isotopes.

The comparative distributions of plutonium in dogs after inhalation of two different types of ^{238}Pu are shown in Table XVIII. After almost 6 years

about 40 percent of the body burden was in the skeleton, nearly 30 percent was in the liver and only about 10 percent was in the thoracic lymph nodes. Distributions of plutonium in tissues of beagle dogs 5 years after inhalation of $^{238}PuO_2$ and $^{239}PuO_2$ are compared in Figure 8. After 5 years only 10 percent of the ^{238}Pu body burden remained in lung, compared with 46 percent of the ^{239}Pu. Accumulations in thoracic lymph nodes were three times greater for $^{239}PuO_2$ than for ^{238}Pu; however, the bone burden of ^{238}Pu was 12 times that of ^{239}Pu. This illustrates that the behavior of $^{238}PuO_2$ in the body may be quite different from that of $^{239}PuO_2$.

Preliminary results of a current experiment reported by Craig ( ) summarize the different behaviors of inhaled transuranic oxides in dogs (Table XIX). All of the oxides were prepared and aerosolized by the same methods. The particle size was less for $^{241}AmO_2$ and $^{244}CmO_2$ than for $^{238}PuO_2$ and $^{239}PuO_2$. The ^{239}Pu was distributed between lungs and thoracic lymph nodes, whereas the ^{238}Pu was distributed among lungs, lymph nodes, liver and skeleton. Translocation of ^{241}Am and ^{244}Cm to skeleton and liver was greater than for ^{238}Pu, but very little ^{241}Am and ^{244}Cm was accumulated in the lymph nodes.

Raabe ( ) has determined solubility rate constants for several transuranic oxides prepared by passing transuranic chloride aerosols through a heated quartz tube. While the results may not be exactly applicable to the aerosols used by Craig, they do tend to agree with the observations made in animal experiments (Table XX). The most soluble were $^{239}PuO_2$ and $^{241}AmO_2$; the least soluble was $^{239}PuO_2$.

Mixed Transuranics

Translocation patterns for transuranics deposited in the respiratory tract as mixtures of soluble or insoluble compounds have not been studied. Data from plutonium studies in which $^{239\text{-}240}Pu$-to-^{241}Am ratios were determined in the inhaled aerosol and in the tissues of dogs that inhaled the aerosols may indicate some differences in translocation (Table XXI). Comparison of the Pu-Am ratio in the aerosols with those in the tissues indicates that Am and Pu were differentially translocated only in the case of inhaled $Pu(NO_3)_4$. Americium was translocated from lung to liver more rapidly than plutonium. Separation of Am from Pu was not detectable in tissues of dogs as long as 6 years after inhalation of ^{239}PuO ( ). However, the validity of extrapolating these results to mixed oxides of uranium, plutonium, americium and curium is not known.

CONCLUSIONS

In recent years experimental animal studies have been extended to include transuranics other than plutonium. The results of these experiments indicate that americium and curium, regardless of the chemical form in which they are inhaled, are largely translocated to liver and skeleton and do not accumulate in thoracic lymph nodes as does $^{239}PuO_2$. There is evidence that $^{238}PuO_2$ also translocates to liver and skeleton, although in lesser amounts than Am and Cm. When considering possible biological effects resulting from inhalation of transuranic elements, therefore, these findings shift some of the emphasis from the lungs to other tissues.

These translocation patterns apply when the transuranics are inhaled individually; they may not apply when transuranics are inhaled in mixed

oxides with uranium, a likely form in the developing breeder reactor program, or in any of the other exotic fuel forms. Biological studies of mixed transuranium oxides and possibly of other fuel forms are urgently needed to determine this.

The finding that americium, curium and sometimes ^{238}Pu deposits in liver and skeleton emphasizes the need for continued development of therapeutic measures to remove the transuranics from blood, skeleton and soft tissues. Of course, we must continue to emphasize the need to develop measures for removing transuranics promptly from the lungs.

In this review I have not discussed the urinary and fecal excretion of inhaled transuranics. This is largely because in recent years we seem to have lost interest in determining the relationships between tissue burdens of the transuranics and rates of excretion. This could be unfortunate because animal data may be very useful in interpreting bioassay data from human exposures.

TABLE I

Gastrointestinal Tract Absorption of Transuranics in Rats
(Percent of Administered Dose)

Transuranic	Compound	Newborn	Adult
^{233}U	Nitrate	7	0.2
^{237}Np	Nitrate	1	0.9
^{238}Pu	Nitrate	2	0.03
^{239}Pu	Nitrate	0.3	0.003
	Chloride	-	0.007
	Oxide	-	0.0001
^{241}Am	Nitrate	9	0.07
	Chloride	-	0.03
	Oxide	0.5	0.01
^{244}Cm	Nitrate	6	0.2
	Chloride	-	0.05
	Oxide (aged in H_2O)	2	0.1
	Oxide (fresh)	0.3	0.03
^{249}Bk	Chloride	-	0.01
^{252}Cf	Nitrate	4	0.1
^{253}Es	Nitrate	4	0.03
	Chloride	-	0.06

Information in this table was developed from published reports from results of current reserach at PNL by M. F. Sullivan.

TABLE II

Absorption of Pu and Es through Intact Skin*

^{239}Pu or ^{253}Es Compound	Animal Species	Duration of Exposure	Percent Absorbed
$Pu(NO_3)_4$ in 10 N HNO_3	Rat	1 Hour	0.05
Pu-tributyl phosphate in CCl_4	Rat	15 Min	0.04
$Pu(NO_3)_4$ in 0.1 N HNO_3	Rat	5 Days	0.1-0.3
$Pu(NO_3)_4$ in 10 N HNO_3	Rat	5 Days	1-2
$Pu(NO_3)_4$	Rabbit	14 Days	0.15
Pu citrate	Swine	10 Days	0.25
Pu in 9% HCl + EDTA	Man	-	0.01
$Pu(NO_3)_4$ in 0.4 N HNO_3	Man	1 Hour	0.002
$Es(NO_3)_3$ in 0.01 N HNO_3	Rat	7 Days	0.05

*Extracted from Durbin [ ]

TABLE III

Retention of Plutonium Deposited in the Lower Respiratory Tract (Alveoli)[a]

Compound	Particle Size (μm)[b] CMD	MMD	Species (Number of Animals)	Duration of Study (days)	Retention Half-Time (days) Whole Body	Lung	Reference
$^{239}Pu(NO_3)_4$	---		Rat	200		50	Ballou [1975]
	(0.1-10)[c]		Rat	32	---	30	Tregubenko (1966)
	0.12	0.6	Dog (11)	100-300	600	120	Part *et al.* (1968)
	---	0.9[d]	Dog (14)	100	500-600	250	Ballou and Park (1972)
	(0.1-10)[c]		Rat	256	---	212	Lyubchansky (1967)
	---	0.3-0.5	Rat (6)	80	---	26-37	Suzuki *et al.* (1971)
$^{238}Pu(NO_3)_4$	---		Rat	200		80	Ballou (1975)
^{239}Pu citrate	(0.1-10)[c]		Rat	64-256	---	137-173	Lyubchansky (1964, 1967)
	---	1.45[c]	Dog (14)	100	900	200	Ballou and Park (1972)
Sodium plutonyl-triacetate (^{239}Pu)	(0.1-10)[c]		Rat	256	---	209	Lyubchansky (1964, 1967)
^{239}Pu (III) chloride	(0.1-10)[c]		Rat	256	---	169	Lyubchansky (1964, 1967)
Ammonium plutonium pentacarbonate in 10% carbonate (^{239}Pu)	(0.1-10)[c]		Rat	256	---	167	Lyubchansky (1964, 1967)
Ammonium plutonium IV pentacarbonate in H_2O (^{239}Pu)	(0.1-10)[c]		Rat	230	---	122	Lyubchansky (1964, 1967)
$^{239}PuF_4$	~0.2	---	Dog (6)[e]	90	240	180	Dilley (1970b)
$^{239}PuO_2$	---	---	Rat	Life Span	---	150	Sanders (1975)
Fume	---	---	Rat	---	---	180	Abrams *et al.* (1946)
350° oxalate	---	---	Mouse (160)	500	---	180-460	Bair *et al.* (1961)
	---	1.1-4.9[f]	Dog (16)	125-468	---	~400	Morrow *et al.* (1967)

TABLE III (contd)

Compound	Particle Size (μm)[b] CMD	MMD	Species (Number of Animals)	Duration of Study (days)	Retention Half-Time (days) Whole Body	Lung	Reference
430° oxalate (dust)	0.60	4.3	Dog (8)	65-105	---	>350	West and Bair (1964)
430° oxalate	0.60	4.3	Dog (4)	270	1600	>1000	Bair and McClanahan (1961)
1000° oxalate	0.51	2.8	Dog (3)	90	1200	780	Bair and Park (1968)
350° oxalate	0.45	2.8	Dog (3)	90	1350	370	Bair and Park (1968)
450° metal	0.50	4.8	Dog (3)	90	2700	840	Bair and Park (1968)
123° metal	0.46	1.3	Dog (3)	90	1600	700	Bair and Park (1968)
900° oxalate	0.05	0.12	Dog (3)	150	700	470	Bair (1970)
350° oxalate	0.3-0.5	3.	Dog (~100)	~12 yr	---	1000	Park *et al.* (1972)
160° peroxide	0.5	---	Baboon (29)	167	---	220-580	H. Metivier (1974)
$^{239}PuO_2$	---	0.30	Man	300	---	240	Johnson *et al.* (1972)
$^{239}PuO_2$, 1200° oxalate	---	6 μm[d]	Man	566	---	290	Ramsden *et al.* (1970)
$PuCl_3$	---	0.16	Man	356	---	<Few days	Ramsden *et al.* (1970)
$^{239}PuO_2$ Field studies[g]	---	10-20	Dog (84)	0-456	---	174	Wilson and Terry (1968)
Field studies[g]	---	10-20	Sheep (132)	14-930	---	399	Wilson and Terry (1968)
Field studies[g]	---	10-20	Burro (84)	7-456	---	155	Wilson and Terry (1968)
$^{239}PuO_2$ 700° oxalate	0.05	0.1	Dog (12)	27-185	900	300	Park *et al.* (1970)
	---	4.4-4.9[f]	Dog (3)	65	---	380	Morrow *et al.* (1970)

TABLE III (contd)

Compound	Particle Size (μm)[b] CMD	MMD	Species (Number of Animals)	Duration of Study (days)	Retention Half-Time (days) Whole Body	Lung	Reference
Crushed microspheres	0.18	0.64	Dog (6)	50-106	2200	600	Willard and Park (1970)
Crushed microspheres	0.18	0.64	Dog	730	5600	1100	Willard and Park (1970)
PuO_2-ZrO_2	0.12	0.26	Dog (3)	90	400	150	Willard and Park (1970)
PuO_2-ThO_2	0.13	0.34	Dog (3)	90	3600	310	Willard and Park (1970)

a. Values shown are means or ranges when more than one individual was observed.
b. Count median diameter (CMD) and mass median diameter (MMD) of the aerosol.
c. Particle size range of the aerosol.
d. Aerodynamic median activity diameter of the aerosol.
e. Three of six dogs treated with DTPA, without affecting retention.
f. Mass median aerodynamic diameter estimated from the mass median diameter and density of the plutonium compound.
g. These animals were exposed to a cloud from the high explosive detonation of a plutonium weapon. The average density of the particles was 4.9 gm/cc, and the mean plutonium content of each particle was estimated to be slightly more than 10%. Other constituents include metal oxides from the device, urarium dioxide, and a minor component from the desert environment. The authors suggest that particles less than 1 μm had a higher density and were composed of uranium and plutonium oxide.

TABLE IV

Retention of Transplutonium Elements in the Lower Respiratory Tract

Compound	Particle Size AMAD	Particle Size σg	Species	Duration of Study (days)	Retention Half-time (days)	Reference
$^{241}AmO_2$	0.82 to 0.99	1.5	Dog	270	140	
$^{244}CmO_{1.73}$	0.5	1.6	Dog	64-256	580 (250-1400)	[ ]
$^{244}CmCl_3$	1.6	1.8	Dog	64-256	580 (250-1400)	[ ]
CmOx	0.5	2	Dog	270	240	[ ]
CmOx	-	-	Rat	Lifespan	70	[ ]
$^{253}Es(NO_3)_3$	-	-	Rat	100	10	[ ]

TABLE V

Disposition of Inhaled Soluble Plutonium Compounds

	Plutonium Citrate					Plutonium Nitrate								PuF4
	Rat Lyubchansky [ ]			Dog Ballou et al. [ ]		Rat Tregubenko [ ]	Dog Bair et al. [ ]	Dog Park et al. [ ]				Dog Ballou & Park [ ]		Dog Dilley [ ]
Days After Exposure	32	128	256	30	100	32	30	75-103	109-138	172-236	303	30	100	90
Tissue	(Percent of Initial Lung Burden)													
Total Body	-			-			91	88	86	80	80			76
Lung	5	3	1.5	37	29	9.7	61	51	46	35	32	32	41	70
Liver	1	0.3	0.3	5.3	16	0.6	12	9.5	8.6	16	12	9	10	0.2
Skeleton	10	8	8	38	38	5.7	18	22	26	24	29	43	28	0.55
Lymph Nodes	-			0.2	0.4	-	0.5	2.6	1.5	1.5	1.6	0.4	0.6	4.8
Turbinates	1			0.4	0.8	-						0.85	0.43	-
Kidney				0.5	0.4	0.2						0.5	0.2	-
Spleen				0.4	0.2	0.2						0.25	0.14	-
All Other				-	-							-	-	1.8
Urine				2	2		0.8	1	1.6	2.1	2.2	1.7	2.3	3.6
Feces				156	208		8.6	11	13	18	18	92	81	20

TABLE VI

Comparative Tissue Distribution of $^{238}Pu(NO_3)_4$ and $^{239}Pu(NO_3)_4$ [ ]

	Inhaled*				Intramuscular**			
	238Pu		239Pu		238Pu		239Pu	
Tissue	30 Day	45 Day	30 Day	45 Day	30 Day	45 Day	30 Day	45 Day
Lung	53	42	40	30	--	--	--	--
Liver	2.2	1.6	1	0.9	3	5	1.2	1.7
Skeleton	18	17	7.6	6.5	48	41	4.8	16
Kidney	0.2	0.2	0.1	0.1	0.9	0.1	0.8	0.2
Feces	24	35	42	57	17	19	2	6
Urine	2.5	3	9	5	13	20	0.9	2.8
Injection Site	--	--	--	--	17	12	90	72

* Values are means of 12 rats, 10 μCi/rat.
** Values are means of 4 to 6 rats, 1 μCi/rat.

TABLE VII

Retention Parameters for Inhaled
Pu and Es Nitrate in Rats [ ]

Compound Inhaled	Lung		Liver		Skeleton	
	Fraction of 1 lb	Teff (Days)	Fraction of 1 lb	Teff (Days)	Fraction of 1 lb	Teff (Days)
$^{239}Pu(NO_3)_4$	0.19	<1	0.02	55	0.11	--
	0.25	7				
	0.46	55				
$^{238}Pu(NO_3)_4$	0.15	<1	0.03	70	0.17	--
	0.70	10				
	0.15	80				
$^{253}Es(NO_3)_3$	0.35	<1	0.035	10	0.35	20
	0.30	3				
	0.35	10				

TABLE VIII

Comparison of Plutonium Content of Rat Lungs After Inhalation of Several Plutonium Compounds [ ] (Percent of Initial Lung Burden)

Plutonium Compound	Valence	pH	1 Day		256 Days	
			Lung	SIO*	Lung	SIO
Plutonium Citrate (2% Citrate)	IV	6.5	47	20	4	22
Sodium Plutonyltriacetate	VI	6.5	70	26	4	26
Ammonium Plutonium Pentacarbonate [10% $(NH_4)_2\ CO_3$]	IV	8	117	11	4	20
Ammonium Plutonium Pentacarbonate [in H_2O]	IV	7.4	85	3	6	11
Plutonium Chloride	III	2	88	14	7	24
Plutonium Nitrate	IV	2	74	3	9	10

* Sum of Internal Organs

TABLE IX

Comparative Pulmonary Retention of Different Plutonium Compounds in Rats 7 Days After Pulmonary Intubation [ ]
(Percent of I.T. Dose)

^{239}Pu Compound	Lungs	Other Tissues
Oxide	58	<0.5
Oxalate	61	27
Citrate	18	70
Nitrate	50	39
DTPA Complex	<0.5	<1

TABLE X

Translocation of Inhaled Cm in Beagle Dogs

	From McClellan et al. [ ]						From Craig et al. [ ]					
	$^{244}CmO_{1.73}$*		$^{244}CmCl_3$**				$^{244}CmO_x$***					
Days	64		128		256		30		90		270	
Tissues:	(Percent of Initial Lung Burden)						(Percent of Body Burden)					
Lung	11	7	4	6	3	3	20	23	18	18	8	15
Liver	66	52	44	61	47	52	37	25	36	48	34	42
Skeleton	44	45	51	35	53	56	20	37	30	25	27	32
TBLN	--	--	--	--	--	--	--	--	--	--	--	--
Muscle	--	--	--	--	--	--	13	9	10	4	27	6
All other	--	--	--	--	--	--	10	6	7	5	5	5
Final Body Burden (μCi)	--	--	--	--	--	--	0.07	0.4	0.2	3.3	0.08	1

* $^{244}CmO_{1.73}$; AMAD = 0.5, σ_g = 1.6

** $CmCl_3$; AMAD = 1.6, σ_g = 1.8

*** Oxalate calcined at 700-750°C; AMAD = 0.5, σ_g = 2.

TABLE XI

Effect of Dose on Distribution of ^{244}Cm in Rats 30 Days After Inhalation of $^{244}CmO_x$ [ ] (Percentage of Initial Alveolar Burden)

Dose - Initial Alveolar Burden (nCi)	0.44	6	32	710	1600
Tissue					
Lungs	5	16	25	15	17
Liver	15	10	19	16	14
Skeleton	10	15	42	52	52
Thoracic Lymph Nodes	--	4	1	0.8	0.7

TABLE XII

Translocation of Inhaled $^{241}AmO_2$ in Beagle Dogs
(Percent of Body Burden)

	From Thomas et al. [ ]*				From Craig et al. [ ]**					
Days	127	256	512	1022	30		90		270	
Tissues:										
Lung	9.9	6.8	3.6	2.6	55	53	29	44	14	17
Liver	41	51	34	24	19	23	39	21	32	49
Skeleton	47	39	59	70	11	17	18	24	45	31
TBLN	0.25	0.14	0.13	0.0005	--	--	--	--	--	--
Body Burden (μCi)	24	15	20	15	0.11	1.3	0.12	1.2	0.15	0.59

* ^{241}Am chloride aerosol passed through heating column at 600°C; AMAD = 0.82 to 0.99, σg = 1.5

** Oxalate calcined at 700-750°C; AMAD = 1.4, σg = 1.7.

TABLE XIII

Distribution of Pu in Hamsters
3-12 Months After Inhalation of PuO_2 [ ]
(Percentage of Initial Lung Burden)

	$^{238}PuO_2$					$^{239}PuO_2$				
Sex	Female		Male			Female			Male	
Initial Alveolar Burden, nCi	10	200	5	15	200	3	35	160	19	160
Tissues										
Lungs	11	34	12	20	37	4	15	41	13	36
Liver	.3	.9	.3	.5	.7	.04	0.07	.08	.5	.1
Skeleton	-	1	.4	.9	1	.1	.2	.2	.2	.2
Thoracic Lymph Nodes	.4	4	-	1	3	.1	1	1	.8	3

TABLE XIV

Effect of Dose on Distribution of ^{238}Pu in Rats at 1-2 Years After Inhalation of $^{238}PuO_2$ [ ]
(Percentage of Initial Alveolar Burden)

Dose - Initial Alveolar Burden (nCi)	7	13	220	890*
Tissues				
Lungs	6	7	9	43
Liver	1	0.7	0.4	0.4
Skeleton	13	3	4	3
Thoracic Lymph Nodes	4	4	2	4

*100-300 Days Postexposure

TABLE XV

Effect of Particle Size on Translocation of Inhaled Monodisperse $^{238}PuO_2$ in Dogs [ ] (32 Days Postexposure)

Particle Size* (μm)	Percent of Body Burden			
	Lung	Liver	Bone	TBLN
0.75	97.3±1.85	0.45±0.41	0.61±0.70	0.56±0.29
1.5	98.8±0.06	0.07±0.02	0.26±0.23	0.86±0.87
3.0	97.8±5.6	0.17±0.16	0.36±0.13	1.32±0.61
1.5 (poly)	97.5	0.09	0.18	2.14

* Aerodynamic Diameter

TABLE XVI

Comparative Disposition of Inhaled Plutonium in Dogs

^{239}Pu Aerosol	Percent of Body Burden				Ref.
	Lung	Liver	Bone	TBLN	
Metal oxidized at 123°*	96	0.04	0.09	3.4	[a]
$PuCl_4$ oxidized at 325°**	79	8.2	11.	0.7	[b]
Oxalate calcined at 350°*	88	0.16	0.16	11.	[a]
Oxalate calcined at 450°*	95	0.06	0.13	4.8	[a]
$PuCl_4$ oxidized at 600°**	94	1.7	8.6	0.93	[b]
$PuCl_4$ oxidized at 900°**	99	0.1	0.3	0.37	[b]
Oxalate calcined at 1000°*	97	0.02	0.03	2.5	[a]
$PuCl_4$ oxidized at 1150°**	99	ND	0.27	0.6	[b]

* 0.5 μm CMD, 3 μm MMD (4.8 μm MMD for 450°, 1.3 μm MMD for 123° aerosols): dogs sacrificed 90 days post exposure.
** 1.9 μm AMAD, 1.8 σg: dogs sacrificed 56 days post exposure.

TABLE XVII

Comparative Distribution of Inhaled $^{238}PuO_2$ and $^{239}PuO_2$ in Rats [ ]
(Percent of Body Burden)

Days Past Exposure	$^{239}PuO_2$				$^{238}PuO_2$						
	13	28	68	113	20	48	78	127	320	465	481
Tissue											
Thoracic Lymph Nodes	0.3	1.4	1.8	--	0.4	0.6	0.8	3.4	3.3	0.1	3.3
Lung	97	96	97	99	82	84	77	78	64	40	68
Spleen	0	0.02	0.04	0	0.13	0.16	0.2	0.2	0.7	0.6	0.5
Kidneys	0	0	0	0	0.5	0.4	0.4	1.1	0.5	3.3	0.5
Liver	0.02	0.4	0.3	0.3	2.4	1.3	1.9	1.7	1.6	3.6	3.6
Skeleton	0.01	0.1	0.1	0.16	11	12	23	15	30	49	23
Terminal Body Burden (μCi)	12.5	4.9	1.5	0.6	9.5	3.8	1.1	0.8	0.38	0.17	0.21

PuO_2 was produced by calcining the oxalate in air at 350°. CMD = 0.1, standard geometric deviation was 1.5-1.9 for ^{238}Pu and 1.7-2.0 for ^{239}Pu.

TABLE XVIII

Comparative Distribution of Two Forms of Inhaled ^{238}Pu in Beagle Dogs [ ]
(Percentage of Final Body Burden)

Time After Exposure (months)	$^{238}PuO_2$ Calcined at 350°								Crushed ^{238}Pu Microspheres							
	23	36	38	54	58	60	62	70	22	34	52	60	62	70	75	76
Tissues																
Lungs	4	32	15	34	6	7	17	23	72	39	16	13	7	8	3	9
Liver	23	23	13	17	23	33	22	28	7	12	31	23	27	15	32	29
Skeleton	64	32	57	41	55	43	47	34	12	24	46	37	32	47	48	41
Thoracic Lymph Nodes	4	10	11	5	10	11	9	10	7	21	3	23	26	19	9	15
Final Body Burden (μCi)	3	8.1	7	2.6	2.5	2.3	2.2	2.6	3.1	1.1	0.2	0.5	2.5	0.8	0.4	1.4

TABLE XIX

Comparative Tissue Distribution of Inhaled Transuranic Oxides in Beagle Dogs* [ ]

Tissue	$^{238}PuO_2$ (~ 370 days)	$^{239}PuO_2$ (~ 370 days)	$^{241}AmO_2$ (270 days)	$^{244}CmO_x$ (270 days)
Lung	56	80	16	12
Thoracic Lymph Nodes	9.5	18	1	0.5
Liver	6.5	0.1	40	38
Skeleton	23	0.9	38	29
Muscle	-	-	3.1	17
Aerosol Properties				
Density (g/cm^3)	10.82	10.38	9.8	11.4
AMAD	2.1	2.3	1.4	0.5
σg	2.3	1.9	1.7	2.1
Ultrofilter ability, %	2.24	0.0002	0.006	0.42

*Prepared by calcining the oxalate at 750°

TABLE XX

Solubility Rate Constants for Americium and Plutonium Oxides [ ]

Oxide	Treatment	Particle Size AMAD (μm)	Solubility Rate Constant (gcm^{-2} day^{-1})
$^{241}AmO_2$	1050°	1.5	4.0×10^{-9}
$^{238}PuO_2$	1050	<1.2	1.2×10^{-8}
$^{239}PuO_2$	1050	<1.2	6.5×10^{-11}

TABLE XXI

$^{239-240}Pu$-^{241}Am Ratios in Dog Tissues
90 Days After Inhalation of Pu

Plutonium Compound	Aerosol	Lung	Tracheobronchial Lymph Nodes	Liver
$^{239}Pu(NO_3)_4$	38	70	50	12
$^{239}PuF_4$	6.5	5.5	5.5	-
	6.5	8.3	6.6	-
	6.5	8.3	6.6	-
$^{239}PuO_2$				
1000° oxalate	14	13	12	-
350° oxalate	13	11	13	-
450° metal	31	32	34	-
123° metal	31	32	30	-
$^{239}PuO_2$ (enriched with ^{240}Pu, ^{241}Pu and ^{242}Pu)	1.9	1.9	1.8	-

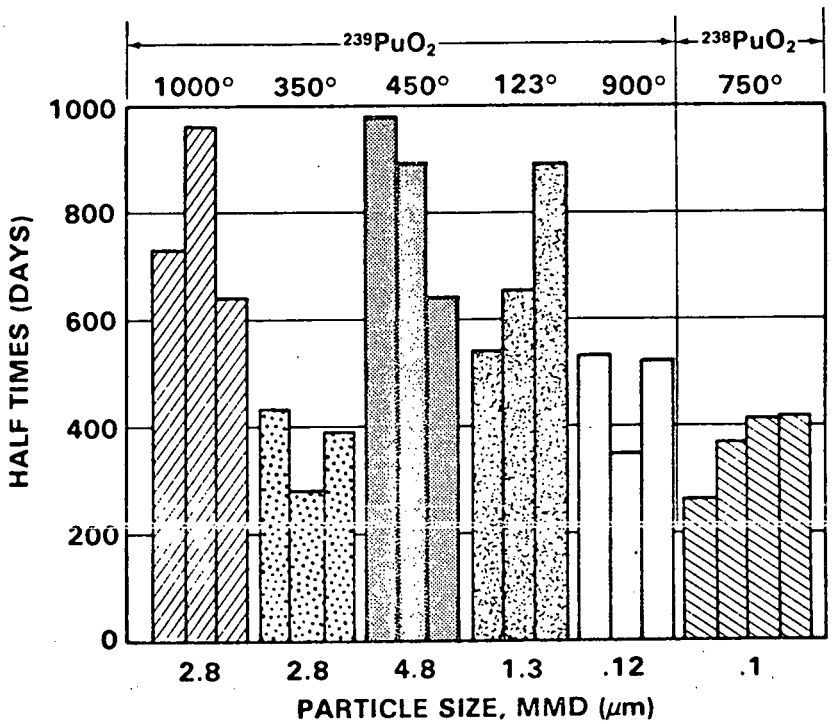

Figure 1

Pulmonary Retention of Inhaled PuO_2 in Dogs

PNL66192-11

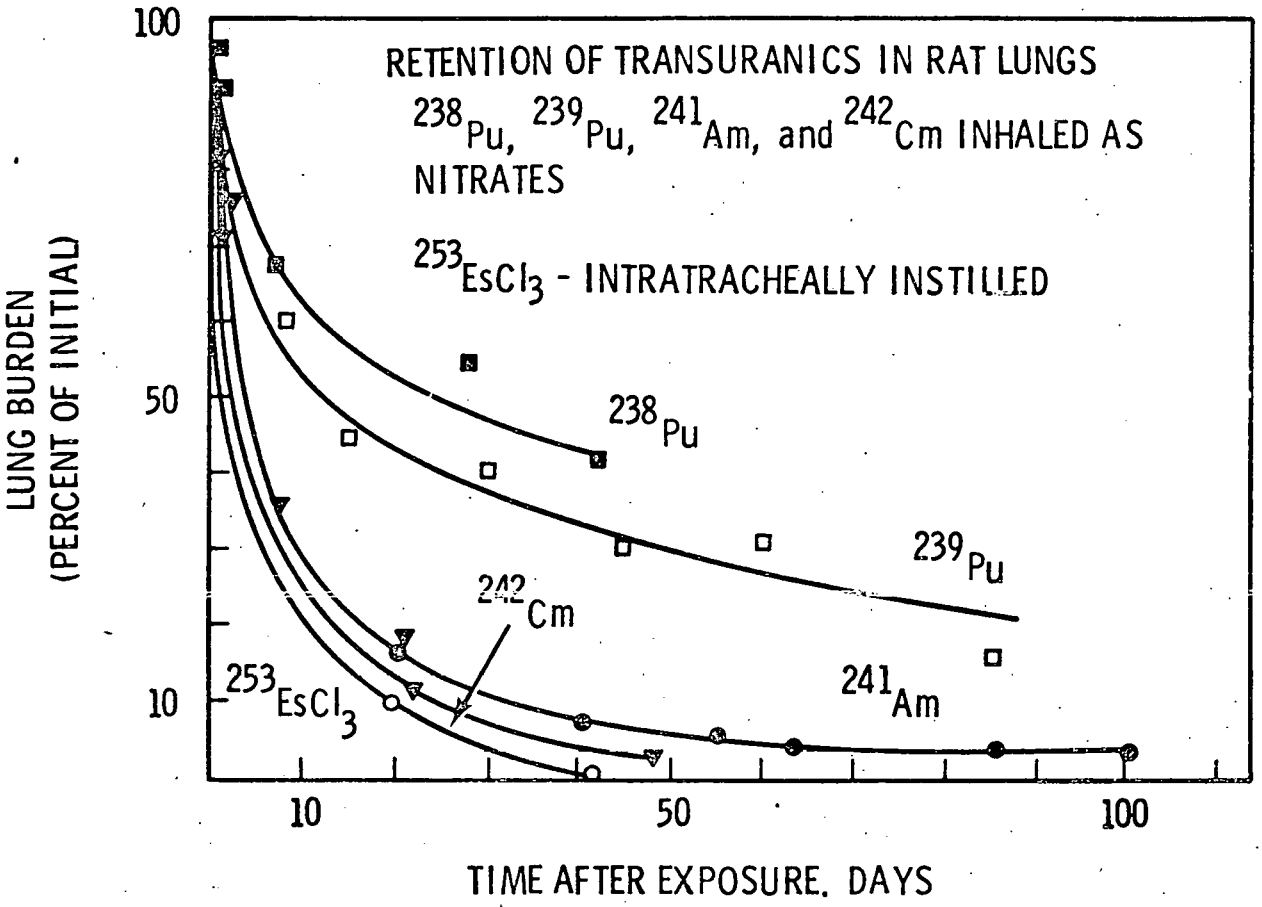

Figure 2

Retention of transuranium elements in rat lungs (^{238}Pu, ^{239}Pu, ^{241}Am and ^{242}Cm - Nenot et al., 1972; $^{253}EsCl_3$ - Ballou et al., submitted for publication)

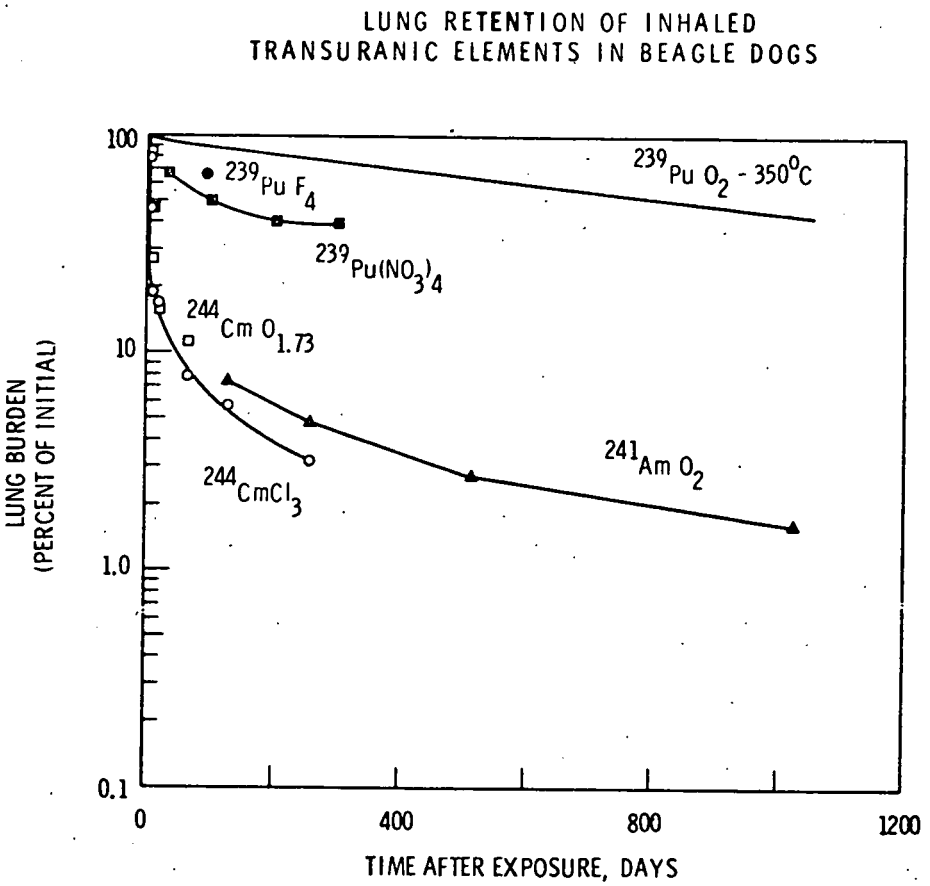

Figure 3

(Redrawn from R. O. McClellan, 1972)

DISTRIBUTION OF PLUTONIUM IN DOGS AFTER INHALATION OF $^{239}Pu(NO_3)_4$

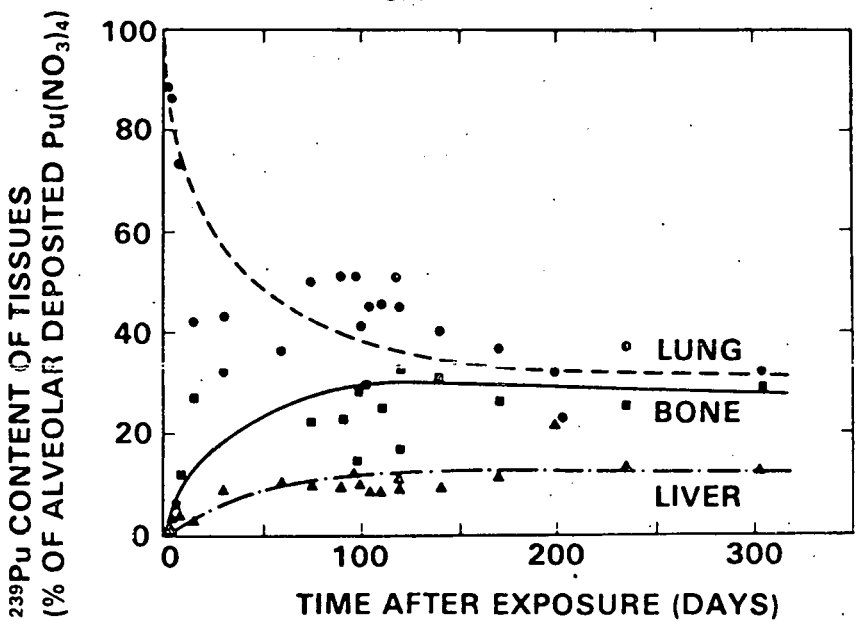

Figure 4

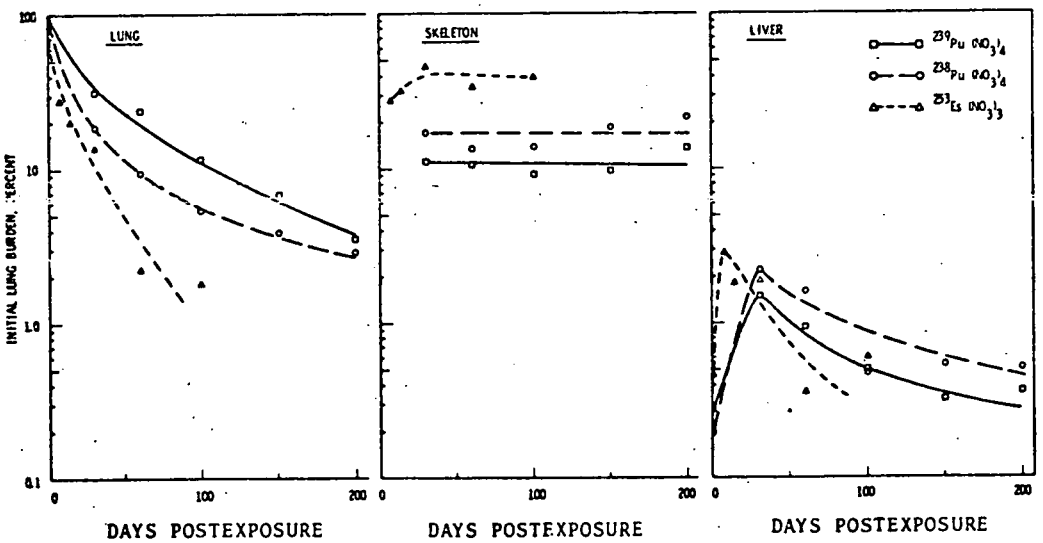

Figure 5

Disposition of Inhaled Plutonium and Einsteinium in Rats

DISTRIBUTION OF PLUTONIUM IN DOGS AFTER INHALATION OF $^{239}PuO_2$

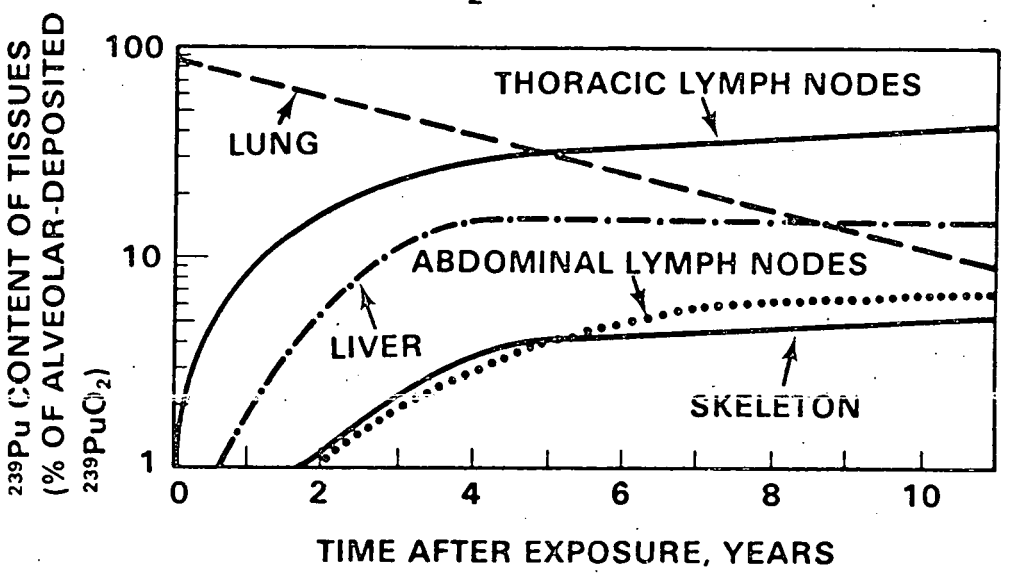

Figure 6

EFFECT OF PARTICLE SIZE ON
FATE OF INHALED $Pu^{239}O_2$
(30 DAYS AFTER EXPOSURE)

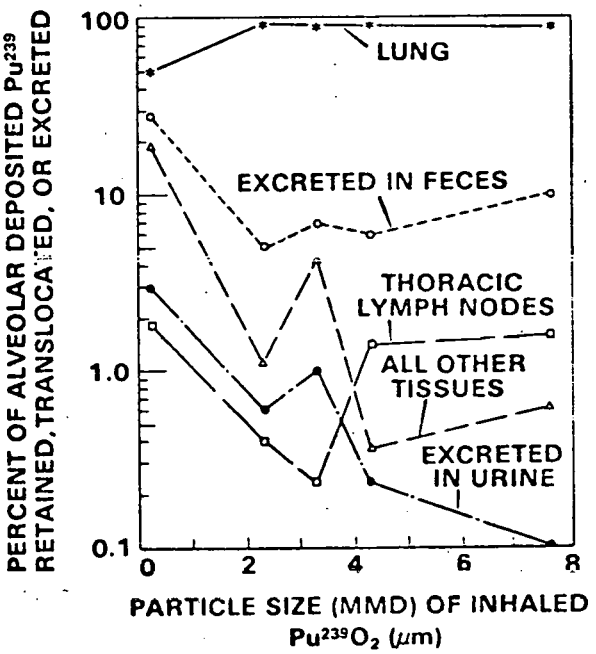

Figure 7

DISTRIBUTION OF PLUTONIUM IN TISSUES OF DOGS
5 YEARS AFTER INHALING $^{238}PuO_2$ OR $^{239}PuO_2$

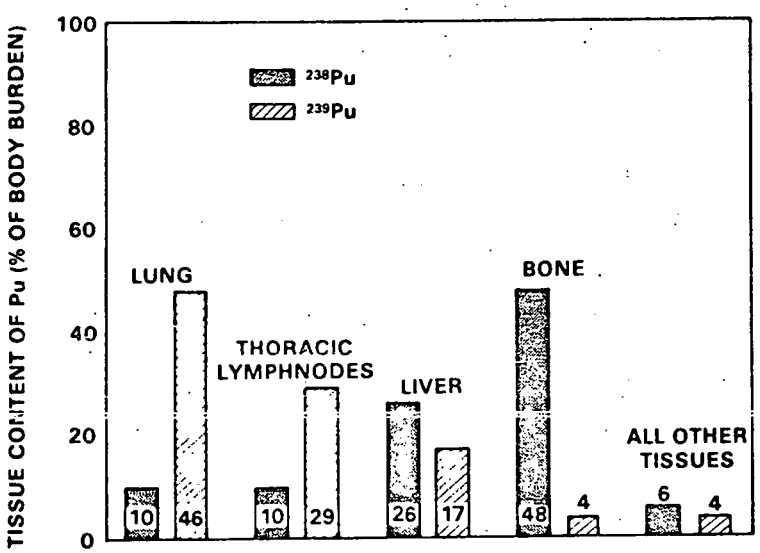

Figure 8