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DEPOSITION, TRANSLOCATION AND EFFECTS OF TRANSURANIC PARTICLES INHALED BY EXPERIMENTAL ANIMALS

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ABSTRACT

Inhalation exposure constitutes the most likely route of entrance for transuranics into the body. Cancer is the most likely consequence of exposure, but several thousand workers have been exposed during the last 30 years without, so far, evidence of exposure-related effects. Because of the difficulties inherent in determining the health risk of airborne transuranics in people, animal inhalation studies are conducted to facilitate risk assessment.

Several soluble and insoluble transuranic compounds have been studied in rodents and dogs, either alone or combined with exposure to other materials (e.g., PuO_2 - UO_2 fuel and Na). These studies have provided a wide variety of spatial and temporal dose distribution patterns in the lung. The distribution and total initial deposition in the respiratory tract is a function of the physical characteristics of the inhaled aerosols (size distribution, shape, hygroscopicity) and of the morphology and physiology of the animal. Translocation rates, organ and tissue distribution and excretion in urine and feces, are a function of the physicochemical characteristics of the deposited material (solubility, specific activity, chemical compound, etc.). Differences in rate of translocation of the solubilized material, primarily to the liver and bone, determines the radiation dose to the various tissues involved. Insoluble particles of plutonium dioxide are transferred to the thoracic lymph nodes, which may be functionally destroyed as a consequence.

Radiation pneumonitis and pulmonary fibrosis are the main causes of death in animals with cumulative radiation doses to the lung of a few thousand rads. The most significant long-term effect of inhaled transuranic compounds in animals is the development of lung and bone tumors. The main type of lung tumor in both dog and rat is the bronchioloalveolar carcinoma (adenocarcinoma). However, tumor type is a function of radiation dose and dose-distribution at high doses. Bone ranks next to lung as the tissue developing the most tumors following inhalation of transuranics.

INTRODUCTION

TYPES OF EXPOSURE

People may be exposed to transuranic materials either as a result of the nature of their work, i.e., occupational exposure, or because of the dissemination of particles to the atmosphere and to water supplies, i.e., environmental exposure. Worldwide distribution of $^{239}PuO_2$ occurred following the extensive testing of nuclear weapons in the atmosphere in the fifties and early sixties, while $^{238}PuO_2$ contamination primarily of the southern hemisphere occurred following the burnup of the SNAP-9A radionuclide thermal generator device during atmosphere re-entry in 1965. These events established low, but measurable, background levels of environmental transuranics to which everyone has been exposed.

DURATION OF POSSIBLE EXPOSURES

Exposure may be acute, as in a short-duration exposure following an accidental release of material, e.g., from a glove box explosion, or in a time-limited planned exposure to deal with a specific problem. It may also be intermittent or repeated, as might occur in periodic air pollution episodes or in repeated activities, even though an attempt is made to eliminate the

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possibility of transuranic releases. Chronic exposure would arise from the continuous release of low levels of transuranic materials into waste water or into the atmosphere.

ROUTE OF EXPOSURE

The possible routes of entry of transuranic materials into the human body are by inhalation, by ingestion in food or water, by absorption through the skin, or by experimental or accidental injection. While people have been exposed by all four routes, inhalation and ingestion are by far the most likely for the largest number of people. A large fraction of ingested plutonium is excreted. Inhalation is more hazardous, because deposited material may be retained in the lung for a long time, available as a long-term source for both local effect and for translocation elsewhere.

Both dose and dose-rate to the various body organs following inhalation of transuranics are likely to be different from those arising following injection (the route of administration used in many studies), the degree of difference depending upon physicochemical characteristics of the material. These characteristics also affect deposition fractions in different regions of the lung (Figure 1), translocation rates, physical growth and dissolution characteristics, etc., that will determine dose to different body organs.

BIOLOGICAL EFFECTS

Depending upon their severity and the relationship between exposure and elapsed time before the effect is observed, these may be classified as acute, subacute and chronic or long term. Acute effects from inhaled transuranic particles include radiation pneumonitis and pulmonary edema which, if severe enough, may lead to early death. The most prominent subacute effect is pulmonary fibrosis, leading to respiratory insufficiency. The chronic or long term effect of most concern following inhalation of transuranic particles is cancer, usually tumors of the respiratory or skeletal systems, the latter only with the more soluble materials.

To date, effects from inhaled radioactive materials have been identified only in experimental animals. Several groups of people who are known to have inhaled measurable quantities of radioactive materials, particularly plutonium compounds, have been under observation for more than 30 years. No effects have been observed, to date, in contrast to the many effects of alpha emitter seen in radium dial painters (ingestion), thorotrast patients (injection), and uranium miners (inhalation), etc.

ANIMAL STUDIES RATIONALE

Although we can make calculations (Figure 2) we cannot, in general, experiment with humans. The purpose, therefore, of animal studies is to develop models that will facilitate risk assessment by studying dose-effect relationships for different materials and combinations of materials of different physicochemical characteristics, determination of tissues at risk, delineation of dose distribution (spatial and temporal) effects and, in addition, to investigate treatments that might reduce the dose commitment, e.g., chelation, lung lavage, excision, innocuous dust exposures, etc.

The studies should be conducted in at least two animal species to reduce the likelihood of being led astray by pecularities (such as the sensitivity of the guinea pig to SO_2) of one species.

CURRENT PNL PROJECTS

Projects involving the inhalation of actinides that are presently under way at PNL are listed in Table 1, which also details the isotopes and compounds being studied and the animal species used. There are currently some 500 dogs and 4000 rats involved, the majority on life span dose-effect and metabolism studies. The remainder are involved with a variety of experiments designed to elucidate the mechanisms of the observed biological effects, mostly in the "Inhaled Transuranics in Rodents" and "Mechanisms of Radiation Effects" projects. These special studies, while potentially of great importance to our understanding of the responses of biological systems to high LET radiation, will not be discussed in this presentation.

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TABLE 1. ISOTOPES, COMPOUNDS AND EXPERIMENTAL ANIMAL SPECIES USED IN PROJECTS INVOLVING INHALATION OF ACTINIDES

Title	Project Manager	Isotopes	Compounds	Animal Species*	Approximate FY 1978 Man Years of Effort
Inhalation Hazards to Uranium Miners	Stuart	^{238}U, ^{230}Th, ^{222}Rn and Daughters	Ore and Gas Molecules	D,H,R	12
Inhaled Plutonium Oxide in Dogs	Park	^{238}Pu, ^{239}Pu, ^{241}Am, ^{244}Cm	High Fired Oxides	D	17
Inhaled Transuranics in Rodents	Sanders	^{238}Pu, ^{239}Pu ^{241}Am, ^{244}Cm, ^{253}Es	High Fired Oxides, Aged in H_2O Oxides, Air Oxidized, Nitrates, Chloride, Hydroxide	H,R	10
Aerosol and Analytical Technology	Cannon	All Actinides Req'd for other Projects	All Compounds Req'd for other Projects	H,R,D,S	3
Fetal and Juvenile Radiotoxicity**	Sikov	^{239}Pu, ^{241}Am	Citrates	R	7
Mechanisms of Radiation Effects**	Frazier	^{238}Pu, ^{239}Pu	High Fired Oxides	D,R	8
Inhaled Plutonium Nitrate in Dogs	Dagle	^{238}Pu, ^{239}Pu	Nitrate	D	8
Toxicity of Thorium Cycle Nuclides	Ballou	^{232}Th, ^{232}U, ^{233}U	Nitrate	R	3
Toxicology of Plutonium-Sodium	Mahlum	^{239}Pu	Oxide	R	5

* D = Beagle Dogs
H = Hamsters
R = Rats
P = Swine

** These studies have an actinide inhalation component but are not exclusively inhalation studies.

METHODS AND MATERIALS

EXPOSURE TECHNIQUES

These have been described in detail in several open-literature publications. For the most part, acute or repeated exposures, lasting less than about 30 minutes for dogs[1] and 3 hours for rodents,[2] have used nose-only techniques. A nose-only exposure technique has also been developed and demonstrated for miniature swine.[3] Such techniques are too stressful for daily exposures lasting for prolonged periods. A head-only exposure technique was developed to minimize contamination of the body fur of beagle dogs during daily exposure for 4 hours to uranium ore dust and radon daughter products for 5 years.[4] These techniques are unsuitable for chronically exposing rodents to test atmospheres and whole-body exposures must be used. A system for exposing 48 rats or 102 hamsters, individually caged on one tier of 3 m^3 aerosol chambers, has been successfully used on a number of life-span rodent studies.[5] Figures 3 and 4 are schematics of the rodent and dog nose-only exposure systems, while Figure 5 shows one of several types of rodent whole-body exposure chambers in use at PNL.

As a general rule, rodents are exposed at a fixed age (8-10 weeks) unless age at exposure is one of the parameters under study. After exposure, they are kept for at least 1 week in a special holding box and/or metabolism cages, from which urine and feces from groups of animals may be collected daily for analyses. Dogs are transferred from runs to metabolism cages 1 month prior to exposure and are subjected to a careful pre-exposure sampling and training regimen which provides adequate background data and minimizes the possibility of an unsuccessful exposure due to the dog's lack of acceptance of the nose-only exposure procedures. This regimen includes the collection of respiration parameters (tidal volume, respiration rate, and minute volume) on several consecutive days under conditions closely approximating those which pertain during aerosol exposure. Following exposure to the desired quantity of transuranic material, the animals are kept in metabolism cages for at least 30 days, during which time urine and fecal samples are collected for analyses according to the experimental protocol; estimates of radioactivity in the dog lungs are obtained from thorax counts made at several postexposure times (e.g., 1, 2, and 4 weeks) and other measurements and/or samples taken as required.

MATERIAL PREPARATION AND AEROSOL GENERATION

The physicochemical nature of an inhaled compound has an important influence on its behavior following deposition in the respiratory system. Accordingly, great care must be taken both in the preparation of the material and in its dispersion as an aerosol to ensure that the experimental animals actually inhale the aerosol which one desires to study. These techniques have been described in various papers during the last 20 years, recently by Craig et al.[6] for oxides and Ballou et al.[7] for nitrates and other soluble materials.

The transuranic oxides have usually been prepared by converting a nitrate solution to the oxalate form, then calcining this in a furnace for 2 to 4 hours at 700 to 750°C, after which it is allowed to cool to room temperature in air. This procedure yields stoichemetric dioxides of the elements plutonium, americium, and curium as verified by X-ray diffraction analyses.

Because of the ease with which aerosols can be generated from small quantities of materials using compressed-air operated liquid nebulizers, this has been the method of choice for the last several years. Water-insoluble materials are generated by nebulizing stirred suspensions of particles in distilled water. The droplets from the nebulizer are passed through a heating column to drive off the water, then diluted with filtered air before introduction to the aerosol exposure chamber. Apart from the stirring, the same procedures are used for generating aerosols from solutions, e.g., 0.27 N nitric acid solution of americium nitrate. The tube passing from the generator to the exposure chamber also serves as a particle charge neutralizer, since particles deposited in it will irradiate the air passing through it with an intense flux of α-particles.

MATERIAL AND AEROSOL CHARACTERIZATION

Several different types of samples are routinely taken from the exposure chambers to permit characterization of the animal exposures. These include filter paper samples for concentration and chemical characterization, cascade impactor samples for aerodynamic equivalent size distribution determination, and thermal or electrostatic precipitator samples (Figure 6) for particle visualization. Ultrafilterability,[8,9] density and X-ray diffraction[8] measurements (Table 2 and 3) are also made on samples of the generator suspension or solution. In some cases, particle size distribution measurements are also made on this material.

These procedures have characterized what the animals have been exposed to and we can duplicate those exposures if necessary or desirable.

TABLE 2. PHYSICAL CHARACTERISTICS OF TRANSURANIUM OXIDES

Item	$^{238}PuO_2$	$^{239}PuO_2$	$^{241}AmO_2$	$^{244}CmO_2$
1. Physical Half Life	87.8 y	24400 y	458 y	18.1 y
2. Wt. % Principal Isotope	80.89	94.21	100	94.34
3. Principal Contaminant	^{239}Pu	^{240}Pu		^{246}Cm
4. Wt. % Princ. Contaminant	14.98	5.35		4.11
5. Lattice Parameter (Å)	5.396	5.393	5.312	5.360
6. Theoretical Density (g/cm^3)	11.41	11.47	11.69	11.90
7. Pycnometrically Determined Density (g/cm^3)	10.82	10.38	9.84*	11.4

* This value may be low due to possibility of transformation to Am_2O_3 or to bubbling of the measurement liquid.

TABLE 3. CHARACTERISTICS OF OXIDE SUSPENSIONS

Characteristic	$^{238}PuO_2$	$^{239}PuO_2$	$^{241}AmO_2$	$^{244}CmO_2$
1. Powder Mass (mg)	5	97.8	100	10
2. Water Volume (ml)	35	30	30	100
3. Mass Conc. ($mg\ ml^{-1}$)	0.143	3.26	3.33	0.10
4. Specific Activity ($mCi\ mg^{-1}$)	12.02	0.0725*	3.242	69.5
5. Initial Suspension Activity	1.719	0.236	10.796	6.950
6. Powder Size Distribution				
(i) MMD (μm)	8.2	15.5	--	--
(ii) GSD	1.88	1.81	--	--
(iii) 10 Wt.% $<d_{10}$ (μm)	3.5	7.2	--	--
(iv) 50 Wt.% $<d_{50}$ (μm)	9.0	20.8	--	--
(v) 90 Wt.% $<d_{90}$ (μm)	19.2	29.0	--	--
7. Supernatant Cond. (Respirable Fraction) ($\mu Ci\ ml^{-1}$)	235	200	2610	2110
8. Ratio Total:Respirable	7.31	1.18	4.14	3.29
9. Initial Ultrafilterability, %	2.24±0.12	0.0002± 0.00001	0.0062± 0.005	0.42±0.021

Note: GSD = Geometric standard deviation
MMD = Mass median diameter

* This value is for PuO_2 containing 94.21% ^{239}Pu and 5.35% ^{240}Pu, the latter having a half-life of 6540 years.

RESULTS AND DISCUSSION

DEPOSITION

To have confidence in the application of results obtained from animal inhalation experiments to man, it is necessary to show, among other things, that there are no startling dissimilarities between man and the experimental animal in the behavior of the inhaled materials. In other words, factors such as the initial deposition patterns, translocation, uptake, and elimination from various body organs as a function of the characteristics of the material inhaled, have to be sufficiently similar for animal and man for extrapolations to be useful.

The alveolar deposition of transuranic aerosols inhaled by rodents has been discussed by Craig and Buschbom.[2] The quantity inhaled is estimated from the product of the aerosol concentration (nCi/ℓ), the exposure time (minutes) and the mean minute volume of the animals (ℓ/min). The pulmonary deposition in each exposed group of rodents is determined from measurements carried out on the first postexposure sacrifice group. Ideally, this would occur at a time when clearance of material initially deposited upon the ciliated epithelium of the tracheobronchial tree and nasopharynx is complete, while early clearance of alveolar-deposited material is small enough to be ignored. Obviously, this is only true for compounds that are relatively insoluble in body fluids. However, for materials that are readily absorbed into the blood, it is the total initial deposition of inhaled material that is of importance rather than just the alveolar deposition.

Other techniques used to arrive at estimates of total and pulmonary deposition of inhaled material include whole body and thorax-counting of exposed animals at various times postexposure, and summation of the quantities of material found in the animals at 30 days postexposure and that excreted in the urine and feces between days 4 and 30.[10] Material excreted during the first 3 days is assumed to come from the ciliated epithelium. Its addition to the above sum gives us an estimate of the total initial deposition.

Percentage deposition is obtained by dividing the quantity deposited by the calculated quantity inhaled and multiplying the quotient by 100. Table 4 presents data obtained for the pulmonary deposition of $^{239}PuO_2$ inhaled by rats. The inverse relationship between percent pulmonary deposition and aerosol particle size (as represented by the activity median aerodynamic diameter, AMAD) is significant at the $p < 0.01$ level,[2] percent pulmonary deposition decreasing as particle size increases over the AMAD range 1 to 4 μm.

Experiments conducted by Sikov et al.[11] have shown that for aerosols of similar particle size distributions, the percentage alveolar deposition is also a function of the age of an animal at the time of exposure. Table 5 compares deposition of aerosols of the different sizes in adult and newborn rats. As might be expected, particularly for the larger aerosols, the fractional deposition is lower for the immature animals with their smaller respiratory passages than for the adults.

A further demonstration of the importance of particle size in determining the percentage of inhaled aerosol that will be deposited is shown in Figure 7. Here, rats were exposed to branched chain aggregate aerosols formed by the vaporization of PuO_2-UO_2 fuel pellets, in the presence or absence of sodium.[12] The AMAD of the resulting aerosol was generally larger (> 2.5 μm) when sodium was present compared to the fuel-only aerosol (about 1 μm) although there were exceptions. Moreover, the physical appearance of the aerosol was changed from a branched chain aggregate to a sphere by the presence of sodium. The fractional deposition of particles 2.5 μm or larger was 6% or less while that of particles smaller than 2.2 μm was 10-15% of the inhaled radioactivity whether sodium was present or not.

In an extensive study on the alveolar deposition of $^{239}PuO_2$ aerosols in dogs, Craig et al.[1] showed that the percentage deposition, determined from 14-day postexposure thorax counts of the plutonium 17-keV X-rays, was significantly correlated with mean tidal volume of the dogs (corrected for the dead space in the valving and nonrespiratory portions of the dog's respiratory tract) and the particle size of the inhaled aerosol. Respiration parameters (tidal volume, respiration rate and minute volume) are measured during aerosol exposures. Separation of expired from inspired air permits separate measurements of the quantity and particle size distribution of material exhaled. Differences beween the concentrations and size distributions (measured with 8-stage cascade impactors) of the inspired and expired aerosols have been used to calculate total initial deposition of aerosols as a function of aerodynamic equivalent size[13] in both dogs (Figure 8) and in Hanford miniature swine (Figure 9). As can be seen, these curves are in good general agreement with the curve derived from the Task Group on Lung Dynamics Report to ICRP

TABLE 4. PERCENTAGE PULMONARY DEPOSITION OF $^{239}PuO_2$ PARTICLES INHALED BY RATS

(48 hr postexposure sacrifice)

Suspension Specific Activity μCi/ml	Aerosol Data			Activity		
	AMAD μm	GSD	CONC. nCi/liter	Inhaled nCi	In Lung nCi	Pulmonary Deposition %
4.14	1.679	1.905	2.99	8.97	0.663	7.36
4.74	1.966	1.774	4.14	12.4	1.52	12.2
4.09	2.177	1.730	7.06	21.2	0.344	1.63
4.32	2.179	1.896	8.86	26.6	1.73	6.51
19.2	2.142	1.739	21.2	63.3	3.35	5.27
97.9	2.077	1.701	37.7	75.4	6.76	8.97
97.9	2.406	1.751	48.6	194	19.6	10.1
97.9	2.684	1.687	111	443	25.7	5.81
97.9	2.596	1.695	126	503	33.9	6.74
91.3	2.584	1.813	126	504	39.4	7.79
93.5	2.245	1.787	170	511	29.1	5.69
93.6	2.273	1.707	285	854	59.6	6.98
432	3.704	1.663	846	3390	79.6	2.35
432	3.92	1.674	1190	4770	281	5.89
1160	3.563	1.722	2100	8400	338	4.03
Mean percentage deposition (%)					6.48	6.48
Pulmonary deposition % = activity in lung 48 hr postexposure as a percentage of activity inhaled						±2.72

AMAD = Activity Median Aerodynamic Activity

GSD = Geometric Standard Deviation

TABLE 5. PERCENTAGE ALVEOLAR DEPOSITION OF $^{239}PuO_2$ PARTICLES: ADULTS VERSUS NEWBORN RATS

AMAD (μ)	% Alveolar Deposition	
	Newborn	Adult
1.1	8.9	9.7
1.4	5.8	10.8
2.4	2.7	5.0
3.0	1.3	3.2

Committee II[14] for man. Cannon et al.[15] have shown that the pulmonary deposition of ^{198}Au labeled, monodispersed Fe_2O_3 aerosols in beagle dogs increases from close to zero between 4 and 7 μm to fairly high values (close to 80%) at 1 μm. There was a considerable scatter in the data points for the five dogs used in this study (Figure 10), not unlike the data Lippmann et al.[16] have obtained in similar studies with people.

TRANSLOCATION

Translocation rates, organ, and tissue distribution, and excretion in urine and feces, all of which affect dose and dose distribution, are a function of the physicochemical characteristics of the deposited material. No effects study is complete without a comprehensive study of the accumulation and elimination of the material in the various tissues of the body as a function of time, since these data enable the relevant dose and dose rate calculations to be made. There are also differences in the metabolism of given compounds between different animal species and sometimes between different strains of the same species. Other factors that have to be considered include the age or maturity of the animals at the time of exposure, the effect of dose on the translocation or redistribution mechanisms, and the possible complication of coincident exposure to other materials.

It is obviously impossible to study all possible permutations and combinations of materials, dose levels and dose distributions, and animal species. In our laboratory, we have attempted to accumulate enough information to enable us to make reasonable predictions for cases that have not been studied with supplementation as needed by data that can be gathered fairly quickly in a limited study.

Thus, long-term effect studies covering a wide range of dose levels (intended to range from a no-detectable-effect level to an as-high-as-possible effect level) have been carried out or are in progress in rats and in dogs for two isotopes of an insoluble and a relatively soluble transuranic compound, namely ^{238}Pu and ^{239}Pu dioxide and nitrate aerosols. In other studies, several other physicochemcial forms of these Pu isotopes and of higher transuranics have been administered to rats and/or hamsters, while more limited metabolism studies have been conducted in dogs for ^{239}Pu citrate,[17] $^{241}AmO_2$,[18] and $^{244}CmO_2$.[19] One study of limited duration has also been conducted on a few miniature swine exposed by inhalation to $^{239}PuO_2$.[3]

Only a few representative examples of the massive amount of data available can be given here. Figure 11 shows the tissue distribution of ^{238}Pu in rats as a function of time after inhalation of $^{238}PuO_2$, while Figure 12 presents similar data for ^{244}Cm following inhalation of $^{244}CmO_2$. Even though these two transuranic oxides were prepared in identical fashion and are considered to belong to the same class of materials (Y) by the ICRP,[20] it is clear that their metabolism in the rat is significantly different. Figure 13 presents retention of inhaled transuranic nitrates in the lungs, liver, and skeleton of rats. Even though all these materials are supposedly soluble in body fluids, there are substantial differences in their clearance rates, which are also as a function of dose level. Figure 14 compares the elimination of ^{239}Pu from the lungs of adult and newborn rats. Even though there were substantial differences in the percentage alveolar deposition, it is apparent that the clearance half-lives are identical.

Table 6 presents the most recent data available for the mean tissue distribution of ^{239}Pu in beagles after inhalation of $^{239}PuO_2$, while Table 7 presents the data for ^{238}Pu. Apart from the much higher translocation rate of ^{238}Pu to the liver and skeleton compared with ^{239}Pu, the most striking feature of this data is the difference after a couple of years of the ^{239}Pu accumulation in the liver at higher dose levels (about 6% at 21-37 months, increasing to about 22% at 53-72 months postexposure for 0.5 to 4 μCi final body burden, compared with < 1% at 25, 43, and 72 months postexposure for 0.074 μCi, 0.0056 μCi, and 0.0017 μCi). There is an apparent difference in retention of ^{239}Pu in the thoracic lymph nodes for these dogs which would be explained if impaired function of the lymph nodes permitted PuO_2 to pass on to the liver.

Prior, coincident or subsequent exposure of animals to aerosols of a different material may have a dramatic effect upon the translocation of material from the lung to other body organs and their retention in those organs. Sanders[21] (Table 8) has shown that exposure of rats to BeO 1, 30, or 60 days prior to their exposure to plutonium dioxide substantially retarded the clearance of Pu from their lungs. On the other hand, Mahlum and Allen[12] have shown that exposure of rats to condensed UO_2-PuO_2 fuel aerosols in the presence of sodium results in a considerable enhancement of Pu translocation to other tissues, particularly skeleton, compared with that occurring for the fuel aerosol alone.

TABLE 6. MEAN TISSUE DISTRIBUTION IN BEAGLES AFTER INHALATION OF $^{239}PuO_2$

Number of Dogs	Time After Exposure, Months	Final Body Burden, Range µCi	Percent of Final Body Burden					Cause of Death
			Lungs	Thoracic Lymph Nodes	Abdominal Lymph Nodes	Liver	Skeleton	
10	<6	0.011-4.8	96.9	1.9	0.01	0.05	0.11	Sacrifice
4	11-15	4.1-12.3	81	17.8	0.32	0.10	0.07	Respiratory Insufficiency
1	13	0.0007	80	15	0.20	0.04	1.6	Sacrifice
1	25	0.074	64	32	---	0.08	0.10	Sacrifice
5	21-37	0.98-3.8	65.4	26.6	0.78	6.04	0.31	Respiratory Insufficienty (1 Lung Tumor)
1	43	0.0056	55	44	0.02	0.17	0.43	Sacrifice
5	53-62	0.67-1.8	45.8	23.6	5.1	21.4	0.76	Lung Tumors
3	69-72	0.59-1.17	36.7	30.7	6.2	22.0	0.65	Lung Tumors
1	72	0.0017	51	43	0.3	0.7	0.7	Sacrifice

TABLE 7. MEAN TISSUE DISTRIBUTION IN BEAGLES AFTER INHALATION OF $^{238}PuO_2$

Number	Time After Exposure, Months	Percent of Final Body Burden				
		Lungs	Thoracic Lymph Nodes	Abdominal Lymph Nodes	Liver	Skeleton
1	0.25	97	0.03	0.02	1.7	0.16
3	1	96	0.75	0.019	0.39	0.83
3	2	89.7	6.47	0.012	0.18	0.46
3	3	89.3	6.13	0.65	0.38	1.0
3	12	51.3	16.3	0.15	10.4	17.7
1	25	19	37	0.08	14	28
3	35-42	21.7	40.0	0.27	16.3	19.7
2	48-50	18.0	30.5	3.71	20.0	23.5

TABLE 8. EFFECT OF BeO DEPOSITION AND CLEARANCE OF PuO_2 INHALED BY RATS

Treatment	Amount of $^{239}PuO_2$ (nCi) Initial Alveolar Deposition	Retained in Lung 30 Days	Total Body Burden 30 Days	Alveolar Deposition Cleared in 30 Days
PuO_2 Only	20	11	12	48
PuO_2 Given 1 Day After BeO	25	18	19	26
PuO_2 Only	30	16	17	50
PuO_2 Given 30 Days After BeO	29	18	19	34
PuO_2 Only	32	16	17	46
PuO_2 Given 60 Days After BeO	38	25	26	30

The effect of animal species may be seen by comparing the tissue distribution of ^{241}Am (Figure 15) and ^{244}Cm (Figure 16) in beagles after inhalation of the respective dioxides of these isotopes, with the data for ^{244}Cm in rats (Figure 12). The general trend of the data for ^{241}Am and ^{244}Cm in rats is similar.[22] The most striking difference between the dog and the rat is in the accumulation of transuranics in the liver. In the dog, transuranics continue to accumulate in the liver throughout the period of the study (810 days) whereas in rats the liver content first rises and then falls rapidly.

In summary, we can say that clearance half-times from the lung increase as particle size increases and decrease as the dissolution rate in body fluids decreases. This occurs with different chemical forms of one isotope (such as chloride to citrate to fluoride to nitrate to oxide), or for the same chemical form of different isotopes or elements (such as einsteinium-253 to curium-244 to americium-241 to plutonium-238 to plutonium-239). Lung clearance rates also change as we go from one animal species to another (e.g., decreasing from dogs to rats to mice, with available evidence suggesting that clearance rates for men might be somewhere between those observed for rats and dogs).

That fraction of deposited transuranic particles that is solubilized, or otherwise rendered capable of being translocated from the deposition site by mechanisms other than mechanical clearance, is accumulated primarily in the liver and bone in rodents and dogs, while considerable quantities find their way to the pulmonary lymph nodes of dogs. As seen in Figures 15 and 16, both Am and Cm continue to accumulate in the liver of the exposed dogs for the duration of the experiments. This is in contrast to the behavior of these isotopes in rats, in which there is a transient increase in liver concentration followed by a decrease. On the other hand, accumulation of transuranics in the skeleton seems to be about the same for both rat and dog.

For the more soluble materials, there is some indication of retention in other soft tissues, such as the muscle. There is no evidence of increasing accumulation of transuranic materials in the gonads of dogs. After the first few postexposure days, most of the elimination from the body was via the feces rather than the urine. This is presumably due to transport from the liver through the bile duct to the G.I. tract. The total body clearance of these transuranic materials (^{241}Am and ^{244}Cm, deposited following inhalation of dioxides) was rather slow, less than 25% of the total initial deposition being excreted over the 27 months of the two studies.

The various studies summarized in this section have provided a wide variety of spatial and temporal dose distribution patterns in the lung in both rats and dogs. Translocation rates to other tissues and to the excreta seem to depend more upon the material involved than on its chemical form, a factor which complicates the studies to define the role of particle size. For some transuranics, indications are that the smaller the particle size, the more rapid the clearance

from the lung. On the other hand, the data presented in Table 6 indicates that the redistribution of transuranics in the body may be altered by the quantity of material (and, therefore, the dose) accumulated in certain organs.

EFFECTS

The biological effects of inhaled transuranics depend upon the quantity and distribution of deposited material and its specific activity and clearance from different organs, i.e., parameters that determine dose and dose rate. The higher dose and dose rates produce acute or subacute inflammatory changes frequently causing death of animals, whereas the lower dose levels may allow the animal to live long enough to develop tumors. The most pronounced effects are observed in the lung since that organ usually receives the most severe dose and dose rate. Since transuranics are generally "bone-seeking" elements, primarily the soluble physicochemical forms, bone tumors are frequently produced. The thoracic lymph nodes can concentrate a considerable amount of transuranics as the particles are filtered out of the lungs, with resultant severe injury.

Pulmonary edema and radiation pneumonitis are the main causes of acute death in animals with cumulative radiation doses to the lung of the order of ten thousand rads or more. The higher the dose, the more severe the response and the earlier the death of the animals. Stuart et al.[23] observed acute deaths in rats exposed to millicurie quantities of ^{238}Pu and ^{239}Pu dioxides as early as a week postexposure. Dogs with initial alveolar burdens in the range 200 μCi to 20 μCi of $^{238}PuO_2$ died from 1 to 6 months postexposure.[24] Cumulative radiation doses of more than a few thousand rads to the lung, cause death of rats 50 to 250 days postexposure (Table 9) and of dogs 1 to 3 years postexposure[25] from pulmonary fibrosis and respiratory insufficiency (Figure 17).

TABLE 9. LIFE SHORTENING EFFECTS OF INHALED Pu NITRATE

Initial Lung Burden (nCi)	Average Lung Dose (Rads)	Average Survival Time (Days)	% of Control Survival
^{239}Pu			
0.058	0.3	697	102
1.246	7	642	94
2.166	10	651	95
2.427	10	662	97
78.2	600	642	94
142.	900	609	89
919.	4500	175	26
Control	----	685	---

The most significant long-term effect of inhaled transuranic compounds in the lungs of animals is the development of lung tumors. In addition to the biological sensitivity of the tissues involved, the dose-effect relationships for the various transuranic isotopes and compounds that have been studied following inhalation are a reflection of the differing degrees and rates of translocation from the lung and/or respiratory tree to other organs and tissues. Table 10 summarizes the tumors that have been seen in the rodent inhalation studies that have been completed at PNL. It is of particular interest to note that there is a clear difference in species susceptibility to high LET radiation induced tumors. While a substantial number of lung tumors were observed in rats for most of the compounds, only one or two were observed in hamsters.[27]

Sanders[10] has shown that the lung tumor incidence in rats is proportional to the quantity of material deposited. Although the first tumor did not appear until nearly a year postexposure, the occurrence was clearly related to quantity deposited (p. 354)[10] providing the dose is not high enough to cause death from radiation pneumonitis. The incidence of lung tumors in rats as a function of mean radiation dose is shown in Figure 20 for $^{238}PuO_2$, $^{239}PuO_2$, and $^{244}CmO_2$[28] while

Figure 21 shows tumor incidence in the lungs of rats after inhalation of soluble compounds.[29] A few lung tumors have been found in rats following inhalation exposure to the dioxide or the nitrate of plutonium at radiation doses roughly estimated to be less than 10 rads, although the peak incidence of 30 to 80 percent does not occur below doses of 100 to 1000 rad.

TABLE 10. TUMORS OBSERVED DURING LIFE SPAN STUDIES IN RODENTS

Actinide	Initial Alveolar Deposition, nCi (Range)	Number of Animals	Number of Tumors	
			Lung	Bone
	RAT			
$^{238}Pu(NO_3)_4$	0.02-1510	301	43	13
$^{239}Pu(NO_3)_4$	0.06-919	378	49	3
$^{238}PuO_2$	0.14-890	344	33	0
$^{239}PuO_2$	0.18-180	343	56	0
"Aged" $^{238}PuO_2$	5.5-64	54	4	2
Air-Oxidized $^{239}PuO_2$	9.5-540	77	12	0
$^{244}CmO_2$	0.4-1600	294	23	12
$^{253}Es(NO_3)_3$	4-1000	180	21	5
$^{241}AmO_2$	0.1-1000*	390	Study in Progress	
$^{239}PuO_2$ + Beryllium Oxide**	3.8-76	383	38	0
	HAMSTER			
$^{238}PuO_2$	5-205	208	1	0
$^{239}PuO_2$	3-200	240	2	0

* Exposures just completed (radioanalyses not completed); values are estimates. All other studies have been completed and all rodents necropsied.

** 0.9 μg to 91 μg Beryllium given by inhalation prior to inhalation of $^{239}PuO_2$.

Rats develop lung tumors earlier than dogs; hamsters rarely develop tumors at any dose.[27] Lung tumors have been observed in rats dying as early as 1 to 2 years postexposure[30] while the earliest tumors seen in dogs did not appear until 3 to 4 years postexposure. The incidence of lung tumors in dogs at radiation doses of greater than 1000 rads is higher than in rodents. Concentration of the alpha dose into fewer but "hotter" particles decreases the lung tumor incidence.[26] The main type of lung tumor in both dog and the rat is the bronchioloalveolar carcinoma (adenocarcinoma). Tumor type in rats has been described by Sanders and Dagle[31] and is a function of radiation dose and dose-distribution at high doses.

Bone ranks next to lung as the tissue developing the most tumors following transuranic inhalation exposure. Osteosarcomas are seen at poorly estimated radiation doses as low as a few rads in rats. Maximum incidences of bone tumors in rats are about 20%; in dogs, the incidence is more than 50% at radiation doses to bone of from 100 rads to 1000 rads. However, bone tumors are seen only after inhalation of soluble transuranics which are translocated from the lung to bone (e.g., ^{238}Pu after inhalation of $^{238}PuO_2$, but not ^{239}Pu after inhalation of $^{239}PuO_2$).

Highly insoluble transuranic compounds like high-fired plutonium-239 dioxide are accumulated in the thoracic lymph nodes in high enough concentrations for the resulting radiation to totally destroy some of these nodes. Another subacute effect observed in dogs, but not in rats is a persistent dose-related lymphocytopenia. This is observed following exposure to both $^{238}PuO_2$ (Figure 18) and $^{239}PuO_2$ (Figure 19), but not following exposure to the soluble transuranic oxides of ^{241}Am and ^{244}Cm. Both the time of onset of lymphocytopenia and the degree of severity are a function of the initial alveolar burden. Only a transient lymphocytopenia was observed in rats, irrespective of the compound to which they were exposed.

The significance of this functional destruction of thoracic lymph nodes in dogs is not known. Although primary cancer of lymphatic tissue has not occurred in these dogs, at least in dogs "one cannot rule out the possibility of a relationship between the reduction of circulating lymphocytes, lymph node pathology, decreased immunological competence, and the pathogenesis of transuranic-induced cancer" (p. 184).[26]

ACKNOWLEDGEMENTS

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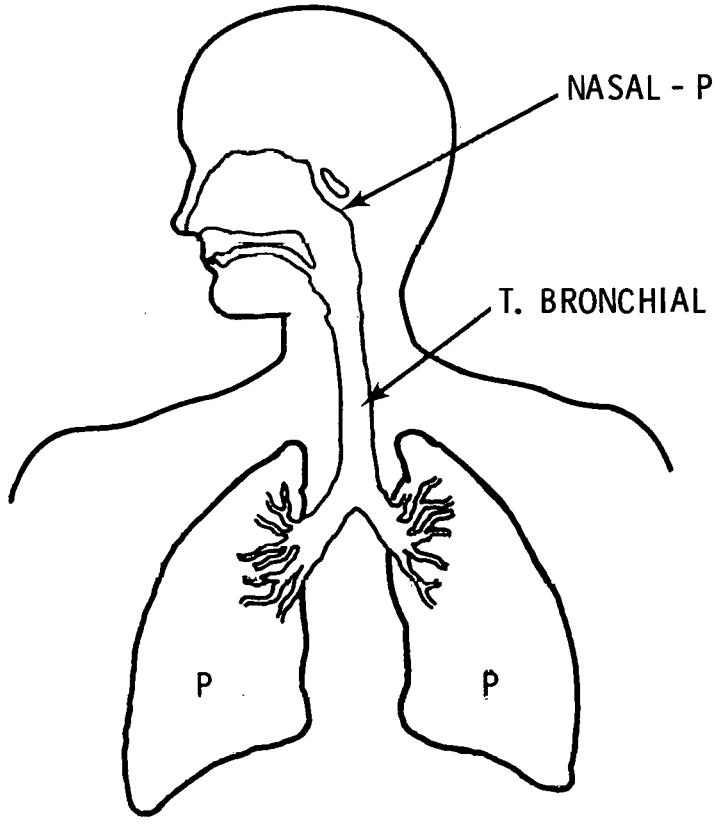
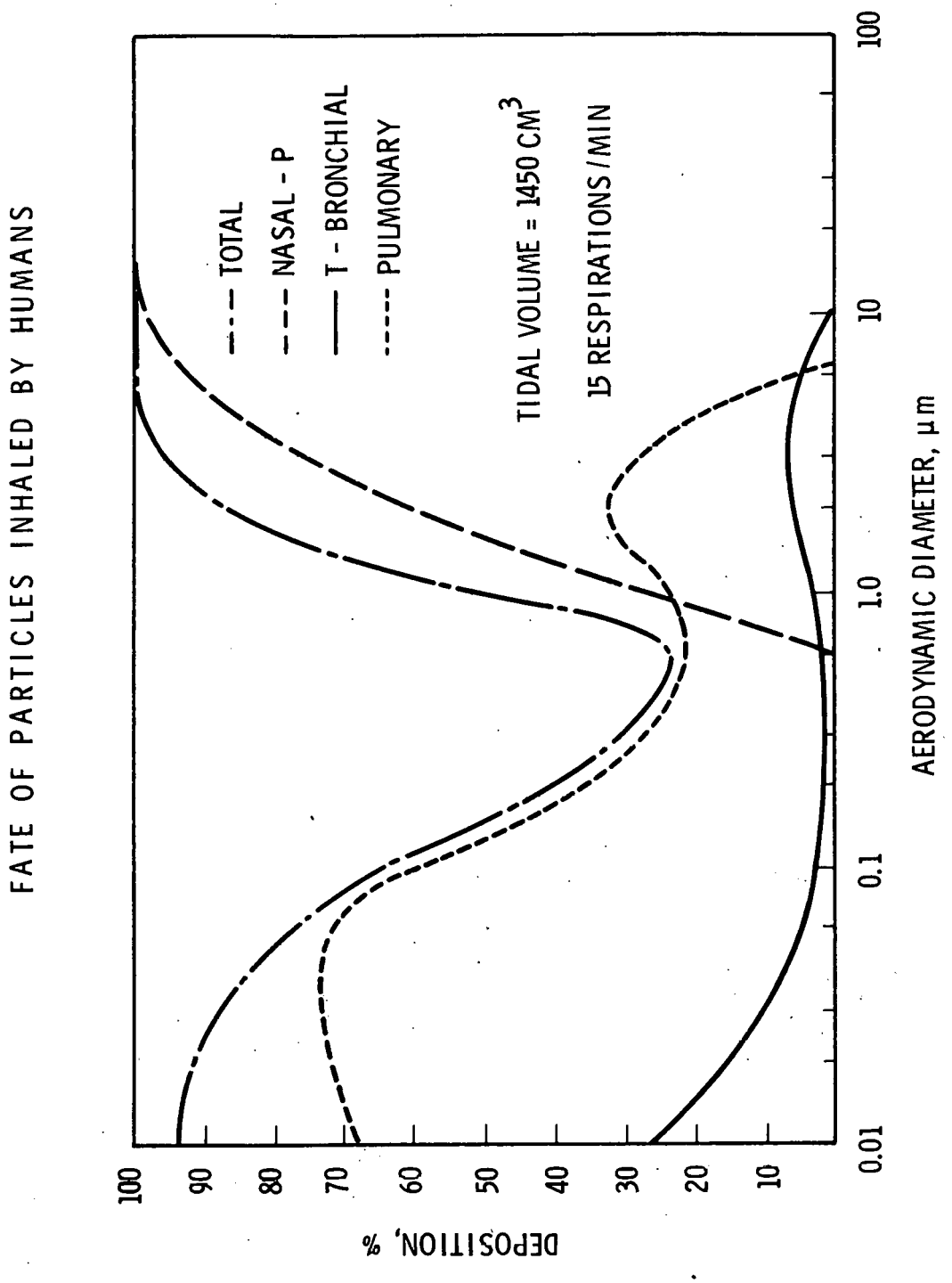


P = PULMONARY REGION

Figure 1. Schematic of human respiratory tract.



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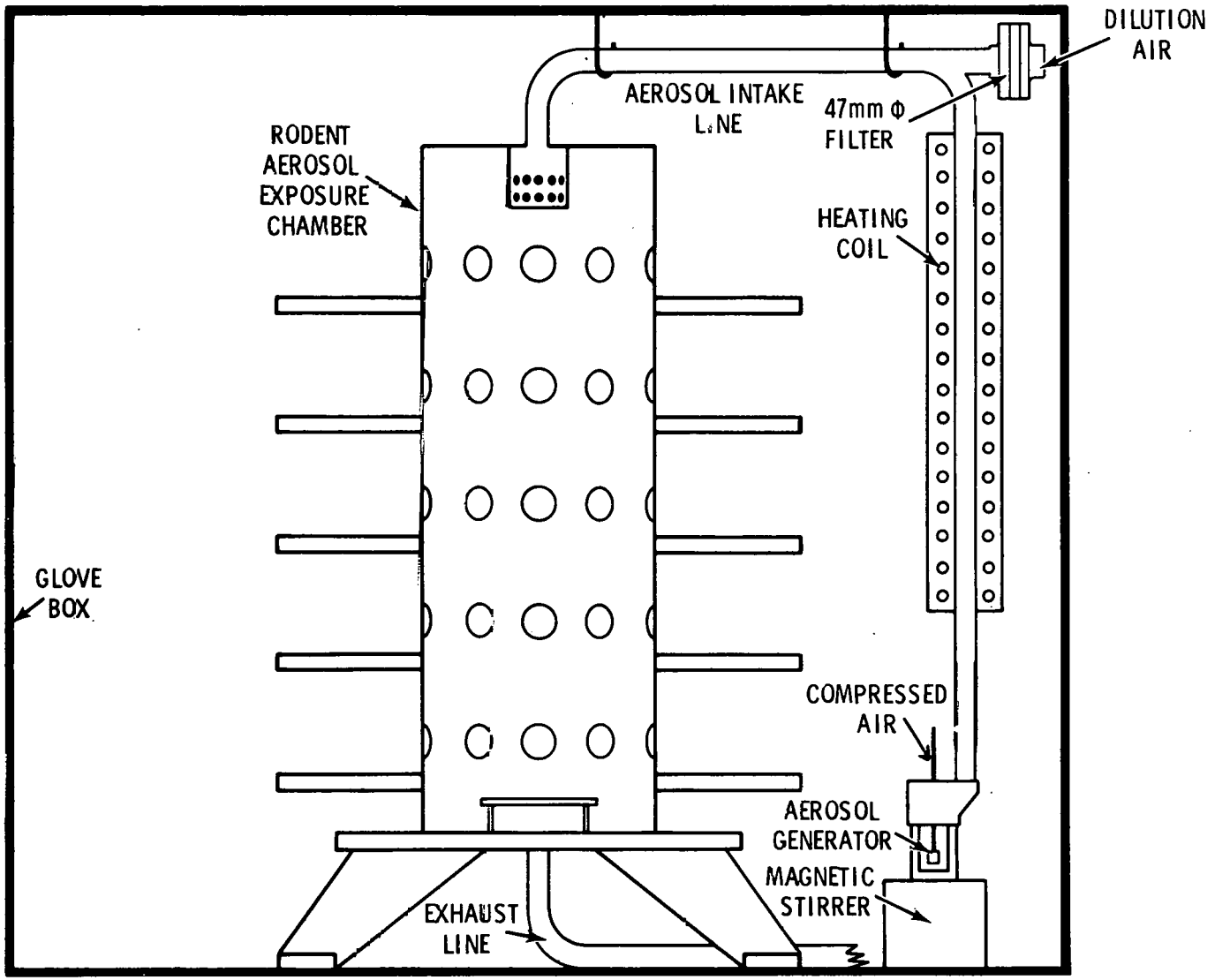
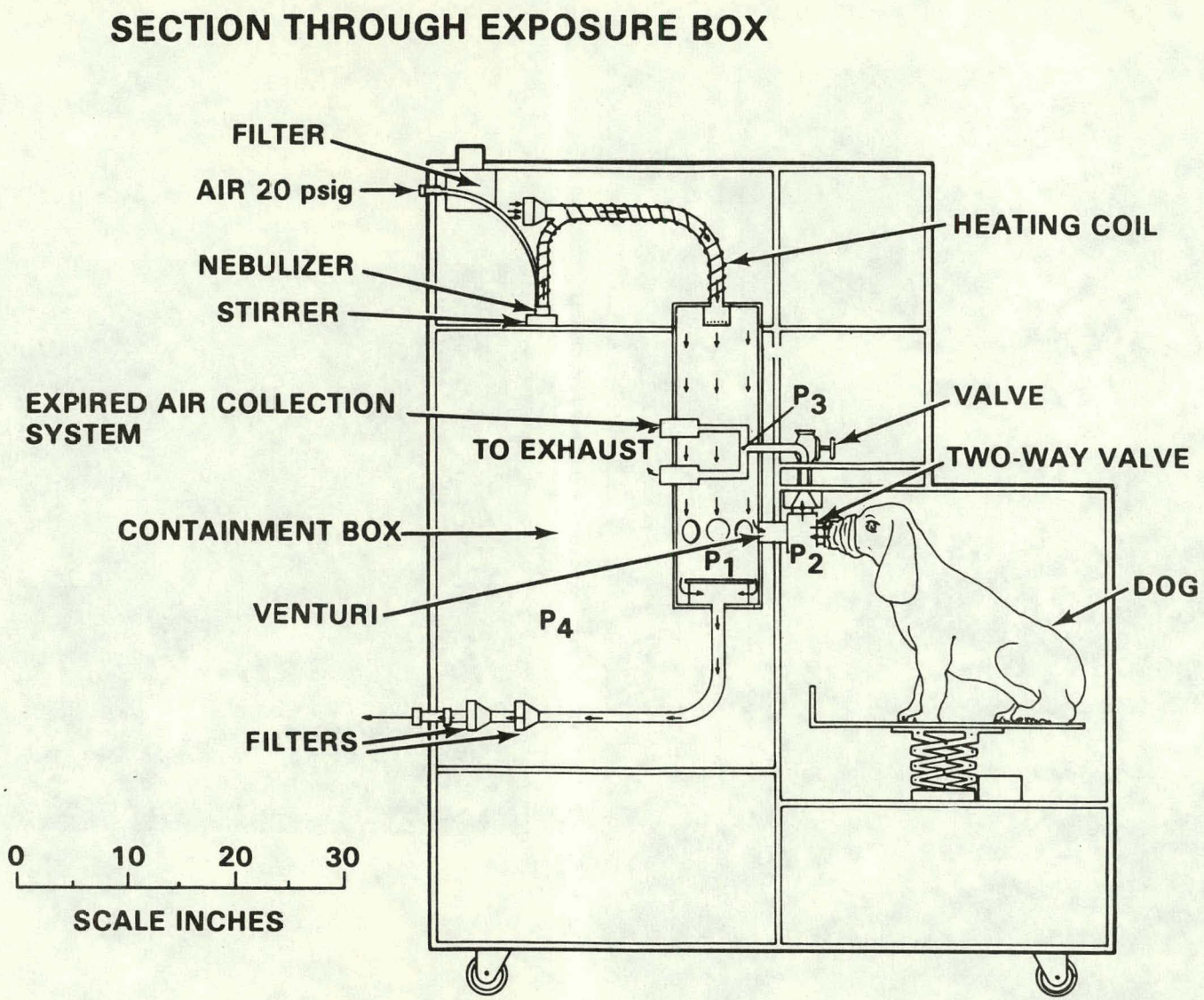


Figure 3. Schematic of rodent nose-only exposure system.



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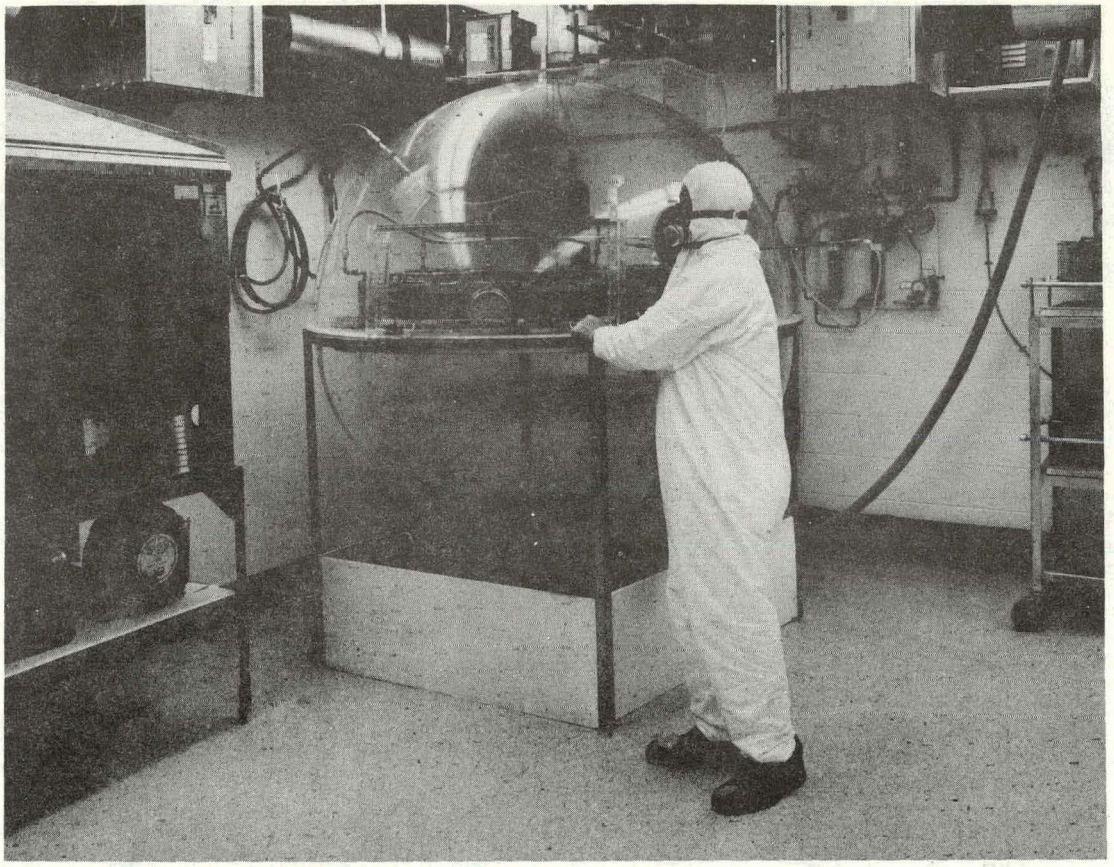

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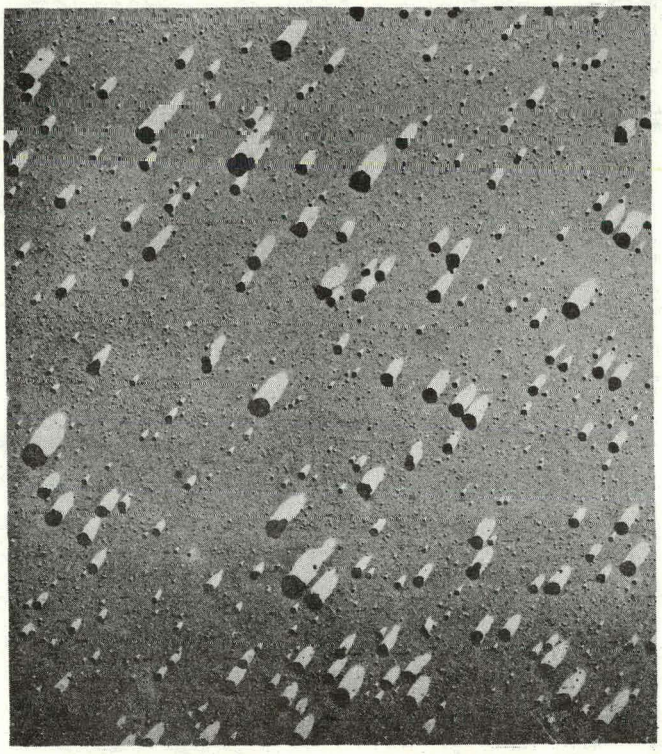

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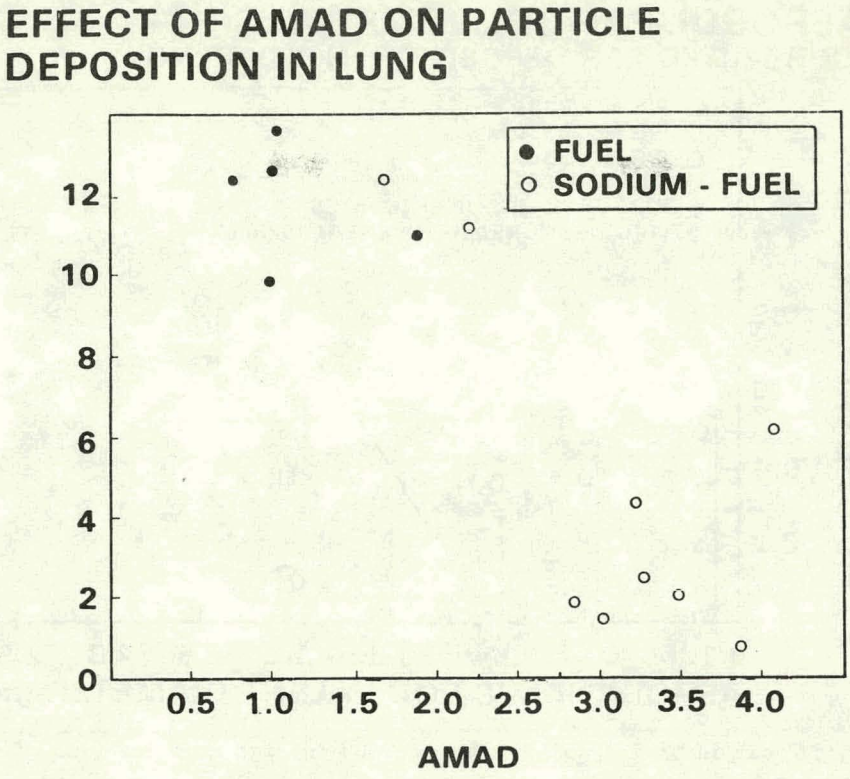

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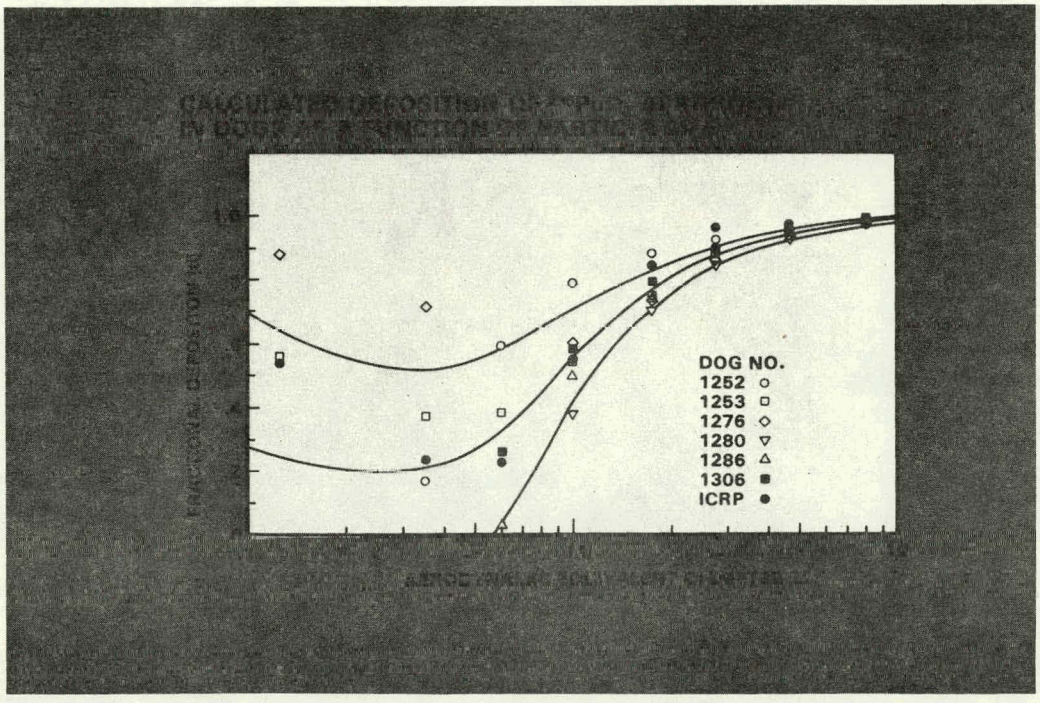

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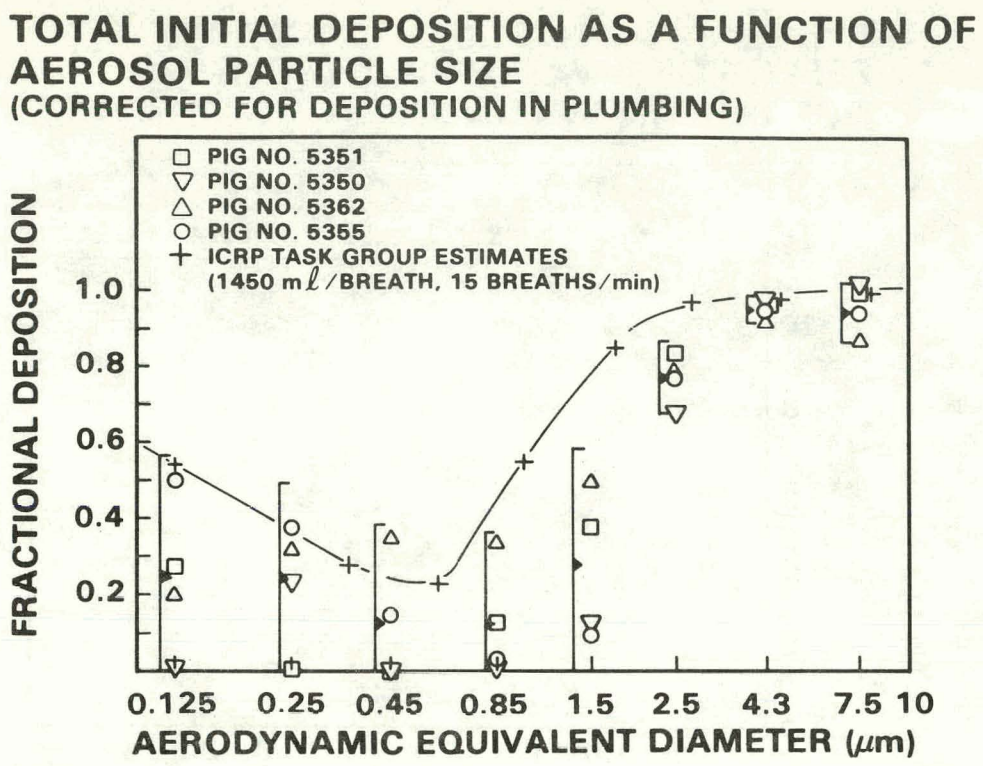

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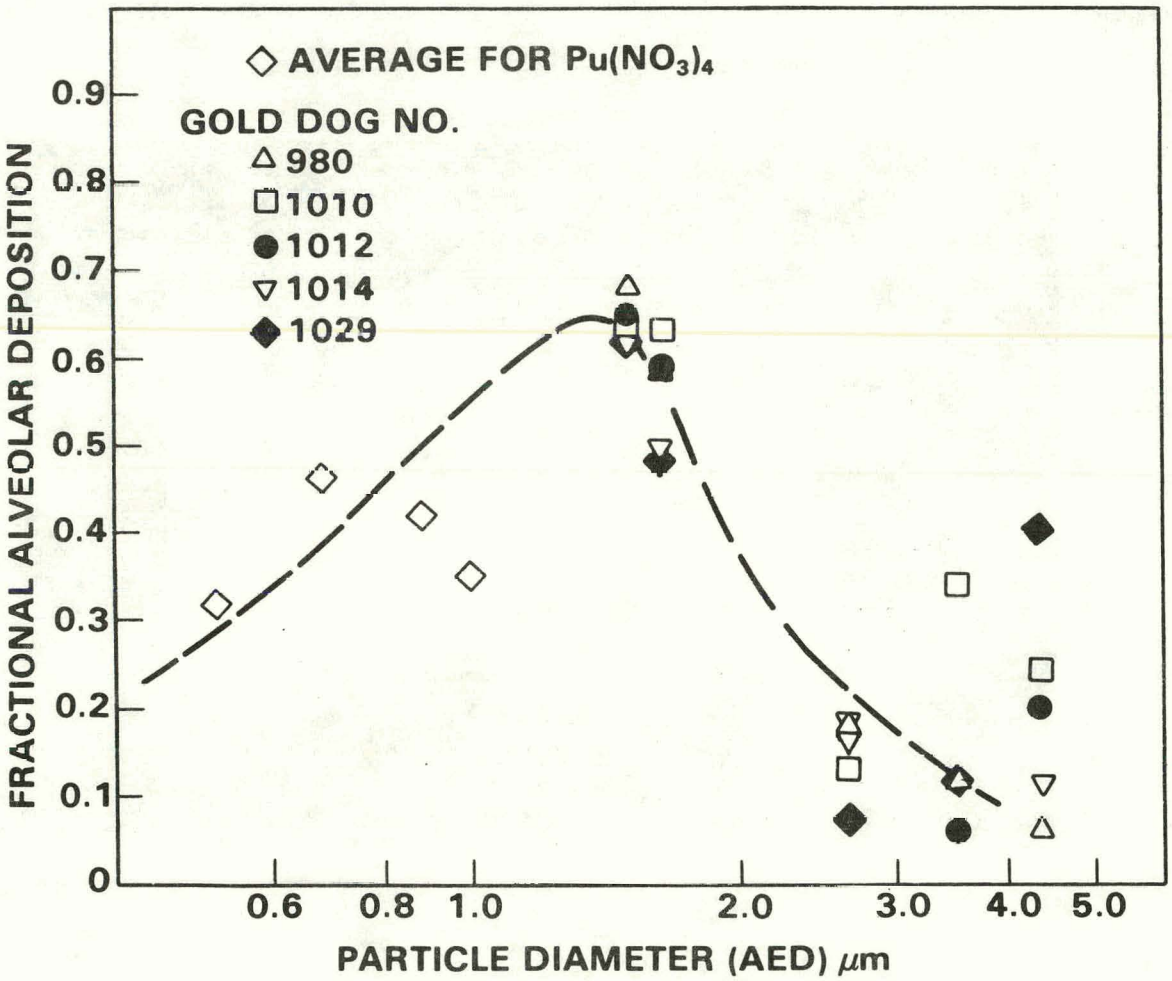

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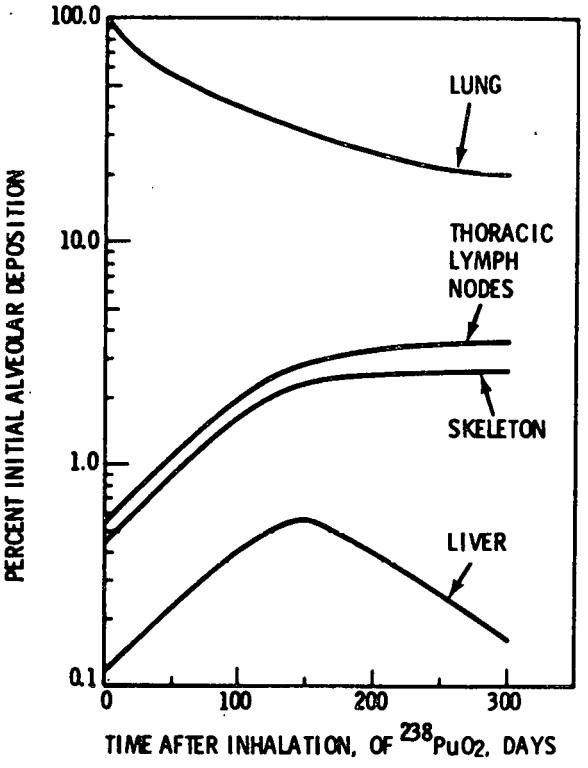
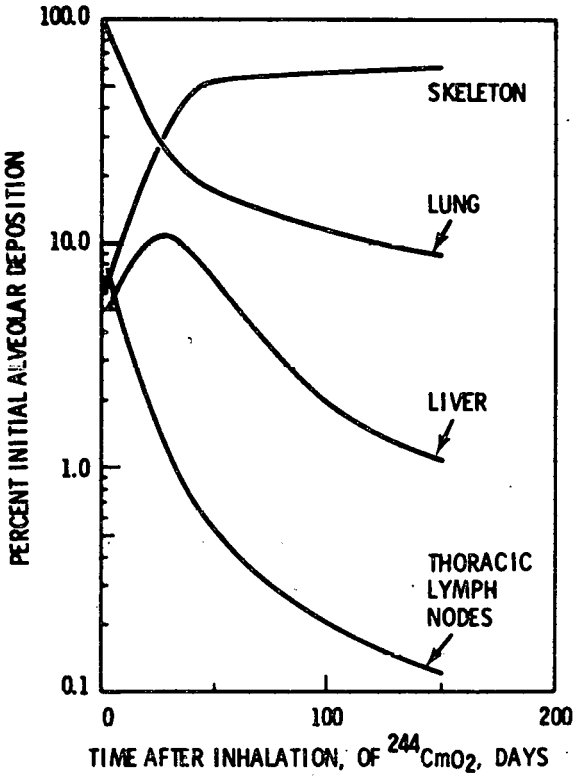


Figure 11. Tissue distribution of ^{238}Pu in rats as a function of time after inhalation of $^{238}PuO_2$.



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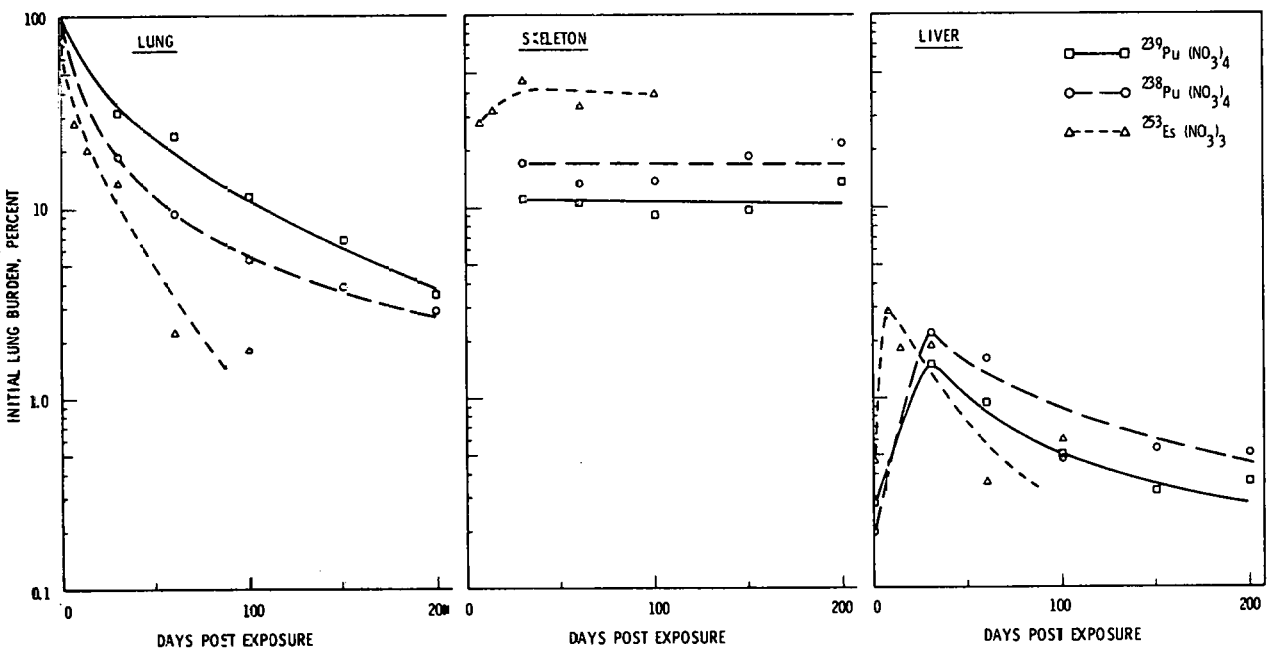

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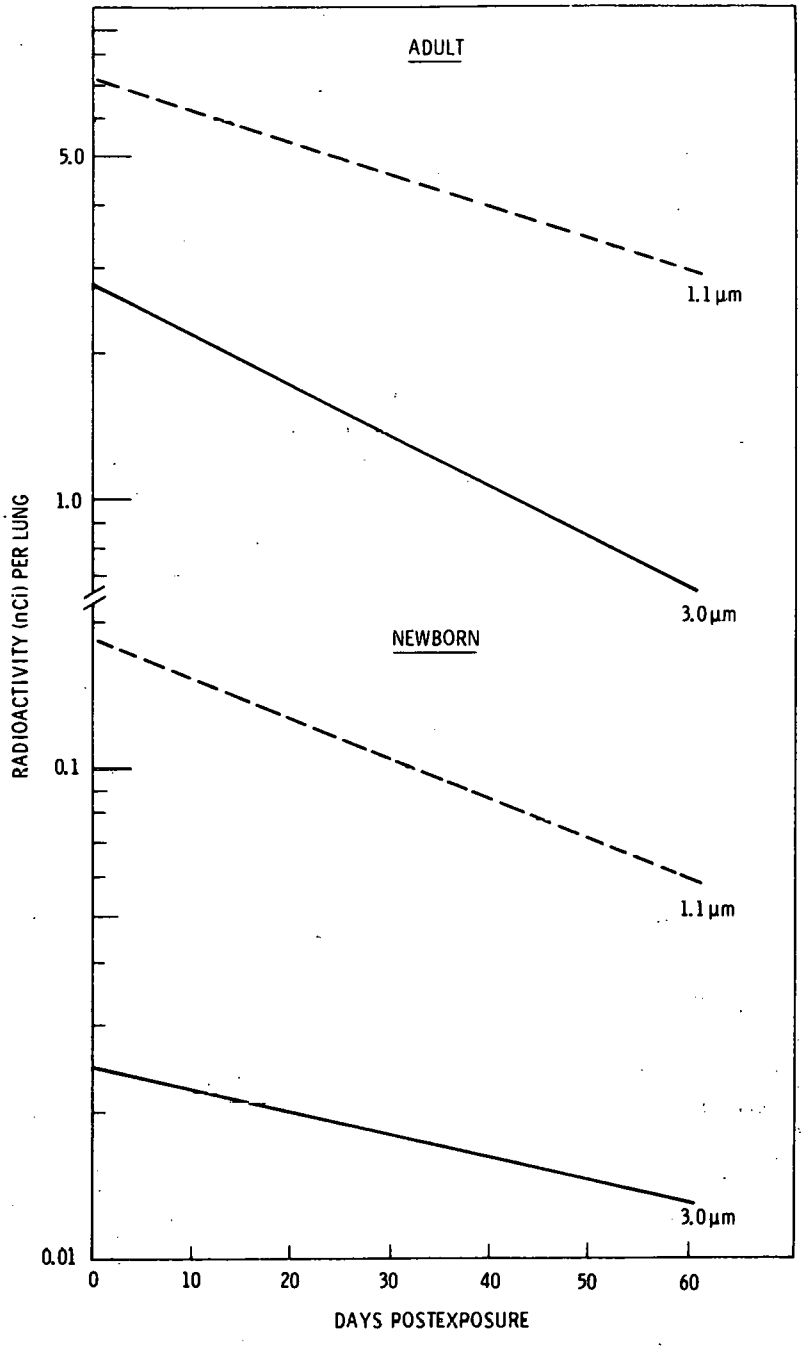

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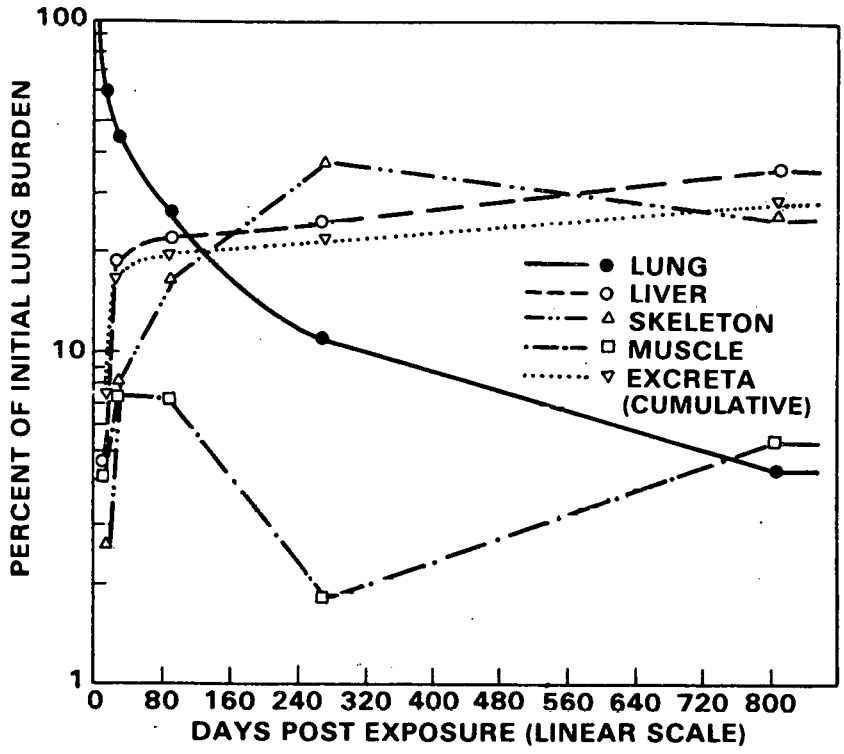


Figure 15. ^{241}Am distribution in beagles as a function of initial lung burden.

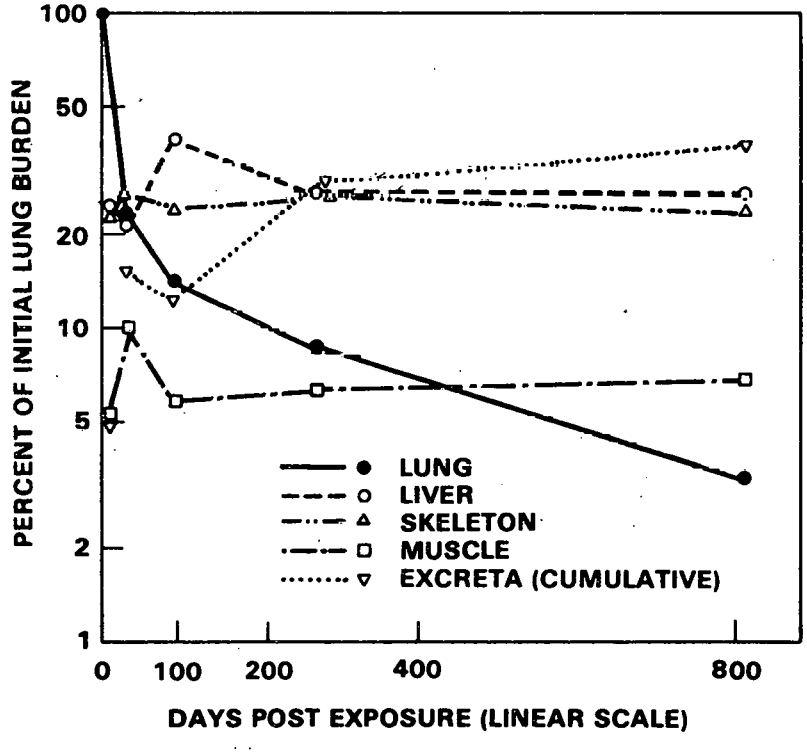


Figure 16. ^{244}Cm distribution in beagles as a function of initial lung burdens.

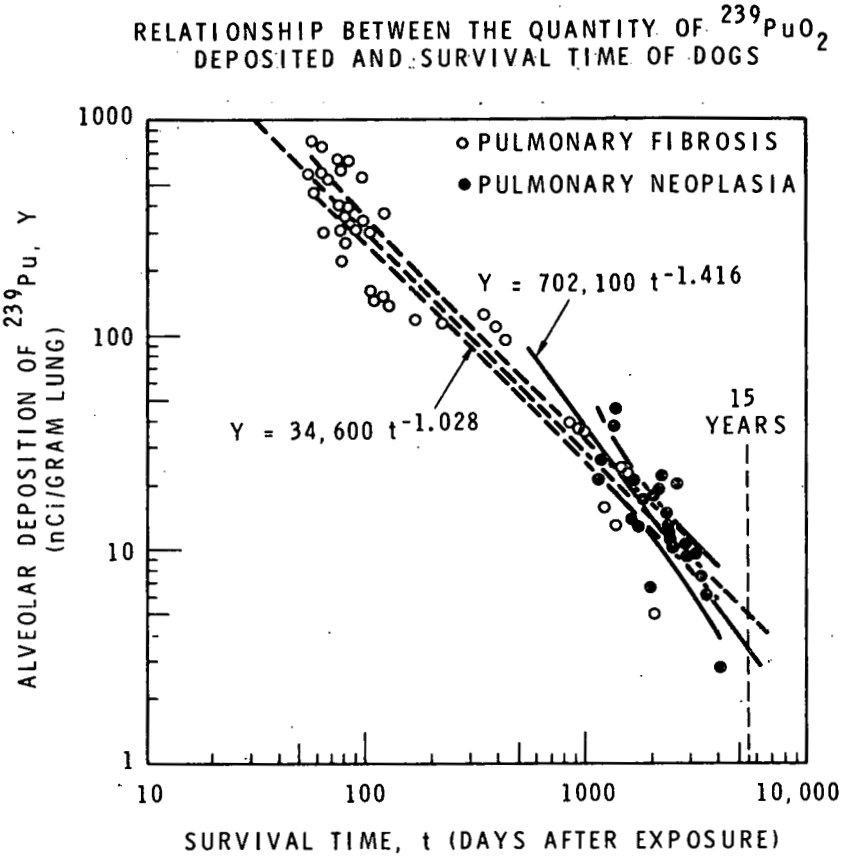


Figure 17. Relationship between quantity of $^{239}PuO_2$ deposited and survival time of dogs.

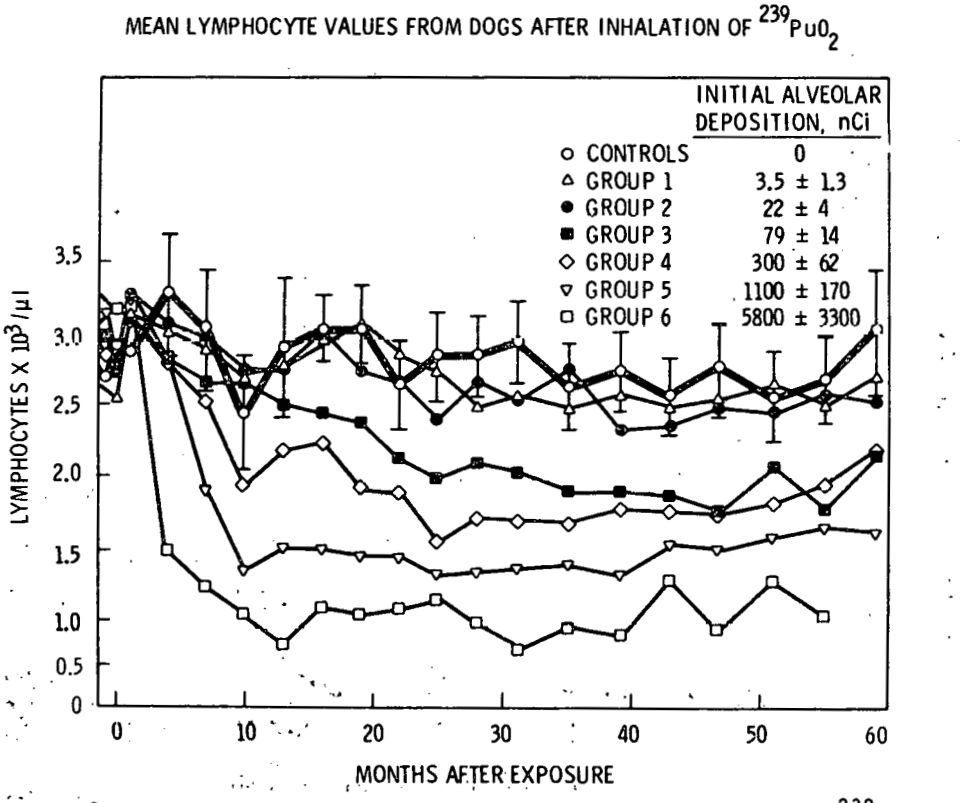
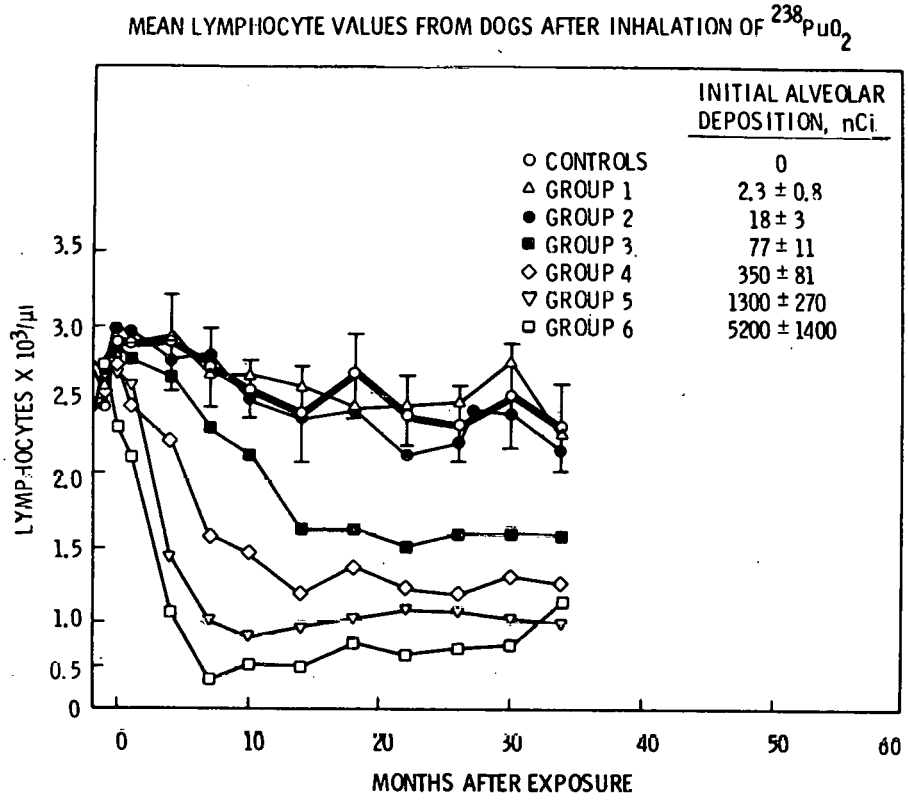


Figure 18. Mean lymphocyte values from dogs after inhalation of $^{239}PuO_2$.



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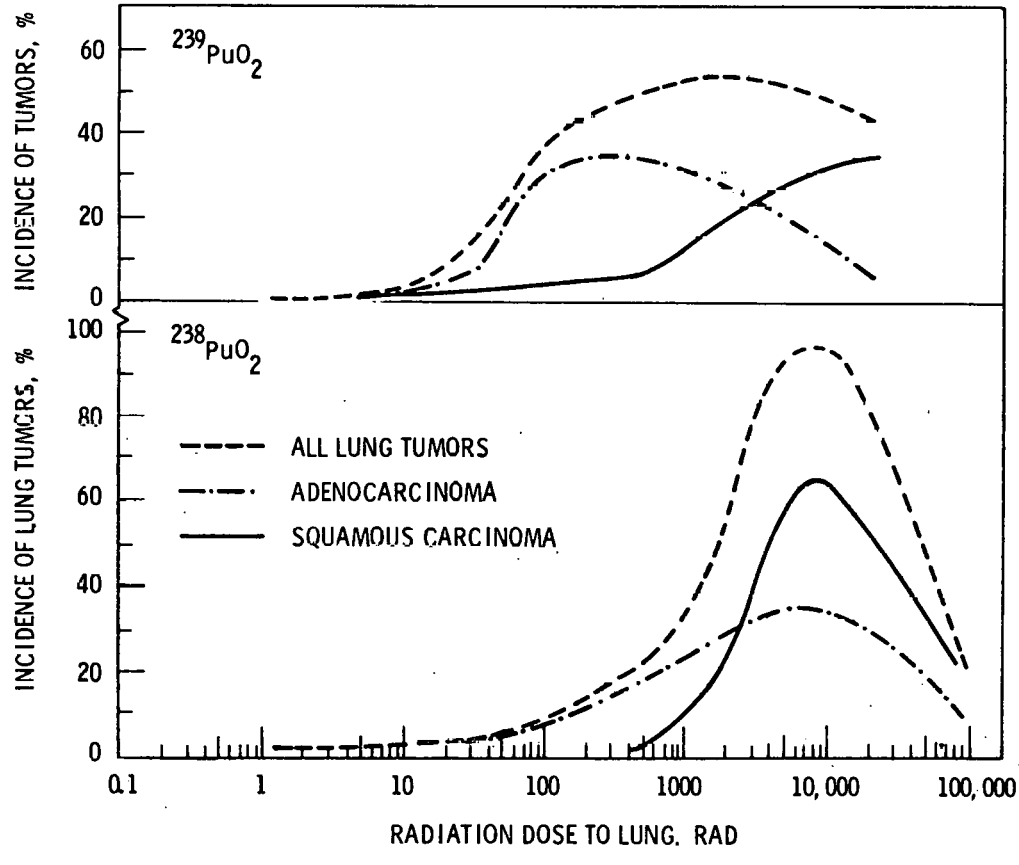

Figure 20. Incidence of lung tumors in rats as a function of mean radiation dose.

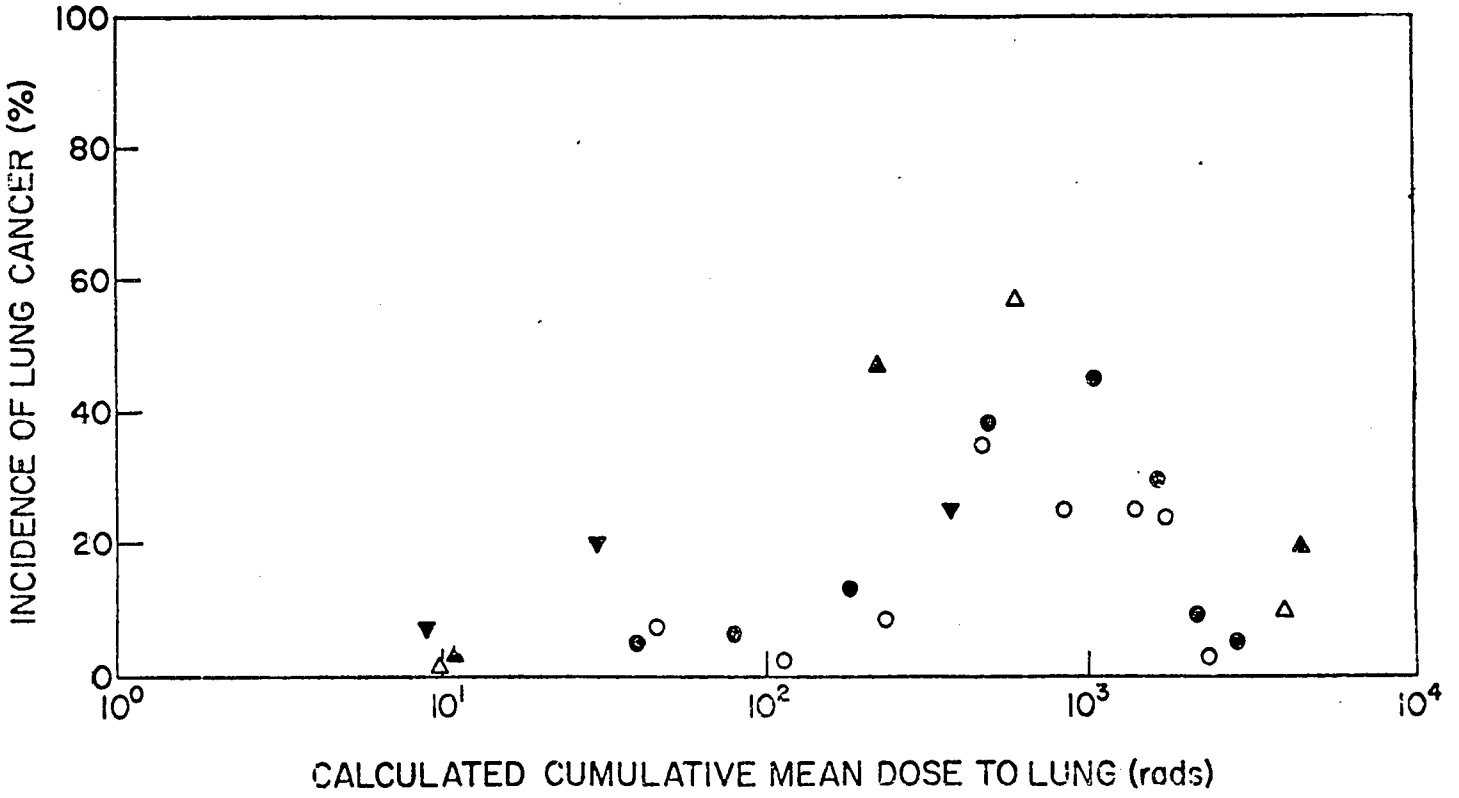

FIGURE 21. Lung cancer in rats after inhalation of soluble plutonium compound as a function of total lung dose.

- ○ ^{239}Pu citrate
- ● ^{239}Plutonyl pentacarbonate
- △ ^{239}Pu nitrate
- ▲ ^{238}Pu nitrate
- ▽ ^{238}Pu - "soluble"