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THE BIOLOGICAL EFFECTS OF TRANSURANIUM ELEMENTS IN EXPERIMENTAL ANIMALS

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The Biological Effects of Transuranium Elements in Experimental Animals

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INTRODUCTION

The toxicity of plutonium has been of concern since milligram quantities were first produced in the Oak Ridge reactor starting in late 1943. In 1944 milligram quantities were allocated for biomedical studies. In 1947 and 1948 the first biological experiments were completed with americium and curium. Since then, biological research has been in progress at several laboratories in the United States and abroad. Most of the reseach effort has been directed towards the compounds of the most common isotope of plutonium, ^{239}Pu. Within the past 10 years as the concept of plutonium recycle and the fast breeder program developed, recognition of the potentially increasing abundance of the transplutonium elements has led to expanded biomedical research on neptunium, plutonium, americium, curium, californium, berkelium, and einstinium.

The purpose of these animal experiments is to enable us to predict the health consequences of transuranium elements in man. These studies have considered two different kinds of contamination events. One of these, occupational exposures to transuranics released into the work environment, involves relatively small numbers of people. Such exposures can be

simulated reasonably well in the laboratory with the expectation of observing unmistakable effects in statistically significant numbers of animals. The second kind of contaminating event of concern is the exposure of large populations to very low levels of the transuranium elements. Such low level exposures cannot be directly simulated in the laboratory because exceedingly large numbers of experimental animals are required to yield meaningful results. Therefore, an understanding of the mechanisms of the biological action of low levels of transuranics is required to predict what cannot be measured in the laboratory.

An overriding concern of all the animal experimentation is the confidence with which the results can be extrapolated to man. While sophisticated experiments can be performed with rodents, dogs, cats, swine, and primates, questions regarding the applicability of the results to man will be settled only as data from human exposure cases become available.

The major health effects of the transuranic elements are due to their emission of alpha radiation and the nature of the effects depends upon which tissues are irradiated. This is determined by the disposition of these radioactive elements in the body which in turn is determined by their chemical and physical properties and their route of entry into the body. Thus, in this presentation, I will review in

a general way the absorption of the transuranic elements into, and the distribution within the body following ingestion, deposition on skin, and inhalation. Then I will summarize the biological effects which have been observed in experimental animals, in particular the late effects resulting from relatively low level radiation exposures. The emphasis will be on plutonium because it is the transuranic element we know most about.

Much of the information included in this presentation has appeared in several recent reviews.

DISPOSITION OF TRANSURANICS IN THE BODY

Transuranium elements released to the environment may reach man through three pathways. Transuranics which become incorporated into foodstuffs may be ingested and absorbed from the gastrointestinal tract, while those dispersed in air may be either deposited on the skin and absorbed, or inhaled and deposited in the respiratory tract. Occupational exposures may include entry through a wound.

ABSORPTION FROM THE GASTROINTESTINAL TRACT

Experiments confirm that most transuranic element compounds are not readily absorbed from the gastrointestinal

tract. The first slide gives values for the gastrointestinal tract absorption of uranium and several transuranic elements in newborn rats and adults. In rats, neptunium nitrate was most readily absorbed, nearly 1 percent. The least absorbed was PuO_2, 0.0001 percent. Gastrointestinal tract absorption was one or two orders of magnitude greater in the newborn rat than in the adult. Americium, curium, berkelium, and einstinium show at least a 10-fold greater absorption than plutonium.

ABSORPTION THROUGH INTACT SKIN

Although percutaneous absorption of all available transuranic elements has not been thoroughly studied, results from experiments with plutonium indicate that absorption through intact skin is a relatively minor route of entry into the body, Slide 2. The highest 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 einstinium, the only other transuranium for which data are available, was absorbed over a period of 7 days through rat skin. Results from animal experiments and human contamination incidents indicate the intact skin to be an effective barrier to the entry of plutonium and einstinium, and probably the other transuranium elements.

RETENTION AND TRANSLOCATION FROM LUNG

Airborne transuranic particles are similar to most other particles when they are inhaled in that deposition in the respiratory tract is primarily dependent upon the physical properties of the particles and the respiratory characteristics of the individual inhaling the particles.

Clearance From Lung

Animal experiments and limited human data provide a range of values for the retention half-times of several plutonium compounds. These are summarized in the next slide for ^{238}Pu and ^{239}Pu. The retention half-times for organic complexes of plutonium, plutonium nitrate and fluoride range from less than 100 days to about 300 days in rats and dogs. The retention half-times for PuO_2 are substantially longer, ranging from 200 to 500 days in rats, 300 to 1000 days in dogs, and 250 to 300 days in human beings. The wide range of values for dogs is largely due to extensive experimentation with a variety of plutonium oxides with different particle size characteristics. The relatively low retention values for human beings, compared with dogs, suggests either that man clears plutonium particles from his lungs more rapidly than do dogs or that the materials inhaled in the human accident cases were more soluble than plutonium dioxide.

Studies with $^{238}PuO_2$ in dogs indicate a much shorter lung retention time than is observed for $^{239}PuO_2$. This appears to be due to instability of $^{238}PuO_2$ particles, possibly caused by radiolysis in tissue fluids.

Pulmonary retentions of inhaled transuranic compounds have been compared in rats and dogs. In rats, both ^{241}Am and ^{242}Cm nitrates were cleared much more rapidly than ^{238}Pu and ^{239}Pu nitrates. Autoradiograms from this study indicated ^{241}Am and ^{242}Cm to be dispersed much more throughout the lung than ^{238}Pu and ^{239}Pu. In another experiment the rate of clearance of intratracheally instilled einstinium chloride was found to be much like that reported for ^{242}Cm nitrate.

The retention rates of several inhaled transuranics in beagle dogs, Slide 5, compare favorably with the results from rat experiments. Plutonium oxide, nitrate and fluoride were retained in the lung much longer than curium and americium oxides.

Spatial Distribution of Transuranics Within Lung

From the moment transuranic elements are deposited in the respiratory tract, biological and physical forces are at work to cause their removal. Thus, it is difficult to visualize plutonium and the other transuranics remaining

static throughout their residence time in lung. It is not possible to document the course of individual particles and aggregates of particles in lung. However, the temporal and spatial characteristics of radioactive particles within tissues can be inferred from autoradiographs of tissue sections prepared from animals exposed to radioactive aerosols.

The first observation is that radionuclides are nonuniformly deposited throughout lung. Further, the radionuclides may deposit unequally among the lung lobes or among portions of lung lobes. Studies of inhaled plutonium and einstinium nitrates show that immediately following the inhalation exposure, the radionuclide is present in both particulate and nonparticulate forms. Autoradiographs prepared from dogs exposed to inhaled $^{239}PuO_2$ show an initial relatively diffuse distribution of particulate plutonium throughout the entire lung.

A fraction of the amount of transuranics deposited in the lung may be dissolved and absorbed into the blood. The remaining transuranic particles and aggregates may be engulfed by macrophages. The alveolar macrophage appears to be capable of transporting transuranic particles and aggregates from the alveoli to the ciliated epithelium lining the bronchioles for removal from the lung in the mucous blanket.

Both soluble and insoluble transuranics not immediately cleared from the lung tend to become further aggregated. This mobility and aggregation of transuranics may have large effects on the temporal and spatial distribution of the alpha radiation dose. For example, a few days after inhalation of plutonium nitrate and other relatively soluble compounds, single tracks in autoradiographs decrease and after several weeks nearly all of the radioactive material appears to be aggregated. The next slide shows aggregation of ^{238}Pu in rat lung 100 days after inhalation of $^{238}Pu(NO_3)_4$. Curium tends to aggregate less than plutonium.

Particles of transuranium elements are transported via lymphatic vessels in the lung and collected in the thoracic lymph nodes. Autoradiographs of lung tissues taken from dogs several weeks and months after inhalation of PuO_2 show alpha stars concentrated in subpleural areas, apparently in lymphatic vessels, Slide 7. Autoradiographs also suggest that radioactive particles become immobilized in scar tissue in subpleural areas. The next slide is an example of a $^{238}PuO_2$ particle located in scar tissue of a dog 5 years after exposure. Areas around the scar tissue appeared to be normal.

Radioactive particles transported to lymph nodes eventually appear sequestered in "hot spots" of scar tissue and do not

appear to be mobile. The residence time for plutonium in lymph nodes appears to be very long.

There is ample evidence that transuranic particles deposited in lung are subjected to biological and physical forces. This argues against either particles or aggregates of transuranium elements remaining static indefinitely, except for that which becomes immobilized in scar tissue. To the contrary, while the rates may be low, movement of transuranic particles within lung tissue by several mechanisms certainly occurs as the lung attempts to expel the radioactive particles and other foreign material which may have been inhaled. The migration of deposited radioactive particles in lung partially compensates for the nonuniformity of the radiation exposure from the particles.

Translocation From Lung to Other Tissues

The relative distribution among body tissues of the transuranics translocated from lung by the circulating blood is essentially the same for all transuranic compounds, but may differ quantitatively depending upon the chemical and physical state of the inhaled material.

In beagle dogs within several months after inhalation of relatively soluble plutonium nitrate, the fraction remaining in lung decreased to 40 percent or less of the amount deposited

in the lower respiratory tract, Slide 9. Translocation of plutonium from lung resulted in bone accumulating about 30 percent, and liver about 10 percent. A small percentage was found in spleen, lymph nodes, and other soft tissues and the remainder was excreted in urine and feces.

When plutonium dioxide is inhaled, the lymphatic system accounts for a large fraction of plutonium cleared from lung, Slide 10. Data from a 11-year study with beagle dogs shows that after 5 years lung and thoracic lymph nodes each contained 30 percent of the plutonium initially deposited in the lower respiratory tract. After 11 years the amount in the lung had decreased to about 10 percent and the thoracic lymph nodes had accumulated 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 radiation doses to these tissues bear the same relationship as the plutonium concentration in the tissues. Average concentrations in lung, liver, and bone were over 1000 times less than those in the thoracic lymph nodes. Thus, the lymph nodes received a much higher average radiation exposure than other tissues in the body.

Data were presented showing that $^{238}PuO_2$ may be cleared from lung more rapidly than $^{239}PuO_2$. It has also been found

that translocation of ^{238}Pu from lung to other tissues in the body may be greater than for ^{239}Pu, Slide 11. Distributions of plutonium in tissues of beagle dogs 5 years after inhalation of $^{238}PuO_2$ and $^{239}PuO_2$ are compared. After 5 years the ^{238}Pu was compared with ^{239}Pu which was in lung and the thoracic lymph nodes.

All of the transuranics tend to translocate from lung to bone and liver and, to a lesser extent, to spleen and kidney. However, the rate at which translocation from lung to these other tissues occurs differs considerably among the transuranics, depending mostly on the in vivo solubility of the compound inhaled. For example, $^{244}CmCl_3$, $^{244}CmO_{1.73}$, and $^{241}AmO_2$ are readily translocated to the bone, similar to plutonium nitrates, Slide 12. Translocation of plutonium occurs very slowly after inhalation of plutonium fluoride and plutonium dioxide.

In dogs exposed to aerosols of oxides of transuranium elements, ^{244}Cm was almost equally distributed among lung, liver, bone, and muscle after one month, Slide 13. The translocation of ^{241}Am was predominately to the liver while translocation of a relatively soluble form of ^{238}Pu, the hydrated oxide, was mainly to bone. More stable ^{238}Pu oxides and $^{239}PuO_2$ showed little translocation from lung to other tissues, but showed greater accumulation in the thoracic lymph nodes than occurred after inhalation of $^{241}AmO_2$ and $^{244}CmO_x$.

The tissue distribution of transuranium elements absorbed through the skin, from wounds or from the gastrointestinal tract is similar to that observed after translocation from the respiratory tract. The rate of translocation may vary, however, because deposition in a wound or in the lung provides a reservoir for continuous absorption into the blood stream. Absorption from skin or the gastrointestinal tract will be of short duration, until the skin has been decontaminated or the GI tract cleared, except in cases of continuous exposure.

DEPOSITION IN GONADS

Because of the concern for possible genetic effects of radionuclides deposited in the body, measurements have been made of the amounts of radionuclide which accumulate in the gonads of experimental animals. This is summarized for plutonium in the next slide. About 0.05 percent of the plutonium in the circulating blood may deposit in testes and only about 0.01 percent in ovaries. In the testes about half of the plutonium appears to be associated with germinal tissue. Few data are available on the deposition of the other transuranics in gonadal tissue but preliminary results suggest that the fractional uptake will be about the same as that for plutonium.

CROSS PLACENTAL TRANSFER

The transfer of transuranics and other radionuclides across the placenta have been studied in rats, Slide 15. Neptunium, plutonium,

and einstinium show significantly less transfer to the fetus as well as to the placenta and the placental membranes than uranium, cesium, and cerium. Preliminary results from studies of ^{241}Am and ^{244}Cm suggest less transfer than has been observed for plutonium. These results show that the placenta is an effective barrier to transuranium elements, and that extremely high levels of contamination would have to occur in the pregnant female before appreciable quantities of transuranium elements would occur in the fetus.

BIOLOGICAL EFFECTS

It has been shown that the distribution of the transuranium elements among the tissues in the body varies depending upon the route of entry, the chemical compound and the radioisotope. The biological effects which may occur will depend upon the radiation exposure and the relative radiation sensitivity of each tissue into which the radionuclide is deposited. These are primarily blood, bone, liver, lung, and the lymphatic system. The biological effects of greatest interest are those that might occur at low doses. Animal experiments have identified neoplasia as the most sensitive response to the long-term effects of transuranic elements deposited in the body.

BLOOD

Transuranic elements are cleared from the circulating blood within a few days after absorption from the site of deposition such as the gastrointestinal tract and lung. Therefore, the major effects seen in blood cells will be due to irradiation of the hematopoietic tissue in which the radionuclides are deposited or to irradiation of blood circulating through tissues containing deposits of the radionuclide.

Most of the hematologic effects observed after deposition of the transuranics in the body occur at relatively high doses, doses above those which have resulted in cancer. Although the transuranics deposit in bone and lymph nodes, leukemia has not been a common finding in animal experiments. It has been reported in less than a dozen rats after intravenous injection of plutonium and americium, in a few rats after intratracheal injection of einstinium, and in one dog (which also had osteosarcoma) after inhalation of ^{238}Pu.

The most consistent hematologic response seen after injection and inhalation of the transuranics is lymphopenia. This is well documented after inhalation of ^{238}Pu, ^{239}Pu, and ^{241}Am. In current experiments with dogs this is the most sensitive indication of a biological effect, occurring at dose levels of inhaled $^{239}PuO_2$ which have not yet shown cancer, Slide 16. The possible health consequences of a

plutonium-reduced level of circulating lymphocytes are not yet known. 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.

BONE

Osteogenic sarcomas appear to be the most sensitive effect following the skeletal deposition of plutonium, americium, curium, and einstinium in mice, rats, and dogs. In most of these experiments the solutions of the transuranics were injected intravenously. However, osteogenic sarcomas have occurred after pulmonary deposition of ^{244}Cm and ^{253}Es in rats and ^{238}Pu in rats and dogs. In these experiments the ^{244}Cm, ^{253}Es, and ^{238}Pu were largely translocated to the skeleton.

The most informative experiment on the effects of transuranics in bone is a beagle dog study with plutonium at the University of Utah. This experiment began in 1952 to compare the long-term effects of intravenously injected plutonium and radium. The objective was to determine the toxicity ratio between plutonium and radium in dogs, so that the radium toxicity data available from human exposures can be used to infer the toxic response to plutonium in man.

The results from the plutonium animals in this experiment are shown in the next slide. There were 9 to 13 animals per exposure group, injected at levels differing by about a factor of three, and ranging from 2.9 μCi/kg to 0.016 μCi/kg. There was a substantial incidence of osteosarcoma, 31 percent at the lowest level. When it became evident that effects were occurring in the lowest exposure groups, additional groups were added to the experiment at levels down to 0.0006 μCi/kg, which is equivalent to the occupationally permissible body burden for man.

A number of long-term studies in rodents have also pointed to osteosarcoma as the most sensitive indicator of plutonium in the skeleton, Slide 18. The incidence of osteosarcoma is plotted against cumulative radiation dose to bone. Each point represents a group of animals at a given dose level; each type of symbol represents a given experiment. The open circles represent the Utah dogs and are quite clearly a separate population from the rodents. From these kinds of data, Mays and Lloyd, assuming a time-independent linear dose-response relationship, have calculated an increased incidence per rad of 0.38 percent for beagles, 0.10 percent for mice, and 0.06 percent for rats. Although few data are available, it appears that doses greater than those which caused bone cancer in dogs do not cause bone cancer in miniature swine.

Of more interest than absolute incidence figures and their uncertain extrapolation to man, is the finding in the Utah studies that plutonium-239 is 5 to 10 times more toxic than radium-226, on the basis of the same total energy delivered to bone. This difference is attributed to the more hazardous localization of plutonium on bone surfaces, whereas radium is distributed more uniformly throughout bone. The cells from which bone tumors originate are located near bone surfaces.

The inhalation of $^{239}PuO_2$ has not led to the development of osteogenic sarcomas in experimental animals. However, osteogenic sarcomas have occurred in dogs after inhalation of $^{238}PuO_2$. These occurred as a result of the translocation of ^{238}Pu from the lung to bone, which received a higher radiation dose than the lungs.

LIVER

Liver is comparable to bone and lung in terms of transuranic content and radiation exposure. However, the liver appears to be less sensitive than bone and lung to the carcinogenic action of alpha radiation. Malignant liver tumors were the primary cause of death in two of 96 plutonium dogs at risk in the Utah experiment. Small, benign bile duct tumors were incidental findings at autopsy in eight other dogs, but these were also seen in controls at a somewhat lower incidence.

The liver tumors had a longer latent period than bone tumors which might explain the lower incidence. Because of this, the possibility remains that liver tumors might predominate at lower doses.

LUNG

Inhalation of relatively soluble plutonium compounds such as organic complexes, plutonium nitrate, and $^{238}PuO_2$ has resulted in primary lung cancer in rodents, rabbits, and dogs in addition to the bone cancer already mentioned. Lung cancer has also occurred in rats given $^{253}EsCl_3$ by intratracheal instillation and in rats after inhalation of ^{244}CmO, $^{244}Cm(NO_3)_3$, $^{238}Pu(NO_3)_4$, $^{241}Am(NO_3)_3$, or $^{241}AmO_2$. Lung cancer has also been observed in beagle dogs, baboons, and rodents after inhalation of $^{239}PuO_2$.

The experimental data on plutonium-induced lung cancer are shown in the next slide, with tumor incidence in percent plotted against the lung dose in rads. These are rat, mouse, and rabbit data except for the results from one dog study represented by the square symbols. The dogs seem to be more susceptible than the rodents; however, there are no dog data below about 1000 rads. Some of the low incidence data are of uncertain significance because there was a low incidence of lung tumors in the controls of some of the

experiments. For both lung and bone tumors, the lowest dose at which a clearly significant affect has been observed is about 30 rads.

In rats given $^{253}EsCl_3$ by intratracheal instillation, the malignant lung tumor incidence was 4 percent for a lung dose of 38 rads and 12.5 percent for a lung dose of 1900 rads.

Other experiments are in progress in the United States and abroad to determine the carcinogenic response of inhaled curium and americium relative to ^{238}Pu and ^{239}Pu. Squamous cell carcinomas and bronchiolo-alveolar carcinomas are being observed in these experiments.

Preliminary results from several laboratories indicate that the transuranics readily induce lung cancer in rats. However, these same laboratories find that Syrian hamsters tend to be much less sensitive to the carcinogenic action of the alpha-emitting transuranium elements than rats. This is in contrast to results being obtained with ^{210}Po introduced by intratracheal injection which show a high incidence of lung cancer.

The available data on plutonium-induced lung cancer has been analyzed to describe mathematically the relationship between cancer incidence and radiation dose. Although other models may have equal merit, a logarithmic probit curve was

selected based on its long usage in toxicology. In the next slide, arithmetic representations of the fitted function are shown by heavy lines for probit curves and linear regressions. Dotted lines show a limited extrapolation of the fitted functions.

This analysis indicates the current status of information on plutonium-induced lung cancer. Studies now in progress are adding substantially to our understanding of the dose-effect response.

LYMPH NODES

It was shown that plutonium accumulates in lymph nodes following deposition of plutonium in the respiratory tract. Months or years after the contaminating event, lymph nodes may attain concentrations of plutonium many times the average concentrations remaining at the site of deposition and consequently the accumulated radiation dose to some lymph nodes may be greater than to any other tissue. The fact that the biomedical significance of plutonium concentrations in lymph nodes is unknown is a major concern in establishing permissible limits for plutonium.

Although dogs have been studied for 11 years after inhaling $^{239}PuO_2$ and rodents have been studied in life span experiments after inhalation of a variety of plutonium and

other transuranic compounds, primary cancer of lymphatic tissue has not occurred. In dogs which had primary cancer, metastasis to mediastinal lymph nodes and lymphatics occured, but only one dog had a possible malignant lymphoma and this was confined to the mesenteric and mandibular lymph nodes. Therefore, it can be concluded that the lymph nodes are not especially susceptible to the carcinogenic action of alpha radiation from plutonium.

RELATIVE SENSITIVITY OF DIFFERENT SEGMENTS OF THE POPULATION

An important question relevant to the establishment of exposure standards for radiation or other potentially hazardous agents is whether all segments of the population are equally sensitive. Research on this question relative to the transuranics has not been extensive; however, some information has been gained from experiments with rats.

Effect of Age on Osteogenic Sarcoma Response to Plutonium

Studies of rats given plutonium intravenously indicate that the newborn and weanling may be slightly more sensitive than the adult to plutonium-induced osteosarcoma.

A similar study with ^{253}Es did not indicate a difference in the incidence of osteogenic sarcoma between the adult and weanling groups at bone doses of 100, 500, and > 2000 rads.

The Effect Of Iron Deficiency

Iron deficiency is common in the human being particularly in pregnant women, pre-menopausal women, and in young children. Because of the metabolic relationship between iron and the transuranics in the blood, iron deficiency could have a bearing on the distribution and subsequent biological effects of the transuranics. In an experiment with mice rendered iron deficient it was found that deposition of intravenously injected plutonium in bone of the iron deficient mice was much greater than in the controls. This suggests that persons deficient in iron could have an increased susceptibility to plutonium-induced osteosarcoma. Iron deficiency did not affect the deposition of plutonium in gonads.

THE "HOT PARTICLE" ISSUE

It was recognized in the early 1940's that plutonium particles deposited in the lung would irradiate cells in the immediate vicinity of the particle rather than the entire lung. This gave rise to the concern that plutonium particles might be exceptionally efficient in causing lung cancer. Research during the past nearly 30 years has provided no evidence for an enhanced effect of the localized radiation dose from plutonium. Although not conclusive, experimental results to date suggest that plutonium particles might be

less hazardous than the same amount of plutonium distributed throughout the lung because many fewer cells would be exposed to alpha radiation. However, experiments to resolve this question are technically difficult because inhaled plutonium does not distribute throughout the lung but tends to aggregate. Also, such experiments require life time studies with large numbers of animals. A few experiments which bear on the issue have been completed with several transuranic compounds, others are still in progress.

Rats exposed to relatively non-particulate soluble ^{238}Pu which was highly dispersed during its relatively short residence time in the lung developed a higher incidence of lung cancer than has been observed for more particulate ^{238}Pu and ^{239}Pu sources (Sanders, 1973). The implication is that the dispersed ^{238}Pu exposed more cells to the carcinogenic action of the alpha radiation than particulate plutonium.

In France the influence of non-uniform distribution of alpha radiation in lung is being studied in about 700 rats exposed to $^{238}Pu(NO_3)_4$, $^{239}Pu(NO_3)_4$, $^{239}PuO_2$, $^{241}Am(NO_3)_3$, $^{241}AmO_2$, or $^{244}Cm(NO_3)_3$. Of these transuranics, ^{244}Cm was the most uniformly distributed throughout the lung and was most effective in reducing survival time followed in descending order by ^{238}Pu, ^{241}Am, $^{239}Pu(NO_3)_4$, and $^{239}PuO_2$ which was the most heterogenously distributed (LaFuma et al., in press).

The relatively uniform distribution of ^{244}Cm in lung is illustrated by the autoradiogram in the next slide. This can be compared with the more aggregated $^{239}Pu(NO_3)_4$ in the next slide. Although the experiment is not yet completed, nearly 200 squamous cell carcinomas and bronchiolo-alveolar carcinomas have been observed. The authors report that the results to date indicate that for lung cancer induction, ^{244}Cm, the most widely dispersed alpha emitter, is more effective than the more particulate transuranics. Again, the implication is that more cells are exposed to the alpha radiation from the dispersed ^{244}Cm than from the other less-dispersed transuranics.

Another experiment was designed specifically to address the "hot particle" issue at the Los Alamos Scientific Laboratory (Richmond and Voelz, 1972, Anderson et al., 1974). It is impossible to distribute alpha emitting sources uniformly throughout the lung by inhalation exposure due to the tendency for such material to be mobilized and aggregated by clearance processes. Therefore, 10 μm zirconium oxide microspheres containing PuO_2 at specific activities corresponding to respirable particles were given intravenously to hamsters. The microspheres were observed to be firmly fixed in the lung vasculature and were highly dispersed throughout the lung. By varying the quantity of Pu in the microspheres the

microdistribution of the radiation dose could be controlled. A total of over 2000 hamsters have been given 2000 to 1,600,000 microspheres ranging in activity from 0.07 to 59 pCi per microsphere. Total lung burdens range from 0.14 nCi to 354 nCi. This study is still in progress. However, nearly 1200 animals have lived their full life span or have been sacrificed. These animals were given a total of about 5.7×10^6 microspheres, each containing in excess of 0.07 pCi. Three malignant tumors were observed. This suggests a tumor risk of about 10^{-7} per particle. The preliminary results from this study do not suggest that particulate sources are more harzardous than equivalent less-particulate sources.

In this experiment and in other experiments with plutonium particles, the lack of significant histopathology in areas adjacent to the particles is a common finding. An example is shown in the next slide which is an autoradiograph of a section from a lung of a rat given $^{239}PuO_2$ by intraperitoneal injection (Sanders, in press). From 0.2 percent to 2 percent of the plutonium was phagocytized and transported to the lung where the particles lodged in the vasculature similar to the microsphere experiment with hamsters. The lungs of these rats surprisingly showed little evidence of pulmonary pathology that could be attributed to the plutonium. The radiation doses to the lungs of the several groups of a

total of 151 rats were 10, 20, 40, 170, and 600 rads. Only one lung tumor occurred; this was observed after 823 days in one rat of 36 which had a lung dose of 10 rads.

Another example of Pu particles residing in lung which shows no evidence of histopathology is illustrated in the next slide. This is an autoradiograph of a histologic section from a lung of a dog about 2 years after inhalation of $^{239}PuO_2$ showing several particles in areas of normal lung. Other sections of the lung from this dog showed evidence of plutonium induced changes. However, normal appearing areas such as this containing plutonium particles are not uncommon in animal experiments.

The pathogenesis of plutonium induced neoplasia is not fully understood. However, observations made during the past 10 years, suggest that phagocytosis of the plutonium particle is one of the steps leading to necrosis and a connective tissue response such as fibrosis and/or an epithelial response such as hyperplasia, metaplasia, and eventually neoplasia.

In agreement with the observations from studies of plutonium and other transuranics deposited in lung are the results from a recent study of the incidence of chromosome aberrations in the liver as a function of the size of the $^{239}PuO_2$ particle administered. For the same total quantity

of plutonium administered, the more uniform dose was more effective in producing chromosome aberrations than the more localized doses (Brooks et al., 1974).

The "hot particle" issue continues to be the subject of controversy and will not be settled to everyone's satisfaction until more of these difficult and expensive experiments are completed. However, the results of relevant experiments at laboratories in the United States, France, and the United Kingdom have led the scientists conducting the experiments to believe that particulate alpha emitting transuranics in the lung do not represent a higher risk of lung cancer than the equivalent quantity of relatively non-particulate transuranium element distributed throughout the lung (LaFuma et al., in press; Dolphin et al., 1974).

COUNTERMEASURES FOR INHALED PLUTONIUM

An important consideration in evaluating the potential health effects of plutonium is the availability of effective countermeasures for plutonium exposures. Since no acceptable therapy exists for radiation exposures, the only really effective countermeasure for inhaled transuranics is their removal from the body. Inhaled insoluble plutonium is not effectively mobilized by a wide variety of agents which have

been tested. The most effective method for removing plutonium from the lung is lavage with isotonic saline. In rats, dogs, and baboons about 50 percent of the lung burden can be removed by lavage.

A chelating agent, Diethylenetriaminepentaacetic acid (DTPA), has had wide application for treating persons occupationally exposed to plutonium. It reduces the liver burden and, to a lesser extent, the bone burden causing an increased urinary excretion of plutonium. DTPA has also been found to be effective in reducing the systemic burden of Am, Cm, and Es. However, it is not effective in removing insoluble transuranics from lung or lymph nodes.

Therefore, it must be recognized that truly effective countermeasures for transuranic contamination have not yet been found, and that for all practical purposes transuranics deposited in the body will remain there until removed by natural processes, most of which are very slow. The development of therapeutic procedures for removing transuranics from the body are high priority research projects in several laboratories.

SUMMARY AND CONCLUSIONS

STATUS OF CURRENT RESEARCH

Research relevant to the problem of low level exposures to transuranium elements has increased significantly during

the past 10 years. Life span animal studies of the biological effects of the transuranium elements have greatly expanded. The current status of our knowledge of plutonium is shown in this slide. The dose levels at which major biological effects have been observed in experimental animals are shown relative to the maximum permissible lung burden of 0.016 μCi for occupational exposures. Lung cancer has been observed at dose levels equivalent to about 100 times the maximum permissible lung burden. Current experiments are directed towards determining whether health effects will occur at lower levels. However, because of logistics and the cost in terms of time and money of such experiments, the most productive research may be that which is directed towards understanding the mechanisms by which alpha emitters induce cancer. Some of these studies are in progress and more are anticipated.

RESEARCH IN PROGRESS

Research is in progress in several laboratories in the United States and abroad to examine the late effects of low levels of transuranic elements. Three dog studies are in progress in the United States. At the University of Utah the late effects of transuranics are being studied after intravenous administration, Figure 26. This study is primarily directed at effects in bone and liver. At the Lovelace

Foundation dogs are being exposed to monodisperse aerosols of ^{238}Pu and ^{239}Pu, Slide 27. A total of 360 dogs are being given single exposures to plutonium aerosols with particle sizes ranging from 0.75 to 3 μm aerodynamic diameter. Initial lung burdens range from 0.1 to 5.6 μCi.

At Battelle-Northwest 221 dogs have been exposed to polydispersed aerosols of $^{238}PuO_2$ and $^{239}PuO_2$, Slide 28. Initial lung burdens ranged from 0.002 μCi to 5 μCi.

In addition to these major dog experiments, all of the available transuranics are being studied in thousands of rats and hamsters following inhalation, ingestion and intravenous injection. These long term animal experiments are being supplemented by increasing levels of research to develop a better understanding of how alpha radiation from the transuranium elements causes cancer and other possible health effects.

No significant surprises are expected from this intensified research effort. The results will help us sharpen our predictions of the health consequences of the expected increased utilization and availability of the transuranium elements.

This work was done by Battelle, Pacific Northwest Laboratories, for the U.S. Energy Research Development Administration under contract AT(45-1)-1830.

TABLE 1

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 and from results of current research at PNL by M. F. Sullivan.

TABLE 2

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

TABLE 3

Relative Concentrations of Plutonium in Tissues of Dogs 7-9 Years After Inhalation of $^{239}PuO_2$

Tissue	Relative Concentration of Plutonium
Lung	1
Thoracic Lymph Nodes	1400
Abdominal Lymph Nodes	100
Liver	0.5
Spleen	0.2
Bone	0.06

TABLE 4

Translocation in Dogs 30 Days After Inhalation
of Oxides of Transuranium Elements

Transuranic Oxides	Particle Size		Tissue Content (Percent of Final Body Burden)					
	AMAD (μm)	GSD	Lung	Thoracic Lymph Nodes	Liver	Bone	Muscle	All Other
$^{244}CmOx$	0.5	2.1	20	0.5	25	25	22	9
$^{241}AmO_2$	1.3	2.	55	-	19	11	11	4
^{238}Pu(hydrated oxide)	0.9	2.6	64	0.5	8	23	2	3
$^{238}PuO_2$ (750°)	2.2	2.3	96	0.8	0.3	0.5	3	0.3
$^{238}PuO_2$ (PPO)	1.9	1.7	96	1	0.2	1	1	1
$^{238}PuO_2$ (PMC)	2.	1.9	94	1	0.6	1.4	1.4	2
$^{239}PuO_2$	2.	2.	97	2	0.01	0.01	0.01	0.2

(Unpublished data provided by D. K. Craig, PNL)

TABLE 5

Deposition of Plutonium in Gonads

	Percent of Pu in Blood
Testes	0.05
Ovaries	0.01

From C. R. Richmond and R. L. Thomas - in press

TABLE 6

Cross-Placental Transfer of Transuranic Elements in Rats

(Percent of Injected Dose per Gram)

Time of Injection (Day of Ingestion)		^{233}U	^{237}Np	^{238}Pu	^{239}Pu	^{239}Pu*	^{253}Es	^{137}Cs	^{144}Ce
15	Fetus	0.01	0.01	0.01	0.01	0.0002	0.002	0.09	0.02
	Placenta	0.01	0.04	0.22	0.40	0.01	0.02	0.16	0.36
	Membranes	0.13	0.81	3.80	1.93	0.03	0.04	0.08	1.79
19	Fetus	0.03	0.02	0.01	0.01	0.0004	0.008	0.08	0.02
	Placenta	0.05	0.18	0.51	0.91	0.02	0.08	0.14	0.39
	Membranes	0.33	1.24	4.30	3.20	0.07	0.05	0.07	1.60

*Polymeric

(Summary of published and unpublished data provided by D. D. Mahlum and M. R. Sikov, PNL)

TABLE 7

Hematologic Effects of Transuranic Elements

Isotope	Species	Dose (μCi/kg)	RBC	Neutro	Lymph	Mono	EOS
I.V.							
^{226}Ra	dog	.06-10.4	±	↓ ↑	↓	↓ ↑	↓ ↑
^{239}Pu	dog	.02-2.9	±	↓ ↑	↓	↓ ↑	↓ ↑
^{228}Th	dog	.02-2.8	±	↓	↓	↓ ↑	↓
^{228}Ra	dog	.05-8.5	±	↓	↓	↓ ↑	↓
^{241}Am	dog	.02-2.8	±	↓	↓	↓ ↑	↓
^{249}Cf	dog	2.8	-	↓ ↑	↓	↓ ↑	↓ ↑
^{253}Es	dog	2.9	↓ ↑	↓ ↑	↓ ↑	↓ ↑	↓ ↑
^{253}Es	pig	3.0	-	↓ ↑	-	↓ ↑	↓ ↑
^{242}Cm	dog	2.6	↓ ↑	↓ ↑	↓	↓ ↑	↓
Inhaled							
^{239}Pu	dog	.08-5.8*	-	-	↓	-	-
^{238}Pu	dog	.14-5.4*	-	±	↓	-	-
^{241}Am	dog	∿ 25	-	↓	↓	↓	↓

*Initial Lung Burden (μCi)
±Depression at highest doses only
↓Sustained depression
↓↑Depression with evidence of recovery
-No effect
(Summary of published and unpublished data provided by H. A. Ragan, PNL)

TABLE 8

Plutonium-Induced Bone Cancers
in Utah Dog Study

Injected Dose (μCi/kg)	Cancer Incidence	Dose to Bone of Cancer Dogs (RAD)
2.9	7/9 = 78%	4900
0.9	12/12 = 100%	1300
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0.1	10/12 = 83%	310
0.05	9/13 = 69%	190
0.016	4/13 = 31%	78
Controls	0	

TABLE 9

Osteosarcoma in Dogs after Inhalation of $^{238}PuO_2$

$^{238}PuO_2$	Survival Time (Months)	Terminal Body Burden (μCi)	Plutonium Distribution (% of Body Burden)				
			Lungs	Thoracic Lymph Nodes	Liver	Bone	Osteo-sarcoma
ined at 350°C	23-70	2.6-3.0	17	9	23	47	5/8*
ned microspheres	22-76	0.2-3	20	12	16	24	4/8**

lung tumor

myelogenous leukemia and 1 fibrosarcoma

k et al., in press)

TABLE 10

Life Span Studies of Intravenously Injected
Transuranium Elements in Dogs at University of Utah
(Numbers of Dogs*)

Nuclide	Age Group of Dogs	Injected Doses, μCi/kg										
		0	.0006	.0016	.005	.01	.015	.05	.1	.3	.9	2.8
^{239}Pu	Juveniles	5					1			4		12
	Young adults	31	26	42	25	36	12					
	Aged									2		3
^{241}Am	Young adults			13	13		12	13	10	16	1	
^{249}Cf	Young adults	6	6		6		6		6	6		
^{252}Cf	Young adults	6	6		6		6		6	6		
^{253}Es	Young adults									3		4

*August, 1974 - 356 dogs

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	Oxide	0.5	0.01
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	Chloride	-	0.05
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Abdominal Lymph Nodes	100
Liver	0.5
Spleen	0.2
Bone	0.06

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Translocation in Dogs 30 Days After Inhalation of Oxides of Transuranium Elements

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$^{241}AmO_2$	1.3	2.	55	-	19	11	11	4
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$^{238}PuO_2$ (PPO)	1.9	1.7	96	1	0.2	1	1	1
$^{238}PuO_2$ (PMC)	2.	1.9	94	1	0.6	1.4	1.4	2
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(Unpublished data provided by D. K. Craig, PNL)

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	Placenta	0.01	0.04	0.22	0.40	0.01	0.02	0.16	0.36
	Membranes	0.13	0.81	3.80	1.93	0.03	0.04	0.08	1.79
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	Placenta	0.05	0.18	0.51	0.91	0.02	0.08	0.14	0.39
	Membranes	0.33	1.24	4.30	3.20	0.07	0.05	0.07	1.60

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^{239}Pu	dog	.02-2.9	±	↓↑	↓	↓↑	↓↑
^{228}Th	dog	.02-2.8	±	↓	↓	↓↑	↓
^{228}Ra	dog	.05-8.5	±	↓	↓	↓↑	↓
^{241}Am	dog	.02-2.8	±	↓	↓	↓↑	↓
^{249}Cf	dog	2.8	-	↓↑	↓	↓↑	↓↑
^{253}Es	dog	2.9	↓↑	↓↑	↓↑	↓↑	↓↑
^{253}Es	pig	3.0	-	↓↑	-	↓↑	↓↑
^{242}Cm	dog	2.6	↓↑	↓↑	↓	↓↑	↓
Inhaled							
^{239}Pu	dog	.08-5.8*	-	-	↓	-	-
^{238}Pu	dog	.14-5.4*	-	±	↓	-	-
^{241}Am	dog	~ 25	-	↓	↓	↓	↓

*Initial Lung Burden (μCi)
±Depression at highest doses only
↓Sustained depression
↓↑Depression with evidence of recovery
-No effect
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			Lungs	Thoracic Lymph Nodes	Liver	Bone	
Calcined at 350°C	23-70	2.6-3.0	17	9	23	47	5/8*
Crushed microspheres	22-76	0.2-3	20	12	16	24	4/8**

* 1 lung tumor

** 1 myelogenous leukemia and 1 fibrosarcoma
(Park et al., in press)

TABLE 10

Life Span Studies of Intravenously Injected
Transuranium Elements in Dogs at University of Utah
(Numbers of Dogs*)

Nuclide	Age Group of Dogs	Injected Doses, μCi/kg										
		0	.0006	.0016	.005	.01	.015	.05	.1	.3	.9	2.8
^{239}Pu	Juveniles	5					1			4		12
	Young adults	31	26	42	25	36	12					
	Aged									2		3
^{241}Am	Young adults			13	13		12	13	10	16	1	
^{249}Cf	Young adults	6	6		6		6		6	6		
^{252}Cf	Young adults	6	6		6		6		6	6		
^{253}Es	Young adults									3		4

*August, 1974 - 356 dogs

TABLE 11

Life Span Study of Inhaled Plutonium

in Dogs at Lovelace

	Particle Size* (μm)	Initial Lung Burden (μCi)	Number of Dogs
$^{238}PuO_2$	1.5	5.6, 3, 1.4, 0.7, 0.3, 0.1	72
$^{238}PuO_2$	3.0	"	72
$^{239}PuO_2$	0.75	"	72
$^{239}PuO_2$	1.5	"	72
$^{239}PuO_2$	3.0	"	72
			360 + 60 controls

*Aerodynamic diameter of monodisperse aerosols

TABLE 12

Life Span Study of Inhaled Plutonium in
Dogs at Battelle-Northwest

$^{238}Pu^{16}O_2$		$^{239}PuO_2$	
Initial Lung Burden (μCi)	No. of Dogs*	Initial Lung Burden (μCi)	No. of Dogs*
.002	20	.004	20
.02	20	.02	20
.08	20	.08	20
.35	20	.3	20
1.3	20	1.1	20
5.2	13	5.8	8
	113		108

*Half male and half female + 40 controls

RETENTION OF PLUTONIUM IN PULMONARY REGION OF LUNG

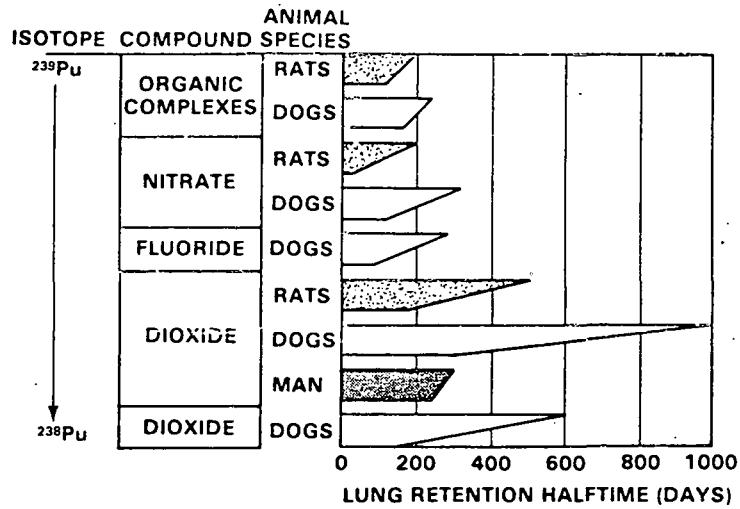

Figure 1

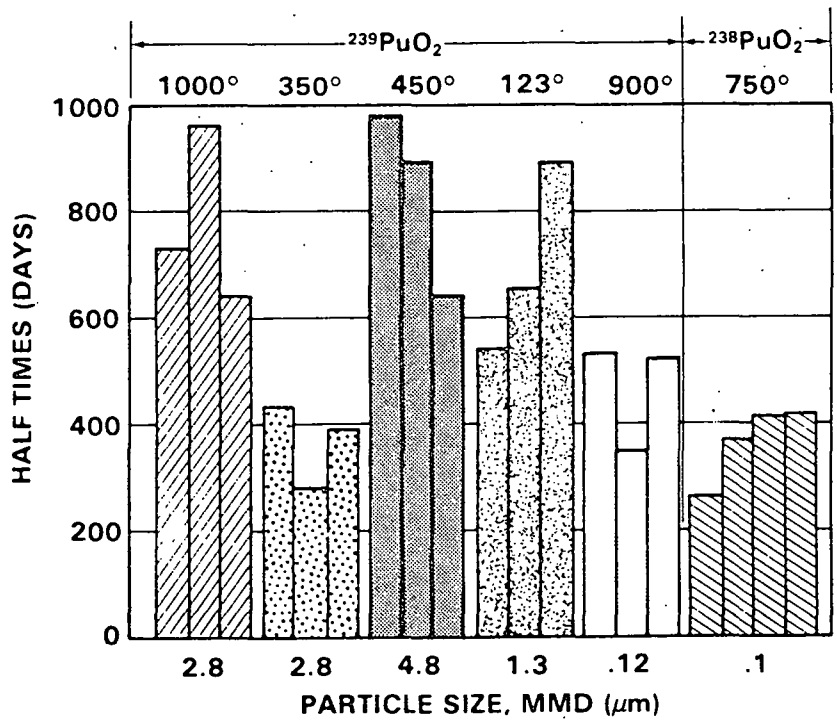

Figure 2

Pulmonary Retention of Inhaled PuO_2 in Dogs

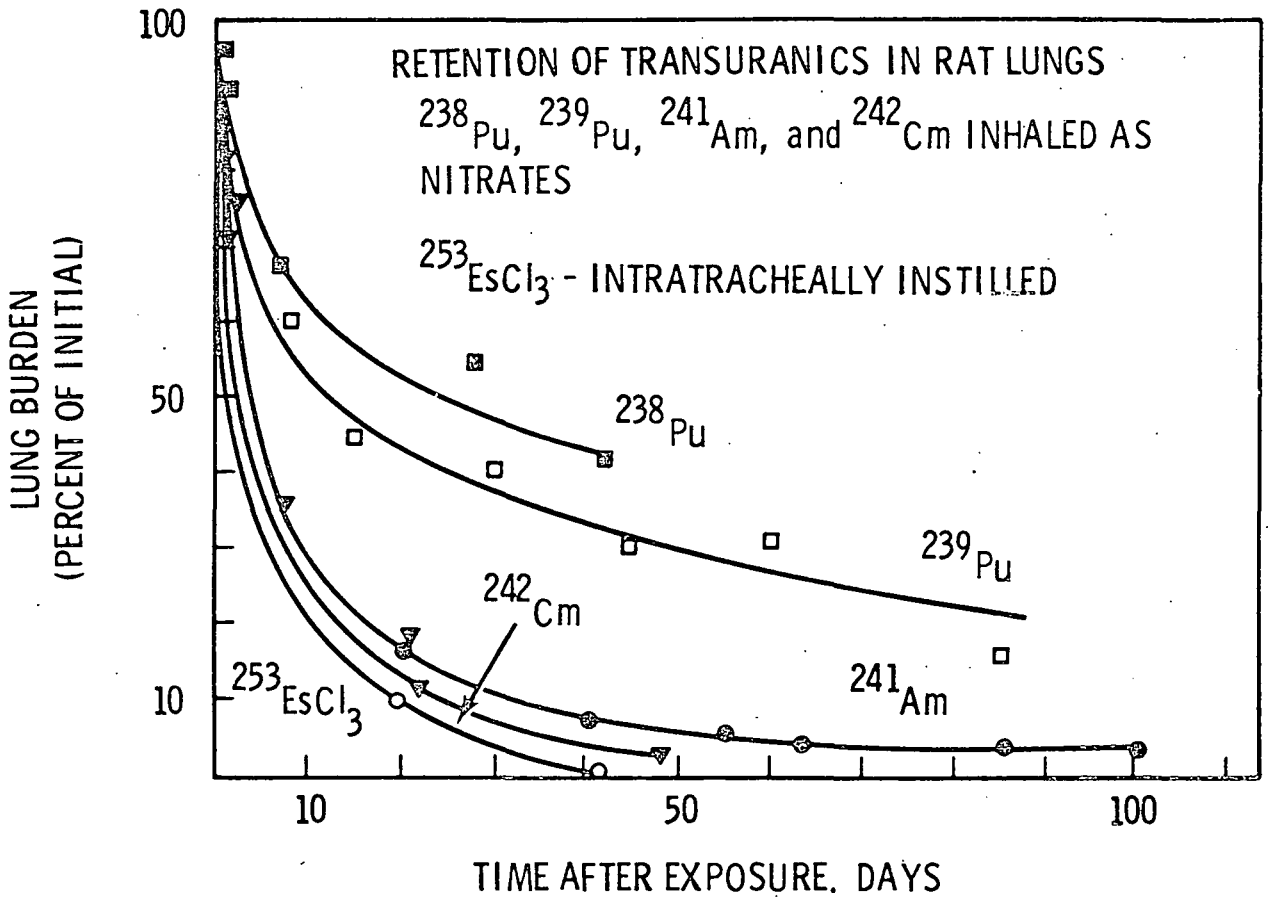

Figure 3

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)

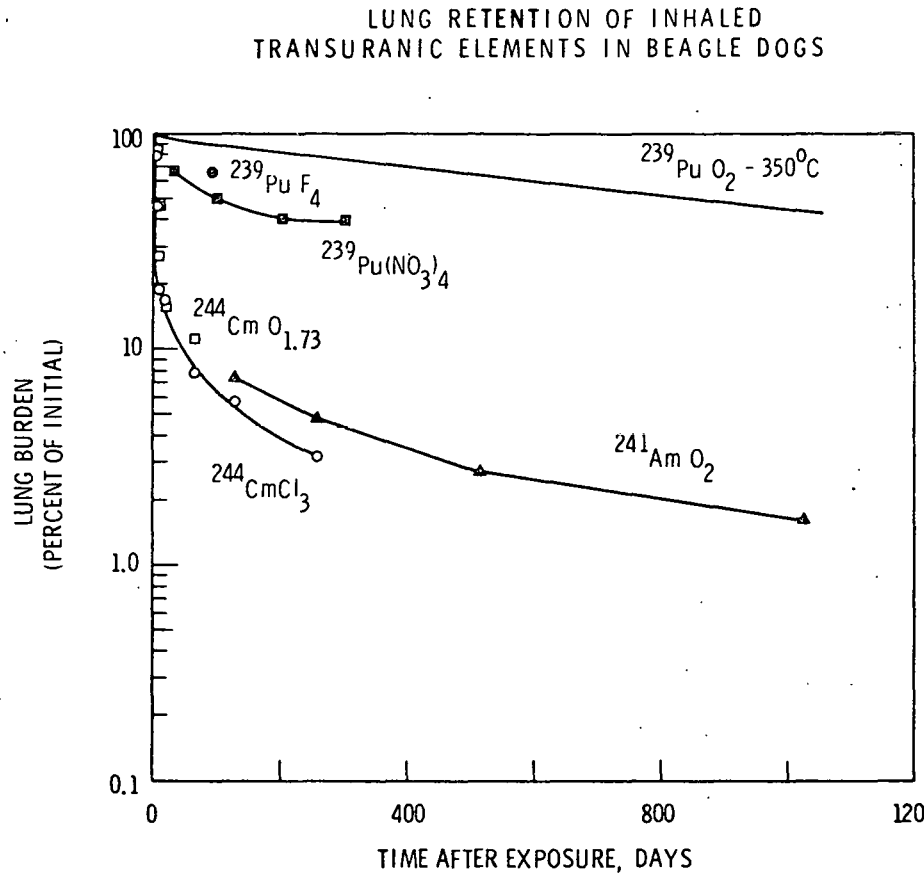

Figure 4

(Redrawn from R. O. McClellan, 1972)

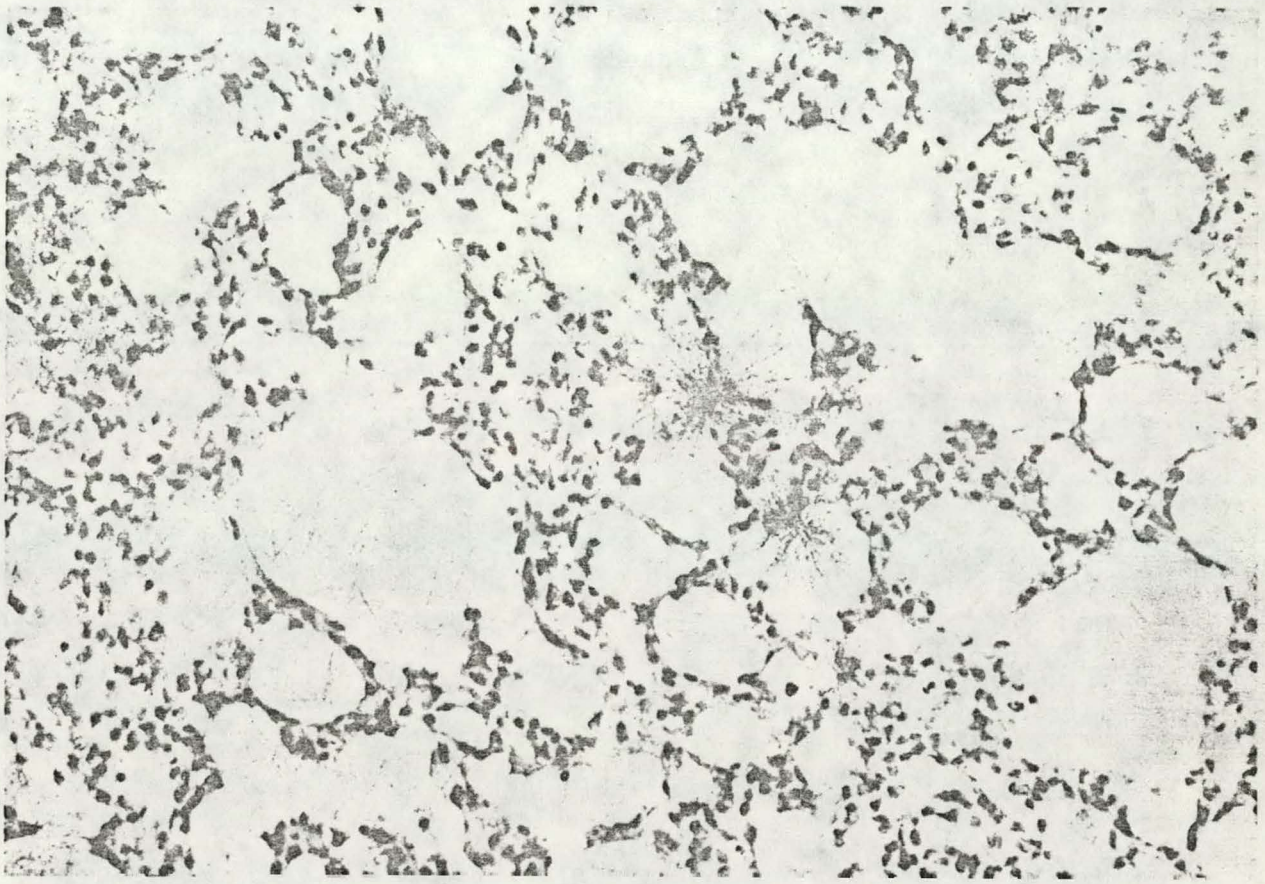

Figure 5

Autoradiograph showing particulate and non-particulate plutonium in lung of a rat immediately after inhalation of $^{239}Pu(NO_3)_4$
(Provided by J. E. Ballou, PNL)

Figure 6

Autoradiograph of a histologic section from a rat lung 7 days after inhalation of $^{253}Es(NO_3)_3$
(Provided by J. E. Ballou, PNL) PNL747349-7

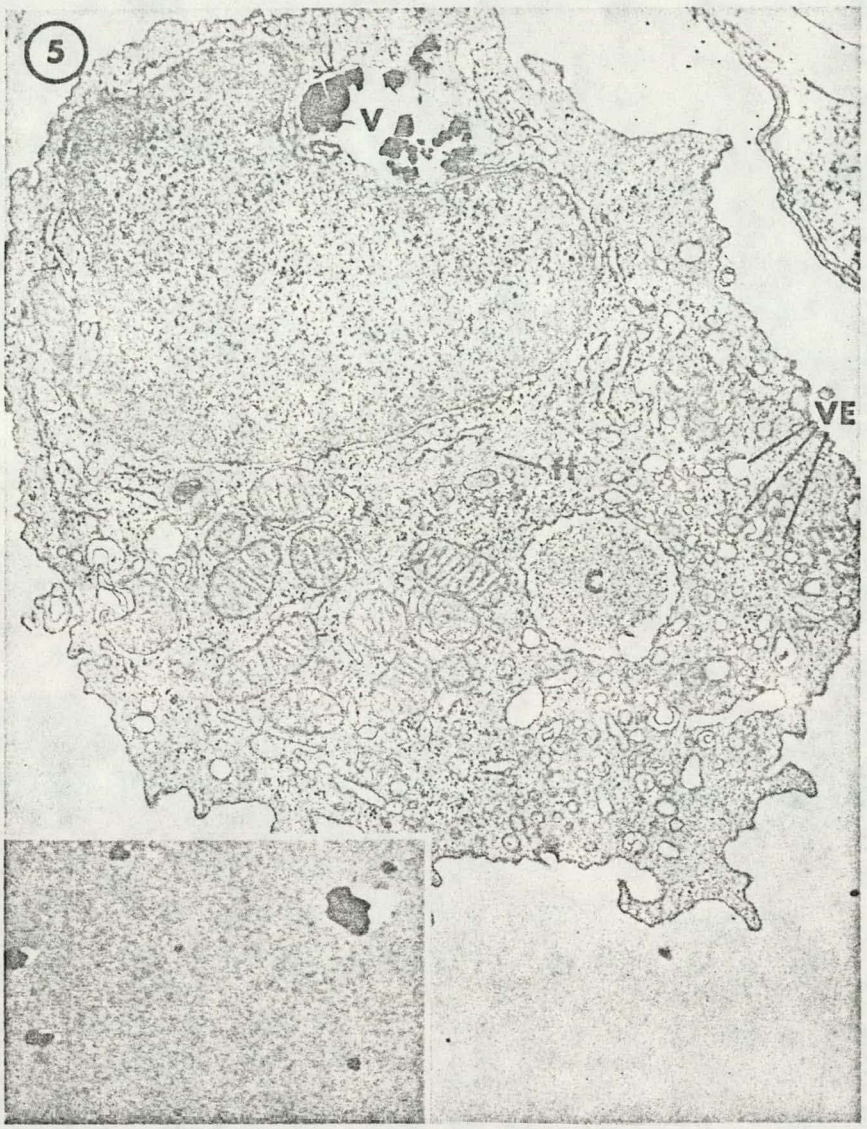

Figure 7

Electromicrograph of plutonium dioxide particles (inset) from an aerosol inhaled by rats and of a cell from the lung of an exposed rat. The dense appearing material in the cell is plutonium dioxide which had been engulfed by the cell.

(Provided by C. L. Sanders and R. R. Adee, PNL) PNL0673470-5

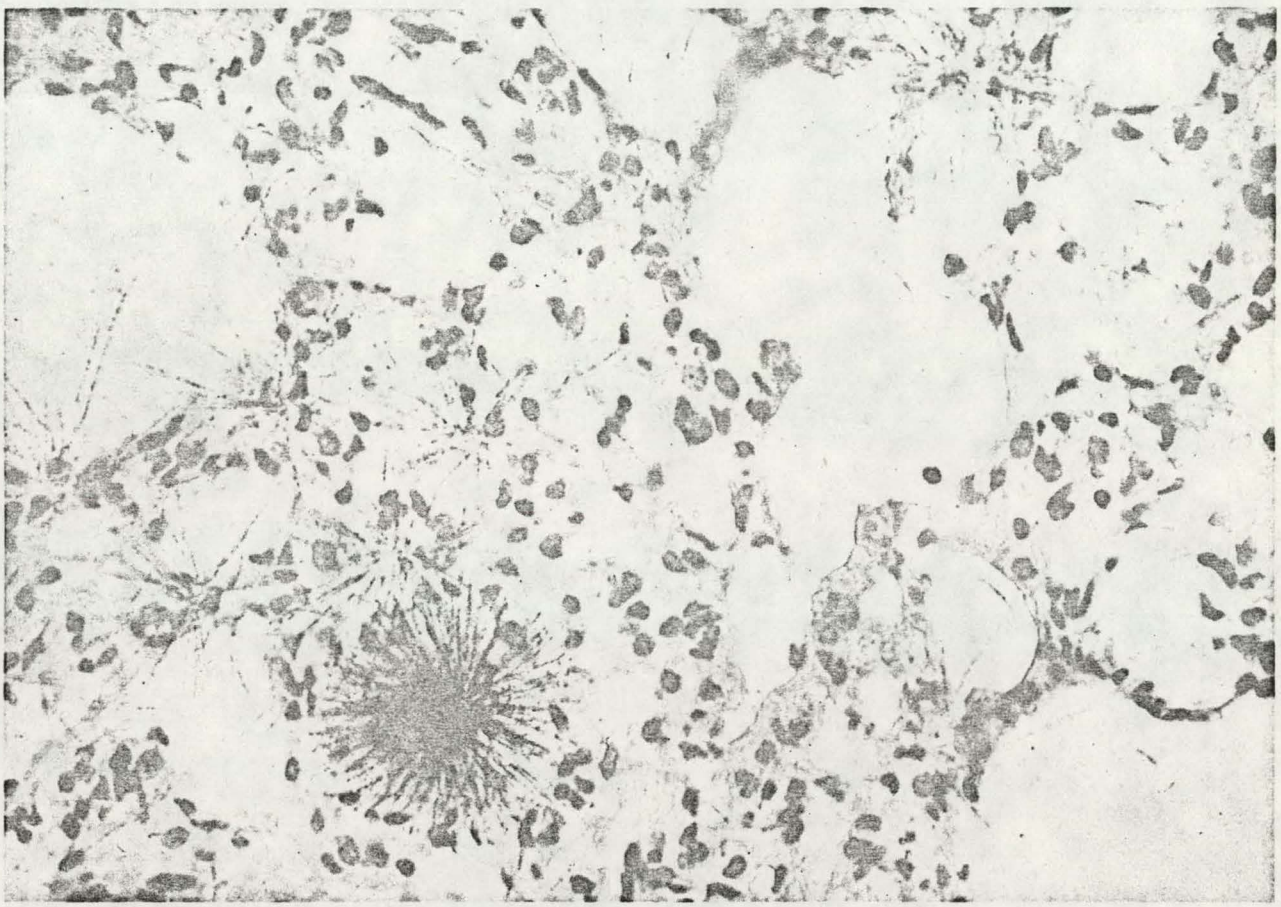

Figure 8

Autoradiograph showing aggregation of ^{238}Pu in a lung of a rat 100 days after inhalation of $^{238}Pu(NO_3)_4$.
(Provided by J. E. Ballou, PNL) PNL747349-3

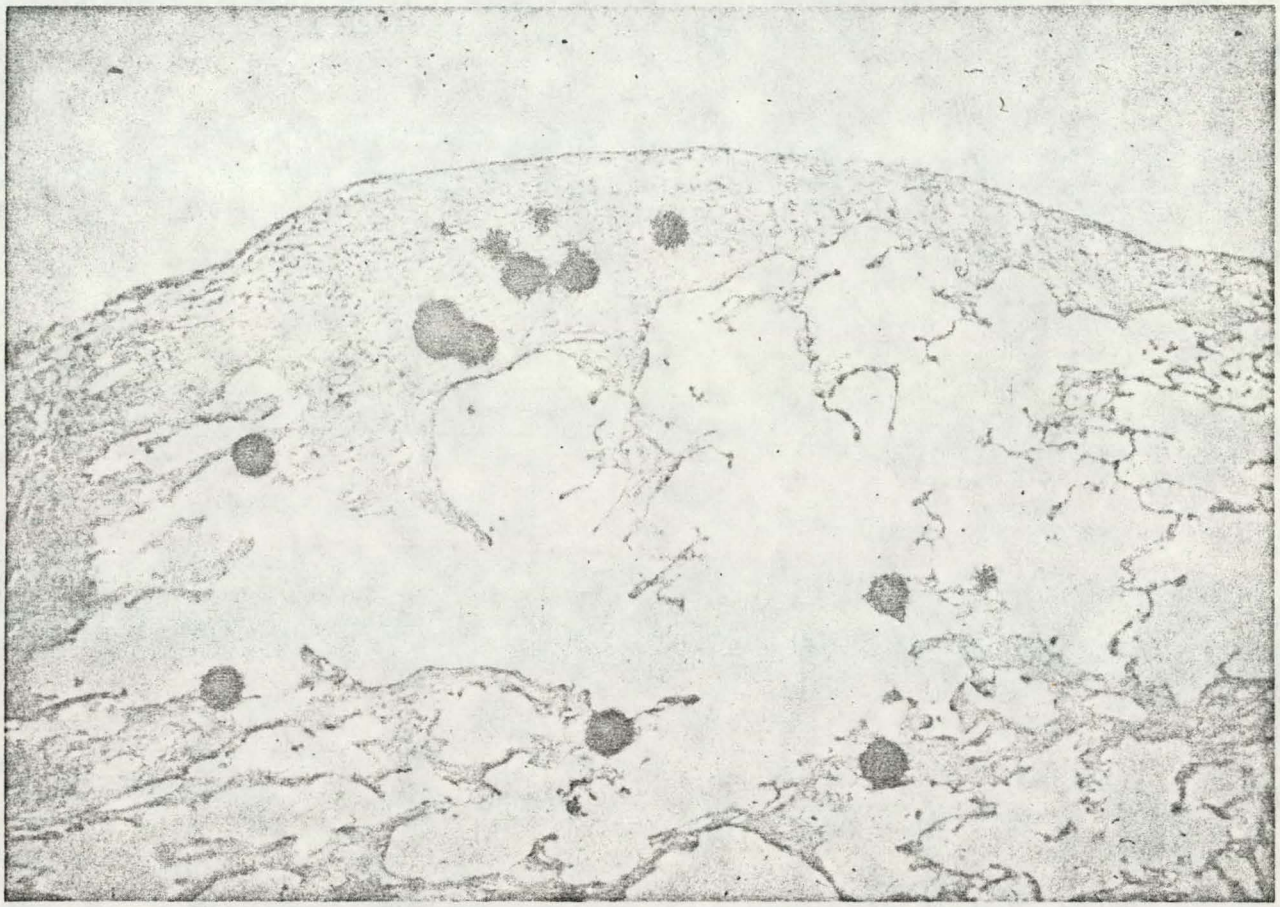

Figure 9

Autoradiograph showing $^{239}PuO_2$ particles in a subpleural area of lung from a dog. (Provided by G. E. Dagle, PNL)
PNL747349-2

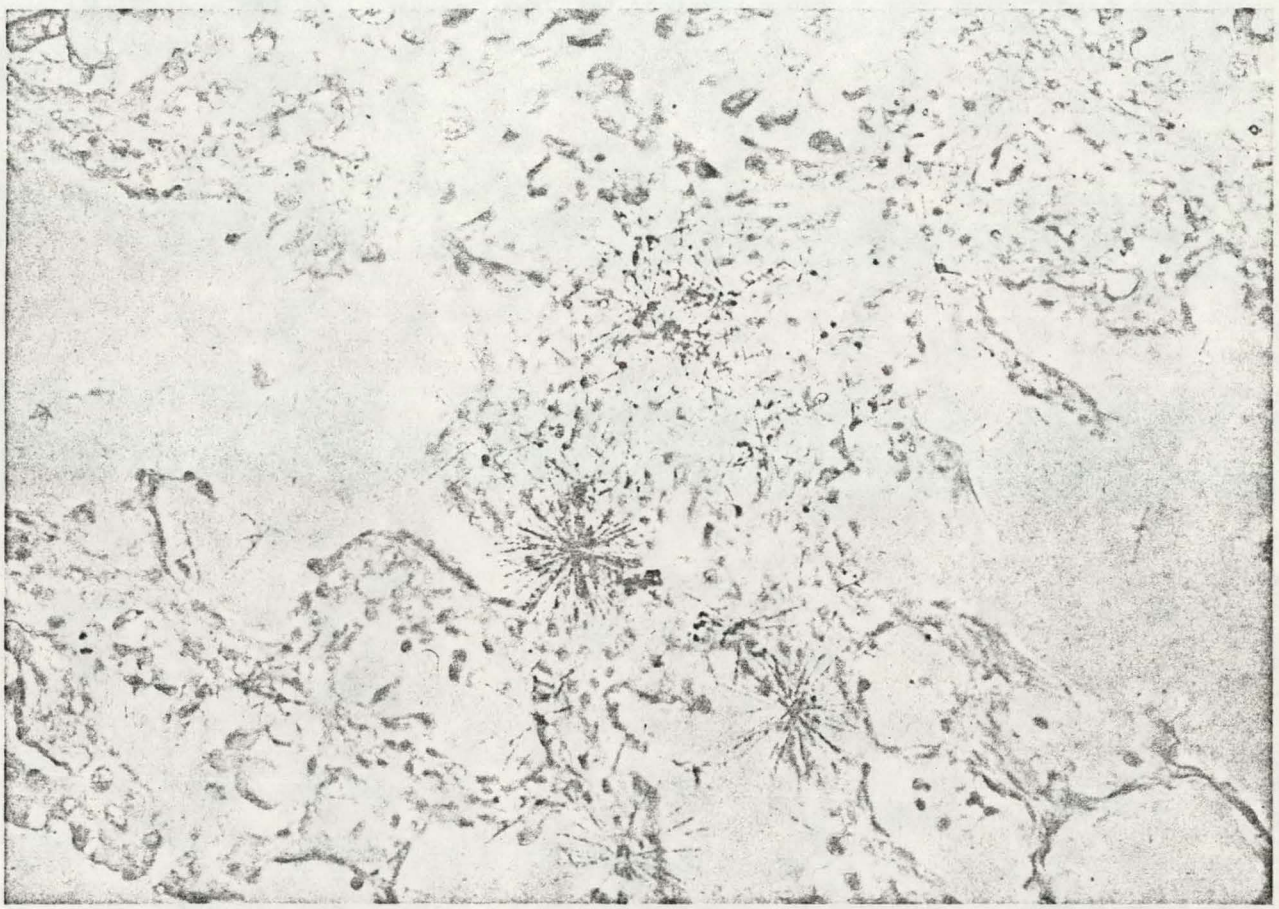

Figure 10

Autoradiograph showing ^{238}Pu particles in scar tissue in a lung of a dog 5 years after inhalation of $^{238}PuO_2$.
(Provided by J. E. Lund) PNL747349-6

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

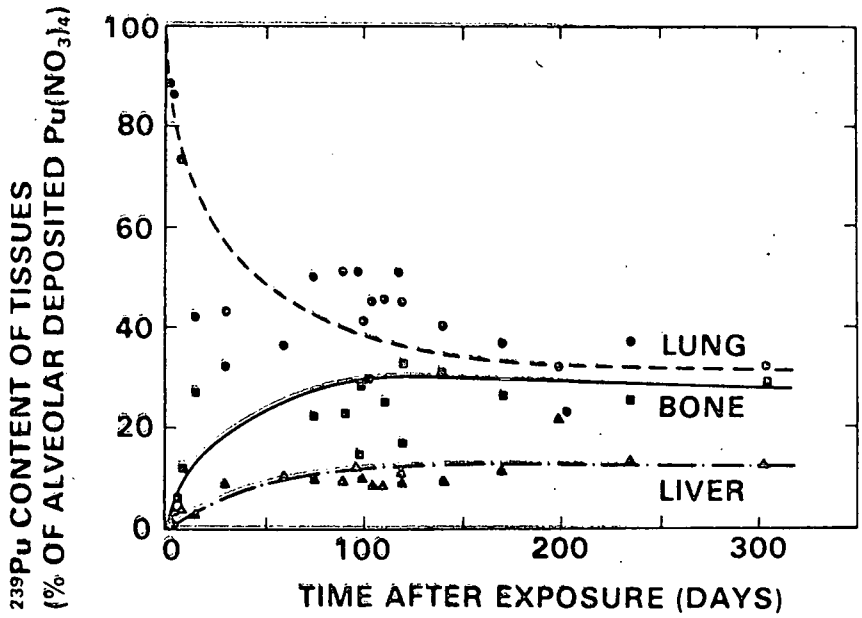

Figure 11

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

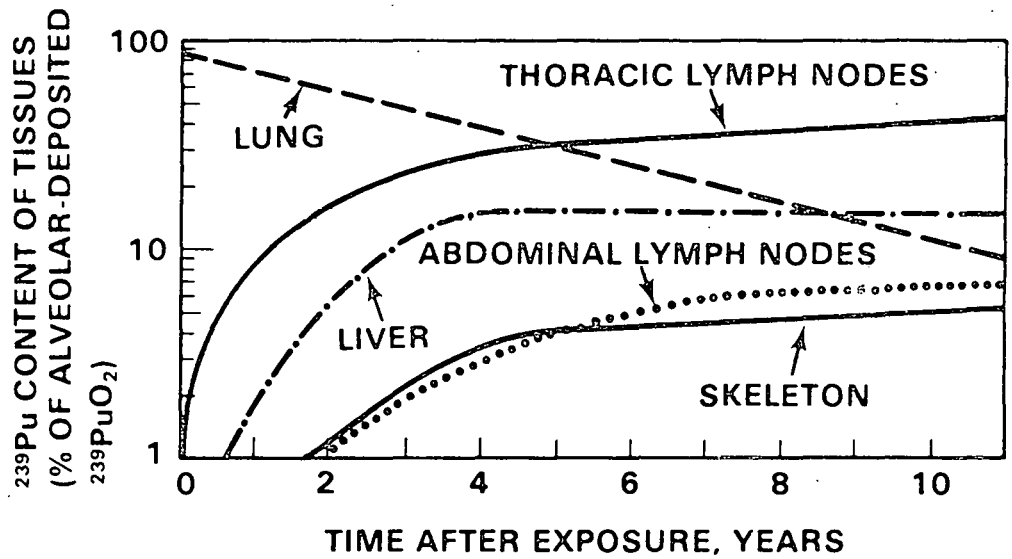

Figure 12

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

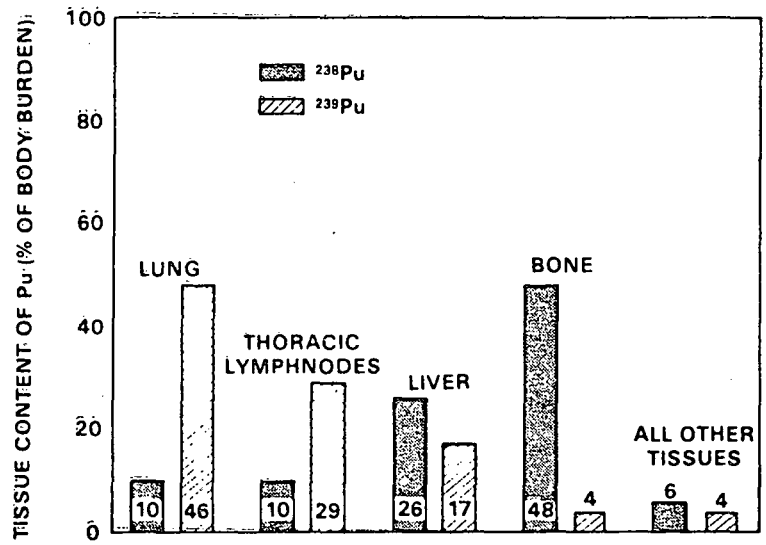

Figure 13

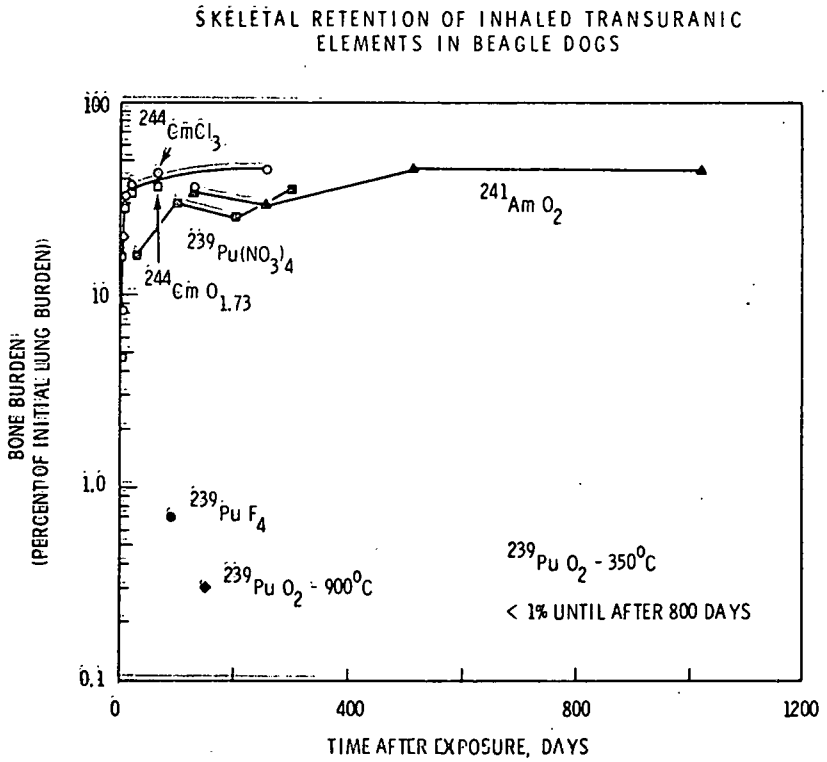

Figure 14

(Redrawn from R. O. McClellan, 1972)

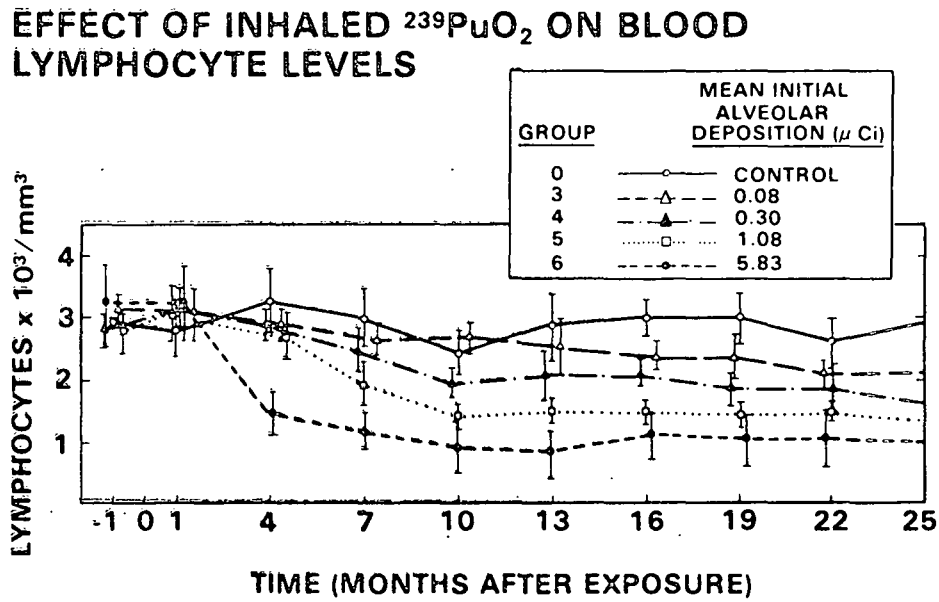
EFFECT OF INHALED $^{239}PuO_2$ ON BLOOD LYMPHOCYTE LEVELS
GROUP
MEAN INITIAL ALVEOLAR DEPOSITION (μ Ci)
0 CONTROL
3 0.08
4 0.30
5 1.08
6 5.83
LYMPHOCYTES x 10^3/mm^3
4
3
2
1
-1 0 1 4 7 10 13 16 19 22 25
TIME (MONTHS AFTER EXPOSURE)

Figure 15

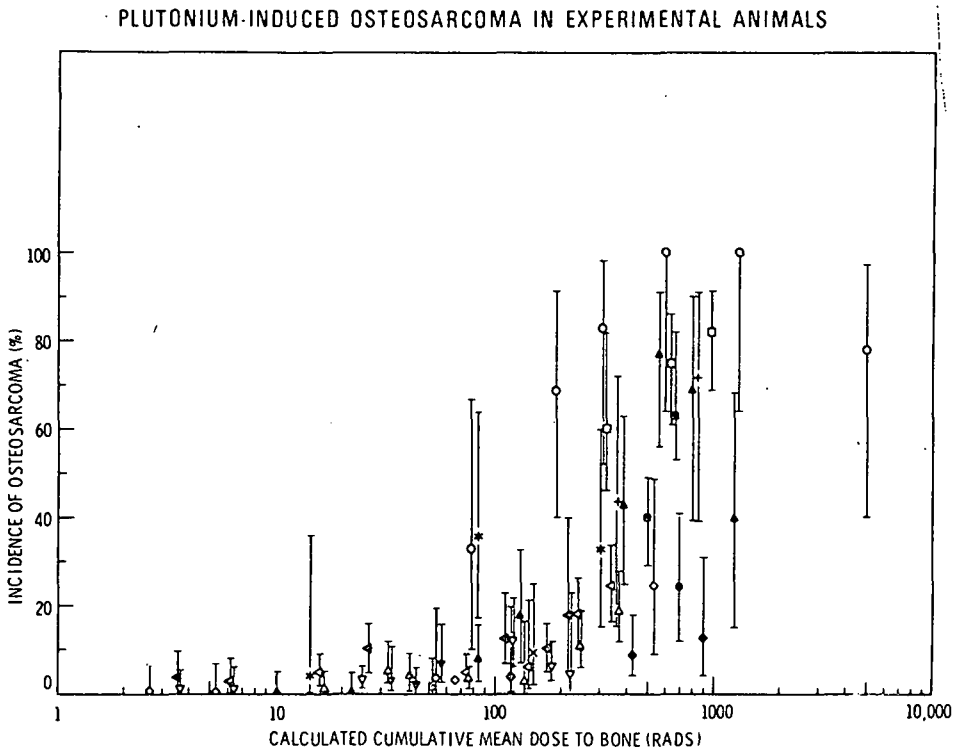

Figure 16

Plutonium-induced Osteosarcoma in Experimental Animals. Mean incidence and radiation dose values are those reported in the literature. Binomial confidence limits were calculated from data included in the referenced literature.

- o ^{239}Pu Citrate, Monomeric - IV - Dogs (from Jee, 1972)
- Δ ^{239}Pu Citrate - Inhaled - Rats (from Buldakov and Lyubchansky, 1970)
- ∇ ^{239}Pu Plutonylpentacarbonate - Inhaled - Rats (from Buldakov and Lyubchansky, 1970)
- ◇ ^{239}Pu Nitrate - Sub- and Intracutaneous - Rats (from Buldakov, et al., 1971)
- ▼ ^{239}Pu Citrate - Oral (Daily) - Rats (from Buldakov et al., 1969)
- ● ^{239}Pu Plutonyltriacetate - I.T. - Rats (from Erokhin et al., 1971)
- ▲ ^{239}Pu Citrate - IV - Mice (from Finkel and Biskis, 1962)
- □ ^{239}Pu Citrate, Monomeric - IV - Mice (from Rosenthal and Lindenbaum, 1967)

▩ ^{239}Pu Citrate, Polymeric - IV - Mice (from Rosenthal and Lindenbaum, 1967)

X $^{238}PuO_2$ - Inhaled - Rats (from C. L. Sanders, 1973)

◈ ^{239}Pu Nitrate - I.T. - Rats (from Erokhin et al., 1971)

+- ^{239}Pu Nitrate - I.T. - Rabbits)from Koshnurnikova et al., 1971)

* ^{239}Pu (Pentacarbonate) - Inhaled - Rabbits (from Koshnurnikova et al., 1971)

◁ ^{239}Pu Citrate - Inhaled - Rats (from Koshnurnikova et al., 1971)

◀ ^{239}Pu Pentacarbonate - Inhaled - Rats (from Koshnurnikova et al., 1971)

(See Bair, 1974 for complete references)

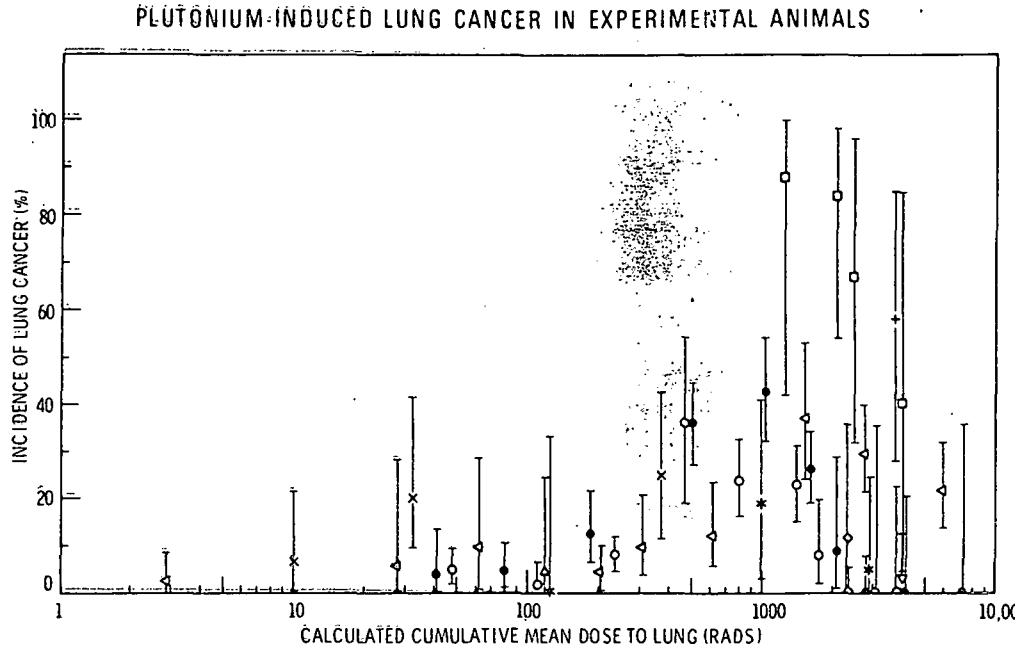

Figure 17

Plutonium-induced Lung Cancer in Experimental Animals
Mean incidence and radiation dose values are those reported in the literature. Binomial confidence limits were calculated from data included in the referenced literature.

- ▣ $^{239}PuO_2$ - Dogs (from Park and Bair, 1972)
- ▽ $^{239}PuO_2$ - Mice (from Temple et al., 1959)
- △ $^{239}PuO_2$ - Mice (from Temple et al., 1959)
- ◈ $^{239}PuO_2$ - Mice (from Wager et al., 1956)
- o ^{239}Pu Citrate - Rats (from Buldakov and Lyubchansky, 1970)
- ● ^{239}Pu - Plutonylpentacarbonate - Rats (from Buldakov and Lyubchansky, 1970)
- x ^{238}Pu - Rats (from C. L. Sanders, 1973)

△ ^{239}Pu - Rats - $Pu(NO_3)_4$ (from Erokhin et al., 1971)

\+ ^{239}Pu - Rabbits - $Pu(NO_3)_4$ (from Koshnurnikova et al., 1971)

* ^{239}Pu - Rabbits - NH_4 Pu Pentacarbonate (from Koshnurnikova et al., 1971)

(See Bair, 1974 for complete references)

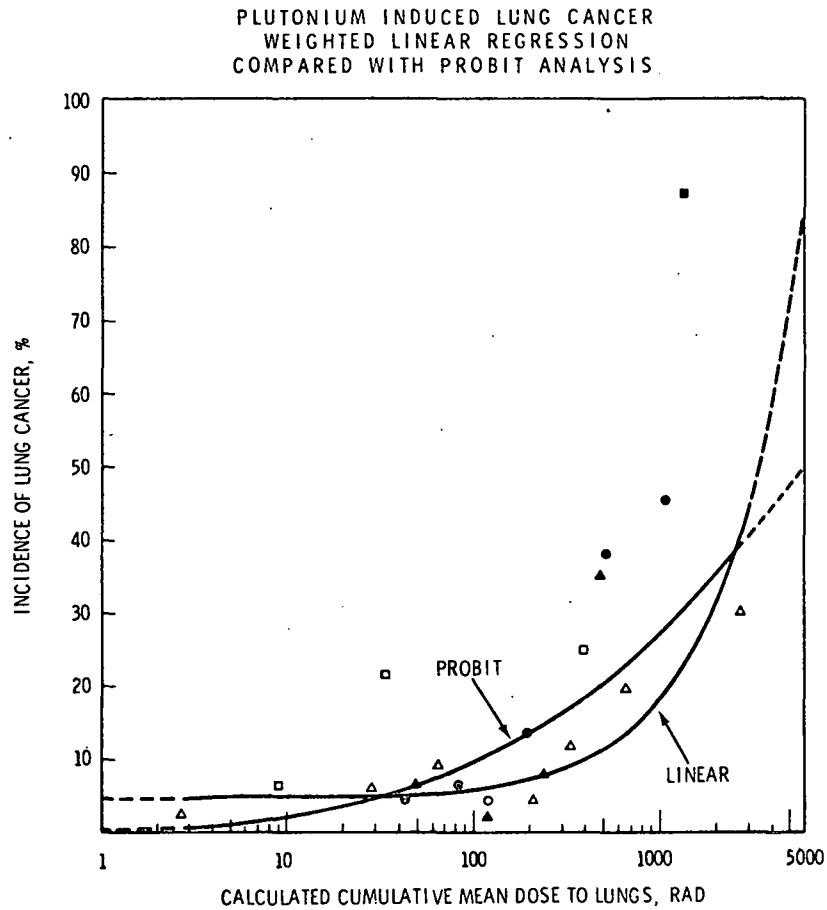

Figure 18

(J. M. Thomas and W. J. Bair, to be published)
PNL66233-1

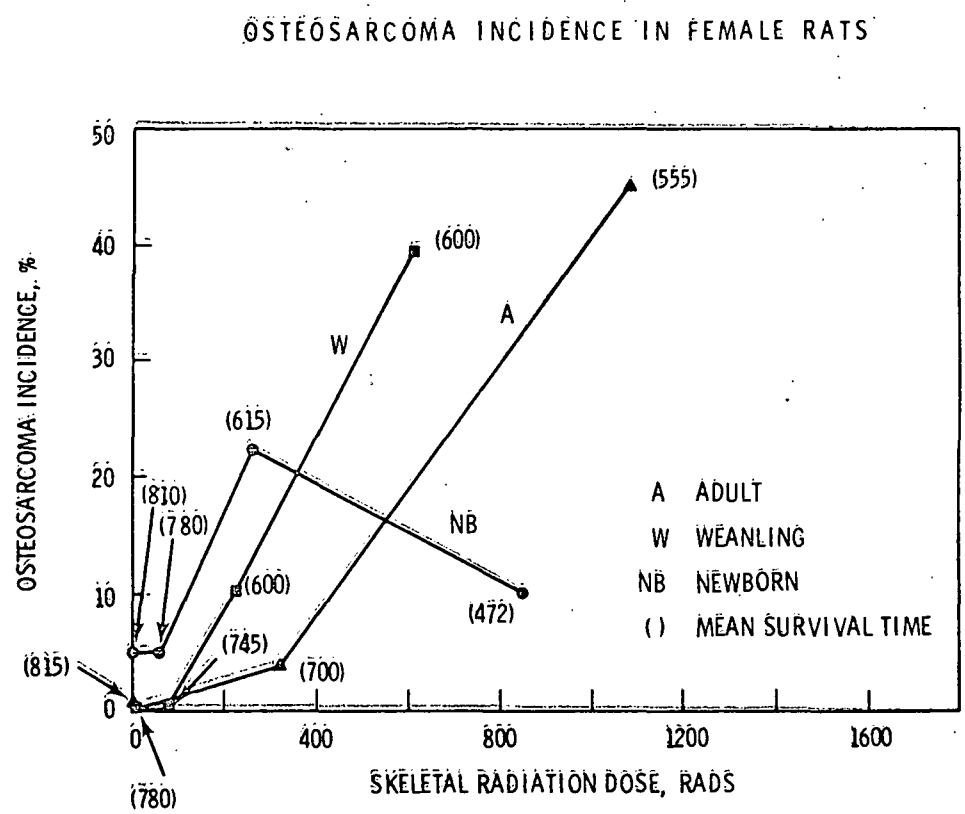

Figure 19

(D. D. Mahlum and M. R. Sikov, PNL, to be published in Pacific Northwest Laboratory Annual Report for 1974) PNL747510-13

Figure 20

Autoradiograph of a histologic section from a lung of a rat after inhalation of $^{244}Cm(NO_3)_3$. (Provided by J. LaFuma, Commissariat a l' Energie Atomique, Association Euratom. C.E.A. CEN. FAR. France.) PNL747596-4

Figure 21

Autoradiograph of a histologic section from a lung of a rat after inhalation of $^{239}Pu(NO_3)_4$. (Provided by J. Lafuma, Commissariat a l' Energie Atomique, Association Euratom. C.E.A. CEN. FAR. France.)PNL747596-1

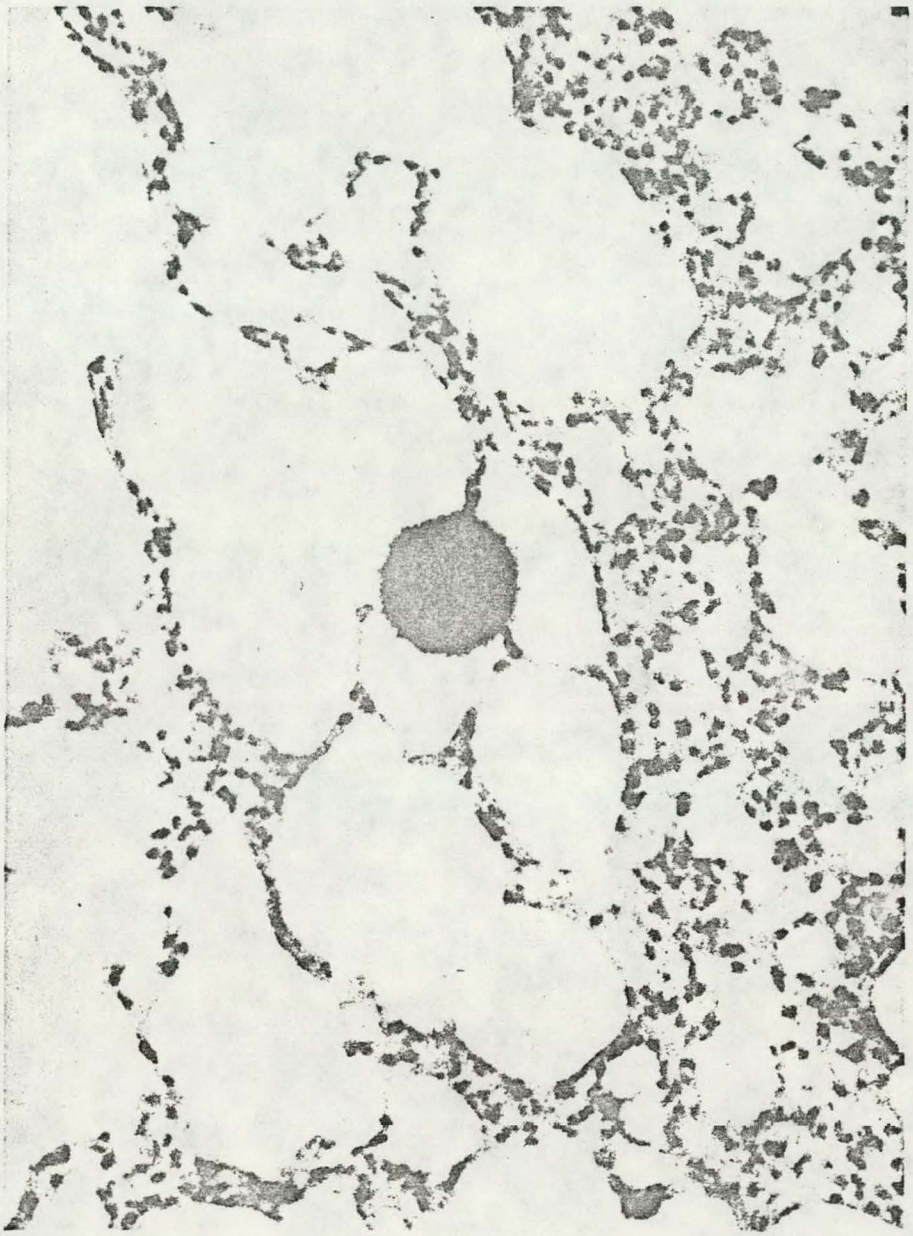

Figure 22

Autoradiograph of a histologic section from a lung of a rat 356 days after intraperitoneal injection of $^{239}PuO_2$ particles. (Provided by C. L. Sanders, PNL) PNL747358-1

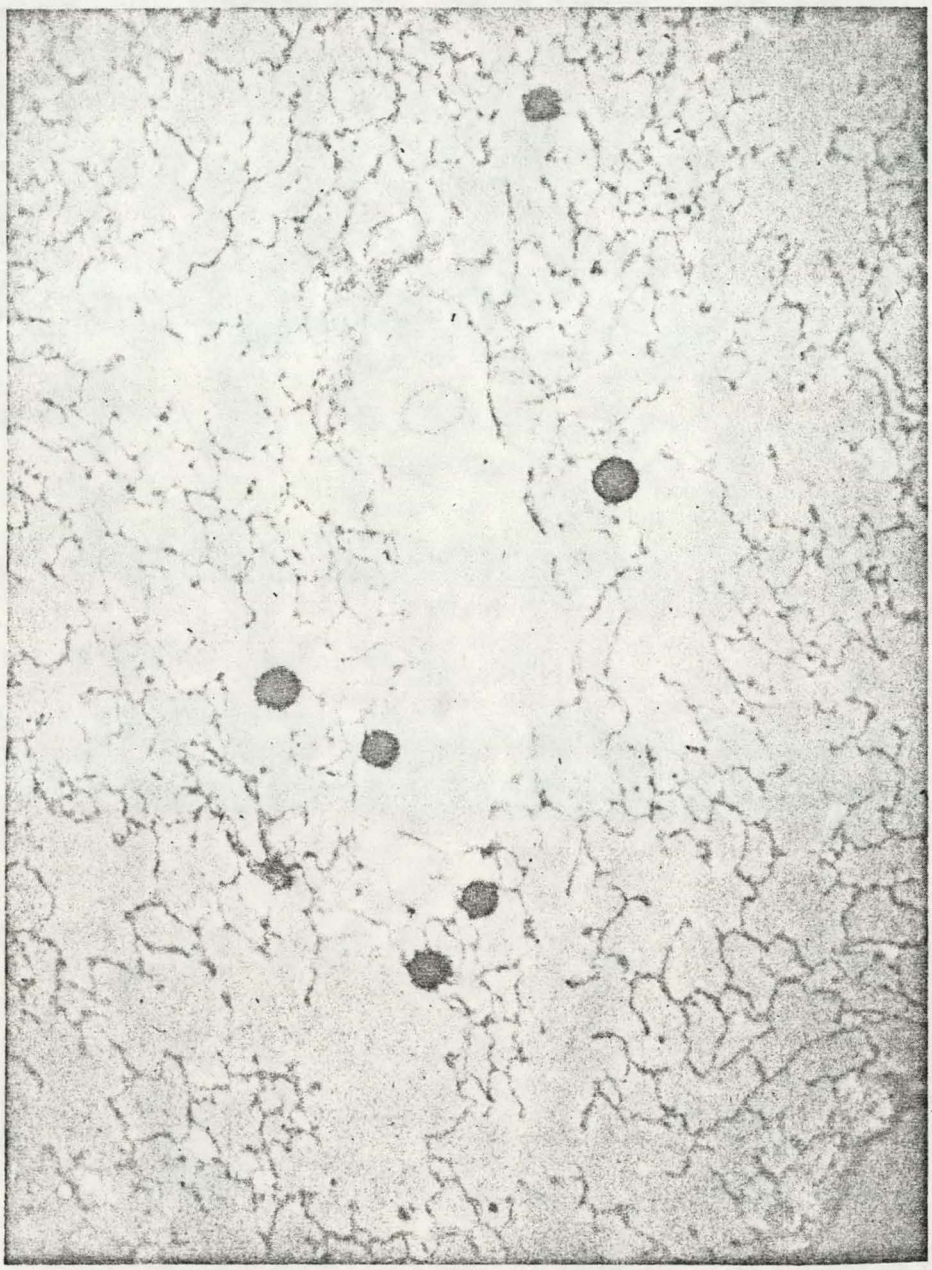

Figure 23

Autoradiogram of a histologic section for a lung of a dog 2 years after inhalation of $^{239}PuO_2$. (Provided by G. E. Dagle, PNL) PNL66199-1

OBSERVED BIOLOGICAL EFFECTS OF INHALED PLUTONIUM

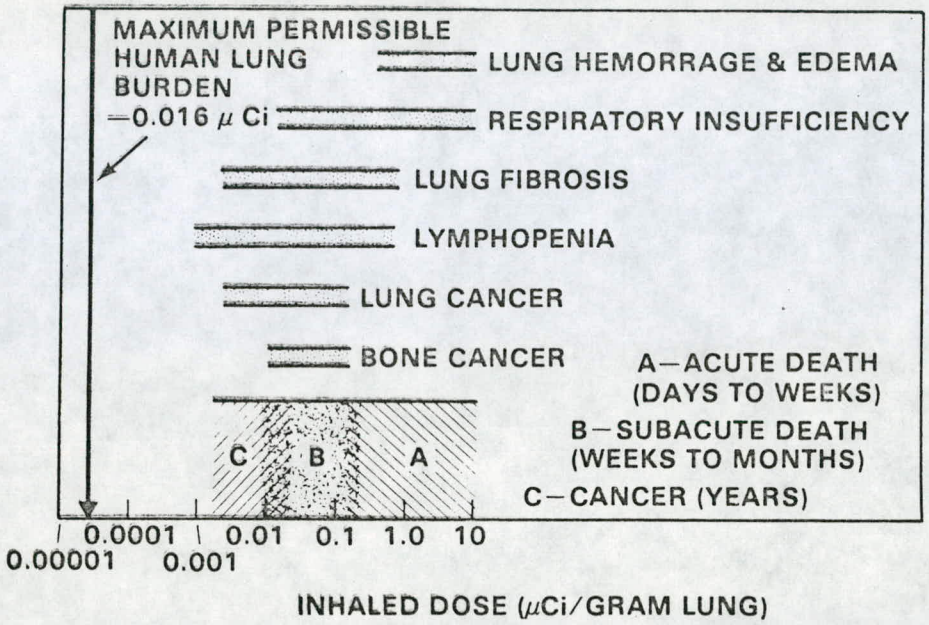

Figure 24

TABLE 11

Life Span Study of Inhaled Plutonium

in Dogs at Lovelace

	Particle Size* (μm)	Initial Lung Burden (μCi)	Number of Dogs
$^{238}PuO_2$	1.5	5.6, 3, 1.4, 0.7, 0.3, 0.1	72
$^{238}PuO_2$	3.0	"	72
$^{239}PuO_2$	0.75	"	72
$^{239}PuO_2$	1.5	"	72
$^{239}PuO_2$	3.0	"	72
			360 + 60 controls

*Aerodynamic diameter of monodisperse aerosols

TABLE 12

Life Span Study of Inhaled Plutonium in Dogs at Battelle-Northwest

$^{238}Pu^{16}O_2$		$^{239}PuO_2$	
Initial Lung Burden (μCi)	No. of Dogs*	Initial Lung Burden (μCi)	No. of Dogs*
.002	20	.004	20
.02	20	.02	20
.08	20	.08	20
.35	20	.3	20
1.3	20	1.1	20
5.2	13	5.8	8
	113		108

*Half male and half female + 40 controls

RETENTION OF PLUTONIUM IN PULMONARY REGION OF LUNG

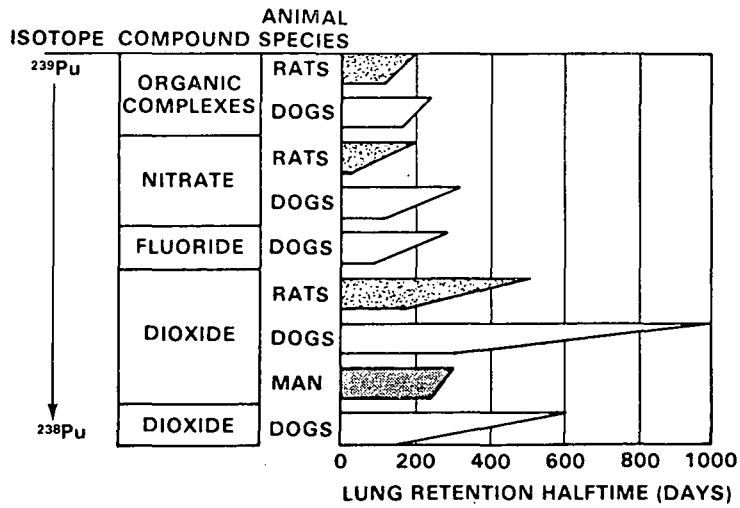

Figure 1

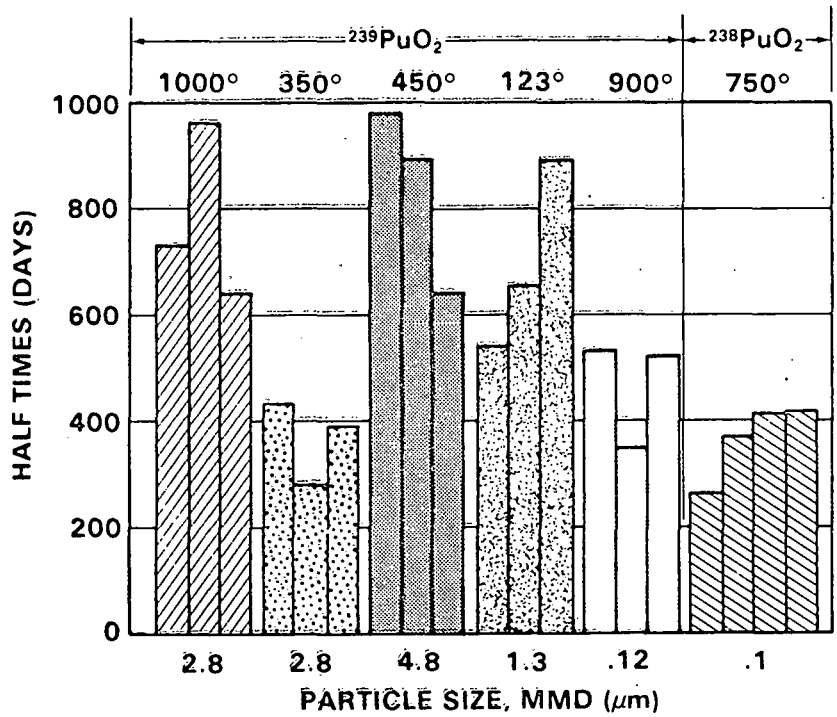

Figure 2

Pulmonary Retention of Inhaled PuO_2 in Dogs

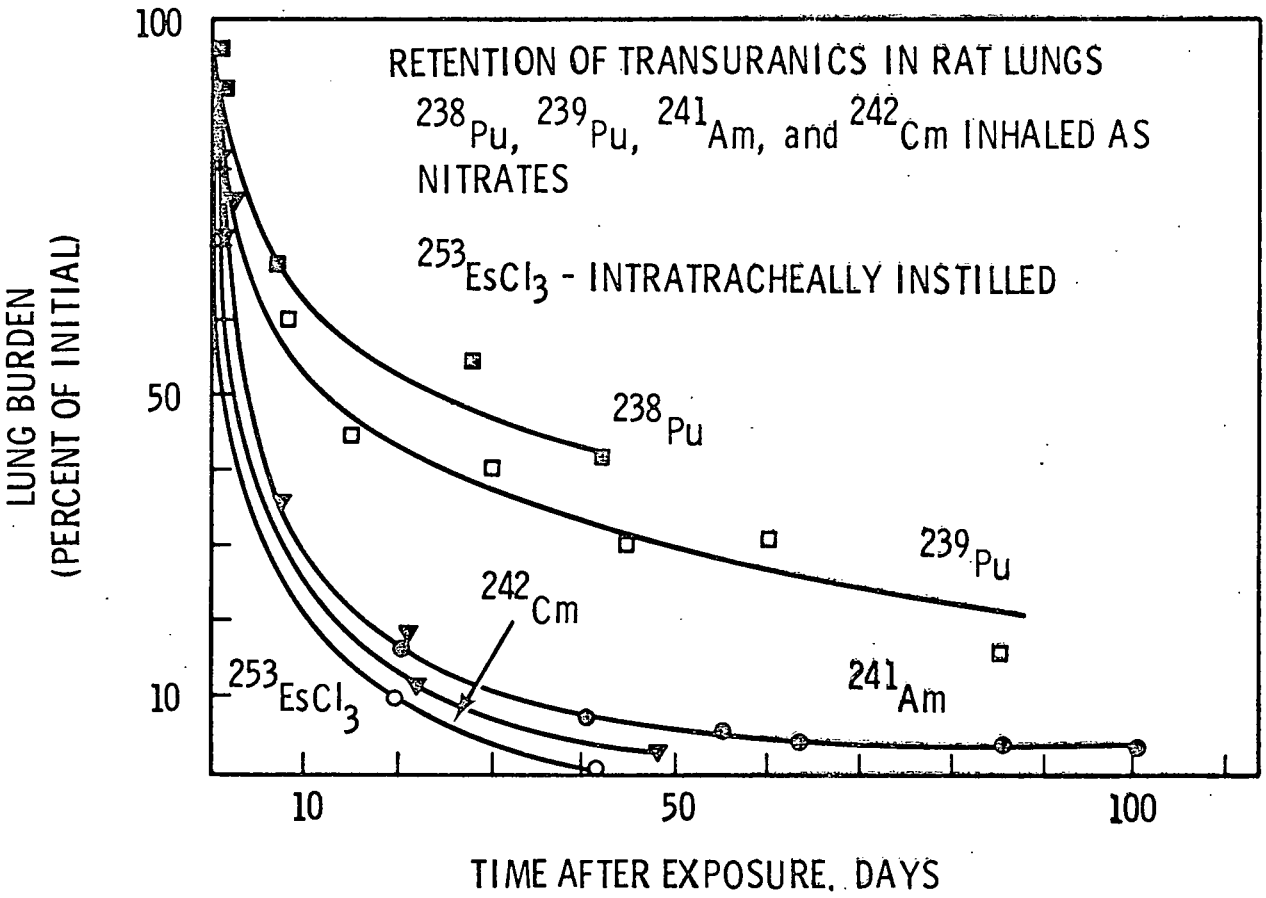

Figure 3

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)

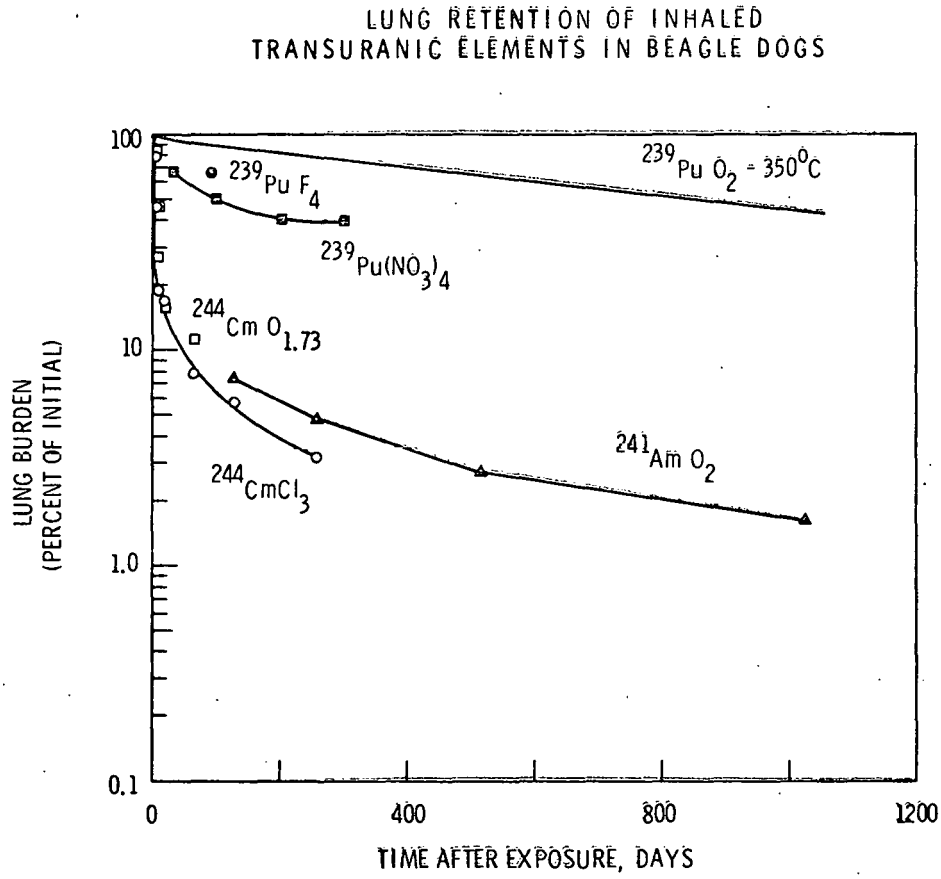

Figure 4

(Redrawn from R. O. McClellan, 1972)

MODELING

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

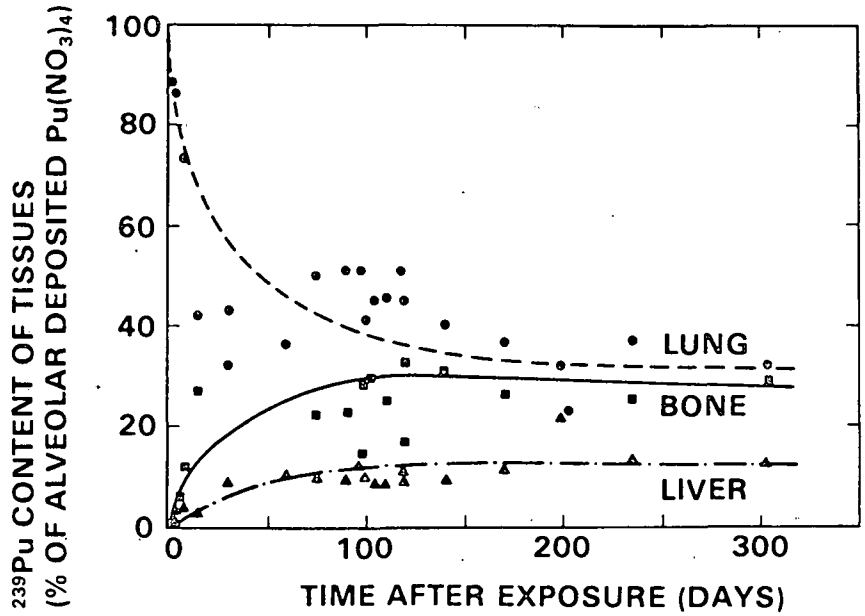

Figure 11

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

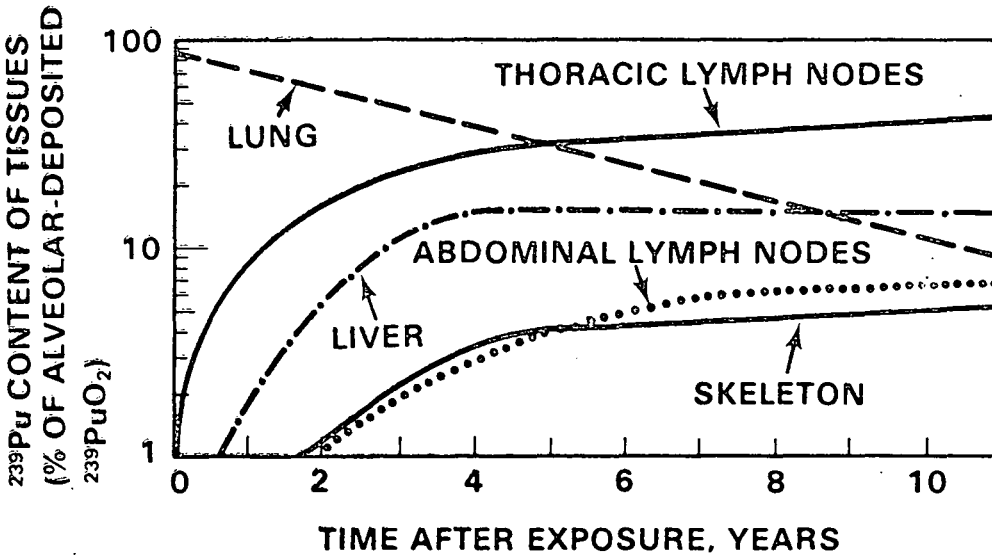

Figure 12

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

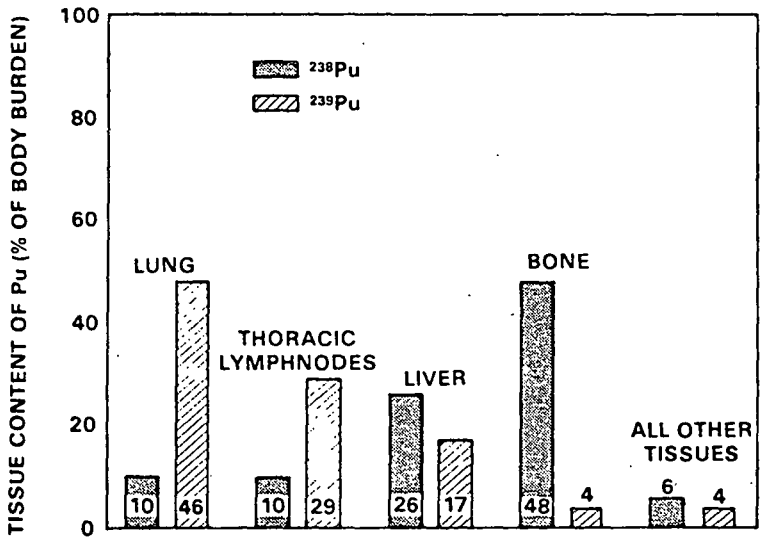

Figure 13

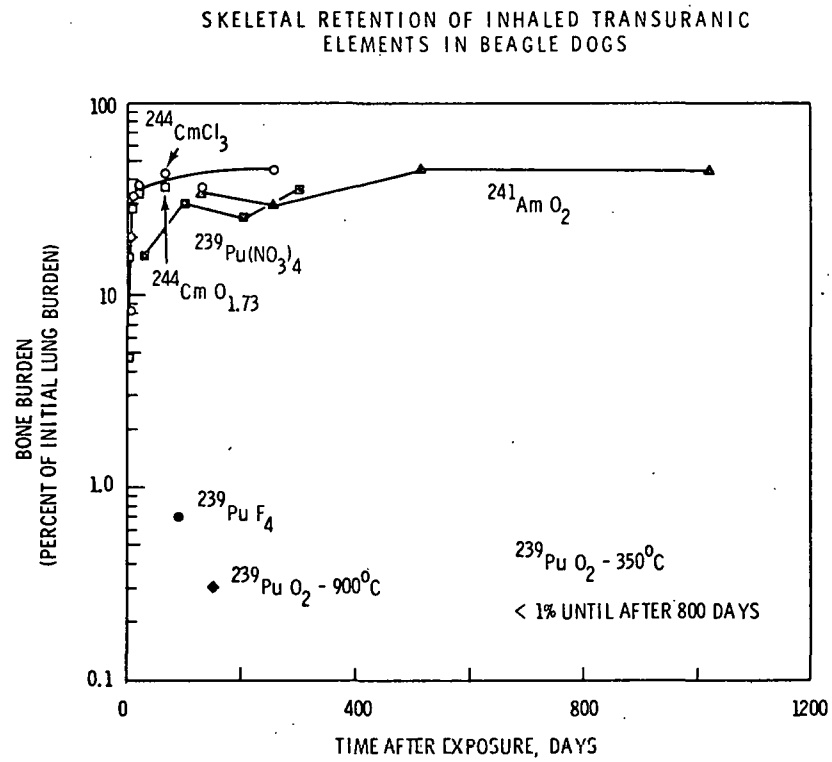

Figure 14

(Redrawn from R. O. McClellan, 1972)

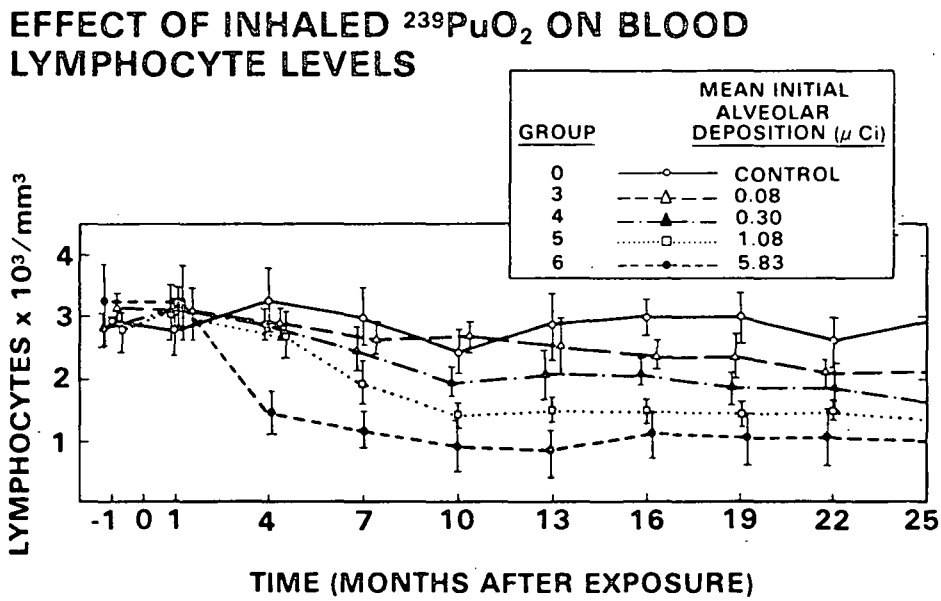
EFFECT OF INHALED $^{239}PuO_2$ ON BLOOD LYMPHOCYTE LEVELS
GROUP
MEAN INITIAL ALVEOLAR DEPOSITION (μ Ci)
0 CONTROL
3 0.08
4 0.30
5 1.08
6 5.83
LYMPHOCYTES x 10^3/mm^3
4
3
2
1
-1 0 1 4 7 10 13 16 19 22 25
TIME (MONTHS AFTER EXPOSURE)

Figure 15

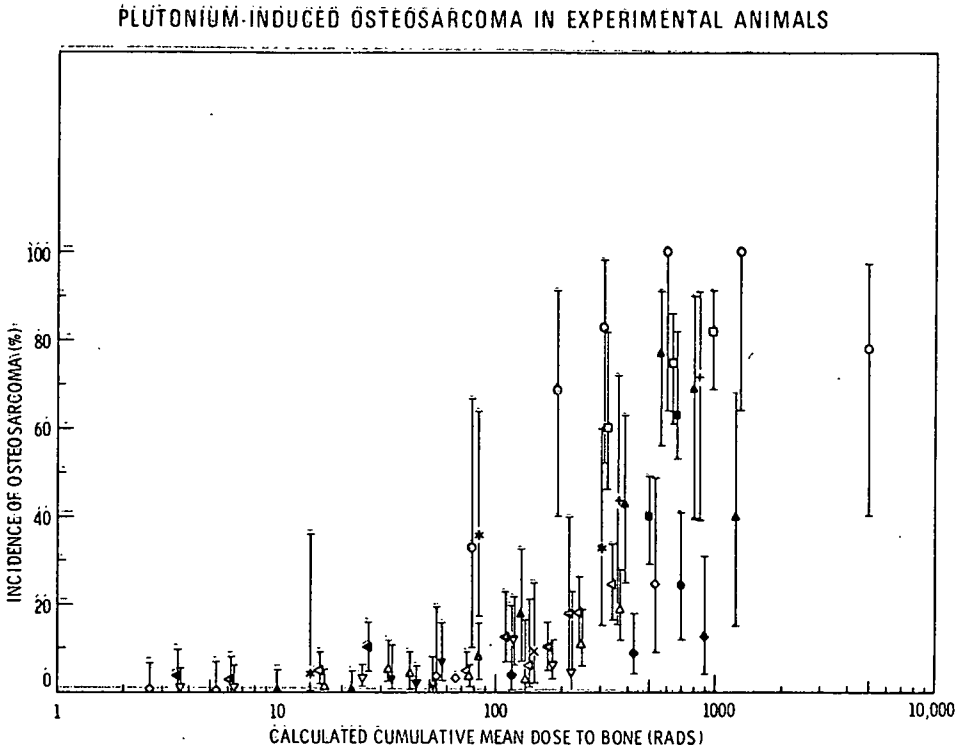

Figure 16

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- ∇ ^{239}Pu Plutonylpentacarbonate - Inhaled - Rats (from Buldakov and Lyubchansky, 1970)
- ◇ ^{239}Pu Nitrate - Sub- and Intracutaneous - Rats (from Buldakov, et al., 1971)
- ▼ ^{239}Pu Citrate - Oral (Daily) - Rats (from Buldakov et al., 1969)
- ⊕ ^{239}Pu Plutonyltriacetate - I.T. - Rats (from Erokhin et al., 1971)
- ▲ ^{239}Pu Citrate - IV - Mice (from Finkel and Biskis, 1962)
- □ ^{239}Pu Citrate, Monomeric - IV - Mice (from Rosenthal and Lindenbaum, 1967)

^{239}Pu Citrate, Polymeric - IV - Mice (from Rosenthal and Lindenbaum, 1967)

X $^{238}PuO_2$ - Inhaled - Rats (from C. L. Sanders, 1973)

^{239}Pu Nitrate - I.T. - Rats (from Erokhin et al., 1971)

\+ ^{239}Pu Nitrate - I.T. - Rabbits)from Koshnurnikova et al., 1971)

* ^{239}Pu (Pentacarbonate) - Inhaled - Rabbits (from Koshnurnikova et al., 1971)

^{239}Pu Citrate - Inhaled - Rats (from Koshnurnikova et al., 1971)

^{239}Pu Pentacarbonate - Inhaled - Rats (from Koshnurnikova et al., 1971)

(See Bair, 1974 for complete references)

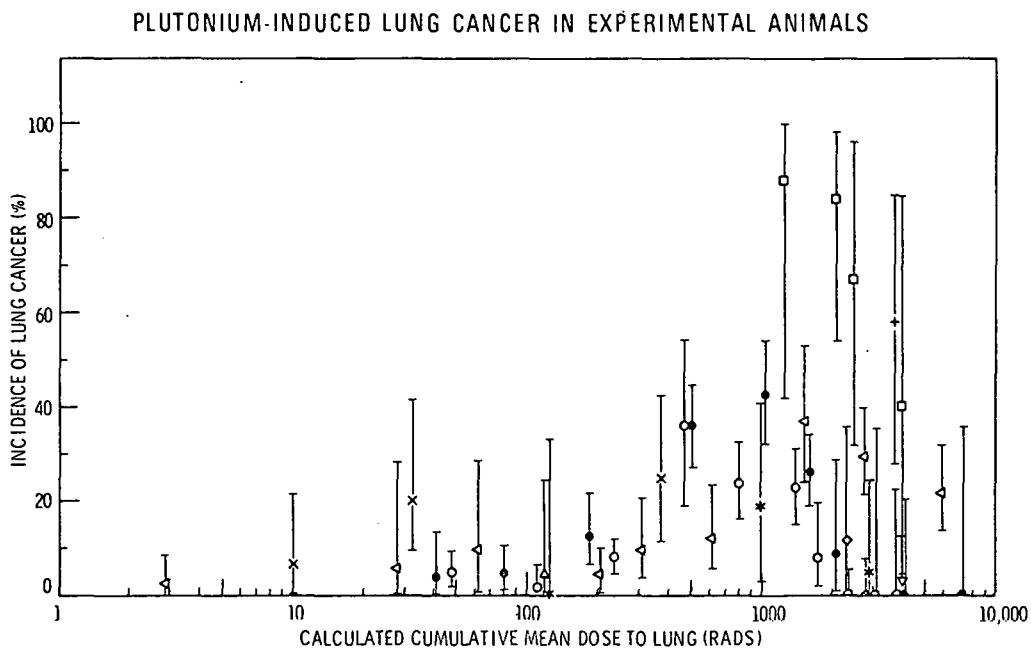

Figure 17

Plutonium-induced Lung Cancer in Experimental Animals
Mean incidence and radiation dose values are those reported in the literature. Binomial confidence limits were calculated from data included in the referenced literature.

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- ∇ $^{239}PuO_2$ - Mice (from Temple et al., 1959)
- Δ $^{239}PuO_2$ - Mice (from Temple et al., 1959)
- ◈ $^{239}PuO_2$ - Mice (from Wager et al., 1956)
- o ^{239}Pu Citrate - Rats (from Buldakov and Lyubchansky, 1970)
- ● ^{239}Pu - Plutonylpentacarbonate - Rats (from Buldakov and Lyubchansky, 1970)
- x ^{238}Pu - Rats (from C. L. Sanders, 1973)

△ ^{239}Pu - Rats - $Pu(NO_3)_4$ (from Erokhin et al., 1971)

\+ ^{239}Pu - Rabbits - $Pu(NO_3)_4$ (from Koshnurnikova et al., 1971)

* ^{239}Pu - Rabbits - NH_4 Pu Pentacarbonate (from Koshnurnikova et al., 1971)

(See Bair, 1974 for complete references)

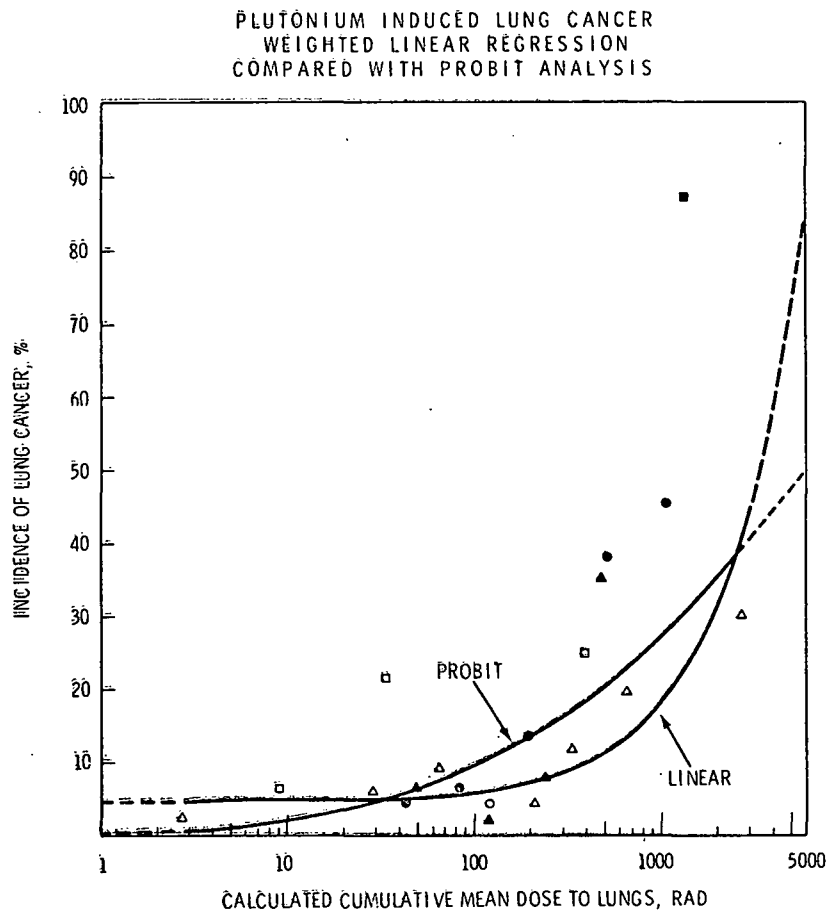

Figure 18

(J. M. Thomas and W. J. Bair, to be published)
PNL66233-1

OSTEOSARCOMA INCIDENCE IN FEMALE RATS

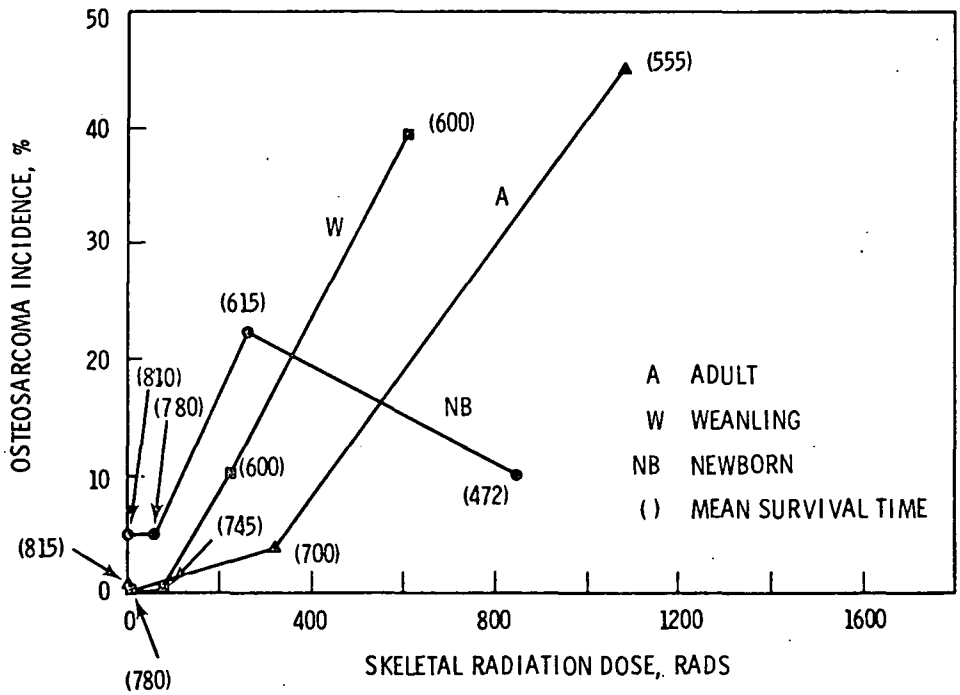

Figure 19

(D. D. Mahlum and M. R. Sikov, PNL, to be published in Pacific Northwest Laboratory Annual Report for 1974) PNL747510-13

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OBSERVED BIOLOGICAL EFFECTS OF INHALED PLUTONIUM

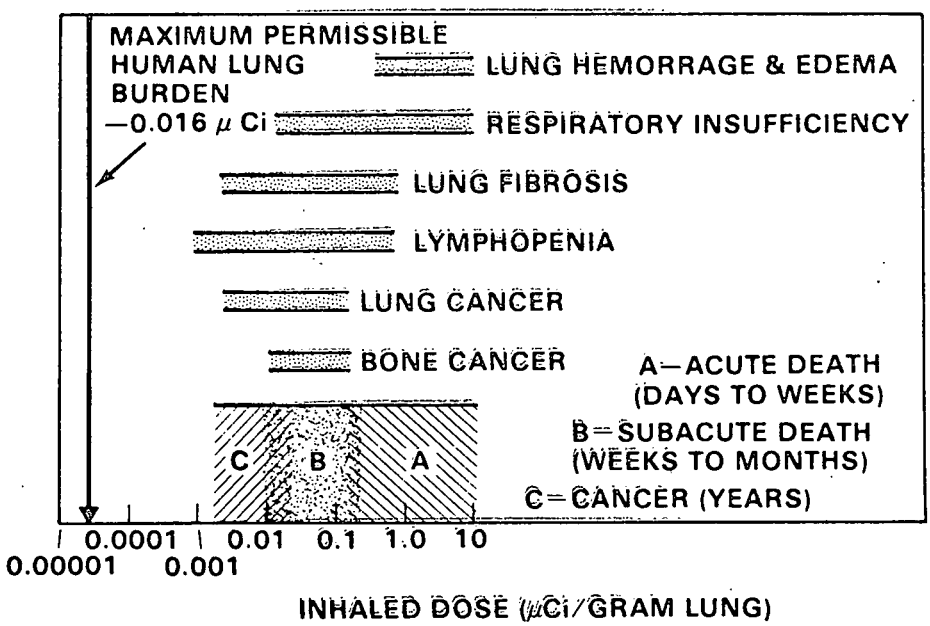

Figure 24