NUREG/CR-4986

Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides

Final Report

Prepared by J. A. Mewhinney

Lovelace Biomedical and Environmental Research Institute

Prepared for
U.S. Nuclear Regulatory
Commission

NUREG/CR-4986
RH

Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides

Final Report

Manuscript Completed: December 1986
Date Published: September 1987

Prepared by
J. A. Mewhinney

Lovelace Biomedical and Environmental Research Institute
Inhalation Toxicology Research Institute
P.O. Box 5890
Albuquerque, NM 87185

Prepared for
Division of Regulatory Applications
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, DC 20555
NRC FIN A1031

PREVIOUS DOCUMENTS IN SERIES

1. Radiation Exposure and Risk Estimates for Inhaled Airborne Radioactive Pollutants Including Hot Particles, Annual Progress Report, 1976-1977, NUREG/CR-0100, 1978.

2. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1977-1978, NUREG/CR-0673, LF-63, 1979.

3. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1978-1979, NUREG/CR-1458, LF-71, 1980.

4. Comparison of Physical Chemical Properties of Powders and Respirable Aerosols of Industrial Mixed Uranium and Plutonium Oxide Fuels, NUREG/CR-1736, LMF-78, 1980.

5. In Vitro Dissolution of Respirable Aerosols of Industrial Uranium and Plutonium Mixed Oxide Nuclear Fuels, NUREG/CR-2171, LMF-79, 1981.

6. Particle Analysis of Mixed-Oxide Nuclear Fuel Materials by Energy Dispersive X-Ray Fluorescence, NUREG/CR-1871, LMF-80, 1981.

7. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1979-1980, NUREG/CR-2246, LMF-86, 1981.

8. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1980-1981, NUREG/CR-2512, LMF-92, 1982.

9. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1981-1982, NUREG/CR-3313, LMF-105, 1983.

10. Radiation Dose Estimates and Hazard Evaluations for Airborne Radionuclides, Annual Progress Report, 1982-1983, NUREG/CR-3870, LMF-109, 1984.

ABSTRACT

This is the final report for a project whose objective was to conduct confirmatory research on physical chemical characteristics of aerosols produced during manufacture of mixed plutonium and uranium oxide nuclear fuel, to determine the radiation dose distribution in tissues of animals after inhalation exposure to representative aerosols of these materials, and to provide estimates of the relationship of radiation dose and biological response in animals after such inhalation exposure. This report is divided into three chapters which summarize the results of these investigations. The first chapter summarizes the physical chemical characterization of samples of aerosols collected from gloveboxes at industrial facilities during normal operations. This chapter provides insights into key aerosol characteristics which are of potential importance in determining the biological fate of specific radionuclides contained in the particulates that would be inhaled by humans following accidental release. The second chapter describes the spatial and temporal distribution of radiation dose in tissues of three species of animals exposed to representative aerosols collected from the industrial facilities. These inhalation studies provide a basis for comparison of the influence of physical chemical form of the inhaled particulates and the variability among species of animal in the radiation dose to tissue. The third chapter details to relationship between radiation dose and biological response in rats exposed to two aerosol forms each at three levels of initial pulmonary burden. This study, conducted over the lifespan of the rats and assuming results to be applicable to humans, indicates that the hazard to health due to inhalation of these industrial aerosols is not different than previously determined for laboratory produced aerosol of PuO_2.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF TABLES (continued)

ACKNOWLEDGEMENTS

PERSONNEL CONTRIBUTING TO THE RESEARCH

Scientific Staff

J.A. Mewhinney	Ph.D.	Radiobiologist
B.B. Boecker	Ph.D.	Radiobiologist
A.F. Eidson	Ph.D.	Chemist
D.H. Gray	M.S.	Radiochemist
F.F. Hahn	D.V.M. Ph.D.	Experimental Pathologist
B.R. Scott	Ph.D.	Biomathematician
F.A. Sieler	Ph.D.	Physicist

Technical Staff

M.F. Conrad	Laboratory Technician
Y.N. Knighton	Radiochemical Analyst
J.A. Romero	Laboratory Technician
B.J. Allmer	Laboratory Technician
C.D. Esquibal	Radiochemical Analyst
H.M. Sedillo	Radiochemical Analyst
K.J. Warner	Research Technologist

It should be emphasized that a listing such as this is rarely comprehensive in acknowledging individuals who have made important contributions to the research. In the unnamed category are the many highly skilled animal care, radiochemical analysts, maintenance, shop, administrative and secretarial personnel whose efforts were essential to the completion of a productive and meaningful research project. Research was performed in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

EXECUTIVE SUMMARY

This final report presents detailed research results for the project entitled "Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides". The three chapters in this report present the results of three areas of the research project. Substantial detail is provided in each chapter to indicate the scope of the research and to facilitate interpretation of the results.

The objective of this project was to conduct confirmatory research on specific aerosol characteristics that may modify the biological fate of the inhaled materials, the patterns of radiation dose distribution in various tissues and organs, and the dose-response relationships following inhalation of these materials. This research involved physical, chemical and biological characterization of aerosols actually present in different process stages used to produce mixed uranium and plutonium oxide nuclear fuel. Since the research involved actual aerosols produced in industrial operations, the research provides a key link between studies with idealized, laboratory-produced aerosols and derived radiation protection standards and hazard analyses.

Industrially-collected aerosol materials were re-aerosolized in the laboratory to determine patterns of deposition, retention, and translocation in laboratory animals as a function of time after an inhalation exposure. The aerosols used were characterized using a number of physical and chemical analysis techniques to determine possible differences between the aerosol and the corresponding bulk powder. These efforts were aimed at determining those characteristics that might help explain the observed patterns seen in animals after exposure. Multiple species (rats, dogs, and monkeys) were used to strengthen the extrapolation of results to man. Finally, the relationship of radiation dose and biological response were determined in rats to provide an estimate of the potential hazard to health of humans that might inhale these materials.

This final report begins with a chapter summarizing the comprehensive analyses of the physical chemical characteristics of 12 aerosol materials collected at various stages of the mixed uranium and plutonium oxide nuclear fuel fabrication process. The aerosol were subjected to a variety of analytical methods including X-ray diffraction, infrared spectroscopy, energy dispersive X-ray fluorescence, alpha spectroscopy and *in vitro* dissolution methods. The results of these individual analyses showed that no biologically significant differences in the aerosols existed prior to sintering of the pressed fuel pellets at high temperature. All of these aerosols consisted of intimately mixed individual particles of UO_2 and PuO_2 such that dissolution of uranium and plutonium proceeded independantly. During sintering at 1750°C, a solid solution of $(U,Pu)O_2$ was formed such that dissolution of the plutonium component of the material was controlled by the dominant mass of uranium. Thus, dissolution of the plutonium component of the

$(U,Pu)O_2$ was slightly more rapid than for PuO_2 particulates. The results of the *in vitro* dissolution studies using a synthetic serum ultrafiltrate were used to calculate a specific constant of dissolution for use in the biokinetic model of the retention, distribution and excretion in three species of animals (chapter #2 of this report). The physical chemical characterizations of these aerosol materials showed that only minor differences exist among the aerosols sampled at many stages of the processing of these fuel materials and that no additional biological studies need to be initiated to study these differences.

The second chapter discusses the formulation and application of a biokinetic model of the retention, distribution and excretion of plutonium and americium in rats, dogs and monkeys after inhalation of aerosols of intimately mixed particulates of UO_2 and PuO_2, of $(U,Pu)O_2$ solid solution particulates or PuO_2. The model used the measured physical chemical characteristics of these particulates to describe the rate of dissolution of material deposited in lung. Good agreement with the observed retention and distribution data for plutonium was obtained for all three species studied. Results of these studies indicated that for a given elemental component of the particulates, slight differences in the retention, distribution and excretion of that element was accounted for by slight differences in the physical chemical characteristics of the aerosol. For a given aerosol, significant differences in retention, distribution and excretion were noted among the three animal species. These differences involved differences in the rates of mucociliary clearance of particles from lung, in the pattern of retention in liver and rates of excretion in urine.

The third chapter examines the relationship between radiation dose and biological response in the lungs of rats that inhaled either $(U,Pu)O_2$ or PuO_2 and three levels of initial pulmonary burden. Biological responses in organs of the rat other than lung were not different for exposed rats compared to control animals. Inhalation exposure to either of these materials resulted in a spectrum of pulmonary cancers, with no discernable difference ascribable to the physical chemical form of the aerosol. Comparison of the crude incidence of pulmonary cancers in rats exposed to these industrial materials containing plutonium were not different from rats exposed to laboratory-produced aerosols of $^{239}PuO_2$. Using a linear dose-effect model, the relative risk of pulmonary cancers following inhalation of these industrial materials was 2.3 ± 1.9 (SE) at a pulmonary dose of 100 rads. This value is in excellant agreement with a relative risk value of 2.2 at an exposure level of approximately 100 rad to lung estimated from the United States uranium miner data cited by the Committee on the Biological Effects of Ionizing Radiation (BEIR III). This suggests that the rat may provide a model useful for estimation of the relative risk for lung cancer induction in people following inhalation of actinide element aerosols. The doubling dose estimated from these studies was 78 ± 63 rads to lung to median lifespan.

PUBLICATIONS IN THE OPEN LITERATURE

1. Eidson, A. F., P. B. DeNee and C. A. Macken, "Particle Analysis of Mixed Oxide Nuclear Fuel Materials by Energy Dispersive X-Ray Fluorescence." Electron Microscopy and X-Ray Applications to Environmental and Occupational Health Analysis. Vol. 2, Chapter 12, pp 233-244, Ann Arbor Science, Ann Arbor, MI, 1981.

2. Stanley, J. A., A. F. Eidson, and J. A. Mewhinney, "Distribution, Retention, and Dosimetry of Plutonium and Americium in the Dog, Rat, and Monkey After Inhalation of an Industrial Mixed Uranium and Plutonium Oxide Aerosol." Health Phys. 43: 521-530, 1982.

3. Eidson, A. F., "Comparison of Physical Chemical Properties of Powders and Respirable Aerosols of Industrial Mixed Uranium and Plutonium Oxide Fuels." Health Phys. 42: 531-536.

4. Eidson, A. F., and J. A. Mewhinney, "In Vitro Dissolution of Respirable Aerosols of Industrial Uranium and Plutonium Mixed-Oxide Nuclear Fuels." Health Phys. 45: 1023-1037, 1983.

5. Hoover, M. D., G. J. Newton, H. C. Yeh, and A. F. Eidson, "Characterization of Aerosols from Industrial Fabrication of Mixed-Oxide Nuclear Reactor Fuels." In Aerosols in the Mining and Industrial Work Environments, Vol. 2, Characterization, Chapter 39, pp 533-548, Eds., V. A. Marple, B. Y. H. Liu, Ann Arbor Sciences, 1983.

6. Mewhinney, J. A., A. F. Eidson, and B. B. Boecker, "Interspecies Comparison of the Metabolism and Dosimetry of Inhaled Mixed Oxides of Plutonium and Uranium." In Radiation-Risk-Protection, Vol. 1, pp 490-493, Proceedings of the 6th Congress of the International Radiation Protection Association; Berlin, Federal Republic of Germany, May 7-12, 1984.

7. Rothenberg, S. J., D. K. Flynn, A. F. Eidson, J. A. Mewhinney, and G. J. Newton, "Determination of Specific Surface Area by Krypton Adsorption; Comparison of Three Methods of Determining Surface Area and Evaluation of Different Specific Surface Area Standards." J. Colloid Interface Sci. 116: 541-554, 1987.

8. Mewhinney, J. A., S. J. Rothenberg, A. F. Eidson, G. J. Newton, and R. C. Scripsick, "Specific Surface Area Determinations of U and Pu Oxide Particles." J. Colloid Interface Sci. 116: 555-562, 1987.

PUBLICATIONS IN THE OPEN LITERATURE (continued)

9. Mewhinney, J. A., A. F. Eidson, and V. A. Wong, "Effect of Wet-Dry Cycles on Dissolution of Relatively Insoluble Particles Containing Plutonium." Health Phys. (submitted).

ABSTRACTS PUBLISHED IN THE OPEN LITERATURE

1. Eidson, A. F., J. A. Mewhinney, J. A. Stanley and T. Mo, "Deposition, Retention, and Excretion in the Beagle Dog of Inhaled Mixed Plutonium and Uranium Oxides as Processed in a Fuel Fabrication Facility." Health Phys. 33:667, 1977.

2. Stanley, J. A., J. A. Mewhinney, A. F. Eidson and T. Mo, "Deposition, Retention and Excretion of Industrial Mixed Oxide Aerosols Using the Laboratory Rat." Health Phys. 33: 666, 1977.

3. Eidson, A. F. and J. A. Mewhinney, "Inhalation Toxicology of Industrial Plutonium and Uranium Oxide Aerosols I: Physical Chemical Characterization." Health Phys. 35: 887, 1978.

4. Stanley, J. A., A. F. Eidson, J. A. Mewhinney, and T. Mo, "Inhalation Toxicology of Industrial Plutonium and Uranium Oxide Aerosols II: Deposition, Retention and Dosimetry." Health Phys. 35: 888, 1978.

5. Stanley, J. A., A. F. Eidson, J. A. Mewhinney, and R. A. Guilmette, "Deposition, Retention and Dosimetry of an Inhaled Industrial Aerosol Containing 750°C Heat Treated Mixed Plutonium and Uranium Oxides in the Rat, Dog and Monkey." Health Phys. 37: 831, 1979.

PRESENTATIONS AT NATIONAL OR INTERNATIONAL SCIENTIFIC MEETINGS

1. Eidson, A. F., J. A. Mewhinney, J. A. Stanley and T. Mo, "Retention, Deposition, and Excretion in the Beagle Dog of Inhaled Plutonium and Uranium Oxides as Processed in a Fuel Fabrication Facility." 22nd Annual Meeting of the Health Physics Society, Atlanta, GA, July 4-8, 1977.

2. Stanley, J. A., J. A. Mewhinney, A. F. Eidson, and T. Mo, "Deposition, Retention, and Excretion of Industrial Mixed-Oxide Aerosols Using the Laboratory Rat." 22nd Annual Meeting of the Health Physics Society, Atlanta, GA, July 4-8, 1977.

PRESENTATIONS AT NATIONAL OR INTERNATIONAL SCIENTIFIC MEETINGS (continued)

3. Eidson, A. F. and J. A. Mewhinney, "Inhalation Toxicology of Industrial Plutonium and Uranium Oxide Aerosols I: Physical, Chemical Characterization." 23rd Annual Meeting of the Health Physics Society, Minneapolis, MN, June 20-23, 1978.

4. Stanley, J. A., A. F. Eidson, J. A. Mewhinney and T. Mo. "Inhalation Toxicology of Industrial Plutonium and Uranium Oxide Aerosols II: Deposition Retention and Dosimetry." 23rd Annual Meeting of the Health Physics Society Meeting, Minneapolis, MN, June 20-23, 1978.

5. Mo, T., "Assay of Uranium, Plutonium, and Americium in Biological Samples by Sequential Separation and Liquid Scintillation Counting." American Chemical Society Meeting, Anaheim, CA, March 15-17, 1978.

6. Newton, G. J., H. C. Yeh, J. A. Stanley, and R. Tamura, "Field Characterization of Plutonium Aerosols in Mixed-Oxide Fuel Fabrication." American Industrial Hygiene Association Conference, Los Angeles, CA, May 9-12, 1978.

7. Eidson, A. F. and P. B. DeNee, "Bulk and Surface Analysis of Mixed Oxide Nuclear Fuels." Aspen Symposium on Electron and X-Ray Applications to Environmental and Occupational Health Analysis, Colorado Springs, CO, September 19-21, 1979.

8. Stanley, J. A., A. F. Eidson, J. A. Mewhinney, and R. A. Guilmette, "Deposition, Retention, and Dosimetry of an Inhaled Industrial Aerosol Containing 750°C Heat Treated, Mixed Plutonium and Uranium Oxides in the Rat, Dog and Monkey." 24th Annual Meeting of the Health Physics Society, Philadelphia, PA, July 8-13, 1979.

9. Hoover, M. D., G. J. Newton, H. C. Yeh, and A. F. Eidson, "Characterization of Aerosols in Fabrication of Mixed-Oxide Nuclear Reactor Fuels." International Symposium on Aerosols in the Mining and Industrial Work Environment, Minneapolis, MN, November 1-6, 1981.

10. Mewhinney, J. A. and A. F. Eidson, "Lung Retention in Rats, Dogs and Monkeys Following Inhalation of Industrial Aerosols Found in Fabrication of Mixed Oxide Nuclear Fuels." 27th Annual Meeting of the Health Physics Society, Las Vegas, NV, June 27-July 1, 1982.

PRESENTATIONS AT NATIONAL OR INTERNATIONAL SCIENTIFIC MEETINGS (continued)

11. Mewhinney, J. A., A. F. Eidson, and V. E. Powers, "The Effect of Wet-Dry Cycles in Dissolution of Particles and Plutonium Oxides." 28th Annual Meeting of the Health Physics Society, Baltimore, MD, June 19-23, 1983.

12. Mewhinney, J. A., A. F. Eidson, and B. B. Boecker, "Interspecies Comparison of the Metabolism and Dosimetry of Inhaled Mixed Oxides of Pu and U." 6th International Congress of the International Radiation Protection Association, Berlin, FRG, May 6-11, 1984.

13. Mewhinney, J. A., "Research on Internal Deposition of Mixed Oxides of Plutonium and Uranium-." Lecture at the Institute for Genetik und Fur Toxicologie von Spaltstoffen, Karlsruhe, Germany, May 4, 1984.

14. Rothenberg, S. J., J. A. Mewhinney, A. F. Eidson, D. K. Flynn, G. J. Newton and R. Scripsick, "Measurement of Specific Surface Areas of Small Powder Samples of Uranium, Plutonium and Mixed uranium and Plutonium Oxides Using ^{85}Kr as Adsorbate." First International Aerosol Conference, Minneapolis, MN, September 17-21, 1984.

Chapter 1. SUMMARY OF THE PHYSICAL CHEMICAL ANALYSES OF MIXED OXIDE NUCLEAR FUEL AS THEY MIGHT INFLUENCE BIOLOGICAL BEHAVIOR AND INTERNAL DOSE

Abstract -- Twelve representative materials that might be accidentally released during the fabrication of mixed-oxide nuclear fuel pellets were studied using X-ray diffraction, infrared spectroscopy, energy dispersive X-ray fluorescence, alpha spectroscopy and *in vitro* dissolution methods. The results are related to a postulated exposure accident and to inhalation experiments using laboratory animals.

PRINCIPAL INVESTIGATORS

A. F. Eidson

J. A. Mewhinney

INTRODUCTION

Many of the steps in the mixed-oxide fuel fabrication process require manual handling of powders in gloveboxes. In the event of an accident, aerosols of uranium and plutonium might escape from the enclosure and be inhaled by a worker. The wide variety of materials with different chemical forms used in the fuel fabrication process precludes study of all potential exposure atmospheres in laboratory animals. Physical and chemical analysis, however, can be applied to a greater number of materials and can identify materials with unique properties that might influence the biological behavior of the materials. Representative powders that might be released in significant quantities were collected from gloveboxes following normal fuel fabrication operations. Aerosols were generated from four of these powders for use in inhalation exposures of laboratory animals as required for the biological phase of the project.

The purpose of this report is to summarize the results of physical and chemical analyses of the industrial materials collected and to relate the results to a postulated worker exposure. Analytical methods were: (1) X-ray diffraction to identify the chemical forms of crystalline phases of the material, (2) infrared spectroscopy to investigate noncrystalline forms, (3) alpha spectroscopy to determine the relative amounts of alpha isotopes present, (4) liquid scintillation counting to determine the amounts of ^{241}Pu and ^{241}Am present, (5) X-ray fluorescence of single particles to investigate the feasibility of single particle analysis, (6) *in vitro* dissolution tests to determine the rates of loss of plutonium and americium from particles.

MATERIALS AND METHODS

Materials

The powders obtained (Table 1.1) represent progressive fabrication steps toward the finished fuel pellet. The PuO_2 powders were prepared at the Hanford Engineering Development Laboratory (HEDL) by calcining plutonium oxalate at 750°C. The process used at the Babcock & Wilcox Facility (B & W) included further calcining at 850°C to ensure uniformity of PuO_2 feedstocks. The calcined PuO_2 lots were screened and blended (Samples 1 and 2) and then blended with UO_2 (Samples 3 and 4). The blended PuO_2 and UO_2 powders were milled to comminute the powders (Samples 5 and 6). The powders were reblended, pressed into slugs and the slugs were granulated. Carbowax and Sterotex organic binders were blended with the powders and the mixture is pressed into pellets (Sample 10). The pressed pellets were sintered at 1750°C in a reducing atmosphere (8% H_2 + 92% Ar) to produce a substoichiometric solid solution of $(U,Pu)O_2$. The pellets were finally ground to design specifications using a centerless grinder (Samples 11 and 12).

Aerosol Generation

Aerosols were generated from powders to provide exposure atmospheres for inhalation toxicity studies in laboratory animals (Ref. 1.1). A powder blower (DeVilbiss Co.) containing 500-700 mg of powder was placed in a water bath in a sonic agitator and aerosols were generated at airflow rates of approximately 2 Lpm. Aerosols were passed through a ^{85}Kr discharger and delivered to the animals. Samples of aerosol particles were collected on 47 mm membrane filters of 0.8 µm pore size (Millipore Corp.). Aerosol particle size distributions were determined using cascade impactors. Aerosol particles for electron microscopy were also collected using a point-to-plane electrostatic precipitator.

Isotopic Analysis

Mixed-oxide aerosol particles collected during animal exposures were dissolved in 2 M HNO_3 for further analysis. Plutonium was separated from the 2 M HNO_3 solutions by ion exchange and then electroplated onto stainless steel planchettes. Alpha spectra were measured using a silicon surface-barrier detector at twelve percent efficiency (Amersham standard source) and 30 keV resolution. The recovery of ^{236}Pu tracer was 76 ± 1%. Americium-241 was separated from plutonium in 2 M HNO_3 solutions by liquid extraction and measured using a Packard liquid scintillation counter at 98% efficiency determined using a standard ^{241}Am source (Amersham). The ^{241}Pu beta activity was counted at 31% efficiency relative to standard ^{3}H-toluene (Packard).

Table 1.1

Industrial mixed-oxide fuel materials collected for characterization prior to selection for study in laboratory animals

Sample Number	Process Step	Source	Chemical Composition	Temperature History of PuO_2	Inhalation Studies	
					Dose Pattern	Dose Response
1.	Screen	B&W	PuO_2	850°C	—	—
2.	Blend	B&W	PuO_2	850°C	rats, dogs, monkeys	rats
3.	Blend	B&W	PuO_2+UO_2	850°C	—	—
4.	Blend	HEDL	PuO_2+UO_2	750°C	—	—
5.	Comminution (ball mill)	HEDL	PuO_2+UO_2	750°C	rats, dogs, monkeys	—
6.	Comminution (jet mill)	B&W	PuO_2+UO_2	850°C	—	—
7.	Blending	B&W	PuO_2+UO_2	850°C	—	—
8.	Slug pressing	B&W	PuO_2+UO_2	850°C	—	—
9.	Slug granulation	B&W	PuO_2+UO_2	850°C	—	—
10.	Pellet pressing	B&W	PuO_2+UO_2 + binders	850°C	rats	—
11.	Pellet grinding	HEDL	$(U,Pu)O_2$	1750°C	rats, dogs, monkeys	—
12.	Pellet grinding	B&W	$(U,Pu)O_2$	1750°C	rats	rats

X-ray Diffraction

A Philips APD-3501 X-ray diffractometer was used to measure crystalline mixed-oxide specimens that were collected on silver membrane filters and covered with Duco® cement dissolved in acetone. Unit cell dimensions were determined using Cu Kα radiation (λ = 1.54056 Angstroms). Silver served as an internal calibration standard.

Infrared Spectroscopy

Desiccated KBr suspensions of powders were analyzed using a Perkin-Elmer Model 621 infrared spectrometer. Aerosols collected on filters were scraped from the filter and mixed with KBr. A correction for the infrared absorption of removed filter material was made using a mixture of pure filter material and KBr.

Energy Dispersive X-ray Fluorescence Analysis

Formvar-coated copper grids containing aerosol particles were removed from the point-to-plane electrostatic precipitator and placed on a carbon substrate for analysis using a JEOL Model SM-35 scanning electron microscope equipped with a Kevex energy dispersive X-ray fluorescence detector. The energy of the analyzing electron beam was 25 keV. Analysis of single particles was achieved by focusing the electron beam (approximate diameter 200 Angstroms) on a single particle. The Lα X-ray lines of uranium and plutonium were observed at 13.6 keV and 14.3 keV, respectively. Atom fractions of uranium to plutonium in a particle or agglomerate were determined from the integrated intensity of the areas of the two emission lines (Ref. 1.2).

In vitro Solubility

A segment was cut from a filter used to collect particles during animal exposures, placed in a filter sandwich assembly (Ref. 1.3, 1.4) and submerged in 200 mL of solvent. The solvent was not stirred. The system retained particles between the two filters, but permitted free diffusion of solvent and solute. The 200 mL volume of solvent was changed every hour for the first day, daily for two weeks and weekly during the remainder of the 30-day experiments. Three solvents were used: 2 M HNO_3, 0.1 M HCl and a simulant of blood serum ultrafiltrate (SUF) (Table 1.2). A chelating agent, diethylenetriaminepentaacetic acid (DTPA) was added to prevent precipitation of dissolved plutonium ions in the experimental apparatus. All chemicals were reagent grade.

Plutonium was separated from americium in the 2 M HNO_3 solvent and both actinides were analyzed in a Packard Tri-Carb liquid scintillation counter. Aliquots of 0.1 M HCl solutions were adjusted to 2 M HNO_3 with nitric acid prior to analysis. The 200 mL SUF + DTPA solutions were evaporated to dryness, dry ashed and wet ashed. Filter sandwiches containing the undissolved fraction of aerosols were dry ashed at 500°C for 8 hours and wet ashed with concentrated HNO_3, 30% H_2O_2 and HF. The resulting solution was adjusted to 2 M HNO_3 for analysis as above. Total uranium was determined by fluorometry after fusion of an aliquot of the 2 M HNO_3 solution in a 2 wt % LiF + 98 wt % NaF salt mixture. Fluorescence intensity was measured using a Jarrel-Ash Model 2600 reflectence fluorometer calibrated with standard solutions of U_3O_8 (New Brunswick Laboratory) dissolved in 2 M HNO_3.

Table 1.2

Composition of simulated serum ultrafiltrate used to study the dissolution of industrial mixed uranium and plutonium oxides

Salt	Molar Concentration
NaCl	0.116
NH_4Cl	0.010
$NaHCO_3$	0.027
Glycine	0.005
Na_3 Citrate	0.0002
$CaCl_2$	0.0002
L-Cysteine	0.001
H_2SO_4	0.0005
NaH_2PO_4	0.0012
DTPA[a]	0.0002
ABDC[b]	50 ppm

[a]Diethylenetriaminepentaacetic acid, not present in blood serum.

[b]Alkylbenzyldimethylammonium chloride added as an antibacterial agent.

The initial micrograms of uranium and nanocuries of plutonium and americium on the filter segment were determined by summing the total amount of each actinide in each solvent sample and the quantity that remained undissolved at the conclusion of the study. The undissolved fraction was expressed as a percentage of the initial quantity and plotted versus time. Two-component exponential equations, equation 1.1, were fitted to these data:

$$\% \text{ undissolved} = A_i e^{-\lambda_i t} , \quad i = 1,2 \qquad \text{(Eq. 1.1)}$$

where: A_i = percentages of the total sample dissolved, λ_i = the corresponding dissolution rate constants (hr^{-1}), and t = elapsed time (hr). Rate curves were fitted to the data points by a nonlinear least squares technique and plotted with the data points.

RESULTS AND DISCUSSION

Particle Size

Particle size distribution parameters of aerosols regenerated in the laboratory were similar to those of aerosols sampled during routine fuel fabrication operations (Ref. 1.5, 1.6) (Table 1.3). The deposition efficiency of inhaled particles in the pulmonary region of the respiratory tract is relatively independent of particle size in this range (Ref. 1.7). Thus,

aerosols regenerated in the laboratory were judged to be suitable simulators of accidentally released industrial aerosols.

Table 1.3

Characteristics of industrially mixed uranium and plutonium oxide fuel aerosols studied

Sample Number	Process Step	Source[b]	Chemical Composition	Temperature History of PuO_2	Aerosol Characteristics[a] Laboratory AMAD[c]	Laboratory GSD[d]	Industrial AMAD	Industrial GSD
2	Blend	B&W[e]	PuO_2	850°C	2.33 ±0.08	2.11 ±0.06	2.1 ±0.3	1.61 ±0.06[f]
5	Ball Mill	HEDL[g]	UO_2+PuO_2	750°C	2.3 ±0.2	1.74 ±0.04	1.9 ±0.4	1.59 ±0.08[h]
10	Pellet Press	B&W	UO_2+PuO_2[i]	850°C	1.7 ±0.6	2.6 ±0.7	1.9 ±0.3	1.54 ±0.04[f]
11	Pellet Press	HEDL	$(U,Pu)O_2$	1750°C	2.6 ±0.1	2.35 ±0.09	2.3 ±0.3	1.6 ±0.1[h]

[a]Mean ± standard deviation.

[b]Sampling site. All PuO_2 was prepared at HEDL prior to shipment to B & W for further processing.

[c]Activity median aerodynamic diameter in μm.

[d]Geometric standard deviation.

[e]Babcock and Wilcox Fuel Fabrication Facility, Park Township, PA.

[f]Reference 5.

[g]Hanford Engineering and Development Laboratory, Richland, WA.

[h]Reference 6.

[i]Sterotex® and Carbowax® binders added to facilitate pellet pressing.

Alpha Radioactivity

The observed alpha radioactivity of industrial powders and aerosols was from ^{241}Am, ^{238}Pu and $^{239,240}Pu$ (Table 1.4). Beta activity of ^{241}Pu was observed in differing amounts. There was generally good agreement among the isotopic compositions measured in powders and aerosols generated from them. The PuO_2 aerosol from the blending process (Sample 2, Table 1.2) contained more ^{238}Pu and less ^{241}Am than the powder. The differences were minor compared to the total plutonium radioactivity and may be related to the nature of the blending process. In this process stage, PuO_2 lots with slightly variable histories and compositions can be blended. The particle size distribution of each PuO_2 lot was retained prior to the particle comminution step. An aerosol generated from a blend that included a PuO_2 lot composed of smaller particles with a relatively large percentage of ^{238}Pu would tend to have increased alpha radioactivity. The opposite might occur for a different PuO_2 blend. Differences between powder and aerosol compositions were reduced in process stages following powder comminution.

Table 1.4

Elemental and isotopic composition of nuclear fuel powders and aerosols studied

	Percent of Alpha Activity ± SD[a]							
	B&W[b] PuO_2 850°C		HEDL[c] UO_2+PuO_2 750°C		B & W UO_2+PuO_2+Binders 850°C		HEDL $(U, Pu)O_2$ 1750°C	
	Blend		Ball Mill		Pellet Press		Pellet Press	
Isotope	Powder	Aerosol	Powder	Aerosol	Powder	Aerosol	Powder	Aerosol
$^{239,240}Pu$	74	69	73	74	82	80	40	43
^{238}Pu	6.1±0.4	17	11	11	7.2±0.3	8.8±0.4	37	35
^{241}Am	20	15	16	15	12	11	23	22
^{241}Pu[d]	12.3	12.0	12.1	13.1	12.5	13.5	20.7	24.9

[a] SD is the standard deviation: ±1% unless specified.

[b] Babcock and Wilcox Fuel Fabrication Facility, Park Township, PA.

[c] Hanford Engineering and Development Laboratory, Richland, WA.

[d] 0.021 MeV beta radiation, values are the beta/total alpha activity ratio ± 5%

X-ray Diffraction

X-ray diffraction (Table 1.5) showed that both powders and aerosols had the face-centered cubic structure of actinide dioxides with unit cell dimensions within ± 0.01 Angstrom of the literature values (Ref. 1.8). Because unit cell dimension differences between powder and aerosol forms were within ± 0.01 Angstrom or less, analysis of the bulk powders serves to characterize the respirable fraction as well. Mixed UO_2 and PuO_2 powders consisted of discrete UO_2 and PuO_2 phases, but the $(U,Pu)O_2$ contained a single solid solution (Ref. 1.9). X-ray diffraction can then be used to identify the sources of a complex mixture of aerosols that might be released from more than one fabrication step.

Infrared Spectroscopy

Infrared spectra of all powders included broad, intense absorption maxima in the 300-600 cm^{-1} region that were assigned to the metal-oxygen stretching frequencies of UO_2 and PuO_2 (Ref. 1.10). Spectra of the pellet pressing powder (Sample 10, Table 1.1) included additional peaks in the 1000-1500 cm^{-1} and 2600-3000 cm^{-1} regions that were assigned to binders added to the mixed-oxide powders to facilitate pellet pressing.

The spectrum of the $(U,Pu)O_2$ aerosol (Sample 11, Table 1.1) showed absorption bands at 916, 1100, 1170, 1400, 1530 and 1640 cm^{-1} (Figure 1.1). Similar bands were observed within ± 10 cm^{-1} in the spectra from all materials in Table 1 except that the spectrum of UO_2 + PuO_2, 750°C material lacked a 1170 cm^{-1} band. The 1100, 1170, 1530 and 1640 cm^{-1} bands were assigned to surface carbonate species (Ref. 1.11, 1.12) and indicate that the particle surfaces were different from the interiors. The 916 cm^{-1} band was assigned to UO_3 or UO_2^{+2} (Ref. 1.13) and indicated a partial reversal at the surface of the reduction that occurred during sintering. The broad band at 1400 cm^{-1} included a KBr contribution that was detected at the higher instrument sensitivity used and was not assigned. The greater intensity of surface species peaks in spectra of aerosols than powders was assumed to result from the greater specific surface area of the aerosol particles.

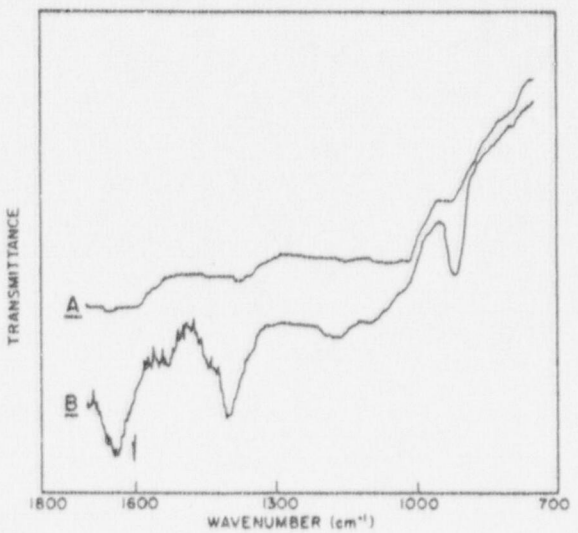


Figure 1.1. Infrared spectra of 1750°C heat-treated $(U,Pu)O_2$ from the pellet grinding operation. (A) powder, (B) aerosol. Ordinate scale expanded 5X. The 1601 cm^{-1} polystyrene absorption peak is shown separately for calibration purposes.

Table 1.5

Unit cell dimensions of industrial mixed uranium and plutonium dioxide fuel powders and aerosols studied

			Unit Cell Dimensions of Face-Centered Cubic Structures $a_o \pm SE$[a] (A)		
			UO_2	PuO_2	
Sample	Material and Source	Process Step and Temperature	a_o = 5.4683 A[b]	a_o = 5.3960 A[b]	$(U,Pu)O_2$
1	PuO_2 B&W	Screen 850°C		5.407 ± 0.002	
2	PuO_2 B&W	Ball Mill 850°C		5.405 ± 0.002[c] (5.402 ± 0.002)[d]	
3	PuO_2+UO_2 B&W	Blend 850°C	5.471 ± 0.001	5.413 ± 0.005	
4	PuO_2+UO_2 HEDL	Blend 750°C	5.472 ± 0.004	5.413 ± 0.005	
5	PuO_2+UO_2 HEDL	Ball Mill 750°C	5.464 ± 0.002[c] (5.459 ± 0.001)[d]	5.404 ± 0.007[c] (5.397 ± 0.003)[d]	
6	PuO_2+UO_2 B&W	Jet Mill 850°C	5.471 ± 0.002	5.412 ± 0.001	
7	PuO_2+UO_2 B&W	Blend 850°C	5.466 ± 0.002	5.411 ± 0.003	
8	PuO_2+UO_2 B&W	Slug Pressing 850°C	5.462 ± 0.002	5.412 ± 0.001	
9	PuO_2+UO_2 B&W	Slug Granulation 850°C	5.472 ± 0.002	5.396 ± 0.001	
10	PuO_2+UO_2 B&W	Pellet Pressing 850°C	5.464 ± 0.003[c] (5.466 ± 0.005)[d]	5.400 ± 0.003[c] (5.405 ± 0.007)[d]	
11	$(U,Pu)O_2$ HEDL	Pellet Grinding 1750°C			5.455 ± 0.004[c] (5.451 ± 0.001)[d]
12	$(U,Pu)O_2$ B&W	Pellet Grinding 1750°C			5.457 ± 0.001

[a] Standard error.

[b] Joint Committee on Powder Diffraction Standards (JCPDS80) values for the cubic unit cell dimension, a_o: UO_2, Card No. 5-055-; PuO_2, Card No. 6-0360.

[c] Powder value.

[d] Aerosol value.

Adsorption of H_2O on PuO_2 calcined at 750°C ranges from 0.2% to 1.5% at 25% to 95% relative humidity with formation of Pu-OH species (Ref. 1.14). Plutonium dioxide rapidly adsorbs 10^{-5} moles CO_2/g when H_2O is excluded (Ref. 1.12) but the Pu-OH species enhance CO_2 adsorption such that one Pu atom in three can be bound (Ref. 1.15). It is difficult to predict atmospheric conditions during an industrial accident, but one can expect that 0.1-1.0% PuO_2 to be in a different chemical form.

Single Particle Analysis Energy Dispersive X-ray Fluorescence Spectroscopy

The analysis of single particles might be required if the only specimen of inhaled material available after an accidental worker exposure consisted of a very small mass, such that other analytical techniques described above could not be applied. Under those circumstances, the major value of a single particle analysis would be to determine whether the inhaled material was a mixture of PuO_2 + UO_2 particles, or a $(Pu,U)O_2$ solid solution.

The atom fraction of uranium in the UO_2 + PuO_2 mixture (Sample 5, Table 1.1) was estimated to be 0.92 with a range of 0.640-0.998 at the 95% confidence level based on the analysis of 13 single particles. This range, although large, includes the uranium atom fraction of 0.69 found for the aerosols by reflectance fluorometry. These results indicate that 13 observations were too few to give a good estimation of the composition of the aerosol. The binomial distribution predicted that 20 particles must be measured to reduce this wide interval to 0.683-0.988 at the 95% confidence level. The calculation of the required number of additional analyses assumed that 0.92 was an accurate initial estimate of the proportion of UO_2 particles in the population. Analysis of additional particles would result in values somewhat altered from 0.92; requiring continuous refinement of the calculations as the analyses progressed. Analysis of 140 particles would be required to estimate the uranium atom fraction in the 0.63-0.79 range with 95% confidence if 0.69 was used as the initial estimate.

The range of the uranium fraction in the $(U,Pu)O_2$ aerosol (Sample 11, Table 1.1) estimated from observations of 9 particles (0.56-0.85 at the 95% confidence level) includes the 0.77 ± 0.03 value determined by reflectence fluorometry. Normally, a higher confidence level is preferred. Using the Student's t distribution, the number of single particle analyses required to increase the confidence level for this range to 99% was calculated to be 19. Similarly, 41 particles should be analyzed to attain a 99.9% confidence level. As in the case of the UO_2 + PuO_2 mixture, each additional measurement would alter the data and require continuous refinement of the calculations. Improved estimates could be obtained by analyzing approximately 40 to 140 particles. These results show that the method is feasible, particularly if automated instrumentation were used.

In vitro Dissolution

Comparisons of dissolution rates for different materials (Tables 1.6 and 1.7) can only be made if the precision of each value is considered. Because the sampling frequency during the first day of the experiment was one change of solvent per hour, the limit of precision for the rapid dissolution half-time was estimated to be ± 0.1 day. The precision of calculated

Table 1.6

In vitro dissolution of industrial mixed uranium and plutonium oxide fuel materials in synthetic serum ultrafiltrate solution Containing DTPA[a]

Process Step, Temperature History	Powder Form	Nuclide	Dissolution Component[b] I A_1 (%)	I $T_{1/2}$ ±0.1[c] (days)	II A_2 (%)	II $T_{1/2}$[d] (days)
Blending	PuO_2	Pu	e	e	100 ± 0.1[f]	20,000 ± 9,000[f]
850°C		Am	e	e	99.6 ± 0.2[f]	6,000 ± 900[f]
Ball Mill	UO_2+PuO_2	Pu	0.4	2.0	99.6	15,000
750°C	Admixture	Am	2.0	1.7	98.6	20,000
		U	37.3	2.3	62.7	400
Pellet	UO_2+PuO_2	Pu	0.1	1.2	99.9	21,000
Press	Admixture	Am	0.6	1.0	99.4	5,400
850°C	+ Binders[g]	U	25.5	2.4	74.5	300
Pellet	$(U,Pu)O_2$	Pu	4.6	2.2	95.4	29,000
Grind	Solid	Am	6.7	1.1	93.3	8,300
1750°C	Solution	U	25.7	1.2	74.3	11,000

[a]Diethylenetriaminepentaacetic acid, not present in blood serum

[b]Two-component exponential dissolution equation of the form % Undissolved = $A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$

[c]Limit of greatest precision based on sampling frequency.

[d]Estimated precision of half-times: 10 to 100 days, ± 25% and >1000 days, ±50%.

[e]Only single component observed.

[f]Mean ± standard deviation of values from duplicate experiments.

[g]Mixture of Sterotex® and Carbowax® added to facilitate pellet pressing.

Table 1.7

In vitro dissolution of industrial mixed uranium and plutonium oxide fuel materials in 0.1M HCl

Process Step, Temperature History	Powder Form	Nuclide	Dissolution Component[a] I A_1 (%)	I $T_{1/2}\pm0.1$[b] (days)	II A_2 (%)	II $T_{1/2}$[c] (days)
Blending	PuO_2	Pu	0.1	0.2	99.9	12,000
850°C						
		Am	0.4	0.2	99.6	5,100
Ball Mill	$UO_2 + PuO_2$	Pu	0.4	0.2	99.6	1,300
750°C	Admixture	Am	4.0	0.1	96.0	2,800
		U	10.0	0.1	90.0	85
Pellet						
Press	$UO_2 + PuO_2$	Pu	0.3	0.2	99.7	6,700
850°C	Admixture	Am	0.8	0.2	99.2	6,100
	+	U	23.0	0.3	77.0	130
	Binders[d]					
Pellet						
Grind	Solid Sol.	Pu	3.2±0.3[e]	0.3±0.1[e]	98.8±0.1[e]	880±90[e]
1750°C	$(U,Pu)O_2$	Am	4.8±0.3[e]	0.2±0.3[e]	95.2±0.3[e]	770±60[e]
		U	9 ±0.3[e]	0.2±0.1[e]	91 ±1[e]	360±90[e]

[a]Two-component exponential dissolution equation of the form

$$\% \text{ Undissolved} = A_1 e^{-\lambda 1 t} + A_2 e^{-\lambda 2 t}$$

[b]Limit of greatest precision based on sampling frequency.

[c]Estimated precision of half-times: 10 to 1000 days, ± 25% and > 1000 days, ±50%.

[d]Mixture of Sterotex® and Carborwax® added to facilitate pellet pressing.

[e]Mean ± standard deviation of values from duplicate experiments.

dissolution half-times greater than 1000 days based on measurements from a 30-day experiment was low, as expected, because accumulated errors were propagated beyond the duration of the experiment. Duplicate plutonium and americium dissolution studies in SUF + DTPA and 0.1 M HCl indicated that the precision of half-times greater than 1000 days was approximately ± 50% and ± 25% for values in the 10-1000 day range. These values are similar to the precision of previously recorded dissolution half-times for similar materials (Ref. 1.6).

Dissolution curves showed biphasic rate profiles with half-times for the rapid initial rates of less than 3 days followed by slower rates with half-times of 100 to 10,000 days. The one exception was the dissolution of PuO_2, 850°C, blender particles in SUF + DTPA, that showed only one rate with a half-time of 20,000 ± 9,000 days. This material showed biphasic disssolution in 0.1 M HCl, however.

The relative dissolution rates of plutonium, americium and uranium from mixed oxides obtained from fabrication steps prior to sintering at 1750°C (Table 1.6) indicated that UO_2 dissolved rapidly and independently of the PuO_2-AmO_2 matrix. The long-term dissolution rates of plutonium and americium in 0.1 M HCl were similar within the limits of experimental precision (Table 1.7). They were not generally similar in SUF + DTPA, however. Plutonium and americium dissolved from all four materials studied in SUF + DTPA with second component half-times greater than 5000 days.

Uranium was the most readily soluble of the three actinides in the $(U,Pu)O_2$, 1750°C, pellet grinding aerosol (Figure 1.2, Tables 1.6 and 1.7). The uranium dissolution half-times during the first phase were not appreciably different from other aerosols, but the half-times for the slower phase were increased in both solvents. Percentages of plutonium and americium dissolved during the early phase were greater than from other aerosols in SUF + DTPA. The same was true for plutonium dissolution in 0.1 M HCl, but the americium percentage was similar to the UO_2 + PuO_2, 750°C, ball mill aerosol value.

Dissolution rates of plutonium from the four industrial aerosols in common solvents were compared. The $(U,Pu)O_2$, solid solution material dissolved differently during the first 100 hours in SUF + DTPA than for the other materials (Figure 1.3), but rates were more similar for all four materials at later times. Plutonium dissolution from the $(U,Pu)O_2$ solid solution was also increased in 0.1 M HCl (Figure 1.4), particularly during the early phase (Table 1.7).

The temperature history of industrial PuO_2 could not be reliably related to plutonium dissolution properties. The fraction of plutonium dissolved from laboratory-produced $^{239}PuO_2$ in 0.1 M HCl within 2 hours decreased with increasing aerosol preparation temperature (Ref. 1.3). No such trend was observed for the industrial aerosols (Table 1.8). The difference between the B & W, 850°C, blending PuO_2 and laboratory-produced, 900°C PuO_2, suggests a strong temperature dependence. No similar difference was observed for HEDL, 750°C, PuO_2 + UO_2 and B & W, 850°C,

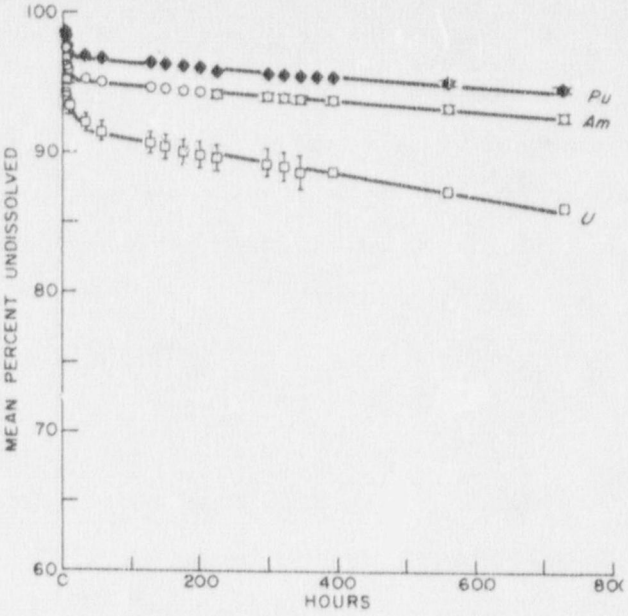


Figure 1.2. Dissolution of plutonium, americium, and uranium from $(U,Pu)O_2$, 1750°C, pellet grinding aerosol in 0.1 M HCl. Mean and range of measurements from duplicate experiments are indicated.

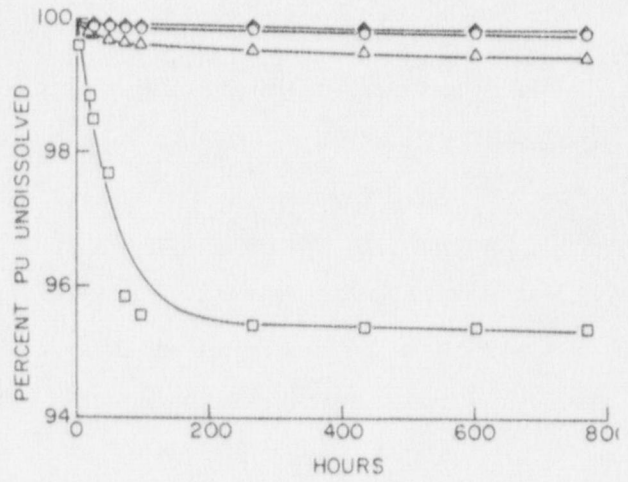


Figure 1.3. Comparison of plutonium dissolution from aerosol samples of four industrial fuel materials in a serum simulant solution containing DTPA. PuO_2, 850°C, blender (◆), UO_2 + PuO_2 + binder, 850°C, pellet press (♢), UO_2 + PuO_2, 750°C, ball mill (△), $(U,Pu)O_2$, 1750°C, pellet grinding (□).

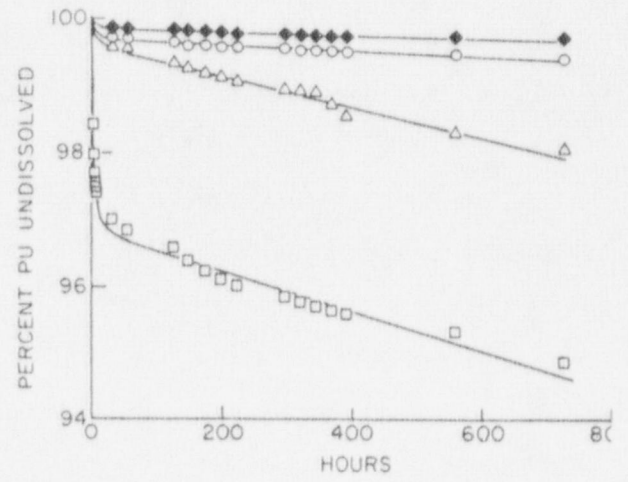


Figure 1.4. Comparison of plutonium dissolution from aerosol samples of four industrial fuel materials in 0.1 M HCl. PuO_2, 850°C, blender (◆), UO_2 + PuO_2 + binders, 850°C, pellet press, (♢), UO_2 + PuO_2, 750°C, ball mill (△), $(U,Pu)O_2$, 1750°C, pellet grinding (□).

Table 1.8

Comparison of dissolution of plutonium from laboratory and industrial produced aerosol particles in 0.1 M HCl

Composition, Industrial Process Step	Source of Aerosol	PuO_2 Temp History	Fraction Pu Dissolved In First 2 Hr	AMAD[a] (μm)	GSD[b]
PuO_2 Blend	Industrial	850°C	7.0×10^{-4}	1.90 ± 0.2	1.68 ± 0.01
UO_2+PuO_2 Ball Mill	Industrial	750°C	1.5×10^{-3}	2.14 ± 0.05	1.71 ± 0.05
UO_2+PuO_2 Pellet Press	Industrial	850°C	1.9×10^{-3}	1.70 ± 0.6	2.6 ± 0.7
$(U,Pu)O_2$ Pellet Grind	Industrial	1750°C	2.0×10^{-2}[c] ± 2.0×10^{-4}	2.5 ± 0.1	1.8 ± 0.2
$^{239}PuO_2$ [d]	Laboratory	600°C	1.2×10^{-2}	1.9	e
$^{239}PuO_2$ [d]	Laboratory	900°C	2.5×10^{-3}	1.9	e
$^{239}PuO_2$ [d]	Laboratory	1300°C	7.8×10^{-5}	1.6	e

[a]Activity median aerodynamic of aerosol generated from dry powder for inhalation exposures of laboratory animals.

[b]Geometric standard deviation.

[c]Mean and standard deviation of duplicate studies.

[d]Table 3 (Ref. 1.3). Produced by nebulization of colloidal $Pu(OH)_n$.

[e]Not given in (Ref. 1.3).

PuO_2 + UO_2, despite the 100°C difference in the PuO_2 temperature history. The presence of UO_2 probably did not cause these differences because the 900°C laboratory PuO_2 and industrial 850°C PuO_2 + UO_2 showed similar dissolution fractions (Table 1.7). No clear trend in initial dissolution rates with temperature was evident in SUF + DTPA (Table 1.6). These results indicate that, in this range, temperature history was a minor factor.

Industrially produced aerosols have greater specific surface area to volume ratios than aerosols of spherical laboratory-produced particles (Ref. 1.3) and would be expected to dissolve differently (Ref. 1.16). The overall plutonium dissolution rate profile of the UO_2 + PuO_2, 750°C, ball mill aerosol (Figure 1.4, Table 1.7) showed slightly increased dissolution in 0.1 M HCl when compared with material heated at 850°C, even though the plutonium fraction dissolved within 2 hours did not correlate with temperature history (Table 1.8). The shorter half-time for the second component of PuO_2 in the ball milling aerosol compared to the blending and pellet pressing aerosols was not the result of differences in particle size distribution (Table 1.1), but was probably the result of differences in specific surface area.

A slightly increased plutonium dissolution from the same aerosol in SUF + DTPA was apparent during the first component, but slower dissolution rates were similar to other aerosols within experimental precision. Slight differences in profiles of the three other materials represented only 0.3% of the initial plutonium present and are not expected to be biologically significant.

Independent dissolution of UO_2 and PuO_2 from industrial mixed oxides containing PuO_2 heated at 750 to 850°C was observed in both solvents and agreed with the results of X-ray diffraction studies showing the aerosols to be admixtures of PuO_2 and UO_2. The major effect of the higher heat treatment on dissolution of industrial mixed-oxide fuels was increased (not decreased) plutonium dissolution caused by sintering at 1750°C. The different dissolution properties of $(U,PU)O_2$, 1750°C, pellet grinding aerosols were attributed to solid solution formation with uranium dioxide.

Greater percentages of plutonium and americium were dissolved from the solid solution in the early phase in both 0.1 M HCl and SUF + DTPA relative to mixed UO_2 and PuO_2 aerosols. Dissolution rates of plutonium and americium were increased in 0.1 M HCl (Table 1.7) and the uranium dissolution was decreased. These results indicate that the major mass component of the solid solution matrix (uranium) modified the dissolution rate of other components in 0.1 M HCl with its rate slightly modified in turn. The major difference in plutonium dissolution from the solid solution aerosol in SUF + DTPA was the greater percentage (4.6%) dissolved in the first component. The increased plutonium solubility from the solid solution matrix was clearly seen when all results were compared at 30 days (Figure 1.5).

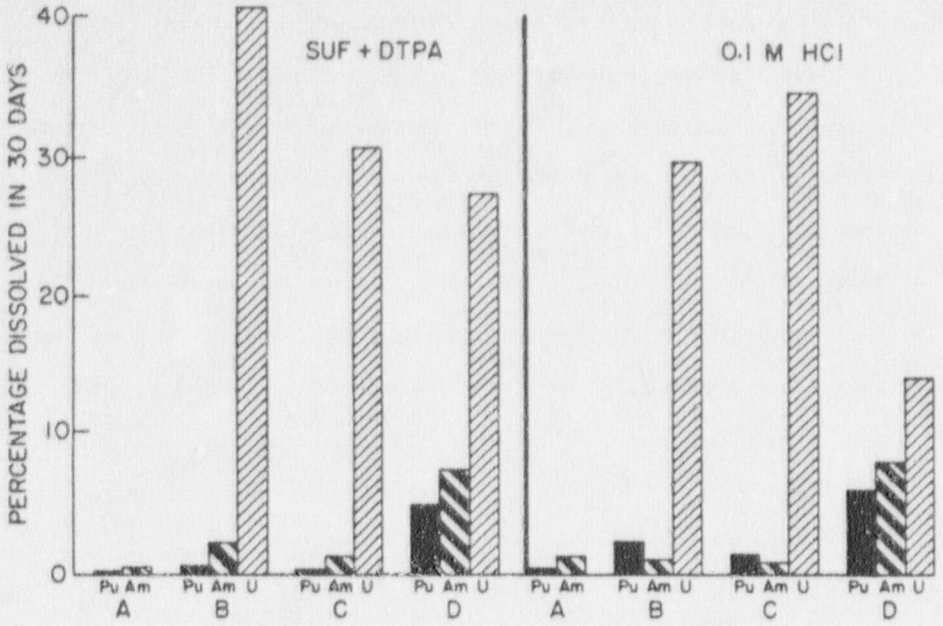


Figure 1.5. Summary of plutonium, americium, and uranium dissolution fractions from four materials in two solvents compared at 30 days after beginning of the experiments. (A) PuO_2, 850°C, blender; (B) $UO_2 + PuO_2$, 750°C, ball mill; (C) $UO_2 + PuO_2$ + binders, 850°C, pellet press; (D) $(U,Pu)O_2$, 1750°C, pellet grinding.

The cause of the rapid initial dissolution phase can be related to two properties of the aerosol particles: specific surface area (Ref. 1.16) and surface composition. Industrial mixed-oxide aerosols are polydisperse and include small particles with rough surfaces that are expected to have high specific surface area and rapid dissolution rate. Further, plutonium and uranium oxides produced in the laboratory (Ref. 1.12) and in industry adsorb atmospheric CO_2 and H_2O that alter the chemical composition at the surface. Formation of a chemically altered surface of a solid results in physical properties different from the interior (Ref. 1.17) and dissolution rates are changed (Ref. 1.18). Thus, the rapid dissolution component of industrial mixed-oxide aerosols can be the result of preferential dissolution of: (1) smaller particles with high specific surface area or (2) an altered surface composition, or both.

Experiments designed to investigate the contribution of surface composition to the initial dissolution rate of mixed actinide oxides showed that specimens that were dried and reintroduced into fresh solvent dissolved 10-38 times faster than their rates prior to drying. The mean plutonium dissolution rate (excluding the first day) from the $UO_2 + PuO_2$, 750°C, ball mill material in 0.1 M HCl was 1.2 ± 0.6 nCi/hr. The plutonium dissolution rate from the same filter assembly that was dried for 7 days and reintroduced into fresh solvent was 45 nCi/hr, representing an initial rate increase by a factor of 38. When the experiment was repeated with the same filter assembly, dried for one day, the plutonium dissolution rate was 12 nCi/hr, a factor of 10 increase. A second experiment using a different filter sandwich assembly showed a plutonium dissolution rate increase by a factor of 10.

A collection of particles exposed to 0.1 M HCl for 30 days and dried in air would be expected to readsorb atmospheric molecules, but would not be expected to have the higher predissolution specific surface area restored. Drying a particle wetted with HCl solution in air would not reproduce exactly the same surface composition formed by exposure to air alone, however, restoration of the rapid initial dissolution rate indicated that differences between the particle surface and interior were important factors in the initial dissolution process in addition to specific surface area effects. The above results qualitatively agree with similar experiments using fused aluminosilicate spheres labeled with ^{137}Cs and 0.15 M NaCl as the solvent (Ref. 1.19).

Biological Implications

Valuable information related to the potential risk to a worker's health from an accidental release can be obtained by analysis of the aerosol involved in an accident. Physical and chemical analysis can identify materials with unique properties that can be related to the biological consequences of an exposure. It is extremely difficult, however, to sample an aerosol that has been released, because such accidents are rare and cannot be anticipated. Powders that might accidentally be released as aerosols may, however, be collected from the enclosure in bulk form after an accident and be analyzed. Other specimens may be obtained from area filter samples, and from surface swipe samples, although they might not be as representative of the inhaled materials. It must be shown whether properties of powders collected from a glove box where an accident occurred are similar to those of the respirable particles in the powder.

X-ray diffraction (Table 1.3) showed that both powders and aerosols have the face-centered cubic structure of actinide dioxides with unit cell dimensions within ± 0.01 Angstrom of literature values (Ref. 1.8). Differences of ± 0.01 Angstrom or less between powder and aerosol forms were not expected to affect toxicity. Mixed UO_2 and PuO_2 powders consisted of discrete UO_2 and PuO_2 phases, but the $(U,Pu)O_2$ contained a single solid solution (Ref. 1.9). X-ray diffraction can, then, be used to identify the sources of a complex mixture of aerosols that might be accidentally released from more than one fabrication step.

Isotopic distributions in powders and aerosols showed that information important for radiation dose to tissue calculations or Pu lung burden estimates can be obtained by analysis of powders. While isotopic analysis of PuO_2 powder from the blending step (Sample 2) might be adequate, analysis of respirable aerosols of this material, and others from steps prior to powder comminution, would be preferred.

If only a few particles of a mixed-oxide aerosol was involved in an accidental exposure of a worker are available, the results of energy dispersive X-ray fluorescence analysis as single particles shows that estimation of the composition of the aerosol is feasible if at least 20 to 200 particles are analyzed.

Results of *in vitro* dissolution studies can be used to predict the potential biological behavior of inhaled mixed-oxide fuel aerosols. Both 0.1 M HCl and SUF + DTPA solvents showed independent UO_2 and PuO_2 dissolution from admixtures and increased plutonium dissolution from the solid solution matrix by approximately 3% to 5%. The true role of dissolution in clearance of inhaled industrial plutonium aerosols and selection of a preferred *in vitro* solvent system can be based on results of kinetic modeling of retention and e· retion of retention and excretion of radioactivity by laboratory animals. Details of the application of *in vitro* dissolution measurements, surface area measurements, and particle density measurements based on X-ray diffraction studies to retention and excretion *in vivo* are discussed later in this report (pp 60 to 88). Table 1.9 summarizes rate constants for dissolution of plutonium from mixed-oxide fuel aerosols that were used in the biokinetic modeling studies (this report, pp 29 to 59).

Table 1.9

Rate constants for dissolution of plutonium

from mixed oxide fuel aerosol particles *in vitro*

Sample Number	Material Source	Temperature Process	Mass Median Diameter (cm)	Density[a] g/cm^{-2}	Dissolution Half Time (days)	Dissolution Rate Constant ($g\ cm^{-2} day^{-1}$)
2	PuO_2 B&W	850°C Blend	4.7×10^{-5}	11.4	2×10^{4}	2.5×10^{-9}
5	UO_2+PuO_2 HEDL	750°C Ball Mill	5.4×10^{-5}	11.5	1.5×10^{4}	4.1×10^{-9}
11	$(U,Pu)O_2$ HEDL	1750°C Pellet Grind	6.6×10^{-5}	11.1	2.9×10^{4}	2.7×10^{-9}

[a]Calculated from X-ray diffraction measurements.

CONCLUSIONS

Results of analyses of representative powders selected from the mixed-oxide fuel fabrication steps showed that a variety of analytical methods might be used to characterize a complex aerosol that might be inhaled by a worker. Although there were differences among materials that could be related to a particular process step, no material or process step was identified as uniquely hazardous. The results summarized here are related to results of inhalation experiments using laboratory animals (this report, pp 29 to 59). None of the materials discussed in this paper had any unique properties that indicate a need for further studies in animals in addition to those completed.

REFERENCES

1.1. Eidson, A. F., "Comparison of Physical Chemical Properties of Powders and Respirable Aerosols of Industrial Mixed Uranium and Plutonium Oxide Fuels," Health Phys. 42 : 531-536, 1982.

1.2. Eidson, A. F., P. B. DeNee, and C. A. Macken, "Particle Analysis of Mixed-Oxide Nuclear Fuel Materials by Energy Dispersive X-ray Fluorescence," in Electron Microscopy and X-ray Applications to Environmental and Occupational Health Analysis, Vol. 2, Chapter 12, P.A. Russell, Ed., Ann Arbor Science, 1981.

1.3. Miglio, J. J., B. A. Muggenburg, and A. L. Brooks, "A Rapid Method for Determining the Solubility of Plutonium Aerosols," Health Phys. 33: 449-457, 1977.

1.4. Eidson, A. F. and J. A. Mewhinney, "In vitro Dissolution of Respirable Aerosols of Industrial Uranium and Plutonium Mixed-Oxide Nuclear Fuels," Health Phys. 45: 1023-1037, 1983.

1.5. Hoover, M. D., G. J. Newton, H. C. Yeh, and A. F. Eidson, "Characterization of Aerosols from Industrial Fabrication of Mixed-Oxide Nuclear Reactor Fuels," in Aerosols in the Mining and Industrial Work Environments, Vol 2, Characterization, Chapter 39, Eds., V. A. Marple, B. Y. H. Liu, Ann Arbor Sciences, 1983.

1.6. Raabe, O. G., G. J. Newton, C. J. Wilkinson, S. V. Teague, and R. C. Smith, "Plutonium Aerosol Characterization Inside Enclosures at a Demonstration Mixed-Oxide Fuel Fabrication Facility," Health Phys. 35: 649-661, 1978.

1.7. ICRP Task Group on Lung Dynamics, "Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract," Health Phys. 12: 123-207, 1966.

1.8. Joint Committee on Powder Diffraction Standards File, Card No. 5-0550 (UO_2) and Card. No. 6-0360 (PuO_2), International Center for Diffraction Data, Swarthmore, Pennsylvania, 1980.

1.9. Russell, L. E., N. H. Brett, J. D. L. Harrison, and J. Williams, "Observations on Phase Equilibria and Centering Behavior in the PuO_2-UO_2 System," J. Nuclear Mater. 5: 216-227, 1976.

1.10. Allen, G. C., "Infrared Spectroscopy of the Uranium/Oxygen System," J. Nuclear Mater. 62: 273-281, 1976.

1.11. Hair, M.L., Infrared Spectroscopy in Surface Chemistry, Marcel Dekker, Inc., New York, p. 204, 1967.

1.12. Colmenares, C. A. and K. Terada, "The Adsorption of Carbon Dioxide on Uranium and Plutonium Oxides," J. Nuclear Mater. 58: 336-356, 1975.

1.13. Tsuboi, M., M. Terada, and T. Shimonouchi, "Optically Active Latice Vibrations of Alpha-Uranium Trioxide," J. Chem. Phys., 36: 1301, 1962.

1.14. Stakebake, J. L., "The Storage Behavior of Plutonium Metal, Alloys and Oxide: A Review," J. Nuclear Mater., 38: 241-259, 1971.

1.15. Toth, L. M. and H. A. Friedman, "The IR Spectrum of Pu(IV) Polymer," J. Inorg. Nucl. Chem., 40: 807-810, 1978.

1.16. Mercer, T. T., "On the Role of Particle Size in the Dissolution of Lung Burdens," Health Phys., 13: 1211-1221, 1967.

1.17. Weyl, W. A., "Effect of the Environment Upon the Properties of Solids," Solid Surfaces and the Gas-Solid Interface, Advances in Chemistry Series No. 33, American Chemical Society, Washington, DC, pp. 72-85, 1961.

1.18. VanLier, J. A., P. L. DeBruyn, and J. T. G. Overbeek, "The Solubility of Quartz," J. Phys. Chem., 61: 1675-1682, 1960.

1.19. Kanapilly, G. M., and C. H. T. Goh, "Some Factors Affecting the In Vitro Rates of Dissolution of Respirable Particles of Relatively Low Solubility," Health Phys., 25: 225-237, 1973.

Chapter 2. DISTRIBUTION OF RADIATION DOSE AFTER INHALATION OF AEROSOLS DERIVED FROM FABRICATION OF MIXED OXIDE NUCLEAR FUELS

Abstract -- The spatial and temporal distribution of radiation dose to tissues of three species of animals was defined following inhalation of one of three particulate materials representative of aerosols produced in the manufacture of mixed uranium and plutonium oxide nuclear fuel. Rats, dogs and monkeys received a single inhalation exposure to one of three materials and groups of five rats, two dogs or one monkey were sacrificed at selected times up to four years after exposure. The three aerosol materials used were a mixture of UO_2 and PuO_2 powders treated at 750°C, a solid solution of $(U,Pu)O_2$ treated at 1750°C, and PuO_2 treated at 850°C. The data defining retention, distribution and excretion of plutonium and americium present in these materials were compared using a biokinetic model to highlight similarities and differences. Lung retention of the plutonium component of these particulates for any one of the three species was not different. In contrast, lung retention of the plutonium component was dependant on the species of animal, apparently due to differences in the rate of mucociliary clearance. The synthesis of information from each aerosol and each species studied indicated that radiation dose distribution in tissue was essentially the same as that measured in animals exposed by inhalation to laboratory-produced aerosols of PuO_2. There was no indication that the hazard to humans exposed to these industrial materials would be appreciably different than has been estimated for laboratory-produced aerosols of PuO_2.

PRINCIPAL INVESTIGATORS

J. A. Mewhinney

A. F. Eidson

B. B. Boecker

INTRODUCTION

Operation of an industrial facility devoted to fabrication of mixed uranium and plutonium oxides involves a complex series of process steps. All operations are carried out within glovebox enclosures to prevent release of these hazardous materials into the working environment. Great care is also taken to prevent release of the materials to the general environment.

All process stages involve the manipulation of dry powders of uranium and plutonium in the oxide form. These processes result in substantial airborne contamination within the glovebox enclosures. The immediate concern for protection of workers is accidental loss of containment. The greatest potential for release to the working environment involves rupture of the rubber gloves used to gain working access to the glovebox. In such case, the radiological hazard for workers is the inhalation of aerosols of the oxides of uranium and plutonium. A complete description of the process stages and a characterization of the aerosols produced within the gloveboxes during routine operation have been presented (Ref. 2.1, 2.2).

To provide an assessment of the hazard represented by inhalation of these mixed uranium and plutonium oxide aerosols, a series of studies was undertaken to determine the radiation dose distribution in tissues of animals after inhalation exposure. Three aerosol forms were selected for study based on their prevalance in the several process stages, the air concentrations routinely observed within the gloveboxes, and measured differences in the physical chemical form of the uranium and plutonium in the particles.

The first aerosol selected for study consisted of a mixture of dry powders of UO_2 and PuO_2 treated at 750°C. This mixture is the form of the fuel material initially processed to achieve uniform distribution of the plutonium in the uranium (25% PuO_2, 75% UO_2 by mass). This material is repeatedly mixed and blended in several process stages, pressed into pellets, reground to powder form, reblended and finally, again pressed into pellets prior to being sintered at high temperature. The mixing, blending, grinding and pressing of dry powders results in substantial airborne contamination within the gloveboxes.

The second aerosol selected for study was a solid solution of $(U,Pu)O_2$ produced by sintering the mixed UO_2 and PuO_2 pellets at 1750°C. for several hours. During sintering, the atoms of plutonium substitute freely into the crystalline structure of the more abundant UO_2 forming the solid solution. After sintering, the pellets are precision ground to design specifications using centerless grinding techniques. This latter operation results in substantial airborne contamination withing the glovebox enclosures.

The third aerosol selected was a PuO_2 powder treated at 850°C used as initial input to the fabrication process. This aerosol provided a key linkage to information from similar studies in animals exposed via inhalation to laboratory-produced aerosols of $^{239}PuO_2$. This comparison allowed a determination of the potential role of the irregular shape of these particles in determining the radiation dose distribution following inhalation.

For each of the selected aerosol materials, three inhalation studies were conducted to determine the patterns of radiation dose distribution in tissues. Each study was conducted using an identical experimental protocol with the single difference among studies being the physical chemical form of the aerosol. Fischer-344 rats provided a link to the large quantity of information on the relationship between radiation dose and biological response following inhalation of PuO_2 (Ref. 2.3, 2.4). Studies using the rat also allowed comparison to previous short-term studies conducted using the rat exposed to mixed oxide aerosols of a slightly different elemental mass ratio (Ref. 2.5, 2.6). Use of Beagle dogs provided a link to a substantial body of information on the dose-response relationships following inhalation of PuO_2 (Ref. 2.7, 2.8, 2.9). In addition, the retention of inhaled, relatively insoluble, particles deposited in lung of dogs is quite similar to that of people. Cynomolgus monkeys provided a unique opportunity to obtain comparative data on radiation dose distribution in a non-human primate.

To compare and contrast the results from the nine inhalation studies reported here, a biokinetic model was formulated. Specific rate constants describing interchange of material among compartments representing specific tissues or organs were initially set to values determined in previous inhalation studies (Ref. 2.10, 2.11). Specific rate constants were then changed to provide predictions of the time course of uptake and retention of plutonium, americium or uranium contained in these particles.

METHODS AND MATERIALS

Aerosol Generation and Characterization

Aerosols used for the animal inhalation exposures were generated from bulk samples of dry powders collected from floors and walls of gloveboxes immediately following a day of routine processing. The inhalation exposure system included a DeVilbiss dry powder blower (Model 175, The DeVilbiss Co., Somerset, PA) containing the powder which was subjected to ultrasound agitation. The aerosol was generated by a moving airstream, passed through a ^{85}Kr discharger to reduce particle agglomeration and then through a tube to the exposure chamber. The entire exposure system was enclosed in a glove-box line to ensure containment of the exposure materials. Each exposure aerosol was characterized with regard to concentration, particle size and size distribution, and morphology using membrane filters, a cascade impactor (Ref. 2.12) and a point-to-plane electrostatic precipitator (Ref. 2.13), respectively. Alpha radioactivity on the membrane filters and the individual cascade impactor stages was quantified by ZnS scintillation counting methods. A lognormal distribution function was fitted to each set of impactor data by a least squares method and the activity median aerodynamic diameter (AMAD) and geometric standard deviation (σ_g) of the distribution were determined. Point-to-plane electrostatic precipitator (ESP) samples were analyzed by transmission electron microscopy.

Animals

Animals were exposed to each of the three aerosol materials as follows. Forty Fischer-344 rats, 20 male and 20 female, born and reared in the Institute's barrier maintained colony and aged 8 to 9 weeks at time of exposure, received their inhalation exposure as a single group using an 80-port chamber (Ref. 2.14). Eighteen purebred Beagles, 9 males and 9 females born and reared in the Institute's colony and aged from 15 to 40 months at exposure, were exposed individually using an exposure apparatus previously described (Ref. 2.15). Nine monkeys (3 Rhesus and 6 Cynomolgus), all males, caught from the wild, received their exposure in the same apparatus used for dogs. The ages of the monkeys, as estimated from body size and dentition, were from 2 to 7 years of age at the time of inhalation exposure.

Rats were exposed to obtain an initial lung burden (ILB) of approximately 50 nCi of alpha activity per animal. The dogs and monkeys were exposed to attain an ILB of approximately 0.07 μCi per kg body weight.

Animal Care and Handling

Rats were housed in pairs in polycarbonate shoe-box cages (25 x 25 x 48 cm) with aspen wood shaving bedding and filter caps. Food and water were provided ad libitum. Rooms housing rats were maintained at 21 ± 2°C with a relative humidity between 20 and 50% and a 12-hour light:12-hour dark cycle starting at 0600 hours. Water bottles were changed twice weekly and bedding material was changed weekly. Selected rats were periodically housed individually in stainless steel metabolism cages for periods of five days for collection of urine and feces.

Dogs were housed singly for 21 days after inhalation exposure in metabolism cages designed for separate collection of urine and feces, and then transferred to standard indoor/outdoor kennel runs, except for periodic 5-day intervals during which additional excreta were collected. Dogs were fed a daily ration of 12 oz. dry kibble food (Allied Mills, Chicago, IL) and water was provided ad libitum. Monkeys were housed singly in metabolism cages for the duration of the study. Each monkey received 8 oz. of dry monkey chow (Ralston Purina Co., St. Louis, MO) and one-half a fruit per day with water provided ad libitum.

Composite 3-day excreta collections were obtained for three of the five rats assigned for sacrifice at 64 days after exposure. Similarly, daily excreta collections from three of the five rats assigned to sacrifice at 2 years after exposure were obtained for the first 64 days after exposure and additionally for three days periods at 12, 18 and 24 weeks and at 6-month intervals thereafter. Daily collections were made for dogs and monkeys for 21 days after exposure and for three-day periods at 12, 18 and 24 weeks and at 6-month intervals thereafter.

Animals were randomly assigned to sacrifice groups at 4 hours, 4 days, 64 days and 1, 1.5, 2, and 4 years after exposure. Animals were sacrificed in groups of five rats, two dogs and one monkey at each sacrifice time. Animals not assigned to specific sacrifice times were maintained as reserves for substitution into sacrifice groups as might be required by death of animals prior to their scheduled sacrifice. After the four-year sacrifices of dogs and monkeys were completed, the remaining reserve animals were kept on study with semiannual excreta collections obtained. At times ranging up to 2079 days (dogs) and 1947 days (monkeys) after inhalation, these reserve animals were sacrificed. This report includes analysis of the data obtained from these reserve animals.

Rats were sacrificed by intraperitoneal injection of T-61 Euthanasia solution (Taylor Pharmacal Co., Decatur IL). Dogs and monkeys were sacrificed by exsanguination performed under sodium pentabarbital anesthesia. A complete postmortem examination was performed on each animal.

Radiochemical Analysis

The plutonium, americium and uranium contents of tissue and excreta samples were determined radiochemically. Briefly, these samples were alternately dry and wet ashed to obtain a clear acid digest. Plutonium was separated from americium by extraction from the aqueous solution with an extractant cocktail containing bis-(2-ethylhexyl)phosphoric acid dissolved in toluene. Radioactivities of $^{238,\ 239}Pu$ and ^{241}Am were measured separately by liquid scintillation counting techniques (Ref. 2.16, 2.17, 2.18). Uranium content was determined from an aliquot of the acid digest solution by fluoresence (Ref. 2.19).

Data Analyses

The initial lung burden (ILB) of each group of rats was estimated from the mean lung content measured for five randomly selected rats sacrificed at 4 days after exposure. For dogs and monkeys, the ILB was estimated for individual animals. Negative exponential functions were fitted to the daily content of Pu or Am in urine or feces for each animal for the period from day 5 after exposure to the day of death. The fitted functions were integrated over this interval to obtain an estimate of the total radioactivity excreted. These values and the total radioactivity measured in the tissue samples obtained at necropsy were summed to estimate the ILB. Radioactivity excreted during the first 4 days after inhalation exposure was excluded because this material largely represented material deposited in the upper respiratory tract and rapidly cleared via the gastrointestinal tract.

To compare the pulmonary retentions of these materials in the three animal species, the radioactivity in lung at each sacrifice time was expressed as a percentage of the ILB. These percentages were fitted to a single-component negative exponential function for each species and for each aerosol material using a nonlinear least squares method (Ref. 20). Using the same method, the uptake and retention of plutonium and americium in the liver and skeleton during the same period were fitted to a function of the form

$$R(t) = A\, e^{-\lambda_1 t}\, (1 - e^{-\lambda_2 t}) \qquad \text{(Eq. 2.1)}$$

To determine if retention data for lung, liver and skeleton were similar for each species and each aerosol material, an F statistic was calculated for each comparison as follows

$$F = \frac{\frac{RSS_g - \Sigma RSS_i}{(m-i)p}}{\frac{\Sigma RSS_i}{n - mp}} \qquad \text{(Eq. 2.2)}$$

where RSS_g = the residual sum of squares of the function fitted to the grouped data,

ΣRSS_i = the sum of the residual sums of squares of the function fitted separately to each subset of data,

m = number of subsets of data in group,

n = total number of data points in grouped data set,

p = number of parameters in the fitting function.

The test of the null hypothesis that the data subsets were from a single population (and therefore not different) is based on the tabulated F statistic. At the stated level of confidence, the null hypothesis cannot be rejected when the calculated F value is less than the appropriate tabulated F value.

Biokinetic Modeling

A second method for highlighting similarities and differences in the retention, distribution and excretion of the plutonium, americium and uranium content in these aerosol materials for each species involved use of a mass balance biokinetic model. The model used represents a synthesis of two previous models found useful for description of similar data from inhalation studies in the Beagle dog involving exposure to aerosols of $^{241}AmO_2$ or $^{238}PuO_2$ (Ref. 2.10, 2.11). The model included the mathematical expression derived by Mercer (Ref. 2.21) to describe the dissolution of particles deposited in the lung. Specifically, dissolution is described as a function of the physical characteristics of the deposited particles as given in the following equations:

$$S(t) = F(B, \sigma_g) \qquad \text{(Eq. 2.4)}$$

and

$$B = \frac{\alpha_s \, kt}{\alpha_v \, \rho \, D_m} \qquad \text{(Eq. 2.5)}$$

where σ_g is the geometric standard deviation of the aerosol size distribution, α_s is the surface shape factor, k is the dissolution rate for the chemical form of interest, t is time in days, α_v is the volume shape factor, ρ is the density of the particles, and D_m is the mean geometric diameter of the particles.

A schematic representation of the model is shown in Figure 2.1. As a starting point in the modeling of plutonium retention, distribution and excretion in dogs exposed to these industrial aerosols, all rate constants for internal organ compartments which communicate with the blood compartment were set identical to the values for these same rate constants used in the model of ^{238}Pu retention, distribution and excretion in dogs over a four-year period following inhalation exposure to $^{238}PuO_2$ (Ref. 2.11). Similarly, for modeling the ^{241}Am component of these industrial aerosols, these rate constants were set equal to values from the model of ^{241}Am retention, distribution and excretion following inhalation of $^{241}AmO_2$ by dogs (Ref. 2.10)

Mucociliary clearance of these materials from lung was described in the model using:

$$M(t) = B_1 e^{-\lambda_1 t} + B_2 e^{-\lambda_2 t} + b3 \qquad \text{(Eq. 2.6)}$$

where B_i and λ_i are empirically determined in the iterative fitting process.

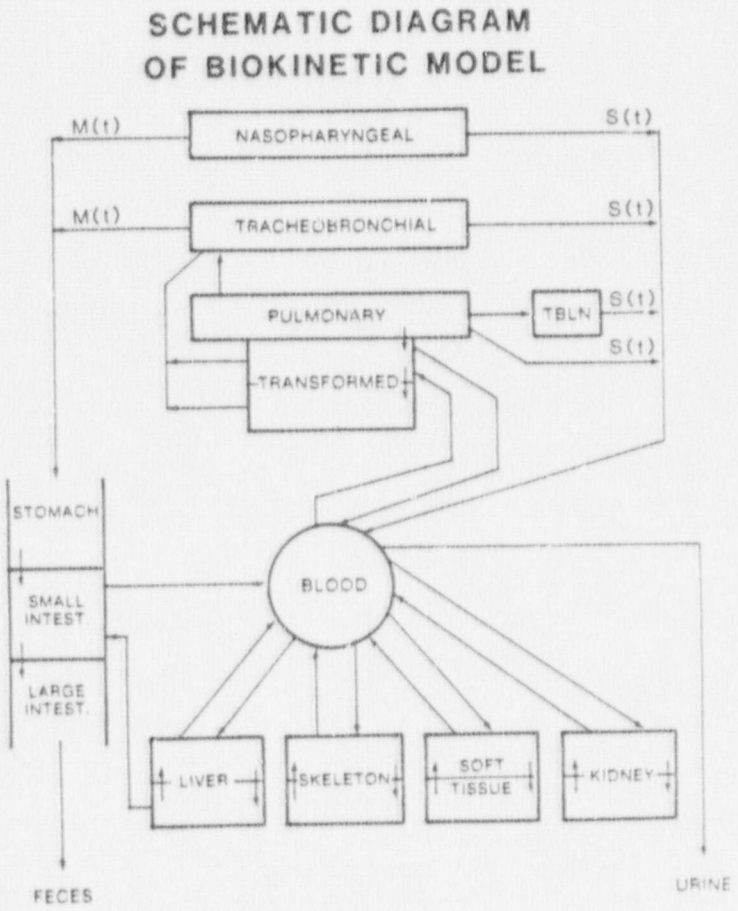


Figure 2.1. Schematic diagram of the biokinetic model used to describe the retention, distribution and excretion of Pu and Am in animals following inhalation of $(U,PU)O_2$ or PuO_2.

The values used for variables in the equations that describe dissolution of Pu or Am from the aerosols (Eq. 2.4, 2.5) were calculated from several types of physical chemical measurements made on samples of the aerosol obtained during animal inhalation exposures. The geometric diameter (D_m) and the geometric standard deviation (σ_g) of the exposure aerosols were determined from cascade impactor data. Density (ρ) was calculated from X-ray diffraction measurements of the crystal lattice unit cell dimensions. Surface shape factor (α_s) and volume shape factor (σ_v) were estimated from measurements of the specific surface area using an ^{85}Kr adsorption technique (Ref. 2.22, 2.23). The dissolution rate constant, (k), was estimated from the results of *in vitro* dissolution studies of aerosol samples using a serum ultrafiltrate (Ref. 2.24).

A departure from the kinetic modeling technique used previously (Ref. 2.10, 2.11) was the insertion of a small fraction of the initial lung burden directly into the blood compartment at time zero in the simulation. For the plutonium component, this fraction amounted to 0.4% of the ILB for the $UO_2 + PuO_2$ material, 4.6% of the ILB for the $(U,Pu)O_2$ material and 0.1% of the ILB for the PuO_2 material. These values represent the percentages of the aerosol which undergoes very rapid dissolution with half-times of less than 2.2 days as determined from *in vitro* dissolution studies (this report, pp 7 to 29). These small percentages of the ILB undergoing rapid dissolution are in contrast to the vast majority of the deposited mass which undergoes very slow dissolution with half-times typically measured in many hundreds of days.

Self-imposed constraints in application of the model simulation procedure included use of a single mechanical-clearance function (Eq. 2.6) for each element (plutonium, americium and uranium) in all three aerosol materials for each species. This constraint recognizes that the elemental components of these aerosols were contained in a single matrix. A second constraint was to modify only those rate constants associated with transport of dissolved material (ie, ionic forms) as the model was extended from consideration of one species to the next for any given element of interest. Thus, the rate of dissolution was considered to be invariant for all animals.

One additional restriction for the modeling of the americium present in these aerosols was to use the identical expression for the rate of mechanical clearance for each species as had been found satisfactory for the plutonium model. This restriction was imposed simply because the americium present was due to the decay of ^{241}Pu present in the particles rather than the presence of seperate particles of AmO_2. Just as for plutonium, the rate constants for all compartments communicating with blood were taken from an identical model used in describing the retention, distribution and excretion of ^{241}Am following inhalation of $^{241}AmO_2$ (Ref. 2.15).

While complete data were available for plutonium and americium in all tissues of each species, the data for uranium were incomplete. Because of the relatively high natural uranium content in tissues and excreta, only data for lung retention and tracheobronchial lymph node uptake and retention of uranium in dogs and monkeys are presented.

The biokinetic model was implemented using a computer simulation language, GASP IV, programmed in Fortran IV (Ref. 2.25) on a VAX computer. The simulations were run iteratively and the results plotted to judge conformance with the data points.

RESULTS

Aerosol characteristics measured during the inhalation exposure of rats, dogs and monkeys to each of the three aerosol materials are summarized in Table 2.1. For comparison, characteristics of the aerosols sampled by cascade impactor during normal operation of the fuel fabrication facility are also given in Table 2.1.

Table 2.1

Aerosol characteristics measured during inhalation exposures of rats, dogs and monkeys, and at the industrial facility during routine processing.

Species or Process Stage	Material	Treatment Temperature (°C)	AMAD (μm)	σ_g
Rat	$UO_2 + PuO_2$	750	2.3	1.8
Dog			2.2	1.8
Monkey			1.5	1.6
Ball Milling			1.9	1.6
Rat	$(U,Pu)O_2$	1750	2.3	1.7
Dog			2.5	1.8
Monkey			2.4	1.7
Centerless Grinding			2.3	1.6
Rat	PuO_2	850	2.2	2.0
Dog			2.2	1.8
Monkey			2.2	1.8
Blending			2.1	1.6

The lung retention of plutonium, americium or uranium in rats was always much different than that observed for either dogs or monkeys. Similarly, the uptake and retention of these elements in liver and skeleton of rats were quite different than was observed for dogs and monkeys.

Values obtained for the parameters of the fitted functions describing the plutonium component of lung retention and liver and skeleton uptake and retention are presented in Tables 2.2, 2.3, and 2.4, respectively, for dogs and monkeys exposed to the three aerosol materials. Also shown in these tables are results from an identical analysis for dogs exposed to laboratory-produced monodisperse aerosols of $^{239}PuO_2$ (Ref. 2.26). The plutonium lung retention data for dogs and monkeys were combined for the three aerosols and a separate fit for the two species obtained, as illustrated in Figure 2.2. Similarly, the liver uptake and retention data for plutonium, along with the fitted functions are shown in Figure 2.3, and for skeletal uptake and retention of plutonium in Figure 2.4.

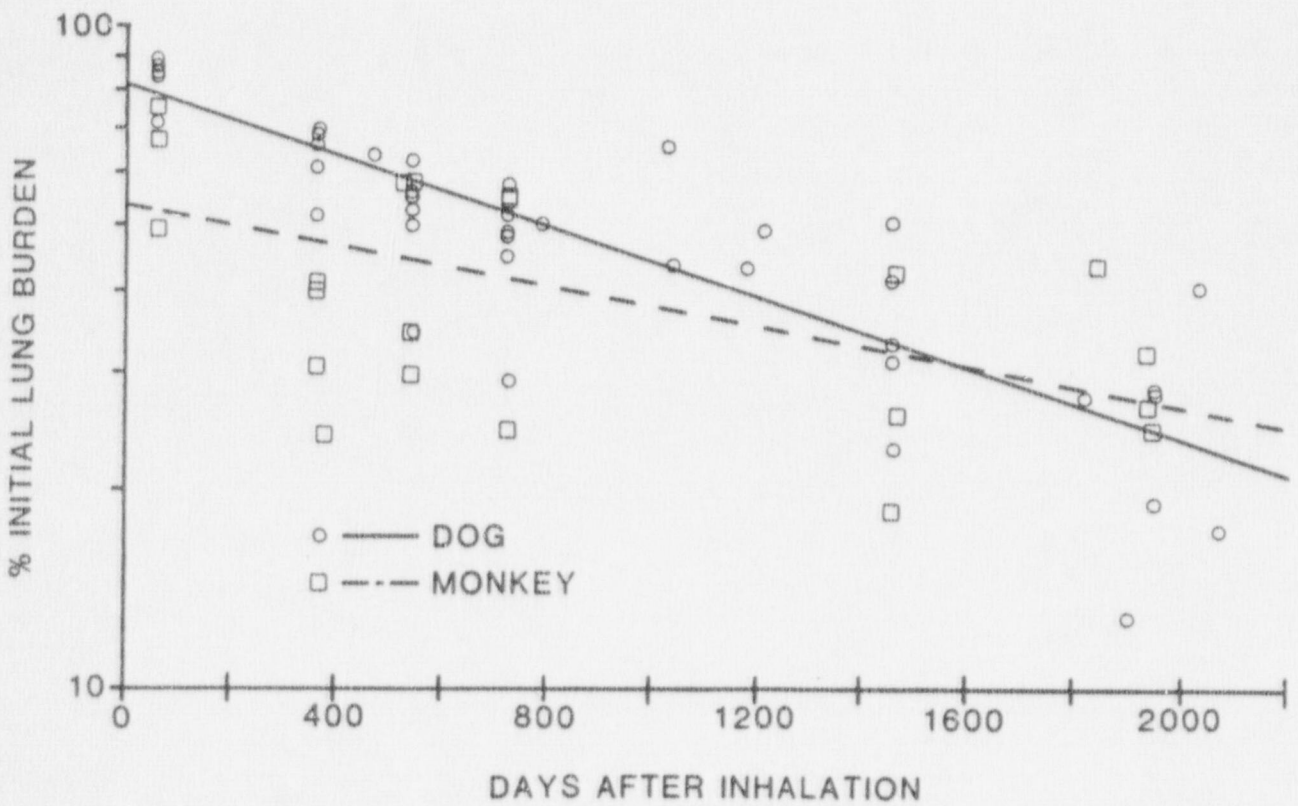


Figure 2.2. Lung retention of the plutonium component of three industrial aerosols in dogs and monkeys. The curves were obtained by nonlinear least squares fitting.

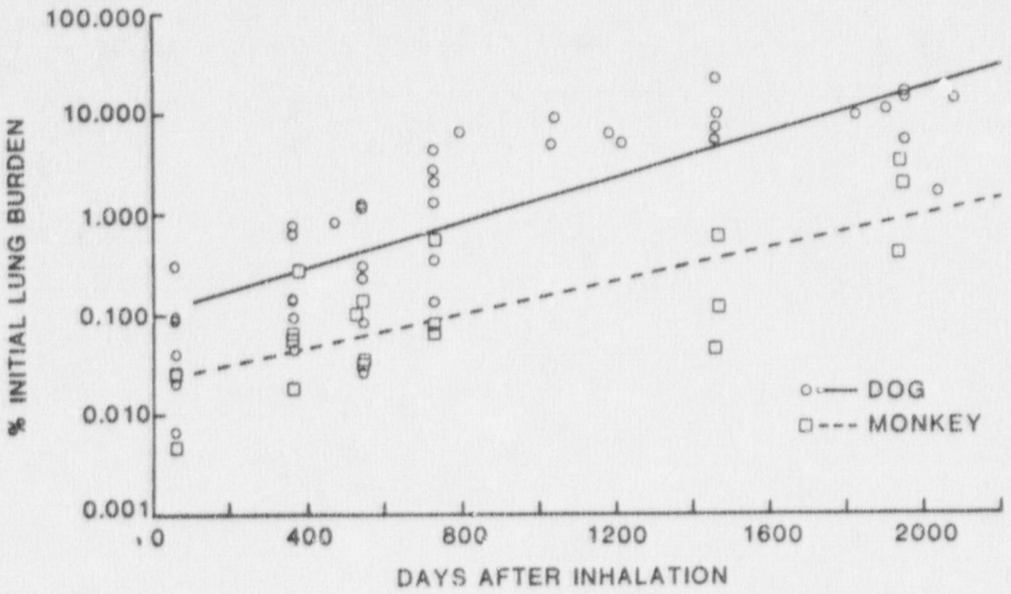


Figure 2.3. Uptake and retention of the plutonium component of three industrial aerosols in the livers of dogs and monkeys. The curves were obtained by nonlinear least squares fitting.

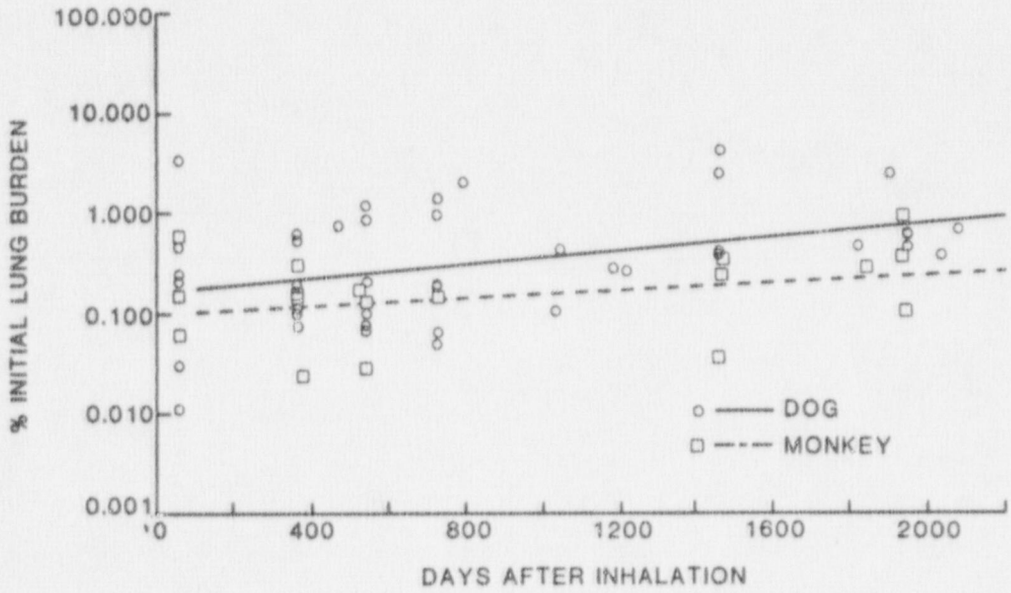


Figure 2.4. Uptake and retention of the plutonium component of three industrial aerosols in the skeletons of dogs and monkeys. The curves were obtained by nonlinear least squares fitting.

Table 2.2

Summary of results of fitting lung retention data for dogs and monkeys exposed to aerosols of UO_2+ PuO_2, $(U,Pu)O_2$, or PuO_2 of industrial origin or laboratory produced aerosols of PuO_2. The fitted function was $LB(t) = A_1 e^{-\lambda_1 t}$.

Data Set	Fitted Parameters A_1	λ_1	Residual Sum of Squares	n	Calculated F	Critical F (95%)
			DOGS			
PuO_2 (LP)[a]	88	-8.7×10^{-4}	580	9		
UO_2+ PuO_2	83	-5.7×10^{-4}	1160	14		
$(U,Pu)O_2$	78	-6.7×10^{-4}	1180	14		
PuO_2	86	-6.3×10^{-4}	792	14		
Combined[b]	82	-6.1×10^{-4}	3560	42	1.27	2.63
Overall[c]	83	-6.4×10^{-4}	4330	51	1.21	2.32
			MONKEYS			
UO_2+ PuO_2	70	-1.2×10^{-3}	1220	7		
$(U,Pu)O_2$	49	-2.0×10^{-4}	362	7		
PuO_2	61	-4.0×10^{-4}	1180	7		
Combined	54	-3.5×10^{-4}	3560	21	1.10	3.06
			DOGS AND MONKEYS			
Combined	72	-5.3×10^{-4}	10060	63	12.2	3.15

[a](LP) refers to data set from dogs exposed to laboratory-produced aerosols of $^{239}PuO_2$.

[b]Combined refers to the grouped data set composed of values for animals exposed to the three industrial aerosols listed just above and excludes data from the LP group.

[c]Overall refers to the grouped data set composed of all dogs exposed to any of the three industrial aerosols plus those exposed to the LP aerosol.

Table 2.3

Summary of results of fitting liver uptake and retention data for dogs and monkeys exposed to aerosols of UO_2+ PuO_2, $(U,Pu)O_2$, or PuO_2 of industrial origin or laboratory produced aerosols of PuO_2. The fitted function was $LB(t) = A_1 e^{-\lambda 1 t}(1 - e^{-\lambda 2 t})$.

Data Set	Fitted Parameters A_1 (% ILB)	$-\lambda_1$	$-\lambda_2$	Residual Sum of Squares	n	Calculated F	Critical F (95%)
			DOGS				
PuO_2 (LP)[a]	0.020	4.0×10^{-2}	-10.	0.37	8		
UO_2+ PuO_2	0.040	3.3×10^{-3}	- 0.46	3.01	14		
$(U,Pu)O_2$	0.39	1.6×10^{-3}	- 1.6	1.77	14		
PuO_2	0.034	3.5×10^{-3}	-99.	3.80	14		
Combined[b]	0.10	2.6×10^{-3}	- 0.23	11.9	42	2.12	1.43
Overall[c]	0.064	3.0×10^{-3}	-99.	13.5	50	2.33	1.61
			MONKEYS				
UO_2+ PuO_2	0.51	6.2×10^{-4}	-30.	0.64	7		
$(U,Pu)O_2$	0.042	1.8×10^{-3}	- 5.4	0.83	7		
PuO_2	0.0058	2.5×10^{-3}	- 1.6	0.81	7		
Combined	0.021	1.9×10^{-3}	- 5.5	3.97	21	1.49	2.50
			DOGS AND MONKEYS				
Combined	0.052	2.6×10^{-3}	- 1.2	27.2	63	14.2	1.15

[a](LP) refers to data set from dogs exposed to laboratory-produced aerosols of $^{239}PuO_2$.

[b]Combined refers to the grouped data set composed of values for animals exposed to the three industrial aerosols listed just above and excludes data from the LP group.

[c]Overall refers to the grouped data set composed of all dogs exposed to any of the three industrial aerosols plus those exposed to the LP aerosol.

Table 2.4

Summary of results of fitting skeletal uptake and retention data for dogs and monkeys exposed to aerosols of $UO_2 + PuO_2$, $(U,Pu)O_2$, or PuO_2 of industrial origin or laboratory produced aerosols of PuO_2. The fitted function was $LB(t) = A_1 e^{-\lambda_1 t} (1 - e^{-\lambda_2 t})$.

Data Set	Fitted Parameters A_1 (%ILB)	λ_1	λ_2	Residual Sum of Squares	n	Calculated F	Critical F (95%)
			DOGS				
PuO_2 (LP)[a]	0.065	1.3×10^{-3}	-32.	0.094	7		
$UO_2 + PuO_2$	0.12	7.5×10^{-4}	-99.	0.56	14		
$(U,Pu)O_2$	0.93	3.0×10^{-4}	-99.	1.38	14		
PuO_2	0.028	1.6×10^{-3}	-10.	0.57	14		
Combined[b]	0.16	8.2×10^{-4}	- 3.7	11.1	42	20.5	1.39
Overall[c]	0.14	8.7×10^{-4}	- 3.0	11.6	49	22.3	1.34
			MONKEYS				
$UO_2 + PuO_2$	0.061	1.2×10^{-3}	-99.	0.66	7		
$(U,Pu)O_2$	0.066	1.0×10^{-3}	- 1.5	0.62	7		
PuO_2	0.21	4.1×10^{-4}	- 4.7	0.82	7		
Combined	0.098	4.7×10^{-4}	- 3.3	2.97	21	0.083	2.50
			DOGS AND MONKEYS				
Combined	0.14	7.0×10^{-4}	- 0.72	15.8	63	2.28	1.15

[a](LP) refers to data set from dogs exposed to Laboratory Produced aerosols of $^{239}PuO_2$.

[b]Combined refers to the grouped data set composed of values for animals exposed to the three industrial aerosols listed just above and excludes data from the LP group.

[c]Overall refers to the grouped data set composed of all dogs exposed to any of the three industrial aerosols plus those exposed to the LP aerosol.

Table 2.5

Measured values for variables in equation describing dissolution of particles deposited in lungs of dogs, monkeys and rats.

Radio-nuclide	Species	Aerosol	Density (g/cm^3)	Particle Diameter ($\times 10^{-4}$ cm)	Geometric Standard Deviation	Specific Constant of Solubility ($g/cm^2/day$)	Surface Shape Factor	p[a]
Plutonium	Dog	$UO_2 + PuO_2$	11.5	0.59	1.8	1.3×10^{-10}	19.3	0.4
		$(U,Pu)O_2$	11.5	0.66	1.8	7.1×10^{-10}	22.0	4.6
		PuO_2	11.5	0.47	1.7	1.5×10^{-10}	108	0.1
	Monkey	$UO_2 + PuO_2$	11.5	0.34	1.6	8.1×10^{-10}	19.3	0.4
		$(U,Pu)O_2$	11.5	0.61	1.7	6.6×10^{-10}	22.0	4.6
		PuO_2	11.5	0.56	1.8	1.8×10^{-10}	108	0.1
	Rat	$UO_2 + PuO_2$	11.5	0.59	1.8	1.4×10^{-9}	19.3	0.4
		$(U,Pu)O_2$	11.5	0.59	1.7	6.4×10^{-10}	22.0	4.6
		PuO_2	11.5	0.56	2.0	1.8×10^{-10}	108	0.1
Americum	Dog	$UO_2 + PuO_2$	11.5	0.59	1.8	9.7×10^{-9}	19.3	2.0
		$(U,Pu)O_2$	11.5	0.66	1.8	2.5×10^{-9}	22.0	6.7
		PuO_2	11.5	0.47	1.7	5.1×10^{-10}	108	0.1
	Monkey	$UO_2 + PuO_2$	11.5	0.34	1.6	6.1×10^{-10}	19.3	2.0
		$(U,Pu)O_2$	11.5	0.61	1.7	2.3×10^{-9}	22.0	6.7
		PuO_2	11.5	0.56	1.6	6.0×10^{-10}	108	0.1
	Rat	$UO_2 + PuO_2$	11.5	0.59	1.8	1.1×10^{-9}	19.3	2.0
		$(U,Pu)O_2$	11.5	0.59	1.7	2.2×10^{-9}	22.0	6.7
		PuO_2	11.5	0.56	2.0	6.0×10^{-10}	108	0.1
Uranium	Dog	$UO_2 + PuO_2$	11.5	0.59	1.8	4.8×10^{-8}	19.3	37.0
		$(U,Pu)O_2$	11.5	0.66	1.8	1.9×10^{-9}	22.0	26.0
	Monkey	$UO_2 + PuO_2$	11.5	0.34	1.6	3.0×10^{-8}	19.3	37.0
		$(U,Pu)O_2$	11.5	0.61	1.7	1.7×10^{-9}	22.0	26.0
	Rat	$UO_2 + PuO_2$[b]						
		$(U,Pu)O_2$						

[a] p = Percentage of initial lung burden dissolving with halftimes less than ≈ 2 days.

[b] Data not available.

A schematic diagram of the biokinetic model showing the rate constants which provided the best overall simulation of data describing retention, distribution and excretion of plutonium for the dog, monkey or rat is shown in Figure 2.5. Where a particular rate constant differed among the three species, the appropriate values are suffixed with a D for dog, M for monkey or R for rat. The rate constants shown apply to the plutonium component of all three aerosol forms in each animal species. Table 2.5 lists the values for variables in the equations (Eq. 2.4, 2.5) used to describe dissolution of plutonium from the three aerosol forms for each species. The adequacy of the model simulation of these data may be judged from Figures 2.6 (dog), 2.7 (monkey) and 2.8 (rat). For Figures 2.6 and 2.7, the symbols represent individual dog or monkey datum points, whereas for Figure 2.8 the symbols each represent a mean value for 5 rats.

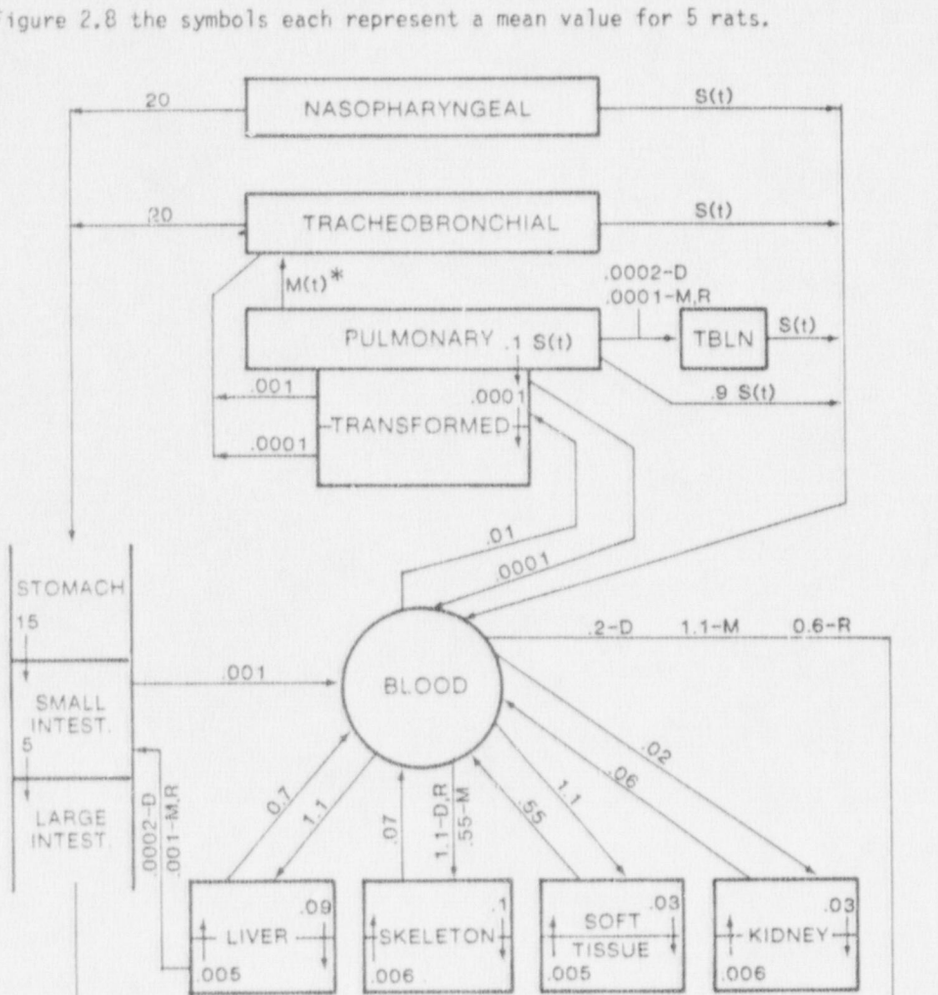
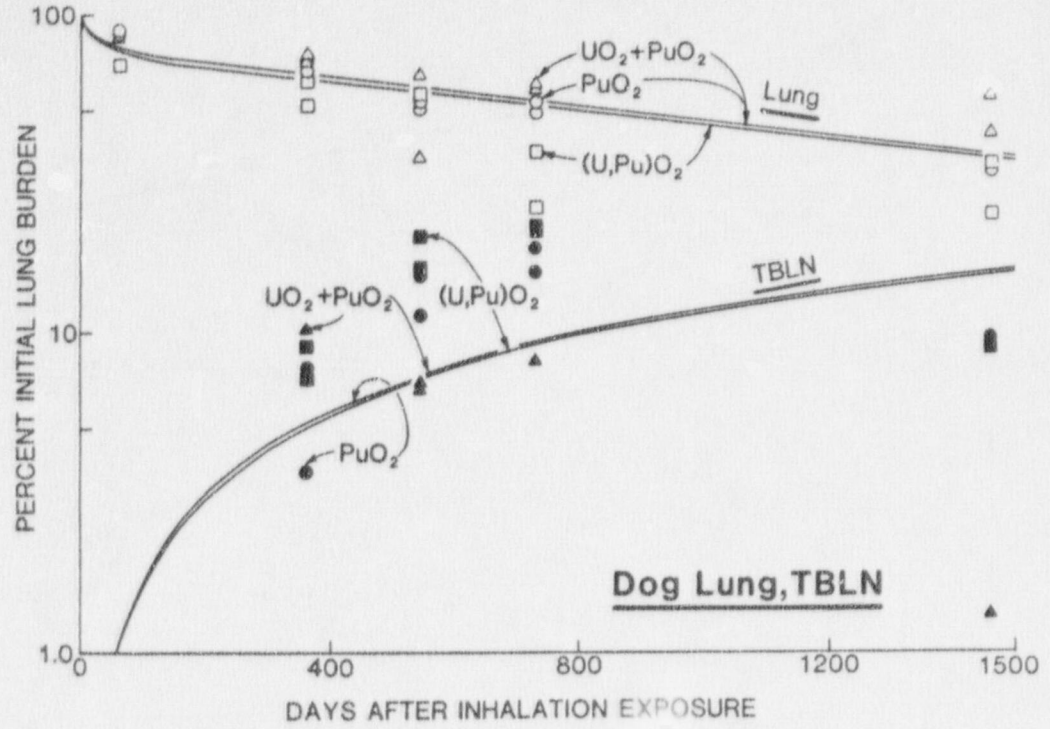


Figure 2.5 Schematic diagram of the biokinetic model used to describe the retention, distribution and excretion of plutonium in dogs, monkeys and rats following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Where more than one rate constant is shown for a given pathway, the suffix letter D (dogs), M (monkeys) and R (rats) indicates which constant is associated with each species.



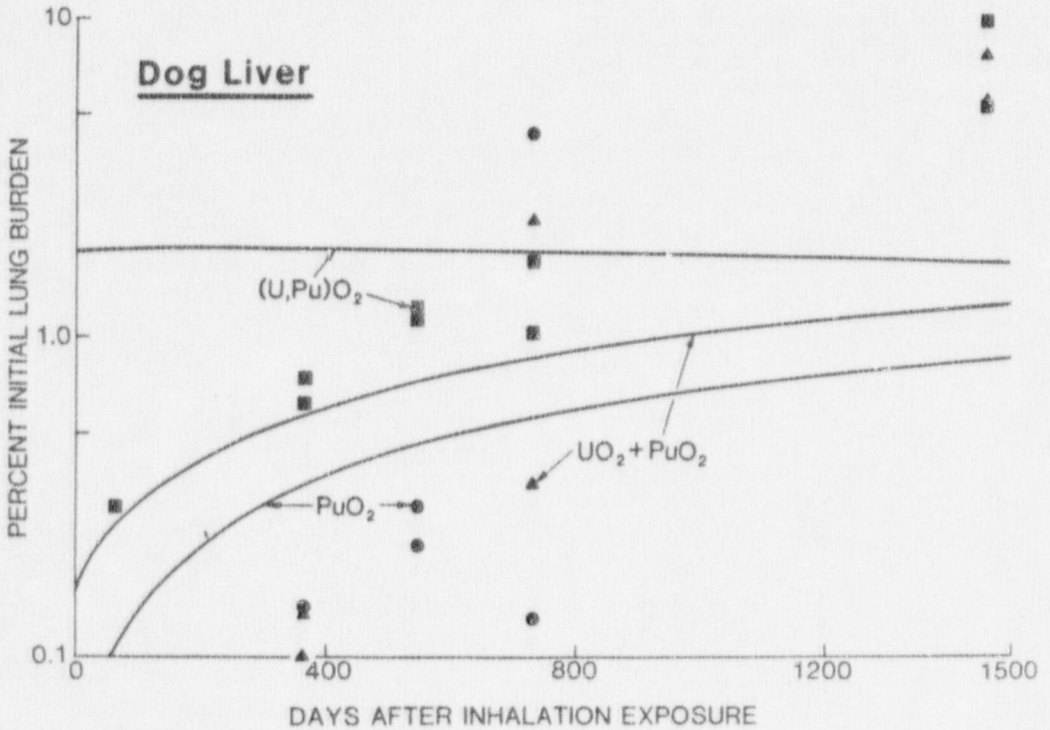
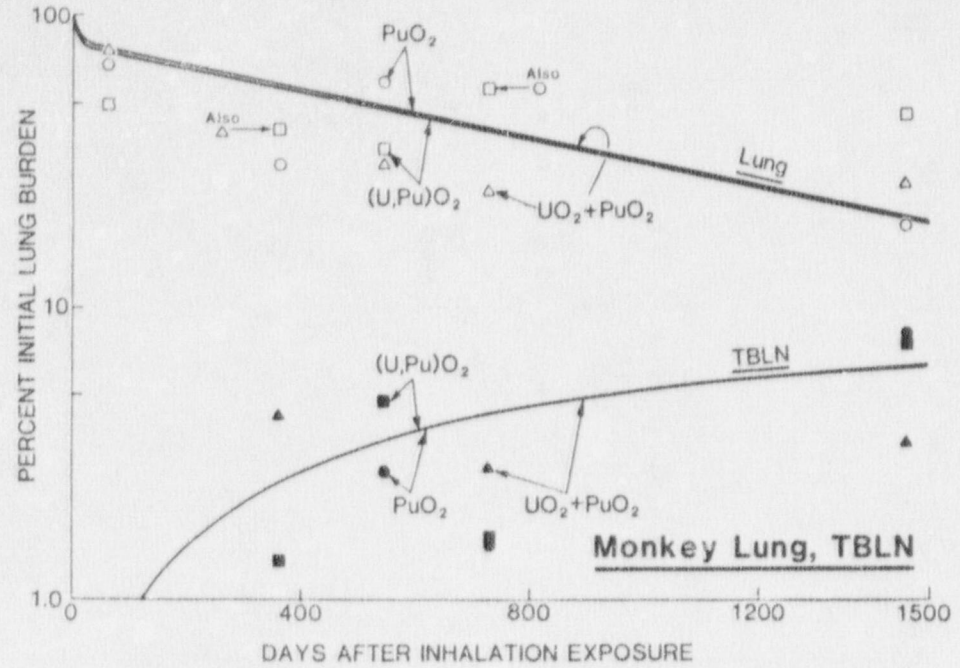


Figure 2.6 Lung retention, and tracheobronchial lymph node and liver uptake and retention of Pu in dogs following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent individual dogs whereas the curves represent model predictions.



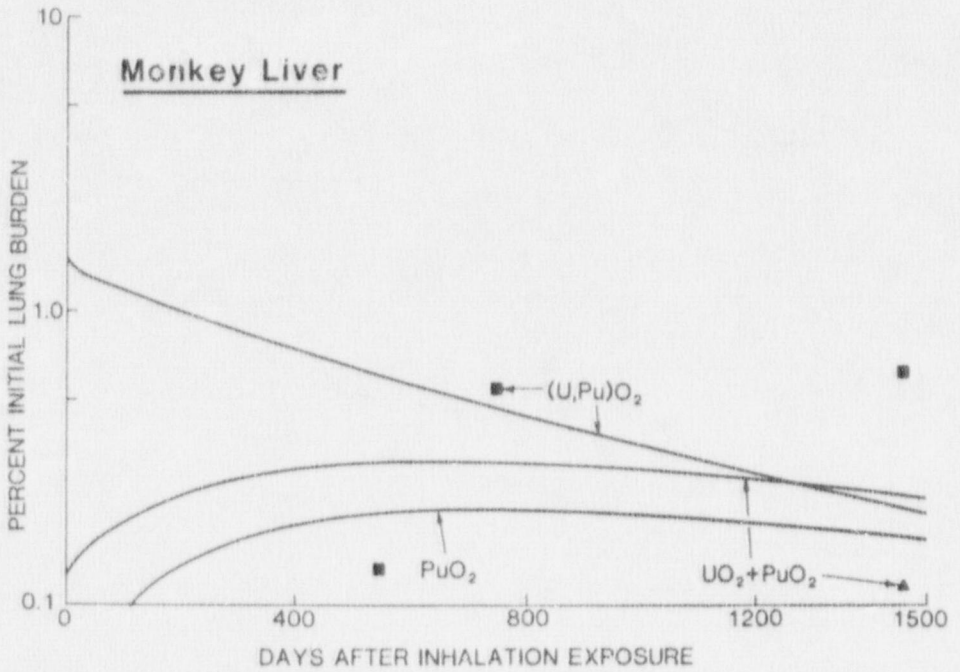
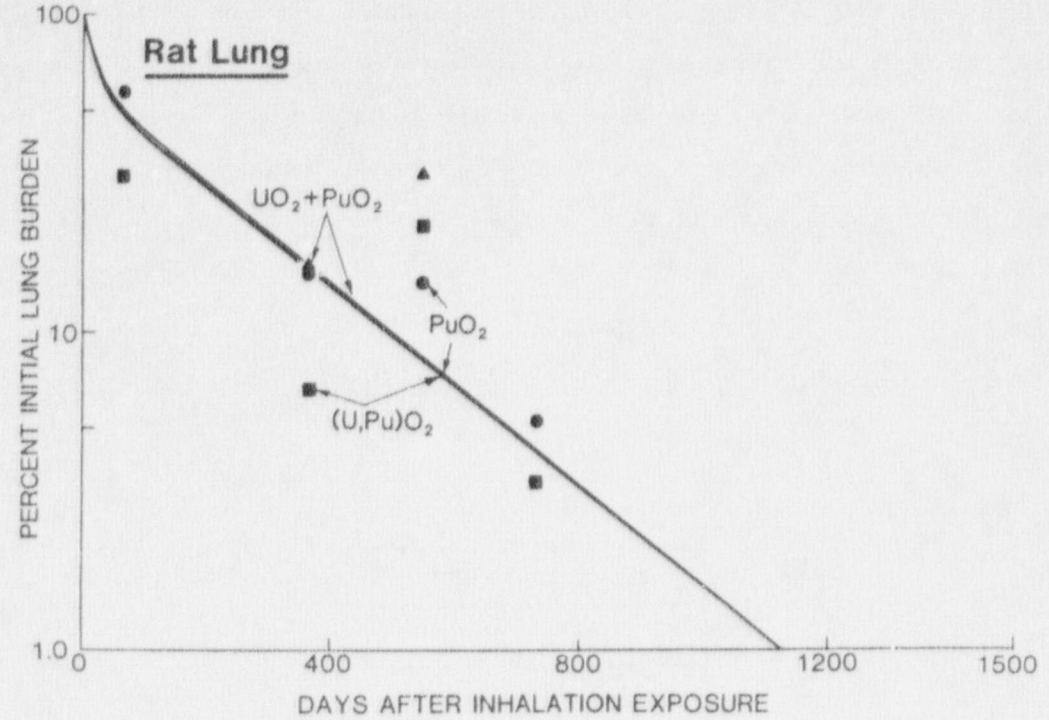


Figure 2.7 Lung retention and tracheobronchial lymph node and liver uptake and retention of Pu in monkeys following inhalation of either UO_2 + PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent individual monkeys whereas the curves represent model predictions.



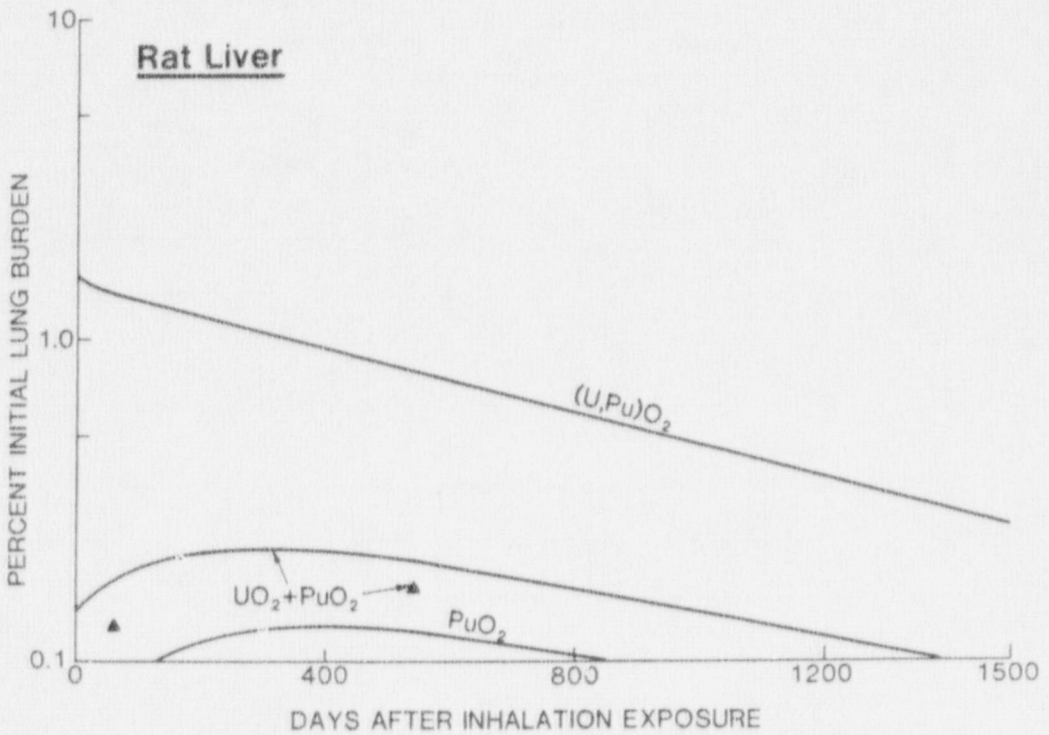


Figure 2.8 Lung retention, and tracheobronchial lymph node and liver uptake and retention of Pu in rats following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent mean of five rats whereas the curves represent model predictions.

A schematic diagram of the model showing the rate constants that provided the best overall simulation of the data describing retention, distribution and excretion of americium for the dog, monkey and rat is shown in Figure 2.9. As was the case for plutonium , these rate constants for americium apply to all three aerosol forms for each species. The values for the variables in the equations describing dissolution of americium from the three aerosol forms for each species are listed in Table 2.5. The adequacy of the model simulation of these data may be judged from Figure 2.10 (dog), Figure 2.11 (monkey) and Figure 2.12 (rat).

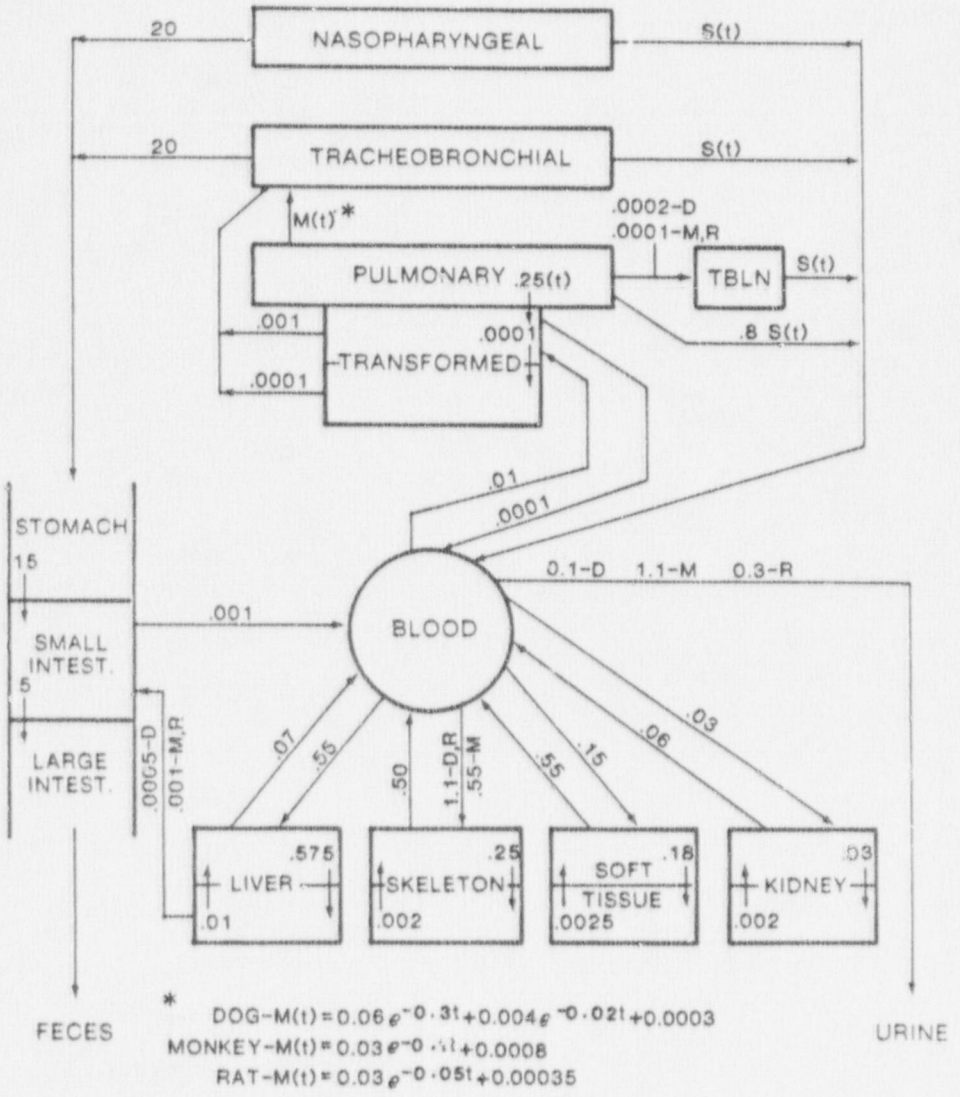
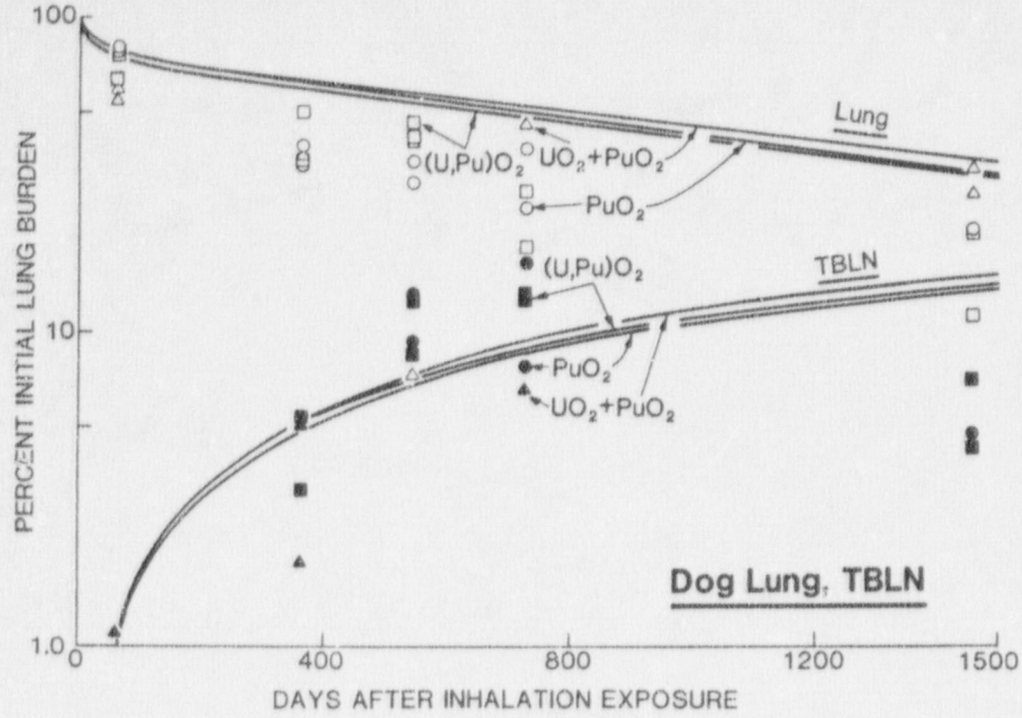


Figure 2.9 Schematic diagram of the biokinetic model used to describe the retention, distribution and excretion of the americium component in dogs, monkeys and rats following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Where more than one rate constant is shown for a given pathway, the suffix letter D (dogs), M (monkeys) and R (rats) indicates which constant is associated with each species.



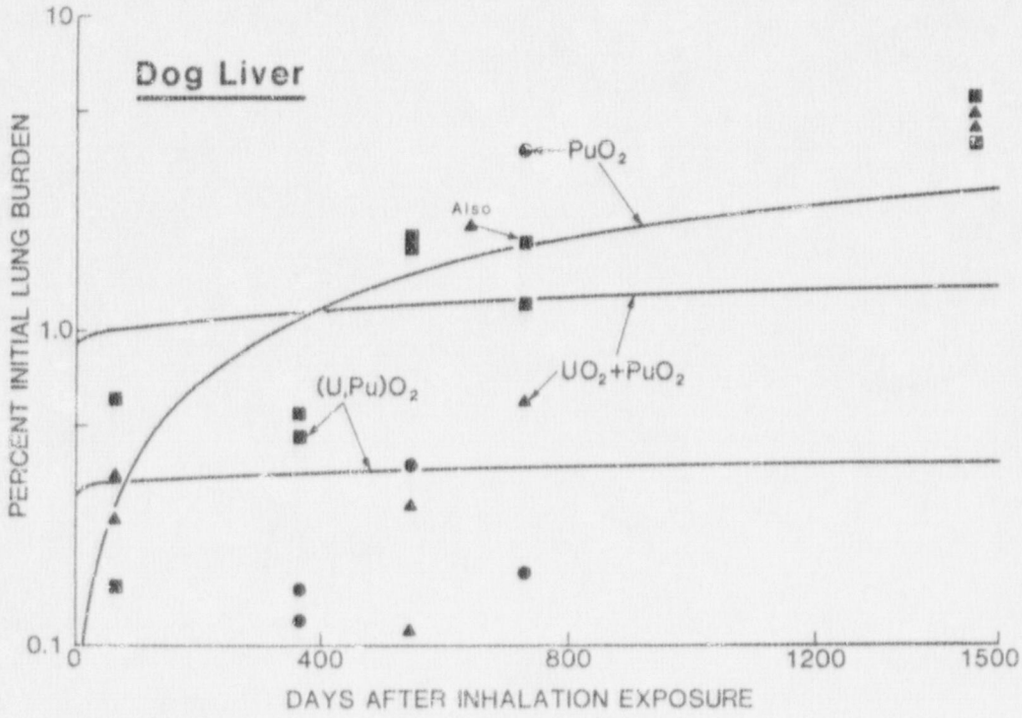
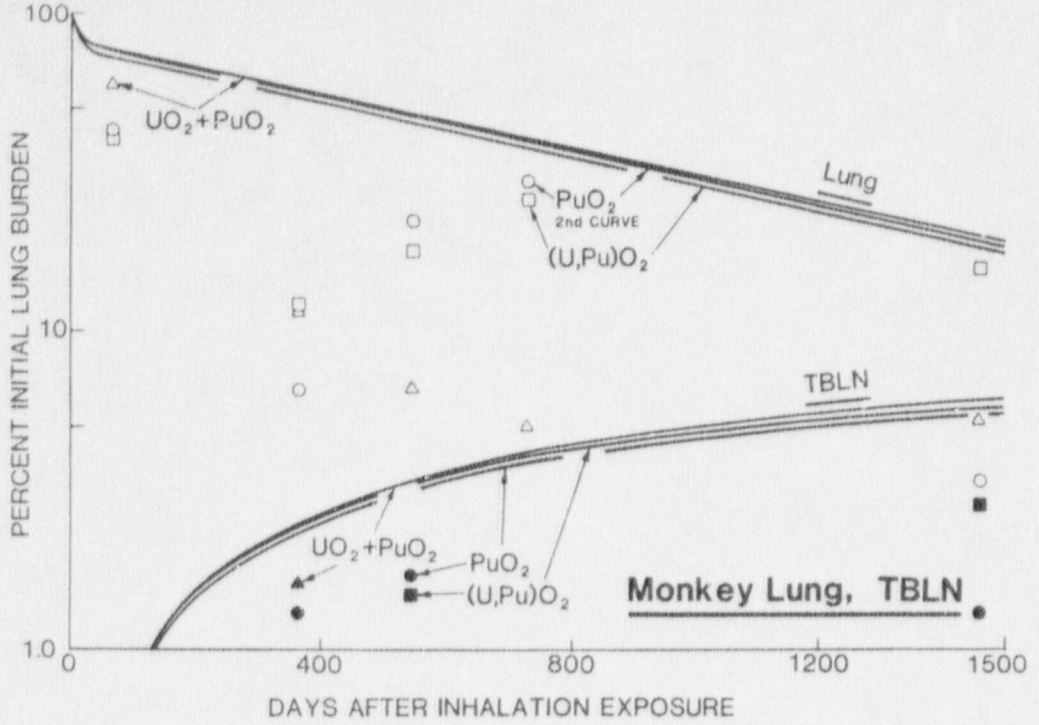


Figure 2.10 Lung retention, and tracheobronchial lymph node and liver uptake and retention of Am in dogs following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent individual dogs whereas the curves represent model predictions.



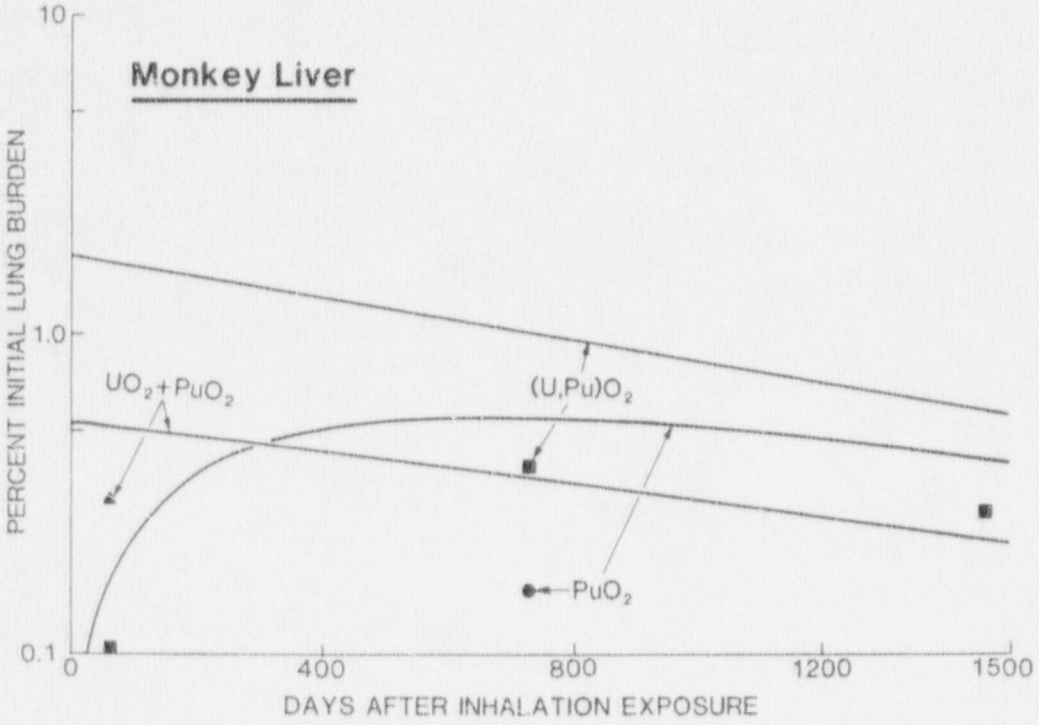
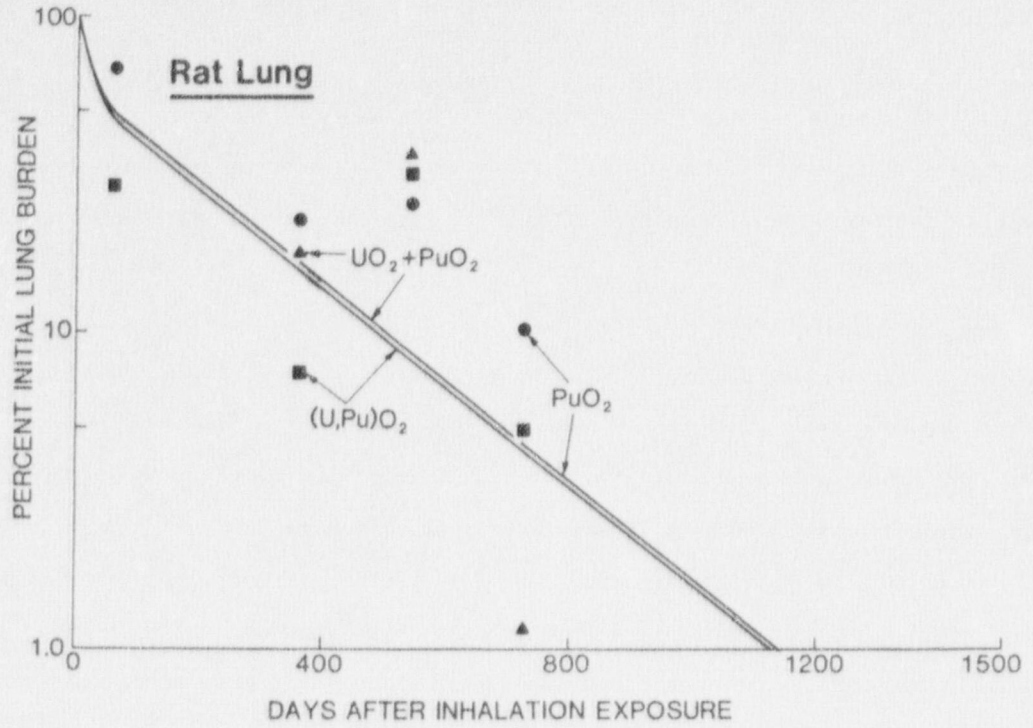


Figure 2.11 Lung retention, and tracheobronchial lymph node and liver uptake and retention of Am in monkeys following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent individual monkeys whereas the curves represent model predictions.



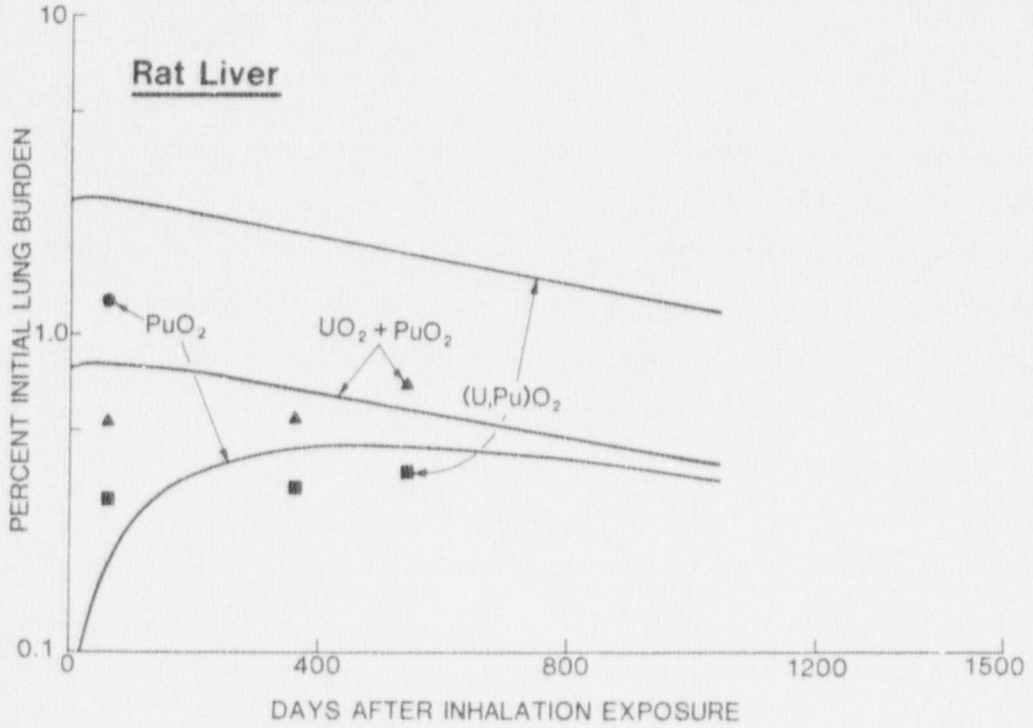


Figure 2.12 Lung retention, and tracheobronchial lymph node and liver uptake and retention of Am in rats following inhalation of either UO_2+ PuO_2, $(U,Pu)O_2$ or PuO_2. Datum points represent mean of five rats whereas the curves represent model predictions.

DISCUSSION

For rats exposed to these industrial aerosols, the lung retention and the uptake and retention in liver and skeleton of the plutonium component of these materials agree with data reported for short-term studies in rats exposed to similar industrial materials (Ref. 2.5, 2.6) or to laboratory-produced $^{239}PuO_2$ aerosols (Ref. 2.4). However, rats rapidly excrete actinide elements initially transported via blood and deposited in liver, whereas dogs do not (Ref. 2.27, 2.28). Further, because the rat skeleton continues to grow throughout the lifespan of rats, deposition and retention of actinide elements in bone are different for rats compared to dogs and monkeys. Therefore, uptake and retention in rats was excluded from further comparison to dogs or monkeys, except by means of the biokinetic model discussed below.

The calculated F statistic for the fit to the combined data set for the plutonium component of each aerosol inhaled by dogs was less than the tabulated value (Table 2.2). This result indicates that, for the dog, the differences in the physical chemical form of the industrial aerosols did not influence the plutonium retention in lung. When the data set for dogs exposed to laboratory produced aerosols of $^{239}PuO_2$ was included in the analysis (shown as "Overall" in Table 2.2), again no difference in retention pattern was evident. The same conclusion was drawn for the plutonium component of the industrial aerosols inhaled by monkeys, i.e. no difference in plutonium lung retention among the three aerosols.

However, when the grouped data for dogs exposed to the industrial materials were compared to the grouped data for monkeys, the F statistic indicated that the retention of the plutonium component in lung was different for the two species. It appears from inspection of Figure 2.2, that the difference between the two species was due to differences in the percentages of the ILB associated with the long-term retention component and the associated half-times of retention. The half-time of the long-term component of plutonium retention for all three aerosol materials was approximately 1100 days for dogs and approximately 2000 days for monkeys. A greater percentage of the ILB of monkeys was removed in the early phase of lung clearance compared to dogs.

When the uptake and retention of the plutonium component of each aerosol material in the dog liver were compared, the calculated F statistic was larger than the tabulated value (Table 2.3), indicating that the three data sets were not from the same population. Examination of the data (Figure 2.3) indicated that the dogs exposed to the $(U,Pu)O_2$ material had greater initial uptake of plutonium than was evident for the other two materials. Inclusion of the data set for dogs exposed to the laboratory-produced aerosol of $^{239}PuO_2$ did not appreciably alter the calculated F value , nor the conclusion of a difference among the aerosols. For monkeys, the F statistic indicated that no differences among the three aerosols were influencing liver uptake and retention.

The fit of the function (Eq. 2.1) to the grouped data for uptake and retention of plutonium in the liver of dogs is not entirely satisfactory. Examination of the data and fitted curve in Figure 2.3 shows that at times from 1000 to 1500 days after inhalation, the fitted curve underestimates the data. Plots of the residuals of the data to the fitted curve show a definite pattern, indicating the function is not providing an unbiased estimate in this time interval. Attempts to weight the data to provide an improved fit were not fruitful. Attempts to fit other functional forms did not improve the situation.

The uptake and retention of plutonium in the liver of monkeys was less than that measured in dogs at all times (Fig. 2.3). This difference may be due to two factors. Less Pu was available for transport from lung to liver in monkeys due to the greater early clearance of the materials from lung. Also, the retention half-time for actinide elements in the liver of monkeys has been reported to be shorter than for dogs (Ref. 2.27). The true retention half-times for plutonium in the liver of either monkeys or dogs cannot be assessed from these studies because uptake of plutonium is continuing throughout the time span of these studies.

An identical analysis of data describing uptake and retention of plutonium in the skeleton of dogs and monkeys was accomplished (Table 2.4, Figure 2.4). A similar conclusion was drawn for the canine skeleton as was concluded for the canine liver, ie. the data for dogs exposed to the three aerosol materials were not from a single population. Again, the data for the $(U,Pu)O_2$ material appeared to be different from data for the other two aerosol materials. For monkeys, no statistically significant differences were discerned in the uptake and retention of plutonium in the skeleton among the three aerosol materials.

The agreement between the curves generated via the biokinetic model and the lung retention, tracheobronchial lymph node and liver uptake and retention data for dogs was quite good (Fig. 2.6). Only slight differences in simulated lung retention of plutonium were noted for the three aerosol forms despite a very large increase in the surface shape factor (Table 2.5) of the PuO_2 aerosol. This larger surface shape factor for the PuO_2 did not appreciably increase the dissolution rate for this material, probably due to the low inherent solubility of PuO_2. As a check on the adequacy of the model in simulating the plutonium retention, distribution and excretion in dogs, the model was applied to the data set from a study which used laboratory-produced aerosols of $^{239}PuO_2$ (Ref. 2.28). For this case, the specific surface area was assumed to approximate that of spheres. No other changes were made in any of the model parameters. The agreement between the model predictions and these data was very good.

The model simulation of lung retention, tracheobronchial lymph node and liver uptake and retention of plutonium in monkeys for each of the aerosols also showed good agreement with the data (Fig. 2.7). Few changes in rate constants were necessary to convert the dog plutonium model

to provide good descriptions of the monkey data (see Fig. 2.5). The mechanical clearance rate, M(t), was altered to provide adequate descriptions of the fecal excretion of plutonium from monkeys. The rate constant describing the rate of transfer from the second liver compartment to the small intestine was increased as was the rate constant describing urinary excretion of plutonium from the blood compartment. The rate constant describing intake of plutonium from blood to skeleton was reduced for monkeys compared to the value for dogs.

The dog model was again modified for modeling the plutonium retention, distribution and excretion in rats. Results of these modifications provided good agreement between the simulation curves and the data for rats (Fig. 2.8). The changes necessary to adapt the model to rats include changes in the time varying rate of mechanical clearance, the rate of transfer from the second subcompartment of liver to small intestine and the rate of urinary clearance (see Fig. 2.5).

These modeling efforts indicate that when the fate of the plutonium component of the three aerosols is compared singly for each species, only very slight differences in lung retention, distribution and excretion can be ascribed to the physical chemical characteristics of the aerosols. This is undoubtably a reflection of the relatively insoluble nature of the plutonium component of these three aerosols. Thus, even though the surface shape factor for the PuO_2 material is a factor of 5 times greater than for the other two materials, the inherently low solubility of the PuO_2 masks expression of this difference. These results tend to confirm the conclusion drawn from the curve fitting analyses noted above of no difference in the lung retention of the plutonium component of the three aerosols.

The opposite conclusion can be made with regard to the role of animal species in determining the retention, distribution and excretion of the plutonium component of the aerosols. To achieve good agreement between the model-generated curves and the data for each species, selected rate constants were adjusted. The adjustments involved the rate of mechanical clearance, urinary excretion, uptake to skeleton and the rate of loss from liver to the small intestine via the biliary route. Retention half-times for the plutonium component in lung for these three aerosols was species dependent and was largely controlled by different rates of mechanical clearance. This result also confirmed the conclusion made from curve fitting regarding the differences among species in lung retention of the plutonium component of these aerosols. These differences were also in accord with observations previously reported for dogs and rats for several inhaled, relatively insoluble materials (Ref. 2.26, 2.27). The same type of differences in uptake and retention of actinide elements in liver of these species have been reported (Ref. 2.26, 2.27).

The simulation modeling of the Am component of these aerosols did not result in completely satisfactory descriptions of the data for the three species. In all cases, the model slightly overpredicted lung retention. Attempts to improve the description of lung retention within the

modeling constraints mentioned above were not successful. In-depth analyses of the cause for this lack of conformity of the model to the data indicated that it might be related to the early, rapid dissolution of the americium from the surface of particles followed by much slower dissolution of americium from the interior of particles. This explanation is supported by the *in vitro* dissolution studies (Ref. 2.24). At times greater than a few days after immersion in solvent, the americium present in these particles dissolves from the PuO_2 matrix much slower ($k > 1 \times 10^{-9}$) than for $^{241}AmO_2$ particles ($k = 1.5 \times 10^{-6}$).

As can be observed from Figures 2.10 (dog), 2.11 (monkey), and 2.12 (rat), lung retention is slightly overestimated; however, tissue distribution and excretion rates are relatively well described. Thus, while the americium model did not provide completely satisfactory descriptions, the fact that the americium content of these particulates is relatively low, and contributes relatively small increments of radiation dose to tissues, use of the model predictions as given in these figures would contribute only a slight over-estimate of total radiation dose to lung of these three species.

The comparison of the lung retention of the plutonium and americium component of these industrial aerosols, which represent the greatest radiological hazard, showed no difference relatable to the physical chemical form of the aerosol. Clear differences were observed when lung retention of plutonium or americium was compared among species for each aerosol. These differences were largely a function of differences in the mucociliary clearance rates for each species. The differences in uptake and retention of these elements in liver were relatable to differences in the half-time of retention in liver. This result agrees with previous reports; the liver of the rat has a short retention time, the monkey is intermediate while the dog retains these elements in liver for very long times. The retention times for these elements in skeleton of these species are all quite long.

CONCLUSIONS

The synthesis of information from these studies indicates that the radiation dose distribution to tissues of animals exposed by inhalation to the industrial aerosols would be essentially the same as would occur following inhalation of PuO_2 aerosols either of industrial or laboratory origin. Further, there is no evidence that the hazard to humans exposed to these industrial aerosols of these mixed oxides would be appreciably different than has been estimated for $^{239}PuO_2$.

REFERENCES

2.1 Newton, G.J., "Mixed-Oxide Fuel Fabrication," in Radiation Exposure and Risk Estimates for Inhaled Airborne Radioactive Pollutants Including Hot Particles, Annual Progress Report for Period July 1976 to June 1977, NUREG/CR-0010, 15-35, 1978.

2.2 Stanley, J.A., and G.J. Newton, "Further Sampling of Aerosolized Mixed-Oxide Nuclear Fuel in a Fabrication Facility," in Radiation Exposure and Risk Estimates for Inhaled Airborne Radioactive Pollutants Including Hot Particles, Annual Progress Report for Period July 1976 to June 1977, NUREG/CR-0010, 9-12, 1978.

2.3 Sanders, C.L., C.E. Dagle, W.C. Cannon, D.K. Craig, G.J. Powers and D.M. Meier, "Inhalation Carcinogenesis of High-Fired $^{239}PuO_2$ in Rats," Radiat. Res. 68: 349-360, 1976.

2.4 Sanders, C.L., C.E. Dagle, W.C. Cannon, G.J. Powers and D.M. Meier, "Inhalation Carcinogenesis of High-Fired $^{238}PuO_2$ in Rats," Radiat. Res. 71: 528-546, 1977.

2.5 Stather, J.W., A.C. James, J.C. Strong and P. Rodwell, "Translocation of Inhaled Industrial Dusts Containing Mixed Actinide Oxides in Rats and Hamsters," in Annual Research and Development Report 1976, NRPB/R&D1, 29-30, 1977.

2.6 James, A.C., J.W. Stather, J.C. Strong, J.E. Hostford, P. Rodwell, A. Hodgson and P. Kay, "Lung Clearance and Translocation in Rats and Hamsters of Inhaled Dust Containing Mixed Actinide Oxides from a Fuel Fabrication Plant," in Annual Research and Development Report 1977, NRPB/R&D2, 57-64, 1978.

2.7 Mewhinney, J.A., F.F. Hahn, B.A. Muggenburg, N.A. Gillett, J.H. Diel, J.L. Mauderly, B.B. Boecker and R.O. McClellan, "Toxicity of $^{238}PuO_2$ in Beagle Dogs: A. Monodisperse 1.5 μm AMAD Particles, B. Monodisperse 3.0 μm Particles, XI." in Inhalation Toxicology Research Institute Annual Progress Report 1984-1984, LMF-113, UC-48, 216-224, 1984.

2.8 Muggenburg, B.A., R.A. Guilmette, F.F. Hahn, B.B. Boecker, R.O. McClellan, J.L. Mauderly and J.A. Pickrell, "Toxicity of Inhaled $^{239}PuO_2$ in Beagle Dogs, A. Monodisperse 0.75 μm AMAD Particles, B. Monodisperse 1.5 μm AMAD Particles, C. Monodisperse 3.0 μm AMAD Particles, VII., in Inhalation Toxicology Research Institute Annual Report for 1983-1984, LMF-113, UC-48, 225-232, 1984.

2.9 Park, J.F., "Inhaled Plutonium Oxide in Dogs," in Pacific Northwest Laboratory Annual Report for 1984 to DOE Office of Energy Research, PNL-5500 PT1, UC-48, 13-22, 1985.

2.10 Mewhinney, J.A., and W.C. Griffith, "Models of Am Metabolism in Beagles," Health Phys. 42: 629-644, 1982.

2.11 Mewhinney, J.A. and J.H. Diel, "Retention of Inhaled $^{238}PuO_2$ in Beagles: A Mechanistic Approach to Description," Health Phys., 45: 39-60, 1983.

2.12 Mercer, T.T., M.I. Tillery and G.J. Newton, "A Multi-stage, Low Flow Rate Cascade Impactor," J. Aerosol Sci. 1: 9-14, 1970.

2.13 Morrow, P.E. and T.T. Mercer, "A Point-to-Plane Electrostatic Precipitator for Particle Size Sampling," Am. Indust. Hyg. Assoc. J. 25: 8-13, 1964.

2.14 Raabe, O.G., J.E. Bennick, M.E. Light, C.H. Hobbs, R.L. Thomas and M.I. Tillery, "An Improved Apparatus for Acute Inhalation Exposure of Rodents to Radioactive Aerosols," Toxicol. Appl. Pharmocol. 26: 264-273, 1973.

2.15 Boecker, B.B., F.L. Aguilar and T.T. Mercer, "A Canine Inhalation Exposure Apparatus Utilizing a Whole-body Plethysmograph," Health Phys. 10: 1077-1089, 1964.

2.16 Keough, A. and G.J. Powers, "Determination of Plutonium in Biological Materials by Extraction and Liquid Scintillation Counting," Anal. Chem. 42: 419-425, 1970.

2.17 Miglio, J.J., "The Determination of Am, Cm, and Cf in Biological Samples by Combined Solvent Extraction-Liquid Scintillation Counting," Int. J. Appl. Radiat. Isot. 129: 581-584, 1978.

2.18 Guilmette, R.A. and A.S. Bay, "Radioassay of Americium or Curium in Biological Material by Isooctyl Acid Phosphate Solvent Extraction and α Liquid Scintillation Counting," Anal. Chem. 53: 2351-2354, 1981.

2.19 Guilmette, R.A., "Analytical Methods for the Quantitative Determination of Uranium in Biological and Nonbiological Material," in Biological Characterization of Radiation Exposure and Dose Estimates for Inhaled Uranium Milling Effluents, Annual Progress Report for the Period April 1,1979 - March 31, 1979, NUREG/CR-1669, LMF-76, 1980.

2.20 SAS Institute Inc. "SAS User's Guide: Statistics," SAS Institute Inc., Cary, NC, 1982.

2.21 Mercer, T.T., "On the Role of Particle Size in the Dissolution of Lung Burdens," Health Phys. 13: 1211-1221, 1967.

2.22 Rothenburg, S.J., J.A. Mewhinney, A.F. Eidson and D.K. Flynn, "Surface Area Measurements. Part B. A Comparison of Three Methods of Determining Specific Surface Area and A Comparison of Three Materials for Surface Area Standards," in Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides - Annual Progress Report for the Period July 1981-June 1982, NUREG/CR-3313, LMF-105, 1983.

2.23 Mewhinney, J.A., S.J. Rothenburg, A.F. Eidson and G.J. Newton, "Surface Area Measurements. Part C. Specific Surface Area Determinations of Mixed U and Pu Oxide Particles," in Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides - Annual Progress Report for the Period July 1981-June 1982, NUREG/CR-3313, LMF-105, 1983.

2.24 Eidson, A.F. and J.A. Mewhinney, "In Vitro Dissolution of Respirable Aerosols of Industrial Uranium and Plutonium Mixed-Oxide Nuclear Fuels," Health Phys. 45: 1023-1037, 1983.

2.25 Pritsker, A.A.B., The GASP IV Simulation Language, New York, Wiley and Sons, 1974.

2.26 Guilmette, R.A., J.H. Diel, B.A. Muggenburg, J.A. Mewhinney, B.B. Boecker, and R.O. McClellan, "Biokinetics of Inhaled $^{239}PuO_2$ in the Beagle Dog: Effect of Aerosol Particle Size," in Inhalation Toxicology Research Institute Annual Report for 1981-1982, LMF-104, UC-48, pp 202-205, 1982.

2.27 Durbin, P.W., "Metabolism and Biological Effects of Transplutonium Elements," in Uranium, Plutonium and the Transplutonium Elements, Handbook of Experimental Pharmacology, Springer-Verlag, New York, 1973.

2.28 Bair, W.J., J.E. Ballou, J.F. Park and C.L. Sanders. "Plutonium in Soft Tissue with Emphasis on the Respiratory Tract," in Uranium, Plutonium and the Transplutonium Elements, Handbook of Experimental Pharmacology, Springer-Verlag, New York, 1973.

Chapter 3. DOSE-RESPONSE STUDY IN F344 RATS EXPOSED TO $(U,Pu)O_2$ OR PuO_2

Abstract -- The relationship of radiation dose to lung and the biological effect observed was investigated following inhalation of two types of plutonium-containing particulate materials in rats. Bulk powder samples of the two materials were obtained from within gloveboxes used in the routine manufacture of mixed plutonium and uranium oxide nuclear fuel. The materials were a solid solution of uranium and plutonium treated at 1750°C and a PuO_2 feedstock. Groups of rats received a single inhalation exposure to a material to achieve one of three levels of initial pulmonary burden. Rats were maintained for their lifespan to observe the biological effects produced. These effects were observed in the lungs of rats exposed to either type of particle. The same types of lung cancer were produced by both particulate materials. The incidences of cancers were also similar at comparable levels of initial pulmonary burden for the two materials. The crude incidence of lung cancers for rats exposed to these materials was not different than those reported for similar studies that used laboratory-produced aerosols of PuO_2. Using a linear dose-effect model, the relative risk of lung cancer for rats exposed to these industrial materials was 2.3 ± 1.0 (SE) at a lung dose of 100 rad. The doubling dose for lung cancers was 78 ± 63 rad to lung to median life span.

PRINCIPAL INVESTIGATORS

J. A. Mewhinney
A. F. Eidson
F. F. Hahn
B. R. Scott
F. A. Seiler
B. B. Boecker

INTRODUCTION

Nuclear fuel for specialized nuclear reactors, especially breeder reactors, may consist of mixed uranium and plutonium oxides. The potential also exists for use of such fuel in light water reactors commonly used in electric power production. Little information exists to describe the potential carcinogenic hazard following inhalation of these materials by workers involved in fabrication of mixed oxide fuel, or to the general population in the event of an accidental release of such material from confinement. The highest potential for internal deposition is by inhalation.

At present, carcinogenic risks for workers or the general population due to internal deposition of aerosolized mixed oxide fuel is likely to be estimated by summing risks for the individual components of the mixtures. Substantial information is available describing the relationship between radiation dose and cancer incidence following inhalation of laboratory-produced PuO_2 or UO_2 in several animal species. However, no such studies have been done using

mixed oxides of uranium and plutonium. Investigations concerning the fate of inhaled mixed U-Pu oxide or PuO_2 aerosols of industrial origin by rats, dogs and monkeys were conducted at this Institute to define the tissue radiation dose distribution (this report, pp 29 to 59). Results from these studies indicated a potential for a greater risk of lung cancer in F344/N rats (Ref. 3.1) compared to previous studies in rats using laboratory-produced aerosols of $^{239}PuO_2$ (Ref. 3.2).

A primary objective of the research reported here was to determine if the dose-response relationship after inhalation of industrial mixed oxides of uranium and plutonium was different than relationships reported for rats that inhaled laboratory-produced aerosols of $^{238}PuO_2$, $^{239}PuO_2$ or UO_2 (Ref. 2.2, 2.3, 2.4, 2.5, 2.6). The second objective was to estimate the potential health risk to humans represented by inhalation of these materials.

In these studies, rats were exposed by inhalation to achieve three levels of radiation dose to lung that was expected to produce significant incidences of lung cancer while having little or no effect on the median life span of the exposed rats compared to sham-exposed rats. Two materials were chosen for study; both were obtained as powder samples from gloveboxes at an industrial plant devoted to production of mixed oxide nuclear fuel. One powder consisted of a mixed oxide of uranium and plutonium treated at 1750°C and the second consisted of PuO_2 powder treated at 850°C.

METHODS AND MATERIALS

Experimental Design

The experimental design for these studies is shown in Table 3.1. F344/N rats (equal numbers of each gender), reared in the Institute's barrier-maintained colony and 10 to 15 weeks of age at the time of exposure, were used. The number of rats in each dose group was selected to allow detection of a 5% increase in lung cancer incidence rate above that measured in previous studies that used laboratory-produced, inhaled $^{239}PuO_2$ aerosols (Ref. 3.7). Each group of rats received a single, brief inhalation exposure to one of the aerosols and was maintained for life span observation. Eight rats were included in each exposed group for sacrifice at seven days after exposure to estimate the initial pulmonary burden for each exposure group. Twenty-four additional rats were included in the medium level exposure group for serial sacrifice in groups of 4 rats at selected times during the first two years after exposure to provide estimates of the retention of $^{238, 239}Pu$ and ^{241}Am in lung and other tissues and to allow calculation of radiation dose in these tissues.

Table 3.1

Experimental design of dose-response study in which rats inhaled graded levels of either $(U,Pu)O_2$ or PuO_2 of industrial origin.

Exposure Level	Desired Initial Pulmonary Burden (nCi)[a]		Number of Rats
	$(U,Pu)O_2$	PuO_2	
low	13.	20.	40
medium	2.6	5.0	80
high	0.52	0.80	120
Control	-	-	160

[a]These desired burdens were calculated from the desired absorbed pulmonary alpha radiation dose using retention functions previously reported for inhalation of $^{239}PuO_2$ by rats (Ref. 3.2).

Inhalation Exposure

Bulk powder samples of $(U,Pu)O_2$ and PuO_2 collected from gloveboxes at an industrial facility that produced mixed plutonium and uranium oxide nuclear reactor fuels (Ref. 3.8, 3.9) were aerosolized for inhalation exposures using a dry-powder blower (Ref. 3.10). The physical chemical form of the aerosols, and the bulk materials from which the aerosols were formed have been described (Refs. 3.11, 3.12). Inhalation exposures of rats were conducted using an apparatus previously described (Ref. 3.13). Duration of the exposures ranged from 10 to 43 minutes depending upon the level of initial pulmonary burden desired. Groups of either 52 or 76 randomly assigned rats were exposed in a series of 6 exposure runs for each aerosol. Four groups of 40 control rats were sham-exposed to room air in an uncontaminated exposure apparatus.

During each inhalation exposure, the aerosol concentration and activity median aerodynamic diameter (AMAD) were characterized by collecting aerosol samples on membrane filters or in cascade impactors (Ref. 3.14). The aerosol size distribution was described by fitting a lognormal distribution to the cascade impactor data using a maximum likelihood approach. Additional samples of the aerosol were collected on electron microscope grids using a point-to-plane electrostatic precipitator (Ref. 3.15) for examination by transmission electron microscopy.

Animal Housing

Immediately after exposure, pairs of rats were placed in polycarbonate cages (20 by 25 by 48 cm) fitted with filter caps. Bedding material (Aspen wood shavings) was changed weekly. Rats were housed for the duration of the experiment in rooms maintained at 21 ± 2°C with a relative humidity between 20 and 50% and a light cycle of 12 hours on (6:00 AM-6:00 PM) and 12 hours off. Food (Lab-Blox, Allied Mills, Chicago, IL) and tap water were available ad libitum. All rats in the study were observed at least twice daily. Body weights of a randomly selected subset of the rats exposed to either of the aerosols and of control rats were measured periodically through the experiment.

Sacrifice and Necropsy

Scheduled sacrifices of randomly designated rats or euthanasia of moribund rats was accomplished by intraperitoneal injection of a lethal dose of T-61 euthanasia solution (Taylor Pharmacal Co., Decatur, IL). Immediately after death, a complete postmortem examination was accomplished that included examination of all organ systems. Samples of tissues from all major organs (lung, liver, kidney, spleen) and lesions observed at necropsy were fixed in 10% neutral buffered formalin. Representative tissue sections were prepared by embedding in paraffin, sectioning at 5 μm and staining with hematoxylin and eosin. The remainder of the major organs and samples of specific tissues were radiochemically analyzed for plutonium, americium, and uranium content.

Radiochemical Analysis

Radiochemical analysis of tissues was accomplished by alternate dry and wet ashing to obtain a clear digest in 2 M nitric acid. An aliquot of each digest was placed in a liquid scintillation vial with an extractant cocktail to quantify the $^{238,239}Pu$ content (Ref. 3.16). Then, an aliquot of the aqueous phase in the vial was carefully withdrawn and placed in a second, clean scintillation vial with Aquasol (New England Nuclear, Inc., Cambridge, MA) scintillation cocktail for determination of the ^{241}Am content.

Initial Pulmonary Burden

The mean initial pulmonary burdens of plutonium, americium, and uranium for each exposure group were estimated by analysis of the content of these radionuclides in the lungs of eight rats (4 of each gender) sacrificed 7 days after exposure. These lung samples consisted of the entire lung, including the two main bronchi. For all rats that died or were sacrificed at times greater than 7 days after exposure, the percentages of the initial pulmonary burden for each rat were determined by dividing its pulmonary content of each element by the mean initial pulmonary burden for that exposure group.

Pulmonary Retention

Comparisons of data sets describing pulmonary retention of plutonium in rats were accomplished through use of nonlinear least squares fitting (Ref. 3.17) and subsequent evaluation of the F statistic. Initially, the data for animals that died or were euthanized in the lifespan studies were segregated by level of initial pulmonary burden (low, medium, and high) for each aerosol. A single exponential function was used because no data were available for times less than 200 days after exposure. Separately, the plutonium pulmonary retention data for animals sacrificed (medium-level exposure group) were fitted using a two-component exponential function (both early and late time data available). The two-component function was forced to pass through 100% retention at seven days after exposure so that the data conformed to the measured pulmonary burdens of rats sacrificed at that time. For each aerosol the combined life-span and sacrifice data were grouped and fitted to the two-component exponential. This latter grouping was also used to compare lung retention of americium from the two aerosols and to compare the americium retention with the plutonium retention in the same animals. Similarly, the lung retention of plutonium was compared for the two genders of rats. All comparisons among data sets were made using the F statistic and a null hypothesis that the subsets of data were from a single population.

Estimation of Radiation Dose to Lung

The initial pulmonary burden for each rat in these studies could not be determined directly because these radionuclides do not emit sufficient penetrating gamma rays for *in vivo* counting, nor were excreta collections possible for the large number of rats used in the studies. Therefore, the initial pulmonary burden for each rat was estimated by extrapolating the pulmonary burden measured at death back to day 7 after exposure using the common retention function determined for rats exposed to that aerosol. Cumulative absorbed alpha radiation dose (hereafter referred to as "dose") to lung was calculated for each rat from time of exposure to time of median lifespan for control rats of each gender (770 days after exposure for females, 700 days after exposure for males) according the equation

$$\text{Cumulative dose (rads)} = \frac{51.2\ E\ f\ g\ A}{W}\int_{t=0}^{t=med} B(t)dt, \qquad \text{(Eq. 3.1)}$$

where 51.2 = proportionality factor, E = alpha particle energy per disintegration in MeV (5.45), f = absorbed fraction of alpha particle energy absorbed in lung (1.0), g=fractional yield of alpha emission per disintegration (1.0), A = initial pulmonary burden in μCi, W = lung weight in grams, B(t) = pulmonary retention expressed as the fraction of the initial pulmonary burden, and limits of integration are from time of exposure (t=0) to time of median life span (t=med).

Survival and Cancer Incidence Analysis

Survival distributions for rats exposed to the two aerosol forms were analyzed separately using the Kaplan-Meier product-limit method (Ref. 3.19). The equality of survival distributions for different groups was tested using the methods of Mantel and Breslow (Ref. 3.19). Analysis of the cumulative incidence of fatal lung cancers as a function of time was accomplished using the Kaplan-Meier method which corrects for competing risks (Ref. 3.19). The potential role of arbitrarily chosen group sizes upon subsequent analysis of the relationship between dose and biological effect was investigated by starting from the ordered initial pulmonary burden data and choosing successive groups of 20, 30 and 40 rats. The Kaplan-Meier method was used to arrive at the cumulative incidence of fatal or fatal plus contributory cancers versus time after exposure for each group size.

Dose-Response Relationships

The cumulative incide of fatal lung cancers, A, was fitted as a linear function of radiation dose, D, to lung at median life span of the rats.

$$A = a_o + (a_2 D) \qquad \text{(Eq. 3.2)}$$

To estimate the intercept, a_o, and the slope, a_2, an iteratively reweighted least squares fitting routine was used (Ref. 3.17) based on the assumption that the cumulative incidence at dose, D, had a binomial distribution. For each iteration, the weights were the inverse of the binomial variance calculated from the estimated incidence. The slope, a_2, and its standard error provided an estimate of the absolute risk per rad and its standard error. To provide an estimate of the relative risk coefficient and its standard error, equation 3.2 was reparameterized as equation 3.3 and the data again fitted using the iteratively reweighted nonlinear least squares.

$$A = a_o + (a_o a_3 D) = a_o (1 + a_3 D) \qquad \text{(Eq. 3.3)}$$

The relative risk, R, at dose, D, was then estimated by

$$R = 1 + (a_3 D). \qquad \text{(Eq. 3.4)}$$

RESULTS

Inhalation Exposure

Characteristics of aerosols measured during rat inhalation exposures are summarized in Table 3.2. Results of X-ray diffraction analysis of samples of the two aerosol materials

Table 3.2

Aerosol characteristics measured during the inhalation exposure of rats in the dose-response studies.

Exposure Level	Aerosol	AMAD[a] (μm)	σ_g[a]	Initial Pulmonary Burden of Plutonium[b] (nCi)
High	$(U,Pu)O_2$	3.38 ± 0.15	1.31 ± 0.04	20.0 ± 8.8
Medium	$(U,Pu)O_2$	3.37 ± 0.14	1.37 ± 0.04	1.2 ± 0.9
Low	$(U,Pu)O_2$	3.64 ± 0.26	1.42 ± 0.03	0.7 ± 0.8
High	PuO_2	2.81 ± 0.30	1.39 ± 0.06	8.2 ± 6.2
Medium	PuO_2	2.11 ± 0.30	1.56 ± 0.17	8.5 ± 6.4
Low	PuO_2	2.47 ± 0.20	1.46 ± 0.04	1.8 ± 2.0

[a]Field measurements of the aerosol size of the $(U,Pu)O_2$ source material at the industrial facility showed an AMAD of 2.08 ± 0.32 μm and a σ_g of 1.61 ± 0.06.

[b]Mean ± SE of eight rats sacrificed at seven days after exposure.

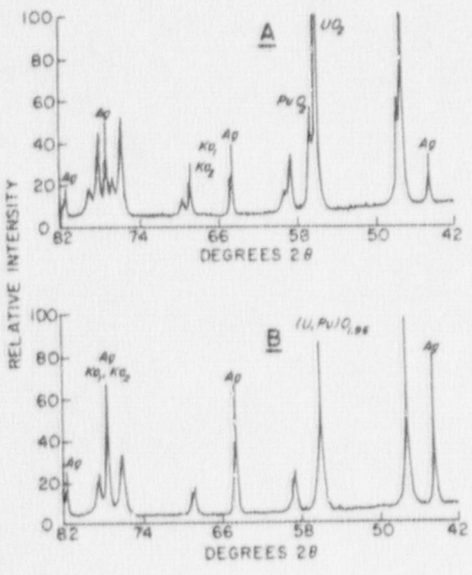


Figure 3.1. X-ray diffraction patterns from aerosols of mixed uranium dioxide and plutonium dioxide (A) and of $(U,Pu)O_2$ (B).

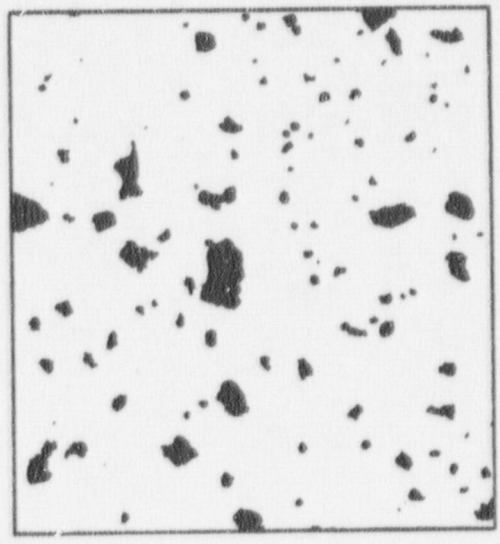


Figure 3.2. Electron micrograph of an aerosol of industrial plutonium dioxide.

collected during rat exposures and for the bulk powder samples obtained at the industrial facility are presented in Figure 3.1. Figure 3.2 is a micrograph of the particles of plutonium dioxide sampled during the exposure of rats. The mean initial pulmonary burdens for rats sacrificed 7 days after exposure for each dose level are also shown in Table 3.2.

Body Weight

The body weights of all rats in the experimental groups, and of a randomly selected subgroup of the control rats, were measured periodically throughout their life span. In Figure 3.3, the values of mean body weight, with a 95% confidence interval, are shown for the control rats. Also shown in Figure 3.3 are curves resulting from fitting a polynomial function of degree two to body-weight data for control rats, rats exposed to the mixed uranium-plutonium oxide aerosol, and for rats exposed to the PuO_2 aerosol.

A further comparison was made to body-weight data for a group of 144 F344/N rats born and raised at this Institute and held as colony controls. The peak body weight attained and the days of age at peak body weight are listed in Table 3.3 for several groups of exposed and control rats.

Table 3.3

Summary of body weight data by gender for rats in the dose-response studies, control groups and colony control groups.

Group	Aerosol	Gender	Peak Weight (g)	Days of Age at Peak Weight
Dose-Response	$(U,Pu)O_2$	F	250	795
Dose-Response	PuO_2	F	270	1050
Dose-Response	Control	F	272	740
Colony Control		F	236	840
Dose-Response	$(U,Pu)O_2$	M	426	565
Dose-Response	PuO_2	M	425	570
Dose-Response	Control	M	411	555
Colony Control		M	396	545

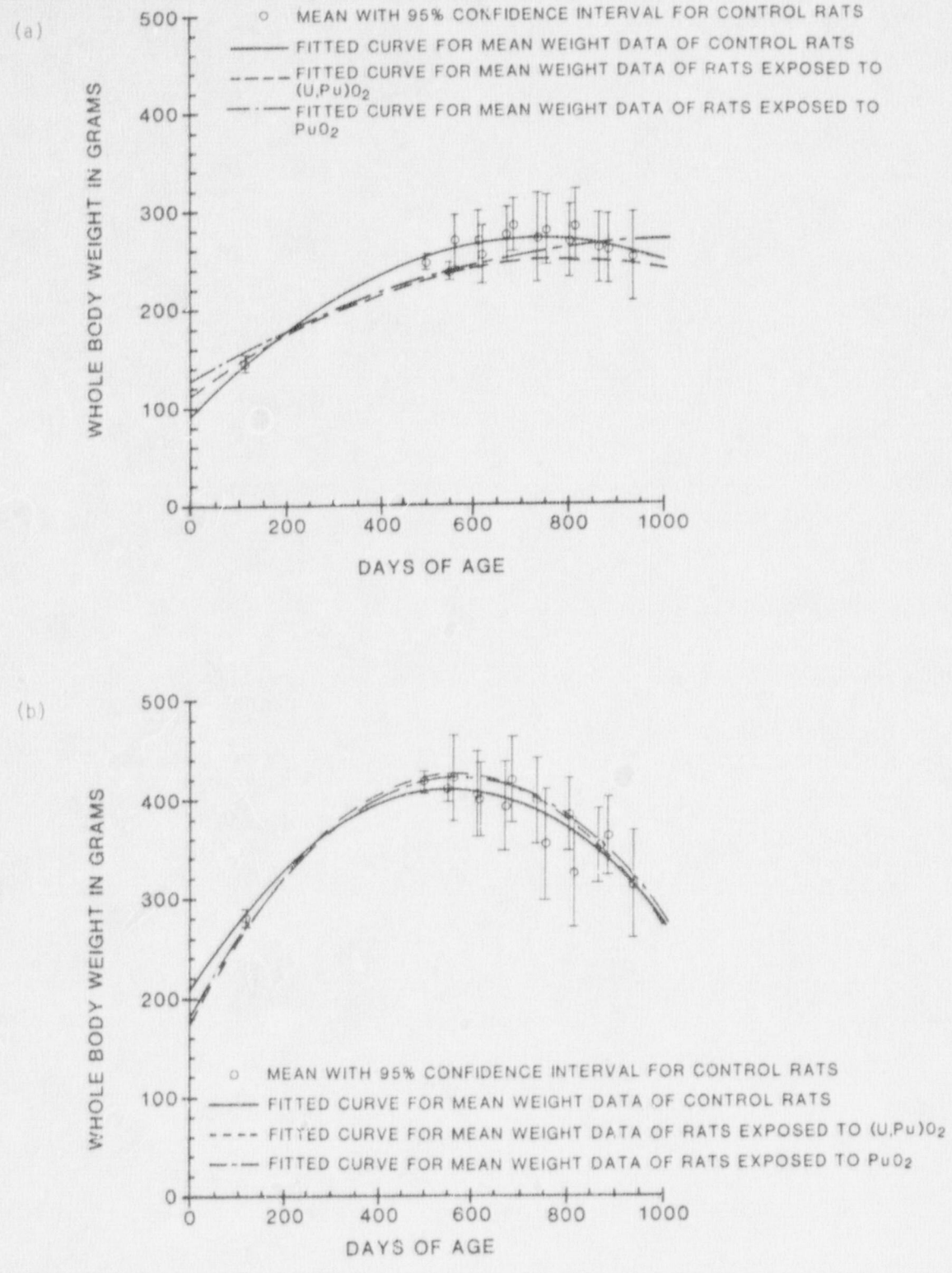
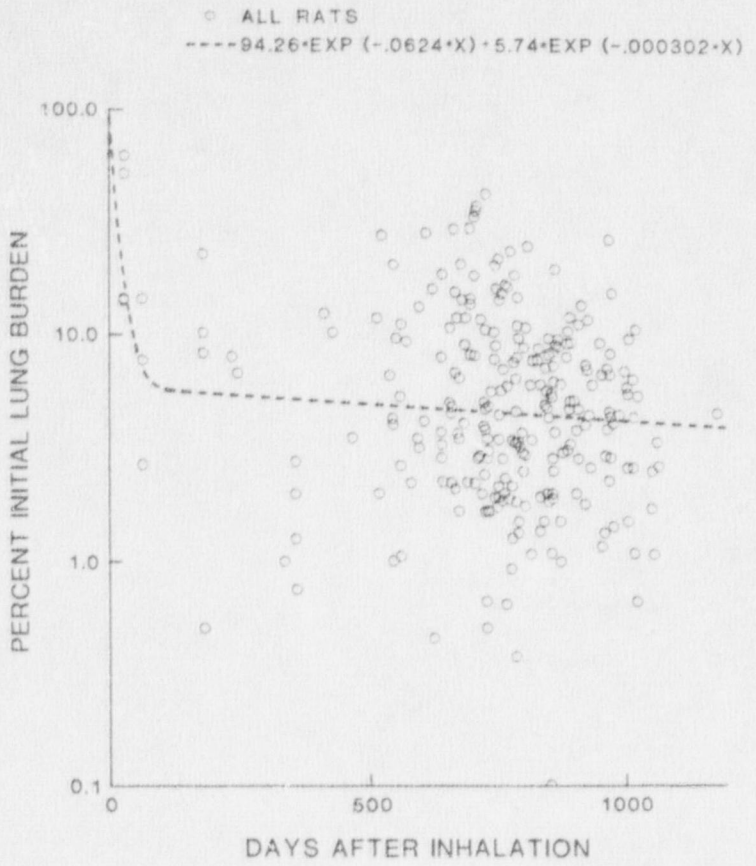


Figure 3.3. Summary of body-weight measurements for F344/N rats. Datum points and intervals represent the means and 95% confidence intervals for control rats while the solid curve represents a least squares fit to these data. The dashed line represents the same type of function fitted to the body weight data of rats exposed to the mixed uranium-plutonium oxide aerosols. The dash-dot line represents the fit to the data for rats exposed to the PuO_2 aerosol. Data for female rats are shown in (a), and for males in (b).

(a)



(b)

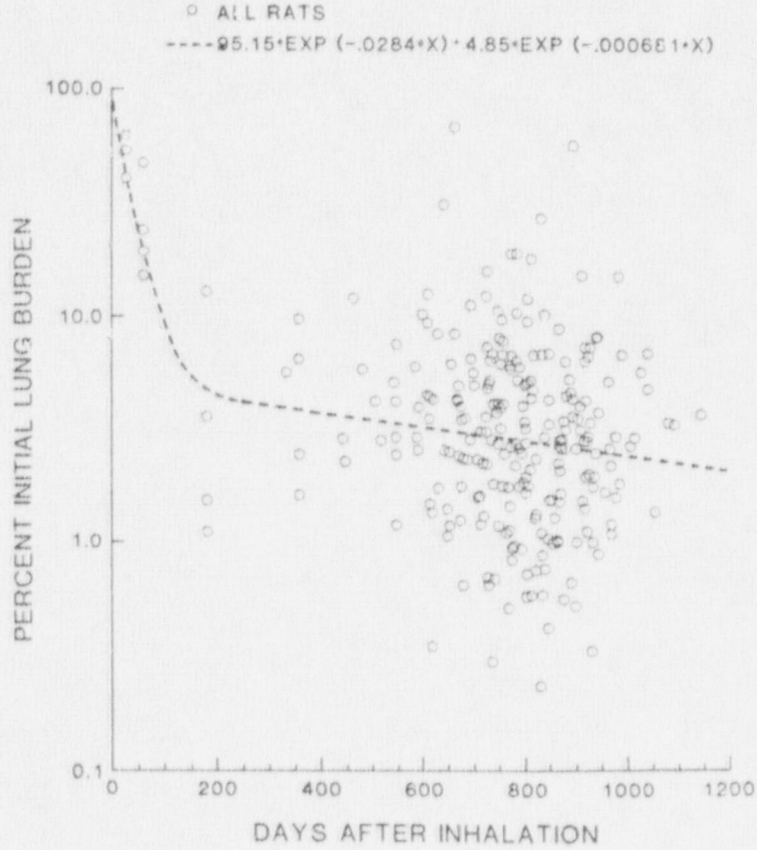


Figure 3.4 Pulmonary retention of Pu in rats exposed to (a) mixed uranium-plutonium oxide or (b) PuO_2. Dashed line represents function fitted to each data set.

Pulmonary Retention and Radiation Dose Determination

The F statistic calculated for the groups of rats exposed to the $(U,Pu)O_2$ aerosol indicated that a difference in Pu retention existed related to dose to lung (Table 3.4). However, the level of significance was only slightly lower than 95%; and the 95% confidence intervals for both fitted parameters overlapped for all three exposure levels. Therefore, this result was considered inconclusive and the pulmonary retention data for the three levels were combined for further comparisons. For rats exposed to PuO_2, the F statistic (Table 3.4) indicated no difference in pulmonary retention of plutonium related to the exposure level. However, when the plutonium pulmonary retention data combined for the three exposure levels of each aerosol were fit, the F statistic indicated a significant difference in plutonium retention in lung did exist. The F statistic indicated no difference in pulmonary retention of Pu related to gender for either aerosol material (Table 3.4).

Values of the parameters of the two-component negative exponential function used to describe the retention of Pu in the lungs of rats exposed to $(U,Pu)O_2$ or PuO_2 and sacrificed from 32 to 730 days after exposure are also listed Table 3.4. The generalized F statistic indicated that the lung retention data sets for these two groups of sacrificed rats exposed to the two materials could be combined and retention expressed as a single fitted function. However, when the Pu pulmonary retention data for the sacrificed rats were combined with the corresponding data for the rats that died or were euthanized for each aerosol, the generalized F statistic (Table 3.4) indicated that the data for the two aerosols were not from a single population.

To determine if the pulmonary retention of Am was similar to that of Pu, the Am retention data were subjected to the same type of comparisons. The results are presented in Table 3.5. These analyses indicated that the pulmonary retention of ^{241}Am was not different from that of Pu. Therefore, pulmonary retention data for Pu and Am were combined for each aerosol and a final set of parameters obtained (Table 3.5); these sets of parameters were then used with Equation 3.1 to calculate dose to lung of each rat in the study. The pulmonary retention data and the fitted functions are shown in Figure 3.4 for each aerosol material. The initial pulmonary burden for each rat in the dose-response study was estimated by extrapolating the pulmonary burden measured at death back to day 7 after exposure using these fitted functions. Figure 3.5 is a bargraph illustrating the distribution of initial pulmonary burdens achieved for each exposure group segregated by gender (95% confidence interval shown).

Table 3.4

Summary of the values for fitted parameters for Pu pulmonary retention in several groupings of rats.

Aerosol	Group	Parameters of Fitted Function (95% confidence limits) A_1	λ_1	A_2	λ_2	Calculated F	Critical F (p=0.05)
				Dose-Response Rats Only			
$(U,Pu)O_2$	Low			10.3 -0.21 to 20.8	-0.000790 -0.00201 to 0.000431		
	Medium			7.3 0.049 to 14.5	-0.000899 -0.00214 to 0.000341		
	High			20.4 -22.4 to 63.2	-0.00181 -0.00463 to 0.00101		
	Combined			9.43 3.01 to 15.9	-0.000879 -0.00171 to 0.00038	2.82	2.40
PuO_2	Low			11.4 -1.69 to 24.5	-0.00182 -0.00322 to -0.000426		
	Medium			4.5 -0.487 to 9.48	-0.000581 -0.00197 to -0.000805		
	High			8.95 -11.7 to 29.6	-0.00111 -0.00406 to -0.00184		
	Combined			7.58 1.86 to 13.3	-0.00122 -0.00216 to -0.000289	1.23	2.41
Both Aerosols				8.35 4.00 to 12.7	-0.00103 -0.00167 to -0.000390	15.0	3.02
$(U,Pu)O_2$	Female			6.32 1.52 to 11.1	-0.000484 -0.00138 to 0.000417		
	Male			14.5 -4.54 to 33.5	-0.00134 -0.00303 to 0.000356	1.19	3.04
PuO_2	Female			10.8 0.549 to 21.1	-0.00148 -0.00262 to -0.000342		
	Male			6.31 -2.33 to 14.9	-0.00118 -0.00293 to 0.000576	2.72	3.04
				Sacrifice Rats Only			
$(U,Pu)O_2$		96.2	-0.0563 -0.0901 to 0.0225	3.84 -0.804 to 8.49	-0.000673 -0.00312 to 0.00177		
PuO_2		97.7	-0.0258 -0.0405 to -0.0112	2.26 -1.55 to 6.08	0.000668 -0.00298 to 0.00382		
Combined		96.8	-0.0358 -0.0502 to -0.0214	3.21 0.344 to 6.09	-0.000158 -0.00194 to 0.00163	1.60	2.85
				Sacrifice + Dose-Response Rats			
$(U,Pu)O_2$		94.3	-0.0624 -0.103 to -0.0112	5.74 2.61 to 8.87	-0.000302 -0.000989 to 0.000386		
PuO_2		95.2	-0.0283 -0.0447 to -0.0115	4.85 1.70 to 8.00	-0.000681 -0.00150 to 0.000135		
Combined		94.7	-0.0384 -0.0544 to -0.0224	5.31 3.04 to 7.58	-0.000498 -0.00104 to 0.000396	10.9	2.61

Table 3.5

Values for the parameters obtained by fitting a two-component negative exponential function to the plutonium, or the americium, or the combined plutonium and americium pulmonary retention data for rats serially sacrificed. Also shown are the values for the parameters of the function fitted to the combined plutonium and americium pulmonary retention data for rats serially sacrificed combined with the data for rats that died or were euthanized in the dose-response studies.

		Parameters (± 1 S.E.)			
Aerosol	Element	A_1[a]	λ_1	A_2	λ_2
$(U,Pu)O_2$	Pu	96.2	-0.0563	3.84	-0.000673
			± 0.0161	± 2.22	± 0.00117
PuO_2	Pu	97.7	-0.0258	2.26	0.000668
			±0.0070	± 1.82	± 0.00151
$(U,Pu)O_2$	Am	94.8	-0.0579	5.24	-0.000336
			± 0.0433	± 3.74	± 0.00154
PuO_2	Am	99.3	-0.0185	0.75	0.00316
			± 0.00459	± 0.97	± 0.00232
$(U,Pu)O_2$	Pu + Am	95.6	-0.0682	4.40	-0.000574
			± 0.0175	± 1.93	± 0.000912
PuO_2	Pu + Am	98.1	-0.0240	1.89	0.00124
			± 0.0046	± 1.26	± 0.00123
$(U,Pu)O_2$[b]	Pu + Am	94.3	-0.0624	5.74	-0.003302
			± 0.0204	± 1.59	± 0.000350
PuO_2[b]	Pu + Am	95.2	-0.0283	4.85	-0.000681
			± 0.0083	± 1.60	± 0.000414

[a] No error is given since $A_1 = 100 - A_2$

[b] These parameters are the result of fitting combined data from sacrificed rats and rats that died in the dose-response studies.

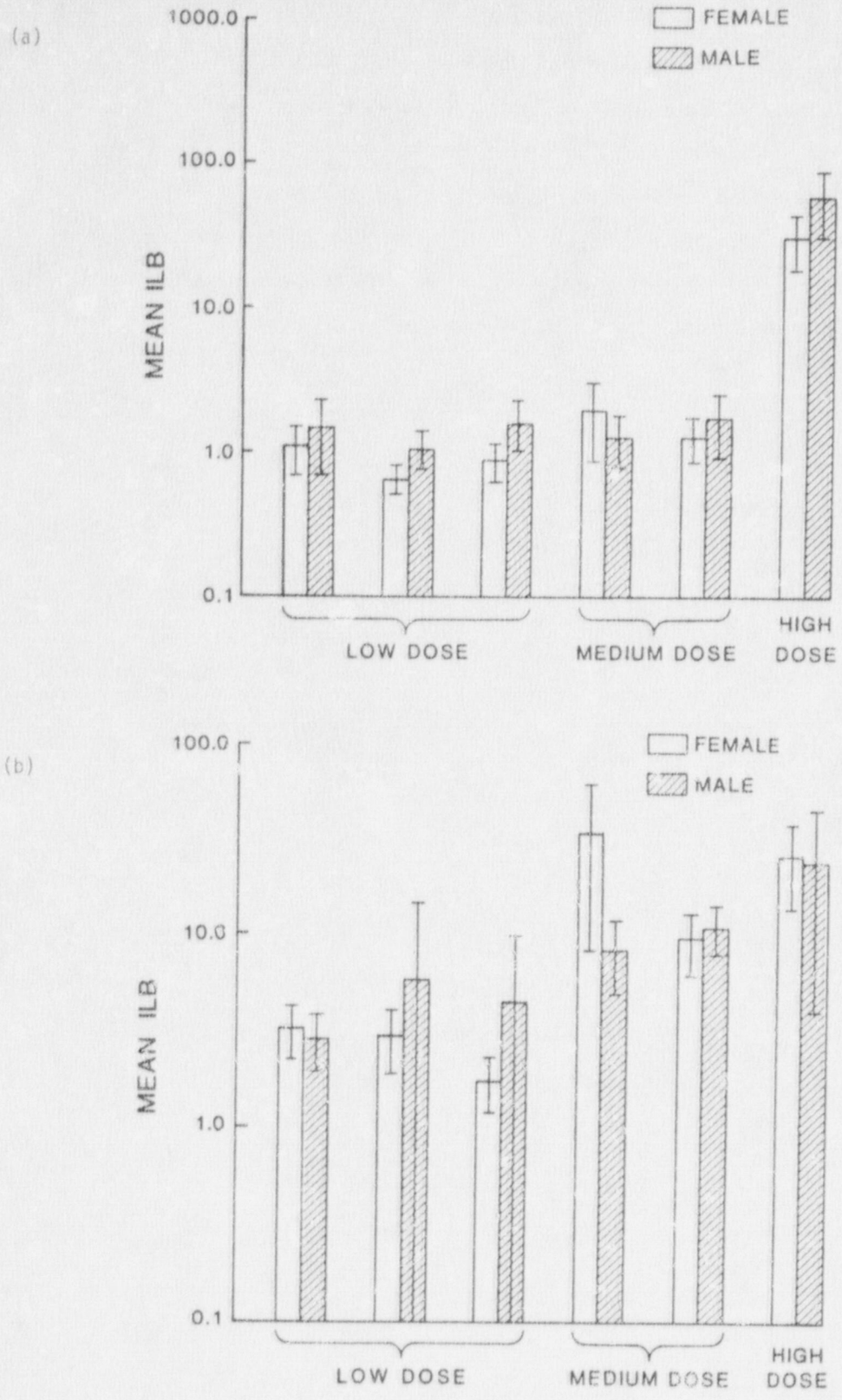


Figure 3.5 The mean initial pulmonary burden for each exposure group of rats exposed to mixed uranium-plutonium oxide aerosol (a) or PuO_2 aerosol(b), (95% confidence interval also shown) for each gender.

Histopathology

Histopathological examination of tissues (lung, liver, kidney, and spleen) and grossly visible tumors in the rats was done by light microscopy. Categories of primary lung cancers identified were papillary adenoma, papillary adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, solid adenocarcinoma, bronchioalveolar adenoma, bronchioalveolar carcinoma, and hemangiosarcoma. In addition, for each cancer identified, the relationship of the cancer to the death of the rat (fatal, contributory to fatality, or incidental) was determined. This categorization was a judgement based on the size, anaplasia and invasiveness of the tumor, the presence of metatases, and the occurrence of the lesion in the body. More than one lung cancer was found in five rats. In these cases, the larger or more aggressive cancer was noted and the second lung cancer was ignored in subsequent analysis. Table 3.6 shows a summary of lung cancers identified in the dose-response study by aerosol and by cancer type.

Table 3.6

Summary of numbers, categories and types of lung cancers found in rats in these dose-response studies.

		$(U,Pu)O_2$			PuO_2		
Exposure Level	Control	Low	Medium	High	Low	Medium	High
Total Number of Rats[a]	160	134	88	43	126	89	44
Total Number of Lung Cancers	3	8	5	21	8	22	8
Crude Incidence (%)[b]	1.9	6.0	5.7	49	6.4	25	18
Cancer Category							
Incidental	0	6	2	4	4	11	2
Contributory	2	1	2	4	1	4	2
Fatal	1	1	1	13	3	7	4
Distribution of Cancer Types							
Papillary Adenocarcinoma			3	6		4	3
Adenosquamous carcinoma				1			
Squamous carcinoma	1			6	1	5	2
Adenocarcinoma	2	3	1	5	3	6	1
Bronchioalveolar carcinoma		2	1	1	1	3	1
Hemangiosarcoma				1	1		
Bronchioalveolar adenoma		3		1	2	4	1

[a]Number of rats in each dose group is slightly larger than shown in Table 3.1 due to inclusion of reserve rats in each exposure group.

[b]Crude Incidence =(Total Number Lung Cancers/Total Number of Rats) X 100.

All of the epithelial lung tumors appeared to arise from the small airways or alveolar portions of the lung and thus could be considered bronchoalveolar neoplasms. Even the squamous cell carcinoma appeared to arise in the periphery of the lung, not the central airways.

The system of lung tumor classification used here is a detailed one and may, with the exception of the squamous cell carcinoma, merely document different phenotypic stages of the same neoplastic process. For example, all of these adenomas and adenocarcinomas would be classified as alveolar bronchiolar neoplasms by workers in the National Toxicology Program. Table 3.7 shows the relationship of histologic tumor type to the cause of death of the rat. It illustrates that the adenomas were all incidental to the animal's death, as would be expected. In addition, a large majority (78%) of the bronchiol-alveolar carcinomas were incidental. In contrast, the majority of the papillary adenocarcinomas (75%) were contributory to death and a majority of the solid carcinomas were fatal (58%). These percentages are consistent with the concept that, as the bronchiolalveolar carcinomas grow, they enlarge and take on the morphological characteristics of the papillary or solid carcinomas.

Numerous tumors in organs other than lung were also identified. The nature and incidence of these tumors in the exposed rats were comparable to the control groups and the historical control rats (Ref. 3.20) and were not considered radiation related. Incidence of tumors in potential target organs other than lung (liver, bone) were similar to incidences measured in control groups or nonexistent (nasal cavity, larynx, and tracheobronchial lymph nodes).

Table 3.7

Relationship of histologic lung cancer type and causes of death in rats exposed to either $(U,Pu)O_2$ or PuO_2 of industrial origin.

Lung Cancer Type	Total Number of Lung Cancers	Percentage of Total Lung Cancers		
		Incidental	Contributory	Fatal
Papillary adenoma	2	100		
Papillary adenocarcinoma	12	17	75	8
Adenosquamous carcinoma	3	33		67
Squamous cell carcinoma	11	18	9	73
Solid adenocarcinoma	19	5	37	58
Bronchiolalveolar carcinoma	9	78		22
Bronchiolalveolar adenoma	16	100		
Hemangiosarcoma	1			100

Dose-response Analysis

For the analysis of the relationship between dose and biological response, rats exposed to each aerosol were ranked according to their individual initial pulmonary burden. As expected, this ordering approximated a continuum of initial pulmonary burdens. No distinct groupings of rats were evident on the basis of initial pulmonary burden due to the overlapping ranges of initial pulmonary burdens produced in each exposure group. All benign and malignant lung tumors noted in Table 3.6 were included in the analysis. This combining is in accordance with the apparent life history of the tumors in progressing from benign to malignant and with recent recommendations on this subject (Ref. 3.21).

The slopes of a linear function with a zero intercept fitted to each data set were obtained for group sizes of 20, 30 and 40 rats for each aerosol. These values are listed in Table 3.8 for both fatal or fatal plus contributory lung cancers. Although similar values for the slopes were obtained for all group sizes, a group size of 40 rats generally provided the smallest standard errors (Table 3.8).

To compare the cumulative lung cancer incidence between the groups exposed to the two aerosol materials, the group size was fixed at 40 rats of both genders and the dose to lung was calculated to the median life span of the control rats (854 and 784 days of age for females and males, respectively) using the retention equation for each aerosol. The rats were then ordered from lowest to highest dose to lung for each aerosol material and arbitrarily selected groups of 40 rats were formed. The slopes of the linear functions fitted to these two data sets are shown in Table 3.9. Comparison of the 95% confidence intervals about these two slope values indicated no significant difference in the slope for the two aerosols. Also, with use of a generalized F statistic, the null hypothesis of a single population could not be rejected. Therefore, the data sets for the two aerosol materials were combined, the entire set reordered by dose to lung and groups of 40 rats were arbitrarily selected again. The combined data and the fitted linear function are shown in Figure 3.6.

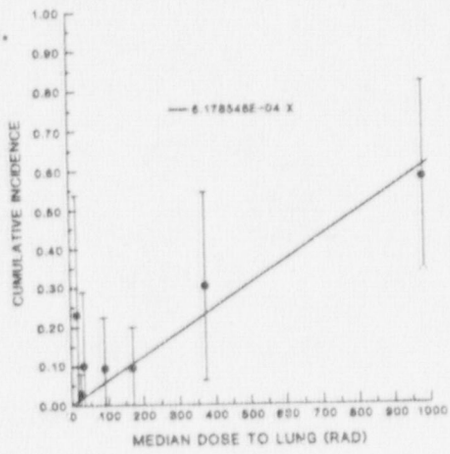


Figure 3.6. Cumulative incidence of fatal lung cancers in rats exposed to an aerosol of either mixed uranium-plutonium oxide or PuO_2 plotted versus median dose (rad) to lung at median lifespan. Group size is 40 rats with 95% confidence interval shown for each group.

To determine if the cumulative incidence of pulmonary tumors in these rats varies systemically with radiation dose, the cumulative incidence of tumors was divided by the median dose to lung for the group and plotted versus the median dose to lung in Figure 3.7. A simple linear function was fitted using the reciprocal of the standard error of the cumulative incidence per rad as a weight for each data value. The slope of the curve fitted to these data was not significantly different from zero indicating that the "effectiveness" of each rad at low dose levels was not greater than a rad at higher dose levels.

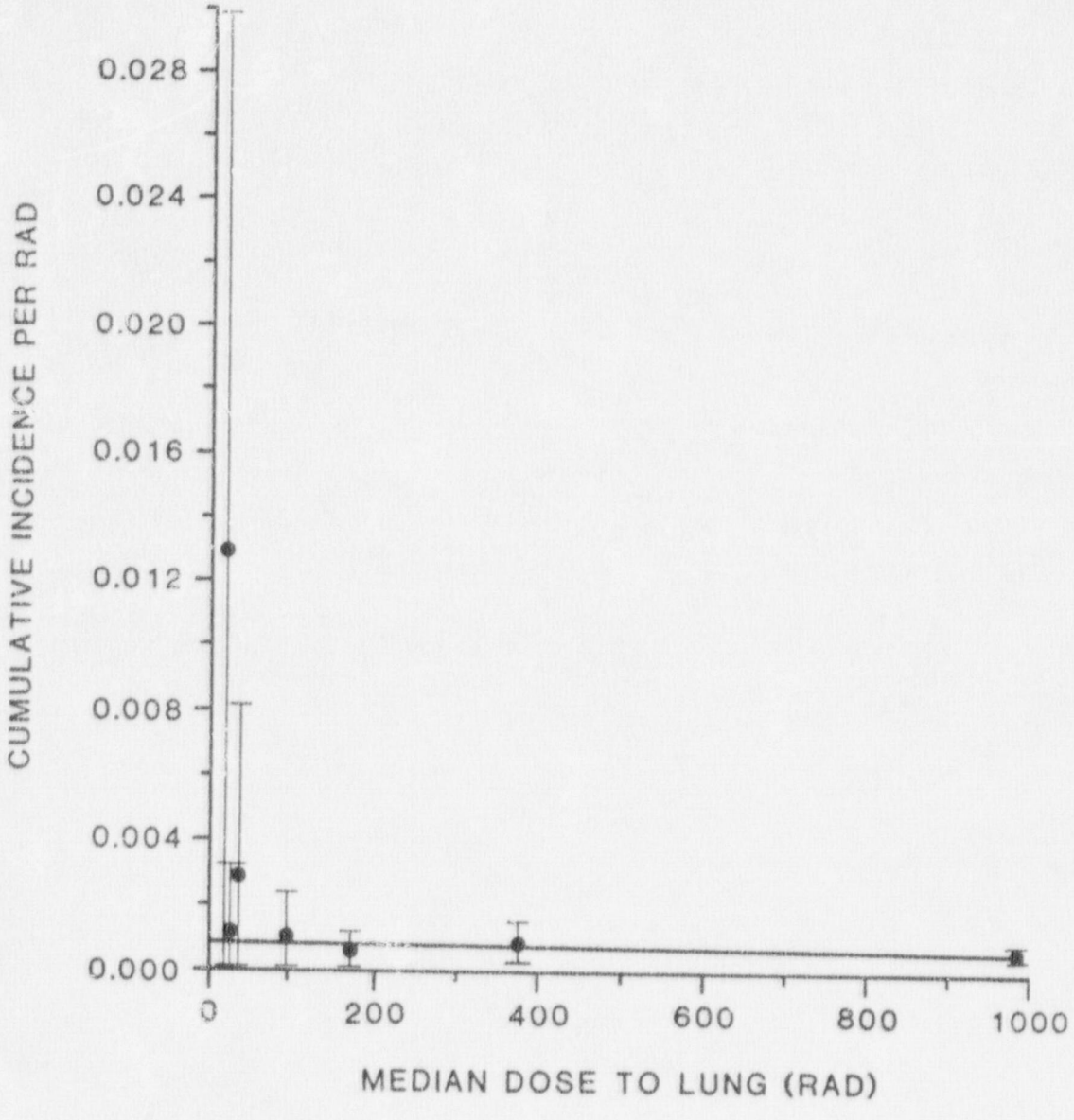


Figure 3.7. Cumulative incidence of pulmonary tumors per rad of radiation dose to lung.

Table 3.8

Slope of the function fitted to the cumulative incidence of fatal or fatal + contributory lung cancers versus the initial pulmonary burden for three different group sizes for the two aerosols used in the dose-response studies.

Aerosol	Number of Rats in Group	Lung Cancer Type	Slope	Std. Err of Slope	95% C.I. (lower limit)	95% C.I. (upper limit)
$(U,Pu)O_2$	20	Fatal	0.0114	0.00129	0.0088	0.0140
	30	Fatal	0.0143	0.00225	0.0098	0.0188
	40	Fatal	0.0160	0.00243	0.0111	0.0209
PuO_2	20	Fatal	0.00445	0.00066	0.0031	0.0058
	30	Fatal	0.00417	0.00056	0.0031	0.0053
	40	Fatal	0.00331	0.00040	0.0025	0.0041
$(U,Pu)O_2$	20	F + C[a]	0.0691	0.01400	0.0411	0.0971
	30	F + C	0.0960	0.01920	0.0576	0.1344
	40	F + C	0.0675	0.00787	0.0518	0.0832
PuO_2	20	F + C	0.00458	0.00080	0.0030	0.0062
	30	F + C	0.00424	0.00065	0.0029	0.0055
	40	F + C	0.00335	0.00047	0.0024	0.0043

[a] F + C is defined as fatal + contributory cancers (see text for explanation).

Table 3.9

Slope of the function fitted to the cumulative incidence of fatal lung cancers versus the dose (rad) to lung to the median survival time of control groups. The results for each aerosol material considered separately and for both aerosols combined are shown.

Aerosol	Slope ($\times 10^3$)	Std. Err of Slope ($\times 10^3$)	Calculated F	Critical F
$(U,Pu)O_2$	1.21	0.190		
PuO_2	0.507	0.129		
Combined	0.706	0.155	7.3	(p=0.05) 5.99 (p=0.01)13.7

Table 3.10

Summary of health risk estimates derived from the dose-response studies.

	Parameter	Estimate
Intercept	a_0	0.043 ± 0.029
Absolute Risk Coefficient (per rad)	a_2	0.00055 ± 0.00014
Relative Risk Coefficient	a_3	0.0128 ± 0.0104
Relative Risk (at 100 rad)	R	2.3 ± 1.9
Doubling Dose (rad)	D	78 ± 63

Dose-Response Relationships

The values estimated for absolute and relative risk of fatal lung cancer in rats exposed to these aerosols are summarized in Table 3.10. Also shown in this table are the calculated values for the dose to lung to median lifespan which is sufficient to increase the incidence of fatal lung cancers by a factor of two (the doubling dose).

DISCUSSION

Inhalation Exposure

The aerosol size distribution measured during the rat inhalation exposures (Table 3.2) indicated that the size distributions of the aerosols were comparable to the values measured within glovebox enclosures at the mixed oxide fuel fabrication facility during normal operations (Ref 3.8, 3.9). Analysis of the X-ray diffraction patterns (Figure 3.1.) clearly indicated that the mixed uranium-plutonium oxide aerosol was a solid solution of uranium and plutonium oxide. The aerosol designated PuO_2 contained no trace of UO_2. The highly irregular shape of individual particles in these aerosols can be observed in Figure 3.2. This particle morphology is typical of the many samples collected during the rat exposures.

The mean initial pulmonary burdens measured (Table 3.2) were somewhat lower than the desired pulmonary burdens. However, recognizing that the variation in pulmonary burdens achieved among rats in the same exposure group was quite large (typically ranging over a factor of 5), subsets of rats received pulmonary burdens within the desired range in each exposure group.

Body Weight

Because the curves fitted to the body weights for the two groups of rats exposed to the $(U,Pu)O_2$ or the PuO_2 aerosol fell within the 95% confidence intervals for control rats, it was apparent that exposure to these two aerosols did not affect body weight. The curves fitted to the body-weight data for colony control rats also fell within the 95% confidence interval of the control rats assigned to this study. The shape of the body weight curves in Figure 3.3 show that differences exist in the rate of weight gain and maximum weight attained for the genders. Table 3.3 presents the maximum weight attained and the age of the rats at maximum weight for experimental and control groups from this study and for the separate group of colony control rats. Again, no discernable differences in maximum weight attained or the age at maximum weight were apparent, except as related to gender.

Pulmonary Retention and Radiation Dose Determination

The conclusions to be drawn from the comparisons of the pulmonary retention of Pu in the various groupings of rats are; 1) no difference in pulmonary retention of the groups of rats exposed at the three levels of initial lung burden and held for lifespan observation may be ascribed to the differences in absorbed dose to lung for either aerosol material inhaled, 2) a difference does exist in pulmonary retention of Pu when the dose-response rats exposed to the $(U,Pu)O_2$ aerosol are compared with those rats exposed to the PuO_2 aerosol, 3) no difference in pulmonary retention was discernable when the genders were compared for either aerosol, 4) no difference in pulmonary retention of Pu was apparent when the two groups of rats that were exposed to the two materials and sacrificed from 32 to 730 days after exposure were compared, and 5) differences were apparent in pulmonary retention of Pu when data for all sacrificed rats and those that died or were euthanized were combined for each aerosol. Therefore, the calculation of dose to lung used different retention function parameters for the two aerosol materials.

Histopathology

No differences between the $(U,Pu)O_2$- or PuO_2-exposed groups of rats were seen in the histological types and distribution of lung cancers. One primary hemagiosarcoma was found in a rat exposed to the $(U,Pu)O_2$ and none was found in rats exposed to PuO_2. In other studies, however, inhaled $^{239}PuO_2$ has been reported to cause hemagiosarcomas of the lung (Ref. 3.2). Thus, the types of lung cancers observed in groups of rats exposed to $(U,Pu)O_2$ and PuO_2 of industrial origin were similar to those reported previously (Ref. 3.2, 3.3).

Dose-response Analysis

The incidence of biological effects in organs other than lung were not different in exposed rats compared to control rats. Little or no translocation of Pu or Am from lung to other tissues or organs occured because of the relatively insoluble nature of the inhaled particles. Thus, the dose to organs or tissues other than lung was of such low magnitude that no effects were expected or observed.

The first order of analysis of lung cancer incidence in these studies was to determine if the gender influenced the incidence of lung cancers. For each gender, the crude incidence of lung cancers (number of lung cancers divided by the number of rats in the group) was plotted versus the initial pulmonary burden for all rats. In all cases, the cancer incidences were not different for the two genders at comparable initial pulmonary burdens and the incidence data for the two genders were comtined for all further analyses.

The second order analysis involved comparisons of the crude incidence of lung cancers from these studies with results from the inhalation of laboratory-produced plutonium aerosols by rats (Ref. 3.2, 3.3, 3.4). For these comparisons, the crude incidence was calculated for all lung cancers (fatal, contributory, and incidental) because these designations were not made for the several published reports (Ref. 3.2, 3.3, 3.4). An approximation of the standard error of the crude incidence for each dose group was calculated by assuming a binomial distribution and using the following equation:

$$\text{Standard error} = \frac{p\,(1-p)}{n} \qquad \text{(Eq. 3.6)}$$

where n = number of rats in the group and p = crude incidence of lung cancers of the group (number of lung cancer bearing rats/total number of rats in group). These comparisons, illustrated in Figure 3.8, showed that the crude incidence of lung cancers following inhalation of $^{239}PuO_2$ (Ref. 3.2, 3.4) or $^{238}PuO_2$ (Ref. 3.3) by rats were of the same order as those observed after inhalation of mixed uranium-plutonium oxides or PuO_2 of industrial origin. It must be noted that the calculation of dose to lung in these studies from the literature did not use the same time span after exposure as was used for the studies reported here. Normalization of the several studies previously reported was not possible because exact retention functions were not presented. Nonetheless, Figure 3.8 clearly indicates that even differences of 30% in the calculated dose to lung for these several studies would not provide a firm basis for concluding that differences exist among the studies.

A question that often arises with this type of analysis is: "What influence does group size have on the calculated slope of the linear portion of the dose-effect curve". The analysis conducted demonstrated that, for fatal cancers, the size of the group did not significantly influence the slope of the linear function (Eq. 3.2) for either aerosol within the range of 20, 30 or 40 rats per group (Table 3.8). Additionally, the inclusion of cancers judged to be contributory to death of the rat, with cancers judged to be fatal, had no major influence on the slope of the fitted curve.

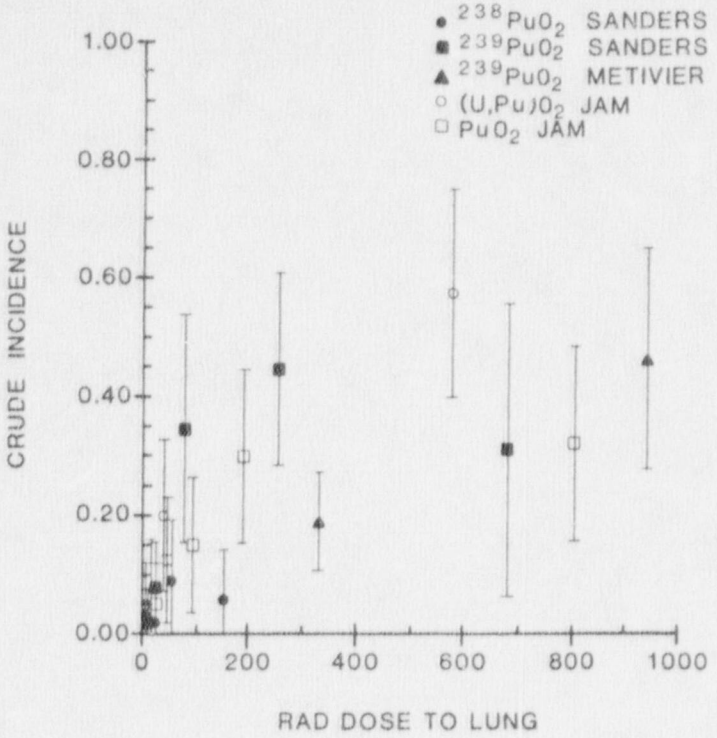
The slopes of linear functions fitted to the cumulative incidence of fatal lung cancers versus the radiation dose (rad) to lung are presented in Table 3.9. The generalized F statistic indicates that the two sets of data were different at the 95% level of confidence, but not different at the 99% level of confidence. However, no consideration was given to uncertainty in this dose calculation. Prentice (Ref. 3.21) has demonstrated that moderate random errors in dosimetry can appreciably alter dose-effect parameter estimates. Considering the fact that the

slopes of the curves fitted to each data set differ by only a factor of 2.4, it would seem prudent not to ascribe any real significance to these differences. Therefore, the data for the two aerosol materials were combined, reordered by dose to lung, from lowest to highest, and the same linear function with a zero intercept fitted. This result, illustrated in Figure 3.9, indicates that the incidence of fatal lung cancers in rats exposed to either of the aerosol materials could be represented by a linear function with intercept equal to 0.043 (± 0.029) and a slope of 0.00055 (± 0.00014) cancer bearers per rad.

Cancer Risk Estimation

The datum points shown in Figure 3.9 represent the relative risk values calculated for each group of rats in these studies and the curve is a theoretical linear curve calculated from Equation 3.2. The risk coefficients calculated from Equations 3.2, 3.3, and 3.4 are shown in Table 3.10. Considering the documented differences among animal species in susceptibility to the induction of lung cancers by radiation and the documented differences in spontaneous or natural lung cancer incidence among laboratory animal species and strains, the absolute risk coefficient derived from this experiment should not be used directly to estimate the risk in humans. Under the assumption that the relative risk coefficient is independent of mammalian species, estimation can then be made of the hazard in humans following inhalation of these industrial materials. The relative risk estimated in this study and its standard error was 2.3 ± 1.9 at a lung dose of 100 rad. This value is in excellant agreement with a relative risk value of 2.2 at an exposure level of approximately 100 rad to lung estimated from the United States uranium miner data cited by the Committee on the Biological Effects of Ionizing Radiation (BEIR III) (Ref. 3.21). This suggests that the rat may provide a model useful for estimation of the relative risk for lung cancer induction in people following inhalation of actinide element in aerosols. The doubling dose estimated from this study was 78 ± 63 rad to lung to median lifespan.

(a)



(b)

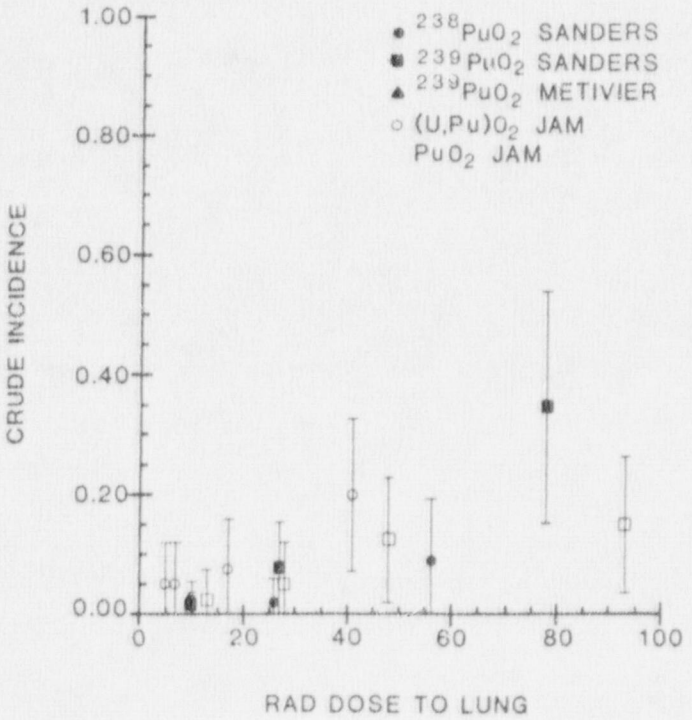


Figure 3.8 Comparison of the crude incidence of lung cancers determined in several studies involving inhalation of $^{238}PuO_2$ (Ref. 3.3), $^{239}PuO_2$ (Ref. 3.2, 3.4) by rats and results from the present studies (a) shows the overall results and (b) represents an expansion of the dose axis to more clearly illustrate the data at low doses to lung.

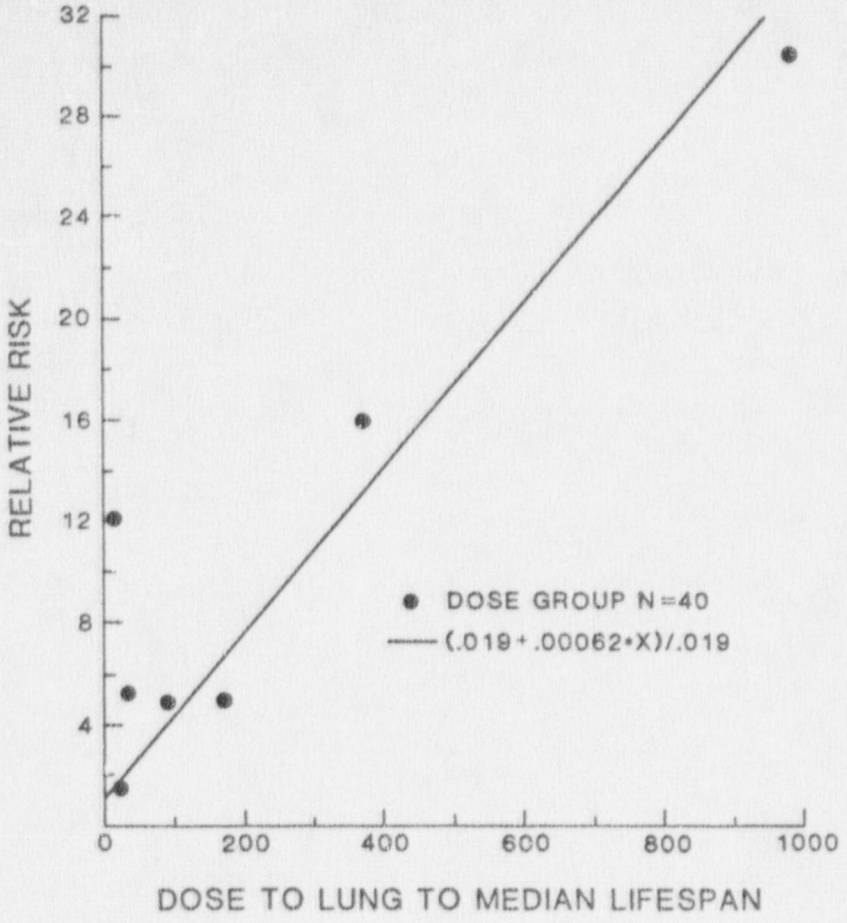


Figure 3.9. Relative risk of fatal lung cancer occurance in rats exposed to aerosols of $(U,Pu)O_2$ or PuO_2 as a linear function of dose to lung to median lifespan of the rats. Data points are for the same groups as shown in Figure 3.6, and the curve represents a calculation from Equation 4.

CONCLUSIONS

Aerosols of mixed uranium and plutonium oxide or PuO_2 used in these inhalation studies were representative in particle size, morphology and chemical form of aerosols produced during normal operation of a nuclear fuel fabrication facility. Inhalation exposure of rats in these studies had no demonstrable effect relatable to dose to lung on the rate of body weight gain or the peak weight attained. A spectrum of lung cancer types occurred in rats exposed to either a mixed oxide form of uranium and plutonium or to plutonium dioxide. However, no differences in the cumulative incidence of lung cancers between groups exposed to either of the two aerosols was discernable. The incidences and types of lung cancers were not different from those that have been reported for rats exposed to laboratory-produced aerosols of PuO_2. The relative risk and its standard error for lung cancers in rats exposed to these industrial aerosols was 2.3 ± 1.9 at a lung dose of 100 rads and the doubling dose and its standard error was 78 ± 63 rad to lung to median lifespan.

The results from these studies imply that these industrially derived aerosols are not more carcinogenic in lung than laboratory-produced aerosols of plutonium of essentially the same chemical form. The relatively insoluble nature of the aerosols, despite the difference in the elemental composition, allows little translocation of the Pu or Am component to other internal organs. The results also indicate that F344/N rats provide a good model for relative risk estimation for lung cancer induction in people following inhalation of actinide element aerosols.

REFERENCES

3.1 Hahn, F.F., J.A. Stanley, A.F. Eidson and J.A. Mewhinney, "Summary of Biological Effects Following Inhalation of Industrial Mixed Oxides (Uranium-Plutonium) or PuO_2 in Rats," in Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides, Annual Progress Report, July 1, 1978-June 30, 1979, NUREG/CR-1458, LF-71, 67-71, 1980*

3.2 Sanders, C.L., C.E. Dagle, W.C. Cannon, D.K. Craig, G.J. Powers and D.M. Meier, "Inhalation Carcinogenesis of High-Fired $^{239}PuO_2$ in Rats," Radiat. Res. 68: 349-360, 1976.

3.3 Sanders, C.L., C.E. Dagle, W.C. Cannon, G.J. Powers and D.M. Meier, "Inhalation Carcinogenesis of High-Fired $^{238}PuO_2$ in Rats," Radiat. Res. 71: 528-546, 1977.

3.4 Metivier, H., J. Wahrendorf and R. Masse, "Multiplicative Effect of Inhaled Plutonium Oxide and Benzo(a)pyrene on Lung Carcinogenesis in Rats," Br. J. Cancer 50: 215-221, 1984.

3.5 Bair, W.J. and R.C. Thompson, "Plutonium: Biomedical Research," Science 183: 715-722, 1974.

3.6 Leach, L.J., C.L. Yuile, H.C. Hodge, G.E. Sylvester and H.B. Wilson, "A Five-Year Inhalation Study with Natural Uranium Dioxide (UO_2) Dust. II. Postexposure Retention and Biologic Effects in the Monkey, Dog and Rat," Health Phys. 25: 239-258, 1973.

3.7 Griffith, W.C., "Design of Dose-response Studies in Fischer-344 Rats," in Radiation Dose Estimates and Hazards Evaluations for Inhaled Airborne Radionuclides, Annual Progress Report, July 1, 1979 to June 30, 1980, NUREG/CR 2246, 52-57, 1981.

3.8 Newton, G.J., "Mixed-Oxide Fuel Fabrication," in Radiation Exposure and Risk Estimates for Inhaled Airborne Radioactive Pollutants Including Hot Particles, Annual Progress Report, July 1, 1976-June 30, 1977, NUREG/CR-0010, 15-35, 1978*

3.9 Stanley, J.A. and G.J. Newton, "Further Sampling of Aerosolized Mixed-Oxide Nuclear Fuel in a Fabrication Facility," in Radiation Exposure and Risk Estimates for Inhaled Airborne Radioactive Pollutants Including Hot Particles," Annual Progress Report, July 1,1976-June 30, 1977, NUREG/CR-0010, 9-12, 1978*

3.10 Eidson, A.F., "An Improved Technique for Aerosolization of Powders of Industrial Uranium and Plutonium Mixed-Oxide Nuclear Fuel Materials," in Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides, Annual Progress Report, July 1, 1978-June 30, 1979, NUREG/CR-1458, LF-71, 5-10, 1980.

3.11 Eidson, A.F., "Comparison of Physical Chemical Properties of Powders and Respirable Aerosols of Industrial Mixed Uranium and Plutonium Oxide Fuels," Health Phys. 42: 531-536, 1982.

3.12 Eidson, A.F. and J.A. Mewhinney, "In Vitro Dissolution of Respirable Aerosols of Industrial Uranium and Plutonium Mixed-Oxide Nuclear Fuels," Health Phys. 45: 1023-1027, 1983.

3.13 Raabe, O.G., J.E. Bennick, M.E. Light, C.H. Hobbs, R.L. Thomas, and M.I. Tillery, "An Improved Apparatus for Acute Inhalation Exposure of Rodents to Radioactive Aerosols," Toxicol. Appl. Pharmocol. 26: 264-273, 1973.

3.14 Mercer, T.T., M.I. Tillery and G.J. Newton, "A Multi-stage Low Flow Rate Cascade Impactor," J. Aerosol Sci. 1: 9-15, 1970.

3.15 Morrow, P.E. and T.T. Mercer, "A Point-to Plane Electrostatic Precipitator for Particle Size Sampling," Am. Ind. Hyg. Assoc. J. 25: 8-14, 1964.

3.16 Keough, A., R.F. and G.J. Powers, "Determination of Plutonium in Biological Materials by Extraction and Liquid Scintillation Counting," Anal. Chem. 42: 419-425, 1970.

3.17 SAS Institute Inc., "SAS User's Guide: Statistics," SAS Institute Inc., Cary, NC, 1982.

3.18 Gallant, A.R., "Nonlinear Regression," American Statistician, 29: 73-81, 1975.

3.19 Dixon, W.J. and M.B. Brown (eds), "BMDP-83, Biomedical Computer Programs, P-Series" Univ. Calif. Press, Berkeley, 1983.

3.20 Prentice, R.L., "Statistical Issues Arising in the Analysis of A-Bomb Survivor Data," in Environmental Epidemiology: Risk Assessment, Proceedings of a SIMS Conference, Alta, Utah, 1982, pp 22-38.

3.21 Committee on Biological Effects of Ionizing Radiation, "The Effects Populations of Exposure to Low Levels of Ionizing Radiation 1980," National Academy Press, Wash, D.C., 1980.

*Available from National Technical Information Service, Springfield, Virginia 22161.

NRC FORM 336 (6 83) U.S. NUCLEAR REGULATORY COMMISSION

BIBLIOGRAPHIC DATA SHEET

1 REPORT NUMBER (Assigned by TIDC and Vol. No. if any)
NUREG/CR-4986

2 Leave blank

3 TITLE AND SUBTITLE
Radiation Dose Estimates and Hazard Evaluations for Inhaled Airborne Radionuclides - Final Report

4 RECIPIENT'S ACCESSION NUMBER
LMF-116

5 DATE REPORT COMPLETED
MONTH: December YEAR: 1986

6 AUTHOR(S)
J. A. Mewhinney, Ph.D.

7 DATE REPORT ISSUED
MONTH: September YEAR: 1987

8 PERFORMING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code)
Inhalation Toxicology Research Institute
Lovelace Biomedical & Environmental Research Institute
P.O. Box 5890
Albuquerque, NM 87185

9 PROJECT/TASK/WORK UNIT NUMBER

10 FIN NUMBER
FIN NO. A1031

11 SPONSORING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code)
Division of Health, Siting and Waste Management
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, DC 20555

12a TYPE OF REPORT
Technical

12b PERIOD COVERED (Inclusive dates)
July 1976 - July 1984

13 SUPPLEMENTARY NOTES

14 ABSTRACT (200 words or less)

This is the final report for a project whose objective was to conduct confirmatory research on physical chemical characteristics of aerosols produced during manufacture of mixed plutonium and uranium oxide nuclear fuel, to determine the radiation dose distribution in tissues of animals after inhalation exposure to representative aerosols of these materials, and to provide estimates of the relationship of radiation dose and biological response in animals after such inhalation exposure. This report is divided into three chapters which summarize the results of these investigations. The first chapter summarizes the physical chemical characterization of samples of aerosols collected from gloveboxes at industrial facilities during normal operations. This chapter provides insights into key aerosol characteristics which are of potential importance in determining the biological fate of specific radionuclides contained in the particulates that would be inhaled by humans following accidental release. The second chapter describes the spatial and temporal distribution of radiation dose in tissues of three species of animals exposed to representative aerosols collected from the industrial facilities. These inhalation studies provide a basis for comparison of the influence of physical chemical form of the inhaled particulates and the variability among species of animal in the radiation dose to tissue. The third chapter details to relationship between radiation dose and biological response in rats exposed to two aerosol forms, each at three levels of initial pulmonary burden. This study, conducted over the lifespan of the rats and assuming results to be applicable to humans, indicates that the hazard to health due to inhalation of these industrial aerosols is not different than previously determined for laboratory produced aerosol of PuO_2.

15a KEY WORDS AND DOCUMENT ANALYSIS
mixed oxide, aerosol, airborne radioactivity
inhalation, exposure, dose, solubility
biological effects

15b DESCRIPTORS
rats, Beagles, monkeys
uranium, plutonium

16 AVAILABILITY STATEMENT
unlimited

17 SECURITY CLASSIFICATION (This report)
UNCLASSIFIED

18 NUMBER OF PAGES

19 SECURITY CLASSIFICATION (This page)

20 PRICE
$

*U.S. GOVERNMENT PRINTING OFFICE: 1987-181-682:60221

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

SPECIAL FOURTH-CLASS RATE
POSTAGE & FEES PAID
USNRC
PERMIT No. G-67

120555078877 1 1AN1RH
US NRC-OARM-ADM
DIV OF PUB SVCS
POLICY & PUB MGT BR-PDR NUREG
W-537
WASHINGTON DC 20555