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Early and Continuing Effects of Combined Alpha and Beta Irradiation of the Lung

Phase II Report

Prepared by B.R. Scott, F.F. Hahn, M.B. Snipes,
G.J. Newton, A.F. Eidson, J.L. Mauderly, B.B. Boecker

Lovelace Biomedical and Environmental Research Institute

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B.R. Scott, F.F. Hahn, M.B. Snipes
G.J.Newton, A.F. Eidson, J.L. Mauderly, B.B. Boecker

S.S. Yaniv, NRC Project Manager

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

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F. F. Hahn, Inhalation Toxicology Research Institute, "Early Mortality Estimate for Different Nuclear Accidents," U. S. NRC Report NUREG/CR-0774, August 1979. Available for purchase from National Technical Information Service, Springfield, VA 22161.

B. R. Scott, et al., Inhalation Toxicology Research Institute, "Experimental Studies of the Early Effects of Inhaled Beta-Emitting Radionuclides for Nuclear Accident Risk Assessment - Phase II Report," U. S. NRC Report NUREG/CR-5025, November 1987. Available for purchase from National Technical Information Service, Springfield, VA 22161.

ABSTRACT

This report summarizes an inhalation exposure experiment that concerns early and continuing effects of combined alpha and beta irradiation of the lung of rats. Both morbidity at 18 months and mortality within 18 months after exposure were examined for rats exposed to the beta-emitter ^{147}Pm, the alpha-emitter ^{238}Pu, or both combined. The results were used to validate hazard-function models that were developed (1) for pulmonary functional morbidity at 18 months and (2) for lethality from radiation pneumonitis and pulmonary fibrosis within 18 months. Both models were found to adequately predict the experimental observations after combined chronic alpha and beta irradiation of the lung. A relative biological effectiveness of approximately 7 was obtained for ^{238}Pu alpha radiation compared to ^{147}Pm beta radiation for both pulmonary functional morbidity and lethality from radiation pneumonitis and pulmonary fibrosis.

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EXECUTIVE SUMMARY

Although current radiobiological research is largely focused on carcinogenic and genetic effects, the casualties caused by the recent Chernobyl nuclear power plant accident in the Soviet Union reemphasized the importance of research on acute radiobiological effects. Recognizing this need years before the Chernobyl accident occurred, the Nuclear Regulatory Commission (NRC) sponsored research on acute and continuing effects of irradiation designed to develop improved radiobiological health-effects models. This report provides experimental and theoretical results on lethality and morbidity effects caused by combined chronic alpha and beta irradiation of the lung, based on research carried out at the Inhalation Toxicology Research Institute (ITRI).

Studying effects of combined alpha and beta irradiation of the lung is important because the transport of radioactive materials associated with the nuclear fuel cycle could result in the accidental or intentional (i.e., by sabotage) release of mixtures of alpha- and beta-emitting radionuclides into the environment. If airborne, the radionuclides could be inhaled by man and could lead to large radiation doses to the lung. A large radiation dose to the lung can cause radiation pneumonitis and pulmonary fibrosis (RPPF) and could prove fatal or lead to impaired pulmonary function for a survivor.

A hazard-function (HF) model was developed at our Institute for predicting the frequency of death from RPPF after complex patterns of beta-gamma irradiation or after combined alpha and beta irradiation of the lung. Several experiments were conducted to validate the mortality model and to provide data to develop a similar model for pulmonary morbidity.

Results of four experiments using rats to test the mortality model for predicting acute effects of complex patterns of beta-gamma irradiation of the lung are in another report (NUREG/CR-5025, 1987). The experiment described in this report was carried out to validate the model for predicting death from RPPF after combined alpha and beta irradiation of the lung and to provide data for developing and validating a similar model for pulmonary morbidity.

Prediction of death from RPPF after combined alpha and beta irradiation of the lung is based on a hazard-function model expressed by the Weibull-type function

$$\text{LETHALITY HAZARD} = \ln(2)\cdot X^{V},$$

where V is a positive parameter that determines the shape of the dose-effect relationship. X is the total alpha plus beta dose in ILB_{50} units. It is calculated by dividing the initial lung burden for the alpha emitter by the median lethal initial lung burden (ILB_{50}) for the alpha emitter resulting in the alpha dose, X_a, in ILB_{50} units for the alpha emitter. A similar procedure is used to derive a similar dose for the beta emitter, X_b. X is then equal to $X_a + X_b$.

Doses X_a, X_b, and X can also be defined in terms of the cumulative radiation dose to the lung evaluated to a fixed time (e.g., 1.5 year dose). To do so, the median lethal radiation dose (D_{50}) must be known for both the alpha and the beta emitter, evaluated to the same fixed time as the cumulative radiation dose.

The lethality risk is related to the lethality hazard by the expression

$$\text{RISK} = 1-\exp[-\text{HAZARD}].$$

The risk for pulmonary morbidity was estimated in a similar way.

To validate the HF model for lethality and to develop and validate a similar model for morbidity, 395 F344/Crl rats, approximately 15 weeks of age were exposed via inhalation to ^{238}Pu only, ^{147}Pm only, or mixtures of both, in insoluble fused aluminosilicate particles (FAP). Control animals were exposed to fused aluminosilicate particles only.

The alpha emitter selected for the study was ^{238}Pu because of its high specific activity. This made it possible to use the same FAP aerosol for both ^{238}Pu and ^{147}Pm, as well as permitting the use of a single radioactive tag, in a single inhalation exposure, thus minimizing the variability in lung deposition of the radionuclides.

Lung tissue content of ^{238}Pu and ^{147}Pm was determined using both whole-body counting of a ^{169}Yb gamma-emitting tag and radiochemical analyses of tissues from sacrificed rats and those dying during the study. The radiochemical procedures included ashing, dissolution, and counting by liquid scintillation methods.

Biological endpoints monitored on all rats during the study were body weights, histological changes, and survival time. The probable cause of death was determined for each rat that died during the 1.5 year followup period. Respiratory function tests were performed on 117 survivors at 1.5 years after inhalation exposure.

For the ^{238}Pu-alpha irradiation of the lung, the ILB_{50} for death within 1.5 years from RPPF was 123 nCi/g-lung, which corresponds to a cumulative 1.5 year radiation dose of 4500 rad (45 Gy) to the lung. For ^{147}Pm-beta irradiation of the lung, the ILB_{50} was 160 μCi/g-lung, which corresponded to a cumulative 1.5 year radiation dose of about 30,000 rad (300 Gy) to the lung. The shape parameter, V, for lethality from RPPF was similar for alpha and beta irradiation of the lung with an average value of approximately 5.

After review of several respiratory parameters, four were selected and used to determine the prevalence of pulmonary functional morbidity. These parameters were vital capacity, quasistatic compliance, CO-diffusing capacity per kg body weight, and slope of phase 3 of the single-breath N_2 washout curve. Vital capacity reflected changes in lung volume; quasistatic lung compliance reflected changes in lung elasticity; the slope of phase 3 of the single-breath N_2 washout reflected the uniformity of gas distribution; and carbon monoxide diffusing capacity per kg body weight reflected alveolar-capillary gas exchange efficiency. Individuals having abnormal values for 3 or more of these 4 functional parameters were judged to have pulmonary morbidity.

For the ^{238}Pu-alpha irradiation of the lung, the ILB_{50} for pulmonary morbidity was 30 nCi/g-lung, which corresponded to a 1.5 year cumulative radiation dose of about 1,100 rad (11 Gy) to the lung. For the ^{147}Pm-beta irradiation of the lung, the ILB_{50} was 40 μCi/g-lung, which corresponded to a 1.5 year cumulative radiation dose of about 7,500 rad (75 Gy) to the lung. The shape parameter, V, was assumed to be the same for both morbidity and lethality. A value of 5 was therefore also used for morbidity.

The results indicate that the same shape parameter can be used for alpha and beta irradiation of the lung and for mortality and morbidity. However, about four times as much dose is required for 1.5-year lethality from RPPF as is required for morbidity.

After adjusting for competing modes of death, 80 rats were judged at risk for death from RPPF after combined alpha and beta irradiation of the lung. Of these, 43 deaths were expected and 54 were observed. Also, for rats receiving combined alpha and beta irradiation of the lung, 21 out of 24 surviving rats were expected to have pulmonary functional morbidity while 22 cases were observed. The results indicate that the hazard-function mortality and hazard-function morbidity models for combined alpha and beta irradiation of the lung should be adequate for reactor accident risk assessment.

CHAPTER 1

INTRODUCTION

The transport of radioactive materials associated with the nuclear fuel cycle could result in accidental or intentional (i.e., by sabotage) release of mixtures of alpha- and beta-emitting radionuclides into the environment. If released, the radioactive substances could become airborne and be inhaled by people leading to irradiation of critical body organs. When radionuclides are inhaled in an insoluble form, the lung is the main organ at risk. Small doses (hundreds of rad) to the lung may result in lung cancer, while large doses (thousands of rad) may result in other morbidity as well as death from radiation pneumonitis and pulmonary fibrosis (RPPF).

The experiment described in this report is the last of a series of inhalation-exposure experiments carried out at the Inhalation Toxicology Research Institute (ITRI) for the Nuclear Regulatory Commission (NRC) to validate an acute mortality model (Scott et al., 1984, 1986). The model was developed for predicting death from RPPF after inhalation exposure of a population to mixtures of beta emitting or mixtures of alpha- and beta-emitting radionuclides. The series of experiments was to also provide morbidity data for developing a similar model to predict morbidity from similar exposures.

The experiment described in this report was carried out to determine if the mortality model adequately predicts lethality from RPPF after combined alpha and beta irradiation of the lung from radionuclides deposited via inhalation. The experiment also provided pulmonary function, body weight, and hematology data to use in an exploratory analysis for morbidity.

Another report (NUREG/CR-5025, 1987) decribes results of inhalation exposure experiments carried out to (1) determine the affect of beta energy on the risk of death from RPPF and (2) to validate model predictions of acute lethalitiy from RPPF after internal exposure of the lung to complex patterns of low linear energy transfer (LET) radiation from beta-emitting radionuclides deposited in the lung.

CHAPTER 2
METHODS

2.1 Animals

Male and female F344/Crl rats were obtained from the Lovelace ITRI breeding colony for use in the study. The colony is free of known rat respiratory pathogens and is tested serologically every three months. The rats were 15 ± 2 weeks of age at exposure.

2.2. Housing of Animals

Before the rats were exposed, each was given a unique ear tag for identification. Rats of each gender were weighed and housed separately (two per polycarbonate cage). The room housing the rats was maintained at 20 to 22°F. The relative humidity was maintained at 20 to 50%. A 12-hour-on 12-hour-off light cycle was used. Rats were fed Lab Blox (Allied Mills, Chicago, IL) and given water ad libitum.

2.3 Experimental Design

Equal numbers of both genders were randomized by body weight into exposure groups as indicated in Table 2.1. Randomization into mortality and hematology groups was constrained such that average body weights were similar over all exposure concentrations and groups for a given gender. Exposure levels L_{01} and L_{50} were based on concentrations intended to produce about 1% and 50% lethality, respectively, from RPPF, for exposure to the alpha-emitter ^{238}Pu or beta-emitter ^{147}Pm only. A gamma-emitting label, ^{169}Yb, was incorporated into each of the FAP aerosols containing ^{147}Pm and for ^{238}Pu to make it possible to estimate the initial lung burdens of these latter two radionuclides by whole-body counting. A uniform distribution of the initial lung burden (ILB) was assumed for each exposure group. Thirty-six rats were included in each of 9 exposure categories (L_{01}, L_{50}, for ^{238}Pu or ^{147}Pm, and combinations of both in the same particle) as indicated in Table 2.1. For example, 36 rats were exposed to the L_{01} (alpha) + L_{01} (beta) combination.

Table 2.1

^{238}Pu-Alpha + ^{147}Pm-Beta Study Design and 1.5-Year Survivors Among F344/Crl Rats Expressed by Exposure Level

Betas (^{147}Pm)	Alphas (^{238}Pu)				
	L_{00}		L_{01}		L_{50}
L_{00}	Mortality (C)* 3/36	Hematology (C1) 0/8	Mortality (A2) 12/36		Mortality (A1) 28/36
L_{01}	Mortality (B2) 3/36		Mortality (AB4) 21/36	Sacrifice (AB5) 50/50	Hematology (AB5) 9/22	Mortality (AB3) 35/36
L_{50}	Mortality (B1) 18/36		Mortality (AB2) 19/36			Mortality (AB1) 35/35

*Items within parentheses represent experimental group designation. Ratios represent number dead at 1.5 years over number exposed. A hematology group (C1) of size 8 at L_{00} + L_{00} level was added after initiation of the study. The hematology group at L_{01} + L_{01} level was taken from animals initially assigned to the sacrifice study. One rat at L_{50} + L_{50} level died at time of exposure. L_{01} was intended to be a 1% affected level. L_{50} was intended to be a 50% affected level. L_{00} represents control exposure to nonradioactive fused aluminosilicate particles.

Fifty additional rats were assigned to the L_{01} (alpha) + L_{01} (beta) exposure level to be sacrificed 6 at a time (3 of each gender) at 0, 4, 14, 30, 60, 90, 120 and 150 days after inhalation exposure to provide needed dosimetry information. The remaining two were used as backups.

Eight rats were added to the L_{00} (control) level and 22 to the L_{01} (alpha) + L_{01} (beta) level to provide hematological data at 7, 14, 30, 60, 90, 180, 365 and 540 days after exposure. The eight control rats were not sham exposed.

2.4 Biological Measurements

Biological endpoints monitored on all rats during the study were body weight, histologic changes and survival time. Body weights were measured before exposure and at monthly intervals to 1.5 years after exposure. Surviving animals were observed twice per day for the 1.5-year observation period. Those moribund or critically ill were euthanized. After death, all animals were examined for gross lesions. The lungs were weighed and fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 microns and stained with hematoxylin and eosin for histologic evaluation. The probable cause of death was determined for each animal that died during the study.

Respiratory-function tests were performed on 117 (60 males and 57 females) survivors at 1.5 years after inhalation exposure using previously reported techniques (Harkema et al., 1982). The distribution of these survivors among exposure concentrations is shown in Table 2.2. Measurements by plethysmography during halothane anethesia included 35 parameters for breathing patterns, lung volumes, lung mechanics, gas distribution, CO diffusing capacity and forced exhalation. Data for all respiratory function parameters were reviewed, then a limited number of parameters reflecting key facets of function were selected for detailed analysis. Vital capacity reflected changes in lung volume, quasistatic lung compliance reflected changes in lung elasticity, the slope of phase 3 of the single-breath N_2 washout reflected the uniformity of gas distribution, and carbon

Table 2.2
Survivors That Were Subjected to Pulmonary Function Testing at 1.5 Years After Inhalation Exposure

Beta Exposure Level	Alpha Exposure Level					
	L_{00}		L_{01}		L_{50}	
	Male	Female	Male	Female	Male	Female
L_{00}	10	10	10	10	10	5
L_{01}	6	10	10	4	--	--
L_{50}	8	5	6	13	--	--

Total males = 60
Total females = 57
Grand total = 117

monoxide diffusing capacity per kg body weight reflected alveolar-capillary gas exchange efficiency.

Hematology was performed only on rats assigned to the hematology group (Table 2.1). Measurements were taken at 7, 14, 30, 60, 90, 180, 360 and 540 days after inhalation exposure. Blood was collected from the retrobulbar sinus in a capillary tube. Blood smears were made and the blood diluted in Unopettes®. Hematocrit, total red and white blood cells and white blood cell differential counts were determined.

2.5 Aerosol Preparation and Generation

Suspensions for aerosol generation were prepared by cation exchange of ^{147}Pm, ^{238}Pu, or ^{169}Yb into montmorillonite clay. The ^{238}Pu and ^{147}Pm were incorporated into separate batches of montmorillonite clay suspended in water. Appropriate aliquots of each batch were mixed together to achieve the desired initial ratios of alpha to beta activity in the exposure aerosol. With this approach, the initial ratio of alpha to beta activity was fixed for each exposure aerosol but differed among them. Polydisperse aerosols were generated with a Lovelace nebulizer and heat treated by passing through a heating column at 1150°C with a flow rate of 2 lpm. The ^{169}Yb gamma-emitting tag was incorporated into the particles in small amounts (Table 2.3) to allow determination of particle retention in the lung through total-body counting.

The ^{238}Pu was selected for this study because of its high specific activity. This made it possible to use the same fused aluminosilicate particle (FAP) aerosols for both ^{238}Pu and ^{147}Pm, as well as permitting the use of a single radioactive tag in a single inhalation exposure, thus minimizing the variability in the lung deposition of the radionuclides. Two separate aerosols would have required two exposures (one for the alpha emitter and one for the beta-emitter) and would have led to larger variability in the initial lung deposition and in the initial alpha to beta activity ratio.

2.6 Total-Body Counting

Shielded NaI(Tl) crystal counters were used to detect gamma radiation from the ^{169}Yb radioactive tag. Each counting unit consisted of three 5 cm by 3 cm sodium iodide crystals with built-in photomultiplier tubes spaced 120° apart around a centrally located sample holder. Detectors were shielded by 10 cm of lead.

2.7 Determination of Lung Radioactivity Content

Rat lung specimens were analyzed for ^{238}Pu and for ^{147}Pm, as detailed below, after the ^{169}Yb had decayed to nondetectable levels. The procedures used included ashing, dissolution, and counting by liquid scintillation methods (Keough and Powers, 1970). This was a double label procedure that required mathematical resolution of the sample content of ^{238}Pu and ^{147}Pm. Quench correction was by the external standard, channels-ratio method.

Tissue samples awaiting analysis were stored in 10% neutral buffered formalin solution in glass vials. For analysis, each sample was transferred to a Pyrex beaker, dried in an oven, dry ashed in a muffle furnace, and wet ashed with HNO_3 and H_2O_2 to destroy the organic matrix. The resulting sample was redissolved in 100 ml of 2 M HNO_3. A 5 ml aliquot of the clear, colorless solution was transferred to a liquid scintillation counting vial. Fifteen ml of Ready-Solv EP liquid scintillation cocktail (Beckman Instruments) was added to the vial. A one-day period was allowed between preparation of a sample and actual counting to allow the sample to stabilize chemically.

Quench correction standards were prepared for ^{238}Pu and ^{147}Pm. These standards were necessary for quench correction and mathematical resolution of the ^{238}Pu and ^{147}Pm activity content in the rat tissues. There were 5 quench correction standards for ^{147}Pm, 5 for ^{238}Pm, and 5 for standards that contained both ^{238}Pu and ^{147}Pm. Five standards were used to provide a range of quenching that covered the anticipated range for the lung tissue samples. The degree of

Table 2.3

Aerosol Concentrations, Aerosol Size, Exposure Run Time and Initial Radionuclide to ^{169}Yb Activity Ratios by Experiment Number

Experiment Group	Aerosol Concentration			Aerosol Size*		^{169}Yb to Nuclide Ratio		Predicted ILB's			Run Time
	^{169}Yb (nCi/l)	^{238}Pu (nCi/l)	^{147}Pm (μCi/l)	AMAD (μm)	σ_g	^{238}Pu	^{147}Pm	^{169}Yb (nCi)	^{238}Pu (nCi)	^{147}Pm (μCi)	(min)
A1	772	550	0	1.60	1.50	2.59	NA	320	230	0	35
A2	775	71.4	0	1.70	1.59	9.56	NA	420	40	0	60
B1	621	NA	132	1.42	1.77	NA	0.0047	447	NA	100	60
B2	943	NA	73	1.44	2.2	NA	0.013	475	NA	40	42
AB1	661	248	107	1.40	1.50	2.67	0.0062	560	210	90	70
AB2	622	72	114	1.27	1.6	12.3	0.0245	450	50	90	60
AB3	541	294	29	1.42	1.56	1.93	0.019	380	210	20	59
AB4	429	45.4	18.1	1.45	1.61	11.2	0.0237	360	40	15	70
AB5	387	44	23.1	1.49	1.58	9.33	0.0167	380	50	20	60

*AMAD represents activity median aerodynamic diameter, σ_g represents the geometric standard deviation.

NA = not applicable.

quenching was controlled by the amount of HNO_3 in the vials. Techniques used for preparation of quenching correction standards were identical to those for preparation of samples. A new series of standards was prepared for each batch of rat tissue.

Samples were counted by liquid scintillation for 20 minutes. The ^{238}Pu and ^{147}Pm activities were counted in two channels (indicated here as A and B) of the liquid scintillation counter. The efficiencies of counting ^{147}Pm and ^{238}Pu in Channel A were indicated by E_{11} and E_{21}, respectively. For Channel B they were indicated by E_{12} and E_{22}, respectively. Sample gross counts in Channels A and B were corrected for background by counting blanks and obtaining net counts per minute (cpm). Net cpm in Channels A and B were represented by CPM_1 and CPM_2, respectively. The counting efficiencies were functions of the external standard channels ratio. Curves were prepared relating counting efficiency to the external standard channels ratio for each radionuclide. Total disintegrations per minute (DPM) for ^{147}Pm and ^{238}Pu, represented by DPM_1 and DPM_2, respectively, were calculated using

$$DPM_1 = [CPM_1*E_{22} - CPM_2*E_{21}]/[E_{11}*E_{22} - E_{12}*E_{21}] \quad (1)$$

$$DPM_2 = [CPM_2*E_{11} - CPM_1*E_{12}]/[E_{11}*E_{22} - E_{12}*E_{21}] \quad (2)$$

After calculating DPM_1 and DPM_2, the total DPM for ^{238}Pu and ^{147}Pm in lung was calculated by multiplying the results by 20, since only 1/20 of each sample was counted.

2.8 Estimation of Initial Lung Burdens

Initial lung burdens for ^{238}Pu and ^{147}Pm were estimated indirectly. First, the initial lung burden of ^{169}Yb was estimated from total-body counts of ^{169}Yb at early times (from 14 to 104 days after exposure). Most of the total-body activity from 14 to 104 days was assumed to be in the lung. A single-component exponential retention function was used to estimate the day 0 intercept for ^{169}Yb, the estimated initial lung burden. Additional total-body activity cleared at early times was excluded. The initial lung burdens of ^{238}Pu and ^{147}Pm were estimated for each animal indirectly by multiplying the initial lung burden of ^{167}Yb by the respective initial activity ratios (^{238}Pu to ^{169}Yb and ^{147}Pm to ^{169}Yb activity ratios).

The aerosol concentrations of ^{238}Pu, ^{147}Pm, and ^{169}Yb were determined by analyzing filters taken during exposure and are given in Table 2.3. Radioactivity counts for ^{238}Pu were obtained using a ZnS scintillation technique; for ^{147}Pm they were achieved using a P-10 gas proportional counter technique; and for ^{169}Yb they were obtained using a NaI(Tl) detector.

2.9 Estimation of Doses to Lung

Separate curves were developed for retention of ^{238}Pu and ^{147}Pm in the lung using initial lung burden estimates and results of radiochemical analysis on specific rats assigned to the study for dosimetry purposes (sacrifice group) and those that died or were euthanized when critically ill. Retention curves for lung were obtained by fitting two-component exponential functions to the radiochemistry data using SAS nonlinear regression software (SAS, 1982).

The cumulative radiation dose to the lung at death and the cumulative dose to a specified time (e.g., 1 year after inhalation exposure) were evaluated by numerical integration over the dose rate pattern for each exposed individual. Numerical evaluation of dose was required because the lung weight changed with time as the animals grew. Instantaneous dose rates DR(t) at any given time t after inhalation exposure were given by

$$DR(t) = 51.2*E*A(t)*f/W(t), \text{ rad/day} \quad (3)$$

where

E = 0.062 MeV for ^{147}Pm

E = 5.5 MeV for ^{238}Pu

A(t) = the activity retained at time t which equals the product of the initial lung burden in μCi and the radionuclide-specific lung retention function

f = fractional energy absorption in the lung; 0.97 for ^{147}Pm betas and 1 for ^{238}Pu alphas (Snipes, 1980)

W(t) = lung weight in g at t days after inhalation exposure

= 0.0050*[Initial body weight in g + 124*GF(t)], females

= 0.0041*[Initial body weight in g + 166*GM(t)], males

where the empirical function GF(t) and GM(t) obtained from an earlier publication (NUREG/CR-5025, 1987) are given by

$$GF(t) = 1 - \exp(-0.0169*t^{0.822}) \quad (4)$$

and

$$GM(t) = 1 - \exp(-0.0133*t^{0.938}). \quad (5)$$

This method of evaluating doses was based on the assumption that the lungs continue to grow in irradiated rats as they do in unirradiated controls. Cumulative radiation doses to the lung for ^{147}Pm betas and ^{238}Pu alphas were evaluated separately at 1, 14, 30, 90, 180, 200, 360, 540, 730 and 1096 days after exposure, for an initial lung burden of 1 μCi/g-lung for ^{147}Pm and 1 nCi/g-lung for ^{238}Pu, using numerical integration with a FORTRAN program. The data obtained for the cumulative dose in rad were then fitted with a two-component exponential function of the form

$$\text{Cumulative dose/unit activity/g-lung} =$$

$$C1*[1 - \exp(-B1*t)] + C2*[1 - \exp(-B2*t)], \quad (6)$$

where the parameters C1, C2, B1 and B2 were positive and depended on the type of radiation. A single set of parameters were determined from the data for exposure to ^{147}Pm only; a single set was obtained for exposure to ^{238}Pu only, and a single set was obtained for exposure to mixtures of ^{147}Pm and ^{238}Pu. The fitted curves for the cumulative dose per μCi ^{147}Pm per g-lung or per nCi ^{238}Pu per g-lung were used to evaluate cumulative rads to the lung at any desired time including the dose to death. To make this evaluation, the cumulative rads per unit initial lung burden (in μCi ^{147}Pm per g-lung or nCi ^{238}Pu per g-lung) at the time of interest were multiplied by the initial lung burden expressed in activity per gram of lung.

CHAPTER 3
RESULTS

3.1 Initial Activity, Biological Clearance and Retention of Radioactive Material in the Lung

Aerosols were polydisperse in their size distribution. Activity median aerodynamic diameters (AMAD) and geometric standard deviations are given in Table 3.1 along with aerosol concentrations and exposure durations. The activity ratios of ^{147}Pm to ^{169}Yb and ^{238}Pu to ^{169}Yb in Table 2.3 were used to estimate actual initial lung burdens from total body ^{169}Yb counts. The desired and actual initial lung burdens (averages) are given, by exposure level, in Table 3.1.

Table 3.1

Desired and Observed Average Initial Lung Burdens of ^{147}Pm and/or ^{238}Pu Inhaled in Fused Aluminosilicate Particles by Rats

^{147}Pm		^{238}Pu Exposure Level					
		L_{00}		L_{01}		L_{50}	
Exposure	Category	Pm (μCi)	Pu (nCi)	Pm (μCi)	Pu (nCi)	Pm (μCi)	Pu (nCi)
L_{00}	Desired	0	0	0	40	0	180
	Observed	0	0	0	24 ± 6	0	130 ± 40
L_{01}	Desired	20	0	20	40	20	180
	Observed	21 ± 12	0	14 ± 5	26 ± 10	13 ± 4	130 ± 44
L_{50}	Desired	100	0	100	40	100	180
	Observed	57 ± 20	0	42 ± 15	26 ± 10	51 ± 20	120 ± 40

Curves for retention of radioactivity in lung (lung-retention functions) that were obtained using two-component exponential functions are plotted in Figures 3.1 and 3.2. Separate lung-retention functions for ^{147}Pm retention were obtained for exposure to ^{147}Pm alone and for exposure to ^{147}Pm in combination with ^{238}Pu (mixture). The lung-retention functions are given in Table 3.2. Separate lung-retention functions were also obtained for ^{238}Pu retention for exposure to ^{238}Pu alone and for exposure to ^{238}Pu in combination with ^{147}Pm.

Table 3.2

Lung Retention Functions for Retention of ^{238}Pu or ^{147}Pm in the Lung of F344 crl Rats*

Radionuclide	Type of Exposure	Retention Function Parameter		
		A1	B1	B2
^{238}Pu	^{238}Pu only	0.41 ± 0.11	0.028 ± 0.022	0.0027 ± 0.00036
^{238}Pu	^{238}Pu + ^{147}Pm	0.69 ± 0.074	0.015 ± 0.0033	0.00094 ± 0.00045
^{147}Pm	^{147}Pm only	0.67 ± 0.10	0.15 ± 0.033	0.0036 ± 0.00059
^{147}Pm	^{238}Pu + ^{147}Pm	0.54 ± 0.023	0.091 ± 0.044	0.0035 ± 0.00016

*Retention function = A1*exp[-B1*t] + (1-A1)exp[-B2*t]), where t is in days.

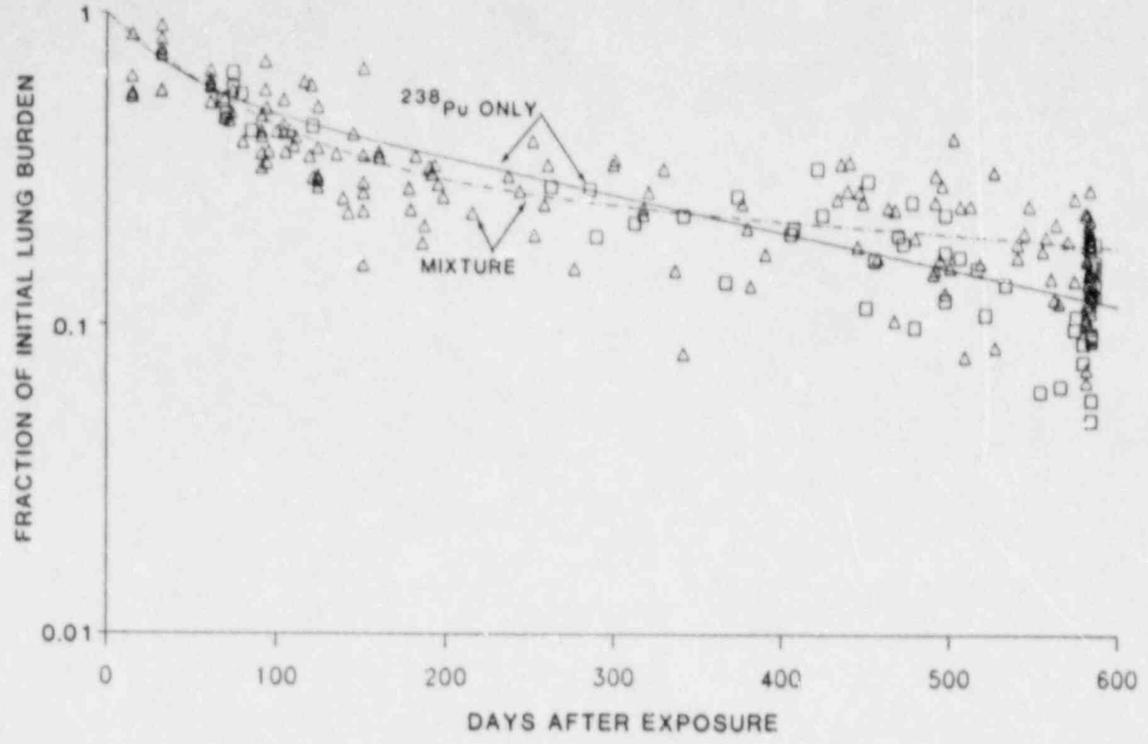

Figure 3.1 Pulmonary retention of ^{238}Pu in F344/Crl rats after (a) inhalation exposure to ^{238}Pu only, in fused aluminosilicate particles and after (b) inhalation exposure to mixtures of ^{238}Pu + ^{147}Pm in the same fused aluminosilicate particle matrix.

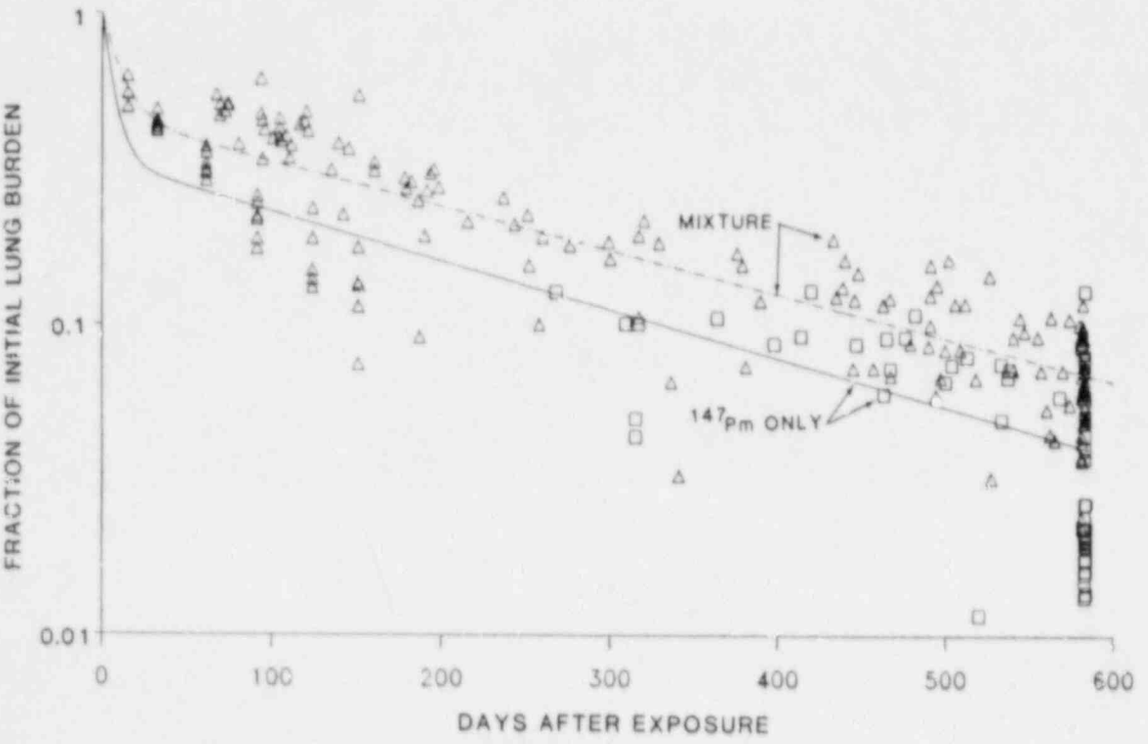

Figure 3.2 Pulmonary retention of ^{147}Pm in F344/Crl rats after (a) inhalation exposure to ^{147}Pm only, in fused aluminosilicate particles and after (b) inhalation exposure to mixtures of ^{238}Pu + ^{147}Pm in the same fused aluminosilicate particle matrix.

Dose accumulation expressed as rads per nCi ^{238}Pu per g-lung or rads per μCi ^{147}Pm per g-lung were first evaluated numerically by gender. Results obtained were essentially the same for both genders so that an average of both was obtained and fitted with a two-component exponential function. The fitted functions obtained are plotted in Figures 3.3 and 3.4 and are given in Table 3.3. These functions were used to calculate radiation doses to the lung to the desired times as described above.

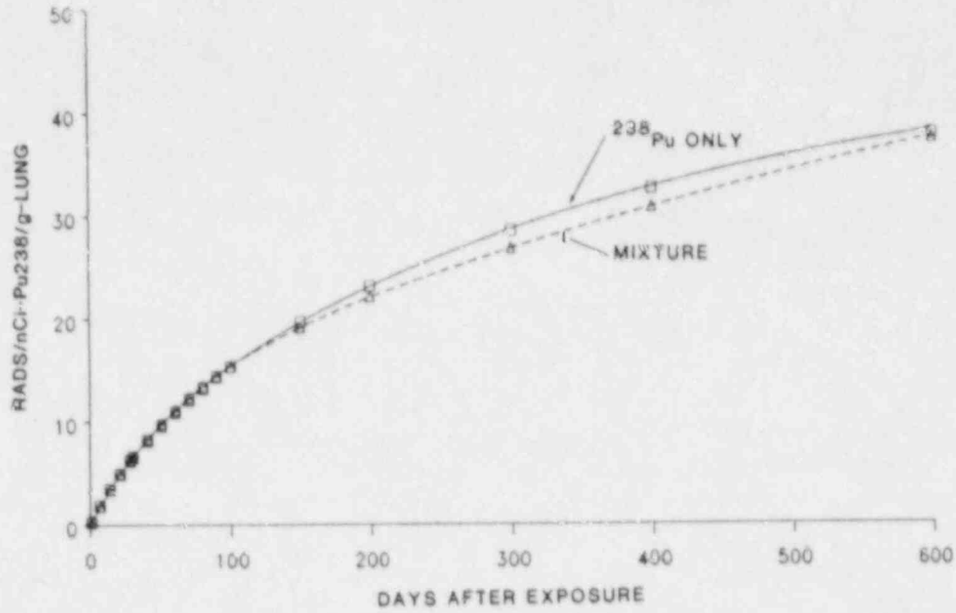

Figure 3.3 Fitted two-component exponential curves for calculating, as a function of time after inhalation exposure, rads per nCi/g-lung due to ^{238}Pu initially deposited in the lung (ILB). Separate curves are provided for exposure to "^{238}Pu only" and for exposure to "^{238}Pu + ^{147}Pm." To get cumulative rads to the lung at a specified time, multiply the value of the curve at that time by the initial lung burden for ^{238}Pu in nCi/g-lung.

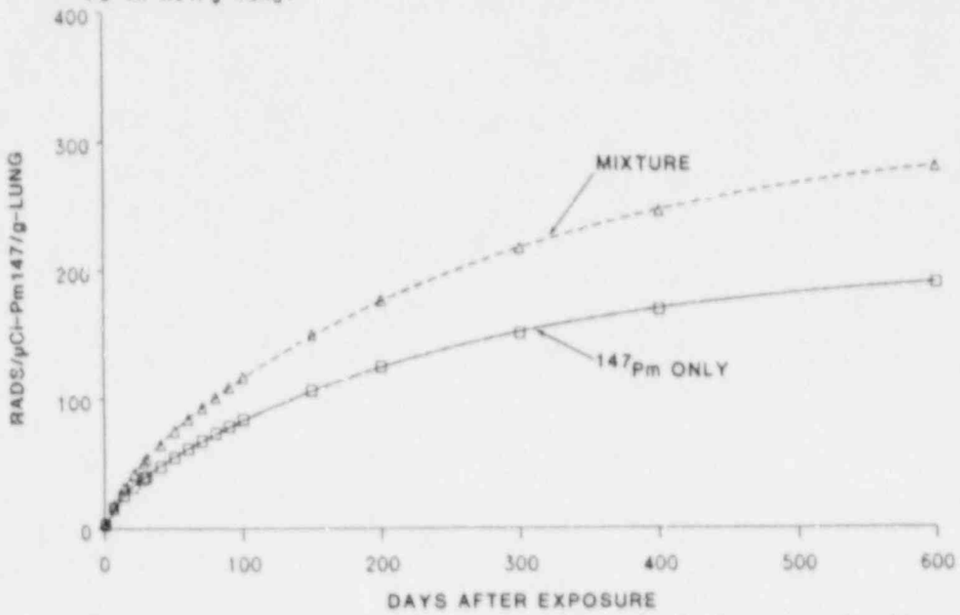

Figure 3.4 Fitted two-component exponential curves for calculating, as a function of time after inhalation exposure, rads per μCi/g-lung due to ^{147}Pm initially deposited in the lung (ILB). Separate curves are provided for exposure to "^{147}Pm only" and for exposure to "^{238}Pu + ^{147}Pm." To get cumulative rads to the lung at a specified time, multiply the value of the curve at that time by the initial lung burden for ^{147}Pm in μCi/g-lung.

Table 3.3

Dose Accumulation Functions for Calculating Cumulative Rads per nCi/g-Lung of ^{238}Pu or per μCi/g-Lung of ^{147}Pm Initially Deposited in the Lung (ILB) as a Function of the Time (t) in Days After Inhalation Exposure of F344/Crl Rats*

Radionuclide	Type of Exposure	Dose Accumulation Function Parameter			
		C1	B1	C2	B2
^{238}Pu	^{238}Pu only	6.10	0.0268	39.2	0.00285
^{238}Pu	^{238}Pu + ^{147}Pm	12.0	0.0176	53.3	0.00109
^{147}Pm	^{147}Pm only	20.7	0.0831	186	0.00411
^{147}Pm	^{238}Pu + ^{147}Pm	30.9	0.0540	283	0.00360

Dose in rad = C1(1-exp[-B1*t]) + C2*(1-exp[-B2*t]).

3.2 Mortality Distribution

The fraction dying from all causes to about 1.5 years after inhalation exposure is shown in Figure 3.5 as a function of exposure level. After adjusting for spontaneous deaths, the results indicate synergistic effects of the alpha and beta radiations for mortality from all causes for three of the four combinations. Adjustments were made by assuming that radiation induced and spontaneous effects were independent. A pronounced synergistic effect was observed for the L_{01} (alpha) + L_{01} (beta) combination. While the L_{01} level beta exposure caused no radiation induced early deaths and the L_{01} alpha level caused 27% lethality, a combination of these two levels caused 54% lethality (all based on adjusted results).

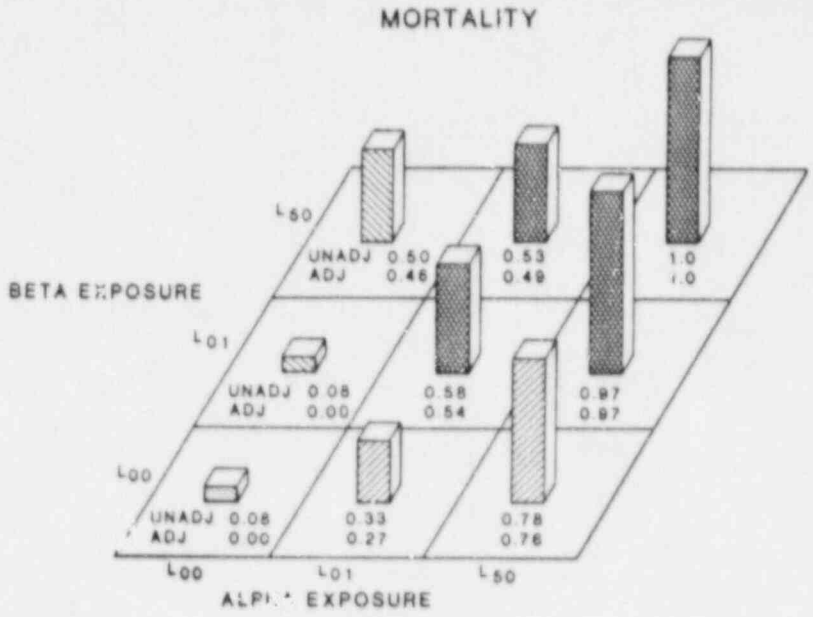

Figure 3.5 Unadjusted (UNADJ) distribution of 1.5 year mortality from all causes of death (except sacrifices) as a function of exposure level. Adjusted values (ADJ) to correct for spontaneous effects are also given and were calculated assuming independence of radiation-induced and nonradiation-induced effects.

Histological examination of the rats that died revealed several causes of death, including RPPF and lung tumors. The major cause of death before 1.5 years was RPPF. It was characterized histologically by increased numbers of vacuolated alveolar macrophages and occasional neutrophils, alveolar hemosiderin, vasculitis and fine alveolar septal fibrosis. Thrombosis was also occasionally present. The cause of death was considered RPPF when these characteristics were found and there was no other obvious cause.

Survival times for death from all causes (except RPPF) vs the initial lung burdens of ^{238}Pu and ^{147}Pm are given in Figure 3.6. Survival times for rats dying from RPPF are given in Figure 3.7 as a function of the initial lung burdens of ^{238}Pu and ^{147}Pm. Note that survival time was inversely related to the total radionuclide activity deposited in the lung.

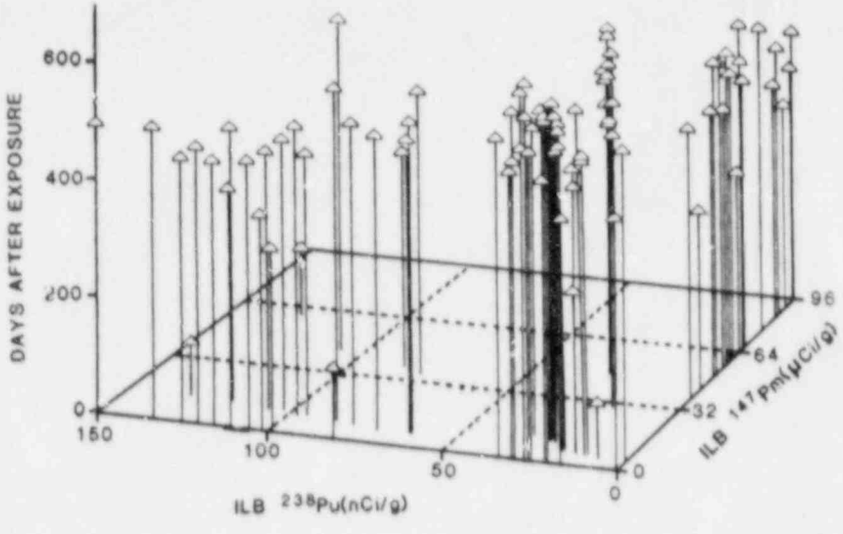

Figure 3.6 Survival time for death from all causes except radiation pneumonitis and pulmonary fibrosis as a function of the intial lung burden of ^{238}Pu in nCi/g-lung and ^{147}Pm in μCi/g-lung. Time to euthanasia of morbid rats was used as estimates of time to death from radiation-induced and natural causes.

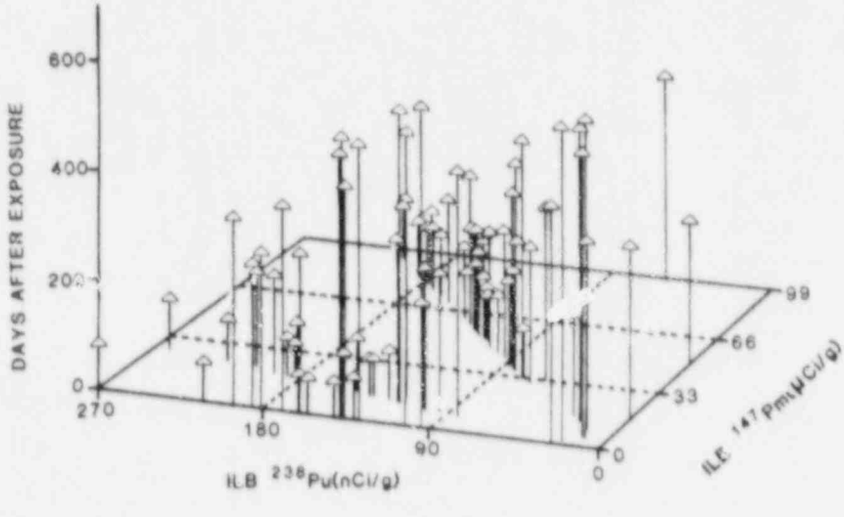

Figure 3.7 Survival time for death from radiation pneumonitis and pulmonary fibrosis. Time to euthanasia of morbid rats was used as an estimate of time to death from radiation induced causes.

Risk estimators were developed for 1.5-year lethality from RPPF after inhalation exposure to only ^{238}Pu and to only ^{147}Pm when inhaled in fused aluminosilicate particles. Use of the maximum likelihood procedure allowed the analysis of individual data without having to form dose groups. This eliminated the systematic error associated with grouping of individuals that had different initial lung burdens. We have used a Weibull type risk function for lethality that depends on the median lethal dose D_{50} and shape parameter ν (Scott et al., 1987). With this risk function model, the lethality hazard H is related to the lethality risk R by

$$R = 1 - \exp(-H) \tag{7}$$

where

$$H = \ln(2)*[ILB/ILB_{50}]^{\nu}. \tag{8}$$

The variable named ILB is the initial lung burden in μCi/g-lung of ^{147}Pm or nCi/g-lung of ^{238}Pu, and ILB_{50} is the median lethal initial lung burden. Once the ILB_{50} is known for ^{238}Pu only or ^{147}Pm only, it can be used to calculate the median lethal dose D_{50} in rads to any specified time (e.g., 1 year). In this case, the ratio ILB/ILB_{50} in the above equation can be replaced by D/D_{50} where D is the dose in rads to the time at which the D_{50} dose is evaluated.

For ^{238}Pu, the median lethal initial lung burden and shape parameter obtained for death from RPPF within 1.5 years, were 123 ± 7.5 nCi/g-lung and 4.7 ± 1.6, respectively. For ^{147}Pm, the corresponding median lethal lung burden and shape parameter estimates were 160 ± 190 μCi/g-lung and 5.4 ± 0.9, respectively. The large uncertainty in the median lethal initial lung burden for ^{147}Pm arises because intended initial lung burdens were not achieved. The rats were underexposed, leading to only one death attributed to RPPF after exposure to ^{147}Pm only. Twenty-five deaths were attributed to other causes, primarily pulmonary tumors. The estimate of 160 μCi/g-lung for the median lethal initial lung burden was identical to that obtained in an earlier experiment where there were many deaths attributed to RPPF (NUREG/CR-5025, 1987).

An attempt was made to use the unimodal Weibull model to characterize dose-effect curves for 1-year lethality from all causes. However, because deaths from causes other than RPPF occurred at doses below the effective threshold for death from RPPF, satisfactory fits to the multimodal data could not be obtained using the unimodal model.

3.3 Expected and Observed Deaths

Based on the hazard function model for predicting the combined effects of high-LET alpha and low-LET beta irradiation of the lung, the lethality hazard for death from RPPF can be predicted in the following way. Divide the ^{147}Pm initial lung burden by the ILB_{50} for ^{147}Pm to obtain the beta dose X_b in units of the ILB_{50}. Also divide the ^{238}Pu initial lung burden by the ILB_{50} for ^{238}Pu to obtain the alpha dose X_a in units of the ILB_{50}. Add X_a and X_b to obtain the total dose X in units of the D_{50}. Next calculate the fraction F_a of the dose X that is due to X_a, where

$$F_a = X_a/X.$$

Also calculate the fraction F_b of the dose X that is due to X_b, where

$$F_b = X_b/X.$$

For exposure to the mixture, the shape parameter V can be obtained using the weighted reciprocal relationship (Scott, 1987; Scott et al., 1986)

$$1/V = F_a/V_a + F_b/V_b \tag{9}$$

where V_a and V_b are the shape parameters for exposure to alphas only and betas only, respectively. The reciprocal relationship is needed only when V_a and V_b differ significantly. When V_a and V_b are approximately equal, V can be calculated as the average of V_a and V_b. This latter averaging procedure has been used here because V_a and V_b were found to be approximately the same. The reciprocal relationship is included for completeness.

Based on the hazard function model of predicting the combined effects of alpha and beta irradiation of the lung, the lethality hazard is given by

$$H = \ln(2)*X^V. \tag{10}$$

Knowing the lethality hazard H, one can then calculate the individual risk of dying from RPPF using the relationship

$$\text{Individual Risk} = 1 - \exp(-H). \tag{11}$$

Adding the individual risks over the dose distribution for the exposed sample of rats leads to the expected cases of deaths when all other competing risks are eliminated. We have used this method to predict the number of deaths from RPPF occurring within 1.5 years after inhalation exposure of F344 rats to mixtures of ^{238}Pu and ^{147}Pm. All rats dying of other competing risks during the 1.5-year interval were excluded from the analysis. Only rats that died from RPPF or survived to 1.5 years were included. The expected and observed numbers of deaths are shown in Table 3.4 and are in good agreement. This indicates that the hazard-function method of predicting the combined lethal effects of alpha and beta irradiation of the lung should be adequate for use in reactor accident consequence modeling.

3.4 Morbidity

3.4.1 Body Weight Changes

A reduced body weight was observed only in rats that died from radiation-induced injury. Average body weights by exposure level are given in Figures 3.8-3.10 for 3, 6 and 12 months after the inhalation exposure. Similar results were obtained at all other times that body weights were recorded. An exploratory analysis of the data revealed that a reduction in body weight mainly occurred in rats that accumulated lethal radiation doses.

3.4.2 Hematology

Hematological measurements were made repeatedly on the same males and females from the L_{01} (alpha) + L_{01} (beta) level and on preselected controls assigned to the hematology group. No significant effects on the peripheral blood were observed. Data for the radiosensitive lymphocytes are given in Table 3.5 where L_c and L_t represent the average control and average test group [L_{01} (alpha) + L_{01} (beta) level] counts at various times after exposure; SL_c and SL_t represent standard deviations for L_c and L_t, respectively. The expression $100L_t/L_c$ with standard deviation SD represents the average test counts expressed as a percentage of the average control value at the specified time. Based on an assumed normal distribution, no significant departure from control values could be demonstrated. None of the other hematological parameters was significantly different from control values.

Table 3.4

Expected and Observed Deaths from Radiation Pneumonitis and Pulmonary Fibrosis Within 1.5 Years After Inhalation Exposure of F344/Crl Rats to Mixtures of ^{238}Pu and ^{147}Pm Inhaled in Fused Aluminosilicate Particles

Experiment Group	Average Initial Lung Burden ^{238}Pu (nCi/g)	Average Initial Lung Burden ^{147}Pm (μCi/g)	Risk Set Size N*	Expected Deaths**	Observed Deaths
AB1	120 ± 40	51 ± 20	32	25 ± 2.4	32
AB2	26 ± 10	42 ± 15	18	1 ± 1	1
AB3	130 ± 44	13 ± 4	22	17 ± 2	21
AB4	26 ± 10	14 ± 5	0	0	0

*After elimination of animals dying within 1.5 years from all causes other than radiation pneumonitis.

**Individual risk = $1 - EXP(-0.693\ X^5)$

$X = X_{PM} + X_{PU}$

$X_{PM} = ILB_{PM}(\mu Ci/G\text{-}LUNG)/160$

$X_{PU} = ILB_{PU}(nCi/G\text{-}LUNG)/123$

Average risk = (Sum of individual risks)/N

Variance = N*(Average risk)(1 - Average risk)

Expected deaths = (Risk set size)*(Average risk)

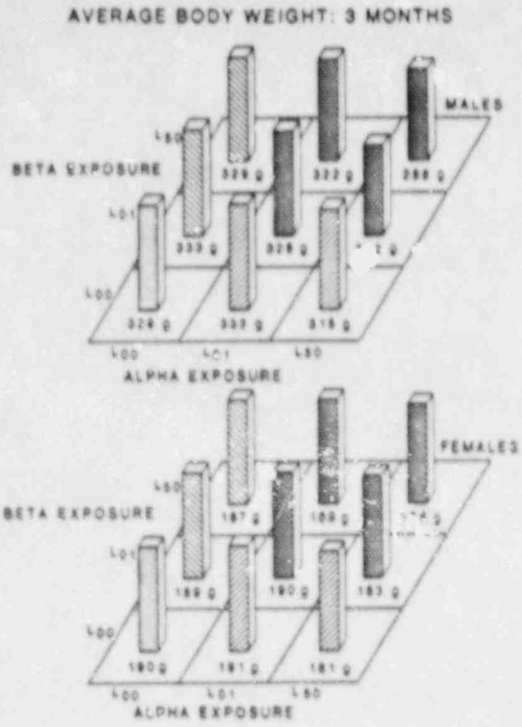

Figure 3.8. Average body weight in grams, as a function of the exposure level, evaluated at 3 months after inhalation exposure; (a) males, (b) females.

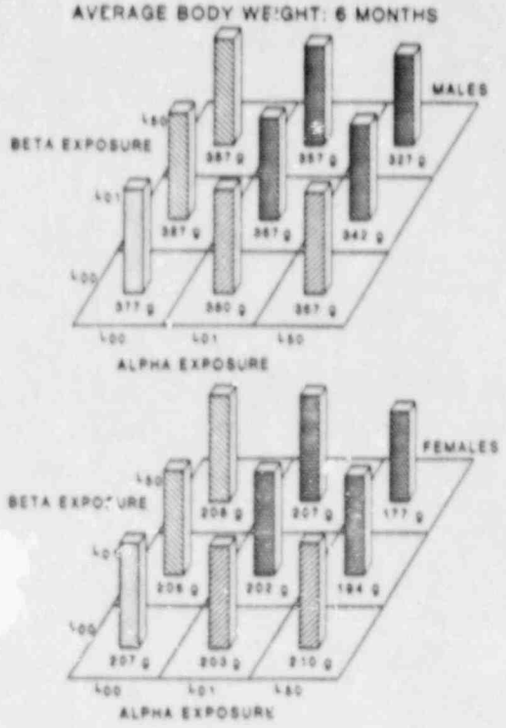

Figure 3.9. Average body weight in grams, as a function of exposure level, evaluated at 6 months after inhalation exposure; (a) males, (b) females.

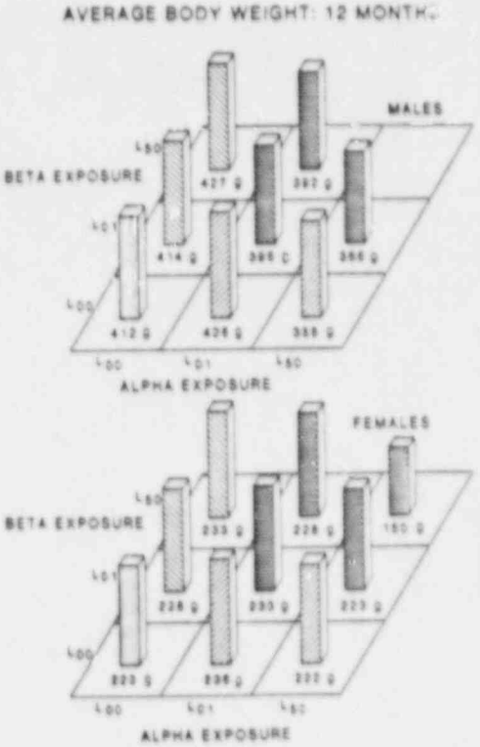

Figure 3.10 Average body weight in grams, as a function of exposure level, evaluated at 12 months after inhalation exposure; (a) males, (b) females.

Table 3.5

Blood Lymphocyte Counts After Inhalation Exposure of Rats to ^{238}Pu + ^{147}Pm Inhaled in Fused Aluminosilicate Particles*

	Controls		L_{01} alpha + L_{01} beta		Average as Percent of Controls	
DPE	Average (L_c)	Standard Deviation (SL_c)	Average (L_t)	Standard Deviation (SL_t)	Average ($100L_t/L_c$)	Standard Deviation (SD)
0	--	--	--	--	100	--
30	7009	1552	7088	2058	101	37
60	7796	1516	9463	4322	121	60
90	7485	2937	6850	1845	92	44
120	7350	2462	7497	3601	102	60
150	8800	4029	8328	3337	95	58
180	5044	2451	5667	4913	112	112
270	5203	1624	5618	3042	108	68
360**	3002	812	3272	974	109	44

*L_c = control group average lymphocyte count (cells/cmm)
L_t = test group (D01 alpha + D01 beta level) average lymphocyte counts (cells/cmm)
$100L_t/L_c$ = average lymphocyte count for test group expressed as percent of average control value at specified time
SL_c = standard deviation of L_c
SL_t = standard deviation of L_t
SD = standard deviation of $100L_t/L_c$
DPE = days after exposure

**Lymphocyte counts as well as other hematological data had systematic error at 360 days. Data were multiplied by correction factor of 2 for sampling volume error correction to reduce systematic error. Systematic error was eliminated by taking ratio L_t/L_c.

3.4.3 Respiratory Function

It is shown in Figures 3.11-3.14 that survivors 1.5 years after inhalation exposure had a reduction in vital capacity (Fig. 3.11), CO diffusing capacity (Fig. 3.12), and quasistatic compliance (Fig. 3.13), and an increase in the slope of phase 3 of the single-breath nitrogen washout curve (Fig. 3.14). These changes reflected the presence of a restrictive lung disorder (smaller, stiffer lungs) with an uneven distribution of lesions (nonuniform gas distribution) and an impairment of gas exchange. The alterations are characteristic of RPPF from internally deposited alpha and beta gamma emitters (Mauderly et al., 1980A, 1980B).

Pulmonary function data were quantified in the following way to develop risk parameters for estimating the prevalance of respiratory dysfunction resulting from irradiation of the lung. Each irradiated rat having a vital capacity measurement less than the lower 95% confidence interval for control values was judged to have a reduced lung volume. Each irradiated rat having a CO diffusing capacity (normalized to kg body weight) less than the lower 95% confidence interval for controls was judged to have abnormal gas exchange in the lung. Each irradiated rat having a quasistatic compliance less than the lower 95% confidence interval for control values was judged to have stiffer than normal lungs. Each rat having a slope of phase 3 of the N_2 washout curve greater than the upper 95% confidence interval for controls was judged to have an abnormal ventilation distribution in the lung.

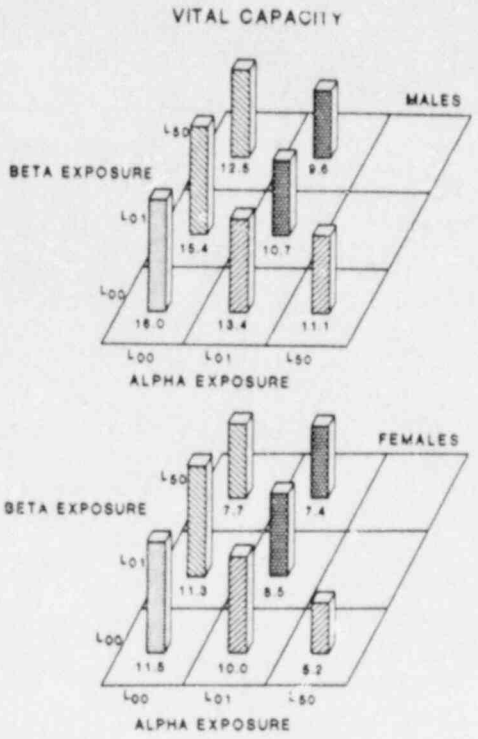

Figure 3.11. Average value for vital capacity in ml, as a function of the exposure level, evaluated at 1.5 years after inhalation exposure; (a) males, (b) females.

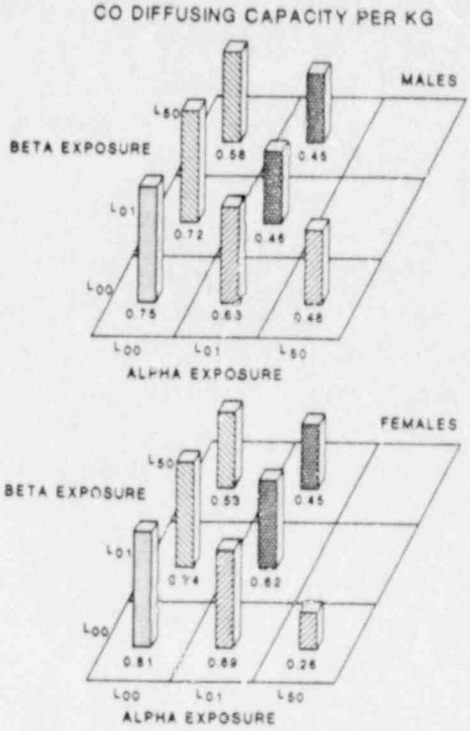

Figure 3.12. Average value for CO diffusing capacity per kg body weight, as a function of the exposure level, at 1.5 years after inhalation exposure, and expressed in ml/min/mmHg/kg; (a) males, (b) females.

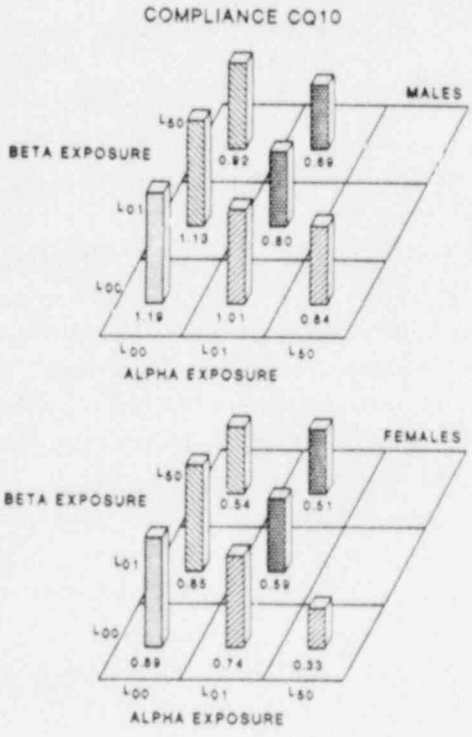

Figure 3.13. Average value for quasistatic compliance (CQ10), in ml/cmH_2O, as a function of the exposure level, at 1.5 years after inhalation exposure; (a) males, (b) females.

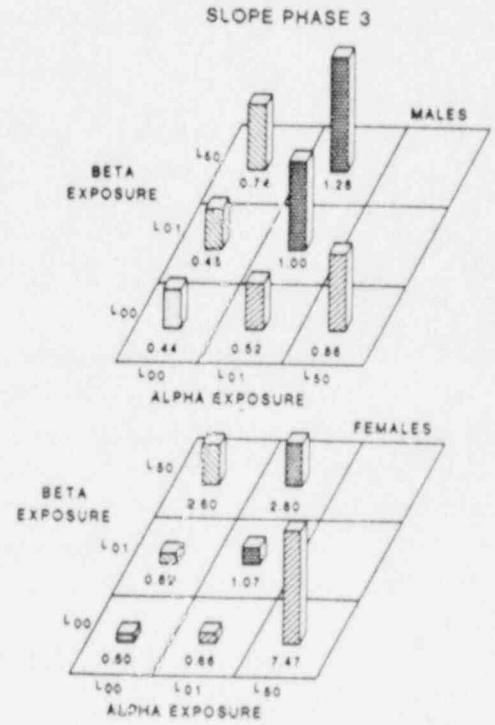

Figure 3.14. Average value for slope of phase III of the single breath nitrogen washout curve expressed in % N_2/ml, as a function of the exposure level, at 1.5 years after inhalation exposure; (a) males, (b) females.

Rats having one or more of these abnormalities were assigned a risk parameter R_1=1; otherwise, R_1=0; rats having two or more abnormalities were assigned a risk parameter R_2=1; otherwise, R_2=0. Rats having three or more abnormalities were assigned a risk parameter R_3=1; otherwise R_3=0. Risk parameters R_1, R_2, and R_3 were examined theoretically to see which would best represent radiation-induced effects.

It is reasonable to assume, for a given gender, that values for the vital capacity, CO diffusing capacity per kg body weight, quasistatic compliance, and slope of phase III of the single breath N_2 washout curve each are normally distributed. If so, R_1 would be expected to lead to the wrong conclusion about radiation induced effects about 20% of the time when there are no radiation induced effects; similarly, the use of R_2 would be expected to lead to the wrong conclusion 1.5% of the time; however, the use of R_3 would be expected to lead to the wrong conclusion only 0.05% of the time. Thus, we selected R_3 as the risk parameter to use in defining the presence or absence of pulmonary functional morbidity after irradiation of the lung. A value of R_3=1 was taken to indicate pulmonary functional morbidity due to injury to the lung. A value of R_3=0 was taken to indicate the absence of pulmonary functional morbidity.

A modified version of the Weibull model was then used to fit the data for the prevalence of pulmonary functional morbidity at 1.5 years after inhalation exposure to ^{238}Pu or ^{147}Pm. Data for combined exposure to both radionuclides were not fitted but were reserved for model validation. The modified model is given by

$$\text{Prevalence} = R_0 + (1-R_0)R \qquad (12)$$

where R is the same type of Weibull function as in Equation 7, and R_0 accounts for effects not due to irradiation. Use of this form of the Weibull model allows the determination of a shape parameter V and ILB_{50} for morbidity even though some rats may have pulmonary morbidity unrelated to irradiation. Using a maximum likelihood approach so that individual datum points could be used, the ILB_{50} was estimated for the prevelance of pulmonary morbidity among rats exposed to ^{238}Pu only or ^{147}Pm only. Because of the small sample sizes used, the shape parameter could not be adequately determined and was therefore assumed to be the same as for lethality from RPPF. For ^{238}Pu, the ILB_{50} for pulmonary morbidity was 30 $\pm$ 3 nCi/g-lung. For ^{147}Pm, it was 40 $\pm$ 4 μCi/g-lung. Corresponding D_{50} values for ^{238}Pu alphas and ^{147}Pm betas, based on cumulative radiation doses to the lung at 1.5 years after inhalation exposure, were 1,100 $\pm$ 110 rad (11 Gy) and 7,500 $\pm$ 750 rad (75 Gy), respectively. The parameter R_0 was found to be zero for these data. However, we have retained the modified model so that results can be compared with those obtained at Pacific Northwest Laboratory (PNL) by Dr. R. Filipy and coworkers who are using the same model.

Because the shape parameters for morbidity could not be adequately determined, a value of 5 was assumed and used. With the ILB_{50}'s and shape parameter given, doses in units of the ILB_{50} could be calculated for those rats exposed to both alpha and beta radiation; this was achieved by dividing the initial lung burden of ^{238}Pu in nCi/g-lung by 30 and dividing the initial lung burden of ^{147}Pm by 40 and adding the results to obtain the total dose X in units of the ILB_{50} or D_{50}. The individual risk for the prevalence of morbidity at 1.5 years was then calculated using

$$\text{Individual risk} = 1 - \exp[-H_m], \qquad (13)$$

where the morbidity hazard H_m is given by

$$H_m = \ln(2)*X^5, \qquad (14)$$

for radiation-induced pulmonary functional morbidity.

Adding the individual risk for a given ILB distribution over a given exposure level and dividing by the number of rats in the level gave the average risk for that level and for that ILB distribution. This average risk can only be used for the specific ILB distribution used to derive it because of the nonlinear shape of the curves for morbidity. The expected number of morbidity cases at a given exposure level is equal to the product of the average risk times the number of rats in the exposure level. Using the same hazard-function approach as was used for mortality from RPPF, the number of morbid rats at 1.5 years after combined alpha and beta irradiation of the lung was predicted for experimental groups AB2 and AB4. Predicted and observed values are given in Table 3.6 and are in good agreement.

Table 3.6

Predicted and Observed Cases of Respiratory Functional Morbidity Among F344/Crl Rats After Combined Alpha and Beta Irradiation of the Lung from Inhaled ^{147}Pm and ^{238}Pu in Fused Aluminosilicate Particles*

Experiment Group	Number Surviving Rats	Dose (Rads)** Alpha	Beta	Predicted Average Risk	Predicted Cases of Morbid Rats	Observed Cases of Morbid Rats
AB2	19	840	10400	0.97	18.5 ± 0.7	18
AB4	5	840	2640	0.54	2.7 ± 1.1	4
C	20	0	0	0	0	0
A1	6	4350	0	1	6	6
A2	19	930	0	0.29	5.5 ± 2.0	5
B1	13	0	8780	0.65	8.5 ± 1.7	10
B2	16	0	2910	0.04	0.7 ± 0.8	1

*Predictions were only made for Groups AB2 and AB4 where rats were exposed to both alpha and beta radiations. There were no survivors in Group AB1 and only one survivor in Group AB3 at 1.5 years. Values listed for Groups C, A1, A2, B1 and B2 are not predictions; data from these groups were fitted with the Weibull dose-response model to obtain model parameters to use to predict the results for Groups AB2 and AB4.

**Group average cumulative 1.5 year radiation dose to lung.

In earlier mortality experiments, in which rats were exposed via inhalation to one or more beta-emitting radionuclides (NUREG/CR-5025, 1987), the shape parameter for lethality from RPPF was also found to be about 5, and seemed to be independent of beta dose rate. It is shown in Table 3.7 that the ILB_{50} for acute lethality is about 4 times larger than that for morbidity. Corresponding doses to 1.5 years after inhalation exposure are given in Table 3.8. These results suggest that the same model used for acute mortality from beta irradiation to the lung could be used for morbidity if the D_{50} parameters for mortality are reduced by a factor of 4 for low energy betas.

A similar analysis of data from previous experiments in which F344/Crl rats inhaled mainly ^{90}Y or an equilibrium mixture of ^{90}Sr + ^{90}Y in fused aluminosilicate particles (NUREG/CR-5025, 1987) did not reveal any significant difference between the median-lethal and median-effective doses for morbidity. Both ^{90}Y and ^{90}Sr are high-energy beta emitters with average energies of 0.935 and 0.196 MeV, respectively; while for ^{147}Pm, the average energy is only 0.062 MeV. The

Table 3.7

Median Lethal Lung Burdens for Death* from Radiation Penumonitis and Pulmonary Fibrosis and Median Effective Lung Burdens for Respiratory Morbidity After Inhalation Exposure of F344/Crl Rats to ^{238}Pu or ^{147}Pm Inhaled in Fused Aluminosilicate Particles

Type of Radiation	Median Lethal	Median Effective	Ratio**
^{238}Pu alphas	123 ± 7.5 nCi/g-lung	30 ± 3 nCi/g-lung	4.1
^{147}Pm betas	160 ± 190 µCi/g-lung	40 ± 4 µCi/g-lung	4.0
		Average Ratio =	4.0

*Death within 1.5 years.

**Median lethal divided by median effective burden.

Table 3.8

Median Lethal 1.5 Year Radiation Doses to the Lung for Death Within 1.5 Years From Radiation Pneumonitis and Pulmonary Fibrosis and Median Effective Doses for Respiratory Morbidity at 1.5 Years After Inhalation Exposure of F344/Crl Rats to ^{238}Pu or ^{147}Pm Inhaled in Fused Aluminosilicate Particles

Type of Radiation	Median Lethal (rads)*	Median Effective (rads)*	Ratio**
^{238}Pu alphas	4,500	1,100	4.1
^{147}Pm betas	30,000	7,500	4.0
RBE***	6.7	6.8	

*1.5 year dose. Multiply beta dose by 0.88 to get 1-year dose. Multiply alpha dose by 0.85 to get 1-year dose.

**Median lethal divided by median effective dose.

***For 1.5 year followup.

results therefore suggest that the factor of 4 derived for comparing lethality and morbidity (respiratory dysfunction) may be applicable to alpha and low-energy beta radiations only.

Data in Table 3.8 were used to estimate the relative biological effectiveness of ^{238}Pu alphas relative to ^{147}Pm betas. An RBE of approximately 7 was obtained for both lethality and morbidity.

Dose-effect surfaces are given in Figures 3.15 and 3.16 for 1.5-year lethality from RPPF and for the prevalence of pulmonary morbidity at 1.5 years after inhalation exposure to a mixture of ^{238}Pu + ^{147}Pm inhaled in an insoluble form. Although the results are based on studies with F344/Crl rats, it is assumed that they are also applicable to man.

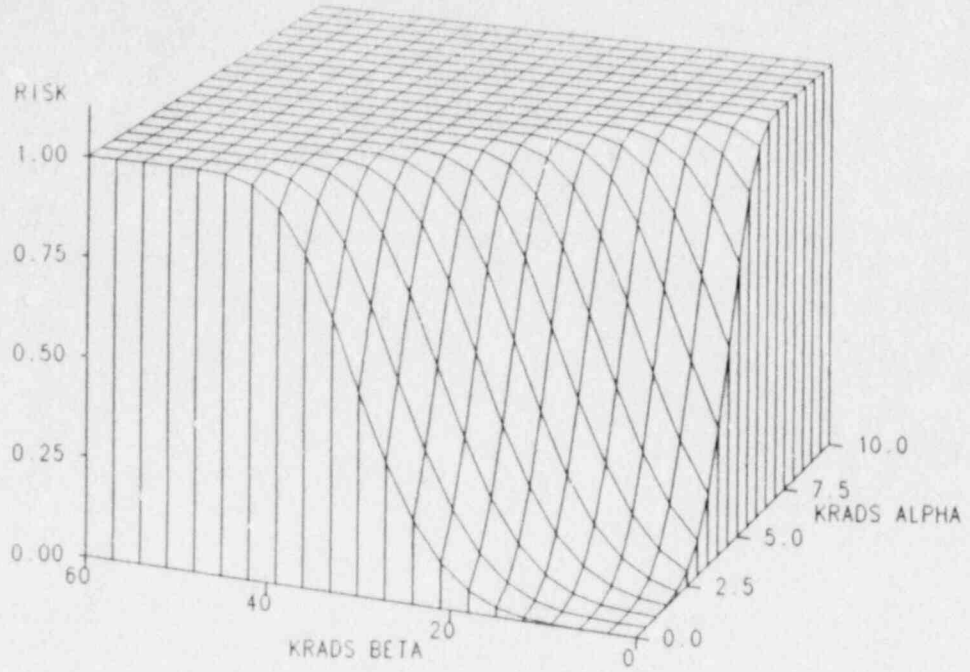

Figure 3.15 Dose-effect surface for F344/Crl rats for estimating the 1.5-year lethality risk for death from radiation pneumonitis and pulmonary fibrosis after inhalation exposure to mixtures of ^{238}Pu + ^{147}Pm inhaled in an insoluble form. Results are based on the hazard-function model. Doses represent 1.5-year doses to the lung.

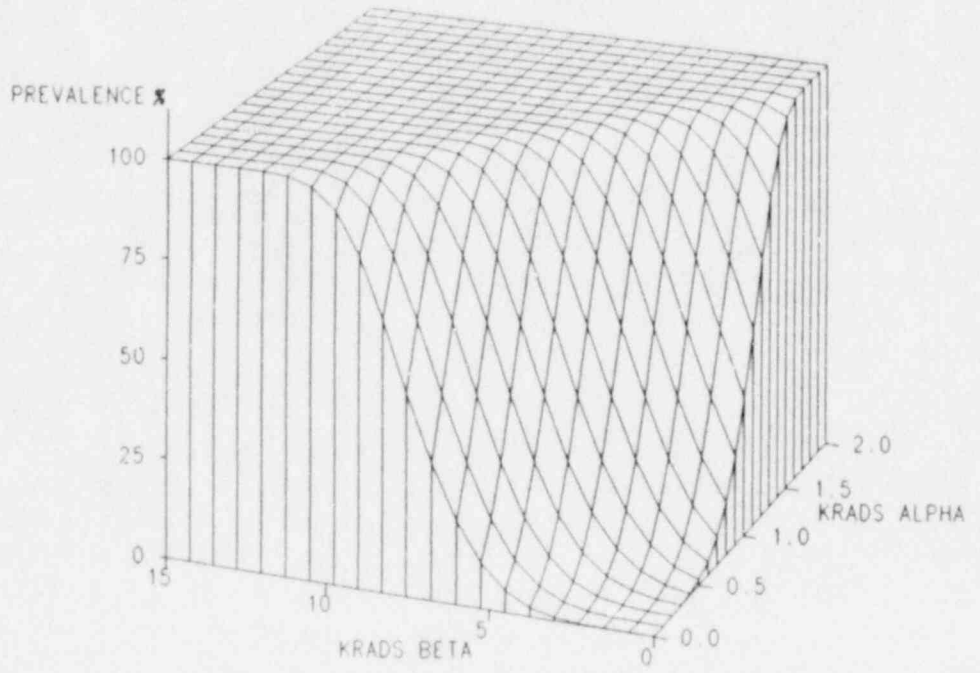

Figure 3.16 Dose-effect surface for F344/Crl rats for estimating the prevalence of respiratory morbidity at 1.5 years after inhalation exposure to mixtures of ^{238}Pu + ^{147}Pm inhaled in an insoluble form. Doses represent 1.5-year doses to the lung.

CHAPTER 4
CONCLUSIONS

The experiment described in this document was part of a series of inhalation exposure experiments carried out at the Inhalation Toxicology Research Institute to validate a mortality model (Scott et al., 1986) developed for predicting deaths from RPPF after inhalation exposure to mixtures of alpha- and beta-emitting radionuclides. Results of the experiment demonstrated that the hazard-function model adequately predicted the observed deaths from RPPF that occurred throughout the 1.5-year observation period.

Hematological evaluations were carried out on rats assigned to the hematology group at various times after inhalation exposure. However, no significant effects on the peripheral blood could be demonstrated. The implications are that low energy betas from ^{147}Pm and alphas from ^{238}Pu deposited in the lung do not deliver significant doses to the radiosensitive bone marrow because of their short range in tissue. In addition, combined alpha and beta irradiation of the blood traversing the lung does not lead to any significant alterations in the cellularity of the peripheral blood of rats.

Body weights of all rats were recorded at various times after inhalation exposure. Significant alterations in body weights were observed mainly in rats with lethal doses to the lung. The results indicate that body weight change is not a good indicator of morbidity among survivors.

Pulmonary function was evaluated in survivors at 1.5 years after inhalation exposure. It was demonstrated using pulmonary function measurements for the vital capacity, CO diffusing capacity, quasistatic compliance, and slope of phase 3 of the N_2 washout curve that irradiation of the lung leads to a reduction in lung volume, a decreased efficiency in gas exchange, a stiffer lung and an altered intrapulmonary gas distribution in some rats. These changes are all characteristic of RPPF and occurred at doses approximately one fourth of that required for acute lethality. A hazard-function model was developed for predicting the prevalence of pulmonary functional morbidity among rats exposed to both alpha and beta radiation. Model predictions were demonstrated to be in good agreement with experimental observations.

Assuming that these results are applicable to man, the implication is that a ^{239}Pu-alpha dose to the lung of approximately 1,100 rad (11 Gy) or a ^{147}Pm-beta dose of approximately 7,500 rad (75 Gy) could cause pulmonary functional morbidity in one-half of those exposed. In a recent report by Muggenburg et al. (1986), it was demonstrated that ^{239}Pu-alpha doses from 240 to 730 rad (2.4 to 7.3 Gy) to the lung of dogs caused clinical signs and pulmonary function values indicating RPPF at 7.1 years after inhalation exposure.

Among 19 rats exposed to ^{238}Pu-alpha doses (1.5 year doses) from 670 to 1,500 rad (6.7 to 15 Gy) to the lung, five had pulmonary functional morbidity, based on the risk parameter R_3. All of these five also had septal fibrosis, suggesting that the fibrosis may have been a cause of the functional morbidity.

Among 29 rats that had 1.5 year ^{147}Pm-beta doses to the lung from 1,100 to 13,000 rad (11 to 130 Gy), 11 had pulmonary functional morbidity, based on the risk parameter R_3. All except one of these 11 rats had septal fibrosis, suggesting that the fibrosis may have been a cause of the functional morbidity.

Together, the results presented imply that doses required for causing acute lethality from RPPF after alpha or low-energy-beta irradiation of the lung are considerably higher than those required for causing pulmonary functional morbidity. The results also indicate that pulmonary functional morbidity can be prevalent after more than a year of prolonged alpha or low-energy-beta irradiation of the lung.

After adjusting for competing modes of death, 80 rats were judged at risk for death from RPPF. Of these, 43 deaths were expected and 54 were observed. Also, for rats receiving combined alpha and beta irradiation of the lung, 21 out of 24 surviving rats were expected to have pulmonary functional morbidity while 22 cases were observed. The results indicate that the hazard-function mortality and hazard-function morbidity models for combined alpha and beta irradiation of the lung should be adequate for reactor accident risk assessment.

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APPENDIX: DATA BASES

Listing of rats exposed to aerosols of alpha- or beta-emitting radionuclides or both in fused aluminosilicate particles (FAP).

1. Rats exposed to aerosols of ^{238}Pu FAP, ^{147}Pm FAP, or ^{238}Pu + ^{147}Pm in FAP.
2. Pulmonary function measurements in rats exposed to aerosols of ^{238}Pu FAP, ^{147}Pm FAP, or ^{238}Pu + ^{147}Pm in FAP.

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2A. PULMONARY FUNCTION MEASUREMENTS FOR RATS EXPOSED VIA INHALATION TO ^{238}Pu, ^{147}Pm OR BOTH IN FAP

ANIMAL NUMBER	EXPERIMENT NUMBER	SEX	MONTHS AFTER EXPOSURE	ILB Pu-238 (nCi/g-LUNG)	ILB Pm-147 (μCi/g-LUNG)	ALPHA RADS	BETA RADS	VITAL CAPAC. (ml)	CO DIFFUSING CAPAC. (ml/min/mm Hg)	DIFFUSING CAPACITY PER Kg BODY WT	QUASISTATIC COMPLIANCE (ml/cm H_2O)	SLOPE PHASE 3
101	3941	F	18	0	0	0	0	10.8	0.19	0.87	0.81	0.60
103	3941	F	18	0	0	0	0	10.6	0.19	0.80	0.79	0.42
105	3941	F	18	0	0	0	0	11.7	0.22	0.87	0.92	0.69
107	3941	F	18	0	0	0	0	12.0	0.23	0.90	0.93	0.35
109	3941	F	18	0	0	0	0	11.4	0.23	0.81	0.86	0.68
111	3941	F	18	0	0	0	0	9.6	0.16	0.70	0.73	0.51
113	3941	F	18	0	0	0	0	11.2	0.22	0.92	0.85	0.47
115	3941	F	18	0	0	0	0	11.9	0.23	0.79	0.89	0.49
117	3941	F	18	0	0	0	0	12.5	0.22	0.67	1.00	0.52
118	3941	F	18	0	0	0	0	13.7	0.25	0.79	1.10	0.27
119	3941	M	18	0	0	0	0	14.3	0.25	0.77	1.03	0.48
121	3941	M	18	0	0	0	0	14.8	0.31	0.84	1.06	0.51
123	3941	M	18	0	0	0	0	17.1	0.35	0.79	1.30	0.48
126	3941	M	18	0	0	0	0	16.9	0.33	0.95	1.22	0.44
127	3941	M	18	0	0	0	0	16.1	0.30	0.74	1.21	0.45
129	3941	M	18	0	0	0	0	17.1	0.38	0.86	1.29	0.38
131	3941	M	18	0	0	0	0	16.4	0.27	0.65	1.27	0.28
133	3941	M	18	.	.	0	0	15.6	0.18	0.44	1.17	0.40
135	3941	M	18	0	0	0	0	16.5	0.35	0.74	1.26	0.42
136	3941	M	18	0	0	0	0	15.1	0.36	0.74	1.13	0.56
201	3942	F	18	115	0	4300	0	4.9	0.06	0.27	0.28	9.01
203	3942	F	18	141	0	5200	0	4.9	0.04	0.23	0.30	8.66
205	3942	F	18	139	0	5200	0	5.2	0.06	0.24	0.32	7.65
209	3942	F	18	114	0	4200	0	4.6	0.05	0.21	0.27	8.82
213	3942	F	18	115	0	4300	0	6.5	0.08	0.34	0.46	3.20
230	3942	M	18	77	0	2900	0	11.1	0.19	0.48	0.84	0.86
301	3943	F	18	25	0	930	0	9.2	0.14	0.65	0.67	0.78
302	3943	F	18	34	0	1300	0	9.9	0.17	0.67	0.69	0.58
303	3943	F	18	19	0	700	0	10.6	0.19	0.73	0.80	0.77
304	3943	F	18	39	0	1500	0	7.2	0.12	0.48	0.50	1.37
305	3943	F	18	26	0	960	0	9.8	0.17	0.69	0.75	0.57
307	3943	F	18	30	0	1100	0	10.0	0.18	0.69	0.74	0.47
309	3943	F	18	22	0	820	0	10.7	0.18	0.70	0.81	0.48
312	3943	F	18	24	0	890	0	10.5	0.15	0.60	0.77	0.45
313	3943	F	18	22	0	820	0	11.1	0.21	0.95	0.84	0.73
314	3943	F	18	18	0	670	0	11.1	0.22	0.83	0.85	0.39
319	3943	M	18	27	0	1000	0	9.1	0.15	0.48	0.72	0.77
320	3943	M	18	30	0	1100	0	15.0	0.31	0.83	1.13	0.46
321	3943	M	18	34	0	1300	0	12.2	0.26	0.72	0.84	0.64
325	3943	M	18	18	0	670	0	11.8	0.23	0.62	0.95	0.30
328	3943	M	18	20	0	740	0	13.8	0.27	0.61	1.08	0.50
330	3943	M	18	21	0	780	0	14.4	0.35	0.87	1.10	0.54
331	3943	M	18	26	0	960	0	15.7	0.27	0.62	1.24	0.36
332	3943	M	18	19	0	700	0	11.9	0.21	0.53	0.84	0.72
333	3943	M	18	20	0	740	0	15.6	0.30	0.68	1.19	0.48
407	3944	F	18	0	59	0	11000	7.2	0.12	0.47	0.46	2.22
408	3944	F	18	0	56	0	11000	7.6	0.14	0.56	0.49	0.82
410	3944	F	18	0	35	0	6600	5.1	0.10	0.39	0.37	8.22
416	3944	F	18	0	53	0	9900	8.5	0.15	0.53	0.59	1.04
418	3944	F	18	0	38	0	7100	10.0	0.18	0.69	0.78	0.56
419	3944	M	18	0	67	0	13000	12.2	0.26	0.67	0.83	0.72
422	3944	M	18	0	64	0	12000	8.0	0.15	0.42	0.54	1.66
429	3944	M	18	0	49	0	9200	15.4	0.27	0.61	1.17	0.36
430	3944	M	18	0	28	0	5200	12.7	0.25	0.58	0.97	0.69
431	3944	M	18	0	27	0	5100	13.0	0.31	0.74	0.94	0.70

2B. PULMONARY FUNCTION MEASUREMENTS FOR RATS EXPOSED VIA INHALATION TO ^{238}Pu, ^{147}Pm OR BOTH IN FAP

ANIMAL NUMBER	EXPERIMENT NUMBER	SEX	MONTHS AFTER EXPOSURE	ILC Pu-238 (nCi/g-LUNG)	ILB Pm-147 (μCi/g-LUNG)	ALPHA RADS	BETA RADS	VITAL CAPAC. (ml)	CO DIFFUSING CAPAC. (ml/min/mm Hg)	DIFFUSING CAPACITY PER Kg BODY WT	QUASISTATIC COMPLIANCE (ml/cm-H_2O)	SLOPE PHASE 3
432	3944	M	18	0	38	0	7100	12.3	0.21	0.53	0.93	0.59
433	3944	M	18	0	52	0	9700	12.2	0.22	0.57	0.89	0.75
436	3944	M	18	0	39	0	7300	14.1	0.24	0.54	1.08	0.42
501	3945	F	18	0	22	0	4100	8.6	0.14	0.63	0.67	0.68
502	3945	F	18	0	20	0	3700	11.5	0.21	0.85	0.87	0.76
504	3945	F	18	0	19	0	3600	11.3	0.19	0.71	0.87	0.44
507	3945	F	18	0	6	0	1100	11.2	0.20	0.76	0.80	0.63
508	3945	F	18	0	7	0	1300	10.5	0.19	0.77	0.75	0.88
509	3945	F	18	0	9	0	1700	12.6	0.23	0.97	0.94	0.65
510	3945	F	18	0	7	0	1300	10.9	0.21	0.85	0.83	0.74
511	3945	F	18	0	12	0	2200	12.7	0.21	0.77	0.99	0.52
513	3945	F	18	0	31	0	5800	11.8	0.10	0.39	0.88	0.51
514	3945	F	18	0	29	0	5400	12.3	0.19	0.71	0.87	0.42
519	3945	M	18	0	10	0	1900	15.4	0.31	0.86	1.13	0.50
521	3945	M	18	0	6	0	1100	14.6	0.17	0.45	1.03	0.52
522	3945	M	18	0	9	0	1700	16.5	0.28	0.74	1.28	0.32
523	3945	M	18	0	14	0	2600	16.2	0.32	0.77	1.17	0.47
524	3945	M	18	0	13	0	2400	15.3	0.31	0.75	1.09	0.34
525	3945	M	18	0	35	0	6600	14.6	0.31	0.77	1.10	0.54
702	3947	F	18	34	53	1200	15000	4.4	0.05	0.24	0.28	12.06
704	3947	F	18	18	30	650	8300	9.3	0.16	0.68	0.67	0.73
705	3947	F	18	15	24	540	6600	9.4	0.15	0.60	0.65	0.67
706	3947	F	18	25	41	900	11000	9.2	0.13	0.48	0.69	0.58
707	3947	F	18	21	34	760	9400	5.2	0.07	0.29	0.33	5.62
708	3947	F	18	23	37	830	10000	6.3	0.09	0.35	0.38	2.47
711	3947	F	18	34	53	1200	15000	5.3	0.07	0.31	0.41	5.09
712	3947	F	18	20	33	720	9100	7.9	0.15	0.59	0.55	1.13
713	3947	F	18	19	31	680	8500	7.8	0.15	0.52	0.57	1.35
715	3947	F	18	29	46	1000	13000	6.2	0.10	0.33	0.43	3.49
716	3947	F	18	19	31	680	8500	8.6	0.12	0.49	0.57	0.68
717	3947	F	18	21	32	760	8800	9.5	0.15	0.54	0.66	0.80
718	3947	F	18	20	32	720	8800	7.5	0.10	0.40	0.49	1.24
719	3947	M	18	33	51	1200	14000	8.2	0.12	0.32	0.60	1.55
725	3947	M	18	25	39	900	11000	9.9	0.21	0.55	0.67	1.39
726	3947	M	18	29	46	1000	13000	7.3	0.14	0.38	0.52	1.92
729	3947	M	18	18	28	650	7700	13.8	0.24	0.55	1.03	0.52
731	3947	M	18	19	30	680	8300	10.4	0.21	0.56	0.78	0.78
732	3947	M	18	27	43	970	12000	8.1	0.13	0.33	0.53	1.51
909	3949	F	18	27	11	970	3000	6.8	0.12	0.48	0.45	1.64
920	3949	M	18	21	8	760	2200	14.7	0.25	0.68	1.14	0.39
922	3949	M	18	19	8	680	2200	10.8	0.13	0.38	0.88	0.67
928	3949	M	18	27	11	970	3000	10.4	0.21	0.50	0.76	0.86
930	3949	M	18	23	10	830	2800	9.5	0.14	0.38	0.70	1.26

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13. ABSTRACT (200 words or less)

This report summarizes an inhalation exposure experiment that concerns early and continuing effects of combined alpha and beta irradiation of the lung of rats. Both morbidity at 18 months and mortality within 18 months after exposure were examined for rats exposed to the beta-emitter ^{147}Pm, the alpha-emitter ^{238}Pu, or both combined. The results were used to validate hazard-function models that were developed (1) for pulmonary functional morbidity at 18 months and (2) for lethality from radiation pneumonitis and pulmonary fibrosis within 18 months. Both models were found to adequately predict the experimental observations after combined chronic alpha and beta irradiation of the lung. A relative biological effectiveness of approximately 7 was obtained for ^{238}Pu alpha radiation compared to ^{147}Pm beta radiation for both pulmonary functional morbidity and lethality from radiation pneumonitis and pulmonary fibrosis.

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